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Expanding the therapeutic landscape: ezetimibe as non-statin therapy for dyslipidemia

Jeongmin Lee[1] and Seung-Hwan Lee[2,3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [3]Department of Medical Informatics, College of Medicine, The Catholic University of Korea, Seoul, Korea

Dyslipidemia is a significant risk factor for atherosclerotic cardiovascular disease (ASCVD), and statins are the primary therapeutic options for reducing low-density lipoprotein cholesterol (LDL-C) levels. However, it can be challenging to achieve optimal LDL-C goals with statin monotherapy. Ezetimibe, a cholesterol absorption inhibitor, offers a potential non-statin therapy to optimize LDL-C management. Key clinical trials, such as IMPROVE-IT and RACING, have demonstrated that the addition of ezetimibe to statin therapy leads to further decreases in LDL-C or significant decreases in major adverse cardiovascular events (MACEs), particularly in patients with high ASCVD risk. Subsequent meta-analyses and clinical trials have further supported the beneficial effect of ezetimibe, suggesting additive decreases in LDL-C and MACEs, as well as pleiotropic effects. This review provides a comprehensive analysis of the clinical implications of ezetimibe for managing dyslipidemia; it also evaluates the available evidence that supports the role of ezetimibe as an adjunct non-statin therapy for long-term use. However, the long-term pleiotropic effects of ezetimibe remain controversial because of limited clinical data. Therefore, additional research is needed to clarify its potential benefits beyond LDL-C reduction. Nonetheless, an understanding of the role of ezetimibe in dyslipidemia management will help clinicians to develop effective treatment strategies.

Keywords: Atherosclerosis; Cardiovascular disease; Dyslipidemias; Ezetimibe

INTRODUCTION

Despite a sustained effort to treat dyslipidemia, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide [1]. Until 2010, ASCVD mortality decreased in South Korea, followed by a steady increase, reaching 123 per 100,000 persons in 2018 [2]. Dyslipidemia, a major risk factor for metabolic diseases and ASCVD, is characterized by an abnormal lipid profile, including high levels of low-density lipoprotein cholesterol (LDL-C) (≥ 160 mg/dL), low levels of high-density lipoprotein cholesterol (HDL-C) (< 40 mg/dL), or high levels of triglycerides (≥ 200 mg/dL). A high LDL-C level is the main risk factor for ASCVD [3]. The prevalence of dyslipidemia has increased by eightfold from 1.5 million in 2002 to 11.6 million in 2018 [4]. The most recent international guidelines for managing dyslipid-

emia recommend reducing LDL-C based on the principle of "lower is better" [5-8]. Recent epidemiological studies and clinical trials have consistently demonstrated that reductions of LDL-C level lower the risk of ASCVD in both primary and secondary settings [9,10]. Among lipid-lowering drugs, statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (an early enzyme in the cholesterol biosynthetic pathway), are the most cost-effective drugs for preventing ASCVD; they are commonly prescribed worldwide, including in Korea [11]. However, the proportion of patients achieving their target LDL-C goal remains low, and only a small percentage of very high-risk patients reach their target LDL-C goal during treatment with statins [12]. Despite sufficient reduction in LDL-C, patients experience an elevated risk of ASCVD, which is attributed to changes in lipid components such as triglycerides, lipoprotein (a),

HDL-C, and chylomicrons [13-15]. Therefore, high-intensity statin therapy or combination therapy involving ezetimibe is increasingly prescribed [16]. Previous studies have shown that the effects of statin/ezetimibe combinations are superior to statin monotherapy in terms of achieving target LDL-C goals in patients with ASCVD or ASCVD risk equivalents. Furthermore, an updated consensus addressed evidence concerning novel medications beyond statin or ezetimibe combination therapy. This review evaluated alternative therapeutic options for non-statin treatments with a focus on ezetimibe, based on the most recent and relevant evidence.

GUIDELINES FOR MANAGING DYSLIPIDEMIA

Global clinical guidelines recommend statins as first-line treatment for reducing the LDL-C level, which is a major target of lipid-lowering therapy. Many studies have established an association between reducing LDL-C and preventing AS-CVD, thereby emphasizing LDL-C management as the primary strategy. Although there are some similarities among clinical guidelines for dyslipidemia, the recommendations display substantial variation. The 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines prioritize statin therapy to reduce LDL-C levels, without emphasizing specific lipids or lipoprotein targets [17]. However, for patients with very high ASCVD risk, an LDL-C threshold of 70 mg/dL is recommended as an indicator of the need for additional non-statin therapy. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines [18], the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) guidelines [19], and the Endocrine Society Clinical Practice Guidelines [20] encourage reducing LDL-C and non-HDL-C levels to targeted thresholds based on a patient's cardiovascular risk profile. However, the most reliable risk estimate system should be based on specific population characteristics and corresponding data. The ESC/EAS guidelines utilize the Systematic Coronary Risk Estimation (SCORE) system, whereas the AHA/ACC guidelines use the Framingham Risk Score (FRS). Nevertheless, most guidelines define the very high-risk group as individuals with documented ASCVD, including acute myocardial infarction, ischemic stroke, and peripheral arterial disease. Numerous lipid experts suggest targeting LDL-C levels below 70 mg/dL and

non-HDL-C levels below 100 mg/dL in patients with clinical ASCVD across all levels of baseline LDL-C or in patients with very high risk. The AACE and ESC/EAS guidelines recommend even lower LDL-C levels, below 55 mg/dL, for patients with very high ASCVD risk. The high-risk group is characterized by chronic kidney disease, diabetes mellitus (DM) with target organ damage, type 1 DM with duration > 10 years, familial hypercholesterolemia, SCORE ≥ 5%, and FRS ≥ 20%. The goal for the high-risk group should be an LDL-C level of < 100 mg/dL and a non-HDL-C level of < 130 mg/dL. The ESC/EAS recommended target LDL-C level for high-risk groups is < 70 mg/dL. Thus, the European guidelines establish a more stringent LDL-C target, compared with other guidelines. In Korea, the delineation of target LDL-C levels based on the presence of cardiovascular disease (CVD) risk factors is consistent with international guidelines. The recommended target LDL-C levels vary according to the level of risk: for the very high-risk group with CVD, the target LDL-C is < 70 mg/dL; for the high-risk group with carotid disease or DM, it is < 100 mg/dL; for the moderate-risk group with more than two major risk factors, it is < 130 mg/dL; and for the low-risk group with one or no major risk factors, it is < 160 mg/dL. However, immediate statin therapy is indicated for acute myocardial infarction, regardless of the baseline LDL-C level [21].

