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New drugs for the treatment of hyperlipidemia in statin-intolerant patients - review

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Abstract

Introduction

Cardiovascular diseases are the most numerous group of diseases prevalent in the world. They are a challenge for many health systems, in terms of keeping life comfortable and also economics. The cause of selected disease entities is too much cholesterol in the blood. The most popular treatment for hypercholesterolemia is based on statins. Many patients are affected by intolerance to these drugs, so an important issue is the discovery and improvement of alternatives to statins.

Purpose of work

The purpose of this review is to collect literature data on the latest treatments for hypercholesterolemia with drugs other than statins and ezetimibe.

Materials and methods

Materials are from a review of recent literature available in PubMed. To search for articles, we used keywords such as: bempedoic acid, non-statin therapy, cardiovascular risk, inclisiran, alirocumab, cardiovascular disease, dyslipidemia, evolocumab.

Summary

Treatment of hypercholesterolemia with statins remains the most popular management strategy. Intolerance to treatment with these drugs creates serious clinical problems for patients. Recently, we could see the emergence of new drugs as alternatives to statins. As the results show, the new drugs can effectively replace statins in the hypolipemic treatment especially of patients who cannot be treated with them.

Keywords: non-statin therapy, dyslipidemia, evolocumab, alirocumab, bempedoic acid, inclisiran, cardiovascular disease, cardiovascular risk.

Introduction

Elevated cholesterol is considered the most important causal factor in the development of ischemic heart disease [1]. Many studies show high correlation in serum lipid levels on risk of myocardial infarction [2]. In view of the numerous reports on the key role of cholesterol, it is reasonable to improve early treatment of hyperlipidemia, including for survivors of acute myocardial infarction [3]. The mainstay of treatment for lipid disorders in both primary and secondary prevention is statins [4]. When statins alone are insufficiently effective, a popular option is to combine with ezetimibe, especially when the goal is to reduce the risk of cardiovascular complications in people with chronic kidney disease and after vascular surgery or acute coronary syndrome [8]. The usual goal of treatment is intensive pharmacotherapy to target values, in people after acute myocardial infarction is an LDL-C level of less than 1.4 mmol/l [5,6]. According to the recommendation the American College of Cardiology (ACC)

and American Heart Association (AHA) for primary prevention for adults 40 to 75 years of age with LDL-C levels are betwen 1.7 to 4.8 mmol/l [7]. However, there are situations in which patients report intolerance to them, in which case the therapeutic options lie in the use of ezetymib, monoclonal antibodies blocking PCSK9 action, inclisiran, bempedoic acid [9]. Statin intolerance is often manifested by muscle pain, elevated liver or muscle enzymes, cognitive impairment or other neurological disorders [11]. In the medical literature, non-statins therapies have shown efficacy and safety in reducing LDL-C in monotherapy or in combination [10, 12]. A multitude of newly emerging drugs allows personalized treatment according to individual patient needs [13]. In this review, we will look at the latest major drugs including monoclonal antibodies blocking PCSK9 action, bempedoic acid and inclisiran.

Methodology

Our research team's queries were based on the principles of preferred reporting elements for systematic reviews. We used PubMed as our main databases for scientific literature. Searches were conducted using keywords such as: Non-statin therapy, dyslipidemia, evolocumab, alirocumab, bempedoic Aacid, Inclisiran, cardiovascular disease, cardiovascular risk. Most of the literature data is not older than 2020. We conducted the extraction of articles in two teams, for the proper selection of materials.

Alternative drugs to statins:

Monoclonal antibodies blocking PCSK9 action

Monoclonal antibodies include alirocumab and evolocumab. These are monoclonal antibodies that bind specifically to human PCSK9 to reduce LDL-C levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases plasma low-density lipoprotein cholesterol (LDL-C) by decreasing expression of the LDL receptor on hepatic cells, alirocumab and evolocumab bind selectively to circulating PCSK9, preventing its interaction with the LDL receptor [14, 39]. PCSK9 inhibitors affect the entire lipid profile: could significantly reduce low-density lipoprotein cholesterol, total cholesterol, triglycerides and increase high-density lipoprotein cholesterol [15]. Many studies have noted a beneficial effect on lipid metabolism and a reduction in cardiovascular mortality [16]. Both drugs described, are also effective in the treatment of familial hypercholesterolemia, especially in terms of

