Novel therapeutic targets and agents for pediatric dyslipidemia

Bhuvana Sunil, Christy Foster, Don P. Wilson and Ambika P. Ashraf

***Abstract*:** Landmark studies have convincingly demonstrated that atherosclerosis begins in youth. While generally asymptomatic, an increasing number of youth with disorders of lipid and lipoprotein metabolism, such as familial hypercholesterolemia, are being identified through selective and universal screening. While a heart healthy lifestyle is the foundation of treatment for all youth with dyslipidemia, lipid-lowering therapy may be required by some to prevent morbidity and premature mortality, especially when initiated at a young age. When appropriate, use of statins has become standard of care for reducing low-density lipoprotein cholesterol, while fibrates may be beneficial in helping to lower triglycerides. Many therapeutic options commonly used in adults are not yet approved for use in youth less than 18 years of age. Although currently available lipid-lowering therapy is well tolerated and safe when administered to youth, response to treatment may vary and some conditions lack an efficient therapeutic option. Thus, newer agents are needed to aid in management. Many are in development and clinical trials in youth are currently in progress but will require FDA approval before becoming commercially available. Many utilize novel approaches to favorably alter lipid and lipoprotein metabolism. In the absence of long-term outcome data of youth who were treated beginning at an early age, clinical registries may prove to be useful in monitoring safety and efficacy and help to inform clinical decision-making. In this manuscript, we review currently available and novel therapeutic agents in development for the treatment of elevated cholesterol and triglycerides.

***Keywords*:** familial hypercholesterolemia, hypercholesterolemia, hyperchylomicronemia, hypertriglyceridemia, pediatric dyslipidemia

Introduction

In 1955, niacin was considered the initial therapeutic option for reducing elevated levels of blood cholesterol.[1] Since that time, the treatment of both elevated levels of cholesterol and triglycerides (TGs) has evolved greatly. With recognition of atherosclerotic cardiovascular disease (ASCVD) as a major public health challenge worldwide, over the past two decades, many newer lipid-lowering therapies (LLT) have been developed. Some have evolved from knowledge gained with the use of targeted treatment of individuals with rare disorders of lipid and lipoprotein metabolism, while others were informed by results of Mendelian randomization studies. While data of LLT initiated in youth and continued for up to 20 years have been promising for familial hypercholesterolemia (FH), treatment of other lipid disorders, such as those with elevated TG have been less successful. In addition, while most currently available LLT options are well tolerated and improve lipid levels, not all youth are able to reach a desirable treatment target. Thus, additional therapeutic options are needed.

In this manuscript, we review currently available and novel therapeutic agents in development for the treatment of elevated cholesterol and TG. We have categorized these novel agents into those that predominantly reduce (1) low-density lipoprotein cholesterol (LDL-C); (2) TG, or (3)

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both. Included in our discussion of the later are agents that reduce Lp(a). Since clinical trials using currently available and evolving novel LLT are limited in youth, much of the evidence supporting the mechanisms of action, safety and efficacy are summarized from data derived from adults, and are so noted. Data for youth have been included whenever available. It should be noted that many, but not all LLT have been FDA approved for youth less than 18 years-of-age.

Therapeutic agents that predominantly lower LDL-C

Traditionally, statins have been the predominate LDL-C lowering agent utilized in clinical practice. Table 1 illustrates the LDL-C lowering medications and their therapeutic targets. Several emerging non-statin therapies that target LDL-C are discussed below.

Therapeutic agents that interfere with dietary absorption of cholesterol

In most individuals, dietary cholesterol contributes about 8–10% of the circulating cholesterol.[2] Currently, there are two medications commonly used to reduce absorption of dietary cholesterol, bile acid sequestrants and ezetimibe. Even though ezetimibe is not a novel therapeutic agent, we have included it in this review to describe current evidence, given the increased use of this drug in youth.

Bile acid sequestrants (BAS). BAS bind to bile acids, removing these from enterohepatic circulation, resulting in up-regulation of LDL-R and increased LDL-C clearance. Colesevelam is the only BAS approved for the treatment of pediatric patients with HeFH, approved for use as an adjunct to diet and exercise in FH, alone or in combination with statin therapy in October 2008. Colesevelam can reduce LDL-C by 7–15%.[3] The side effect profile includes bloating, constipation, and malabsorption of fat-soluble vitamins, all of which interferes with adherence.[4] Both colestipol and cholestyramine have been studied in pediatric patients but are not FDA approved and can bring LDL-C levels down by 10–20%.[5–7]

Ezetimibe

Mechanism: Ezetimibe is a selective cholesterol absorption inhibitor approved by the FDA in 2002 for cholesterol lowering. Ezetimibe reduces absorption of cholesterol and plant sterols from the intestinal brush border by blocking the Niemann–Pick C1-like intracellular cholesterol transporter 1 (NPC1 L1) at the cell surface.[8] Since its systemic absorption is negligible, ezetimibe does not potentiate the toxicity of any other lipid-lowering agents, making it a useful agent for combination therapy. Its LDL-C lowering effect is additive and independent of the action of statins.

Clinical data: In adults, The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial evaluated the benefit for reduction in ASCVD with the addition of ezetimibe *versus* placebo.

With a median follow-up of 6 years, the study showed that compared to placebo, ezetimibe resulted in incremental lowering of LDL-C levels and improved cardiovascular outcomes.[9] A 2018 meta-analysis illustrated moderate to high-quality evidence that ezetimibe had modest beneficial effects on lowering risk of ASCVD endpoints, primarily driven by a reduction in non-fatal myocardial infarction (MI) and non-fatal stroke, but little or no effect on fatal endpoints.[10]

Pediatric data: Ezetimibe 10 mg/day is approved by the FDA for use in youth 10 years-of-age and older. Pediatric data on the use of ezetimibe is derived from two small studies. In a randomized controlled trial (RCT) evaluating ezetimibe in 138 children, most of whom had heterozygous familial hypercholesterolemia (HeFH), and others with LDL-C persistently >160 mg/dL, the use of ezetimibe resulted in greater reductions in LDL-C and total cholesterol[11] than placebo. Another multicenter, randomized, double-blind, placebo-controlled study of adolescents with HeFH followed up to 53 weeks showed that co-administration of ezetimibe with simvastatin was safe, well tolerated, and provided higher LDL-C reduction compared with simvastatin alone.[12] For children between the ages of 5–9 years, limited data are available.[13,14]

Ezetimibe is also used in youth with homozygous familial hypercholesterolemia (HoFH) as an adjunct to statins and apheresis, in sitosterolemia as an adjunct to dietary therapy, in HeFH and mixed hyperlipidemia as an adjunct to dietary changes and statins, or as monotherapy in the rare event statins are not tolerated. While safe and effective, because of its modest ability to lower

Table 1. Novel therapeutic agents for lowering low-density lipoprotein cholesterol.

