Do we need new lipid-lowering agents in the era of PCSK9 inhibitors? Recent advances

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ABSTRACT

Atherosclerotic disease remains the leading cause of death worldwide. Much of atherosclerotic disease initiation and progression is driven by dyslipidemia. With the advent of statins, ezetimibe, and more recently the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, physicians across all specialties have access to an armamentarium to address this major pathophysiological driver. Nevertheless, there is still a large unmet need in terms of optimizing pharmacotherapeutic lipid lowering strategies. This article will review the evidence pertaining to the major lipid-lowering agents that have been introduced lately, or still are under development, after the advent of statins, ezetimibe and PCSK9 inhibitors. There is cumulating evidence suggesting that there soon will be a broad specter of differential therapies across a variety of mechanistic pathways that will enter clinical medicine. Knowledge about these potential recent advances and various upcoming therapeutic options will make choice easier for physicians, and will lead to more personalized selections of available treatments.

Key words: lipid lowering agents, LDL cholesterol, PCSK9 inhibitors, atherosclerotic disease, RNA-based therapy

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide [1]. The newest statistics from the World Health Organization (WHO) show that 17.9 million people die yearly of CVD worldwide, an estimated 32% of all deaths. Of those, approx. Eighty-five percent are attributable to myocardial infarctions and strokes.

Recent guidelines on CVD prevention pinpoint the role of elevated low-density lipoprotein cholesterol (LDL-C) as one of the most important contributors to atherosclerotic CVD [2]. Since elevated LDL-C concentrations are amenable to pharmacological lowering, the pertinent European and US dyslipidemia guidelines have put forward treatment goals in different patient categories, to emphasize the need for robust LDL-C lowering in patients at high risk of CVD, or those with established CVD. Statins have been established as the gold standard for the management of cholesterol in primary and secondary prevention for nearly two decades. In recent years, the second drug added to statin treatment has been ezetimibe. Ezetimibe inhibits cholesterol absorption from the intestine, providing additional LDL-C reduction.

Despite the success of statins, registry data show that there is underuse of currently available therapies. The NOR-COR (NORwegian CORonary) study from Norway published in 2017 showed that among patients who had survived an acute myocardial infarction, 57% had LDL-C levels above 1.8 mmol/l; 22% above 2.5 mmol/l; and 10% above 3.0 mmol/l at a time-point between 2 and 36 months post-infarction [3]. In the POLASPIRE study, conducted in 2017–2018 as part of the EUROASPIRE V study, target levels for LDL-C were met by only 20% of women and 25% of men [4]. According to current guidelines,

these patients should aim for an LDL-C level of 1.4 mmol/l or lower [2]. Achieving current recommendations of even lower LDL-C concentrations than at the time of these studies constitutes a major challenge in clinical practice.

Among the particular high-risk groups of patients are those with familial hypercholesterolemia (FH). Due to high cholesterol levels from birth, individuals with FH face a substantially higher risk for CVD than those with a later onset of hypercholesterolemia [5]. Most patients with FH do not reach their LDL-C treatment goals. In a Norwegian cohort 25% of patients in primary prevention and only 8% of patients in secondary prevention attained LDL-C goals of below 2.5 mmol/l and below 1.8 mmol/l, respectively, on treatment mainly with statins and ezetimibe [6]. As in the case of secondary prevention, treatment goals in FH were substantially lowered in the 2019 joint Guidelines for the Management of Dyslipidaemias from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), to LDL-C <1.8 mmol/l in primary prevention and <1.4 mmol/l in secondary prevention, underscoring the need for new treatment options [7].

Another problem in preventive cardiology is that of residual risk driving recurrent events in patients with established CVD despite current preventive therapies. Recently the role of triglyceride-rich lipoproteins in contributing to the progression of atherosclerosis and CVD has been recognized [7]. These particles may mediate cholesterol accumulation within the arterial intima and activate pro-inflammatory pathways. While fibrate drugs have substantial triglyceride-lowering properties their success in lowering cardiovascular events has been limited, leading to an interest in drugs that modify or lower cardiovascular risks associated with these lipoproteins. Another factor increasing residual risk is elevated lipoprotein(a) [Lp(a)] concentration. Lp(a) is a genetically determined LDL-like particle characterized by the addition of apolipoprotein(a) [apo(a)] to an apolipoprotein B100-based particle. Up to 20% of populations exhibit levels that may increase their CVD risk. Major lipid-lowering therapies have little effect on Lp(a) concentrations, but new gene-based therapies specifically targeting apo(a) are being developed.