beneficial effects on the vascular endothelium [17] [18]. Compared to placebo, the 4-year risk of adverse cardiovascular events (MACE) and death was lower with alirocumab [19]. More than one year of alirocumab therapy significantly regresses coronary lesions and improves their hemodynamics compared to placebo [20]. A comprehensive 2022 meta-analysis including a total of 53,484 patients proved the positive effects in preventing MACE and stroke of both alirocumab and evolucumab. In the same study, evolucumab reduced the risk of acute myocardial infarction, while no such effect was observed with alirocumab, suggesting greater efficacy of the evolucumab [21]. Noteworthy is the fact of beneficial, safe effects also for people with chronic kidney disease [22]. Of the drugs mentioned in this review, monoclonal antibodies have functioned the longest among the other drugs, and are therefore a natural replacement in the first instance for statin intolerance, due to their known profile of action and predictable side effects. Nevertheless, these drugs need further observation in improving the quality of life of people especially with cardiovascular diseases.

Bempedoic acid

The mechanism of action of bempedoic acid is to inhibits the enzyme adenosine triphosphate (ATP)-citrate lyase, which lies two steps upstream from β-hydroxy β-methylglutaryl-CoA reductase in the cholesterol biosynthesis pathway, therefore participates in a similar process as statins [23]. The CLEAR Serenity study found that bempedoic acid significantly reduces both LDL-C and hsCRP compared with placebo and is well tolerated in patients with statin intolerance [24]. In addition the recent National Institute of Health and Care Excellence (NICE) (UK) technology appraisal guidance [TA694] published in April 2021 recommended bempedoic acid with ezetimibe as a treatment option for primary hypercholesterolaemia or mixed dyslipidaemia if statins are not tolerated or contraindicated and if there is inadequate control of LDL-C with ezetimibe alone [25]. It is noteworthy that bempedoic acid shows good results in the treatment of hypercholesterolemia in people diagnosed with diabetes, and more than that it does not raise the risk of diabetes, according to a study involving 13,970 patients [26]. Bempedoic acid with a single daily dose (180 mg) reduces LDL-C by a mean 24.5% when given alone [27]. A 2023 meta-analysis involving 18,315 patients showed was associated with a reduced risk of MACE (OR 0.86, 95% CI 0.79-0.95), myocardial infarction (OR 0.76, 95% CI 0.64-0.88) and unstable angina (OR 0.69, 95% CI 0.54-0.88) compared to control [28]. Of the side effects of bempedoic acid, they mainly include hyperuricemia and an increase in blood creatinine levels, so a completely different

spectrum than treatment with statins [29]. The approval of Bempedoic acid for use in the United States in 2020, and for use in the European Union in 2020 for the treatment of people with hypercholesterolemia, raises another possibility in the pharmacotherapy of statin-intolerant patients that is worth considering in clinical practice.

Inclisiran

Inclisiran is the first cholesterol-lowering small interfering RNA (siRNA) conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc) to be approved for treatment in 2020 [30]. The mechanism involves prevents hepatic synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby decreasing circulating low-density lipoprotein cholesterol (LDL-C) [31]. Inclisiran is well-tolerated in primary prevention patients with elevated LDL-C, who derived significant reductions in atherogenic lipoprotein levels with twice-yearly maintenance dosing [32]. The main side effects are the main adverse events were injection site pain, back pain, nasopharyngitis, headache, upper respiratory tract infection, and flu-like symptoms (7.5%), which clearly distinguishes these effects from statins [33]. Studies show the drug is effective after just one subcutaneous dose with the maximal reduction between Day 30 and Day 60 [34]. Such a drug delivery system could also affect the adjustment of health care systems so that the drug is administered in the same way as vaccines for seasonal diseases, which would also translate into economic considerations for therapy [35]. Noteworthy is the ORION-5 study where patients with homozygous familial hypercholesterolemia and elevated LDL-C levels were studied, in this study involving 56 patients, no statistical differences were observed between the drug and placebo [36]. In 2020 meta-analysis involving 3,660 patients showed that incisiran lowered LDL cholesterol by 51% (95% confidence interval, 48 to 53%; $p < 0.001$) compared with placebo, over to There were no differences in adverse events, abnormalities in liver function tests or creatine kinase levels between treatment strategies, making it a good alternative to statin therapy [37]. An important feature that distingui inclisiran from Monoclonal Antibodies Blocking PCSK9 Action is more favorable dosing regimen with biannual application that might improve therapeutic adherence significantly [38]. These data show inadequacies that require further research all the time, while the undoubted benefit is convenient dosage, which can translate into better control and regularity of treatment.

