Scholars Journal of Applied Medical Sciences (SJAMS) **ISSN 2320-6691 (Online)**
Sch. J. App. Med. Sci., 2015; 3(3F):1450-1456 **ISSN 2347-954X (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublishers.com DOI: 10.36347/sjams.2015.v03i03.084

Review Article

Dyslipidaemia: Current Therapy and Future Prospectus

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Abstract: Dyslipidaemia is a major cause of atherosclerosis and atherosclerosis-induced conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease and peripheral vascular disease. These conditions cause morbidity or mortality in a majority of middle-aged or older adults and account for about one-third of all deaths of persons in this age range. The incidence and absolute numbers will likely increase over the next decade because of the epidemic of obesity and the aging of the population. When pharmacotherpy is indicated, providers can choose from multiple agents with proven efficacy i.e. statins are the first-line drugs for treatment of dyslipidemia, but they do not address all CVD risk. Recognition that dyslipidemia is a risk factor has led to the development of drugs that modify cholesterol levels. The ongoing development of novel therapies include (i) Low-density-lipoprotein (LDL) cholesterol concentrations reduction by the use of antibodies to proprotein convertase subtilisin/kexin-9, antisense oligonucleotide inhibitors of apolipoprotein B production, acyl-coenzyme A cholesterol acyl transferase inhibitors and microsomal transfer protein (MTP) inhibitors; (ii) Triglyceride-rich lipoproteins level reduction with ω-3 fatty acids, inhibitors of MTP and diacylglycerol acyl transferase-1; and (iii) increase the level of high-density-lipoprotein (HDL) cholesterol levels, HDL particle numbers, and/or HDL functionality using cholesteryl ester transfer protein inhibitors, agents derived from HDL, apolipoprotein AI mimetic peptides, and microRNAs. This review article focuses on the currently available hypolipdemic drugs, their limitation and novel strategies for treatment of dyslipidaemia.
Keywords: Dyslipidaemia, Lipoprotein, Statins, CETP inhibitor, PCSK-9 inhibitor.

INTRODUCTION

Lipids are insoluble or sparingly soluble molecules. These are essential for membrane biogenesis, maintenance of membrane integrity, as energy sources and as signaling molecules etc [1]. It is known fact that atherosclerosis risk is associated with increased concentrations of LDL particles as well as TG and decreased concentrations of HDL [2-4]. The various role players in lipid metabolism are (a) Lipid (b) Lipoprotein (c) Apo-lipoprotein (d) Lipoprotein receptors and (e) various enzymes i.e. Lipoprotein lipase etc.

Normal lipoprotein metabolism

Normal lipoprotein metabolism is categorized into 3 steps [5]:

- Assembly
- Intravascular metabolism
- Receptor mediated clearance.
- **Assembly**

During this step lipoprotein are synthesized and released into the blood stream. Lipoproteins are assembled in the enterocyte from dietary fat and in hepatocytes from endogenous lipid. These two pathways are known as exogenous and endogenous pathway respectively (Fig 1).

- **Intravascular metabolism**

During this step lipoprotein molecules are taken up by the peripheral tissues and degraded to release FFA and TG by the action of Lipoprotein lipase which is present on endothelial surface of capillaries in muscle & fat tissue. Apoprotein C-II helps to bind LPL however Apoprotein C-III inhibit LPL activity.

- **Receptor mediated clearance**

This is final step of lipoprotein metabolism. During this step Cholesterol + Apo E are taken up by liver and the cholesterol is used to synthesize VLDL [endogenous pathway] and to some extent HDL. Apo A-I and Apo A-II are useful during HDL particle

synthesis. Apart from it PCSK-9, Apo CI/II and Apo C-III also play their role in normal lipoprotein metabolism.

Disorders of lipid metabolism

Disorders of lipid metabolism are defined as Dyslipidaemia and it is further classified [6] as (a) Primary due to some genetic reason (Table 1) and (b) Secondary due to some systemic disorder i.e. DM/Hypothyroidism/Hypopituitarism etc.