In the following article, we will review the evidence pertaining to major lipid-lowering agents that have been introduced lately, or still are under development, after the advent of statins and ezetimibe.

PROPROTEIN CONVERTASE SUBTILISIN/ /KEXIN TYPE 9 (PCSK9) INHIBITION

PCSK9 is an enzyme expressed in many tissues and cells. It binds to the LDL receptor on hepatocyte membranes, targeting the receptor for degradation intracellularly in the lysosomes. LDL receptors not bound to PCSK9 may be recirculated more than 100 times. Blocking PCSK9 leads to an increase of functional LDL receptors, increased transportation of LDL particles from the extracellular to the intracellular space, and thereby a reduction of LDL-C concentration in the blood (Figure 1). The first two PCSK9 inhibitors, alirocumab and evolocumab, were approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) in 2015 as injections once every two weeks or once monthly. A recent meta-analysis in individuals with atherosclerotic CVD, but not FH, comprising 66 478 patients who took part in 39 randomized controlled trials found that PCSK9 inhibitors achieve an approx. 60% reduction in LDL-C. This reduction was associated with a lower risk of myocardial infarction (relative risk [RR], 0.80; 95% confidence interval [CI], 0.74–0.86; $P<0.0001$), ischemic stroke (RR, 0.78; 95% CI, 0.67–0.89; $P=0.0005$), and coronary revascularization (RR, 0.83; 95% CI, 0.78–0.89; $P<0.0001$) compared with controls. However, the effects of PCSK9 inhibition on all-cause death and cardiovascular death were not statistically significant during the mean follow-up time of 2.3 years; a time frame that possibly was too short to demonstrate effects on mortality. The use of these PCSK9 inhibitors was not associated with an increased risk of neurocognitive adverse events, liver enzymes elevations, rhabdomyolysis, or new-onset diabetes mellitus [8].

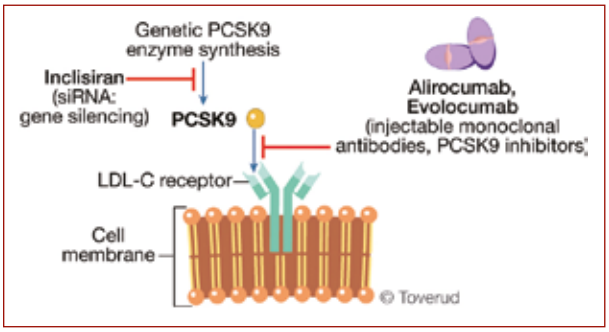

Figure 1. Mechanisms of PCSK9-targeting therapies

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA; LDL-C, low-density lipoprotein cholesterol

In randomized, double-blind studies with alirocumab and evolocumab in patients with heterozygous FH on stable lipid-lowering therapy, mainly with statins and ezetimibe, LDL-C concentrations were reduced by 50%–60% to around 1.8 mmol/l [9, 10]. Approximately 60% of patients may achieve LDL-C treatment goals of below 1.8 mmol/l [8, 9]. Results from long-term open-label treatment studies with alirocumab and evolocumab have been reassuring, with sustained LDL-C lowering, low discontinuation rates due to side effects, and low prevalence of anti-drug antibodies [11, 12]. In the rare disorder homozygous FH (i.e., FH-causing mutations inherited from both parents), little or no residual LDL receptor activity remains. Therefore, drugs acting by upregulation of LDL receptors, including statins and ezetimibe, have limited effect. PCSK9 inhibitors also upregulate LDL receptors, but in homozygous FH patients who retain some residual LDL receptor function, PCSK9 inhibitors may be effective to varying degrees [13, 14].

