Lipid Association of India Expert Consensus Statement on Management of Dyslipidemia in Indians 2020: Part III

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Introduction

India is in the middle of an epidemic of atherosclerotic cardiovascular disease (ASCVD) which is showing no signs of abating.[1,2] Coronary artery disease (CAD) manifests almost a decade earlier in India than in Western countries.[3] Further, the incidence of CAD is increasing most rapidly among patients younger than 40 years of age. About 10%-25% of myocardial infarctions (MI) in India occur before the age of 40 years[4,5] and more than 50% of CAD-associated deaths in India occur before the age of 50 years.[3-5]

Although multiple risk factors including smoking, sedentary lifestyle, obesity, hypertension and diabetes are all important contributors to ASCVD, dyslipidemia is the major condition necessary for the atherosclerotic process. Alarmingly, the prevalence of dyslipidemia [defined according to National Cholesterol Education Programme (NCEP) guidelines][6] in Indians is very high with 79% of subjects having at least one lipid abnormality, with decreased high density lipoprotein cholesterol (HDL-C) levels in 72.3% subjects, hypertriglyceridemia in 29.5% subjects and elevated low density lipoprotein cholesterol (LDL-C) levels in 11.8% of subjects.[7] Hence, optimal management of dyslipidemia is key to stem the epidemic of ASCVD along with control of other risk factors.

The appropriate approach to management of dyslipidemia includes identification of subjects with dyslipidemia, increasing the usage and adherence of statins in suitable subjects, focus on achievement of LDL-C goals proposed by Lipid Association of India (LAI),[8] identification and application of lipid markers like lipoprotein (a) [Lp(a)] and apolipoprotein B (apo B) for risk stratification and control of vascular inflammation. Since significant residual risk persists even after high-intensity statin therapy[9] and further lowering of LDL-C beyond that achieved by statins has been shown to further reduce CV risk by addition of non-statin lipid-lowering drugs in recent large randomized trials,[10-12] LAI proposes lower LDL-C goals.[13]

The foundation for prevention of ASCVD is appropriate lifestyle changes. The section on lifestyle changes guides the physicians regarding various interventions based on scientific evidence. The section on low LDL-C levels sums the evidence to the present date and gives justification for lower proposed LDL-C goals. Since hypertriglyceridemia as a component of atherogenic dyslipidemia is highly prevalent, a section on triglycerides discusses the evidence and gives recommendations for approach to patients with hypertriglyceridemia.

Increased Lp(a) levels are also highly prevalent but are a neglected entity. Hence, the section on Lp(a) deliberates on the evidence and recommends universal screening of Lp(a) to estimate CV risk. The section on C-reactive protein discusses the current evidence

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on the role of inflammation in ASCVD and gives criteria for its use in clinical practice. Most importantly, the risk of ASCVD events may be underestimated by use of LDL-C alone to estimate CV risk especially in subjects with atherogenic dyslipidemia. Normal or mildly elevated LDL-C levels may give a sense of complacency regarding estimation and management of lipid risk. Hence LAI proposes that apo B be universally measured to estimate the true risk. Because one molecule of apo B is present on all atherogenic lipoprotein particles, apo B levels will clearly categorize these patients. In the section on apo B, LAI has given cut-offs for risk stratification.

Finally, the LAI recommends non-HDL-C as a co-primary target, as important as LDL-C (a position endorsed by LAI since 2016), for lipid lowering therapy. The monitoring of non-HDL-C is 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 triglyceride targets.

The Lipid Association of India started the process of developing this updated consensus statement in August 2018. It was a two step process. In the first phase we developed the recommendations (August 2018 to June 2019). In the second phase validation cohort was taken comprising physicians from across the country (May 2020 and July 2020). To ensure that the recommendations in this statement reflected expert opinion among lipid specialists throughout India, a series of 19 meetings were conducted in 13 cities involving 162 expert health care providers over 11 months. Subsequently a total of 55 webinars (duration 150 minutes each) were held across the country over 3 months period between May 2020 and July 2020 involving local physicians where new Indian guidelines were presented and discussed and comments recorded. The recommendations presented in this document represent information collected during these series of meetings and summarized here in this consensus document. These recommendations are not binding and are aimed to provide general guidance regarding dyslipidemia management to clinicians. The clinical judgment is of paramount importance in individual cases and all decisions must be taken after counseling and informing the patient in detail (shared decision).

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Lifestyle Modification in the Prevention of Atherosclerotic Cardiovascular Disease

Lifestyle modification plays an enormously important role in the reduction of risk of MI and stroke, two major cardiovascular killers globally. Lifestyle modification is the cornerstone of ASCVD prevention. Lifestyle modification includes attention to diet, physical activity, alcohol consumption, tobacco usage and stress management.

The importance of lifestyle-related risk factors and their role in ASCVD were clearly highlighted by two landmark studies-the INTERHEART[1] and the INTERSTROKE[2] study. The INTERHEART study, which was a large, standardized, case-control study of acute myocardial infarction (MI) patients in 52 countries, showed that the two risk factors, smoking and abnormal lipids, accounted for about two-thirds of the population attributable risk (PAR) of an acute myocardial infarction and both showed a graded relationship with the odds of a myocardial infarction. Besides, regular consumption of fruits and vegetables were associated with 30% risk reduction. In addition, it demonstrated that eating fruits and vegetables, undertaking regular physical activity and avoiding tobacco usage (smoking) could lead to about 80% lower relative risk for MI. The study also found markedly lower prevalence of physical activity and regular intake of fruits and vegetables in South Asians than the western population. Besides, regular alcohol consumption was not found to be protective among south Asians. The INTERSTROKE study complimented the above observations and concluded that 5 risk factors (hypertension, abdominal obesity, diet, physical inactivity and current smoking) accounted for >80% of global risk of all strokes. In terms of prevention, it was demonstrated that intake of fish and fruits (Mediterranean pattern diet) was associated with greatest risk reduction. It was thus concluded that modifications in BP, physical activity, smoking, and diet could substantially reduce the burden of stroke worldwide.

Regarding obesity and diabetes mellitus (DM), which are closely linked with ASCVD, the role of lifestyle cannot be underscored. In a prospective community-based study- The Indian diabetic prevention program (IDPP-1),[3] the progression of DM and effects of interventions were studied in native Indians who were younger, leaner and more insulin resistant, with impaired glucose tolerance (IGT). Compared to the control group, the relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin alone and 28.2% with lifestyle modification with metformin, clearly delineating the key role of life style in diabetes progression and prevention.

In the subsequent sections, we describe the various components of lifestyle management and propose LAI recommendations.

1. Dietary changes

There can be no single diet which can be prescribed to everyone. Diet prescription should be "individualized" based on the metabolic status, body mass index (BMI), age and should accommodate patient's lifestyle, eating habits, concurrent diseases, financial status, along with cultural and ethnic background. For instance, the American Diabetes Association (ADA) in 2019 noted that there is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins, which can be prescribed for people with diabetes. The macronutrient distribution, should be individualized while keeping total calorie and metabolic goals in mind.[4]

More important than a specific distribution of carbohydrates, fats, and proteins is the overall dietary pattern. The 2019 American College of cardiology/American heart association (ACC/AHA) Guidelines on the Primary Prevention of Cardiovascular Disease, effectively summarized the recommended diet pattern: 'all adults should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish and minimizes the intake of trans fats, red meat and processed meats, refined carbohydrates, and sugar-sweetened beverages. For adults with overweight/obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss.[5] While no specific limitation in total fat from calories is specified, a recommendation to keep saturated fat intake to under 7% of calories and avoidance of trans-fats is noted.

Evidence related to diet and CHD

A number of studies indicate that diets using whole grains as the main form of carbohydrates, non-hydrogenated unsaturated fats as a predominant form of dietary fat and abundance of fruits and vegetables with adequate omega-3 fatty acids can offer significant protection against CAD.[6] In the Indo-Mediterranean study, the intervention groups consumed more fruits, vegetables, legumes, walnuts and almonds than did controls with reduction in CHD events in Asian Indians.[7]

The Lyon Diet Heart Study[8] was a randomized single blind secondary prevention trial aimed at testing a Mediterranean-type diet vs. a prudent western diet. It showed nearly 70% reduction in cardiac events with the Mediterranean type of diet. Various other dietary interventional studies have also shown similar reduction in cardiac events with diets rich in omega-3 fatty acids.[9-11] The PREDIMED (Prevention Con Delta Mediterranean) Study was a primary prevention dietary intervention trial and showed that among persons at high risk of cardiovascular disease (CVD), a Mediterranean diet supplemented with extra virgin olive oil or nuts reduced the incidence of major CV events.[12] The AHA Guidelines subsequently also favored a Mediterranean type of dietary pattern.[13]

However, after the Prospective Urban Rural Epidemiology (PURE) study,[14] several controversial findings emerged although many experts have raised concerns because of many methodological issues concerning this study. In this study, 135,335 people from 18 countries were followed up for 7.4 years. The main findings from the PURE study were: higher intake of fat (saturated and unsaturated) was associated with a lower risk of mortality, higher carbohydrate intake

(>60% of diet) was associated with a higher risk of mortality, with no association between demonstrated with intake of total fat or types of fat on CV mortality. This study has been criticized by many experts in nutrition, in part, due to the limited range of fat intake among the populations studied. The recommendation of the guidelines restricting total fat to <30% or saturated fat to <10% total fat was not supported by this study. In general, raw vegetables appeared to be more protective than cooked vegetables and a balanced diet of >3-4 daily servings of fruit, vegetables and legumes was associated with lower mortality.

1a. Diet Patterns:

It is now understood that the dietary pattern rather than individual nutrient components are a better approach to study and recommend to the patients. As a result, several diet patterns are promoted as *heart healthy dietary patterns*. The most relevant ones are briefly discussed below:

Bergeron et al (2019) conducted a study to test whether levels of atherogenic lipids and lipoproteins differed significantly following consumption of diets with high red meat content compared with diets with similar amounts of protein derived from white meat or non-meat sources, and whether these effects were modified by concomitant intake of high compared with low SFAs. Subjects were healthy men and women, 21-65 years, BMI 20-35 kg/m^2, were randomly assigned to 1 of 2 parallel arms (high or low SFA) and within each, allocated to red meat, white meat, and non-meat protein diets consumed for 4 weeks each in random order. LDL-C and apo B were higher with red and white meat than with non-meat, independent of SFA content (P <0.0001 for all, except apo B: red meat compared with non-meat [P =0.0004]). This was due primarily to increases in large LDL particles, whereas small LDL-C and HDL-C were unaffected by protein source. The findings were in keeping with recommendations promoting diets with a high proportion of plant-based food.[15]

Mediterranean Diet

The Mediterranean diet has been shown to reduce CV morbidity and mortality in both primary and secondary prevention.[16] A typical Mediterranean diet is moderate in total fats, low in saturated fats, has a high fibre content and high PUFA (omega-3). Its constituents are fruits, vegetables, fatty fish, whole grains, low amounts of red meat, lower fat or fat free dairy products, nuts, olive or canola oil and moderate amounts of red wine. It is proposed that Mediterranean diet when combined with regular physical activity and no smoking, can help avoid 90% of type 2 DM, 80% of CAD, 1/3rd acute MI and 70% of strokes.[17]

To summarize, the protective effect of the Mediterranean diet on chronic diseases is provided by antioxidants, anti-inflammatory agents and bioactive components found in the nutrient contents. The diet has a protective effect against obesity due to the high fibre content which requires increased time in chewing thereby enhancing satiety and also facilitates the secretion of cholecystokinin, a known anorexigenic factor. These effects also reduce the risk of developing chronic diseases caused by obesity.

Indo-Mediterranean Diet

For Indians with typically different patterns which also varies by region, a single dietary recommendation is difficult to implement. However, an Indo-Mediterranean diet is proposed that focuses on consumption 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. Extra-virgin olive oil (an unrefined oil) can be used for cooking but it has a lower smoke point than many other oils, which means it burns at a lower temperature. Besides cooking and baking, it is recommended that it be used for dipping bread, dressing, dips, cold dishes. However, this diet pattern has been criticized for not adequately being supported by robust data.[18] It has recently been suggested that adherence to the intake of Indo-Mediterranean style diets could markedly reduce the incidence of heart failure as well as cardiac arrhythmias. The cardioprotective effects of diets rich in flavonoids and long-chain omega-3fatty acids (PUFA) are most likely associated with their potent antioxidant and anti-inflammatory actions.[19]

Dietary Approaches to Stop Hypertension (DASH) diet

This is a dietary pattern similar to the Mediterranean diet that also advocates intake of fruits, vegetables, whole grains, low fat dairy products, legumes, poultry, fish, nuts and non-tropical oils. It limits the intake of sweets, sugar sweetened beverages and red meat. Sodium intake in DASH diet is limited to no more than 2400 mg of sodium/day. In patients with hypertension, DASH diet has proven to be effective in reducing BP even more than a sodium restricted diet alone. In a meta-analysis which included seventeen trials on the effect of diet on BP, found that DASH diet, Nordic diet, and Mediterranean diet significantly lowered systolic and diastolic BP by 4.26 and 2.38 mmHg, respectively. These diets are rich in fruit, vegetables, whole grains, legumes, seeds, nuts, fish, and dairy and low in meat, sweets, and alcohol. Further research is needed to establish the effect of dietary patterns on BP in different cultures other than those identified in this review.[20]

Emerging Diet trends

Ketogenic diet

The ketogenic diet encourages high fat and protein intake, while restricting carbohydrate consumption to as low as 20-50 g daily.[21,22] The diet is intended to induce a state of ketosis in the body, promoting fat loss. The high fat and protein content of the diet may decrease hunger and promote satiety and several meta-analyses have produced contrasting results of weight loss, cardiovascular health benefits, and long-term mortality.[23] The impact of the ketogenic diet on cardiovascular health remains unclear and does not appear in recommendations by any major society.

Intermittent Fasting

Intermittent fasting is the practice of alternating periods of normal food intake with periods of little to no caloric intake. A popular weekly regimen is 5 days of normal eating with 2 days of restricted eating (about 400 calories per day). Initial results have been promising, with several studies showing reduced LDL-C levels, decreased systolic and diastolic blood pressure, decreased systemic inflammatory biomarkers, and improved glycaemic profile.[21] However, this diet may be challenging or even dangerous for those with pregnancy, diabetes or eating disorders.

Apart from diet patterns, oils as cooking media and as dressings has always attracted much attention. There has been lot of information about the various types of oils available and their merits/demerits.

1b. Oils

Since no single oil is ideal, combining various oils is recommended so that a balance of different fatty acids can be maintained. Coconut oil (CO) and ghee need special mention as their use is significantly prevalent in India and continues to be hotly debated regarding CV risk. Ghee, also known as clarified butter, has been utilized for thousands of years in *Ayurveda* as a therapeutic agent and in ancient India; ghee was the preferred cooking oil. In the last several decades, ghee has been implicated in the increased prevalence of CHD in Asian Indians due to its content of saturated fatty acids and cholesterol. Ghee (clarified butter) is rich in conjugated linoleic acid, a fatty acid known to be protective against carcinogens, artery plaque formation and DM. One tablespoon of ghee has approximately 135 calories, all of which come from fat. It also has a higher smoking point and a more complex flavor profile.[24]

As of now, there are no large randomized controlled trials on ghee consumption. It is another matter that in India, ghee is commonly used in many households as daily ritual. There are few small studies in humans in this regard. A study in a rural population in India showed a significantly lower prevalence of CHD in men who consumed higher amounts of ghee.[25] In a study conducted to assess serum lipid response to introducing ghee as a partial replacement for mustard oil in the diet of healthy young Indians (63 healthy, young, physically active adult volunteers (52 male, 11 female) showed that serum total cholesterol level rose significantly in the experimental group at 4 weeks; the rise persisted at 8 weeks. A similar rise was also seen in HDL-C. Hence the total cholesterol/HDL-C ratio did not change significantly. The study did not indicate any adverse effect of ghee on the lipoprotein profile.[26] The large amounts of saturated fat contained in ghee, however, makes it non-ideal and not recommended for heart health.

Coconut oil (CO) is commonly used edible oil in many countries, and there is mixed evidence for its effects on lipid profiles and CVD risk. CO has generated discussions about its possible effects on health, especially for being oil rich in saturated fat, which is known to contribute to the development of atherosclerosis and CVD. On the other hand, CO contains high levels of lauric acid that is directly absorbed by enterocytes and may prevent the fat deposition in blood vessels. In addition, flavonoids and polyphenols present in CO may be beneficial in reducing the oxidative stress involved in the etiology of various diseases, like CVD and cancer. CO is predominantly composed of saturated fatty acids (SFA), corresponding to approximately 90% of its total composition. In nutritional terms, a tablespoon of CO (13 g) contains about 120 kcal, 12 g of total fats, 11.2 g of SFA, 0.7 g of monounsaturated fatty acids (MUFA) and 0.2 g of polyunsaturated fatty acids (PUFA). The main fatty acids (FA) found in CO are the lauric (12:0), myristic (14:0) and palmitic (16:0) acids, which represent 46%, 17% and 9% of the FA, respectively. Unlike the long-chain FAs, which require the aid of lipoproteins that can be deposited in various organs, CO mostly consists of medium chain FAs, which are directly absorbed by the intestine and sent to the liver to be used as energy source.[27]

A study to examine the association between CO consumption and lipid profiles in a cohort of 1,839 Filipino women (age 35-69 years) provided one of the earliest evidence for a relationship between high CO consumption and beneficial lipid profiles in the Philippines.[28] However, no convincing evidence exists that consumption of CO, as opposed to consumption of unsaturated oils, led to a decreased risk of CVD.[29] A meta-analysis of 60 controlled trials showed that the main fatty acid in coconut fat, lauric acid has the greatest cholesterol raising effect of all FAs, but much of this is due to HDL-C. As a result, lauric acid had a more favorable effect on total: HDL-C than any other FA, either saturated or unsaturated. LDL-C/HDL-C ratio among CO users is significantly lower than the same ratio in Palm oil (monounsaturated fatty acid rich) and corn oil (polyunsaturated fatty acid rich) consumers.[30] A recent systematic Review and Meta-Analysis of Clinical Trials showed that coconut oil consumption results in significantly higher LDL-cholesterol than non-tropical vegetable oils.[31] The AHA had issued a scientific advisory statement in 2017 to replace saturated fats (including coconut and other tropical oils) with unsaturated fats. The AHA advised against the use of CO, and suggested limiting all saturated fat. For those at risk for or who have heart disease, they advise no more than 6% of total calories from saturated fat, or about 13 g based on a 2000-calorie diet. One tablespoon of CO comes close to that limit at about 12 g of saturated fat.[32] Despite the rising popularity of coconut oil because of its purported health benefits, Coconut oil should not be viewed as healthy oil for cardiovascular disease risk reduction and limiting coconut oil consumption because of its high saturated fat content is warranted.

Key points on oils

- Smoke point has to be considered when choosing oils for frying.
- Mustard and Canola oil appear to be most heart healthy as they are low in saturated fat, high in MUFA and PUFA and they have the highest N-3/N-6 ratio.
- To achieve best health benefits, oils rich in PUFA should be used in combination with those rich in MUFA like olive oil, mustard oil or groundnut oil.
- A combination of oils may be better rather than relying on single oil. Use of both MUFA (Mustard) and PUFA (Sunflower) oils.
- Trans fats (hydrogenated fat): Trans fats are produced when polyunsaturated vegetable fats are artificially hydrogenated, a process that increases both their firmness and their resistance to oxidative spoilage. TFA are present in *vanaspati*, and reused oil that crosses the "smoke point". Trans fats can be found in many foods – including fried foods like doughnuts, and baked goods including cakes, pie crusts, biscuits, frozen pizza, cookies, crackers, and stick margarines and other spreads. The amount of trans fats in a particular packaged food is mentioned on the packaging. However, products can be listed as "0 grams of *trans* fats" if they contain less than 0.5 grams of trans fat per serving. Current US recommendations support the avoidance of trans fats in any amount.

• Cooking oils should never be re-used as they turn rancid and increase the trans-fatty acids.[4]

• Ordinary home cooking does not lead to a significant production of *trans* fats but avoid reaching a point where oils starts to smoke, the "Smoke Point."

A brief list of various cooking oils according to the types of fatty acids present in them is mentioned in Table 1.

Refined versus unrefined oils

Unrefined oil is processed with minimal or no heat. They are usually referred to as cold pressed or expeller pressed oil. These are also labeled as raw, pure or virgin oils. Refined oils, on the other hand, have been bleached or deodorized to extract the maximum amount of oil. It can be as simple as filtration to more complex processes like degumming or acid refining. This process reduces the nutrients in the oil and compromises its effectiveness. Some oils, like coconut oil, do not require any refining and can be used as such while some, like palm oil, need refining. Some examples of unrefined oils are extra virgin olive oil, avocado oil, sesame oil and macadamia oil. Some examples of refined oils include canola oil, rice bran oil, soya oil and sunflower oil.

