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Dyslipidemia and Atherosclerotic Cardiovascular Disease: Flash Back and Vision Ahead

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Abstract: Dyslipidemia is the most common modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD). There is unequivocal evidence that Low Density Lipoprotein Cholesterol (LDL-C) is the main culprit. Statins, ezetimibe, bempedoic acid and Proprotein Convertase Subtilisin/ Kexin Type 9 (PCSK9) inhibitors are used to target LDL-C. Statin is always utilized as the first line therapy and they decrease LDL-C by approximately 1 mmol/l (40 mg/dL). If the LDL goals are not achieved ezetimibe is used and this decreases LDL-C by 15-20%. Bempedoic acid can also be utilized to lower LDL-C before initiating PCSK9 inhibitors but this is not available in India as yet. PCSK9 inhibitors decrease LDL-C by 1 to 1.5 mmol/l (40-60 mg/dL) on top of all lipid lowering therapy and with this very low LDL-C level targets of < 55 or even < 40 mg/dL can be achieved in very high risk patient. After the LDL-C goal is achieved, non HDL-C is targeted if the triglycerides (TG) levels are above 200 mg/dL. Targeting HDL-C with drugs is not recommended because all trials of HDL-C elevating drugs on top of statins have been negative. The role of TG has a causal factor for ASCVD is still in the process of evolution. Icospent ethyl in REDUCE IT trial has shown reduction in ischemic cardiovascular events in patients with established CVD or diabetics with other risk factors on statins and elevated TG between 135-499 mg/dL. but the mechanism of benefit does not seem to be related to lowering of TG because the benefit was similar in subgroup of patients with TG > 150 <150 mg/dL. Inclisiran which blocks the synthesis of PCSK9 is emerging as very exciting molecule for the future. It decreases LDL-C by 50% which remains there for six months after a single injection of 300 mg.

Keywords: LDL-C Main Culprit of ASCVD, Statins First Drug for Dyslipidemia, Proprotein Convertase Subtilsin-kexin Type 9

1. Introduction

Dyslipidemia is a major modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD). As per WHO 50% of cardiovascular events are attributed to dyslipidemia (Figure 1) and the rest 50% is related to non-lipid atherogenic risk factors.

Amongst lipids, LDL-C and Non-HDL-C are the principal targets. ApoB is also a target but usually it is not utilized because lack of facilities for estimating it and an idea about its level is obtained from Non HDL-C. All trials of HDL-C elevation on top of statins have been flop trials and there is no evidence of benefit of pharmacological elevation of HDL-C. In fact HDL-C has become a fallen angel. Triglycerides (TG) are still in the process of evolution as a casual factor for atherosclerosis.

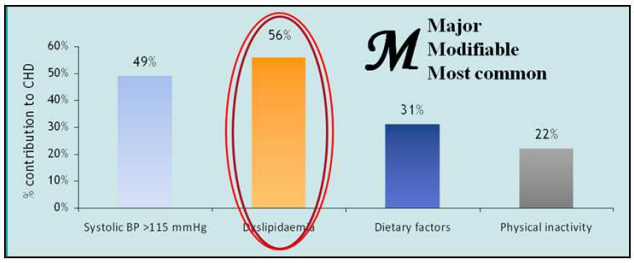

Figure 1. *Relation of lipids to coronary heart disease.*

2. Drugs for lowering LDL-Cholesterol

2.1. LDL-C Cholesterol

Drugs like statins, ezetimibe, bempedoic acid and PCKS-9 inhibitors are used to target LDL- cholesterol.

2.1.1. Statins

Statins have emerged as uncontested king for lipid management. We are witnessing the statin era for last 33 years and there is voluminous data on statins. They are class IA recommendation for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) and primary prevention in high risk patients. They are highly effective drugs and have minimal side effects. For every 10000 cases treated for 5 years with atorvastatin 40 mg, there are 5 cases of myopathy, 50-100 new cases of diabetes mellitus (DM), 5-10 hemorrhagic strokes, no cognitive decline in RCTs.

