Research advances in current drugs targeting hyperlipidemia (Review)

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Abstract. Hyperlipidemia is a disorder of lipid metabolism. With rapid economic development, unhealthy diets and lack of exercise, the incidence of hyperlipidemia has been increasing year by year. In adults, hyperlipidemia is a major risk factor for cardiovascular diseases, especially atherosclerotic cardiovascular disease (ASCVD), and the current goal of treating hyperlipidemia is to prevent and manage ASCVD. In terms of etiology, hyperlipidemia is divided into primary and secondary types. Common primary hyperlipidemias include familial hypercholesterolemia, mixed familial hyperlipidemia, type III hyperlipoproteinemia and familial chylomicronemia syndrome. In addition to statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors, a number of new and emerging drugs for lowering cholesterol and triglycerides are being developed to regulate lipid levels and prevent cardiovascular diseases. The present review summarized the classification and composition of lipoproteins, the pathogenesis of common primary hyperlipidemias, secondary factors affecting dyslipidemia, modern common lipid-lowering drugs and the latest clinical progress in emerging lipid-lowering therapies.

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1. Introduction

Hyperlipidemia (HLP) is a common lipid metabolism disorder and dyslipidemia (1-4). Blood lipids refer to the total cholesterol, triglycerides (TG) and lipids in the serum. The main characteristics of HLP are elevated levels of total cholesterol, TG, and low-density lipoprotein cholesterol (LDL-C) in the blood, along with a decrease in high-density lipoprotein cholesterol (HDL-C) levels (5). Due to the fact that blood lipids are not soluble in water, they must combine with proteins called apolipoproteins (Apo) to form lipoproteins in order to dissolve in the blood and be transported to tissues for metabolism (6). Lipoproteins can be classified into chylomicrons (CM), very low-density lipoprotein (VLDL), intermediate-density lipoprotein, LDL, high-density lipoprotein (HDL) and lipoprotein(a) [Lp (a)] (7-17). The classification, main components, sources and functions of lipoproteins are shown in Table I. HLP also represents an abnormality of lipoproteins.

Cardiovascular disease (CVD) is the leading chronic non-communicable disease threatening human life and health in modern society (18,19), including atherosclerosis, stroke and myocardial infarction. Atherosclerosis is a chronic disease that primarily occurs in medium or large arteries, caused by the accumulation of lipids and complex carbohydrates in the vascular endothelium, forming hard structures known as plaques, which can lead to narrowing of the vascular lumen and ultimately result in deformation or even death of myocardial cells (20,21). HLP is one of the independent risk factors for atherosclerotic CVD (ASCVD) (21). A previous study demonstrated that the prevalence of dyslipidemia has markedly increased in low- and middle-income countries, especially in East and Southeast Asia (22). Since 2012 to 2018, the prevalence of dyslipidemia among adults in China has remained at high levels (23-26). In China, 26% of patients with ASCVD are classified as very high-risk (27). Preventing and treating HLP is an effective and commonly used method to reduce the incidence of CVD (28,29).

With the in-depth understanding and research of the molecular basis and genetic origins of dyslipidemia, the treatment options for dyslipidemia are continuously increasing. This present review summarizes the classification and pathogenesis of HLP, as well as the latest clinical research progress on statins, ezetimibe, proprotein convertase subtilisin/kexin type

9 (PCSK9) monoclonal antibodies, volanesorsen targeting ApoC3, bile acid sequestrants and various other drugs including evinacumab that can lower LDL-C, along with newly launched and other emerging drugs, providing reference for the treatment of HLP and its associated diseases and drug research.

2. Classification of the causes of primary HLP

Primary HLP refers to lipid abnormalities caused by non-secondary factors (such as unhealthy diet, diseases and medications), usually resulting from mutations in a single gene or multiple genes, and is characterized by familial clustering and has a considerable genetic tendency, especially in cases of single gene mutations (Table II).

Familial hypercholesterolemia (FH). FH is an autosomal, single-gene hereditary disorder of cholesterol metabolism, usually inherited in a dominant manner, with recessive inheritance being relatively rare (30). It is one of the most common single-gene genetic disorders (31). Its characteristic is an increase in LDL-C (32), this is mainly caused by genetic defects in the LDL clearance pathway. The three most common explicit genetic factors are: LDL receptor (LDLR), ApoB and PCSK9, among which the most common is the LDLR gene mutation, accounting for ~90%. LDLR gene mutations leads to a decrease in LDLR activity (33). Secondly, pathogenic mutations of ApoB account for 5-10% and the proportion is higher among patients in China (34), this gene mutation impairs ligand-receptor mediated LDL binding (33); PCSK9 accounts for ~2% (35), PCSK9 can lead to the degradation of LDLR, therefore, gain-of-function mutations in the PCSK9 gene can also increase LDL by weakening LDLR activity (33). Mutations in the ApoB and PCSK9 genes rarely lead to hypercholesterolemia (36,37). Extremely rare recessive hypercholesterolemia is caused by homozygous mutations in the gene encoding LDLR adaptor protein 1 (36).

FH includes heterozygous FH (HeFH) and homozygous FH (HoFH), with HeFH being more common. A systematic review and meta-analysis reported that the overall prevalence of FH in the HeFH group is 1 in 200-250 individuals, while in the HoFH group it is 1 in 100,000-160,000 individuals (38). Due to the high cholesterol levels from birth, patients with FH have a markedly increased risk of cardiovascular disease, with severe atherosclerotic events occurring even in early childhood, leading to premature mortality (32,39-41). Although the majority of patients with FH have hypercholesterolemia caused by a single gene, there are still several patients with FH whose hypercholesterolemia is caused by polygenic, environmental or unknown single-gene factors (39). With the development of gene sequencing technology, more and more genes such as signaling transducer and activator of transcription 1, lysosomal acid lipase and apolipoprotein E (ApoE) have been considered potentially associate with the pathogenesis of FH (42).

Mixed familial HLP (FCHL). FCHL is caused by polygenic inheritance with a complex genetic pattern, characterized by elevated levels of ApoB100 and TG in plasma (43-47). FCHL may be caused by a lipid disorder, where adipocytes have a poor ability to retain TGs, leading to an increased release of free fatty acids (48,49). The lipid genes located on chromosome 11 and genes associated with endoplasmic reticulum VLDL processing (such as uncoupling stimulus factor 1) exacerbate this phenotype (47). In addition, upstream transcription factor 1 is also associated with FCHL (50).

Familial dysbetalipoproteinemia (FD). FD, also known as type III hyperlipoproteinemia, is a hereditary lipid disorder with low penetrance associated with ApoE mutations (51,52). ApoE can bind to LDLR and heparan sulfate proteoglycan receptor with high affinity (52,53), ApoE can inhibit the breakdown of lipoprotein lipase (LPL) and TG-rich lipoproteins (54), high ApoE levels are associated with cardiovascular and cancer mortality, while low ApoE levels are linked to mortality associated with dementia (51,55).

