Management of Dyslipidemia in India: What should be Our Approach in View of the Differing Guidelines

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SCOPE OF THE GUIDELINES

There are two major lipid guidelines- ESC and the ACC/AHA guidelines. The major differences are- 1. The scope of ACC/AHA is limited to randomized trials only, which excludes a significant body of data and promotes essentially a statin centric approach only. 2. The abolition of low-density lipoprotein cholesterol (LDL-C) targets in favour of specific statin regimens producing a 30–50% reduction in LDL-C may confuse many physicians and may compromise medication adherence. 3. The absence of target LDL-C levels in very high-risk patients may discourage clinicians to consider the addition of lipid modification treatments and individualize patient care. 4. A reduction in the threshold for treatment in primary prevention will result in a greater number of patients being prescribed statin therapy, which is potentially good in young patients with high life time risk, but will result in a very large number of older patients offered therapy. 5. The mixed pool risk calculator used to asses CVD risk in the guidelines for primary prevention has not been fully evaluated[1].6. ESC/EAS guidelines provide guidance on elevated triglycerides (TG) including the relevance of identifying and treating secondary causes, recommending pharmacological intervention, if fasting TGs are >2.3 mmol/L, using fibrates. The ACC AHA guidelines don't recommend any other drugs beside statins and deals with risks rather than goals. 7. The guideline doesn't adequately address the management of the group who cannot tolerate recommended statin doses. But both the guidelines ESC and ACC/AHA identifies LDL as the most important risk factor and both recommend behavioural and lifestyle modifications concurrent to drug therapy.

WHOM TO TREAT

Both sets of guidelines have categorised four major patient groups who would benefit from lipid modification therapy. These include individuals with established CVD, diabetes mellitus, and familial hypercholesterolaemia. The fourth group contains those individuals not included in the first three, but who after undergoing global risk assessment (based on age, gender, smoking status, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol;HDL-C) seem to be at increased CVD risk. The definition of ASCVD varies between guidelines as the ACC/AHA defines this as acute coronary syndromes, previous myocardial infarction, stable angina, prior coronary or other revascularization, ischaemic stroke or

transient ischaemic attack, and atherosclerotic peripheral arterial disease. In contrast, the ESC/EAS include all those mentioned in the ACC/AHA guidelines, but also include any pre-clinical evidence for atherosclerotic disease on the basis of any imaging modality. Importantly, the ACC/AHA guidelines do not include chronic kidney disease (CKD), whereas the ESC/EAS guidelines consider those with CKD (as defined by a GFR ,60 mL/min/1.73 m2) as a very high-risk group who require lipid management with a target LDL-C of <1.8 mmol/L or a 50% reduction in LDL-C. The ESC/EAS guidelines also recognize that, while traditional risk factors are the basis of global risk assessment, there may be other factors such as elevated TG, social deprivation, central obesity, elevated lipoprotein (a), subclinical atherosclerosis, or family history of premature CVD which may further modify absolute risk.

The policy change that will have the largest impact on the healthcare system is the ACC/AHA statement that statin treatment is recommended for primary prevention in individuals with a 10-year ASCVD risk of 7.5% or higher when compared with previous guideline on the treatment of blood cholesterol recommendations that considered a substantially higher threshold for 10-year risk of fatal and non-fatal coronary heart disease (CHD). The ACC/AHA 10-year threshold of 7.5% corresponds to a 2.5% risk for CVD death over 10 years in the SCORE model. In SCORE, those with a 10-year risk of fatal CVD of 2.5% are considered at moderate risk, and the ESC/EAS recommendation is that an LDL-C of <3 mmol/L is achieved. Thus, while the ESC/EAS guidelines allows some scope by virtue of an LDL-C goal for lifestyle before medication are added, patients are more likely to receive medications under the new ACC/AHA guidelines. The consequence will be a greater expenditure to the public health budget.

The prescription of moderate to high intensity statins to persons having the 10 Yr ASCVD risk>7.5% will provide certain benefit of high dose statins but the impact of such a dose on tolerance in such a wide group is not clear. One important benefit of lowering the threshold for statin initiation in the primary prevention setting is that those young people with low short-term CVD risk but high-lifetime risk will be initiated on statins earlier and will have a greater impact on the disease process. However practically all older individuals (>70 years) because of the

impact of age on 10-year ASCVD risk, will now be offered moderate- to high-intensity statins. As co-morbidities and tolerability of these agents becomes more of a concern in this age group, the potential for harm is much greater. However, the guideline committee considered that there was lack of data on lifetime CVD risk, on long-term (i.e. >15 years) follow-up of treatments tested in RCTs, on long-term safety of statins, and on the effects of treatment initiation before the age of 40.

