Korean Circ J. 2024 Sep;54(9):545-548
https://doi.org/10.4070/kcj.2024.0195
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Check for updates

Exploring New Combination Strategy of Lipid-Lowering Therapies for Primary Prevention of Cardiovascular Disease

Jun Hwan Cho, MD[1,2], Eun Jeong Cho, MD, PhD[1,2], and Young-Hoon Jeong, MD, PhD[1,2]

[1]CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea
[2]Division of Cardiology, Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

▸ See the article "Comparison of Statin With Ezetimibe Combination Therapy Versus Statin Monotherapy for Primary Prevention in Middle-Aged Adults" in volume 54 on page 534.

OPEN ACCESS

Received: Jul 1, 2024
Accepted: Jul 24, 2024
Published online: Jul 25, 2024

Correspondence to
Young-Hoon Jeong, MD, PhD
CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, 110, Deokan-ro, Gwangmyeong 14353, Korea.
Email: goodoctor@naver.com
younggoodoctor@gmail.com

ORCID iDs
Jun Hwan Cho
https://orcid.org/0000-0003-2158-8272
Eun Jeong Cho
https://orcid.org/0000-0003-3345-2516
Young-Hoon Jeong
https://orcid.org/0000-0003-0403-3726

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Cardiovascular disease (CVD) is the leading cause of death globally. Metabolic, behavioral, environmental, and occupational risk factors significantly influence the incidence and progression of CVD. Among the top cardiovascular risk factors are high blood pressure, dietary risks, and elevated levels of low-density lipoprotein cholesterol (LDL-C).[1] Therefore, lowering LDL-C levels is one of the most effective strategies for preventing CVD. Statin therapy is the cornerstone of this approach, with numerous randomized controlled trials (RCTs) demonstrating its effectiveness in the primary prevention of CVD (**Table 1**).[2-5] According to a recent meta-analysis (23 RCTs and 3 observational studies; n=513,291), statin therapy for the primary prevention of CVD was associated with a reduced risk of all-cause mortality (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.87–0.98) and CVD events (HR, 0.72; 95% CI, 0.64–0.81).[6] Benefits of statin therapy appeared to be present across diverse demographic and clinical populations. Consequently, the US Preventive Services Task Force recommends statin use for primary prevention in individuals aged 40 to 75 years with no history of CVD, who have one or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater.

Ezetimibe inhibits the absorption of biliary and dietary cholesterol from the intestine. The Ezetimibe Lipid-Lowering Trial On Prevention of Atherosclerosis in 75 or older (EWTOPIA-75) trial focused on individuals aged 75 and older without history of CVD (n=5,333) (**Table 1**). Lipid lowering therapy with ezetimibe demonstrated significant decreases of LDL-C level (absolute difference; 18 mg/dL at 1 year) and CVD (HR, 0.66; 95% CI, 0.50–0.86) compared with placebo treatment.[7] Since the inhibition of hepatic cholesterol synthesis by statins is generally followed by a compensatory increase in cholesterol absorption, combining statins with ezetimibe is more effective in reducing LDL-C levels. Furthermore, adding ezetimibe has demonstrated a significant LDL-C-lowering effect while reducing the dose-dependent adverse effects associated with statins, thereby improving medication adherence.

Table 1. Representative large-scale clinical trials of lipid-lowering strategies for primary prevention