It is advisable to avoid refined oils, since during the refining process; oils are heated to high temperatures resulting in their degradation and generation of toxic substances. Refined oils, particularly high in PUFAs, degrade easily and therefore, should be avoided for frying. In contrast, oils high in saturated fats (like ghee) can be used for Indian cooking, as they are comparatively stable during frying.[33]

Key Points on diet

• Dietary *patterns* are more important rather than individual dietary *components* hence adopt a dietary pattern that emphasizes intake of vegetables, fruits, whole grains, low fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts etc.

• Carbohydrates (table 2) can be simple and complex. Examples of simple are Maida, sugar, honey, fruit juice and cola. Simple carbohydrates are sugars that should largely be avoided. Complex ones are cereals, pulses, vegetables and fruits. According to Indian Council of Medical Research ICMR 2018 guidelines, carbohydrate content should be 55-60%. However, the consensus statement from lipid association of India (LAI) restricts carbohydrate consumption between 50-60%.[34]

The recommendations for macronutrient intake are summarized in table 3.[35-36]

Excessive intake of salt or sodium chloride can accentuate hypertension and also cause water retention. Limit the use of salt to no more than 6g/day which is equivalent to 2.4g sodium. Processed (canned and frozen) foods tend to be the major source of sodium in the diet; however, use of salt at the table should of course be limited.

Tips to reduce sodium in diet include: Avoid adding table salt on top of prepared food. Always wash canned foods to remove excess salts. Limit the intake of high salt foods such as processed foods (pickles, chutneys and preserved foods), salted nuts. To limit salt intake, add lemon juice for flavor.

Fruit and Vegetable intake: these reduce incidence of stroke, CHD and DM. They also result in substantial improvement in BP, lipid levels, insulin resistance, adiposity and endothelial function. Flavonols, powerful health-giving chemicals which can protect against heart disease, are found in fruits and vegetables. Red onions are full of flavonols whereas white onions have practically none. Unlike many vitamins flavonols are not easily destroyed by cooking; 4 to 5 servings of fruits and vegetables daily are recommended. Fruits and vegetables are also the richest source of fibre. Raw foods contain more fibre than the processed ones. Choose fresh, colorful fruits rather than canned fruits or juices. Have a salad every day.

Seeds and Beans: They lower the incidence of CHD and DM, lower LDL-C, inflammation and improve endothelial dysfunction.

Nuts: Modest nut consumption lowers cardio metabolic risk. Active components are fibre, folate, phenols, tocopherols and plant proteins. A growing body of scientific evidence suggests potential beneficial effects from the ingestion of tree nuts such as walnuts, almonds and pecans. They contain high amount of monounsaturated fat in the form of oleic acid. Magnesium and copper present in the nut may protect against CHD. Since they are rich in calories and fat, nuts should be consumed in small quantities. Almonds are the best source of alpha-tocopherol form of vitamin-E and among the best whole food sources. 70% of fats in almonds is MUFA which helps reduce cholesterol. Eating almonds consistently lowers total cholesterol and LDL-C, respectively by 4-5%. Walnuts contain high concentration of omega-3 fatty acids, alpha linolenic acid. Walnuts have highest antioxidant activity.

Fibre: Beneficial effects of fibre operate via different mechanisms throughout the digestive system including the mouth, stomach and small and large intestine; some of which are still not completely understood. Insoluble fibres include cellulose, hemi-celluloses and lignin and soluble fibres include pectins, β-glucan and hydro-colloids. Systematic reviews of trials and cohorts support that high fibre consumption is associated with reductions in the risk for cardiovascular disease (both heart disease and stroke) and lower risk of type 2 diabetes, lower LDL-cholesterol, lower blood pressure, and some cancers.[37] However, consumption of fibres is far less than what is recommended. The average American gets about 16 grams of fibre a day[38] as opposed to the recommended 30 grams.[39]

Fish and fish oils: Modest consumption, particularly, non-fried, oily fish, (2 servings/week) lowers CHD mortality. Omega-3 FAs are the key beneficial component responsible for this benefit. Fish oils contain the omega-3 PUFAs- eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which has pleiotropic, anti-inflammatory, antioxidant, and anti-platelet properties. Fish oil causes a decline in hepatic VLDL production and increase VLDL clearance. By increasing LPL activity, it enhances clearance of TG rich lipoproteins. At a dose of fish oil of 3-4g/day, plasma TG levels are reduced by about 25-50% after 1 month of treatment. Higher consumption of fish and n-3 fatty acids were associated with multiple measures of lipoproteins that were mostly consistent with cardiovascular prevention, (reduced total cholesterol, LDL cholesterol, apolipoprotein B, and

Table 1: Brief list of various cooking oils used in India according to the types of fatty acids (% of total fatty acids)[41]

Fats/oil	SFA	MUFA	LA	ALA
High (Medium Chain) SFAs				
Coconut	92	6	2	-
Palm Kernel	83	15	2	-
Butter/Ghee	68	29	2	1
High SFAs and MUFAs				
Palmolein	39	46	11	<0.5
High MUFAs and Moderate LA				
Groundnut	19	41	32	<0.5
Rice bran	17	43	38	1
Sesame	16	41	42	<0.5
High LA				
Cotton seed	24	29	4	1
Corn	12	35	50	1
Safflower	9	13	75	-
Sunflower	12	22	62	-
LA and ALA				
Soya bean	14	24	53	7
Canola	6	60	22	10
Mustard/rape seed	4	65	15	14
Flax seed	10	21	16	53
High TFAs				
Vanaspati	46	49	4	-

SFA=Saturated Fatty Acids, TFAs=Trans Fatty Acids, MUFA=Monounsaturated Fatty Acids, LA=Linoleic Acid, ALA=Alpha Linolenic Acid

Table 2: Complex carbohydrate and fiber content of cereals which are commonly used in different parts of India.

Geographic Region in India	High Carbohydrate Less Fibre	High Carbohydrate Moderate Fibre	Low Carbohydrate High Fibre
South	Maida	Finger millet Red rice Parboiled rice Brown Rice	Green gram whole/Muttar Black gram whole/Kali Urad Bengal gram whole/Chole Black Kidney beans/Rajma
North	Maida	Jawar / Sorghum Buckwheat/Kuttu Whole wheat flour Barley	Black Kidney beans Green gram whole Red gram Bengal gram whole
West	Maida	Brown Rice Buckwheat/Kuttu Whole wheat flour Maize	Red gram Chole /Bengal gram whole Muttar/Green gram whole Kali /Black gram whole
East	Maida	Brown Rice Buckwheat/Kuttu Whole wheat flour Maize	Rajma/Black Kidney beans/Green gram whole Kali Urad/Black gram whole Chole/Bengal gram whole

Table 3: LAI Recommendations for daily intakes of macronutrients:

Carbohydrates	Proteins	Fats	Fruits, fibres and sodium
50-60% energy intake/day	10-15% energy/day	15-30% energy/day	
Prefer complex carbohydrates. Low glycemic index and low glycaemic load foods are preferable	Sources- Non-vegetarian: fish, lean meat, egg whites, low fat dairy products Vegetarian: Pulses, legumes, whole grams etc.	Components: - Saturated fats: 10% - Trans fats: nil - MUFA:10% - PUFA:8-10% (omega-6: 5-8%, omega-3: 1-2%, omega-6/omega-3 ratio: 5-10)	4-5 servings of fruits and vegetables daily of 100 g each/day
More than 50% grains should be whole grains daily		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.soyabean/mustard/ canola oils, flax seeds, fenugreek seeds, green leafy vegetables, walnuts etc. * Eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA)-oily fish * Cholesterol 200-300 mg/ day	Higher intake of fibres (25-40 g/day)
Sugars- <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.			Reduce sodium intake <2400 mg/day

larger LDL size.[40]

Meat: Red meat such as from beef and lamb is a major source of saturated fat in the diet, which can significantly raise blood cholesterol levels. Processed meats more than unprocessed meats increase the risk of diabetes and coronary heart disease (CHD).

Dairy: Consumption of low and especially fat-free dairy products (like skimmed milk and yoghurt) is associated with lower CHD/DM/stroke.

• Tea/Coffee: There is little evidence related to the beneficial effect of these beverages. It is however believed that green tea (>2 servings/d) lowers CHD, stroke and diabetes risk. Green tea lowers LDL-C, and it contains more polyphenols than black tea. The polyphenols present in tea prevent the oxidation of low-density lipoprotein by inhibiting formation of atherosclerotic plaques. Frequent (>2 servings/day) coffee intake also reduces risk of diabetes.

2. Physical Activity:

2a. Benefits of exercise

Exercise has always been highlighted as a cost-effective prevention strategy for CVD. Both human and animal studies have demonstrated multifactorial effects of exercise,[42] including skeletal muscle growth, vascular remodeling, and beneficial effects on metabolism.

CVD: A number of studies have shown a strong inverse relationship between habitual exercise and the risk of CHD, cardiac events, and CV death for both primary and secondary prevention.[43,44] Exercise also induces structural changes in cardiac muscle, which helps to protect against ischemic damage.[41] Intervention studies have reported that both aerobic and strength training have favorable effects on CV risk factors in individuals at high risk for CVD.[45-47]

Diabetes: Aerobic exercise may improve glycemic control and insulin sensitivity and may prevent the development of T2DM in high-risk groups.

Cancer prevention and

treatment: Exercise may provide modest protection against breast, intestinal, bladder, kidney, lung, stomach, esophageal, prostate, endometrial, and pancreatic cancers.[44,48]

Obesity: Compared with a weight loss diet alone, diet coupled with either exercise or exercise and resistance training is associated with a greater reduction in body fat and enhanced preservation of body lean mass, compared with weight loss diet alone.

Osteoporosis: Weight bearing exercise is associated with an increase in bone mineral density in men and women.

Gallstones: Physical activity is associated with a decreased risk of cholelithiasis.

Cognition: Exercise has been associated with improved cognitive function in both young and older adults.[49]

Psychological: Regular exercise is associated with improved sleep, reduced stress and anxiety, and a lower risk of depression.[50]

Physical activity thus has linear relation with multiple health benefits.[51,52] It increases left ventricular ejection fraction, arrhythmia threshold, HDL-C, promotes fibrinolytic activity, insulin sensitivity and psychological wellbeing.[53] It decreases non-HDL-C, TG, LDL-C, total cholesterol, platelet aggregation, abdominal obesity and body weight. Further exercise has also been shown to reduce PCSK-9 levels.

In the HERITAGE family study, the largest published interventional study, 675 normo-lipidemic subjects were given 20 weeks of supervised exercise. Their HDL-C concentration increased by 3.6 ± 11 % in both males and females compared to baseline but with significant inter-individual variability. A significant reduction ($p<0.01$) from baseline levels in plasma total and VLDL was also observed only in the 24h post training specimens reflecting a response to the last bout of exercise.[54] As for LDL-C physical activity alone has shown no significant effect as shown in several systemic reviews.[55,56] Nevertheless, resistance training over longer periods may reduce LDL-C also. [57] Physical activity appears to increase the average size of LDL particles and reduce the number of more atherogenic, small, dense LDL particles.[58] This observation is of particular importance to Indians, who have increased proportions of small, dense LDL particles.

A Longitudinal Analyses in the UK Biobank Study involving a large cohort of 502, 635 individuals, 40 to 69 years of age, analyzed the associations of objective and subjective measures of fitness and physical activity with 6 CV outcomes and total mortality, and explored these associations in individuals with different genetic burden for CVD. Study revealed that Fitness and physical activity has inverse associations with incident CVD in the general population, as well as in individuals with elevated genetic risk for these diseases.[59] Among those at high, intermediate, or low genetic predisposition for CHD and AF, there was a graded inverse association with these parameters among each stratum of genetic risk. UK Biobank Study also suggested that in the longer term, identifying subgroups based on genetic risk that benefit most from lifestyle interventions could help personalize prevention strategies of chronic diseases. Furthermore, personalized prevention and treatment strategies could help motivate individuals more efficiently compared with general guidelines.

Physical inactivity - Indian scenario

The World Health Organization (WHO) in 2010 stated that physical inactivity was the fourth leading cause of mortality globally.[57]

According to ICMR in 2014[60], 392 million people were inactive in India representing nearly one third of our population. There was high prevalence of obesity, T2DM, metabolic syndrome and CHD in India. The Indian diet and lifestyle were the main reason for premature CHD and also early onset of type-2 diabetes.[61-63]

The evidence-based Guidelines on physical activity have been proposed by the WHO[57], AHA[64] and US department of health and Human services.[65]

2b. Classification of exercise

Exercise has been classified as isotonic, isometric and aerobic.[65] Dynamic (isotonic) refers to regular, purposeful movement of joints and large muscle groups. Isometric exercise involves the static contraction of muscles without joint movement while aerobic exercise is any activity which uses large muscle groups and results in greater oxygen consumption by the body than it would do while resting. However, the benefits of exercises are related to the "dose" – which encompasses its duration, intensity and frequency. The intensity of exercise is generally categorized as either moderate- intensity dynamic aerobic exercise or vigorous- intensity dynamic aerobic exercise. When using absolute terms, exercise can be categorized as- Light intensity activities: 1.1 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, and Vigorous-intensity activities: ≥6.0 METs of energy expended during an activity.

There is no single exercise prescription for all adults; exercise should be individualized to suit the patient's capabilities and to prevent injuries and to maximize incentives for maintaining a consistent regimen. In general, reasonable weekly goals for dynamic aerobic exercise are at least, 150 min of moderate-intensity physical activity (approximately 30 min/day, ≥5 days/week) or at least, 75 min of vigorous- intensity physical activity (approximately 30 min/day, ≥3 days/week). For additional or more extensive health benefits, adults should increase their aerobic physical activity to 300 min/week of moderate intensity or 150 min/week of vigorous intensity activity. A combination of moderate and vigorous intensity activity can also be implemented.

The most extensively studied form of exercise is dynamic aerobic exercise which is regular and purposeful movement of large muscle groups in moderate and/or vigorous activity that places stress on the CV system. Examples include: brisk walking, jogging, dancing, cycling, swimming and using certain exercise equipment. The evidence on dynamic resistance exercise is limited. Common type of dynamic resistance exercise is weight lifting often with the use of exercise equipment. These types of exercises are typically performed with a goal of progressively increasing muscle strength.

2c. Risks of Exercise

In the majority of patients, the benefits of physical activity far outweigh the possible associated risks. Musculoskeletal injury is the

Table 4: Salient points from relevant guidelines on physical activity.

US Department of Health and Human Services	WHO	AHA	Indian Consensus Document
Avoid inactivity	-	-	Physical inactivity should be avoided as much as possible
Aerobic Physical Activity			
Adults should do at least 150 min/week of moderate intensity activity	Adults aged 18-64 should do at least 150 min of moderate intensity aerobic physical activity throughout the week.	Adults should do at least 150 min/week of moderate intensity activity	A total of 60 min of physical activity daily, which includes aerobic activity, and muscle-strengthening activity.
OR		75 min/week of vigorous intensity aerobic exercises	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
75 min/week of vigorous intensity aerobic exercises	At least 75 min of vigorous intensity aerobic physical activity throughout the week		
OR			
An equivalent combination of moderate and vigorous intensity aerobic exercises	An equivalent combination of moderate and vigorous intensity activity	A combination of moderate and vigorous intensity aerobic activity	Aerobic activity should be performed in bouts of at least 10 min duration
Aerobic activity should be performed in episodes of 10 min and be spread throughout the week	Aerobic activity should be performed in bouts of a least 10 min duration.	Aerobic activity should be performed in episodes of 10 min and be spread throughout the week	
AND			
Muscle strengthening Adults should do muscle strengthening activities that are moderate or high intensity and involve all major muscle groups on ≥2 days/week	Muscle – strengthening activities should be done involving major muscle groups on ≥2 days/week	For lowering blood pressure and cholesterol, an average 40 min of moderate- to vigorous intensity aerobic activity, 3 or 4 times/week	Adults should increase their moderate- intensity aerobic physical activity to 300 min/week,
For additional health benefits 300 min/week of moderate intensity activity.	Adults should increase their moderate – intensity aerobic physical activity to 300 min/week, or		Engage in 150 min of vigorous intensity aerobic physical activity/week
150 min/week of vigorous intensity aerobic exercises	Engage in 150 min of vigorous-intensity aerobic physical activity/week		
OR			
An equivalent combination of moderate and vigorous intensity aerobic exercises	An equivalent combination of moderate- and vigorous- intensity activity.		An equivalent combination of moderate- and vigorous intensity activity.

most common risk of exercise. More serious but much less common risks include arrhythmia, sudden cardiac arrest and MI. Those who engage in sports activities run a higher risk of incurring minor injury but people who do not participate in regular exercise are more likely to incur more severe injuries when engaging in such activity. Myocardial infarction or Sudden cardiac death (SCD) is rare but may occur during physical activity, particularly among those with multiple cardiac risk factors and those who exercise infrequently.[66,67]

Rhabdomyolysis — Subclinical myoglobinemia, myoglobinuria, and elevation of creatine kinase (CK) are common following physical exertion. The CK levels can rise several-fold, particularly after intense exercise for extended periods of time (e.g. marathon running).[68]

Bronchoconstriction — Exercise-induced bronchoconstriction occurs in the majority of patients with current symptomatic asthma.[69] Other effects — Hypothermia, hyperthermia, and dehydration are potential preventable risks associated with physical activity.[70] Table 4 summarizes the salient features from the recommendations of the major organizations for physical activity, including the Indian consensus document.[71]

Ideal Body Weight

Maintaining an ideal body weight is essentially related to diet and physical activity. The cut-off of increased BMI for Indians is 23 kg/m^2. The Asian Indian-specific guidelines for defining and managing overweight and obesity have defined normal BMI as 18.0–22.9 kg/m^2, overweight as those with BMI between 23.0–24.9 kg/m^2 and obesity as those having BMI ≥25.0 kg/m^2.[72]

While BMI remains the most widely used clinical method of measuring obesity, in the case of the Indian population, the measurement of waist circumference (WC), should also be considered as important as BMI, if not more. The recommended waist circumference for Indian men is 90 cm or 35.4 inch (it is 102 cm/40.1 inch globally) and 80 cm or 31.5 inch for Indian women (as opposed to 88 cm/34.6 inch globally). Asians and South Asians in particular, have more severe inflammation, insulin resistance, and liver fat even when non-obese by BMI standards used for Caucasians.[72,73] In addition to increasing the risk of hypertension, overweight and obesity increase CV risk through adverse effects on lipids, insulin resistance, and other cardio-metabolic processes.

3. Alcohol

An updated meta-analysis of 34 prospective studies showed a J-shaped relationship between alcohol and total mortality in both men and women.[74] Consumption of alcohol up to 4 drinks/day in men and 2 drinks/day in women was inversely associated with total mortality in western population. Heavy drinking was associated with an increase in mortality, hypertension, alcoholic cardiomyopathy, cancer and cerebrovascular events including cerebrovascular hemorrhage. A host of mechanisms have been postulated to explain the benefit that light to moderate alcohol intake has on the heart, including an increasing HDL-C, increase in fibrinolysis, reduction in plasma viscosity and fibrinogen concentration, decrease in platelet aggregation, reduction of inflammation, improvement in endothelial function and promotion of antioxidant effects.[75]

Observational studies provide strong evidence that moderate amounts of all alcoholic drinks are linked with

lower risk. Thus, the substantial portion of benefit is from alcohol rather than other components of each type of drink (e.g. beer, wine or spirits).[76] However, it is important to note that most of the benefits of moderate alcohol consumption apply to the Western population. In the INTERHEART study, regular alcohol consumption did not demonstrate protective effect on CHD among South Asians.[77] Hence, alcohol intake even in moderation should be avoided by Indians, since it has no virtues to offer. However, the per capita alcohol consumption in India increased from 2.4 liters in 2005 to 4.3 liters in 2010 and 5.7 litres in 2016.[78]

Patients with ASCVD who have never tasted alcohol should not be encouraged to take up regular alcohol consumption. However, for patients who drink, alcohol should not exceed up to 2 drinks /day for men and 1drink/day for women. (1 drink =1.5 oz distilled spirits, 5 oz wine, 12 oz beer. A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol.

4. Tobacco

Smoking is a major cause of CVD and an independent risk factor for atherosclerosis, CHD and peripheral artery disease. It causes approximately 1of every 4 deaths from CVD, according to the 2014 US Surgeon General's Report on smoking and health.[79] Globally, cigarette smoking is a predominant form of tobacco consumption whereas in India, *Beedi* and tobacco chewing are widely prevalent. There is a dose-response relationship between the number of cigarettes smoked/day and CV mortality and morbidity.[80] Cigarette smoke contains more than 4000 chemical substances, including nicotine and carbon monoxide (CO) that can have harmful effects on cardiovascular function. These basic ingredients of tobacco smoke cause an increase in oxidative stress, endothelial damage and dysfunction, and are associated with significantly higher serum concentrations of total cholesterol and TG, and lower levels of the cardio protective HDL. By causing intravascular inflammation, smoking promotes the development of atherosclerosis and cardiovascular disease. Nicotine deregulates cardiac autonomic function, boosts sympathetic activity, and increases heart rate (HR) at rest, while blunting HR elevation during progressive exercise and lowering the maximum HR that can be achieved. Smoking and tobacco chewing have equal and comparable adverse effects on the lipid profile and therefore raise the CV risk in same proportion. Smoking cigarettes with lower levels of tar or nicotine does not reduce the risk for CVD.