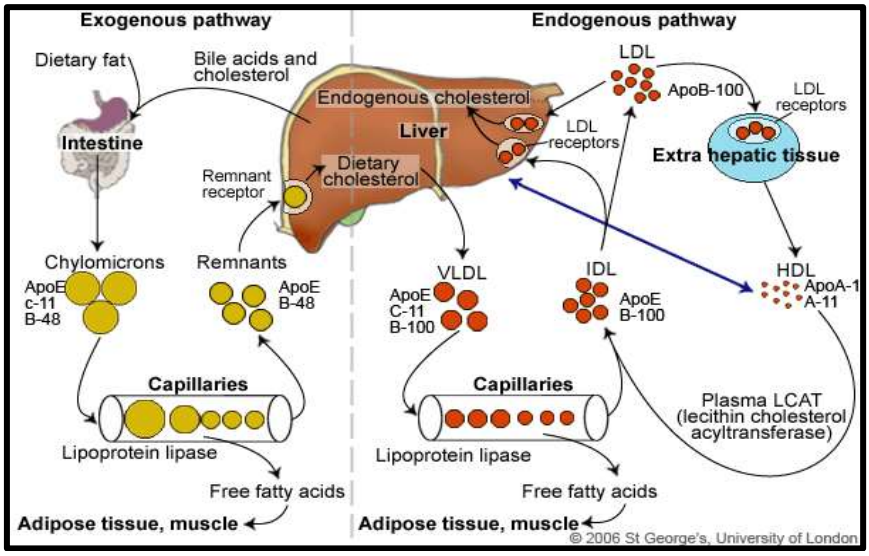

Fig. 1: Lipoprotein metabolism – exogenous and endogenous pathway

Table 1: Examples of primary hyperlipidaemias and the associated lipoprotein abnormalities

Type	Disorder	Cause	Elevated plasma lipoprotein	Atherosclerosis risk	Drug treatment
I	Familial lipoprotein lipase deficiency	Genetic	Chylomicron	NE	None
IIa	Familial hypercholesterolaemia	Genetic	LDL	High	Statin +/- Ezetimibe
IIb	Polygenic hypercholesterolaemia	Multifactorial	LDL	High	Fibrates, Statin, Nicotinic acid
III	Familial dysbetalipoproteinaemia	Genetic	IDL, Chylomicron remenants	Moderate	Fibrates
IV	Hypertriglyceridaemia	Multifactorial / Genetic	VLDL	Moderate	Fibrates
V	Familial combined hyperlipidaemia	Genetic	VLDL, LDL	High	Fibrates, fish oil, Niacin & statin combination

CURRENTLY AVAILABLE AGENTS

The earliest lipid-lowering drug—niacin—was discovered in 1955, and bile acid sequestrants and fibrates were developed in the 1960s. These drugs have been almost completely replaced by statins, which are more effective in reducing LDL-C. Fibrates primarily reduce TG levels and have lesser effects on LDL-C while marginally increasing HDL-C levels, but their main action is to increase LDL and HDL particle sizes [7]. Niacin increases HDL-C levels by 20–25% in a dose-dependent manner, reduces LDL-C and TGs by up to, 5%-25% and 20%-50%, respectively [8]. Bile acid sequestrants are positively charged molecules that act by binding negatively charged bile acids and preventing the opsonization of lipid-rich particles, and subsequent cholesterol absorption, in the gut.

