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Additive Effects of Ezetimibe and Statins in Managing Elevated LDL-C: An Approach to Reducing Cardiovascular Risk

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Abstract

Elevated low-density lipoprotein cholesterol (LDL-C) is a key modifiable risk factor for cardiovascular disease. While statins are the cornerstone of LDL-C-lowering therapy, their long-term use may result in dose-dependent adverse effects. Ezetimibe, a Niemann–Pick C1-Like 1 inhibitor, reduces intestinal cholesterol absorption and complements the reduction of hepatic cholesterol synthesis achieved through statin therapy. Evidence from major trials, including IMPROVE-IT, SHARP, RACING, and EWTOPIA 75, demonstrates that combination therapy achieves greater LDL-C reduction and provides modest improvements in clinical outcomes compared with statin monotherapy, while maintaining a favorable safety profile. The early initiation of combination therapy may permit the use of lower statin doses, thereby reducing adverse effects such as insulin resistance and hepatotoxicity. The co-administration of ezetimibe with statins, when implemented alongside guideline-recommended strategies, represents a rational and patient-centered approach for high-risk individuals. This strategy offers enhanced lipid control and improved safety outcomes compared with statin monotherapy.

Keywords: LDL, Ezetimibe, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Cardiovascular Diseases, Hyperlipidemias

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Dear Editor

Hyperlipidemia, particularly elevated levels of low-density lipoprotein cholesterol (LDL-C), remains one of the most significant modifiable risk factors for cardiovascular diseases (CVDs) (1, 2). Statins have long been the foundation of treatment for reducing LDL-C, demonstrating considerable efficacy in lowering cardiovascular events and mortality (3). Statins exert their effects by inhibiting HMG-CoA reductase, the enzyme responsible for cholesterol synthesis in the liver (4). This inhibition leads to a decrease in hepatic cholesterol production, which stimulates the liver to increase LDL receptor expression and thereby reduces circulating LDL particles. Statins are well documented for their capacity to lower LDL-C and diminish the risk of atherosclerotic cardiovascular diseases (5). However, although statins effectively reduce LDL-C, their potential to cause adverse effects, including hepatotoxicity, myopathy, and impaired glucose tolerance, raises concerns regarding their safety, particularly with

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long-term therapy (6–8).

Ezetimibe, in contrast, acts by selectively inhibiting the Niemann–Pick C1-like 1 (NPC1L1) protein in the intestine, thereby preventing the absorption of cholesterol from both dietary and biliary sources (9). This mechanism produces a modest reduction in LDL-C levels and serves to complement the LDL-lowering effects of statins. The addition of ezetimibe to statin therapy has been shown to reduce LDL-C levels markedly without significantly increasing the risk of adverse effects (10). Additionally, large-scale evidence supports its use in combination therapy. The IMPROVE-IT trial demonstrated incremental risk reduction in post–acute coronary syndrome patients treated with ezetimibe plus simvastatin compared to single simvastatin application (11). The SHARP trial, conducted among patients with chronic kidney disease—of whom approximately one-fifth had diabetes mellitus and one-sixth had vascular disease—showed that allocation to ezetimibe plus simvastatin was not associated with an excess risk of myopathy, hepatic toxicity, or biliary complications during the first year of follow-up and was also clinically beneficial (12). Similarly, the EWTOPIA 75 study in elderly Japanese patients confirmed the clinical benefit of ezetimibe across diverse populations (13). Furthermore, the RACING trial demonstrated that a regimen of moderate-dose statin plus ezetimibe was noninferior to high-intensity statin monotherapy in achieving LDL-C targets and may also improve tolerability (14). Taken together, these studies indicate that the effect of ezetimibe combined with statins is additive and clinically meaningful (Table 1).

Current ESC and ACC/AHA guidelines recommend a stepwise approach: initiate moderate- to high-intensity statin therapy, add ezetimibe if LDL-C levels remain above target, and escalate to PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitors or newer agents such as inclisiran or bempedoic acid in refractory cases (3, 15).

