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Review Article

CURRENT TRENDS IN MANAGING HYPERLIPIDEMIA- REVIEW ARTICLE

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A B S T R A C T

Hyperlipidemia is an increase in the plasma lipids like triglycerides, cholesterol, phospholipids and low density lipoproteins (LDL) with reduction in high density lipoproteins (HDL). Elevated LDL meanwhile is accepted as the leading factor which causes atherosclerosis from decades. Therapeutic control beginning with statins and fibrates has kept it under the bar to some extent but myalgia and other side effects are worrisome due to them. Many new drug targets to treat hyperlipidemia are available now. The review focuses on new strategy as well as new lipid lowering agents available for this major risk factor for cardiovascular diseases.

INTRODUCTION

Hyperlipidemia is characterized by abnormally high lipids (fats) in the blood. While fat plays a vital role in the body's metabolic processes, high blood levels aggravates the risk of coronary heart diseases (CHD). It is believed that CHDs will be the major cause of death worldwide by 2020. [1] Decline in HDL and elevation of serum triglycerides can also increase the deposition of lipids in the arteries leading to cardiac ailments, especially in people who are obese or have diabetes.[2] Advancement in treating hyperlipidemia is occurring every hour and various drugs from statins to PCSK9 inhibitors are available. But still it's a major risk factor for cardiovascular event.

HMG-CoA-Reductase Inhibitors

HMG-CoA-Reductase Inhibitors are the first class of hypolipidemic drugs. Production of HMG-CoA-Reductase enzyme and of the LDL receptors is transcriptionally regulated by the content of cholesterol in the cell. Elevation in the cholesterol level is in well known association with cardiovascular diseases (CVD), and these enzyme inhibitors i.e. statins are the most common drugs used in its prevention.[3, 4]. Recently the new recommendations for giving statins for atherosclerotic cardiovascular disease prevention divides it into two groups, on the basis of dose, known as high intensity statins which lowers the LDL cholesterol by 50% of the baseline and low intensity statins which decreases LDL cholesterol by 30%, merely a difference of 20%.[5]

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Side effects– Commonly seen are transient gastritis, headache, myalgias and drowsiness. High intensity statins causes more side effects than low intensity. Myopathy is one of the rare side effect which has prevalence of 1/10,000 persons per year, most of which recovers spontaneously after treatment is discontinued. Very rarely autoimmune myopathy occurs in some patients which may causes significant muscle necrosis.[6,7,8]. These also causes diabetes mellitus, poor sleep quality and rhabdomyolysis especially if given in combination with fibrates.[9]

Fibrates

Fibrates mainly decreases triglycerides along with increases in the HDL-cholesterol levels although to a lesser extent. It acts on PPAR-α receptor leading to increased β-oxidation in the liver, causing decline in synthesis of triglycerides. It also accentuates the activity of lipoprotein lipase causing decline in VLDL levels and elevation of HDL along with increased clearance of remnant particles.[10]

Side Effects includes myopathy, arrhythmias, skin rashes, deranged liver and renal functions and gallstones.[1] As fibrates has major emphasis on raised triglycerides and low high-density–lipoprotein cholesterol levels which directly doesn't have any clinical benefit but have significant impact in diabetic patients and mixed dyslipidemia.[12] It is proven in studies that the combination therapy of fenofibrates and simvastatins has no benefit in reducing rate of fatal cardiovascular events, nonfatal myocardial infarction, stroke, in comparison with single line treatment with simvastatin alone. [13]

Classification of drugs on the basis of mechanism of action is as follows

Classification	Drugs
HMG - CoA - Reductase inhibitors	Atorvastatin Lovastatin Fluvastatin Pravastatin Rosuvastatin Simvastatin Pitavastatin
Fibrates	Bezafibrate Ciprofibrate Clofibrate Gemfibrozil Fenofibrate
Nicotinic acid derivatives	Niacin
Bile acid sequestrants	Colestipol Cholestyramine Colesevelam
Cholesterol absorption Inhibitor	Ezetimibe
CETP(Cholesteryl Ester Transport Protein) Inhibitors	Torcetrapib Dalcetrapib Evecetrapib Anacetrapib
Apolipoprotein B synthesis Inhibitor	Mipomersen
Microsomal triglyceride transfer protein inhibitor	Lopitamide
Pcsk9(ProproteinConvertase Subtilisin / Kexin 9) Inhibitors	Bococizumab Evolocumab Alirocumab Inclisiran
Angiopoietin-like 3 (ANGPTL3) inhibitor	Evinacumab