Conclusions

Hypercholesterolemia often accompanies cardiovascular disease and is the cause of the development of many disease entities that, if untreated, can be life threatening. Several decades ago, the advent of statins in treatment revolutionized the treatment of hyperlipidemia, which directly contributed to slowing the progression of diseases underlying atherosclerosis. This group of drugs has made a real contribution to prolonging the life of the population, both in terms of primary and secondary prevention. Unfortunately, over the past years, there has been a large group of people who have not tolerated the treatment. In response, new blood lipid-lowering formulations have been emerging. At the present time, new drugs such as evolocumab, alirocumab, bempedoic acid, inclisiran create a good alternative for people with intolerance to statins, in lowering cholesterol, triglycerides which directly affects the reduction of cardiovascular risk in the form of hospitalization for emergency events and even death. Due to the prevalence of cardiovascular disease in society, it is extremely necessary and crucial to continue research developing the topic of alternatives to statins, which will translate directly into the quality of life of the general population of affected patients.

Author's contribution:

Conceptualization, Wojciech Płonka; methodology, Damian Chruściki, Marcin Pelc; software, Krzysztof Banach; check, Joanna Liber; formal analysis, Marta Żerek; investigation, Aleksandra Pławiak; resources, Gracjan Sitarek; data curation, Monika Bułatowicz; writing - rough preparation, Krzyszrof Banach; writing - review and editing, Wojciech Płonka; visualization, Damian Chruścicki; supervision, Monika Bułatowicz; project administration, Marcin Pelc;

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Bibliography

[1] Nordestgaard, Børge G., and Anette Varbo. "Triglycerides and cardiovascular disease." The Lancet 384.9943 (2014): 626-635.

[2] Doi T, Langsted A, Nordestgaard BG. Elevated Remnant Cholesterol Reclassifies Risk of Ischemic Heart Disease and Myocardial Infarction. J Am Coll Cardiol. 2022 Jun 21;79(24):2383-2397. doi: 10.1016/j.jacc.2022.03.384. PMID: 35710189; PMCID: PMC8972554.
[3] Princip M, von Känel R, Sivakumar S, Jellestad L, Pazhenkottil AP, Langraf-Meister RE, Znoj H, Schmid JP, Barth J, Schnyder U, Zuccarella-Hackl C. Longitudinal association between positive affect and blood lipids in patients following acute myocardial infarction. PLoS One. 2023 Nov 2;18(11):e0287166. doi: 10.1371/journal.pone.0287166. PMID: 37917632; PMCID: PMC10621864.
[4] National Clinical Guideline Centre (UK). Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London: National Institute for Health and Care Excellence (UK); 2014 Jul. PMID: 25340243.
[5] Wambua PM, Khan Z, Kariuki CM, Ogola EN. A Retrospective Study on the Adoption of Lipid Management Guidelines in Post-Myocardial Infarction Patients in a Tertiary Care Centre. Cureus. 2023 Jul 5;15(7):e41402. doi: 10.7759/cureus.41402. PMID: 37546064; PMCID: PMC10402653.
[6] Hong SJ, Lee YJ, Lee SJ, Hong BK, Kang WC, Lee JY, Lee JB, Yang TH, Yoon J, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Hong MK; LODESTAR Investigators. Treat-to-Target or High-Intensity Statin in Patients With Coronary Artery Disease: A Randomized Clinical Trial. JAMA. 2023 Apr 4;329(13):1078-1087. doi: 10.1001/jama.2023.2487. PMID: 36877807; PMCID: PMC9989958.
[7] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 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. Circulation. 2019 Jun 18;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625. Epub 2018 Nov 10. Erratum in: Circulation. 2019 Jun 18;139(25):e1182-e1186. Erratum in: Circulation. 2023 Aug 15;148(7):e5. PMID: 30586774; PMCID: PMC7403606.
[8] Agabiti Rosei E, Salvetti M. Management of Hypercholesterolemia, Appropriateness of Therapeutic Approaches and New Drugs in Patients with High Cardiovascular Risk. High Blood Press Cardiovasc Prev. 2016 Sep;23(3):217-30. doi: 10.1007/s40292-016-0155-2. Epub 2016 Aug 27. PMID: 27567901; PMCID: PMC5014894.
[9] Ferri N, Ruscica M, Fazio S, Corsini A. Low-Density Lipoprotein Cholesterol-Lowering Drugs: A Narrative Review. J Clin Med. 2024 Feb 7;13(4):943. doi: 10.3390/jcm13040943. PMID: 38398257; PMCID: PMC10889346.
[10] Bosco G, Di Giacomo Barbagallo F, Spampinato S, Lanzafame L, Di Pino A, Piro S, Purrello F, Scicali R. Management of Statin Intolerant Patients in the Era of Novel Lipid Lowering Therapies: A Critical Approach in Clinical Practice. J Clin Med. 2023 Mar 22;12(6):2444. doi: 10.3390/jcm12062444. PMID: 36983444; PMCID: PMC10055622.
[11] Feingold KR. Cholesterol Lowering Drugs. 2024 Feb 12. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 27809434.

