



Defining the Place of Ezetimibe/Atorvastatin in the Management of Hyperlipidemia

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Abstract Statin–ezetimibe combinations are a potentially advantageous therapeutic option for high-risk patients who need additional lowering of low-density lipoprotein cholesterol (LDL-C). These combinations may overcome some of the limitations of statin monotherapy by blocking both sources of cholesterol. Recently, a fixed-dose combination with atorvastatin, one of the most extensively studied statins, was approved and launched in several countries, including the USA. Depending on atorvastatin dose, this combination provides LDL-C reductions of 50–60%, triglyceride reductions of 30–40%, and high-density lipoprotein cholesterol (HDL-C) increases of 5–9%. Studies comparing the lipid-lowering efficacy of the atorvastatin–ezetimibe combination with the alternatives of statin dose titration or switching to a more potent statin consistently showed that combination therapy provided greater LDL-C reduction, translating into a greater proportion of patients achieving lipid goals. Simvastatin–ezetimibe combinations have been shown to reduce the incidence of major atherosclerotic events in several clinical settings to a magnitude that seems similar to that observed with statins for the same degree of absolute LDL-C lowering. The atorvastatin–ezetimibe combination has also been shown to induce the regression of coronary atherosclerosis measured by intravascular ultrasound in a significantly greater proportion of patients than atorvastatin

alone. Atorvastatin–ezetimibe combinations are generally well tolerated. Previous concerns of a possible increase in the incidence of cancer with ezetimibe were dismissed in large trials with long follow-up periods. In this paper, we examine the rationale for an atorvastatin–ezetimibe combination, review the evidence supporting it, and discuss its potential role in the management of dyslipidemia.

Key Points

Statin–ezetimibe combinations are a realistic treatment option for patients who do not achieve low-density lipoprotein cholesterol (LDL-C) targets while receiving statin monotherapy and for patients prone to dose-dependent statin side effects.

The IMPROVE-IT trial was the first to demonstrate a reduction in cardiovascular events with ezetimibe.

Recently, combination therapy with atorvastatin plus ezetimibe was also associated with greater coronary plaque regression than atorvastatin alone.

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1 Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, despite recent improvements in both [1]. Large epidemiological studies established hypercholesterolemia as one of the most important risk factors for myocardial infarction and ischemic stroke at the population level [2, 3]. The notion

that low-density lipoprotein cholesterol (LDL-C) plays a causal role in atherosclerotic disease is further supported by genetic studies [4–6] and by a large number of randomized controlled trials (RCTs) showing that lipid-lowering interventions reduce the risk of cardiovascular events proportionally to their LDL-C reduction efficacy (reviewed in three meta-analyses) [7–9]. HMG Co-A reductase inhibitors (statins) are the cornerstone of pharmacological lipid-lowering treatment to reduce cardiovascular risk. Statins act by decreasing the hepatic production of LDL-C, enabling reductions in serum LDL-C levels of up to 50–60% when high doses are used [10]. Although these agents transformed the management of dyslipidemia in the last 30 years, an unquestionable ‘residual risk’ for cardiovascular morbidity and mortality remains despite statin therapy [11]. This ‘residual risk’ prompted the search for additional lipid-lowering therapies that could offer further cardiovascular risk reduction. Ezetimibe, an inhibitor of intestinal cholesterol absorption, was approved for clinical use in 2002 and has been available as a single agent and in combination with simvastatin. Recently, a fixed-dose combination with atorvastatin, one of the most extensively studied statins, was also approved and launched in several countries, including the USA. The interest in these statin–ezetimibe combinations has now been strengthened by the publication of much awaited data showing cardiovascular risk reduction with ezetimibe in patients with acute coronary syndromes (ACS) [12]. In this article, we examine the rationale for an atorvastatin–ezetimibe combination, conduct a narrative review of the evidence supporting it, and discuss its potential role in the management of dyslipidemia.

1.1 Rationale for Combination Therapy

Even though statins are unquestionably the mainstay of the pharmacological treatment of hypercholesterolemia, they are unable to fulfill the clinical needs of a significant proportion of patients. The underlying reasons are discussed below.

1.1.1 Variability in Individual Response to Statin Therapy

A large variability in individual response has been demonstrated for several different statins and doses [13, 14]. A recent meta-analysis using individual subject data collected from 32,258 patients treated with atorvastatin 10–80 mg, rosuvastatin 5–40 mg, or simvastatin 10–80 mg showed that the standard deviation of LDL-C reduction for all statins and doses ranged from 13 to 18%, whereas the percentage of patients experiencing a suboptimal response (<30% reduction in LDL-C) ranged from 5 to 53% [15]. This somewhat unpredictable response to

statins is thought to be due to a complex interplay between genetic and environmental factors [16, 17] that translates into a large variability in the balance between cholesterol synthesis and absorption and, at least in part, a compensatory increase in intestinal cholesterol uptake [18, 19]. Recently, the PRECISE-IVUS (Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial found that sterols (lathosterol, campesterol, and sitosterol) and their ratio to cholesterol increased with atorvastatin monotherapy but decreased with the atorvastatin–ezetimibe combination. Interestingly, the campesterol-to-cholesterol ratio reduction was positively related to a reduction in percent atheroma volume [20]. The notion that statin–ezetimibe combination therapy might reduce the variability in LDL-C-lowering response is also supported by a recent analysis of patient-level data pooled from 27 double-blind controlled studies [21].

