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Review

2024 KSoLA Update on New Lipid-Lowering Agents: Inclisiran and Bempedoic Acid

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ABSTRACT

Inclisiran and bempedoic acid (BA) are non-statin lipid-lowering agents that have been approved for use in the US and Europe. Inclisiran, a subcutaneously administered small interfering RNA targeting proprotein convertase subtilisin/kexin type 9 messenger RNA, is effectively delivered to the liver via lipid nanoparticles and conjugation. In several phase 3 trials, it has successfully reduced low-density lipoprotein cholesterol (LDL-C) by 50% and has an acceptable safety profile. Currently, the results of clinical outcome studies are awaited. While it is indicated for both primary and secondary cardiovascular prevention, it is selectively recommended after statin-based regimens. BA, an oral inhibitor of adenosine triphosphate-citrate lyase, decreases cholesterol production and enhances LDL uptake by hepatocytes. This enzyme is absent in muscle cells, and BA has fewer muscle-related adverse events. In clinical trials, it lowered LDL-C by 17%–21% compared to placebo and showed a clinical outcome benefit in patients with statin intolerance. This agent modestly increases the incidence of gout and cholelithiasis. For primary and secondary prevention, it may be recommended as a non-first-line agent, either alone or in combination therapy.

Keywords: Coronary artery disease; Pharmacology; Lipoproteins; Safety

INTRODUCTION

Numerous articles have recently been published on inclisiran and bempedoic acid (BA). Given that these agents were only recently released, there is significant interest and a need for in-depth knowledge about them. This update provides essential pharmacological information, key results from clinical trials, and an overview of their approval status and recommendations worldwide. Although official recommendations are limited, we have endeavored to summarize the available data as objectively as possible. We hope this article will assist physicians and researchers interested in lipid disorders, cardiovascular prevention, and new lipid-lowering agents.[1-3]

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Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

Conceptualization: Lee SH; Investigation: Kim HL, Cha JJ; Project administration: Lee SH; Visualization: Kim HL, Cha JJ; Writing - original draft: Kim HL, Cha JJ, Lee SH; Writing - review & editing: Lee SH.

INCLISIRAN

Inclisiran, a small interfering RNA (siRNA) agent, functions by inhibiting the production of proprotein convertase subtilisin/kexin type 9 (PCSK9). It effectively lowers low-density lipoprotein cholesterol (LDL-C) levels and requires administration only once every six months, demonstrating a favorable safety profile. This article provides a comprehensive overview of inclisiran's development, pivotal clinical findings, and potential clinical implications.

1. Background of development

PCSK9 regulates the lifespan of LDL receptors. When PCSK9 binds to an LDL receptor, it leads to its degradation and diminishes the ability of liver cells to uptake LDL from the bloodstream.[4] A gain-of-function mutation in the PCSK9 gene is linked to the development of familial hypercholesterolemia (FH).[5] Conversely, in individuals with a nonsense mutation in the *PCSK9* gene, the blood LDL-C concentration is lower than in those who do not have such a mutation.[6] Monoclonal antibodies targeting PCSK9 have been developed, and clinical trials have shown that these medications not only reduce LDL-C levels but also effectively decrease cardiovascular risk.[7,8] However, PCSK9 antibodies have several disadvantages, including bi-monthly injections, injection site reactions, and high costs. Inclisiran has been developed as an alternative agent to these agents.

2. Action mechanism and pharmacological characteristics

When long hairpin structured double-stranded RNA enters the cytoplasm, it is processed by Dicer, which cleaves it into 19-21 base pair siRNAs. These siRNAs, upon binding with other proteins, form the RNA-induced silencing complex. Once assembled, the complex allows the siRNA to unwind from its double-stranded form into a single strand, which then binds to a complementary messenger RNA (mRNA), leading to the cleavage and degradation of the mRNA.[9-11] Inclisiran is an siRNA specifically designed to target and degrade the mRNA for PCSK9. By doing so, it inhibits the production of PCSK9 protein, increases the number of LDL receptors, and consequently lowers the blood LDL-C concentration (**Fig. 1**).[12]

