Lipid Association of India (LAI) expert consensus statement on management of dyslipidaemia in Indians 2017: part 2


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Lipid Association of India (LAI) expert consensus statement on management of dyslipidaemia in Indians 2017: part 2


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ABSTRACT
These Lipid Association of India (LAI) recommendations refer to specific patient populations. They follow the previously published LAI part 1 recommendations. These part 2 LAI recommendations focus on specific patient groups. These include patients with heart failure, chronic kidney disease, non-alcoholic fatty liver disease, cerebrovascular disease, thyroid disorders, inflammatory joint diseases, familial hypercholesterolaemia and human immunodeficiency virus infection. We also consider women, the elderly and post-transplantation patients. The current recommendations are based, as much as possible, on available data from Indian populations.

Abbreviations: 4D: Die Deutsche Diabetes Dialyses Studie; ABCD: Amsterdam Born Children and Their Development; ACC: American College of Cardiology; ACCF: American College of Cardiology Foundation; ACCORD: Action to Control Cardiovascular Risk in Diabetes; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention study; AHA: American Heart Association; AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglyceride; ALA: Alpha Linolenic Acid; ALERT: Assessment of Lescol in Renal Transplantation; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; APO A: Apolipoprotein A; APO B: Apolipoprotein B; APO C: Apolipoprotein C; APO E: Apolipoprotein E; AS: Ankylosing Spondylitis; ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm; ASCVD: Atherosclerotic Cardiovascular...
Dyslipidaemia is widely prevalent and is one of the most important risk factors for atherosclerotic cardiovascular disease (ASCVD). Accordingly, effective management of dyslipidaemia is an important goal for the prevention of ASCVD.

Numerous leading international societies have published guidelines for the management of dyslipidaemia but these guidelines are not directly applicable to Indians because of various reasons. Indians have an unusually high prevalence of dyslipidaemia comprising of low high-density lipoprotein cholesterol (HDL-C), high triglycerides (TG), moderately elevated low-density lipoprotein cholesterol (LDL-C) and high lipoprotein (a), particularly at a younger age; this pattern of dyslipidaemia is also distinct compared with Western populations. The distribution and interplay of various other ASCVD risk factors and genetic susceptibility may also be different. In addition, population awareness about prevention of ASCVD, cultural beliefs, socio-economic conditions, diet and other factors contribute to their adverse risk profile. For these reasons, it is important to formulate policies and guidelines that accommodate these differences and propose recommendations that are specific to the Indian population. To meet this objective, the Lipid Association of India (LAI) has

1. Introduction

Dyslipidaemia is widely prevalent and is one of the most important risk factors for atherosclerotic cardiovascular disease (ASCVD). Accordingly, effective management of dyslipidaemia is an important goal for the prevention of ASCVD.

Because of various reasons, Indians have an unusually high prevalence of dyslipidaemia comprising of low high-density lipoprotein cholesterol (HDL-C), high triglycerides (TG), moderately elevated low-density lipoprotein cholesterol (LDL-C) and high lipoprotein (a), particularly at a younger age; this pattern of dyslipidaemia is also distinct compared with Western populations. The distribution and interplay of various other ASCVD risk factors and genetic susceptibility may also be different. In addition, population awareness about prevention of ASCVD, cultural beliefs, socio-economic conditions, diet and other factors contribute to their adverse risk profile. For these reasons, it is important to formulate policies and guidelines that accommodate these differences and propose recommendations that are specific to the Indian population. To meet this objective, the Lipid Association of India (LAI) has
produced a consensus document on the management of dyslipidaemia in Indians. Part 1 of the document dealt with all the common issues related to lipid management encountered during routine clinical practice and was published last year [1, 2]. The present document – part 2 of the consensus document – outlines the management of dyslipidaemia in specific patient populations.

2. Methodology

The LAI initiated the process of developing this consensus document by inviting leading experts from various specialties including Internal Medicine, Cardiology, Endocrinology, Nephrology, Neurology, Pharmacology and Vascular Surgery to participate in this process. A series of regional meetings were held with these experts in different parts of the country. In all, there were 8 meetings held at Delhi, Patna, Mumbai, Chennai and Jaipur with 213 experts from 17 states, 2 union territories and 33 cities of India. In addition, two experts were from the UK and 1 from the USA.

These meetings followed a standard format. First, the key issues related to lipid management in specific patient populations were presented to the entire group in the form of lectures, followed by extensive discussion among experts on these topics. The discussions held in the meetings were recorded. Subsequently, the experts of the core committee reviewed the discussions of all the meetings and prepared a consensus draft. This draft was circulated to the remaining experts for their suggestions and approval. Suggestions were re-evaluated by the core committee and were incorporated in the recommendations. After the final round of discussion, the expert panel prepared the final document, considering the following main objectives:

- To ensure that the document remained simple, yet scientifically robust.
- To be informative rather than prescriptive.
- To maximally utilise the available Indian data for evidence-based practice.
- To ensure practical applicability of the recommendations to the Indian population.

3. Dyslipidaemia in heart failure (HF)

3.1. Cholesterol levels in HF

Low total cholesterol levels have been shown to be associated with increased cardiovascular (CV) events and mortality in HF patients in several studies [3, 4]. In a Korean HF Registry, patients ($n = 2797$; 44% with ischemic HF) were stratified into quartiles of serum total cholesterol [5]. Patients with lower serum total cholesterol had lower blood pressure, lower haemoglobin, low serum sodium and increased brain natriuretic peptide (BNP) levels, suggesting that low total cholesterol coexists with other markers of poor risk. Low total cholesterol was associated with increased risk for death and readmission due to HF. However, propensity score matching analysis revealed that low cholesterol itself did not affect outcome [hazard ratio, HR, 1.12]. Hence, low cholesterol may merely be a consequence of advanced HF and has no pathophysiologic role. In vitro studies have implicated cytokines, such as tumour necrosis factor, as a causative factor in the hypocholesterolaemia of inflammatory conditions through mechanisms such as decreased hepatic lipoprotein production and increased low-density lipoprotein (LDL) receptor activity.

Further, low cholesterol is a marker of cachexia related to HF [6, 7].

3.2. Statins in HF

Several randomised trials have shown that statins reduce major adverse CV events in patients with risk factors for, or clinically apparent, ASCVD. However, these studies have excluded HF patients. The relative risk reduction (RRR) of cardiac events was seen regardless of baseline LDL-C levels.

The beneficial effects of statins in HF were demonstrated in various registries, observational studies and post hoc analyses of randomised clinical trials [9]. However, two large randomised controlled trials failed to confirm the benefit of statins in HF. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [10] and GruppoItaliano per lo Studio dellaSopravvivenzanell’InfartoMiocardico Heart Failure (GISSI-HF) [11] trials evaluated the use of statins in patients with symptomatic HF and reduced left ventricular ejection fraction (LVEF).

The CORONA trial [10] randomised 5011 patients aged $\geq$ 60 years (mean age 73 years) with ischemic HF, LVEF $\leq$ 40% and New York Heart Association (NYHA) class II-IV symptoms to 10 mg/day rosuvastatin vs. placebo. The GISSI-HF trial [11] randomised 4574 patients aged $\geq$ 18 years (mean age 68 years) with NYHA class II-IV symptoms; HF aetiology being ischemic (40%), non-ischemic (35%) or other causes (25%) with LVEF $\leq$ 40% (or $>40%$ if hospitalised within the past year) also to 10 mg/day rosuvastatin vs. placebo. There was no statistically significant difference in the primary endpoint of death from CV causes, nonfatal MI and nonfatal stroke in CORONA and co-primary endpoints of time to death, or admission to hospital for CV reasons in GISSI-HF between the rosuvastatin and placebo groups. It is noteworthy that both trials included older and sicker patients with high mortality rates in both the treatment and placebo groups signifying advanced HF. Further, most of the deaths in the
two trials were arrhythmic or due to progressive HF. There were only few deaths attributed to myocardial infarction (MI) or stroke. Since statin therapy is likely to be beneficial for plaque stabilisation or pleiotropic effects, perhaps it could not affect mortality due to the low incidence of MI or stroke. Nevertheless, pleiotropic effects also failed to show any effect on primary endpoint in this population with advanced HF [10, 11]. However, an individual-level pooled data re-analysis of both trials demonstrated a significant 19% reduction in risk of MI among patients with ischemic HF [12].

As per the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines [13], statins have class IA recommendation in stage B ischemic HF (post-MI without symptoms of HF) to prevent progression of HF. In symptomatic HF patients, statins have class III recommendation meaning that statins are not useful as adjunctive therapy in the absence of other indications for their use [13]. However, the recent 2016 American College of Cardiology (ACC) expert consensus document recommends that patients with HF in NYHA class II to III due to ischemic aetiology may be given statins [14]. The role of statins in non-ischemic or dilated cardiomyopathy is more controversial especially in advanced HF as in the negative GISSI-HF trial where 34.5% of the participants had non-ischemic cardiomyopathy [11].

The low uptake of hydrophilic rosuvastatin by the heart (approximately 1% of that by liver) compared with the lipophilic simvastatin (approximately 80%) has been postulated to explain the lack of benefit with rosuvastatin in the CORONA and GISSI-HF trials. A meta-analysis of 17 studies showed that atorvastatin but not rosuvastatin increased LVEF and decreased BNP levels in HF patients [15]. However, no randomised trial has been carried out with atorvastatin in HF.

Coenzyme Q10 (CoQ10) plays an essential role in the mitochondrial respiratory chain through oxidative phosphorylation with the concomitant production of adenosine triphosphate. Statins block production of farnesyl pyrophosphate, an intermediate in the synthesis of CoQ10 or ubiquinone. A meta-analysis showed that statins significantly reduced plasma CoQ10 concentrations [16]. Whether depletion of CoQ10 by statins could actually worsen HF is highly debated. In the CORONA study, lower CoQ10 levels were associated with several other markers of greater disease severity like older age, higher N-terminal pro-BNP (NT-proBNP) levels, lower lipid levels, lower LVEF and lower glomerular filtration rate. Rosuvastatin 10 mg/day significantly reduced plasma CoQ10 by 39% [17]. Multivariable models demonstrated no independent relationship between CoQ10 levels and muscle pain or CV outcomes [17]. Review of the data on coenzyme Q10 depletion and statin myopathy did not find definitive evidence for either a causative role or a therapeutic benefit from coenzyme Q10 supplements [18, 19].

There is evidence suggesting that cumulative exposure to lifelong low LDL C is likely to confer more protection than when treatment is delayed and the cumulative exposure to LDL C remains high [20, 21]. Similarly, it is likely that in the HF trials, sicker patients with advanced HF failed to derive benefit from statins because of delayed treatment. In fact, in a post hoc analysis of the CORONA study, NT-proBNP was measured in 3664 (73% of total cohort) patients. The mid-tertile included values between 868 and 2348 pg/ml. Patients in the lowest tertile of NT-proBNP had the best prognosis and if assigned to rosuvastatin rather than placebo had a greater reduction in primary endpoint (HR0.65, p = 0.019) than patients in higher tertiles. Patients with ischemic HF who have NT-proBNP values < 868 pg/ml may benefit from rosuvastatin resulting in fewer atherothrombotic events and sudden deaths. This occurred despite similar effects of rosuvastatin on the lipid profile and high-sensitivity C-reactive protein (hsCRP) in each ter-
tile of NT-proBNP [22]. These findings suggest that rosuvasta-
tin was effective in patients with less advanced disease.

Galectin-3 is a biomarker of myocardial fibrosis and may play a role in the pathophysiology of HF through promotion of myocardial fibrosis and inflammation thereby influencing ventricular remodelling [23]. Galectin-3 levels correlate with severity of HF [24]. In the CORONA trial, patients with plasma galectin-3 levels less than the median (≤19.0 ng/ml) benefited more from statin therapy and had a lower primary event rate (HR 0.65; p = 0.014), lower total mortality (HR 0.70; p = 0.038), lower all-cause mortality and HF hospitalisations (HR 0.72; p = 0.017) compared with placebo, raising the possibility that it might be used to define HF subtypes that respond differently to rosuvastatin. The combination of concurrently low concentrations of galec-
tin-3 and NT-proBNP (<868 pg/ml) identified patients with a greater benefit from rosuvastatin (HR 0.33; p = 0.002) [25]. There is insufficient evidence to support that heart failure improves with use of ezetimibe.

### 3.3. LAI recommendations

- Besides lifestyle measures, statins may be adminis-
tered to patients with ischemic HF with NYHA Class II-III symptoms.
- Patients with advanced symptomatic HF require individualised care, e.g. if a coronary artery disease (CAD) patient who was on statins develops symptomatic HF, statins may be continued. In these groups, intensive statin therapy with a goal to achieve 50% reduction in LDL-C levels is justified.
- Statins are also recommended for ischemic HF patients awaiting heart transplantation.
LDL-C levels. However, on progression to ESRD, LDL-C and total cholesterol levels remain low to normal in the majority of patients [31, 32]. In advanced CKD patients with decreased LDL-C levels, there are increased levels of small dense LDL particles, so that the small dense LDL particle to normal size LDL particle ratio is significantly elevated [33]. There is some evidence that statins can improve the LDL subclass distribution in patients on haemodialysis [34].

Several randomised, large-scale trials in CKD patients such as the Die Deutsche Diabetes Dialyses Study (4D) [35], A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [36], Study of Heart and Renal Protection (SHARP) [37] and Assessment of Lescol in Renal Transplantation (ALERT) trial [38] have provided the basis for guidelines on the management of dyslipidaemia in CKD by organisations such as Kidney Disease: Improving Global Outcomes (KDIGO) [39], the Joint British Society (JBS3) [40] and Canadian Society of Nephrology [41]. It is also important to note that there is paucity of data on dyslipidaemia management in Indian patients with CKD. Of the above, the KDIGO guidelines include a detailed analysis and discussion on relevance and management of dyslipidaemia in CKD. Hence, the executive summary of these guidelines is mentioned below. The salient features of KDIGO guidelines on management of dyslipidaemia [39] include:

- A full evaluation of lipid profile in all subjects with CKD at the time of diagnosis. This includes all subjects receiving dialysis and kidney transplant recipients.
- Routine follow-up measurement of lipid levels is not recommended, except to establish adherence to treatment and documentation of >30% reduction in LDL-C.
- All adults with CKD should receive therapeutic lifestyle advice.
- Treatment with statins or statins/ezetimibe combination is recommended for all adults equal to or greater than 50 years with an eGFR < 60 mL/min/1.73 m².
- In adults between the ages of 18 and 49 with CKD should be treated with statins if they have one of the following:
  - Known CAD, stroke or peripheral arterial disease
  - Diabetes mellitus
  - Estimated 10-year risk of coronary death or MI > 10%
- ESRD patients who are on lipid-lowering therapy at the time of starting dialysis should continue to receive these agents.

4. Dyslipidaemia in chronic kidney disease

Chronic kidney disease (CKD) is defined as structural or functional kidney abnormalities persisting for > 3 months with or without a decrease in estimated glomerular filtration rate (eGFR) [27]. CKD is divided into five stages, with stage 1 indicating relatively preserved renal function with eGFR > 90 mL/min/1.73 m², with steady decline in renal function on progression to stage 5 defined as an eGFR < 15 mL/min/1.73 m². Several studies have conclusively demonstrated progressive increase in CV morbidity and mortality on progression from stage 1 to stage 5 CKD [28]. CKD stage 5D or end stage renal disease (ESRD) increases the risk of CV disease (CVD) several fold, irrespective of age. In this context, young people with ESRD are at 10–30-fold higher risk for CV mortality than age-matched healthy counterparts [29]. The Indian subcontinent faces a higher burden of CKD [30], which is often considered a CAD equivalent.

CKD is a risk factor for atherogenic dyslipidaemia [31] and hence, management of dyslipidaemia can potentially reduce mortality in these patients. CKD is associated with high TG, high very low-density lipoprotein cholesterol (VLDL-C) levels, low HDL-C levels and modestly elevated LDL-C levels. However, on progression to ESRD, LDL-C and total cholesterol levels remain low to normal in the majority of patients [31, 32]. In advanced CKD patients with decreased LDL-C levels, there are increased levels of small dense LDL particles, so that the small dense LDL particle to normal size LDL particle ratio is significantly elevated [33]. There is some evidence that statins can improve the LDL subclass distribution in patients on haemodialysis [34].

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- In adults between the ages of 18 and 49 with CKD should be treated with statins if they have one of the following:
  - Known CAD, stroke or peripheral arterial disease
  - Diabetes mellitus
  - Estimated 10-year risk of coronary death or MI > 10%
- ESRD patients who are on lipid-lowering therapy at the time of starting dialysis should continue to receive these agents.
• In statin-naive adult dialysis patients, initiation of statins is not recommended.
• All adult kidney transplant recipients should receive statin therapy.
• Statins should be started at a lower dose in subjects with eGFR < 30 ml/min with gradual escalation to the recommended dose along with monitoring for any adverse events.