ROLES OF NON-STATIN THERAPIES IN CLINICAL GUIDELINES

In the last few years, complementary therapies for HMG-CoA reductase inhibitors have emerged as additional options for LDL-C reduction. These therapies include the use of ezetimibe, an inhibitor of the Niemann-Pick C1-Like 1 (NPC1L1) transporter responsible for cholesterol absorption [21], and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, which interferes with the degradation of LDL receptors in hepatocytes [22]. By targeting different metabolic pathways, these therapies offer new treatment options for patients with dyslipidemia who have a high ASCVD risk. Recent studies regarding the addition of ezetimibe to statin therapy, including Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [23], and studies focused on PCSK9 inhibitors [24-26] revealed further decreases in LDL-C levels and CVD events. Current guidelines recommend these non-statin therapies

when maximally tolerable statin dosage has been reached or when a switch to another class has not achieved sufficient reduction in LDL-C; thus, the strength of the recommendation is increased. Among newly developed treatments, ezetimibe and/or PCSK9 inhibitors have emerged as the primary non-statin therapies. In 2022, the ACC released the expert decision pathway for non-statin therapy, which recommends novel therapies (e.g., bempedoic acid, inclisiran [small interfering RNA], and evinacumab) but prioritizes ezetimibe and/or PCSK9 inhibitors because of their superior outcome data [6]. Global perspectives based on all clinical guidelines are consistent in recommending statins as first-line treatment; non-statin therapies, such as ezetimibe and/or PCSK9 inhibitors, remain second-line options. More options are available to achieve target LDL-C levels and improve CVD outcomes with the emergence of novel therapies for dyslipidemia.

EZETIMIBE AS FIRST-LINE NON-STATIN THERAPY FOR LDL-C MANAGEMENT: EVIDENCE AND IMPLICATIONS

Considering the large amount of data supporting the clinical effectiveness of statin therapy and the current guidelines that prioritize statin prescriptions, the number of clinical trials assessing ezetimibe monotherapy has been relatively limited. A meta-analysis of eight randomized controlled trials (RCTs) regarding the clinical effectiveness of ezetimibe monotherapy (10 mg/d) for 12 weeks demonstrated a mean LDL-C level reduction of 18.58%. Additionally, there were substantial reductions in total cholesterol (13.49%) and triglycerides (8.6%), compared with the placebo group [27]. According to a recent meta-analysis, the pooled prevalence of statin intolerance is 9.1% [28]. In patients who cannot tolerate statin therapy, non-statins are recommended as alternative treatment options. In confirmed CVD cases with statin intolerance or contraindications, ezetimibe monotherapy is cost-effective relative to no treatment. Ezetimibe monotherapy reduces LDL-C levels by 18.56% relative to no treatment [29]. The GAUSS-3 trial investigated the effectiveness of two non-statin therapies, ezetimibe (10 mg/d) and evolocumab (a PCSK9 inhibitor, 420 mg/mo), in 419 patients with statin intolerance [30]. At week 24, the average percentage changes in LDL-C level were −16.7% with ezetimibe and −52.8% with evolocumab. One study (EWTOPIA

75), conducted among Japanese patients aged ≥ 75 years, demonstrated the effectiveness of non-statin monotherapy using a 10 mg dose of ezetimibe to prevent CVD. The study revealed a hazard ratio of 0.66 (95% confidence interval [CI] 0.50–0.86), indicating a reduced risk of CVD, along with a substantial reduction (25.9%) in LDL-C levels [31]. Nevertheless, evidence regarding ezetimibe monotherapy as first-line treatment for primary prevention and its effectiveness in preventing ASCVD is insufficient, compared with statin therapy. Consequently, further research is needed to better understand the potential benefits and efficacy of ezetimibe in these areas.

ADD-ON EZETIMIBE WITH STATIN THERAPY: EFFECTS ON ASCVD OUTCOMES

LDL-C levels are affected by endogenous cholesterol synthesis, cholesterol absorption, and clearance [32]. Statin-mediated inhibition of hepatic cholesterol synthesis can paradoxically enhance cholesterol absorption, leading to a smaller lipid-lowering effect of statin therapy [33]. This problem can be overcome by incorporating a cholesterol-absorbing inhibitor, such as ezetimibe, to complement the statin treatment. As previously noted, ezetimibe monotherapy reduces LDL-C levels by 13–20%. The combination of ezetimibe with statin therapy results in an additional 21–27% decrease in LDL-C levels [34,35]. Several meta-analyses have consistently shown that combination therapy with ezetimibe and a statin is more effective in reducing LDL-C, compared with a twofold increase in the statin dose [36]. In terms of preventing major adverse cardiovascular events (MACEs), most clinical trials focused on secondary prevention among patients with a history of ASCVD (Table 1). Combination therapy demonstrated a superior drop in LDL-C levels and a 17% proportional decrease in MACEs in the Study of Heart and Renal Protection (SHARP) trial, which included individuals with chronic kidney disease who had no history of ASCVD [37]. These results are consistent with previous findings that combination therapy in the vascular surgical setting is protective against MACEs during the first year of follow-up [38]. The IMPROVE-IT study, which is the largest and longest study (enrolling 18,144 participants over 6 yr), showed that the MACE rate in the combined group was lower than the rate in the simvastatin monotherapy group, with absolute risk reduction of 2% (hazard ratio 0.936) [23]. The results