1.1.2 Side Effects of Statins

Statins are generally well tolerated. The most common side effects are muscle-related symptoms and elevated serum transaminases, both of which are more frequent when high doses are used. Statin-associated myopathy is a rare but serious side effect, affecting 1 per 100 to 1 per 10,000 people receiving standard statin doses. Perhaps more importantly, up to 7–29% of patients experience some type of statin-associated muscle symptoms that may lead to drug discontinuation [22].

Statin therapy was also recently shown to carry a small increase in the risk of developing type 2 diabetes mellitus [23]. The underlying mechanism remains to be elucidated, but the issue was considered sufficiently important for the US FDA to change their labeling requirements for statins to include a warning about the possibility of increased blood sugar and glycated hemoglobin (HbA_{1c}) levels. The risk of new-onset diabetes is relatively circumscribed to patients who already have one or more risk factors for developing this disease [24, 25] and seems to be higher with intensive statin therapy than with moderate-dose therapy [26]. Although some drugs may be more harmful than others [27, 28], the current evidence is insufficient to recommend specific statins based on their diabetogenic potential [29, 30]. Although the benefits of statin therapy seem to largely outweigh the risk of inducing diabetes, concern remains that some individuals might experience this side effect without deriving any benefit (i.e., individuals who would not experience a cardiovascular event even if left untreated).

Since these side effects seem to be dose dependent, the use of combination therapy as part of a statin dose-sparing strategy may be an attractive approach, particularly for

patients who cannot tolerate high-dose statins or who are prone to statin-induced myopathy (the elderly, Asian patients, or those with renal insufficiency) [31]. This reasoning relies on the assumption that a second drug (such as ezetimibe) results in cardiovascular event reductions that are similar to those observed with statins for the same degree of LDL-C lowering, an idea for which there is growing evidence [5, 12].

1.1.3 Inability of Some Patients to Attain Desirable Low-Density Lipoprotein Cholesterol (LDL-C) Levels (or Percent LDL-C Reductions) with Statin Monotherapy

The usefulness of treatment goals has been one of the most controversial issues in clinical lipidology in recent years, particularly after the publication of the contemporary American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol [32]. These guidelines represented a major paradigm shift and sparked considerable controversy because they abandoned the traditional treat-to-target approach [33]. Even though the strategy of treating patients to a specific level of LDL-C has never been formally tested in large trials assessing cardiovascular morbidity and mortality, treatment goals might still be useful as a means to ensure that the aggressiveness of therapy is matched to absolute risk for an event [34]. LDL-C levels achieved with treatment correlated well with the incidence of major atherosclerotic cardiovascular events in four meta-analyses [7–9, 13] and a large analysis of 40,000 patient records [35]. Acknowledging the new evidence of cardiovascular event reduction with ezetimibe and the potential role of the recently approved monoclonal antibodies to proprotein convertase subtilisin/kexin 9 (PCSK9), the American College of Cardiology issued an expert consensus document on the role of non-statin therapies for LDL-C lowering [36]. Although LDL-C goals are not exactly reinstated, percent LDL-C reduction (or, alternatively, absolute LDL-C levels) are included in the proposed decision algorithms.

Apart from the cholesterol targets controversy, a large body of data shows that a sizeable proportion of patients do not achieve desirable LDL-C levels (or expected percent LDL-C reductions) despite statin treatment. DYSIS (Dyslipidemia International Study) was a cross-sectional observational study conducted in Europe and Canada that assessed the prevalence of persistent dyslipidemia in patients treated with statins. Overall, 48.2% of patients did not achieve their LDL-C goal (according to European Society of Cardiology [ESC] recommendations) [37]. Among high-risk patients (defined as established CVD, diabetes, or ESC-SCORE $\geq 5\%$), 46.8% did not attain an LDL-C level < 97 mg/dl [38]. The more recent DYSIS-II

study, which enrolled 3867 patients with recent ACS and 6794 patients with stable coronary heart disease (CHD), showed that, among those receiving lipid-lowering treatment, only 26% of patients with ACS and 31% of those with stable CAD achieved an LDL-C < 70 mg/dl. The median distance to target was 34 and 29 mg/dl, respectively [39]. Finally, EUROASPIRE IV was a cross-sectional survey undertaken in 24 European countries where the medical records of 7998 patients with established CHD were reviewed. Among those receiving lipid-lowering medication, only one-fifth reached LDL-C < 70 mg/dl [40].

It can be argued that these poor results from the ‘real world’ are largely the consequence of using only moderately intensive statin therapy; however, clinical trial data show that a significant proportion of patients still do not reach LDL-C goals, even with high doses of statins. In a recent meta-analysis of eight RCTs including 18,677 patients treated with high-dose statins (defined as either rosuvastatin 20 mg or atorvastatin 80 mg), 40% of patients did not reach an LDL-C < 70 mg/dl [13].

In summary, the potential usefulness of adding a second lipid-lowering drug to baseline statin therapy is essentially twofold: (1) to increase the efficacy of treatment when the achieved LDL-C reduction is deemed insufficient and (2) to allow the use of a lower statin dose in patients who cannot tolerate, or may experience important side effects with, higher doses. Other less studied potential advantages of combination therapy include a decrease in LDL-C-lowering variability and possible improvements in patient adherence (because of the lower number of daily pills).