The statins acts by inhibiting the hydroxymethylglutaryl-CoA (HMG-CoA) reductase enzyme and provide multifaceted actions for preventing ASCVD (Table 1).

Table 1. *Multifaceted actions of statins.*

1	Improves endothelial function.
2	Delipidates atherosclerotic plaques.
3	Increase thickness of fibrous cap.
4	Decreases inflammation.
5	Promotes calcification of plaque.
6	Decrease thrombogenecity of blood.

CTT meta-analysis Collaboration has shown that high intensity statins on an average decrease LDL-C by 1 mmol and this reduction is seen across the range of LDL-C and this translates into reduction of CV events by 20-25% approximately irrespective of baseline LDL-C. According to the reduction in LDL-C levels statins have been categorized into high, moderate and low intensity statins (Table 2). For secondary prevention of ASCVD high intensity statins like atorvastatin 80 mg or rosuvastatin 40 mg are utilized. For primary prevention depending on the atherogenic risk the dose of an appropriate statin is selected. For primary prevention in non diabetic individuals if the ASCVD risk > 7.5% a moderate intensity statin is recommended.

Table 2. *Categorization of statins into high moderate and low intensity statins.*

Parameter	High intensity	Moderate Intensity	Low Intensity
LDL-C reduction	50%	30-50%	<30%
drug & dose in mg	Atorvastatin 80	Rosuvatatin 20 mg	Simvastatin 10 mg
	Rosuvastatin 40	Atorvastatin 40 mg	Pravastatin 10-20 mg
		Simvastatin 20-40 mg	Lovastatin 20 mg
		Pravastatin 40-80 mg	Fluvastatin 20-40 mg
		Lovastatin 40 mg	Pitavastatin 1 mg
		Fluvastatin XL 80 mg	
		Fluvastatin 40 mg bid	
		Pitavastatin 2-4 mg	

The goals for LDL-C reduction are getting lower and lower and the current goals as per ESC Guidelines-2019 [1] are outlined in Table 3.

Table 3. *Goals for LDL-C for different ASCVD risk sub group.*

Sr. no.	ASCVD Risk	Score %	LDL C target mg/dL/ mmol/L
1.	Low	<1	116 / 3.0
2.	Moderate	>1 <5	100 / 2.6
3.	High	>5 <10	70 / 1.8
4.	Very High	> 10	55 / 1.4

In those with recurrent ASCVD events within 2 years while taking maximally tolerated statin therapy, a goal of <1.0 mmol/L (<40 mg/dL) for LDL-C should be considered.

The Guideline of other professional bodies has also recommended nearly same targets [2, 3]. The lipid association of India [4] has recommended an LDL goal of 50 mg/dL for the very high risk patients.

2.1.2. Legacy Effects of Statins

Statins also have a legacy effect as shown by the long term follow up of WOSCOPS trial. It showed that after taking statin for 5 years, the beneficial effect persisted for the next 20 years. There was statistically significant reduction of 27% in the coronary heart disease mortality (P<0.001), all cause mortality decreased by 13% P<0.001, revascularization decreased by 19%, P=0.0032, heart failure decreased by 31% P=0.0068. Stroke only showed a numerically decrease of 10% P=0.19.

2.1.3. Statin Discontinuation Syndrome

Sudden withdrawal of statin at the onset of acute coronary syndrome is associated with increased incidence of cardiovascular events and mortality due to endothelial dysfunction and increased thrombogenicity of blood. This was demonstrated in the PRISM trial. Therefore statin should never be discontinued at the onset of ACS and if patient is not on high intensity statin, it should be initiated.

