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Review Article

Adaptation of 2016 European Society of Cardiology/European Atherosclerosis Society guideline for lipid management to Indian patients – A consensus document

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ABSTRACT

In the year 2016, European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provided recommendations on dyslipidemia management. The recommendation from these guidelines are restricted to European subcontinent. To adapt the updated recommendations for Indian subset of dyslipidemia, a panel of experts in management of dyslipidemia provided their expert opinions. This document provides expert consensus on adapting 2016 ESC dyslipidemia guidelines recommendations in Indian setting. The document also discussed India-specific relevant literature to support the consensus opinions provided in management of dyslipidemia.

1. Introduction

Dyslipidemia being a known modifiable risk factor for cardiovascular (CV) disease, demands attention from patients, physicians and policy makers to reduce the morbidity and mortality from CV disease. In India, the burden of dyslipidemia is substantial. Significant prevalence of reduced high density lipoprotein cholesterol (HDL-C) and raised triglycerides (TGs) characterizes the Indian dyslipidemia.[1] The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study reported low HDL-C in 72.3% and raised TGs in 29.5% of study population as against raised total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) in only 13.9% and 11.8% respectively of the study population.[2] it is well known that dyslipidemia is central to the pathophysiology of atherogenesis and is associated with an increased CV risk.[3]

2. Need for India-specific dyslipidemia management recommendations

Evidence-based guidelines are published internationally from time to time to provide newer recommendations in dyslipidemia management. European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) released guideline for the management of dyslipidemia in 2016.[4] However, as is evident in various studies, dyslipidemia in Indian population is characterized by low HDL-C and high TG instead of a raised TC and LDL-C, which are much less commonly seen. Moreover, there are significant lifestyle, genetic, socioeconomic, and cultural differences between Indian and European populations. All these factors demand specific approach for optimal management of dyslipidemia and CV disease for the Indian subcontinent. In addition, the prevalence and pattern of various other risk factors that decide the category of CV disease risk also differ between the two populations and hence the risk assessment score varies. Apart from this, the economic constraint on healthcare expenditure and high cost of newer

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agents also demands different treatment approaches amongst treating physicians in the two continents. As is also reported, the side effect profiles of the drugs used to treat dyslipidemia, notably statins, also varies from the European to the Indian population. Thus though the available expert consensus documents provide effective recommendations on dyslipidemia management in Indians,[5,6] there is constant need to update these recommendations with availability of new evidence and with specific assessment and treatment goals more suited to the target population. Since changing global evidence-based recommendations are incorporated in international guidelines, ESC/EAS 2016 guidelines recommendations were considered for appraisal with their applicability to Indian patients.

To address the above differences and challenges, this expert consensus document was prepared to guide Indian physicians on treatment approaches for Indian patients with dyslipidemia based on the widely accepted recent ESC guidelines. However, this document only represents the common consensus amongst experts through in-depth study of ESC guidelines and available scientific evidences with an intent to assist clinical decision making. The final decision for patient should be taken by the treating physician based on individual patient clinical profile.

3. The expert panel

The expert panel consisted of 19 cardiologists and physicians involved in the management of dyslipidemia from various parts of India and meeting of these experts was held to discuss on these specific issues. Involving experts from different locations was based on consideration of geographical and dietary differences in Indian setting. These experts have provided India specific consensus opinions for management of dyslipidemia after discussion of the recent ESC guideline recommendations pertaining to following issues –

- CV risk factors and risk assessment
- Laboratory parameters assessment
- Treatment goals and targets
- Treatment recommendations
- Follow up monitoring
- Safety assessments

The opinions of experts were counted on majority. Following sections provide practically applicable ESC recommendations with expert opinions on each of them for adaptation in an Indian setting.

4. CV risk factors and risk assessments

The 2016 ESC dyslipidemia guidelines provided Systemic Coronary Risk Estimation (SCORE) charts for assessment of total CV risk score in men and women which were based on age, gender, smoking, systolic blood pressure (SBP) and TC levels.[4] The expert panel agreed on the 5 standard risk factors considered in risk calculation but they felt a need to additionally consider risk factors like diabetes, metabolic syndrome, family history of premature coronary artery disease (CAD) and other lipid parameters like TGs, and non-HDL. It was opined that as the SCORE chart has not been validated in Indian setting, its adaptation may lead to erroneous estimation of CV risk. This was based on the fact that even ESC recommends use of low risk and high risk charts separately in different countries within Europe.[4] Considering these differences, panel suggested to use QRISK®2 calculator for estimating CV risk as it incorporates ethnicity in CV risk estimation. The QRISK®2 score calculation is shown in Table 1. Panel suggested that QRISK®2 is associated with least underestimation of CV risk in Indians. To define CV risk categories, it was suggested to develop India specific risk score. However, in absence of valid randomized controlled trials (RCTs), panel found that it is difficult to derive any specific risk score for Indian patients. Few studies have comparatively evaluated risk scores in Indian population. A study by Bansal et al[7] compared various risk scores in patients with first myocardial infarction (MI) (n = 149). World Health Organization (WHO) risk prediction charts were found to have lowest risk estimate compared to Framingham Risk score (FRS), American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations and the 3rd Joint British Societies' (JBS3) risk calculator (86.6% Vs 61.7%, 69.8% and 44.1% patients at <20% 10-year risk respectively). Another study from Rao et al[8] assessed 434 Indians using FRS, JBS (2nd) and QRISK®2 scoring systems. They found 15% patients with 10-years CV risk of >20% with QRISK®2. In three risk calculators, study reported a moderate agreement for risk determination. However, evaluation from Tillin et al[9] in adult white Europeans, South Asians and African Caribbeans suggested

