Insights into the current management of dyslipidemia from a clinical pharmacological perspective

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Abstract

The low-density lipoprotein cholesterol (LDL-C) is established as a causative agent of atherosclerotic cardiovascular disease (ASCVD) and lowering plasma LDL-C levels represents the main approach to reduce the risk of cardiovascular events. Statins remain the cornerstone of drug therapy for dyslipidemia. Although moderate- to high- intensity statin therapy has demonstrated consistent benefits for secondary prevention of cardiovascular events, statin monotherapy is insufficient to achieve the guideline-recommended LDL-C levels for high- and very high-risk patients. Some patients cannot tolerate statins, especially when taking long-term high doses. Several non-statin drugs that have a complementary mechanism of action to statins are now available, including ezetimibe, monoclonal antibodies targeted to proprotein convertase subtilisin/kexin type 9 (PCSK9 mAb), and, more recently, inclisiran, bempedoic acid, and evinacumab. Considering the recommendations from guidelines by domestic and international cardiovascular associations, combining these drugs should be contemplated to attain treatment goals for patients.

Keywords: *dyslipidemia, atherosclerotic cardiovascular disease, lipid-lowering drugs, familial hypercholesterolemia, hypertriglyceridaemia, nonstatin therapies.*

1. INTRODUCTION

The pharmacological control of plasma low-density lipoprotein cholesterol (LDL-C) levels is the major route to prevent cardiovascular (CV) outcomes and therapy intensification associated with a significant reduction of CV event incidence in high and very high-risk patients. LDL-C reduction with statin treatment remains the cornerstone of lipid-lowering therapy for primary and secondary prevention of CV events. Increased research on new non-statin drugs having mechanisms of action that can "complement" the effect of statins enriching the tools for dyslipidemia treatment. Reaching LDL-C goals and reducing cardiovascular disease (CVD) risk is more difficult in patients with familial hypercholesterolemia (FH) [1]. Recently, new and promising pharmacological strategies have become available to solve this difficulty. In this section, we summarize the pharmacology of lipid-lowering drugs, provide updates on the treatment of dyslipidemia based on guidelines from global and Vietnamese cardiovascular associations, and review new therapeutic approaches for dyslipidemia treatment, including medication options that have undergone phase II clinical trials.

2. OVERVIEW OF THE PHARMACOLOGY OF THE MAJOR LIPID-LOWERING DRUGS

2.1. Statin (rosuvastatin, pitavastatin, and atorvastatin)

2.1.1. Mechanism of action

Statins competitively inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, preventing the conversion of HMG-CoA to mevalonic acid. Low intracellular cholesterol concentrations result in increased expression of LDL receptor at the surface of the hepatocytes, which in turn results in increased uptake of LDL from the blood, and decreased plasma concentrations of LDL-C and other ApoB-containing lipoproteins, including triglyceride (TG)-rich particles.

2.1.2. Pharmacokinetics

Following oral administration, statin is rapidly absorbed and reaches maximum plasma concentrations in approximately 4 hours. Lipophilic statins oxidative metabolism by cytochromes P450 (CYP450) is the major route, with the CYP3A4 isoenzyme playing the greatest role and excretion primarily in bile. Muscle toxicity is more prominent with these statins and is also most

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commonly associated with drug interactions due to CYP450 inhibition. Hydrophilic statins are actively transported into the liver, metabolized less by the CYP enzymes, and actively excreted through the kidneys.

2.1.3. Effects of statin

LDL-C reduction by statin therapy is dose-dependent, and varies among different statins. Interindividual variations in statin responses. With the same dose of statin, the response should be monitored on initiation of therapy. *Triglycerides:* statins reduce TG levels by 10 - 20% of baseline values. Particularly, strong statins (rosuvastatin, pitavastatin, and atorvastatin) have a high TG-lowering effect, especially at high doses and in patients with elevated TGs. *HDL-C:* HDL cholesterol levels varied with dose among respective statins, ranging from 1 - 10%. However, because ApoB-containing lipoproteins are markedly reduced with statin, the modest effect on HDL-C levels might contribute to overall CV risk reduction. *Lipoprotein(a) [Lp(a)]:* Statins only marginally affect Lp(a) plasma levels with reports of either no effect on or an increase of Lp(a) levels after statin treatment. *Effect on CV morbidity and mortality:* Statin reduced the risk of major CV events by 22%, major coronary events by 23%, coronary artery disease (CAD) death by 20%, total stroke by 17%, and total mortality by 10% over 5 years per 1 mmol/L LDL cholesterol reduction. For each 1 mmol/L reduction in LDL-C, statin therapy reduced the risk of all-cause mortality by 9% in participants without a history of vascular disease. In the long term, statins had an 18% reduced risk of all-cause mortality over 20 years. Statins are effective for the prevention of ASCVD in the elderly, including those aged > 75 years [2].