Therapeutic targets for LDL-C lowering			Mechanism of action
Site of action	**LDL-C contribution**	**Medications**	
Intestine	8–10%	Ezetimibe Colesevelem	Blocks the internalization of the NPC1 L1/cholesterol complex Binds bile acids, prevents reabsorption, and reduces cholesterol stores
Hepatic synthesis	90%	Statins Bempedoic acid	HMG-CoA reductase inhibitor—a rate-limiting step in cholesterol biosynthesis ATP citrate lyase inhibitor—upstream of HMG-CoA reductase inhibition
LDL-R Mediated Metabolism	Two-third of circulating LDL removed by liver	PCSK9 mAb (evolocumab, alirocumab) SiRNA that controls PCSK9 production (inclisiran)	Inhibits PCSK9 mediated LDL-R degradation Inhibits intracellular PCSK9 synthesis in hepatocytes by cleaving mRNA molecules encoding PCSK9
LDL-R independent LDL-C lowering		apoB ASO (mipomersan) MTP inhibitor (lomitapide) ANGPTL3 inhibitors ANGPTL3 mAb (evinacumab) Anti-ANGPTL3 ASO (vupanorsen)	Pairs with apoB mRNA preventing its translation Inhibits MTP—blocks apoB loading onto TG, blocking VLDL assembly and secretion Blocks lipases, promotes VLDL remodeling, causes clearance of VLDL remnants via LDL-R independent uptake—evinacumab as a mAb that blocks ANGPTL3 and vupanorsen by blocking ANGPTL3 synthesis

ANGPTL3, angiopoietin-like 3 protein; apoB, apolipoprotein B100; ASO, anti-sense oligonucleotide; ATP, adenosine triphosphate; HMG-CoA, hydroxymethylglutaryl-coenzyme A; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-R, LDL receptor; mAb, monoclonal antibody; mRNA, messenger RNA; MTP, microsomal triglyceride transfer protein; NPC1 L1, Niemann–Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; SiRNA, small interfering RNA; TG, triglyceride; VLDL, very-low-density lipoprotein.

LDL-C when used as a monotherapy, ezetimibe tends to be a preferred second-line, add-on therapy.

Therapeutic agents that reduce hepatic synthesis of cholesterol

About 90% of cholesterol synthesis occurs in the liver.

Statins. Traditionally, statins have been the primary LDL-C lowering agents, recommended as first-line treatment in all lipid guidelines. Statins act by inhibiting HMG-CoA reductase. In response to reduced intrahepatic cholesterol, LDL receptor (LDL-R) activity is upregulated, enhancing cellular uptake of circulating LDL. They have a favorable safety profile and excellent short- and long-term data with benefits outweighing the risks. The FDA has approved lovastatin (1987), pravastatin (1991), simvastatin (1991), fluvastatin (1993), atorvastatin (1996), rosuvastatin (2003), and pitavastatin (2009)[15] for use in children. The use of these medications is supported by multiple clinical trials,[13,16–25] with significant LDL-C reduction, favorable effect on

ASCVD risk and overall low adverse effects. Recently, long-term follow-up data have showed that initiation of statin therapy during childhood in patients with FH slowed the atherosclerotic progression and reduced the risk of cardiovascular disease in adulthood.[26,27]

Bempedoic acid

Mechanism: Bempedoic acid is a pro-drug which when selectively activated in the liver, inhibits ATP citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase. It primarily lowers LDL-C by competitively inhibiting conversion of mitochondrial-derived citrate to cytosolic acetyl CoA[28] creating less substrate for cholesterol and fatty acid synthesis.[29] It does not utilize the cytochrome P 450 enzyme pathway and is considered relatively safe.

Clinical data: Thus far, five clinical trials have demonstrated the safety of bempedoic acid and bempedoic acid/ezetimibe combination therapy and its efficacy in lowering LDL-C in adults with ASCVD, HeFH and those who are statin intolerant.[30–34] Overall, it lowered LDL-C levels by 15–25% when used alone and up to 38% when combined with ezetimibe. In one of the pivotal studies, patients who received bempedoic acid in addition to a statin experienced a dose-dependent LDL-C reduction of 17–24% compared with placebo.[35] Bempedoic acid also decreased apoB, non-high-density lipoprotein cholesterol (non-HDL-C), and total cholesterol (TC) levels to a greater extent than placebo.[35] The anticipated results of the CLEAR OUTCOMES trial in 2022 (NCT02993406) will determine if treatment with bempedoic acid decreases the ASCVD in adults who are statin intolerant.[36] Bempedoic acid was approved in February 2020 in the United States for treatment of adults with HeFH or established ASCVD who require additional LDL-C lowering. It is administered orally, with or without food, at a dose of 180 mg once daily.[37] Bempedoic acid-ezetimibe combination therapy has also been approved.

Hyperuricemia has been reported with the use of bempedoic acid, secondary to inhibition of renal tubular secretion of uric acid.[37] Adverse events included nasopharyngitis, myalgia, upper respiratory tract infections, dizziness, and diarrhea.[38] In the CLEAR HARMONY trial, adverse events occurred with similar frequency in those who received bempedoic acid and placebo. In addition to uric acid, bempedoic acid was associated with mild increases in blood urea nitrogen and creatinine and decreases in hemoglobin.[39] The risk of myotoxicity and rhabdomyolysis is considered low since the drug is not activated in skeletal muscles.

Pediatric data: Safety and effectiveness have not been established in youth <18 years-of-age.

Therapeutic agents that act through LDL-R-mediated metabolism

This class of medications include PCSK9 inhibitors (PCSK9i)–PCSK9 monoclonal antibodies (PCSK9 mAb) and small RNA molecules that interfering with PCSK9 production (inclisiran).

PCSK9i is an excellent example of groundbreaking research that has been successfully translated from bench-to-bedside. In 2003, a gain-of-function mutation of *PCSK9* was described in individuals with autosomal dominant hypercholesterolemia.[40] In 2005, *PCSK9* sequencing of 128 individuals of African descent with low LDL-C and a history of reduced risk of ASCVD showed two loss-of-function mutations.[41] These findings, corroborated in subsequent studies, were supportive of PCSK9 gain-of-function increasing risk of ASCVD.[42,43]

PCSK9 monoclonal antibodies. Following the completion of multiple compelling clinical trials, PCSK9 mAb were approved in 2015, leading to a paradigm shift in primary and secondary prevention.