Table 1
QRISK®2 score parameters.

Age
TC: HDL ratio
Systolic blood pressure
Smoking status
Body mass index
Family history of coronary heart disease in first degree relative under 60 years (yes/no)
Townsend deprivation score
Treated hypertension (yes/no)
Self-assigned ethnicity (white (or not recorded)/Indian/Pakistani/Bangladeshi/other Asian/black African/black Caribbean/other (including mixed))
Type 2 diabetes mellitus (yes/no)
Rheumatoid arthritis (yes/no)
Atrial fibrillation (yes/no)
Renal disease (yes/no)
Age × BMI
Age × Townsend score
Age × SBP
Age × family history of CV disease
Age × current smoking
Age × treated hypertension
Age × type 2 diabetes
Age × atrial fibrillation

inconsistent performance of QRISK®2 and FRS necessitating further validation of QRISK®2 in multi-ethnic groups.

In consideration of premature CV disease in family, panel thus suggests that cut-off age for Indians can be reduced by a decade (<55 years and <50 years in females and males, respectively). Further, consideration of lipid parameters like TC, TGs, and non-HDL (if TGs > 200 mg/dL) are suggested for Indian setting. More technical details of QRISK®2 risk calculation can be obtained at https://qrisk.org/2016/.[10]

Expert Opinion: Use QRISK®2 risk calculator for estimating CV risk in Indian subset of dyslipidemia.

5. Laboratory parameters assessment

5.1. Fasting vs non-fasting assessments

Assessment of lipid parameters is crucial to determine CV risk and to decide on the treatment of an individual. Routinely, assessments are done in fasting state. ESC dyslipidemia guideline opined that both fasting and non-fasting assessment of TC, LDL-C and HDL-C show similar levels, whereas higher TG levels (~27 mg/dL) are observed in non-fasting state depending on time and composition of the last meal. In Indian setting, this is important due to high content of carbohydrates in meal and it is necessary to decide whether to assess fasting or non-fasting levels. The increase in TG levels in non-fasting state seemed important as TGs are considered as strong CV risk factors for Asian Indians and is a characteristic dyslipidemic component in Indians.[11,12] Besides, panel discussed some practical issues pertaining to the lipid assessment in Indian setting. *Non-fasting assessments* were deemed helpful so that overcrowding of laboratory in morning will be reduced and allows freedom to patient to visit laboratory in day-time so that patients' preference to perform lipid assessment increases. However, non-fasting lipid assessment has disadvantage of unclear evidence on time of assessment after meal (whether 1 h, 1.5 h, 2 h and so), meal load or composition before assessment, and non-fasting cut-off levels for each of lipid component. Thus, panel thus suggests fasting lipid assessment to be performed whenever feasible. Panel identifies that non-fasting is feasible in situations like CV risk assessments, in diabetic patients, patients residing at distant region (first-hand opportunity to screen for dyslipidemia with follow up fasting evaluation at 3 months). Further the panel recommends that for a LDL-centric management, i.e. when physicians treating dyslipidemia has to keep the target of achieving LDL-C to a goal irrespective of the other lipid levels, a non-fasting measurement may prove to be equally useful as fasting measurements. This was also recommended by the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine.[13] However, National Institute for Health and Care Excellence (NICE) lipid guidelines 2014 recommended fasting levels.[14]

Expert Opinion: Fasting assessment are to be done when feasible and in follow-up monitoring of lipids. Non-Fasting testing can be done in situations like CV risk assessment, diabetes, and distant residence of a patients where the current visit might be the only chance of assessing lipid levels of the patient.

5.2. Lipid parameters for CV risk classification

LDL-C was identified as primary lipid parameter to be used for screening, risk estimation, diagnosis and management by ESC dyslipidemia guidelines[4] and was unarguably accepted by the panel for Indian setting as well. *TGs* estimation was also advised as an additional tool for assessment of CV risk. *Non-HDL* was recommended for risk estimation in patients with high TG (>200 mg/dL) by ESC guidelines and the panel as well.