2.1.4. Side effects

On muscle: rhabdomyolysis is the most severe form of myotoxicity caused by statins, characterized by severe muscle pain, muscle necrosis, and myoglobinuria that can potentially lead to renal failure and death. In rhabdomyolysis, creatine kinase (CK) levels increase ≥ 10-fold and often ≥ 40-fold the upper limit of normal (ULN). The estimated incidence of rhabdomyolysis is 1 - 3 cases/100,000 patient-years. *On the liver:* mildly elevated alanine transaminase (ALT) occurs in 0.5 - 2% of patients, more commonly with strong or high-dose statins. Progression to liver failure is extremely rare, so routine ALT monitoring is not recommended. *Increased risk of new-onset diabetes mellitus:* dose-related, increased risk with intensive dose statin and is higher in the elderly, and in the presence of risk factors such as being overweight or insulin resistant. However, the benefit of absolute reduction in CVD risk in high-risk patients outweighs the side effect of slightly increasing the incidence of diabetes. *Increased risk of hemorrhagic stroke*: the risk increased by 21% per 1 mmol/L decrease in LDL-C level. However, other meta-analyses have yielded conflicting findings and there is a need for further exploration of the risk of hemorrhagic stroke in particular types of patients. The overall benefit greatly outweighs this small (and uncertain) hazard. *Side effects on kidney function*: no clear evidence. An increased frequency of proteinuria is seen with all statins. Proteinuria is of tubular origin, usually transient and due to reduced tubular reabsorption and not due to glomerular dysfunction [2].

2.2. Cholesterol absorption inhibitors (ezetimibe)

Mechanism of action: is mediated by targeting the sterol transporter Neimann-Pick C1 Like 1 (NPC1L1), which is localized at the border cells in the small intestine. Binding to the transporter inhibits it and decreases the absorption of cholesterol, further decreasing cholesterol circulation through the liver, and finally increasing the clearance of cholesterol from blood. *Administration:* 10 mg taken by mouth once per day, dose adjustment is not recommended in patients with mild hepatic impairment or mild to severe renal impairment. *Effects:* is mostly observed when combined with statins, reducing LDL-C by 10 - 15%, varies among different statins combined. Many studies have shown good effects when combining ezetimibe with bempedoic acid, with an average difference in LDL-C of 38% compared to placebo. Monotherapy is also acceptable, especially in patients who are statin intolerant and require moderate LDL-C reduction, providing an 18% reduction in LDL-C compared with placebo. *Side effects:* ezetimibe has a good safety profile, with few or no side effects reported. Life-threatening liver failure with ezetimibe monotherapy or in combination with statins is rare [3].

2.3. Bile acid sequestrants (cholestyramine, cholestipol, colesevelam)

Mechanism of action: by binding the bile acids, the drugs prevent the reabsorption of cholesterol into the blood, and thereby remove a large portion of the bile acids from the enterohepatic circulation. The depletion of hepatic cholesterol due to increased diversion to bile acid synthesis leads to increased hepatic LDL receptor expression, which

results in a decrease in circulating LDL. *Effects:* at daily doses of 24 g cholestyramine, 20 g colestipol, or 4.5 g colesevelam, LDL cholesterol is reduced 18-25%, without effect on HDL-C. Colesevelam may reduce glucose concentrations in hyperglycemic patients. *Side effects:* The main side effects limiting the use of them are those associated with the gastrointestinal tract (flatulence, constipation, indigestion, and nausea), even at low doses. These side effects can be reduced by starting at a low dose, increasing the dose slowly, and drinking plenty of fluids. Reduced absorption of fat-soluble vitamins has been reported. The drug may increase TG levels in some patients. *Interactions:* bile acid sequestrants interact with some commonly prescribed drugs, so it must be taken 4 hours before or 1 hour after other drugs. Colesevelam is better tolerated has fewer interactions than other drugs, and can be taken with statins and some other drugs [2]**.**