4.1. LAI recommendations

A full evaluation of lipid profile (total cholesterol, LDL-C, HDL-C and TG) is recommended in all CKD patients (including patients with ESRD and renal transplant recipients) at the time of diagnosis.

• Follow-up measurement of lipid levels should be performed routinely (at treating physicians’ discretion) in subjects with CKD until the LDL-C and non-HDL-C target is achieved.
• Therapeutic lifestyle modification should be recommended to all patients.
• A combination of statins/statin plus ezetimibe is recommended for all adults over the age of 40 years with eGFR < 60 mL/min/1.73 m².
• Adults between the ages of 18 and 39, with CKD should be treated with statins if they have one of the following:
  ◦ Known CAD, stroke or peripheral arterial disease
  ◦ Diabetes mellitus
  ◦ Life time risk of ASCVD >30%
• Patients who are already receiving lipid-lowering therapy at the time of starting dialysis should continue to receive these agents.
• In adults with dialysis-dependent CKD who are not on statins, statins could be considered at the lowest dose possible and should be titrated up carefully to achieve the LDL-C level for very high risk patients (see Table 1).
• All adult kidney transplant recipients should receive statin therapy.

Statins should be started at a lower dose in all subjects with eGFR <30 ml/min with gradual escalation to the recommended dose along with monitoring for any adverse events (see Table 1).

4.2. Rationale for LAI recommendations

Experts at LAI are largely in agreement with the KDIGO regarding lipid-lowering therapy in CKD patients. The expert opinion differs in the following aspects:

• Recommendations for pursuing target LDL-C and non-HDL-C levels
• Age cut-off for initiation of statin therapy has been lowered to 40 years
• Initiation of statin therapy in dialysis patients

CKD patients remain at high risk for CVD; hence, it is prudent to check the lipid profile at the time of diagnosis of CKD, whatever the stage of renal failure, including patients who have undergone renal transplantation. Secondary causes of dyslipidaemia should be ruled out. Follow-up lipid profile should be checked in order to ensure compliance with medications and to achieve target LDL-C and non-HDL-C levels. South Asians have an atherogenic lipid profile at baseline and are at risk for premature and severe CVD compared with Caucasians [42, 43]. This underlying risk multiplies with development of CKD. Hence, it is prudent to mitigate the risk associated with dyslipidaemia as early and as effectively as possible.

The use of statins in early stages of CKD has modest cardio-protective benefit, though less than what has been noted in general population and the magnitude of benefit decreases as the CKD stage increases [44]. The SHARP trial, a large randomised trial evaluating the use of simvastatin (20 mg)/ezetimibe (10 mg) combination vs. placebo in both dialysis and non-dialysis patients, reported a 17% proportional reduction in major atherosclerotic events, significant reductions in non-haemorrhagic stroke and arterial revascularisation procedures in CKD-ND (non-dialysis) patients [37]. In contrast, large randomised trials in ESRD patients on dialysis like 4D (with atorvastatin) [35] and AURORA (with rosuvastatin) [36] failed to show cardio-protective or mortality benefit. Hence, international recommendations do not favour initiation of statins in dialysis patients. We differ from the KDIGO guidelines [39] in this regard, the reasons being that the Indian population

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<th>Drug</th>
<th>Estimated glomerular filtration rate</th>
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<tr>
<td></td>
<td>&gt;30 ml/min/1.73 m²</td>
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<tr>
<td>Atorvastatin (mg/day)</td>
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<td>Simvastatin (mg/day)</td>
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<td>Pravastatin (mg/day)</td>
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has a higher risk for both CAD and ESRD compared with the Western population which may have a genetic basis and an associated accelerated CVD and CAD [42]. In addition, it is to be noted that the dialysis population in India is younger (mean age 44 years) compared with the Western population [30]; hence, therapies to mitigate CV risk instituted earlier have the potential to reduce mortality in this population of Indian origin. In such a situation, where Indian data are limited, we encourage informed and shared decision-making. We emphasise that other reversible and modifiable risk factors for ESRD and CVD need to be strictly controlled as well.

KDIGO states an age cut-off of 50 years or greater for initiation of statins in CKD patients. This age cut-off was based on a Canadian cohort study consisting predominantly of Caucasians. The age cut-off of 40 years in our expert opinion is based on the risk factor profile of our population, as discussed above [42, 43].

Management of dyslipidaemia in kidney transplant recipients is discussed in the solid organ transplantation section.

In patients with nephrotic syndrome (NS), the concentration of VLDL, IDL and lipoprotein (a) is higher with increasing content of TG within the lipoprotein particles. They exhibit exaggerated post-prandial hyperlipidaemia. Reduced lipoprotein lipase activity, increased PCSK9 activity, increased Acetyl CoA Acyl Transferase 2 (ACAT-2) activity and increased 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG Co-A reductase) activity have all been implicated in the generation of dyslipidaemia of NS [45, 46]. Treatment of dyslipidaemia has not been shown to reduce the risk of renal failure; however, there is some evidence that statins reduce proteinuria and the reduction in, as well as deterioration of, eGFR in these patients [47, 48]. However, caution should be exercised in using rosuvastatin in this group of patients due to reported increase in proteinuria and deterioration of renal function [47, 48].

Consideration has to be given to the dose of statins with respect to an individual’s renal function in order to avoid adverse reactions. Table 1 shows the dose adjustment of commonly available statins. Major trials mentioned earlier such as 4D [35], AURORA [36], SHARP [37] and ALERT [49] utilised renal dosing for atorvastatin, rosuvastatin, simvastatin/ezetimibe and fluvastatin, respectively. In all these trials, there was no statistically significant increase in adverse reactions related to statins. For clinical practice, statin monotherapy can be used since trials in the general population have shown desirable effects of monotherapy with statins. Combination with ezetimibe can be used if a desirable LDL-C level has not been achieved.

Currently, there is no good evidence to support the routine use of fibric acid derivatives for management of hypertriglyceridaemia in CKD patients due to high toxicity of these drugs (rhabdomyolysis and acute kidney injury) in patients with renal dysfunction [52, 54]. In cases with serum TG > 500 mg/dL despite lifestyle modification and statin therapy, a fibric acid derivative may therefore be considered but due care should be taken in patients with renal impairment as fibrates are renally excreted [52]. The National Kidney Foundation recommends that the dose of fenofibrate should be reduced by 50% in patients with GFR of 60–90 ml/min/1.73 m² and about 75% if GFR is between 15 and 59 ml/min/1.73 m² and avoid using fibrates if GFR is < 15 ml/min (https://www2.kidney.org/professionals/kdoqi/guidelines_lipids/iii.htm).

5. Dyslipidaemia and non-alcoholic fatty liver disease (NAFLD)

NAFLD is associated with metabolic factors and evidence suggests that CVD is the most common cause of death in patients with NAFLD. Statins are used to treat atherogenic dyslipidaemia to reduce atherosclerotic cardiac events. However, statins are known to elevate liver enzymes and hence there is significant concern among physicians to prescribe statins in NAFLD. There is evidence that suggests that statins may improve liver enzymes and histology in NAFLD [55–57].

NAFLD is an important health issue in India and is closely associated with marked metabolic derangements such as insulin resistance and the metabolic syndrome, which are important determinants of T2DM and CVD [58]. Hence, there are two important issues that need to be addressed: Should statins be used to treat dyslipidaemia in NAFLD and can statins be used for NAFLD/non-alcoholic steatohepatitis (NASH) for primary prevention?

5.1. Evidence from meta-analyses

The Prospective Pravastatin Pooling (PPP) project [59] was a prospective analysis of three major large, placebo-controlled trials of pravastatin: West of Scotland Coronary Prevention Study (WOSCOPS) [60], Cholesterol and Recurrent Events (CARE) study [61] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study [62] which included 19,768 patients treated for 5 years (Table 2). Its aim was to assess potential safety issues and concluded that 40 mg of pravastatin was well tolerated, with no serious adverse events, including liver function abnormalities.

One meta-analysis of randomised control trials (RCTs) of statins for primary or secondary prevention included a total of 49,275 patients from 13 trials. The duration of the included trials varied from 48 weeks to 6 years. The results showed that low to moderate doses of pravastatin, lovastatin and simvastatin were not associated with a significant
risk of liver test abnormalities and that monitoring was not warranted in patients taking a low-to-moderate dose other than at the onset of therapy [63].

Another meta-analysis of 75,317 subjects addressed the issue of effect of higher vs. lower intensity statin therapy on liver toxicity [64]. It included 23 statin arms for 0.9–6 years of follow-up. Liver enzymes increased significantly with higher statin dose while there was no significant relationship between LDL-C reduction and liver damage. It concluded that the risk of statin-associated rise in liver enzymes is not related to the magnitude of LDL-C lowering but is more likely determined by drug and dose-specific effects.

5.2. Should statins be used to treat dyslipidaemia in patients with NAFLD?

NAFLD is characterised by the presence of hepatic steatosis by imaging or histology and absence of secondary causes of fat accumulation in the liver. It is divided into two types on the basis of histological findings: NAFLD and NASH. NAFLD is generally associated with metabolic disorders like obesity, insulin resistance, diabetes mellitus and dyslipidaemia [65]. Aggressive treatment of dyslipidaemia is essential in the management of patients with NAFLD. However, there is concern that patients with NAFLD and dyslipidaemia who are treated with statins may develop abnormal liver tests [66].

A post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study evaluated the risk-to-benefit ratio of using a statin to treat dyslipidaemia in patients with NAFLD [67]. The GREACE study randomised 1600 patients with CAD to receive statin or usual care, which could include statins. Participants were randomised to receive either usual care or structured care with atorvastatin (10–80 mg) to achieve an LDL-C below 100 mg/dL. The primary endpoints were the first occurrence of any CV event and the secondary endpoints were elevation of liver enzymes or liver-related adverse effects. Post hoc analysis of 437 out of total cohort of 1600 patients with baseline elevation in the liver enzymes [<3 times upper limit of normal (ULN)] showed that 227 subjects treated with a statin had significant improvement in liver tests, whereas 210 participants who were not treated with a statin had further increases of liver enzymes. Other causes of elevated liver enzymes like alcohol, hepatitis B and C and autoimmune hepatitis were ruled out. CV events occurred in 22 (10%) of 227 patients with deranged liver enzymes who received statins (3.2 events/100 patient-years) and 63 (30%) of 210 patients with deranged liver enzymes who did not receive statins (10 events/100 patient-years). There was a 68% RRR in patients with abnormal liver tests on statins vs. 39% RRR in patients with normal liver tests on statins [67, 68]. Importantly, patients with increase in liver enzymes up to 3 times the ULN showed improvement in liver tests with statins compared with a further rise in liver tests in patients not treated with statins. The relationship between statins, hepatic TG content and serum alanine aminotransferase (ALT) levels was examined in 2264 Dallas Heart Study participants and it concluded that there was no association between statins and hepatic steatosis or serum ALT abnormalities, even among those with hepatic steatosis [69].

In another study, 342 hyperlipidaemic patients with elevated baseline liver enzymes were prescribed a statin and the incidence of mild-moderate and severe elevations in liver enzymes was 4.7 and 0.6%, respectively. It concluded that individuals with deranged liver enzymes did not have higher risk for hepatic adverse effects due to statins [70].

High-dose pravastatin (80 mg/day) when used for the treatment of dyslipidaemia in patients with chronic liver disease significantly lowered LDL-C, total cholesterol and TGs compared with placebo and it was well tolerated [71]. Similar findings were noted in a small prospective study involving 23 dyslipidaemic patients with biochemical evidence of NAFLD, where rosuvastatin 10 mg/day for 8 months normalised liver function tests in all patients [72].
In a prospective study of 25 dyslipidaemic and NAFLD patients with elevated baseline liver enzymes, the ALT levels returned to normal in 36.3% of patients after 6 months and 20% after 12 months of treatment with atorvastatin [73]. In another randomised study, pitavastatin and atorvastatin equally reduced LDL-C and significantly reduced ALT in patients with hypercholesterolaemia and elevated ALT concentration [74].

5.3. Should statins be used to specifically treat NAFLD?

Statins have pleiotropic effects besides lipid lowering which include anti-thrombotic, anti-inflammatory and antioxidant effects. Hence, they have been considered as therapeutic agents in NAFLD because inflammation and oxidative stress play a major role in the pathogenesis of NAFLD [75].

An additional benefit seen in the post hoc analysis of GREACE study was the reduction in ALT and aspartate aminotransferase (AST) levels during treatment in patients with NAFLD on statins. Nearly 47% reduction in AST levels and 35% reduction in ALT levels were noted. In addition, 89% of the participants on statins had normal liver enzymes and gamma-glutamyl transferase levels at the end of the three-year period. A 12% increase in AST and ALT was noted in patients with NAFLD who did not receive statins at the end of the three-year period. A rise in liver enzymes more than 3 × ULN was observed in only 10 of 880 patients taking statins. In three of these patients, the liver enzymes normalised after dose adjustment of the statin. Only seven (<1%) patients on statins had to discontinue therapy because of liver-related side effects [68].

While the GREACE study included patients with CAD and NAFLD, another study – ATTEMPT [76] – was carried out in patients with MetS (some with NAFLD) but without CVD or DM. The ATTEMPT was a prospective, randomised trial in 1123 MetS patients (aged 45–65 years), followed up for 42 months. Patients received intensive lifestyle intervention and pharmacotherapy: atorvastatin in all patients (LDL-C targets of <100 mg/dL or <130 mg/dL), inhibitors of the renin–angiotensin–aldosterone axis for hypertension, metformin for dysglycaemia and for obesity [77]. A post hoc analysis was carried out to assess the effects of multifactorial intervention on liver tests and their association with CAD in subjects with MetS but without CVD and DM. Among the whole population, 326 patients had elevated liver tests and evidence of NAFLD on imaging studies. Of these, 165 patients received an average of 34 mg/day of atorvastatin to attain the LDL-C < 100 mg/dL target (Group A). The remaining 161 patients received an average of 24 mg/day of atorvastatin to attain the LDL-C < 130 mg/dL target (Group B). NAFLD resolved during the 42-month treatment period in 86% of patients in the high atorvastatin group and in 74% of patients in the low atorvastatin group. Nearly 90% of patients attained their target lipid goals. There were no CVD events in group A, whereas five non-fatal events occurred in group B. No major adverse events were reported [78].

A Cochrane database review of 653 records assessed the effects of statins on all-cause and liver-related mortality, adverse events, histological, biochemical and imaging responses in patients with NAFLD or NASH. It found only two RCTs eligible but neither reported on histological changes, liver-related morbidity or mortality. It concluded that statins may improve liver enzymes as well as ultrasound findings but that larger trials are needed [79].

Dongiovanni et al. studied the relationship between statins, genetic risk factors and liver damage in 1201 Europeans who underwent a liver biopsy for suspected NASH [80]; 107 of these patients received simvastatin or rosuvastatin. There was a significant reduction in fibrosis score 48–91% and NASH by 38–76% independent of steatosis, while significant fibrosis was almost halved.

An open-label study evaluated the efficacy of pitavastatin for the treatment of NASH with dyslipidaemia. Follow-up biopsies available for 13 NASH patients showed a slight reduction of NASH activity score although there was no significant change in the fibrosis stage [55]. In another open-label study by the same authors in patients with NASH and dyslipidaemia [56], atorvastatin was administered to the patients and follow-up biopsies were carried out after 24 months. There was significant improvement in liver macrovascular steatosis and NASH activity score in both studies but some patients had increased fibrosis stage. The population-based Rotterdam Study was carried out in 2578 subjects who underwent liver ultrasonography. A lower prevalence of liver steatosis in the patients treated with statins for >2 years was reported [57].

In another study, patients with NASH were randomised to receive simvastatin or placebo. There was no statistically significant improvement in serum ALT, hepatic steatosis, necro-inflammatory activity or stage of fibrosis [81, 82].

A post hoc analysis of the IDEAL trial (n = 8863) suggested that the CV benefit of intensive lipid lowering with atorvastatin compared with a more moderate regimen with simvastatin was generally greater in patients with mild-to-moderately elevated baseline ALT than patients with normal baseline ALT [83]. The statin treatment was safe.

A recent review concluded that the prevalence of NAFLD is increasing in South Asians with male predominance. South Asians develop NAFLD at an earlier age as compared with the Western population. BMI does not fully appreciate the risk of developing NAFLD due to variation in ethnic distribution of fat. This increasing prevalence
5.4. LAI recommendations

- The available evidence suggests that the risk for serious liver injury from statins is quite rare and patients with NAFLD and dyslipidaemia are not at an increased risk for statin-induced hepatotoxicity. Hence, statins could be used by physicians to treat dyslipidaemia in patients with NAFLD.
- There are few data to suggest usage of statins as a treatment option for NAFLD. However, it continues to be a matter of debate and treatment of NAFLD with statins cannot be recommended at present. Larger trials with histological evidence or use of follow-up Fibroscan are required to investigate the efficacy of statins in NAFLD.