INCLISIRAN

Inclisiran (Leqvio®) is a small interfering RNA (siRNA) that inhibits translation of the protein PCSK9 (Figure 1). The efficiency of this drug was investigated on top of statins in three trials enrolling patients with either heterozygous FH or with established CVD [15]. The primary endpoint in these studies was the reduction in LDL-C, and administration of the drug or placebo was subcutaneously at baseline and at months 3, 9, and 15. Overall, the decrease in LDL-C was around 45%. So far, no study has documented morbidity or mortality benefits, but these are underway. Inclisiran was approved for commercialization by the EMA in 2020 and the FDA in 2021. Interestingly, the National Institute for Health and Care Excellence in the UK (NICE) advocated its use in general practice in the UK even before any outcome studies were published. One of the advantages of inclisiran is its pharmacokinetics resulting in long-lasting reductions in LDL-C concentrations. Inclisiran is administered at 0 and three months and then twice yearly, which assures improved compliance. On the other hand, possible adverse events may persist; however, its safety profile is excellent to date. In all trials, inclisiran was used together with established lipid-lowering treatment.

LOMITAPIDE

Lomitapide, an inhibitor of microsomal triglyceride transfer protein, inhibits the assembly of apolipoprotein B containing lipoproteins in the intestine and liver, thereby lowering serum LDL-C, independently of LDL receptors (Figure 2). Dose-dependently, LDL-C concentrations may be reduced by around 50% [16]. Add-on treatment with lomitapide may prolong intervals between LDL-apheresis in selected and motivated patients with homozygous FH. Side effects include gastrointestinal disturbances, elevated liver enzymes, and increased liver fat. Lomitapide (Lojuxta®) was approved for the treatment of homozygous FH in adults in 2013. On a different note, costs are very high, limiting availability.

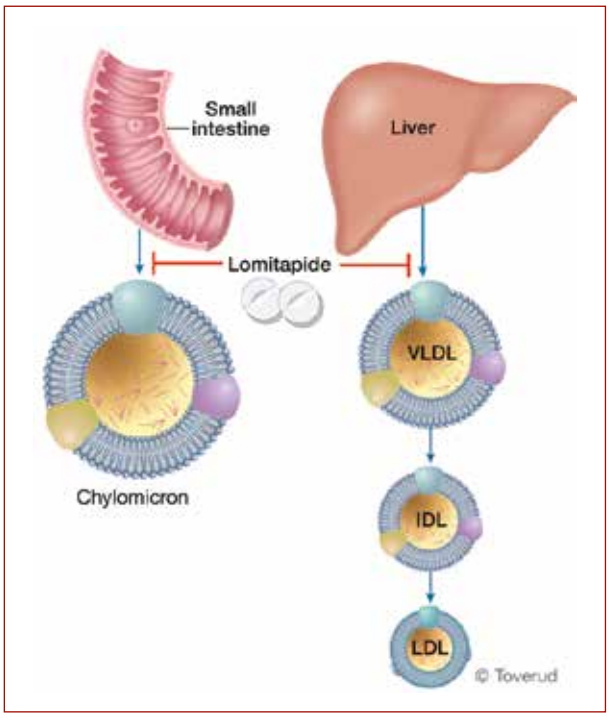

Figure 2. Mechanism of action of lomitapide

Abbreviations: IDL, intermediate density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein

BEMPEDOIC ACID

Bempedoic acid is approved in the European Union (Nilemdo®) and in the United States (Nexletol®) for treatment of hypercholesterolemia. As a prodrug bempedoic acid requires activation by very-long-chain-acyl-CoA synthetase-1, which is primarily expressed in the liver (but not in skeletal muscles). The active metabolite inhibits adenosine triphosphate citrate lyase, an essential enzyme in the cholesterol synthetic pathway upstream of 3-hydroxy-3-methylglutaryl-CoA reductase (Figure 3). As with statins, inhibition of cholesterol synthesis leads to upregulation of LDL receptors and thereby clearance of LDL particles. With a half-life of 15–24 hours, bempedoic acid may be administered once daily orally. As monotherapy, bempedoic acid reduced LDL-C concentrations by up to 25% (placebo-subtracted) in patients with baseline levels of 3.4–5.7 mmol/l [17].

