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Newer Lipid Guidelines: Interpretation and Applications for Indians

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ABSTRACT

There are number of guidelines and recommendations for managing cholesterol.American College of Cardiology [ACC] / American Heart Association [AHA] guidelines 2013 focussed on Atherosclerotic Cardiovascular risk and not on lipid goals. International Atherosclerosis Society [IAS] published global recommendations in the same year for the management of dyslipidemia. National Lipid Association [NLA] guidelines were published in 2014.Lipid Association of India [LAI]has released Expert Consensus Statement on Management of Dyslipidemia in Indians in 2016. European Guidelines on cardiovascular disease prevention in clinical practice was published in 2016..This chapter on Newer Lipid Guidelines : focuses on interpretation of these international guidelines including recommendations of LAI which may be applicable for Indians. Many aspects of lipid management targeting LDL- c and other lipoproteins are discussed in detail. Indians have typical elevations of triglyceride with low levels of HDL-c and almost normal LDL- c levels. Atherogenic dyslipidemia which is the characteristic feature of Metabolic syndrome [MetS] and diabetes is characterised by an increase in triglyceride levels with low HDL –c and increase in small dense LDL-c.In view of increasing prevalence of obesity, MetS and diabetes, there is a need for different approach in managing mixed dyslipidemia.Randomised Control Trials [RCTs] focussing on lipid lowering therapy have to be conducted for evidence and to develop guidelines for Indian patients. Patient centric approach with evidence obtained from epidemiological / observational data on the prevalence and type of dyslipidemia was given importance in the recommendations of LAI which are highlighted in this chapter.

INTRODUCTION : WHY DO WE NEED GUIDELINES ?

Many times we get conflicting data in guidelines. What is reasonable to do for overall approach to make sense of the totality of data ? What we should aspire to do at a population level is to standardise care and avoid inequalities. RCTs systematically test effects of an intervention on pre-specified outcomes in defined populations. Their use minimizes confounding. Their ability to generalize results to real-world patients may be limited due to exclusion criteria. Observational / Epidemiologic studies have world-wide in scope and may assess ASCVD risk across populations.Cohort studies : evaluate mortality and morbidity within populations. Guidelines are published based on robust evidence from RCTs, observational / epidemiological & cohort studies. Experimental data are taken into account.

Atherosclerosis is a preventable disorder. Of all the lipoproteins, it is the LDL Cholesterol which plays a central role not only in the initiation of atherosclerosis but also in the progression of atherosclerosis ending in clinical cardiovascular events. Most robust evidence for the role played by LDL –C comes from RCT's which had used statins. The evidence clearly shows that by reducing LDL –c, we get substantial reduction in CV morbidity & mortality. Many secondary prevention trials, primary prevention trials, and trials conducted in high risk groups, clearly demonstrated the important role of LDL-C reduction and the potency of statins in reducing the atherosclerotic cardiovascular risk.

NCEP ATP III Guidelines : Many guidelines were published by various academic bodies across the globe. After the publication of National Cholesterol Education Program – Adult Treatment Panel - III [NCEP ATP III] Guidelines in the year 2001, we had also seen an updated recommendation from the same organisation in the year 2004. ACC/AHA recommendations on lipid lowering was released in the year 2006, mostly concurring with ATP III recommendations. Recommendations are : LDL-C Goals for High Risk Patients : < 100 mg/dl in patients with CHD or CHD risk equivalents including 10 years risk > 20 % and <70 mg/dl as option for very high risk patients. If it is not possible to attain LDL-C < 70 mg/dl because of a high baseline LDL-C, it is generally possible to achieve LDL-C reductions of >50% with more intensive LDL-C lowering therapy including drug combinations[1]. ATP III also recommended lowering of Non HDL -c as a secondary goal when Hypertriglyceridemia exceeds 200 mg/dl.

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce atherosclerotic cardiovascular risk in adults : Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline circulation JACC, Nov 12, 2013.

Main focus on ASCVD risk reduction : 4 statin benefit groups in secondary and primary prevention are identified for high-intensity and moderate intensity statin therapy.

1. Individuals with clinical ASCVD : [Seconday Prevention] Atherosclerotic CVD includes CHD,

Table 1: High & Moderate Intensity Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL-c on average, by approximately ≥50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%
Atorvastatin (40)-80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20-40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg

stroke, and PAD:High-intensity statin therapy should be used to achieve at least a 50% reduction in LDL - C unless otherwise contraindicated. For those older than 75 yrs, moderate dose statin may be used.

