Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2016: Part 1


Why this Document?

The burden of atherosclerotic cardiovascular disease (ASCVD) in India is alarmingly high and is a cause of concern. Indians are not only at high risk of developing ASCVD, they usually get the disease at an early age, have a more severe form of the disease and have poorer outcome as compared to the western populations. Access to health care is also not optimal in India, and the treatment of ASCVD remains expensive. For all these reasons, prevention of ASCVD should take priority, not only from the perspective of governmental agencies and health care providers, but of all Indians.

There are many correctable risk factors for ASCVD. Of these, dyslipidemia has the highest population attributable risk for myocardial infarction (MI), both because of its high prevalence and also because of its direct pathogenic association with atherosclerosis. Accordingly, effective management of dyslipidemia remains one of the most important healthcare targets for prevention of ASCVD.

Management of dyslipidemia presents unique challenges in Indians. Not only the prevalence of dyslipidemia is constantly increasing in Indians, particularly at a younger age, the pattern of dyslipidemia is also distinct as compared to the western populations. The distribution and interplay of comitant cardiovascular (CV) risk factors and genetic susceptibility are also different. Furthermore, the population awareness about prevention of ASCVD, cultural beliefs, socioeconomic conditions,

1Chair, Sr. Consultant and Head, Department of Cardiology, Manjul Hospital, Bangalore, Karnataka; 2Chair, Sr. Consultant Cardiology, Indraprastha Apollo Hospitals, New Delhi; 3Chair, Former Adjunct Professor of Medicine, The Tamil Nadu Dr MGR Medical University and Managing Director, SNN Specialities Clinic, Chennai, Tamil Nadu; 4Prof. of Endocrinology, Department of Endocrinology, Indraprastha Apollo Hospitals, New Delhi; 5Chairman and Chief Diabetologist, Department of Diabetology, Madras Diabetes Research Foundation, Chennai, Tamil Nadu; 6Sr. Consultant Cardiology, Fortis Hospital, Shalimar Bagh, New Delhi; 7Director, Department of Diabetes and Metabolic Diseases, Fortis Hospital, New Delhi; 8Sr. Consultant Endocrinology, ACCR, Chennai; 9Sr. Consultant Cardiology, Kokilaben Dhirubhai Ambani Hospital; Director, Centre for Cardiac Sciences, Mumbai, Maharashtra; 10Sr. Consultant, Department of Preventive Cardiology and Internal Medicine, Eternal Heart Care and Research Institute, Jaipur, Rajasthan; 11Sr. Consultant Cardiology, Apollo First Med and Apollo Hospitals, Chennai, Tamil Nadu; 12Sr. Consultant Cardiology, Asian Heart Institute and Research Centre, Mumbai, Maharashtra; 13Former Director and Ex. Officer Secretary to Govt., Shere-Kashmir Institute of Medical Sciences, Srinagar, Jammu Kashmir; 14Chairman, Clinical and Preventive Cardiology, Medanta the Medicity, Gurgaon, Haryana; 15Sr. Consultant Cardiology, Fortis Hospital, Shalimar Bagh, New Delhi; 16Prof. and Head, Department of Cardiology, Vivekanand Institute of Medical Sciences, Kolkata, West Bengal; 17Sr. Consultant Cardiology, Apollo Glenage Hospital, Kolkata, West Bengal; 18Sr. Consultant Endocrinology, PD Hinduja Hospital and Medical Research Centre, Mumbai, Maharashtra; 19Prof of Endocrinology and Metabolism, Shri Ram Chandra University, Chennai, Tamil Nadu; 20Prof and Unit Head, Department of Cardiology, Madras Medical College, Chennai, Tamil Nadu; 21Sr. Consultant Cardiology, Max Care Hospital, Hitech City, Hyderabad, Telangana; 22Sr. Consultant Endocrinologist, Artemis Hospital, Gurgaon, Haryana; 23Prof and Head, Department of Cardiology, King George Medical University, Lucknow, Uttar Pradesh; 24Assistant Prof, Department of Endocrinology, PGIMER, Chandigarh; 25Sr. Consultant Physician and Managing Director, AG Hospital, Thirupur, Tamil Nadu; 26Sr. Consultant Endocrinology, CRL Group of Hospitals, Indore, Madhya Pradesh; 27Sr. Consultant Endocrinology, Chennai, Tamil Nadu; 28Prof. of Cardiology, International Hospital and Excel Hospital, Guwahati, Assam; 29Sr. Consultant Cardiology and Director Interventional cardiology, Apollo Hospitals Bhubaneswar, Odisha; 30Sr. Consultant and Head, Department of Cardiology, Ruby Hospital, Patna, Bihar; 31Sr. Interventional Cardiologist and Managing Director, Care Institute of Medical Sciences, Ahmedabad, Gujarat; 32Sr. Consultant Endocrinology, Pt. BDSPGIMS, Rohtak, Haryana; 33Sr. Consultant, Department of Medical Medicine, Sahyadri Speciality Hospital, Pune, Maharashtra

Corresponding Author: Raman Puri, MD, DM
Lipid Association of India, A-26, 2nd Floor, South Extension Part-2, New Delhi-110049, India e-mail: lipidaoi@gmail.com
relevant topics was given to all the participating experts to collect their responses about each specific aspect of lipid management in Indians. The proceedings of these meetings were video recorded for future reference.

Apart from these meetings, a questionnaire was also sent to experts who could not attend the meetings due to any reason.

The information thus collected through the questionnaires was collated and summarized and the key findings were then further discussed among the members of the core expert group. After this 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 more informative rather than prescriptive,
• To maximally utilize the available Indian data, and
• To make all the efforts to ensure practical applicability of the recommendations to the Indian population.

However, while every effort has been made to ensure that the recommendations presented in this document are based on the most update scientific evidence, it is important to remember that “Medicine is a constantly evolving field, and we often have to deal with moving targets. The recommendations made in the consensus statement are not a mandate to the medical community. Keeping patient’s wellbeing uppermost in mind, clinicians should use their judgment and experience in applying these recommendations to their patients.”

This consensus document is divided in two parts. Part 1, the present document, deals with all common issues related to lipid management encountered during routine clinical practice. Part 2, which will be released subsequently, will deal with management of dyslipidemia in special patient populations such as those with acute coronary syndrome, familial dyslipidemias, chronic kidney disease, etc.

**Epidemiology of Dyslipidemia in India**

‘Global Burden of Metabolic Risk Factors Study’ reported trends in total cholesterol levels in different countries and world regions from the years 1980 to 2008. It was concluded that total cholesterol levels increased in India and other low-income and lower-middle income countries over this period. The levels declined in most high income countries. These trends were derived using mathematical modeling from sparse epidemiological studies in a number of countries. Good quality data were available from high-income countries (e.g. USA, UK, Germany, Japan, etc.) due to periodic nationwide surveys. On the other hand, in low and lower-middle countries such as India, where most of the CV and coronary heart disease (CHD) mortality occurs, high quality epidemiological data were not available.

In India, only limited number of large-scale studies exist on epidemiology of cholesterol and other lipid components. We reviewed all the population based epidemiological studies that focused on CV risk factors and found that there were only six multisite studies with sample size ranging from 2,000-15,000. None of these are nationally representative. The only studies that had a large sample size were Indian Industrial Population Surveillance Study (n=10,442), India Migration Study (n=1983), Indian Council of Medical Research (ICMR) Integrated Disease Surveillance Project (urban N=15223, rural N=13517, slum/peri-urban N=15751), Indian Women...
Health Study (n=4624),
India Heart Watch (n=6123) and INDIAB study (n=2500).
Prevalence of hypercholesterolemia in these studies is shown in Table 1 and varies from 10-15% in rural to 25-30% in urban populations.

However, an important shortcoming of Indian epidemiological studies is the lack of detailed information about the patterns of dyslipidemia. When compared with the western populations, Indians and migrant South Asians tend to have higher triglyceride (TG) levels and lower high-density lipoprotein cholesterol (HDL-C) levels but the total cholesterol levels are generally lower than in the US or the UK populations. The low HDL-C level and hypertriglyceridemia are metabolically interlinked and their combination has been termed as atherogenic dyslipidemia. It is often accompanied by increased levels of small-dense low density lipoprotein (LDL) particles and insulin resistance. Atherogenic dyslipidemia is particularly common in South Asians and has been shown to have a strong association with type 2 diabetes mellitus, metabolic syndrome and CHD. However, only a few large studies have reported prevalence of different forms of lipid abnormalities among Indians. India Heart Watch study was conducted among urban middle class subjects in 11 cities of India. Prevalence of various lipid abnormalities after age-adjustment in men and women, respectively were: total cholesterol ≥200 mg/dL in 25.1 and 24.9%, LDL cholesterol (LDL-C) ≥130 mg/dL in 16.3 and 15.1% and ≥100 mg/dL in 49.5 and 49.7%, HDL-C <40 mg/dL (men) and <50 mg/dL (women) in 33.6 and 52.8%, total cholesterol: HDL-C ratio ≥4.5 in 29.4 and 16.8% and TG≥150 mg/dL in 42.1 and 32.9%. The prevalence rates of various forms of dyslipidemia in the first phase of ICMR INDIAB study were similar in South Asians as compared to other ethnic groups.

Jaipur Heart Watch, a series of cross sectional studies in an Indian urban population, reported secular trends in cholesterol and other lipoproteins over a 20-year period. Increasing levels of total cholesterol, LDL-C, TG with decreasing levels of HDL-C were reported. However, these were small studies and not nationally representative.

There are no studies that have prospectively evaluated

### Table 1: Prevalence of hypercholesterolemia (≥200 mg/dL) in multisite Indian studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year reported</th>
<th>Sample size</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indian Industrial Population Surveillance Study</td>
<td>2006</td>
<td>10,442</td>
<td>25.1</td>
</tr>
<tr>
<td>India Migration Study: Rural</td>
<td>2010</td>
<td>1,983</td>
<td>21.1</td>
</tr>
<tr>
<td>ICMR IDSP: Urban</td>
<td>2010</td>
<td>15,223</td>
<td>31.7</td>
</tr>
<tr>
<td>ICMR IDSP: Rural</td>
<td>2010</td>
<td>13,517</td>
<td>19.5</td>
</tr>
<tr>
<td>ICMR IDSP: Periurban/Urban Slum</td>
<td>2010</td>
<td>15,751</td>
<td>24.8</td>
</tr>
<tr>
<td>Indian Women’s Health Study: Urban</td>
<td>2013</td>
<td>2,008</td>
<td>27.7</td>
</tr>
<tr>
<td>Indian Women’s Health Study: Rural</td>
<td>2013</td>
<td>2,616</td>
<td>13.5</td>
</tr>
<tr>
<td>India Heart Watch</td>
<td>2014</td>
<td>6,123</td>
<td>25.1</td>
</tr>
<tr>
<td>ICMR INDIAB Study</td>
<td>2014</td>
<td>2,042</td>
<td>13.9</td>
</tr>
</tbody>
</table>

IDSP: Integrated Disease Surveillance Project

The relative importance of different lipid components in causing acute MI in different ethnic groups has been highlighted in the INTERHEART study (Table 2). Overall, apolipoprotein A-I (Apo A-I) was a better marker of protection (odds ratio 0.72, 95% confidence interval 0.66-0.78) than HDL-C (odds ratio 0.97, 95% confidence interval 0.90-1.05) while raised apolipoprotein B (Apo B): Apo A-I was the best indicator of risk. However, the risk associated with 1 standard deviation change in total cholesterol, non-HDL-C, Apo B_{100}, total cholesterol: HDL-C ratio or Apo B_{100}/Apo A-I ratio was similar in South Asians as compared to other ethnic groups.

<table>
<thead>
<tr>
<th>Study</th>
<th>South Asians</th>
<th>European</th>
<th>Chinese</th>
<th>Latin American</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>1.23 (1.14-1.31)</td>
<td>1.08 (1.02-1.15)</td>
<td>1.16 (1.09-1.23)</td>
<td>1.05 (0.97-1.14)</td>
<td>1.16 (1.13-1.19)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.97 (0.90-1.05)</td>
<td>0.78 (0.73-0.83)</td>
<td>0.83 (0.78-0.88)</td>
<td>1.03 (0.94-1.13)</td>
<td>0.85 (0.83-0.88)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.23 (1.15-1.31)</td>
<td>1.17 (1.10-1.24)</td>
<td>1.24 (1.18-1.31)</td>
<td>1.04 (0.96-1.28)</td>
<td>1.21 (1.17-1.24)</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>0.72 (0.66-0.78)</td>
<td>0.70 (0.66-0.75)</td>
<td>0.67 (0.63-0.71)</td>
<td>0.67 (0.61-0.74)</td>
<td>0.67 (0.65-0.70)</td>
</tr>
<tr>
<td>Apo B</td>
<td>1.38 (1.29-1.48)</td>
<td>1.24 (1.16-1.32)</td>
<td>1.28 (1.20-1.36)</td>
<td>1.18 (1.09-1.28)</td>
<td>1.32 (1.28-1.36)</td>
</tr>
<tr>
<td>Total cholesterol: HDL-C ratio</td>
<td>1.10 (1.04-1.17)</td>
<td>1.31 (1.21-1.42)</td>
<td>1.34 (1.24-1.45)</td>
<td>0.97 (0.90-1.05)</td>
<td>1.17 (1.13-1.20)</td>
</tr>
<tr>
<td>Apo B: Apo A-I ratio</td>
<td>1.53 (1.42-1.64)</td>
<td>1.47 (1.37-1.59)</td>
<td>1.77 (1.63-1.92)</td>
<td>1.27 (1.17-1.38)</td>
<td>1.59 (1.52-1.64)</td>
</tr>
</tbody>
</table>
the importance of various lipid abnormalities in causation of CHD in India. A small study in patients with existing CHD evaluated long-term CV mortality in about 500 patients. High total cholesterol level (200-239 mg/dL and >240 mg/dL) were associated with a greater hazard of adverse events over a mean follow-up of 5 years. The ongoing PURE (Prospective Urban Rural Epidemiology) study and other prospective studies in India shall provide answers to this important question.

Summary and recommendations:

- Although data are sparse, the available evidence suggests that the cholesterol levels are steadily rising among Indians, a trend which is opposite to what is observed in western populations.
- Compared with the western populations, Indians tend to have higher TG levels and lower HDL-C levels but the total cholesterol and LDL-C levels are generally lower.
- Among various lipid markers, the ratio of Apo B: Apo A-I appears to be the best indicator of CV risk.

Value of Primordial Prevention

“Lest we forget”

Primordial prevention is defined as prevention of the development of risk factors.

Logically, the first and foremost step in the prevention of ASCVD should be to prevent development of risk factors which are responsible for ASCVD. Atherosclerosis starts in the youth; hence it makes sense to start primordial prevention early-on in life. It is said that the period of first 1000 days from conception to preschool ages is the stage where there is maximal developmental plasticity.

Attention to diet, physical activity, body weight and avoidance of tobacco use would certainly reduce the risk of developing CV risk factors and consequently the risk of falling prey to ASCVD. The Special Turku Coronary Risk Factor Intervention Project for Children study, a longitudinal, randomized atherosclerosis prevention trial showed that early dietary intervention was effective in the prevention of metabolic syndrome later in adolescence. Another prospective study followed up 88940 women in the age group 27 to 44 years for 20 years. Women with healthy life style were compared to those not practicing a healthy life style. It was concluded that primordial prevention by way of maintaining a healthy life style amongst young women was likely to significantly lower the burden of ASCVD. Similar findings were reported by yet another study from Sweden. A total of 20721 men with no history of cancer, ASCVD, diabetes, hypertension, or high cholesterol levels were followed up for 11 years. It was found that men having 5 low-risk health behaviors (a healthy diet, moderate alcohol consumption, no smoking, being physically active and having no abdominal adiposity) had 86% lower risk of MI compared with those with none of these low-risk health behaviors.

Governmental agencies and health education of the populace have a major role to play in primordial prevention. Policies have to be formulated and methods need to be devised to decide whom to target and when to intervene in a sustainable manner. Though many feel that primordial prevention does not fall within the purview of doctor-patient relationship, clinicians can contribute to the process by counseling family members accompanying the patients of ASCVD and also the patients presenting with non-cardiac illnesses or those undergoing preventive health checks.

Since it is our collective responsibility, it is high time we took the first step in this direction!

Cardiovascular Risk Stratification in Indians

In patients with established ASCVD, treatment decisions pertaining to the use of preventive cardiovascular therapies are relatively straightforward as all patients require aggressive risk reduction. However, in patients who do not have pre-existing ASCVD, i.e. those requiring primary prevention of ASCVD, wide heterogeneity in the likelihood of developing ASCVD necessitates some form of risk stratification. This is required so that the intensity of preventive therapies can be appropriately matched with the individual’s risk of developing a CV event. Such a strategy not only facilitates cost effective utilization of the limited healthcare resources but also avoids unwarranted side-effects and cost burden in those who do not need such therapies. Moreover, the knowledge of the anticipated ASCVD risk may also help improve patients’ health-related behaviors and improve the compliance to the interventions.

A number of risk assessment tools are currently available for predicting future risk of ASCVD events but none of them has been validated in Indian populations. Several recalibrations methods have been proposed to overcome this limitation. However, in the absence of prospective data, these re-calibrated risk estimates also remain only approximations at best. Moreover, the use of many of the currently available risk assessment tools requires access to a computer, and for some algorithms even internet access, which limits their wider applicability. Considering these issues, LAI proposes, as described below, a simpler risk algorithm which categorizes individuals in to various risk categories based only on the presence or absence
4. High blood pressure (≥140/90 mm Hg or on blood pressure medication)
5. Low HDL-C (males <40 mg/dL and females <50 mg/dL)

The non-conventional risk factors are categorized as high risk or moderate-risk (Table 3, Figure 1). The presence of any high-risk non-conventional risk factor (e.g., coronary artery calcium [CAC] score ≥300 Agatston units) puts the patient at high risk of having ASCVD whereas the presence of one or more of moderate-risk non-conventional risk factors should lead to re-designation of the individual to a higher risk category than the risk perceived based on the presence of major conventional risk factors alone. For example, lipoprotein (a) [Lp(a)] level of 20-49 mg/dL in a patient with 2 other major ASCVD risk factors should result in reclassification of this individual as high-risk.