2 Key Data on Ezetimibe, Atorvastatin, and their Combination

Ezetimibe inhibits the intestinal absorption of biliary and dietary cholesterol by interacting with the Niemann-Pick C1-like 1 (NPC1L1) sterol transporter located on the brush border membrane of enterocytes in the proximal jejunum [41, 42]. The resulting reduction in liver cholesterol levels triggers an upregulation of hepatic LDL-C receptors, thereby causing increased clearance of cholesterol from the blood. Both ezetimibe and its active glucuronide metabolite undergo extensive enterohepatic circulation, ensuring repeated delivery to the site of action and limiting systemic exposure. Recent Mendelian randomization studies have supported the rationale of targeting intestinal absorption through this pathway. Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL-C levels and a reduced risk of CHD. Moreover, the effect of lower LDL-C on the risk of CHD mediated by polymorphisms in NPC1L1, HMG Co-A reductase, or both was approximately the same per unit

lower LDL-C [5, 6]. The group with polymorphisms in both NPC1L1 and HMG Co-A reductase showed a largely additive effect in LDL-C lowering and in risk reduction of CHD (odds ratio [OR] 0.892, 95% confidence interval [CI] 0.854–0.932) compared with the reference group.

2.1 Lipid-Lowering Efficacy of the Ezetimibe/Atorvastatin Combination

Ezetimibe monotherapy (10 mg per day) significantly reduces LDL-C levels by roughly 20% compared with placebo [43, 44]. When added to statins, ezetimibe also provides statistically significant improvements in triglycerides, HDL-C, non-HDL-C, apolipoprotein B (ApoB), and high-sensitivity C-reactive protein (hsCRP). Effects on these parameters are consistently observed in different patient populations, including those with metabolic syndrome and diabetes mellitus [45]. Despite focusing on the short-term safety and laboratory effects of statin-ezetimibe combinations, the following studies provided important information on their impact on lipid profiles. The lipid-lowering efficacy of the ezetimibe–atorvastatin combination was assessed in several clinical trials enrolling patients who did not attain LDL-C goals while receiving atorvastatin monotherapy (Table 1).

EZ-PATH was a multicenter randomized double-blind study that included 579 high-risk patients with LDL-C levels between 70 and 160 mg/dl while receiving

atorvastatin 40 mg per day. Patients were randomly assigned to receive (1) atorvastatin 40 mg plus ezetimibe 10 mg per day or (2) atorvastatin 80 mg per day for 6 weeks. Combination therapy resulted in a significantly greater reduction in LDL-C than did doubling the atorvastatin dose (–27 vs. –11%, respectively) [46]. The TEMPO trial used a similar design in patients with moderately high risk unable to meet LDL-C goals with atorvastatin 20 mg. Adding ezetimibe to atorvastatin 20 mg resulted in a greater LDL-C reduction than did doubling the statin dose to 40 mg (–31 vs. –11%, respectively) [47]. Another multicenter randomized double-blind study compared the efficacy and safety of ezetimibe 10 mg plus response-based atorvastatin titration versus response-based atorvastatin alone in the attainment of LDL-C goals in 621 high-risk patients with LDL-C \geq 130 mg/dl on the starting dose of atorvastatin. The proportion of subjects reaching their target LDL-C goal of \leq 100 mg/dl was significantly higher in the coadministration group than in the atorvastatin monotherapy group (22 vs. 7%). At 4 weeks, LDL-C levels were reduced significantly more by combination therapy than by doubling the dose of atorvastatin (–22.8 vs. –8.6%) [48]. All dose combinations of ezetimibe–atorvastatin were simultaneously assessed in a large prospective randomized double-blind clinical trial. In this study, 628 patients with baseline LDL-C 145–250 mg/dl were randomly assigned to receive one of the following for 12 weeks: ezetimibe 10 mg/day, atorvastatin (10, 20, 40, or

Table 1 Summary of key data from lipid-lowering efficacy trials of ezetimibe–atorvastatin combinations

Trial	Baseline pt characteristics	Treatment arms	Main results
EZ-PATH [46]	579 high-risk pts with LDL-C 70–160 mg/dl with ATO 40 mg/day	EZE 10 mg/day + ATO 40 mg/day vs. doubling ATO dose to 80 mg/day	Adding EZE to ATO 40 mg/day resulted in significantly greater reductions in LDL-C and significantly more pts achieving LDL-C <70 mg/dl
TEMPO [47]	184 moderately-high risk pts with LDL-C levels 100–160 mg/dl receiving ATO 20 mg/day	EZE 10 mg/day + ATO 20 mg/day vs. doubling ATO dose to 40 mg/day	Adding EZE to ATO 20 mg resulted in significantly greater reductions in LDL-C and significantly more pts achieving LDL-C <100 mg/dl
Stein et al. [48]	621 high-risk pts with LDL-C \geq 130 mg/dl despite treatment with ATO 10 mg/day	EZE 10 mg/day + ATO 10 mg/day followed by response-based ATO dose titration up to 40 mg/day vs. monotherapy with ATO 20 mg/day with response-based ATO dose titration up to 80 mg/day	Adding EZE to ATO 10 mg/day followed by ATO dose titration was more effective in reducing LDL-C and significantly increased the proportion of pts achieving LDL-C \leq 100 mg/dl
Ballantyne et al. [49]	628 pts with primary hypercholesterolemia and baseline LDL-C 145–250 mg/dl	Ten treatment groups: EZE 10 mg/day + ATO (10, 20, 40, or 80 mg), ATO (10, 20, 40, or 80 mg), EZE 10 mg/day, or placebo	Adding EZE to ATO (pooled doses) was significantly more effective at reducing LDL-C than ATO monotherapy (pooled doses)
Bays et al. [50]	1547 high-risk pts with LDL-C > 100 mg/dl despite treatment with ATO 10 mg/day	EZE 10 mg + ATO 10 mg/day vs. ATO 20 mg/day vs. ROS 10 mg/day	EZE + ATO 10 mg/day reduced LDL-C significantly more than ATO 20 mg or ROS 10 mg

