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CLINICAL EFFICACY OF COMBINED LIPID-LOWERING THERAPY IN ISCHEMIC HEART DISEASE: OUTCOMES OF STATIN AND EZETIMIBE THERAPY

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Abstract: Ischemic heart disease (IHD) is one of the most important manifestations of atherosclerotic cardiovascular disease and remains a major cause of recurrent myocardial infarction, coronary revascularization, heart failure, and cardiovascular mortality. Low-density lipoprotein cholesterol (LDL-C) is a causal factor in the development and progression of atherosclerosis, making intensive LDL-C reduction a cornerstone of secondary cardiovascular prevention. Although statins remain the first-line pharmacological treatment, a substantial proportion of patients do not achieve recommended LDL-C targets with maximally tolerated statin therapy alone. The addition of ezetimibe provides a complementary mechanism of LDL-C reduction by inhibiting intestinal cholesterol absorption. This literature review evaluates the clinical efficacy of combined statin and ezetimibe therapy in patients with IHD. Evidence from randomized controlled trials, comparative studies, and contemporary clinical guidelines was analyzed. The IMPROVE-IT trial demonstrated that adding ezetimibe to statin therapy after acute coronary syndrome produced additional LDL-C reduction and a significant decrease in major cardiovascular events [1]. The RACING trial subsequently showed that moderate-intensity rosuvastatin combined with ezetimibe was non-inferior to high-intensity rosuvastatin monotherapy for a composite cardiovascular outcome, while achieving higher rates of LDL-C target attainment [2]. Current evidence therefore supports combination therapy as an effective strategy for patients who do not achieve LDL-C targets with statin monotherapy or who require intensive lipid lowering while minimizing statin-related intolerance.

Keywords: ischemic heart disease, coronary artery disease, statins, ezetimibe, LDL cholesterol, lipid-lowering therapy, combination therapy, cardiovascular events, myocardial infarction, secondary prevention.

Introduction

Ischemic heart disease (IHD), primarily caused by atherosclerotic coronary artery disease, remains a major contributor to cardiovascular morbidity and mortality. Patients with established coronary artery disease have a high or very high risk of recurrent cardiovascular events and therefore require long-term secondary prevention. Among the modifiable risk factors, low-density lipoprotein cholesterol (LDL-C) has a central causal role in atherosclerotic cardiovascular disease. Persistent exposure to elevated LDL-C promotes lipid accumulation within the arterial wall, progression of

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atherosclerotic plaques, and an increased risk of myocardial infarction and other cardiovascular events [3].

Statins are the cornerstone of lipid-lowering therapy because they effectively reduce LDL-C and have a well-established effect on cardiovascular outcomes. However, even high-intensity statin therapy may not reduce LDL-C sufficiently to achieve recommended targets in many patients. Furthermore, some patients are unable to tolerate high-intensity statin doses because of adverse effects or clinically significant statin-associated symptoms. These limitations have increased interest in combination lipid-lowering therapy.

Ezetimibe is a selective inhibitor of intestinal cholesterol absorption. When added to statin therapy, it provides an additional reduction in LDL-C without requiring further escalation of the statin dose. This pharmacological complementarity makes statin–ezetimibe therapy particularly relevant for patients with established IHD who remain above their LDL-C target despite maximally tolerated statin treatment [4].

The importance of combination therapy has been reinforced by contemporary guidelines. The 2025 Focused Update of the ESC/EAS dyslipidaemia guidelines maintains statins as the first-line therapy and recommends the addition of non-statin agents with demonstrated cardiovascular benefit when LDL-C goals are not achieved with the maximally tolerated statin dose. The update also emphasizes early intensification of lipid-lowering therapy following acute coronary syndrome and considers initiation of high-intensity statin plus ezetimibe during hospitalization in treatment-naïve patients when the LDL-C goal is unlikely to be achieved with statin monotherapy [5].

Aim of the review. The aim of this literature review was to evaluate the clinical efficacy of combined statin and ezetimibe therapy in patients with ischemic heart disease, with particular attention to LDL-C reduction, cardiovascular outcomes, safety, and achievement of therapeutic targets.

Materials and Methods

This study was designed as a narrative literature review. Published randomized controlled trials, comparative clinical studies, meta-analyses, and international clinical practice guidelines concerning statin and ezetimibe combination therapy were reviewed.

The analysis focused primarily on patients with established atherosclerotic cardiovascular disease, including patients with chronic coronary artery disease and those who had experienced acute coronary syndrome. Particular attention was given to studies comparing statin monotherapy with statin–ezetimibe combination therapy.

The principal outcomes considered were LDL-C reduction, achievement of guideline-recommended LDL-C targets, major adverse cardiovascular events, myocardial infarction, stroke, coronary revascularization, cardiovascular death, treatment adherence, and safety.

The evidence base included the IMPROVE-IT randomized controlled trial, the RACING randomized non-inferiority trial, contemporary ESC/EAS recommendations, and other relevant clinical evidence [1, 2, 5].