2.4. Proprotein convertase subtilisin/kexin type 9 inhibitors (alirocumab, evolocumab)

Two monoclonal antibody inhibitors of PCSK9 that were approved by the FDA are alirocumab and evolocumab. *Mechanism of action:* PCSK9 is a serine protease mainly expressed in the liver that targets LDL-R. It leads the receptors to lysosome-mediated degradation, thus diminishing their recycling. The monoclonal antibodies alirocumab and evolocumab inhibit PCSK9 binding to LDL receptors, increase recycling of LDL receptors, and indirectly lower circulating LDL cholesterol levels by increasing LDL cholesterol uptake. *Pharmacokinetics:* peak concentrations of alirocumab are achieved within 3 - 7 days and 3 - 4 days for evolocumab. The bioavailability of alirocumab and evolocumab is approximately 85 and 72%, respectively. *They have two phases of elimination*: predominantly through saturable binding to PCSK9 at lower concentrations and a nonsaturable proteolytic pathway at higher concentrations. Alirocumab has a half-life of 17 - 20 days and evolocumab has a half-life of 11 - 17 days [4]. *Effects:* monotherapy or combination therapy reduces LDL-C by an average of 60% depending on the dose. Combination with high-intensity or maximally tolerated statins reduced LDL-C by 46 - 73% more than placebo and 30% more than ezetimibe. Evolocumab reduced TG by 26% and increased HDL-C and ApoA-I by 9% and 4%, respectively; results were similar to alirocumab. Unlike statins, PCSK9i reduces Lp(a) by about 30 - 40%. The ODYSSEY OUTCOMES trial showed that alirocumab reduced the primary endpoint and deaths from any cause by 15% over a median follow-up period of 2.8 years [5]. The FOURIER trial showed that evolocumab treatment reduced the primary endpoint by 15% and key secondary endpoints by 20% over an average follow-up period of 2.2 years [6]. In other studies, PCSK9i has been shown to reduce the lipid core of atherosclerotic plaques. After six months of PCSK9i with alirocumab, it resulted in reduced lipid content by 17%, without significant changes in the lumen/wall area or in the inflammatory index Ktrans [7]. Lepor et al analyzed carotid atherosclerotic plaques by MRI after 3, 6, and 12 months of treatment with PCSK9i, showing a regression in plaque composition and neovasculature [8]. *Side effects:* are usually mild, include upper respiratory tract infections, injection site reactions, and nasopharyngitis. To date, only very few cases of anti-drug antibodies have been reported, and no reduction in LDL-C lowering has been observed, but monitoring is required during long-term use. *Dosage:* The dose of alirocumab is 75 mg once every two weeks. If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg every two weeks. The dosing of evolocumab is 140 mg every two weeks or 420 mg once monthly administered subcutaneously.

2.5. Fibrates (gemfibrozil, fenofibrate, pemafibrate)

Mechanism of action: fibrates are agonists of PPAR- α, acting via transcription factors regulating, among other things, various steps in lipid and lipoprotein metabolism. Fibrates have good efficacy in lowering fasting TG levels, as well as post-prandial TGs and TG-rich lipoprotein (TRL) remnant particles. *Effects:* reduce TG by 50%, reduce LDL-C by ≤ 20% and increase HDL-C by ≤ 20%, depending on the initial lipid concentration. The clinical effects of fibrates were reported in 6 RCTs: HHS, VA-HIT, BIP, LEADER, FIELD and ACCORD. The overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Recently, a newer dialysis PPAR-α modulator (pemafibrate) has been reported to be effective in significantly reducing TRL. Overall, the cardiovascular benefits of fibrates require further confirmation. *Side effects:* fibrates are generally well tolerated with mild side effects, gastrointestinal disturbances in < 5% of patients, and skin rash in 2%. Myopathy, increased liver enzymes, and gallbladder stones are side effects commonly associated with fibrates. The risk of myopathy is 5.5 times greater with fibrate monotherapy (mainly with gemfibrozil) than with statins. Because fenofibrate does not share the same pharmacokinetic pathway

as gemfibrozil, the risk of myopathy is less. Fibrates increase blood creatinine and homocysteine levels and slightly increase the risk of pancreatitis [2].

