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# Short Review: Lipid-Lowering Therapies, Where are we Heading?

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**Abstract**

Times are exciting when it comes to numerous new treatment options for dyslipidaemia. Here, we provide a short update on the developments over the last year. While expectations are high, and affordability of new therapies are a concern, their ultimate application still largely depends proof of reduced morbidity and mortality from atherosclerotic cardiovascular disease.

**Keywords:** Atherosclerotic Cardiovascular Disease (ASCVD); Cholesterol; Future Drug Research; ApoC3; ANGPTL3; LDLc; Lp(a); Triglycerides

## Introduction

With the presently available drugs, low-density lipoprotein cholesterol (LDL-c) can be reduced to current guideline recommendations. Despite very low LDL-c, patients continue to experience atherosclerotic cardiovascular disease (ASCVD) complications. To address this "residual" risk, new potentially manageable lipoproteins have become the next therapeutic targets, i.e. Lp(a) and triglyceride rich lipoproteins (TRL). We recently summarized the evidence and rationale of targeting these risk factors and concluded that despite good perspectives on the efficacy and safety of these new lipid-lowering drugs in clinical trials, high costs of approved and upcoming drugs are a serious concern [1]. Here we provide a short update on the new promising treatment methods and their potential implications.

## Description

Since the publication of our review last year, new drugs that target LDL-c have shown promising outcomes. The very recently approved NEXLETOL (Bempedoic acid) and NEXLIZET (Bempedoic acid and Ezetimibe) effectively lower LDLc by 16,5% and 36,2% after 12 weeks, respectively, on top of maximally tolerated statin therapy in adults at high risk of ASCVD or heterozygous familial hypercholesterolemia [2,3]. Bempedoic acid is a small molecule inhibitor that like statins targets the de novo cholesterol synthesis pathway but through inhibition of ATP Citrate Lyase. Since it concerns a prodrug which is activated by a hepatic enzyme [4] reduced adverse effects on skeletal muscle and glucose metabolism may offer advantage over statins.

Competition for the same group of patients comes from PCSK9 inhibitors. The monoclonal antibodies Evolocumab and Alirocumab reduce LDLc up to 59% while surpassing the burden of daily oral intake by sub-cutaneous injection every 2-4 weeks [5]. PCSK9 inhibitors are currently higher priced than oral drugs but the price is coming down in part due to increased competition as well as less than expected prescriptions [5,6]. A potential competitor from Novartis is Inclisiran, which through siRNA lowers hepatic PCSK9 production and lowers LDLc by more than 50% with only bi-annual injections [7,8]. The UK has set up a unique population-level arrangement with Novartis to test the efficacy of this drug in a primary prevention setting that will include 40.000 high-risk patients [9]. The same company also conducted the ORION-4 trial for secondary prevention of ASCVD, with the UK as the global trial centre. A current pause in the enrolment of patients in clinical trials due to the COVID-19 pandemic could cause some delays [10].

As companies are striving for prolonged drug effects, an upcoming transformative technology, with preclinical proof-of-concept data, includes adenine base editing (ABE) to permanently turn off a 'cholesterol-raising genes' in the liver. In June 2020, Verve Therapeutics reported effective gene editing of PCSK9 and ANGPTL3 in non-human primates to lower LDLc and/or triglyceride (TG) levels [11]. The speed of technical development taking daily drug intake towards once in a lifetime medication is astounding. Caution may; however, be needed as at this point the consequences of a permanent silencing of these genes in the liver is not known. On the other hand, exclusive targeting of e.g. PCKS9 in the liver may limit unwanted effects of inhibition in other organs.

This brings us to the most recent news on drugs targeting TRL or Lp(a) (1 for more detail). Besides ABE for ANGPTL3, monoclonal antibody therapy and antisense oligonucleotides (ASO) have already proven efficacy in phase I and II clinical trials [1]. The monoclonal antibody Evinacumab reduces TG as well as LDLc levels via mechanisms other than affecting the LDL receptor (LDLR) pathway [12] and can therefore be particularly interesting for patients with defective LDLR. Evinacumab showed positive effects in the recent phase III trial (ELIPSE) by a 49% reduction in LDLc after monthly injections in 65 patients suffering from homozygous familial hypercholesterolemia. The versatility of ANGPTL3 antagonism is shown by positive news from a phase II trial in patients with hypertriglyceridemia or type 2 diabetes with use of antisense oligonucleotides (ASOs) targeting RNA [13].

Patients suffering from hypertriglyceridemia may in the future also benefit from ASOs targeting APOC3. Promising results of a phase II trial with APOC3 in hypertriglyceridemic patients with a diagnosis or high risk of CVD, was published in January 2020 [14]. Following a monthly dose of 50 mg for minimally 6 months, 90% of patients (compared

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to 5% in the placebo group) achieved TG levels <150 mg/dL (mean baseline: 285 mg/dL). Akcea Therapeutics, however, indicated that the drug will first be used to treat familial chylomicronemia syndrome, a rare lipid disorder, to reduce the risk of pancreatitis. Whether the drug will eventually also become available for patients with mild hypertriglyceridemia at an affordable price is not known.

To date there are no registered drugs to effectively lower Lp(a). A retrospective study to improve knowledge about the epidemiology of Lp(a) in patients with CVD was initiated in April 2019 (NCT03887520). Since December 2019, patients in the US with Lp(a) levels >70 mg/dL are recruited for the first phase III double-blind Lp(a) HORIZON trial that will be completed in 2024 (NCT04023552). Over 7600 participants will receive monthly subcutaneous injection of ASOs against LPA. Tsimikas S., emphasized that 30% of the global population has Lp(a) levels in the atherogenic range [15]. This suggests that many could benefit from this drug but we have to await outcomes and learn how treatment costs will compare to apheresis, which is currently the only option to reduce high Lp(a).

## Conclusion

Summarizing, a range of therapeutic modalities are likely to offer improved ASCVD risk reduction in the near future with potential advantages over generic lipid-lowering medication (reduced adverse effects, no daily intake, etc). The currently tested arsenal of experimental drugs offers great opportunities for more personalized care for especially high risk patients but it remains to be seen whether such treatments will be affordable for the common patient with an increased ASCVD risk. The success of ongoing trials will provide insights into how much ASCVD residual risk remains (room for e.g. targeting inflammation) but most promises fall short in the end and we still need proof that these new treatments modalities can securely reduce ASCVD-related morbidity and mortality.

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