ESC recommended *apolipoprotein B* (ApoB) as an alternative marker for risk assessment, especially in those with elevated TGs.[4] However, panel suggests that ApoB is expensive for Indian setting. Hence, it is suggested that Apo B should not form a part of routine dyslipidemia management in Indian setting.

Lipoprotein (a) [Lp (a)] was advised by ESC guideline as marker for estimation in patients with history of premature CV disease in family and in those with borderline CV risk.[4] Although, evidence suggests positive association of Lp (a) with atherosclerosis and coronary artery disease (CAD),[15,16] panel disagrees on routine Lp (a) estimation due to several reasons. Most importantly, panel questioned that as Lp(a) estimation techniques were not validated in most laboratories in India, Lp (a) testing was liable to technical errors giving false positive or false negative results. A recent evaluation from Banerjee et al[17] reported non-significantly higher trend for elevated Lp(a) association with ischemic heart disease (IHD) in Asian Indians [Odds ratio (OR) 2.0] and Chinese (OR 4.8) than non-Hispanic Whites (OR 1.4).

Lp (a) assessment is best considered in following conditions-

- Premature (at age <40 years) or recurrent CVD
- Familial hypercholesterolemia
- History of premature CVD in family
- Borderline high risk of CV disease

Expert Opinion: LDL-C is a primary target for dyslipidemia management including CV risk assessment. TGs and non-HDL-C can be considered additional targets in whom these levels are abnormal. Apo-B is not routinely recommended for risk assessment and management. Lp (a) estimation is recommended in select conditions as described above.

6. Treatment goals and targets

LDL-C has been recommended as a primary target for treatment by ESC guidelines[4] and was accepted by all the panellists. TC has been suggested as alternative target if other lipid parameters are not available. However, panel opined that its optimal cut-off levels are still debatable. Alternatively, low HDL can be present even in normal TC levels. Low HDL is considered as risk factor for CAD since long.[18,19] However, recent Framingham Offspring Study[20] showed that isolated low HDL is probably not a factor contributing to high CV risk and association with other lipid abnormalities was found to increase CV risk. Thus, function of HDL was postulated to differ according to associated lipid abnormalities. A recent Canadian study observed a J shaped curve of HDL-C level and CAD, a higher risk was seen with both too low and too high levels of HDL-C that are observed in untreated population.[21]

6.1. CV disease prevention: targets

A multimodal approach needs to be adopted for CV disease prevention. ESC recommends cessation of tobacco in any form, healthy diet, physical activity (moderate-vigorous 2.5–5 h per week), body weight maintenance, BP control and glycemia control (glycated hemoglobin <7%).[4] Expert panel also agreed on these interventions. However, it was pointed out that healthy diet is one of the most deficient means acknowledged in CV disease prevention in India. Reducing carbohydrate intake was recommended. Being culturally diverse, India witnesses large variety in staple food consumption and cooking oil utilization. ICMR National Institute of Nutrition Research recommends visible fat intake of 50

gm per person per day.[22] Panel thus recommends limiting the use of coconut oil, *vanaspati*, and animal fats on account of high amount of saturated fatty acids present in these sources. Further, they it is advised to avoid olive oil for cooking in India as it has lower smoking point and may get denatured at cooking temperatures (deep frying) used routinely.[23] Besides these, weight maintenance is also recommended. Here, panel calls for lower waist circumference (WC) cut-off for males (<90 cm) and females (<80 cm) contrasting to ESC recommendation of <94 cm and <80 cm respectively.[4] Also, body mass index (BMI) cut-off was opined to be below 23 kg/m^2 against ESC recommendation of 20–25 kg/m^2.[4] This was in line with recommendation of lower BMI and WC cut-off for South Asian population.[24,25] Alcohol has not been found to be cardiac friendly for Indian population as opposed to most other ethnic groups.[26]

Expert Opinion: Avoidance of tobacco in any form, physical activity, BP and glycemic control are integral targets for CV risk reduction. Healthy diet in the form of lesser intake of carbohydrate and saturated fats, higher intake of green-leafy vegetables, cereals and fruits and optimal protein intake should be implemented. Salt restriction and reduction or avoidance of alcohol is advised. A cut-off for WC is <90 cm *and* <80 cm *in Indian males and females respectively and cut-off for BMI is* <23 kg/m^2.