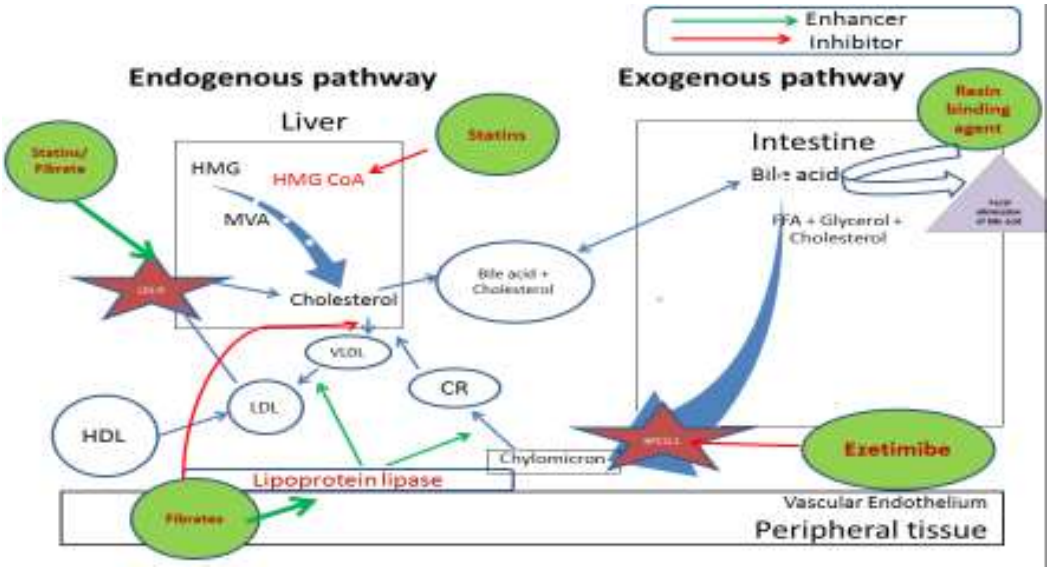

Fig. 2: Currently available hypo-lipidemic drugs and their site of action

LIMITATION WITH CURRENTLY AVAILABLE HYPO-LIPIDAEMIC DRUGS

Statins: Statins are drugs of choice for lowering LDL-C, but these do not address the entire spectrum of CVD risk

- Statins have Non-linear dose effect
- Maximum doses are limited by side effects i.e. myalgia, Increase transaminase, statin intolerance etc.
- Combination with Niacin: increased risk of myopathy
- Co-administration with Gemfibrozil: increased risk of Rhabdo-myolysis

Fibrates

- Fibrates show NO benefit on fatal CHD events, stroke or mortality
- Fibrates associated with increase in serum creatinine [reversible] and venous thrombosis
- Fibrates can decrease HDL-C if used in combination with PPAR or retinoid-X receptor acting drug such as PPAR-Y agonist

Bile acid sequestrants

- Significant bloating and dyspepsia limit patient compliance
- Decrease absorption of fat-soluble vitamins: bleeding may result due to vitamin K deficiency

Niacin

- flushing due to PGD2 and PGE2 synthesis
- Hepatotoxicity
- New cases of type II DM
- Excess infections
- Hyperuricaemia occurs in 20% of patients and may precipitate gout

Ezetimibe

- Inhibition of cholesterol absorption by Ezetimibe leads to a compensatory increase in hepatic cholesterol synthesis
- Minimal impact on surrogate outcome for Statin-Ezetimibe combination as compared with high dose statin monotherapy or Statin-Niacin combination therapy [9]

FUTURE PROSPECTUS: NOVEL APPROACH FOR TREATMENT OF DYSLIPIDAEMIA

Even after high dose of currently available hypo-lipidaemic drugs target level of LDL-C is not achieved. Desired reduction in dys-lipidaemia associated morbidity and mortality is still a challenge. Considering the facts newer therapeutic target have been identified and are being explored for useful drug to treat dyslipidaemia. These novel therapeutic approachs are being focused for below mentioned objectives:

To lower LDL-C level

- PCSK-9 inhibitor
- ASO inhibitors of Apo-B production
- MTP inhibitors
- Acyl CoA cholesterol acyl transferase [ACAT] inhibitor