Table 1. Trials assessing EZT with statins for prevention of cardiovascular events

Trial/author	Year	Country	Number	Follow-up (yr)	Intervention/comparison	Clinical setting	Outcome	Findings
SHARP [37]	2011	UK	9,270	4.9	SIMV 20 mg + EZT 10 mg SIMV 20 mg alone	CKD	MACE	The combination therapy reduced the incidence of MACE (17%) in advanced CKD.
Kouvelos [38]	2013	Greece (single center)	262	1	RSV 10 mg + EZT 10 mg RSV 10 mg alone	Undergoing elective vascular surgery	MACE	The combination therapy exhibited a robust protective effect against the occurrence of cardiovascular events in the first year of follow-up.
IMPROVE-IT [23]	2015	USA (multinational)	18,144	6	SIMV 40 mg + EZT 10 mg SIMV 40 mg + placebo	ACS	MACE	Combination therapy resulted in a significantly lower risk of cardiovascular events than that with statin monotherapy (HR 0.936)
Wang [39]	2016	China (single center)	106	1	RSV 10 mg+ EZT 10 mg RSV 10 mg alone	CAD	MACE	The primary endpoint decreased more effectively in the combination group.
HIJ-PROPER [40]	2017	Japan (multicenter)	1,734	3.9	PTV 2 mg + EZT 10 mg PTV 2 mg alone	ACS	MACE	The combination therapy did not reduce MACE in comparison with s statin monotherapy.
Liu [41]	2017	China (single center)	264	1	ATV 10 mg + EZT 10 mg ATV 20 mg	ACS	MACE	The rate of MACE in the combination treatment was similar with double-dose ATV group.
Hibi [42]	2018	Japan (multicenter)	128	3	PTV 2 mg + EZT 10 mg PTV 2 mg alone	ACS	1. non-culprit coronary plaque volume on IVUS 2. MACE	There was no significant difference in the incidence of MACE.
Ogiso [43]	2020	Japan (multicenter)	1,702	3.8	PTV 2 mg + EZT 10 mg PTV 2 mg alone	ACS	MACE	The benefits of combination were enhanced in ACS patients with single vessel disease (HR 0.72).
RACING [44]	2022	South Korea (multicenter)	3,780	3	RSV 10 mg+ EZT 10 mg RSV 20 mg alone	ACS	MACE	The combination therapy was found to be non-inferior to high-intensity statin monotherapy in terms of the composite endpoint MACE (absolute difference −0·78%).

ACS, acute coronary syndrome; ATV, atorvastatin; CAD, coronary artery disease; CKD, chronic kidney disease; EZT, ezetimibe; HR, hazard ratio; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular event; PTV, pitavastatin; RSV, rosuvastatin; SIMV, simvastatin.

concerning MACE risk were inconsistent in Asian patients with ASCVD [39-43]. The Heart Institute of Japan-Proper Level of Lipid Lowering with Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROPER) trial and post hoc analysis of that study demonstrated different results. In HIJ-PROPER, combination therapy did not improve MACE outcomes compared with monotherapy, despite reduction of LDL-C levels [40]. Post hoc analysis of 1,702 patients with ASCVD revealed a significant benefit of combination therapy regarding single vessel disease (hazard ratio 0.72, 95% CI 0.55–0.94) [43]. In a recent large, randomized, open-label study (the randomized comparison of efficacy and safety of lipid lowering with statin monotherapy versus statin–ezetimibe combination for high-risk cardiovascular disease [RACING] trial), combination therapy in patients with high ASCVD risk was non-inferior to high-intensity statin monotherapy (absolute difference -0.78%; 90% CI -2.39 to 0.83) [44]. The previous trials were based on the additive effect of ezetimibe while maintaining a single statin dosage, whereas the RACING trial compared the efficacies of combination therapy comprising moderate-intensity statin with ezetimibe (10 mg rosuvastatin with 10 mg ezetimibe) and monotherapy involving high-intensity statin (20 mg rosuvastatin). Although clinical trials have shown heterogeneous results, pooled analysis of MACEs using a fixed-effects model indicated that combination therapy with ezetimibe resulted in a lower risk of MACEs, compared with the control group. The risk ratio was 0.94 (95% CI 0.90–0.98), indicating a significant benefit [45]. These trial results indicate that patients with higher risk can achieve risk reduction by adding ezetimibe to a statin therapy regimen. Overall, the findings support ezetimibe as a second-line treatment option.

PLEIOTROPIC EFFECTS OF EZETIMIBE IN CLINICAL TRIALS

Clinical trials spanning over one year revealed diverse benefits of Ezetimibe, encompassing anti-atherosclerotic effects, anti-inflammation, impact on lipoprotein oxidation, and involvement in glucose metabolism and insulin resistance. These findings provide insights into the multifaceted advantages of Ezetimibe therapy (Table 2).