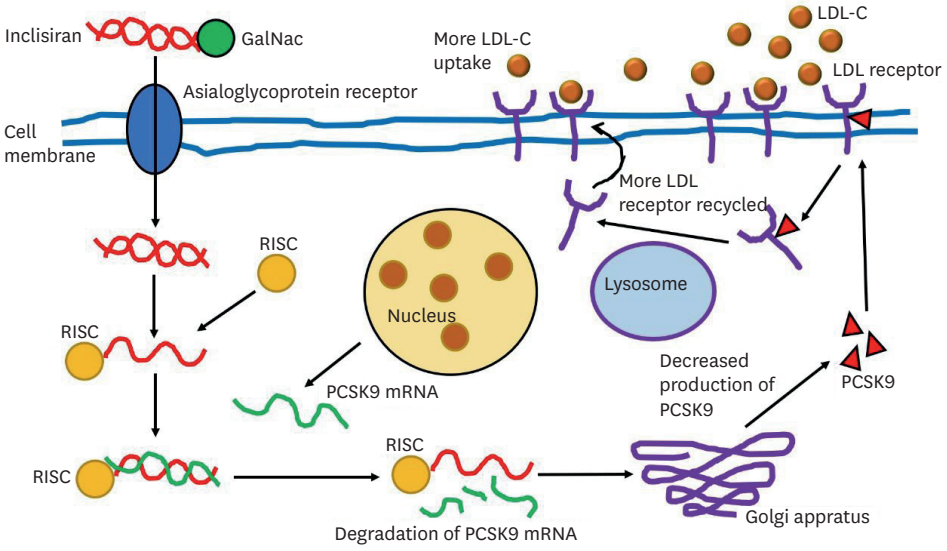

Fig. 1. Mechanism through which inclisiran reduces LDL-C levels in hepatocytes.
LDL-C, low-density lipoprotein cholesterol; GalNac, N-acetylgalactosamine; RISC, RNA-induced silencing complex; PCSK9, proprotein convertase subtilisin/kexin type 9; mRNA, messenger RNA.

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When synthesized siRNA is injected into the body, it faces several biological barriers before reaching the cytoplasm of liver cells, where it can perform its intended function. This journey involves overcoming various obstacles.[10,13] To overcome these numerous barriers, inclisiran is modified with lipid nanoparticles (LNPs) and conjugated with a specific ligand.[14] LNPs encapsulate the siRNA, protecting it from degradation and enhancing cellular uptake. They are particularly effective in targeting the liver due to their natural uptake via the liver's scavenger receptors.[15] Additionally, conjugation with specific ligands, such as N-acetylgalactosamine, further enhances uptake by hepatocytes.[16,17] These delivery methods are crucial for ensuring that siRNA therapies like inclisiran effectively reach their target cells in the liver and carry out their gene-silencing functions.[14] In an animal study, the ALN-PCS molecule, a precursor to inclisiran, was incorporated into LNPs and achieved a 70% reduction in PCSK9 mRNA in transgenic mice expressing human PCSK9. This resulted in an approximate 60% decrease in LDL-C levels in the blood.[18]

The peak blood concentration is achieved about 4 hours after injection and the concentration is undetectable at 48 hours. Inclisiran has an elimination half life about 9 hours, and 16% is cleared by kidney.[19] Patients with renal impairment revealed up to 3.3-fold increase in inclisiran maximum plasma concentration (C_{max}) and up to 2.3-fold increase in inclisiran area under the concentration-time curve. No dose adjustment is required for individuals with renal impairment.[19] Patients with hepatic dysfunction had up to 2.1-fold increase in inclisiran C_{max} and up to 2.0-fold increase in area under the concentration-time curve. Dose adjustment is not necessary in individuals with mild to moderate hepatic dysfunction.[19]

3. Results of clinical trials

In a phase 1 trial, administering a single intravenous dose of ALN-PCS, a synthetic siRNA against PCSK9 developed by Alnylam, at 0.4 mg/kg resulted in a 70% reduction in circulating PCSK9 levels and a 40% reduction in LDL-C levels over 30 days.[20] The subsequent development of ALN-PCSsc, synthetic siRNA against PCSK9 that is conjugated to triantennary N-acetylgalactosamine carbohydrate enabled its administration via subcutaneous injection. In another phase 1 trial, doses of 300 mg or more, whether given once or multiple times, led to reductions in PCSK9 and LDL-C levels by 84% and 60%, respectively, lasting at least 6 months.[21] The adverse events observed were generally mild. In the phase II ORION-1 trial, a single 300 mg dose of subcutaneous injection lowered LDL-C by 38% at day 180 in patients with high-risk cardiovascular disease (CVD) and elevated LDL-C levels, despite 70%–80% of them being on statin therapy. The adverse reactions were tolerable, with 11% of patients in the inclisiran group experiencing serious adverse events (AEs), compared to 8% in the placebo group.[22]