6.2. Treatment goals

ESC guidelines recommends LDL-C goal of <70 mg/dL in very high risk cases.[4] Panel opined that achievement of LDL-C <70 should be the goal for all cases with established atherosclerotic cardiovascular disease (ASCVD). However, a lower target LDL-C levels (<50 mg/dL) was suggested in high-risk cases which include –

- post-MI
- post percutaneous coronary intervention (PCI)
- post-coronary artery bypass graft (CABG)
- premature CVD with multiple risk factors
- recurrent CV events with optimum statin therapy

Further, the panel suggested that a target of <50 mg/dL of LDL-C as against <70 mg/dL should be optional as numbers have psychological consequences on patient compliance to therapy. As primary care physicians (PCPs) are largely involved in the management of dyslipidemia in India, panel feels the need to percolate these numbers to PCPs as non-achievement of these targets will result in higher risk for CAD. Evidence also suggests that physician often undertreat even the high risk patients.[27] With regards to HDL-C and TGs, panel agreed to recommendations of ESC guidelines with no specific target for HDL-C but levels >40 mg/dL in men and >48 mg/dL in women and TGs <150 mg/dL indicate lower risk.

Panel identifies 4 measures to raise HDL-C and reduce TG levels for Indian patients viz; physical activity, cessation of smoking and alcohol, weight reduction and control of hyperglycemia.

Expert Opinion: LDL-C <70 mg/dL *is the target in all ASCVD cases with optional target of <50* mg/dL *in very high-risk cases mentioned above. Physicians should understand the treatment target in each patient to provide optimal treatment. Lifestyle changes and glycemia control are necessary to raise HDL-C and reduce TGs. Treatment should be tailored to achieve HDL-C >40* mg/dL *in men and >48* mg/dL *in women and TGs <150* mg/dL *with optional lowering to <100* mg/dL *in high-risk cases.*

7. Treatment recommendations

7.1. Drugs for dyslipidemia

Statins remain the cornerstone for treatment of dyslipidemia. Statins are recommended in highest recommended or tolerated dose to reach the lipid levels goal and their use was agreed unanimously by the panel. Panel identified three potential statins – atorvastatin, rosuvastatin and pitavastatin for clinical use in India. Descriptive studies in India have reported maximum utilization of atorvastatin and rosuvastatin to a large extent (over 95% of prescriptions) as compared to other statins.[28,29]

ESC recommends use of ezetimibe, bile acid sequestrant, and cholesterol absorption inhibitors in a sequential manner as additional agents if the goal is not reached with statin alone. In cases with very high risk who failed to achieve treatment goal, addition of PCSK 9 inhibitors should be considered.[4] Panel suggests that when lipid goals are not reached, causes of secondary dyslipidemia should be ruled out.

Dysglycemia is hugely prevalent in Indian subset and prevalence of any dysglycemia was reported to be 51.7 per 1000 person-years.[30] Niemen-Pick C1L1 (NPC1L1) protein expression is increased in dysglycemic individuals. NPC1L1 is reported to be a target for ezetimibe action.[31] This dictates the use of ezetimibe in combination with statin to achieve the lower LDL-C levels. With ezetimibe, the evidence is convincing especially in diabetic subgroup of patients. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed additional lipid lowering when ezetimibe was added to statin treatment versus statin alone.[32] A subgroup analysis in diabetic subset showed significant benefits in terms of CV event reduction.[33] Addition of ezetimibe to statin is reported to be associated with reduction in both LDL-C and high sensitivity C-reactive protein (hs-CRP) and this dual reduction was associated with improved outcome in a multivariate analysis.[34]

Since increase in blood sugar with statins was reported in Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,[35] a concern is raised for using high-dose statin even in high risk cases. Intensive statin therapy has been reported to be associated with 12% increase in new onset diabetes compared to placebo.[36] Panel suggested to use lower bracket dose of a high-intensity statin (e.g. atorvastatin 40 mg instead of 80 mg and rosuvastatin 20 mg instead of 40 mg) with addition of ezetimibe. This may help reduce the lipids without significant side effects of statin including hyperglycemic effect which may be concern to some patients.

Expert Opinion: To achieve LDL-C target, statins are first line agents. In India, rosuvastatin (5–40 mg*), atorvastatin (10–80* mg*), and pitavastatin (1–4* mg*, only as moderate intensity statin) may be used as first choice. If there is a failure to achieve LDL-C goal with statin alone, ezetimibe (10* mg*) as second agent followed by bile acid sequestrant, and cholesterol absorption inhibitors may be added. A combination of statin (in modest dose – e.g. atorvastatin 40* mg *instead of 80* mg *or rosuvastatin 20* mg *instead of 40* mg*) with ezetimibe may be considered in patients who have significant adverse effects with statins or who are diabetic or at high CV risk.*