Anti-atherosclerotic effect based on intima-media thickness or plaque volume

Cholesterol-rich particles infiltrate the walls of arterial blood vessels, causing retention of LDL particles [46]. The ENHANCE trial [47], the Stop Atherosclerosis in Native Diabetics Study (SANDS) [48], and the Vytorin on Carotid Intima-Media Thickness and Overall Arterial Rigidity (VYCTOR) Study [49] evaluated the change in carotid intima-media thickness (CIMT). Despite achieving substantial reduction (16.5%) in LDL-C levels, combination therapy comprising ezetimibe with a statin did not produce a significant difference in CIMT during the ENHANCE trial of patients with familial hypercholesterolemia. In contrast, a benefit with ezetimibe was observed in the SANDS and VYCTOR trials, which were conducted in high-risk patients; a decrease in atherosclerosis was observed upon reduction of the CIMT. In the SANDS, the aggressively treated group exhibited CIMT regression from baseline among patients receiving ezetimibe (-0.025 mm) and non-ezetimibe (-0.012 mm) regimens. Follow-up measurements revealed significant reduction of 0.90–0.93 mm in the CIMT. The mean baseline CIMT values were thicker in these two trials (0.69 and 1.33 mm) than in the ENHANCE study (0.69 mm). The Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) trial enrolled participants with high ASCVD risk [50]. In this trial, the combination therapy demonstrated lower LDL-C levels and slower progression of coronary atherosclerosis, with a substantial difference of 20%. Thus, combination therapy involving ezetimibe reversed atherosclerosis in patients with greater baseline CIMT. The Ezetimibe In Addition To Atorvastatin Therapy On The Plaque Composition In Patients With Acute Myocardial Infarction (OCTIVUS) trial investigated the effect of adding ezetimibe to statin therapy on atheroma volume and plaque composition in patients with acute myocardial infarction [51]. The results showed that the combination therapy reduced atheroma volume. The levels of matrix metalloproteinase-9 (MMP-9), an extracellular protein hydrolysate, show similar relationships in human and animal models [52]. Plaque stability is a crucial factor in atherosclerosis development and progression. Wang et al. [39] demonstrated that ezetimibe reduces MMP-9 levels. Consistent with this finding, recent trials in patients with ASCVD showed that MMP-9 levels decrease after 6 months of combination therapy and at the 24-month follow-up [53].

Table 2. Pleiotropic effects of EZT in clinical trials with > 1 year of follow-up

Trial/author	Year	Country	Number	Follow-up (yr)	Intervention/comparison	Clinical setting	Outcome	Findings
ENHANCE [47]	2008	USA (multinational)	720	2	SIMV 80 mg + EZT 10 mg SIMV 80 mg alone	Familial hypercholesterolemia	CIMT	Combination therapy did not reduce CIMT.
SANDS [48]	2008	USA (multicenter)	499	3	Statin + EZT	Type 2 diabetes without CAD	CIMT	CIMT regressed in the aggressive group.
VYCTOR [49]	2009	Mexico (single center)	60	1	SIMV 20–40 mg + EZT 10 mg SIMV 40–80 mg PITV 40 mg + EZT 10 mg	High risk of CAD	CIMT	Combination therapy reduced CIMT.
PRECISE-IVUS [50]	2015	Japan (multicenter)	246	1	ATV 10-20 mg + EZT 10 mg ATV alone	ACS	Change percent atheroma volume	The absolute change in percent atheroma volume showed superiority for the combination.
OCTIVUS [51]	2017	Denmark (single center)	87	1	ATV 80 mg + EZT ATV 80 mg + placebo	ASCVD	1. Change in necrotic core 2. Total atheroma volume and percentage atheroma volume	1. Necrotic volume did not differ. 2. Total volume and percentage atheroma volume was decreased in EZT group.
Luo [56]	2014	China (single center)	84	1	ATV 10 mg + EZT 10 mg ATV 10 mg alone	CAD	hsCRP	The reduction in the hsCRP was more significant in the combined group
Ren [57]	2017	China (single center)	135	1	RSV 10 mg + EZT 10 mg RSV 10 mg only	ASCVD	hsCRP	The combination therapy led to greater reduction of hsCRP.
Wang [58]	2017	China (single center)	100	1	ATV 20 mg +EZT 10 mg ATV 20 mg alone	Type 2 diabetes with CAD	hsCRP	hsCRP in combination group was much lower.
Wang [39]	2016	China (single center)	106	1	RSV 10 mg + EZT 10 mg RSV 10 mg alone	CAD	hsCRP, IL-6, MMP-9	The combination decreased hsCRP, IL-6, and MMP-9 levels at six and 12 months after treatment.
Tan [53]	2021	China (single center)	200	2	ATV 10 mg + EZT 10 mg ATV 40 mg	ACS	hsCRP, MMP-9	The combination therapy provides remarkable effects on alleviating the inflammatory state.
ESSENTIAL [83]	2022	Korea (single center)	70	2	RSV 5 mg +EZT 10 mg RSV 5 mg	Hypercholesterolemia with NAFLD	Liver fat MRI-PDFF	The combination therapy significantly reduced liver fat compared with monotherapy.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; ATV, atorvastatin; CAD, coronary artery disease; CIMT, carotid intima-media thickness; EZT, ezetimibe; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MMP, matrix metalloproteinase-9; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; PTV, pitavastatin; RSV, rosuvastatin; SIMV, simvastatin.

Anti-inflammatory effect

Inflammation is associated with atherosclerosis [54]. High-sensitivity C-reactive protein (hsCRP) is a marker for CVD [55]. In the initial stage of atherosclerosis, hsCRP triggers monocyte attachment to the arterial wall. Several clinical trials have shown that ezetimibe as an add-on to statin therapy decreases inflammatory markers as a primary outcome [56-58]. According to a recent meta-analysis, ezetimibe treatment was more effective in decreasing hsCRP levels, compared with a statin or a PCSK9 inhibitor (mean difference −0.64 mg/L, 95% CI −1.07 to −0.21 mg/dL) [59]. However, cautious interpretation is needed because low levels of hsCRP are not necessarily associated with reduced ASCVD risk. In an animal study regarding ezetimibe treatment, adipocyte size and pro-inflammatory cytokine accumulation decreased [60]. A clinical trial by Wang et al. [39] demonstrated that the levels of interleukin (IL)-6 and hsCRP were lower in the combined group than in the monotherapy group. A recent clinical trial involving patients with ASCVD revealed that phospholipase A2 and IL-1β levels were significantly decreased in response to combined therapy involving ezetimibe [61]. In patients who had isolated dyslipidemia without ASCVD, combination therapy decreased the levels of tumor necrosis factor-α and free fatty acids [62]. Based on a meta-analysis involving 12 studies, significant decreases in IL-6 levels were observed in Asian individuals aged ≥ 60 years, particularly when interventions were maintained for > 3 weeks [63]. The impact of combination therapy on systemic inflammation was greater in individuals with higher LDL-C levels and longer intervention durations.