Step 3: Estimate lifetime ASCVD risk in all low-risk individuals

Lifetime ASCVD risk should be estimated in all individuals who are considered to have low
Fig. 1: Recommended approach to ASCVD risk stratification in Indians

10-year ASCVD risk. If the absolute lifetime risk is 30-44%, it is considered moderately-high and if it is ≥45%, it is considered very high. The individuals who have moderately-high or high lifetime ASCVD risk should be treated on par with those who have moderate 10-year ASCVD risk.

Formal ASCVD risk estimation

Although the above risk assessment approach should be sufficient in most individuals, a more formal risk assessment may be used by clinicians according to their personal preferences and familiarity with the risk scores.

Unfortunately, as mentioned earlier, none of the currently available risk algorithms has been validated in Indian populations and therefore accurate ASCVD risk
Table 4: Treatment goals and statin initiation thresholds according to ASCVD risk categories

<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></td>
<td>(preferably in all)</td>
<td>(preferably in all)</td>
</tr>
<tr>
<td>High risk</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
</tr>
<tr>
<td></td>
<td>(preferably in all)</td>
<td>(preferably in all)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
</tr>
<tr>
<td></td>
<td>(preferably in all)</td>
<td>(preferably in all)</td>
</tr>
<tr>
<td>Low risk</td>
<td>≤ 100</td>
<td>&lt; 130</td>
</tr>
</tbody>
</table>

*After an initial adequate non-pharmacological intervention for at least 3 months

assessment in Indians is currently not feasible. Nonetheless, of all the available risk scores, the risk calculator proposed by the Joint British Societies 3rd Iteration (JBS3) appears to provide the most accurate risk estimates in Indians.\(^48,49\) The greater accuracy of JBS3 risk score may be due to the fact that it has already been validated in ethnic Indians, though non-resident ones. Moreover, unlike most other risk algorithms, JBS3 risk score includes several non-conventional yet important risk factors such as family history of premature ASCVD, obesity, etc. The risk calculator can be accessed at www.jbs3risk.com.

An alternate approach may be to recalibrate the estimated 10-year Framingham risk score by multiplying it with a calibration factor. The second Indo-US Health Summit task force recommended a calibration factor of two for Indians,\(^48\) whereas the recent UK lipid-lowering guidelines have proposed a multiplication factor of 1.4 for men of South Asian origin.\(^56\)

In comparison, the International Atherosclerosis Society has proposed calibration factors of 1.81 and 1.54 for urban men and women and 1.0 and 0.8 for rural men and women respectively. This is a very simple risk algorithm which takes in to consideration only 4 risk factors: cigarette smoking, diabetes, total cholesterol level and systolic blood pressure. While the first two are considered to be major risk factors, the remaining two are categorized in to minor, moderate and major on the basis of actual levels. Based on the number of minor, moderate and major risk factors present in a given individual, his/her lifetime ASCVD risk is estimated. Since this algorithm is based on data derived from a Caucasian population in the U.S., the International Atherosclerotic Society has also proposed ethnic-specific calibration factors for rendering it applicable to other ethnic groups. Although this algorithm appears to be very simple to use, a major problem with its application in Indian subjects is that using this algorithm almost every urban Indian man will be considered to have high lifetime ASCVD risk. This happens because in men, the presence of just one minor risk factor (systolic blood pressure equal to or above 120 mmHg or total cholesterol equal to or above 180 mg/dL) imparts 25% lifetime ASCVD risk which when multiplied with 1.8 (calibration factor for urban Indian men) translates into 45% risk for ASCVD, which is the threshold for defining high-risk.

Treatment goals and thresholds for initiation of statin therapy according to the estimated ASCVD risk

Table 4 outlines the recommended treatment goals and thresholds for initiation of statin therapy in various risk categories. It should be noted that therapeutic lifestyle change is recommended in all individuals who have LDL-C or non-HDL-C values above the desired goals, and preferably in everyone regardless of their cholesterol levels.
Non-Conventional Cardiovascular Risk Factors

As discussed in the previous section, estimation of ASCVD risk is an essential, initial step in the management of individuals requiring primary prevention of ASCVD. In the context of lipid management, such a risk estimate forms the basis for several key therapeutic decisions, such as the need for and the aggressiveness of statin therapy.

Traditionally, the estimation of ASCVD risk has been performed by incorporating information about the major and minor conventional ASCVD risk factors in to one of the several risk algorithms that are currently available. However, these algorithms have certain important limitations that warrant attention—1) while the accuracy of these algorithms is well-established at population level, their performance at the individual level is only sub-optimal, 2) using these algorithms, a vast majority of the individuals are identified to be at intermediate risk of ASCVD but the actual ASCVD risk in them varies widely, and 3) many individuals do not have any of the major conventional ASCVD risk factors but they still develop clinical ASCVD. Therefore, to overcome these limitations and to improve the accuracy of risk prediction with these algorithms, several alternate or non-conventional markers of ASCVD risk have been proposed. These markers can be considered to be useful only if they can be measured readily, add value to existing diagnostic paradigms, enhance clinician’s decision making ability, and the most importantly, improve patient management. Considering these factors, the risk markers that appear to be relevant to regular clinical practice are briefly discussed below.

Coronary artery calcium

CAC reflects the anatomic presence of coronary atherosclerosis as calcium is deposited in coronary arteries primarily in the atherosclerotic plaques only.51 Accordingly, total CAC score, as measured using computed tomography, correlates directly with the total atherosclerotic burden in the coronaries.52

Numerous studies have demonstrated that CAC score correlates with various ASCVD risk factors and the risk of CV events.53-58 In a study of 6093 patients for whom CAC score, lipids, personal health history, and body morphology were recorded, both LDL-C and HDL-C were found to be independent predictors of CAC with the relative risk being 1.05 times higher for each 10 mg/dL increase in LDL-C (P < 0.001).53 The correlation between HDL-C and CAC was three times that of LDL-C.

The association between CAC and the risk of CV events has been established for several years establishing its prognostic value in ASCVD risk prediction.54-58 A meta-analysis was performed of six large, prospective studies with a total of nearly 30,000 subjects.59 Compared with zero CAC score (Agatston units), those with any measurable CAC had a relative risk of 4.3 for ASCVD death or MI over a 3–5 years follow-up. Additionally, there was a graded relationship between CAC score and the risk of vascular events with the annual event rates being 0.4%, 0.7%, 2.1%, 4.6% and 7.1% in patients with CAC score 0, 1–112, 100–400, 400–999 and ≥1000, respectively.59

CAC has been evaluated in a few studies from India also.80,61 In a study of 388 individuals undergoing coronary angiography, any CAC score above 0 had a sensitivity of 95% for detecting significant CAD whereas a score of >400 had 100% specificity.60 In another study, Wasnik and coworkers provided reference percentile values of CAC score for Indian subjects, though it was only a cross-sectional study.81 Given the robust evidence supporting excellent predictive accuracy of CAC, it is recommended as an optional measure for ASCVD risk stratification in individuals who do not have any traditional high risk features.43 However, its cost, relatively limited availability and radiation exposure are major limitations to its wider use.

Carotid intima media thickness

CIMT is a widely recognized imaging marker of generalized atherosclerosis. A large number of trials have shown association of CIMT with ASCVD risk factors, already existing ASCVD and the future risk of vascular events.62-69 Furthermore, reduction in CIMT has been demonstrated with various non-pharmacological and pharmacological measures aimed at prevention of ASCVD.70-78

A meta-analysis of eight observational population based studies that had enrolled 37197 subjects reported a strong association between CIMT and ASCVD risk.79 Overall, for an absolute CIMT difference of 0.1 mm, the future risk of MI increased by 10-15% and the stroke risk increased by 13-18%. Furthermore, the predictive accuracy of CIMT has been shown to be incremental to conventional risk factors or Framingham risk score. Similarly, analysis of 9 lipid-lowering trials has reported strong correlation between CIMT and LDL-C reduction.80 A 10% reduction in LDL-C per year accounted for a reduction of CIMT by 0.73.

A number of studies have evaluated the role of CIMT in Indians also and have shown that CIMT correlates with ASCVD risk factors and the presence and extent of CAD.81-89 Recently, a large-scale study has also described normal distribution of CIMT in Indian subjects.90 However, so far no prospective study has been performed demonstrating utility of CIMT in Indians.

Thus, the available evidence
suggests that CIMT can reliably predict ASCVD risk and has incremental value above conventional risk factors for this purpose. However, despite this, the net reclassification with CIMT is not large enough to justify its routine use. Therefore, CIMT remains an optional marker for ASCVD risk assessment. However, both CAC and CIMT have an added advantage that these modalities, by demonstrating ongoing atherosclerosis, can favorably modify patients’ behavior towards preventive therapy.

Compared with CIMT, carotid plaques, even when non-stenotic, have been shown to be associated with significantly higher risk of vascular events. Therefore, the presence of carotid plaques should be considered to be a marker of already existing ASCVD and not just a marker of future ASCVD risk.

Aortic pulse wave velocity

Aortic PWV is a measure of arterial stiffness. Arterial stiffness is a pathological manifestation of the cumulative vascular damage resulting from various known and unknown ASCVD risk factors. Increased arterial stiffness has been shown to have excellent predictive value for ASCVD mortality, total mortality, fatal and non-fatal coronary events and fatal strokes in a wide variety of patient subsets, and the predictive value has often been incremental to conventional ASCVD risk factors. However, it must be noted that arterial stiffness is primarily a manifestation of atherosclerosis, rather than atherosclerosis. Therefore, measurement of arterial stiffness appears to be the most useful in conditions associated with atherosclerosis such as hypertension, end-stage renal disease and ageing.

Several devices are currently available for non-invasive assessment of arterial stiffness. Using these devices, arterial stiffness can be measured as carotid-femoral or brachial-ankle PWV, both of which quantify aortic stiffness. In addition, central aortic pressure and central augmentation index can also be derived with the help of these devices.

Currently, measurement of aortic PWV is recommended during work-up of hypertensive subjects but its role in ASCVD risk stratification in general is uncertain at present.

C-reactive protein

C-reactive protein (CRP) is one of the most extensively studied protein biomarkers for inflammation in ASCVD and the association between elevated CRP levels and ASCVD is well established. Whether CRP rises nonspecifically in response to the inflammation involved in ASCVD or whether it is a direct contributor to atherosclerosis progression and its sequelae is still not clear. Nevertheless, CRP has been proposed as a potentially useful non-traditional risk factor in the assessment of ASCVD risk in those without known ASCVD. In addition, CRP is also a target for lipid-lowering therapy as demonstrated in the JUPITER (Justification for the use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) study. The study showed a significant ASCVD risk reduction with statin in individuals with elevated CRP despite relatively normal LDL-C.

However, CRP is a non-specific marker for inflammation and is elevated in the presence of any inflammatory condition in the body. The utility of CRP for ASCVD risk assessment is therefore limited to individuals without any apparent cause of active inflammation. In such individuals, an elevated CRP level can be considered to be a marker for ongoing atherosclerosis, and therefore, increased ASCVD risk. Since the CRP levels are much lower in these settings than during commonly encountered inflammatory conditions, high sensitivity assays are required for accurate estimation of CRP levels. Therefore, high-sensitive CRP (hs-CRP), and not the conventional CRP, is recommended for ASCVD risk stratification. A value of ≥2 mg/l of hs-CRP indicates increased ASCVD risk. When the value is >10 mg/L, it usually indicates a non-atherosclerotic cause of inflammation and should not be considered as a marker of increased ASCVD risk.

CRP has been evaluated in a few cross-sectional studies in Indians also. In a study of 1021 subjects, comprising 774 with established CAD, plasma hs-CRP levels were found to have strong correlation with the presence of CAD. Levels of hs-CRP were higher among subjects who suffered a repeat coronary event as compared to those who remained event free and subjects in the top quartile of hs-CRP (>3.58 mg/L) were found to have a fourfold higher risk. However, despite these evidences, the utility of hs-CRP in Indian settings remains uncertain. Quality control and proper standardization of hs-CRP assays is essential and is challenging in India. Moreover, due to the confounding effect of high prevalence of overt or subclinical infection, the true prognostic value of hs-CRP is difficult to ascertain in Indian subjects. Therefore, routine measurement of hs-CRP for ASCVD risk stratification in Indians is not recommended at the present moment.

Lipoprotein (a)

Lp(a) is a genetically modified form of LDL-C particle and has greater propensity, than LDL-C, to bind to oxidized lipoproteins. As a result, elevated Lp(a) levels accentuate the risk imparted by several other ASCVD risk factors such as diabetes, low HDL-C and high LDL-C.

Lp(a) appears to be a particularly important ASCVD risk factor for Indians as Indians tend to have high prevalence of elevated
Lp(a). Enas et al were the first to report high levels of Lp(a) in Asian Indians. Elevated Lp(a) level was the most common risk factor in the CADI (Coronary Artery Disease in Asian Indians) study. Subsequent studies have confirmed elevated Lp(a) levels in Asian Indians in the U.S. and Singapore showed that the Lp(a) levels in Asian Indian newborns were significantly higher than in Chinese and the differences in Lp(a) levels in cord blood paralleled the 3 to 4-fold differences in adult CAD mortality between these two populations. In the U.K, Lp(a) levels in Asian Indians are significantly higher than whites but identical to their siblings living in India. Also, Asian Indians with CAD and their offspring in the U.K. had higher Lp(a) levels than white CAD patients and their offspring. More importantly, at least 10 angiographic and case-control studies in India have shown elevated Lp(a) levels to be a powerful risk factor for premature CAD, especially under the age of 40.

Based on these evidences, estimation of Lp(a) levels is strongly recommended for ASCVD risk stratification in Indian subjects, particularly in those who have family history or premature CAD. A level ≥20 mg/dL indicates increased ASCVD risk in Indians. However, choice of Lp(a) assay is crucial as several Lp(a) isoforms are known to exist and most of the Lp(a) assays are affected by the relative proportion of different isoforms. It is therefore recommended to use an assay that is unaffected by the isoform size.

Homocysteine

Several studies have identified elevated homocysteine level as a risk factor for CAD, stroke, peripheral arterial disease, aortic atherosclerotic disease and deep vein thrombosis. A metaanalysis of 27 studies showed that 5 µmol/L increase in homocysteine level was associated with the odds ratio of 1.6 and 1.8 for CAD in men and women respectively. The atherogenicity of homocysteine may involve several mechanisms including LDL-cholesterol oxidative modification, and HDL-cholesterol decrease. However, there is no definitive evidence of a causal relationship between the two. Moreover, there is currently no evidence to show that lowering serum homocysteine levels with folic acid or vitamin B12 supplementation reduces the risk of ASCVD. For these reasons, routine estimation of homocysteine for ASCVD risk stratification is not recommended.

Nonetheless, homocysteine levels are reported to be higher among Asian Indians than whites in several countries. Refsum et al have recently reported a very high prevalence of hyperhomocystinemia (>15 µmol/L) in 75% of subjects in India, which was strongly correlated with cobalamin deficiency (and not folic acid deficiency, which was rare). Thus, impaired cobalamin status appears more important than folate deficiency among Asian Indians.

Other markers

It is well established that obesity and metabolic syndrome are associated with increased risk of diabetes and ASCVD. However, the excess ASCVD risk imparted by these two conditions manifests over a much longer-term than the relatively shorter 5- or 10-year period, whereas diabetes manifests much earlier. Therefore, the presence of obesity and/or metabolic syndrome in an individual who is otherwise at low 10-year risk of ASCVD should indicate high lifetime ASCVD risk.

There are several other markers that have been associated with increased risk of ASCVD. These include- fibrinogen, plasminogen activator inhibitor1, platelet count, lipoprotein associated phospholipase A2, non-alcoholic fatty liver disease, vitamin D, F2-isoprostanes, etc. However, their utility for routine clinical use is not established.

Summary and recommendations:

• There is robust evidence to support prognostic value of CAC for ASCVD risk assessment. However, its cost, relatively limited availability and radiation exposure are major limitations to its wider use. It is therefore recommended as an optional tool for ASCVD risk assessment in individuals at low- to moderate-risk. A CAC score ≥300 Agatston units indicates high ASCVD risk.

• Compared with CAC, CIMT is simpler to perform, more widely available and completely safe but its accuracy for ASCVD risk prediction is inferior to that of CAC.

• Aortic PWV is a measure of arterial stiffness which is primarily a marker of arteriosclerosis. Measurement of aortic PWV is most useful in hypertensive subjects.

• Although there is enough evidence to support value of hs-CRP as a ASCVD risk marker, its routine use in Indians is not recommended due to issues related to standardization of assays and the high prevalence of infectious diseases in our country.

• Lp(a) appears to be an important marker for ASCVD risk in Indians, particularly in those with family history of premature CAD. Lp(a) value of ≥20 mg/dL indicates increased ASCVD risk in Indians. Only those assays that are not influenced by Lp(a) isoform size should be used for its estimation.

• Homocysteine estimation is not recommended in asymptomatic individuals.

• Obesity and metabolic syndrome are associated with significantly increase risk of diabetes in the short term and
increased risk of ASCVD in the long-term.

The approach to integration of these non-conventional risk factors in the overall ASCVD risk stratification is discussed in the preceding section on ‘RISK STRATIFICATION’.