2.6. n-3 fatty acids (EPA, DHA)

Mechanism of action: it impact serum lipids and lipoproteins, especially VLDL concentrations. The mechanism is not well understood, possibly related to its ability to interact with PPAR and reduce ApoB secretion. *Effects:* n-3 fatty acids reduce TG, but the effect on other lipoproteins is insignificant. 3 recent studies in high TG people using EPA showed significant dose-dependent reductions in blood TG concentrations of up to 45%. The REDUCE-IT trial using a high dose of EPA (2 g twice daily) compared with placebo resulted in a 25% relative risk reduction in major CV events. *Dosage:* the recommended dose of total EPA and DHA to reduce TG is 2 - 4 g/day. *Side effects:* appears to be safe with no clinically significant interactions. The most common side effect is digestive disorders. Antithrombotic effects may increase the risk of bleeding, especially when used with aspirin/clopidogrel. Recently, data from a study showed an increased risk of prostate cancer with high doses of n-3 PUFA [2].

2.7. Nicotinic acid

Mechanism of action: it has main site of action in both liver and adipose tissue. In the liver, it inhibits diacylglycerol acyltransferase-2 leading to decreased secretion of VLDL particles, reducing plasma concentrations of both IDL and LDL. Nicotinic acid primarily increases HDL-C and ApoA1 by stimulating ApoA1 production in the liver. *Effects:* 2 large randomized trials: one with extended-release niacin and one with niacin plus laropiprant showed no benefit but an increased incidence of serious side effects. There are no medicines containing nicotinic acid currently approved in Europe [2]

3. UPDATED GUIDELINES FOR THE MANAGEMENT OF DYSLIPIDEMIA

3.1. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice [9]

Table 1. Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age

Recommendations	Class	Level
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group	**I**	**A**
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of ≥50% from baseline should be considered in apparently healthy persons <70 years at very high risk	**IIa**	**C**
An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of ≥50% from baseline should be considered in apparently healthy persons <70 years at high risk	**IIa**	**C**
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDLC vs. baseline is recommended	**I**	**A**
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended	**I**	**B**
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered	**IIb**	**C**
For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended	**I**	**A**
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended	**I**	**C**

If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered	**IIa**	**B**
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered	**IIb**	**C**
If the goal is not achieved, statin combination with a bile acid sequestrant may be considered	**IIb**	**C**
Statin therapy is not recommended in premenopausal female patients who are considering pregnancy or are not using adequate contraception	**III**	**C**

Table 2. Recommendations for drug treatments of patients with hypertriglyceridaemia

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridemia [triglycerides >2.3mmol/L (200 mg/dL)]	**I**	**A**
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered	**IIa**	**B**
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) may be considered in combination with a statin	**IIa**	**B**

3.2. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults [10]