Lipoprotein oxidation

The oxidation of LDL particles (producing oxidized LDL [oxLDL]) is widely recognized as the key atherogenic change in LDL and a factor contributing to atherosclerosis onset. A previous study showed that ezetimibe alone or as an add-on to statin therapy prolongs the lag time for LDL-C oxidation [64]. Several clinical trials revealed that oxLDL levels significantly decreased by 8 to 15% after combination treatment [65-67]. Despite the higher rate of LDL-C target achievement with combination therapy, a 12-week treatment regimen did not result in a significant change in oxLDL levels [68]. It remains uncertain whether the reduction in oxLDL levels with combination therapy is beneficial.

Glucose metabolism and insulin resistance

Several randomized trials, observational studies, and meta-analyses have revealed increased risks of new-onset DM or dysglycemia in individuals with DM, particularly during high-dose statin therapy [69-71]. The diabetogenic effects of statin therapy have been linked to the underlying mechanisms, particularly effects on β-cell function and insulin sensitivity [72]. The effect of ezetimibe on glucose metabolism has been sparsely reported, compared with the effects of statins. A study of Korean patients with dyslipidemia showed that ezetimibe could attenuate statin-induced dysglycemia [73]. After an 8-week treatment period, glycated hemoglobin levels increased by 3% in the 20 mg atorvastatin group and 1.2% in the 5 mg rosuvastatin group, whereas they decreased by 0.4% in the 5 mg atorvastatin plus 5 mg ezetimibe group ($p = 0.03$). However, there was no significant change in the homeostasis model assessment of insulin resistance (HOMA-IR). A Japanese study involving obese patients with dyslipidemia showed that ezetimibe monotherapy significantly decreased HOMA-IR and fasting insulinemia [74,75]. In contrast, ezetimibe therapy in patients with non-alcoholic fatty liver disease (NAFLD) led to increased glycated hemoglobin levels in a small study [76]. Ezetimibe directly inhibits cholesterol absorption, leading to decreased levels of free fatty acids. These reductions in free fatty acids contribute to decreased gluconeogenesis, thereby improving insulin resistance [77]. However, the precise mechanism underlying the ezetimibe-mediated improvement in glucose metabolism is not fully understood.

Non-alcoholic fatty liver disease

NAFLD encompasses a range of histological presentations, beginning with simple steatosis and extending to non-alcoholic steatohepatitis, which can involve varying levels of fibrosis and are accompanied by various metabolic diseases [78]. Ezetimibe targets NPC1L1, which is expressed in the small intestine and liver; it reduces cholesterol by inhibiting NPC1L1 expression. Ezetimibe reduces liver susceptibility to oxidative injury, modulates autophagy, and influences the hepatocyte-driven exosome pathway [79]. In a study evaluating the long-term effects of ezetimibe monotherapy on hepatic steatosis, 45 patients with biopsy-proven NAFLD were treated for 2 years. The study showed a significant decrease in histologically assessed hepatic steatosis and NAFLD activity scores after treatment [80]. Another study investigating the effects of ezetimibe monotherapy revealed

improvements in fibrosis stage and ballooning score [76]. In a subanalysis of the IMPROVE-IT study, the combination of ezetimibe and simvastatin led to a substantial decrease in absolute risk (3.7%) and a relative risk reduction of 15% in recurrent cardiovascular events in the high-risk NAFLD subgroup, but the low-risk group did not experience a similar benefit [81]. A meta-analysis demonstrated that ezetimibe significantly decreased the NAFLD activity score compared with statin monotherapy [82]. A more recent clinical trial involving participants with dyslipidemia and NAFLD showed that ezetimibe and rosuvastatin combination therapy significantly decreased liver fat compared with statin monotherapy [83].

EZETIMIBE TOLERABILITY AND SAFETY

The use of high-intensity statins is often linked to statin intolerance, which is frequently associated with muscle-related adverse events. Although various interpretations of statin intolerance have been described in the literature, the definition most widely used by the EAS focuses on the probability of statin-associated muscle symptoms (SAMS) linked to statin usage. This likelihood assessment considers the nature of the muscle symptoms; the elevation of creatine kinase (CK) levels; and temporal relationships with the initiation, discontinuation, and re-initiation of statin therapy [84]. Comprehensive large-scale clinical studies regarding alternatives to statin therapies have demonstrated substantial reduction in statin-associated side effects, including SAMS, accompanied by improvements in clinical outcomes [24,30,85].

In contrast to statins, ezetimibe has not been associated with an increase in muscle toxicity. An analysis of eight RCTs indicated that ezetimibe therapy did not consistently lead to a clinical increase in CK level ($\geq$ 10 times the upper limit of normal); the incidence was < 1% [27]. A comprehensive pooled safety analysis, involving 17 RCTs and 4,558 patients, conclusively showed that combination therapy involving ezetimibe does not worsen SAMS or increase their incidence [86]. Furthermore, a subanalysis from the RACING trial indicated that the rate of SAMS-related discontinuation or therapeutic reduction was lower in the combination therapy group (4.5%) than in the statin monotherapy group (7.9%) [87]. An RCT involving ezetimibe monotherapy demonstrated that myopathy was slightly more common in the ezetimibe group than in the placebo group (5 vs. 4%) without

an increase in CK level [88]. However, some case reports of myopathy (muscle pain with increased CK levels) have been linked to the addition of ezetimibe to statin therapy [89,90]. In these cases, ezetimibe withdrawal led to normalization of the CK level and reduction of muscle pain. One plausible mechanism involves glucuronidation. Statins undergo cytochrome P450 hydrolysis and glucuronidation; ezetimibe can also undergo glucuronidation [91]. Another possible underlying mechanism is the obstruction of fatty acid oxidation by ezetimibe [89]. Fatty acids are crucial constituents for energy production and the maintenance of muscle function. Therefore, the effects of ezetimibe on fatty acid oxidation may lead to changes in energy metabolism and function within muscle. The exact mechanisms by which ezetimibe causes muscle-related side effects are currently under investigation.