Trials	Inclusion criteria	Follow-up duration (years, median)	Intervention vs. comparator (number)	Primary endpoint	HR (95% CI)
Statin					
ASCOT-LLA[2] (2003)	Aged 40 to 79 years with hypertension ≥3 CVD risk factors Total cholesterol ≤251 mg/dL Triglyceride <399 mg/dL	3.3	Atorvastatin 10 mg/d (n=5,168) vs. placebo (n=5,137)	Fatal CHD, or non-fatal MI	0.64 (0.50–0.83)
MEGA[3] (2006)	Aged 40 to 70 years No history of CVD or stroke events Total cholesterol 220 to 270 mg/dL	5.3 (mean)	Diet + pravastatin 10–20 mg/d (n=3,866) vs. diet only (n=3,966)	CHD events	0.67 (0.49–0.91)
JUPITER[4] (2008)	Men ≥50 years or women ≥60 years No history of CVD CRP ≥2.0 mg/L LDL-C <130 mg/dL Triglyceride <500 mg/dL	1.9	Rosuvastatin 20 mg/d (n=8,901) vs. placebo (n=8,901)	CV death, MI, stroke, revascularization, or hospitalization for unstable angina	0.56 (0.46–0.69)
HOPE-3[5] (2016)	Men: aged ≥55 years Women: aged ≥65 years ≥1 CVD risk factor Women ≥60 years with ≥2 CVD risk factors	5.6	Rosuvastatin 10 mg/d (n=6,361) vs. placebo (n=6,344)	CV death, non-fatal MI or stroke	0.76 (0.64–0.91)
Ezetimibe					
EWTOPIA-75[7] (2019)	Aged ≥75 years No history of CHD LDL-C ≥140 mg/dL	2.6	Ezetimibe 10 mg/d (n=1,716) vs. placebo (n=1,695)	CV death, MI, stroke or coronary revascularization	0.66 (0.50–0.86)
Bempedoic acid					
CLEAR Outcomes[8] (2023)	Aged 18 to 85 years Statin intolerance LDL-C ≥100 mg/dL High SCORE risk Coronary calcium score ≥400 Agatston units, or women ≥65 years or men ≥60 years with diabetes	3.3	Bempedoic acid 180 mg/d (n=2,100) vs. placebo (n=2,106)	CV death, non-fatal MI, stroke, or coronary revascularization	0.70 (0.55–0.89)

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CHD = coronary heart disease; CI = confidence interval; CLEAR = Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen; CRP = C-reactive protein; CV = cardiovascular; CVD = cardiovascular disease; EWTOPIA-75 = Ezetimibe Lipid-Lowering Trial On Prevention of Atherosclerosis in 75 or older; HOPE-3 = Heart Outcomes Prevention Evaluation-3; HR = hazard ratio; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI = myocardial infarction; SCORE = systemic coronary risk evaluation.

Conflict of Interest

Dr Jeong has received honoraria for lectures from Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Daewoong Pharmaceuticals and research grants or support from Samjin Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals, Biotronik Korea, and U and I Corporation. The remaining authors have nothing to disclose.

Data Sharing Statement

The data required to reproduce findings cannot be shared as this paper is an editorial.

Author Contributions

Conceptualization: Cho JH, Jeong YH; Resources: Cho JH, Jeong YH; Writing - original draft: Cho JH; Writing - review & editing: Cho EJ, Jeong YH.

Ezetimibe is recommended as a second-line treatment for patients who do not achieve their LDL-C goals on maximum tolerated statin therapy, according to guidelines for both primary and secondary prevention. Compared to the beneficial effects of their combination therapy in secondary prevention, its efficacy in primary prevention remains controversial. In the Study of Heart and Renal Protection trial (n=9,270), the simvastatin-ezetimibe treatment significantly reduced the incidence of major cardiovascular events in patients with chronic kidney disease (11.3% vs. 13.4%; HR, 0.83; 95% CI, 0.74–0.94; log-rank p=0.0021) compared with placebo.[9] This trial targeted selective patients at very high CVD risk and compared the combination therapy with a placebo, making it difficult to generalize the results.

In this issue of the *Korean Circulation Journal*, Cha et al.[10] presented the clinical outcome of healthy middle-aged adults treated with a combination of statin with ezetimibe vs. statin monotherapy, using the Korean National Health Insurance Service (NHIS) database. After propensity score matching, 46,078 participants were treated with the combination strategy, while another 46,078 were treated with statin monotherapy. Over a period of 2.9±0.3 years, the incidence of composite clinical outcomes was monitored. The combination therapy showed no difference in composite clinical outcomes compared to statin monotherapy (HR, 1.022; 95% CI, 0.980–1.064; p=0.309). However, combining ezetimibe with statin

kcj
Korean Circulation Journal

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

significantly decreased the risk of all-cause mortality compared to statin monotherapy (HR, 0.595; 95% CI, 0.460–0.769; p<0.001). This analysis significantly contributes to the existing literature by demonstrating the role of ezetimibe and statin combination therapy in the primary prevention of CVD using a large-scale real-world database. However, the study design has limitations, including the inability to ascertain patients' CVD risk, LDL-C levels during the follow-up period, the type and intensity of statin used, and the occurrence of statin intolerance and adverse events.