3.2.1. The Management of Dyslipidemia in Primary Prevention

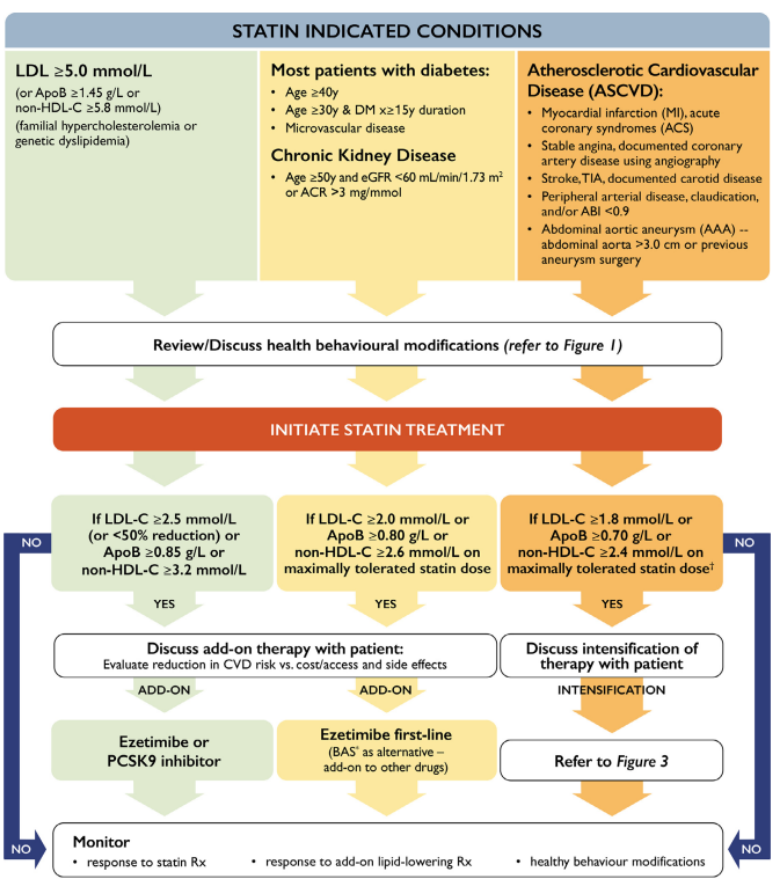

Figure 1. Treatment approach for patients with a statin-indicated condition

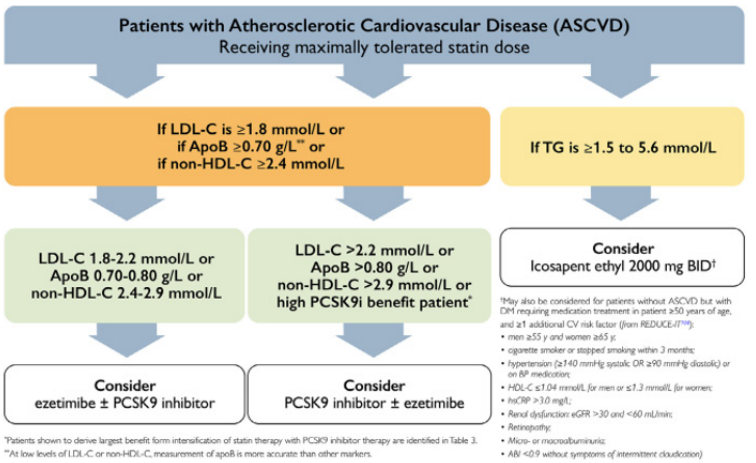

Figure 2. Treatment intensification approach for patients with atherosclerotic cardiovascular disease

3.2.2. The Management of Dyslipidemia in Secondary Prevention

RECOMMENDATION

1. We recommend use of high-intensity statin therapy in addition to appropriate health behaviour modifications for all secondary prevention CVD patients. For patients who do not tolerate a high-intensity statins, we recommend the maximally tolerated statin dose (Strong Recommendation; High-Quality Evidence).

2. We recommend intensification of lipid-lowering therapy with a PCSK9 inhibitor (evolocumab or alirocumab) - with or without the additional use of ezetimibe—for secondary CV prevention patients shown to derive the largest benefit from PCSK9 inhibitor therapy in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose (Fig. 2; Strong Recommendation; Moderate-Quality Evidence).

3. We recommend intensification of lipid-lowering therapy with ezetimibe and/or PCSK9 inhibitor therapy for all secondary prevention CVD patients in whom LDL-C remains ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) while receiving the maximally tolerated statin dose. (Strong Recommendation; High-Quality Evidence). If ezetimibe is used initially and LDL-C remains ≥ 1.8 mmol/L (or nonHDL-C ≥ 2.4 mmol/L or ApoB ≥ 0.7 g/L) PCSK9 inhibitor therapy is recommended (Strong Recommendation; High-Quality Evidence).