Ezetimibe is metabolized in the small intestine and liver [91]. Nevertheless, the incidence of increased serum transaminases ($\geq$ 3 times the upper limit of normal) was not affected by ezetimibe monotherapy [27]. Current guidelines indicate that ezetimibe can be used without dose modification in patients with mild hepatic insufficiency. However, these guidelines may not support the use of ezetimibe for individuals with moderate or severe hepatic insufficiency [92].

CONCLUSION

Current guidelines recommend ezetimibe as cost-effective second-line therapy. The addition of ezetimibe to statin therapy produces favorable outcomes in terms of further decreases in LDL-C levels and MACE risks in patients with established ASCVD or high ASCVD risk. The pleiotropic effects of ezetimibe in clinical trials may be linked to improvements in ASCVD outcomes. These effects include protection against atherosclerosis; reduction of inflammation; modulation of lipoprotein oxidation; and potential benefits regarding glucose metabolism, insulin resistance, and NAFLD. However, the long-term pleiotropic effects of ezetimibe remain controversial because clinical trial data have been limited. Further research is needed to explore the benefits of ezetimibe beyond LDL-C reduction.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. Circulation 2022;145:e153-e639.

2. Lee HH, Cho SMJ, Lee H, et al. Korea heart disease fact sheet 2020: analysis of nationwide data. Korean Circ J 2021;51:495-503.

3. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. Nat Rev Cardiol 2021; 18:689-700.

4. Cho SMJ, Lee H, Lee HH, et al.; Korean Society of Lipid and Atherosclerosis (KSoLA) Public Relations Committee. Dyslipidemia fact sheets in Korea 2020: an analysis of nationwide population-based data. J Lipid Atheroscler 2021;10:202-209.

5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/ AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:3168-3209.

6. Writing Committee; Birtcher KK, Allen LA, Anderson JL, et al. 2022 ACC expert consensus decision pathway for integrating atherosclerotic cardiovascular disease and multimorbidity treatment: a framework for pragmatic, patient-centered care: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023;81:292-317.

7. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. Can J Cardiol 2021;37:1129-1150.

8. Visseren FLJ, Mach F, Smulders YM, et al.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.

9. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41:2313-2330.

10. Kunutsor SK, Laukkanen JA. Further proof of a paradoxical relationship between high-density lipoprotein levels and adverse cardiovascular outcomes: are there implications for cardiovascular disease prevention? Eur J Prev Cardiol 2023;30:290-292.

11. Rhee EJ, Kim HC, Kim JH, et al.; Committee of Clinical Practice Guideline of Korean Society of Lipid and Atherosclerosis. 2018 guidelines for the management of dyslipidemia in Korea. J Lipid Atheroscler 2019;8:78-131.

12. Lee SH, Song WH, Jeong MH, et al. Dyslipidemia and rate of under-target low-density lipoprotein-cholesterol in patients with coronary artery disease in Korea. J Lipid Atheroscler 2019; 8:242-251.

13. Yang Y, Han K, Park SH, Kim MK, Yoon KH, Lee SH. High-density lipoprotein cholesterol and the risk of myocardial infarction, stroke, and cause-specific mortality: a nationwide cohort study in Korea. J Lipid Atheroscler 2021;10:74-87.

14. Hong SP, Kim CY, Jung HW. The comparison of the associations of lipoprotein(a) and the atherogenic index of plasma with coronary artery calcification in patients without high LDL-C: a comparative analysis. J Lipid Atheroscler 2023;12: 152-163.

15. Kim KA, Park HJ. New therapeutic approaches to the treatment of dyslipidemia 2: LDL-C and Lp(a). J Lipid Atheroscler 2023; 12:37-46.

16. Kim K, Bang WD, Han K, Kim B, Lee JM, Chung H. Comparison of the effects of high-intensity statin therapy with moderate-intensity statin and ezetimibe combination therapy on major adverse cardiovascular events in patients with acute myocardial infarction: a nationwide cohort study. J Lipid Atheroscler 2021;10:291-302.

17. Grundy SM, Stone NJ. 2018 American Heart Association/ American College of Cardiology/multisociety guideline on the management of blood cholesterol-secondary prevention. JAMA Cardiol 2019;4:589-591.

18. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-188.

19. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm - 2020 executive summary. Endocr Pract 2020;26:1196-1224.

20. Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2020;105: dgaa674.

21. Sweeney ME, Johnson RR. Ezetimibe: an update on the mechanism of action, pharmacokinetics and recent clinical trials. Expert Opin Drug Metab Toxicol 2007;3:441-450.

22. Zhang DW, Lagace TA, Garuti R, et al. Binding of proprotein

convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation. J Biol Chem 2007;282:18602-18612.

23. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-2397.

24. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-1722.

25. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-2107.

26. 26. Schwartz GG, Szarek M, Bhatt DL, et al.; ODYSSEY OUTCOMES Investigators. Transiently achieved very low LDL-cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial. Eur Heart J 2023;44:1408–1417.

27. Pandor A, Ara RM, Tumur I, et al. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. J Intern Med 2009;265:568-580.

28. Bytyçi I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J 2022;43:3213-3223.

29. Ara R, Pandor A, Tumur I, et al. Cost effectiveness of ezetimibe in patients with cardiovascular disease and statin intolerance or contraindications: a Markov model. Am J Cardiovasc Drugs 2008;8:419-427.

30. Nissen SE, Stroes E, Dent-Acosta RE, et al.; GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. JAMA 2016;315:1580-1590.

31. Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older (EWTOPIA 75): a randomized, controlled trial. Circulation 2019;140:992-1003.

32. Maxfield FR, Tabas I. Role of cholesterol and lipid organization in disease. Nature 2005;438:612-621.

33. Duan Y, Gong K, Xu S, Zhang F, Meng X, Han J. Regulation of cholesterol homeostasis in health and diseases: from mechanisms to targeted therapeutics. Signal Transduct Target Ther 2022;7:265.

34. Lee J, Egolum U, Parihar H, Cooley M, Ling H. Effect of ezetimibe added to high-intensity statin therapy on low-density lipoprotein cholesterol levels: a meta-analysis. Cardiol Res 2021; 12:98-108.

