

Review



Pharmacological Strategies beyond Statins: Ezetimibe and PCSK9 Inhibitors

Jah Yeon Choi , Jin Oh Na

Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea

OPEN ACCESS

Received: May 6, 2019

Revised: Aug 22, 2019

Accepted: Sep 3, 2019

Correspondence to

Jin Oh Na

Cardiovascular Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.

E-mail: koolup93@gmail.com

Copyright © 2019 The Korean Society of Lipid and Atherosclerosis.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Jah Yeon Choi

<https://orcid.org/0000-0002-6793-4137>

Jin Oh Na

<https://orcid.org/0000-0002-5096-4428>

Funding

None.

Conflict of Interest

The authors have no conflicts of interest to declare.

ABSTRACT

Dyslipidemia, highly elevated, low-density lipoprotein (LDL) cholesterol, is a major cardiovascular risk factor. Statins have been proven to effectively reduce the risk of atherosclerotic cardiovascular disease (ASCVD) and are recommended as a first-line therapy for the primary and secondary prevention of ASCVD. However, statins may not be sufficient in decreasing LDL cholesterol levels and pose a significant on-treatment residual risk of major cardiovascular events (i.e., residual cholesterol risk) according to meta-analyses of statin trials. Current guidelines for cholesterol management to achieve additional LDL cholesterol reduction and reduce ASCVD risk recommend two hyperlipidemic agents besides statins. Use of ezetimibe, a cholesterol absorption inhibitor, leads to additional LDL cholesterol reduction and decreased ASCVD risk, when added to statin therapy, without raising significant safety concerns. Furthermore, in combination with a mild-to-moderate statin intensity, ezetimibe is used in situations of statin-associated adverse effects such as myalgia and the combination therapy is relatively safer. Monoclonal antibody of proprotein convertase subtilisin/kexin type 9 (PCSK9), alirocumab, and evolocumab, have been approved to lower LDL cholesterol level. While there are drawbacks to the use of PCSK9 inhibitors, including high cost and adverse events such as injection site reaction, they significantly decreased serum LDL cholesterol levels and thereby ASCVD risks when added to maximally tolerated statin therapy.

Keywords: Dyslipidemia; Ezetimibe; Alirocumab; Evolocumab

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is still the leading cause of death in the world and dyslipidemia, especially high levels of low density lipoprotein (LDL) cholesterol, are known to be a well-established risk factor. Statins, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, effectively block the cholesterol synthesis pathway in the liver and decrease serum LDL cholesterol up to 50% from baseline according to their potency. During the past few decades, statins have played a central role in the treatment of dyslipidemia and decrease ASCVD risk by 15%–37%. High-intensity statin therapy additionally lowers LDL cholesterol level and cardiovascular events when compared to moderate intensity statins.¹

However, there is still a residual risk of recurrent ASCVD, along with unmet issues as to how we could optimize the treatment for patients with a higher risk of ASCVD² who would benefit from new drug combinations beyond statins.³ In this review, we will discuss pharmacological strategies for dyslipidemia beyond statins, especially two recommended hyperlipidemic agents, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, by recent guidelines.^{4,5}

RECENT AMERICAN HEART ASSOCIATION/ AMERICAN COLLEGE OF CARDIOLOGY (AHA/ACC), EUROPEAN SOCIETY OF CARDIOLOGY/EUROPEAN ATHEROSCLEROSIS SOCIETY (ESC/EAS) GUIDELINES AND KOREAN GUIDELINE ON THE MANAGEMENT OF BLOOD CHOLESTEROL FOR SECONDARY PREVENTION

The 2018 AHA/ACC and 2016 ESC/EAS guidelines recognized that the principle of “the lower, the better” in cholesterol management. Many studies suggest that the ideal total cholesterol level is about 150 mg/dL and LDL cholesterol at or below 100 mg/dL. Especially if patients have a history of ischemic heart disease or stroke, the cholesterol level should be lower than 70 mg/dL or a reduction of at least 50% of baseline for secondary prevention. Statins are thus used, and dose escalation is recommended to achieve optimal cholesterol level.^{4,5} The adopted Korean guideline for management of dyslipidemia revised in 2018 also recommends a treatment target below 70 mg/dL or a 50% reduction of baseline level in patients with an extremely high cardiovascular risk, such as coronary artery disease, ischemic cerebrovascular disease, and peripheral artery disease.⁶

