European Journal of Internal Medicine 112 (2023) 19–20

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Commentary

Novel LDL-cholesterol lowering therapies: A step forward a personalized medicine

Maurizio Averna [a,b,*], Angelo B. Cefalù [a]

[a] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), Università degli Studi di Palermo, Via del Vespro 129, 90127, Palermo, Italy
[b] Istituto di Biofisica, Consiglio Nazionale delle Ricerche, Via U. La Malfa 153, 90146, Palermo, Italy

The Low-density lipoproteins (LDL) as well as all the ApoB-containing lipoproteins (VLDL remnants and Lp(a)) are etiological factors of atherosclerotic cardiovascular diseases (ASCVD). Several published consensuses [1–3] have reached this conclusion based on the evidence of experimental, observational, and randomized controlled interventional studies. Overall randomized controlled trials (RCTs) and Mendelian randomization studies have determined that a reduction of 1 mmol/L of LDL-C results in a short term (5 years) 22% reduction and in a lifetime reduction of 50% of the relative risk of ASCVD. The success of a pharmacological treatment in reducing ASCVD events and cardiovascular mortality in high and very high-risk patients in a setting of secondary cardiovascular prevention depends on the absolute reduction of LDL-cholesterol and more in general of ApoB plasma levels. The 2019 EAS/ESC Guidelines [4] have recommended new therapeutic goals for the target LDL-C: <70 mg/dL for the high-risk patient category, <55 mg/dL for the very high-risk category and <40 mg/dl for patients who have experienced recurrent vascular events in a recent short period of time despite the LDL-C lowering treatment. Moreover, a reduction of 50% of LDL-C is always mandatory. Since the 4S, the first pivotal trial with simvastatin, the RCTs have shown that a more intensive reduction of LDL-C – high intensity vs low intensity statins, statins vs combination therapy with ezetimibe and PCSK9 inhibitors vs combination therapy- have always added a clinical benefit without no evidence of a low threshold for LDL-C [5]. The RCTs results support the concept the lower is better and the Mendelian randomization studies that earlier is better. According to the available evidence we can safely reach levels of LDL-C between 25 and 50 mg/dL, although a single trial [6] has shown a further clinical benefit and no harms for achieved LDL-C levels of <10 mg/dl. The EAS/ESC 2019 and the ESC 2021 guidelines recommend a stepwise approach to intensify preventive treatments and achieve the LDL-C goals, but this approach has been criticized because it can favor the medical inertia and the loss of patients' compliance. Moreover, with the new LDL-C goals the use of a single drug strategy will fail to achieve the objective while a combined lipid-lowering therapy with two drugs – high intensity statin and ezetimibe- and in a near future possibly with three drugs, is an effective way to reduce LDL-C. In Europe several position papers [7–9] have in some extent corrected the guidelines stepwise approach suggesting that starting with a combination therapy is more effective in high and very high risk and in Familial Hypercholesterolemia patients. In addition, real word surveys and registries data [10,11] have documented that most patients in secondary prevention are not at the LDL-C goals recommended by the recent guidelines and that the cardiovascular benefits are greater when the goals are achieved as quick as possible. A further benefit of the earlier intensive approach is represented by the effects on the atherosclerotic anatomical lesions. Recent imaging studies have shown that a rapid and aggressive reduction of LDL-C in acute coronary syndrome-ACS- patients stabilizes the atherosclerotic coronary plaques by reducing the atheroma volume, the core lipid content and by increasing the atheroma fibrous cap [12,13]. In such a complex scenario characterized by a persistent gap between the guidelines and the clinical reality due to the medical inertia or the presence of true obstacles to achieve the goals such as the case of FH patients or of the statin-intolerant patients, it is necessary to build a precision-medicine based approach. In this perspective novel and innovative drugs, to enlarge our therapeutic armamentarium and to allow the individual treatment tailoring, are welcome as reviewed by Elis A in the Journal [14].