To lower TG level

- ω-3 fatty acid
- Diacylglycerol transferase-1 [DGAT-1] inhibitor
- MTP inhibitors

To increase HDL level and/or enhance HDL functionality

- Cholesteryl ester transfer protein [CETP] inhibitor
- HDL derived protein
- Apo A-1 mimetic peptides
- Reconstituted HDL infusion
- HDL delipidation strategies

- Micro-RNA [miRNA]
- PCSK-9 inhibitors

PCSK-9 [Pro-proconvertinsubtilisn kinase-9]

It is involved in Autosomal Dominant Hypercholesterolemia [10]. It is a glycoprotein which contains 692 amino acids. It is secreted by Liver, small intestine, Kidney & CNS. It is found that loss of PCSK-9 lead to Hypocholesterolemia with no apparent associated side effect [11]. PCSK-9 plays a central role in cholesterol homeostasis by enhancing lysosomal degradation of hepatic LDL-C receptor thereby modulating plasma LDL-C level. It affects both fasting and post-prandial lipid metabolism. It is associated with hormonal control of lipid metabolism by estrogen, androgen, GH etc [12]. Therefore, PCSK9 inhibitors reduce plasma LDL-C by increasing the numbers of LDL receptors available at the cell surface.

PCSK9 inhibitors currently under development are (alirocumab (Sanofi-Aventis/Regeneron; Paris, France; Tarrytown, NY), evolocumab (Amgen, Thousand Oaks, CA), and bococizumab (Pfizer, New York, NY)) [13].

Antisense oligonucleotides

These are short single stranded synthetic analogs of neutral nucleic acid designed to specifically bind to a target mRNA. They specifically reduce or silence gene expressions. The genetic assessment verified that ASO may lead to Hypo beta-lipoproteinemia and decrease Apo-B & LDL-C with normal life expectancy [14]. A new Apo-B ASO [Mipomersen] has been studied widely. Mipomersen [Apo-B ASO] decreases Apo-B 100/LDL-C/non HDL-C & TG in patients treated with statin or other LLD [15, 16]. The side effect observed injection site reaction and hepatic steatosis.

Another Apo CIII ASO is under evaluation. It is secreted in Liver. Genetic study indicated that decrease Apo CIII is associated with decrease TG and decrease CVD and extended life [17].

ACAT inhibitor

Acyl cholesteryl acetyl transferase enzyme plays its role in lipoprotein metabolism. It casues esterification of cholesterol. During atherogenesis, cholesterol accumulates in arterial wall and foam cell generated due to esterification of cholesterol in macrophages [18]. However, non selective ACAT inhibitors like Avasimibe and Pactimibe failed to decrease atherosclerosis progression. Therefore selective inhibitor of ACAT-1like K-604, are being considered under-development [19].

Microsomal transfer protein inhibitors

MTP are required for formation and secretion of Apo-B containing lipoprotein from hepatic/intestinal cell. MTP mutation is found to be associated with abeta-lipoproteinemia [Autosomal recessive condition] [20]. MTP inhibition in pre-clinical study showed decrease TG & cholesterol level. Implitapide lead to decreases LDL-C and the side effect are GIT related/Hepatic fat accumulation. Due to which its development discontinued. Lomitapide, approved in Dec-2012 for HoFH, found to be useful in moderate hypercholesterolemia either alone or in comination with ezetimibe [21,22]. The side effects observed include increased transaminase and increased fat in liver. Due to limitation with non-specific MTP inhibitor gut targeted MTP inhibitor are being explored to decrease plasma TG. One such compound SLX- 4090, decreases both VLDL & Chylomicron and cause weight loss without increase in hepatic fat or enzyme [clinical study ongoing] [23].

ω-3 fatty acid

They are recommended either as monotherapy or in combination with statin/fibrate [24]. These agents are usually used in high doses [3-4gm per day]. For example EEPA /DOHA are useful in hypertriglyceridemia.