There are three common alleles of ApoE, namely ε2, ε3 and ε4, which can form six genotypes (ε2ε2, ε2ε3, ε2ε4, ε3ε3, ε3ε4 and ε4ε4). FD characteristics include mixed HLP, which is characterized by elevated cholesterol and TGs in the plasma and can also present primarily as hypercholesterolemia or hypertriglyceridemia (HTG), associated with an increased risk of ASCVD (51). The main genetic mutation of FD is the homozygosity of the ε2 allele (ε2ε2 genotype), but only 15% of patients with ε2ε2 will develop FD (52). Compared with ε3 homozygotes, the majority of ε2 allele carriers have lower LDL-C levels and higher TG levels, with ε2 homozygotes having even higher TG levels (52). The risk of coronary heart disease and stroke is reduced for ε2 carriers, but the risk for ε2 homozygotes is not reduced (56-58). The ε4 allele is associated with elevated LDL-C levels and the risk of coronary heart disease and stroke (56,57). In addition, the ε4 allele is also associated with Alzheimer's disease (59).

Familial chylomicronemia syndrome (FCS). CM and VLDL are collectively referred to as triglyceride-rich lipoprotein (TRL), which is one of the CVD risk factors for certain special populations (8-12). TRL is cleared by LPL located in the capillaries of adipose tissue and muscle, and the hydrolyzed fatty acids are stored in these adipose tissues and capillaries or used for fuel. FCS, a rare autosomal recessive genetic disorder, is usually caused by homozygous or compound heterozygous mutations in the LPL gene that lead to loss of LPL function or reduced function (60,61), which can lead to the accumulation of CMs in the plasma and HTG. FCS caused by loss-of-function mutations in the ApoC2, ApoA5, GPIHBP1 and LMF1 genes is even rarer (60,61). Compared with patients with non-LPL mutations, those with LPL mutations often have increased TG levels. Due to lifelong persistent chylomicronemia, patients with FCS have an increased likelihood of developing acute pancreatitis (62).

Others. In addition to the aforementioned four common types of primary HLP, there are also Tangier disease (ApoA-I deficiency) (63), familial lecithin-cholesterol acyltransferase (LCAT) deficiency (64) and other types of primary HLP which are beyond the scope of the present review.

3. Secondary HLP

Secondary HLP is dyslipidemia caused by unhealthy diet, systemic diseases or medications. In this section, the effects of

Table I. Classification, main components, sources and functions of lipoproteins.

First author/s, year	Classification	TG, %	FC and CE, %	PL, %	Apolipoprotein		Sources	Functions	Other	(Refs.)
					Main	Other				
Corvilain, 1997; Errico *et al*, 2013	CM	90-95	2-5	2-5	B48	A, A2, A4, A5	Small intestine synthesis	Transport triglycerides and cholesterol from the small intestine to other tissues.	The largest lipoprotein in the blood, with the lowest density.	(6,7)
Mach *et al*, 2020; Chapman *et al*, 2011 Chait *et al*, 2020; Vallejo-Vaz *et al*, 2018; Raposeiras-Roubin *et al*, 2021	VLDL	50-70	15-20	12-15	B100 C3, E, A5	A1, C2,	Liver synthesis	Transport endogenous triglycerides to peripheral tissues, releasing free fatty acids after lipase hydrolysis.	Together with CM, they are collectively referred to as triglyceride-rich lipoprotein (TRL), which is one of the CVD risk factors for certain special populations (such as patients with diabetes) apart from LDL-C.	(8-12)
Corvilain, 1997; Errico *et al*, 2013	IDL	25-40	25-40	15-25	B100	C2, C3, E	Forms after the hydrolysis of TG in VLDL by lipase.	LDL precursor	N/A	(6,7)
Borén *et al*, 2020	LDL	4-6	40-50	22-26	B100		Forms after the hydrolysis of TG by lipase in VLDL and IDL.	The main carrier of cholesterol is taken up and utilized by peripheral tissues mediated by LDL receptors.	Carries out a key role in the occurrence and development of atherosclerosis.	(13)
Gotto *et al*, 2004	HDL	7	15-25	55	A1	A2, C3, E, M	Mainly synthesized in the liver and small intestine.	Transporting cholesterol to the liver or other tissues.	The smallest particles of lipoprotein are negatively associated with coronary heart disease.	(14)
Li *et al*, 2022; Mehta *et al*, 2022; Ong *et al*, 2021	Lp (a)	4-8	40-55	17-24	Apo(a)	B100	Complex formed by Apo(a) with LDL through disulfide bonds in the liver or outside the liver.	The function is unclear.	Lp (a) is an independent risk factor for atherosclerotic CVD and calcific aortic valve stenosis.	(15-17

CVD, cardiovascular disease; CM, chylomicrons; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp (a), lipoprotein(a); TG, triglycerides; FC, free cholesterol; CE, cholesteryl ester; PL, phospholipids; Apo(a), Apolipoprotein(a); TRL, triglyceride-rich lipoproteins; N/A, not available.

Table II. Classification of primary hyperlipidemia, pathogenic genes and their effects on blood lipids.

First author/s, year	Disease name	Pathogenic genes	Effects on blood lipids	(Refs.)
Vrablik *et al*, 2020; Sun *et al*, 2018;	HeFH	LDLR, ApoB, PCSK9	LDL-C increased	(33-36)
Benito-Vicente *et al*, 2018; Sawhney and Madad, 2024	HoFH	LDLR, ApoB, PCSK9, LDLRAP1	LDL-C increased	
Wierzbicki *et al*, 2022; Naukkarinen *et al*, 2006	Mixed familial hyperlipidemia	UCP1, USF1	LDL-C and VLDL-C increased	(47,50)
Heidemann *et al*, 2022; Koopal *et al*, 2017	Familial dyslipoproteinemia	ApoE	IDL and βVLDL increased	(51,52)
Goldberg and Chait, 2020; Hegele *et al*, 2018	Familial CM syndrome	LPL, ApoC2, ApoA5, GPIHBP1, LMF1	CM and VLDL-C increased	(60,61)
Koseki *et al*, 2018	Tangier disease (without α-lipoproteinemia)	ABCA1	HDL-C decreased	(63)
Vitali *et al*, 2022	Familial LCAT deficiency	LCAT	HDL-C decreased	(64)

HeFH, heterozygous familial cholesterolemia; HoFH, homozygous familial hypercholesterolemia; LCAT, lecithin cholesterol acyltransferase; LDLR, low density lipoprotein receptor; Apo, apolipoprotein; PCSK9, proprotein convertase subtilisin-kexin type 9; LDLRAP1, low density lipoprotein receptor adaptor protein 1; LPL, lipoprotein lipase; GPIHBP1, glycerophosphatidylinositol-anchored high-density lipoprotein binding protein 1; LMF1, lipase maturation factor 1; ABCA1, ATP-binding cassette transporter A1; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; βVLDL, β-very low density lipoprotein; HDL-C, high density lipoprotein cholesterol; CM, chylomicrons; USF1, upstream transcription factor 1; UPC1, uncoupling protein .

unhealthy diet, some systemic diseases and gut microbiota on blood lipids are briefly described.