Besides, exposure to second hand smoke causes heart disease and stroke even in nonsmokers.[81] There is no safe lower limit of exposure to secondhand smoke.[82] More than 41,000 preventable deaths occur in United States from CHD caused by exposure to second hand smoke. Therefore, 2019 AHA/ACC guidelines on the primary prevention of CVD recommend that patients be advised to take precautions against exposure to secondhand smoke and aerosol from all tobacco products.

Electronic Nicotine Delivery Systems

Electronic nicotine delivery systems (electronic cigarettes, e-cigarettes or vaping devices) deliver nicotine by heating a solution, called e-liquid, that contains nicotine, propylene glycol and a wide range of additives and flavoring agents. Because they do not burn tobacco, e-cigarettes expose the user to fewer and lower levels of the harmful chemicals found in cigarette smoke. Therefore, they are likely to be less harmful than continuing to smoke, even though they are not harmless because users are exposed to nicotine and other chemicals. According to a white paper on e-cigarettes by the Indian Council of Medical Research (ICMR), depending on the battery output voltage used nicotine solvents can release in varying amounts, potential carcinogens such as acetaldehyde, formaldehyde and acetone. The liquid-vaporizing solutions also contain "toxic chemicals and metals that can cause several adverse health effects including cancers and diseases of the heart, lungs and brain". E-cigarettes also contain volatile organic compounds, heavy metals, such as nickel, tin and lead. E-cigarettes are increasingly popular among youth and dual use with cigarettes is often seen.[83] E-cigarettes are however, banned in India.

The consumption of tobacco products in any form, including flavored or unflavored E-cigarettes should be avoided completely. Since nicotine is a highly addictive substance, quitting tobacco use can be challenging. Healthcare professionals play an important role in tobacco cessation interventions; in fact, advice from a physician increases by 66% the chance that a smoker will make a successful quit attempt.[84] Smokers who quit start to improve their heart health and reduce their risk for CVD immediately. Within a year, the risk of heart attack drops dramatically, and even people who have already had an MI can cut their risk of having another if they quit smoking. Within 5 years of quitting, smokers lower their risk of stroke to about that of a person who has never smoked.

The 5A's strategy is suggested for achieving avoidance of tobacco products in clinical practice.[85]

Ask: systematically identify all tobacco users at every visit.

Advise: strongly urge all tobacco users to quit.

Assess: determine willingness to make a quitting attempt.

Assist: aid every willing patient in quitting by behavioral counseling and pharmacotherapy

Arrange: schedule for follow-ups

For those requiring pharmacotherapy to aid in quitting, nicotine gums, lozenges, patches, inhalers, nasal spray are available.[86] Nicotine replacement therapy (NRT) is available even without a doctor's prescription. Medicines for which a prescription is needed are bupropion and varenicline. Pharmacotherapy is generally safe, and is clearly safer than continuing to use tobacco products. Despite some controversy regarding the safety of bupropion and varenicline, regulatory agencies consider these drugs as having a favorable benefit/risk profile. However, given the high rate of psychiatric comorbidity in dependent smokers, practitioners should closely monitor patients for neuropsychiatric symptoms. Second-line pharmacotherapies include nortriptyline and clonidine.

A recent study among the general public showed that tobacco cessation therapy did not increase the risk of serious CV events.[86]

5. Stress management

According to the INTERHEART study stressful life events were more common within the prior year in patients with MI than among controls.

Psychological stress is also a predictor of fatal ischemic strokes. Most of the associations can be explained by behavioral changes such as lack of physical activity, diet, smoking etc., which are commonly associated with altered psychological states.[87] Depression is among the most common psychosocial issues among patients with a prevalence of up to 30% in those with cardiovascular disease, roughly 2-3-fold greater than those without cardiovascular disease. Simple screening tools such as the Patient Health Questionnaire-9 (PHQ-9), are recommended in clinical practice, especially in those with known cardiovascular disease. A simple algorithm for management of depression has been recommended by the American Heart Association based on scores obtained from the PHQ-9.[88]

Several different stress management and reduction approaches are available. These include advice related to proper sleep, changes in behavior (behavior therapy) and advice against use of harmful substances like alcohol or narcotic drugs as a remedy to manage stress. Meditation has been considered as a useful stress management and CV risk reduction tool in recent years and has been systematically studied for its various psychological and physiological benefits.

5a. Role of meditation in stress management and CV risk reduction

Meditation is an ancient Indian discipline which has been practiced for several hundred years as an approach to attaining union with the ultimate (yoga). Several different types of meditation have been prevalent with the common features being contemplative inward attention, leading to a state of absorption. Recently, lot of attention has been garnered by the meditation practices owing to the corollary health benefits that accrue in those who practice it. Systematic studies with different types of meditation have demonstrated that it is an active process that results in significant short- and long-term physiological alterations, all of which are favorable for overall health and well-being. The greatest advantage is that all these benefits are obtained without any harmful side effects.

As expected, the maximal benefit has been on the ability of meditation to reduce perceived stress in the practitioners. Stress is a powerful risk factor for CVD which largely goes undetected, is not managed appropriately and is thus increasing to epidemic proportions. Antidepressants/ anxiolytics have multiple, bothersome side effects and interactions-owing to which they are not preferred by the patients as well as physicians, particularly for long-term use. Several studies have been published regarding the role of meditation in stress management. A meta-analysis of 47 studies in >3000 subjects demonstrated that the effect size of meditation was comparable to anti-depressant medications without any attendant side effects.[45] Meditation is thus an integral part of stress management programs and is being encouraged at all levels by governments, corporate sector for its employees, in the armed forces, educational institutions, as well as in hospital settings for the patients as well as physicians and nurses.

Several studies have also evaluated the role of meditation in impacting other risk factors like elevated BP, blood sugar and dyslipidaemia.[89-92] Acknowledging these findings, the AHA recommends meditation as a life-style intervention for overall CV risk reduction.[61] However, not all meditation practices are equal. Some are quite cumbersome, not widely available, require considerable training, involve expense and are not widely available.

Heartfulness is a heart-centered system of practices, based on the ancient raja yoga (yoga of the mind) which originated in India more than a century ago. Currently being practiced in >150 countries of the world, it is widely being practiced in India too. It is offered free of cost, is undemanding and can be incorporated in the daily life quite easily by everybody. This simple but effective system has also been explored for its scientific benefits and has demonstrated consistent health benefits. In a study on heartfulness and heart rate variability, it was shown that the practice resulted in beneficial alteration of sympatho-vagal balance, reduction in heart rate, as well as BP.[93] In another study, a short duration of heartfulness practice resulted in positive psychological changes, reduced burnout, as well as impacted the telomere length of the practitioners in a healthcare setting.[94] However, the reported studies have several limitations and larger studies are needed to confirm these findings. Even then, meditation is widely being accepted as a safe and effective tool for CVD risk reduction that can be easily incorporated in the daily routine.

Summary and LAI recommendations

Diet

- The overall dietary pattern is more important for cardiovascular health than the specific composition of individual macronutrients. Thus, we recommend the adoption of a DASH-like or Mediterranean dietary pattern that emphasizes intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, nuts, etc. A combination of monounsaturated and polyunsaturated oils may be considered. Oils rich in PUFA should be used in combination with those rich in MUFA like olive oil, mustard oil or groundnut oil. It is advisable to avoid refined oils, since during the refining process; oils are heated to high temperatures resulting in their degradation and generation of toxic substances. We do not recommend use of coconut oil, and suggest limiting all saturated fats. We also recommend limiting intake of sweets, sugar sweetened beverages and meat. This above can be achieved by adopting a diet pattern such as Mediterranean or Indo-Mediterranean diet as described above.

Incorporating dietitians into clinical practices can provide a valuable resource for patients and healthcare providers alike. Multiple sessions with such trained lifestyle interventionalists over several months are often needed to achieve adequate adherence to dietary recommendations.

Physical activity for adults

- Physical inactivity is harmful and should be avoided. For substantial health benefits adults should do at least 150 min/week of moderate intensity, or 75 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous intensity aerobic activity. Aerobic activity should preferably be spread throughout the week. Aerobic activity can also be performed in episodes of at least 10 min, 3 times/day.
- For additional and more extensive health benefits, adults should increase

their aerobic physical activity to 300 min / week of moderate-intensity, or 150 min / 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 are also advised to do muscle strengthening activities that are moderate or high intensity and involve all major muscle groups on ≥2 days/ week. However, time spent in muscle-strengthening activities does not count towards the aerobic activity guidelines.

• Including exercise physiologists in healthcare practices can be a valuable resource for patients and healthcare providers alike and such lifestyle interventionalists should meet regularly with patients to assure adequate adherence to physical activity recommendations.

Alcohol

• Alcohol intake should preferably be avoided by Indians, or whenever possible kept to a maximum of one drink daily for women and two drinks daily for men. One drink is considered to be 1 oz of spirits, 4 oz of wine, or 12 oz of beer.

• Patients with who do not consume alcohol should never be encouraged to start drinking it.

Tobacco products

• Complete abstinence from tobacco products, including all vaping products and exposure to secondhand smoking is recommended. Healthcare providers should incorporate the five A's as described above when counseling patients with tobacco use.

Stress management

• In view of the widespread availability in rural as well as urban areas of the country, its simple and secular nature and availability of studies demonstrating its salutary effects, LAI recommends that heartfulness practices be included in the daily routine of all individuals. Adequate sleep should also be encouraged.

Conclusions

Lifestyle management forms the foundation of ASCVD risk reduction and should be implemented in all patients with the appropriate guidance from lifestyle interventionalists such as dietitians and exercise physiologists, ideally in multiple sessions done over several months. Incorporating dietitians and exercise physiologists into medical practices throughout India will be important to accomplish this. Indians are at increased risk of ASCVD primarily owing to the composition of the native diet and inadequate physical activity. Evidence based interventions which are also easily followed and tailored to local needs should be implemented. These guidelines are a step in this direction and aim to reduce the risk of ASCVD in the Indian population. Widespread availability and awareness about these will go a long way in this direction.

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Low Density Lipoprotein Cholesterol Targets in Secondary Prevention of Atherosclerotic Cardiovascular Disease

Background and Introduction

A German pathologist, Rudolf Virchow in 1856 suggested that blood lipids accumulate in arterial wall.[1] In 1977, the Framingham study showed that elevated low density lipoprotein-cholesterol (LDL-C) and reduced high density lipoprotein-cholesterol (HDL-C) levels independently predict risk for developing atherosclerotic cardiovascular disease (ASCVD). LDL-C contributes significantly to the initiation and progression of atherosclerosis through a pathway involving endothelial cell dysfunction, formation of oxidized LDL, foam cell formation and inflammation.[2]

In 2001, ATP III guidelines focused on intensive treatment of patients with coronary heart disease (CHD) and recognized significant 'CHD risk' in persons with multiple risk factors. LDL-C <100 mg/dl was identified as optimal and LDL-C was considered the primary target of therapy with non–HDL-C <130 mg/dl as a secondary target in patients with hypertriglyceridemia.[3]

The 2004 update of ATP III considered 5 major clinical outcome trials- HPS, PROSPER, ALLHAT-LLT, ASCOT-LLA and PROVE-IT TIMI 22 published between 2001 and 2004, that addressed issues not previously focused upon in clinical trials of cholesterol lowering. It recognized the following- diabetes as a CHD risk equivalent, an optional goal of LDL-C less than 70 mg/dl in very high-risk patients, and combination therapy of statins with non-statins in patients with hypertriglyceridemia or low HDL.[4]

These goals served as the standard of care for patients with dyslipidemia for more than a decade. LDL-C continues to be the lipoprotein of interest as recommended by ATP III (Adult Treatment Panel III), AHA/ACC (American Heart Association/American College of Cardiology), IAS (International atherosclerosis society), EAS/ESC (European Atherosclerosis Society/European Society of Cardiology), CCS (Canadian Cardiovascular Society), and NLA (National Lipid Association).[5-9] These organizations recommended an LDL-C less than 70 mg/dl in very high risk persons or for secondary prevention.

A lower treatment goal of LDL-C <50 mg/dl for very high-risk Indians was recommended by the Lipid Association of India (LAI) in March, 2016.[10] Subsequently in 2017, a goal of LDL-C <55 mg/dl in patients with extreme risk and ACS patients with DM was put forward by AACE (American Association of Clinical Endocrinologists) and Taiwan guidelines respectively.[11,12] The LAI subsequently in December 2017 published dyslipidemia management guidelines in special patient populations.[13] Most recently, the ESC (European Society of Cardiology) has recommended a treatment goal of <55 mg/dl for LDL-C for those patients at very high risk, including all patients with ASCVD, with optional consideration of an LDL-C <40 mg/dl for those who have had a recurrent event within the past two years.[14]

Indians develop ASCVD at a younger age, have malignant disease and high case fatality rates.[15] Hence, the ever-expanding epidemic of ASCVD among Indians warrants further lowering of LDL-C especially in patients with extreme risk of recurrence of CV events.

Linear correlation between LDL-C lowering and risk of ASCVD

A series of meta-analyses calculated the effect of long-term exposure to lower levels of LDL-C on the risk of CHD mediated by 9 polymorphisms in 6 different genes. All 9 polymorphisms were associated with significant reduction in the risk of CHD per unit lower LDL-C. Non-overlapping data from 312,321 participants in a meta-analysis with natural random allocation to long-term exposure to lower LDL-C was associated with 54.5% reduction in the risk of CHD per mmol/L lower LDL-C. This correlates to nearly a 3-fold greater reduction in the risk of CHD per mmol/L lower LDL-C than that noted during treatment with a statin started later in life.[16]

Recently, European Atherosclerosis Society assessed meta-analyses of over 200 prospective cohort studies, Mendelian randomization studies, and randomized trials of more than 2 million participants with over 20 million person-years of follow-up and over 150,000 cardiovascular events and stated that irrespective of any mechanism of lowering LDL-C, there is a positive linear relationship between risk of ASCVD reduction and absolute reduction in LDL-C. The risk of ASCVD is also directly related to cumulative duration in reduction of LDL-C. There is a consistent dose-dependent log-linear association between magnitude of exposure of the vasculature to LDL-C and the risk of ASCVD; and this effect appears to increase with increasing duration of exposure to LDL-C.[17]

A meta-analysis of nearly 175,000 participants in 27 randomized trials of statins including 22 trials of statin versus control (n=134,537; mean LDL-C difference 1.08 mmol/L; 4.8 years) and five trials of intensive versus moderate statin therapy (n=39,612; mean LDL-C difference 0.51 mmol/L; 5.1 years) was carried out by the Cholesterol Treatment Trialists (CTT) collaborators. It concluded that a reduction of 1 mmol/L (38.7 mg/dl) in LDL-C levels brings about a 21% reduction in the risk of major vascular events over 5 years, irrespective of age, sex, baseline LDL-C levels and previous vascular disease. An additional 15% reduction in ASCVD risk was noted in the intensive statin trials following lowering of LDL-C by an additional 0.5 mmol/L.[18]

Magnitude of ASCVD problem in India

Cardiovascular diseases have attained epidemic proportions worldwide with mortality declining in developed nations while rising in the developing nations due to epidemiological transition.[19] Mortality rates from CHD and stroke have shown an obvious decline in the western world, with age-adjusted mortality rates having dropped by one-third from

Table 1: The achieved LDL-C levels on moderate versus high intensity statins

Trial	Number of patients	LDL-C achieved on moderate dose statins	LDL-C achieved on intensive dose statins	Percent of patients suffering events on intensive doses
PROVE IT-TIMI 22[26]	4162	95 mg/dl	62 mg/dl	22.4%
IDEAL[27]	8888	104 mg/dl	81 mg/dl	12.0%
TNT[28]	10,001	101 mg/dl	77 mg/dl	8.7%

Table 2: The adjusted hazard ratios based on achieved LDL-C levels in a meta-analysis of eight major trials[31]

LDL-C I (mg/dl)	<50 mg/dl (n=4375)	50-75 mg/dl (n=10,375)	75-100 mg/dl (n=10,091)	100-125 mg/dl (n=8953)	125-150 mg/dl (n=3128)	150-175 mg/dl (n=836)	>175 mg/dl (n=375)
Major CV events	0.44 (0.35-0.55)	0.51 (0.42- 0.62)	0.56 (0.46-0.67)	0.58 (0.48- 0.69)	0.64 (0.53- 0.79)	0.71 (0.56- 0.89)	1.00 (ref)

1960 to 2000.[20] The Global Burden of Disease Study of 2016 for India reported an estimated 32.7% increase in years of life lost (YLL) from 1990 until 2016 whereas YLL declined in United States by 62.4% and in European countries by 72.2%. Disability adjusted life years (DALYs) for ischemic heart disease in India doubled from 19.77 million/year in 1990 to 40.29 million in 2016.[21]

Ischemic heart disease is the leading cause of premature deaths with a 53% rise from 2005 to 2016 as per India Health Metrics.[22] The prevalence of dyslipidemia is 79% among Indians which is higher than 53% reported among the US population.[23,24]

A study from India, providing estimates of 333 diseases and 84 risk factors from different states, covering the period from 1990 to 2016 reported that CVD and diabetes accounted for 15.9 and 8.9% of the disability-adjusted life years respectively. Change in DALYs and percent change in rates for the leading 30 causes during the period 1990–2016 in India showed that ischemic heart disease has moved up to the first position.[25]

Residual risk following intensive statin therapy: LDL cholesterol

Three trials[26-28] compared higher vs. lower intensity statin therapy resulting in lower achieved LDL-C to prevent major events in patients with history of CHD or ACS. There were statistically significant reductions in LDL-C but a significant quantity of residual risk was noted (Table 1). Superko mentioned that while 22.4% of subjects in the intensively treated group in the PROVE-IT TIMI 22 achieved an LDL-C<70 mg/dl, they still experienced a clinical event.[29]

Hence, despite intensive statin therapy significant residual risk contributes to future adverse CV events. Further aggressive lowering of LDL-C along with more intensive control of other risk factors may prove beneficial to reduction of recurrent events and mortality.

Does further LDL-C lowering from 70 mg/dl to 30 mg/dl reduce cardiovascular events?

Evidence from randomized trials and meta-analysis for LDL-C lowering from 70 mg/dl to 50 mg/dl

4162 patients with a median LDL-C of 102 mg/dl were enrolled in the PROVE-IT TIMI 22 study. It compared intensive therapy (80 mg of atorvastatin) versus moderate therapy (40 mg of pravastatin) in patients following acute coronary event.[30] The safety and efficacy of achieving very low LDL-C levels with intensive statin therapy was evaluated by a sub study of PROVE IT-TIMI 22. The median LDL-C achieved in the atorvastatin group was 62 mg/dl. The distribution of LDL-C levels after 4 months was divided into 4 groups- <40 mg/dl (11%), >40-60 mg/dl (34%), >60-80 mg/dl (31%) and >80-100 mg/dl (14%). There were 193 patients in the group that achieved an LDL-C of less than 40 mg/dl. The hazard ratio was lowest in this group with fewer cardiac events.[30] No significant increase in adverse effects was observed while 39% RR reduction in MACE was recorded in the group with achieving LDL-C less than 40 mg/dl as compared to those with LDL-C levels >80-100mg/dl.

A meta-analysis of 8 major trials- 4S (Scandinavian Simvastatin Survival Study), AFCAPS/TexCAPS (Air Force/ Texas Coronary Atherosclerosis Prevention study), LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease), TNT (Treating to New Targets), IDEAL (Incremental Decrease in Endpoints Through aggressive Lipid Lowering), JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) and CARDS (the Collaborative Atorvastatin Diabetes Study)- with determination of lipids and apolipoproteins at baseline and at 1-year follow-up, revealed 54% reduction in major CV events. It included 38,153 patients allocated to statin therapy and a total of 6,286 cardiovascular events occurred in 5,387 study participants during follow-up. Compared to patients who achieved an LDL-C >175 mg/dl, it was noted that those who achieved an LDL-C of 75-100 mg/dl, 50-75 mg/dl and <50 mg/dl had adjusted hazard ratios for major CV events of 0.56 (95% CI 0.46-0.67), 0.51 (95% CI 0.42-0.62) and 0.44 (95% CI 0.35-0.55), respectively. There was a 19% relative risk reduction (adjusted hazard ratio 0.81; 95% CI 0.70-0.95) in MACE in the group with LDL-C less than 50 mg/dl compared to LDL-C of 75-100 mg/dl. No increase in the adverse effects was noted (Table 2).[31]

The landmark IMPROVE-IT trial (15281 participants) concluded that in post-acute coronary syndrome patients (within 10 days of index event), ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing CV events in long term at follow up of 7 years. Baseline LDL cholesterol levels was 95 mg/dl in the participants of both groups. The median follow-up levels were 53.7 mg/dl versus 69.5 mg/dl in the ezetimibe/simvastatin and simvastatin arms, respectively at the end of one month.[73] No rise in muscle complaints, liver enzymes, cancer, cataract, neurocognitive defects and diabetes was noted.[73] The results of this study supported LDL-C lowering down to around 55 mg/dl.