7.2. Strategies to control plasma triglycerides

ESC recommended that statin should be given to all high-risk patients with TG >200 mg/dL and addition of fenofibrate to statin to be considered if target TG of <200 mg/dL is not reached with statin alone.[4] Panel agrees to this approach for raised TGs. However, panel advised caution while using statin together with

fenofibrate because of increased risk of renal damage.[37–39] Chronic kidney disease (CKD) and CV disease are interrelated with each one imposing a significant risk on the other. The risk of CV disease morbidity and mortality is increased significantly in case where estimated glomerular filtration (eGFR) is <15 ml/min/1.73 m^2.[40] Using fenofibrate with statin thus demands lower dosage (<75 mg/day) of fenofibrate. Further, reported prevalence of CKD in Indians is 17.2% with further increase in diabetic subset (18.8%) suggests significant burden of CKD.[41] Panel is of the opinion that when eGFR is <60 ml/min/1.73 m^2, dose of fenofibrate should not be increased. In patients who have TGs >200 mg/dL, panel recommends use of fenofibrate in a low dose with caution in CKD cases and strict implementation of lifestyle modification as a treatment strategy. In CAD cases, who have LDL-C <70 mg/dL with TG >200 mg/dL and HDL-C <35 mg/dL, panel suggests the use of fenofibrate (75 mg/day) in addition to statin. Use of higher dose needs monitoring of eGFR in patients. Where fibrate is contraindicated or not tolerated, there is some evidence of biochemical benefit with saroglitazar, a dual PPAR agonist. This is safe in combination with statin but as yet there is no evidence of its clinical benefit.

Expert Opinion: If target TGs <200 mg/dL *is not achieved with statin, add fenofibrate to statin treatment. However, cautious use of fenofibrate is warranted in patients with CKD. Consider low dose fenofibrate (75* mg*) especially when eGFR <60* ml/min/*1.73* m^2*. If higher dose to be used for very high TG levels (>500* mg/dL*), monitor renal function and intensify lifestyle modification. For CAD with high TGs, low HDL-C with controlled LDL-C, add low dose (75* mg*) fenofibrate to statin therapy.*

7.3. Familial hypercholesterolemia (FH)

ESC guidelines recommend use of Dutch Lipid Clinic Network diagnostic criteria for FH screening (Table 2).[4] In India, sporadic case reports of FH are available in literature suggesting its existence even in Indian population.[42–46] However, panel feels that there is need to prospectively screen patients for FH and suggested the use of clinical criteria for screening of FH in India. Panel stresses on assessing for arcus cornealis before the age of 45 years especially in upper cornea as simple tool to start screening FH. In association with raised LDL-C (>250 mg/dL), this criteria can provide a clue to the diagnosis of FH. Genetic screening may be positive in ~60% cases which were classified as definite FH by clinical criteria.

ESC recommends test for FH in children by age 5 years or even in early years if homozygous FH is suspected. LDL-C goal of <135 mg/dL is recommended from over 10 years of age.[4] Panel agrees upon these recommendations. Though the arbitrary incidence of heterozygous FH being 1 in 300, physicians including specialists have been missing identification of FH cases in Indian set up. So, panel stresses for more appropriate clinical screening of FH as mentioned above. Compared to another criteria, the Simon Broome criteria for diagnosis of FH,[47] panel suggested the use of Dutch criteria as it is easy to understand and there has a higher consideration of clinical profile. Further, cascade screening of FH may help identify more number of patients in families.[47]

Target LDL-C in FH recommended by ESC guidelines is <100 mg/dL and <70 mg/dL without or with CVD respectively. In high risk cases or in those with CVD or statin intolerance, PCSK9 inhibitor is recommended as treatment.[4] As PCSK9 inhibitor is not routinely available for clinical use in India, panel suggested use of stain and ezetimibe combination in optimally tolerated doses. With this combination, ~40% of the patients may not reach their LDL-C goal. Lipoprotein apheresis can be an option in treatment of FH,[48,49] but is not widely available in India.

Expert Opinion: Use Dutch criteria described above for diagnosis of FH. LDL-C goal should be <70 and <100 mg/dL *in patients with and without CVD respectively. Statin and ezetimibe in combination is a primary treatment for FH in India until PCSK9 inhibitors become available for clinical use. Cascade screening is advised in family members.*

Table 2
Dutch criteria for familial hypercholesterolemia.[4]

Criteria	Points
Family History	
First-degree relative with	
• Premature coronary/vascular disease (M < 55 yrs, F < 60 yrs), OR	1
• LDL-C >95th percentile, OR	
• Tendinous xanthoma and/or arcus cornealis, OR	
• Children <18 yrs with LDL-C >95th percentile	2
Clinical History	
• Premature CAD	2
• Premature cerebral or peripheral vascular disease	1
Physical Examination	
• Tendinous xanthoma	6
• Arcus cornealis in <45 years	4
LDL-C levels	
• >325 mg/dL	8
• 251–325 mg/dL	5
• 191–250 mg/dL	3
• 155–190 mg/dL	1
Genetic (DNA) analysis	8
Total Score	
• >8 points: Definite FH	
• 6–8 points: Probable FH	
• 3–5 points: Possible FH	