6. Statins and cerebrovascular disease

The crude prevalence of stroke in India is estimated as 1.27–2.20 per 1000 and a higher rate is recorded in the Parsi community. A large number of these are ischemic strokes compared with haemorrhagic strokes. Of the total number of strokes, 10–15% are in the young; hypertension, smoking and hyperlipidaemia contribute to stroke risk, especially in the young. There is also a higher prevalence of haemorrhagic stroke in the young [85, 86].

Statins are the lipid-lowering agents most commonly prescribed to reduce the risk of cerebrovascular events. But what is the evidence supporting their use in different cerebrovascular conditions? Can they cause any harm? We briefly discuss the current evidence for and against the use of statins in various cerebrovascular diseases.

SPARCL is a prospective double-blind placebo-controlled trial in 4731 patients with stroke or TIA randomised either to placebo or atorvastatin 80 mg (4.9 years of follow up). Those with haemorrhagic stroke without risk factors for ischemic stroke were excluded from the trial. Several subgroup analyses from this important multicentre study have been published [87–91].

(1) The primary endpoint – fatal or non-fatal stroke – was less frequent in the atorvastatin group with a RRR of 16% ($p = 0.03$ CI 0.71–0.99). This was mostly driven by reduction in acute stroke with RRR of 43% with no effect on non-fatal stroke. Atorvastatin reduced ischemic stroke by 21% and the partial attenuation to 16% was due to increase in haemorrhagic stroke. Those with haemorrhagic stroke did not benefit from treatment (HR 2.82; 95% CI 0.89–0.90).

(2) There was a reduction of TIA and stroke by 23% and TIA alone by 26%.

(3) Major coronary events, revascularisation and any CV event were reduced by 35% (HR 0.65, CI 95% 0.49–0.87), 45% (HR 0.55, 95% CI 0.43–0.72) and 42% (HR 0.58, 95% CI 0.46–0.73), respectively although there was no difference in total mortality. In patients with >50% reduction in LDL-C, a combined risk reduction of fatal and non-fatal stroke was seen and no increase in risk of intracerebral haemorrhage (ICH) was seen in those with the greatest reduction of LDL-C.

(4) Primary endpoint was a 10% RRR in the elderly (over 65 years) group compared with 26% in the younger (HR 0.74, 0.57–0.96, $p = 0.02$).

(5) The risk reduction in stroke in those with carotid stenosis confirmed by ultrasound was (HR0.67 CI 0.47–0.94; $p = 0.02$); an annual risk reduction of 2.5% was observed with NNT of 8 comparable to carotid endarterectomy but without the problems associated with surgery. As carotid artery evaluation was not required by the SPARCL protocol, carotid imaging carried out by the local investigator was used in the study.

Studies aimed at patients with coronary heart disease (CHD) showed a decrease in stroke by one-quarter by addition of a statin [8].

6.1. Acute ischemic stroke

An important question in patients with acute ischemic stroke is whether statins should be started in those who are not already on statins. There is a lack of robust clinical evidence supporting this. However, several studies have shown that statins have many pleiotropic effects viz. expression of endothelial nitric oxide synthase which causes vasodilatation and enhancement of cerebral blood flow, enhancement of collateral circulation, angiogenesis, anti-inflammatory action, stabilisation of the endothelial layer and enhancement of tissue plasminogen activator. All these effects are thought to benefit by reducing infarct volume in acute ischemic stroke [92]. In addition, a recent meta-analysis of mainly observational studies has suggested that immediate statin therapy in acute ischemic stroke might improve functional disability and short-term mortality [93]. Although the American Stroke Association (ASA) Guidelines [94] do not provide any specific recommendation as to if and when to start statins in patients of acute ischemic stroke, it seems prudent to initiate statins in acute ischemic stroke.

The contention that statins may be beneficial in acute ischemic stroke was supported in a small randomised study of 89 patients already taking chronic statins at the...
time of ischemic stroke, where brief withdrawal of statins during the acute period was associated with increased odds of death or dependency at 3 months [95]. Based on these observations, it is recommended to continue statin therapy among patients already taking statins at the time of onset of ischemic stroke (AHA/ASA Classification of Recommendations and Level of Evidence: class IIa; level of evidence B) [94].

6.2. Statins and thrombolysis
A meta-analysis of three studies totalling 4339 ischemic stroke patients treated with thrombolysis showed an association between statins and increased fatality at 90 days. However, this association was no longer present after adjusting for age and stroke severity in the largest study [96]. On the other hand, a more recent thrombolysis and statins (THRaST) study reported that statin use within 72 h after stroke was associated with favourable functional outcome and a reduced risk of mortality at 90 days in 1844 patients treated with intravenous thrombolysis [97].

Therefore, in an acute stroke patient eligible for thrombolysis and already taking statin, thrombolysis is not contraindicated, and statins should not be discontinued. If the patient is not already on a statin, then a statin should be started (as per THRaST study).

6.3. Acute ICH
Several studies have shown that low serum total cholesterol level is associated with increased risk of ICH [87, 98–100].

However, in a meta-analysis of 31 randomised controlled trials, active statin therapy was not associated with significant increase in the risk of ICH. A significant reduction in all strokes and all-cause mortality was observed with statin therapy [101].

A prospective study from Canada in patients of ICH demonstrated that prior use of statins is not associated with worse outcome and patients who discontinue their statin therapy after admission to hospital have higher mortality and bad prognosis [102].

Based on these observations, in patients of acute haemorrhagic stroke, it is best not to start a statin, but if the patient is already on statin, it is prudent not to discontinue it.

6.4. Prevention of ischemic stroke
6.4.1. Primary prevention
The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) found a 24% reduction in strokes (95% CI, 6–39%; \( p = 0.01 \)) among 5963 diabetic individuals treated with a statin in addition to best medical care [8].

The Collaborative Atorvastatin Diabetes Study (CARDS) reported that in patients with type 2 diabetes with at least one additional risk factor (retinopathy, albuminuria, current smoking or hypertension) and an LDL-C \( \geq 160 \text{ mg/dL} \) but without a prior history of CVD, treatment with a statin resulted in a 48% reduction in stroke (95% CI, 11–69%) [103].

Based on the above, statin treatment along with lifestyle changes is recommended in adults with diabetes, especially those with additional risk factors, or CAD, to lower the risk of a first stroke (AHA/ASA class I; level of evidence A) [104].

6.4.2. Secondary prevention
A meta-analysis of several studies has shown that statins are beneficial in preventing a second ischemic stroke, but do not prevent fatal stroke [105].

As per ACC/ASA guidelines, therapy with a high intensity statin is recommended if LDL-C level is \( \geq 100 \text{ mg/dL} \) (AHA/ASA class I; level of evidence B) [106].

Therapy with high intensity statin is also recommended if LDL-C level is <100 mg/dL, (AHA/ASA class I; level of evidence C) [106].

As per 2013 ACC/AHA cholesterol guidelines, patients with ischemic stroke or transient ischemic attacks should be managed with lifestyle modification, dietary recommendations and medication recommendations [107] (AHA/ASA class I; level of evidence A) [106].

However, for the Indian population, treatment goals and statin intervention thresholds are as per LAI part 1 recommendations [1].

6.5. Patients with previous haemorrhagic stroke
Notwithstanding older studies suggesting a higher incidence of ICH in patients on aggressive statin therapy, recent large studies do not indicate that long-term statin treatment confers a higher risk of ICH [108]. Although they may be associated with a non-significant risk of haemorrhage, other benefits may outweigh this risk, and the current recommendation is to use statins, preferably at a lower dose. However, in patients of chronic haemorrhage who have low risk of ischemic stroke or MI but high risk of ICH recurrence, for example, after primary lobar haemorrhage, statins are best avoided [109, 110].

6.6. LAI recommendations
• 
Acute ischemic stroke: Starting a statin is probably beneficial. Continue statin if patient is already receiving it. Statins are not contraindicated if patient is
and Lande, who in 1922 demonstrated an association between thyroid function/dysfunction was first reported by Epstein et al. [117, 118]. However, total cholesterol and LDL-C levels are not completely normalised with thyroxine replacement. The higher the degree of hypercholesterolaemia, the more reversible with thyroid hormone replacement [113–116]. The amount of oxidised LDL particle, apolipoprotein A-1 (Apo A1), lipoprotein (a) [Lp(a)] and apolipoprotein B (ApoB), has also been reported to be elevated in hypothyroidism [121, 122]. Overt hypothyroidism has also been reported to be associated with increase in TG in some, but not all patients [123]. The elevation in TG levels is associated with increased levels of VLDL and occasionally fasting chylomicronaemia [124]. The VLDL and intermediate density lipoprotein (IDL) particles in hypothyroidism are rich in cholesterol and apolipoprotein E (Apo E), thus resembling VLDL particles of type III hypolipoproteinaemia [125]. HDL-C has also been reported to be normal or marginally elevated in overt hypothyroidism [124].

Sub-clinical hypothyroidism has also been reported to be associated with increase in total cholesterol and LDL-C level [126, 127]. The other abnormalities mentioned above in overt hypothyroidism are usually not seen in subclinical hypothyroidism [128]. Even within the normal range, there is a positive association between the thyroid stimulating hormone (TSH) level and the cholesterol level [129].

Thyrotoxicosis is associated with not only weight loss, but also lipid changes opposite to those seen in hypothyroidism. LDL-C and TG levels are reduced in thyrotoxicosis [130, 131].

7. Mechanism of thyroid-related dyslipidaemia

Thyroid hormone triiodothyronine increases intestinal cholesterol absorption and the activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis [132]. But it also increases the expression of LDL receptors in liver [133, 134]. Though the former two mechanisms increase cholesterol levels, the latter mechanism dominates and the net result is an increase in cholesterol level in hypothyroidism and the reverse in thyrotoxicosis. Triiodothyronine can influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL₂ to VLDL and TG in the opposite direction. Triiodothyronine stimulates the activity of lipoprotein lipase (LPL), which catabolises the TG-rich lipoproteins, and decreases TG concentration. They also activate hepatic lipase, which hydrolyses HDL₂ to HDL₃. These, mechanisms contribute to the conversion of IDL to LDL and in turn LDL to small-dense LDL [121].
The metabolic effects of thyroid hormone are through both nuclear receptor and non-receptor mechanisms [135, 136]. Its effects on lipid and glucose metabolism are through TR-β subunit activation predominantly [137]. It indirectly activates peroxisome proliferator-activated receptor (PPAR)-α and PPAR-γ receptors as well [138]. It also activates the respiratory chain [139]. Recently, it has been found that thyroid hormone also increases browning of adipose tissue in individuals with severe insulin resistance [140].

7.3. Cardiovascular risk in hypothyroidism

Apart from dyslipidaemia, obesity, increased waist circumference, increased homocysteine level, high-hsCRP, hypercoagulability, hypertension and increased arterial stiffness are other mechanisms through which hypothyroidism contributes to CV risk [141]. Hypothyroidism has been found to be associated with increased carotid intima thickness (cIMT) and impaired endothelial function [142].

7.4. Clinical epidemiology

As hypothyroidism (including subclinical hypothyroidism) is a common condition, lipid abnormalities and thyroid disorders coexist in a substantial number of individuals. The prevalence of dyslipidaemia in subjects with clinically overt significant hypothyroidism is reported as high as 80% [143]. Among individuals with hypercholesterolaemia, the reported prevalence of elevated TSH is around 15% [144–146]. However, the majority of them have sub-clinical hypothyroidism [144]. According to a study, 13% of individuals in the general population had sub-clinical hypothyroidism and 25% of them had lipid abnormalities [147]. Therefore, hypothyroidism is an important cause of secondary dyslipidaemia and all subjects with dyslipidaemia should be screened for hypothyroidism.

7.5. Management of dyslipidaemia in thyroid disorders

All patients with dyslipidaemia and overt hypothyroidism should be treated with thyroxine initially. A period of 4–6 weeks of thyroxine replacement therapy is usually needed to correct the dyslipidaemia [148]. As this treatment may exacerbate myocardial ischaemia in patients with underlying CAD, it is recommended to start treatment at lower doses (25 μg/day) and titrate gradually (12.5–25.0 μg increments) at intervals of 4–6 weeks with monitoring of clinical features, TSH levels and electrocardiogram. If adequate response is not seen with thyroxine treatment alone after 4–6 weeks of therapy, lipid-lowering medications can be then initiated [149]. Use of statins in hypothyroidism with dyslipidaemia should be customised. In patients not known to have underlying CAD or risk for CAD, it is better to wait until the patient becomes euthyroid. A repeat lipid profile will help to proceed according to the existing guidelines [107]. In presence of underlying CAD or acute coronary syndrome, statins should be started along with levothyroxine replacement [150]. Use of statins or fibrates alone or in combination in patients with dyslipidaemia and uncontrolled hypothyroidism carries a higher risk of myopathy [151]. Risk of myopathy may also be associated with the co-administration of statins with thyroxine [152]. It is generally agreed that thyroid replacement therapy has beneficial effects on serum lipid profile and CVD risk in overt hypothyroid patients, but no clear consensus has been established regarding the treatment of sub-clinical hypothyroidism subjects. Some of the points put forth by researchers in favour of providing treatment to patients with sub-clinical hypothyroidism are that treatment will prevent progression to overt hypothyroidism and will also reduce future risk for CVD [153]. However, these findings are yet to be strengthened by definitive evidence. There is no clear consensus on whether thyroid replacement therapy with thyroxine has beneficial effects on serum lipid profile and CVD risk in subclinical hypothyroidism patients [154]. Thyroid replacement in patients with subclinical hypothyroidism is recommended if serum TSH is >10 mIU/L, patients have high initial cholesterol levels or are elderly, are smokers or are positive for anti-thyroid peroxidase antibodies.

The treatment of hyperthyroidism is directed towards lowering the serum concentration of thyroid hormones and to re-establish a eumetabolic state. The management of lipid levels in patients with hyperthyroidism should be based on the existing guidelines [107]. Sewerynek et al. suggested that treatment with methimazole in patients with hyperthyroidism can be protective against the oxidative stress induced by overproduction of thyroid hormones [155].

7.6. LAI recommendations

1. All patients with dyslipidaemia should be screened for thyroid dysfunction.
2. Patients with dyslipidaemia and overt hypothyroidism should be treated initially with thyroxine.
3. In patients with underlying risk for CAD, start low dose thyroxine and titrate upwards slowly. Assess CVD risk and start lipid-lowering drugs as per LAI recommendation for primary prevention of CVD.
4. Patients without underlying risk for CAD: wait for the patient to become euthyroid.
(5) Statins or fibrates alone or in combination in patients with dyslipidaemia and uncontrolled hypothyroidism carry a higher risk of myopathy.

(6) Thyroid replacement in patients with sub-clinical hypothyroidism if serum TSH is >10 mIU/L, patients have high initial cholesterol levels or are elderly, are smokers or are positive for anti-thyroid peroxidase antibodies.

(7) In patients with established vascular disease requiring thyroxine and lipid-lowering therapy, caution should be exercised with thyroxine dose to prevent onset of ischemic symptoms.

8. Management of ASCVD risk in inflammatory joint diseases

Inflammatory joint disorders (IJDs) include rheumatoid arthritis (RA), spondyloarthritis [including ankylosing spondylitis (AS)] and psoriatic arthritis (PsA) and many others. The first two are the main groups of joint disorders that have been evaluated and managed for CVD in clinical practice. These two conditions are associated with an excess of CVD morbidity and mortality. Systemic lupus erythematosus, progressive systemic sclerosis, etc. are other autoimmune conditions (not strictly “IJDs”) associated with excess CVD morbidity, but compared with IJDs, these conditions have been subjected to less scrutiny vis-à-vis their CVD potential. The following discussion therefore focuses on the CVD risk and its management in the IJDs only (namely RA, AS and PsA).

IJDs are being managed with increasingly effective medications like biologic disease modifying anti-rheumatic drugs (DMARDs) and targeted synthetic DMARDs (tsDMARDs) [156, 157]. The excess morbidity and mortality of IJDs are no longer attributed to musculoskeletal factors, but are more due to increased CV events [158, 159]. The main reasons for the excess CVD in IJDs include: (a) presence of systemic inflammation that also causes vascular inflammation [160], (b) the deleterious effect of non-steroidal anti-inflammatory drugs (NSAIDs) and long-term steroids, used for managing IJDs [161] and (c) a reduced ability of patients with IJD to exercise [162] and lifestyle-related factors (smoking in particular). Indeed, the risk of CVD in RA patients rivals the risk of CVD in diabetic patients [158]. Also, AS and PsA have now been studied for their CVD potential [159, 163] and their CVD assessment and treatment may soon follow a path similar to the one followed for RA.