Mechanism: PCSK9 mAb strongly bind to circulating PCSK9 preventing it from binding to the LDL-*R* (Figure 1). Inhibition of PCSK9 mediated LDL-R degradation enables the LDL-Rs to return to the surface of the liver. Upregulation of LDL-R activity results in increased catabolism of circulating LDL and reduction of LDL-C levels in the blood.[44]

Clinical data: Evolocumab and alirocumab are the two commercially available PCSK9 mAb. They reduce LDL-C by 60–70% when used alone or in combination therapy with statins.[45–55] They also reduce levels of lipoprotein(a) (Lp(a)] by 18–36% and TG by 12–31%.[52,56–59] Meta-analysis of data from subjects treated with PCSK9 mAb has shown reduced all-cause mortality, cardiovascular mortality, and myocardial infarction.[56,60]
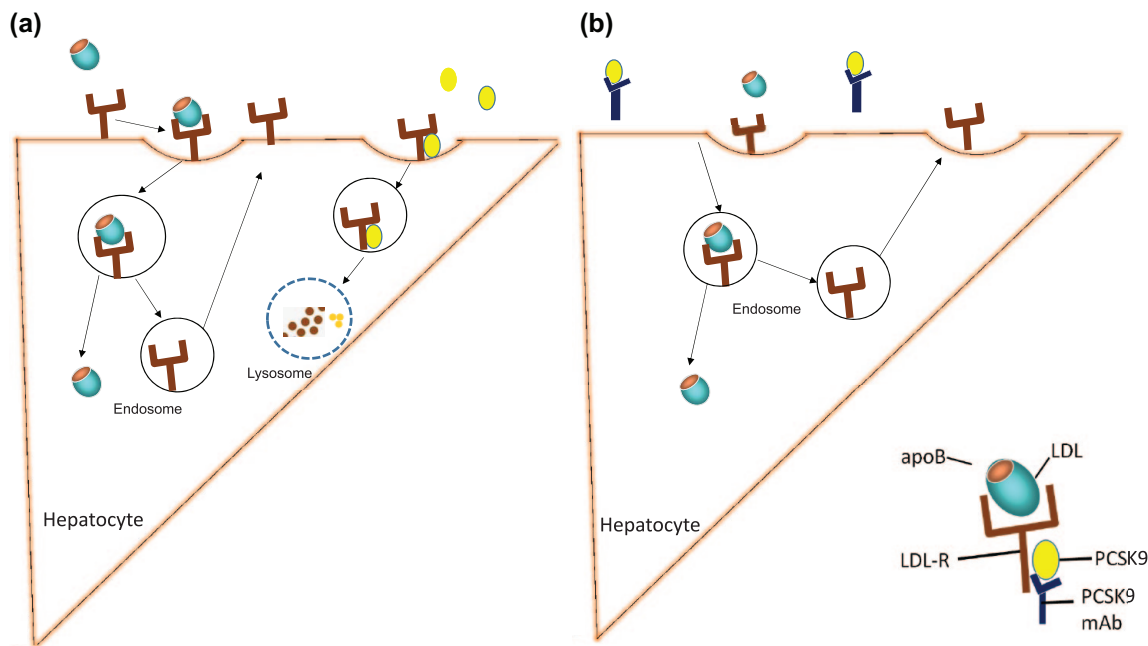
Figure 1. The mechanism of action of PCSK9 inhibitors. (a) Shows that LDL-C attaches to LDL-R to incorporate it into the hepatocyte. This can either be recycled when not attached to PCSK9. When the secreted PCSK9 attaches to the LDL-R, it eventually leads to lysosomal degradation of PCSK9. (b) Illustrates that in the presence of PCSK9 monoclonal antibody, the PCSK9 is inactivated, preventing the LDL-R from being degraded. This allows for the LDL-R to be recycled, prompting LDL-C uptake, and reducing LDL-C levels in the serum. LDL-C, low-density lipoprotein cholesterol; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; mAb, monoclonal antibody; apoB, apolipoprotein B100; mAb, monoclonal antibody.
The inset figure depicts the representation of various components of the figure.

Evolocumab is administered subcutaneously as either 140 mg every 2 weeks or 420 mg once a month.[37] Alirocumab is administered subcutaneously as either 75 mg or 150 mg every 2 weeks or 300 mg once a month.[37] Adverse events include headaches and injection site reactions, nasopharyngitis, influenza, and upper respiratory infections.[50,57,61–64] There have been no reported incident risk of type-2 diabetes.

Pediatric data: Evolocumab is approved in combination with diet and other LDL-C-lowering therapies in youth ⩾12 years-of-age with HoFH who require additional LDL-C lowering. Alirocumab is not yet approved for pediatric use. Current information regarding the efficacy and safety of evolocumab in the pediatric population comes mostly from patients with HoFH. In 2015, the effect of evolocumab as an adjunctive therapy in HoFH was evaluated in the TESLA Part B trial, in which 420 mg of evolocumab administered every 4 weeks was well tolerated and significantly reduced LDL-C.[65] At 12 weeks, LDL-C was lowered by up to 30%.[54,65,66] In 2020, 300

patients with HoFH (14 patients; <18 years of age) or severe HeFH ⩾12 years of age enrolled in the TAUSSIG study were treated with 420 mg monthly.[62] Changes in LDL-C and adverse events were monitored over a period of 4 years. Mean change in LDL-C from baseline to week 12 was 21% in HoFH and 54.9% in those with severe HeFH; and sustained over time. The adjudicated cardiovascular event rate was 2.7% per year.[62] The HAUSER-RCT study of 157 pediatric patients with HeFH reported a mean percent change in LDL-C of 44.5% in the evolocumab group with good drug tolerability.[61]

The ODYSSEY KIDS study, a phase-2 trial, assessed the efficacy, safety, and dose selection of alirocumab in HeFH. Youth 8–17 years of age were included who, despite the use of optimal LLT, had an LDL-C ⩾130 mg/dL.[64] Subjects were divided into four cohorts, utilizing multiple doses with a maximum dose of 300 mg every 2 weeks. At week 8, the cohort receiving the highest dose was found to have the greatest reduction in LDL-C.[64]
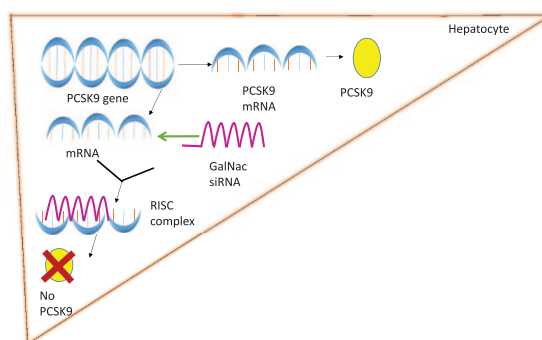
Figure 2. The mechanism of action of Inclisiran within the hepatocyte. Incisiran is an siRNA Blocking PCSK9 Transcription. Inclisiran is conjugated to GalNac for liver specific entry. The PCSK9 gene transcription results in PCSK9 mRNA. Inclisiran binds to PCSK9 mRNA, forms RISC complexes, and thereby promotes PCSK9 mRNA degradation and prevents synthesis of PCSK9.
PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; RNA, ribonucleic acid; mRNA, messenger RNA; siRNA, small interfering RNA; RISC, RNA-induced silencing complex; GalNac, N-acetylgalactosamine.