Results and Discussion

Rationale for combined statin and ezetimibe therapy. The therapeutic rationale for combining statins with ezetimibe is based on their complementary mechanisms of action. Statins inhibit hepatic cholesterol synthesis through inhibition of HMG-CoA reductase, resulting in increased hepatic LDL receptor expression and enhanced clearance of circulating LDL particles. Ezetimibe, in contrast,

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inhibits intestinal cholesterol absorption by targeting the Niemann-Pick C1-like 1 protein. The combination therefore reduces cholesterol availability through two different pathways.

This complementary mechanism is clinically important because patients with IHD frequently require substantial LDL-C reductions. High-intensity statin therapy may reduce LDL-C by approximately 50% or more, but individual responses vary and treatment may be limited by intolerance. Addition of ezetimibe can provide a further reduction in LDL-C without requiring further escalation of statin intensity [4].

The 2025 ESC/EAS focused update confirms that non-statin lipid-lowering therapies with demonstrated cardiovascular benefit should be added when LDL-C targets cannot be achieved with the maximum tolerated statin dose [5]. This approach represents a shift from a purely drug-centered strategy toward a target-oriented treatment model.

Evidence from the IMPROVE-IT trial. The strongest evidence supporting the cardiovascular efficacy of statin–ezetimibe combination therapy comes from the IMPROVE-IT trial. This double-blind randomized controlled trial enrolled 18,144 patients who had been hospitalized for acute coronary syndrome. Participants were assigned to receive either simvastatin 40 mg plus ezetimibe 10 mg or simvastatin 40 mg plus placebo [1].

The addition of ezetimibe resulted in a significantly lower LDL-C concentration compared with statin monotherapy. More importantly, the reduction in LDL-C translated into a statistically significant reduction in the composite primary cardiovascular endpoint. The primary endpoint occurred in 32.7% of patients receiving ezetimibe plus simvastatin compared with 34.7% receiving simvastatin alone during the study period [1].

The absolute difference was modest but clinically meaningful given the high baseline risk of the population. The study provided important evidence that additional LDL-C reduction beyond that achieved with statin monotherapy can produce further cardiovascular benefit.

The findings of IMPROVE-IT are particularly relevant to patients with IHD because the trial population consisted of individuals with recent acute coronary syndrome, a group characterized by a high risk of recurrent cardiovascular events. Therefore, the results support the use of combination therapy when aggressive LDL-C lowering is required.

Combination therapy and achievement of LDL-C targets. One of the principal advantages of combining ezetimibe with a statin is the increased likelihood of achieving LDL-C targets. In patients with very high cardiovascular risk, the LDL-C target is substantially lower than conventional historical thresholds. Current European recommendations retain very-low LDL-C targets for patients with established atherosclerotic cardiovascular disease [5].

Achieving these targets with statin monotherapy may be difficult, particularly in patients with high baseline LDL-C concentrations. Addition of ezetimibe increases the magnitude of LDL-C reduction and may therefore allow clinicians to achieve therapeutic goals without further increasing the statin dose.

This approach may be particularly valuable in patients with statin-associated muscle symptoms or other intolerance. Rather than discontinuing lipid-lowering therapy or maintaining a suboptimal statin dose, combination treatment can provide substantial LDL-C reduction through complementary pharmacological mechanisms.

Evidence from the RACING trial. The RACING trial provided further evidence regarding the role of combination therapy in patients with established atherosclerotic cardiovascular disease. In this

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randomized open-label non-inferiority trial, 3,780 patients were assigned to either moderate-intensity rosuvastatin 10 mg plus ezetimibe 10 mg or high-intensity rosuvastatin 20 mg [2].

After three years, the primary composite cardiovascular endpoint occurred in 9.1% of patients receiving combination therapy compared with 9.9% of patients receiving high-intensity statin monotherapy. The combination strategy therefore demonstrated non-inferiority to high-intensity statin monotherapy [2].

Importantly, combination therapy was associated with a higher proportion of patients achieving LDL-C targets. The study also provides clinically relevant evidence for patients who cannot tolerate high-intensity statin treatment. A moderate statin dose combined with ezetimibe may achieve comparable cardiovascular protection while reducing exposure to higher statin doses.

Thus, the RACING trial expands the clinical rationale for combination therapy beyond the simple concept of "add-on treatment." In selected patients, statin–ezetimibe combination therapy may serve as an alternative strategy for achieving intensive lipid lowering while maintaining treatment tolerability.

Effect on myocardial infarction and other cardiovascular events. The principal objective of lipid-lowering therapy in IHD is not simply to improve laboratory lipid parameters but to reduce clinically important cardiovascular events. Evidence from IMPROVE-IT demonstrated that additional LDL-C lowering through ezetimibe was associated with a reduction in the composite of cardiovascular death, major cardiovascular events, and non-fatal myocardial infarction [1].