[12] Toth PP, Bray S, Villa G, Palagashvili T, Sattar N, Stroes ESG, Worth GM. Network Meta-Analysis of Randomized Trials Evaluating the Comparative Efficacy of Lipid-Lowering Therapies Added to Maximally Tolerated Statins for the Reduction of Low-Density Lipoprotein Cholesterol. J Am Heart Assoc. 2022 Sep 20;11(18):e025551. doi: 10.1161/JAHA.122.025551. Epub 2022 Sep 8. PMID: 36073669; PMCID: PMC9683660.
[13] Michaeli DT, Michaeli JC, Albers S, Boch T, Michaeli T. Established and Emerging Lipid-Lowering Drugs for Primary and Secondary Cardiovascular Prevention. Am J Cardiovasc Drugs. 2023 Sep;23(5):477-495. doi: 10.1007/s40256-023-00594-5. Epub 2023 Jul 24. PMID: 37486464; PMCID: PMC10462544.
[14] Kasichayanula S, Grover A, Emery MG, Gibbs MA, Somaratne R, Wasserman SM, Gibbs JP. Clinical Pharmacokinetics and Pharmacodynamics of Evolocumab, a PCSK9 Inhibitor. Clin Pharmacokinet. 2018 Jul;57(7):769-779. doi: 10.1007/s40262-017-0620-7. PMID: 29353350; PMCID: PMC5999140.
[15] Geng Q, Li X, Sun Q, Wang Z. Efficacy and safety of PCSK9 inhibition in cardiovascular disease: a meta-analysis of 45 randomized controlled trials. Cardiol J. 2022;29(4):574-581. doi: 10.5603/CJ.a2021.0110. Epub 2021 Sep 28. PMID: 34581425; PMCID: PMC9273234.
[16] Altschmiedová T, Todorovová V, Šnejdrlová M, Šatný M, Češka R. PCSK9 Inhibitors in Real-world Practice: Analysis of Data from 314 Patients and 2 Years of Experience in a Center of Preventive Cardiology. Curr Atheroscler Rep. 2022 May;24(5):357-363. doi: 10.1007/s11883-022-01008-8. Epub 2022 Mar 25. PMID: 35332442; PMCID: PMC9810794.
[17] Luthra G, Shahbaz M, Almatooq H, Foucambert P, Esbrand F, Zafar S, Panthangi V, Cyril Kurupp AR, Raju A, Khan S. Exploring the Efficacy of Alirocumab and Evolocumab in Reducing Low-Density Lipoprotein (LDL) Cholesterol Levels in Patients With Familial Hypercholesterolemia: A Systematic Review. Cureus. 2022 Sep 8;14(9):e28930. doi: 10.7759/cureus.28930. PMID: 36237809; PMCID: PMC9547534.
[18] Di Minno A, Gentile M, Iannuzzo G, Calcaterra I, Tripaldella M, Porro B, Cavalca V, Di Taranto MD, Tremoli E, Fortunato G, Rubba POF, Di Minno MND. Endothelial function improvement in patients with familial hypercholesterolemia receiving PCSK-9 inhibitors on top of maximally tolerated lipid lowering therapy. Thromb Res. 2020 Oct;194:229-236. doi: 10.1016/j.thromres.2020.07.049. Epub 2020 Jul 31. PMID: 33213848.
[19] Chiang CE, Schwartz GG, Elbez Y, Szarek M, Bhatt DL, Bittner VA, Diaz R, Erglis A, Goodman SG, Hagström E, Jukema JW, Liberopoulos E, Loy M, Pordy R, White HD, Simon T, Steg PG; ODYSSEY OUTCOMES Investigators. Alirocumab and Cardiovascular Outcomes in Patients With Previous Myocardial Infarction: Prespecified Subanalysis From ODYSSEY OUTCOMES. Can J Cardiol. 2022 Oct;38(10):1542-1549. doi: 10.1016/j.cjca.2022.05.021. Epub 2022 May 27. PMID: 35644332.
[20] Bär S, Kavaliauskaite R, Otsuka T, Ueki Y, Häner JD, Siontis GCM, Stortecky S, Shibutani H, Temperli F, Kaiser C, Iglesias JF, Jan van Geuns R, Daemen J, Spirk D, Engstrøm T, Lang I, Windecker S, Koskinas KC, Losdat S, Räber L. Impact of alirocumab on plaque regression and haemodynamics of non-culprit arteries in patients with acute myocardial infarction: a prespecified substudy of the PACMAN-AMI trial. EuroIntervention. 2023 Jul 17;19(4):e286-e296. doi: 10.4244/EIJ-D-23-00201. PMID: 37341586; PMCID: PMC10333923.
[21] Wang HF, Mao YC, Xu XY, Zhao SY, Han DD, Ge SY, Song K, Geng C, Tian QB. Effect of alirocumab and evolocumab on all-cause mortality and major cardiovascular events: A meta-analysis focusing on the number needed to treat. Front Cardiovasc Med. 2022 Dec 2;9:1016802. doi: 10.3389/fcvm.2022.1016802. PMID: 36531722; PMCID: PMC9755489.
[22] Igweonu-Nwakile EO, Ali S, Paul S, Yakkali S, Teresa Selvin S, Thomas S, Bikeyeva V, Abdullah A, Radivojevic A, Abu Jad AA, Ravanavena A, Ravindra C, Balani P. A Systematic