Although high-intensity statins demonstrated a significantly reduced level of LDL cholesterol and cardiovascular events, there is still concern for a “residual cholesterol risk” in patients with ASCVD. Among the pharmacological strategies beyond statins, ezetimibe and an PCSK9 inhibitor are most commonly used as non-statin therapies and have demonstrated additional benefits in lowering LDL cholesterol and reducing residual cardiovascular risks in recent clinical trials^{7,11} and are approved by current guidelines.^{4,6} In patients with a high cardiovascular risk with persistent high LDL cholesterol despite high-intensity statins or maximum tolerated statin dose, ezetimibe is indicated to achieve the treatment goal of LDL cholesterol and secondary prevention. If patients cannot achieve LDL cholesterol targets after maximum tolerable dose statins plus ezetimibe, a PCSK-9 inhibitor can be considered.^{4,6}

EZETIMIBE

Ezetimibe, by targeting the Niemann-Pick C1-like 1 (NPC1L1) protein, inhibits the absorption of cholesterol from the intestine and thereby reduces LDL cholesterol levels.¹² In clinical studies, ezetimibe as a monotherapy reduces LDL cholesterol in patients with dyslipidemia by 18%.¹³ When combined with a statin, ezetimibe provides additional reduction of LDL cholesterol by 15%–20%, leading to a 34%–61% reduction of total LDL cholesterol level.³ One comprehensive study regarding LDL cholesterol effects of ezetimibe was published in 2015

and involved 27 different trials, 21,671 patients, and ezetimibe add-on therapy. It showed a significant LDL cholesterol-lowering effect when compared to statin monotherapy.¹⁴

A number of clinical trials have demonstrated additional benefits of ezetimibe add-on therapy.^{10,15} Among them, a large randomized study, “IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),” reported that adding ezetimibe to statins decreased LDL cholesterol by 24% and reduced cardiovascular events in patients with acute coronary syndrome.¹⁰ It was a double-blind, randomized trial involving 18,144 patients with acute coronary syndrome. In the trial, the simvastatin-ezetimibe group showed a 2% lower rate of primary end points including cardiovascular death, nonfatal myocardial infarction, hospitalization due to unstable angina, coronary revascularization, and nonfatal stroke, compared to the simvastatin monotherapy group ($p < 0.05$). In a subgroup analysis of IMPROVE-IT, the beneficial cardiovascular effect was consistent regardless of sex or the presence of diabetes.^{16,17} Studies reported that ezetimibe has additional benefits in ischemic stroke and cardiovascular-related hospitalization.^{18,19}

Ezetimibe is well-tolerated and associated with adverse events such as myopathy and abnormalities in liver function tests. In a pre-specified safety analysis and IMPROVE-IT trial, patients who achieved an LDL cholesterol level of < 30 mg/dL were compared with those achieving higher LDL cholesterol. There was no significant increase in 9 pre-specified safety outcomes, including myalgia, hepatobiliary events, and neurocognitive disorders.^{5,10} Myalgia is one of the most frequent statin-associated side effects, reported in 10%–25% of patients^{20,21} and is often a result of statin non-adherence. As statin-associated myalgia is thought to be dose dependent, it seems that an ezetimibe add-on to low-dose statin therapy is a treatment option to achieve a target LDL cholesterol level and decreased cardiovascular risk without adverse effects.²² In the most recent guidelines, ezetimibe is to be considered in combination with low-dose statins to manage statin-attributed muscle symptoms.^{5,22,23}

Regarding the effect of ezetimibe on diabetes, a recently published systemic review of randomized controlled trials (RCTs) including 2,440 patients with dyslipidemia reported that ezetimibe did not cause any adverse effects such as increased levels of fasting blood glucose or hemoglobin A1c. Compared with high-dose statin therapy, ezetimibe add-on to low-dose statins may even have beneficial effects on glycemic control.²⁴ By inhibiting the intestinal cholesterol absorption and the NPC1L1 at the hepatic level, ezetimibe decreases hepatic insulin resistance and improves insulin sensitivity and glycemic control in metabolic syndrome.²⁵ However, further study is needed for the clarification of ezetimibe's effect on metabolic disease.