2. Individuals with primary elevations of LDL–C ≥190 mg/dL [Primary Prevention] High-intensity statin therapy should be used to achieve at least a 50% reduction in LDL -C unless otherwise contraindicated.3.Individuals between 40 and 75 years of age with diabetes & without clinical ASCVD with LDL-C 70-189 mg/dL : A moderate-intensity statin- that lowers LDL-C 30% to 49%. High-intensity statin is a reasonable choice if the patient also has a 10-year risk of ASCVD exceeding 7.5%

4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher : A Moderate - or High-intensity statin therapy.

High & Moderate Intensity Statin Therapy : Ref Table 1

Statins and doses that are approved by the U.S.FDA but were not tested in the RCTs reviewed are listed in italics.

New perspective on LDL and / or Non HDL-C Treatment Goals : The expert panel included RCTs with robust evidence for framing guidelines and was unable to find RCT evidence to support continued use of specific LDL-c and / or Non-HDL –c treatment targets. Global risk assessment for primary prevention is recommended by using new pooled cohort equations to estimate 10-year ASCVD risk by a new risk calculator. 7.5% risk threshold for primary prevention was selected based on analyses. Some patients do not tolerate statins and may require treatment with lower doses. With few exceptions, use of lipid-modifying drugs other than statins is discouraged. Only statins have data of CV protection.Non-statin lipid lowering drugs have no evidence of CV protection. Measuring lipids during follow-up of drug-treated patients is done to assess adherence to treatment and not to see whether a specific LDL-C target has been achieved.

Implementation of ACC / AHA Guidelines in clinical practice in India : Is this possible ?

These guidelines are intended for US population. It is very difficult to implement the same for Indians for the following reasons : Use of high dose statin may be difficult in patients with multiple co-morbidities & in Asian patients.Over estimation of CV risk by presently developed calculator was highlighted in the subsequent publications. There was no recommendation for LDL goal. This becomes difficult in Indian scenario. Asian subjects were not considered who have high TG and low HDL. MetS was totally neglected for recommendation in spite of an increasing prevalence in US. We have problems of overweight,Obesity and MetS with > 69 million people suffering from diabetes in India. Atherogenic dyslipidemia is the risk factor in MetS and in diabetes which was not addressed. Lower statin dose are frequently used in our population. Adequacy of statin therapy cannot be determined without measuring on treatment LDL. ACC/AHA Guidelines2013 raised several questions that need to be answered.

Indian Scenario on Lipids and Lipoproteins

India Heart WATCH Study which evaluated for dyslipidemia prevalence in a population of 6400 subjects revealed higher TG levels with low HDL –c with normal or marginally elevated LDL –c levels.

High prevalence of Metabolic syndrome among urban subjects in India was highlighted in a multisite study[2]: 33.3% of men and 40.4% of women are having metabolic syndrome features with constellation of multiple risk factors.Atherogenic dyslipidemia was typically seen in this study.

ICMR – INDIAB Study 2014 : Prevalence of Dyslipidemia in urban and rural India was evaluated in this study. Higher prevalence of TG [29.5%] with higher prevalence of low HDL [72.3%] and 13.9% subjects were seen with Hypercholesterolemia.

Non HDL-C is a better indicator of residual risk than LDL-C

Meta analysis of 62,154 statin-treated patients in 8 trials [4S, AFCAPS, LIPID, CARDS, TNT, IDEAL, SPARCL, JUPITER] published between 1994 and 2008 revealed the following: 1 SD increase in LDL-C, Apo B and Non HDL increase the risk of CV events by 13%, 14%, and 16% respectively indicating the strength of association with CVD is greater for non HDL-C than for LDL-C and ApoB [3]. People who had LDL levels < 100 mg/dl with Non-HDL level of > 130 mg/dl had hazard ratio of 1.32 indicating CV risk of 32% when compared to people who had uncontrolled LDL levels of > 100 mg/dl with Non HDL level of < 130mg/dl had hazard ratio of 1.02 indicating CV risk of 2%. Conclusion : Non HDL-C is associated with increased risk for future CV events, even if LDL is under control with statins.

AACE [American Association of Clinical Endocrinologists] Guidelines for management of Dyslipidemia and prevention of Atherosclerosis – 2012 : Calculate Non–HDL-C in patients with moderately elevated TG (200-500 mg/dL) with DM and/or established CHD.In patients with insulin resistance, AACE recommends evaluating Non – HDL-C to gain useful information on total atherogenic lipid burden[4]. AACE 2013 Diabetes Guidelines : Non HDL goal to be achieved with TG lowering therapy after achievement of desirable LDL-C level.[5]

Role of Apo-B

Apo-B is the key atherogenic lipoprotein which is a more sensitive measure of risk than LDL-c.It provides information on LDL particle size which is difficult to measure directly. A recent analysis of the combined data set from the TNT and IDEAL studies showed that on-treatment level of apo-B was clearly superior to that of LDL-c as a predictor of CV events, but it was not superior to non - HDL-c[6].