35. Gudzune KA, Monroe AK, Sharma R, Ranasinghe PD, Chelladurai Y, Robinson KA. Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy: a systematic review. Ann Intern Med 2014;160:468-476.

36. Toth PP, Bray S, Villa G, et al. Network meta-analysis of randomized trials evaluating the comparative efficacy of lipid-lowering therapies added to maximally tolerated statins for the reduction of low-density lipoprotein cholesterol. J Am Heart Assoc 2022;11:e025551.

37. Baigent C, Landray MJ, Reith C, et al.; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-2192.

38. Kouvelos GN, Arnaoutoglou EM, Matsagkas MI, et al. Effects of rosuvastatin with or without ezetimibe on clinical outcomes in patients undergoing elective vascular surgery: results of a pilot study. J Cardiovasc Pharmacol Ther 2013;18:5-12.

39. Wang X, Zhao X, Li L, Yao H, Jiang Y, Zhang J. Effects of combination of ezetimibe and rosuvastatin on coronary artery plaque in patients with coronary heart disease. Heart Lung Circ 2016;25:459-465.

40. Hagiwara N, Kawada-Watanabe E, Koyanagi R, et al. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. Eur Heart J 2017;38:2264-2276.

41. Liu Z, Hao H, Yin C, Chu Y, Li J, Xu D. Therapeutic effects of atorvastatin and ezetimibe compared with double-dose atorvastatin in very elderly patients with acute coronary syndrome. Oncotarget 2017;8:41582-41589.

42. Hibi K, Sonoda S, Kawasaki M, et al.; Ezetimibe-ACS Investigators. Effects of ezetimibe-statin combination therapy on coronary atherosclerosis in acute coronary syndrome. Circ J 2018; 82:757-766.

43. Ogiso M, Yamaguchi J, Kawada-Watanabe E, et al. Effect of aggressive lipid-lowering therapy in single-vessel vs. multivessel coronary artery disease patients with acute coronary syndrome - Heart Institute of Japan-Proper Level of Lipid Lowering With Pitavastatin and Ezetimibe in Acute Coronary Syndrome (HIJ-PROPER) Substudy. Circ Rep 2020;2:128-134.

44. Kim BK, Hong SJ, Lee YJ, et al.; RACING investigators. Long-

term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet 2022;400:380-390.

45. Zhan S, Tang M, Liu F, Xia P, Shu M, Wu X. Ezetimibe for the prevention of cardiovascular disease and all-cause mortality events. Cochrane Database Syst Rev 2018;11:CD012502.

46. Bernardi S, Marcuzzi A, Piscianz E, Tommasini A, Fabris B. The complex interplay between lipids, immune system and interleukins in cardio-metabolic diseases. Int J Mol Sci 2018;19:4058.

47. Kastelein JJ, Akdim F, Stroes ES, et al.; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358:1431-1443.

48. Howard BV, Roman MJ, Devereux RB, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA 2008;299:1678-1689.

49. Meaney A, Ceballos G, Asbun J, et al. The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. J Clin Pharmacol 2009;49:838-847.

50. Tsujita K, Sugiyama S, Sumida H, et al.; PRECISE–IVUS Investigators. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. J Am Coll Cardiol 2015; 66:495-507.

51. Hougaard M, Hansen HS, Thayssen P, et al. Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: Intravascular ultrasound with iMap: the OCTIVUS trial. Cardiovasc Revasc Med 2017;18: 110-117.

52. Newby AC. Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture. Physiol Rev 2005;85:1-31.

53. Tan H, Liu L, Zheng Q, et al. Effects of combined lipid-lowering therapy on low-density lipoprotein cholesterol variability and cardiovascular adverse events in patients with acute coronary syndrome. Adv Ther 2021;38:3389-3398.

54. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circ Res 2019;124:315-327.

55. Ridker PM. A test in context: high-sensitivity C-reactive protein. J Am Coll Cardiol 2016;67:712-723.

56. Luo P, Li L, Wang LX, et al. Effects of atorvastatin in combination with ezetimibe on carotid atherosclerosis in elderly patients with hypercholesterolemia. Genet Mol Res 2014;13: 2377-2384.

57. Ren Y, Zhu H, Fan Z, Gao Y, Tian N. Comparison of the effect of rosuvastatin versus rosuvastatin/ezetimibe on markers of inflammation in patients with acute myocardial infarction. Exp Ther Med 2017;14:4942-4950.

58. Wang J, Ai XB, Wang F, Zou YW, Li L, Yi XL. Efficacy of ezetimibe combined with atorvastatin in the treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease. Int Angiol 2017;36:467-473.

59. Yang W, Cai X, Lin C, et al. Reduction of C-reactive protein, low-density lipoprotein cholesterol, and its relationship with cardiovascular events of different lipid-lowering therapies: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore) 2022;101:e30563.

60. Cho Y, Kim RH, Park H, Wang HJ, Lee H, Kang ES. Effect of ezetimibe on glucose metabolism and inflammatory markers in adipose tissue. Biomedicines 2020;8:512.

61. Sun C, Zheng W, Liang L, Liu Z, Sun W, Tang R. Ezetimibe improves rosuvastatin effects on inflammation and vascular endothelial function in acute coronary syndrome patients undergoing PCI. J Interv Cardiol 2021;2021:2995602.

62. Krysiak R, Zmuda W, Okopien B. The effect of simvastatin-ezetimibe combination therapy on adipose tissue hormones and systemic inflammation in patients with isolated hypercholesterolemia. Cardiovasc Ther 2014;32:40-46.

63. Mostafa Arabi S, Sadat Bahrami L, MalekAhmadi M, et al. The effect of combination therapy with statins and ezetimibe on proinflammatory cytokines: a systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol 2022;113(Pt B):109477.

64. Hussein O, Minasian L, Itzkovich Y, Shestatski K, Solomon L, Zidan J. Ezetimibe's effect on platelet aggregation and LDL tendency to peroxidation in hypercholesterolaemia as monotherapy or in addition to simvastatin. Br J Clin Pharmacol 2008;65: 637-645.