More clinical trials are underway that are further supportive of the use of these medications in children with HoFH (NCT03510715) and HeFH (NCT03510884). Of these, NCT03510715 is an open-label trial with alirocumab causing significant LDL-C reductions and a favorable safety profile in children with HoFH.

Overall, PCSK9 mAb therapy has demonstrated an ability to substantially lower LDL-C with minimal adverse events. Even when used as monotherapy, PCSK9 mAb has demonstrated robust activity, and there is a monotonic relationship between achieved LDL-C and major cardiovascular outcomes.[67] Evolocumab and alirocumab are fourth-generation IgG monoclonal antibodies that are fully humanized, thus greatly reducing the potential for therapy-associated production of anti-drug or neutralizing antibodies. Current evidence supports their use in individuals with HoFH or HeFH who require additional lowering of LDL-C, despite maximum statin therapy. Response to treatment in those HoFH is variable, depending on residual LDL-R activity (LDL-R defective *vs* LDL-R null).

Both drugs have a favorable safety profile. There are no risks of rhabdomyolysis, myopathy, neutralizing antibodies, or incident risk of type-2 diabetes. Evolocumab administered 420 mg once monthly is approved for >13 years with HoFH in combination with other lipid-lowering therapies. In 2021, FDA has approved its usage to those 10 years and older with HeFH. Alirocumab is not yet approved for youth <18 years of age.

Small interfering RNA (SiRNA) that control PCSK9 production (inclisiran). In 2006, the Nobel Prize in Physiology or Medicine was jointly awarded to Andrew Fire and Craig Mello for their discovery of RNA interference – gene silencing by double-stranded RNA, a discovery eventually responsible for the development of inclisiran.[68] It is an incremental therapeutic advancement from PCSK9 mAb.

***Mechanism*:** Inclisiran is a siRNA, which inhibits intracellular PCSK9 synthesis in hepatocytes (Figure 2).[69,70] SiRNA bind intracellularly to the RNA-induced silencing complex, thus enabling it to cleave messenger RNA molecules that encode PCSK9. This unique mechanism allows them to reduce both intra- and extracellular PCSK9 levels, resulting in an extended reduction of LDL-C. The silencing complex remains active after mRNA degradation contributing toward long-term efficacy. SiRNA delivered to the hepatocyte can interfere with the expression of multiple mRNA molecules. This limits its translation and therefore reduces synthesis of PCSK9, leading to a decrease in serum LDL-C.[70]

Clinical data: The ORION trials studied the utility of inclisiran in clinical practice. ORION-9 included 482 adults with HeFH randomized to either 300 mg inclisiran or placebo at baseline, 3 months and then every 6 months for a total of four doses. The data showed an LDL-C reduction of 47.9% at day 510 and a time-averaged LDL-C reduction of 44.3% over the 18-month trial.[71] Using a similar design, 1,561 patients with ASCVD were assessed in ORION-10 and 1,617 patients in ORION-11.[72] Inclisiran lowered TC, non-HDL-C, apoB and TG as well as reducing Lp(a) by 18.6–25.6%, the latter a known independent, causative CVD risk factor. Though not yet approved for clinical use in the USA, based upon data from these trials, it is anticipated that the subcutaneous dose will likely be 300 mg twice a year. Twice a year dosing will likely enhance adherence to inclisiran.[73] The European Commission granted marketing authorization for inclisiran in Europe in December 2020.[74]

The most frequently reported adverse events include a self-limiting rash, hyperpigmentation, cough, musculoskeletal and back pain, and acute nasopharyngitis.[70,75,76] In one study, serious adverse events occurred in 11% of patients who received inclisiran compared to 8% of those who received placebo. Injection site reactions occurred in 5% of the subjects who received inclisiran.[76]

Pediatric data: In 2016, the initial phase-1 trial in youth was conducted on 24 healthy volunteers with LDL-C greater than 100 mg/dL, utilizing doses ranging from 25 to 800 mg. At 12 weeks, the maximal reduction of the PCSK9 concentration was 74.5% after the 300-mg dose. LDL-C concentration was reduced maximally by 50.6% with a dose of 500 mg.[70] ORION 16 (NCT04652726) is an ongoing clinical trial to evaluate safety, tolerability and efficacy of inclisiran in adolescents with HeFH and elevated LDL-C on stable lipid-lowering therapy, while ORION 13 will assess youth with HoFH (NCT04659863).

LDL-R-independent reduction of LDL-C
The main therapeutic agents in this category include mipomersan, lomitapide, and evinacumab.

Mipomersen. The first antisense oligonucleotide (ASO) to be used in dyslipidemia management, mipomersen, was approved in 2013. It is a second-generation ASO directed toward the coding region of apoB RNA.[77]

Mechanism: Mipomersen inhibits hepatic apoB production by pairing with apoB mRNA, preventing its translation. This decrease in apoB synthesis results in a reduction in hepatic very-low density lipoprotein (VLDL) production, eventually leading to a decrease in levels of LDL.[78,79]

Clinical data: In a phase 3 trial in adults, mipomersen administered subcutaneously to 34 HeFH subjects for 26 weeks significantly reduced LDL-C by 25% from baseline. In a separate trial, 124 subjects with HeFH on maximally tolerated statin were randomized to weekly subcutaneous mipomersen 200 mg or placebo for 26 weeks. In this study, LDL-C was lowered by ~28% and and apoB by 26%.[80] A meta-analysis included six RCTs involving 444 subjects. Compared with the placebo group, patients who received mipomersen therapy had a significant reduction in LDL-C (33.13%), as well as a reduction in non-HDL-C (31.70%), apoB (33.27%), and LP(a) (26.34%).[81] Adverse effects included injection site reactions, flu-like symptoms and elevated liver enzymes.[81]

Pediatric data: In a post hoc analysis of a phase-3 trial, seven HoFH youth between the ages of 12–18 years were randomized to 200 mg weekly of mipomersen for 24 weeks. The three youth who received mipomersen experienced mean reductions from baseline of 43% and 46% in LDL-C and apoB, respectively.[82]

Use of mipomersen in youth has primarily been in those with HoFH with the goal of achieving additional LDL-C lowering in those unable to reach their LDL-C target.[83] In January 2013, the FDA approved mipomersen in the United States as an orphan drug for the management of HoFH, provided physicians registered in a Risk Evaluation and Mitigation Strategy (REMS). In Europe, the Committee for Medicinal Products for Human declined to approve mipomersen for clinical use, citing the potential risks outweighed the benefit of the drug. The product was withdrawn from the market in 2019 secondary to hepatotoxicity.[37]

Microsomal triglyceride transfer protein (MTP) inhibitor: lomitapide. In 2012 lomitapide became the first MTP inhibitor approved by the FDA for HoFH as an adjunct to diet and other lipid-lowering therapies.