In the ODYSSEY LONG TERM study- 2341 high risk patients on statins were administered alirocumab subcutaneously in a dose of 150 mg once every two weeks and compared to placebo in a 2:1 ratio. The mean LDL at baseline was 120 mg/dl. The mean percentage change in LDL cholesterol level from baseline to week 24 was

Table 3: Lipid Association of India 2016 LDL-C and non-HDL-C goals

Treatment goals and statin initiation thresholds according to ASCVD risk categories (2016) (Lipid Association of India)				
Risk category	Treatment goals		Consider drug therapy	
	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
Very high risk	<50	<80	≥50 (preferably in all)	≥80 (preferably in all)
High risk	<70	<100	≥70 (preferably in all)	≥100 (preferably in all)
Moderate risk	<100	<130	≥100	≥130
Low risk	<100	<130	≥130*	≥160*

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

−61.0% with alirocumab versus 0.8% with placebo. The mean absolute LDL cholesterol level at week 24 was 48 mg/dl and 119 mg/dl in the alirocumab and placebo groups respectively. After 78 weeks treatment with alirocumab, LDL-C levels were 53.1 mg/dL resulting in 48% relative risk reduction of CV events as compared to the placebo. The number of participants with adverse events was similar in the 2 groups.[33]

Similar results were noted with evolocumab in the OSLER trial. It included two extension studies with 4465 patients on standard therapy and evolocumab or standard therapy alone in a 2:1 ratio. Evolocumab reduced the LDL-C levels by 61%, from a median of 120 mg/dl to 48 mg/dl contributing to 53% reduction in CV outcomes when compared to the placebo group at the end of approximately 1 year of treatment.[34]

The post hoc analysis of 10 Odyssey trials including 4974 patients (3182 on alirocumab, 1174 on placebo, 618 on ezetimibe) evaluated the relationship between on-treatment LDL-C levels and percent reductions in LDL-C from baseline with MACE (coronary heart disease death, non-fatal myocardial infarction, ischemic stroke, or unstable angina) in multivariate analyses. Almost 33.1% of the pooled cohort achieved average LDL-C <50 mg/dl: 44.7% to 52.6% allocated to alirocumab, 6.5% allocated to ezetimibe, and 0% allocated to placebo. MACE was inversely correlated to the percent reductions in LDL-C down to 25 mg/dl. MACE appeared to be 24% lower for every 39 mg/dl lower achieved LDL-C.[35]

Based upon these data from RCTs and meta-analysis, LAI released its first expert consensus statement on management of dyslipidemia in Indian population in March 2016 (Table 3).[10] LDL-C was the primary target with non-HDL-C as co-primary target.

The ODYSSEY OUTCOMES study compared the safety and efficacy of alirocumab with placebo among patients with recent acute coronary syndrome (ACS) already on intensive statin therapy. Participants were enrolled to receive either alirocumab (n =9,462) every 2 weeks subcutaneously or placebo (n =9,462). The dose was titrated between 75 and 150 mg to keep LDL-C between 25 and 50 mg/dl, but above 15 mg/dl. The duration of follow up was 2.8 years.[36] The mean LDL-C was 87 mg/dl at baseline and 53.3 mg/dl on treatment at 44 months. LDL-C reduction in alirocumab vs. placebo was 62.7% (37.6 mg/dl vs 93.3 mg/dl) at 4 months; 50% (48 mg/dl vs 96.4 mg/dl) at 12 months and 54.7% (53.3 mg/dl vs 101.4 mg/dl) at 2.8 years.[37] In patients on alirocumab, 15% reduction in CV events and all cause deaths was noted. Non-fatal MI reduced by 14%, stroke by 27% and unstable angina by 39%. The primary endpoint of MACE was significantly lower in the alirocumab group versus the placebo group (9.5% vs 11.1%).[36] No effect on CV death was observed. Adverse effects were comparable in both groups except minor injection-site reactions in the alirocumab group. This trial too supported benefit of lowering LDL-C to levels around 50 mg/dl.

Benefit of further lowering of LDL-C to 30 mg/dl and below

Only more recently, however, has evidence accumulated to support the benefit of attaining levels of LDL-C even below 50 mg/dl. In the IMPROVE-IT trial of patients with an acute coronary syndrome within 10 days, 6.4% (971) patients achieved LDL-C <30 mg/dl (Figure 1). There were significant 21% relative risk reduction as compared to those who achieved LDL-C ≥70 mg/dl (adjusted HR 0.79; P =0.001). There were no significant adverse events in those with achieved LDL-C below 30 mg/dl.[32]

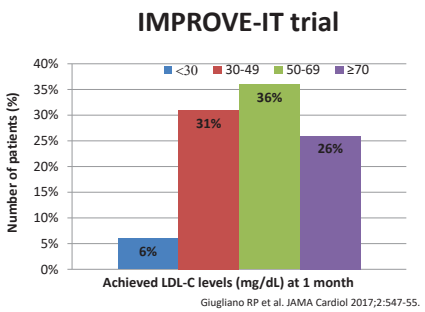


Fig. 1: The distribution of achieved LDL-C levels at one month in 15,281 patients in the IMPROVE-IT trial

The FOURIER study randomized 27,564 patients with ASCVD and LDL-C ≥70 mg/dl on maximally tolerated statin therapy to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo as subcutaneous injections. At 48 weeks, the mean percentage reduction in LDL-C levels with evolocumab was 59%, from a median baseline value of 92 mg/dl to 30 mg/dl. Significant reduction in the risk of the primary and secondary end points was noted. LDL-C values reduced to ≤70 mg/dl in 87% versus 18%, to ≤40 mg/dl in 67% versus 0.5% and to ≤25 mg/dl in 42% versus less than 0.1% in the evolocumab versus placebo groups respectively. The event rates of primary end point and secondary end point were 11.3% and 7.4% in placebo group while they were 9.8% and 5.9% in the evolocumab group respectively at the end of 2.2 years.[37] This contributed to ARR of 1.5% and NNT of 67 for primary endpoint. No significant effect on CV death was observed. No significant difference in the rates of muscle-related events, cataract, neurocognition and hemorrhagic stroke was observed between the two groups. Injection-site reactions though rare, were more frequent with injection evolocumab. New binding antibodies developed in 43 patients (0.3%) but no neutralizing antibodies were noted.[38]

A risk reduction of 17% was noted in key secondary endpoint among patients in the top quartile for baseline LDL-C, in whom evolocumab lowered LDL-C level from 126 mg/dl to 43 mg/dl and a 22% risk reduction was noted in the key secondary endpoint among the patients in the lowest quartile for baseline LDL, in whom evolocumab lowered LDL-C from 73 mg/dl to 22 mg/dl.[37] A

Table 4: Relationship between achieved LDL-C levels, CV events and relative risk reduction in FOURIER Study[38]

Patients	Achieved LDL-C levels at 4 weeks	Kaplan Meier Event rates	Relative risk reduction (RRR)
2669 (10%)	<0.5 mmol/l (<20mg/dl)	10.3%	24%
8003 (31%)	0.5 to <1.3 mmol/l (20 mg/dl to <50 mg/dl)	12.4%	15%
3444 (13%)	1.3 to <1.8 mmol/l (50 mg/dl to <70 mg/dl)	13.6%	6%
7471 (29%)	1.8 to <2.6 mmol/l (70 mg/dl to <100 mg/dl)	13.7%	3%
4395 (17%)	≥2.6 mmol/L (≥100 mg/dl)	15.5%	-

Table 5: Meta-analysis of statin and non-statin data in populations with baseline LDL-C values of ≤70 mg/dl[41]

Groups	Baseline mean LDL-C mg/dl	Vascular Events	Risk Ratio per 38.7 mg/dl (1 mmol/l) reduction of LDL-C
Statins only	65.7 mg/dl	1922	0.78 (0.65-0.94)
Non-statins added to statins	63-70 mg/dl	9570	0.79 (0.70-0.88)
Statins only + Non-statins added to statins combined			0.79 (0.71-0.87)

linear relationship was noted between achieved LDL and CV outcomes in a pre-specified secondary analysis of FOURIER trial (Fig. 2). Approximately 504 patients achieved median LDL-C levels of 7 mg/dl at 4 weeks with more cardiovascular efficacy and no worsening of adverse effects (Table 4).[39]

A post-hoc analysis of ODYSSEY OUTCOME study concluded that the hazard ratio for all-cause death by baseline LDL subgroups was the lowest in the group with baseline LDL-C of at least 100 mg/dl with absolute risk reduction of 1.6% (relative RR of 29%) in this group and 3.4% absolute risk reduction (relative RR of 24%) for CV events.[36]

An analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration concluded that lowering LDL-C with a PCSK9 inhibitor reduces the risk of major events by the same amount as statins per mmol/L reduction in LDL-C. In the FOURIER trial, treatment with evolocumab during the

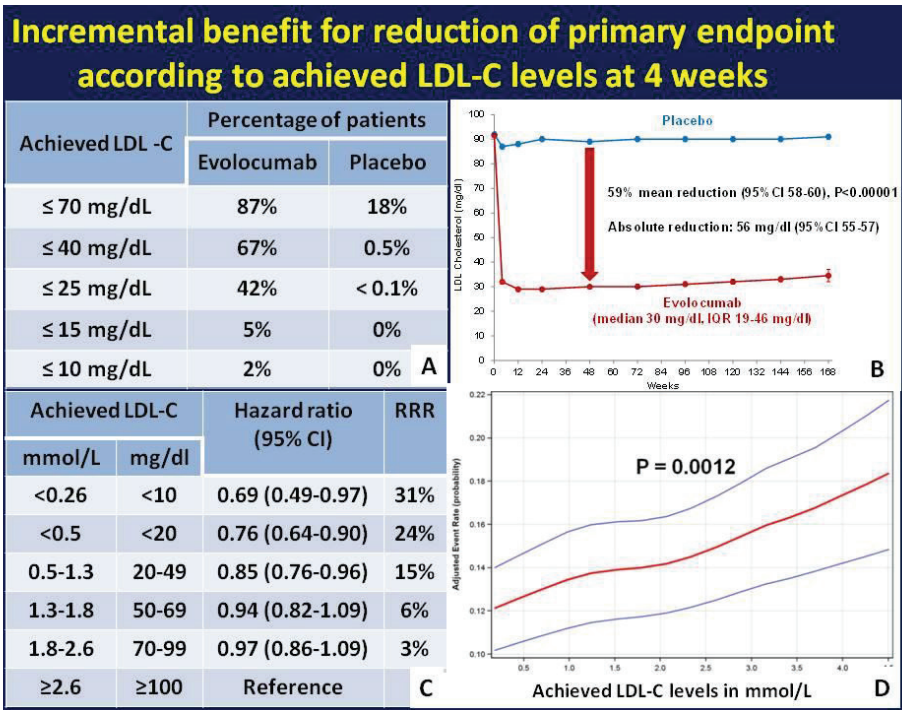


Fig. 2: The incremental benefit for reduction of primary endpoint according to achieved LDL-C levels at 4 weeks. A: The percentage of patients with different levels of achieved LDL-C levels in the two study groups; B: Mean reduction in LDL-C levels in the evolocumab group compared to placebo; C: The relative risk reduction (RRR) with evolocumab based on the achieved LDL-C levels; D: The relationship between achieved LDL-C levels and adjusted event rates showing significantly decreased event rates with further lowering of LDL-C levels down to <20 mg/dL

second year of the trial reduced the risk of multiple cardiovascular outcomes by 18–23% per mmol/L reduction in LDL-C, which is very similar to the 22–25% reduction in risk for these same outcomes observed during the second year of treatment in the statin trials.[40]

A meta-analysis of Cholesterol Treatment Trialists Collaboration (CTTC) for statin data and Medline database for non-statin data was carried out to evaluate safety and efficacy of further lowering LDL-C levels in populations with average LDL-C levels of 70 mg/dl (1.8 mmol/L) or below. The non-statin trials include Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Patients With Elevated Risk (FOURIER) and Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) (Table 5). The data suggests treating patients with mean LDL-C level of 65 mg/dl (1.7 mmol/L) and achieving LDL as low as a median of 21 mg/dl (0.5 mmol/L) achieved further cardiovascular benefits with no observed adverse effects.[41]

Evidence from Imaging Trials

Multiple imaging trials have proven that aggressive lowering of LDL-C level to 50 mg/dl or less contributes to significant reduction of progression of atherosclerotic plaques and CV events.[42-48] Patients who underwent PCI were randomly assigned to 20 mg atorvastatin monotherapy versus 20 mg atorvastatin plus 10 mg of ezetimibe daily in PRECISE-IVUS study.[46] Serial volumetric IVUS was performed at baseline and again at 9 to 12 months to quantify the coronary plaque response in 202 patients. Combination therapy resulted in lower levels of LDL-C than monotherapy (63.2 ± 16.3 mg/dl vs 73.3 ± 20.3 mg/dl; p <0.001). Coronary plaque regression on IVUS was achieved in more patients on combination therapy than those who received monotherapy (78% vs 58%; P=0.004). Side-effect profiles were similar in both groups.[46]

In Yellow trial there was significant reduction in LCBI (lipid core burden index) using Near infrared spectroscopy (NIRS) with short duration (6 to

8 weeks) intensive statin therapy (Rosuvastatin) as compared to standard therapy. Mean achieved LDL-C level with rosuvastatin 40 mg/d was 60 mg/dl compared to 82 mg/dl with standard therapy.[47]

Recently, GLAGOV trial[48] evaluated the effect of evolocumab on progression of coronary atherosclerosis in statin treated patients. 968 participants on statins with angiographic coronary artery disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injections for 76 weeks. Mean baseline LDL-C level was 92.5 mg/dl. The LDL cholesterol at 76 weeks was 36.6 mg/dl in the evolocumab group versus 93.0 mg/dl in the placebo group. Change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging was the primary efficacy endpoint. Change in total atheroma volume (TAV) and demonstration of plaque regression was secondary efficacy endpoint.

Compared with placebo, the evolocumab group achieved lower mean LDL-C levels (93.0 vs 36.6 mg/dl; difference, -56.5 mg/dl; P <0.001). PAV increased by 0.05% with placebo versus decrease by 0.95% with evolocumab, while TAV decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (difference, -4.9 mm^3; P <0.001). Plaque regression was noted in a greater percentage of patients on evolocumab than placebo (64.3% vs 47.3%; difference, 17.0%; P <0.001 for PAV). A LOESS plot showed a linear relationship between achieved LDL-C level and PAV for LDL-C levels ranging from 110 mg/dl to as low as 20 mg/dl.[48]

Plaque composition changes were determined in 331 patients with radiofrequency analysis of the ultrasound backscatter signal. No changes were observed between the evolocumab and placebo groups in changes in calcium, fibrous, fibrofatty and necrotic volumes. Hence, evaluation of plaque morphology using virtual histology imaging may provide no additional information about the plaque effects of evolocumab beyond measurement of plaque burden.[49] However, LDL-C lowering was associated with an increase in plaque calcification and reductions in the size of all other plaque components.[49]

Hence, it can be presumed that LDL-C level of 30 mg/dl is safe, at least within the duration of follow-up time available from the supporting clinical trials, and there is also evidence of further significant reduction in ASCVD events as compared to LDL-C of 50 mg/dl with no increase in adverse effects.

Which group of patients would benefit from aggressive LDL-C lowering?

Based on available data and evidence, the benefit from aggressive LDL-C lowering therapies depends on the following:

1. Absolute reduction in LDL-C levels
2. Baseline LDL-C cholesterol levels
3. Baseline cardiovascular risk
4. Duration of LDL-C lowering

Absolute reduction in LDL cholesterol

As discussed previously reducing LDL-C down to 30 mg/dl or below has been shown to significantly reduce ASCVD events.[36-41] Further in the ODYSSEY OUTCOMES trial, of the 9462 patients randomized to receive alirocumab, 730 (7.7%) patients reached very low LDL-C (<15 mg/dl) and were switched to placebo after a median 8.3 months after randomization. Using propensity score matching, they were compared (3:1) with 2152 patients initially assigned to placebo. Despite being switched to placebo, patients with very low LDL-C on alirocumab had fewer MACE than matched patients from the placebo group (6.4% vs 8.5%; HR 0.71, P=0.039). The very low LDL-C levels on alirocumab were not associated with risk of new-onset diabetes, neurocognitive events or haemorrhagic stroke. This clearly demonstrates the extended benefit of very low levels of LDL-C even after the discontinuation of pharmacotherapy.[50]

Baseline LDL cholesterol levels

In the 4S study, the mean LDL-C was 190 mg/dl. Treatment with simvastatin resulted in 34% RRR in CHD death or nonfatal MI and 30% reduction in total mortality. In the CARE study, mean LDL-C was 139 mg/dl and treatment with 40 mg pravastatin resulted in 24% RRR in CHD death or non-fatal MI and 8.3% reduction in total mortality. This suggests that benefits are higher in patients with higher baseline LDL-C.[51,52]

The ODYSSEY OUTCOMES study concluded that MACE benefit was largely driven by patients with LDL-C values of 100 mg/dl or more. The hazard ratio for primary outcome was 0.91 (0.81-1.02) in those with LDL less than 100 mg/dl as compared to 0.76 (0.65-0.87) in those with higher LDL-C (≥100 mg/dl) values. Absolute risk reduction due to CHD, CV death and all cause death was 1.0%, 1.3% and 1.7% in those with LDL-C less than 100 mg/dl as compared to 1%, 4% and 6% in those with LDL-C ≥100 mg/dl.[37]

In SPIRE-1 and SPIRE-2 studies, patients with elevated cardiovascular risk with two varying baseline levels of LDL-C were assigned to either the PCSK9 inhibitor bococizumab or placebo. In the lower-risk arm, patients had a baseline LDL-C of ≥70 mg/dl. At median follow-up of 7 months, major events occurred in 173 patients each in the bococizumab group and the placebo group (hazard ratio, 0.99; 95% confidence interval [CI], 0.80 to 1.22; P =0.94). In the higher-risk arm, patients had baseline LDL-C ≥100 mg/dl. At median follow-up of 12 months, major cardiovascular events occurred in 179 and 224 patients in the bococizumab group and the placebo group, respectively (HR 0.79; P =0.02). Thus, the benefit was seen only in patients with higher baseline LDL-C levels.[53]

Baseline cardiovascular risk

Baseline cardiovascular risk is a major determinant of risk of future adverse ASCVD events in patients with CAD. In secondary prevention setting, the risk is predominantly defined by number, type and severity of baseline risk factors like older age ≥75 years, diabetes mellitus, hypertension, smoking, eGFR <60 ml/min, peripheral artery disease, prior stroke, prior CABG and CHF.[64] FOURIER study showed those with a recent MI (<2 years), multiple MIs, multivessel CAD, or PAD benefited the most.[54] The Odyssey Outcomes study showed those with disease in multiple vascular beds or defined as "very high risk" benefitted the most.[55,56] The absolute risk reduction (ARR) was 1.4, NNT =71 for patients with arterial disease in one

Table 6: Subgroup analysis of 4S study: Relative risk of major endpoints in simvastatin treated diabetics versus non-diabetics[63]

Endpoints	Diabetics	Non-Diabetics
Total Mortality	0.57	0.71
Atherosclerotic Event	0.63	0.74
CHD Event	0.45	0.68

vascular bed versus ARR of 13.0, NNT =8 for patients with arterial disease in three vascular beds, suggesting that alirocumab was 9 times more beneficial in patients with polyvascular disease.[55] In primary prevention, persons with homozygous or heterozygous familial hypercholesterolemia are at substantial baseline risk due to their lifetime of elevated LDL-C levels. In addition, those with diabetes, especially when accompanied with multiple risk factors are at high or very high risk.[57,58] The aim of determining baseline CV risk is to identify patients who require more intensive risk factor control and management.

Diabetes- From CHD risk equivalent to extremely high-risk category

In a Finnish population-based study, the incidence of myocardial infarction among 1373 non-diabetics was compared to 1059 diabetic subjects over 7-year period. The incidence in non-diabetic subjects was 18.8% and 3.5% versus 45.0% and 20.2% in diabetic subjects with and without previous myocardial infarction respectively. In an 18-year follow-up study of Finnish subjects, type 2 diabetes is a "CHD equivalent" if prior myocardial infarction was used to define CHD. When less stringent criteria for prior CHD were used (myocardial infarction or ischemic ECG changes or angina pectoris), type 2 diabetes carried a larger risk than prior CHD, especially in women.[57] Hence, it can be concluded that cardiovascular risk factors in diabetic patients must be treated as aggressively as non-diabetic patients with prior myocardial infarction.[58] However, several years later a meta-analysis of over a dozen studies examining this issue showed overall that those with DM without a prior MI had a 43% lower risk of future CHD compared to those with a prior MI without DM.[59] Finally, data from the Multiethnic Study of Atherosclerosis examining CHD and CVD event rates according to levels of

Table 7: Absolute risk reduction (ARR) in diabetics versus non-diabetics

Trial	Absolute Risk Reduction (ARR) in Diabetics	Absolute Risk Reduction (ARR) in Non-Diabetics
Fourier[38]	2.7% (NNT 37)	1.6% (NNT 62)
Odyssey outcomes[36,37]	2.3% (NNT 43)	1.2% (NNT 83)
Improve-IT[32,73]	5.5% (NNT 18)	0.6% (NNT 166)

NNT: number needed to treat

coronary calcium in adults with DM or metabolic syndrome shows a 10-fold variation in event rates. For example in those with DM with a 0 calcium score, CHD event rates were 0.4% per year, compared to 4% per year in those with calcium scores of 400 or greater.[60] Most recently, Rana and colleagues showed among a large registry of DM patients from Kaiser Permanente pointed that those DM patients with a duration of DM of 10 years or more have a risk similar to those with pre-existing CHD.[61] These studies support the more contemporary concept that not all with DM are CHD risk equivalents, but that risk assessment is important in those at DM to identify those at highest risk who need even more intensive therapy.