8.1. Evidence from clinical trials for the beneficial role of statin use in RA

One landmark study published in 2004 (the “TARA” trial) evaluated the disease-modifying effect of a statin in the treatment of RA. The authors postulated that statins might reduce inflammation, its associated CV (cardiovascular) implications and could therefore be potentially disease-modifying (akin to methotrexate (MTX) and prednisolone) in reducing arthritis. Patients \( n = 116 \) with RA were randomised in a double-blind placebo-controlled trial to receive 40 mg of atorvastatin or placebo on the background of standard disease-modifying therapy. The findings at the end of 6 months revealed a statistically significant but clinically modest reduction in arthritis scores in the atorvastatin groups. However, these scores were not enough to qualify as “disease modification” by current Biologic and DMARD standards in RA treatment [164].

In another trial, 30 patients with early RA received either MTX plus prednisolone or MTX plus prednisolone plus a statin (atorvastatin 40 mg/day). The parameters of inflammation that included tissue necrosis factor (TNF)-alpha levels, lipid profiles, serum malondialdehyde (MDA) and brachial artery flow-mediated dilatation (FMD) were evaluated before and 6 months after treatment. The results favoured the atorvastatin group for an overall improvement in the endothelial function and CV risk benefit (clinical parameters were not compared) [165].

In another trial which studied the effect of intensive lipid-lowering strategies in patients with RA and a previous MI (“IDEAL trial”) showed that RA patients with a previous MI had comparable reduction in lipid levels and rates of CV events when compared with patients without RA [166].

8.2. General recommendations

Recommendations for CVD risk assessment and its management in RA and AS or PsA have been published (“EULAR recommendations-2009”) [167]. These have been updated with modifications based on new data from clinical and epidemiological studies [168]. Briefly, the updated recommendations are: 1) TC/HDL-C ratio is preferred over individual lipid components when calculating CVD risk in RA patients and the values should be assessed when the patient is in complete remission or has stable activity, 2) The use of an RA-adapted risk prediction model was recommended over the use of an un-adapted general population model. Moreover, the general population risk CVD risk algorithm should have a multiplication factor of 1.5 for all RA patients (and not just with long-standing seropositive disease as was recommended by the 2009 EULAR recommendation), 3) CVD risk assessment should apply for RA as well as other IJDs like AS and PsA and assessments should be repeated every 5 years by the treating rheumatologist and 4) Disease control for all IJDs (RA, AS, PsA) is mandatory and should be the first step for reducing CVD risk.

Most rheumatologists will target complete remission or low disease activity, both for RA and SpA/PsA. A complete
remission would logically reduce the disease-related vascular inflammation, and would therefore be the single most important factor for reducing CVD events in IJDs. Correction of hypertension and lipid abnormalities is only the next step for reducing CVD in IJDs, as discussed in the following paragraphs. Treatment with medications including NSAIDs, steroids, biologics DMARDs (bDMARDs) and tDMARDs is followed based on guidelines published by the American College of Rheumatology [169].

The recommendations for the management of RA and AS published from India [169, 170] can also be referred to, but their relevance to current management is limited given their date of publication (2010 and 2012). Simpler algorithms have been published for the management of early RA [171] and established RA [172] and are inclusive of bDMARDs and conventional DMARDs. These may instead be used for management decisions especially for Indian patients. The rheumatologist/physician/musculoskeletal expert should evaluate and manage CVD risk in all patients of IJDs, with input from cardiologists/neurologists/physicians [167, 168].

The treating physician should be wary of the low levels of LDL-C, HDL-C and total cholesterol in untreated and active disease with RA [173], which when used for CVD risk calculation in these patients will underestimate the risk. This paradox of low lipid levels with a higher propensity to CVD is partly because the HDL is dysfunctional and its protective role is compromised in active inflammation [174, 175]. Similar abnormalities (low LDL-C and low HDL-C) are also found in sepsis/infections, trauma, etc. and this phenomenon may be due to cytokine-mediated activation of the reticulo-endothelial system which mops up the lipid particles [173]. Successful anti-inflammatory treatment increases both the LDL-C and HDL-C [176], but the level of the HDL-C is raised more than the LDL-C and therefore there is a net anti-atherogenic shift in total cholesterol/HDL-C ratio. Also, the use of conventional synthetic DMARDs (csDMARDs) like MTX and hydroxychloroquine in RA patients has resulted in a consistent overall improvement in the lipid profile, insulin resistance and cIMT [177]. The remission induction and successful treatment of RA with csDMARDs and bDMARDs have registered benefits for CVD morbidity and mortality in large populations of RA patients (real-world registry data from various countries, BIOBADASER database, biologic registries from UK, US, etc.) [178, 179].

The Prospective Randomised Evaluation Of Celecoxib Integrated Safety VS Ibuprofen Or Naproxen (PRECISION) trial’s results bring new NSAID data to the forefront, in which it was found that celecoxib was non-inferior to naproxen as regards safety of CVD events in a large cohort of osteoarthritis and RA patients combined [180]. Another important finding from the study includes: for all-cause mortality in patients with RA patients alone, treated with naproxen, (hitherto considered the safest NSAID as far as CVD risk is concerned) the risks for CVD and all-cause mortality were higher when compared with celecoxib [selective cyclooxygenase-2 (COX-2) inhibitor, hitherto considered higher CVD risk as compared with conventional NSAIDs]. Therefore, it may be pertinent to consider selective COX-2 inhibitor celecoxib as the NSAID of choice for treating at least the elderly RA patients with comorbid gastrointestinal risk. On the other hand, for most osteoarthritis patients regardless of age, either celecoxib or naproxen may be used depending on patient/physician preference. At the time of the baseline visit and at each follow-up visit of IJD patients, the rheumatologist should assess adherence to diet and exercise. Cessation of smoking should be discussed with the patient if applicable.

A study showed that various biomarkers were affected in an Indian population with RA. CRP, TNF-α, serum nitrite, DAS-28 and depleted EPC population predicted endothelial dysfunction. Age, IL-6, HDL, LDL and depleted EPC population predicted accelerated atherosclerosis. Also, flow-mediated dilation and cIMT were also impaired in RA [181].

8.3. LAI recommendations

- CVD risk assessment for IJD patients should be carried out [including total cholesterol and HDL-C (fasting or non-fasting)] during the stable disease state once every 5 years [168].
- The use of statins and CVD risk management should follow the same principles as discussed in the Part1 of this consensus document [1]. As discussed, the Joint British Societies 3rd version (JBS3) risk calculator should be the preferred calculator as other conventional calculators when used for CVD risk assessment in active RA and IJD patients underestimate CVD outcomes over time [182]. This is because the low lipid levels underlie the true state of vascular inflammation. Statins should not be used solely for disease modification since trials like the TARA trial have shown a clinically insignificant arthritis-reducing result in RA. Statins have to be used in AS/PsA patients with a lower threshold for lipid abnormalities (statins lowered CVD mortality by 32% in a population of AS/PsA patients from UK – The Health Improvement Network-database UCL) [183]. For hypertension management, the Indian guidelines or the European Society Guidelines should be followed and minor adjustments may be made depending on the comorbid conditions of the patient. Use of steroids should be at the lowest dose possible for the shortest duration. At each follow-up visit, the
Concerns regarding safety, life expectancy, comorbidities, and cost–benefit analysis have excluded older patients from participation in some studies [189, 190]. However, various randomised trials have shown that LDL-C-lowering therapy should be greater than in younger individuals [191, 192]. Similarly, another concern is that side effects are more common in the elderly. However, many trials have shown that there is no significant increase in side effects compared with placebo in the elderly taking statins [193, 194].

9. Dyslipidaemia in the elderly

The World Health Organization (WHO) defines elderly as an individual aged ≥ 65 years, although racial variations may exist. The absolute risk of CAD and death due to CAD rises in both men and women with increasing age. In males, after the onset of puberty, cholesterol levels keep increasing until 50 years of age and plateau until 70 years followed by a slight fall in the levels. In females between 20 and 25 years, the cholesterol levels are higher than in men, and thereafter, it rises at a slower rate than in males. Cholesterol levels are almost equal between males and females aged 55–60 years. LDL-C mainly contributes to the increase in total cholesterol with age [184]. This is probably due to the decreased ability of hepatic LDL receptors to metabolise LDL with age [185]. The HDL-C values do not change much with age in both males and females. CV risk is predicted by serum cholesterol levels. High LDL-C and low HDL-C have been shown to be risk factors in the elderly for CAD both in the Framingham Heart Study and the Systolic Hypertension in the Elderly Program (SHEP) studies [186, 187]. The Framingham Heart Study showed that men and women had 1.5 and 2.3 relative risk of developing asymptomatic CAD when the serum cholesterol was above 200 mg/dL [188]. Low HDL-C (<35 mg/dL) is also a risk factor contributing to increased deaths due to CAD in the elderly above 70 years of age, with a relative mortality of 4.9 in males and 2.0 in females [188].

Although the relative increase in mortality that is seen with elevated cholesterol levels declines with age, the absolute risk increases with increasing age because of other comorbidities [187]. The higher absolute risk in older adults suggests that the benefit from cholesterol-lowering therapy should be greater than in younger individuals [189, 190]. However, various randomised trials with statins have excluded older patients because of concerns regarding safety, life expectancy, comorbidities in the elderly and cost–benefit analysis. Further, statins are also withheld in elderly patients because of the belief that LDL-C-lowering therapy requires many years before the course of atherosclerosis can be altered. However, many studies have observed clinical benefits as early as 6 months to 2 years [191, 192]. Similarly, another concern is that side effects are more common in the elderly. However, many trials have shown that there is no significant increase in side effects compared with placebo in the elderly taking statins [193, 194].

9.1. Benefits of lipid lowering in older adults

Subgroup analysis of various secondary prevention trials of LDL-C lowering show that elderly patients derive similar benefit from lipid-lowering therapy as younger ones [8, 195, 196]. The CARDS study and the HPS showed similar reductions in serum lipids in elderly and younger individuals, with significant reduction in all-cause mortality, mortality from CAD, major coronary events and the number of revascularisation procedures in elderly patients [8, 197, 198]. The LIPID trial which included a large number of patients between the ages of 65 and 75 years (n = 3514) who had a prior MI or unstable angina with a baseline serum cholesterol of 155 to 271 mg/dL showed greater absolute benefit of pravastatin in elderly patients [195]. This was due to increased baseline risk of CV events in the elderly. In the Treating to New Targets (TNT) study, atorvastatin 80 mg was compared with 10 mg in 10,003 patients (of these, 3809 were ≥ 65 years) with stable CAD. High dose atorvastatin therapy significantly reduced major CV events compared with low dose without any increase in creatine kinase (CK) levels suggesting a role for aggressive statin therapy in the elderly [199]. In a study of 7220 patients with angiographically proven CAD followed up for a mean of 3.3 years, statin therapy reduced mortality across all age groups including the very elderly (≥80 years) [200]. However, in this study, the elderly were significantly less likely to be prescribed statins. Similarly, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [201] and the Study Assessing Goals in the Elderly (SAGE) trial [202] showed mortality reduction with intensive statin therapy in patients aged ≥ 65 years with a history of or risk factors for vascular disease. Importantly, in the PROSPER study, pravastatin had no significant effect on cognitive function.

Primary prevention trials of statins, including the Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TexCAPS) and Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA), found similar results on clinical endpoints in younger and older individuals [203–205]. The JUPITER trial in which rosuvastatin was administered to patients with low-to-average LDL-C levels with elevated CRP levels, patients 70 years
and older (32% of total cohort) derived greater absolute risk reduction than younger patients [205].

The secondary causes of dyslipidaemia, e.g. hypothyroidism, diabetes mellitus, CKD, thiazide diuretics, should be ruled out and managed. The prevalence of subclinical and overt hypothyroidism increases with age and hence needs to be routinely ruled out [206]. Similarly, CKD is common in the elderly and kidney function should be evaluated in an elderly patient with dyslipidaemia [207]. Lifestyle measures including smoking, exercise and dietary saturated fat restriction are as important in the elderly as in the younger population. However, aggressive dietary restrictions may be inappropriate in the elderly as they are at high risk of malnutrition as dementia and physical disabilities may limit their access to adequate nutrition. Elderly patients are frequently treated with multiple medications and so carry the risk of drug interactions (e.g. administration of macrolide antibiotics can raise statin levels and increased risk of muscle toxicity). The adherence to statins declines substantially with time in elderly patients [208]. This occurs even when the cost is not an issue.

9.2. Summary

The event rates in elderly subjects are proportionately higher than for younger subjects in both primary prevention and secondary prevention studies emphasising increased absolute risk. Hence, instituting statin therapy is important for appropriate subjects. Both chronological and physiologic age should be taken into consideration before deciding to treat high or high-normal serum cholesterol in elderly patients [209]. Fibric acid derivative should be used with caution in those with renal impairment. The treatment should be individualised – a patient with a projected limited life span due to comorbidities may not be a candidate for statins, whereas an otherwise healthy older adult individual should not be denied drug therapy simply on the basis of age alone [190].

Many trials support the use of lipid-lowering therapy for secondary prevention in older patients with established CAD who do not have life-limiting comorbid disease [8, 197, 199]. The data from the Cardiovascular Health Study suggest significant benefit from primary prevention in patients aged ≥65 years [210]. However, despite proven benefit, statins are largely underutilised in elderly patients even in those with increased baseline risk [211].

9.3. LAI recommendations

- CVD is the most common cause of death in the elderly. As in the young, elderly patients with dyslipidaemia have an increased risk for CVD.

- Secondary causes of dyslipidaemia such as hypothyroidism, diabetes, CKD and drug effects should be considered in elderly patients.

- The RRR of lipid-lowering therapy in elderly patients is similar to that in younger patients; however, the absolute benefit is higher than in younger patients.

- Reductions in events with statin therapy are apparent within a few weeks to months even in older patients.

- In general, side effects of lipid-lowering therapy are similar in the old and young. However, in very elderly frail patients, lower doses may be appropriate.

- Secondary prevention: Statin therapy should be instituted in all appropriate elderly patients as above with treatment goals similar to younger patients. Dose of statins may need to be individualised in the elderly based on frailty and other comorbidities.

- Primary prevention: Elderly subjects with a reasonable life expectancy should be treated similar to younger patients as per risk stratification algorithm proposed in the previously published LAI expert consensus statement [1].

10. Dyslipidaemia in women

Heart disease remains the leading killer of women. After MI, women are more likely than men to develop HF or die within 5 years of the event [212].

Management of dyslipidaemia in women requires consideration of gender-specific differences in CV risk, evidence from the available trials and the potential risks and benefits of lipid-lowering therapies.

Despite the importance of ASCVD as a health concern for women, they have historically been under-represented in RCTs of lipid-lowering therapies. In the statin trials that have included women, there have been no gender-specific differences in the observed lipid responses to statin therapy, with similar reductions in total cholesterol, LDL-C and TG, and increases in HDL-C among men and women [213].

10.1. Physiology of lipoproteins in women

Women experience a number of hormonal changes throughout their lifetime, beginning from puberty, through pregnancy and up to menopause. LDL-C levels tend to increase in both men and women after the age of 20 years, but do so more rapidly in men [184]. There is a rise in the number of hormones including human chorionic gonadotropin hormone, beta-estradiol, insulin and progesterone during pregnancy which is associated with increases in total cholesterol, TG and LDL-C [214, 215]. Additionally, pregnancy is also associated with an increase
in total HDL-C and Apo A1 concentration, with maximum levels at week 25 of pregnancy [214, 215].

After menopause, women have increased levels of LDL-C, total cholesterol and Apo B compared with premenopausal women [216]. There is a transition in LDL particles to more atherogenic smaller and more dense particles [217]. Total HDL-C and HDL2 also decrease in postmenopausal women [218]. Lipoprotein (a) levels increase after menopause and decrease in those on hormone replacement therapy (HRT) [219, 220].

10.2. Evidence for the role of lipid pharmacologic therapy in women

Studies have demonstrated gender differences in the burden of CV outcomes for patients with dyslipidaemia. Farahani et al. investigated the evolving pattern of sex/gender disparity in participants of RCTs on statins between 1990 and 2010. This study observed a significant progress in the inclusion of women in RCTs involving statins [221].

10.2.1. Statins in women

The JUPITER primary prevention trial included 6801 women and 11,001 men. The post-treatment changes in lipid parameters and hsCRP levels were similar in men and women as was the primary endpoint which was a composite of MI, stroke, hospitalisation for unstable angina, arterial revascularisation or ASCVD death [222].

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study which included highest percentage of women in any statin trial to date (7832 subjects with 5356 women – 68% and 2476 men – 22%) studied the usefulness of pravastatin in primary prevention of CV events in adult Japanese women [223]. The incidence of CV events was 2–3 times lower in women compared with men. There was a non-significant 25% risk reduction in CAD in women on pravastatin compared with a non-significant 35% CAD risk reduction in men.

The Cholesterol Treatment Trialists' (CTT) collaborators conducted a meta-analysis of 27 primary and secondary prevention RCTs with 174,249 participants [46,675 (27%) women] to examine gender differences in the efficacy and safety of statin therapy [224]. The meta-analysis showed similar reductions in events in men and women.