Mechanism: Lomitapide works through the inhibition of MTP in the endoplasmic reticulum of hepatocytes and enterocytes (Figure 3). MTP is required for assembly and secretion of apoB-containing lipoproteins in the intestines (chylomicrons) and liver (VLDL). Following hepatic excretion, VLDL is converted to LDL in the circulation. Reduction in VLDL leads to decrease substrate for conversion to LDL[84] and a decrease in measured LDL-C concentration.

Lomitapide was approved by the FDA in 2012.[79] The drug is given orally, once a day, initial as a 5 mg dose. If tolerated, the drug is titrated to a maximum dose of 60 mg a day.[37] The chief adverse events of lomitapide include diarrhea and hepatic steatosis—both likely linked to the intracellular increase in TG associated with impaired assembly and secretion of apoB-containing lipoproteins. Close monitoring of dietary fat intake is required with use of lomitapide.
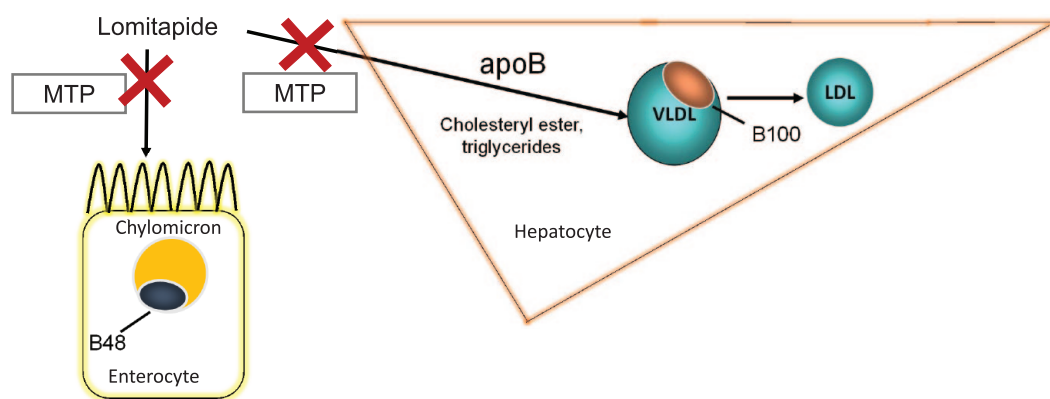
Figure 3. The mechanism of action of lomitapide. MTP is required for assembly and secretion of apoB-containing lipoproteins in the liver (apoB100) and intestine (apoB48). After production in the liver, VLDL is released into the plasma, where the TG content of the VLDL is hydrolyzed into free fatty acids, eventually forming LDL. By inhibiting MTP, lomitapide reduces the production and release of VLDL and LDL levels in plasma while at the same time reducing TG levels by reducing intestinal chylomicron formation.
MTP, microsomal triglyceride transfer protein; apoB, apolipoprotein B; VLDL, very-low density lipoprotein; LDL, low-density lipoprotein; mAb, monoclonal antibody; TG, triglyceride.

Clinical data: Lomitapide has been shown to lower LDL-C by more than 50%.[85] The long-term safety and efficacy of lomitapide in HoFH has been reported in several clinical trials. In a dose-dependent manner, lomitapide reduced LDL-C by 46–51% and apoB by 24–56%.[86–88] It also reduced TC by 25%, TG by 55% and non-HDL-C by 47%.[89] In a phase-3 trial involving 29 European adults, approximately three quarters of subjects treated with lomitapide for at least 2 years reached LDL-C goals of 100 mg/dL.[90]

Adverse events include gastrointestinal symptoms, liver dysfunction, and hepatic steatosis.[85,91,92] Lomitapide impair the absorption of fat-soluble vitamins as well.[93] Because a high-fat meal can potentiate GI side effects, dietary fat should be limited in individual receiving this drug. In pediatric case series, GI side effects included nausea, vomiting, and reduced appetite. Two youth had thickened cardiac valves.[94]

Pediatric data: In youth, a case series demonstrated improvement in LDL-C in 11 subjects with HoFH whose mean LDL-C at baseline was greater than 400 mg/dL. Following the addition of lomitapide, six subjects achieved their target LDL-C of less than 135 mg/dL.[94] The safety and efficacy of lomitapide in youth with HoFH is being evaluated in an ongoing clinical trial. (NCT04681170)

Lomitapide is approved for treatment of adults with HoFH through REMS. Used with caution, the drug has the potential of mitigating ASCVD risk, especially in those who do not meet their LDL-C targets with statins, ezetimibe, resins, and PCSK9i. In addition, it may improve quality of life by reducing the need for or frequency of lipid apheresis, and provide an alternative to those who do not have access to or decline apheresis. At this time, lomitapide it is not approved for pediatric use.

Inhibition of angiopoietin like 3 (ANGPTL3). The role of ANGPTL3 in lipoprotein metabolism was initially defined in obese KK mice. This mouse model exhibits a mutant phenotype characterized by abnormally high levels of plasma insulin (hyperinsulinemia), glucose (hyperglycemia), and lipids (hyperlipidemia), although one strain (KK/San) was found to have abnormally low plasma lipid levels (hypolipidemia).[95] When the region including *ANGPTL3* loss-of-function variant was introduced to atherogenic apoE-knock out mice, the prevalence of baseline atherosclerotic lesions declined.[96] In human studies, genetic variants in *ANGPTL3* showed a strong association between plasma levels of *ANGPTL3* and TG.[97] Addition publications support the association of ANGPTL3 loss-of-function and low cholesterol levels.[98,99] These findings support development of drugs targeting ANGPTL3 inhibition as a therapeutic strategy.
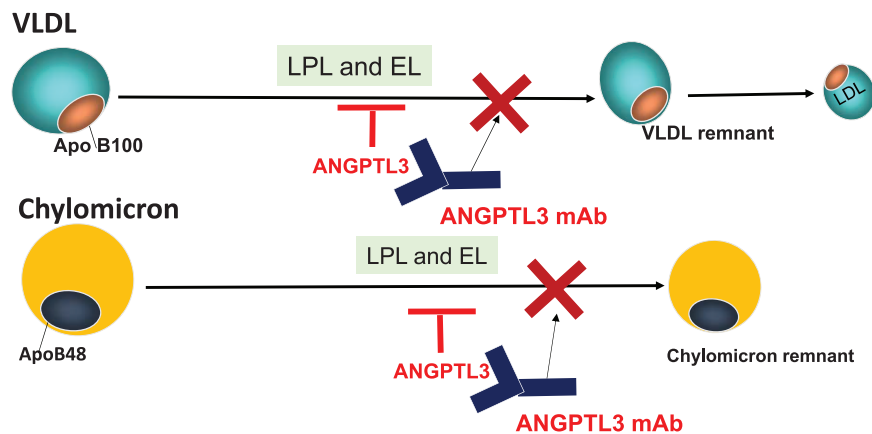
Figure 4. Mechanism of action of ANGPTL3 inhibition. ANGPTL3 is synthesized and secreted by hepatocytes. It inhibits LPL and endothelial lipase and thereby regulates the concentrations of apoB-containing lipoprotein turnover – namely VLDL, IDL and LDL. Since it causes clearance of triglyceride-rich lipoproteins upstream of LDL production, it can cause an LDL-R independent reduction in apoB-containing lipoproteins.
ANGPTL3, Angiopoietin-like 3 protein; LPL, lipoprotein lipase; EL, Endothelial lipase; VLDL, very-low density lipoprotein; LDL, low-density lipoprotein.