**Low-Density Lipoprotein Cholesterol: Is Lower the Better?**

Clinical data has suggested a linear relation between LDL-C lowering and ASCVD risk reduction, supporting a favorable benefit-risk ratio for attaining low levels of LDL-C to minimize the risk of CV events. In a meta-analysis that included more than 175,000 participants in 27 randomized trials of statins, the Cholesterol Treatment Trialists (CTT) collaborators found that, on average, a reduction of 1 mmol per liter (38.7 mg per deciliter) in LDL-C levels yielded a consistent 21% reduction in the risk of major vascular events over 5 years, irrespective of age, sex, base line LDL-C levels and presence or absence of vascular disease. Additionally, the high-dose statin trials actually lowered LDL-C by an additional 0.5 mmol per liter, effectively offering an additional 15% reduction in ASCVD risk.

There is ample evidence to show that more-aggressive lipid-lowering therapy more effectively reduces the incidence of CV events than does a less-aggressive lipid-lowering strategy. Following the publication of National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP) III recommendations, 5 major clinical trials evaluating the beneficial impact of aggressive statin therapy on clinical end points were published. This led to major modifications in ATP-III recommendations in 2004. The goal for LDL-C lowering was reduced to of less than 70 mg/dL in very high risk patients and less than 100 mg/dL in high risk group. Subsequent studies and meta-analysis have revealed that achieving LDL-C levels even lower than these recommended targets further reduces ASCVD risk, thus lending further support to the concept- “lower the LDL-C the better”.

In the JUPITER trial, the subjects with no prior ASCVD or diabetes with LDL-C ≤130 mg/dL and hsCRP ≥2 mg/L were treated with rosuvastatin 20 mg/d. The median LDL-C level achieved with treatment was 55 mg/dL, as compared to 108 mg/dL at baseline. Those who achieved LDL-C <50 mg/dL had 65% reduction in the risk of major CV events and 46% reduction in total mortality. Approximately 23% of the subjects reached LDL-C level of <40 mg/dL. In a post-hoc analysis, no adverse effects were seen in this group.

In the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), that included patients with ACS, on-treatment mean level of LDL-C was 69.9 mg/dL in the simvastatin group and 53.2 mg/dL in the simvastatin-ezetimibe combination group. After a median follow-up of 7 years, primary endpoint comprising CV death, MI, hospitalization for unstable angina, coronary revascularization (>30days), or stroke occurred in 34.7% of the simvastatin group versus 32.7% of the simvastatin plus ezetimibe group, representing an absolute risk reduction of 2% (numbers needed to treat- 50) and 6.4% relative risk reduction (hazard ratio 0.936, CI 0.887-0.988, p=0.016). No safety issues were observed during the trial and there were no significant differences in cancer or muscle-related events.

A meta-analysis of individual patient data from 8 landmark randomized controlled trials [including AFCAPS/TexCAPS (Air Force/ Texas Coronary Atherosclerosis Prevention study), LIPID, JUPITER, TNT (Treating to New Targets), IDEAL (Incremental Decrease in Endpoints Through aggressive Lipid Lowering), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)], in which conventional lipids and apolipoproteins were determined at baseline and at 1-year follow-up, revealed 54% reduction in major CV events among individuals who achieved LDL-C level less than 50 mg/dL.

Genetic studies of ‘loss of function’ mutations in the proprotein convertase subtilisin/kexin-9 (PCSK9) have also shown markedly reduced LDL-C with concomitant CHD reduction in patients carrying these mutations. It has been demonstrated that 12%-28% reduction in LDL-C in patients with loss-of-function mutation resulted in 46-88% reduction in CHD risk. This further supports the concept that not only lower LDL-C level is better but the earlier it is achieved, greater is the reduction in CV events. Based on these observations, novel lipid lowering agents targeting PCSK9 have become available for clinical use and have been shown to reduce LDL-C levels by as much as 60%. In the ODYSSEY long term study involving 2341 high risk patients receiving ‘standard of care’ lipid lowering therapy, alirocumab, a PCSK9 inhibitor administered subcutaneously in a dose of 150 mg once every two weeks, was compared with placebo. A 78 weeks treatment with alirocumab lowered LDL-C to 53.1 mg/dL resulting in 48% relative reduction in the risk of CV events as compared to the placebo. Similar results have been obtained with yet another PCSK9 inhibitor- evolocumab- also. In the OSLETER trial, two extension studies with 4465 patients on ‘standard of care’, addition of evolocumab in 2976 patients resulted in median LDL-C level of 48mg/dL and a 53% reduction in CV outcome as compared to patients on ‘standard of care’ treatment in a pre-specified but exploratory
Various imaging trials and meta-analysis have also shown that more aggressive lowering of LDL-C level to 50 mg/dL or less results in significant reduction in atheroma volume and CV events (Table 5). In the ASTEROID intravascular ultrasound (IVUS) trial, patients with stable CAD were treated with intensive statin therapy (40 mg/d of rosuvastatin) for 24 months. The treatment with 40 mg rosuvastatin per day achieved mean LDL-C level of 60.8 mg/dL compared with 130 mg/dL in the placebo group. This resulted in atherosclerosis regression as evidenced by an increase in the minimum lumen diameter and a decrease in percent diameter stenosis. There was significant reduction in all 3 pre-specified IVUS measures of disease burden (change in percent atheroma volume, change in atheroma volume in the 10-mm sub-segment with greatest disease severity at base line and change in normalized total atheroma volume for the entire coronary artery).

In the PRECISE-IVUS study, eligible patients who underwent PCI were randomly assigned to atorvastatin (20 mg) alone or atorvastatin (20 mg) plus ezetimibe (10 mg) daily. Serial volumetric IVUS was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients. The combination of atorvastatin/ezetimibe resulted in lower levels of LDL-C than atorvastatin monotherapy (63.2 ± 16.3 mg/dL vs. 73.3 ± 20.3 mg/dL; p < 0.001). Significantly more patients who received dual therapy had coronary plaque regression on IVUS in comparison to those who received monotherapy (78% vs 58%; P=0.004). Side-effect profiles were acceptable with both strategies.

These imaging studies have shown that aggressive LDL-C lowering reduces lipid rich necrotic core, significantly reduces increase in atheroma volume, reduces mean diameter stenosis, and improves coronary flow physiology in addition to causing plaque stabilization. In this context, it is important to note that the ratio of LDL-C to HDL-C is important in determining the benefit of LDL-C lowering, particularly in patients in the very high and high risk groups. Most of the imaging trials have shown that regression of atheroma is confined mainly to the individuals with LDL-C to HDL-C ratio ≤ 1.5.
Safety of very low LDL-C levels

Most of the available evidence from large-scale trials shows that individuals with very low LDL-C levels are generally healthy and have low ASCVD risk. No clear increased risk of cancer has been identified in humans with very low LDL-C levels regardless of whether the LDL-C levels were inherently low or were achieved with aggressive statin-therapy. Although data is sparse, LDL-C <50 mg/dL does not appear to be inherently unsafe. As already mentioned above, the pooled analysis by CTT collaborators did not find any evidence for increased risk of cancer, hemorrhagic stroke, non-CV death or neurocognitive dysfunction with very low LDL-C levels.

Summary and recommendations:

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

Non-High-Density Lipoprotein Cholesterol: Should it be the Primary Target for Lipid Lowering Therapy?

Of all the lipoproteins, it is the LDL which plays a central role in atherogenesis, right from its initiation in the form of endothelial dysfunction, to its eventual manifestation as clinical ASCVD. Accordingly, reduction of LDL-C results in substantial reduction of ASCVD risk. There is robust evidence from large scale randomized clinical trials, mostly using statins, to this effect. Many primary prevention trials, secondary prevention trials and trials conducted in high risk populations have clearly proven the role of LDL-C in causation of ASCVD and the potency of statin in reducing this ASCVD risk. The dominant role of LDL is further exemplified by patients of Familial Hypercholesterolemia, who commonly develop premature atherosclerosis and clinical ASCVD even in the absence of any other risk factors. Based on these evidences, our prime focus for prevention of ASCVD must be on lowering LDL-C and keeping it low throughout life.

However, there are several other atherogenic lipoproteins in blood and LDL accounts for only about 75% of them. The other significant contributors are cholesterol-enriched remnants of TG-rich lipoproteins such as very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL) etc. These non-LDL lipoproteins may account for a significant proportion of ASCVD risk, particularly in patients who have elevated TG levels or those in whom LDL-C has already been lowered with statins. The large scale statin trials have shown that despite marked ASCVD risk reduction, the residual risk of ASCVD in statin-treated patients remains as high as 55%-70%. It is thus evident that in order to reduce ASCVD effectively, we need to concentrate on all atherogenic lipoproteins, and not just LDL alone.

Non-HDL-C as an indicator of ASCVD risk

Non-HDL-C is defined as total cholesterol minus HDL-C. Since HDL is the only anti-atherogenic lipoprotein, non-HDL-C effectively measures all atherogenic lipoproteins in blood, including LDL, VLDL, IDL, Lp(a), etc. (Figure 2). For this reason, it is expected to be a more accurate predictor of ASCVD risk as compared to LDL-C. Several large scale studies have indeed proven this hypothesis, showing that non-HDL-C is a much stronger predictor of all-cause and ASCVD mortality as compared to LDL-C. For example, in the Lipid Research Clinics Program, 4462 middle aged individuals who were free from ASCVD were followed up for an average of 19 years. It was found that non-HDL-C was a much stronger predictor of ASCVD outcomes as compared to LDL-C (chi square 24.3 for non-HDL-C and 5.0 for LDL-C). A 30 mg/dL increase in non-HDL-C resulted in 19% increase in mortality in men and 11% increase in women compared to 15% and 8% respectively for LDL-C.

Non-HDL-C has also been compared with Apo B for its ability to predict ASCVD risk. Since all
atherogenic lipoproteins, whether LDL, VLDL or Lp(a), contain one molecule of Apo B, Apo B is considered to be the most accurate predictor of ASCVD risk. This was confirmed by the INTERHEART study which showed that the ratio of Apo B to Apo A-I (the protein moiety present in HDL) was the strongest determinant of MI risk in the studied individuals. Since non-HDL-C measures cholesterol component of all Apo B containing lipoproteins, it correlates with the circulating levels of Apo B. In the Women Heart Study, the highest quintile of non-HDL-C had similar relative risk for major ASCVD events as the highest quintile of ApoB. However, in the Health Professionals Follow-up study, non-HDL-C was found to be an inferior predictor of CV events as compared to Apo B. Nevertheless, it is important to note that in both these studies, non-HDL-C was a better predictor of ASCVD risk than LDL-C.

Finally, there is robust evidence to show that non-HDL-C is an accurate predictor of residual ASCVD risk in patients already on statin therapy. A meta-analysis of 62,154 statin-treated patients in 8 trials published between 1994 and 2008 revealed that one standard deviation increase in LDL-C, Apo B and non-HDL-C increased the risk of CV events by 13%, 14%, and 16% respectively indicating that the strength of association with ASCVD was greater for non-HDL-C than for LDL-C or even Apo B. Compared with the patients who had LDL-C <100 mg/dL and non-HDL-C <130 mg/dL, those who had elevated non-HDL-C (i.e. >130 mg/dL) but low LDL-C levels (i.e. <100 mg/dL) had a hazard ratio of 1.32 indicating 32% excess ASCVD. In contrast, the hazard ratio was only 1.02 when LDL-C was elevated but non-HDL-C was low. These findings strongly suggest that increased non-HDL-C is associated with increased risk of future CV events, even if LDL-C is under control with statins.

Other advantages of non-HDL-C

Apart from being a wholesome ASCVD risk marker, non-HDL-C offers several other advantages that are relevant to clinical practice:

- Estimation of non-HDL-C does not require any additional testing. It can be easily calculated by subtracting HDL-C from total cholesterol.
- Unlike LDL-C, measurement of non-HDL-C does not need fasting blood sampling because both total cholesterol and HDL-C are not acutely affected by feeding.
- Since non-HDL-C includes both LDL-C and the TG rich non-LDL lipoproteins, using a non-HDL-C based approach obviates the need to look at TG levels separately. Furthermore, as LDL-C is the major component of non-HDL-C, focusing on non-HDL-C maintains focus on LDL-C, the primary target for ASCVD risk reduction.
- Non-HDL-C also covers, to some extent, the excess ASCVD risk imparted by the small dense form of LDL, which is significantly more atherogenic than the normal large buoyant particles. Small dense LDL is the dominant form of LDL particles in patients with elevated TG levels. Unfortunately, LDL-C levels do not provide any information about the LDL particle size but an elevated non-HDL-C, being a surrogate for elevated TG, indirectly suggests greater proportion of the small dense variety of LDL particles.

What do the guidelines suggest?

Based on the accumulated and emerging evidence, it is being increasingly recognized by most experts worldwide that non-HDL-C would be a better target for lipid lowering therapy than LDL-C alone. Most of the current guidelines have incorporated this in their recommendations. The JBS3 consensus recommendations for the prevention of ASCVD state that non–HDL-C should be used in preference to LDL-C as the treatment goal for lipid lowering therapy. Following the same concept, the 2014 National Institute for Health and Care Executive(NICE) lipid management guidelines recommend... Before starting lipid modification therapy for the primary prevention of ASCVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL-C, non-HDL-C, and TG concentrations. A fasting sample is not needed. Similarly, the U.S. National Lipid Association guidelines have also placed a greater emphasis on non-HDL-C than LDL-C. The International Atherosclerosis Society has also recommended non-HDL-C alongside LDL-C as a target for therapy.
However, the recently published ACC/AHA guidelines for lipid management, in 2013, have not provided any specific recommendation about using LDL-C or non-HDL-C as the primary target for therapy. The primary reason for this is that these guidelines have focused on ASCVD-risk based approach rather than lipid-level based approach for initiation and follow-up of statin therapy.

**What should be recommended for Indians?**

Several studies have shown that Indians have high prevalence of diabetes, obesity and metabolic syndrome, all of which are characterized by high TG levels, low HDL-C and higher prevalence of small dense LDL particles, which is also known as atherogenic dyslipidemia. Accordingly, as discussed in the section on ‘Epidemiology’ and in other relevant sections in this document, high prevalence of elevated TG and low HDL-C has been documented in various epidemiological studies conducted in Indian subjects. For this reason, it appears that non-HDL-C is likely to be an important target for therapy for Indians. Furthermore, even though most of the trials have shown ASCVD risk reduction mainly with statins, there is evidence from other studies that addition of a fibrate to statin therapy leads to incremental ASCVD risk reduction in patients with atherogenic dyslipidemia. Accordingly, the Lipid Association of India recommends non-HDL-C as a co-primary target, as important as LDL-C, for lipid lowering therapy.

- The Lipid Association of India recommends non-HDL-C as a co-primary target, as important as LDL-C, for lipid lowering therapy.
- Monitoring of non-HDL-C will provide a simple, practical tool for treatment decisions relating to lipid-lowering therapy since it does not require a fasting blood sample and takes care of both LDL-C and TG targets.
- In all individuals, the non-HDL-C level should be kept within 30 mg/dL of LDL-C levels.
- Statins remain the first line agent for lipid lowering, regardless of whether LDL-C is the target for therapy or non-HDL-C.
- Increasing the dosage of statin or switching to a more potent statin and intensifying lifestyle measures should be the first step to achieve further non-HDL-C lowering when LDL-C target has already been reached. Adding a non-statin drug such as ezetimibe or a fibrate should be considered when above measures prove inadequate.

**Relevance of High TG Levels**

Epidemiologic studies have suggested that TG is a relevant measure in evaluating CHD risk. However, the extent to which TG serves as an independent CHD risk factor has proved elusive because of its tight-knit association with other covariates. In the largest population-based prospective study, which included more than 300,000 men and women, the strong linear association between TG levels and CHD risk persisted until adjustment for non–HDL-C and HDL-C. Although this attenuated association may have reflected statistical over-adjustment, because TG is a core component of VLDL (the predominant lipoprotein represented in non–HDL-C), several fundamental reasons exist for not discarding TG as an important biomarker of CHD risk. In contrast to cholesterol, TG is readily metabolized, and its hydrolytic byproducts, free fatty acids, serve as a mammalian energy source. However, although TG itself is not taken up by vascular wall macrophages and does not contribute to atherosclerotic plaques, free fatty acids may activate pro-inflammatory signaling pathways that may contribute to insulin resistance and atherogenicity.

Evidence available from data

The evidence that raised concentrations of remnant cholesterol, marked by raised TG, are an additional causal risk factor for ASCVD and all-cause mortality is increasing. Rare mutations that disrupt APOC3 function were associated with lower levels of plasma TG and APOC3. Carriers of these mutations were found to have a reduced risk of CHD. Conversely, data from randomized controlled trials have consistently demonstrated that placebo-treated individuals with mixed hyperlipidemia, defined by either the lipid triad (elevated LDL-C, elevated TG, and low HDL-C) in the Scandinavian Simvastatin Survival Study (4S) or the combination of high TG (>200 mg/dL) and elevated LDL-C in the Helsinki Heart Study and Bezafibrate Infarction Program (8, 9) were at the highest risk of CHD events. This clearly highlights the importance of elevated TG in determining CHD risk.

Furthermore, in a subgroup analysis of the ACCORD lipid study, there was a suggestion that patients with higher baseline TG and lower HDL-C levels benefited from fenofibrate therapy in addition to pre-existing simvastatin, which was similar to the findings in the post-hoc
subgroup analyses performed in the Helsinki Heart Study, Bezelfibrate Infarction Prevention and FIELD studies.\textsuperscript{181,182} A meta-analysis of 18 trials providing data for 45058 participants, including 2870 major CV events, 4552 coronary events, and 3880 deaths confirmed these findings.\textsuperscript{183} It was found that fibrates could reduce the risk of major CV events predominately by prevention of coronary events, and might have a role in individuals at high risk of CV events and in those with combined dyslipidemia.