ATO atorvastatin, EZE ezetimibe, LDL-C low-density lipoprotein cholesterol, pt(s) patient(s), ROS rosuvastatin

80 mg/day), ezetimibe 10 mg plus atorvastatin (10, 20, 40, or 80 mg/day), or placebo [49]. Depending on atorvastatin dose, the ezetimibe–atorvastatin combination provided LDL-C reductions of 50–60%, triglyceride reductions of 30–40%, and HDL-C increases of 5–9%. Coadministration of ezetimibe with atorvastatin 10 mg afforded a 50% reduction in LDL-C, similar to the 51% reduction obtained with high-dose atorvastatin (80 mg) monotherapy. Compared with the LDL-C level obtained by atorvastatin alone, the average incremental LDL-C reduction achieved by coadministration of ezetimibe with atorvastatin was 22%. Finally, Bays et al. [50] studied 1547 high-risk subjects who did not achieve LDL-C <100 mg/dl while receiving atorvastatin 10 mg per day. Patients were randomly assigned to one of three treatment options: adding ezetimibe 10 mg to stable atorvastatin 10 mg, doubling atorvastatin to 20 mg, or switching to rosuvastatin 10 mg. After 6 weeks of treatment, ezetimibe plus atorvastatin 10 mg reduced LDL-C significantly more than did atorvastatin 20 mg or rosuvastatin 10 mg (−22.2 vs. −9.5% vs. −13.0%, respectively) [50]. In all these trials, the larger LDL-C reduction provided by the ezetimibe–atorvastatin combination translated into a greater proportion of patients achieving lipid goals compared with statin monotherapy.

2.2 Previous Clinical Experience with Simvastatin–Ezetimibe Combinations

It is important to emphasize that the main purpose of treating hypercholesterolemia is to prevent atherothrombotic events. Favorable effects on lipid profile are a necessary but not sufficient condition for a lipid drug to be truly beneficial. Drugs such as niacin, fibrates, and torcetrapib have failed to clearly demonstrate cardiovascular event reduction (and in some cases have proved harmful) despite their apparently salutary effect on lipid blood tests [51–53]. Evidence for cardiovascular risk reduction with statin–ezetimibe combination therapy has been sought in RCTs performed in several clinical settings. Although they were all performed using simvastatin, their results serve as a ‘proof-of-concept’ for the clinical benefits of other statin–ezetimibe combinations. A brief review of these trials is presented below and summarized in Table 2.

The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial was the first to study the potential anti-atherogenic effect of ezetimibe added to statin therapy. ENHANCE was an RCT in patients with heterozygous familial hypercholesterolemia (FH) to assess the effect of simvastatin 80 mg plus ezetimibe 10 mg daily versus simvastatin 80 mg alone on the carotid intima-media thickness (cIMT), used as a surrogate marker of subclinical atherosclerosis. Despite a 16.5% greater reduction in LDL-C in the combination

therapy arm, no change was observed in the primary outcome, the change from baseline mean cIMT [54]. The trial results generated a great deal of controversy, and several possible explanations were promptly pointed out, including the study population, previous treatment with statins, a relatively short follow-up period, the variability of cIMT measurements, and the possibility that ezetimibe would decrease LDL-C without affecting the atherosclerotic process. Recent evidence strongly suggests that change in cIMT (the chosen primary outcome) is in fact an inadequate surrogate marker of atherosclerosis progression [55, 56]. Nowadays, most scientific societies do not recommend the use of cIMT for cardiovascular risk assessment (class III recommendation, level of evidence A/B) [57, 58]. The ENHANCE results, together with those from subsequent studies, highlighted the need for trials assessing cardiovascular outcomes rather than surrogate markers.

In the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial, 1873 patients with asymptomatic mild to moderate aortic stenosis (AS) were randomly assigned to receive simvastatin 40 mg plus ezetimibe 10 mg versus placebo. The primary outcome was a composite of major atherosclerotic and valvular events (death from cardiovascular causes, aortic valve replacement, non-fatal myocardial infarction, hospitalization for unstable angina, and non-hemorrhagic stroke). After a median follow-up period of 52 months, the primary outcome occurred in 35.3% of patients in the combination therapy arm and in 38.3% of patients in the placebo arm, failing to reach statistical significance [59]. Similar studies failed to show a benefit from lipid-lowering therapy in slowing or halting the progression of AS, suggesting that the pathophysiology of this valvular disease may be predominantly driven by tissue calcification of valve leaflets and not atherosclerosis [60, 61]. However, in SEAS there was a 22% relative risk reduction in ischemic cardiovascular events (a pre-specified secondary endpoint) in the simvastatin–ezetimibe group (15.7 vs. 20.1%, hazard ratio [HR] 0.78; $p = 0.02$). A substudy of the SEAS trial suggested that the degree of LDL-C reduction obtained with simvastatin–ezetimibe was closely related to the extent of ischemic event reduction in patients with mild AS, but not in those with more severe AS [62].