High Intensity Statins	Atorvastatin 40 - 80 mg Rosuvastatin 40 - 80 mg
Low Intensity Statins	Atorvastatin 10 -20 mg Rosuvastatin 5 -10mg Simvastatin 20 -40mg Pravastatin 40 -80mg Lovastatin 40mg Fluvastatin XL 80mg Fluvastatin 40mg BD Pitavastatin 2- 4 mg

Nicotinic acid derivatives

Nicotinic acid also known as vitamin B_3 reduces the production of triglycerides and VLDL as well as increases the HDL. It is the nicotinic acid form of niacin that plays the major role. Nicotinic acid significantly increases the HDL levels, greater than any other lipid lowering agents.[14] The most common side effects of nicotinic acid are intense cutaneous flush, itching, headache, nausea and abdominal pain and elevated liver enzymes.[15] Study comparing combination of extended-release niacin–laropiprant to statin in peoples having atherosclerotic vascular disease shows no reduction in the risk of major vascular events but it leads to increase in various adverse effects.[16]

Bile acid sequestrants

These are a group of medications that binds to components of bile in the gastrointestinal tract disrupting the enterohepatic circulation and prevents their reabsorption from the gut. [17] It leads to greater synthesis of bile acids i.e. almost ten times that of normal resulting in increased conversion of cholesterol into bile. It also increase HDL levels to some extent.[18] It has been seen that second generation bile acid sequestrants like colesevelam and colestimide also have a glucose-lowering effect thus can be beneficial in diabetes mellitus patients.[19]

Cholesterol Absorption Inhibitor

Ezetimibe is the first member of this group of drugs which acts by inhibiting intestinal absorption of phytosterols and cholesterol, and has improved the treatment of hypercholesterolemia.[20] Common side effects of Ezetimibe includes back pain, arthralgia, diarrhea, sinusitis, abdominal pain, pharyngitis, coughing, viral infection and fatigability.[21] When combination of ezetimibe and statins are used, it is seen that it accentuates the lowering of LDL cholesterol levels and improves cardiovascular outcomes[22]. Whether this combination is beneficial is still not established as one other study shows that Ezetimibe±simvastatin had inconsistent effects on important outcomes with adverse effects.[23]

CETP (Cholesteryl Ester Transport Protein) Inhibitors

These acts by inhibiting the transfer of triglyceride and cholesteryl ester (CE) between lipoproteins. When this pathway is inhibited, it leads to markedly increase in HDL levels. First CETP inhibitor that came into use was torcetrapib.[24] It has also shown beneficial effects in declining cardiovascular risk as it markedly elevates HDL-C and apolipoprotein A-1 (apoA1) levels. Use of it increases the risk of mortality and morbidity due to unknown mechanism. Torcetrapib raises blood pressure and increases the concentration of serum aldosterone which raises risk of cardiovascular events.[25] After torcetrapib, dalcetrapib is the second CETP modulator which came into use but it only elevates HDL and has negligible effect on lowering LDL. Use of dalcetrapib in patients who had recent acute coronary syndrome increases the HDL cholesterol levels but there is no reduction in the risk of repeated cardiovascular events.[26] Two other CETP inhibitors, anacetrapib and evacetrapib, are undergoing phase III clinical trials. Both molecules have effects on increasing HDL-C and decreasing LDL-C levels. Although evacetrapib had favorable effects on lowering LDL, it did not result in a lower rate of cardiovascular events among patients with high cardiovascular risk.[27] Anacetrapib still bears as hope in this class of drugs.It had significant effects on LDL and HDL cholesterol, less side-effects, and, and also it do not have adverse cardiovascular effects.[28]