These findings are particularly relevant for us as in our country, atherogenic dyslipidemia triad is encountered quite frequently with elevated TG found in 29.5% and low HDL-C in 72.3% individuals.\textsuperscript{11} Hypertriglyceridemia and atherogenesis

The plasma TG level represents in part, the concentration of TG-rich lipoproteins: VLDL, chylomicrons and their remnants. Although chylomicrons and probably VLDL are both too large to penetrate the arterial wall, their remnants are small enough to do this, and have been demonstrated in human and animal atherosclerotic plaques. Because of the strong association between plasma TG and remnant lipoprotein concentration, high TG serves as a biomarker for the presence of atherogenic circulating remnant particles.\textsuperscript{184}

A second significant consequence of hypertriglyceridemic states is a relative change in the composition of LDL and HDL particles. It is important to know that small dense LDL particles are proportional to the levels of circulating TG and that small dense LDL is more atherogenic than the large buoyant LDL.\textsuperscript{176} A threshold appears to exist for a fasting TG concentration above which there will be a predominance of small, dense LDL particles (phenotype B) and below which large, more buoyant particles will predominate (phenotype A).\textsuperscript{168-170} The TG concentration that produces a shift from one subclass pattern to another varies with each patient. At a fasting TG concentration <100 mg/dL, 85% of the population has pattern A, whereas at a fasting TG concentration >250 mg/dL, 85% will have pattern B.\textsuperscript{185} Keeping TG at 200-250 mg/dL may not be optimal to reduce atherosclerosis. Most patients have a threshold for shifting LDL-C subclass pattern within the range of 100 to 250 mg/dL and since small dense LDL-C is known to be more atherogenic, keeping TG even at 200-250 may not reduce atherosclerosis completely. A target of TG < 100 mg/dL should, therefore be considered.

Insulin resistance, a classical hypertriglyceridemic state, is associated with the diminished activity of adipocyte lipoprotein lipase, leading to free fatty acid mobilization, hepatic VLDL overproduction, and up-regulation of cholesteryl ester transfer protein (CETP). Increased CETP activity facilitates the transfer of TG to LDL and HDL in exchange for cholesteryl ester. TG-enriched LDL particles are further hydrolyzed by hepatic lipase, resulting in small dense LDL particles that exhibit increased susceptibility to oxidative modification as compared to the larger, buoyant LDL particles. This is followed by unregulated uptake of LDL particles and their incorporation by scavenger receptors residing on the surface of the arterial wall.\textsuperscript{185,186} Another significant event is that the TG-enriched HDL particles may be less efficient in reverse cholesterol transport.\textsuperscript{187} TG may also stimulate atherogenesis by other mechanisms, which include the production of proinflammatory cytokines, fibrinogen and coagulation factors and impairment of fibrinolysis. Thus, the role of TG in atherogenesis has a basic biological plausibility.\textsuperscript{188} The combination of elevated TG and elevated LDL-C signals greater CHD risk compared with LDL-C elevation alone. Conversely, individuals who live in regions of the world that maintain low lipid levels retain an overall low risk of CHD.\textsuperscript{189-192}

Classification of fasting TG Levels

The generally followed classification for TG values based on fasting lipid profile is:\textsuperscript{131}

- **Desirable** <150 mg/dL
- **Borderline high** 150-199 mg/dL
- **High** 200-499 mg/dL, and
- **Very high** >500 mg/dL

Non-fasting versus fasting concentrations

Traditionally, a blood sample for lipid profile is taken in the fasting state. Several recent studies have not shown any advantage of performing a fasting lipid profile testing. Rather, there is an advantage of non-fasting fasting lipid profile measurements in that the blood-sampling process is simplified for patients, general practitioners, and hospitals, and therefore probably increases compliance to lipid-lowering therapy and monitoring.

In most patients, there is usually a clinically unimportant increase in TG concentrations, by 0·2–0·4 mmol/L (18-36 mg/dL) on average, two to six hours after eating normal meals.\textsuperscript{193-195} Besides, even a non-fasting concentration predicts increased CV risk.\textsuperscript{195} Also, it is important to note that most people eat regularly throughout the day and are therefore usually fasting (defined as at least 8 h since the last meal) only for a few hours in the morning. For all these reasons, non-fasting lipid concentrations might be a better indicator of average lipid concentrations in the blood rather than fasting concentrations.\textsuperscript{196,197} Secondary causes of elevated TG

There are numerous conditions that can result in increase in serum TG levels. It is important to be aware of these conditions to be able to better manage patients who present with hypertriglyceridemia—

- **Diabetes**
- **Hypothyroidism**
- **Nephrotic syndrome**
levels, rule out secondary causes of the same and intensify lifestyle modification, which can reduce TG by as much as 50%.

- Unless TG is very high (>500 mg/dL), statin should be the first drug to be prescribed in all patients requiring lipid lowering therapy. Routine addition of a fibrate or another non-statin drug must be avoided.

- Only when TG is not sufficiently lowered with above measures, a non-statin drug should be added.

**Summary and recommendations**

- Elevated TG is associated with increased risk of ASCVD, independent of LDL-C levels. A combination of high TG and LDL-C imparts even greater risk.
- High TG is often accompanied by low HDL-C levels and increased proportion of small-dense LDL-C, a pattern known as atherogenic dyslipidemia.
- Keep TG <150 mg/dL, preferably <100 mg/dL.
- In patients with elevated TG levels, rule out secondary causes of the same and intensify lifestyle modification, which can reduce TG by as much as 50%.

**High-Density Lipoprotein Cholesterol**

HDL is a class of heterogeneous lipoproteins that are the only anti-atherogenic lipid particles in blood. The cardio-protective effects of HDL-C have been attributed to its role in reverse cholesterol transport, its effects on endothelial cells, and its antioxidant activity. HDL particles are characterized by high density (>1.063 g/mL), and small size (Stoke’s diameter 5-17 nm).
In general, large prospective epidemiological studies, such as the Framingham Heart Study in the United States and the PROCAM (Prospective Cardiovascular Munster) study in Europe, have found that low HDL-C is independently associated with increased risk for CAD. However, the overall activity of HDL-C may be influenced by certain unmeasured variables, including genetic and acquired factors. It is increasingly being recognized that the concentration of HDL subclasses and the kinetics of HDL metabolism and not the absolute quantity of HDL, may be the primary determinants of its anti-atherogenic effects. Factors affecting HDL-C levels

The HDL-C level and function depend on several genetic and acquired factors. There are several genetic disorders of the molecules involved in HDL metabolism that alter the HDL biology but no significant or consistent association between atherosclerosis and genetic HDL forms has ever been observed. Several monogenic forms of hypo-alpha-lipoproteinemia (mutations involving ApoA1, LCAT, ABCA1, SCARB1 and CETP) and few conditions of polygenic origin are known that result in extreme HDL-C levels. More commonly, there are certain acquired conditions which result in low HDL-C levels. These secondary factors associated with low HDL-C are- obesity, physical inactivity, smoking, high carbohydrate diet, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, chronic renal failure, human immunodeficiency virus infection, systemic lupus erythematosus and drugs (corticosteroids, beta blockers, retinoids, protease inhibitors, sirolimus, and atypical antipsychotic agents). Except smoking, all the others are also associated with elevated TG.

HDL-C and atherosclerosis risk (HDL hypothesis)

Low serum concentrations of
HDL-C have consistently been considered as an independent risk factor for CHD. The cardio-protective effects of HDL were initially suggested by the strong inverse relationship between plasma HDL-C levels and ASCVD risk in observational studies. However, more recently, several pharmacological and genetic studies have raised the questions of whether HDL-C is a reliable biomarker of HDL functionality and, in a further erosion of the HDL hypothesis, whether HDL function itself is of any importance, especially once plaques advance significantly or LDL-C is sufficiently lowered.25 This controversy has obscured the preclinical and human studies to date that have generally shown that when the levels of functional HDL particles are increased, either by stimulating endogenous production of (lipid-poor) Apo A-I or by providing HDL or Apo A-I exogenously, regressive changes in plaques occur that would be expected to translate in to the reduction in ASCVD risk. Besides, other conflicting information about this baffling lipoprotein is also emerging. A Canadian cohort study of 631,762 individuals with no prior cardiac conditions, with a mean follow up of 4.9 years, showed that low and very high levels of HDL-C were associated with an increased risk of death from both CV and non-CV causes, compared with intermediate HDL-C levels. This suggests that there is a U shaped HDL-C mortality curve and that HDL-C levels are unlikely to represent a specific cardiovascular risk factor. Despite the incompleteness of our current clinical and preclinical knowledge, if further investigations continue to support the power of HDL to favorably modify plaque biology, rather than abandon the HDL hypothesis entirely as a therapeutic strategy, then a more prudent approach would be to shift the target of simply increasing HDL-C to that of increasing the supply of functional HDL particles or the intrinsic functions through other means.257 However, most of the current guidelines continue to recommend HDL-C level for CHD risk assessment. In the recent ACC/AHA guidelines, low HDL-C is defined as less than 40 mg/dL in men and as less than 50 mg/dL in women for use in the Pooled Cohort Equation.41

Atherogenic dyslipidemia in South Asians

Low HDL-C and elevated TG, especially when combined with high LDL-C to produce the phenotype of mixed or atherogenic dyslipidemia, are commonly encountered in clinical practice in our country.

As per the INTERHEART Study1, the prevalence of low HDL-C levels was much higher in the South Asian populations than in the other populations (82% vs 60% of acute MI cases). Besides, the presence of higher levels of HDL-C correlated with a decreased risk of MI. The extent of decrease in risk with increase in HDL-C seemed to be less prominent for South Asians than for the other Asians. One standard deviation increase in HDL-C was associated with a mere 13% reduction in MI risk in South Asians as compared to 23% risk reduction in the other Asians. In the same context, a study revealed high prevalence of most of the ASCVD risk factors, specially diabetes, hypertension and dyslipidemia in Indian patients undergoing coronary artery bypass surgery. In this study, 13.9% of the subjects studied had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and 79% had abnormalities in at least one of the lipid parameters11. A pattern of Apo A1 single-nucleotide polymorphism observed in 94 unrelated South Asian immigrants may be contributing to decreased levels of HDL-C leading to an increased risk for developing CAD in this population.268 Also, higher prevalence of metabolic syndrome in our country, which is associated with insulin resistance leading to increase in small dense LDL particles with reduction in HDL-C, HDL particle size and number, may also be a reason.

The patients with low HDL-C are three times more likely to die after an acute coronary event.269 Also, the presence of metabolic syndrome which is usually associated with low HDL-C, increases the risk of early recurrent events after acute coronary event.210

Management of Low HDL-C275

Lifestyle modification

Smoking cessation, weight loss, aerobic exercise, and moderate alcohol intake are known to increase HDL-C.

In general, physically active individuals have higher HDL-C as compared to people with sedentary lifestyle.211,212 Also, it has been shown in randomized studies that aerobic exercise results in an increase in HDL-C from the baseline.213,214 The most notable and largest of such studies was the HERITAGE (Health Risk Factors Exercise Training and Genetics) Family Study,215 where HDL-C concentrations increased by 3.6±11% in both males and females at the end of 20 weeks, compared with baseline. A key feature observed was significant individual variability in the response to exercise in this study. The variability in response could possibly be explained by genetic factors and different baseline TG values.

The dietary advice given to patients with dyslipidemia also is applicable for elevating HDL-C, though with some caveats. A diet rich in polyunsaturated fatty acids (PUFA), which is known to lower LDL-C may actually lower HDL-C along with TG. Similarly, increasing monounsaturated fatty acids (MUFA) in diet has no effect on HDL-C.231 Consumption of foods with trans-fatty acids is the most harmful and results in reduction
in HDL-C along with elevation of LDL-C and TG. A diet rich in fruits and vegetables is most useful in reducing TG and LDL-C and raising HDL-C.

Pharmacologic therapy

a. Statins- Statins, though primarily used to lower LDL-C levels, also raise HDL-C levels by 5% to 15%. However, due to their profound ASCVD risk reduction ability through multiple mechanisms, statins should be used as first-line agents in patients with low HDL-C also, whether or not LDL-C is elevated. Aggressive statin monotherapy in ASTEROID study resulted in the lowest level of LDL-C and the greatest increase in HDL-C ever observed in a major statin outcomes trial. These changes in lipid levels were accompanied by regression in all three pre-specified IVUS measures of disease burden. Similar observations were made in the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) and METEOR studies also.

b. Niacin- Niacin is the most effective HDL-C-raising pharmacologic agent, currently available for clinical use. Niacin reduces ApoB secretion, thereby lowering both VLDL cholesterol and LDL-C, increasing ApoA-I, and lowering Lp(a). The HDL Atherosclerosis Treatment Study (HATS) randomized 160 patients with established CAD and low HDL-C to simvastatin plus niacin or to their placebo, and to antioxidant vitamins (E, C, β-carotene, and selenium) or to their placebo. Patients given simvastatin and niacin had a virtual halting of the progression of coronary stenosis while those given only placebos had, on an average, 3.9% worsening of stenosis. The ARBITER-2 and ARBITER-3 trials were the first to demonstrate an atherosclerosis treatment benefit with the addition of niacin to an established statin regimen. Mean reduction in CIMT was observed when extended release niacin at bedtime was added to ongoing statin therapy. Niacin therapy was shown to improve clinical outcomes also in previous studies such as the Coronary Drug Project and the Stockholm Ischaemic Heart Disease trial. However, two recent large-scale studies-HPS2-THRIVE (Heart Protection Study 2- Treatment of HDL to Reduce the Incidence of Vascular Events) and the AIM-HIGH (Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High TG) provided contrasting results. Both these trials failed to show any benefit when niacin was added to background statin therapy with regard to short-term and long-term CV risk reduction. Moreover, there was some suggestion of harm also with niacin therapy. Although the exact reasons underlying these paradoxical results remain debatable, niacin is currently not recommended for clinical use as an HDL-C-raising agent.

c. Fibrates- Fibrates are peroxisome proliferator-activated receptor (PPAR)-α ligands and result in enhanced catabolism of TG-rich particles. Fibrates also increase the expression of Apo A-I and Apo A-II, with the net result of decreasing hypertriglyceridemia and increasing HDL-C. As a result, fibrates are used in combination with statins in patients who continue to have elevated TG and/or HDL-C despite optimum statin therapy and adequate lifestyle changes. The post-hoc analysis of FIELD study showed 27% reduction in cardiac events with fenofibrate in patients with high TG and low HDL-C. Similarly, in the ACCORD trial, the patients with high TG and low HDL-C appeared to benefit with addition of fenofibrate to simvastatin.

d. Newer drugs

CETP inhibitors- CETP inhibitors lower LDL-C by 30%-40% and increase HDL-C, often by greater than 100%, and may provide CV benefits because of LDL-C reduction. However, studies with two CETP inhibitors- torcetrapib and dalcetrapib- have not shown any clinical benefit and torcetrapib even resulted in harm. The two other CETP inhibitors- anacetrapib and evacetrapib- are under trials presently.

Emerging approaches- Several other innovative approaches for raising HDL-C are being currently evaluated. These include:

- Infusion of mutant forms of Apo A-I, such as Apo A-I Milano,
- Oral Apo A-I mimetics, Apo A-I Milano gene transfer,
- Reconstituted or delipidated HDL-C infusions,
- Activators of the nuclear receptors liver X receptor and farnesoid X receptor, which may also stimulate reverse cholesterol transport,
- PPAR agonists targeting one or more of PPAR-α, -β, and -γ, etc.

Summary and recommendations

- Low HDL-C is an independent risk factor for ASCVD. It becomes even more relevant when LDL-C is not elevated.
- Life style modification plays an important role in raising HDL-C.
- Among pharmacological agents, statins remain mainstay
Risk factors for ASCVD

Prevention of ASCVD

Approach to Primary Prevention of ASCVD

Unlike the developed countries where the incidence and prevalence of ASCVD have been steadily declining over the past 2-3 decades, in India, the burden of ASCVD is growing exponentially. Not only this, ASCVD tends to occur at a younger age among Indians, resulting in much greater loss of productive life. As per the official Government projections, in India, 40% of the CHD related deaths in 2015 were expected to be in persons less than 45 years of age. If this trend continues, in 2020, 2.6 million Indians would die of CHD, and 50% of them would be in the age group 30 to 69 years. That will truly be a disaster for the families of the patients, for the society and for the nation as a whole. This also underscores the need for aggressive efforts for primordial and primary prevention of ASCVD.

Risk factors for ASCVD

A brief overview of the major risk factors responsible for causation of ASCVD in India is provided below to highlight the focus areas for prevention of ASCVD. Risk factors for ASCVD are broadly categorized as modifiable or non-modifiable risk factors.

A. Non-modifiable risk factors:
   - Heredity
   - Gender
   - Age
   - Ethnicity

Ethnicity is a significant risk factor for development of ASCVD. Multiple studies of migrant South Asian populations have consistently shown a 3- to 5-fold higher risk for MI and ASCVD death as compared with other ethnic groups. Even among South Asians, Asian Indians have one of the highest rates of CAD amongst the ethnic groups that have been studied.

B. Modifiable risk factors: These are many conventional and non-conventional modifiable risk factors for ASCVD, but the most robust are diabetes, tobacco use, high BP, lipid abnormalities and obesity. These factors have been identified consistently and conclusively through animal experiments, human epidemiologic studies, and randomized clinical trials of lifestyle modifications and medications.

Primary prevention should focus on controlling conventional risk factors for ASCVD. Less often and in selected situations, one may look for the novel risk factors or markers of subclinical atherosclerosis for the ASCVD risk and management. In addition, one must also be aware of the disease conditions and drugs that may cause secondary dyslipidemia (Table 6).