Table 1. Key Clinical Trials of Statin–Ezetimibe Combination Therapy.

Trial (Year)	Population	Intervention	Comparator	LDL-C Reduction	Clinical Outcomes
IMPROVE-IT (2015)	18,144 pts with ACS	Simvastatin 40 mg + ezetimibe 10 mg	Simvastatin 40 mg	~24% additional LDL-C reduction	Relative risk reduction in composite CV events
SHARP (2011)	9,438 pts with CKD	Simvastatin 20 mg + ezetimibe 10 mg	Placebo	Average LDL-C differences of 43 mg/dL at 1 year and 33 mg/dL at 2.5 years	18% relative risk reduction in major atherosclerotic events
EWTOPIA 75 (2019)	3,796 Japanese pts ≥75 yrs	Ezetimibe 10 mg	Dietary counselling only	~25.9% LDL-C reduction	40% reduction in composite CV events; 34% relative risk reduction in primary cardiovascular outcomes
RACING (2022)	3,780 Korean pts with ASCVD (of whom 1,511 [40%] were very high risk)	Rosuvastatin 10 mg + ezetimibe 10 mg	Rosuvastatin 20 mg	LDL-C significantly lower with combination therapy vs high-intensity statin (VHR, 1 yr: 57 vs 65 mg/dL; non-VHR, 1 yr: 58 vs 68 mg/dL; P < .001)	Noninferior for CV outcomes; fewer drug discontinuations (VHR, 4.6% vs 7.7%; P = .02; non-VHR, 5.0% vs 8.7%; P = 0.001)

ACS = acute coronary syndrome, CKD = chronic kidney disease, ASCVD = atherosclerotic cardiovascular disease, VHR = very high risk, CV = cardiovascular.

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Within this framework, the authors argue that an optimal strategy may involve initiating combination therapy with potent statins, such as rosuvastatin or atorvastatin, together with ezetimibe from the outset, rather than deferring the addition of ezetimibe until statin monotherapy proves insufficient. If applied in clinical practice, a fixed-dose combination (FDC) could support this approach by improving adherence and persistence, which in turn may potentiate LDL-C reduction (16). The early combination of these agents has the potential not only to achieve superior LDL-C reduction but also to decrease the long-term risk of adverse effects associated with high-dose statin therapy, including insulin resistance and hepatotoxicity. Meta-analytic evidence supports this strategy, demonstrating that ezetimibe use in patients with NAFLD/NASH significantly lowered serum AST and GGT levels without worsening fibrosis (17). Moreover, a systematic review reported that higher statin doses (20 mg vs. 5 mg) were associated with greater increases in fasting glucose and insulin levels, with incident type 2 diabetes occurring in 3.4–44% of statin users compared with 1.2–5.8% of non-users, risks that increased further with long-term exposure (18). Thus, adopting early combination therapy may reduce the need for escalating statin doses, thereby improving the overall safety and efficacy of treatment for high-risk patients, including those with acute coronary syndromes, chronic kidney disease, diabetes mellitus, and elderly populations (19).

Regardless of the chosen strategy, careful safety monitoring is essential. Baseline ALT (Alanine Aminotransferase) assessment, CK (Creatine Kinase) testing in symptomatic patients, and evaluation of diabetes risk must be incorporated into clinical management, while cost-effectiveness should guide decisions regarding newer lipid-lowering agents (20). Beyond statin–ezetimibe therapy, PCSK9 inhibitors, inclisiran, and bempedoic acid provide additional therapeutic options for patients at high risk or those intolerant to statins, offering substantial LDL-C reduction with proven clinical benefits (21–23). In conclusion, although the LDL-C–lowering effect of ezetimibe combined with statin therapy is largely additive, robust evidence supports its use in high-risk patients for whom statins alone are insufficient. The early integration of ezetimibe, within the framework of guideline-based stepwise strategies, represents a practical and clinically relevant approach to reducing cardiovascular risk.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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