Mechanism: Normally, ANGPTL3 inhibits lipases–LPL and endothelial lipase (EL). ANGPTL3 binds LPL attached to the cell surface, promotes dissociation and induces the cleavage of the enzyme – this causes reduced clearance of TG-rich lipoproteins (TRLPs). It regulates apoB-containing lipoprotein turnover. EL is an extracellular lipase, which increases the catabolism of high-density lipoprotein (HDL) particles.

Monoclonal antibodies, which target ANGPTL3, inhibit both lipases and promotes VLDL remodeling, causing preferential removal of TRLPs. As a consequence, reduced levels of VLDL limit LDL production, and lower circulating LDL-C.[100,101]

Evinacumab: This fully humanized ANGPTL3-blocking monoclonal antibody works by binding and reducing the activity of ANGPTL3 (Figure 4).

Clinical data: In adult studies, LDL-C was reduced by 45–50% with the use of evinacumab;[102–105] and in those with HTG, a dose-dependent TG reduction of 77–83%.[106]

Reported adverse events with use of evinacumab included headache and upper respiratory infections. Urinary tract infection, arthralgia, and myalgia also occurred. Elevated liver enzymes have reported in some individuals treated with evinacumab.[103,107,108]

Pediatric data: Prior studies of adolescents with HoFH 12 years-of-age or older showed a decrease in LDL-C of 47%.[102] Clinical trials are currently assessing evinacumab in youth with HoFH between the ages of 5–11 years (NCT04233918).

Evinacumab has been shown to be effective as an adjunctive therapy in HoFH and HeFH patients receiving maximally tolerated doses of statin; and approved for youth ≥12 years with HoFH in February 2011.[109] Efficacy is dependent upon residual LDLR activity (defective > null). However, some lipid-lowering effect may be seen in those with complete absence of the LDL-*R* (null-null variants), a group relatively unresponsive to PCSK9 inhibition. For youth 12 years of age and older, evinacumab is administered intravenously at a dose of 15 mg/kg/dose every 4 weeks.

Clinical application: In general, the need for new and novel therapeutic agents is less critical in youth with hypercholesterolemia since statins have been shown to be both effective and safe, and unlike the experience in adults, rarely associated with side effects. All commercially available statins are FDA approved with pravastatin, rosuvastatin, and pitavastatin starting at age 8 and all others at age 10, for treatment of persistently elevated LDL-C ≥160 mg/dL after 3–6 months of lifestyle modification and clinical findings consistent with FH.[110] At this time, some of the newer agents could be considered in specific pediatric patients.

For example, in patients with HoFH who cannot reach the recommended LDL-C levels with current lipid-lowering therapies, the management approach may include maximally tolerated high intensity statin along with ezetimibe and BAS. If feasible, plasmapheresis weekly/ biweekly is recommended in this scenario. If the LDL-C is still elevated, drugs acting through LDLR such as a PCSK9 inhibitor (i.e., evolocumab from age 13 and alirocumab from age 18) can be tried. Drugs acting independently of LDL-R such as ANGPTL3 inhibition (evinacumab from age 12) and lomitapide from age 18 can also be considered. With the degree of LDL-C reduction, although improvement in long-term clinical outcomes is expected. Comparative studies to understand the sequence in which these advanced therapies should be selected are needed.

Therapeutic agents to lower TG

Historically, effective therapies that target TG lowering have been challenging. Fibrates, though not approved for use in youth less than 18 years-of-age, have been extensively used for treatment of hypertriglyceridemia (HTG) in adults. There is no evidence in youth that omega-3-fatty acids (O3FAs) have been effective in the treatment of mild-to-moderate HTG. Several promising investigational therapeutic agents, which act through the lipoprotein lipase (LPL) complex, are currently in development: (1) antisense oligonucleotides (Volanesorsen® and AKCEA-APO-CIII-LRx) which reduce apoC3 and (2) Monoclonal antibodies (evinacumab) and GalNac conjugated ASO which targets ANGPTL3 mRNA in the liver (Vupanorsen/IONIS-ANGPTL3-LRX). Lomitapide, which inhibits MTP and is currently approved for treatment of HoFH as an adjunct to diet and other lipid-lowering therapies, can also lower TG. While O3FAs are generally of limited benefit in youth, iIcosapent ethyl (VASCEPA®), an ethyl ester of eicosapentaenoic acid (EPA), has been used by some for management of HTG. Safety and effectiveness of icosapent ethyl in youth have not been established. Table 2 illustrates novel medications lowering TG levels.

Inhibition of apoC3

Antisense oligonucleotide (ASO) inhibiting apoC3 (Volanesorsen). Mechanism: Volanesorsen is a second-generation antisense oligonucleotide. It selectively binds the apoC3 messenger ribonucleic acid (mRNA), preventing translation and allowing mRNA degradation, thereby promoting TG clearance and the lowering plasma TG levels through LPL-independent pathways (Figure 5). The results of early clinical trial data were quite promising.[111–113]

ApoC3 is an apolipoprotein synthesized in the liver, and a component of atherogenic TG rich lipoproteins (TRLPs) such as VLDL, chylomicrons and remnant lipoproteins. ApoC3 affects TG levels by inhibiting of LPL dependent and independent pathways. It may also directly regulate enterocyte metabolism of TGs. It reduces receptor-mediated clearance of TRLPs by the liver, inhibits hepatic lipase, and increases intrahepatic assembly and secretion of TG rich VLDL. In humans, loss-of-function mutations of the *APOC3* gene results in lower levels of plasma TG and LDL-C, increased HDL-C levels and reduced ASCVD risk.[114]

Clinical data: In clinical trials of individuals with genetically confirmed familial chylomicronemia syndrome (FCS), volanesorsen lowered TG levels below 750 mg/dL in 77%–overall, TG levels were reduced by 53% at 6 months and 40% at 12 months.[115] Clinical studies in individuals with non-FCS HTG also experienced significant TG lowering.[116] In addition, efficacy in a small study of individuals with familial partial lipodystrophy reported reduction in apoC3 of 88% and TG by 69%, while HDL-C increased 42%.[117]

Despite the impressive ability of volanesorsen to lower TGs, the occurrence of thrombocytopenia and injection-site reactions have raised concerned about its use. Up to 30% of subjects discontinued use of the drug in phase-3 studies due to unpredictable thrombocytopenia, which required the drug administration schedule to be changed, interrupted or discontinued. The European Medicines Agency gave conditional marketing authorization of the drug for patients with confirmed FCS provided that extra data were collected in a registry study.[118] In 2018, the US FDA refused to approve volanesorsen for the treatment of FCS based on safety issues of thrombocytopenia and risks of bleeding. No pediatric data are available.