Regarding cost-effectiveness, ezetimibe showed favorable results. Pre-specified analysis of the IMPROVE-IT study reported adding ezetimibe to statin in patients with acute coronary syndrome led to a reduction of cardiovascular-related hospitalization and costs compared to a statin placebo.¹⁸ In patients with high cardiovascular risk, ezetimibe may lead to cost savings in the health care system.¹⁸

The recommended ezetimibe dosage is 10 mg daily, regardless of food intake. When used in combination with bile acid sequestrates, it should be taken either 2 hours before or 4 hours after the bile acid sequestrants.²⁶ Ezetimibe has a favorable drug–drug interaction profile, so that there was no clinically significant interaction between ezetimibe and other drugs used in patients with dyslipidemia, such as statins.⁵ Exceptionally, some reports have demonstrated

interaction between fibrates and ezetimibe due to competition for the same glucuronide clearance pathways.²⁶ Finally, timing of the administration of ezetimibe had no effect on its potency or metabolism. **Tables 1** and **2** show a brief summary and clinical trials of ezetimibe.

PCSK-9 INHIBITORS

PCSK9 is a serine protease that plays a major role in cholesterol metabolism in the liver. Circulating PCSK9 binds to the LDL receptors (LDLR) on the liver surface, internalizes LDLR into the lysosome, and enhances their clearance in the hepatocyte so as to prevent the recycling of LDLRs back to the cell surface.²⁷⁻²⁹ By promoting degradation of LDLR, PCSK9 decreases the clearance of LDL cholesterol from the blood.³⁰ PCSK9 inhibitors block the pathway of PCSK9

Table 1. A brief summary of ezetimibe⁶

Characteristics	Summary
Usage/dosage	10 mg once daily
Follow-up test	Lipid profile tests every 3–6 months
Adverse reactions	- Abdominal pain, diarrhea, flatulence, fatigue, indigestion, gastroesophageal reflux, reduced appetite, arthralgia, muscle spasm, and chest pain - Elevated transaminase, gamma-glutamyl transferase, and creatinine kinase
Contraindications	- Drug hypersensitivity - Pregnancy and breastfeeding - Acute liver disease or moderate to severe chronic liver dysfunction

Table 2. Major clinical trials of ezetimibe

Characteristics	ENHANCE (2008) ⁴¹	SEAS (2008) ¹⁵	SHARP (2011) ¹¹	IMPROVE-IT (2015) ¹⁰
Study type	Phase III	Phase III	Phase III	Phase III
Drug	Ezetimibe	Ezetimibe	Ezetimibe	Ezetimibe
Intervention	Simvastatin 80 mg + ezetimibe vs. simvastatin 80 mg + placebo	Simvastatin 40 mg + ezetimibe vs. simvastatin 40 mg + placebo	Simvastatin 20 mg + ezetimibe vs. simvastatin 20 mg + placebo	Simvastatin 40 mg + ezetimibe vs. simvastatin 40 mg + placebo
Study population	720 patients with familial hypercholesterolemia with untreated LDL cholesterol \geq 210 mg/dL	1,873 patients with mild-to-moderate asymptomatic AS	9,270 patients with chronic kidney disease without history of MI or coronary revascularization	18,144 patients who had been hospitalized for an ACS within the preceding 10 days and 50 mg/dL \leq LDL cholesterol \leq 100 mg/dL with lipid lowering therapy or 50 mg/dL \leq LDL cholesterol \leq 125 mg/dL without lipid lowering therapy
Median duration of follow-up	24 mon	52.2 mon	4.9 yr	6 yr
Primary efficacy endpoint	Change in the mean carotid-artery intima-media thickness	Composite of MACE: cardiovascular death, AVR, nonfatal MI, hospitalization for unstable angina, HF, CABG, PCI, and non-hemorrhagic stroke	First major atherosclerotic event: non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure	Composite of MACE: cardiovascular death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization (\geq 30 days after randomization), or nonfatal stroke
Results	The mean (\pm SE) change in the carotid-artery intima-media thickness, was 0.0058 \pm 0.0037 mm in the simvastatin-only group and 0.0111 \pm 0.0038 mm in the simvastatin-plus-ezetimibe group ($p=0.29$)	Composite of MACE occurred in 333 patients (35.3%) in the simvastatin-ezetimibe group and in 355 patients (38.2%) in the placebo group (HR, 0.96; $p=0.59$)	- 17% reduction first major atherosclerotic event in ezetimibe group - 526 (11.3%) in the simvastatin-ezetimibe group and in 619 patients (13.4%) in the placebo group (RR, 0.83; log rank $p=0.0021$)	2.0% absolute risk difference: 32.7% in the simvastatin-ezetimibe group, 34.7% in the simvastatin-monotherapy group (HR, 0.936; $p=0.016$)