SHARP (Study of Heart And Renal Protection) was a large randomized outcomes controlled trial assessing the efficacy and safety of simvastatin 20 mg plus ezetimibe 10 mg versus placebo in 9270 patients with moderate to severe chronic kidney disease (CKD) defined as being on dialysis or having a serum creatinine of at least 1.7 mg/dl in men and 1.5 mg/dl in women. After a median follow-up of 4.9 years, simvastatin–ezetimibe therapy resulted in a mean reduction in LDL-C of 33 mg/dl and a 17% relative risk reduction (HR 0.83; $p = 0.002$) in major

Table 2 Randomized controlled trials assessing the effect of simvastatin/ezetimibe combinations on cardiovascular outcomes

Study ^a	Population	Treatment	Clinical endpoints	Median follow-up	Main findings
SEAS [59]	1873 pts with asymptomatic aortic stenosis	SIM 40 mg + EZE 10 mg vs. PL	Composite of death from CV causes, aortic valve replacement, non-fatal MI, hospitalization for UA, coronary revascularization, HF, and non-hemorrhagic stroke	4.3 years	Non-significant reduction in primary endpoint 22% RRR (4.4% ARR) in ischemic events (pre-specified secondary endpoint)
SHARP [63]	9270 pts with moderate to severe CKD ($\approx 1/3$ on dialysis)	SIM 20 mg + EZE 10 mg vs. PL	Composite of death from CAD, non-fatal MI, non-hemorrhagic stroke, or any revascularization procedure	4.9 years	17% RRR (2.1% ARR) in primary endpoint
IMPROVE-IT [12]	18,144 pts with stabilized ACS	SIM 40 mg + EZE 10 mg vs. SIM 40 mg	Composite of CV death, nonfatal MI, UA requiring rehospitalization, coronary revascularization, or nonfatal stroke	6 years	6.4% RRR (2.0% ARR) in primary endpoint

^a See the main text for full study names

ACS acute coronary syndrome, ARR absolute risk reduction, CAD coronary artery disease, CKD chronic kidney disease, CV cardiovascular, EZE ezetimibe, HF heart failure, MI myocardial infarction, PL placebo, *pt(s)* patient(s), SIM simvastatin, RRR relative risk reduction, UA unstable angina

atherosclerotic events (defined as death from coronary artery disease, non-fatal myocardial infarction, non-hemorrhagic stroke, or any revascularization procedure). There was no significant effect on survival or prevention of renal disease progression [63]. The SHARP trial was particularly important to clarify the role of lipid-lowering therapy in preventing atherosclerotic events in patients with CKD, since similar trials (performed in patients receiving hemodialysis) had failed to demonstrate significant benefits from statin therapy [64, 65]. Moreover, the safety of the simvastatin-ezetimibe combination in the context of renal insufficiency was made clear.

Despite the positive results of the SEAS trial and SHARP, evidence for reduction of cardiovascular events with ezetimibe remained elusive, since it was unclear whether the observed benefit resulted from both simvastatin and ezetimibe or from simvastatin alone (with ezetimibe possibly acting as an ineffective bystander). Moreover, these trials were performed in specific populations (patients with asymptomatic AS and CKD, respectively) and results could not easily be generalized to individuals without these conditions. This clinical framework meant the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) results were eagerly awaited.

IMPROVE-IT was a multicenter double-blind controlled trial of 18,144 high-risk patients with stabilized ACS. Patients were randomly assigned to receive simvastatin 40 mg plus ezetimibe 10 mg versus simvastatin 40 mg alone. To ensure most of the study subjects would attain an LDL-C <70 mg/dl with the study medications

(recommended target at the time) [66], patients could only be included if their LDL-C was between 50 and 100 mg/dl (or <125 mg/dl for those without previous lipid-lowering medication). Mean LDL-C levels at baseline were 95 mg/dl in both arms. The study primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days after randomization), or nonfatal stroke. The median follow-up was 6 years. Mean LDL-C at 1-year follow-up was 69.9 mg/dl in the simvastatin arm and 53.2 mg/dl in the combination therapy arm (absolute reduction of 16.7 mg/dl; $p < 0.001$). The primary endpoint occurred in 2742 (34.7%) patients receiving simvastatin alone versus 2575 (32.7%) patients receiving combination therapy (HR 0.936; 95% CI 0.89–0.99; $p = 0.016$). This 2% absolute risk reduction in the primary endpoint translates into a number needed to treat (NNT) of approximately 50 patients for the trial duration. No significant differences were noted on overall mortality, cardiovascular deaths, or deaths due to CHD. However, there was a significant 13% relative risk reduction in the incidence of myocardial infarction ($p = 0.002$) and a 21% relative risk reduction in the incidence of ischemic stroke ($p = 0.008$) in the simvastatin–ezetimibe arm compared with simvastatin monotherapy [12]. This long trial also confirmed the good safety profile of ezetimibe.