Antisense oligonucleotide inhibiting apoC3 with GalNac adult (AKCEA-APOC3-L$_{Rx}$)

Mechanism: AKCEA-APO-CIII-L$_{Rx}$ is a third-generation ligand-conjugated antisense (LICA) drug with an N-acetylgalactosamine-containing additive (GalNac). The drug targets *APOC3*. It is anticipated

Table 2. Medications lowering triglyceride levels.

Therapeutic target/agent	Medications	TG-lowering mechanism
Fibric acid derivatives	Gemfibrozil	Decrease VLDL-C production and increase LPL activity
	Fenofibrate	
Omega 3 Fatty acid	EPA/DHA	Inhibit DGA, reduce VLDL-C synthesis, and increase rate of peroxisomal beta oxidation in the liver
	Icosapent ethyl	
ApoC3	Volanesorsen (ASO)	Targets mRNA to reduce apoC3 production Eventually promotes hydrolysis of TG by LPL
	Anti apoC3 ASO conjugated to GalNac	
MTP	Lomitapide	Reduces intestinal chylomicron and hepatic VLDL and LDL production
ANGPTL3	Evinacumab (ANGPTL3 mAb)	Blocks lipases, promotes VLDL remodeling ASO reducing ANGPTL3 synthesis
	Vupanorsen (ASO targeting ANGPTL3 mRNA in the liver)	

ANGPTL3, angiopoietin-like 3 protein; ApoC3, apolipoprotein C3; ASO, antisense oligonucleotide; DGA, diacylglycerol acyltransferase; DHA, docosahexanoic acid; EPA, eicosapentanoic acid; GalNac, triantennary *N*-acetyl galactosamine; LDL, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; mAb, monoconal antibody; mRNA, messenger RNA; MTP, microsomal triglyceride transfer protein; TG, triglyceride; VLDL, very-low-density lipoprotein.
None of these medications shown are FDA approved for children <18 years-of-age.

to increase first pass clearance, and lower the risk of thrombocytopenia due to higher tissue selectivity. Because of its longer half-life, lower dosing preparations may be required for effective TG lowering, a potential advantage over Volanesorsen.[119]

Clinical data: Clinical trials have shown dose-dependent mean reductions in fasting apoC3 and TG levels.[120] No injection site or flu-like reactions, renal impairment, or thrombocytopenia were noted in these studies. Adult Phase-3 trials to evaluate the efficacy of AKCEA-APOC3-L$_{Rx}$ on TG lowering are underway (NCT04568434). Since this technology is in its initial stages, there are no pediatric data or ongoing pediatric clinical trials at this time.

Inhibition of angiopoietin like 3 (ANGPTL3)
This class of therapeutic agents is capable of lowering both LDL-C and TG.

Evinacumab. This fully humanized ANGPTL3-blocking monoclonal antibody can reduce both LDL-C and TG (please refer to the section on LDL-C lowering). In 2002, ANGPTL3 knock out mice were shown to have abnormally low lipid levels. By 2010, ANGPTL3 loss-of-function carriers were shown to have extremely low levels of LDL-C, VLDL-C, HDL-C, and TGs. These findings lend support to drug development targeting inhibition of ANGPTL3 as a therapeutic strategy (See 1.a.3. Inhibition of Angiopoietin Like 3 (ANGPTL3) for additional details.)

Antisense oligonucleotide (ASO) targeting ANGPTL3 mRNA in the liver
Mechanism: Vupanorsen (formerly known as IONIS-ANGPTL3-LRx and AKCEA-ANGPTL3-LRx) is an antisense oligonucleotide targeted to the liver, which selectively inhibits ANGPTL3 protein synthesis. The drug's down-
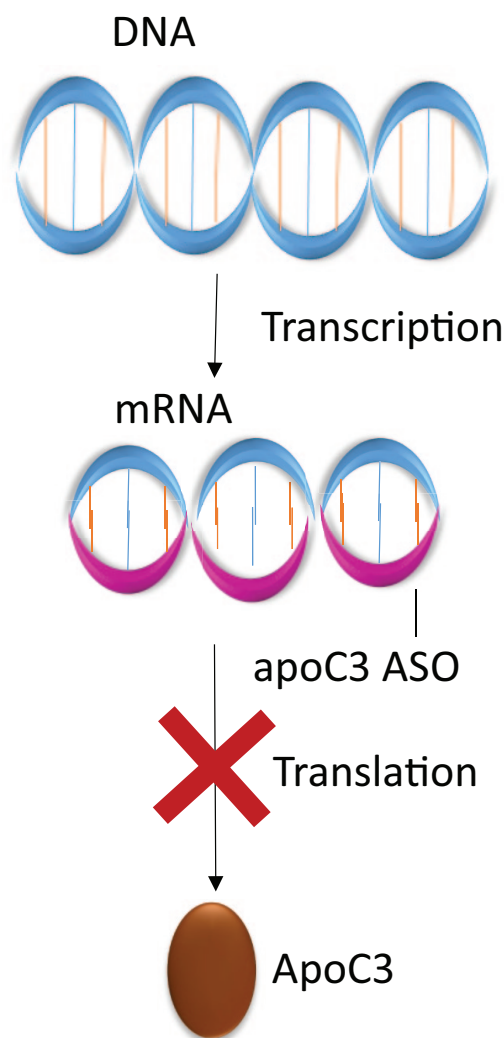
Figure 5. The mechanism of action of an ASO targeting apoC3. Volanesorsen is an ASO that binds to apoC3 mRNA, leading to its degradation, and preventing translation of apoC3 protein. This allows ribonuclease H1-mediated mRNA degradation, thereby promoting TG clearance through LPL-independent mechanisms.
ASO, anti-sense oligonucleotide; apoB, apolipoprotein B100; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; mRNA, messenger RNA; apoC3, apolipoprotein C3; TG, triglyceride; LPL, lipoprotein lipase.

stream mechanism of action is, therefore, similar to evinacumab.