It has been observed that elimination of health risk behaviors, like unhealthy diet, excess energy intake, physical inactivity, and smoking might prevent 80% of heart disease, stroke, and type 2 diabetes mellitus, as well as 40% of cancers. Thus, adoption of a healthy lifestyle forms the foundation of lifetime prevention. A healthy lifestyle mainly includes smoking cessation, an LDL-lowering diet, weight control, and regular physical activity. A healthy lifestyle can be promoted through both public health and clinical strategies.

Table 6: Drugs and disease conditions that may cause secondary dyslipidemia

<table>
<thead>
<tr>
<th>Drugs and diseases that increase LDL-C levels</th>
<th>Drugs and diseases that increase TG levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Drugs</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Beta-blockers (especially non-beta 1-selective)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>Fibrates (in severe hypertriglyceridemia)</td>
<td>Bile acid sequestrants</td>
</tr>
<tr>
<td>Long chain omega-3 fatty acids (in severe hypertriglyceridemia)</td>
<td>Oral estrogens</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Tamoxifen, Raloxifene</td>
</tr>
<tr>
<td>Some progestins</td>
<td>Retinoids</td>
</tr>
<tr>
<td>Danazol</td>
<td>Immunosuppressive drugs (cyclosporine, sirolimus)</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Cyclosporamide</td>
</tr>
<tr>
<td>Immunosuppressive drugs (cyclosporine)</td>
<td>Interferons</td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotic drugs</td>
</tr>
<tr>
<td></td>
<td>(fluperlapine, clozapine, olanzapine)</td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase</td>
</tr>
</tbody>
</table>

in the treatment of low HDL-C also. Although several other agents have been tried specifically for raising HDL-C, none of them has been shown to result in clinical benefit.

For the latest information on therapies for ASCVD and other diseases, please refer to the latest issue of the Journal of The Association of Physicians of India.
What are the conventional risk factors for ASCVD in Indians?

Various studies, most notably the Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, and the Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study, have provided a convincingly clear answer to the question.

INTERHEART Study

It was a case-control study of acute MI in 52 countries. 15152 cases and 14820 controls were studied. Nine risk factors were considered- smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors.

These nine risk factors accounted for most of the risk of MI globally, in both genders and in all age groups. Of these, the two most important risk factors were smoking and abnormal lipids, accounting for about two-thirds of the population attributable risk (PAR) for an acute MI.

Analysis of data from Asian subjects in the INTERHEART study

In the INTERHEART study, there were 5,731 cases of acute MI and 6,459 control subjects from 65 centres in Asia. A greater proportion of Asian subjects (both cases and controls) had LDL-C levels of ≤100 mg/dL (25.5% and 32.3% in Asians vs. 19.4% and 25.3% in non-Asians respectively) but low HDL-C was also more common amongst South Asians. However, despite the lower baseline levels of LDL-C amongst South Asians, the associated risk of acute MI was similar to that in non-Asians. Based on these findings, the authors suggested that it was time to rethink the treatment thresholds and targets for LDL-C in South Asian populations.

Another analysis from the INTERHEART study evaluated the association of risk factors with acute MI in younger age groups and compared South Asians with other populations. The analysis included 1732 cases with acute MI and 2204 controls recruited from 5 South Asian countries and 10 728 cases and 12 431 controls from other countries. Out of the 9 INTERHEART risk factors, 8 accounted for the majority of acute MI cases in South Asian countries also. Alcohol consumption was not found to be a risk factor for South Asians. Importantly, it was found that the earlier age of acute MI in South Asians was largely due to higher risk factor levels at younger ages in them.

INTERSTROKE study

This case control study from 22 countries studied 3000 cases of stroke and 3000 controls. The study found that 10 risk factors i.e. smoking, hypertension, diabetes, diet, physical activity, waist to hip ratio, cardiac causes, alcohol intake, psychosocial stress and depression were associated with 90% of risk of stroke globally. Ratio of Apo B to Apo A-I was a strong predictor of ischaemic stroke.

Benefits of risk factor reduction

Numerous studies have established beyond doubt the benefits of risk factor reduction in primary prevention of ASCVD. Although a detailed discussion about approaches for ASCVD risk factor reduction is included in subsequent sections, a broad overview is provided below.

Smoking

Smoking is the single most important risk factor for ASCVD, next only to ageing. This applies to passive smoking and all forms of tobacco consumption. Smoking increased the risk for CAD and stroke by 2 to 4 fold and smokers lose about 10 years of life on an average. Smoking adversely affects BP, sympathetic nervous system, haemostasis (platelets, fibrinogen) and myocardial oxygen supply. It enhances LDL-C oxidation, impairs endothelial function and raises CRP levels.

It is never too late to quit smoking. After quitting smoking, the ASCVD risk decreases by 50% within 2 years.

In India, smoking is increasing, particularly amongst the poorly educated sections in the urban areas and among younger subjects. Government policies, antismoking campaigns and health education should effectively combat the menace of smoking.

Physical inactivity

Sedentary life confers an increased risk for mortality. Sedentary life as compared to those with regular exercise was shown to be associated with an almost 8-fold increase in age adjusted all-cause mortality.

There is adequate epidemiologic evidence that regular physical exercise results in reduced risk of CV morbidity and mortality, and all-cause mortality across age, gender and ethnicity. Furthermore, exercise also decreases the risk of diabetes and various forms of cancers.

A complete exercise program includes aerobic exercise, resistive training, and stretching. More frequent exercise, preferably daily, provides more benefit.

Diet

A healthy diet helps in reducing the risk of ASCVD, by way of weight reduction as well as improvements in diabetic state, blood pressure and lipid levels. The following are some general instructions:

- Achieve and maintain ideal body weight by limiting foods high in calories and low in nutrition, including those high in sugar, such as soft drinks and candy.
- Eat a variety of fruits, vegetables, legumes, nuts, soy products, low-fat dairy
products and whole grain breads, cereals, and pastas.

- Eat baked or broiled fish at least twice per week.
- Choose oils and margarines low in saturated fat and high in omega-3 fat, such as canola, soybean, walnut, and flaxseed oils.
- Avoid foods high in saturated and trans-fats, such as red meat, whole milk products, and pastries, deep fried items.
- Limit alcohol consumption to no more than 2 drinks per day for a man or 1 drink per day for a woman. It is preferable to completely abstain.
- Eat <6 g of salt or <2400 mg/d of sodium per day.

**Hypertension**

Hypertension is a major risk factor for ASCVD. It increases the risk for CAD, heart failure, stroke, peripheral arterial disease, aortic aneurysm, atrial fibrillation, renal failure and total mortality. The data show that mortality due to CAD and stroke increases progressively from a BP level of 115/75 mmHg onwards. Hypertension also affects cognitive functions and increases the risk of dementia. Effective treatment of hypertension reduces the ASCVD risk substantially.\(^{244}\)

Prevalence of hypertension in India at present is roughly 25 to 40% among urban adults and 10 to 15% among rural adults.\(^{245}\)

Healthy life style (healthy diet, regular exercise, maintaining ideal bodyweight, no tobacco, and minimizing alcohol consumption) can greatly reduce the risk of hypertension. Pharmacological treatment is required in those who have higher BP levels not controlled with lifestyle management alone.

**Diabetes**

Diabetes is a major, independent risk factor for ASCVD. In some populations, the risk associated with type 2 diabetes approaches that seen with already existing CAD, though it is not true for all the populations.

The prevalence of diabetes in India has increased to 10-15% in urban and 3-5% in rural areas.\(^{246}\)

**Tight glycemic control reduces risk of microvasculopathy of diabetes and there is a trend toward benefit in macrovascular complication as well.** At the same time, in a diabetic patient, it is extremely important to effectively manage other risk factors to reduce the incidence of major coronary events.

**Dyslipidemia**

The prevalence of dyslipidemia, particularly atherogenic dyslipidemia is high amongst Indian subjects. It has been noted that there is a progressive increase in the mean levels of TC, LDL-C and non-HDL-C and a decline in the HDL-C levels amongst urban Indians.\(^{19}\)

The longer the LDL level is kept low, the better it is for risk reduction. The lower the level that is achieved, the greater the risk reduction will be, particularly in people with advanced atherosclerotic disease.\(^{247}\)

### Role of statins in low ASCVD risk population

Two extensive reviews have tried to answer the question whether statins, used for primary prevention, reduce the risk of ASCVD in low risk populations.\(^{248}\)

From 18 randomized controlled trials dating from 1994 to 2008, 56934 patients were studied. Mean age was 57 years (range 28-97) and 60.3% were men. The results and adverse events with relative risk/odds ratio are summarized in Tables 7a and 7b.

There was clear evidence in reduction of all-cause mortality, major vascular events and revascularization with no excess risk of adverse events. The benefits were similar in trials stopped early and in those running their planned course. It was estimated that treatment of 1000 patients with a statin for five years would prevent 18 major ASCVD events.\(^{249}\)

This analysis included 22 trials of statin versus control (n= 134537; LDL-C difference of 1.08 mmol/L with median follow up of 4.8 years) and 5 trials of more versus less intensive statin therapy (n= 39612; LDL-C difference of 0.51 mmol/L with median follow up of 5.1 years).

Based on the 5 year major vascular events in the control group, the subjects were divided into 5 risk categories - <5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, ≥30%. In each of these risk categories, the event rate ratio per 1.0 mmol/L LDL-C reduction was estimated.

Overall, 1 mmol/L reduction in LDL-C with a statin was associated with 21% reduction in the risk of major vascular events, irrespective of age, sex, baseline LDL-C or previous vascular disease. In individuals with 5-year risk of major vascular events <10%, each 1 mmol/L reduction in LDL-C produced an absolute reduction in major vascular events of about 11
per 1000 over 5 years. This benefit greatly exceeds any known hazards of statin therapy. As per the existing guidelines, such individuals would not typically be regarded as suitable for LDL-C lowering statin therapy. This suggests that the treatment thresholds for initiating statin therapy for primary prevention need to be revised. The thresholds recommended by the Lipid Association of India are described in the section on ‘Risk stratification’.

**Statins have a legacy effect!**

The WOSCOPS study had showed that in a primary prevention setting, treatment with 40 mg pravastatin for 5 years resulted in 31% reduction in the risk of nonfatal MI or death from cardiovascular causes as compared with placebo. More recently, 20-year follow-up data from the same study were presented. It was found that the benefits accrued during the active phase of the study were sustained over the course of two decades such that a gain of 5 event free years was seen in the individuals initially treated with pravastatin. These findings suggest that statins indeed have a ‘legacy effect’.

### Table 7b: Cochrane review of the studies evaluating role of statins in primary prevention of ASCVD - Adverse effects

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Relative risk / odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>1.01</td>
</tr>
<tr>
<td>Myalgia or muscle pain</td>
<td>1.03</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.18</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.97</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>1.16</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>1.00</td>
</tr>
<tr>
<td>Stopping treatment due to adverse events</td>
<td>0.86</td>
</tr>
</tbody>
</table>

As compared to 22% in women. Similar findings were observed for all CV end-points separately as well as for all-cause mortality. No adverse effect on rates of cancer incidence or non-cardiovascular mortality was noted for either sex. This analysis concluded that in men and women at an equivalent risk of ASCVD, statin therapy was of similar effectiveness for the prevention of major vascular events.

**Aspirin in Primary Prevention**

Role of aspirin in primary prevention of ASCVD remains controversial. A systematic review six trials including 95000 subjects and comparing long-term aspirin therapy with control was performed. A risk reduction from 0.57% to 0.51% per year of serious vascular events was found. This 12% proportional risk reduction was due mainly to a reduction in non-fatal MI. There was a slight increase in hemorrhagic stroke and a reduction of ischemic stroke. The net effect on stroke was not statistically significant. Major gastrointestinal and extra-cranial bleeds increased by 0.03% per year. Risk of vascular mortality was not changed by treatment with aspirin. Given the increased risk of bleeding, aspirin is not recommended for routine use for primary prevention of ASCVD. However, low-dose aspirin therapy is reasonable for individuals in whom the benefits clearly outweigh the risks. Thus, in individuals with annual ASCVD event rate of ≥2% and low bleeding risk, low-dose aspirin seems to be clearly warranted whereas in those with the annual event rate 1-2%, the decision to prescribe or not to prescribe aspirin should be left to the physician’s discretion and to the patient’s preferences. Aspirin is clearly not warranted in individuals with lower risk of ASCVD.

**A call to save preventable death from ASCVD**

In 2011, a UN high-level meeting on non-communicable diseases (NCDs) set a target of reducing premature mortality by 25% by 2025 (i.e. ‘25X25’). One year later, major cardiovascular societies across the globe came together to publicize important steps that needed to be taken to achieve this goal, given that ASCVD accounted for nearly half of all NCD deaths. The targets that were recommended are:

- 10% reduction in the prevalence of insufficient physical activity,
- 25% reduction in the prevalence of raised blood pressure,
- 30% reduction in salt or sodium intake (goal of <5 g salt or <2000 mg sodium per day)
- 30% reduction in the prevalence of tobacco smoking,
- 15% reduction of saturated fat intake,
- halving the prevalence of obesity,
- 10% reduction in alcohol intake and, and
- 20% reduction in the prevalence of elevated cholesterol

In addition to above, certain healthcare delivery goals were also set. It was recommended that by 2025, at least 50% of the eligible people should be receiving counseling and drug therapy required to prevent heart attacks and strokes. Simultaneously, the availability of basic technologies and generic essential medicines required to treat major NCDs also needed to be raised to at least 80% in both public and private facilities.

**Summary and recommendations**

- Primary prevention of ASCVD should occupy the prime place in clinical practice.
- Screen for ASCVD all adults at 20 years of age/college entry.
- Assess ASCVD risk and discuss the health program with the individual.
- Follow the “magnificent seven”:
  1. No tobacco
2. Physical activity: ≥150 min moderate intensity or equivalent exercise per week
3. Body-mass index <23 kg/m²
4. Healthy diet: achieving at least four of the five important dietary components, focusing on fruits and vegetables, fish, fibre, and sodium intake and sweetened beverage intake
5. LDL-C level should be below 100mg/dl
6. Blood pressure: <120/80 mmHg
7. Fasting plasma glucose level: <100 mg/dL
- Stains are safe and effective in both primary and secondary prevention in ASCVD

“Clearly, it is time to take a break from reading and get up and take a walk” - Neil Skolnik

**Therapeutic Lifestyle Changes**

The importance of lifestyle related risk factors and their role in ASCVD were brought out by two landmark studies of recent times- The INTERHEART study and the INTERSTROKE study. The INTERHEART study, which was a large, international, standardized case-control study of acute MI patients in 52 countries, showed that the two most important risk factors for acute MI were Apo A-I: ApoB ratio and smoking. Regular consumption of fruits and vegetables was associated with a 30% relative risk reduction. Thus, according to the findings of the study, eating fruits and vegetables, undertaking exercise, and avoiding smoking could lead to about 80% lower relative risk for MI. The study also showed that the protective lifestyle factors such as leisure time physical activity and regular intake of fruits and vegetables were markedly lower among South Asians than in the western population while harmful risk factors such as elevated ApoB/ APO A-I ratio were higher in South Asians. Regular alcohol consumption was not found to be protective among South Asians. Similar findings were reported from the INTERSTROKE study also. Five risk factors (hypertension, abdominal obesity, diet, physical inactivity and current smoking) accounted for more than 80% of global risk of all stroke. Alcohol had a J-shaped association with stroke and psycho-social stress in the form of depression was also associated with increased risk. Intake of fish and fruits (Mediterranean pattern diet) was associated with the greatest risk reduction. It was concluded that modifications in BP, physical activity, smoking, and diet could substantially reduce the burden of stroke worldwide.

As evident from the above two studies, lifestyle plays a very important role in the reduction in the risk for MI and stroke, the two major cardiovascular killers globally. The other pandemics are obesity and diabetes which are closely linked with ASCVD. The role of lifestyle cannot be underscored in these diseases also. In a prospective community based study- The Indian diabetic prevention program (IDPP-1), the progression of diabetes and effects of interventions was studied in native Indians with IGT who were younger, leaner and more insulin resistant. As compared to the control group, the relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin and 28.2% with lifestyle modification with metformin, clearly underscoring the key role of life style in diabetes progression and prevention.

In the subsequent section, we outline the various components of life style management and propose our recommendations.

**Physical activity and maintenance of ideal body weight**

**Benefits of exercise**

Physical activity has a linear relationship with health benefits. It increases HDL-C, left ventricular ejection fraction, arrhythmia threshold, promotes fibrinolytic activity, insulin sensitivity and psychological well-being. It decrease non-HDL-C, TG, LDL-C, total cholesterol, platelet aggregation, abdominal obesity, body weight, colon and breast cancers and risk of death from non-communicable diseases. Furthermore, exercise has been shown to reduce the levels of PCSK9 also.

In the HERITAGE Family Study, the largest published interventional study, 675 normolipidemic subjects were given 20 weeks of supervised exercise and their HDL-C concentration increased by 3.6 ± 11% in both males and females compared with baseline but with significant inter-individual variability. A significant reduction (P <0.01) from baseline levels in plasma total and VLDL TG was also observed only in the 24-hour post-training specimens, reflecting a response to the last bout of exercise. As for LDL-C, physical exercise alone has shown no significant effect as reported in several systemic reviews. However, resistance training over longer periods may reduce LDL-C. Although the effects of physical exercise on LDL-C are mixed, it appears to increase the average size of LDL particles and reduce the number of more atherogenic, small-dense LDL particles. This is of particular importance to Indians who are known to have increased proportions of small-dense LDL. Thus, in effect, physical exercise directly improves “atherogenic dyslipidemia”, which is frequently present among Indians.