ORION-9, a phase III trial, was conducted in patients with heterozygous FH, with approximately 90% of participants receiving statin therapy. The between-group difference in the percent change of LDL-C reduction at day 510 was −48%, and the time-adjusted percent change of LDL-C from day 90 to 540 was −44%. Although AEs and serious AEs were similar between the two groups, more injection site reactions occurred in the inclisiran group.[23] ORION-10 and ORION-11, both phase III clinical trials, included patients with atherosclerotic cardiovascular disease (ASCVD) or its equivalent who had elevated LDL-C despite maximal statin therapy. The between-group differences in the percent change of LDL-C at day 510 ranged from −50% to −52%, while the time-adjusted percent changes from day 90 to day 540 ranged from −49% to −54%. AEs were generally similar between the groups.[24] The ORION-3 study, an extension of ORION-1, assessed the long-term efficacy and safety of biannual inclisiran injections, demonstrating sustained LDL-C reduction over 4 years with acceptable

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Table 1. Results of clinical trials on inclisiran

Trials	Participants	Regimens and endpoints	Findings	Clinical implications
ORION-1[21]	n=501; At high risk of CVD; elevated LDL-C; statin users 67%–83%	Single-dose SC injection of placebo or 200, 300, or 500 mg inclisiran or two doses of these at days 1 and 90; least-square mean % change in LDL-C at 180 days	Mean reduction of LDL-C of 28%–42% after single dose inclisiran; 36-53% after two doses; serious AEs in 11% of inclisiran and 8% of placebo groups	Inclisiran lowered PCSK9 and LDL-C in patients with high cardiovascular risk and LDL-C.
ORION-9[22]	n=482; heterozygous FH; statin users 90%	SC injection of inclisiran (300 mg) or placebo on days 1, 90, 270, 450; % change in LDL-C on day 510; Time-adjusted % change in LDL-C between days 90 and 540	–40% in inclisiran group and 8% in the placebo group at day 510 (difference –48%), Time-adjusted change in LDL-C –38% in inclisiran and 6% in placebo groups (difference –44%); AEs/serious AEs were similar	Among adults with heterozygous FH, inclisiran reduced LDL-C with infrequent dosing and acceptable safety.
ORION-10[23]	n=1,561; ASCVD, elevated LDL-C after MTD statin	Inclisiran (284 mg) or placebo on days 1 and 90, and every 6 months up to 540 days; placebo-corrected % change in LDL-C to day 510, time-adjusted % change in LDL-C after day 90 to day 540	LDL-C –52% in the inclisiran group, time-adjusted –54%; AEs were similar, injection-site reactions were more frequent in inclisiran group	An LDL-C reduction of approximately 50% was obtained with inclisiran SC every 6 months.
ORION-11[23]	n=1,617; ASCVD or ASCVD risk equivalent, elevated LDL-C after MTD statin	Same as ORION-10	LDL-C –50%, time-adjusted –49%; AEs were similar, injection-site reactions were more frequent in the inclisiran group	Same as ORION-10.
ORION-3[25]	n=382; At high cardiovascular risk and elevated LDL-C	4-year open label extension of ORION-1, twice-yearly 300 mg inclisiran (inclisiran-only arm) and 140 mg evolocumab until day 360 transitioning to inclisiran (switching arm); % change in LDL-C with inclisiran from ORION-1 start to day 210 of extension (570 days of total exposure)	In the inclisiran-only arm, LDL-C –48% at day 210 and sustained, 4-year averaged LDL-C –44%; AEs at the injection site occurred in 14% in the inclisiran-only arm and 14% in the switching arm	First prospective long-term study to assess repeated exposure to inclisiran.
ORION-5[26]	n=56; Homozygous FH	300 mg open-label inclisiran or placebo for part 1 (6 months), placebo-treated patients transitioned to inclisiran in part 2 (18 months); % change in LDL-C to day 150	Placebo-corrected change in LDL-C to day 150 –2% (difference not significant), placebo-corrected change in PCSK9 at day 150 –61%	Inclisiran did not reduce LDL-C in patients with homozygous FH.

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; SC, subcutaneous; AE, adverse event; PCSK9, proprotein convertase subtilisin/kexin type 9; FH, familial hypercholesterolemia; ASCVD, atherosclerotic cardiovascular disease; MTD, maximally tolerable dose.

safety results.[25] However, the ORION-5 trial, which included 56 patients with homozygous FH, showed that the placebo-corrected percentage change in LDL-C from baseline to day 150 was –1.7% and not significant (**Table 1**).[21-23,25-27] The ORION-10 and ORION-11 trials suggested a potential reduction in major adverse cardiovascular events (MACE), although clinical outcome results are not yet available. The ORION-4 and VICTORION-2P outcome trials are currently ongoing and are expected to conclude in 2026 and 2027, respectively.