Similar conclusions were derived from the data collected in 6 different countries for the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry. In the registry, 21% of 1718 were diabetic patients. The mortality was highest amongst diabetics. Diabetes independently predicted mortality, CV death, new myocardial infarction, stroke, and congestive heart failure.[62] A post-hoc subgroup analysis of 4S study including 202 diabetic patients and 4,242 non-diabetic patients with previous cardiac event, elevated cholesterol and triglycerides analysis was carried out. Patients were assigned to double-blind treatment with 20 mg simvastatin with dose titration to 40 mg daily, according to cholesterol response during the first 6-18 weeks, or placebo. The relative risk (RR) of major endpoints in simvastatin-treated diabetic vs non-diabetic patients as shown in table 6.[63]

Higher absolute risk of recurrent CV and other atherosclerotic events in diabetics corresponds to greater absolute clinical benefit achieved by cholesterol lowering in diabetics than in nondiabetics.[63]

In a Korean study, 2438 patients post PCI following myocardial infarction were stratified to four groups according to the presence of DM or hypertension and followed up for 1 year. MACE was 15.9% in non-diabetic/non-hypertensive vs 22.9% in hypertensives vs 28.8% in diabetics vs 37.0% in hypertensive and DM group. The combination of DM and hypertension had higher mortality than either alone.[64]

Further, the ARR was higher amongst the diabetics as compared to the non-diabetics in the 3 major trials as shown in table. It can be concluded that patients with higher baseline risk derive higher benefits from further aggressive LDL-C reduction (Table 7).

LDL-C risk curve concept

The concept of a "risk curve" correlates to the absolute risk of a patient for future CV events over a varying range of LDL-C levels. An analysis to probe the relationship between LDL-C and CVD risk for the placebo and active-controlled trials was done and the risk curves were constructed. The rationale was to identify patients who require aggressive LDL cholesterol-lowering therapy. The position on the curve is based not only on the baseline LDL-C levels but also on the presence or absence of diabetes, metabolic syndrome and IFG. Patients who are high risk based on their position on the risk curve require further LDL-C reduction as well as aggressive risk factor control to shift their position downwards on the risk curve.[65]

In LDL-C and CVD risk curve, when LDL-C is reduced from 100 to 70 mg/dl, the absolute risk reduction is 6% in patients of CHD plus diabetes compared to 3% in those with CHD without diabetes or metabolic syndrome or impaired glucose tolerance over period of 5 years. Residual risk for 5 years, at an LDL level of 40 mg/dl for CHD subjects with and without diabetes is 10 % and 8% respectively. The number-needed-to prevent an event at LDL-C 40 mg/dl is 23 in patients with CAD and DM which is lower than NNT of 45 for patients with CAD without DM, metabolic syndrome or IFG. Hence, aggressive therapy is reserved for those at the highest risk.[65]

Table 8: Reduction in primary endpoint in the evolocumab group based on the presence or absence of high-risk features

Presence or absence of high-risk features	Evolocumab group-Number needed to treat (NNT)	Primary endpoint	
		RRR	ARR
Multivessel Disease	28	21%	3.6
No multi-vessel disease	83	7%	1.2
Qualifying MI < 2 years	30	20%	3.4
Qualifying MI > 2 years	125	5%	0.8
2 or more prior MIs	27	18%	3.7
1 prior MI	77	8%	1.3

Efficient risk stratification to identify high risk groups for secondary prevention

The TIMI Risk score identified 9 independent clinical indicators in TRA 2°P-TIMI 50 [Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-TIMI 50]- age, diabetes mellitus, hypertension, smoking, peripheral arterial disease, previous stroke, previous coronary bypass grafting, heart failure, and impaired renal function. In this study, 8598 placebo patients with a prior MI were followed for 2.5 years. High-risk patients (≥3 risk indicators) had a 3.2% absolute risk reduction in cardiovascular disease/MI/ischemic stroke (NNT-31) as compared to intermediate-risk patients (1-2 risk indicators) who had a 2.1% absolute risk reduction (P<0.001) with NNT of 48. Higher the number of risk factors, greater was the number of MACE-3.5% in those with no risk factors and 58.6% in presence of 7 or more risk factors. The greater reduction in ARR in cardiac events with vorapaxar in high risk patients as compared to the intermediate risk concludes that stratification of baseline atherothrombotic risk can assist with therapeutic decision making for secondary prevention post MI.[66]

Another study applied this score to 17,717 post-ACS patients randomized either to ezetimibe and simvastatin or to placebo and simvastatin in IMPROVE-IT study. High-risk patients with ≥3 risk indicators, had a 6.3% ARR in events at 7 years with ezetimibe/simvastatin, thus translating to a number-needed-to-treat (NNT) of 16. Intermediate-risk patients with 2 risk factors had a 2.2% ARR with NNR =45. Thus, risk stratification identifies high risk patients who will benefit most from additional lipid lowering with non-statin therapy (ezetimibe) over and above statin treatment for secondary prevention. This benefit was seen without any increase in adverse events over 7-year period.[67]

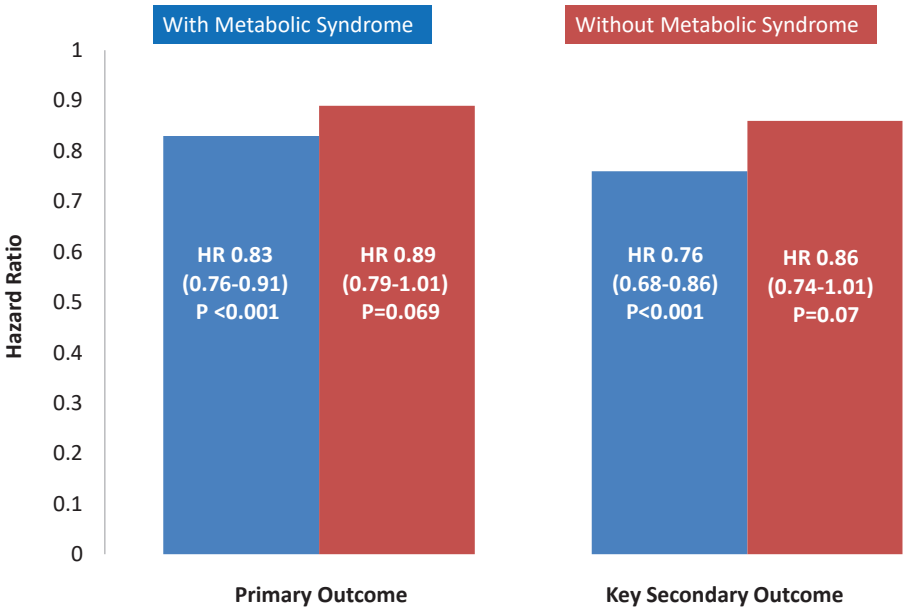


Fig. 3: Effect of evolocumab treatment in patients with and without the metabolic syndrome (Fourier Trial)

Similarly, TIMI Risk Score for Secondary Prevention (TRS 2°P) showed a strong graded relationship with the rate of CV death, MI or stroke when applied to 27,564 patients with atherosclerotic heart disease and LDL-C ≥70 mg/dl randomized to evolocumab or placebo in FOURIER study. Intermediate risk patients demonstrated a 1.9% ARR (NNT 53) in CV death, MI or stroke at 3 years with evolocumab while high-risk patients had a 3.6% ARR (NNT 28).[68]

The Dyslipidemia International Study (DYSIS II) CHD study was a cross-sectional observational study of 3,867 ACS and 6794 patients with stable coronary heart disease (CHD) across 18 countries including India. Hypertension (96.0%) and diabetes mellitus (40.3%) were the most common risk factors noted in the DYSIS II population and 2.0% of patients had a TIMI risk score for secondary prevention (TRS 2°P score) of zero and 3.7% had a score of ≥5. The DYSIS II CHD population displayed a greater number of TRS 2°P risk factors as compared to IMPROVE-IT study which had 12% of the patients in the simvastatin treatment group with zero score and 2% had a score of ≥5. The event rate would have been higher for the DYSIS II patients observed by extrapolating the event rate of IMPROVE-IT. MACE were noted in 68% of the simvastatin-treated patients in IMPROVE-IT with a TRS 2°P of ≥5. The benefits of ezetimibe addition to the statin therapy were observed in the patients with higher TRS 2°P values, which indicates that use of ezetimibe would have even greater benefits for the higher risk DYSIS II CHD population.[69] Thus in real world patient population significant proportion of patients are very high risk suggesting that additional LDL-C lowering with non-statin therapies is likely to confer further risk reduction.

In an analysis of FOURIER study, 22,351 post-MI patients were grouped based on presence of high-risk features following myocardial infarction. The high-risk features were <2 years from qualifying MI, ≥2 prior MIs or residual multivessel disease. The 8343 patients (37% of prior MI population) had zero risk features and demonstrated 6% RRR and 0.5% ARR with the NNT being as high as 200. The remaining 13,973 (63% of prior MI population) showed at least a single risk feature and showed 22% RRR and 2.5% ARR with the NNT of 41.[54] The detailed analysis of each risk feature is mentioned in the Table 8.

Benefits in peripheral artery disease

3642 patients (13.2%) had PAD (1505 with no prior myocardial infarction or stroke) in the FOURIER study.[70] Patients with PAD had much higher ARR for the primary end point (3.5% with PAD, 1.6% without PAD) and secondary end point (3.5% with PAD, 1.4% without PAD) with evolocumab due to higher attributable risk. There was significant reduction (42% RRR) in major adverse limb events in the evolocumab group as compared to placebo. A consistent relationship between lower achieved LDL-C and reduced risk of limb events (P=0.026 for the beta coefficient) that extended down to <10 mg/dl was noted.[70]

The long-term cardiovascular risk associated with polyvascular disease, type II diabetes, and their combination in patients with CAD was assessed in an exploratory analysis of IMPROVE-IT study. Patients in the IMPROVE-IT trial with polyvascular disease with concomitant type 2 diabetes were at very high risk (60% MACE rate at 7 years) compared to those without diabetes and polyvascular disease (29.6% MACE rate at 7 years), P <0.0001. The absolute risk reduction with ezetimibe 10 mg/d on the background of simvastatin 40 mg/d was 9.1% in polyvascular disease with concomitant type 2 diabetes compared to 1.7% in those without diabetes and polyvascular disease over 7 years, P <0.0001.[71]

The ODYSSEY Outcomes Trial also showed that patients with recent ACS and dyslipidemia despite being on intensive statin therapy, polyvascular disease (concurrent peripheral artery disease, cerebrovascular disease, or both), carry a higher risk of MACE and death, and alirocumab leads to large absolute reductions in the risk.[55]

Benefits in metabolic syndrome

Participants with metabolic syndrome achieved a greater risk reduction for the primary endpoint (HR = 0.83; 95% CI, 0.76-0.91) vs. those without metabolic syndrome (HR =0.89; 95% CI, 0.79-1.01). Similarly, 24% risk reduction for secondary endpoints in those with metabolic syndrome (HR = 0.76; 95% CI, 0.68-0.86) versus 14% risk reduction for those without metabolic syndrome (HR = 0.86; 95% CI, 0.74-1.01) was noted in an analysis of data from FOURIER study in adults with/without metabolic syndrome (Fig. 3).[72]

Duration of LDL-C Lowering

A series of meta-analyses were carried out to quantify the effect of long-term exposure to lower LDL-C on the risk of CHD mediated by 9 polymorphisms. These Mendelian studies were combined in a meta-analysis to compare it with the clinical benefit associated with the same magnitude of LDL-C reduction with statin treatment.

These polymorphisms were associated with consistent reduction in the risk of CHD per unit lower LDL-C. In a meta-analysis of 312,321 participants, naturally random allocation to long-term exposure to lower LDL-C led to 54.5% reduction in the risk of CHD for each mmol/l (38.7 mg/dl) lower LDL-C. This represents nearly 3-fold greater reduction in the risk of CHD than that observed during treatment with a statin started later in life.[16]

Evidence from Guidelines

Various international bodies have also recognized the impact of lowering LDL to less than 50 mg/dl in patients with very high risk of events in the future. In 2016, Lipid Association of India (LAI) brought out a consensus document which set lower, stricter treatment goals of LDL-C <50 mg/dl and non-HDL-C <80 mg/dl- for very high-risk Indians. The very high-risk category included patients with pre-existing ASCVD, diabetics with 2 or more major risk factors or evidence of end-organ damage and homozygous familial hypercholesterolemia.[10]

This was soon followed by AACE recommending an LDL-C goal of less than 55 mg/dl in patients at extreme risk. This group included progressive ASCVD, established clinical ASCVD with diabetes, CKD stage 3 or 4, and/or HeFH, or individuals with premature ASCVD (<55 years of age in males or <65 years of age in females).[11] In 2017, Taiwan lipid guidelines for high risk patients recommended that a lower target of LDL-C <55 mg/dl can be considered in ACS patients with DM.[12] This was based on the findings of IMPROVE IT study.[73] Recent EAS/ESC 2019 guidelines advocated that very high-risk patients should achieve a goal LDL-C level of <55 mg/dl. It recognized that ACS patients are at very high risk of recurrent events and those who experience a second vascular event within 2 years on maximally tolerated statin therapy, an LDL-C goal of <40 mg/dL be considered.[14]

Recently Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy endorsed Interdisciplinary Expert Position Statement Recommendation for the management of dyslipidemia in Poland. This document recommended LDL-C of less than 35 mg/dl in extreme risk group patients.[74]

Newer lipid-lowering drugs

PCSK 9 inhibitors in high-risk patients

Although various guidelines suggest the use of PCSK9 inhibitors is appropriate in indicated patients, the use is minimal due the perceived expense. Various models focusing on cost-effectiveness analyses have produced widely varying and confusing results.[75,76] The 'highest risk–highest benefit' concept has been recommended by Annemans et al as a strategy to assist in the identification of patients who will derive maximum benefit from PCSK9 therapy.[77] The former part is to identify those with the 'highest baseline event rate' primarily for secondary prevention- polyvascular disease, ASCVD with co-morbidities such as chronic kidney disease or diabetes with end-organ damage or FH patients with a CVD event. FH with high LDL-C despite statin therapy is the only criteria for primary prevention. The latter part is to identify patients who would get 'highest benefit'. The RRR is proportionate to the absolute decrease in LDL-C. Estimated NNT is lower in patients with the highest CVD risk and largest absolute LDL-C reduction.[77]

Robinson and Watson proposed that NNT can provide the basis for shared decision making by patients and clinicians. They identified three phenotypes- extremely high risk, very high risk and high risk and LDL-C thresholds for each group that would aid in the identification of patients most likely to benefit from adding ezetimibe or a PCSK9 inhibitor. An NNT of less than 25 for PCSK9 inhibitors and

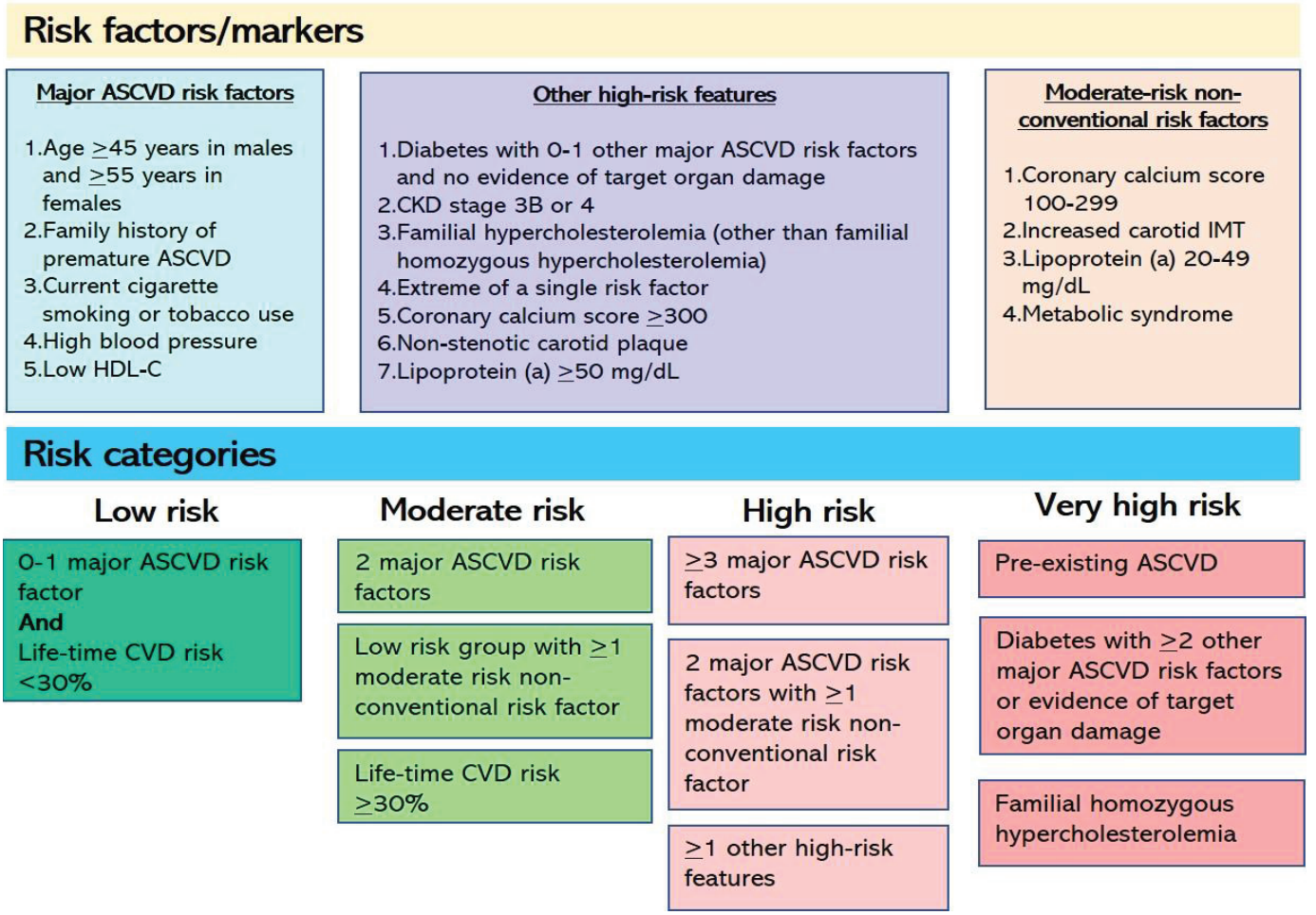


Fig. 4: Risk stratification approach previously recommended by the Lipid Association of India in 2016

NNT less than 30 for ezetimibe were considered to make these cost-effective in deserving candidates.[78]