Review on the Safety and Efficacy of PCSK9 Inhibitors in Lowering Cardiovascular Risks in Patients With Chronic Kidney Disease. Cureus. 2022 Sep 13;14(9):e29140. doi: 10.7759/cureus.29140. PMID: 36128564; PMCID: PMC9477547.
[23] Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of Bempedoic Acid in Clinical Practice. Cardiovasc Drugs Ther. 2021 Aug;35(4):853-864. doi: 10.1007/s10557-021-07147-5. Epub 2021 Apr 5. Erratum in: Cardiovasc Drugs Ther. 2021 Apr 19;: PMID: 33818688; PMCID: PMC8266788.
[24] Laufs U, Banach M, Mancini GBJ, Gaudet D, Bloedon LT, Sterling LR, Kelly S, Stroes ESG. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. J Am Heart Assoc. 2019 Apr 2;8(7):e011662. doi: 10.1161/JAHA.118.011662. PMID: 30922146; PMCID: PMC6509724.
[25] Alam U, Al-Bazz DY, Soran H. Bempedoic Acid: The New Kid on the Block for the Treatment of Dyslipidemia and LDL Cholesterol: A Narrative Review. Diabetes Ther. 2021 Jul;12(7):1779-1789. doi: 10.1007/s13300-021-01070-6. Epub 2021 May 26. PMID: 34037950; PMCID: PMC8266948.
[26] Ray KK, Nicholls SJ, Li N, Louie MJ, Brennan D, Lincoff AM, Nissen SE; CLEAR OUTCOMES Committees and Investigators. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial. Lancet Diabetes Endocrinol. 2024 Jan;12(1):19-28. doi: 10.1016/S2213-8587(23)00316-9. Epub 2023 Dec 4. PMID: 38061370.
[27] Ruscica M, Sirtori CR, Carugo S, Banach M, Corsini A. Bempedoic Acid: for Whom and When. Curr Atheroscler Rep. 2022 Oct;24(10):791-801. doi: 10.1007/s11883-022-01054-2. Epub 2022 Jul 28. PMID: 35900636; PMCID: PMC9474414.
[28]- De Filippo O, D'Ascenzo F, Iannaccone M, Bertaina M, Leone A, Borzillo I, Ravetti E, Solano A, Pagliassotto I, Nebiolo M, Bruno F, Giacobbe F, Muscoli S, Monticone S, Brizzi MF, Biondi Zoccai G, De Ferrari GM. Safety and efficacy of bempedoic acid: a systematic review and meta-analysis of randomised controlled trials. Cardiovasc Diabetol. 2023 Nov 28;22(1):324. doi: 10.1186/s12933-023-02022-z. PMID: 38017541; PMCID: PMC10685600.
[29] Jialal I, Ramakrishnan N. Bempedoic acid: a novel oral LDL-cholesterol lowering agent. Int J Physiol Pathophysiol Pharmacol. 2022 Apr 15;14(2):84-89. PMID: 35619668; PMCID: PMC9123472.
[30] Lamb YN. Inclisiran: First Approval. Drugs. 2021 Feb;81(3):389-395. doi: 10.1007/s40265-021-01473-6. Erratum in: Drugs. 2021 Jun;81(9):1129. PMID: 33620677; PMCID: PMC7900795.
[31] Frampton JE. Inclisiran: A Review in Hypercholesterolemia. Am J Cardiovasc Drugs. 2023 Mar;23(2):219-230. doi: 10.1007/s40256-023-00568-7. Epub 2023 Mar 4. PMID: 36869996.
[32] Ray KK, Kallend D, Leiter LA, Raal FJ, Koenig W, Jaros MJ, Schwartz GG, Landmesser U, Garcia Conde L, Wright RS; ORION-11 Investigators. Effect of inclisiran on lipids in primary prevention: the ORION-11 trial. Eur Heart J. 2022 Dec 21;43(48):5047-5057. doi: 10.1093/eurheartj/ehac615. PMID: 36331315; PMCID: PMC9769955.
[33] Grześk G, Dorota B, Wołowiec Ł, Wołowiec A, Osiak J, Kozakiewicz M, Banach J. Safety of PCSK9 inhibitors. Biomed Pharmacother. 2022 Dec;156:113957. doi: 10.1016/j.biopha.2022.113957. Epub 2022 Nov 8. PMID: 36411665.
[34] Luo Z, Huang Z, Sun F, Guo F, Wang Y, Kao S, Yang G, Huang J, Li J, Zhao S, He Y. The clinical effects of inclisiran, a first-in-class LDL-C lowering siRNA therapy, on the LDL-C levels in Chinese patients with hypercholesterolemia. J Clin Lipidol. 2023 May-Jun;17(3):392-400. doi: 10.1016/j.jacl.2023.04.010. Epub 2023 Apr 29. PMID: 37164838.
[35] Albosta MS, Grant JK, Taub P, Blumenthal RS, Martin SS, Michos ED. Inclisiran: A New Strategy for LDL-C Lowering and Prevention of Atherosclerotic Cardiovascular Disease.