Body weight is closely related to diet and physical activity. There have been various parameters proposed to assess ideal body
Table 8: Salient points from four relevant guidelines on physical activity

<table>
<thead>
<tr>
<th>US Department of Health and Human Services(^{270})</th>
<th>WHO(^{263})</th>
<th>AHA(^{271})</th>
<th>Indian Consensus Document(^{272})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Avoid inactivity</strong></td>
<td>-</td>
<td>-</td>
<td><strong>Physical inactivity should be avoided as far as possible.</strong></td>
</tr>
<tr>
<td><strong>Aerobic Physical Activity</strong></td>
<td>Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week.</td>
<td>Adults should do at least 150 min/week of moderate-intensity activity</td>
<td><strong>A total of 60 min of physical activity daily, which includes aerobic activity, work-related activity and muscle-strengthening activity.</strong></td>
</tr>
<tr>
<td>OR</td>
<td>At least 75 min/week of vigorous intensity aerobic exercises</td>
<td>75 min/week of vigorous intensity aerobic exercises</td>
<td>At least 30 min of moderate-intensity aerobic activity (e.g., brisk walking, jogging, hiking, gardening, bicycling, etc.), 15 min of work-related activity (e.g., carrying heavy loads, climbing stairs, etc.) and 15 min of muscle-strengthening exercises</td>
</tr>
<tr>
<td>OR</td>
<td>An equivalent combination of moderate and vigorous intensity aerobic exercises</td>
<td>An equivalent combination of moderate and vigorous intensity aerobic activity</td>
<td><strong>Aerobic activity should be performed in bouts of at least 10 minutes duration.</strong></td>
</tr>
<tr>
<td><strong>AND</strong></td>
<td>Aerobic activity should be performed in episodes of 10 minutes and be spread throughout the week</td>
<td>Aerobic activity should be performed in bouts of at least 10 minutes duration.</td>
<td>Aerobic activity should be performed in bouts of at least 10 minutes duration.</td>
</tr>
<tr>
<td><strong>Muscle strengthening</strong></td>
<td>Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.</td>
<td>For lowering blood pressure and cholesterol, an average 40 minutes of moderate-to-vigorous-intensity aerobic activity, 3 or 4 times per week</td>
<td>Adults should increase their moderate-intensity aerobic physical activity to 300 min per week,</td>
</tr>
<tr>
<td>OR</td>
<td>Adults should do at least 300 min/week of moderate-intensity activity</td>
<td>Adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or</td>
<td>Engage in 150 min of vigorous-intensity aerobic physical activity per week</td>
</tr>
<tr>
<td>OR</td>
<td>150 min/week of vigorous intensity aerobic exercises</td>
<td>-</td>
<td>Engage in 150 min of vigorous-intensity aerobic physical activity per week</td>
</tr>
</tbody>
</table>

weight of an individual. Broca’s index is a commonly used simple clinical parameter to get the ideal body weight. It calculates the ideal body weight in kilograms as height in centimeters minus 100. Body mass index can also be used to calculate the ideal body weight. The recommended body mass index for Indians is 18-23 kg/m\(^2\). The cornerstone of achieving weight loss is calorie restriction to achieve the ideal body weight while the cornerstone of maintaining weight loss is a regular exercise program.

**Physical inactivity: scenario in India**

As per the World Health Organization (WHO), in 2010, physical inactivity was the 4th leading factor for mortality globally.\(^{263}\)

As per the ICMR in 2014, 392 million people were inactive in India which represented nearly 1/3rd of our population. There was a high prevalence of metabolic syndrome, obesity, type 2 diabetes and CAD in India. The Indian diet and lifestyle was the main reason associated with premature CAD and early onset of diabetes in our society.\(^{265-267}\)

**Existing guidelines**

The most well-known evidence-based physical activity recommendations for public health were first issued by the AHA,\(^{268}\) the American College of Sports Medicine\(^{269}\) and the US Department of Health and Human Services\(^{270}\) and these have been modified over
the years. These guidelines have been adopted by various countries and organizations including WHO.260 Recently, revised lifestyle management guidelines were published by the American Heart Association Working Committee in 2013.271 Table 8 summarizes salient points from 4 relevant guidelines on physical activity.

Intensity of exercise

The intensity of exercise can be described either in absolute terms or in relative terms. When using absolute terms, exercise can be categorized as:

- Light-intensity activities - 1.1 MET to 2.9 METs of energy expended during an activity.
- Moderate-intensity activities - 3.0 to 5.9 METs of energy expended during an activity.
- Vigorous-intensity activities - 6.0 METs or more of energy expended during an activity.

Alternately, intensity of exercise can also be defined relative to the fitness of the individual, with the intensity expressed as percentage of a person’s maximal heart rate, heart rate reserve, or aerobic capacity reserve. Yet another way to describe exercise intensity is to use a scale of 0 to 10, where 0 is the level of effort of sitting, and 10 is maximal effort. Relatively moderate-intensity activity is a level of 5 or 6 and vigorous-intensity activity 7 or 8 on this scale.

Dietary changes

Evidence

Substantial evidence indicates that diets using non-hydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD.274

A review of 146 prospective studies and 43 randomized control trials concluded that strong evidence supports valid associations of protective factors, including intake of vegetables, nuts, and “Mediterranean” and high-quality dietary patterns with CHD.274

The Lyon Diet Heart Study, a randomized, single-blind secondary prevention trial aimed at testing a Mediterranean-type diet vs a prudent Western, one of the largest intervention trials and showed nearly 70% reduction in cardiac events. Various other dietary intervention trials showed similar reduction in cardiac events with diets rich in omega 3 fatty acids.275-277 In the Indo-Mediterranean study, the intervention group consumed more fruits, vegetables, legumes, walnuts, and almonds than did controls with reduction in CHD events in Asian Indians.278 The PREDIMED (Prevention Con Delta Mediterranea) study was a primary prevention, dietary intervention trial and showed that among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events.279 The recent American Heart Association guidelines also favor a Mediterranean dietary pattern.271

Diet pattern

Several different diet patterns have been promoted as ‘heart friendly diets’. Of these, the most relevant ones are briefly discussed below.

Mediterranean diet

It has been proposed that a diet pattern that is consistent with Mediterranean diet, when combined with physical activity and no smoking, can help avoid 90% of the type 2 diabetes, 80% of CAD, 1/3 acute MI and 70% of the strokes.280 A typical Mediterranean diet is moderate in total fats, low in saturated fats, has high fiber content and high PUFA (omega-3). Its constituents are fruits, vegetables, whole grains, fatty fish, low amounts of red meat, lower-fat or fat-free dairy products, nuts, olive or canola oil and moderate amounts of red wine.

Indo-Mediterranean diet

For Indians, with a typically different diet pattern in comparison to the west, an Indo-Mediterranean diet can be proposed by including lot of fruits, vegetables, whole grains like unpolished rice, whole wheat and millets; fatty fish for non-vegetarians and fenugreek seeds, mustard seeds, flax seeds, soya bean oil, mustard oil for vegetarians (as sources of omega-3 fatty acids); and nuts to work as a cardio-protective diet.

Dietary Approaches To Stop Hypertension (DASH) diet279

This is a dietary pattern that emphasizes intake of fruits, vegetables, whole grains, low fat dairy products, legumes, poultry, fish, nuts, non-tropical oils; limits intake of sweets, sugar sweetened beverages and red meats. Sodium intake is limited in DASH pattern to no more than 2,400 mg of sodium/day. In patients with hypertension, DASH diet pattern has shown to be very effective in reducing blood pressure.

Macro and Micro-nutrients

Composition of a healthy diet can be described in terms of daily intake of various macro- and micro-nutrients also. The recommendations for macronutrient intake are summarized in the Table 9. 281, 282

Below is a brief list of various cooking oils according to the types of fatty acids present in them:

- High MUFA: olive oil
- High MUFA and moderate omega-6: groundnut, rice bran, sesame
- High LA (omega-6): corn, sunflower, safflower
- High LA (omega-6) and high ALA (omega-3): mustard, soybean, canola, flaxseed
- High trans-fatty acids: vanaspati
Since no single oil is ideal, combining various oils is recommended to maintain a balance of different fatty acids.\textsuperscript{285} Some of the recommended combinations of oils in Indian cooking are:

- Oil containing LA and oil containing both LA and ALA (1:1):
  - Groundnut / sesame / rice bran + mustard
  - Groundnut / sesame / rice bran + canola
  - Groundnut / sesame / rice bran + soybean

- Oil containing high LA and oil containing moderate or low LA (1:1):
  - Sunflower/safflower + olive
  - Safflower / sunflower + groundnut / sesame / rice bran

### Alcohol

A meta-analysis of 34 prospective studies by Castelnuovo et al showed a J-shaped relationship between alcohol and total mortality in both men and women.\textsuperscript{284} Consumption of alcohol, up to 4 drinks per day in men and 2 drinks per day in women, was inversely associated with total mortality in the western population. Heavy drinking was associated with an increase in mortality, hypertension, alcoholic cardiomyopathy, cancer, and cerebrovascular events, including cerebrovascular hemorrhage. Numerous mechanisms have been proposed to explain the benefit that light-to-moderate alcohol intake has on the heart, including an increase of HDL-C, reduction in plasma viscosity and fibrinogen concentration, increase in fibrinolysis, decrease in platelet aggregation, improvement in endothelial function, reduction of inflammation, and promotion of antioxidant effects.\textsuperscript{285} Results from observational studies, where alcohol consumption can be linked directly to an individual’s risk of CHD, provide strong evidence that moderate amounts of all alcoholic drinks are linked with lower risk. Thus, a substantial portion of the benefit is from alcohol rather than other components of each type of drink.\textsuperscript{286}

However, most of the benefits of moderate alcohol consumption apply to the western populations. Regular alcohol consumption did not have protective effect on CAD amongst South Asians in the INTERHEART study.\textsuperscript{285} Similarly, a cross sectional study by Roy et al. suggests that alcohol use is not protective against CHD in Indian men. Rather, it is associated with possible harm. Hence, alcohol intake even in moderation should be avoided by Indians.\textsuperscript{287}

### Tobacco products

Globally, cigarette smoking is the predominant form of tobacco consumption, whereas in India, beedi and tobacco chewing are more widely prevalent. Cigarette smoking is an important and independent risk factor for atherosclerosis, coronary artery disease and peripheral vascular disorders. There is a dose response relationship between the number of cigarettes smoked per day and cardiovascular morbidity and mortality.\textsuperscript{288} Smoking and tobacco chewing have equal and comparable adverse effects on lipid profile and therefore raise the cardiovascular risk in same proportion.\textsuperscript{289}

The consumption of tobacco products should be avoided completely. The 5A’s strategy is suggested for achieving this goal in clinical practice.\textsuperscript{290}

1. **Assess**: determine willingness to make a quitting attempt.
2. **Advise**: strongly urge all tobacco users to quit.
3. **Ask**: systematically identify all tobacco users at every visit.
4. **Assist**: aid every willing patient in quitting by behavioral counseling and pharmacotherapy.

### Table 9: Recommendations for daily intake of macronutrients

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>Proteins</th>
<th>Fats</th>
<th>Fruits, fibers and sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 50–60% energy intake/day</td>
<td>• 10–15% energy/day</td>
<td>• 15–30% energy/day</td>
<td>• 4-5 servings of fruits and vegetables daily of 100 gmeach/day</td>
</tr>
<tr>
<td>• Prefer complex carbohydrates. Low glycemic index and low glycemic load foods are preferable. More than 50% grains should be whole grains daily</td>
<td>• Sources- - Non-veg: fish, lean meat, egg whites, low fat dairy products - Veg: Pulses, legumes, whole grains, etc.</td>
<td>• Components- - Saturated fats: &lt; 7% - Trans-fats: nil - MUFA: 10% - PUFA: 8-10% (omega-6:5-8%, omega-3:1-2%, omega-6 / omega-3 ratio: 5-10)</td>
<td>• Higher intake of fibers (25–40 g/day)</td>
</tr>
<tr>
<td>• Sugars- - &lt;10% of total calories from sugar - Minimize sucrose intake when substituting for starch - Avoid sugar-sweetened beverages and sweets - Substitute with water, buttermilk, tender coconut water, green tea, etc.</td>
<td></td>
<td>• Sources of PUFA- - Omega-6 Linoleic acid (LA): most vegetable oils, except coconut oil - Omega-3: • Alpha-linolenic acid (ALA, the parent compound of omega 3): e.g. soybean/mustard/canola oils, flax seeds, fenugreek seeds, green leafy vegetables, walnuts, etc. • Eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) – oily fish</td>
<td>• Reduce sodium intake &lt;2400 mg/day</td>
</tr>
<tr>
<td>• More than 50% of total calories from sugars - More than 50% grains should be whole grains daily</td>
<td></td>
<td>• Cholesterol 200-300 mg/d</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular disease and tobacco consumption**

Smoking and tobacco chewing are the predominant form of tobacco consumption, whereas in India, beedi and tobacco chewing are more widely prevalent. Cigarette smoking is an important and independent risk factor for atherosclerosis, coronary artery disease and peripheral vascular disorders. There is a dose response relationship between the number of cigarettes smoked per day and cardiovascular morbidity and mortality.\textsuperscript{288} Smoking and tobacco chewing have equal and comparable adverse effects on lipid profile and therefore raise the cardiovascular risk in same proportion.\textsuperscript{289}

The consumption of tobacco products should be avoided completely. The 5A’s strategy is suggested for achieving this goal in clinical practice.\textsuperscript{290}

1. **Assess**: determine willingness to make a quitting attempt.
2. **Advise**: strongly urge all tobacco users to quit.
3. **Ask**: systematically identify all tobacco users at every visit.
4. **Assist**: aid every willing patient in quitting by behavioral counseling and pharmacotherapy.
Non-nicotine replacement options include—
• Nicotine replacement therapies such as nicotine gums, patches, inhalers, nasal sprays, and
• Non-nicotine replacement options such as bupropion, varenicline, etc.

Stress management

As per the INTERHEART study, stressful life events were more common within the prior year in patients with MI than among controls. Psychological distress is also a predictor of fatal ischemic stroke, and depression seems to be an important factor. Most of the association can be largely explained by behavioral changes like smoking, diet, lack of physical activity, etc. which are commonly associated with disturbed psychological states.

Performing simple physical exercises called yogasanas along with meditation is an ancient Indian system practiced by sages of old times for keeping themselves physically fit and mentally agile. Of late, the practice has become very popular among the western countries owing to its simple nature, ease of doing it at no cost and multiple health benefits, most prominent being stress reduction. Different forms of this practice called “yoga” with various combinations of physical postures, breathing exercises and meditation techniques have become popular. Several scientific studies have also been undertaken for the same reason to evaluate the efficacy in terms of demonstrable end points. In one such study, women suffering from end stage renal disease. Several studies have shown cardio protective effects of yoga like reduction of blood pressure, blood sugar, weight and favorable changes in lipid profile.

Summary and recommendations

Physical activity for adults
• All adults should avoid inactivity.
• For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week.
• For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate-intensity, or 150 minutes (2 hours 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate-and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount.
• Adults should also do muscle-strengthening activities that are moderate or high intensity and involve all major muscle groups on 2 or more days a week. However, time spent in muscle-strengthening activities does not count toward the aerobic activity guidelines.

Diet
• Dietary patterns are more significant rather than individual dietary components. Thus, we recommend the adoption of a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, nuts, etc.
• Limit intake of sweets, sugar-sweetened beverages, and red meat.
• This above can be achieved by adopting a diet pattern such as Mediterranean or Indo-Mediterranean diet as described above.

Alcohol
• Alcohol intake, even in moderation should preferably be avoided by Indians.
• Patients with ASCVD who do not consume alcohol should not be encouraged to start regular drinking.
• However, for patients who drink, alcohol should not exceed 1 drink per day for women or up to 2 drinks per day for men (1 drink = 12 oz beer, 5 oz wine or 1.5 oz distilled spirits).

Tobacco products
• Complete abstinence from tobacco products is recommended.

Stress management

• Though no clear, large-scale studies are available with different forms of practice, we recommend that all Indians should be encouraged to incorporate yogasanas and meditation in daily life.

Usage of Statins for Lipid Management

Of all the lipid lowering drugs currently available, statins are the drugs of choice because of multiple reasons. Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase, the key enzyme involved in cholesterol synthesis by liver. Besides, they also increase
expression of LDL receptors, thereby increasing removal of LDL particles from the blood stream. As a result, statins act as powerful LDL-C lowering drugs. In addition, they also lower VLDL-C, the other atherogenic lipoprotein, and raise HDL-C levels. The net effect of statins on lipid profile is roughly 25-55% reduction in LDL-C, 15-51% reduction in non-HDL-C, 7-30% reduction in TG and approximately 5-15% increase in HDL-C. Apart from these lipid modifying actions, statins also have numerous pleiotropic effects as described below. Collectively, all these actions result in profound ASCVD risk reduction with statins.

Several large scale randomized clinical trials have demonstrated that statins significantly reduce ASCVD morbidity and mortality, in both primary and secondary prevention settings (Table 10). In the randomized trials with 5-years follow-up, the relative risk reduction with statins has been in the range of 25-45%; and it is estimated that longer-term treatment would produce even greater risk reduction. Similar to these clinical benefits, statins have also been shown to slow down the progression, or even promote regression, of coronary and carotid atherosclerosis various imaging trials (Table 5). 

Pleiotropic beneficial effects

The inhibition of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase also leads to inhibition of the synthesis of isoprenoid-intermediates. Isoprenylation of proteins is involved in the activation of inflammatory pathways and in vascular remodeling in disease states such as atherosclerosis and diabetes. Blocking this metabolic pathway by statins protects against the progression of atherosclerosis.