As noted above, the need for greater reductions in LDL-C than those obtained with statins alone has emerged, and bempedoic acid may play a role. In patients receiving background statin therapy whose LDL-C remained between

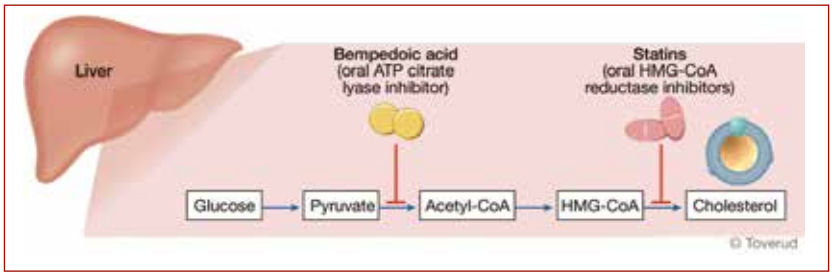

Figure 3. Mechanism of action of bempedoic acid and statins

Abbreviations: ATP, adenosine triphosphate; CoA, coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A

3.0–5.7 mmol/l, bempedoic acid 180 mg daily reduced LDL-C further by ~20% despite targeting the identical cholesterol biosynthesis pathway as statins, though at different enzymes [18]. Rates of adverse events including muscle-related symptoms were similar to placebo [19]. Likewise in patients with atherosclerotic cardiovascular disease or FH or both whose LDL-C remained >1.8 mmol/l on maximally tolerated lipid therapy (including a statin), reductions in LDL-C of 17%–18% were observed [20]. A similar reduction was observed in a parallel study of similar patients with LDL-C >2.6 mmol/l at their initial screening, which did not require patients to be taking a statin to enter the trial [21]. Common side effects of bempedoic acid include elevations of uric acid [20, 21] and an increase in gout [21, 22]. A tendency to worsen renal function has been indicated in a recent meta-analysis [21].

The need for management of lipids in patients who are unable to tolerate statins has emerged in recent years. While randomized controlled trials show low rates of muscle symptoms, observational data have indicated that up to one-third of statin-treated patients experience total intolerance or inability to take adequate doses to reach LDL-C goals [22]. In a substantial number of patients; however, symptoms thought to be side effects of statins are probably nocebo effects. Studies in patients experiencing muscle-related symptoms while on statin therapy show that most people are unable to distinguish periods with placebo therapy from periods with statin therapy [23, 24].

Studies have focused on using bempedoic acid in patients with statin intolerance [25] and as add-on therapy to ezetimibe [26]. In patients with statin intolerance, LDL-C reductions of >21% were seen in patients with LDL-C of 4.1 mmol/l, of whom <10% were taking a low-dose statin [25]. In a study of statin-intolerant patients taking ezetimibe, of whom one-third were taking a low-dose statin, LDL-C concentrations were reduced by >28% [27]. Bempedoic acid was well tolerated in these populations with no increase in muscle symptoms.

Given the costs of PCSK9 inhibitors, further studies have focused on trying to achieve as low LDL-C concentrations as provided by PCSK9 inhibitors. In a fixed-dose study of bempedoic acid plus ezetimibe in patients with high cardiovascular risk and mean baseline LDL-C of 3.9 mmol/l despite maximal statin therapy, reductions of LDL-C were substantial (>38%) though less than expected with a PCSK9 inhibitor [28]. Triple therapy with bempedoic acid, ezetimibe, and atorvastatin (20 mg/day) gave approximately equivalent LDL-C reductions of >64% as would be expected with a PCSK9 inhibitor [29] though head-to-head studies have not been published. Adding bempedoic acid to background therapy with once-monthly evolocumab 420 mg significantly reduced LDL-C by nearly 30% [29].

Generally, reductions in LDL-C with bempedoic acid appear to be slightly greater in populations not taking a statin [18–20]. With regard to other lipid fractions, bempedoic acid reduces apolipoprotein B, triglycerides, and non-high-density lipoprotein cholesterol (non-HDL-C) concentrations. Reductions in CRP concentrations observed in several studies may be promising but require further understanding of the mechanism [21, 22, 26].

The future role of bempedoic acid appears to be in (1) patients with statin intolerance, most often in combination with other tolerated lipid-lowering agents; and (2) patients needing additional therapies to achieve LDL-C goals. The ongoing cardiovascular outcomes trial (CLEAR Outcomes) in patients with history of, or at high risk for CVD, statin intolerance and LDL-C ≥2.6 mmol/l will further clarify the role of the drug and whether potential reductions in clinical endpoints relate solely to the lipid-reduction or also to reductions in CRP.