7.4. Dyslipidemia in type 2 diabetes and metabolic syndrome (MetS)

ESC guidelines described that dyslipidemia in MetS is a cluster of lipoprotein abnormalities. They recommend non-HDL-C <130 mg/dL and <100 mg/dL in high risk and very high-risk cases respectively. Higher WC and TGs were identified as tools to find high-risk patients with MetS. In treating dyslipidemia, statins are recommended in type 1 diabetes and in presence of micro-albuminuria and/or renal disease irrespective of baseline LDL-C. LDL-C <70 mg/dL (primary) and non-HDL-C <100 mg/dL (secondary) are recommended in type 2 diabetes and CVD/CKD as well as in patients aged >40 years without CVD but with one or more CVD risk factor. Further, LDL-C <100 mg/dL (primary) and non-HDL-C <130 mg/dL (secondary) is advised in type 2 diabetes without any risk factor and/or evidence of target organ damage.

Panel was unanimous on these recommendations of EAS/ESC guidelines. In India, diabetes occurs at a younger age.[50,51] Panel feels age should be no bar for treating dyslipidemia. As prevalence of low HDL-C, a risk factor for CVD, is significantly high in diabetic population,[52,53] panel suggested that all diabetics should receive treatment with statin to reach the LDL-C <70 mg/dL. This will ensure aggressive treatment with statin with better containment of CV disease in diabetes since control of dyslipidemia in diabetes is reported to be poor in India.[2,53] Further, addition of ezetimibe to statin therapy is to be considered as it has been reported to improve LDL-C reduction in diabetic and MetS population.[54] However, it should be kept in mind that statins are contraindicated during pregnancy and proper caution and counselling must be done while using statins in females of child bearing age.

In statin intolerant patients, panel suggested the use of alternative strategies. Besides strategies of using alternate statin or low dose statin or use of a statin with lesser frequency like alternate day or thrice a week, other agents like ezetimibe, fibrates, niacin, bile acid sequestrant and PCSK9 inhibitors alone or in combination can be used.[55] In patients with diabetes or MS and statin intolerance, Rivers et al[56] assessed efficacy and safety of colesevelam hydrochloride (HCl) and ezetimibe combination therapy. In 16 cases analyzed, 75% had type 2 DM, and 25% had MetS. This combination treatment resulted in significant reductions in mean levels of TC (27.5%), LDL-C (42.2%), and non-HDL-C (37.1%). Besides, 50% patients achieved LDL-C goal of <100 mg/dL. Treatment was safe and well tolerated. Use of combination therapy of these non-statin agents has also been recommended by the American Academy of Clinical Endocrinology (AACE) guidelines.[57] In another study, Backes et al,[58] used every other day rosuvastatin approach in statin intolerant cases and observed that 72.5% (37/51) of patients tolerated the statin. Over mean duration of 4 months, a mean dose of 5.6 mg rosuvastatin resulted in 34.5% reduction in mean LDL-C ($p < 0.001$). These approaches can thus be adopted for statin intolerant cases.

Expert Opinion: LDL-C goal is <70 mg/dL in high risk diabetic cases. Modest dose statin with addition of ezetimibe is advised to achieve the desired goal and to improve the dyslipidemia control in Indians which will reduce the CVD risk.

7.5. Dyslipidemia in acute coronary syndrome (ACS) and in PCI cases

ESC recommends early high-dose statin for all cases with ACS and those undergoing PCI despite normal baseline LDL-C levels. Addition of ezetimibe and PCSK9 inhibitors should be considered if LDL-C target is not reached with statin alone. In statin-intolerant cases, the ezetimibe and PCSK9 inhibitor may be used alone or in combination. A goal LDL-C is <70 mg/dL or 50% reduction from the baseline value. Re-evaluation at 4–6 weeks is recommended. A loading of high-dose statin before elective PCI or in patients with non-ST elevation ACS should be considered when patients are already receiving statins. Panel suggested that when baseline LDL-C is <100 mg/dL in any ACS patients, a target should be 50% reduction from baseline. When the target of <50 mg/dL is desirable and is not achieved with statin alone, addition of ezetimibe may be considered. It has been reported that nearly 68–96% of high-risk population did not achieve LDL-C <70 mg/dL.[59] This necessitates intensification of statin therapy and use of combination treatments in high-risk cases like ACS.