Vasc Health Risk Manag. 2023 Jul 6;19:421-431. doi: 10.2147/VHRM.S338424. PMID: 37434791; PMCID: PMC10332363.
[36] Raal F, Durst R, Bi R, Talloczy Z, Maheux P, Lesogor A, Kastelein JJP; ORION-5 Study Investigators. Efficacy, Safety, and Tolerability of Inclisiran in Patients With Homozygous Familial Hypercholesterolemia: Results From the ORION-5 Randomized Clinical Trial. Circulation. 2024 Jan 30;149(5):354-362. doi: 10.1161/CIRCULATIONAHA.122.063460. Epub 2023 Oct 18. PMID: 37850379; PMCID: PMC10815002.
[37] Khan SA, Naz A, Qamar Masood M, Shah R. Meta-Analysis of Inclisiran for the Treatment of Hypercholesterolemia. Am J Cardiol. 2020 Nov 1;134:69-73. doi: 10.1016/j.amjcard.2020.08.018. Epub 2020 Aug 15. PMID: 32892993.
[38] Arnold N, Koenig W. PCSK9 Inhibitor Wars: How Does Inclisiran Fit in with Current Monoclonal Antibody Inhibitor Therapy? Considerations for Patient Selection. Curr Cardiol Rep. 2022 Nov;24(11):1657-1667. doi: 10.1007/s11886-022-01782-6. Epub 2022 Sep 10. PMID: 36087240; PMCID: PMC9729136.
[39] Stein EA, Swergold GD. Potential of proprotein convertase subtilisin/kexin type 9 based therapeutics. Curr Atheroscler Rep. 2013 Mar;15(3):310. doi: 10.1007/s11883-013-0310-3. PMID: 23371064.