2.1.4. Ezetimibe and Bempodoic Acid

Statins are the first drug of choice for treating high LDL-

C. If the LDL goal are not achieved with maximally tolerated statins, than ezetimibe can be added in doses of 10 mg/day as shown in the IMPROVE IT Trial [5]. It is safe, well tolerated and has hardly any side effects. Bempidoic acid, approved by USFDA can also be utilized before initiating PCSK 9 inhibitors but this is available in USA and not in India as yet. It inhibits synthesis of cholesterol in the liver. It can be used in doses of 180 mg orally daily. It decreases LDL by 15-20% and is not associated with muscle toxicity. If the LDL-C goals are still not achieved, PCSK9 inhibitors like evolocumab and alirocumab can be used.

2.2. PCSK9 Inhibitors

Monoclonal antibodies to PCSK9 have been tried in 2 CV OUTCOME trials [4, 5]. The PCSK9 inhibitors produce an additional reduction of LDL-C by 40-60%, LP (a) is reduced by approximately 25% and other lipoprotein are also favourably altered. Both these molecules have been approved for clinical use. Evolocumabis commercially available in India.

2.2.1. Evolocumab

This molecule was evaluated in FOURIER trial [4] which compared evolcoumab with placebo in 27,564 patients with ASCVD having an LDL-C of more than 70 mg /dL with a median follow up 2.2 years. There was a 15% relative risk reduction in the primary end point of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. (hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001).

In FOURIER study [6], LDL-C decreased from median base line value of 92 mg/dl to 30 mg/dl, i.e., approximately by 60% (P<0.001), 42% had LDL-C <25 mg / dL. Despite such low levels of LDL-C there was no evidence of muscle, liver toxicity, diabetogenecity or neurocognitive decline. The dedicated sub-study, EBBINGHAUS also confirmed lack of neurocognitive decline with its use. The only side effect which was seen with evolocumab was injection site reactions, 2.1% (evolocumab) vs 1.6% (Placebo). The study therefore demonstrated incredible safety on top of statins. The benefit was seen across the range of LDL up to 20-25 mg/dl. All quartiles benefitted, highest as well as lowest. There was no J curve so lower is better is also validated for super low LDL-C. The FOURIER trial showed reduction in MI by 27% p=<0.001, stroke by 21%, p=0.01 and coronary revascularization by 22%, P=<0.001. There was no significant decrease in all cause or CV mortality.

It is available as 1ml pen containing 140 mg. It is given in doses of 140 mg. biweekly / 420 mg. monthly sc.

2.2.2. Alirocumab

The ODYSSEY OUTCOMES [7] compared alirocumab with placebo in 18,924 post ACS patients 1-12 months after the acute event having LDL-C level of >70 mg/dL. The median duration of follow-up was 2.8 years. The composite primary end-point of ischemic event showed a relative risk reduction of 15% (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). There was no statistically significant decrease in CHD mortality or all cause of mortality. Patients with LDL-C > 100 mg/dL benefited more and also showed decrease in all cause mortality. This is approved for clinical use and is commercially available as 1 ml pen containing 75 mg which is given every two weeks or 150 mg which is given monthly.

Both evolocumab and alirocumab are very well tolerated and besides local injection site reactions there are hardly any side effects. In FOURIER trial, the safety of LDL-C has been proven upto 10 mg /dL

2.2.3. Bococizumab

The SPIRE 1 and 2 trial with Bococizumab was prematurely terminated because of presence of neutralizing antibody in 29% and antidrug antibodies in 48% of patients taking the drug. This is because Bococizumab is partly murine partly human monoclonal antibody unlike Evolocumab and Alirocumab which are fully humanized monoclonal antibodies.

Although both SPIREI and SPIRE II trials were prematurely terminated, the SPIRE II which had LDL-C > 100 mg/dL showed a reduction in CV events by 21% at 12 months hinting that the drug is also useful for primary prevention. The SPIRE I trial which enrolled comparatively lower risk population (LDL-C> 70) did not showed any benefit.

The current indications PCSK9 MoAbs are outlined in Table 4.