3.3. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk [11]

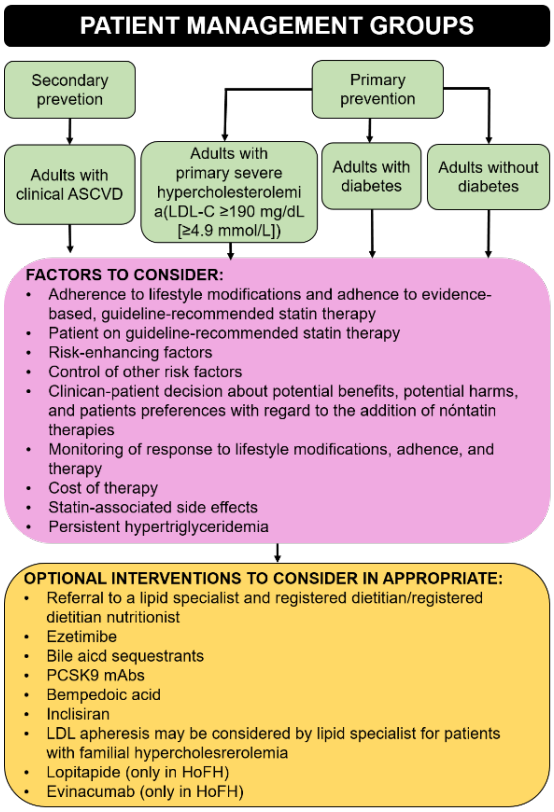

Figure 3. Summary Graphic: Patient Populations Addressed and Factors and Interventions to Consider

3.4. 2022 Vietnam National Heart Association Guidelines on cardiovascular disease prevention in clinical practice [12]

Table 3. Recommendations for medications to reduce LDL-C for patients < 70 years old

Recommendations	Class	Level
A high-intensity statin is prescribed up to the highest tolerated dose to reach the LDL-C goals set for the specific risk group is recommended	I	A
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/ dL) and LDL-C reduction of ≥ 50% from baseline should be considered in apparently healthy persons <70 years at very high risk	IIa	C
An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of ≥ 50% from baseline should be considered in apparently healthy persons <70 years at high risk	IIa	C
Lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥ 50% reduction in LDLC vs. baseline is recommended in patients with established ASCVD	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, a combination with ezetimibe is recommended	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered	IIb	C

For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended	**I**	**A**
Combination therapy including a PCSK9 inhibitor is recommended for very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe	**I**	**C**
Ezetimibe should be considered if a statin-based regimen is not tolerated at any dosage (even after rechallenge).	**IIa**	**B**
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered	**IIb**	**C**
If the goal is not achieved, statin combination with a bile acid sequestrant may be considered	**IIb**	**C**
Statin therapy is not recommended in premenopausal female patients who are considering pregnancy or are not using adequate contraception	**III**	**C**

Table 4. Strategies to control blood triglycerides

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridemia [triglycerides >2.3 mmol/L (200 mg/dL)]	**I**	**A**
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered	**IIa**	**B**
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 2 g/day) may be considered in combination with a statin	**IIa**	**B**

4. NEW DRUGS AND THERAPEUTIC APPROACHES IN TREATMENT OF DYSLIPIDEMIA

4.1. Bempedoic acid

Bempedoic acid is a prodrug and the active metabolite ESP15228 inhibits ATP citrate lyase - an enzyme upstream of HMG-CoA reductase in the biochemical cholesterol synthesis pathway. Inhibition of ATP citrate lyase prevents endogenous cholesterol synthesis and indirectly increases the expression of LDL receptors, thereby increasing the clearance of LDL-C. It has been approved by the FDA and EMA for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or ASCVD who require additional LDL-C lowering. The recommended dosage is 180 mg taken orally once daily. Five clinical trials have demonstrated the safety and efficacy of bempedoic acid: HARMONY, WISDOM, SERENITY, TRANQUILITY and OUTCOMES. The HARMONY and WISDOM studies showed that after 12 weeks of treatment, LDL-C levels decreased by 16.5% in the group of patients receiving bempedoic acid and 15.1% in the control group treated with high-dose statins. The TRANQUILITY study provided substantial safety data and the drug was well tolerated. The drug does not cause myopathy like long-term statin treatment. Common side effects include upper respiratory tract infections, urinary tract infections, joint pain, muscle spasms, and diarrhea; however, these symptoms were also observed in the placebo group. In the SERENITY trial, one observation showed increased blood uric acid levels, but other trials did not support this finding [3].