Clinical data: A phase-2 study with vupanorsen in individuals with HTG and hepatic steatosis showed a 36–56% reduction in serum TG levels, 38% reduction in remnant cholesterol, 19% reduction in TC, 18% reduction in non-HDL-C, and 9% reduction in apoB. The most frequent adverse events were erythema and pruritus at the injection-site.

With TRLPs increasing recognized as being associated with increased ASCVD risk,[121] potent TG, and non-HDL-C lowering therapy such as vupanorsen could provide additional cardiovascular benefits. No pediatric data or ongoing trials in youth are available at the time.

Lomitapide

Lomitapide can reduce levels of both LDL-C and TG (See d.2. Microsomal TG transfer protein (MTP) inhibitor: lomitapide for more details)

Icosapent ethyl: Vascepa®

Mechanism: Icosapent ethyl is a purified eicosapentaenoic acid (EPA). It reduces hepatic synthesis and/or secretion of VLDL-TG) and enhances TG clearance from circulating VLDL particles.[122] It received initially approved by the FDA in 2012 for adults with severe HTG.

Clinical data: In 2011, the MARINE study evaluated 229 adults with fasting $TG > 500$ mg/dL. With a baseline TG level >750 mg/dL, icosapent 4 g/day reduced the placebo-corrected TG levels by 45%. Both 2 and 4 g per day of icosapent lowered non-HDL and VLDL-C.[123] Bhatt *et al.* performed a multicenter, randomized, double-blind, placebo-controlled trial of 8000 adults with established CVD, diabetes and elevated fasting TG who were receiving statin therapy. A total of 8179 adults were enrolled and followed for 4 years with a primary endpoint of cardiovascular death, stroke, or myocardial infarction. A primary endpoint event occurred in 17.2% in the icosapent ethyl group, compared with 22.0% in the placebo group.[124] The ANCHOR study demonstrated that 4 and 2 g/day significantly decreased TG levels by 21.5% ($p < 0.0001$) and 10.1% ($p = 0.0005$), respectively. In the REDUCE-IT Cardiovascular Events, Vascepa reduced CVD-related events by 25% in patients with either CVD or diabetes mellitus.[125] The most common treatment-emergent adverse events were gastrointestinal (i.e. diarrhea, nausea, and eructation).[123] Individuals with shellfish allergies should avoid Vascepa. In the REDUCE-IT trial, a larger percentage of those in the icosapent ethyl treatment *vs* the placebo group were hospitalized for atrial fibrillation or flutter.[124]

Pediatric data: The pharmacokinetics of icosapent ethyl has not been studied youth less than 18 years of age. Engler *et al.*[126] have shown that DHA can lower low-density lipoprotein subclass 1 and high-density lipoprotein subclass 2. Omega-3 fatty acid (O3FA) supplementation can have beneficial effects on preclinical atherosclerosis markers in youth with CVD risk factors, including increased artery vasodilation.[127] Therefore, it has been suggested that the use of O3FA dietary supplements in youth may improve future cardiovascular outcomes.

In a Commentary by the ESPGHAN Committee on Nutrition, addressing the various health claims made to support the use of O3FA in children, insufficient evidence was found toward supplementation of long-chain polyunsaturated fatty acids on cognitive function, attention-deficit hyperactivity disorder (ADHD), visual function in phenylketonuria, major clinical outcomes in cystic fibrosis or in asthma.[128]

Vascepa has been approved as an adjunct to diet to reduce TG levels in adults with severe HTG ($\geq$500 mg/dL). It is not approved for pediatric use at this time.

Clinical application: Management of hypertriglyceridemia varies depending on the severity of HTG. In the case of TG between 150–399 mg/dL, statins are the first line of therapy in addition to dietary and lifestyle changes. The treatment goal is non-HDL-C < 130 mg/dL to reduce premature CVD risk. In the case of moderate HTG 400–999 mg/dL, fibrates are used along with dietary and lifestyle changes. The role of O3FA in pediatric HTG is still being evaluated. Although urgently needed, particularly in those with severe HTG (hyperchylomicronemia), currently, there are no FDA-approved TG-lowering medications in youth. Currently, in patients with severe HTG strict dietary fat restriction is the standard of care treatment. Theoretically, Evinacumab, which is approved for HoFH from age 12, could reduce TG in hyperchylomicronemia. In patients older than 18, lomitapide and volanesorsen are also clinical options in Europe for FCS and severe hypertriglyceridemia.

Novel agents that target elevated Lp(a)
The National Lipid Association recommended Lp(a) be selectively measured in youth <20 years of age: (1) in clinically suspected or genetically confirmed FH; (2) if there is a significant family history of ASCVD; (3) a history of ischemic stroke of unknown etiology; or (4) if there is a family history of a parent or sibling with elevated Lp(a).[129,130] At present, screening for Lp(a) is limited, which may be due a lack of uniformity in Lp(a) screening guidelines among various professional organizations, an incomplete understanding of age-based normative values and treatment goals, and lack of commercially available targeted Lp(a) therapeutic agents. However, pending the result of ongoing clinical trials, this may change.

Of the agents mentioned above, PCSK9i, inclisiran, mipomersan, and APO(a)-L$_{Rx}$ antisense therapy can all potentially reduce Lp(a) levels.[131] On an average, the PCSK9 inhibitors can reduce Lp(a) by 20–25%[132–134] and inclisran by 17%.[72] The ASOs targeting hepatic *LPA* messenger RNA by conjugation with GalNAc$_3$, named APO(a)-L$_{Rx}$ specifically reduced plasma levels of Lp(a) by 66–92% in a dose-dependent in participants with established cardiovascular disease and elevated Lp(a) levels.[135]

While statins significantly reduce LDL-C levels, in some, they may modestly increase Lp(a). The overall cardiovascular impacts of these effects are incompletely understood. Although niacin and estrogen can both reduce Lp(a) levels, neither is recommended for this indication.[131]

Conclusion
Over the past two decades, improvements in our knowledge of genetic disorders and advances in biomedical technology have prompted the discovery of novel targets for management of acquired and genetic lipid and lipoprotein disorders. This collaboration of basic science, biotechnology, and robust clinical research has facilitated the development of an increasing number of new therapeutic options to aid in ASCVD prevention. While several safe and effective therapeutic options are currently available for use in youth, more are needed, especially in those with TG elevations. Development of novel therapeutic agents and their subsequent approval for clinical use should include youth less than 18 years of age. While data from adult clinical trials are informative, more studies are needed in the pediatric population. If proven safe and effective, early intervention with newer therapeutic alternatives and additives have

the potential of significantly reducing CVD risk and prevention of future ASCVD-related events in this unique population.

Author contributions
B.S. drafted the initial manuscript, and reviewed and revised the manuscript. A.P.A. conceptualized and designed the manuscript, drafted some sections of the manuscript, and critically reviewed the manuscript for important intellectual content. C.F. and D.P.W critically reviewed the manuscript for important intellectual content and revised the manuscript.

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