Diet. Consuming a diet rich in saturated fatty acids (SFAs) and cholesterol can lead to an increase in cholesterol levels. Factors such as excessive intake of high carbohydrates and excessive alcohol consumption may also cause abnormal blood lipid levels. Animal fat is often rich in SFAs, which is the dietary factor with the greatest influence on LDL-C levels (65). Trans fatty acids (TFAs) are found in full-fat dairy products, butter and meat from ruminants such as cattle, sheep and goats, as well as in industrial production (66,67), TFAs can increase the level of LDL-C, reduce the level of HDL-C and promote the formation of atherosclerosis through sphingolipids, which increases the risk of ASCVD (68). ApoC3 expression induced by a high-sugar diet can reduce or reverse cholesterol transport, decrease LPL activity and affect TG hydrolysis in CM and VLDL (69,70). In addition, a high-fat diet may also affect the lipid metabolism of the body by interacting with intestinal microflora. For example, SFA can cause the increase of Gram-negative bacteria in intestinal microflora, increase serum endotoxin level, increase intestinal permeability and cause lipid metabolism disorders (71). By adjusting the dietary structure, reducing the intake of high-energy foods such as high oil and high sugar and reducing the intake of related lipids from exogenous pathways, it is beneficial to regulate blood lipid levels to a certain extent and reduce cardiovascular diseases caused by HLP.

Systemic disease. Systemic diseases include obesity, diabetes, hypothyroidism, kidney disease, liver disease and autoimmune diseases (such as systemic lupus erythematosus). A variety of diseases interact with each other, involving lipid metabolism, glucose metabolism, protein digestion and absorption, and amino acid metabolism in a variety of tissues and organs, forming a complex pathogenesis of dyslipidemia.

After the occurrence of obesity, lipid accumulation is obvious, the increase of adipose tissue mass leads to the increase of total free fatty acid (FFA) in the circulation system and organs (such as liver) will also receive different degrees of damage. Insulin can considerably inhibit the lipolysis process in adipose tissue by inhibiting the activity of hormone-sensitive lipase, the key enzyme of lipid metabolism in cells and control the production and secretion of FFA in plasma (72). Insulin also activates the degradation of ApoB48 and ApoB100 and inhibits secretion of CM and VLDL by stem cells (73). Insulin resistance leads to increased hepatic lipogenesis and fatty acid metabolism in adipose tissue, leading to dyslipidemia (74). In addition, insulin can also upregulate LPL and insulin resistance will reduce LPL activity and HDL-C levels, thereby affecting TG levels (75). Therefore, HTG and low HDL-C are common in patients with diabetes (76).

Nesfatin-1 is an 82-amino acid bioactive fragment derived from the cleavage of nucleobindin-2 (NUCB2) by PC enzymes and is currently the only known bioactive product of NUCB2 (77). Serum nesfatin-1 was demonstrated to be markedly decreased in patients with non-alcoholic fatty liver disease (78); in mice, nesfatin-1 was demonstrated to attenuate lipid accumulation in hepatocytes through a pathway mediated by AMP-activated protein kinase (79). Nesfatin-1-like peptide with high similarity to nesfatin-1 also reduced lipid accumulation in hepatocytes (80). PCSK9 mediates ApoB100 and TG synthesis as well as VLDL assembly pathways and upregulation of PCSK9 causes excess VLDL production in the liver (81). Visceral adipose tissue releases adipokines such as tumor necrosis factor-α and IL-6, which not only cause chronic

inflammation but may also affect insulin signaling in hepatocytes and disrupt insulin sensitivity (82). Downregulation of adiponectin gene expression in adipocytes in metabolically associated dyslipidemia, circulating adiponectin levels are markedly reduced and inversely associated with the degree of visceral lipid accumulation (73), enhanced ApoA1 catabolism and decreased plasma HDL-C levels (83), which promote the accumulation of FFA in atherosclerosis and hepatocytes.

Relative to euthyroid individuals, patients with hypothyroidism have reduced thyroid hormone levels and are more likely to be obese, especially severely obese (84). Thyroid hormones exert biological effects by interacting with thyroid hormone receptor (TR). The TR has two isoforms, TRα and TRβ. The TRα mainly regulates thermogenesis, while TRβ mainly regulates cholesterol metabolism and lipogenesis (85). Synthetic TRβ agonists reduce cholesterol, TGs and obesity in rats and primates, suggesting a potential therapeutic mechanism (86,87). In addition, decreased thyroid hormone levels reduce the amount of LDLR in the liver and the synthesis of bile salts, increasing the absorption of cholesterol from the gastrointestinal tract. Decreased thyroid hormone levels also decrease the activities of cholesterol 7α-hydroxylase (CYP7A1) and ATP-binding cassette transporter G5/8 by reducing ATP-binding cassette transporter A1 and cholesteryl ester transfer protein (CETP) (88), and the production of dysfunctional HDL impairs cholesterol reverse transport, reduces the activity and amount of LPL and hepatic lipase and reduces cholesterol clearance (89).

Serum angiopoietin-like protein (ANGPTL3) levels are significantly positively associated with TG and cholesterol levels in patients with primary nephrotic syndrome. In addition, ANGPTL8 can promote ANGPTL3 cleavage and bind to the N-terminus of ANGPTL3 to form an N-terminal complex, which synergistically inhibits LPL activity and inhibits the clearance process of LDL and VLDL (90). In chronic kidney disease, ApoA1 and HDL levels are decreased, and LCAT deficiency and acyl-CoA cholesterol acyltransferase upregulation mediated by ApoA1 may lead to defective HDL maturation and impaired cholesterol reverse transport (91), thereby increasing TG levels.

In patients with lupus, LPL activity is compromised, leading to CM and VLDL accumulation followed by increased TG levels and decreased HDL levels (92,93). In addition, in patients with lupus, a notable proportion of HDL is dysfunctional and fails to inhibit LDL oxidation, a pro-inflammatory HDL that has been demonstrated to be an independent risk factor for carotid atherosclerosis (94,95).

Gut microbiota. Gut microbiota can regulate host metabolism and body weight through the gut-brain axis. The imbalance of intestinal flora can lead to the proliferation of potential pathogenic bacteria, activate innate immune recognition and initiate inflammatory responses, which in turn causes insulin resistance and fat accumulation, resulting in lipid metabolism disorders (96,97), it can also regulate lipid metabolic balance by changing the integrity of epithelial cells and the intestinal barrier, regulating cholesterol metabolism in the liver and lipid storage in adipose tissue (98).

Short-chain fatty acids (SCFAs), which are mainly composed of acetate, propionate and butyrate, are indirect nutrients produced by various intestinal microorganisms in the glycolysis of carbohydrates. In rodent administration studies, SCFAs have been reported to have effects on preventing weight gain and reducing weight gain (99). Although data in humans are limited, increased colonic propionate has been demonstrated to regulate appetite and prevent weight gain in overweight adults (100-103).

Bile acid is the main component of bile, which is released into the small intestine after eating. Bile acid can be broken down by intestinal microorganisms into secondary bile acids, including deoxycholic acid, lithocholic acid and ursodeoxycholic acid (secondary cholic acid in humans and primary cholic acid in rodents). Bile acids are considered to be key regulators of systemic metabolism, capable of regulating cholesterol metabolism and energy expenditure throughout the body (104). Gut microbes affect the metabolic reactions in which they participate by altering the bioavailability and biological activity of bile acids. In the small intestine, bile acid activation of faridoid X receptor (FXR) promotes fibroblast growth factor (FGF) 19/FGF15 release from intestinal epithelial cells and inhibits CYP7A1 transcriptional process, thereby increasing liver cholesterol levels (105). The activation of FXR is tissue-specific. The activation of FXR in the liver controls the process of adipogenesis, while the activation of FXR in the intestine reduces the absorption of lipids in the intestine and carries out a lipid-lowering role (106).

