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Newer Strategies in Treatment of Dyslipidaemia Overriding the Conventional Therapy: A Review Article

Rasmirekha Behera*
Professor Pharmacology
IMS & SUM Hospital, Bhubaneswar, Odisha, India
**Corresponding Author: Rasmirekha Behera, Professor Pharmacology, IMS &SUM Hospital, Bhubaneswar, Odisha, India*

ABSTRACT:
Cardiovascular disease (CVD) is among the primary causes of morbidity and mortality world wide.Hyperlipidemia is the cornerstone of CVD development and progression.Decreasing low-density lipoprotein cholesterol (LDL-C) is the main objective of hypolipidemic therapy.LDL particles constitute the end product of lipoprotein metabolism and must be cleared via an endosomal pathway by hepatic lipoprotein receptors such as the LDL receptor and LDL receptor related protein.Statins are the primary hypolipidemic treatment because by decreasing LDL-C levels,they reduce CVD in both primary and secondary prevention.Statins are among the most widely used medication for dyslipidemia.Apart from statins other therapeutics that reduce LDL levels have been shown to be effective in decreasing the risk of cardiovascular events.The aim of the article to review the role of new therapeutic approaches in treatment of dyslipidaemia.
Key words*: Dyslipidemia, Statins, Bempedoic Acid,Inclisiran,PCSK9 inhibitor*

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I. INTRODUCTION:

Cardiovascular disease (CVD) is among the primary cause of morbidity and mortality worldwide.(1)Apart from well-known risk factors such as hypertension,diabetes mellitus and smoking dyslipidaemia plays an important role in the development of cardiovascular disease,people with elevated serum lipoprotein levels have a two times greater chance of developing CVD than those without.(2,3)Dyslipidaemia,a crucial correctable predictive factor for coronary artery disease,are defined as alteration of the plasma lipid profile:increased levels of total cholesterol,LDL cholesterol or triglycerides or a low plasma concentration of HDL cholesterol or a combination of these features.(4)Hypercholesterolemia the most common form of dyslipidemia,is associated with elevated LDL cholesterol levels,which have been shown to be an important causal factor for ischemic heart disease and ischemic stroke in both developed and developing countries.(4)Dyslipidaemias are divided into primary or familial dyslipidaemias or secondary to other conditions such as diabetes mellitus,thyroid diseases,obesity and unhealthy life style,the latter being more common.(4)Familial forms account for less than 2% of all dyslipidaemias are caused by genetic defect of a single gene (monogenic) or multiple genes (polygenic).(5)Homozygous familial hypercholesterolemia (HoFH) is an autosomal co-dominant disorder caused primarily by a number of mutations in the LDLR gene,although mutations in the genes for apoB 100,PCSK9 and clathrin adaptor protein-1 can also give rise to phenotypic FH.(6)Dyslipidaemias are usually defined as those with elevated total and LDL cholesterol those with elevated triglycerides and those with both elevated LDL cholesterol and elevated triglycerides,with considerable attention also paid to elevate Lp(a) and low HDL cholesterol.Significant number of CV events persist despite maximal therapy,it has been necessary to combine different therapeutic approaches and test several new drugs to reduce the burden of CVD.(7)The primary emphasis of lipid lowering therapy is LDL-C reduction.(8)LDL particles constitute the end product of lipoprotein metabolism and must be cleared via an endosomal pathway by hepatic lipoprotein receptors such as the LDL receptor and LDL receptor related Protein 1.Cardiovascular risk associated with elevated LDL-C and the benefits of lowering LDL-C well below the generally recommened 70mg/dl for patients at high risk or with a history of prior ASCVD adverse events.(9)Currently secondary dyslipidaemias related to diabetes mellitus,obesity and unhealthy lifestyle.One of the primary methods of atherosclerotic CVD (ASCVD) prevention and treatment is lipid lowering therapy an area of great complexity and efficacy.Measuring serum lipid levels,defining risk-stratified lipid goals,assessing response to lipid lowering therapy and determining individual ASCVD risk.(10,11)

The most frequently measured and clinically utilized components within the lipid panel include total cholesterol,triglycerides,low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein(HDL-

C).While not specifically noted on the standard lipid panel,very low density lipoprotein cholesterol(VLDL-C) is an additional key component and atherogenic lipoprotein.(8)With regards to other lipoprotein targets,Lp(a) lipoprotein (a) is a lipoprotein compromised of apo(a) and apoB proteins covalently linked by a disulfide bond.(12)Lp(a) is thought to mediate cardiovascular risk throughinflammatory,atherogenic and thrombotic mechanisms.(13)Several clinical studies have demonstrated the role of low density lipoprotein cholesterol (LDL-C) in the development of atherosclerosis and CVD.(14)Treatment initiation achievement of goal LDL-C levels and maintenance of lipid lowering therapies remain suboptimal .(15,16)Because a significant number of Cardio Vascular events persist despite maximal therapy,it has been necessary to combine different therapeutic approaches and several new drugs to reduce the burden on cardiovascular deaths.(7)
The article will review the recent concept of lipid lowering drugs the in treatment of dyslipidemia.