WHAT TO TREAT

The ESC/EAS guidelines place considerable weight to the measurement of LDL-C to determine future CVD risk and provide an algorithm which combines SCORE risk with measured LDL-C levels. This is of advantage as for general physicians it highlights the importance of screening for genetically elevated LDL-C levels. Additionally, LDL-C measurement is recommended for CVD risk assessment among those with established CVD, hypertension, smoking, type 2 diabetes, obesity, family history of pre-mature CVD or familial hypercholesterolaemia, CKD, or chronic inflammatory disease. However new ACC/AHA guidelines doesn't mandate LDL-C measurement, if absolute risk is high enough to warrant statin therapy. Thus adoption of the ESC/EAS guidelines will allow many more cases of undiagnosed familial hypercholesterolaemia to be identified which are much more common than the 1:500 that is generally perceived.

The ACC/AHA guidelines discard the lipid targets as there is no RCT conducted based on such targets. While the ACC/AHA guidelines treat risk alone, the ESC/ EAS guidelines treat risk, create a greater understanding of the role of LDL-C in CVD risk assessment, and use LDL-C monitoring for measuring therapeutic efficacy and patient compliance. Furthermore, the ESC/EAS guidelines have given importance on the role of other lipid fractions such as TG-rich lipoproteins, remnants, and conditions associated with low HDL-C where LDL-C may not be as informative as non-HDL-C or apolipoprotein B (apoB), but for which there are clear data (Class IIa, Level B).

The ESC/EAS guidelines allow us to individualize patient care by potentially assessing other more appropriate factors driving lipid mediated so-called 'residual risk'. For instance among patients with diabetes and low HDL-C, it is not uncommon to see an LDL-C level <1.8 mmol/L, but their non-HDL-C can be as high as 3.0 mmol/L thus above the 2.6 mmol/L target. In such situations which are now more common with the growing population of patients with diabetes or the metabolic syndrome, the ESC/EAS guideline allows greater flexibility to tailor individual care by using additional therapies to lower the non-HDL-C or apoB. In the ACC/AHA guidelines, those patients would not be considered for treatment optimization, but left to a trial-based regimen of high intensity statin with no additional consideration to residual risk.

HOW TO TREAT

The ACC/AHA guidelines essentially recommend either high intensity or moderate-intensity statin treatment.

High-intensity statin treatment is defined as those regimens which reduce LDL-C by 50%. Of note, while atorvastatin 40, 80mg and rosuvastatin 20mg are endorsed as RCT outcomes tested high intensity statins, rosuvastatin 40mg is not, even though it is Food and Drug Administration (FDA) approved. Moderate-intensity statin treatment (assessed in outcomes studies) is defined as regimens which reduce LDL-C by 30–50% (atorvastatin 10 mg, simvastatin 20 or 40 mg, pravastatin 40 mg, fluvastatin 40 mg bd, rosuvastatin 10 mg), again note that atorvastatin 20 mg and rosuvastatin 5 are not included as those doses were not used in outcomes studies but are FDA approved doses. In these ACC/AHA recommendations, there is no mandated requirement to measure LDL-C levels or to attain a specific LDL-C goal as the recommendations draw on dosage of statin rather than specific LDL-C level attainment. However, they suggest that in high risk patients, therapy could be intensified, if 50% reduction in LDL-C is not achieved (50% being the proxy for response to high-intensity statins among adherent patients) at the doctor's discretion. The 50% reduction does not seem to have a hard RCT evidence base which was claimed to be the sole criterion of the ACC/AHA guidelines. This is a marked divergence from existing ATP-III guidelines and other international guidelines which all recommend specific LDL-C goals. The remaining role of LDL-C measurements seems to be for monitoring adherence to lifestyle and medication, suggesting a fasting lipid panel at 4–12weeks and every 3–12 months thereafter. This seems a futile exercise, if the physician is not advised to consider residual risk or a specific target.

Another practical problem of the recommendations regarding percentage reductions as treatment objectives instead of an on treatment LDL-C target is that the baseline LDL-C may not be known when the patient is already taking a low-dose statin. Hence percentage reductions may be quite complicated in settings such as primary care. Another controversial issue in the ACC/AHA guidelines is the recommendation that physicians should consider decreasing the statin dose if LDL-C is <1.03 mmol/L on two occasions. This contradicts the genetic lifetime data on safety and the observational data from RCTs.

Recent ESC 2016 guideline is a more elaborate and practical guide specially in our context given in Table 1.

HOW AND WHY INDIANS ARE DIFFERENT ?