4.2. Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) that targets PCSK9, interferes with the translation of PCSK9 by cleaving messenger RNA, thereby decreasing PCSK9 production. The absence of PCSK9 results in the upregulation of LDL receptors and, consequently, reduces circulating cholesterol levels [13]. It is available as a pre-filled syringe for subcutaneous injection, containing 284 mg inclisiran in 1.5 ml solution. An additional advantage is the method of administering the drug: subcutaneous injection on day 1, day 90, day 180 and then every 6 months with the recommended dose is 284mg [13]. The effects was observed in the ORION trials: LDL-C levels were reduced by approximately 50% compared with placebo. Although these results showed slightly lower

efficacy compared with PCSK9 inhibition, patient compliance was better. ORION studies also showed that the drug is well tolerated and safe to use in all patients without dose adjustment. The drug has few side effects. Local reactions at the injection site, myalgia, and upper respiratory tract symptoms were common side effects, but the frequency was similar in the inclisiran and placebo groups [4, 13]. Inclisiran has been approved by the FDA and EMA for patient with ASCVD and HeFH.

4.3. Evinacumab

Angiopoietin-like 3 (ANGPTL3) is an inhibitor of lipoprotein lipase and endothelial lipase enzymes. Complete ANGPTL3 deficiency showed no evidence of coronary atherosclerotic plaque. Evinacumab is a fully human monoclonal antibody that inhibits ANGPTL3. Dosing is 15 mg/kg administered by intravenous infusion once monthly. Effectively reduced LDL-C by 47.1% compared to a 1.9% increase in the placebo group. Evinacumab has very few side effects, mainly upper respiratory tract infections and flu-like syndrome. Like other intravenous drugs, evinacumab has the potential to cause allergic reactions and even anaphylaxis[14]. Currently, evinacumab is approved by the FDA and EMA for the treatment of HoFH.

4.4. Lomitapide

Lomitapide directly binds and inhibits microsomal triglyceride transfer protein (MTP), which is an enzyme required for the transfer of triglycerides to Apo B and the assembly of VLDL particles. Inhibition of MTP causes a reduction in Apo B secretion in the liver and a reduction in total cholesterol levels. Lomitapide showed a significant dose-dependent reduction in LDL-C, both as monotherapy: 19% at 5 mg, 26% at 7.5 mg, and 30% at 10 mg, and in combination with ezetimibe: LDL-C decreased further by 35%, 38%, and 46%, respectively [15]. It is administered orally at a dose of 5 - 10 mg. The drug is generally safe, the most serious side effect is increased liver enzymes. Lomitapide has been approved by both FDA and EMA for the treatment of adult HoFH patients.

4.5. Pelacarsen

Pelacarsen is an antisense oligonucleotide that binds to hepatocyte apo(a) mRNA and forms an ASO/mRNA complex that prevents the translation of apolipoprotein(a), leading to decreased apolipoprotein(a) production and thus reduces circulating Lp(a) levels. Clinical trials of pelacarsen are still underway, and the published results are quite optimistic. Pelacarsen was administered subcutaneously at doses of 20 mg every 4 weeks, 20 mg every 2 weeks, 20 mg every week, 40 mg every 4 weeks, and 60 mg every 4 weeks, with a reduction in circulating Lp(a) of 35%, 58%, 80%, 56%, and 72% respectively [16]. Most side effects were mild to moderate, with 5% of patients discontinuing treatment because of muscle pain, joint pain, discomfort, or injection site reactions.

4.6. Volanesorsen

Volanesorsen is an antisense oligonucleotide that binds to the ApoC-III mRNA and disrupts apoC-III translation, leading to lower apoC-III levels and lower levels of chylomicrons and triglycerides. Phase III clinical trial results published in 2021 showed that after 3 months, TG concentrations decreased by 71.8% compared to the placebo group. Additionally, pancreatitis events were reduced, with five events of acute pancreatitis in the placebo group versus none in the volanesorsen treatment group. Specifically, patients eligible for the Phase III clinical trial are those diagnosed with Familial Chylomicronaemia Syndrome (FCS). Based on these results, volanesorsen was approved by the EMA for the treatment of hypertriglyceridemia and FCS. Although the results are quite optimistic, the safety is not completely clear. The most common side effect is injection site reaction; Severe thrombocytopenia has been seen. Volanesorsen is injected subcutaneously at a dose of 285 mg once a week. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks [3].