High costs limit the availability of PCSK9 inhibitors. With the advent of biosimilars and other modes of PCSK9 inhibition, prices may come down in the future, making this effective and well-tolerated therapy available for a broader range of patients.

TRIGLYCERIDES/COMBINED HYPERLIPIDEMIA — TARGETING THERAPIES

High triglycerides despite LDL-C lowering therapies remain one of the most frequently confronted dilemmas in clinical practice. Patients with hypertriglyceridemia may carry a high residual risk of cardiovascular disease [30]. Given that lifestyle stands out as the major cause of hypertriglyceridemia in patients with metabolic syndrome, abdominal obesity, or type 2 diabetes mellitus (T2DM), as well as persons who overconsume alcohol or are physically inactive, what more can a physician do to address these risk factors? While diet, activity, and weight reduction are cornerstones of treatment, genetics and other unmodifiable factors also play a role. For example, patients with familial combined hyperlipidemia commonly present in clinical practice and may exhibit hypertriglyceridemia despite normal body weight [31]. A very rare condition is monogenic familial hyperchylomicronemia syndrome.

Evidence from epidemiology and genetics has supported the hypothesis that variants of several key genes of triglyceride metabolism affecting triglycerides, and triglyceride-rich and remnant lipoproteins are causally related to cardiovascular disease and all-cause mortality [32]. This evidence has given rise to new therapies to target these manifestations.

EICOSAPENTAENOIC ACID

Fish oil supplements have been touted for decades for their cardiovascular benefits. They have also been implemented quite extensively in clinical practice to reduce triglyceride concentrations, but trials of omega-3 fatty acids have not proved their protection against CVD [33]. Thus, the results of the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) came as a surprise. They

show a 25% reduction in the primary endpoint of a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in patients assigned to receive 4 g of icosapent ethyl daily or mineral-oil containing placebo [34]. Further analysis revealed consistent benefits across patient subgroups and reduction in total (first and subsequent) ischemic events by 31% [35]. The majority of patients included in the trial were based on established CVD (71%); nearly 60% had diabetes and the median triglyceride level was 2.4 mmol/l. Thus, the impressive reduction in events occurred in a population at high cardiovascular risk, of which well over 90% were treated with moderate or high-intensity statins.

Since this publication, questions have focused on the difference between icosapent ethyl used in REDUCE-IT and omega-3 carboxylic acid, composed of a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid. This compound was used in a 4 g/day dose in the STRENGTH (Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial, a study that did not show a reduction in cardiovascular events [36]. Whether these differences are explained by potential harms of docosahexaenoic acid or the higher dosage of EPA in REDUCE-IT versus STRENGTH has not been completely clarified. Another explanation that has been proposed is the choice of placebo in REDUCE-IT. In the mineral oil control group levels of LDL-C, apolipoprotein B, and C-reactive protein increased by 10.9%, 7.8%, and 32.3%, respectively, indicating that the benefits of icosapent ethyl may have been partly confounded by harms in the control group [34, 37]. However, EPA may have characteristics that mitigated some of these differences.

The mechanisms of the benefits observed in REDUCE-IT may be multifactorial as the reductions in risks observed exceeded expectations regarding the degree of triglyceride lowering. The median change in the triglyceride level was a decrease of 18.3% (–0.44 mmol/l) in the icosapent ethyl group versus an increase of 2.2% in the placebo group. Due to variability in triglycerides, about 10% of participants had normal levels, but risk reductions were consistent across all baseline triglyceride levels. Omega-3 fatty acids may reduce inflammation, affect arrhythmias due to modulation of membrane fluidity and attenuate atherosclerotic plaque formation and progression [38]. Notably, while on the one hand, a marked reduction of 30% in sudden cardiac deaths occurred in the icosapent ethyl group in REDUCE-IT (a tertiary analysis), the rate of atrial fibrillation was significantly higher in the icosapent ethyl group than in the placebo group (5.3% vs. 3.9%) [34].