Tryptophan is an essential amino acid for protein synthesis and a key contributor to microbial influences on body weight and metabolism (107). The aryl hydrocarbon receptor (AhR) is a sensor of environmental and physiological signals and a potent regulator of intestinal barrier integrity, immunity and metabolism. Tryptophan catabolites, such as tryptamine, indole-3-acetic acid and 3-indole-propionic acid, are natural ligands for AhR (108). Reduced microbial production of AhR ligands leads to reduced secretion of glucagon-like peptide and defective mucosal barrier integrity, which may ultimately contribute to the development of metabolic syndrome, BMI, type 2 diabetes and hypertension (108-110).

In past studies, a variety of probiotics including *Lactobacillus* (*L*) *plantarum*, *L. sakei, L. forementum, L. hamnosus, L. cidophilus, L. Paracasei*, *Pediococcus pentosaceus* and *bifidobacterium* were reported to alleviate diet-induced lipid metabolism disorders by improving lipid and glucose metabolism, inhibiting metabolic inflammation and regulating the homeostasis and metabolites of gut microbiota (111-115). In a recent lipid-lowering activity screening study of 2,250 human gut strains, *Blautia Producta* demonstrated the strongest inhibition of cellular lipid accumulation and improvement of HLP in mice fed a high-fat diet. Its active metabolite, 12-methylmyristic acid can improve glucose metabolism by activating G protein-coupled receptor 120 to an exert anti-hyperglycemic effect (116). In addition, as a low-cost, high-safety functional food, probiotics have developed into an innovative strategy to prevent or improve diet-induced lipid metabolism disorders in the special context of rising medical costs for chronic diseases (111).

4. Clinical classification of HLP

In addition to the classification of HLP according to its cause, dyslipidemia can be divided into four types for practical use in clinical settings (Table III).

Table III. Simple clinical classification of hyperlipidemia and its lipid characteristics.

Classification	Total cholesterol	Triglyceride	High density lipoprotein cholesterol
Hypercholesterolemia	Increased	-	-
Hypertriglyceridemia	-	Increased	-
Combined hyperlipidemia	Increased	Increased	-
Low high-density lipoprotein cholesterol	-	-	Decreased

Lipid-lowering agents. In lipid-lowering treatment, it is recommended to improve lifestyle to a healthy one, including reasonable diet, moderate exercise, weight control, reducing smoking and drinking (117,118). Regarding dietary changes, it is recommended to reduce the intake of high-energy foods such as high oil and sugar, limit the intake of SFAs and trans-fatty acids, and increase the intake of fruits, vegetables, dietary fiber and fish (118). Lipid-lowering drugs should be considered to control lipid levels when lifestyle is not effective or lipid lowering targets are achieved (118). The mechanism of action of lipid-lowering therapy (Fig. 1). Emerging lipid-lowering drugs are shown in Table IV.

Statins. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. By competitively binding to the active site of HMG-CoA, statins prevent the conversion of HMG-CoA to mevalonate, reduce hepatic cholesterol synthesis and upregulate cellular LDLR. This increases LDL particle catabolism and decreases plasma LDL-C levels (119). In addition, statins also slightly reduce ApoB secretion (120), slightly reduce TG and increase HDL-C (121). Currently, there are seven types of statins used for treatment, including fluvastatin, lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin and pitavastatin.

Multiple studies have reported pronounced ASCVD risk reductions with moderate-intensity statin therapy (122-126). ASCVD risk was further reduced with high-intensity statin therapy (123). However, due to statin intolerance, high-intensity statin therapy may be associated with more adverse events, such as myotoxicity, hepatotoxicity, nephrotoxicity and diabetes (127). Initiating a standard-dose or moderate-intensity statin is therefore recommended. In addition, the majority of patients who are intolerant to one statin can successfully switch to another (128).

Ezetimibe and hyzetimibe. Ezetimibe is a cholesterol absorption inhibitor that inhibits the absorption of cholesterol in the intestine by inhibiting Niemann-Pick C1-like protein 1 in the upper small intestine (129). Standard-measured ezetimibe reduces LDL-C levels by 18 to 25% (130). The combination of ezetimibe and statin resulted in a 70% reduction in LDL-C (130). The addition of ezetimibe to simvastatin can further reduce cardiovascular events in patients with ACS (131). Combination therapy also improves cardiovascular outcomes in patients with chronic kidney disease (132). Hyzetimibe is a cholesterol absorption inhibitor recently marketed in China (www.nmpa.gov.cn; H20210030, H20210031). Its mechanism of action, usage and lipid-lowering efficacy are similar to ezetimibe, which provides an additional treatment option for patients (133-136).

Bile acid chelator (BAS). BAS are an alkaline anion exchange resin that can block the reabsorption of cholesterol from intestinal bile acids, reduce the inflow of bile acids into the liver and promote the synthesis of bile acids in the liver to deplete cholesterol in the body (137). Commonly used types of BAS in clinical practice are colestyramine, colestipol and colesevelam. BAS combined with statins can markedly improve lipid-lowering efficacy (138). BAS is insoluble in water and not easily absorbed by the human body. The common adverse effects of BAS include gastrointestinal discomfort and constipation, which can be relieved by adjusting the dose and increasing the intake of dietary fiber and water. In addition, it should be noted that BAS can elevate serum TG (139). Therefore, BAS drugs are contraindicated in patients with high TG.

PCSK9 inhibitors. PCSK9 is synthesized by the liver and can bind to LDLR and allow it to be transferred to lysosomes for degradation, thereby reducing the clearance of serum LDL-C by LDLR (140,141). At present, PCSK9 inhibitors mainly include PCSK9 monoclonal antibody and PCSK9 small interfering RNA. Currently, there are two major monoclonal antibodies against PCSK9, evolocumab and alirocumab, which are marketed in multiple countries. Both drugs reduced LDL-C and ASCVD events when combined with statins (142). Evolocumab induces regression and reversal of coronary plaques (143), evolocumab considerably reduced LDL-C and other atherogenic lipid components in patients with type 2 diabetes and HLP or mixed dyslipidemia in the setting of atorvastatin therapy and was well tolerated, with no marked effect on glycemic measures [national clinical trial (NCT) no. 02662569) (144). In long-term evolocumab studies, rates of serious adverse events, muscle related events, new-onset diabetes, hemorrhagic stroke and neurocognitive events were similar to placebo (NCT nos. 02867813 and 03080935) (145). In a randomized clinical trial, 615 high cardiovascular risk patients with HLP, were administered alirocumab or ezetimibe for 6 months, and LDL-C was reduced by 56 and 20.3%, respectively (146). In addition, evolocumab and alirocumab also reduced TG and Lp (a) levels and increased HDL-C levels (147-149). Evolocumab and alirocumab are effective in the vast majority of patients, including patients with HeFH and HoFH who have residual LDLR function and have a poor response in patients with LDLR receptor-deficient HoFH (150).