In a meta-analysis that included 40,275 women from 18 primary and secondary prevention RCTs with gender-specific outcomes, a statistically significant decrease in the primary endpoint was observed among women in both primary and secondary prevention [225]. Another meta-analysis of 37 prospective, multinational studies demonstrated that the relative risk (RR) for fatal CHD associated with diabetes is nearly 50% higher in women (RR 3.5; 95% CI 2.7–4.5) than it is in men (RR 2.06; 95% CI 1.81–2.34) after adjustment for major coronary risk factors, although the absolute ASCVD risk may remain lower in women with diabetes compared with men with diabetes [226].

Based on the above information, statins are the first-line cholesterol-lowering drug therapy for women as per the risk stratification algorithm of LAI [1].

10.2.2. Non-statin therapy in women

10.2.2.1. Niacin. The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) [227] was a large trial conducted in 25,673 patients with established vascular disease (4444 women, 17.3%). Participants were randomly assigned to receive 2 g of extended release niacin and 40 mg of laropiprant or a matching placebo daily. Women randomised to niacin and laropiprant had an excess of events compared with those randomised to placebo with a trend towards harm compared with benefit in men, but this gender difference was not statistically significant.

In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) [228] study, 3414 patients (14.8% women) with established ASCVD were randomised to extended release niacin 1500 to 2000 mg/day or matching placebo in addition to simvastatin and ezetimibe in all the patients. Following a 36-month follow-up, the trial was terminated due to lack of clinical benefit from the addition of extended release niacin to statin therapy. There was no heterogeneity by gender.

Nicotinic acid preparations are available for use in some countries including India. Care should be taken when prescribing niacin in view of the side effects.

10.2.2.2. Fibrates. Two large RCTs of fenofibrate have included women as well as men: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies [229, 230]. The FIELD study included 9795 (37.3% women) type II diabetic patients aged 50–75 years of age and not taking statin therapy at study entry. Approximately 22% of patients had pre-existing ASCVD. Patients were randomly assigned to micronised fenofibrate 200 mg/day or matching placebo and followed-up for 5 years. Although the study was not adequately powered for gender-specific analysis, women had a statistically significant 18.9% relative reduction in total CV events (9.5% for placebo vs. 7.7% for fenofibrate, p = 0.04). There were no significant gender-specific differences in adverse effects of treatment with fenofibrate [229].

The ACCORD trial included both primary and secondary prevention patients (women 1694(31%), men 3824)
with type 2 diabetes [230]. Participants were randomised to simvastatin plus fenofibrate 160 mg or placebo and followed for 4.7 years for the primary outcome, and 5.0 years for all-cause death. In the subgroup analysis, men seemed to benefit from fenofibrate therapy, whereas there was a trend towards harm among women. The ACCORD study results are in contrast to the FIELD study results where no significant interaction was seen between treatment and sex on outcomes.

10.2.2.3. Ezetimibe. A gender subset analysis (women, \( n = 1066 \); men, \( n = 796 \)) on data pooled across four randomised, double-blind trials showed that statin/ezetimibe combination decreased LDL-C equally in men and women [231]. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) included 18,144 patients (24% women) with acute coronary syndrome < 10 days duration who were randomised to simvastatin 40 mg + ezetimibe 10 mg daily or simvastatin monotherapy [232]. Incremental lowering of LDL-C levels and improved CV outcomes were observed in the combination group. No statistically significant gender difference was observed in CV events.

10.2.2.4. Omega-3 fatty acids/fish oils. The Japan EPA Lipid Intervention Study (JELIS) evaluated the effects of statin plus highly purified eicosapentaenoic acid (EPA) ethyl ester 1800 mg daily (600 mg three times a day after meals) or usual care (no EPA) in 18,645 (68% women) Japanese primary and secondary prevention patients [233]. There was no heterogeneity by gender for the relative reduction in the occurrence of coronary events, although women had a lower absolute risk of events (2.7% control vs. 2.0% EPA group) compared with men (4.2% control vs. 3.5% EPA group).

The Alpha Omega trial randomised post-MI patients who were on the state-of-art treatment to margarine supplemented with a combination of EPA and docosahexaenoic acid (DHA), a margarine supplemented with alphalinolenic acid (ALA), a margarine supplemented with EPA-DHA and ALA or placebo margarine [234]. Overall, there was no benefit; however, there was non-significant 27% reduction in major CV events with ALA among women (HR 0.73, \( p = 0.07 \)).

Not much gender-specific data are available presently for PCSK9 inhibitors, microsomal triglyceride transfer protein inhibitors and Apo B inhibitors. In the recently published Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, which included 27,564 patients (25% women), the beneficial effects of evolocumab were similar in men and women [235].

10.2.3. Non-pharmacological approaches

Therapeutic lifestyle changes are required for the optimal management of dyslipidaemia in women, including dietary changes, increases in physical activity and exercise and smoking cessation, all of which have been shown to reduce overall CV risk factors and to contribute to a decline in CAD. Among 84,129 women in the Nurses’ Health Study, 82% of CAD events were attributed to lack of adherence to lifestyle guidelines [236].

Tobacco use is a major preventable cause of CAD in women. Moderate (e.g., 1–2 drinks/day) alcohol consumption increases HDL-C in women and may be cardioprotective, but because of other concerns (increased risk of breast cancer, liver disease, alcoholism, etc.), it is difficult to routinely recommend regular alcohol consumption to non-drinkers.

In addition to dietary restrictions in saturated fat, trans fatty acids and cholesterol, some studies have reported that increased intake of soy or soy protein, especially as a replacement for animal protein, resulted in small, but at times, statistically significant, lipid improvements in women [237].

10.3. Gender differences in adverse effects

Meta-analyses have shown no evidence for an increase in non-CV mortality, specifically no increase in cancer, associated with statin therapy in women [224]. In JUPITER, women (\( n = 6801 \)) were significantly older, more likely to have hypertension and the metabolic syndrome and had a higher body–mass index and lower eGFR compared with men (\( n = 11,001 \)). The rates of muscle-related adverse events were similar among women and men regardless of assignment to statin or placebo [222].

Nevertheless, gender differences in body fat, muscle mass, CoQ10 levels, pain perception and reporting of adverse reactions and underlying genetic factors (polymorphisms associated with cytochrome P450 isoenzymes, drug transporters or myocyte metabolism) may play a role in the increased frequencies of adverse drug effects reported by women [238].

10.4. Special situations

10.4.1. Pregnancy

A steady rise of lipoprotein levels occurs throughout pregnancy; however, in uncomplicated pregnancy, neither total cholesterol nor TG exceeds 250 mg/dL [239]. TG levels exceeding 250 mg/dL are associated with pregnancy complications, including pregnancy-induced hypertension, preeclampsia, gestational diabetes and more for gestational age babies [240]. Secondary causes of
hypertriglyceridaemia should be ruled out as in non-pregnant women. The Amsterdam Born Children and Their Development (ABCD) study showed that atherogenic lipid profiles during the first trimester confer an increased risk of adverse pregnancy outcomes including maternal morbidity, mortality and preterm delivery [240].

The American Association of Physicians/American College of Obstetricians and Gynecologists Guidelines for Perinatal Care recommend lipid assessment annually for all age groups [241]. The best time to screen for dyslipidaemia is prior to pregnancy and monitor during the pregnancy if values are elevated. Follow-up should be performed routinely after the pregnancy is over, usually by the 6-week postpartum visit.

10.4.1.1. Treatment of dyslipidaemia during pregnancy. Appropriate diet, weight management and exercise are essential for management during pregnancy. For women on lipid-lowering medications prior to pregnancy, all except bile acid sequestrants are currently recommended to be stopped in preparation for pregnancy [242]. The Food and Drug Administration (FDA) has classified statins as category X (Table 3).

Controlling glycaemia is central to managing increased TG in women with gestational diabetes or diabetes present prior to pregnancy. Very high TG (≥500 mg/dL is associated with a higher risk for pancreatitis) may be treated with diet/lifestyle management plus omega-3-fatty acids and/or with fenofibrate early in the second trimester based on clinical judgement [243].

It is recommended that lipids should be monitored every trimester, or within 6 weeks of an intervention. Hypercholesterolaemia during pregnancy, especially in women with familial hypercholesterolaemia (FH), may be treated with bile acid sequestrants as they are not absorbed systemically. Bile acid sequestrants like colesevelam may increase TG levels. However, diet and exercise continue to be the mainstay of treatment during pregnancy. Women with FH may also be treated with LDL apheresis.

10.4.2. Breast feeding

Appropriate diet and exercise should be continued following pregnancy during breast feeding. Patients with FH can receive bile acid sequestrants, and drug therapy for severe hypertriglyceridaemia may be continued (as above). In the Nurse’s Health Study, there was a 23% lower incidence of MI in women in their 60s if they had breast fed [236].

10.4.3. Polycystic ovary syndrome (PCOS)

PCOS affects 4–22% of reproductive age Indian women [244, 245]. Women with PCOS are at increased risk for metabolic syndrome, diabetes mellitus and complications of pregnancy [246], as well as endometrial cancer [247]. Insulin resistance is associated with dyslipidaemia in women with PCOS, independent of obesity and the lipid profile is significantly different (high TG, total cholesterol and lower HDL-C) compared with insulin-sensitive women [248].

As per the National Lipid Association (NLA) Expert Panel, patients with PCOS irrespective of their age should undergo initial lipid and diabetes screening, typically with fasting glucose or glycated haemoglobin and should have screening (at least every 2 years) if initial values are normal [249]. Dyslipidaemia should be treated as per the LAI recommendation[1].

10.4.4. Menopause

Both LDL-C and Apo B increase in the few years prior to menopausal symptoms, peak and then plateau. HDL-C tends to decrease after menopause. The absolute risk for ASCVD increases substantially during the menopause transition for women [250].

In postmenopausal women, use of HRT with unopposed oestrogen is associated with significantly higher HDL-C and lower LDL-C compared with premenopausal women [251]. Combination HRT appears to negate the increases in HDL-C seen with oestrogen monotherapy. In the Postmenopausal Oestrogen and Progesterone Interventions trial, investigators noted that combination HRT, which included progesterone, was associated with a significantly smaller increase in HDL-C and TG as compared with oestrogen-only HRT [252].

While epidemiologic and observational studies suggested a CV benefit of HRT, data from randomised controlled trials failed to confirm these benefits. In the Heart and Oestrogen/Progestin Replacement Study, 4 years follow-up of 2763 postmenopausal women, use of HRT was associated with an 11% reduction in LDL-C and a 10%
increase in HDL-C, but this beneficial lipid change was not associated with significant improvement in CAD [253]. The Women’s Health Initiative study [254] was stopped early due to a significant increase in the risk of stroke in the oestrogen-only-treated women and the oestrogen and progesterone therapy terminated due to increase in breast cancer cases.

Based upon these randomised controlled trials, treatment guidelines were subsequently changed with removal of the recommendation for use of HRT in women to prevent CAD events [255].

10.4.5. Contraception

Oral contraceptive pill (OCP) can have estrogenic, progestational, androgenic, anti-estrogenic and anti-androgenic effects. The major risk associated with their use is thrombotic, including venous and arterial events. Women with comorbidities, older age and, most importantly, current smokers are at greater risk for CV events.

The oestrogen contained in OCP will frequently increase TG and HDL-C, and lower LDL-C [256]. Androgenic progestins (such as norgestrel and levonorgestrel) can raise LDL-C and lower HDL-C. The other progestational agents are usually lipid-neutral. The more oestrogen an OCP contains, the greater TG raising effect it will generally have; these agents may cause severe hypertriglyceridaemia in women with high baseline TG [257].

Transdermal or vaginal contraceptives (oestrogen plus progestin) do not have a lower thrombotic risk compared with OCP, but transdermal contraceptives are less prone to producing clinically important elevations in TG concentration [258]. Progestin-only containing oral contraceptives are available and may be used if estrogenic preparations are contraindicated. They are, however, associated with greater risk for breakthrough bleeding and are not as effective for contraceptive purposes.

10.5. LAI recommendations

Based on all the evidence from primary and secondary RCTs, meta-analysis and the various available guidelines, the recommendations in Indian women can be summarised as:

10.5.1. General recommendations

- Women with collagen vascular disorders, PCOS, preeclampsia, pregnancy-induced hypertension and gestational diabetes are at higher ASCVD risk.
- In general, the dyslipidaemia management is similar in both men and women. However, in elderly frail women, treatment should be started with low dose statin in view of higher incidence of muscle-related adverse effects except in the very high risk group.
- Statins remain the first-line cholesterol-lowering drug therapy for primary and secondary prevention in women. Statin dosage should be increased to the maximally tolerated dose before adding a non-statin drug if goal levels of LDL-C and non-HDL-C are not achieved.
- Non-statin drugs may be considered as a primary drug for women with contraindications for, or intolerance to, statin therapy.

10.5.2. Recommendations in pregnancy

- Lipid-lowering drugs must be stopped if pregnancy is planned, during pregnancy and during breast feeding.
- Diet and exercise continue to be the mainstay of treatment during pregnancy. Statins are contraindicated. Only the bile acid sequestrants are considered safe for use during pregnancy.
- Very high TG (≥500 mg/dL) may be treated during pregnancy and breast feeding with diet/lifestyle management plus omega-3 fatty acids [259]; fenofibrate or gemfibrozil may be considered [260]. During pregnancy there is a high risk of developing pancreatitis. Although apheresis may be useful in pregnant women, it is not available in India.

10.5.3. Recommendations for PCOS

- All patients with PCOS should undergo initial lipid and diabetes screening and regular follow-up is recommended.
- Therapeutic management of dyslipidaemia in PCOS should focus on diet, exercise and lipid-lowering medication (as above).

10.5.4. Recommendations for menopause

- Hormone therapy should not be used for prevention or treatment of ASCVD.
- Hormone therapy is an option for treatment of significant menopausal symptoms during menopause transition for women at minimal risk for ASCVD.

10.5.5. Recommendations for contraception

- Contraceptive pills derange lipid profiles and should be used carefully especially by women who use tobacco/tobacco products as it increases risk of thrombosis. LAI recommends annual lipid assessment in women using oral contraceptive pills for long duration.
11. Familial hypercholesterolaemia (FH) – an Indian perspective

FH is the most common monogenic disorder of lipoprotein metabolism, mostly with an autosomal dominant inheritance [261]. This condition, also called as Fredrickson type 2a hyperlipidaemia, is characterised by elevated total cholesterol and LDL-C concentration. An estimated 14–34 million people are likely to have this condition worldwide but <1% of those individuals have been diagnosed with only half of them receiving optimal treatment [262]. The affected individuals have a high risk for developing premature ASCVD and through appropriate intervention to reduce LDL-C concentration, significant reduction in mortality can be achieved [263].

CVD is the leading cause of death attributing to 28% of the total mortality in the Indian population with an average age of onset below 55 years [264]. However, the contribution of FH to premature CVD in Indians is unknown, mainly due to the lack of awareness of this condition among both health care providers and the general population. A recent survey in Tamil Nadu suggested a substantial deficit in awareness and knowledge of FH among medical practitioners [265].

11.1. Pathophysiology of FH

FH is caused by mutations in the genes of the LDL receptor (LDLR) or Apo B or PCSK9 that interfere with clearance of LDL-C by the liver [266]. An autosomal recessive rare form affecting LDL receptor adaptor protein 1 gene has also been described as causing FH [267]. The most common cause among Indians is a mutation in the LDLR gene, accounting for up to 85–90% of all cases of FH [268]. Over 1000 mutations have been described; however, the Pro685Leu mutation in exon 14 of LDLR has been shown to be particularly common accounting for 50% of all FH mutations in Indian migrants from South Africa [269]. The prevalence of FH is high in Indians living in South Africa and it is possible that it is due to the “Founder effect”. However, in a study of 16 homozygous subjects, no mutation was seen in exons 3, 9 and 14 of the LDLR gene, which were considered to be the hot spots in studies done on Asian Indians in South Africa [270]. FH occurs clinically as heterozygous FH (HeFH) or homozygous FH (HoFH). HeFH occurs when the affected individual inherits one mutant gene and is characterised by LDL-C concentration that is 3–4-fold higher compared with the general population. Such patients typically develop lipid stigmata that include corneal arcus and tendon xanthoma and develop premature CVD in their 4th decade, although women may develop these later. In contrast, those with HoFH inherit the defective genes from both the parents, have an LDL-C concentration that exceeds 4–8-fold that of the general population and they develop cutaneous stigmata and atherosclerotic CVD in their teens [271].

11.2. Diagnosis of FH

Different diagnostic criteria have been proposed by different authorities/investigators. The Simon Broome Criteria, commonly used in the United Kingdom, take into consideration total cholesterol and LDL-C concentrations, presence of tendon xanthoma, presence of family history of premature vascular disease and cholesterol concentration in the family members [272] (Figure 1). According to these criteria, the index patient is categorised into “definite FH” or “possible FH” depending on certain predefined parameters:

- **Diagnose definite FH** if the following are met:
  - Total cholesterol > 250 mg/dL or LDL-C > 150 mg/dL in a child less than 16 years or total cholesterol > 300 mg/dL and LDL-C > 190 mg/dL in an adult with tendon xanthomas or evidence of these signs in a first- or second-degree relative
  - DNA-based evidence of an LDLR mutation, familial defective Apo B-100 or a PCSK9 mutation.