The IMPROVE-IT trial may be considered a milestone in clinical lipidology, not only for being the first to prove the cardiovascular benefit of adding a lipid-lowering agent (ezetimibe) to a statin but also for confirming the ‘LDL

hypothesis' that additional reductions in LDL-C translate into further reductions in atherosclerotic events (namely myocardial infarction and ischemic stroke). Despite the positive results, the trial received some criticism, mostly for the relatively modest reduction in cardiovascular events (6.4% relative risk reduction in the primary endpoint) and for the lack of benefit in terms of total and cardiovascular mortality. These findings should be put into context, since the trial was conducted in patients with relatively low LDL-C baseline levels (mean LDL-C level in patients treated with statin alone was 69.9 mg/dl) and combination therapy was compared with statin monotherapy (and not placebo). In fact, according to the results of the CTT (Cholesterol Treatment Trialists) meta-analysis, the observed relative risk reduction is in line with the expected risk reduction for the 16 mg/dl absolute difference in LDL-C recorded between both arms [7]. In light of this knowledge, it might be speculated that using combination therapy in patients with higher LDL-C levels could produce greater absolute reductions in LDL-C and translate into more significant cardiovascular risk reductions [67]. As for the lack of mortality benefit, the IMPROVE-IT trial was probably underpowered to demonstrate it. Again, in the CTT meta-analysis, pooled data from five RCTs of more-versus less-intensive statin therapy also failed to show a significant reduction in death from CHD [7], possibly due to the influence of competing risks that affect mortality but are unrelated to lipid levels [68]. One important limitation is that the statin treatment used in the monotherapy arm was not intensive statin therapy, raising some questions on the applicability of these results in that setting.

In light of the IMPROVE-IT results, a recent study sought to assess the potential use of ezetimibe in a large cohort of 219,625 patients with ACS. Of these patients from the Veterans Affairs healthcare system, 69,508 (31.6%) would qualify for ezetimibe therapy using the IMPROVE-IT criteria. Of the remaining who did not meet the trial criteria, 28% were receiving treatment with a more potent statin, 7.1% had a confirmed intolerance to statins, and 10.4% had LDL-C levels >125 mg/dl [69]. These results suggest that a large proportion of patients with ACS could qualify for ezetimibe therapy.

Since the publication of the IMPROVE-IT trial, several sub-studies have been published or presented, warranting some discussion. A pre-specified exploratory analysis censored follow-up data 30 days after the last dose of study drug. In this 'on-treatment' analysis, the absolute risk reduction in the primary endpoint rose to 2.6% (reducing the NNT to 38), and the relative risk reduction increased to 7.6% (HR 0.924; 95% CI 0.868–0.983; $p = 0.012$). These unpublished data seem important, since 42% of the IMPROVE-IT patient population discontinued the study drug prematurely, raising concerns that study withdrawals

could dilute the treatment effect and reduce the power of the study in intention-to-treat analyses. Possible reasons for this high withdrawal rate include the long study duration and, importantly, the negative publicity regarding ezetimibe in both scientific and lay media following the presentation of the SEAS trial results.

Another substudy expanded the analysis to include not only first but also subsequent events. Overall, there were 9545 total primary endpoint events in the IMPROVE-IT trial (56% first events and 44% subsequent). Total events were significantly reduced by 9% with ezetimibe–simvastatin versus simvastatin monotherapy (HR 0.91; 95% CI 0.85–0.97; $p = 0.007$). Reductions in total primary endpoint events, driven by reductions in myocardial infarction and stroke, more than doubled the number of events prevented compared with examining only the first event. The number of cardiovascular deaths remained similar between treatment groups [70].

Another interesting IMPROVE-IT substudy assessed the impact of achieving a dual treatment target (LDL-C <70 mg/dl and hsCRP <2 mg/l). More patients treated with simvastatin–ezetimibe met this combined goal than those treated with simvastatin alone (50 vs. 29%; $p < 0.001$). Importantly, those attaining both targets had lower event rates than those meeting neither of them (28.0 vs. 38.9%; adjusted HR 0.73; 95% CI 0.66–0.81; $p < 0.001$). Reaching both goals was associated with improved outcomes even after multivariable adjustment [71]. These findings support the use of treatment targets to guide the introduction of drugs such as ezetimibe.

Finally, a pre-specified subgroup analysis showed that the simvastatin–ezetimibe combination resulted in a greater decrease in LDL-C levels in patients with type 2 diabetes mellitus than in patients without diabetes (–16.6 vs. –14.3 mg/dl; $p = 0.003$). This greater reduction in LDL-C translated into a greater reduction in primary endpoint events (HR 0.86; $p = 0.023$). Among patients with diabetes, a very high-risk subpopulation of patients with ACS, combination therapy achieved remarkable relative risk reductions in myocardial infarction (–24%) and ischemic stroke (–39%). In contrast, in patients without diabetes, there was no significant difference in the primary endpoint between those who received ezetimibe and those who received placebo (30.2 vs. 30.8%, respectively). Although these post hoc findings should be interpreted with caution, they seem to indicate that patients with diabetes mellitus obtain greater benefit from intensive lipid-lowering with simvastatin–ezetimibe after an ACS than patients without diabetes. Other analyses put forward other markers of benefit such as prior coronary artery bypass grafting [72], suggesting a powerful interaction between patient risk and benefit from ezetimibe. Further studies are warranted to understand whether the greater benefit observed in patients

with diabetes is a consequence of their greater absolute risk or of the greater lipid-lowering efficacy of combination therapy in those patients, or both.