In view of such conflicting strategies advocated in the accepted guidelines it would be reasonable to have individual assessment of every patient and accordingly plan for management. To treat our native patients it is important to understand the nature of metabolic and lipid derangements prevalent in our country. The Pooled Cohort Equation for calculating the estimated CV risk needs further validation in our population as the pattern of metabolic abnormalities seem to differ in this subset. We need to develop our own risk calculator on the basis of large scale studies and apply those in future. South Asians are prone to develop CHD at a younger age, often before the age of 40 years in men.[4] Compared with whites,

Table 1: Treatment targets and Goals for Cardiovascular Disease Preventin	
Smoking	No exposure to tobacco in anby form
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish
Physical activity	2.5 – 5 h moderately vigorous physical activity per week or 30-60 min most days.
Body weight	BMI 20-25 kg/m^2, waist circumference <94 cm (men) and <80 cm (women).
Blood pressue	<140 / 90 mmHg
Lipid LDL-C is the primary target	Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate –risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<8.6 mmol/L)

South Asians are more likely to have an anterior location of infarction.[5] They are more likely to have significant left main, multivessel, and distal coronary artery disease.[6] Numerous case-control studies documenting premature CHD in South Asians demonstrate similar or lower prevalence of traditional risk factors than with other populations. However unlike other traditional risk factors, the prevalence of diabetes mellitus is uniformly higher in South Asians.[7] Compared with European populations, South Asians have increased abdominal visceral fat and greater insulin resistance at BMI levels that are traditionally considered "ideal" (<25 kg/m^2).[8] This body type, often termed "thin-fat phenotype" (muscle thin but body fat) is associated with an increased risk of developing diabetes. A more appropriate estimate of visceral fat and insulin resistance in South Asians may be measurement of waist circumference.[9] Hence we need to restratify our population and set up our own risk scores.

Although South Asians have levels of LDL cholesterol comparable to other populations, LDL particle size tends to be smaller[10]. Small LDL particles, are more atherogenic due to increased susceptibility to oxidation than larger particles. The serum triglyceride levels are highest in urban Asian Indians residing in India and migrant Asian Indians. Further, even the average serum triglyceride level of rural-based Asian Indians is higher than Caucasians. A close association between Sst I polymorphism in the 3' untranslated region of the apolipoproteinC3 (*APOC3*) gene and levels of plasma triglycerides (TG) had been reported in North India. Gupta et al (1997) showed that ~24% of the urban population of north India had low levels of HDL-cholesterol [11]. HDL particle size, in addition to the actual level of HDL cholesterol, also appears to be an important predictor of CHD risk. South Asians not only have lower HDL levels but also have a higher concentration of small, less-protective HDL particles[12]. Asian Indian males have a higher prevalence of low HDL_{2b}, which suggests impaired reverse cholesterol transport. Among the emerging risk factors, elevated lipoprotein(a), apolipoprotein B, homocysteine, plasminogen activator inhibitor-1, fibrinogen, and C-reactive protein (CRP) have considerable importance. Lipoprotein(a), homocysteine, and plasminogen activator inhibitor-1 levels tend to be higher in South Asians than in white populations, although fibrinogen levels appear to be similar[13]. These factors support a prothrombotic milieu. Microalbuminuria is recognized as an independent cardiovascular disease risk factor. Numerous studies have suggested that altered adipokine production or action may play a role in the heightened vascular risk observed in South Asian patients. Altered adipokines may explain why lean nondiabetic Asian Indians have decreased insulin sensitivity compared with others.

So Indians are many way different heterogenous population where atherogenic dyslipidemia prevails and that is why treatment schedule should be individualized here, approach should be extended beyond conventional stereotyped guidelines. For effective lipid lowering in Asian Indians, the following principles and interventions may be adopted:

1. The therapeutic strategy likely to confer the greatest benefit to a South Asian individual is one of moderate weight loss through regular exercise and dietary restriction. Reduction of abdominal obesity through lifestyle measures can improve all components of the metabolic syndrome and likely delay the development of both diabetes and atherosclerosis.

   Beyond lifestyle intervention, optimal management of risk factors to evidence-based targets is essential. At present, there is no evidence to suggest that treatment targets should differ between ethnic

groups. Importantly, evidence-based treatments should be optimized in South Asians at risk, including the use of aspirin, lipid-lowering agents, blood pressure control, and renin-angiotensin inhibition.

2. It is advisable to increase intake of ω-3 polyunsaturated fatty acids in diets, particularly for the vegetarians which leads to effective lowering of serum triglyceride levels and increase HDL-cholesterol levels.