- **Diagnose possible FH** if the following are present:
  - Cholesterol concentrations defined as above
  - AND at least one of the following:
    - Family history of MI in a first-degree relative younger than 60 years or a second-degree relative younger than 50 years, or
    - Family history of raised total cholesterol – >300 mg/dL in an adult first- or second-degree relative or >260 mg/dL in a child, brother or sister aged younger than 16 years.

The Dutch criteria use a point system for LDL-C concentration, presence of xanthoma and presence of CVD and a total score of over 8 is considered as definite FH and 6–8 as probable FH [273]. The US Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria uses age- and relative-specific LDL-C concentration for diagnosing FH [274].

The LAI expert consensus recommends universal screening of all individuals prior to the age of 20 years or at the time of college entry [1] or earlier if there is a family history of HeFH/HoFH or premature CAD. If all efforts are directed to implement this concept of screening, it may be possible to detect more cases of FH patients in India. This requires coordinated efforts from both government agencies and health care providers.

LAI recommends the Simon Broome criteria for diagnosis of FH because of ease of remembering the criteria in
LAI recommends training health professionals in basic genetics as well as training in construction of the family tree. An online guidance will be available for that on the LAI website (www.lipid.net.in). Cascade testing requires time and in India, where most of the medical care is provided through a fee-paying structure, unless the government issues policies to assist case-finding, health professionals are likely to face barriers on financial grounds alone from individuals and family. Health professionals may also face difficulties in testing the young because their parents may not give consent to confirm a diagnosis for fear of not being able to marry their children due to the perceived stigma of a genetic diagnosis. LAI will work towards establishing awareness programmes within communities and provide access to information on the importance of testing family members. LAI would recommend testing children at age 2 if there is a family history of FH. Due to pubertal changes in cholesterol levels, the recommendation from different expert panels is to test children before age of 10 or after puberty [277, 278].

11.2.2. Molecular diagnosis
A diagnosis of FH can be confirmed by genetic testing. LAI recommends that molecular testing should be available to confirm the diagnosis of FH. However, it should be understood by health care providers that failure to detect a mutation does not exclude a diagnosis of FH and intervention with lipid-lowering therapy is required if the diagnosis

Figure 1. Peripheral stigmata included in familial hypercholesterolemia.
Food items such as burgers, pastries, pizzas and patties should be strictly avoided to reduce fat consumption. The meals should be based around high fibre-containing carbohydrates and proteins and should include plenty of fruits and vegetables.

A concern in paediatric patients consuming a low-fat and low-cholesterol diet is regarding the compromised growth, nutrition and psychosocial issues. Retarded growth rates were demonstrated in an eight-year study of growth patterns in 13 children with hypercholesterolaemia receiving <30% of total calories from fat. However, most of the recent studies suggest that a moderate dietary fat restriction does not affect growth [281–283]. Overall, paediatric subjects may need to be closely monitored for potential nutritional deficiencies because of a more limited food selection. Adolescents and adults with FH are encouraged to be physically active, avoid smoking and alcohol intake and strive to achieve the ideal body weight for their age.

There is no need to risk stratify this population as statin therapy is mandatory [271, 272, 284]. The cumulative exposure to elevated LDL-C levels from birth results in a high vascular risk. Statins at high doses is the mainstay of therapy with or without ezetimibe [271, 285]. If intolerant to maximal doses of statin, low dose statin with bile acid resins is an option in other countries. The LAI expert consensus recommends pharmacological intervention with high doses of atorvastatin or rosuvastatin for adults with a diagnosis of HoFH [1].

In children with FH with LDL-C of >160 mg/dL, treatment with statin should be started at the age of 8 years. Pravastatin or atorvastatin may be used with or without ezetimibe in children with a modest additional reduction of 15–20% [286–288]. There are controversies about earlier intervention with statins in children. The safety of statins in children as young as 8 years has been established [289,
If a woman with FH has significant CAD, she should be advised against pregnancy as appropriate in view of the risk of CV complications. Young women who need contraception should be advised regarding lipid-friendly contraceptives.

11.4. LAI recommendations

- Lipid profile estimation of children to be done at 2 years of age in those with family history of FH and premature ASCVD.
- Universal screening of lipids to be carried out at age 20 years or at the time of college admission.
- LAI recommends the Simon Broome criteria for the diagnosis of FH.
- In an established case of FH, LAI recommends estimation of Lp(a) levels.
- Genetic testing and cascade screening should be performed wherever feasible.
- Look for other ASCVD risk factors and manage them appropriately.
- Strict dietary recommendations and lifestyle modifications as advised.
- Drug therapy to be started at age 8 years or earlier in individualised cases.
- LDL-C targets to be achieved: <70 mg/dL for HoFH and <100 mg/dL for HeFH in children and in adults <50 mg/dL in HoFH and 70 mg/dL in HeFH or at least 50% reduction in LDL-C from the baseline.

12. Inherited hypertriglyceridaemia

Hypertriglyceridaemia is defined as elevated fasting TG concentrations above the 95th percentile for age and gender in a given population [304]. In all cases of raised TG levels, secondary causes such as obesity, diabetes, renal and liver diseases, as well as concomitant medication that may raise TG must be ruled out [305–308]. If the raised TG levels cannot be explained by a secondary cause, a diagnosis of primary hypertriglyceridaemia should be considered [309]. Less than 5% of all hypertriglyceridaemia are primary and <1% are due to a monogenic cause [310]. Loss of function mutations in apolipoprotein C3 (Apo C3) results in low levels of TG. A recent genetic study involving >75000 participants showed that heterozygosity for loss-of-function mutations in Apo C3 was associated with 44% lower levels of non-fasting TG levels with 41% reduction in the risk for CVD and 36% reduction in the risk for CAD [311]. Apart from increased ASCVD risk with raised TG, TG levels > 1000 mg/dL are associated with an increased risk for acute pancreatitis [312].
Dietary TG is absorbed and assembled as chylomicrons in the gut, which enter the circulation. These particles undergo a lipolytic process, whereby the free fatty acid and TG are removed through lipoprotein lipase (LPL) enzyme activity. After the initial phase of lipolysis, the chylomicron remnant that remains in the circulation is cleared by a receptor-mediated mechanism with the help of Apo E, which acts as a ligand [313].

The majority of inherited lipoprotein disorders that fall under the Fredrickson classification are characterised by elevated TG concentrations except for FH (type IIa hyperlipidaemia) [314].

12.1. Classification of inherited forms of lipoprotein disorders

Inherited conditions with raised TG concentration include [314]:

- Chylomicronaemia syndrome or type 1 hyperlipidaemia
- Familial combined hyperlipidaemia or type 2b hyperlipidaemia
- Dysbetalipoproteinaemia or type 3 hyperlipidaemia
- Familial hypertriglyceridaemia or type 4 hyperlipidaemia
- Type 5 hyperlipidaemia

These conditions are described in greater detail below. All these conditions exacerbate the degree of hypertriglyceridaemia of pregnancy, especially the type 1 and type 5, with the added risk of complications resulting in maternal and fetal mortality due to acute pancreatitis [315].

12.2. Diagnosis of hypertriglyceridaemia

Hypertriglyceridaemia results from increased production or reduced clearance of TG-rich particles in the circulation. It can either be a result of excessive circulating free fatty acids reaching the liver and increasing the synthesis or de novo synthesis of VLDL in the liver [313, 316]. Insulin resistance contributes to both increased free fatty acid concentration and lipogenesis in the liver through the increased production of VLDL [313, 316]. The relationship between VLDL production and insulin resistance can vary across different ethnicities and gender [317].

LAI recommends assessing TG concentrations in a fasting state [1]. A non-fasting lipid profile may be performed as an initial step in all individuals above 20 years of age or at the time of college admission. If the TG level is high in an non-fasting sample, then fasting TG estimation is needed, with a repeat measurement performed every 5 years [189, 318]. Thresholds for diagnosis of hypertriglyceridaemia are the same as those mentioned in the LAI part 1 expert consensus statement, National Cholesterol Education Program or Endocrine Society Clinical Practice Guideline for the management of hypertriglyceridaemia [189, 318] (Table 4).

12.2.1. Physical examination in a patient with severe hypertriglyceridaemia

All patients with elevated TG levels should undergo a full clinical examination and assessment to evaluate their CV risk, and those with very high TG levels should also be assessed for acute pancreatitis. Careful search for any underlying secondary cause of hypertriglyceridaemia should be made (Table 5). Signs indicating a secondary cause, such as pedal oedema as part of nephrotic syndrome, should not be missed. Physical assessment should include evaluation of any lipid stigmata. Any individual presenting with lipid stigmata as described below should have a full fasting lipid profile, and if necessary, further biochemical investigations should be carried out to evaluate the possibility of an inherited form of hypertriglyceridaemia.

<table>
<thead>
<tr>
<th>Category</th>
<th>Fasting serum triglyceride concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150 mg/dL (&lt;1.7 mmol/L)</td>
</tr>
<tr>
<td>Borderline-high or mildly raised</td>
<td>150–199 mg/dL (1.7–2.3 mmol/L)</td>
</tr>
<tr>
<td>High or moderately raised</td>
<td>200–499 mg/dL (2.3–5.6 mmol/L)</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;500 mg/dL (5.6 mmol/L)</td>
</tr>
</tbody>
</table>

Table 4. Classification of fasting serum triglyceride concentration (National Cholesterol Education Programme Adult Treatment Panel III classification) [189].

Physiological conditions/diseases

- Pregnancy: physiological triglyceride concentrations double during the third trimester
- Obesity
- Metabolic syndrome
- Alcohol consumption
- Diabetes mellitus, particularly type 2
- Renal disease, especially nephrotic syndrome/chronic renal failure
- Hypothyroidism
- Paraproteinaemia
- Liver disease
- Certain glycogen storage diseases

Medications

- Corticosteroids
- Oestrogens, especially those taken orally
- Tamoxifen
- Anti-hypertensives e.g. non-cardioselective β-blockers, thiazides.
- Isotretinoin
- Bile-acid-binding resins
- Cyclophosphamide
- Antiretroviral regimens
- Psychotropic medications
- Anabolic steroids

Table 5. Secondary causes for hypertriglyceridaemia.
12.2.1. Lipid stigmata in hypertriglyceridaemia (Figure 3) [316]

- Eruptive xanthomata: These erupt as small yellow papules found most commonly on the buttocks, shoulders, back, arms and legs. They do not appear on the face. They can be painful, tender and are often itchy. These lesions resolve when TG concentrations fall, as a result of treatment or aggressive lifestyle changes. They are often seen in type 1 hyperlipidaemia. Type 4 and 5 hyperlipidaemias may also present eruptive xanthomata. Infants and children with type 1 hyperlipidaemia or chylomicronaemia syndrome can manifest these lesions.

- Palmar xanthoma: Found on palmar creases; they are pathognomonic of type 3 hyperlipidaemia.

- Tubo-eruptive xanthomata: Appear as clusters of small papules on elbows, knees and buttocks. They can grow to the size of grapes. They are pathognomonic of type 3 hyperlipidaemia.

- Xanthelasma: Distributed as soft, velvety, yellow and flat topped papules and plaques in the upper and lower eyelids. These can also occur in people with normal lipids. Often these lesions are seen in those with hypothyroidism or liver disease, with or without increased lipid levels.

- Lipoaemiaretinalis: This is a milky appearance of the retinal vein when viewed through a fundoscope and is commonly seen in patients with severe hypertriglyceridaemia and can be associated with visual problems.

12.2.2. General investigations

12.2.2.1. Following investigations are required to exclude secondary causes [319]

- Urine dipstick test to rule out proteinuria, thereby excluding nephrotic syndrome and some other forms of renal disease.

12.2.3. Special Investigations

The various investigations to rule out different types of primary hyperlipidaemias are discussed below.

12.2.3.1. Type 1 hyperlipidaemia or chylomicronaemia syndrome. This is an autosomal recessive condition characterised by excessive circulating chylomicrons due to defective or absent LPL activity [320, 321]. Usually it is seen in children or in the adolescent age group. The patients present with recurrent acute pancreatitis and very high TG levels (values reaching to about >1000 mg/dL), mostly contributed by chylomicrons. They develop extensive eruptive xanthomata and carry a high risk for recurrent acute pancreatitis. They may also present with hepatosplenomegaly that resolves with reduction in TG levels [320–322]. As the patient ages, the phenotype changes and subjects may present as type V hyperlipidaemia.

The prevalence is one in a million, but higher prevalence is possible in communities in India where history of consanguinity is not uncommon.

Genetic testing is available for the diagnosis of the condition. Additional proteins involved in lipolysis are Apo CII, Apo A5, Lipase Maturation factor 1 (LMF1) and glycosylphosphatidyl inositol anchoring high-density lipoprotein binding protein 1 (GPIHBP1). Mutations involving these proteins can also cause type 1 hyperlipidaemia [323].

Figure 3. Lipid stigmata in hypertriglyceridaemia.
12.2.3.3. **Type 3 hyperlipidaemia or dysbetalipoproteinemia.** This condition is more common than that the above-mentioned lipoprotein disorders. The defect is in the Apo E, a ligand that facilitates removal of chylomicron remnant particles to the liver through a receptor-mediated mechanism [316]. It is an autosomal recessive condition, often the phenotypic expression requiring the presence of a second hit mechanism such as obesity, hypothyroidism, diabetes and excessive alcohol consumption in addition to the genotype [328]. A rare autosomal dominant form also exists [329]. Raised chylomicron remnants' level in this condition is associated with an increased risk for all forms of ASCVD, including MI, stroke, peripheral arterial disease as well as renal artery disease [330]. Palmar xanthomas are pathognomonic of this condition. Soft tissue xanthomata may also be seen. Cholesterol and TG increases are more often in the equimolar range. The gene for Apo E exists in three isoforms – 2, 3 and 4. Each individual inherits two genes in any combination, one from each of the parents. Apo 3, 3 is considered as normal with all others being the mutant form with the 2, 2 isoform causing the dysbetalipoproteinemia syndrome [316].

12.2.3.1.1. **Investigations.** The simplest test involves placing the tube in which the blood sample was centrifuged in a refrigerator to demonstrate the creamy layer with a clear serum layer separating it from the red cells. High TG levels interfere with measurement of LDL-C and other analytes like sodium concentration depending on the method used [324].

- A full lipid profile: often calculated LDL-C is not available as the TG level is high and the Friedewald formula for calculating LDL-C is inaccurate.
- Lipoprotein Lipase: Mass or activity measurement of LPL is rarely available in routine laboratories. This measurement requires administration of 60 to 100 IU of heparin/kg to mobilise the LPL bound to the endothelium. These assays are only available in specialist centres [325].
- Genetic testing.

The United Kingdom Genetic Testing Network recommends that patients with type 1 hyperlipidaemia be tested to confirm the molecular defect, if they satisfy the following criteria (https://ukgtn.nhs.uk/)

- TG > 2000 mg/dL (>20 mmol/L)
- History of acute pancreatitis
- Secondary causes excluded
- Known family mutation

Genetic testing is available in many international centres for diagnosis of this condition. LPL gene sequencing is essential for confirming a diagnosis; however, as mentioned above, genetic defects in other proteins involved in the lipolysis such as Apo C2 and A5, LMF1 and GPIHBP1 can also cause type 1 hyperlipidaemia. Therefore, current recommendation is for full gene sequencing of LPL and the genes for other four co-factors involved in lipolysis [323].

Genetic testing is not widely available in India, and should be set up (perhaps in a reference centre) to provide a diagnostic service for these patients.

12.2.3.3. **Type 3 hyperlipidaemia or dysbetalipoproteinemia.** This condition is more common than that the above-mentioned lipoprotein disorders. The defect is in the Apo E, a ligand that facilitates removal of chylomicron remnant particles to the liver through a receptor-mediated mechanism [316]. It is an autosomal recessive condition, often the phenotypic expression requiring the presence of a second hit mechanism such as obesity, hypothyroidism, diabetes and excessive alcohol consumption in addition to the genotype [328]. A rare autosomal dominant form also exists [329]. Raised chylomicron remnants’ level in this condition is associated with an increased risk for all forms of ASCVD, including MI, stroke, peripheral arterial disease as well as renal artery disease [330]. Palmar xanthomas are pathognomonic of this condition. Soft tissue xanthomata may also be seen. Cholesterol and TG increases are more often in the equimolar range. The gene for Apo E exists in three isoforms – 2, 3 and 4. Each individual inherits two genes in any combination, one from each of the parents. Apo 3, 3 is considered as normal with all others being the mutant form with the 2, 2 isoform causing the dysbetalipoproteinemia syndrome [316].