Role of Triglycerides

Prove IT-TIMI 22 trial conducted in ACS patients stressed the role of high triglyceride as a risk factor after reaching the LDL goal of 70mg/dl with high dose Atorvastatin 80 mg/day. People who had >200 mg/dl of triglyceride had higher CV risk of sudden cardiac death, fatal and non-fatal reinfarction in a 30 day follow up compared with people who had < 200 mg/dl of triglyceride. Clinicians need to focus on the residual risk contributed by high triglycerides.[7] Meta-analysis of 5 landmark trials (ACCORD, BIP, FIELD, HHS, VAHIT) with 7389 patients with diabetes and or CVD, concluded that lowering TG in people who had elevated levels > 200mg/dl with PPAR alpha agonists-Fibrates reduced

CV events by 25%.[8] In different studies in the last 2-3 decades, TG reduction, with or without statin, has shown to cause significant risk reduction in patients with high TG and low HDL-C (Atherogenic Dyslipidemia)[9]. Triglycerides can be measured in the non-fasting or fasting states. RCTs showing CV benefit of triglyceride reduction are scanty. Lowering triglycerides reduces the risk of CVD is still debated[10]. Saroglitazar, a novel lipid lowering drug which has both PPAR alpha and gamma agonistic activity has shown in clinical trials to lower triglycerides markedly in diabetics. This is a promising molecule which has been approved in India for managing diabetic dyslipidemia.

Role of HDL-C : Trials to raise HDL-C levels by using CETP Inhibitors like Torcetrapib,failed to show beneficial effects in spite of having a favorable HDL rise in number of studies. Therapeutic Lifestyle Changes, such as smoking cessation, weight loss,physical activity,moderate alcohol consumption,w-3 fatty acids have been found to show beneficial effects in increasing HDL. However, there is still lack of evidence that raising HDL reduces CV Risk. HDL-C is not recommended as a target of therapy[11].

Role of Lp(a): Lp(a) >50mg/dl independently predicts the presence of symptomatic & angiographic CAD. Primary objective is to treat LDL and Non-HDL aggressively with high dose statin. Niacin is the only drug that lowers Lp(a). Novel Lipid lowering drugs like Apo B blockade by AntiSense Oligonucleotide (ASO) [Mipomersen] MTP Inhibitor [Lomitapide] and PCSK9 inhibitors [Evolocumab] have shown reduction in Lp (a) with marked reduction of LDL – c. European Atherosclerosis Society recommends screening for elevated Lp(a) in those at moderately high or high ASCVD risk.

International Atherosclerosis Society : Global recommendations for the management of dyslipidemia:[12] LDL –C and Non-HDL-C as target of Therapy : LDL is the major atherogenic lipoprotein and VLDL is an additional atherogenic lipoprotein. Non-HDL includes LDL + VLDL. LDL –C is the traditional primary target for clinical intervention and Non-HDL-C is also an appropriate target for clinical intervention based on huge body of evidence. Advantages of Non-HDL –C as Target : It does not require fasting for accurate measurement.Non HDL subsumes most cases of elevated triglycerides

Growing evidence favor Non HDL has greater predictive power than LDL-C.Non –HDL is also considered equivalent to apo lipoprotein- B in predictive power.

Secondary Prevention : Achieving an optimal atherogenic cholesterol level : The optimal LDL-C in patients with established ASCVD is < 70 mg/dl or non-HDL-C of < 100 mg/dl. Most patients with ASCVD deserve maximal statin therapy when it is tolerated. To achieve an LDL-C < 70 mg/dl, some patients will require add on drugs to statins [i.e.ezetimibe and / or bile acid resins]

Secondary Prevention : Patients with Hypertriglyceridemia :For those with high triglycerides, Nicotinic acid or a Fibrate are alternative add on drugs.However, risk reduction with combined drug therapy comparable to that with high-dose statins has not been documented in RCTs.Subgroup analysis of RCTs and atherosclerosis imaging provides some evidence of benefit of combined drug therapy.