65. Pesaro AE, Serrano CV Jr, Fernandes JL, et al. Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin. Int J Cardiol 2012;158:400-404.

66. Moutzouri E, Liberopoulos EN, Tellis CC, Milionis HJ, Tselepis AD, Elisaf MS. Comparison of the effect of simvastatin versus simvastatin/ezetimibe versus rosuvastatin on markers of inflammation and oxidative stress in subjects with hypercholesterolemia. Atherosclerosis 2013;231:8-14.

67. Sakuma M, Toyoda S, Hashimoto R, et al. Add-on ezetimibe treatment to low-dose statins vs medium-intensity statin monotherapy in coronary artery disease patients with poorly controlled dyslipidemia. Hypertens Res 2019;42:1923-1931.

68. Takase S, Matoba T, Nakashiro S, et al. Ezetimibe in combination with statins ameliorates endothelial dysfunction in coronary arteries after stenting: the CuVIC trial (effect of cholesterol absorption inhibitor usage on target vessel dysfunction after coronary stenting), a multicenter randomized controlled trial. Arterioscler Thromb Vasc Biol 2017;37:350-358.

69. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380:565-571.

70. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015;58:1109-1117.

71. Agarwala A, Kulkarni S, Maddox T. The association of statin therapy with incident diabetes: evidence, mechanisms, and recommendations. Curr Cardiol Rep 2018;20:50.

72. Betteridge DJ, Carmena R. The diabetogenic action of statins - mechanisms and clinical implications. Nat Rev Endocrinol 2016;12:99-110.

73. Her AY, Kim JY, Kang SM, et al. Effects of atorvastatin 20 mg, rosuvastatin 10 mg, and atorvastatin/ezetimibe 5 mg/5 mg on lipoproteins and glucose metabolism. J Cardiovasc Pharmacol Ther 2010;15:167-174.

74. Adachi H, Nakano H, Yamamoto K, et al.; ERASE METS Study Investigators. Ezetimibe ameliorates atherogenic lipids profiles, insulin resistance and hepatocyte growth factor in obese patients with hypercholesterolemia. Lipids Health Dis 2015;14:1.

75. Ohbu-Murayama K, Adachi H, Hirai Y, et al. Ezetimibe combined with standard diet and exercise therapy improves insulin resistance and atherosclerotic markers in patients with metabolic syndrome. J Diabetes Investig 2015;6:325-333.

76. Takeshita Y, Takamura T, Honda M, et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism: a randomised controlled trial. Diabetologia 2014;57:878-890.

77. Zhong Y, Wang J, Gu P, Shao J, Lu B, Jiang S. Effect of ezetimibe on insulin secretion in db/db diabetic mice. Exp Diabetes Res 2012;2012:420854.

78. Zeng KY, Bao WY, Wang YH, et al. Non-invasive evaluation of liver steatosis with imaging modalities: new techniques and applications. World J Gastroenterol 2023;29:2534-2550.

79. Kim SH, Kim G, Han DH, et al. Ezetimibe ameliorates steatohepatitis via AMP activated protein kinase-TFEB-mediated activation of autophagy and NLRP3 inflammasome inhibition. Autophagy 2017;13:1767-1781.

80. Park H, Shima T, Yamaguchi K, et al. Efficacy of long-term ezetimibe therapy in patients with nonalcoholic fatty liver disease. J Gastroenterol 2011;46:101-107.

81. Simon TG, Corey KE, Cannon CP, et al. The nonalcoholic fatty liver disease (NAFLD) fibrosis score, cardiovascular risk stratification and a strategy for secondary prevention with ezetimibe. Int J Cardiol 2018;270:245-252.

82. Lee HY, Jun DW, Kim HJ, et al. Ezetimibe decreased nonalcoholic fatty liver disease activity score but not hepatic steatosis. Korean J Intern Med 2019;34:296-304.

83. Cho Y, Rhee H, Kim YE, et al. Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: an open-label randomized controlled trial (ESSENTIAL study). BMC Med 2022;20:93.

84. Stroes ES, Thompson PD, Corsini A, et al.; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:1012-1022.

85. Cha JJ, Hong SJ, Kim JH, et al. Effect of rosuvastatin 20 mg versus rosuvastatin 5 mg plus ezetimibe on statin side-effects in elderly patients with atherosclerotic cardiovascular disease: Rationale and design of a randomized, controlled SaveSAMS trial. Am Heart J 2023;261:45-50.

86. Davidson MH, Maccubbin D, Stepanavage M, Strony J, Musliner T. Striated muscle safety of ezetimibe/simvastatin (Vytorin). Am J Cardiol 2006;97:223-228.

87. Lee YJ, Cho JY, You SC, et al. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. Eur Heart J 2023;44:972-983.

88. Dujovne CA, Ettinger MP, McNeer JF, et al.; Ezetimibe Study Group. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1092-1097.

89. Phillips PS. Ezetimibe and statin-associated myopathy. Ann Intern Med 2004;141:649.

90. Fux R, Mörike K, Gundel UF, Hartmann R, Gleiter CH. Ezetimibe and statin-associated myopathy. Ann Intern Med 2004;140:671-672.

91. Nutescu EA, Shapiro NL. Ezetimibe: a selective cholesterol ab-

sorption inhibitor. Pharmacotherapy 2003;23:1463-1474.

92. Newman CB. Safety of statins and nonstatins for treatment of dyslipidemia. Endocrinol Metab Clin North Am 2022;51:655-679.

Correspondence to
Seung-Hwan Lee, M.D., Ph.D.
Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-6069, Fax: +82-2-595-2534
E-mail: hwanx2@catholic.ac.kr
https://orcid.org/0000-0002-3964-3877

CRedit authorship contributions
Jeongmin Lee: conceptualization, writing - original draft; Seung-Hwan Lee: conceptualization, writing - review & editing, project administration

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