3. Statins are very effective in reducing LDL-cholesterol levels. The newer statins (Atorvastatin and Rosuvastatin) reduce serum triglyceride levels by nearly 15-20% and also increase the LDL particle diameter[14], but have relatively milder effect on HDL-cholesterol levels.

4. Fibrates are more effective than statins in reducing serum triglyceride levels and increasing HDL-cholesterol levels[15] . Atherogenic dyslipidemia in Asian Indians may be well managed by the use of fibrates. Fibrates decrease TG levels by 20-50%, and increase HDL-C by 10-20%. They also reduce small, dense LDL particles by promoting a shift to larger, more buoyant particles which have higher binding affinity for the LDL receptor Fibrates decrease fibrinogen levels and factor VII level, increase fibrinolysis ,decrease CRP & vascular inflammation , inhibit vascular smooth muscle proliferation and improves glucose tolerance. Subgroup analysis of FIELD and ACCORD trials showed that there was a possible benefit of fenofibrate in those with a triglyceride more than 204 and an HDL less than 34. There were around 2014 patients in the FIELD trial who showed a CV event reduction of 27% while in the 941 patients of ACCORD trial there was a CV endpoint reduction of 31%.

Fibrate monotherapy was shown to reduce events in those with HDL-C concentrations less than 40 mg/dL in the VA-HIT trial (Veterans Affairs HDL Intervention Trial) and in those with triglyceride concentrations of 200 mg/dL or greater in the Bezafibrate Infarction Prevention trial. FIELD trial demonstrated a more certain preventive effect in patients with both triglyceride levels greater than 200 mg/dL and HDL-C levels less than 40 mg/dL.

Fibrates along with Simvastatin have shown a favourable trend in those diabetics with hypertriglyceridemia and low HDL in ACCORD Trial.

5. Recent evidence indicates that combination of statins and fibrates is well tolerated [16]. Adequate spacing of administration of both the drugs by several hours, gradual upward dose titration, and careful monitoring of liver function and creatine phosphokinase levels is essential to minimize adverse effects.

6. Fibrates and ω-3 polyunsatalso have anti-inflammatory and anti atherogenic properties, and may be additionally useful in Indians who have high prevalence of subclinical inflammation although there is no hard evidence supporting their use.

7. In IMPROVE-IT, the addition to statin therapy of a nonstatin agent, ezetimibe, which reduces the absorption of cholesterol from the gastrointestinal tract, lowered LDL cholesterol by approximately 24%.The combination of simvastatin and ezetimibe also resulted in a significantly lower risk of cardiovascular events than that with statin monotherapy, with a 2.0-percentage point lower rate of the primary composite end point of cardiovascular death, major coronary events, or nonfatal stroke (hazard ratio, 0.936).

7. Non-HDL cholesterol, which is derived from subtracting HDL cholesterol concentration from total cholesterol level, representing the sum of all atherogenic lipoproteins, has been identified as a secondary target of therapy in patients with elevated triglyceride levels. There is evidence to suggest that, in patients with diabetes, non-HDL cholesterol is a stronger predictor of mortality from coronary disease than LDL cholesterol. In a post hoc analysis of patients with diabetes from four prospective cohort studies—the Framingham Cohort Study, the Framingham Offspring Study, the Lipid Research Clinics Prevalence Follow-Up Study, and the usual-care group of the Multiple Risk Factor Intervention Trial—the relative risk of death for diabetic (compared with nondiabetic) patients was 7.2 for those with elevated non-HDL cholesterol ≥ 130 mg/dl) and low LDL (< 100 mg/dl) and 5.7 for those with low non-HDL cholesterol (< 130 mg/dl) and elevated LDL (≥ 100 mg/dl). Managing and monitoring nonHDL cholesterol may be particularly important for Asian Indians where, the prevalence of CHD is nearly two-fold higher in presence of combination of hypertriglyceridemia, low HDL-cholesterol level and higher prevalence of metabolic syndrome.

Thus one needs to individualize each patient based on clinical judgement and experience. Initiation of therapy should be done considering an individual's clinical as well as laboratory parameters including lipid levels. The high risk patients should undergo moderate to high intensity statin therapy depending on clinical perspectives. LDL-C should be monitored for adequate control, assessing drug compliance and addition of other drugs needs to be considered once optimal LDL-C lowering is not achieved though there is no strong evidence supporting their use. The use of fibrates and other group of drugs in addition to statins also may be appropriate if lipid fractions other than LDL-C are elevated, specialy in diabetics and those with atherogenic dyslipidemia. Setting a target will lead to better drug monitoring on the part of the physician and

also better drug compliance on the part of the patient. Time has come to set up our own set of guidelines that can be applied to our indigeneous population. As a foundation to that goal we need our own data and hence future large scale trials are necessary.

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