4. Approval and recommendation of inclisiran

Inclisiran was approved in the European Union (EU) in December 2020. It is available under the brand name Leqvio and contains 284 mg of inclisiran in a volume of 1.5 mL. It is approved for use in adults with primary hypercholesterolemia (FH and non-familial)[28,29] or mixed dyslipidemia, as an adjunct to diet therapy. It is recommended for use alongside statins or statin-based combination lipid-lowering therapy (LLT).[30] In the United Kingdom, inclisiran is approved for individuals who meet both of the following criteria: 1) patients with a history of CVD (including coronary heart disease, ischemic stroke, or peripheral arterial disease) and 2) LDL-C levels greater than 2.6 mmol/L (100 mg/dL) despite using the maximum tolerable LLT with or without ezetimibe, or when statins are not tolerated or contraindicated. The Food and Drug Administration, USA, approved inclisiran in December 2021 for adults with FH or clinical ASCVD who require additional LLT. This indication was expanded in July 2023 to include patients at high risk of ASCVD. Inclisiran was also approved in China and Japan in 2023. In Korea, it received approval in June 2024 with indications very similar to those in the EU, including primary hypercholesterolemia (FH and non-familial) and mixed dyslipidemia as an adjunct to diet therapy. In Korea, the cost is ₩5,400,000 in the first year and per year and ₩3,600,000 per year thereafter.

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Table 2. Approval and recommendations for inclisiran and BA

Drugs	Inclisiran	BA
Approval date	Dec 2020 (EU), Dec 2021 (US), 2023 (China, Japan), Jun 2024 (Korea)	Feb 2020 (US), Apr 2020 (EU)
Indication	· Adults with primary hypercholesterolemia (FH and non-FH) or mixed dyslipidemia, as adjunct to diet therapy; use with statins or statin-based combination (EU) · History of CVD and LDL-C ≥100 mg/dL despite using maximally tolerable LLT, or when statins are not tolerated (UK) · FH or clinical ASCVD who need additional LLT; Expanded indication for primary prevention (patients at high risk of ASCVD) (Jul 2023) (US)	· Adults who are unable to take statins and with established CVD, or at high risk for CVD events to reduce cardiovascular risk; adjunct to diet, in combination with other LLTs or alone · In adults with primary hyperlipidemia, including heterozygous FH · Expanded indications for primary/secondary prevention, and primary hyperlipidemia, with/without statin (Mar 2024)
Recommendation	May be considered for adults with/without ASCVD; not at LDL-C target after maximally tolerable statins; after shared decision-making with patients; poor adherence to PCSK9 mAbs[30]	Mentioned as next priority of ezetimibe or PCSK9 mAbs[30]

BA, bempedoic acid; EU, European Union; US, United States; FH, familial hypercholesterolemia; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; UK, United Kingdom; ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin 9; mAb, monoclonal antibody.

The 2022 consensus on the role of non-statin therapies for LDL-C lowering from the American College of Cardiology stated that inclisiran may be considered for patients with the following conditions: 1) adults with or without ASCVD, 2) those not at LDL-C target after maximally tolerated statin therapy, 3) following shared decision-making regarding the addition of non-statin therapy, 4) poor adherence to PCSK9 monoclonal antibodies or inability to self-inject (**Table 2**).[31]

5. Future perspectives

The lipid-lowering efficacy of inclisiran, combined with its favorable safety profile and the convenience of a semi-annual dosing schedule, positions it as a powerful tool in managing hypercholesterolemia. A significant clinical benefit of inclisiran is its potential to enhance patient adherence. Future research may explore its use in pediatric populations or in combination with other LLTs. Ongoing and forthcoming longitudinal studies are expected to shed light on the long-term advantages and possible risks of sustained PCSK9 inhibition. Future discussions and studies should therefore concentrate on assessing the cost-effectiveness of inclisiran, especially in terms of its ability to decrease cardiovascular events and healthcare expenditures over time.