12.2.3.4. **Type 4 hyperlipidaemia.** This disorder, often called familial hypertriglyceridaemia, is associated with mutations in the Apo A5 or lipase 1 gene and is of polygenic origin [328]. The patients often present with low HDL-C, obesity or diabetes. Association with elevated ASCVD risk has been established [333]. This has a pseudo-
autosomal dominant inheritance. No genetic testing is available. With additional metabolic risk factors such as obesity and diabetes, these subjects can deteriorate to type 5, but the TG concentration rarely rises to levels that increase the risk for acute pancreatitis.

12.2.3.4.1. Investigations. Investigations are limited, except for a full lipid profile. The VLDL fraction is increased along with raised TG and a low HDL-C. The concentration of TG usually ranges from 300 to 900 mg/dL. Total cholesterol and non-HDL-C are high due to the increased VLDL component that also explains the association with increased risk for vascular disease [333].

12.2.3.5. Type 5 hyperlipidaemia. This condition is caracterised by raised VLDL fraction and chylomicrons. There is increased risk for acute pancreatitis due to high concentration of chylomicrons [313].

12.3. Management
Patient with hypertriglyceridaemia should be referred to a specialist centre in the following situations:

- Primary hypertriglyceridaemia
- Treatment failure in primary care (a minority of patients with very high levels of TG may require multiple drugs)
- Pregnancy: high TG during treatment prior to pregnancy and hypertriglyceridaemia identified during pregnancy
- Pharmacological intervention leading to increase in:
  - TG levels, e.g. anti-retroviral therapy (ART), where important interactions between anti-retroviral drugs and lipid-lowering drugs are possible.
  - Raised CK, induced by drugs such as lipid-lowering drugs in any muscle disease, as these patients may require combination therapy with statin and fibrate which further increases the potential for muscle side effects.
  - Liver function test abnormalities – increase in transaminase activity (>3 times ULN).

12.3.1. Non-pharmacological therapy of hypertriglyceridaemia
The following are non-pharmacological treatment options for management of hypertriglyceridaemia [189, 318]:

- Weight loss for patients who are obese (diet and exercise)
- Strict glycaemic control if diabetes is present
- Treatment of hypothyroidism
- Avoidance of excessive alcohol consumption

- Avoidance of TG raising medications
- Low fat diet – <30% of calories as fat, and in severe hypertriglyceridaemia reduce to <15%
- Refrain from simple sugars and high carbohydrate diet
- A diet moderate in total fats, low in saturated fats, low in simple sugars, with high fibre content and high omega-3 fatty acids is beneficial in hypertriglyceridaemia. A dietary pattern that emphasises intake of vegetables, fruits and whole grains, low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts with limited intake of sweets, sugar-sweetened beverages and red meat should be encouraged [334, 335].

- Including fresh vegetables, complex carbohydrates, fatty fish for non-vegetarians and fenugreek seeds, mustard seeds, flax seeds, soybean oil, mustard oil, etc. for vegetarians (as sources of omega-3 fatty acids) and nuts in the diet can be a step towards a good dietary pattern in these patients [334, 335].

- In patients with type 1 hyperchylomicronaemia syndrome, a very low fat diet < 15 g/day and caloric supplementation with oils rich in medium chain TG should be used, as they bypass intestinal absorption and directly enter portal circulation [1].

The harmful effects of partially hydrogenated vegetable oil containing high proportion of trans-fats are well-known. There is an increased consumption of such oils by the Indian population. Although, there is a legal requirement for the manufacturers to reduce the amount of trans-fat content, it is not strictly followed [336]. Many commonly used bakery products and Indian snacks that are commercially fried are rich in trans-fat [335, 336]. Patients should be advised to specifically avoid these products. Use of saturated fat such as coconut oil and palm oil should also be discouraged [337].

12.3.2. Pharmacotherapy
The basic principles of pharmacotherapy are described below [338]:

- In subjects with TG concentrations between 150 and 199 mg/dL, non-pharmacological therapy (as described above) may be sufficient. ASCVD risk assessment is essential and statin use indicated if ASCVD risk is high.
- TG concentrations between 199 and 500 mg/dL with a high non-HDL-C concentration will require lifestyle changes along with pharmacotherapy. LDL-C reduction should be the primary aim. Statin is the drug of choice; appropriate doses of atorvastatin or rosuvastatin should be used. The effect of statins on
TG levels depend on the LDL-C-lowering effect and initial TG level.

- When TG concentrations is > 500 mg/dL, start with a fibric acid derivative such as fenofibrate and add a statin if non-HDL-C is high as defined in the LAI consensus Part 1 statement [1].
- Additional TG reduction can be obtained by adding an omega-3 acid ester concentrate.
- Nicotinic acid use is debatable.

Controlling TG levels in patients with type 1 hyperlipidaemia can be challenging. New therapies are being investigated in type 1 hyperlipidaemia, including lomitapide, which is a microsomal TG transfer protein inhibitor, and also gene therapy [338–340].

Fibric acid derivatives [338, 341] are the drug of choice in type 3 hyperlipidaemia. When combination therapy with a statin and a fibric acid derivative is prescribed, the risk for muscle-related side effects such as myalgia, myositis and rhabdomyolysis is increased. Thus, appropriate monitoring with CK and renal function tests should be performed after the initial 8 weeks, and if necessary, with every dose escalation [338, 341, 342].

Treatment of severely high TG is more challenging than severe hypercholesterolaemia. Differentiating subjects who might develop ASCVD and/or acute pancreatitis is difficult. Very strict dietary practice may be essential in managing subjects with very high TG. Secondary factors can exacerbate a primary hyperlipidaemia. It is essential that physicians managing these patients are advised to obtain or seek specialist knowledge and skill essential for managing patients with high TG [189, 318].

In patients of acute pancreatitis and severe hypertriglyceridaemia (TG > 1000 mg/dL), plasma apheresis is a treatment option [343].

12.4. LAI recommendations

- All subjects should be screened for hypertriglyceridaemia with a fasting lipid profile. A non-fasting lipid profile may be performed as an initial step, but fasting TG estimation will be needed if TG is found to be high in the non-fasting sample
- Exclude and treat secondary causes
- Aggressive therapeutic lifestyle changes should be implemented
- Subjects with TG > 200 mg/dL and <500 mg/dL – treat with a statin
- Subjects with TG ≥ 500 mg/dL – treat with fibrates to prevent acute pancreatitis and later add statin to achieve non-HDL-C goal
- Preferred drugs: Fibrates and high dose omega fatty acids; the role of niacin is controversial.

13. Dyslipidaemia in heart transplantation

13.1. General considerations

Dyslipidaemia is common in patients after heart transplantation, with a prevalence of 60–80% [344]. Dyslipidaemia can occur as a pre-existing condition or can be a side effect of immunosuppressive therapy, leading to an increased risk for CV morbidity and mortality. Typically, dyslipidaemia worsens in post-transplantation period as immunosuppressive therapy with cyclosporine, sirolimus and corticosteroids and to a lesser extent tacrolimus and everolimus adversely affects the lipid levels [345–348]. Immunosuppression also increases the incidence of hypertension, diabetes and can cause nephrotoxicity thus increasing the overall CV risk (Table 6). A significant association has been shown between increased total cholesterol and CV events after heart transplantation and dyslipidaemia represents one of the major modifiable risk factors [349]. Interestingly, for the same level of dyslipidaemia, there is a significant increase in intimal thickness, greater angiogenesis and higher accumulation of T-lymphocytes within the allograft vasculature compared with native vessels. This suggests an additional role of immune mechanisms in the pathogenesis of allograft vasculopathy beyond that of high cholesterol [350].

Cardiac allograft vasculopathy (CAV) is an accelerated form of obliterative CAD that occurs in heart transplant recipients. It is one of the leading causes of mortality

<table>
<thead>
<tr>
<th>Effects of drugs</th>
<th>Sirolimus</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Mycophenolate mofetil</th>
<th>Azathioprine</th>
<th>Prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunosuppressive potency</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td><strong>New diabetes</strong></td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<tr>
<td><strong>Nephrotoxicity</strong></td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<td>–</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
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<td>+</td>
<td>–</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
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<td>–</td>
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<td>+</td>
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<td>–</td>
</tr>
<tr>
<td><strong>Leucopenia</strong></td>
<td>+</td>
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</table>
Among long-term cardiac transplant recipients, CAV affects approximately 8, 30 and 50% of patients who survive 1, 5 and 10 years post-transplant [352]. Histologically, CAV is characterised by concentric intimal thickening, smooth muscle cell proliferation, inflammatory cell infiltration, along with lipid deposition resulting in diffuse narrowing along entire length of the vessel [353]. Although the pathogenesis of CAV involves both immunological and non-immunological mechanisms, dyslipidaemia is an important factor in the development of CAV [354].

As CAV involves both epicardial and intramural arteries, procedures to reopen epicardial coronary arteries like angioplasty and bypass graft surgery have only limited efficacy. CAV is irreversible and is associated with poor prognosis, therefore the key is prevention. Even though various pre-transplant and post-transplant strategies can be used to prevent the development of CAV, dyslipidaemia management remains one of the most important and essential approaches in heart transplant recipients [355, 356].

### 13.2. Role of immunosuppressive drugs

Calcineurin inhibitor-based therapy (cyclosporine and tacrolimus) remains the mainstay in immunosuppressive protocols used after heart transplantation because of its proven efficacy. Maintenance therapy should include a calcineurin inhibitor in all paediatric heart transplant recipients as per International Society for Heart and Lung Transplantation guidelines [357]. Mycophenolate mofetil, everolimus or sirolimus as tolerated should be included in contemporary immunosuppressive regimens as these drugs reduce onset and progression of CAV [357].

Cyclosporine inhibits the enzyme 26-hydroxylase and also inhibits binding of LDL to LDLR resulting in an increase in circulating LDL-C of up to 31% (Table 7). Lovastatin, simvastatin and atorvastatin are mainly metabolised by the CYP3A4 pathway. Fluvastatin metabolism predominantly occurs via the CYP2C9 enzyme with minimal need for CYP3A4 activity. Since cyclosporine inhibits CYP3A4 activity, markedly increased levels of statins metabolised by CYP3A4 may occur with concomitant administration of cyclosporine [54, 358]. Thus, cyclosporine not only increases LDL-C levels but it also inhibits the metabolism of statins. The higher statin levels increase the risk of myopathy and rhabdomyolysis. Rhabdomyolysis has been reported with all statins except pravastatin and fluvastatin. Cyclosporine increases plasma concentrations of statins by manifold; atorvastatin: 6-fold, pravastatin: 5-fold, simvastatin: 3-fold and lovastatin: 20-fold [54].

Despite both cyclosporine and tacrolimus inhibiting CYP3A4, only the cyclosporine–statin interaction may be clinically relevant. Although data are limited on tacrolimus, its interaction with statin may not raise plasma levels of statins to the same degree as cyclosporine [359, 360].

The mTOR (mammalian target of rapamycin) inhibitors sirolimus and everolimus are potent immunosuppressive agents, allowing the dose of nephrotoxic calcineurin inhibitors cyclosporine and tacrolimus to be decreased in solid organ transplant recipients. Dyslipidaemia is very common with mTOR inhibitors, with an estimated prevalence of up to 75% [345]. The mTOR inhibitors reduce the catabolism of circulating lipoproteins by inhibiting the activity of lipases, resulting in dyslipidaemia. Of the mTOR inhibitors, everolimus has less deleterious effects on lipids than sirolimus [346]. Everolimus and sirolimus with cyclosporine increase serum cholesterol by about 16% and 20–46%, respectively, and serum TG by 4% and 21–57%, respectively, in heart transplant recipients. The incidence of new onset diabetes (NOD) is 5–32% and 20–27% with everolimus and sirolimus, respectively, adding to the CV risk [347]. Corticosteroids induce peripheral insulin resistance and an ensuing inability to activate lipid storage, which stimulates a reflex increase in total cholesterol [348, 361]. The diabetogenic potential of these drugs needs to be considered in the presence of statins which can also cause NOD [362].

### 13.3. Statins in heart transplant recipients

The beneficial effects of statins after heart transplantation correspond to cholesterol control, anti-inflammatory and immunomodulatory effects. Statins inhibit the production of proinflammatory cytokines and reduce the expression of several immunoregulatory molecules, including major histocompatibility complex class II (MHC-II) molecules. Statins effectively suppress the induction of MHC-II expression by interferon-gamma and inhibit MHC class II-dependent activation of T-lymphocytes [363, 364]. Statins cause a significant reduction in incidence of severe acute rejection and CAV and increase long-term survival [365, 366]. Unfortunately, statins, which rarely cause myopathy in non-transplant general population, may do so in transplant patients. In fact, in early experience, 40–80 mg lovastatin in heart transplant patients resulted in 4 out of 5 developing rhabdomyolysis [367]. Low doses

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**Table 7. Lipid abnormalities with immunosuppressive drugs [345–348].**

<table>
<thead>
<tr>
<th>Immunosuppressive drug</th>
<th>Lipid abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td>TG ↑↑, LDL-C ↑</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Total cholesterol ↑, LDL-C ↑</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Total cholesterol ↑</td>
</tr>
<tr>
<td>Sirolimus and everolimus</td>
<td>TG ↑↑, total cholesterol ↑</td>
</tr>
<tr>
<td>Mycophenolate mofetil, azathioprine</td>
<td>Lipid neutral</td>
</tr>
</tbody>
</table>

Note: LDL-C: low-density lipoprotein cholesterol, TG: triglycerides.
of statins are however relatively well tolerated [367] but it is at the cost of decreased cholesterol-lowering efficacy.

In a landmark study, which paved the way for routine statin therapy in post-transplant patients, 97 heart transplants were randomly assigned to pravastatin 40 mg/day (47 patients) or no pravastatin (50 patients) in addition to their immunosuppressive treatment with cyclosporine, prednisolone and azathioprine [365]. The pravastatin group had lower mean cholesterol levels than the control group (193 ± 36 vs. 248 ± 49 mg/dL, p < 0.001), decreased incidence of coronary vasculopathy (3 vs. 10 patients, p = 0.049) and improved survival (94 vs. 78%, p = 0.025) at 12 months follow-up. Pravastatin did not change the overall incidence of cardiac rejection, but it decreased the rate of rejection accompanied by haemodynamic compromise, resulting in better survival. During long-term follow-up, 81% of the control patients were eventually placed on statin therapy. In the intention-to-treat analysis, pravastatin group had increased 10-year survival (68 vs. 48%, p = 0.026). The 10-year freedom from angiographic CAV and/or death in pravastatin group was significantly greater compared with the control group (43 vs. 20%, p = 0.009) [366].

Similar salutary benefits of statins have also been demonstrated with simvastatin [368] and rosuvastatin [369]. Seventy-two heart transplant recipients receiving standard triple immuno suppression (cyclosporin, azathioprine and prednisolone) were randomly assigned to simvastatin (n = 35) or a control group (n = 37). Over 4 years follow-up, the simvastatin group had significantly lower LDL-C than the control group (115 ± 14 vs. 156 ± 17 mg/dL, p = 0.002), a significantly better long-term survival (88.6 vs. 70.3%, p = 0.05) and a lower incidence of CAV (16.6 vs. 42.3%, p = 0.045). Intracoronary ultrasound performed after 4 years in a subgroup of 27 patients showed less intimal thickening in patients with LDL-C levels of < 110 mg/dL [368].

The long-term safety of rosuvastatin 10 mg was evaluated in 30 heart transplant patients who failed to achieve cholesterol goals (LDL-C > 100 mg/dL) despite statin therapy. All patients received oral prednisone and a combination of ≥2 of the following three drug groups: (i) cyclosporine or tacrolimus, (ii) everolimus or sirolimus and (iii) mycophenolate formulation. At baseline, median total cholesterol was 236 mg/dL (range: 214–264) and median LDL-C was 142 mg/dL (range: 125–162). The average absolute reduction of total cholesterol was −48.7 mg/dL and LDL-C was −46.6 mg/dL, with 57% patients achieving a serum LDL-C < 100 mg/dL. Nearly 90% patients continued on long-term therapy with rosuvastatin over a median of 3.6 years. Rosuvastatin was discontinued in only two (6.7%) patients due to muscle toxicity and in one (3.3%) patient due to liver toxicity [369].

Two head-to-head comparisons between pravastatin and equipotent dosages of simvastatin in heart transplant recipients did not find any statistically significant differences in rejection or survival outcomes [370, 371]. Despite known drug interactions with calcineurin inhibitors, the use of statins is highly recommended in current guidelines [357]. Hydrophilic statins (e.g. pravastatin, rosuvastatin) undergo limited metabolism by the cytochrome P3A4 isoenzyme system and are less likely to cause toxicity seen with lipophilic statins (e.g. simvastatin, atorvastatin, lovastatin). The recommended daily doses of statins are: pravastatin (20–40 mg), simvastatin (5–20 mg), atorvastatin (10–20 mg), lovastatin 20 mg and rosvastatin (5–20 mg) [54, 357].