Despite some uncertainties, a review of icosapent ethyl (Vazkepa®) by EMA led to approval of the medication in 2021 as treatment to reduce the risk of cardiovascular events in high-risk statin-treated patients with elevated triglycerides (≥1.7 mmol/l) and established CVD (or diabetes and one or more additional cardiovascular risk factors).

PEMAFIBRATE

Fibrates are peroxisome proliferator-activated receptor (PPAR) agonists that have been used as triglyceride-lowering drugs for decades. Because most studies have included wide ranges of participants, their cardioprotective effects have been questioned and are seen mainly in study subgroups with hypertriglyceridemia [39]. Pemafibrate stands out as a novel highly selective PPAR-α modulator causing marked reductions of triglycerides and remnant cholesterol particles. A recent study, however, found no significant reductions in non-HDL-C [40], indicating that potential beneficial effects may be related primarily to triglyceride and triglyceride remnant reductions. The ongoing PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study has randomized over 10 000 participants with T2DM (primary or secondary prevention), triglycerides of 2.26–5.64 mmol/l and HDL-C levels <1.03 mmol/l, to pemafibrate or placebo, with the study endpoint driven by events. Results are expected to be presented shortly [41]. Positive outcomes could significantly improve treatment of patients with T2DM.

APOLIPOPROTEIN C-III AND ANGIOPOIETIN-LIKE PROTEIN THERAPIES

Control of triglyceride metabolism involves a number of proteins and enzymatic pathways. Triglycerides in chylomicrons and very low-density lipoproteins undergo intravascular lipolysis by lipoprotein lipase to release free fatty acids that are used for fuel or stored. Pivotal proteins regulating these processes are apolipoprotein C-III (ApoCIII), angiopoietin-like protein 3 (ANGPTL3), and ANGPTL4, all potent inhibitors of lipoprotein lipase (Figure 4).

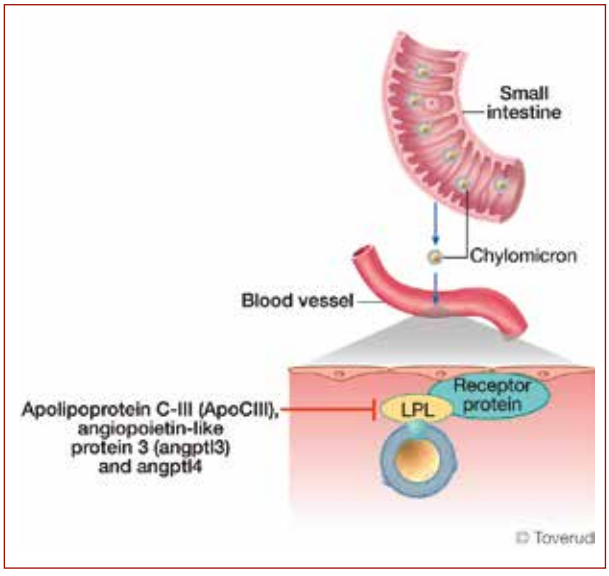

Figure 4. Mechanisms of ApoCIII — targeting therapies
Abbreviations: ApoCIII, apolipoprotein C-III; LPL, lipoprotein lipase

Genetic evidence links the loss-of-function variants of ApoCIII to reduced triglyceride levels and cardiovascular risk [42]. Furthermore, ApoCIII appears to contribute to the atherogenicity of various lipoproteins to which it attaches, including HDL [43]. Notably, the low risk of CVD in ApoCIII loss-of-function heterozygotes appears to be mediated by its association with low remnant cholesterol and not with low LDL-C [44], further establishing the role of triglyceride remnants in atherosclerosis. These findings from genetics and pathophysiology have acted as key catalysts for the development of therapeutic drugs targeting hypertriglyceridemia by inhibiting ApoCIII.

A recent study found that ANGPTL3 concentrations remained independent predictors of cardiovascular events after adjustment for traditional risk factors and lipid-lowering medications [45].

In accordance with this, loss-of-function mutations in the *ANGPTL3* gene are shown to associate with hypobetalipoproteinemia and decreased levels of triglycerides, and LDL-C and HDL-C levels, as well as risk of coronary heart disease [44] while mutations in the *ANGPTL4* gene are associated with decreased triglycerides and increased HDL cholesterol levels [45]. Subjects with ANGPTL3 deficiency showed no coronary atherosclerosis [46] leading to the conclusion that ANGPTL3 blockers could be promising risk-reducing agents. On the other hand, the development of angptl4 inhibitors has been impeded by the observation of lipogranulomatous lesions in the intestines of angptl4 deficient mice.