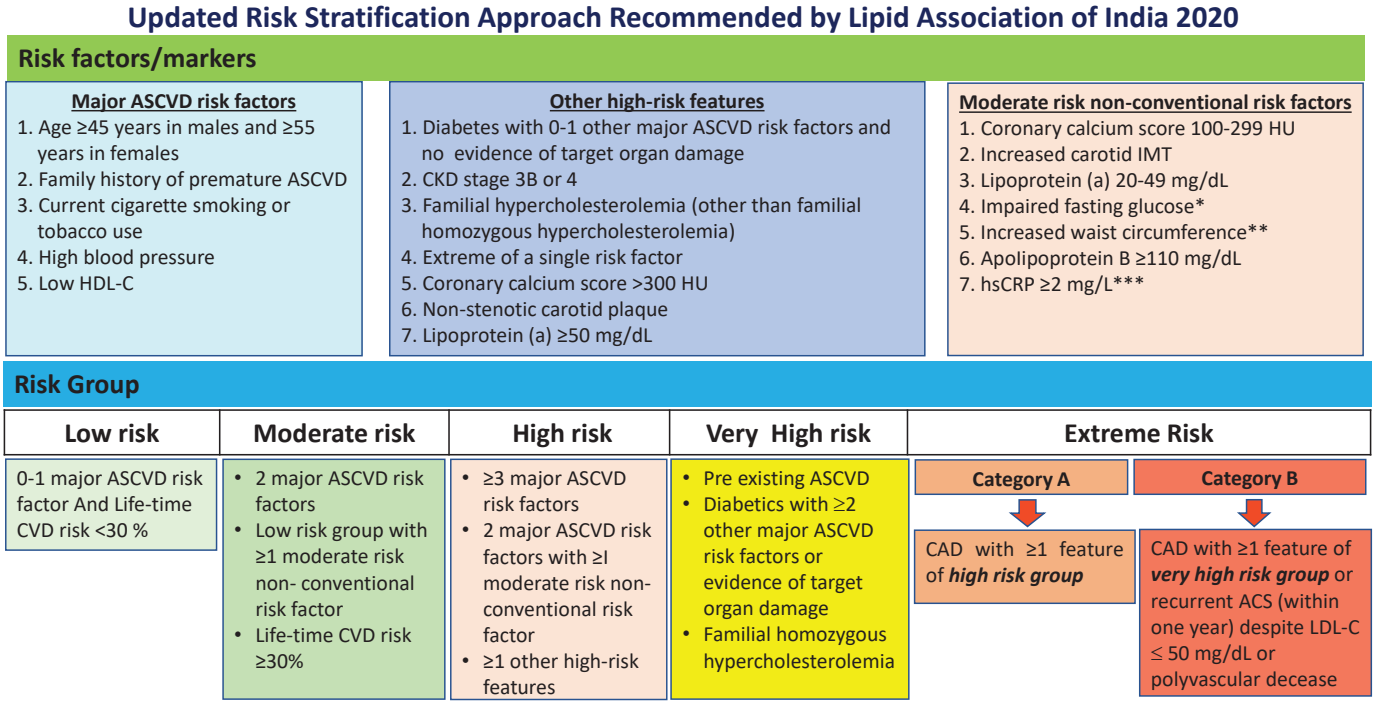
Bempedoic Acid

Bempedoic acid (ETC-1002) is a prodrug that requires conversion by acyl-CoA synthease-1 to its active moiety, ETC-1002-coenzyme A (ETC-1002-CoA). The active form of bempedoic acid is a competitive inhibitor of the enzyme adenosine triphosphate (ATP)-citrate lyase (ACL) and reduces the production of cytosolic acetyl coenzyme A (acetyl-CoA), the final substrate for both fatty acid and sterol synthesis, located upstream of HMG-CoA in the cholesterol biosynthesis pathway. It is an oral, once-daily, non-statin LDL-C lowering drug.[79]

After small studies including by Thompson et al who reported that bempedoic acid reduced LDL-C levels by 28.7% more than placebo in a randomized, placebo-controlled study of 56 patients hypercholesterolemic patients with statin intolerance, bempedoic acid has been studied four phase III clinical trials representing more than 3,600 patients.[80] The CLEAR Harmony trial randomized 2230 patients (2:1) with ASCVD, heterozygous familial hypercholesterolemia, or both on maximally tolerated statin with LDL-C levels ≥70 mg/dl to bempedoic acid or placebo. The mean LDL-C level decreased by 19.2 mg/dl (16.5% decrease from baseline levels, P <0.001) at 12 weeks. The overall incidence of adverse events (78.5% patients) in the bempedoic acid group compared to with placebo group (78.7% patients) was similar. However the incidence of gout (18 patients [1.2%] vs. 2 [0.3%]) was higher with bempedoic acid.[81]

The CLEAR Wisdom trial randomized 779 patients (2:1) with ASCVD, heterozygous familial hypercholesterolemia, or both on maximally tolerated statin with LDL-C levels ≥70 mg/dl to bempedoic acid or placebo while receiving maximally tolerated lipid lowering therapy. The addition of bempedoic acid (180 mg) to maximally tolerated lipid-lowering therapy significantly lowered LDL-C levels compared with placebo (-15.1 vs. 2.4%, P <0.01) at 12 weeks. The bempedoic acid also significantly decreased non-HDL-C (-10.8% vs. 2.3%), total cholesterol (-9.9% vs. 1.3%), apolipoprotein B (-9.3% vs. 3.7%) and high-sensitivity CRP (-18.7% vs. -9.4%) compared to placebo.[82]

In a pooled analysis of 3623 patients included in four randomized trials with ASCVD or HeFH or both, the mean baseline LDL-C level was 107.6 mg/dL. At week 12, the LDL-C level change from baseline was −16.0% with bempedoic acid vs 1.8% with placebo (P <0.001). Patients with statin intolerance had a mean baseline LDL-C level of 144.4 mg/dL. The changes in LDL-C levels at week 12 were −23.0% in the bempedoic



Clinical judgment to be used if the patient has atherosclerotic peripheral arterial disease instead of coronary artery disease; *A fasting blood sugar level from 100 to 125 mg/dl. It should be confirmed by repeat testing; **Waist circumference is to be measured at the superior border of the iliac crest just after expiration. Increased waist circumference is defined as >90 cm in men and >80 cm in women. If increased waist circumference is the only risk factor, it should again be measured after 6 months after initiating heart healthy lifestyle measures; ***On two occasions at least 2 weeks apart. For reclassifying moderate risk group only

Fig. 5: Updated 2020 risk stratification approach recommended by the Lipid Association of India

acid group and 1.5% in the placebo group (P <0.001). The decrease in LDL-C levels with bempedoic acid was sustained during long-term follow-up in both groups (patients with ASCVD or HeFH or both receiving a maximally tolerated statin, LDL-C change of −12.7% at week 52; patients with statin intolerance, LDL-C change of −22.2% at week 24). Treatment-emergent adverse events associated more frequently with bempedoic acid than with placebo included increased blood uric acid level (2.1% vs 0.5%), gout (1.4% vs 0.4%), decreased glomerular filtration rate (0.7% vs <0.1%), and increased of hepatic enzyme levels s (2.8% vs 1.3%).[83]

The US Food and Drug Administration approved bempedoic acid for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional lowering of LDL-C on February 21, 2020. On February 26, the FDA also cleared a fixed-dose combination containing bempedoic acid and ezetimibe.[79] This combination therapy provides LDL-C reductions in the range of 35%, making this a very useful option for additional LDL-C lowering beyond maximally tolerable statin.

Although the LDL-C lowering effects and safety profile of bempedoic acid are encouraging, it's effect on clinical endpoints are yet to be determined. CLEAR Outcomes trial is an ongoing study to assess major adverse cardiovascular events in patients with, or at high risk for cardiovascular disease who are statin intolerant treated with bempedoic acid or placebo.[79]

Physiological levels of LDL-C

Experimentally, healthy baboons show LDL-C levels of approximately 40 to 80 mg/dl.[84] There is evidence from hunter-gatherer populations demonstrating no evidence of atherosclerosis, even in individuals living into the seventh and eighth decades of life.[85] Their total cholesterol levels are approximately 100 to 150 mg/dl with estimated LDL cholesterol levels of about 50 to 75 mg/dl. Neonates are born with LDL values in the range of 30-70 mg/dl.[86] A theory suggests that an LDL value of 25 mg/dl in the plasma is enough to provide nourishment to the body cells with cholesterol.[87]

In a prospective cohort study of 27,937 women from Women's Health Study (primary prevention study) followed up for a mean period of 19.3 years it was found that LDL-C of less than 70 mg/dl and low triglyceride levels were associated with increased risk of hemorrhagic stroke. One should appreciate that this is a primary prevention study restricted to female gender and study had limited power of determining hemorrhagic stroke subtype and, other confounding variables were menopausal status, availability of only baseline lipid values and low statin usage.[88]

Hence, based on the above data there is no evidence at present to suggest any safety concern with pharmacologically achieved LDL-C levels less than 30 mg/dl in extremely high-risk individuals.

Updated Recommendations by LAI

The Lipid Association of India published a practical algorithm for risk evaluation amongst Indians in 2016 (Figure 4).[10] It included four risk categories- Very high, High, Moderate and Low risk.

Table 9: Proposed LDL-C goals in very high risk and extreme risk group patients

Risk group		
Very High Risk group (VHRG)	**Extreme Risk group**	
	Category A	**Category B**
LDL-C goal		
LDL-C goal of <50 mg/dl	LDL-C goal of <50 mg/dl (Indispensable) LDL-C goal of ≤30 mg/dl (optional)[Δ]	LDL-C goal of ≤30 mg/dl[Δ]
High-risk conditions		
Any one of following:	**CAD° with ≥1 of following:**	**CAD° with ≥1 of following:**
ASCVD (CAD/PAD/TIA or stroke) Homozygous familial hypercholesterolemia Diabetes with ≥3 major ASCVD risk factors*/target organ damage	Diabetes without target organ damage/0-2 major ASCVD risk factors Familial hypercholesterolemia ≥3 major ASCVD risk factors CKD stage 3B and 4 ≥2 major ASCVD risk factors with ≥1 moderate non-conventional risk factor[#] Lp(a) ≥50 mg/dl Coronary calcium score ≥300 HU Extreme of a single risk factor PAD H/o TIA or stroke	Diabetes + polyvascular disease/≥3 major ASCVD risk factors*/target organ damage Recurrent ACS (within 12 months) despite on LDL-C goal Homozygous familial hypercholesterolemia

[Δ]The LDL-C goal of ≤30 mg/dl must be pursued after detailed risk-benefit discussion between physician and patient

°Clinical judgment to be used in decision making if the patient has disease/risk factors not covered in the table, eg. PAD or cerebrovascular disease

Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; polyvascular disease: evidence of atherosclerotic disease in at least two vascular territories: coronary artery disease (CAD), peripheral arterial disease (PAD) and history of (H/o) transient ischemic attack (TIA) or stroke, CKD: chronic kidney disease; Lp(a): lipoprotein(a)

[*]**Major ASCVD risk factors:** 1. Age- male ≥45 years, female ≥55 years, 2. Family h/o premature CAD- male <55 years, female <65 years, 3. Smoking/tobacco use, 4. Systemic hypertension, 5. Low HDL (males <40 mg/dl and females <50 mg/dl)

[#]**Moderate non-conventional risk factors:** 1. Coronary calcium score 100-299 HU, 2. Increased carotid intima-media thickness, 3. Lp(a) ≥20-49 mg/dl, 4. Impaired fasting glucose, 5. Increased waist circumference, 6. Apolipoprotein B ≥110 mg/dl, 7. hsCRP ≥2 mg/L

Table 10: Newer treatment goals and statin initiation thresholds based on the risk categories proposed by LAI in 2020

Risk group	Treatment Goals		Consider Drug Therapy	
	LDL-C (mg/dl)	Non-HDL (mg/dl)	LDL-C (mg/dl)	Non-HDL (mg/dl)
Extreme Risk Group Category A	<50 (Optional goal ≤30)	<80 (Optional goal ≤60)	≥50	≥80
Extreme Risk Group Category B	≤30	≤60	>30	>60
Very High Risk	<50	<80	≥50	≥80
High Risk	<70	<100	≥70	≥100
Moderate Risk	<100	<130	≥100	≥130
Low Risk	<100	<130	≥130*	≥160*

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

Additional Category in the Risk Stratification Algorithm

Considering the elevated risk of malignant nature of ASCVD in Indians and availability of evidence supporting the benefits and safety of lowering LDL below 30 mg/dl, an *Extreme Risk Category* has been incorporated in the existing risk stratification algorithm by Lipid Association of India (Fig. 5).

Extreme Risk category includes:

1. CAD with features of high-risk group (Extreme risk group category A)

2. CAD with features of very high-risk group or recurrent ACS (within one year) even after LDL-C target of less than 50 mg/dl is achieved (Extreme risk group category B)

The Extreme Risk Group category is divided into category A and category B depending on the underlying risk conditions. An optional LDL-C of ≤30 mg/dl is proposed for Category A while ≤30 mg/dl is recommended for those in category B.

Justification for Extreme Risk Group

CAD is designated as very high-risk category in 2016 LAI consensus statement on management of dyslipidemia.[10] However, all CAD patients do not have the same prognosis. Selected CAD patients have higher risk of future adverse CV events because of presence of risk factors, comorbidities and extent of atherosclerosis. The number, type and severity of risk factors determine the risk of subsequent adverse CV events. This has been discussed in detail above. To adequately manage the risk in patients with increased risk, LAI proposes a new category- Extreme risk. These "Extreme risk" patients require aggressive management to decrease future ASCVD events (Table 9). Further, more aggressive LDL-C goals in Indians are needed compared to the western countries as prevalence of coronary artery disease as well as cardiovascular events in south Asians is 1.5- to 2-fold higher compared to native US population.[89] Besides CAD is malignant in Indian subcontinent with more than 50% of CAD associated death in India occurring before the patient reaches the age of 50 years and 25% of myocardial infarctions occur before the age of 40 years[15] necessitating vigorous and determined measures to stem the ASCVD epidemic.

Statins are the mainstay of treatment to prevent future CV events. However significant residual risk persists despite statin therapy. This risk is significantly more in patients with additional risk factors. Recent non-statin trials have shown that further risk reduction can be achieved by LDL-C lowering regardless of means of LDL-C lowering. We have recently proposed aggressive lowering of LDL-C for secondary prevention through improved usage of high-intensity statins with ezetimibe, possibly in combination with PCSK9 inhibitor monoclonal antibodies.[90,91] Bempedoic acid has been recently approved by US FDA for LDL-C lowering in HeFH and established ASCVD.[79] It can be considered on the background of other lipid lowering agents prior to addition of PCSK9 inhibitors.

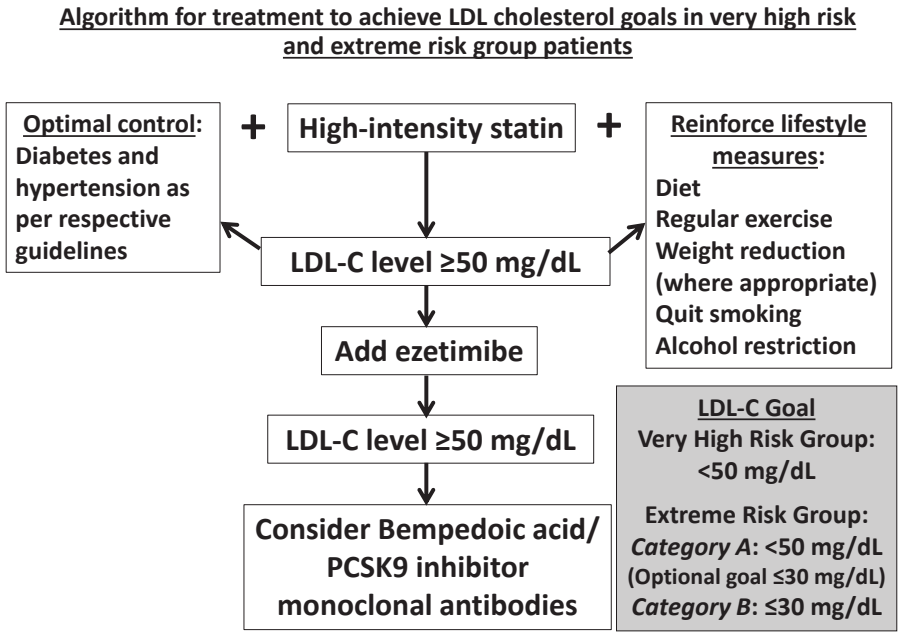


Fig. 6: Algorithm for treatment in very high risk and extreme risk group patients to achieve LDL-C goals. Refer to table 9 for criteria of very high risk and extreme risk group

Treatment Goals

The different treatment goals and statin initiation thresholds based on the risk categories are proposed in the table.

Recommended Treatment Protocol

The 2020 Lipid Association of India LDL-C and non-HDL-C treatment goals and algorithm are given in Table 10 and Figure 6.

Shared decision-making

As highlighted above, there is ample evidence to justify aggressive LDL-C lowering to very low levels in patients with "extreme risk" for ASCVD. However, such intensive LDL-C lowering involves use of high-intensity statin therapy combined often with ezetimibe and/or PCSK9 inhibitors leading to issues related to cost and patients' concerns about side-effects of medications as well as of very low LDL-C levels. Recognizing this, the LAI strongly emphasizes the role of shared decision-making when recommending treatment to this group of patients. Moreover, a comprehensive discussion about lifestyle management should always be central to the patient-clinician discussion. All the benefits and risks of therapy should be discussed with the patient and the patient family before reaching a joint decision about further lipid-lowering in any given patient.

Conclusions

• Children are born with an LDL-C level of about 30 mg/dl.

• Hunter gatherers had low cholesterol with a very low prevalence of CAD.

• The Extreme risk group is an additional ASCVD risk category indicating greater atheroma load and greater risk of MACE.

• The Extreme risk group is divided in two categories:

• Category A- CAD with ≥1 high-risk group feature with LDL-C goal of <50 mg/dl (recommended) and ≤30 mg/dl (optional)

• Category B- CAD with ≥1 very high-risk group features with LDL-C goal of ≤30 mg/dl (recommended).

• Extreme low levels of LDL-C (≤30 mg/dl) can be achieved with newer drugs and should be considered as an option in patients at extreme risk to further reduce ASCVD events (MI/ stroke/ revascularization)

• Maximal tolerated doses of statins with or without ezetimibe, adequate lifestyle interventions and treatment of all modifiable factors must be investigated carefully prior to addition of newer drugs such as PCSK9 inhibitors.

• The calculated LDL-C includes the cholesterol contained in Lp(a). The Lp(a) cholesterol is not reduced by statins. Hence individuals with elevated Lp(a) may have a less-than-anticipated response in LDL-C reduction on statin therapy. This should raise the suspicion of a markedly elevated Lp(a).

• Identification of highest risk groups who would benefit maximally with efficient drug therapy is probably the missing key.

However, the final decision should follow a detailed discussion between the patient and treating physician (shared decision).

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Triglycerides and Atherosclerotic Cardiovascular Disease

Epidemiologic studies have suggested that triglycerides (TGs) are a significant factor in evaluating coronary heart disease (CHD) risk.[1-3] However, the extent to which TG serves as an independent CHD risk factor has proved elusive because of its close association with other covariates. In the largest population-based prospective study of nearly 300,000 men and women, linear association between TG levels and CHD risk was noted until adjustments are made for non-HDL-C and HDLC.[4] Compared with cholesterol, TG is readily metabolized to free fatty acids which serve as a source of energy. The free fatty acids activate pro-inflammatory pathways which possibly contribute to insulin resistance and atherogenicity.[5] TGs are metabolized by most cells, are not taken up by the macrophages and do not contribute directly to the plaque formation.

Current evidence

Available evidence points towards remnant cholesterol, marked by raised TG, as an additional causal risk factor for ASCVD and all-cause mortality.[2,3] Mutations that disrupt apo C3 function were associated with lower levels of plasma TG and apo C3.[6] Subjects with these mutations were found to have a reduced risk of ischaemic cardiac events. Genome Wide Association Studies (GWAS) have found a causal association of raised TGs with CHD. Nearly 30 gene variants can modestly increase TG. Of these, 6 different genes- Lipoprotein lipase (LPL), apo C2, apo A5, lipase maturation factor (LMF1), glycosylphosphatidylinositol-anchored HDL-binding protein-1 (GPIHBP1), and glycerol-3-phosphate dehydrogenase 1A (GPD1A) can increase TG substantially. These are monogenic disorders and numerous studies have linked high TG with increased CV risk.[7] Lipoprotein lipase is the principal TG-metabolizing enzyme and its action is modulated by various proteins like apo C3 and apo A5. Hence targeting these proteins may yield reduced CV risk.[7]

Data from randomized trials have consistently shown that individuals with mixed hyperlipidaemia, defined by either the lipid triad (elevated LDL-C, elevated TG, and low HDL-C) in the 4S or the combination of high TG (≧200 mg/dl) and elevated LDL-C in the Helsinki Heart Study and Bezafibrate Infarction Program carried the highest risk of CHD events.[8,9] This emphasizes the importance of elevated TG in determining CHD risk, thereby suggesting that high TGs potentiate the risk of elevated LDL-C levels.