In addition, statins also act at several other steps involved in the process of atherosclerosis. They reduce platelet activation and aggregability in both cholesterol dependent and cholesterol independent manner, reduce the pro-atherogenic effects of oxidized LDL; improve endothelial function by promoting endothelial progenitor cell proliferation, migration and survival; reduce vascular smooth muscle cell migration and proliferation, two key steps of atherogenesis; stabilize atherosclerotic plaque though lipid lowering and by decreasing the expression of matrix metalloproteinases and tissue factor; and also decrease myocardial remodeling following MI by inhibiting some effects of angiotensin II such as cardiac fibroblast proliferation, collagen synthesis, and induction of cardiomyocyte proliferation. A proposed mechanism for the anti-inflammatory effects of statins following an acute coronary event is through the reduction of phospholipase A2 biomarkers.

Initiation of statin therapy

Evidence suggests that the clinical benefit of statins is largely independent of the type of statin used, but depends primarily on the extent of LDL-C reduction achieved. Hence, the type of statin and dose to be used should be based on the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient. The recommended LDL-C targets for various ASCVD risk categories are provided in Table 4. It is important to remember that statins have proven to be remarkably safe for most patients. The risk for serious side effects with statins is low whereas the benefit for patients at risk for ASCVD is substantial.

Atleast moderate- or high-intensity statin therapy is required to bring about a clinically meaningful reduction in LDL-C in most patients. Moderate-intensity statin therapy is defined as a statin dose that is expected to reduce LDL-C by at least 30 to <50% whereas high-intensity statin therapy is one that is expected to reduce LDL-C by at least 50% from the baseline. The expected magnitude of LDL-C reduction with the different dosages of commonly used statins is provided below-

- ≥ 50% reduction from baseline (i.e. high-intensity therapy) - Rosuvastatin 20-40 mg/d - Atorvastatin 40-80 mg/d
- 30 to <50% reduction from baseline (i.e. moderate-intensity therapy) - Rosuvastatin 5-10 mg/d - Atorvastatin 10-20 mg/d - Simvastatin 20-40 mg/d - Pitavastatin 2-4 mg/d - Pravastatin 40-80 mg/d - Lovastatin 40 mg/d

Clinicians need to make decisions regarding high- or moderate-intensity therapy depending on the clinical situations they encounter. Discussion with the patient regarding statin therapy, highlighting the advantages and disadvantages with their use, is an integral component of good clinical practice.

Summary and recommendations

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

Statin Intolerance

Lowering LDL-C with the use of statins has consistently been shown to reduce mortality and the risk of recurrent CV events, resulting in improved outcomes, in both primary as well as secondary prevention scenarios. Despite their proven efficacy and extreme
utility in achieving LDL-C targets, the use of standard and high-dose statins has to be limited in some patients due to side effects.

There are adverse effects of statin therapy for which there is definitive evidence such as myopathy, deranged LFT and new onset diabetes. However, numerous other adverse effects that have been anecdotally attributed to statin treatment have no objective evidence to support any cause-and-effect relationship. For instance, careful long-term controlled follow-up of 170,000 patients showed that statins do not increase incidence of cancer, cerebral hemorrhage, kidney disease, liver disease, dementia, memory impairment, or fatigue.  

Several studies have evaluated the incidence of adverse events during statin therapy. In a meta-analysis of over 70,000 subjects in 18 primary and secondary prevention placebo-controlled trials, the number needed to harm for any adverse event with statins was 197 versus 27, which was the number needed to treat to prevent one CV event. In other words, treating 1,000 patients with a statin would prevent 37 CV events and cause 5 adverse events. In this analysis, serious adverse events, such as serum creatine kinase (CK) level elevation to greater than 10 times upper limit of normal (ULN) or rhabdomyolysis were very rare. 

**Statins and skeletal muscle**

The most frequently reported symptoms include myalgia, fatigue, weakness, generalized aching, and low back ache or proximal muscle pain. There have been less frequent complaints of tendon pain and nocturnal muscle cramps. According to well accepted definitions, myopathy is a general term for disease of the muscles, and it is usually characterized by weakness. In the setting of statin treatment, myopathy is used to describe any muscle problem, whether or not it is actually related to the statin use; myalgia is defined as muscular symptoms without CK elevations; myositis refers to muscle symptoms with marked CK elevations; myositis refers to muscle symptoms with CK elevation; and rhabdomyolysis is defined as muscle symptoms with marked CK elevations (> 10 times ULN) with an elevated plasma creatinine and the occasional presence of brown urine.

In a systematic review of

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**Table 10: Major randomized clinical trials with statins**

<table>
<thead>
<tr>
<th>Trial, year</th>
<th>Statin</th>
<th>Setting</th>
<th>Baseline LDL-C level (mg/dL)</th>
<th>Duration; No. of patients</th>
<th>Primary findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S, 1994</td>
<td>Simvastatin</td>
<td>Secondary prevention</td>
<td>188</td>
<td>5.4 years; 4444</td>
<td>All-cause mortality reduced by 30%, coronary mortality reduced by 42%</td>
</tr>
<tr>
<td>WOSCOPS, 1995</td>
<td>Pravastatin</td>
<td>Primary prevention</td>
<td>192</td>
<td>4.9 years; 6595</td>
<td>Non-fatal MI and CHD deaths reduced by 31%</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS, 1998</td>
<td>Lovastatin</td>
<td>Primary prevention</td>
<td>150</td>
<td>5.2 years; 6605</td>
<td>37% reduction in first acute major coronary event</td>
</tr>
<tr>
<td>CARE, 1996</td>
<td>Pravastatin</td>
<td>Secondary prevention</td>
<td>139</td>
<td>5.0 years; 4159</td>
<td>Non-fatal MI and/or CHD deaths reduced by 24%</td>
</tr>
<tr>
<td>LIPID, 1998</td>
<td>Pravastatin</td>
<td>Secondary prevention</td>
<td>150</td>
<td>6.1 years; 9014</td>
<td>CHD deaths reduced by 24%</td>
</tr>
<tr>
<td>HPS, 2002</td>
<td>Simvastatin</td>
<td>Both (65% with ASCVD)</td>
<td>131</td>
<td>5.0 years; 20536</td>
<td>13% reduction in all-cause mortality, coronary mortality reduced by 17%</td>
</tr>
<tr>
<td>PROSPER, 2002</td>
<td>Pravastatin</td>
<td>Both (high risk older adults)</td>
<td>147</td>
<td>3.2 years; 5804</td>
<td>15% reduction in the composite of CHD deaths, nonfatal MI and fatal or nonfatal stroke</td>
</tr>
<tr>
<td>ASCOT-LLA, 2004</td>
<td>Atorvastatin 10 mg/d</td>
<td>Primary prevention (high risk hypertensives)</td>
<td>131</td>
<td>3.3 years; 10305</td>
<td>Non-fatal MI and/or CHD deaths reduced by 36%</td>
</tr>
<tr>
<td>PROVE-IT, 2004</td>
<td>Atorvastatin 80 mg/d, Pravastatin 40 mg/d</td>
<td>Secondary prevention (recent acute coronary event)</td>
<td>106</td>
<td>2 years; 4162</td>
<td>16% reduction with atorvastatin in the composite of death from any cause, MI, unstable angina requiring re-hospitalization, revascularization and stroke</td>
</tr>
<tr>
<td>JUPITER, 2008</td>
<td>Rosuvastatin</td>
<td>Primary prevention</td>
<td>108</td>
<td>1.9 years; 17802</td>
<td>44% reduction in the composite of cardiovascular death, MI, unstable angina requiring re-hospitalization, revascularization, and stroke</td>
</tr>
<tr>
<td>TNT, 2005</td>
<td>Atorvastatin 10 mg/d and 80 mg/d</td>
<td>Secondary prevention</td>
<td>98</td>
<td>4.9 years; 10001</td>
<td>22% reduction in the composite of CHD death, nonfatal non–procedure-related MI, resuscitation after cardiac arrest, or fatal nonfatal stroke</td>
</tr>
</tbody>
</table>

4S- Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS- Air Force/ Texas Coronary Atherosclerosis Prevention study; ASCOT-LLA- Anglo-Scandinavian Cardiac Outcomes Trial– Lipid Lowering Arm; CARE- Cholesterol and Recurrent Events; CHD- coronary heart disease; HPS- Heart Protection Study; JUPITER- Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C- low density lipoprotein cholesterol; LIPID- Long-Term Intervention with Pravastatin in Ischaemic Disease; MI- myocardial infarction; PROSPER- Pravastatin in elderly individuals at risk of vascular disease; PROVE-IT TIMI 22- Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; TNT- Treating to New Targets; WOSCOPS- West of Scotland Coronary Prevention Study.
20 clinical trials, Law and Rudnicka\textsuperscript{328} reported that the incidence of myopathy and minor muscle pain incidence was 195 cases per 100,000 patient-years [95% confidence intervals (CI) 38 to 410]. The incidence of rhabdomyolysis was 1.6 cases per 100,000 patient-years (95% CI 2.4 to 5.5). In the Prediction of Muscular Risk in Observational Conditions (PRIMO) study, over 7,900 hyperlipidemic patients treated with high-dose statin therapy were enrolled in a 12-month, prospective observational follow-up.\textsuperscript{329} Muscle symptoms were reported by 11% of patients. This figure has been confirmed by others also. Hence, we can reasonably state that statin induced myopathy may affect approximately 10-15% of statin users.\textsuperscript{329} Clinical factors that predispose patients to a higher incidence of side effects include being female, older age, low body weight, pre-existing renal or hepatic dysfunction, multi-organ disease, and concurrent alcohol abuse.\textsuperscript{330}

Statin-related side effects mostly occur during the early phase of treatment. In 75% of all cases, the symptoms appear within 3 months, and in 90% cases within first 6 months, after initiation of the treatment or increase in statin dose.\textsuperscript{331,332} Pain is more common in the lower extremities, including the thighs and calves, than in the upper extremities or trunk. These symptoms are particularly exaggerated in athletes.

Although the exact mechanisms causing statin induced myopathy have not been determined, several hypotheses have been proposed. In the PRIMO study, patients with a family history of muscle pain during lipid-lowering therapy had double the risk of muscle-related symptoms compared with patients who did not.\textsuperscript{333} This finding suggests underlying genetic mechanism for statin induced myopathy and hints at the prospects of identifying particular genes or single-nucleotide polymorphisms that may increase the risk of myopathy or reduce the maximal tolerated dose.

Routine measurement of CK during statin therapy is not required. However, caution must be exercised in prescribing statins to patients at risk of having statin induce myopathy, either due to concomitant illness or due to concomitant medications.

**Statins and liver**

Although biochemical tests for liver function may be outside the normal range in 0.1% to 3% of subjects receiving high doses of a statin, the blood tests soon return to the normal range when the statin is stopped. CV and liver outcomes were assessed in 437 patients presenting with abnormal liver enzymes (<3 times ULN), possibly due to non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), in a post-hoc analysis of the GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study.\textsuperscript{334} Patients with abnormal liver tests who received a statin experienced significantly lower CV events (68% relative risk reduction, p<0.0001). This CV benefit was significantly greater (p=0.0074) in patients with abnormal liver tests than it was in patients with normal liver tests. Less than 1% of the patients on statin discontinued statin treatment because of liver related adverse effects (LFT >3times ULN).

Based on the available evidence, there is no need to routinely monitor liver function tests during statin therapy. It is sufficient to perform it before starting statin. Permanent liver damage is extremely rare (less than 1 in 2 million treated subjects).

**Statins and new onset diabetes**

Recently, statins have been found to be associated with the risk of new-onset diabetes mellitus. However this risk is small and is significantly outweighed by the benefits of statins. A recent meta-analysis of 13 randomized controlled trials including 91940 subjects showed that treatment of 255 people with statins for 4 years would result in 1 additional case of diabetes mellitus but would prevent 5.4 deaths or MI, apart from also preventing a number of strokes and revascularization procedures.\textsuperscript{335} Overall, the risk of new onset diabetes with intensive statin therapy is approximately 3 per 1000 patient-years and with moderate intensity statin therapy 1 per 1000 patient-years.\textsuperscript{373}

In this context, it is important to note that new cases of diabetes occur predominantly in subjects already predisposed to develop diabetes, such as those with obesity, metabolic syndrome, pre-diabetes, family history of diabetes, etc. In these subjects, statins seem to merely predate rather than causing de-novo development of diabetes. However, since the prevalence of these disorders is high in our country, we need to carefully screen such patients by performing fasting blood sugar and HbA1c before starting statin therapy. Periodic monitoring is recommended on an annual basis for early diagnosis of new onset diabetes. Aggressive life-style management must be encouraged in all individuals at risk of developing diabetes.

**Statins and memory loss**

There have been case reports suggesting that memory loss or cognitive impairment may occur rarely with statin therapy.

A meta-analysis of eight prospective cohort studies with a 4-year follow-up reported a 38% reduction in dementia which suggests that statins may actually have a beneficial effect on the occurrence of dementia.\textsuperscript{336}

However, more definitive, large, randomized clinical trials do not support a relationship between statins and cognitive changes, either detrimental or beneficial. Cognitive function was systematically assessed 6 times during a 42-week follow-up period.
in the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial in the 70- to 82-year-old patients who initially had a Mini-Mental State Examination score of greater than or equal to 24. No differences were detected (beneficial or detrimental) in cognitive functioning. A Cochrane review of three double-blind, randomized controlled clinical trials of statins versus placebo utilizing two well-established cognition tests, the Alzheimer’s Disease Assessment Scale and the Mini-Mental State Examination, also reported no differences in the treatment groups.

In 2012, the U.S. Food and Drugs Administration (FDA) reported that it continued to receive reports of ill-defined cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use from health professionals, patients, and manufacturers.

If a patient experiences symptoms of impaired cognition while receiving statin therapy, other etiologies should be ruled out, and if none are found, statin therapy may be withdrawn for 1 to 3 months. If improvement is not observed, statin therapy should be restarted. However, if improvement is observed off-statin, re-challenge with another statin, preferably one that is hydrophilic and less likely to cross the blood–brain barrier (e.g., pravastatin, rosuvastatin) in a small dose is warranted to attain the benefit of LDL-C lowering with a statin while avoiding problems in cognition.

Statins and strokes

Statins have been shown to have neuroprotective effects, including an improvement in endothelial function, modulation of brain endothelial-derived nitric oxide synthase, inhibition of inflammatory processes associated with brain injury, and stabilization of cerebrovascular atherosclerotic plaques. Statins have also been shown to significantly reduce the risk of ischemic stroke in CHD patients.

A number of individual statin outcome trials have reported a significant reduction in ischemic strokes when statins were given to patients with coronary or other vascular disease. The meta-analysis by the CTT in 170,000 individuals showed a 21% risk reduction in the incidence of ischemic strokes.

The first study to evaluate the benefit of statin therapy exclusively in a patient population with a history of a stroke or transient ischemic attack, and not CHD, was the SPARCL study. There was a significant reduction in the ischemic events. However, the study reported a significant increase in hemorrhagic strokes in those receiving atorvastatin. A multivariable Cox regression analysis showed that the occurrence of hemorrhagic strokes occurred mostly in individuals who had a history of hemorrhagic stroke at study entry and had elevated blood pressure readings (especially systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) on the visit before the event. Neither total cholesterol nor LDL-C at baseline or at the visit before the hemorrhagic stroke was associated with an increased risk of hemorrhagic stroke, even in those patients with on-treatment LDL-C levels less than 40 mg/dL.

The CTT meta-analysis also reported a non-significant excess of hemorrhagic stroke of 12% per 39-mg/dL LDL-C reduction in statin-treated patients. When the results of SPARCL and the CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) trial, (a study of statins vs. placebo therapy in 5000 individuals older than 60 years with systolic heart failure that reported a very small increase in hemorrhagic strokes) studies were added to the CTT meta-analysis, a hemorrhagic stroke rate ratio of 1.21 (95% CI 1.05–1.41; P = 0.01) per 39 mg/dL reduction of LDL-C was reported. The CTT investigators interpreted this outcome as indicating that a few extra hemorrhagic strokes would occur per 10,000 patients treated with a statin, whereas a few hundred ischemic strokes would be avoided per 10,000 patients treated with a statin within a population of people with a high risk of vascular events.

The conclusion is that a very small relationship exists between statin therapy and hemorrhagic stroke, which is clustered in patients who have had a previous hemorrhagic stroke and who have poorly controlled blood pressure.

Statins and peripheral neuropathy

The potential risk of peripheral neuropathy with statin therapy is very small but in an article that examined this issue, the neurologists concluded that “statin neuropathy occurs much less frequently than recently thought, and the statin class appears to be neuroprotective in some settings.”

Large randomized clinical trials are required to address this issue further. However, at present, there is little or no proof of a causal association. The U. S. National Lipid Association (NLA) Statin Safety Task Force recommends that routine monitoring of patients for changes indicative of peripheral neuropathy is not necessary but systematic evaluation of patients who develop symptoms of peripheral neuropathy while taking a statin is a reasonable approach to rule out secondary causes (e.g., diabetes, renal insufficiency, alcohol abuse, vitamin B12 deficiency). If another etiology is not identified, statin therapy should be withdrawn for 3 to 6 months to establish whether an association with the statin exists.

Statins and cancer

There have been a lot of concern initially that a low cholesterol level somehow contributed to an increased death rate, and later,
with the advent of statins and their ability to significantly lower blood cholesterol levels, that statins themselves might cause cancer. This became a greater concern when an excess of gastrointestinal cancer in the PROSPER trial and of breast cancer in the CARE (Cholesterol and recurrent events) trial was reported, despite the lack of corroborating evidence from other trials.

The CTT meta-analysis in 2012 studied more than 10,000 cancers occurring in 175,000 participants in 27 statin outcome trials. There was no increase in cancer risk in any of the 23 individual sites, including gastrointestinal and breast cancers, nor was there any increased risk of death from cancer at any individual site. Additionally, because lowering of LDL-C had been put forward as a potential cause of cancer risk, CCT scientists also examined whether there was any increased incidence of first cancers yearly over the 5-year follow-up period but found none. Further, no association was found between on-treatment LDL-C levels and cancer rates, but surprisingly, there were actually fewer cancers among statin-treated participants who had lower LDL-C levels (P = 0.008). They concluded that statin therapy had no effect on the incidence of, or mortality from, any type of cancer (or the aggregate of all cancers).