BEMPEDOIC ACID

1. Action mechanism and pharmacological characteristics

BA is an inhibitor of adenosine triphosphate-citrate lyase (ATC or ACLY), functioning within the same cholesterol production pathway as 3-hydroxy-3-methylglutaryl coenzyme A (CoA) reductase inhibitors (statins).[32] Bempedoil CoA, which is the active form of BA, inhibits ACLY in the cytoplasm of hepatocytes, thereby reducing cholesterol synthesis. Additionally, bempedoil CoA lowers acetyl CoA levels and increases LDL uptake by upregulating LDL receptors, which leads to a decrease in blood LDL-C levels.[32-34]

BA is considered suitable for daily use due to its 23-hour half-life, high absorption rate, and minimal pharmacokinetic changes in individuals with impaired renal function.[33,34] The high bioavailability of BA can be attributed to its molecular size and efficient absorption in the intestines.[35] BA reaches peak levels 3.5 hours post-administration.[32,36,37] Approximately 70% of BA and its active metabolite, bempedoil-CoA, are cleared by the renal system, while the liver eliminates the remaining 30%.[38] BA is a prodrug that requires activation by a liver-specific enzyme, very long-chain acyl-CoA synthetase-1.[33] This enzyme is present in hepatocytes but

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absent in skeletal muscle cells.[33] The lack of muscle-associated complaints may be attributed to its preferential absorption by hepatocytes.

2. Results of clinical trials

Trials of BA have primarily focused on its role in treating patients with elevated LDL-C, especially those at high cardiovascular risk or those who are statin-intolerant. The CLEAR Harmony trial enrolled 2,230 patients with ASCVD or heterozygous FH who were receiving maximally tolerated statin therapy. The trial found that AEs were comparable between the BA and control groups, although there were higher rates of discontinuation and gout in the BA group. The percentage change in LDL-C was –16.5% at week 12, with a between-group difference of –18.1%.[39] The CLEAR-Wisdom trial, which included 779 patients with ASCVD or heterozygous FH on maximally tolerated LLT, reported that the percentage change in LDL-C in the BA group was –15.1% (with a between-group difference of –17.4%) at 12 weeks. Common AEs included nasopharyngitis, urinary tract infections, and hyperuricemia. These trials highlighted the potential of BA as an additional LLT beyond statins.[40] The CLEAR Tranquility and CLEAR Serenity trials assessed the effects of BA in patients with a history of statin intolerance and, in some cases, concomitant LLT. At week 12, the BA group exhibited LDL-C reductions of 28.5% and 21.4% more than the placebo, respectively. Treatment-emergent AEs were similar between the BA and placebo groups.[41,42] A 78-week open-label extension study following the CLEAR Harmony trial was conducted with 1,462 patients divided into BA and placebo groups. This study confirmed the sustained lipid-lowering efficacy of BA for up to 2.5 years and a safety profile consistent with the original study.[43]

The largest trial on BA, known as CLEAR Outcomes, was conducted with 13,970 statin-intolerant patients and evaluated clinical outcome benefits, focusing on both primary and secondary prevention. This trial reported a between-group LDL-C difference of 21.1% at 6 months and a significantly lower risk of MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) in the BA group, with a hazard ratio of 0.87 (11.7% and 13.3% in the BA and placebo groups, respectively) after a median follow-up of 40.6 months. The incidences of gout and cholelithiasis were higher in the BA group.[44] Further analysis of a subgroup of primary prevention patients (n=4,206) showed that BA was associated with a lower cardiovascular risk, with a hazard ratio of 0.70 (5.3% and 7.6% in the BA and placebo groups, respectively).[45] Among patients with diabetes (n=6,373), BA reduced the MACE risk with a hazard ratio of 0.83 (absolute risk reduction 2.4%). The proportion of new-onset diabetes in individuals without diabetes at baseline was similar between the BA and placebo groups. These results suggest that BA could be a viable clinical option for individuals with or without diabetes (**Table 3**).[24,25,38,39,42-44]

3. Approval and recommendation of BA

BA has been approved in several regions, including the USA under the name Nexletol (February 2020) and the EU under the name Nilemdo (April 2020), for the treatment of certain types of hyperlipidemia or mixed dyslipidemia. These approvals underscore its utility as an adjunct to diet and maximally tolerated statin therapy. The inclusion in clinical guidelines and its acceptance in international directives can vary, reflecting the dynamic nature of cardiovascular risk management. The indications for BA in the USA and the EU are similar. Initially, it was indicated for the following conditions: 1) adults who are unable to take statin therapy[46,47] and who have established CVD, or are at high risk for CVD events, to reduce cardiovascular risk; 2) as an adjunct to diet, in combination with other LLTs, or alone when concomitant LLT is not possible, in adults with primary hyperlipidemia, including heterozygous FH. In March 2024, the

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Table 3. Results of clinical trials on BA