Apolipoprotein B - Synthesis Inhibitors

Mipomersen is an antisense oligonucleotide inhibitor of apoB-100 which is an essential component of lipoproteins such as VLDL and LDL. The dose of it is 200 mg/week subcutaneously. Side Effects includes injection site reaction ,influenza like symptoms, nausea and hepatic steatosis[29] It has significant effect in improving all lipid parameters but it doesn't have any effect on HDL levels.[30]

Microsomal triglyceride transfer protein inhibitor

Lomitapide acts by inhibiting cholesterol through microsomal

triglyceride transfer protein (MTP). MTP acts by causing adhesion of triglyceride on apolipoprotein B100, and form very low density lipoprotein (VLDL) which later converts into LDL. Lomitapide causes reduction in VLDL release and VLDL-mediated triglyceride secretion which overall leads to reduction in LDL.[31] It has common side effects like diarrhoea, nausea, vomiting, and constipation along with elevation liver enzymes.[32] It is mainly approved for the treatment of homozygous familial hypercholesterolemia. It is thus an alternative for patients who suffers from homozygous familial hypercholesterolemia who fails to achieve LDL-C goal or cannot tolerate statin therapy.[33, 34, and 35]

PCSK9 Inhibitors

The PCSK9 protein is produced by the hepatocytes. It binds with the complex of LDL receptor and LDL-C and get internalized into the liver cell. It causes lysosomal catabolism of receptors within the hepatocyte, thus preventing the process of LDL-R recycling.[36] The first two proprotein convertasesubtilisin/kexin type 9 (PCSK9) inhibitor approved in July 2015 by the US Food and Drug Administration were Evolocumab and Alirocumab.

Evolocumab when used alone has no significant effects but when given with statin, it has lowered LDL cholesterol level below current targets leading to major reduction in cardiovascular events. It should always be given in the background of statins.[37] One study shows that there is no decline in cognitive functions seen in patients taking evolocumab as presumed.[38] Treatment with other PCSK9 inhibitor like bococizumab has less or negligible benefit in low risk patients but have significant effects in higher risk patients. [39] Alirocumab also has the same effect in lowering the LDL as above but it has been seen in trials that anti drug antibodies are found in some patients treated with it.[40 41] It can be used as a single line therapy in patients not responding to statins and having significant hypercholesterolemia.[42] Side effects of alirocumab includes hypersensitivity, rash and pruritus.[43] Inclisiran is the only parenteral long-acting RNA interference (RNAi) therapeutic inhibitor of proprotein convertase subtilisin–kexin type 9 (PCSK9). It is effective in lowering low-density lipoprotein cholesterol in healthy volunteers. Its effects remains sustained for 6 months after single dose, thus twice yearly administration is needed only.[4]

Angiopoietin-like 3 (ANGPTL3) Inhibitor

Angiopoietin-like 3 (ANGPTL3) is a protein secreted and expressed in liver. It causes increase plasma levels of triglycerides, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol.[45] Evinacumab is an Angiopoietin-like 3 (ANGPTL3) protein inhibitor. Its use in homozygous familial hypercholesterolemia, leads to decline LDL cholesterol levels. Genetics as well as pharmacological antagonism of ANGPTL3 was associated with decrease in of all the three major types of lipid fractions, and decrease the risk of cardiovascular events too.[46]

New targets in dyslipidemia

Autoantibodies against GPIHBP1

It is a protein present on capillary endothelial cells called GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1). It acts by binding to the lipoprotein lipase and transport it to its site of action in the capillary lumen. GPIHBP1 deficiency will lead to severe hypertriglyceridemia (chylomicronemia). Autoantibodies formed against it are responsible for significant hypertriglyceridemia thus an important concern.[47]

Small nucleated RNA

These are chemically modified, small interfering RNA conjugates to the trivalent N-acetylgalactosamine therapeutics.It causes the destruction of RNA before the synthesis of lipoproteins. It will be added soon in strategy to lower the cholesterol.[48]