ENHANCE, Efficacy and Safety Study of Prolonged-Release Fampridine in Participants With Multiple Sclerosis; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL, low-density lipoprotein; AS, aortic stenosis; MI, myocardial infarction; ACS, acute coronary syndrome; MACE, major adverse cardiovascular events; AVR, aortic valve replacement; HF, heart failure; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SE, standard error; HR, hazard ratio; RR, relative risk.

and decrease LDLRs degradation and increase the surface expression of the LDLRs on liver, which in turn enhance LDLRs recycling and reduce level of serum LDL cholesterol.³¹

Although various investigation has been done regarding PCSK9 inhibition, the human data are only available for the monoclonal antibody of PCSK9. The best-studied PCSK9 inhibitors are alirocumab and evolocumab, which are currently Food and Drug Administration-approved drugs. In a clinical trial involving 77 patients with heterozygous familial hypercholesterolemia, alirocumab reduced LDL cholesterol by 29%–43% with monthly injections of 150–300 mg and by 68% with biweekly injections of 150 mg.²⁸ Furthermore, the higher doses of alirocumab and biweekly injections of 150 mg showed a significant increase in high-density lipoprotein (HDL) cholesterol and ApoA1 by 6.5% and 8.8%, respectively, and a decrease in ApoB and non-HDL cholesterol.²⁸ In the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS) trial, evolocumab dose-dependency induced a significant decrease in LDL cholesterol levels from 41%–51% compared to baseline in patients with statin-intolerance.²⁷ Contrary to bococizumab, the humanized antibody inhibits PCSK9, a recently reported substantive attenuation of a LDL cholesterol-lowering effect due to immunogenicity,³² evolocumab showed sustained lipid lowering effect to 48 weeks,³³ and alirocumab showed a sustained lipid-lowering effect until 78 weeks; both drugs showed a reduction of major adverse cardiovascular events.^{9,33}

Recently, large-scale RCTs have been performed for monoclonal antibody therapies that inactivated PCSK9. In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) trial, a total of 27,564 patients with ASCVD and suboptimal LDL cholesterol levels despite maximally tolerate statin therapy were enrolled and randomly assigned to receive evolocumab or a placebo.⁸ Regarding a primary end point, which was a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization, the evolocumab group showed significant risk reduction ($p < 0.001$) compared to placebo with no significant difference in adverse events. The Odyssey Outcomes trial confirmed the benefit of alirocumab to reduce ASCVD risk.⁷ The relative risk reduction of 15% was similar to that in the FOURIER trial. While the FOURIER trial enrolled patients with stable ischemic disease, the Odyssey Outcomes trial enrolled patients with recent ACS, which resulted in consistent results in the reduction of all-cause mortalities.

Another PCSK9 inhibitor, inclisiran, a small interfering RNA that silences target RNA and prevents PCSK9 synthesis in the liver, resulted in a decrease in LDL cholesterol up to 53% at day 180 after a second injection.³⁴ Further study is needed for clarification of the cardiovascular effect of inclisiran, and the Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4) trial, which will include 15,000 participants, is expected to provide evidence for the safety and effectiveness of inclisiran on ASCVD patients.