STATINS:

Statins are most widely used medications and are the first therapeutic choice for dyslipidemia particularly for elevated LDL cholesterol levels.(17)They act as antagonists for 3-hydroxy-3-methyl glutaryl coenzyme A reductase and by inhibiting the enzyme HMG-3-CoA,reductase blocks the endogenic cholesterol synthesis pathway,resulting in the lower LDL cholesterol serum levels.(18)The reduction in intracellular cholesterol leads to an upregulation of LDL receptors on the surface of hepatocytes,which augments their LDL clearing capacity.Statins have also been shown to have anti-inflammatory properties at the sites of endothelial dysfunction and atheroma,which helps to restore endothelial function and stabilize plaque.(19,20,21)Statin therapy has also been shown to reduce acute ASCVD events in primary prevention as well as in patients with diabetes mellitus,hypertension and heightened systemic inflammatory tone.Statin therapy is universally recommended as first line in both primary and secondary CVD prevention.(22,23)Side effects such as new onset of diabetes has earned attention,in those starting statin therapy.(24,25) In those with objective muscle weakness ,checking creatinine kinase to evaluate for rhabdomyolysis is recommended as it requires statin cessation .(10)

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 CVD.(14)Treatment initiation achievement of goal LDL-C levels

And maintenance of lipid lowering therapies remain suboptimal.(26,27)Therefore several new molecules have been introduced to reduce to treat dyslipidemia and reduce CVD risk.This narrative review will provide an overview of new drugs used in the treatment of dyslipidemia.

Newer Approaches in Dyslipidemia:

Bempedoic acid:

Bempedoic acid is an adenosine triphosphate (ATP) citrate lyase inhobitor that inhibits cholesterol biosynthesis and increases LDL receptor expression.ATP citrate lyase is 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 cholesterol.(27)Bempedoic acid is a prodrug that requires activation and the active metabolite inhibits ATP citrate lyase.(28)The enzyme acyl-CoA synthetase 1(ACSVL 1),

expressed primarily in the liver,converts the prodrug Bempedoic Acid in to the active metabolite.After activation,Bempedoic Acid inhibits adenosine triphosphate citrate lysase,resulting in a reduction in acetyl-CoA levels at a level in the cholesterol synthesis pathway upstream of HMG-CoA reductase,the

molecular target of statins.This results in a decrease cholesterol synthesis,thus leading to an upregulation of LDL-R and a subsequent lowering of LDL-C levels.(14)In addition activation of AMP-activated protein kinase leads to inhibitory phosphorylation of HMG-CoA reductase and acetyl-CoA carboxylase,improves glucose regulation and reduces proinflammatory cytokines production chemokines in human macrophages.(29,30)The capacity of bempedoic acid to reduce risk of acute cardiovascular events is being evaluated in the CLEAR Outcomes trial,which will campare bempedoic acid to placebo against a no-statin background.(31)The efficacy and safety of BA in combination with ezetimibe was investigated in the CLEAR Traquilly study (III).Bempedoic Acid reduced LDL-C levels by 28.5% compared to placebo.The association was found to be safe and effective,with no significant difference in side effects compared to placebo.(32)

Inclisiran:

One of the most recently approved drugs for the treatment of dyslipidemia is inclisiran.It is a small interfering ribonucleic acid (siRNA) that targets PCSK9.PCSK9 is an important protein involved in LDL receptor degradation.Inclisiran an siRNA,interferes with the translation of PCSK9 by cleaving messenger RNA,there by decreasing PCSK9 production.The absence of PCSK9 results in upregulation of LDL receptor

and consequently lowers the circulating level of LDL cholesterol.(33,34)The use of small interfering RNA(siRNA) represents another strategy to reduce PCSK9 secretion.siRNAs block the expression of specific

genes with complementary nucleotide sequences by selectively silencing the translation of their complementary Nucleotide sequences by selectively silencing the translation of their complementary nucleotide sequences by selectively silencing the translation of their complementary target mRNAs.(35)PCSK9 is a serine protease found in many tissues but mainly expressed in the liver that targets LDL-R.It leads the receptors to lysosome-mediated degradation,thus diminishing their recycling and decreasing the removal rate of circulating LDL-C with a subsequent increase concentration in the blood.(36,37,38)Although these results indicate slightly lower efficacy than that of monoclonal PCSK9 inhibitors,patient compliance with inclisiran therapy is believed to be better because of infrequent

administration.(33)Adverse effects are uncommon with inclisiran therapy and has been approved by the FDA and EMA for the treatment of mixed dyslipidaemia and hypertriglyceridemia.

PCSK9 Inhibitors:

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new generation of lipid-lowering drugs with many clinical trials suggesting very good LDL cholesterol lowering results.PCSK9 plays an important role in LDL receptor downregulation.LDL receptors are found on hepatocytes and play a role in the removal of circulating LDL cholesterol from blood.When the PCSK9 protein binds to the LDL receptor,it starts the process of degrading the receptor,thus increasing LDL cholesterol levels.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.(39)Alirocumab and evolocumab are administered subcutaneously once every two weeks.Steady concentration of both the drugs were achieved within 4-6weeks from the start of the treatment.(40,41)Most limiting factor for wider use of PCSK9 inhibitors is their cost.The benefits of these monoclonal antibodies surpass their relative high cost for certain indications.(42)

ANGPTL3 Inhibitors:

One of the new possible targets for the treatment of dyslipidaemia is angiopoietin-like 3 protein(ANGPTL3),which is currently one of the main focal points of lipidology studies.ANGPTL3 acts as an inhibitor of lipoprotein lipase(LPL) and endothelial lipase (EL) enzymes.(43)Both enzymes are important in the serum increase in triglycerides and LDL cholesterol,so inhibition of ANGPTL3 protein leads to the disinhibition of LPL and EL and therefore a decrease in triglycerides and LDL cholesterol levels in circulation.(44,45) The first drug in the class of ANGPTL3 inhibitors is evinacumab,a monoclonal antibody already approved by the FDA and EMA for the treatment of familial hypercholesterolemia.

Evinacumab has very few reported adverse effects with most being upper respiratory tract infections and flu-like syndromes.Evinacumab has potential to cause serious allergic reactions or even anaphylaxis.(46)Another possibility to target ANGPTL3 is the antisense oligonucleotide vupanorsen.Vupanorsen is a liver-targeted antisense oligonucleotide that inhibits the synthesis of ANGPTL3.It shows increase in alanine aminotransferase(ALT) and aspartate aminotransferase (AST) were observed as adverse effects.(47)

Vaccines against PCSK9:

Proprotein convertase subtilisin/kexin type 9(PCSK9) represents a new therapeutic target in the management of dyslipidemias.PCSK9 is a secretory protein,primarily produced by hepatocytes,but many other tissues and cell types have been proven to express the PCSK9 gene.(48)After initial secretion,PCSK9 circulates in the bloodstream and binds to the LDL-R predominantly on the surface of hepatocytes via binding to the growth factor like repeat A catalytic domain,which is responsible for the circulation of the LDL-R to the cellular surface.PCSK9 synthesized in the liver interacts with the LDLR(49) Thus leading to its internalization and subsequent lysosomal degradation.(50,51) and the subsequent down regulation of the number of cell-surface LDLR molecules.(52) Vaccines against PCSK9,which should trigger the generation of host anti-PCSK9 antibodies and consequently neutralize PCSK9 PCSK9/LDL receptor interactions.

II. CONCLUSIONS:

Increase in CVD in recent years imposes enormous costs in terms of mortality and morbidity.Lowering LDL-C levels and reducing CVD risk in both primary and secondary prevention is one of the main goals supported in European and American guidelines.(53,54) Currently there are numerous new agents aimed at lowering lipid levels and thus decreasing the morbidity and mortality of cardiovascular diseases.Statins are the standard therapy for treatment of hypercholesterolemia.However some patients do not achieve optimal LDL-C goals or do not tolerate statins especially at high dose.These patients are at high risk of CVD.New therapeutic agents have been investigated and introduced into clinical practice to address this difficulty.Further clinical trials

are needed to provide valuable information on the efficacy of these agents and their role in reducing CVD in patients with dyslipidemia.

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