The 2013 ACC/AHA guidelines on cholesterol management recommend high intensity statin therapy in patients with established ASCVD, thus lowering LDL-C by approximately ≥50% [107]. The role of such an approach in solid organ transplantation is unclear.

### 13.4. LAI recommendations

- Baseline lipid levels should be obtained for all patients after heart transplantation.
- The strict control of modifiable risk factors including hypertension, diabetes, dyslipidaemia, smoking and obesity should be reinforced.
- In adults, the use of statins beginning 1 to 2 weeks after heart transplantation is recommended regardless of cholesterol levels [357].
- Pravastatin shows the least interaction with cyclosporine to produce myopathy, making it the drug of choice. Rosuvastatin up to 10 mg/day may be given as a second choice. Addition of a statin to a cyclosporine–sirolimus regimen produces multiple beneficial effects like reduced cholesterol levels, decreased acute rejection episodes, decreased incidence of CAV and improved survival.
- In heart transplant recipients, a strategy of lowest achievable LDL-C levels with maximally tolerated dose of statin by slowly up-titrating the statin dose is justified.
- Owing to pharmacologic interactions with cyclosporine and risk for toxicity, initial statin doses should be lower. In paediatric patients with evidence of hyperlipidaemia, CAV or after re-transplantation and increased risk of rejection use of statins is recommended [357]. All patients should be actively monitored for development of myopathy with regular monitoring of CK.
- In the absence of RCTs and very limited data, use of non-statin lipid-lowering drugs is not recommended.
Dyslipidaemia in other solid organ transplantation

Dyslipidaemia is common after solid organ transplantation with a prevalence of 30–70%. CVD is the most important cause of death in solid organ transplant recipients who have a functioning graft [375]. The incidence of CVD in renal transplant recipients is 3–5 times higher and in chronic haemodialysis patients 10–20 times higher than that of general population [376]. Although several factors (e.g. hypertension and left ventricular hypertrophy) contribute to CVD morbidity and mortality, dyslipidaemia plays an important role. The factors contributing to dyslipidaemia include abnormal renal function and impaired glucose metabolism, in addition to those mentioned above for heart transplantation [377].

In the ALERT study, 2102 cyclosporine-treated stable renal transplant recipients were randomised to fluvastatin 40–80 mg daily or placebo. Although on initial analysis the primary composite cardiac endpoint was not significantly reduced, the extended follow-up for up to 8 years was associated with a 35% reduction in the composite endpoint of cardiac death or non-fatal MI [38, 49]. Total mortality and graft loss did not differ between the two groups. Importantly, early introduction of statin therapy was associated with increased survival benefit [38, 49]. Interestingly, the CV events in renal transplant recipients may be not only because of conventional CVD risk factors but also due to a high prevalence of renal dysfunction, hypertension and left ventricular hypertrophy. The management of dyslipidaemia in solid transplant recipients has three major components – lifestyle modification, lipid-lowering drugs and fine tuning the immunosuppressive regimen. The KDIGO 2013 lipid management guidelines [378] recommend statins in all adult renal transplant recipients above the age 30 years.

The 2012 Practice Guideline of the American Association for the Study of Liver Diseases and the American Society of Transplantation recommends an annual fasting lipid profile for healthy liver transplant recipients and recommend cut-off of LDL-C levels > 100 mg/dL irrespective of presence of hypertriglyceridaemia as the target for initiation of statins [379].

14.1. LAI recommendations

- In the absence of available robust data for heart transplantation, measurement of fasting serum total cholesterol, LDL-C and TG is recommended after a solid organ transplant and at 6 months post-transplant, thereafter annually or if there is a change in immunosuppressive medication.
- Statin therapy should be initiated in all adult renal and in liver transplant recipients if LDL-C levels are >100 mg/dL. For second-line drug use and management of hypertriglyceridaemia, the same recommendations as given for heart transplantation should be followed.

15. Dyslipidaemia in human immunodeficiency virus infection

15.1. Introduction

There is an increased mortality and morbidity associated with human immunodeficiency virus (HIV)-related conditions [380] and ART has changed the course of HIV to a chronic disease. With this change, the treatment-induced risk for comorbidities has increased, in particular CVD. Patients with HIV infection have been shown to have an increased risk for CVD compared with the general population [381, 382]. Furthermore, dyslipidaemia in HIV infection is well recognised and its treatment is associated with abnormalities in lipid metabolism. The hall mark findings are high TGs and low HDL-C [383]. Increased TNF and IL-6 are the predominant cytokines involved in pathogenesis of dyslipidaemia; HIV in addition has an independent effect on cardiovascular risk [384]. ART may also increase the incidence of metabolic risk factors like insulin resistance,
lipoatrophy, dyslipidaemia and abnormalities of fat distribution in HIV patients [385]. It is important to recognise that as patients live longer, they became vulnerable to age-related complications, prominently CVD.

Although there are many different lipoproteins in particles, the cornerstone of lipid therapy has traditionally focused on LDL-C. Years of research have demonstrated that LDL-C is the primary atherogenic particle which is directly associated with the development of CVD and therefore the target of lipid-lowering therapy [304, 385]. There are currently no long-term epidemiologic studies or randomised clinical trials demonstrating the efficacy of lipid medication or benefits of lowering LDL-C on cardiovascular event outcomes in patients with HIV.

Dyslipidaemia is being increasingly recognised in patients on Protease Inhibitor (PI) based regimens [386]. The majority (70–80%) have high TGs and LDL-C and decreased HDL-C and accumulation of ApoE and ApoC III. There is also central obesity, lipoatrophy and insulin resistance [387]. This is due to stimulation of hepatic synthesis of TGs and inhibition of lipogenesis, adipocyte differentiation and decreased hepatocyte clearance of chylomicrons and VLDL [388, 389]. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) also cause high TGs and lipoatrophy although less seen with tenofovir [390]. Abacavir and didanosine (NRTIs) were found to be independent risk factors for MI in the data collection on adverse events of Anti-HIV Drugs (DAD) study. Nevirapine has been shown to increase the HDL-C concentration and efavirenz produces increase in total cholesterol and TGs [391] Dyslipidaemia, insulin resistance and diabetes has been shown with use of ART medication in HIV patients [392].

Unfortunately, there are scant data on the effect of HIV infection on CHD prevalence and outcomes in resource-poor countries like India. Because of the connection of lipid abnormalities with CVD, the understanding of the pathophysiology of the disorders in lipid metabolism and the management of lipid disorders in HIV infected individuals is important.

15.2. Epidemiology

Dyslipidaemia is highly prevalent among patients with HIV infection with and without antiretroviral therapy and can contribute to the increased CVD risk [393, 394]. CVD is an increasing health problem affecting HIV-infected patients [395, 396]. Antiretroviral therapy has remarkably improved the survival of HIV-infected patients [397, 398]; however, the mortality rates in HIV patients are still higher than in the general population also due to non-HIV-related causes including CVD [399, 400]. Patients with HIV have increased traditional cardiovascular risk factors including dyslipidaemia, smoking and glucose abnormalities [396]. Studies have shown that children receiving antiretroviral therapy had higher total cholesterol and TGs, and increased CIMT; thus, cardiovascular risk may be higher among HIV patients even at a young age [393, 401, 402]. In a multicenter cross-sectional study of elderly individuals with HIV, dyslipidaemia was found in 54%, CVD in 23% and lipodystrophy in 58% [403]. Hejazi et al. found that dyslipidaemia is common in HIV subjects receiving antiretroviral medication: it reached 82.3% among 1583 patients in their Malaysian study [404].

15.3. Dyslipidaemia in HIV a challenge to manage

Cardiovascular morbidities are observed in HIV/AIDS especially in older and obese patients. Chu et al. found prevalence rates of 26, 48 and 13% for hypertension, dyslipidaemia and diabetes, respectively. Hence, the treatment of the comorbidities may improve outcome due to the modifiable nature of cardiovascular risk [405]. Increased prevalence of dyslipidaemia is also seen in infected HIV children [396] and they are at increased risk of premature CAD.

Before the availability of highly active antiretroviral therapy, Grunfeld et al. found that patients with AIDS had elevated plasma TG and free fatty acid levels, whereas HIV-infected patients without AIDS had decreased total cholesterol and HDL-C.

In another multicentre study, total cholesterol, HDL-C and LDL-C levels declined following HIV seroconversion [406]. In these patients, total cholesterol and LDL-C levels rose but HDL-C remained decreased after initiation of highly active antiretroviral therapy.

In the Swiss HIV Cohort Study, HIV protease inhibitor (PI) use was found to be associated with an increase in plasma total cholesterol and TGs [407]. Discontinuation of antiretroviral therapy in the The Strategies for Management of Antiretroviral Therapy (SMART) Study resulted in a decline in total cholesterol and LDL-C, but HDL-C declined as well, leading to an unfavourable increase in the total cholesterol/HDL-C ratio [408]. Recently, Duprez et al. [409] showed that cardiovascular risk in HIV patients was associated with lower levels of small and large HDL-particle concentration independently of other cardiovascular risk factors. Patients with HIV-associated fat redistribution are even more likely to have dyslipidaemia, possibly related to excess visceral adipose tissue accumulation [397].

15.4. Pathogenesis of HIV-associated CAD

This is primarily due to interaction of inflammation, endothelial dysfunction and coagulation disorders leading to atherosclerosis. The typical plaque is non-calcified in HIV-infected individuals. However, they may have calcium
oxalate crystal while on ART therapy [406]. cIMT and coronary CT angiography studies show increased prevalence of subclinical atherosclerosis in HIV-positive patients [410–412]. More vulnerable plaques in patients with low CD4 counts have also been observed [382]. C-reactive protein, IL-6, TNF levels are high in HIV-positive patients [413, 414]. Patients with complete virological suppression may still continue to have inflammation and increased immune activation. This predisposes risk of CAD [415]. Similarly endothelial function improvement after suppression of HIV viraemia proves that it is one of the significant factors for atherosclerosis [416]. Coagulopathy reflected as increased D-dimer, fibrinogen, factor VII, etc. was shown to be associated with risk for CVD deaths in the SMART study [410]. Tissue factor activation is also seen. Platelet activation is another observation made in HIV patients [417].

### 15.5. Evaluation and treatment of dyslipidaemia in HIV patients

Guidelines and recommendations for the evaluation and management of dyslipidaemia in HIV-infected adults put forth by the Infectious Disease Society of America (IDSA) and the Adult AIDS Clinical Trials Group (ACTG) in 2003 [418] support the use of the updated recommendations from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III (ATP III)) [419]. Of note, since the IDSA/ACTG Guidelines were written, a more recent update was published for the NCEP ATP III Guidelines in 2004 [420] that should be taken into consideration when relevant. As recommended in the NCEP ATP III and IDSA/ACTG Guidelines [418], lifestyle counselling on diet and exercise should generally be instituted first. Other modifiable cardiovascular risk factors such as smoking, hypertension and diabetes mellitus should also be addressed. When medications become necessary, then identification of the lipid abnormality needs to be made and the choice of therapy should target the specific abnormality. Silverberg et al. [421] found that lipid-lowering therapies are generally well tolerated in HIV-infected patients but hypertriglyceridaemia can be more difficult to treat in HIV-infected patients compared with non-HIV-infected patients.

### 15.6. Risk scores

Traditional scores either underestimate or overestimate cardiovascular risk in HIV patients irrespective of being on ART or not. Hence, there is a need to identify specific cardiovascular risk equations [422]. ART use in the past, including duration of use of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, was not associated with myocardial infarction [423]. A risk calculator including both traditional risk and exposure to individual ART therapy has been developed [424]; the Veterans Aging Cohort study (VACS) is one such score. A model using traditional risks and HIV specific risks like CD4 + Count, abacavir use exposure to Protease Inhibitors (PIs) and NRTI has better prediction. But validation is not yet confirmed [425]. Non-invasive risk stratification using coronary computed tomography angiography (CCTA) and cIMT can help in identifying HIV patients at risk [392, 426, 427]. The ASCVD risk stratification algorithm in Indians (Figure 4) given by LAI can be used in HIV patients to take into account conventional risk factors in addition to ART.

### 15.7. Lipid targets for patients living with HIV

The NCEP ATP III recommends achieving LDL-C targets as a “first priority” unless TG are >500 mg/dL at baseline when the first priority is to lower TG levels to prevent acute pancreatitis. The European AIDS Society has set up a target of <155 mg/dl for total cholesterol and <80 mg/dl for LDL-C [383]. However, the IDSA and others emphasise the need for more stringent targets as in non-HIV patients [384]. However, HIV status is not considered in the NCEPATPIII guidelines [428] Table 8 lists the lipid targets recommended by LAI to be used in HIV patients.

### 15.8. Management of hyperlipidaemia in HIV patients

Most of the patients of HIV with dyslipidaemia require treatment. Lifestyle modifications like weight reduction with caloric restriction should be an important component for management. HMG-Co-A reductase inhibitors, known as statins, are the most widely used and researched medications for the treatment of dyslipidaemia. They are primarily used to lower LDL-C and have a modest effect on raising HDL-C and lowering TGs. In addition, they also lead to improvement in endothelial function, decreased platelet aggregation and reduced inflammation [429]. As statins differ in their pharmacokinetic properties, drug interaction profiles, risk of myopathy, many issues regarding the use in patients infected with HIV are still unclear including metabolism and efficacy, not only for LDL-C lowering but also regarding their effect on CVD events and mortality (Table 9).

In a recently published meta-analysis [430], the authors concluded that in HIV-positive patients on combination antiretroviral therapy (cART), statins prescribed for primary prevention showed a good safety profile and were effective for improving dyslipidaemia. Rosuvastatin 10 mg showed greater reductions of TC, LDL-C and TGs and significantly increased HDL-C; pravastatin 40 mg mildly
decreased TC, LDL-C and triglycerides, but was unable to significantly increase HDL-C. Atorvastatin showed controversial safety results and its prescription should be carefully monitored. Simvastatin, despite proving to be safe and effective, should not be prescribed concomitantly with PIs due to pharmacokinetic interactions. Fluvastatin appeared to be safe and efficacious, though the results were based on a single study. Combination antiretroviral therapy does not appear to affect the safety of dose-adjusted statins.

Table 8. Lipids targets in HIV patients as recommended by LAI.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Treatment goal</th>
<th>Consider drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C (mg/dL)</td>
<td>Non-HDL-C (mg/dL)</td>
</tr>
<tr>
<td>Very high risk</td>
<td>&lt;50</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High risk</td>
<td>&lt;70</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Low risk</td>
<td>&lt;100</td>
<td>&lt;130</td>
</tr>
</tbody>
</table>

<sup>a</sup>After an initial adequate non-pharmacological intervention for at least 3 months.
15.10. Conclusions

Prevention of CVD in HIV patients is an increasing priority. The challenge of more CAD in HIV patients as longevity increases on account of ART is considerable. Our understanding of the complex interaction of traditional risk factors and HIV-specific factors has improved. Diagnosis and treatment of dyslipidaemia remains an integral part of this prevention effort. Current guidelines including the NCEP ATP III [428] as well as the IDSA/ACTG Guidelines [439] for the evaluation and management of lipid disorders in HIV patients can be used to help guide therapy. Lifestyle counselling on diet and exercise should be emphasised in every patient with dyslipidaemia. Special consideration to potential drug–drug interactions needs to be taken when lipid-lowering therapy is initiated in patients with HIV.

15.11. LAI recommendations

- Lifestyle modifications with special emphasis on smoking cessation, weight reduction and calorie restriction are important.
- The recommendations for the evaluation and treatment of dyslipidaemia as suggested by LAI regarding target goals for lipids should be strictly followed to help guide therapy. At least, evidence available in the Indian population suggests the same.
- Different types of statins are available to lower plasma lipids to guideline levels in patients with HIV, but they differ in their pharmacokinetic properties and drug interaction profiles. Simvastatin and lovastatin are contraindicated in patients taking PIs. The other statins atorvastatin and rosuvastatin (apart from simvastatin and lovastatin) have better therapeutic effect in lowering LDL-C in HIV dyslipidaemia. The addition of ezetimibe is another option [432, 433]. Fenofibrate [440] and fish oil [441, 442] can be used in statin-unresponsive HIV dyslipidaemia.
16. Concluding statement
The ASCVD risk stratification should be completed as per the LAI recommendation part 1 and the treatment goals and statin intervention thresholds should consider the additional risk for all special populations. In inherited hyperlipidaemia, the recommended levels of <50 mg/dl should be reached if ASCVD risk is very high and <70 mg/dl if risk is high. Other targets and threshold for familial forms have been discussed in the relevant sections. This comprehensive recommendation developed by the expert committee has tried to base all recommendations on the available data from Indian population, while also critically reviewing and incorporating the available evidence worldwide. In this context, if Indian data were lacking, inferences have been drawn from appropriate international studies and guidelines to formulate these recommendations.

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