EVINACUMAB

Evinacumab is a fully human monoclonal antibody that binds to and inhibits angptl3, thereby increasing lipoprotein lipase activity (Figure 5). Evinacumab reduces elevated triglycerides, although not in those with severely elevated triglycerides due to the lack of lipoprotein lipase activity in rare familial hyperchylomicronemia syndrome [47, 48]. Evinacumab also reduces LDL-C by a mechanism independent of LDL receptors, which is not fully understood. In a recent phase 3 study in patients with homozygous FH, monthly intravenous infusions of evinacumab reduced LDL-C by 47% (49% vs. placebo) and seemed to be a promising new treatment option for these difficult-to-treat patients [49]. Flu-like symptoms occurred more often in patients receiving evinacumab. Long-term side effects on atherosclerosis and pregnancies are being collected from an ongoing registry of users. Evinacumab (Evkeeza®) was approved in 2021 for the treatment of homozygous FH from 12 years of age.

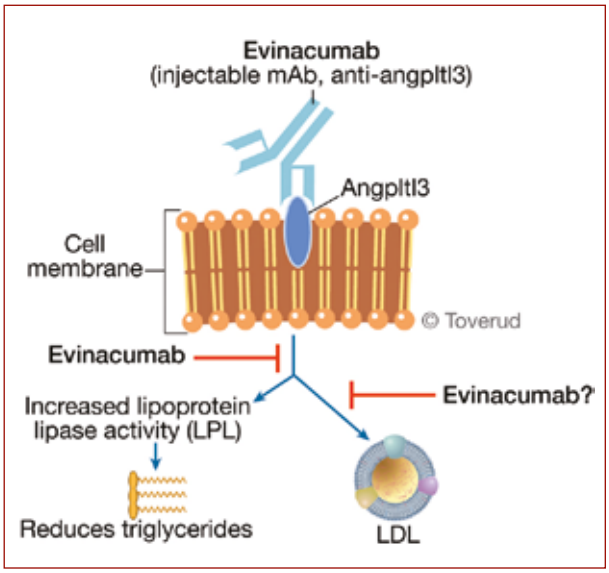

Figure 5. Mechanism of evinacumab

Abbreviations: mAb, monoclonal antibody; other — see Figures 2 and 4

VUPANORSEN

Vupanorsen is an antisense oligonucleotide to ANGPTL3 mRNA that is being developed as potential treatment for dyslipidemias [50]. In patients with diabetes, hepatic steatosis, and hypertriglyceridemia, the drug decreased substantially triglycerides and total and non-HDL cholesterols without reducing platelet counts [51].

VOLANESORSEN

Volanesorsen is an antisense oligonucleotide against ApoCIII mRNA that robustly decreases triglyceride and ApoCIII concentrations through lipoprotein lipase independent pathways (Figure 4). Randomized controlled clinical trials have found reductions of about 70% in triglyceride levels and a reduced risk of acute pancreatitis associated with hypertriglyceridemia [52]. A major step forward in the treatment of rare diseases was made in patients with familial chylomicronemia syndrome, a rare and potentially fatal genetic disorder due to loss of lipoprotein lipase activity, characterized by chylomicronemia with recurrent pancreatitis and few therapeutic options. Volanesorsen lowered triglyceride levels by 77%, and most participants reached triglyceride levels below 8.5 mmol, a threshold associated with a substantially lowered risk of pancreatitis [53]. Volanesorsen lowered apolipoprotein B-48 by 76%, but increased LDL-C by 136%, and total apolipoprotein B by 20%. While these findings may reflect a possible increased cardiovascular risk, levels of atherogenic lipoproteins were very low, as typically seen in patients with familial chylomicronemia.

A major adverse effect of volanesorsen is thrombocytopenia, which led the FDA to refuse approval, as did concerns about serious bleeding. However, thrombocytopenia is reversed by stopping the drug. EMA has approved volanesorsen (Waylivra®) in adult patients with familial chylomicronemia syndrome in 2019.