Trials	Participants	Regimens and endpoints	Findings	Clinical implications
CLEAR-Harmony[38]	n=2,230; ASCVD, heterozygous FH, or both, LDL-C ≥70 mg/dL after MTD statins	BA (180 mg) or placebo up to week 52; primary: safety, secondary: % change in LDL-C at week 12 of 52 weeks	Incidences of AEs and serious AEs were similar; discontinuation (11% and 7%) and gout rates (1.2% and 0.3%) were higher in the BA group; BA reduced LDL-C more (−18%) at week 12	BA did not lead to higher overall AEs and led to lower LDL-C.
CLEAR-Widson[39]	n=779; ASCVD, heterozygous FH, or both, at high LDL-C after MTD LLT	BA (180 mg) or placebo for 52 weeks; % change in LDL-C from baseline to week 12	BA lowered LDL-C more at week 12 by 17%, a greater reduction of other components of the lipid profile including non-HDL-C was also found; common AEs included nasopharyngitis and urinary tract infection	BA resulted in a significant LDL-C reduction at week 12.
CLEAR-Harmony OLE[42]	n=1,462, ASCVD and/or heterozygous FH enrolled in CLEAR-Harmony trial	Open-label extension following CLEAR-Harmony for 78 weeks; % change in LDL-C	LDL-C and other lipid parameter reductions remained stable through 78 weeks; treatment-emergent AEs and AEs were similar in patients receiving 130 weeks and 78 weeks of BA	BA was generally well tolerated and exhibited sustained efficacy up to 2.5 years.
CLEAR-Outcomes[43]	n=13,970, patients with statin intolerance and had or at high risk for CVD	BA (180 mg) or placebo; 4-component MACE (cardiovascular death, nonfatal MI, nonfatal stroke, or coronary revascularization)	LDL-C reduction was greater with BA by 21%, primary end-point (11.7% and 13.3%; HR, 0.87), cardiovascular death, nonfatal stroke, nonfatal MI were lower with BA; the incidence rates of gout and cholelithiasis were higher with BA	Among statin-intolerant individuals, BA was associated with lower MACE rates.
CLEAR-Outcomes, primary prevention[44]	n=4,206, statin-intolerant patients, primary prevention patients	BA (180 mg) or placebo, 4-component MACE	At a median follow-up of 39.9 months, BA was associated with reduction of MACE (5.3% and 7.6%; adjusted HR, 0.70); AEs with BA included higher rates of gout and cholelithiasis	In subgroup of primary prevention, BA was associated with lower cardiovascular risk.
CLEAR-Outcomes, with and without diabetes[24]	n=13,970, CLEAR-Outcomes participants	Prespecified analysis; 4-component MACE, using ITT stratified by baseline glycemia status, risk of new-onset diabetes and HbA1c	At a median follow-up of 3.4 years, patients with diabetes had relative (HR, 0.83) and absolute risk reduction (2.4%) with BA without effect modification across glycemic strata; the proportions of patients developing new-onset diabetes were similar between the BA and placebo groups	The efficacy and metabolic safety of BA make it clinical option for those with or without diabetes.

BA, bempedoic acid; ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MTD, maximally tolerable dose; AE, adverse event; LLT, lipid-lowering therapy; HDL-C, high-density lipoprotein cholesterol; OLE, open-label extension; CVD, cardiovascular disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; HR, hazard ratio; ITT, intention-to-treat; HbA1c, hemoglobin A1c.

indications for BA were expanded to include both primary and secondary prevention, as well as primary hyperlipidemia, with or without statin therapy. As of October 2024, BA has not yet been approved in Korea and the price is undecided either.

As of August 2024, BA is not prominently featured in major LLT guidelines. The 2022 American College of Cardiology consensus on non-statin therapies lists it as a next option to ezetimibe or PCSK9 monoclonal antibodies.[31] This may be attributed to its range of benefits, safety concerns, and the necessity for more competitive pricing. A further analysis of BA's benefits relative to its costs could be crucial in determining its role and deeper integration into clinical practice (**Table 2**).

CONCLUSIONS

Inclisiran and BA are non-statin lipid-lowering agents that were approved in the 2020s. Inclisiran is notable for its long-lasting effects, and results from its outcome trials are anticipated. BA has demonstrated an outcome benefit, particularly in patients with statin intolerance, although it is associated with increased AEs, such as gout. Currently, these agents are recommended as non-first-line therapies for selected patients.