Expert Opinion: LDL-C goal in ACS cases or in patients undergoing PCI is <70 mg/dL or 50% reduction from baseline. Statin in high-dose is first-line treatment with addition of ezetimibe to achieve the lipid levels goal. Goal of <50 mg/dL may be considered in very high-risk patients specially with multiple risk factors.

7.6. Dyslipidemia in heart failure and valvular disease

ESC guidelines recommend that though not harmful, lipid lowering treatment is not necessary in HF or in aortic valvular stenosis in absence of CAD or other indications for their use. Omega-3 polyunsaturated fatty acids can be considered in HF patients treated with optimal medical therapy.[4] Panel agrees to these recommendations.

Expert Opinion: Statin therapy is not advised in HF unless complicated by CAD or other compelling indications for their use.

7.7. Dyslipidemia in moderate to severe CKD

ESC guidelines identified that CKD stage 3 to 5 are high or very high risk for CV disease. Statin with or without ezetimibe is recommended in non-dialysis-dependent CKD. Statin, ezetimibe, or their combination should be continued at the time of dialysis initiation in all and especially in CV disease cases.[4] The expert panel agrees to the recommendations of ESC guidelines. They further reviewed recent evidences regarding statin use in CKD. In Study of Heart and Renal Protection (SHARP) trial,[60] simvastatin 20 mg plus ezetimibe 10 mg per day (n = 4650) and placebo (n = 4620) were compared in CKD patients, of which 3023 patients were on dialysis. Patients had no previous history of CV disease or revascularization procedure. In median 4.9 years of follow-up, the combination treatment resulted in 17% reduction in atherosclerotic events. In another study from Aftab et al.[61] in patients of end-stage renal disease (ESRD) on hemodialysis awaiting renal transplant, statin use was associated with a lower mortality (hazard ratio 0.30, 95% confidence interval 0.11, 0.79, $p = 0.01$) in a multivariate analysis. These data supported the use of statins in CKD including hemodialysis cases which are the high-risk for CV disease. Panel suggested the use of high dose statin in CHD patients who have CKD based on results of Treating to New Targets (TNT) trial sub-analysis[62] where atorvastatin 10 mg and 80 mg were compared in stable CAD with CKD cases (n = 3107). Compared to normal eGFR, patients with CKD had significantly higher risk of major CV events (HR 1.35, 95% CI 1.18–1.54; $p < 0.0001$). In CKD cases, compared to 10 mg, atorvastatin 80 mg was reported to reduce the relative risk of major CV events by 32% (HR = 0.68; 95% CI 0.55–0.84; $p = 0.0003$) whereas it was reduced by 15% in patients with normal eGFR (HR = 0.85; 95% CI 0.72–1.00; $p = 0.049$).

Panel reviewed the evidence from Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease (PLANET I) trial comparing atorvastatin and rosuvastatin in diabetic CKD, high dose rosuvastatin resulted in better reduction in lipid parameters at 52 weeks. However, atorvastatin showed better renoprotection than rosuvastatin.[63]

Thus, choice of statin in CKD may vary depending on the treatment goal. Recommended dose of atorvastatin by NICE guidelines for primary or secondary prevention of CVD in CKD cases is 20 mg/day. These guidelines further advocated consultation of nephrologist if eGFR is <30 ml/min/1.73 m^2 and need higher dose of atorvastatin.[14] But, as recommended by ESC guidelines, the panel opined that any dose of statin may be initiated to achieve the LDL-C target of <70 mg/dL. Panel further suggested that the consultation with nephrologist should be done more often to manage the dyslipidemia in CKD cases especially when eGFR is <30 ml/min/1.73 m^2 and in patients receiving hemodialysis.

Expert Opinion: Statin with or without ezetimibe is to be used only in non-dialysis-dependent CKD patients. In CKD, LDL-C goal is <70 mg/dL*. Statin in high-dose is advised in cases where eGFR is above 30* ml/min/*1.73* m^2*. Consultation with nephrologist is necessary to use high doses in ESRD on hemodialysis. At the time of hemodialysis initiation, if patient is already receiving statin/ezetimibe or combination, continue the same.*

7.8. Dyslipidemia and stroke prevention

For primary prevention of stroke, statin treatment is recommended to achieve desired goals in high-risk and very high CV risk cases. For secondary prevention of stroke, intensive statin treatment is recommended by ESC guidelines.[4] Panel agrees on these recommendations and advised high dose statin for both primary as well as secondary stroke prevention.

Expert Opinion: Use high-dose statin for primary and secondary prevention of stroke.

8. Follow-up monitoring

ESC recommends that two measurements should be done, 1–12 weeks apart, before initiating lipid lowering treatment except for known case of ACS or a high risk patient.[4] Panel disagrees on this recommendation and suggested the use of one lipid assessment to initiate treatment with statin for two major reasons – cost and low probability of patients returning with second measurement. One lipid assessment with clinical history and estimation of CV risk should guide the treatment initiation.