DGAT inhibitor

Di-acyl glycerol acetyl transferase enzyme plays its role lipoprotein metabolism. It causes esterification of cholesterol. DGAT is involved in TG synthesis in adipose tissue/intestine & liver. These are involved in incorporation of free fatty acid. Decreased activity of DGAT-1 showed reduced TG synthesis, hepatic steatosis and obesity [25]. They show improvement in insulin resistance. DGAT-1 inhibitors are used in hyper TG with Lipoprotein lipase deficiency. A numbered compound LCQ-908, new DGAT-1 inhibitor, decreases fasting TG level. Its clinical trial is underway.

CETP inhibitor

CETP involved in transfer of cholesteryl esters from HDL to the apoB-containing lipoproteins, with a parallel reverse exchange of TGs. CETP inhibitors presentlty under clinical development, includes torcetrapib, dalcetrapib, anacetrapib and evacetrapib. the ILLUMINATE trial with torcetrapib was terminated as a result of excessive serious adverse effects in the active arm [26], whereas dalcetrapib development was suspended after findings of futility in the dal-OUTCOMES trial [27]. The REVEAL outcome trial is currently ongoing for anacetrapib [28]. Effects of evacetrapib on plasma lipids are similar to those of anacetrapib, involving increase in HDL-C by 54–130% and reductions in LDL-C by 14–36% in monotherapy or when added to statin therapy [29].

HDL derived agent

These are isolated, partially delipidated HDL protein. Native Apo-A1 or its genetic variant i.e. Apo A1 Milano complexed with phospholipid. These are functional, non antigenic and not instantly degraded in kidney.

HDL infusion

There are a number of compounds which are being explored for infusion purpose. ETC-216 is a recombinant apo A1 milano/phospholipid disc. It is recommended as five weekly IV infusion. It reduces coronary atherosclerosis [30]. CSL-111 is a purified human apo A1 combined with soybean phosphotidylcholine. It has a favorable effect on plaque morphology however no significant effect on plaque volume [31]. CER-001 is an engineered pre β-like HDL recommended as weekly IV infusion. In animal model- it increases reverse cholesterol transport & decreases atherosclerotic burden [32].

Apo A-1 mimetic is an oral D-4F. It causes regression of atherosclerotic lesion independent of both plasma cholesterol level and statin therapy [33,34]. ATF-5261 is a potent cellular cholesterol efflux activity [35]. It help reducing atherosclerosis.

HDL delipidation techniques involves removal of HDL particles from the circulation with delipidation and subsequent reinfusion of cholesterol depleted functional pre β-HDL by the apheresis process. It is shown to reduce carotid atheroma volume [36].

miRNA

These are noncoding RNA of 20-22 nucleotide long chain. These agent acts at post transcriptional level. They repress gene expression via mRNA translational repression or destabilization and play role in HDL metabolism & reverse cholesterol transport [37]. They control cholesterol efflux i.e. miR-33, miR-758, miR-26, miR-106, miR-144 etc. and may control B1 mediated HDL-C uptake i.e. miR-223, miR-455-5p, miR - 96, miR-185 & miR-125a etc. Spcifically miR-33 has shown efficacy in plasma HDL-C level modulation [38] however miR-30c independently control both hepatic lipid synthesis & apo-B containing lipoprotein secretion [39].

CONCLUSION

Statins comprises the cornerstone of lipid-lowering therapy with a strong evidence based in terms of both efficacy and safety. Absolute reduction in LDL-C levels correlates with reduction in the rate of cardiovascular events. Novel approaches using gene technology and translational mechanisms resulted in considerable progress in the development of newer therapeutic agents to reduce the levels of proatherogenic lipoproteins and lipids and/or by increasing levels of antiatherogenic lipoproteins. However, safety concerns and the high price of many of these orphan drug therapies is likely to severely limit their availability. Therefore, further studies are needed to explore the safety of these agents and to define their effect on clinical outcomes.

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