OLEZARSEN

Olezarsen is an antisense oligonucleotide targeted to hepatic ApoCIII mRNA to inhibit ApoCIII protein production (Figure 4). In a recent study, treatment with olezarsen for

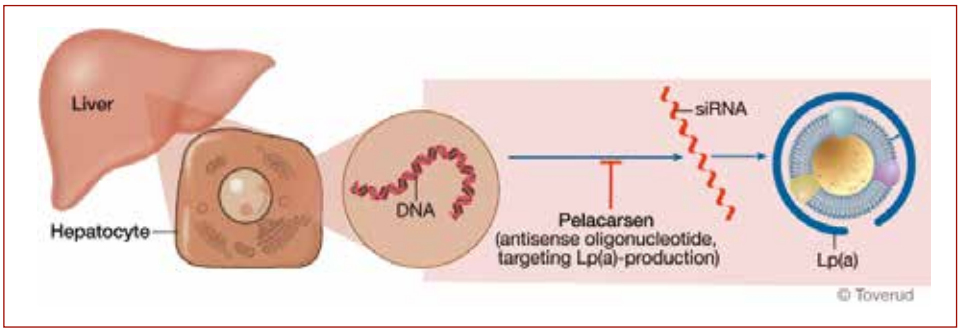

Figure 6. Mechanism of action of pelacarsen

Abbreviations: Lp(a), lipoprotein (a); other — see Figure 1

6–12 months dose-dependently reduced triglycerides by 23%–60%, without changes in platelet count, liver, or renal function changes, in participants with elevated triglycerides and high cardiovascular risk or disease [51].

THERAPIES TARGETING ELEVATED LIPOPROTEIN (A)

The association between elevated Lp(a) and cardiovascular disease has been established through studies following the identification of the molecule in 1968 by Berg in Oslo, Norway. A meta-analysis of prospective studies has shown an approximate increase of 1.16 (1.11–1.22) per 3.5-fold higher Lp(a) concentration in the risk of coronary heart disease, which decreases only slightly to 1.13 (1.09–1.18) following adjustment [54].

Associations between Lp(a) and mortality have also been shown, as well as stroke, peripheral artery disease, and calcific aortic valve stenosis. This brief review targets only specific therapies for apo(a). It is thought that while some studies have found that reductions in Lp(a) by 20%–25% did not demonstrate lowered cardiovascular risk beyond concomitant reductions in LDL-C, this observation could be explained by the notion that large reductions in absolute levels are needed, as seen in studies of the following novel therapies [55].

PELACARSEN

Pelacarsen is the antisense oligonucleotide targeting hepatic apo(a) production that has made most progress regarding studies that are completed or initiated (Figure 6). Compared to placebo, pelacarsen reduced Lp(a) concentrations dose-dependently and consistently by up to 80% in patients with elevated levels and established CVD [56].

Furthermore, reductions in oxidized phospholipids on apolipoprotein B and apo(a), components of Lp(a) with probable proinflammatory effects, were seen. The Lp(a) HORIZON study is a randomized double-blind, placebo-controlled multicenter trial assessing the effect of pelacarsen on major cardiovascular events in patients with established CVD and Lp(a) concentrations ≥175 nmol/l [57].

SMALL INTERFERING RNA THERAPY

Olpasiran, a small interfering molecule designed to directly inhibit Lp(a) messenger RNA, showed large, dose-dependent, and long-lasting reductions of 71%–97% in Lp(a) concentrations with effects persisting for several months [58].

Recently the results of an escalating study of another small interfering RNA therapy (SLN360) inhibiting translation of the gene encoding apo(a) in hepatocytes and also given as a single dose was reported. Median reductions of Lp(a) of 98% were observed in the group receiving the highest dose after up to 150 days [59].

Safety questions related to both of these therapies will require longer and larger studies.

CONCLUSION

Taken together, there is an unmet need for more efficient lipid-lowering therapies, as well as an expansion of today's therapeutic armamentarium. Recent advantages in pharmacotherapy point to a number of possible mechanistic and pharmacological pathways deployed to reach the goal of getting more patients to lipid targets. The field is moving more rapidly than in the last decades and may lead to significant changes in how we approach the global atherosclerotic burden.

Article information

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