Recently, a new PCSK9 monoclonal antibody, tafolecimab, has been approved in China for the treatment of adult patients

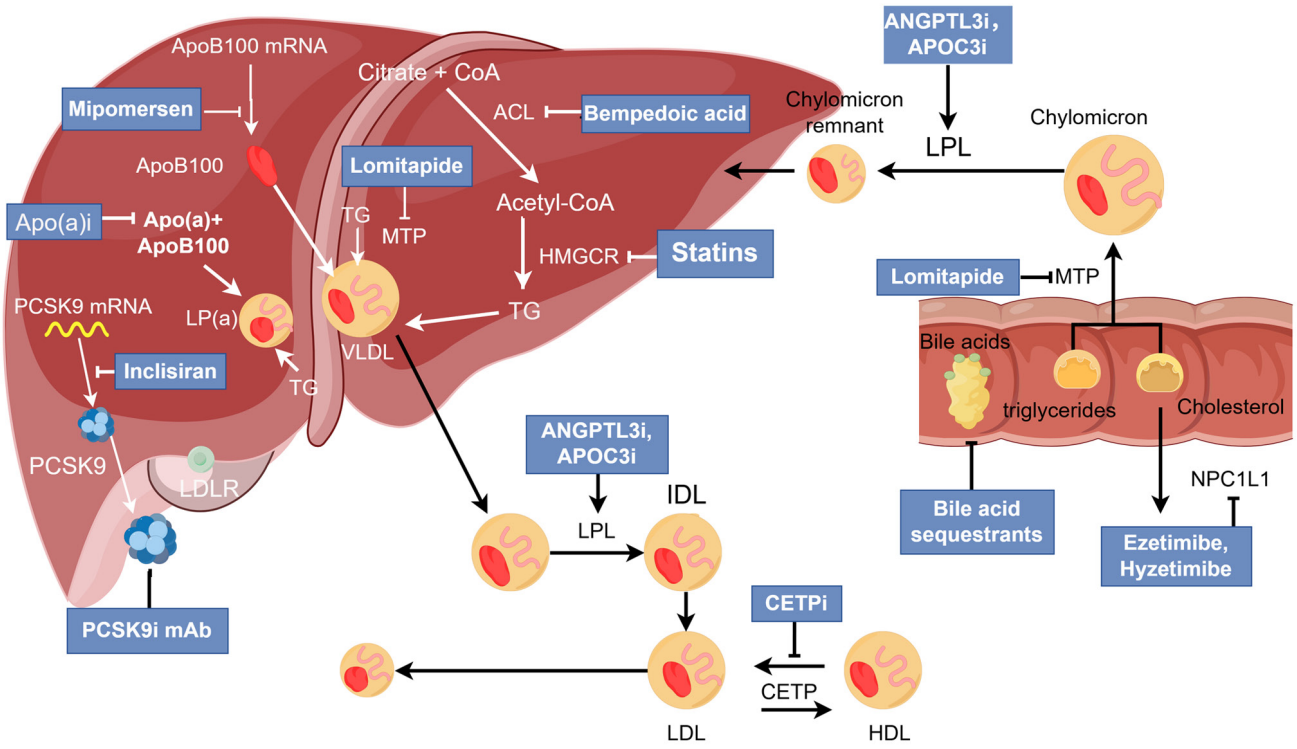

Figure 1. Mechanism of action of lipid-lowering therapy. Mipomersen targets ApoB100 mRNA. Apo(a)is inhibit Lp (a) synthesis by blocking Apo(a). Inclisiran targets PCSK9 mRNA. PCSK9i mAb blocks PCSK9 binding to the LDLR. Lomitapide inhibits the assembly of VLDL and chylomicrons by inhibiting MTP in the liver and small intestine. Bempedoic acid blocks cholesterol synthesis by inhibiting ACL. Statins inhibit cholesterol synthesis by blocking HMGCR. ANGPTL3i and ApoC3i enhance the function of LPL. Bile acid sequestrants bind bile acids in the small intestine. Ezetimibe and hyzetimibe inhibit NPC1L1 to inhibit cholesterol absorption in the intestine. CETPi primarily block the net mass transfer of cholesterol from high-density lipoprotein to very low-density lipoprotein and low-density lipoprotein. Apo, apolipoprotein; Apo(a)i, apolipoprotein (a) inhibitors; PCSK9, proprotein convertase subtilisin-kexin type 9; PCSK9i mAb, PCSK9 inhibitor monoclonal antibody; LDLR; low-density lipoprotein receptor; VLDL, very low-density lipoprotein; MTP, microsomal triglyceride transfer protein; ACL, ATP citrate lyase; HMGCR, 3-hydroxy-3-methylglutarylcoenzymereductase; ANGPTL3i, angiopoietin-like 3 protein inhibitors; ApoC3i, apolipoprotein C3 inhibitors; LPL, lipoprotein lipase; NPC1L1, Niemann-Pick C1-like protein 1; CETPi, cholesteryl ester transfer protein inhibitors; IDL, intermediate density lipoprotein; TG, triglycerides.

with primary HLP and mixed dyslipidemia who have not achieved LDL-C targets on moderate or higher doses of statins to reduce LDL-C, TC and ApoB levels (151). Its phase III clinical trials, CREDIT-2 (NCT no. 04179669) (152) and CREDIT-4 (NCT no. 04709536) (153), reported that at week 12 of tafolecimab treatment, compared with placebo, there was a ≥50% reduction in LDL-C levels in Chinese patients with HeFH or non-HeFH at high or very high cardiovascular risk, with comparable adverse events in both groups. This indicates that tafolecimab had robust short-term lipid-lowering efficacy and a good safety profile (152,153). In a trial evaluating the long-term efficacy and safety of talfolecimab, adverse events were similar in patients treated with tafolecimab vs. placebo after 48 weeks (NCT no. 04289285) (154). Tafolecimab may provide a novel treatment option with longer dosing intervals for Chinese patients with hypercholesterolemia.

Inclisiran is a small interfering (si)RNA targeting PCSK9 that binds to triantennary N-acetylgalactosamine (GalNac) and is an ultra-long-acting PCSK9 inhibitor approved for use in the European Union and Canada (www.ema.europa.eu, www.canada.ca; drug name, Leqvio). Studies have demonstrated that inclisiran can effectively reduce PCSK9 and LDL-C after a single injection for 6-12 months (155,156). In three randomized clinical trials involving a total of 3,660 patients, inclisiran reduced LDL-C by 51%, TC by 37%, non-HDL-C by 45% and ApoB by 41% compared with placebo. Inclisiran reduced the risk of major ASCVD and, in addition to a minor increase in injection-site reactions, reduced the risk of major ASCVD (157-159). Adverse effects did not differ between groups (159). Results from a phase 3 open-label study (ORION-8) demonstrated that inclisiran was consistently effective in lowering LDL-C and was well tolerated in patients at high cardiovascular risk, with a maximum exposure time of 6.8 years and a mean exposure time of 3.7 years. Treatment-related adverse events occurred at the injection site in 5.9% of patients and no new safety signals were identified (NCT no. 03814187) (160).