References

1. Jorgensen, T., Capewell, S., Prescott, E., Allender, S., Sans, S., Zdrojewski, T. Population-level changes to promote cardiovascular health. *Eur. J. Prev. Cardiol*., 2013; 20(3):409-21.
2. *Robert A. Kreisberg Jane E.B. ReuschHyperlipidemia (High Blood Fat) The Journal of Clinical Endocrinology & Metabolism*, 2005;90,3 Pages E1,
3. Ray KK, Seshasai SR, Erqou S. Statins and all-cause mortality in high-risk primary prevention: a meta analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med*, 2010, 170(12), 1024-31
4. Stone NJ, Robinson J, Lichtenstein AH, *et al*. ACC/AHAguideline on the treatment of blood cholesterol to reduce athero-sclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force1.
5. Hansen KE, Hildebrand JP, Ferguson EE, Stein JH. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* 2005;165:2671-6.
6. Echaniz-Laguna A, Mohr M, Tranchant C. Neuromuscular symptoms and elevated creatine kinase after statin withdrawal. *N Engl J Med* 2010;362:564-5
7. Klein M, Mann H, Pleštilová L, *et al*. Increasing incidence of immune-mediated necrotizing myopathy: single-centre experience. *Rheumatology* (Oxford) 2015; 54:2010-4.
8. Paul M RidkerCirculation: Cardiovascular Quality and Outcomes. 2009;2:279-285
9. Wiggins BS1, Saseen JJ Gemfibrozil in Combination with Statins-Is It Really Contraindicated? *CurrAtheroscler Rep*. 2016 Apr;18(4):18
10. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, Pilote L, Genest J, Eisenberg MJ. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. *Am J Med*, 2009, 122(10), 962-962.
11. Kishor, S., Kathiravan, M., Somani, R., Shishoo, C.H. The biology and chemistry of hyperlipidemia.*Bioorg. Med. Chem.,*2007; 15(14): 4674-4699.
12. Allison B. Goldfine, M.D., Sanjay Kaul, M.D., and William R. Hiatt, M.DFibrates in the Treatment of Dyslipidemias - Time for a Reassessment; *NEngl J Med* 2011; 365:481-484
13. The ACCORD Study Group*Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus *N Engl J Med* 2010; 362:1563-1574
14. Bhatt *et al*. Effects of antioxidant vitamins along with atorvastatin and atorvastatin–niacin combination on