National Lipid Association [NLA] recommendation for management of dyslipidemia[11] : An elevated level of atherogenic cholesterol – cholesterol carried by apo B-containing lipoprotein particles (non-HDL-C and LDL-C) – is causally related to the development of atherosclerosis. Targets of Therapy : Atherogenic cholesterol (non-HDL-C and LDL-C) levels are the primary targets of therapy. Elevations in apo B-containing particles, and cholesterol carried by those particles, are considered a " root cause" of atherosclerosis, and of primary importance for prevention. Non-HDL-C testing is universally available, requires no additional cost, and may be measured in the non-fasting state. An elevated triglyceride level is not a target of therapy per so, except when very high [severe]. Moderate or high-intensity statin therapy should be the first line agent.Starting with a moderate dose and titrating as necessary to achieve treatment goals is a reasonable approach. An alternate

drug : Bile Acid Sequestrant [BAS] Cholesterol absorption inhibitor like Ezetimibe,Fibrate and Niacin. These drugs may be considered in those with contraindications to statin.

What is needed for Indians ?

Number of guidelines were published with a focus on LDL lowering. We don't have cholesterol management guidelines for Indians. We have a huge burden of CV disease in our country.CV deaths are increasing in alarming preportions. Young people are getting affected with CAD. This occurs one decade earlier when compared to western counterparts. Moreover CAD is diffuse with multi vessel involvement, predominantly affecting LAD. There is a need for development of risk calculator taking into account conventional risk factors and other risk factors which are peculiar to Indians. We are currently witnessing overweight, obesity, features of metabolic syndrome with insulin resistance. There is an increasing prevalence of diabetes which had crossed 69 million with features of atherogenic dyslipidemia in nearly 90% of diabetics. Hence we need individualised, patient centric approach to bring down the CV risk. We require separate guidelines to suit our patients. High dose statin are preferred for high risk and very high risk individuals, whereas moderate dose statin with uptitration to high dose may be the correct approach for Indian subjects. Indians respond quickly to moderate dose statin therapy and statin intolerance has been reported which needs to be tackled. We require LDL goals to have a good adherence for lifestyle modification and pharmacotherapy. If we are not able to reach the goal of LDL with high dose statin we may have to add Ezetemibe not only to reduce the LDL but also to reduce CV risk as has been highlighted in the recent studies. We require non statin drugs like Fibrates, Nicotinic acid, and omega 3 fatty acids to tackle high triglyceride levels in specific situations. At present we may not consider HDL as target of therapy. We need to pay more attention to non HDL which covers LDL and VLDL. Statins will play a major role in bringing down non HDL levels. Though we don't have convincing data for marked CV risk reduction with TG lowering therapy, we are forced to continue the combination of drugs in view of predominant peculiar dyslipidemia in our population. Emphasis has to be given for therapeutic lifestyle changes which is a corner stone in the management of dyslipidemia not only in primary prevention but also in secondary prevention. It is appropriate to say that we need patient centric approach with our own recommendations/guidelines.

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Low-Density Lipoprotein cholesterol

LDL-C should be the primary target for therapy. LDL-C lowering to a low level is essential to achieve the desired reduction in the risk of vascular disease. In those with elevated levels of ASCVD risk, lower LDL-C levels are associated with better outcomes. LDL-C levels <50mg/dL is safe.

Non HDL-c (Non-High-Density lipoprotein Cholesterol)

Non-HDL-C, which is equal to total cholesterol –HDL-C and this includes all atherogenic lipoproteins.It is more accurate predictor of ASCVD risk, particularly in patients who have elevated TG (e.g. diabetes, obese persons, those with metabolic syndrome) and those already on statin therapy. LAI recommends non-HDL-C as a co-primary target, as important as LDL-C, for lipid lowering therapy. Non-HDL-C level should be kept within 30mg/dL of LDL-C levels. Statins remain the first line agent for lipid lowering, regardless of whether LDL-C is the target for therapy or non-HDL-C.

Relevance of HighTG Levels

Elevated TG is associated with increased risk of ASCVD, independent of LDL-C levels. A combination of high TG and LDL-C imparts even greater risk. High TG is one of the components of atherogenic dyslipidemia.Keep TG<150 mg/dL, preferably <100mg/dL. In patients with elevated TG levels, rule out secondary causes of the same and intensify lifestyle modification, which can reduce TG by as much as 50%. Unless TG is very high (>500 mg/dL), statin should be the first drug. Routine addition of a fibrate or another non-statin drug must be avoided. Only when TG is not sufficiently lowered with above measures, a non-statin drug should be added.