Another study using the NHIS database compared the clinical outcomes during a combining low- or moderate-intensity statin with ezetimibe vs. high-intensity statin monotherapy for primary prevention of CVD. The combination of moderate-intensity statin with ezetimibe was only found to be superior to high-intensity statin monotherapy in preventing the composite outcomes (HR, 0.84; 95% CI, 0.77–0.92), as well as individual outcomes of myocardial infarction (HR, 0.81; 95% CI, 0.71–0.94) and stroke (HR, 0.78; 95% CI, 0.65–0.93).[11] These clinical benefits from this combination strategy in primary prevention may be associated with the additional reduction of LDL-C levels, the high attainment rate of LDL-C goals, and high drug adherence due to fewer side effects, as demonstrated in secondary prevention. Additionally, these benefits might be related to the pleiotropic effects of ezetimibe, such as improving platelet aggregation, oxidative stress, inflammatory activity and endothelial dysfunction.[7] As the clinical effect of adding ezetimibe to statin therapy for primary prevention remains unclear, more research and RCTs are needed to fully understand the benefits of this combination therapy in primary prevention. Nonetheless, an understanding of the role of ezetimibe in dyslipidemia management will help clinicians to develop effective treatment strategies.

We now have another alternative to control LDL-C levels: bempedoic acid, in addition to statins and ezetimibe. Bempedoic acid inhibits cholesterol synthesis by inhibiting adenosine triphosphate citrate lyase (ACL), a cytosolic enzyme that acts before 3-hydroxy-3-methyl-glutaryl coenzyme reductase in the cholesterol biosynthetic pathway. alternative to statins. According to a subgroup analysis from the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial (n=4,206) (**Table 1**), bempedoic acid of 180-mg daily lowered LDL-C levels by 30.2 mg/dL (21.3%) and reduced major cardiovascular events for primary prevention of CVD in statin-intolerant patients (HR, 0.70; 95% CI, 0.55–0.89) compared with placebo.[8] For patients who cannot achieve their target LDL-C levels, or who are intolerant to statins, bempedoic acid could be an excellent alternative or adjunctive to statin.

Cumulative exposure to LDL-C is a key driver of CVD risk.[12] For primary prevention, the consideration of estimated CVD risk guides decisions regarding the use of statin and other therapies. Defining risk-enhancing factors (e.g. high-sensitivity C-reactive protein) and coronary artery calcium scoring may enable personalized risk assessment and decision-making. In patients with diabetes, lipid-lowering therapy is recommended for most to reduce CVD risk, with opportunities to tailor therapy based on additional risk factors. Patients with familial hypercholesterolemia are at elevated risk, and LDL-C lowering with statin therapy is often combined with non-statin therapies to prevent CVD occurrence. Therefore, the 'new wave' of lipid-modifying drugs with innovative treatment modalities is expected to further reduce patients' risk of adverse cardiovascular events. With this arsenal of new drugs, we will eventually be able to personalize lipid-lowering treatment according to patient-specific needs.

https://doi.org/10.4070/kcj.2024.0195

REFERENCES

1. Hwang IC, Kim CH, Kim JY, et al. Changes in risk factor status and risk of future ASCVD events in primary prevention. *Korean Circ J* 2024;54:354-6. PUBMED | CROSSREF
2. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58. PUBMED | CROSSREF
3. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* 2006;368:1155-63. PUBMED | CROSSREF
4. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207. PUBMED | CROSSREF
5. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2021-31. PUBMED | CROSSREF
6. Chou R, Cantor A, Dana T, et al. Statin use for the primary prevention of cardiovascular disease in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2022;328:754-71. PUBMED | CROSSREF
7. 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. PUBMED | CROSSREF
8. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA* 2023;330:131-40. PUBMED | CROSSREF
9. Baigent C, Landray MJ, Reith C, et al. 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;377:2181-92. PUBMED | CROSSREF
10. Cha JJ, Hong SJ, Lim S, et al. Comparison of statin with ezetimibe combination therapy versus statin monotherapy for primary prevention in middle-aged adults. *Korean Circ J* 2024;54:534-44. PUBMED | CROSSREF
11. Jun JE, Jeong IK, Ahn KJ, Chung HY, Hwang YC. Combination of low- or moderate-intensity statin and ezetimibe versus high-intensity statin monotherapy on primary prevention of cardiovascular disease and all-cause death: a propensity-matched nationwide cohort study. *Eur J Prev Cardiol*. 2024 [Epub ahead of print]. PUBMED | CROSSREF
12. Yoon M, Lee CJ, Park S, Lee SH. Statins and clinical outcomes in patients with low to moderate risk but with non-obstructive carotid plaques: the SCOPE-CP study. *Korean Circ J* 2022;52:890-900. PUBMED | CROSSREF