In Europe two novel drugs have been approved by EMA "in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet and in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is

* Corresponding author.
E-mail address: maurizio.averna@unipa.it (M. Averna).

https://doi.org/10.1016/j.ejim.2023.04.026
Received 14 April 2023; Received in revised form 26 April 2023; Accepted 28 April 2023
Available online 1 May 2023

contraindicated". The two drugs are bempedoic acid and Inclisiran. In some European countries are already available for prescription and in other countries are in stand-by. Bempedoic acid (BA) is an oral, once-daily, small molecule, which has a peculiar mechanism of action like that of statins because inhibits the ATP-citrate lyase (ACLY), a step upstream the HMGCR in the enzymatic chain of the cholesterol synthesis. ACLY has been validated as pharmacological target by Mendelian randomization [15]. Differently from statins BA does not have skeletal muscle activity since as a pro-drug is activated by an acyl-CoA synthase present only in the liver and thus BA is the ideal agent to treat statin-intolerant patients. Moreover, BA decrease the fatty acids hepatic synthesis, increases their beta-oxidation and by inhibiting the AMP-activated protein kinase has a glucose lowering effect [16]. Studies of phase 3 have demonstrated the efficacy of BA in presence of a background statin therapy, in statin intolerant patients and in fixed dose combination with ezetimibe, reducing LDL-C in these settings respectively by 18%, 24% and 38%. BA is overall well tolerated. Recently the results of the cardiovascular outcome trial (Clear Outcome) [17] in statin-intolerant high-risk patients, have been published showing a significant reduction of the primary (MACE-4, HR 0.83) and secondary endpoints (non-fatal and fatal myocardial infarction, HR 0.77), confirming the overall safety. BA will offer a therapeutic opportunity not only to high-risk statin-intolerant patients but also to patients in secondary prevention who do not have access to PCSK9i and to diabetics who are worrying about the metabolic effects of statins. Inclisiran is a high technology drug which mimics the physiologic mechanism of RNA-interference. It is designed to be directed to the hepatocytes via the GaLNaC- asialoglycoprotein receptors (ASGPR) where it downregulates the PCSK9 gene expression and in this way a higher number of LDL receptors are expressed. In the phase 3 trials (Orion program) Inclisiran has been studied in ASCVD patients with/out familial hypercholesterolemia, in heterozygous FH patients and in established and ASCVD risk-equivalent patients. The results have shown a sustained reduction of plasma LDL-C by about 50% after a subcutaneous injection of 300 mg every 6 months. The pharmacokinetics of Inclisiran explains the safety data. The drug rapidly disappears from the plasma and in completely up taken by the liver which is its site of action and in the liver is slowly degraded. In the liver Inclisiran does not interfere with the cytochromes and no drug-drug interactions are expected. Inclisiran can be administered in subjects with hepatic impairment from mild to moderate without any warning signals. The kidney eliminates 16% of the drug and the safety profile of inclisiran was unaffected by renal impairment. Moreover, the real-world data available today confirm the efficacy and safety of Inclisiran shown in the registration trials; according to a single center experience 46,3% of patients has reduced LDL-C by more than 50% and 46,3% of patients reached LDL-C levels below 54 mg/dl. The FH status did not affect the response and patients on statin therapy showed a higher reduction. It is still debated whether or not Inclisiran will improve the patients' adherence to the cholesterol lowering therapy; future data from the real word will clarify if Inclisiran will be preferred to PCSK9i that have shown very high rates of adherence and persistence [18]. A key role will be played by the patients' preferences. We still do not have data on the clinical benefits because the Inclisiran outcomes trials are still ongoing. However, a pooled phase 3 trials analysis indicated a reduction of HR of MACE of about 25% with a reduction of LDL-C of 50% [19].

Taken together these data show that the new drugs have the potential to improve our clinical practice, to narrow the gap between the guideline's recommendation and the real world and to help the clinicians to make personalized medical choices.

References

[1] Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020;41(24):2313–30. https://doi.org/10.1093/eurheartj/ehz962.

[2] Ginsberg HN, Packard CJ, Chapman MJ, Borén J, Aguilar-Salinas CA, Averna M, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. Eur Heart J 2021;42(47):4791–806. https://doi.org/10.1093/eurheartj/ehab551.