3 Safety of the Ezetimibe–Atorvastatin Combination

Ezetimibe, administered as monotherapy or as combination therapy, is generally well tolerated. Despite some isolated reports of myopathy attributable to ezetimibe [73], the adverse event profile in several large trials was similar to that of placebo [74]. Studies assessing specifically the short-term safety of the atorvastatin–ezetimibe combination showed similar results, with no significant differences in the incidences of laboratory and clinical adverse events, including gastrointestinal, liver, or muscle effects [46–50]. Concerns that ezetimibe could increase the risk of cancer were raised by the SEAS trial. New cases of cancer were reported in significantly more patients receiving combination therapy than in those receiving placebo (105 vs. 70) over a follow-up period of 4.4 years [59]. However, pooled preliminary data, the final results of the SHARP and IMPROVE-IT trials (with larger populations and longer follow-up periods), and a recent meta-analysis refuted this hypothesis and proved that no significant increase in cancer is associated with ezetimibe [12, 63, 75, 76]. A large 4-year FDA-sponsored post-marketing analysis focusing on cancer-associated adverse events among patients treated with ezetimibe also reinforced that this drug does not increase the risk of cancer [77].

Importantly, unlike statins, ezetimibe does not seem to increase the risk of new-onset diabetes mellitus. A recent retrospective study including 877 subjects treated for dyslipidemia suggested that the addition of ezetimibe to statin treatment did not increase the risk of incident diabetes among individuals with pre-diabetes (adjusted OR 0.89; $p > 0.5$). A significantly higher risk of incident diabetes was found in patients receiving high-intensity than in those receiving moderate-intensity statin therapy (adjusted OR ratio 2.1) and those not receiving a statin (adjusted OR 4.9) [78]. Unpublished data from the IMPROVE-IT trial also support the lack of a diabetogenic effect of ezetimibe. A subgroup analysis from this trial was performed in the 12,254 patients who did not have diabetes prior to enrolment. Of these, 1414 (11.5%) developed diabetes during a mean follow-up of 75 months. There was no significant difference in the incidence of new-onset diabetes mellitus in patients treated with simvastatin–ezetimibe compared with simvastatin alone (HR 1.04; 95% CI 0.94–1.15; $p = 0.46$) (data presented at the ESC 2015 Congress).

4 Impact of the Atorvastatin–Ezetimibe Combination on the Progression of Coronary Atherosclerosis

Since it would be virtually impossible to conduct large-scale trials such as IMPROVE-IT using each of the available statins, clinicians must use the available evidence and their clinical judgment when deciding to prescribe other statin–ezetimibe combinations. Recent evidence on the atorvastatin–ezetimibe combination supports the use of this specific compound to slow or halt the progression of atherosclerosis. The PRECISE-IVUS trial was a prospective randomized controlled multicenter study conducted in Japan. Patients undergoing percutaneous coronary intervention for stable angina or ACS were randomly assigned to atorvastatin alone or atorvastatin plus ezetimibe 10 mg daily. Serial volumetric intravascular ultrasound (IVUS) was performed at baseline and again at 9–12 months to quantify the coronary plaque response in 202 patients. As expected, the atorvastatin–ezetimibe combination resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 vs. 73.3 mg/dl; $p < 0.001$). More importantly, a significantly greater percentage of patients who received atorvastatin–ezetimibe experienced coronary plaque regression (78 vs. 58%; $p = 0.004$) [20]. An interesting substudy of this trial showed that achieved LDL-C was the strongest independent predictor of reduction in coronary atheroma volume [79]. Even though this was a single trial assessing an imaging parameter, IVUS studies are regarded as one of the most reliable surrogate markers of cardiovascular benefit [80].

5 Atorvastatin–Ezetimibe Combinations: Approved Indications and Current Positioning in International Guidelines

In the USA, atorvastatin–ezetimibe combinations are currently indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, ApoB, and non-HDL-C in patients with primary hyperlipidemia. A request to expand the use of ezetimibe for reduction of cardiovascular events in patients with CHD was rejected by the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA. This controversial decision was based on the opinion of several panel members who considered the effect of ezetimibe in the IMPROVE-IT trial to be relatively weak and the proposed indication too wide.

In Europe, a similar request for an expanded indication was granted approval. Besides their previously acknowledged role in hypercholesterolemia, statin–ezetimibe combinations are now indicated to reduce the risk of

Table 3 Selected guidelines and scientific recommendations mentioning the role of ezetimibe in the management of hyperlipidemia

