Cardiovascular Diabetology

COMMENT

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Moderate-intensity statin plus ezetimibe as an alternative to high-intensity statin therapy

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To the Editor:

Following our recent meta-analysis demonstrating that ezetimibe combined with moderate-intensity statin therapy is associated with a significantly lower risk of new-onset type 2 diabetes (NO-T2DM) compared with high-intensity statin monotherapy [1], we aim to highlight the potential clinical implications of these findings for individualized cholesterol management. Specifically, combination therapy was associated with an 18% lower risk of NO-T2DM (RR = 0.82, 95% CI: 0.77–0.87) compared with high-intensity statin monotherapy, while no significant difference was observed compared with moderate-intensity statin alone (RR = 1.04, 95% CI: 0.94–1.14).

High-intensity statin therapy remains the standard for patients at high and very high cardiovascular risk [2]. Although this strategy is highly effective for lowering low-density lipoprotein cholesterol (LDL-C), robust evidence indicates a dose-dependent increase in NO-T2DM, particularly among individuals with prediabetes, obesity, or metabolic syndrome [3]. This raises a critical clinical question: can comparable cardiovascular protection be achieved while minimizing metabolic harm?

Accumulating evidence from randomized trials and meta-analyses indicates that moderate-intensity statin therapy combined with ezetimibe provides cardiovascular efficacy comparable to high-intensity statin monotherapy in patients with established atherosclerotic cardiovascular disease (ASCVD). Across pooled randomized data, including post–acute coronary syndrome and post–percutaneous coronary intervention populations, no significant differences in major adverse cardiovascular events have been observed over follow-up periods of up to three years [4–6]. In parallel, multiple analyses demonstrate that this combination strategy achieves LDL-C reductions comparable to high-intensity statins and enables attainment of guideline-recommended LDL-C targets in both stable coronary disease and post-acute coronary syndrome settings [7, 8].

Importantly, metabolic safety distinguishes these two approaches. High-intensity statin therapy has been consistently associated with a higher risk of NO-T2DM, confirming a dose-related dysglycemic effect [3]. Recent individual participant data meta-analyses from the Cholesterol Treatment Trialists' Collaboration further demonstrate that statin therapy is associated with a dose-dependent increase in incident diabetes, with higher risk observed with intensive-dose statin regimens, particularly among individuals with predisposing metabolic risk factors [9]. In contrast, pooled evidence from randomized trials and observational studies shows that moderate-intensity statin plus ezetimibe is associated with lower incidence of NO-T2DM, fewer treatment-limiting adverse effects, and improved treatment adherence, particularly among patients with underlying metabolic risk [5, 10, 11]. These findings are concordant with landmark trials such as IMPROVE-IT and RACING, which demonstrated non-inferior cardiovascular outcomes, effective LDL-C lowering, and superior tolerability with combination therapy compared with high-intensity statin regimens in high-risk ASCVD populations [12, 13]. The observed balance between effective LDL-C lowering and reduced diabetes risk underscores the potential value of combination therapy in patients with overlapping

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cardiovascular and metabolic risk profiles. This approach may be particularly relevant in individuals with prediabetes, obesity, or metabolic syndrome, where treatment decisions must simultaneously address both atherosclerotic and glycemic outcomes.

While the available evidence is generally consistent, several limitations should be considered. First, most studies have follow-up durations of up to three years, which may not fully capture long-term cardiovascular and metabolic outcomes. Second, variability in study populations, including differences in baseline cardiometabolic risk profiles, may limit the generalizability of the findings. In addition, residual confounding cannot be excluded in observational analyses. Therefore, these findings should be interpreted with appropriate caution.

Taken together, current evidence suggests that moderate-intensity statin plus ezetimibe represents a clinically effective and metabolically safer alternative to high-intensity statin monotherapy for appropriately selected patients, particularly those at elevated risk of diabetes. These findings may help inform future guideline discussions and support a more individualized, cardiometabolic approach to lipid-lowering therapy. Nevertheless, further long-term studies are needed to better define optimal patient selection and to confirm these observations.

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References

1. Albawa'neh AS, Alqasrawi MN, Al-Mahayri ZN, Albawaana A, Ahmed G, Al-Rifai RH, et al. Ezetimibe and the risk of new-onset type 2 diabetes: a systematic review and meta-analysis. Ann Med. 2025;57(1):2594355. https://doi.org/10.1080/07853890.2025.2594355.
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC guideline on the management of blood cholesterol. Circulation. 2019;139(25):E1082–143. https://doi.org/10.1161/CIR.0000000000000625.
3. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735–42. https://doi.org/10.1016/S0140-6736(09)61965-6.
4. Yun J, Yang S, Hwang D, Kang J, Yang HM, Park KW, et al. Comparative outcomes of moderate-intensity statin with ezetimibe vs high-intensity statin therapy: a retrospective observational cohort study. J Clin Lipidol. 2026;20(1):87–95. https://doi.org/10.1016/j.jacl.2025.09.020.
5. Lee YJ, Hong BK, Yun KH, Kang WC, Hong SJ, Lee SH, et al. Alternative LDL cholesterol-lowering strategy vs high-intensity statins in atherosclerotic cardiovascular disease: a systematic review and individual patient data meta-analysis. JAMA Cardiol. 2025;10(2):137–44. https://doi.org/10.1001/jamacardio.2024.3911.
6. Kelly FA, de Moraes FCA, Lôbo AOM, Siebel VM, Leite M, de Almeida AM, et al. Safety and efficacy of moderate-intensity statin plus ezetimibe versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease: a meta-analysis. J Clin Lipidol. 2024;18(6):e893–904. https://doi.org/10.1016/j.jacl.2024.07.013.
7. Ah YM, Jeong M, Choi HD. Comparative safety and efficacy of low- or moderate-intensity statin plus ezetimibe combination therapy and high-intensity statin monotherapy: a meta-analysis of randomized controlled studies. PLoS ONE. 2022;17(3):e0264437. https://doi.org/10.1371/journal.pone.0264437.
8. Yasmin F, Moeed A, Umar M, Zaidi F, Khan MS, Alraies MC. Efficacy and safety of moderate-intensity statin and ezetimibe combination therapy versus high-intensity statin monotherapy in patients with cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. J Lipid Atheroscler. 2025;14(2):145–58. https://doi.org/10.12997/jla.2025.14.2.145.
9. Cholesterol Treatment Trialists' (CTT) Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. Lancet Diabetes Endocrinol. 2024;12(5):306–19. https://doi.org/10.1016/S2213-8587(24)00040-8.
10. Choo EH, Moon D, Choi IJ, Lim S, Lee J, Kang D, et al. Efficacy and diabetes risk of moderate-intensity statin plus ezetimibe versus high-intensity statin after percutaneous coronary intervention. Cardiovasc Diabetol. 2024;23(1):396. https://doi.org/10.1186/s12933-024-02498-3.
11. Sydhom P, Al-Quraishi B, El-Shawaf M, Osman MT, Naji N, Awwad N, et al. The clinical effectiveness and safety of low/moderate-intensity statins & ezetimibe combination therapy vs. high-intensity statin monotherapy: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2024;24(1):660. https://doi.org/10.1186/s12872-024-04144-y.
12. Lee SJ, Cha JJ, Choi WG, Lee WS, Jeong JO, Choi S, et al. Moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients at very high risk of atherosclerotic cardiovascular disease: a post hoc analysis from the RACING randomized clinical trial. JAMA Cardiol. 2023;8(9):853–8. https://doi.org/10.1001/jamacardio.2023.2222.
13. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387–97. https://doi.org/10.1056/NEJMoa1410489.

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