Probucol. Probucol is a synthetic antioxidant agent used in the treatment of patients with FH for the prevention and treatment of ASCVD and xanthelasoma, hepatic cholesterol 7 α-hydroxylase activity was increased by probucol, it lowers serum cholesterol mainly by increasing catabolic excretion of cholesterol into bile (161). While Probucol was discontinued in Western countries, as it caused a decrease in HDL-C levels and prolonged QT time (162), it is still used in Japan and China.

Bempedoic acid. Bempedoic acid inhibits hepatic cholesterol synthesis and is approved by the Food and Drug Administration (FDA) for lipid-lowering use. Bempedoic acid, which targets

Table IV. Emerging lipid-lowering drugs.

Classification	Name of drug	Target	Maximum development phase
ANGPTL3 inhibitors	Evinacumab	ANGPTL3 protein	Publicly available
	Vupanorsen	ANGPTL3 mRNA	Development stopped
	Zodasiran	ANGPTL3 mRNA	Phase 3 clinical trial
ANGPTL3/8 complex inhibitor	LY3475766	ANGPTL3/8 protein complex	Phase 1 clinical trial
ApoC3 inhibitors	Volanesorsen	ApoC3 mRNA	Publicly available
	Olezarsen	ApoC3 mRNA	Phase 3 clinical trial, application for listing
	Plozasiran	ApoC3 mRNA	Phase 3 clinical trial
Apo(a) inhibitors	Pelacarsen	Apo(a) mRNA	Phase 3 clinical trial
	Olpasiran	Apo(a) mRNA	Phase 3 clinical trial
	Zerlasiran	Apo(a) mRNA	Phase 2 clinical trial
	Muvalaplin	KIV8 domain of structure	Phase 2 clinical trial

Apo, apolipoprotein; ANGPTL3, serum angiopoietin-like protein.

ATP citrate lyase upstream of HMG-CoA, inhibits hepatic cholesterol synthesis through the mevalonate pathway while upregulating LDLR to promote LDL particle catabolism (163). Bempedoic acid and its combination with ezetimibe can considerably reduce LDL-C levels in patients with high-intensity statin therapy and statin intolerance, and has a good safety profile (164,165). In addition, a recent meta-analysis demonstrated that bempedoic acid is a safe and effective alternative to statins and reduces the risk of adverse cardiovascular events in high-risk patients with statin intolerance (166).

CETP inhibitors. CETP is a plasma glycoprotein secreted by the liver, which mediates the bidirectional transport of cholesteryl ester and TG between HDL, VLDL and LDL particles. CETP activity results in a net mass transfer of cholesterol from HDL to VLDL and LDL, and CETP inhibition reduces these exchanges, resulting in increased HDL-C levels and lower concentrations of cholesterol (such as VLDL and LDL) in ApoB particles (167). Previously, several CETP inhibitors, including torcetrapib, evacetrapib and anacetrapib, have been discontinued due to reasons such as side effects and poor therapeutic efficacy (130,168). There are two other CETP inhibitors, dalcetrapib and obicetrapib. Dalcetrapib failed in the dal-OUTCOMES trial due to its lack of HDL-C-raising power, but studies of the genome have demonstrated that dalcetrapib may be effective in subjects with a specific genotype, such as those with the AA genotype (genes at the same locus on homologous chromosomes are completely identical) of rs1967309 in the ADCY9 gene (NCT no. 02525939) (168-170), and further relevant clinical trials are ongoing (NCT no. 05918861). Obicetrapib in ROSE2, combination therapy with ezetimibe (all in addition to high-intensity statin therapy) markedly reduced levels of LDL-C, non-HDL-C, ApoB, total LDL particles, small LDL particles, small dense LDL and Lp (a) and increased HDL-C levels (NCT no. 05266586) (171). Currently, obicetrapib is being studied in fixed-dose combinations of ezetimibe and obicetrapib in addition to maximally tolerated lipid-lowering therapy (NCT no. 06005597). There are a total of three relevant phase 3 clinical trials of obicetrapib in patients with HeFH and cardiovascular disease, including efficacy, safety and tolerability (NCT nos. 05142722, 05425745 and 05202509).

Mipomersen. Mipomersen, an antisense oligonucleotide targeting ApoB100 mRNA (172), has been approved by the FDA. A meta-analysis reported that mipomersen reduced LDL-C by a mean of 26% (173). However, mipomersen caused elevated liver enzymes, injection-site reactions and flu-like symptoms compared with placebo, and ≤20% of subjects discontinued the drug (173,174). Long-term follow-up data from a 2-year open-label extension study demonstrated similar adverse effects (175), the pathological examination of liver biopsy demonstrated that the majority of patients had hepatic steatosis (176), these safety concerns have limited the use of mipomersen (174). Currently, the use of mipomersen is limited to patients with HoFH (177).

Lomitapide. Lomitapide, an inhibitor of microsomal TG transporter, is approved by The European Medicines Agency and the US FDA for the treatment of patients with HoFH (177,178). Lomitapide is able to cause a large reduction in LDL-C, but it causes an increase in liver enzymes and hepatic steatosis (179). A total of two phase 3 extension studies of lomitapide now demonstrate the long-term safety and efficacy of lomitapide in lowering lipid levels in patients with HoFH (180,181).

Fibrates. Fibrates include gemfibrozil, fenofibrate, bezafibrate and ciprofibrate, which activate peroxisome proliferator-activated receptor α (PPARα) and LPL, downregulate ApoC3 expression and upregulate ApoA1. Thus, levels of serum TG were decreased and HDL-C levels were increased (182-184). Current fibrate drugs either target PPARα or activate all three

PPAR isoforms and while the efficacy of fibrate drugs to lower TG is well established (182-184), their clinical benefit in reducing cardiovascular events is not convincing (185). Fibrates are used primarily to treat patients with severe HTG to reduce the risk for acute pancreatitis (186).

Pemafibrate, a novel PPARα agonist, is currently available in Japan (187). Pemafibrate is able to be metabolized and excreted into bile in the liver and therefore can be used in patients with renal insufficiency, as demonstrated in clinical trials (188,189). However, whether pemafibrate treatment markedly reduces cardiovascular events in patients with atherogenic dyslipidemia is unknown (185).

Niacin. Niacin can effectively reduce TG and LDL-C levels, increase HDL-C levels and reduce Lp (a) levels, but the mechanism is still unknown (190). The common adverse reactions of niacin are dizziness, skin flushing and pruritus, gastrointestinal discomfort, liver damage, hyperuricemia and deterioration of glucose tolerance. In two trials of niacin, there was no cardiovascular benefit and an increase in adverse effects (191,192).

ω-3 fatty acids. ω-3 fatty acids mainly include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are mainly found in marine animals and plant oils. ω-3 fatty acids inhibit *de novo* lipogenesis by inhibiting the cholesterol regulatory element binding protein gene and reducing TG levels by increasing fatty acid oxidation and TG catabolism by non-specific activation of peroxisome proliferator gene family members (193). ω-3 fatty acids are mainly used to treat THG. Icosapent ethyl IPE (EPA only) is clinically beneficial for cardiovascular diseases (194), ω-3 fatty acids with EPA and DHA also reduced cardiovascular events, but to a lesser extent when compared with IPE (195). In addition, randomized trials evaluating the efficacy of statins combined with EPA for secondary prevention have suggested that EPA has a certain coronary vascular protective effect (196).