The meta-analysis of 5 landmark trials (ACCORD, FIELD, BIP, HHS and VA-HIT) which included 4726 patients proved that PPAR-α agonists reduced CV events by 35% in patients with high TG ≥204 mg/dl and low HDL ≤34 mg/dl.[10,11] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study aimed at assessing the effect of fenofibrate on cardiac events in diabetics. A reduction of total CV disease events from 13.9-12.5% was noted though it did not reduce the risk of the primary outcome of coronary events.[12] However, no benefit was noted and the combination of fenofibrate and simvastatin did not reduce the rate of CV events in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial.[13]

These findings are relevant for Indians as atherogenic dyslipidaemia is highly prevalent. Globally, every 3 out of 4 diabetic suffers from dyslipidaemia. However, almost 9 out of 10 diabetics have dyslipidaemia in India.[14,15] An epidemiological study, ICMR INDIAB study across 15 states of India revealed that the prevalence of dyslipidaemia, hypertriglyceridemia and low HDL-C as 79.6%, 29.5% and 72%, respectively.[16]

TGs in stable CHD

The Cholesterol and Recurrent Events trial (CARE) and the Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID) trials were secondary prevention trials evaluating pravastatin. Both concluded that TG levels remain a CVD risk factor in patients treated with statins. There was a consistent rise in CVD event rates in those with TG levels ≥150 mg/dl in the pravastatin groups in both studies compared with placebo.[17]

TG in acute coronary syndrome (ACS)

In PROVE IT-TIMI 22 study, elevated TGs ≥150 mg/dl increased the risk of myocardial infarction, ACS or death (HR 0.84) within 30 days to 2 years of follow up compared to those with TG <150 mg/dl (HR 0.72) despite patients having achieved a LDL-C goal of <70 mg/dl with high dose of atorvastatin.[18]

In dal-OUTCOMES, long-term risk increased across quintiles of baseline triglycerides, highest/lowest quintile (>175/≤80 mg/dl) with hazard ratio 1.61 (P <0.001). In the atorvastatin group of MIRACL, short-term risk increased across tertiles of baseline triglycerides (HR 1.50, P =0.03) in highest/lowest tertiles (>195/≤135 mg/dl). The relationship of triglycerides to risk was independent of LDL-C levels in both studies.[19]

TGs and CVD

Twenty two year follow up of the Bezafibrate Infarction Prevention (BIP) study and registry concluded that in patients with established CHD, higher TGs levels are independently associated with increased 22-year mortality. Mortality increased by 68% in those with TGs ≥500 mg/dl compared with patients with TGs <100 mg/dl.[20]

3216 American Indians with no CVD at baseline were followed for 17.7 years. Subjects with high TG and low HDL-C levels had a 1.32-fold higher HR (95% CI 1.06-1.64) for CHD than those with normal TG and normal HDL-C levels.[21] Among diabetics, HR for CHD with high TG (>150 mg/dl) and low HDL-C (<40 mg/dl) was 1.54 fold higher compared with those without high TG and low HDL-C indicating a relative risk of 54% for CHD. Similarly, the HR for stroke was 2.13 fold higher among diabetics with high TG and low HDL-C values.[21]

Hypertriglyceridaemia and atherogenesis

The plasma TG level represents the concentration of TG-rich lipoproteins: VLDL, chylomicrons and their remnants (Figure 1). Although chylomicrons are too large to penetrate the arterial wall, VLDL and remnants (chylomicron remnants, VLDL remnants, and intermediate-density lipoproteins) are small enough to enter the arterial wall, and have been identified in human and animal atherosclerotic plaques. Because of the strong association between plasma TG and remnant lipoprotein concentration, high TG levels serve as a biomarker for the

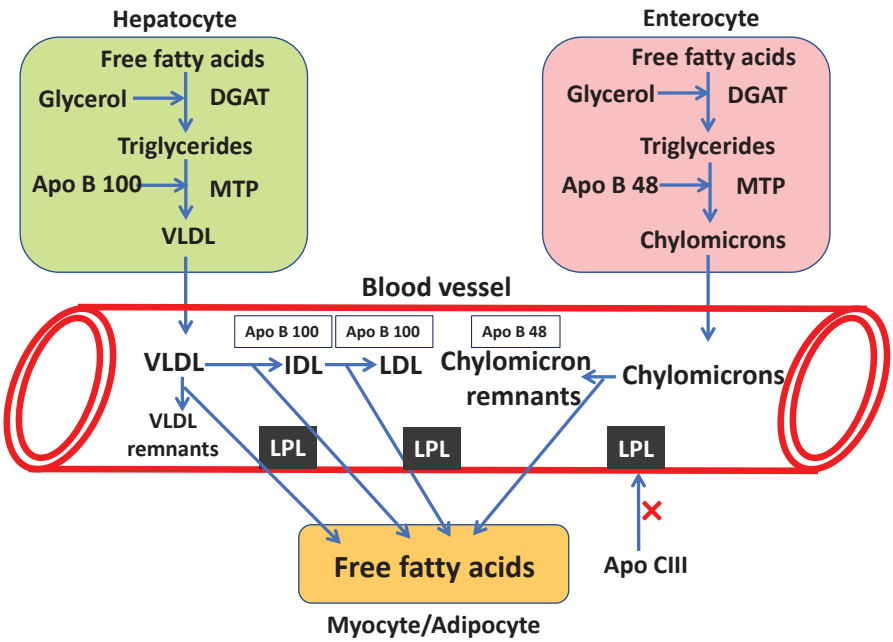

Fig. 1: Triglyceride metabolism. Abbreviations: Apo CIII: Apolipoprotein CIII, DGAT: diacylglycerol acyltransferase, IDL: Intermediate density lipoprotein, LDL: Low density lipoprotein, LPL: Lipoprotein lipase, MTP: Microsomal triglyceride transfer protein, VLDL: Very low density lipoprotein

presence of atherogenic circulating remnant particles.[22]

A second consequence of hypertriglyceridemia is a relative change in the composition of LDL and HDL particles. The small, dense LDL particles share a linear relation with the levels of circulating TG and are more atherogenic than large buoyant LDL.[23] Above a threshold of fasting TG concentration, there will be a predominance of small, dense LDL particles (phenotype B) and below the threshold large, more buoyant particles will predominate (phenotype A).[23,24]

The TG concentration that produces a shift from one subclass pattern to another varies with each patient. A fasting TG concentration of <100 mg/dl favors pattern A in 85% of the population whereas a fasting TG concentration ≥250 mg/dl favors pattern B in 85% of the population. Therefore, maintaining TGs at 200-250 mg/dl may not be optimal for regression of atherosclerosis.[25] Most patients have a threshold of 100 to 250 mg/dl for shifting LDL-C subclass pattern and since small, dense LDL-C is more atherogenic, keeping TG even at 200-250 may not reduce atherosclerosis completely. A target of TG <100 mg/dl may be preferable.

A classical hypertriglyceridaemic state is insulin resistance which 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 acted upon by hepatic lipase, resulting in small, dense LDL particles that are subjected to oxidative modification as compared with the larger, buoyant LDL particles. This is followed by increased uptake of LDL particles and their incorporation by scavenger receptors on the surface of the arterial wall.[25,26] Further TG-enriched HDL particles may be less efficient in reverse cholesterol transport.[27]

Triglyceride metabolism. The free fatty acids are esterified with glycerol in a multistep process involving diacylglycerol acyltransferase (DGAT) in the hepatocyte and enterocyte resulting in the formation of triglycerides. The apolipoproteins and phospholipids are added to triglycerides in the process involving microsomal triglyceride transfer protein (MTP) with apo B100 added in the liver and apo B48 added in the intestine resulting in formation of VLDL in the liver and chylomicrons in the intestine. VLDL produced from liver enters the circulation where triglycerides are hydrolysed by endothelium derived lipoprotein lipase (LPL) to form VLDL remnants. VLDL remnants are hydrolysed to form IDL, which are further hydrolysed to form LDL. The chylomicrons are hydrolysed by lipoprotein lipase resulting in formation of chylomicron remnants. Lipoprotein lipase hydrolyses triglycerides thereby releasing free fatty acids which are taken up by the myocytes and adipocytes (Figure 1). Apo CIII inhibits LPL activity.

TG stimulates the production of proinflammatory cytokines, fibrinogen and coagulation factors and impairs of fibrinolysis.[28] The combination of elevated TG and elevated LDL-C contributes to elevated CHD risk vs 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.[29-32] The blood samples of 523 healthy Tarahumaras Indians of Mexico (ages 5-70 years) were surveyed for lipids and lipoproteins. All atherogenic lipoproteins including TGs were below normal range. Particularly notable was the virtual absence of the hypertension, obesity, and the usual age related increase of the serum cholesterol in adults. Hence, the regular diet of the Tarahumaras is adequate in all nutrients, low in lipids and is presumably antiatherogenic.[29]

Though previous studies in Melanesians of Papua New Guinea have documented low serum cholesterol concentrations and a virtual absence of CHD, modernization has brought in dyslipidaemia and unless effective preventative strategies can be developed, one can expect an increasing incidence of CHD.[30] Consumption of freshwater fish (300-600 g daily) was associated with raised plasma concentrations of omega-3 polyunsaturated fatty acids, lower blood pressure, and lower plasma lipid concentrations in a village in Tanzania.[31]

Classification of fasting TG Levels

The generally followed classification for TG values based on fasting lipid profile is tabulated.[1]

• Optimal	<100 mg/dl (<1.1 mmol/l)
• Normal	<150 mg/dl (<1.7 mmol/l)
• Borderline high	150-199 mg/dl (1.8-2.2 mmol/l)
• High	200-499 mg/dl (2.3-5.6 mmol/l)
• Very High	>500 mg/dl (>5.65 mmol/l)

Non-fasting vs fasting TG concentrations

Although traditionally a blood sample for lipid profile is taken in the fasting state, recent studies have not shown any advantage of performing a fasting lipid profile, unless obtaining an LDL-C requires use of the Friedwald formula (when TG <400 mg/dl). Rather, there is an advantage of non-fasting fasting lipid profile measurements in that the blood sampling process is simplified for patients, doctors and hence increases adherence to drug therapy and monitoring.

In most patients, there is usually a clinically unimportant increase in TG concentrations, by 18-36 mg/dl (0.2-0.4 mmol/L) on average, 2-6 hours after eating normal meals.[33-35] Even a non-fasting concentration predicts increased CV risk. Most people eat regularly throughout the day and are 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.[36,37]

Fasting and post-prandial TG and CV risk

Some studies support the hypothesis that non-fasting TG levels may be more significant predictors of CVD risk than fasting levels. The increasing levels of non-fasting TGs were associated with increased risk in the Copenhagen City Heart Study and Copenhagen Population Study, with TG of 585 mg/dl (6.6 mmol/l) versus 71 mg/dl (0.8 mmol/l), the age-adjusted and sex-adjusted hazard ratios [HR] were 5.1 (95% CI 3.5–7.2) for myocardial infarction, 3.2 (2.5–4.1) for ischaemic heart disease, 3.2 (2.2–4.7) for ischaemic stroke, and 2.2 (1.8–2.7) for all-cause mortality.[3]

Indications for fasting lipid profile testing

- Non-fasting TGs ≥400 mg/dl (4.5 mmol/l)
- Familial dyslipidemia
- Follow up patient with hypertriglyceridemia
- Recovering from hypertriglyceridemia-related acute pancreatitis
- Patients with premature ASCVD
- Baseline TG levels before start of drugs known to increase TG levels
- Additional laboratory tests requested that require fasting or morning samples (e.g. fasting glucose, therapeutic drug monitoring)
- To confirm adherence to therapy
- To estimate residual risk in patients on maximal intensity statin therapy
- To judge effectiveness of treatment on LDL-C or need for additional LDL-C lowering, a fasting lipid profile or direct LDL-C measurement is recommended (Figure 2).

Situations where a non-fasting lipid profile may be done

- In primary prevention setting, e.g. mass screening of a community
- Initial lipid profile testing in any patient, especially those who have not been fasting
- For CV risk assessment
- Emergency assessment of pancreatitis patient
- Patients admitted with ACS
- In children
- If preferred by the patient
- In diabetic patients [due to hypoglycemia risk]
- In the elderly
- When extreme levels are observed, for example approximately ≥500 mg/dl, treatment may be started immediately with repeat fasting lipids done after initiation of treatment

Significance of methods of estimation

The Friedewald LDL-C equation was originally derived in fasting patients. Now it is increasingly utilized in the non-fasting setting to guide management to lower LDL-C. However, it cannot be used if TGs are >400 mg/dl and in rare type III lipid abnormality. Martin et al analysed samples of 1 million patients to compare the Friedewald-estimated and directly measured LDL-C. Among patients with Friedewald-estimated LDL-C <70 mg/dl, nearly 23% had LDL-C ≥70 mg/dl by direct measurement (39% when concurrent TG values were 150 to 199 mg/dl and 59% when concurrent TG values were 200 to 399 mg/dl). The authors concluded that the Friedewald equation underestimated LDL-C when TG levels were ≥150 mg/dl and especially, at TG levels >200 mg/dl.[38] A recent analysis[39,40] showed that the Friedewald equation leads to more errors in non-fasting samples compared with fasting ones. The maximal errors are observed at LDL-C <70 mg/dl which is most significant in those at very high risk.[41]

The Martin-Hopkins LDL-C method has converted the LDL-C measurement to a more individualized approach. It has replaced the fixed factor of 5 used for the triglyceride to VLDL-C ratio by 1 of 180 patient-specific variables.[42] These variables are calculated based on serum TG and non-HDL-C concentrations. More than 97% of patients have errors <10 mg/dl, even in the non-fasting state.[40]

How does the Martin-Hopkins calculation differ from the Friedewald calculation for LDL-C

It provides greater customization to a patient's specific TG level by using a more "personalized" factor to calculate VLDL-C from TG. The adjustable factor ranges from 3.1 to 11.9. It is derived from an analysis of TG -to-VLDL-C ratios in more than 1.3 million people. The factor is lowest for patients with very low levels of TG and high levels of non-HDL-C and highest for those with very high levels of TG and low levels of non-HDL-C. It correlates better with direct LDL-C measurements. The primary advantage of the Martin-Hopkins equation is that it is applicable to low LDL-C levels even in the presence of elevated TG concentrations.[42]

Secondary causes of Hypertriglyceridemia

There are numerous conditions that can result in increase in serum TG levels.[43]

1. Diabetes
2. Obesity
3. Metabolic syndrome
4. Alcohol consumption
5. Insufficient physical activity
6. Acute pancreatitis
7. Hypothyroidism
8. Pregnancy
9. Nephrotic syndrome
10. Chronic renal failure
11. Obstructive liver disease
12. Autoimmune disorders
13. Drugs such as steroids, beta-blockers, protease inhibitors for treatment of HIV infections, steroids,

Lipid Association of India: Lipid Profile assessment for Indian population

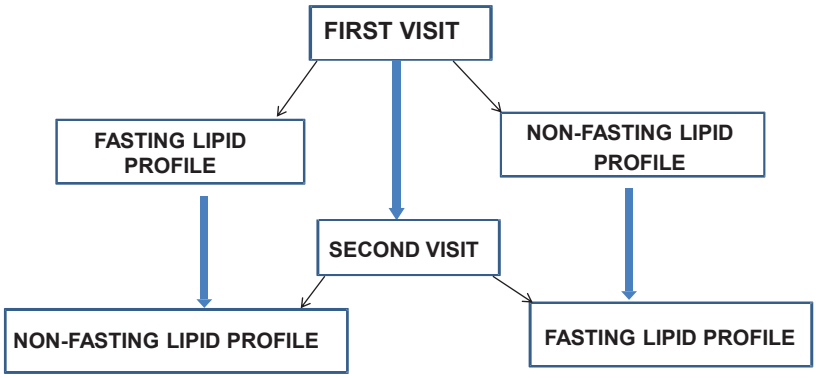

Fig. 2: In Indian subjects with dyslipidemia, both the fasting and non-fasting lipid profile should be known. A fasting lipid profile or direct LDL-C measurement is recommended to judge whether LDL-C goals have been achieved and to determine the need for additional LDL-C lowering. Non-fasting lipid profile is required to determine post-prandial hypertriglyceridemia

estrogens, tamoxifen, retinoic acid, certain drugs used in chemotherapy and anti-psychotic medications

Pharmacological agents for managing hypertriglyceridemia

The conventional medications for lowering of triglycerides (TGs) are tabulated.[43]

Medication	Reduction of TG levels
Fibrates	30 - 50%
Niacin	20 - 50%
Omega-3 fatty acids	20 - 50%
Statins*	10 - 30%
Ezetimibe	5 - 10%

*High potency statins and higher doses of statins result in greater triglyceride reduction. Patients with higher baseline triglyceride levels achieve greater reduction with same dose of statin.

While statins can lower TG levels modestly, recent data show that among US adults on statin therapy, one-fourth still have borderline or elevated levels of TG (≥150 mg/dl), even when LDL-C is <100 mg/d, indicating the need for additional lifestyle and where indicated, pharmacologic therapies to address this residual hypertriglyceridemia.[44]

Available Data on Newer Drugs

1. Eicosapentaenoic acid (EPA)-Icosapent ethyl ester

Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid that is incorporated into membrane phospholipids and atherosclerotic plaques. The EE (ethyl ester) form of omega-3 fatty acids must be converted into FFA (free fatty acids) by pancreatic lipase while the FFA forms are not dependent on pancreatic enzyme activity and are more readily absorbed.

In Japan the average fish intake is about 5 times higher than other countries. The Japan eicosapentaenoic acid (EPA) Lipid Intervention Study (JELIS) randomized 18,645 hypercholesterolaemic patients to 1800 mg of EPA (EPA ethyl ester is purified from n-3 polyunsaturated fatty acids present in fish oil) daily combined with statin or statin only. The primary endpoint of any major coronary event was reduced from 3.5% in the statin alone group to 2.8% in the combination group on five years follow-up, a 19% relative risk reduction (p=0.01). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group.[45] Of note, in the pre-specified subgroup with TG >150 mg/dl and HDL-C <40 mg/dl, there was a 53% risk reduction associated with the EPA treatment.[46]

But given the statin dosages used in JELIS were lower and baseline plasma EPA levels much higher than in the US and Europe, a large multinational trial was needed to further confirm these results.

The REDUCE-IT trial was a multinational double-blind, placebo-controlled study designed to evaluate whether treatment with icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester 4 g/day vs placebo reduces CV events in patients who despite statin therapy had elevated TGs and other CV risk factors. Patients (n =8179; 70% with previous CVD, the remainder with diabetes and multiple risk factors) were on stable statin therapy and were followed for a median of 4.9 years and the median LDL-C was 75 mg/dl. The triglyceride levels decreased from baseline to one year by 18.3% (39 mg/dL decrease) and non-HDL-C decreased by 12.2%. The primary end-point event occurred in 17.2% of those in the icosapent ethyl group vs 22.0% of those in the placebo group (P <0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (P <0.001), respectively.[47] The dose of purified eicosapentaenoic acid (EPA) (4 g/day) was higher than what was tested in other clinical trials. The rates of the primary and secondary composite CVD endpoints were reduced by 25% and 30%, respectively, as well as all individual secondary endpoints except for all-cause mortality in the icosapent ethyl group.[47] This is one of the first non-LDL-C targeted trials to show a CV benefit. As similar benefit was found in those who attained on-treatment TG levels of <150 mg/dl versus ≥150 mg/dl, the CV benefits of icosapent ethyl may be due to other mechanisms such as anti-inflammatory or anti-oxidant activity present in the product.

The hypothesis of EVAPORATE trial is that icosapent ethyl 4 g/d in addition to statin therapy would reduce the progression of plaque volume over 9 to 18 months compared with the use of statin therapy alone on a multidetector computed tomography angiography (MDCTA) population of statin-treated patients with elevated TG levels of 200-499 mg/dl.[48] Patients with known angiographic disease on statins (n=80) were randomized to either icosapent ethyl (IPE) 4 g/day or placebo. The final results after 18 months of follow-up showed a significant difference in the change in the primary endpoint of low attenuation plaque volume, which was reduced by IPE by 17%, but increased by 109% in the placebo group (p <0.01); significant differences in rates of progression between IPE and placebo at study end were also seen for fibrous, and fibrofatty (FF) plaque volumes which regressed in the IPE group and progressed in the placebo group (P < 0.01 for all).[49]

2. Epanova (Omega-3 carboxylic acids)

Epanova is a combination of omega-3 free fatty acids and can lower TGs by up

to 31%. The STRENGTH Study evaluated the efficacy of epanova (omega 3 carboxylic acids) 4 grams daily as an adjunct to statin therapy in high-risk subjects with hypertriglyceridemia and low HDL-C levels in the prevention and reduction of major CV events.[50] The study had enrolled 13,086 patients, but was prematurely terminated on Jan. 13th 2020 as preliminary analysis showed that Epanova had a low likelihood of showing benefit.

3. PPAR alpha agonist- Pemafibrate

Pemafibrate is a PPARα agonist and is >2500-fold more potent than fenofibric acid, the active metabolite of fenofibrate, for human PPARα with >5000-fold activity for PPARα than either PPARγ or δ. The PROMINENT Study is evaluating of Pemafibrate to reduce CV outcomes by reducing TGs in diabetics with atherogenic dyslipidaemia despite statin therapy. It includes 10,000 participants and expected to complete in 2022. Pemafibrate leads to marked reduction of TGs, non-HDL-C, VLDL, apo B100, apo B48, remnant cholesterol and apo CIII and increase in HDL-C.[51]

4. Dual PPAR agonists

Saroglitazar is a novel non-thiazolidinedione, dual peroxisome proliferator activated receptor (PPAR) agonist which shows an improvement in lipid and glycaemic parameters through the PPAR-α and γ agonist actions, respectively. A consistent reduction in TG levels (up to ~45% to 62%), non-HDL-C levels (up to ~21% to 36%) and glycosylated hemoglobin levels (up to ~0.7% to 1.6%) with an increase in mean HDL-C levels (up to 9%) was reported in an analysis of 18 studies enrolling 5824 patients in India.[52] The Drug Controller General of India (DCGI) approved the drug for the treatment of diabetic dyslipidemia and hypertriglyceridemia in patients with type 2 diabetes not controlled by statins alone in 25 Feb 2013. In January 2020, saroglitazar got approval for the treatment of type-2 diabetes mellitus and on 5th March 2020 DCGI has granted approval for saroglitazar to treat non-cirrhotic non-alcoholic steatohepatitis (NASH) in India. However, no large CV outcome studies are available at present.