High Density Lipoprotein Cholesterol

Low HDL-C is an independent risk factor for ASCVD. It becomes even more relevant when LDL-C is not elevated. Life style modification plays an important role in raising HDL-C. Among pharmacological agents, statins remain mainstay in the treatment of low HDL-C also. Although several other agents have been tried specifically for raising HDL-C, none of them has been shown to result in clinical benefit.

Usage of statins for Lipid Management

The clinical benefit of statins depends primarily on the extent of LDL-C reduction and not on the type of statin used. The type of the statin and dose to be used should be based on the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient. Atleast moderate- or high intensity statin therapy is required to bring about a clinically meaningful reduction in LDL-C in most patients.

The ACC/AHA 2013 guidelines on the treatment of blood cholesterol to reduce ASCVD risk : A comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011.[13] Recommendations from LAI has been added apart from NLA & IAS for comparison.[14] Ref. Tables 2, 3, 4 & 5

THE BAD : Comparison of International Guidelines

ACC/AHA and ESC/EAS guidelines seek to lower LDL-C with statin therapy as their principal aim LAI also recommends the same. ACC/ AHA Guidelines : Treats risk alone with guidance only on treating ASCVD risk

and discard the use of lipid targets It is simply fire and forget approach.Do not recommend additional lipid-lowering therapies among those with high residual risk despite achievement of 50% reduction in LDL-C. ESC/EAS Guidelines & LAI recommendations : Treats risk and more : Treats CVD risk, create a greater understanding of the role of LDL-C in CVD assessment (LDL-C monitoring). Individualized patient care approach : assessing other lipid-mediated factors "residual risk" :TG-rich lipoproteins remnants, HDL-C, Non-HDL-C & Apo B. Recommends LDL-C and other lipid measures for monitoring efficacy, compliance, assessing residual risk and allow a greater scope for modifying individual patient care by considering additional therapies if clinically warranted.

2016 ACC Expert Consensus Statement : This is a different compared to ACC/AHA Guidelines 2013. The statement stressed the role of Non-statin therapies for LDL-C lowering in the management of ASCVD risk. Non HDL-C thresholds are included in high risk patients. Ezetimibe is preferred as the initial non statin therapy. Colesevelam has a modest hypoglycemic effect that may be of benefit in some diabetic patients with fasting triglycerides <300 mg/dl or in patients who are ezetimibe intolerant.

2016 European Guidelines on CVD prevention in clinical practice : Total CV risk should guide the intensity of the intervention. Non HDL –c is included as a target. Non statin therapy mainly Ezetimibe is recommended.

CONCLUSION

There is a need for absolute risk assessment in everyone and this is the best approach in managing Lipids. We need to assess the risk and then go with which ever is

Table 2: Comparison of International Guidelines Including recommendations of LAI

	ACC/ AHA	ESC/ EAS	NLA	IAS	LAI
Highlight the role of Lifestyle	√	√	√	√	√
Highlight the need to engage the patient as a partner	√	√	√	√	√
Highlight the role of lipid modification in the prevention of CVD	√	√	√	√	√
Highlight the need for risk assessment	√	√	√	√	√
In general use an absolute risk strategy	√	√	√	√	√
Risk categories easy to identify and agreed	√	√	√	√	√
Good summary of RCT data	√	√	√	√	√

Table 3: The Approach : Comparison of International Guidelines

	ACC/ AHA	ESC/ EAS	NLA	IAS	LAI
Use doses seen in trials scenarios	√	√	√	√	√
Emphasis on higher intensity statins for established ASCVD	√	√	√	√	√
Plus TARGETS		√	√	√	√
% Reductions	√	√			

Table 4: The Bad : Comparison of International Guidelines

	ACC/ AHA	ESC/ EAS	NLA	IAS	LAI
Targets	X	√	√	√	√
Lower is better	X	√	√	√	√
Scope for other atherogenic lipids	X	√	√	√	√
Scope for other LLT	X	√	√	√	√
CKD as a high risk group	X	√	√	√	√

Table 5: The Uncertain : Comparison of International Guidelines

	ACC/AHA	ESC/EAS	NLA	IAS	LAI
What to do at the extremes of age	?	?	?	?	?
A new risk calculator	?				Promoting JBS 3 score
Reducing the primary Prevention threshold [For Young]	√	?	√	-	√
Reducing the primary prevention threshold [For Old]	X	?	-	-	?
What do our patients want	?	?	?	?	?

greater i.e. a 50% LDL-C reduction or a target. In those at highest absolute risk we have to maximise the dose of the statin. We need to decide whether this is enough for this person's level of risk or should we go lower ? Lower could be a greater percentage reduction in LDL-C or a target.

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