ANGPTL3 inhibitors. ANGPL3 is synthesized in the liver and regulates lipid metabolism mainly by inhibiting LPL and endothelial lipase (197). Loss-of-function variants in ANGPTL3 cause panhypolipidemia, and heterozygous carriers of ANGPTL3 loss-of-function mutations have a 41% lower risk of coronary artery disease when compared with non-carriers (198). These properties make ANGPTL3 a novel target for the treatment of hypercholesterolemia and severe HTG. Currently, ANGPTL3 inhibitors mainly include ANGPTL3 monoclonal antibody (evinacumab), antisense oligonucleotide (ASO) targeting ANGPTL3 mRNA (vupanorsen) and the small interfering RNA (siRNA) targeting ANGPTL3 mRNA (zodasiran or ARO-ANG3).

Evinacumab is approved for the treatment of HoFH in the European Union, the United Kingdom and the United States (www.ema.europa.eu; products.mhra.gov.uk; www.fda.gov; drug name, Evkeeza). A clinical trial demonstrated that evinacumab can further reduce LDL-C by nearly 50% in patients with HoFH beyond existing lipid-lowering therapies (NCT no. 03399786) (199). A study of evinacumab in 14 pediatric patients with HoFH who were treated with lipid-lowering therapy demonstrated rapid and durable reductions in LDL-C levels with evinacumab and only two reported adverse events (nausea and abdominal pain) considered to be related to treatment. evinacumab provides a new treatment for pediatric patients with HoFH that is poorly controlled despite lipid-lowering therapy (NCT no. 04233918) (200).

Another trial of long-term evinacumab therapy (median, 104.3 weeks) revealed that in a large cohort of patients with HoFH (116 patients), evinacumab was generally well tolerated and notably reduced LDL-C regardless of age and sex, and was associated with a marked reduction in LDL-C. Its efficacy and safety can be maintained over an extended period (NCT no. 03409744) (201). In addition, a recent phase 2 placebo-controlled randomized trial revealed that among three groups of patients with severe HTG (all with a history of acute pancreatitis), TG levels did not decrease in group I patients with FCS; in the second group of patients with multifactorial CM syndrome caused by heterozygous loss-of-function mutation of LPL, TG levels markedly decreased. In group 3, patients with multifactorial CM syndrome without LPL pathway mutations had greater decreases in TG levels (NCT no. 03452228) (202). These results also indicate that evinacumab can effectively reduce TG when LPL has a certain activity, and can be used to treat the majority of patients with severe HTG. However, a phase II trial in patients with severe HTG (history of acute pancreatitis) was stopped in 2023 because of unfavorable recruitment (203).

Vupanorsen is a GalNac-bound ASO that targets ANGPTL3 mRNA, thereby inhibiting ANGPTL3 synthesis. A phase 2b trial revealed that vupanorsen caused a dose-dependent increase in liver fat fraction (NCT no. 04516291) (204,205); this liver-related toxicity was not observed with evinacumab or in patients with ANGPTL3 loss-of-function mutations (206,207). Possibly due to its adverse reactions and the availability of better alternatives, the development of the drug was discontinued.

ARO-AGN3 (zodasiran) is an siRNA that targets ANGPTL3. In a phase 1 trial involving 52 healthy induviduals and 9 individuals with hepatic steatosis, ARO-AGN3 produced substantial and sustained reductions in serum ANGPTL3 concentrations of up to 92.7% from baseline in healthy individuals. Meanwhile, serum TG and atherogenic lipoproteins (LDL-C, non-HDL-C and VLDL-C) also decreased. ARO-AGN3 similarly reduced atherogenic lipoproteins in a small subset of participants with hepatic steatosis, and no increase in liver fat was observed with repeated dosing. In addition, ARO-ANG3 demonstrated durable pharmacological effects that lasted >3 months after the current administration. Injection-site reactions were the most common adverse events (NCT no. 03747224) (208). A double-blind, placebo-controlled, dose-ranging, phase 2b trial involving 204 patients with mixed HLP, almost all of whom had a background in statin therapy, revealed dose-dependent notable reductions of ≥50% in ANGPTL3 levels with Zodasiran at 24 weeks of treatment, as compared with baseline. TG levels were also decreased by ≥50% in a dose-dependent manner and LDL-C, non-HDL-C and ApoB levels were also decreased. Zodasiran also did not cause increases in liver fat content or serum aminotransferase levels, and symptoms of thrombocytopenia were not observed (NCT no. 04832971) (209). This suggests that the toxicity of vupanorsen is not caused by ANGPTL3 inhibition. A phase

3 clinical trial in Chinese patients with HoFH is currently planned to evaluate the efficacy and safety of zodasiran in patients with HoFH (NCT06712771).

ANGPTL3/8 complex inhibitors. ANGPTL8 is a cofactor for the efficacy of ANGPTL3, which can synergistically inhibit LPL activity by promoting the molecular cleavage of ANGPTL3 and forming an ANGPTL3/8 complex by binding to the N terminus of ANGPTL3, thereby increasing TG levels (90). The loss-of-function mutant of ANGPTL8 is associated with reduced TG and LDL-C levels and increased HDL-C levels compared with the ANGPTL3 loss-of-function mutant, but because this mutant is rare, there is insufficient evidence to assess its cardiovascular protective effects (203,210). The inhibition of LPL by the ANGPTL3/8 complex is 100-fold more potent than ANGPTL3 alone, making it a potential target for the treatment of hypercholesterolemia and HTG (211). A phase 1 clinical trial of a monoclonal antibody directed against the ANGPTL3/8 complex, LY3475766, has been completed, but the results have not yet been reported (NCT no. 04052594).

ApoC3 inhibitors. ApoC3 can increase plasma TG levels by reducing LPL activity, inhibiting the clearance of TG from the circulation and promoting the secretion of hepatic VLDL into plasma (212). Functional mutations in ApoC3 are associated with lower TG levels and reduced risk of ischemic CVD (213,214). Human genetic studies have confirmed ApoC3 as a therapeutic target for severe and mild-to-moderate HTG for the prevention of acute pancreatitis and ASCVD (215-220).

Volanesorsen, the first ASO RNA drug to be developed against ApoC3 (2'-O-methoxyethyl-modified ASO), is available in the European Union and the United Kingdom (www.ema.europa.eu; products.mhra.gov.uk; drug name, Waylivra). A 52-week phase III trial of Volanesorsen in 66 patients with FCS (APPROACH; NCT no. 02211209) (221), after treatment, mean TG levels decreased by 77%. Another phase 3 trial of volanesorsen was carried out in 114 patients with multifactorial severe HTG or FCS (COMPASS; NCT no. 02300233) (222), after 3 months of treatment, plasma TG levels were reduced by 71%. In both theses phase 3 trials, adverse events of thrombocytopenia were noted in a number of patients receiving volanesorsen, and platelet counts normalized after treatment discontinuation. This may be due to the chemical properties of the drug rather than a generic effect of all drugs that target ApoC3. A phase 3 long-term open-label treatment of volanesorsen revealed sustained reductions in plasma TG levels in patients with FCS, with common adverse events of injection-site reactions and reductions in platelet counts, which are consistent with previous studies (221-223).