ESC recommends lipid testing after 8 (±4) weeks once treatment is initiated or after adjustment of treatment until the target levels are reached and thereafter annually (except non-compliance or any other reason that demands repeat measurement).[4] Panel agrees upon these recommendations even for Indian patients.

Expert opinion: Single fasting lipid assessment may be sufficient to initiate statin treatment especially in high risk cases. Follow-up testing is advised after 12 weeks till goal levels are reached and then it can be done annually.

9. Safety assessments

In consideration of safety of statins, ESC guidelines recommend liver enzyme assessment, especially alanine aminotransferase (ALT), at baseline, and once 8 to 12 weeks post-treatment or after increase in dose. Routine monitoring with ALT thereafter is not recommended during therapy. If elevation of liver enzymes is over 3 times the upper limit of normal (ULN), reduce the dose/stop the drug and recheck liver enzymes in 4 to 6 weeks. Reintroduction should be cautiously done after ALT has returned to normal with lower dose at the start and then gradual increase with monitoring of enzymes. Persistent elevation in enzymes excludes lipid lowering therapy as a culprit for liver damage. With regards to muscle damage, guideline recommends creatinine kinase (CK) assessment at baseline. If elevation of CK is 4x ULN, do not start treatment. Routine monitoring is not necessary unless patients complains of myalgia. Elevation of CK during therapy to 10x ULN demands discontinuation of drug and bimonthly monitoring of CK and renal function. With asymptomatic CK elevation to <10x ULN, continue treatment and monitor CK bimonthly whereas in symptomatic elevation of CK to <10x ULN, discontinue treatment, monitor CK and restart at lower dose after CK is normalized. Panel agrees to these recommendations and suggest a cautious use of statins in cases of hypothyroidism and vitamin D deficiency.

Expert Opinion: Initial pre-treatment assessment and post-treatment monitoring of liver function is necessary to initiate or modify treatment as described. CK monitoring is not advised except in patients with myopathy or those at high risk of muscle damage. Modification in treatment can be done based on CK levels as discussed above.

10. Summary of recommendations for Indian dyslipidemic patient

- Assess CV risk with QRISK®2 calculator in all patients in India.
- Fasting lipid assessment should be routine except in cases of CV risk assessment, in diabetes and distant locality of patients where non-fasting lipid assessment can be done.
- Five primary targets for CV risk reduction include no tobacco, physical activity, healthy diet, blood pressure control, and lowering of glycemic load.
- LDL-C being a primary target, non-HDL-C can be considered as secondary targets after achieving primary LDL-C target, if TGs remain high (>200 mg/dl). LDL-C <70 mg/dL is target for all ASCVD cases with optional reduction to <50 mg/dL in very-high risk cases.
- Statins are first-line drugs for dyslipidemia. Rosuvastatin, atorvastatin and pitavastatin can be used in India. Ezetimibe should be second agent to statin to achieve the desired lipid targets. Other agents can be considered after statin and ezetimibe. Lower statin dose in combination with ezetimibe may be considered in patients with significant statin related side effects.
- Addition of fenofibrate may be considered to statin to lower TGs <200 mg/dL in India. Monitor creatinine with use of fenofibrate. Use low dose of fenofibrate in existing renal failure cases. Intensification of lifestyle measures should be done.
- For diagnosis of FH, use Dutch clinical criteria. LDL-C goal should be <70 and <100 mg/dL in patients with CVD and without CVD respectively. Statin and ezetimibe in combination is recommended as the primary treatment for FH in India until PCSK9 inhibitors become available for clinical use.
- In diabetes with high CV risk, LDL-C goal is <70 mg/dL. Combination of modest dose statin with ezetimibe should be considered to control dyslipidemia in diabetes.
- In ACS and in patients undergoing PCI, LDL-C goal is <70 mg/dL with optional lowering to <50 mg/dL in very-high risk cases. Statin (high dose) with addition of ezetimibe is suggested to achieve these lipid targets.
- In non-dialysis dependent CKD, statin ± ezetimibe is advised to achieve LDL-C goal of <70 mg/dL. eGFR should guide choice of dose. Use of high-dose statin in those with eGFR <30 ml/min/1.73 m^2, consultation with nephrologist is necessary.
- For primary and secondary stroke prevention, high-dose statins are recommended for Indians.
- Follow-up monitoring is advised after 12 weeks till goal are reached and then annually.
- Liver function assessment at baseline and post-treatment (after 4–6 weeks) should be done. CK levels should be assessed in

patients with myopathy or in those at high-risk of muscle damage.

Conflicts of interest

Authors declare no conflict of interest.

Contributors

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