**Approach to management of suspected statin intolerance**

A practical approach to management of statin intolerance is provided below-

1. **Look for reversible causes**-
   - Drug interaction,
   - Hypothyroidism,
   - Hypovitaminosis D, etc.

2. **Reduce the dose of statin or stop it depending on the severity of symptoms**-
   - With mild symptoms, reduce the dose
   - With severe symptoms, stop the statin

3. **Once symptoms disappears, restart statin**-
   - Reduced dose of same or different statin
   - Use statin twice or thrice a week
   - Alternatively, use statin with ezetimibe or bile acid sequestrants

4. **If symptoms recur, use non-statin drugs such as ezetimibe or bile acid sequestrant (e.g. colesevelam)**

5. **Encourage therapeutic life change to all**

**Summary and recommendations:**

**Statin and muscle-related side effects**
- Its true frequency is unknown; however, reported incidence is around 10%.
- Routine monitoring is not needed.
- When patients present with symptoms, check serum CK level and rule out drug-drug interactions, vitamin D deficiency, hypothyroidism and other potential causes of statin induced myopathy. Treatment options include using statin treatment in lower doses, reduced frequency or use of alternative statins.

**Statin and liver**
- An asymptomatic rise in hepatic enzyme activity is one of the most common adverse effect of statin therapy but the incidence of elevated aminotransferase activity >3 times ULN is still no greater than 3%. Hepatitis, cholestasis and acute liver failure are extremely rare.
- In patients with NAFLD/NASH statin treatment is safe, and it may even contribute to the resolution of NAFLD/NASH, and substantially reduce ASCVD risk by a greater margin than in those with normal liver function.

**Statin and new onset diabetes**
- Although statins are associated with an increase in the risk of new onset diabetes, this risk is significantly outweighed by the benefits.
- The risk is greater with intensive statin therapy and in patients already predisposed to develop diabetes.
- Patients with risk factors for diabetes mellitus should be screened with fasting blood glucose or HbA1c, ideally prior to starting statin therapy. Thereafter, monitoring should be repeated within 1 year of initiation and at intervals no longer than 3 years.

**Aggressive lifestyle management is very important in preventing development of diabetes in patients receiving statin therapy.**

**Statin and neurological side-effects**
- A very small relationship exists between statin therapy and hemorrhagic stroke, mainly in patients who have had a previous hemorrhagic stroke and who have poorly controlled blood pressure. However, this risk is generally outweighed by the reduction in ischemic stroke with statins.
- There is no definitive evidence to suggest that statins lead to cognitive impairment or peripheral neuropathy.

**If a patient presents with symptoms suggestive of cognitive impairment or peripheral neuropathy and no alternate etiology is found, statins may have to be withdrawn temporarily.**

**Statin and cancers**
- Statin therapy had no effect on the incidence of, or mortality from, any type of cancer (or the aggregate of all cancers).
Role of Non-Statin Drugs in Lipid Management

The significance of LDL-C in the pathophysiology of atherosclerosis is well established. Accordingly, the use of LDL-C-lowering medications has been shown to result in significant reduction in ASCVD risk in both primary and secondary prevention settings. Statins are the cornerstone of therapy for lowering LDL-C levels. Many large-scale trials have clearly demonstrated that statins significantly and substantially reduce morbidity and mortality from all forms of atherosclerotic disease, especially CHD and stroke, regardless of the starting levels of LDL-C and the underlying absolute risk of CHD in the population. Furthermore, the CHD outcome trials have also shown that the lower LDL-C levels attained are associated with lower risk of CHD events. The most effective of the statins at their highest doses reduce LDL-C by 55% on an average. However, many individuals at risk for ASCVD fail to achieve the desired LDL-C goals. These include the patients with familial hypercholesterolemia, and many patients with established CHD who cannot reach their LDL-C target despite maximum dose statin therapy. In addition, several patients are intolerant to statins due to side effects, mostly myalgia and weakness, especially at high statin doses.

Failure to achieve LDL-C targets even with high doses of statins or inability to use the required doses of statins due to side effects/tolerance are the major challenges with the use of statin therapy. Herein lays the utility and the need for non-statin cholesterol modifying medications. These non-statin lipid lowering agents are also needed for modifying other lipid components such as elevated TG, low HDL-C, etc. Among these alternative agents are fibrates, niacin, ezetimibe, omega 3 fatty acids, bile acid sequestrants, and dual (α/γ) agonists of PPAR such as saroglitazar.

Various leading societies have different recommendations regarding the use of non-statin drugs. Although the ACC/AHA guidelines overtly emphasize on the role of statins, they have stated that non-statin therapies should be used in high-risk patients who have a less-than-anticipated response to statins, those who are unable to tolerate the recommended intensity of a statin, and those who are completely statin intolerant. However, these guidelines have highlighted the lack of any convincing evidence demonstrating benefit with the use of non-statin medications, either alone or in combination with statins. The Endocrine Society differs from the ACC/AHA guidelines regarding treatment of dyslipidemia, particularly hypertriglyceridemia. It encourages the use of non-statin drugs in combination with statins for treating varying levels of TG. It recommends that fibrate be used as a first-line agent for reduction of TG in patients at risk for TG-induced pancreatitis. It also states that fibrates, niacin and omega-3 fatty acids, either alone or in combination with statins, be considered as treatment options in patients with moderate to severe TG levels. The American Association of Clinical Endocrinology (AACE), in its lipids and atherosclerosis guidelines, recommends that statins remain as the drug of choice for LDL-C reduction. Fibrates are recommended for use in the treatment of severe hypertriglyceridemia (TG>500 mg/dL), and the adjunct use of 2 to 4 g of omega 3 fish oil is also recommended, when necessary, to achieve satisfactory TG lowering.

Fibrates are PPAR-α receptor agonists. Various studies have evaluated the effects of fibrates on CV outcomes. The Helsinki Heart Study used gemfibrozil for primary prevention. It showed significant reduction in major coronary events and in non-fatal MI with gemfibrozil. The Bezafibrate Infarction Prevention study and VA-HIT (Veterans Affairs HDL Intervention Trial) were secondary prevention trials that showed improvement in CV outcomes with fibrates. Patients with mixed dyslipidemia associated with insulin resistance syndromes such as type 2 diabetes mellitus or metabolic syndrome derived the greatest benefit from fibrate therapy. However, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial used fenofibrate and found that it did not significantly reduce the risk of the primary outcome of coronary events; although it did reduce the total cardiovascular events.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) study results also did not support the routine use of fenofibrate-simvastatin combination to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. However, in both FIELD and ACCORD studies, improvements in CV outcomes were observed in the subgroup of patients having elevated TG levels and low HDL-C. Currently, fibrates are recommended for use in the treatment of severe hypertriglyceridemia (TG>500 mg/dL) and are also indicated for use as an add-on to statin in combined dyslipidemia. Among the fibrates, gemfibrozil should not be used with a statin due to the increased risk of adverse effects. Renal function needs to be assessed when using fenofibrate.

Niacin, or extended release nicotinic acid, has several side effects and is currently not used for any form of dyslipidemia. There is no incremental benefit of niacin, used as add-on to statin, in reducing CV events. With the use of niacin, there is a concern for a rise in liver transaminases, persistent severe cutaneous symptoms,
dependent manner. It is available
LDL-C by 5-30% in a dose-
colesevalam monotherapy lowers
increase in cholesterol uptake.
into bile acid and a compensatory
conversion of hepatic cholesterol
colesevelam. Bile acid sequestrants
cholestyramine, colestipol and
trial for omega 3 fatty acids is
absorption of fat-soluble vitamins.
gastrointestinal and reduced
The adverse effects are mainly
Twice-daily dosing, after meals.
362 mg tablet; 6 tablets are
patients. A large CV outcome
incidence of major adverse coronary
doses (1.8 g/day) reduced the
Intervention Study), EPA in high
to achieve non-HDL-C targets (9,
statin in combined dyslipidemia
used as add-on to statin for LDL-C
and add-on to statin and fenofibrate in mixed dyslipidemia.
In the IMPROVE-IT, the addition of
ezetimibe to simvastatin resulted
in incremental lowering of LDL-C
levels with improvement in CV
outcomes. However, ezetimibe
can result in an increase in liver
transaminases when combined
with statin.
Omega 3 fatty acids reduce
TG by interfering with many
transcription factors. They have
been recommended for use in
severe hypertriglyceridemia
(TG>500 mg/dL) and as add-on to
statin in combined dyslipidemia
to achieve non-HDL-C targets (9,
In the JELIS (Japan EPA Lipid
Intervention Study), EPA in high
doses (1.8 g/day) reduced the
incidence of major adverse coronary
events in hypercholesterolemic
patients. A large CV outcome
trial for omega 3 fatty acids is
ongoing and is expected to be
completed in 2017.
Bile acid sequestrants include
cholestyramine, colestipol and
colesevelam. Bile acid sequestrants
promote the excretion of bile acids
by interrupting their enterohepatic
circulation. This results in increased
conversion of hepatic cholesterol
into bile acid and a compensatory
increase in cholesterol uptake.
Colestevalam monotherapy lowers
LDL-C by 5-30% in a dose-
dependent manner. It is available
as a 625 mg tablet; 6 tablets are
to be taken daily, in once-daily/
twice-daily dosing, after meals.
The adverse effects are mainly
intestinal and reduced
absorption of fat-soluble vitamins.
Bile acid sequestrants should not be
used if TG are more than 300 mg/
dL, or in the presence of type III
hyperlipoproteinemia.
PPAR agonists improve lipid
levels by modulating the activity
of PPAR-α. Saroglitazar is a
dual PPAR-α/γ agonist which
has recently become available
for clinical use. It has been
found to be an effective and safe
therapeutic option for improving
hypertriglyceridemia in patients
with type 2 diabetes mellitus.
Due to its agonist activity on
PPAR-γ, it leads to an improvement
in glycemic parameters also. It
has been approved by the Drug
Controller General of India for the
treatment of diabetic dyslipidemia
(i.e. hypertriglyceridemia with
type 2 diabetes), not corrected with
statin therapy alone. However,
large-scale CV outcomes studies
are needed to clearly establish
the role of saroglitazar in the
management of dyslipidemia.
Various other agents that produce
significant LDL-C reduction have
been either recently approved or are
currently in advanced large-scale
trials. Alirocumab and evolocumab
are monoclonal antibodies against
PCSK9, that have been recently
approved by the U.S. FDA for use in
patients with heterozygous familial
hypercholesterolemia. Currently
these have also been approved for
use in patients with Homozygous
Familial hypercholesterolemia
and Clinical ASCVD who require
additional lowering of LDL-C.
Mipomersen, an Apo B antisense
drug, and lomitapide, a micromosual
TG transport protein inhibitor,
have also been approved by the
FDA, solely for the treatment of
homzygous familial
hypercholesterolemia, although
they carry black-box warnings
about significant side effects and
are prescribed only under a risk
evaluation and mitigation strategy
(REMS) program.

Summary and recommendations
• LDL-C remains the primary
target for lipid-lowering
therapy and statins remain
the first choice for LDL-C
lowering.
• Non-statin drugs may be used
in the following settings-
  - As alternative to statins
  when the patient is completely
  statin intolerant,
  - In combination with statins
  when the desired dose of
  statin cannot be used due
to intolerance,
  - In combination with
  statins when serum TG
  levels remain persistently
  elevated despite optimum
dose of statins, adequate
  life-style modifications,
  and correction of other
  treatable causes of
  hypertriglyceridemia (e.g.
  uncontrolled diabetes),
  - As first-line of treatment,
  before adding a statin,
  when serum TG levels are
  very high (>500 mg/dL).

Abbreviations
4S: Scandinavian Simvastatin
Survival Study; AACE:
American Association of Clinical
Endocrinology; ACC: American
College of Cardiology; 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 Lenolenic
Acid; Apo A: Apolipoprotein A;
Apo B: Apolipoprotein B; Apo C:
Apolipoprotein C; Apo E:
Apolipoprotein E; ARBITER:
Arterial Biology for the
Investigation of the treatment
effects of reducing
Cholesterol; ASCOT-LLA:
Anglo-Scandinavian Cardiac
Outcomes Trial–Lipid Lowering
Arm; ASCVD: Atherosclerotic
Cardiovascular Disease; ATP:
Adult Treatment Panel; CAC:
Coronary Artery Calcium; CAD:
Coronary Artery Disease; CADI:
Coronary Artery
Disease in Asian Indians; CARE: Cholesterol and Recurrent Events; CETP: Cholesteryl Ester Transfer Protein; CHD: Coronary Heart Disease; CIMT: Carotid Intima Media Thickness; CK: Creatine Kinase; CORONA: Controlled Rosuvastatin Multinational Study in Heart Failure; CRP: C-Reactive Protein; CTT: Cholesterol Treatment Trialists; CV: Cardiovascular; DASH: Dietary Approaches To Stop Hypertension; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; EPIC-Norfolk: European Prospective Investigation into Cancer and Nutrition-Norfolk; FDA: Food and Drug Administration; GREACE: Greek Atorvastatin and Coronary Heart Disease Evaluation; HDL: High-Density Lipoprotein; HDL-C: High-Density Lipoprotein Cholesterol; HERITAGE: Health Risk Factors Exercise Training and Genetics Family Study 209; HPS: Heart Protection Study; HPS2-THRIVE: Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; hs-CRP: High sensitive C-Reactive Protein; ICMR: Indian Council of Medical Research; IDEAL: Incremental Decrease in Endpoints Through aggressive Lipid Lowering; IDL: Intermediate Density Lipoprotein; IVUS: Intravascular Ultrasound; JBS: Joint British Society; JELIS: Japan EPA Lipid Intervention Study; JUPITER: Justification for the use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin; IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LA: Linoleic Acid; LAL: Lip Association of India; LCAT: Lecithin Cholesterol Acyl Transferase; LPL: Lipoprotein Lipase; LDL: Low-Density Lipoprotein; LDL-C: Low-Density Lipoprotein Cholesterol; LIPID: Long-Term Intervention with Pravastatin in Ischaemic Disease; Lp(a): Lipoprotein (a); MI: Myocardial Infarction; MUFA: Monounsaturated Fatty Acids; NAFLD: Non-alcoholic Fatty Liver Disease; NASH: Non-alcoholic Steatohepatitis; NCEP: National Cholesterol Education Program; NICE: National Institute for Health and Care Executive; NIRS: Near-infrared spectroscopy; NLA: National Lipid Association; Non-HDL-C: Non-High-density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin Kexin Type 9; PL: Phospholipid; PLTP: Phospholipid Transfer Protein; PPAR: Peroxisome Proliferator-Activated Receptor; PREDIMED: Prevention Con Delta Mediterranea; PROCAM: Prospective Cardiovascular Munster; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT TIMI 22: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; PUFA: Polyunsaturated Fatty Acid; PURE: Prospective Urban Rural Epidemiology; PWV: Pulse Wave Velocity; REMS: Risk evaluation and mitigation strategy; SHEP: Systolic Hypertension in the Elderly Program; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SR-BI: Scavenger receptor class B type I; TG: Triglyceride; TNT: Treating to New Targets; ULN: Upper Limit of Norm; VLDL: Very Low-density Lipoprotein; WHO: World Health Organization; WOSCOPS: West of Scotland Coronary Prevention Study.

Specialty-wise List of the Expert Panel Members

(In alphabetical order)

**Cardiology**

1. Abraham Oommen, Chennai, Tamil Nadu
2. Aditya Kapoor, Lucknow, Uttar Pradesh
3. Akhayaya Pradhan, Lucknow, Uttar Pradesh
4. Ananda Bagchi, Kolkata, West Bengal
5. Anil Bansal, New Delhi, Delhi
6. Animesh Mishra, Shillong, Meghalaya
7. Anurag Malhorta, Mohali, Punjab
8. Arup Dasbiswas, Kolkata, West Bengal
9. Asha Mahilmaran, Chennai, Tamil Nadu
10. Ashok Kumar, Lucknow, Uttar Pradesh
11. Ashwani Mehta, New Delhi, Delhi
12. Aziz Khan, Nagpur, Maharashtra
13. Balbir Singh, Gurgaon, Haryana
14. Bhaskar Shah, Mumbai, Maharashtra
15. Bipin Daxini, Mumbai, Maharashtra
16. Brian Pinto, Mumbai, Maharashtra
17. Chetan Shah, Mumbai, Maharashtra
18. D P Sinha, Kolkata, West Bengal
19. D Prabhakar, Chennai, Tamil Nadu
20. D Ramesh, Bengaluru, Karnataka
21. Deepak Koshal, Gurgaon, Haryana
22. Dhiman Kahali, Kolkata, West Bengal
23. Girish Parmar, Mumbai, Maharashtra
24. Guru Prasad, Chennai, Tamil Nadu
25. Harshwardhan, New Delhi, Delhi
26. Hemant Malhotra, Noida, Uttar Pradesh
27. J C Mohan, New Delhi, Delhi
28. J P S Sawhney, New Delhi, Delhi
29. Jamshed J Dalal, Mumbai, Maharashtra
30. Joy M Thomas, Chennai, Tamil Nadu
31. Justin Paul, Chennai, Tamil Nadu
32. K K Saxena, New Delhi, Delhi
33. K K Trivedi, Baroda, Gujarat
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**Endocrinology**

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**Internal Medicine and Diabetology**

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Nephrology
147. Ankur Kumar, Lucknow, Uttar Pradesh

Vascular Surgery
151. N Shastry, New Delhi, Delhi

Neurology
153. V Ramachandran, Chennai, Tamil Nadu

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