There are several obstacles to the clinical use of the PCSK9 inhibitor. In a phase 2 trial of alirocumab, even though the adverse events were slightly higher in the alirocumab group, there was no increase in any specific organ systems and no difference in liver and muscle enzymes. One patient terminated the study due to an injection-site reaction.²⁸ In a phase 2 trial of evolocumab, nasopharyngitis, cough, upper respiratory tract infections, influenza, arthralgia, and injection site reactions were reported.³⁵ However, in phase 3 trial RCTs, adverse events associated with the PCSK9 inhibitor were variable compared to the placebo except for injection site reactions.^{7-9,33} A meta-analysis of 35 RCTs, including 45,539 patients, reported no

significant difference in neurocognitive adverse events, myalgia, levels of creatine kinase, and alanine or aspartate aminotransferase, which showed a high tolerance of PCSK9 inhibitors.³⁶

Another important barrier for PCSK9 inhibitors in clinical use is cost. There have been several studies regarding the cost-effectiveness of the PCSK9 inhibitor using various economic models.³⁷ Many investigators have agreed that PCSK9 inhibitors will markedly increase medical budgets over the cost savings from preventing cardiovascular events. All models revealed that incremental cost-effectiveness ratio, the value of cost-effectiveness, is unfavorable due to the drug's high price.³⁷ One simulation study, based on the cohort of National Health and Nutrition Examination Surveys (NHANES), suggested that a price reduction by 71% would be needed to avoid excessive cost burden in the health care system.³⁸ Although further investigation is needed, many investigators agree that reducing the price of PCSK9 inhibitors is needed to enhance the long-term adherence of individual patients and achieve any potential health benefits.³⁷⁻⁴⁰

The characteristics and major clinical trials of PCSK9 inhibitors are summarized in **Tables 3 and 4**.

Table 3. A brief summary of PCSK9 inhibitors⁶

Characteristics	Summary
Usage/dosage	Alirocumab: subcutaneous injection of 75 mg or 150 mg Evolocumab: subcutaneous injection of 140 mg/mL in 2-week interval or 420 mg in 1-month interval
Follow-up test	Lipid profile
Adverse reaction	Adverse reactions in the injection site, nasopharyngitis, urinary tract infection, upper respiratory tract infection
Contraindications	Hypersensitivity to alirocumab or evolocumab

Table 4. Major clinical trials of PCSK9 inhibitors

Characteristics	GLAGOV (2016) ⁴²	FOURIER (2017) ⁸	ODYSSEY LONG TERM (2015) ⁹	ODYSSEY OUTCOMES (2018) ⁷
Study type	Phase III	Phase III	Phase III	Phase III
Drug	Evolocumab	Evolocumab	Alirocumab	Alirocumab
Intervention	Statin + evolocumab vs. statin + placebo	Statin + evolocumab vs. statin + placebo	Statin + alirocumab vs. statin + placebo	Statin + alirocumab vs. statin + placebo
Study population	- 968 patients with coronary atherosclerosis - At least 4 weeks of statin therapy with LDL cholesterol ≥ 80 mg/dL or 60 mg/dL \leq LDL cholesterol ≤ 80 mg/dL with 1 major or 3 minor CV risk factors	27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol ≥ 70 mg/dL	2,341 patients at high risk for cardiovascular events who had LDL cholesterol ≥ 70 mg/dL with maximum tolerated dose of statins	18,924 patients with ACS 1 to 12 months earlier and LDL cholesterol ≥ 70 mg/dL, non-HDL cholesterol ≥ 100 mg/dL, apolipoprotein B ≥ 80 mg/dL with high intensity/maximum tolerated dose of statins
Median duration of follow-up	76 wk	2.2 yr	80.9 wk	2.8 yr
Primary efficacy endpoint	Nominal change in PAV from baseline to week 78, measured by serial IVUS imaging	Composite of MACE: cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization	Percentage change in calculated LDL cholesterol level from baseline to week 24	Composite of MACE: coronary heart disease death, MI, ischemic stroke, and unstable angina requiring hospitalization
Results	PAV: - Increased by 0.05% in placebo group - Decreased by 0.95% in evolocumab group	- LDL cholesterol: 59% reduction compared to placebo - Major cardiovascular events: ARR by 1.5%	LDL change at week 24, the difference between the alirocumab and placebo groups -62% ($p < 0.001$); the treatment effect remained consistent over a period of 78 weeks	Composite of MACE: 9.5% in alirocumab group vs. 11.1% in placebo (HR, 0.85; $p < 0.001$)