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REFERENCES

1. Tarim BA, Fici F, Tengiz I, Avunduk S, Ozcan Y, Faikoglu G, et al. Do statins counteract the effect of antidiabetic drugs? Results of the SCEAD study. Yonsei Med J 2023;64:175-180. PUBMED | CROSSREF
2. Kang Y, Park JM, Lee SH. Moderate-intensity rosuvastatin/ezetimibe combination versus quadruple-dose rosuvastatin monotherapy: a meta-analysis and systemic review. Yonsei Med J 2024;65:19-26. PUBMED | CROSSREF
3. Cha JJ, Hong SJ, Lim S, Kim JH, Joo HJ, Park JH, et al. Comparison of statin with ezetimibe combination therapy versus statin monotherapy for primary prevention in middle-aged adults. Korean Circ J 2024;54:534-544. PUBMED | CROSSREF
4. Catapano AL, Pirillo A, Norata GD. New pharmacological approaches to target PCSK9. Curr Atheroscler Rep 2020;22:24. PUBMED | CROSSREF
5. 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
6. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 2005;37:161-165. PUBMED | CROSSREF
7. 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
8. 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
9. Hu B, Zhong L, Weng Y, Peng L, Huang Y, Zhao Y, et al. Therapeutic siRNA: state of the art. Signal Transduct Target Ther 2020;5:101. PUBMED | CROSSREF
10. Kanasty R, Dorkin JR, Vegas A, Anderson D. Delivery materials for siRNA therapeutics. Nat Mater 2013;12:967-977. PUBMED | CROSSREF
11. Dana H, Chalbatani GM, Mahmoodzadeh H, Karimloo R, Rezaiean O, Moradzadeh A, et al. Molecular mechanisms and biological functions of siRNA. Int J Biomed Sci 2017;13:48-57. PUBMED | CROSSREF
12. Zhang Y, Chen H, Hong L, Wang H, Li B, Zhang M, et al. Inclisiran: a new generation of lipid-lowering siRNA therapeutic. Front Pharmacol 2023;14:1260921. PUBMED | CROSSREF
13. Nikam RR, Gore KR. Journey of siRNA: clinical developments and targeted delivery. Nucleic Acid Ther 2018;28:209-224. PUBMED | CROSSREF
14. Ebenezer O, Comoglio P, Wong GK, Tuszynski JA. Development of novel siRNA therapeutics: a review with a focus on inclisiran for the treatment of hypercholesterolemia. Int J Mol Sci 2023;24:4019. PUBMED | CROSSREF
15. Landen CN Jr, Chavez-Reyes A, Bucana C, Schmandt R, Deavers MT, Lopez-Berestein G, et al. Therapeutic EphA2 gene targeting *in vivo* using neutral liposomal small interfering RNA delivery. Cancer Res 2005;65:6910-6918. PUBMED | CROSSREF
16. Nair JK, Willoughby JL, Chan A, Charisse K, Alam MR, Wang Q, et al. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. J Am Chem Soc 2014;136:16958-16961. PUBMED | CROSSREF
17. Foster DJ, Brown CR, Shaikh S, Trapp C, Schlegel MK, Qian K, et al. Advanced siRNA designs further improve *in vivo* performance of GalNAc-siRNA conjugates. Mol Ther 2018;26:708-717. PUBMED | CROSSREF
18. Frank-Kamenetsky M, Grefhorst A, Anderson NN, Racie TS, Bramlage B, Akinc A, et al. Therapeutic RNAi targeting PCSK9 acutely lowers plasma cholesterol in rodents and LDL cholesterol in nonhuman primates. Proc Natl Acad Sci U S A 2008;105:11915-11920. PUBMED | CROSSREF
19. European Medicines Agency. Leqvio 284 mg solution for injection in pre-filled syringe: summary of product characteristics [Internet]. European Medicines Agency; 2021 [cited 2024 Nov 11]. Available from: http://www.ema.europa.eu/.
20. Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, Liebow A, Bettencourt BR, Sutherland JE, et al. Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. Lancet 2014;383:60-68. PUBMED | CROSSREF

21. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. N Engl J Med 2017;376:41-51. PUBMED | CROSSREF
22. 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
23. Raal FJ, Kallend D, Ray KK, Turner T, Koenig W, Wright RS, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med 2020;382:1520-1530. PUBMED | CROSSREF
24. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med 2020;382:1507-1519. PUBMED | CROSSREF
25. Ray KK, Nicholls SJ, Li N, Louie MJ, Brennan D, Lincoff AM, et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial. Lancet Diabetes Endocrinol 2024;12:19-28. PUBMED | CROSSREF
26. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol 2023;11:109-119. PUBMED | CROSSREF
27. Raal F, Durst R, Bi R, Talloczy Z, Maheux P, Lesogor A, et al. Efficacy, safety, and tolerability of inclisiran in patients with homozygous familial hypercholesterolemia: results from the ORION-5 randomized clinical trial. Circulation 2024;149:354-362. PUBMED | CROSSREF
28. Li BV, Laurie AD, Reid NJ, Leath MA, King RI, Chan HK, et al. Association of clinical characteristics with familial hypercholesterolaemia variants in a lipid clinic setting: a case-control study. J Lipid Atheroscler 2024;13:29-40. PUBMED | CROSSREF
29. Yang JH, Cho KH, Hong YJ, Kim JH, Kim HY, Shin MH. Enhancing familial hypercholesterolemia detection in South Korea: a targeted screening approach integrating national program and genetic cascade screening. Korean Circ J 2024;54:726-738. PUBMED | CROSSREF
30. Lamb YN. Inclisiran: first approval. Drugs 2021;81:389-395. PUBMED | CROSSREF
31. Writing Committee, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM, et al. 2022 ACC Expert Consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022.80:1366-1418. PUBMED | CROSSREF
32. Pinkosky SL, Newton RS, Day EA, Ford RJ, Lhotak S, Austin RC, et al. Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. Nat Commun 2016;7:13457. PUBMED | CROSSREF
33. Amore BM, Sasiela WJ, Ries DK, Tresh P, Emery MG. Pharmacokinetics of bempedoic acid in patients with renal impairment. Clin Transl Sci 2022;15:789-798. PUBMED | CROSSREF
34. Ruscica M, Sirtori CR, Carugo S, Banach M, Corsini A. Bempedoic acid: for whom and when. Curr Atheroscler Rep 2022;24:791-801. PUBMED | CROSSREF
35. Tummala R, Gupta M, Devanabanda AR, Bandyopadhyay D, Aronow WS, Ray KK, et al. Bempedoic acid and its role in contemporary management of hyperlipidemia in atherosclerosis. Ann Med 2022;54:1287-1296. PUBMED | CROSSREF
36. Powell J, Piszczatoski C. Bempedoic acid: a new tool in the battle against hyperlipidemia. Clin Ther 2021;43:410-420. PUBMED | CROSSREF
37. Wichaiyo S, Supharattanasitthi W. Bempedoic acid: a new non-statin drug for the treatment of dyslipidemia. Clin Drug Investig 2021;41:843-851. PUBMED | CROSSREF
38. Biolo G, Vinci P, Mangogna A, Landolfo M, Schincariol P, Fiotti N, et al. Mechanism of action and therapeutic use of bempedoic acid in atherosclerosis and metabolic syndrome. Front Cardiovasc Med 2022;9:1028355. PUBMED | CROSSREF
39. Ray KK, Bays HE, Catapano AL, Lalwani ND, Bloedon LT, Sterling LR, et al. Safety and efficacy of bempedoic acid to reduced LDL cholesterol. N Engl J Med 2019;380:1022-1032. PUBMED | CROSSREF
40. Goldberg AC, Leiter LA, Stroes ESG, Baum SJ, Hanselman JC, Bloedon LT, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom randomized clinical trial. JAMA 2019;322:1780-1788. PUBMED | CROSSREF
41. Ballantyne CM, Banach M, Mancini GBJ, Lepor NE, Hanselman JC, Zhao X, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195-203. PUBMED | CROSSREF
42. Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8:e011662. PUBMED | CROSSREF

43. Ballantyne CM, Banach M, Bays HE, Catapano AL, Laufs U, Stroes ESG, et al. Long-term safety and efficacy of bempedoic acid in patients with atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia (from the CLEAR Harmony Open-Label Extension study). Am J Cardiol 2022;174:1-11. PUBMED | CROSSREF

44. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 2023;388:1353-1364. PUBMED | CROSSREF

45. Nissen SE, Menon V, Nicholls SJ, Brennan D, Laffin L, Ridker P, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. JAMA 2023;330:131-140. PUBMED | CROSSREF

46. Kim KS, Hong S, Han K, Park CY. Clinical characteristics of patients with statin discontinuation in Korea: a nationwide population-based study. J Lipid Atheroscler 2024;13:41-52. PUBMED | CROSSREF

47. Patel R, Sharma JB, Rajput S. Statins, ticagrelor and rhabdomyolysis: a coincidence or a drug interaction? J Lipid Atheroscler 2024;13:61-68. PUBMED | CROSSREF