Olezarsen, an ASO conjugated to GalNac, is another form of volanesorsen and is currently applying for marketing in the United States (www.fda.gov; drug name, Tryngolza). In the phase 2 clinical trial of Olezarsen, 114 patients with moderate HTG received olezarsen or corresponding placebo for 6-12 months, which markedly reduced the level of TG, ApoC3, non-HDL-C and ApoB. The most common adverse event was mild erythema at the injection site and no participants presented symptoms of thrombocytopenia (NCT no. 03385239) (224). The recent phase 2b trial of olezarsen showed that two doses (50 or 80 mg; administered subcutaneously every 4 weeks) of olezarsen or matching placebo were used to treat 154 patients with moderate HTG and elevated cardiovascular risk or severe HTG for 6-12 months. Olezarsen at both 50 and 80 mg reduced TG levels by 49 and 53%, respectively, as well as markedly reduced ApoC3, ApoB and non-HDL-C levels. Risks of adverse events and serious adverse events were similar among the three groups (NCT no. 05355402) (225). Currently, a number of clinical trials are ongoing or planned to evaluate the efficacy and safety of olezarsen in different types of patients (NCT nos. 04568434, 05130450, 05681351, 05185843, 05610280, 05552326 and 05079919).

Plozasiran (also known as ARO-APOC3) is a GalNac-conjugated siRNA targeting ApoC3 mRNA in hepatocytes (226). A phase 2b study of Plozasiran (SHASTA-2), in which 229 patients with severe HTG received two subcutaneous injections of plozasiran (10, 25 or 50 mg) or matching placebo at day 1 and week 12 and were followed up to week 48, revealed dose-dependent reductions in TG levels. An average reduction of 57% was observed and there was a dose-dependent increase in LDL-C levels, but not ApoB levels. In these patients, non-HDL-C levels decreased considerably at all doses (NCT no. 04720534) (227). In another 48-week clinical trial of 353 patients with mixed HLP (of which, ~60% patients also had diabetes), participants who received plozasiran had a marked reduction in fasting TG levels at week 24, with a mean reduction of ≥50% compared with placebo; in addition, ApoC3, ApoB and non-HDL-C were also notably decreased, while HDL-C was increased (NCT no. 04998201) (228). Multiple phase 3 trials of plozasiran are currently under way (NCT nos. 05089084, 06347133, 06347003 and 06347016).

Apo(a) inhibitors. Lp (a) is considered to be an independent risk factor for ASCVD and calcific aortic stenosis (16,17,229). Proinflammatory activation of circulating monocytes is a potential mechanism of Lp (a)-mediated CVD (230). Several inhibitors that inhibit Lp (a) formation are currently in clinical trials, such as pelacarsen, olpasiran, zerlasiran and muvalaplin.

Pelacarsen, also known as AKCEA-Apo(a)-LRx or TQJ230, is an ASO that binds GalNac to target APO(a) mRNA in hepatocytes (231). In the pelacarsen phase 2 trial of pelacarsen, which treated 286 patients with established CVD and high levels of Lp (a) or matching placebo, the pelacarsen group revealed a dose-dependent reduction in Lp (a) levels of ≤80%. Adverse events were similar when compared with placebo (NCT no. 03070782) (232). In addition, Pelacarsen decreased the expression of pro-inflammatory genes in monocytes from patients with CVD with elevated Lp (a). Although PCSK9ab treatment reduced Lp (a) by 16% and LDL-C by 65%, it did not alter monocyte transcriptomic or functional properties (233). These data support that substantial Lp (a) reduction produces beneficial effects in patients with elevated Lp (a). Multiple clinical trials of pelacarsen in the population, efficacy, safety, tolerability and pharmacokinetics are ongoing or planned (NCT nos. 04023552, 05305664, 05646381 and 06267560).

Olpasiran (AMG-890) is an siRNA that targets Apo(a) (234). The phase 2 OCEAN (a)-DOSE study of olpasiran revealed that 281 patients with confirmed ASCVD and high levels of Lp (a), the majority of whom had a background

in lipid-lowering therapy, were treated with different doses of olpasiran or matching placebo. In the olpasiran group, Lp (a) decreased in a dose-dependent manner. At week 36, patients receiving ≥75 mg every 12 weeks had >95% reduction in Lp (a) levels. The incidence of adverse events was similar in olpasiran and placebo groups, and the most common adverse event was injection-site reaction (NCT no. 04270760) (235). A phase 3 clinical trial of olpasiran is currently underway (NCT no. 05581303).

Zerlasiran (SLN360) is also an siRNA targeting Apo(a). In a recent phase 2 trial of Zerlasiran, 178 patients with ASCVD with high Lp (a) levels who were treated with zerlasiran or matching placebo had a mean reduction in Lp (a) levels of >80% at week 36 in the zerlasiran group, as compared with the placebo group. The most common adverse events were mild injection site reactions (NCT no. 05537571) (236).

Muvalaplin (LY3473329) is the first small molecule drug in the world to enter phase 2 clinical trials, which can effectively lower Lp (a) (237). Lp (a) is generated by Apo(a) by first binding to the lysine residue of ApoB100 on LDL via the Kringle IV 7 and 8 (KIV8) domains, followed by the formation of a disulfide bond between Apo(a) and B100 (238-241). Muvalaplin is a trimeric molecule that binds three KIV8 domains simultaneously. In cynomolgus monkeys, muvalaplin reduced Lp (a) levels by 71% from baseline in a dose-dependent manner (237). A phase 2 trial of muvalaplin is currently under way (NCT no. 05563246).

Conclusions

Advancements in science and technology have allowed for a deeper understanding of the mechanisms underlying dyslipidemia. This allows for the development of new biotherapies specifically targeting molecules of core metabolic importance. Lipid-lowering therapies carry out a central role in the prevention of ASCVD. The main existing lipid-lowering medications include statins, ezetimibe, BAS, monoclonal antibodies that inhibit PSCK9, mipomersen, lomitapide and ω-3 fatty acids. Even when used in combination, they cannot meet current clinical needs due to various reasons such as intolerance, applicable populations and adverse reactions. Combining new therapeutic drugs, such as inclisiran, hyzetimibe, bempedoic acid, CETP inhibitors, ANGPTL3 inhibitors, ANGPTL3/8 complex inhibitors, ApoC3 inhibitors and Apo(a) inhibitors, with existing lipid-lowering medications, may help to meet the unmet clinical needs. Additionally, a reasonable dietary structure and appropriate exercise may help improve lipid levels and promote overall health, and the development of drugs targeting relevant points on the microbiome-gut-brain axis also demonstrates potential for therapeutic application.

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Authors' contributions

HZ drafted the original manuscript and prepared the figures. YW, YL and RC conducted the literature search and contributed to the writing of the paper. HZ and WC proposed the research design, conducted literature research and contributed to the writing of the paper. Additionally, WC provided professional advice and revisions. All authors critically reviewed the content. Data authentication not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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