Guideline	Recommendations
2016 European Guidelines on Cardiovascular Disease Prevention [58]	<p>Data indicate that combination therapy with EZE also brings a benefit that is in line with the CTT collaboration meta-analysis supporting the notion that LDL-C reduction is key to the achieved benefit</p> <p>Selective cholesterol absorption inhibitors (...) are recommended as combination therapy with statins in selected pts when a specific goal is not reached with the maximal tolerated dose of a statin</p> <p>More recent trial evidence shows a clear cardiovascular benefit of lowering LDL-C with EZE on top of a statin in pts with T2DM</p> <p>It must be stressed that the only combination with evidence of clinical benefit (one large RCT) is that of a statin combined with EZE. Based on the relatively limited body of evidence, clinicians may restrict the use of this combination to pts at high or very-high risk of CVD</p>
2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk [36]	<p>Stable clinical ASCVD, on statin for secondary prevention</p> <p>Although there is a gap in RCT evidence demonstrating outcomes benefits of using combination therapy in pts with stable clinical ASCVD, the expert consensus writing committee supports consideration of adding EZE 10 mg daily as the first non-statin agent, given the benefits on ASCVD outcomes and demonstrated safety of EZE in patients with ACS treated with EZE-SIM vs. SIM monotherapy</p> <p>Clinical ASCVD and baseline LDL-C ≥ 190 mg/dl not due to secondary causes, on statin for secondary prevention</p> <p>Although there is a gap in the evidence demonstrating outcomes benefit when combined with high-intensity statin therapy, the addition of EZE may be considered based upon the improved ASCVD outcomes and demonstrated safety of the combination of EZE with moderate-intensity SIM vs. SIM monotherapy</p> <p>In a patient with ASCVD and baseline LDL-C ≥ 190 mg/dl with $< 50\%$ reduction in LDL-C (and may consider LDL-C ≥ 70 mg/dl) it is reasonable to consider a PCSK9 inhibitor as a first step rather than EZE or bile acid sequestrant given the greater LDL-C lowering efficacy of PCSK9 inhibitors</p> <p>Adults aged 40–75 years without ASCVD, but with diabetes and LDL-C 70–189 mg/dl, on statin for primary prevention</p> <p>EZE is the preferred initial non-statin therapy because of its tolerability, convenience, and single-tablet daily dose</p> <p>Adults aged 40–75 years without clinical ASCVD or diabetes, with LDL-C 70–189 mg/dl and an estimated 10-year risk for ASCVD of $\geq 7.5\%$, on statin for primary prevention</p> <p>For primary prevention pts with high-risk markers who have achieved a less-than-anticipated response to maximally tolerated statin therapy with $< 50\%$ LDL-C reduction (and may consider LDL-C ≥ 100 mg/dl), EZE (or a bile acid sequestrant as a second-line agent) may be considered as a potential additional agent</p>
2015 National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia [34]	<p>Combination drug therapy with a statin plus a second (or third) agent that further lowers non-HDL-C and LDL-C may be considered for pts who have not attained their atherogenic cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy</p>
2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation [81]	<p>In pts with LDL-C ≥ 70 mg/dl despite a maximally tolerated statin dose, further reduction in LDL-C with a non-statin agent^a should be considered. Class IIa recommendation, level of evidence B</p>
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults ^b [32]	<p>Clinicians treating high-risk pts who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a non-statin cholesterol-lowering therapy. (...) In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences</p>

ACC American College of Cardiology, ACS acute coronary syndrome, AHA American Heart Association, ASCVD atherosclerotic cardiovascular disease, CVD cardiovascular disease, ESC European Society of Cardiology, EZE ezetimibe, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, PCSK9 proprotein convertase subtilisin/kexin 9, *pt(s)* patient(s), RCT randomized controlled trial, SIM simvastatin, T2DM type 2 diabetes mellitus

^a At the time of finalizing the guidelines, this recommendation applied only to EZE

^b Published before the IMPROVE-IT trial

cardiovascular events in patients with CHD and a history of ACS, either previously treated with a statin or not. Even though the IMPROVE-IT trial was performed with simvastatin–ezetimibe, the European Medicines Agency (EMA) did not limit the new indication to that particular statin combination. Recently, the UK National Institute for Health and Care Excellence (NICE) re-evaluated ezetimibe and considered it a clinically useful and cost-effective drug to be used in addition to statins (in high-risk patients) or when statins are not tolerated.

Table 3 provides a brief summary of the proposed role for ezetimibe in international guidelines and scientific recommendations.

6 Conclusion

Statins are the cornerstone of pharmacological lipid-lowering treatment to reduce cardiovascular risk. However, even with the most effective agents, up to 40% of patients do not achieve desirable LDL-C levels. Ezetimibe, an inhibitor of intestinal cholesterol absorption, has complementary and additive therapeutic lipid effects when combined with statins, providing marked LDL-C reductions and substantially improving the attainment of guideline-recommended cholesterol levels.

In placebo-controlled trials, simvastatin–ezetimibe combinations have been shown to reduce the incidence of ischemic events in patients with asymptomatic AS, and the incidence of major atherosclerotic events in patients with CKD. Compared with simvastatin monotherapy, simvastatin–ezetimibe also significantly reduced non-fatal myocardial infarction and ischemic stroke in patients with recent stabilized ACS. Notably, the magnitude of cardiovascular event reduction seen with ezetimibe seems similar to that observed with statins for the same degree of absolute LDL-C lowering. Atorvastatin–ezetimibe has also been shown to induce the regression of coronary atherosclerosis measured by IVUS in a significantly greater proportion of patients than atorvastatin alone.

Ezetimibe is generally well tolerated and has a favorable safety profile. The addition of ezetimibe to statin therapy allows the use of lower statin dosages without compromising efficacy, thus reducing the likelihood of dose-dependent statin adverse effects. Importantly, unlike statins, ezetimibe does not seem to be related to incident diabetes.

Until recently, the lack of evidence of cardiovascular event reduction and cost issues were regarded as the main obstacles to a more widespread use of ezetimibe. The IMPROVE-IT trial results and the upcoming generic are likely to change this. Only time will tell whether these will be enough to make combination therapy the rule in the management of hyperlipidemia, as we already see in

hypertension. In any case, the IMPROVE-IT trial results and the availability of an atorvastatin–ezetimibe combination are certainly welcome, since they extend the number of potential therapies we have to offer our patients as options to prevent cardiovascular events.

Compliance with Ethical Standards

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