The relationship between LDL-C reduction and cardiovascular risk is consistent with the broader evidence base from statin and non-statin trials. Lower LDL-C concentrations are associated with lower risks of myocardial infarction, ischemic stroke, and coronary revascularization [3, 6].

For patients with IHD, this is especially important because the residual risk after an initial coronary event remains substantial. Even when patients receive statins and standard secondary prevention, recurrent events may occur. Intensification of lipid-lowering treatment may therefore contribute to further risk reduction.

Effect on recurrent angina and clinical symptoms. The effect of statin–ezetimibe combination therapy on angina symptoms requires a somewhat different interpretation. Ezetimibe is not an anti-anginal drug, and its primary clinical benefit is the reduction of atherosclerotic cardiovascular events rather than immediate relief of myocardial ischemia.

Nevertheless, sustained LDL-C reduction may contribute to stabilization of coronary atherosclerotic plaques and reduction of progressive coronary disease. This mechanism may indirectly reduce the likelihood of recurrent ischemic events and subsequent deterioration in symptoms.

Patients with IHD should therefore not discontinue anti-anginal therapy solely because LDL-C has reached the desired target. Conversely, improvement in angina symptoms should not be interpreted as evidence that lipid-lowering treatment is no longer necessary. Symptom control and atherosclerotic risk reduction represent separate but complementary treatment objectives.

Safety and treatment adherence. An important clinical advantage of ezetimibe is its favorable tolerability profile. Because it does not require further escalation of statin dosage, it may be useful for patients who experience adverse effects at higher statin intensities.

The RACING trial demonstrated that the combination strategy was associated with fewer treatment discontinuations or dose reductions due to intolerance compared with high-intensity statin

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monotherapy [2]. This finding has practical importance because long-term adherence is essential for successful secondary cardiovascular prevention.

In real-world clinical practice, the effectiveness of a lipid-lowering strategy depends not only on its pharmacological potency but also on whether patients can continue treatment over an extended period. A moderately intensive statin combined with ezetimibe may therefore represent an attractive strategy for selected patients when high-intensity statin therapy is poorly tolerated.

Role of combination therapy after acute coronary syndrome. Patients who have recently experienced acute coronary syndrome represent a particularly high-risk population. The early period after an acute coronary event is associated with a substantial risk of recurrent ischemic complications. Therefore, delaying intensification of lipid-lowering therapy may leave patients exposed to preventable residual risk.

The 2025 ESC/EAS focused update specifically emphasizes early intensification of lipid-lowering treatment during hospitalization for ACS. For treatment-naïve patients, initiation of high-intensity statin plus ezetimibe should be considered when the LDL-C target is not expected to be achieved with statin therapy alone [5].

This recommendation is important because it supports an early combination strategy rather than waiting for a later outpatient reassessment before adding ezetimibe. The clinical rationale is to shorten the time required to reach the LDL-C target during a period when cardiovascular risk is particularly high.

Comparison with other non-statin therapies. Although ezetimibe represents an established second-line therapy, it is not the only option for patients who remain above their LDL-C target. PCSK9 inhibitors can produce substantially larger LDL-C reductions and have demonstrated cardiovascular benefit in high-risk populations [7, 8]. Bempedoic acid is another option, particularly for patients with statin intolerance [5].

Nevertheless, ezetimibe has several practical advantages, including oral administration, relatively favorable tolerability, established cardiovascular outcome evidence, and generally lower treatment complexity than injectable PCSK9 inhibitor therapy.

Therefore, treatment selection should be individualized according to baseline LDL-C, the magnitude of reduction required, cardiovascular risk, statin tolerance, adherence, cost and accessibility, and patient preferences.

Conclusion

The available evidence demonstrates that combined statin and ezetimibe therapy is an effective strategy for patients with ischemic heart disease who require intensive LDL-C reduction. The IMPROVE-IT trial provided direct evidence that adding ezetimibe to statin therapy after acute coronary syndrome produces additional LDL-C lowering and reduces major cardiovascular events [1].

The RACING trial further demonstrated that moderate-intensity rosuvastatin combined with ezetimibe was non-inferior to high-intensity rosuvastatin monotherapy for major cardiovascular outcomes, while providing better LDL-C target attainment and potentially improving treatment tolerability [2].

The contemporary treatment strategy is therefore increasingly based on achieving individualized LDL-C targets rather than simply prescribing a fixed statin dose. Current ESC/EAS recommendations support the addition of ezetimibe when LDL-C goals cannot be reached with maximally tolerated

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statin therapy and emphasize early combination treatment in selected patients with acute coronary syndrome [5].

Overall, statin–ezetimibe combination therapy should be considered an important component of secondary prevention in IHD. Its principal clinical value lies in achieving greater and sustained LDL-C reduction, improving the probability of reaching recommended therapeutic targets, and reducing the risk of recurrent cardiovascular events. Future clinical research should continue to evaluate personalized combination strategies, treatment adherence, long-term outcomes, and cost-effectiveness in different IHD populations.

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