Given the lack of long-term safety and efficacy data on these agents, they are not recommended for use for primary prevention except in patients with familial hypercholesterolemia. The data of PCSK9 inhibitors for primary prevention like high risk diabetics is yet to evolve out.

Table 4. *Indications of PCSK9 inhibitors.*

1	Failure to achieve LDL-C goals with optimal doses of statins in patients with ASCVD
2	Statin intolerance
3	Familial hypercholesterolemia

For patients with homozygous hypercholesterolemia (HoFH) the LDL-C goals are difficult to achieve. Besides statins, ezetimibe and PCSK9 inhibitors, on occasions one has to use other drugs like of lomitapide [8], mipomersen [9], and even LDL apheresis to achieve LDL-C goals.

3. Role of Triglycerides (TG)

TG is commonly elevated in diabetes. In Indian context too, there is often high TG and low HDL and it is often claimed that raised TGs may be playing an important role in the Indian dyslipidemia but there is no randomized trial as yet to establish it as a causal factor for atherosclerosis. It is important to realize that it is ApoB particles which enters the vessel wall and not TG per se. The risk of atherosclerosis is related to the number of atherogenic particles and each

atherogenic lipoprotein particle contains a single molecule of ApoB. Therefore the concentration of ApoB provides a direct measurement of the number of circulating atherogenic lipoprotein. In most hypertriglceridemic (HyperTG) patients including diabetics, LDL particles make up 85-90% of total ApoB particles and the contribution of VLDL is only 10-15%. Fibrates only lower LDL particle by only about 10% and therefore fibrates at most may only play a minor role. The Quebec cardiovascular study also showed that if there is HyperTG with normal ApoB levels, there is no increase in Odds ration of Ischemic Heart Disease (IHD) but if there is HyperTG with increased ApoB levels, the odds ratio of IHD are significantly increased.

All randomized trial of TG lowering with fibrates on top of statins has failed to show any CV benefit. The ACCORD LLA trial [10] did not show benefit of fibrates on top of statins. The subgroup analysis of TG more 204 mg/dL and HDL-C < 34mg/dL has shown reduction in the CV events. This is hypothesis generating but is not yet tested in any randomized control trial. A meta-analysis of fibrates [11] has shown benefit but all trials in this meta analysis were not done on top of statins.

REDUCE IT Trial

The REDUCE IT Trial [12], evaluated patients with established CVD or with diabetes and other risk factor who have been on statins with LDL-C levels of 41 to 100 mg/dL and TG levels were between 135 to 499 mg/dL. Icosapent ethyl 2gm twice daily was compared with placebo over a period of 4.9 years and showed reduction of 25% in the composite primary end point of ischemic events (HR, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001). Atrial fibrillation was more often seen with icosapent ethyl compared to placebo (3.1% vs. 2.1%, P=0.004). Serious bleeding was also observed in more number of patients with icosapent ethyl compared to placebo, 2.7 vs. 2.1 (P=0.06). The trial was positive but sub group analysis showed that the benefit was similar in groups with TG<150 mg/dL and >150 mg/dL indicating the mechanism of benefit is not related lowering of TG. Saroglitazar in dose of 4 mg /day has been used to treat hypertriglycedemia but there is no outcome data with it.

4. Newer Agents for Lipid Management

Inclisiran a small interfering RNA inhibits synthesis of PCSK9 and a single injection of 300 mg decreases LDL-C levels by 50% and this remains there for 6 months [13]. It is emerging as an important competitor for PCSK9 monoclonal antibodies but it is still undergoing evaluation. A single injection of PCSK9 vaccine decreases LDL-C by 50% which lasts for 12 months. If the human trial comes to out to be positive, a yearly booster dose of this vaccine will be the new way to target ASCVD.

5. Conclusion

The treatment of dyslipidemia has improved tremendously during the last couple of years. The goals for LDL-C are getting lower and lower and these are providing incremental reduction in ASCVD events. It seems that the new emerging drugs like incilisran will further brighten the prospects of ASCVD in future.

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