PCSK9, proprotein convertase subtilisin/kexin type 9; GLAGOV, GLocal Assessment of Plaque regression With a PCSK9 antibody as Measured by IntraVascular Ultrasound; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk; LDL, low-density lipoprotein; CV, cardiovascular; ACS, acute coronary syndrome; HDL, high-density lipoprotein; PAV, percent atheroma volume; IVUS, intravascular ultrasonography; MACE, major adverse cardiovascular events; MI, myocardial infarction; ARR, absolute risk reduction; HR, hazard ratio.

CONCLUSION

In recent years, the concept of residual cholesterol risk among statin treated patients has emerged and efforts to reduce this risk have been made. Ezetimibe and PCSK9 inhibitors are drugs which have abundant clinical evidence and are frequently used in the clinical field. Recognition that there is still room for improvement in clinical outcomes for patients with dyslipidemia and ACSVD and understanding the optimal indication for dyslipidemia medication beyond statins is needed to achieve clinical benefits.

REFERENCES

1. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.
[PUBMED](#) | [CROSSREF](#)
2. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation* 2015;132:1667-1678.
[PUBMED](#) | [CROSSREF](#)
3. Ahn CH, Choi SH. New drugs for treating dyslipidemia: beyond statins. *Diabetes Metab J* 2015;39:87-94.
[PUBMED](#) | [CROSSREF](#)
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:e285-350.
[PUBMED](#) | [CROSSREF](#)
5. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;37:2999-3058.
[PUBMED](#) | [CROSSREF](#)
6. Rhee EJ, Kim HC, Kim JH, Lee EY, Kim BJ, Kim EM, et al. 2018 guidelines for the management of dyslipidemia. *Korean J Intern Med* 2019;34:723-771.
[PUBMED](#) | [CROSSREF](#)
7. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097-2107.
[PUBMED](#) | [CROSSREF](#)
8. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-1722.
[PUBMED](#) | [CROSSREF](#)
9. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-1499.
[PUBMED](#) | [CROSSREF](#)
10. 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;372:2387-2397.
[PUBMED](#) | [CROSSREF](#)
11. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson 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;377:2181-2192.
[PUBMED](#) | [CROSSREF](#)
12. Phan BA, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. *Vasc Health Risk Manag* 2012;8:415-427.
[PUBMED](#)
13. Pandor A, Ara RM, Tumor I, Wilkinson AJ, Paisley S, Duenas A, 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.
[PUBMED](#) | [CROSSREF](#)
14. Descamps O, Tomassini JE, Lin J, Polis AB, Shah A, Brudi P, et al. Variability of the LDL-C lowering response to ezetimibe and ezetimibe + statin therapy in hypercholesterolemic patients. *Atherosclerosis* 2015;240:482-489.
[PUBMED](#) | [CROSSREF](#)

15. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;359:1343-1356.
[PUBMED](#) | [CROSSREF](#)
16. Kato ET, Cannon CP, Blazing MA, Bohula E, Guneri S, White JA, et al. Efficacy and safety of adding ezetimibe to statin therapy among women and men: insight from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *J Am Heart Assoc* 2017;6:e006901.
[PUBMED](#) | [CROSSREF](#)
17. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018;137:1571-1582.
[PUBMED](#) | [CROSSREF](#)
18. Pokharel Y, Chinnakondapalli K, Vilain K, Wang K, Mark DB, Davies G, et al. Impact of ezetimibe on the rate of cardiovascular-related hospitalizations and associated costs among patients with a recent acute coronary syndrome: results from the IMPROVE-IT Trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circ Cardiovasc Qual Outcomes* 2017;10:e003201.
[PUBMED](#) | [CROSSREF](#)
19. Bohula EA, Wiviott SD, Giugliano RP, Blazing MA, Park JG, Murphy SA, et al. Prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2017;136:2440-2450.
[PUBMED](#) | [CROSSREF](#)
20. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403-414.
[PUBMED](#) | [CROSSREF](#)
21. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012;6:208-215.
[PUBMED](#) | [CROSSREF](#)
22. Saxon DR, Eckel RH. statin intolerance: a literature review and management strategies. *Prog Cardiovasc Dis* 2016;59:153-164.
[PUBMED](#) | [CROSSREF](#)
23. Wilson PW, Polonsky TS, Miedema MD, Khera A, Kosinski AS, Kuvin JT. Systematic review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;73:3210-27.
[PUBMED](#) | [CROSSREF](#)
24. Wu H, Shang H, Wu J. Effect of ezetimibe on glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Endocrine* 2018;60:229-239.
[PUBMED](#) | [CROSSREF](#)
25. Deushi M, Nomura M, Kawakami A, Haraguchi M, Ito M, Okazaki M, et al. Ezetimibe improves liver steatosis and insulin resistance in obese rat model of metabolic syndrome. *FEBS Lett* 2007;581:5664-5670.
[PUBMED](#) | [CROSSREF](#)
26. Kosoglou T, Statkevich P, Johnson-Levonos AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005;44:467-494.
[PUBMED](#) | [CROSSREF](#)
27. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, GebSKI V, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA* 2012;308:2497-2506.
[PUBMED](#) | [CROSSREF](#)
28. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet* 2012;380:29-36.
[PUBMED](#) | [CROSSREF](#)
29. Reiss AB, Shah N, Muhieddine D, Zhen J, Yudkevich J, Kasselmann LJ, et al. PCSK9 in cholesterol metabolism: from bench to bedside. *Clin Sci (Lond)* 2018;132:1135-1153.
[PUBMED](#) | [CROSSREF](#)
30. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;34:154-156.
[PUBMED](#) | [CROSSREF](#)

31. Lagace TA. PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells. *Curr Opin Lipidol* 2014;25:387-393.
[PUBMED](#) | [CROSSREF](#)
32. Ridker PM, Tardif JC, Amarenco P, Duggan W, Glynn RJ, Jukema JW, et al. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med* 2017;376:1517-1526.
[PUBMED](#) | [CROSSREF](#)
33. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1500-1509.
[PUBMED](#) | [CROSSREF](#)
34. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med* 2017;376:1430-1440.
[PUBMED](#) | [CROSSREF](#)
35. Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. *Circulation* 2014;129:234-243.
[PUBMED](#) | [CROSSREF](#)
36. Karatasakis A, Danek BA, Karacsonyi J, Rangan BV, Roesle MK, Knickelbine T, et al. Effect of pcsk9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc* 2017;6:e006910.
[PUBMED](#) | [CROSSREF](#)
37. Hlatky MA, Kazi DS. PCSK9 Inhibitors: Economics and Policy. *J Am Coll Cardiol* 2017;70:2677-2687.
[PUBMED](#) | [CROSSREF](#)
38. Kazi DS, Penko J, Coxson PG, Moran AE, Ollendorff DA, Tice JA, et al. Updated cost-effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial. *JAMA* 2017;318:748-750.
[PUBMED](#) | [CROSSREF](#)
39. Virani SS, Akeroyd JM, Nambi V, Heidenreich PA, Morris PB, Nasir K, et al. Estimation of eligibility for proprotein convertase subtilisin/kexin type 9 inhibitors and associated costs based on the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk): insights from the Department of Veterans Affairs. *Circulation* 2017;135:2572-2574.
[PUBMED](#) | [CROSSREF](#)
40. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated cost-effectiveness assessments of PCSK9 inhibitors from the perspectives of the health system and private payers: insights derived from the FOURIER trial. *JAMA Cardiol* 2017;2:1369-1374.
[PUBMED](#) | [CROSSREF](#)
41. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431-1443.
[PUBMED](#) | [CROSSREF](#)
42. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA* 2016;316:2373-2384.
[PUBMED](#) | [CROSSREF](#)