4.7. Olezarsen

Similar to volanesorsen, olezarsen is an antisense oligonucleotides (ASOs) targeting apoCIII, and through apoC-III translation disruption, chylomicrons and triglyceride levels are reduced. It is currently in phase III clinical trials. The first results of the Phase II trial were published in early 2022. The treatment regimens tested were 10 mg every 4 weeks, 15 mg every 2 weeks, 10 mg every week, and 50 mg every 4 weeks, subcutaneously. Evaluation was performed after 6 months of treatment with TG reductions of 23%, 56%, 60%, and 60%, respectively. Compared to volanesorsen, olezarsen does not cause thrombocytopenia and the main side effects are mild injection site reactions [17].

4.8. Mipomersen

Mipomersen is an antisense oligonucleotide that targets apolipoprotein B (Apo B) mRNA and interferes with translation, thereby decreasing Apo B levels, thus reducing LDL-C and total cholesterol levels in the blood. In studies, LDL-C levels decreased

by 24.7% over 26 weeks compared to placebo. In 2012, the FDA approved mipomersen subcutaneous injection at a dose of 200 mg once weekly in patients with HoFH. However, mipomersen has significant side effects, ranging from local injection reactions to flu-like symptoms, causing many patients to discontinue treatment. The most serious side effect is hepatotoxicity, which increases liver enzymes and accumulates fat in the liver. Therefore, after initial FDA approval, mipomersen was given a special warning about hepatotoxicity and later discontinued from market [3].

4.9. Lerodalcibep

Lerodalcibep is a recombinant fusion protein of a PCSK9-binding domain (adnectin) and human serum albumin, inhibits PCSK9 by gene editing, using CRISPR-Cas9 techniques. It has a half-life of 12 - 15 days, allowing it to be injected only once a month. A phase II study of 300 mg once monthly in patients with LDL-C > 2.0 mmol/L (~ 80 mg/dL) despite maximally tolerated statin therapy, resulted in a reduction of more than 70% LDL-C after 12 weeks. The rate of side effects was roughly equivalent to placebo. An extension of this study showed a sustained mean LDL-C reduction of 60% over 36 weeks. The ORE trial focusing on HoFH, CVD prevention, and high-risk primary prevention is ongoing and includes six phase III trials [18].

4.10. Vaccines against PCSK9

Another strategy is based on vaccines against PCSK9, which induce a sufficient production of antibodies against PCSK9, which should neutralize the interaction between PCSK9 and LDL-R. L-IFPTA (liposomal immunogenic fused PCSK9-tetanus peptide plus Alum adjuvant) is a recently designed novel PCSK9 vaccine. The efficacy of the L-IFPTA vaccine has been shown in different animal models [19]. The vaccine induced the safe and long-lasting production of functional anti-PCSK9-specific antibodies in BALB/c mice and reduced LDL-C and VLDL-C levels by up to 51.7% and 19.2% in C57BL/6 mice without any significant side effects [20].

5. CONCLUSION

The increase in cardiovascular disease in recent years has brought a huge medical burden and increased risks for mortality. This requires rapid intervention and aggressive modification of risk factors for atherosclerotic. In particular, reducing LDL-C levels and reducing the risk of cardiovascular disease in primary and secondary prevention is one of the main goals mentioned in the guidelines of cardiovascular associations in Vietnam and around the world. Statins are the drugs of first choice for treating dyslipidemia with well-established efficacy, and use at maximum tolerated doses in combination with ezetimibe usually allows the achievement of LDL-C goals. However, some patients do not achieve optimal LDL-C goals or do not tolerate statins, especially at high doses. These patients are at high risk of cardiovascular disease. Therefore, several new drugs discussed in this review have been introduced to reduce the risk of cardiovascular disease (alirocumab, acid bempedoic, volanesorsen, olezarsen, lomitapide,...), and extensive research is focusing on new drugs for the treatment of hypercholesterolemia, which hold promise in treatment of dyslipidemia.

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