diet-induced hypercholesterolemia in rats. *Int J Physiol Pathophysiol Pharmacol*, 2010, 2(1), 57-63.
15. Safeer, R. S., Lacivita, C.L. Choosing drug therapy for patients with hyperlipidemia. *Am. Fam. Physician.,* 2000; 61(11): 3371-82.
16. The HPS2-THRIVE Collaborative Group*Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients *NEngl J Med* 2014; 371:203-212
17. Wong NN. Colesevelam: a new bile acid sequestrants. Heart disease, 2001, 3(1), 63-70
18. Arnold, M.A., Swanson, B.J., Crowder, C.D., Frankel, W.L., Lam-Himlin, D., Singhi, A.D., Stanich, P.P., Arnold, C.A. Colesevelam and colestipol: novel medication resins in the gastrointestinal tract. *Am. J. Surg. Pathol.;* 2014; 38(1)
19. MD, PhD Franklin J. Zieve *et al.* Results of the glucose-lowering effect of WelChol study (GLOWS): A randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. *clinthera*.2007.01.003
20. Nutescu, E. A., Shapiro, N. L. Ezetimibe: a selective cholesterol absorption inhibitor. *Pharmacotherapy*., 2003; 23(11): 1463-74.
21. Jigna Patel, PHARMD CANDIDATE,1 Valerie Sheehan, PHARMD,1 and CheryleGurk-Turner, RPH1Ezetimibe (Zetia): a new type of lipid-lowering agentProc (BaylUniv Med Cent). 2003 Jul; 16(3): 354–358.
22. Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D.*et al*. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes *NEngl J Med* 2015; 372:2387-2397
23. Battaggia A, Donzelli A, Font M, Molteni D, Galvano A (2015) Clinical Efficacy and Safety of Ezetimibe on Major Cardiovascular Endpoints: Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS ONE 10(4): e0124587
24. Mohammadpour AH1, AkhlaghiF. Future of cholesteryl ester transfer protein (CETP) inhibitors: a pharmacological perspective *ClinPharmacokinet.* 2013 Aug;52(8):615-26.
25. Philip J. Barter, M.D., Ph.D., Mark Caulfield, M.D., M.B., B.S., Mats Eriksson, M.D., Ph.D.*et al*, Effects of Torcetrapib in Patients at High Risk for Coronary Events *NEngl J Med* 2007; 357:2109-2122
26. Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D., *et al* Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome *NEngl J Med* 2012; 367:2089-2099
27. A. Michael Lincoff, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Jeffrey S. Riesmeyer, M.D., Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* 2017; 376:1933-1942
28. Christopher P. Cannon, M.D., Sukrut Shah, Ph.D., R.Ph., Hayes M. Dansky, M.D., Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease. *NEngl J Med* 2010; 363:2406-2415
29. Klaus G ParhoferMipomersen: evidence-based review of its potential in the treatment of homozygous and severe heterozygous familial hypercholesterolemia CoreEvid. 2012; 7: 29-38.
30. RajuPanta, MD, MS, KhagendraDahal, MD Sumit Kunwar, Efficacy and safety of mipomersen in treatment of dyslipidemia: A meta-analysis of randomized controlled trials, *Journal of clinical lipidology*, 2015 , 9, Issue 2,217-225
31. Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. *Circulation*. 2014;129:1022–32
32. European Medicines Agency. 2013. Lojuxta: EPAR – Product Information Sep [updated Dec 12 2014; cited Dec 15 2014].
33. Kyle A. Davis, Marta A. MiyaresLomitapide: A novel agent for the treatment of homozygous familial hypercholesterolemia; *American Journal of Health-System Pharmacy* June 2014, 71 (12) 1001-1008
34. Marina Cuchel, M.D., Ph.D., LeAnne T. Bloedon, M.S., R.D., Philippe O. Szapary, M.D., Inhibition of Microsomal Triglyceride Transfer Protein in Familial Hypercholesterolemia *NEngl J Med* 2007; 356:148-156
35. Cuchel M1, Meagher EA, du Toit Theron H; Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study *Lancet*. 2013 Jan 5; 381(9860):40-6.
36. Bifadel M, Varret M, Rabès JP, *et al*. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003; 34:154-156.
37. Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease *NEngl J Med* 2017; 376:1713-1722
38. Robert P. Giugliano, M.D., François Mach, M.D., Kenton Zavitz, Ph.D., Cognitive Function in a Randomized Trial of Evolocumab *NEngl J Med* 2017; 377:633-643
39. Paul M Ridker, M.D., James Revkin, M.D., Pierre Amarenco, M.D.Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients *NEngl J Med* 2017; 376:1527-1539
40. Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events *NEngl J Med* 2015; 372:1489-1499
41. Eli M. Roth, M.D., Anne C. Goldberg, M.D. Antidrug Antibodies in Patients Treated with Alirocumab *NEngl J Med* 2017; 376:1589-1590
42. Erik Stroes, John R. Guyton, Norman Lepor Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study *journal of the American Heart Association*. 2016;5:e003421
43. Praluent (alirocumab) injection [prescribing information]. Bridgewater, NJ: sanofi-aventis US; Tarrytown, NY: Regeneron Pharmaceuticals; October 2015.
44. Shigeo Masuda, M.D., Ph.D.ShigeruMiyagawa, M.D., Ph.D.YoshikiSawa, M.D., Ph.D. correspondence A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. *N Engl J Med* 2017; 376:e38

45. Daniel Gaudet, M.D., Ph.D. Daniel A. Gipe, M.D. correspondence Robert Pordy, M.D.ANGPTL3 Inhibition in Homozygous Familial Hypercholesterolemia. *NEngl J Med* 2017; 377:296-297
46. Frederick E. Dewey, M.D., ViktoriaGusarova, Ph.D., Richard L. Dunbar, M.D. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease *NEngl J Med* 2017; 377:296-297
47. Anne P. Beigneux, Ph.D., Kazuya Miyashita, B.Sc., Michael Ploug, Ph.D. Autoantibodies against GPIHBP1 as a Cause of Hypertriglyceridemia. *NEngl J Med* 2017; 376:1647-1658
48. Anastasia Khvorova, Ph.D. Oligonucleotide Therapeutics - A New Class of Cholesterol-Lowering Drugs; *N Engl J Med* 2017; 376:4-7

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