[3] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022;43(39):3925–46. https://doi.org/10.1093/eurheartj/ehac361.

[4] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al., ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

[5] Cholesterol Treatment Trialists' (CTT) Collaboration Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, 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(9753):1670–81. https://doi.org/10.1016/S0140-6736(10)61350-5.

[6] Gaba P, O'Donoghue ML, Park JG, Wiviott SD, Atar D, Kuder JF, et al. Association between achieved low-density lipoprotein cholesterol levels and long-term cardiovascular and safety outcomes: an analysis of fourier-ole. Circulation; 2023. https://doi.org/10.1161/CIRCULATIONAHA.122.063399.

[7] Averna M, Banach M, Bruckert E, Drexel H, Farnier M, Gaita D, et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: a statement from a European Atherosclerosis Society Task Force. Atherosclerosis 2021;325:99–109. https://doi.org/10.1016/j.atherosclerosis.2021.03.039.

[8] Ray KK, Reeskamp LF, Laufs U, Banach M, Mach F, Tokgözoğlu LS, et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. Eur Heart J 2022;43(8):830–3. https://doi.org/10.1093/eurheartj/ehab718.

[9] Banach M, Penson PE, Vrablik M, Bunc M, Dyrbus K, Fedacko J, et al. ACS EuroPath Central & South European Countries Project. Optimal use of lipid-lowering therapy after acute coronary syndromes: a Position Paper endorsed by the International Lipid Expert Panel (ILEP). Pharmacol Res 2021;166:105499. https://doi.org/10.1016/j.phrs.2021.105499.

[10] Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol 2021;28(11):1279–89. https://doi.org/10.1093/eurjpc/zwaa047.

[11] Kotseva K, De Backer G, De Bacquer D, Rydén L, Hoes A, Grobbee D, Maggioni A, Marques-Vidal P, Jennings C, Abreu A, Aguiar C, Badariene J, Bruthans J, Castro Conde A, Cifkova R, Crowley J, Davletov K, Deckers J, De Smedt D, De Sutter J, Dilic M, Dolzhenko M, Dzerve V, Erglis A, Fras Z, Gaita D, Gotcheva N, Heuschmann P, Hasan-Ali H, Jankowski P, Lalic N, Lehto S, Lovic D, Mancas S, Mellbin L, Milicic D, Mirrakhimov E, Oganov R, Pogosova N, Reiner Z, Stöerk S, Tokgözoğlu L, Tsioufis C, Vulic D, Wood D. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol 2019;26:824–35. https://doi.org/10.1177/2047487318825350.

[12] 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(22):2373–84. https://doi.org/10.1001/jama.2016.16951.

[13] Räber L, Ueki Y, Otsuka T, Losdat S, Häner JD, Lonborg J, et al. PACMAN-AMI collaborators. effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. JAMA 2022;327(18):1771–81. https://doi.org/10.1001/jama.2022.5218.

[14] Elis A. Current and future options in cholesterol lowering treatments. Eur J Int Med 2023;112:1–5. https://doi.org/10.1016/j.ejim.2023.02.010.

[15] Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, et al. Mendelian randomization study of ACLY and cardiovascular disease. N Engl J Med 2019;380(11):1033–42. https://doi.org/10.1056/NEJMoa1806747.

[16] 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. https://doi.org/10.1038/ncomms13457.

[17] Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, et al., CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 2023. https://doi.org/10.1056/NEJMoa2215024.

[18] Padm P, Barton L, Wilson S, David A, Walji S, de Lorenzo F, et al. Lipid lowering with inclisiran: a real-world single-centre experience. Open Heart 2022;9(2):e002184. https://doi.org/10.1136/openhrt-2022-002184.

[19] Ray KK, Raal FJ, Kallend DG, Jaros MJ, Koenig W, Leiter LA, et al., ORION Phase III investigators. Inclisiran and cardiovascular events: a patient-level analysis of phase III trials. Eur Heart J 2023;44(2):129–38. https://doi.org/10.1093/eurheartj/ehac594.