5. Antisense oligonucleotides

Angiopoietin-like protein 3 (ANGPTL3) inhibits lipoprotein lipase, the enzyme that breaks down triglycerides. Participants with heterozygous loss-of-function variants in ANGPTL3 had lower levels of TG, HDL-C and LDL-C than participants without these variants in the DiscovEHR study.[53] Further the loss-of-function variants in ANGPTL3 were associated with reduced risk of CHD with an odds ratio for CHD of 0.61 (95% CI, 0.45 to 0.81) among patients with such variants, as compared with patients without them.[53]

Antisense oligonucleotides (ASO) targeting mouse ANGPTL3 retarded the progression of atherosclerosis and reduced levels of atherogenic lipoproteins in mice. Similar strategy was applied to target human ANGPTL3 reduced levels of atherogenic lipoproteins in humans.[54] Human participants (n=44) with TG levels 90 to 150 or >150 mg/dl depending on the dose group received subcutaneous injections of placebo or an antisense oligonucleotide targeting ANGPTL3 mRNA in a single dose (20, 40 or 80 mg) or multiple doses (10, 20, 40 or 60 mg/week for 6 weeks). After 6 weeks of treatment, subjects in the multiple dose groups had reductions in levels of ANGPTL3 protein (-46.6 to -84.5%, P<0.01), triglycerides (-33.2 to -63.1%), LDL-C (-1.3 to -32.9%), VLDL-C (-27.9 to -60.0%), non-HDL-C (-10.0 to -36.6%), apo B (-3.4 to -25.7%), and apo C-III (-18.9 to -58.8%).[54] Recently, Evinacumab, a fully human anti-ANGPTL3 monoclonal antibody, caused a dose-dependent placebo-adjusted decrease in fasting TG levels of up to 76% and LDL-C levels of up to 23%.[53] New approaches that increase lipoprotein lipase activity, including ANGPTL3 inhibition, represent a fresh frontier in the treatment of hypertriglyceridemia and CHD.[55] Similarly ANGPTL4 is an inhibitor of LPL and a potential novel therapeutic target for reducing triglycerides and treatment of metabolic syndrome.[56]

Another target of therapy is inhibition of apo C3. Loss of function mutations in the gene encoding apo C3 leads to low TG levels and a decreased risk for CVD and overexpression of apo C3 is associated with hypertriglyceridemia. Volanesorsen is an antisense oligonucleotide against apo C3 mRNA and reduces apo C3 production and TG concentration.[57] The APPROACH trial randomized 66 patients with familial chylomicronemia syndrome with fasting TG ≥750 mg/dL (mean TG levels: 2209 mg/dL) to 300 mg of volanesorsen injected subcutaneously weekly for 52 weeks or placebo. Volanesorsen reduced triglycerides by a mean of 77% and reduced recurrence of pancreatitis. Thrombocytopenia was observed in 5 patients.[58] The COMPASS trial randomized 75 patients with fasting triglyceride values ≥500 mg/dl to weekly subcutaneous injections of 300 mg of volanesorsen or placebo for 26 weeks. Treatment with volanesorsen yielded 72.7% reduction in triglycerides at 3 months, and significantly reduced pancreatitis compared with placebo (0 vs. 6 cases, P <0.01).[59] In May 2019, volanesorsen was approved in the EU for the treatment of adult patients with familial chylomicronemia syndrome.[57]

6. Gene therapy

Alipogene tiparvovec is LPL gene therapy that utilizes adeno-associated viral vector 1 (AAV1) combined with a gain-of-function LPL variant, which encodes the protein, LPLS447X. It is used for patients with hyperchylomicronemia syndrome due to lipoprotein lipase deficiency. It was approved in Europe in 2012. However high cost and rarity of disease resulted in premature withdrawal from market.[60]

7. MTTP (Microsomal triglyceride transfer protein) inhibitor

Lomitapide, a microsomal triglyceride transfer protein [MTP] inhibitor is also available and FDA approved for homozygous familial hypercholesterolemia. In addition to LDL-C lowering properties, trials have shown up to a 45% reduction in plasma TG levels.[61] The common side-effects are nausea, vomiting and diarrhea which necessitate slow upward dose titration. Hepatic steatosis is more serious side-effect. However it is not yet approved for hypertriglyceridemia and has been used for this indication on compassionate grounds.

8. Diacyl glycerol acyl transferase (DGAT) inhibitors

The synthesis and metabolism of cardiac triglyceride play a pivotal role in the regulation of lipid metabolism and function of the heart. The last step in TG synthesis is catalyzed by diacyl glycerol acyl transferase (DGAT). There are two DGAT isoforms, DGAT1 and

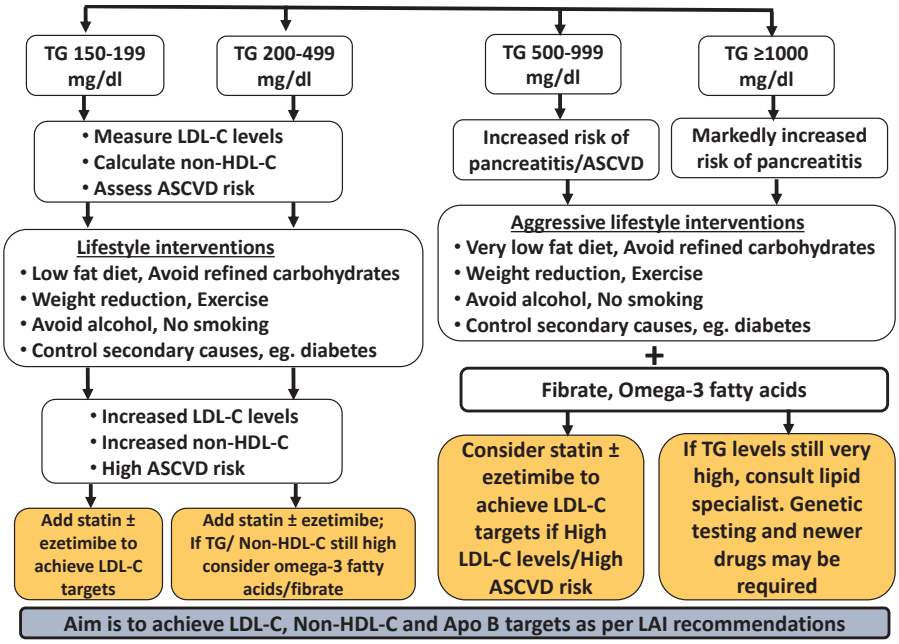

Fig. 3: Treatment algorithm for hypertriglyceridemia based on baseline triglyceride levels

DGAT2, in the mammalian heart but their roles are poorly defined. A study showed that inhibition of DGAT1 or DGAT2 in adult mouse heart results in a suppression of TG synthesis and turnover. This protects the heart against high fat diet-induced lipid accumulation.[62]

LAI recommendations

Both fasting and non-fasting lipid profiles are important for managing Indian patients with dyslipidemia. For routine screening, a fasting lipid profile is not mandatory.

1. Direct LDL-C measurement is preferred if TG is ≥200 mg/dl or LDL-C is <70 mg/dl.

2. There is substantial evidence that triglyceride rich lipoproteins play a causative role in atherosclerosis and CHD. TG levels remain a significant predictor of residual risk and focus on non-HDL-C after control of LDL-C levels is recommended. A combination of high TG and LDL-C imparts even greater CV risk.

3. All patients with hypertriglyceridemia should be evaluated for ASCVD risk.

4. High TG is often accompanied by low HDL-C levels and increased proportion of small dense LDL-C, a pattern known as atherogenic dyslipidemia.

5. Maintain TG <150 mg/dl, preferably <100 mg/dl.

6. In patients with elevated TG levels, rule out secondary causes for hypertriglyceridemia.

7. Lifestyle changes are recommended for all patients with hypertriglyceridemia: Regular exercise, maintenance of appropriate body weight, avoidance of alcohol and smoking, eating a diet with reduced saturated fat and refined carbohydrates. Lifestyle modification can reduce TG by as much as 50% (Figure 3).

8. Adequate glycaemic control in DM will result in substantial fall in triglyceride levels.

9. If TG is ≥150 mg/dl but <500 mg/dl: consider statin ± ezetimibe as the first line drug therapy. First priority is achievement of LDL-C target to reduce ASCVD risk; if TG remains ≥200 mg/dl calculate non-HDL-C level, if above goal, a non-statin drug can be added to achieve the non-HDL-C goal. For those with ASCVD or diabetes and multiple risk factors IPE can be considered in those with TG of 150 mg/dL or higher to provide further risk reduction benefit beyond a statin.

10. Unless TG is very high, ≥500 mg/dl, a statin ± ezetimibe, with the option to consider IPE for those with TG of 150 mg/dL is preferred before considering a fibrate or other non-statin drug.

11. If TG is ≥500 mg/dl the primary objective is to reduce the risk of acute pancreatitis by lowering TG first. Start treatment with a non-statin drug (e.g., fenofibrate) and then add statin to achieve LDL-C and non-HDL-C goals.

12. Among non-statin drugs, omega-3 fatty acids especially icosapent ethyl in dose of 4 grams per day is preferred as it has been shown to reduce adverse CV events in patients with ASCVD or diabetes and multiple risk factors. In subjects with very high TG levels, fibrates are to be initiated first with simultaneous identification and control of secondary causes.

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Lipoprotein(a) and ASCVD risk

Lipoprotein(a) [Lp(a)] was discovered in 1963 by Kare Berg as a new antigen associated with LDL. The new antigen was called Lp(a) after lipoprotein, and (a) as this was the accepted terminology to name antigens in human immunogenetics.[1] The LPA gene is located on chromosome 6q26-27 region encoding the apo(a) component of Lp(a).

Lp(a) is an LDL like particle with a molecule of apo B-100 linked to apo(a) by a disulphide bridge (Figure 1). The apo(a) component shares structural homology to plasminogen and competes with plasminogen binding sites– resulting in reduced fibrinolysis.[2] Lp(a) is also thought to speed up the process of atherosclerosis by binding to LDL, calcium and other components into the blood vessel wall in an atherosclerotic plaque. Lp(a) has proinflammatory properties too.

The serum Lp(a) levels are reported to remain same throughout life without intervention. However, in women, estrogen therapy decreases Lp(a), while after the menopause Lp(a) levels increase. Growth hormone increases Lp(a) levels. Surprisingly, exercise and dieting have been shown to increase Lp(a) levels. It is possible that the proportion of the isoforms of Lp(a) which are less atherogenic are elevated by therapeutic life style changes.[3]

Clinical Studies (Epidemiology and Genetics)

Mendelian randomization data support a causal role for Lp(a) in CAD.[4] In this analysis, three studies from Denmark were included: the Copenhagen City Heart Study with 16 years of follow-up (total number 8637 and MI events 599); the Copenhagen General Population Study (total number 29,388 and MI events 994); and the Copenhagen Ischemic Heart Disease Study (total number 2461 and MI events 1231). Genetically elevated Lp(a) was associated with an HR of 1.22 per doubling of the Lp(a) level.[4] These data support causal association between elevated Lp(a) levels and increased risk of MI.

In a genome wide association study, 3145 patients with CHD and 3352 control subjects were studied.[5] It identified two LPA variants that showed strong association with an increased level of Lp(a) lipoprotein and an increased risk of CHD. This further supports a causal role of Lp(a) lipoprotein in CHD.

In a meta-analysis of 36 prospective studies, involving a total of 126,634 individuals who had no known prior history of CHD, the relationship of Lp(a) concentration with risk of major vascular and non-vascular outcomes was analysed.[6] The study concluded that there were continuous, independent, and modest associations of Lp(a) concentration with risk of vascular outcomes (CHD and stroke).

In the INTERHEART-Lp(a) study[7], 6086 cases of first myocardial infarction (MI) and 6857 controls were included in the analysis of 7 ethnic groups. There were 775 Africans, 4443 Chinese, 1352 Arabs, 1856 Europeans, 1469 Latin Americans, 1829 South Asians, and 1221 Southeast Asians. Serum Lp(a) levels were measured using an isoform insensitive assay. Lp(a) concentration ≥50 mg/dL was associated with an increased risk of MI (odds ratio, 1.48; 95% CI, 1.32-1.67; p<0.001). This association was independent of other ASCVD risk factors (diabetes mellitus, smoking, high BP, and apo B and apo A ratio). The population-attributable risk of high Lp(a) for MI varied from 0% in Africans to 9.5% in South Asians (Table 1).

Indian studies

Lp(a) may have particular relevance for Indians in causing ASCVD. The coronary artery disease in Asian Indians (CADI) study showed that levels of Lp(a) are significantly elevated among Indians.[8] Approximately 25% of Indians and other South Asians have elevated

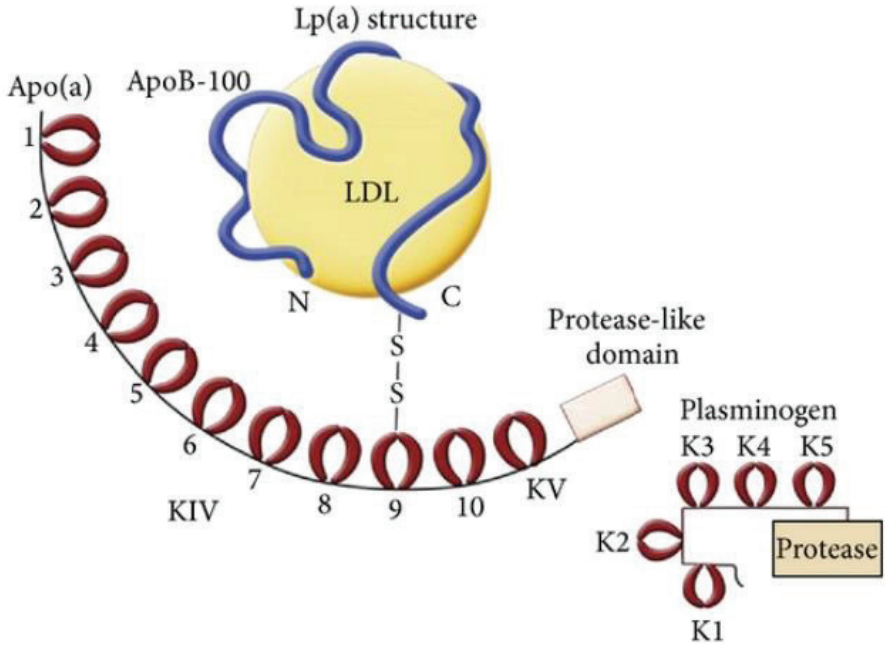

Fig. 1: Structural characteristics of Lp(a) and structural homology between Lp(a) and plasminogen (from *Disease Markers* 2013; 35:551-559, an open access article)

Table 1: Prevalence, odds ratio, and population-attributable risk (PAR) for acute myocardial infarction in South Asians in the INTERHEART Study[7]

Risk factors	Prevalence %	Odds ratio (OR)	PAR%
High apoB/ apoA1 ratio	44	2.57	47%
Current smoking	41	2.57	38%
Hypertension	13	2.92	19%
Diabetes mellitus	10	2.52	12%
Lipoprotein(a) >50 mg/dL	9	2.14	10%

Table 2: Lipoprotein(a) levels in Indians with CAD or stroke compared to age-matched control (Age group 45 years or less) (9-13)

Author	Number		Mean Lp(a) level		P value
	Cases	Control	Cases	Control	
Christopher R[9]	50 stroke	50	23.1 ± 24.3	11.7 ± 11	<0.001
Gambhir JK[12]	50 CAD	50	35.0 ± 32.4	20.3 ± 17.0	<0.002
Isser HS[13]	50 AMI	50	22.28 ± 5.4	9.28 ± 22.59	<0.002
Angeline T[10]	65 AMI	50	58.6 ± 3.20	19.70 ± 0.18	<0.05
Wadhwa A[11]	40 AMI	40	38.74 ± 26.15	20.54 ± 16.27	<0.05

Lp(a) levels (≥50 mg/dL), rendering it a highly prevalent risk factor in the population. Numerous studies have shown that elevated Lp(a) is significantly associated with premature and malignant CHD among Indians[9-13] (Table 2).

The recently published INTERHEART-Lp(a) also demonstrated that South Asians (including Indians) had the second highest Lp(a) levels after Africans among various ethnic groups and had the highest risk of MI from elevated Lp(a).[7] Enas et al[14] emphasized the importance and usefulness of estimating Lp(a) levels in assessing the risk of acute MI in South Asians who, as shown in the study by Pare et al[7] have the highest risk and population attributable risk.

Lp(a) and calcific aortic valve disease (CAVD)

Lp(a) may also predispose to aortic valve calcification in familial hypercholesterolemia (FH) patients.[15] CAVD remains the leading cause of aortic valve replacement in the developed world, yet there is no drug therapy to slow the disease progression. In the ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial, elevated Lp(a) levels were linked to echocardiographically measured progression of aortic stenosis, as well as the need for aortic valve replacement (AVR).[15] The patients with elevated Lp(a) and oxidized phospholipids (OxPL) on apo B-100 (OxPL-apoB) levels had the fastest progression rate and higher need for AVR.[15]

Torzewski et al[17] demonstrated the presence of Lp(a)-associated molecules in plasma and in aortic valve leaflets of patients with calcific aortic valve stenosis. These data support the hypothesis that Lp(a) is a key etiologic factor in patients with calcific aortic valve stenosis. In another study, the prevalence of elevated Lp(a) (≥30 mg/dL) in patients undergoing transcatheter aortic valve replacement (TAVR) was 35%; these patients more often had coronary artery disease (CAD) requiring revascularization compared with patients with normal Lp(a) (65% vs 47%; p=0.047). Patients with Lp(a) ≥30 mg/dL also had higher incidence of paravalvular leak compared with those with normal Lp(a) (13% vs 4%; p=0.04).[18]

Lp(a) and stroke

In a meta-analysis of 31 studies comprising of 56,010 subjects and >4609 stroke events, it was concluded that elevated Lp(a) was a risk factor for incident stroke.[19] Lp(a) amplifies the impact of high LDL-C, low HDL-C, systemic hypertension, DM and hyperhomocysteinemia.[20,21] The risk of recurrent events doubles when Lp(a) levels are high as compared to low Lp(a) levels. Further, the levels correlate with the severity of the disease.[21]

Therapeutics

Among various lipid-lowering agents, statins have negligible effect on Lp(a) but niacin significantly reduces it. Unfortunately, two major studies with niacin- AIM-HIGH and HPS-THRIVE showed no significant clinical benefit and hence, niacin is no longer used as a lipid-lowering agent for the purposes of cardiovascular risk reduction.[22,23] However, recently, the interest in Lp(a) has received a positive thrust by the finding of nearly 25% reduction in Lp(a) with PCSK-9 inhibitors.[24] One of the proposed mechanisms of action of PCSK-9 inhibitors is that the increased number of LDL-C receptors also bind to Lp(a) particles and remove them from circulation.[25] In the FOURIER trial, the patients with higher baseline Lp(a) exhibited greater lowering of Lp(a) with evolocumab and derived greater coronary benefit.[26] Alirocumab, another PCSK9 inhibitor, reduced Lp(a) by 23% but did not significantly reduce MACE when adjusted for LDL-C lowering. However, when baseline Lp(a) was >50 mg%, the association between Lp(a) reduction and MACE remained significant in a fully adjusted model.[27] In a pre-specified analysis of the ODYSSEY Outcomes trial in patients with recent acute coronary syndrome (ACS)[28] to evaluate whether alirocumab-induced changes in lipoprotein(a) and LDL-C independently predicted major adverse cardiovascular events (MACE), it was found that lipoprotein(a) and corrected LDL-C levels and their reductions by alirocumab predicted the risk of MACE after recent ACS. The authors concluded that "Lipoprotein(a) lowering by alirocumab is an independent contributor to MACE reduction, which suggests that lipoprotein(a) should be an independent treatment target after ACS". In another study, anacetrapib, a CETP inhibitor, reduced Lp(a) by 36.4% and the best outcome results were achieved with the lowest achieved LDL-C and the lowest achieved Lp(a).[29]

Although it is indisputable that elevated Lp(a) is a strong risk factor for ASCVD, only PCSK9 inhibitors are currently available for lowering Lp(a)[24-28] Therefore, at present, LDL-C reduction and effective control of other risk factors remain the primary goals of therapy. When Lp(a) is >50 mg/dl, aggressive LDL-C lowering with statins should be achieved to reduce the multiplicative effect of LDL-C and Lp(a). With PCSK9 inhibitors showing reduction of Lp(a), further data showing the clinical impact of Lp(a) reduction is now eagerly awaited.[30]

New therapeutic agents

APO(a)-LRx, an oligonucleotide targeting apo(a), is a novel therapy to reduce Lp(a) concentrations and Lp(a)-mediated CV risk. A phase II trial[31] assessed the effect of IONIS-APO(a)Rx, a ligand-conjugated antisense oligonucleotide designed to be highly and selectively taken up by hepatocytes, in participants with elevated Lp(a) levels. It was a dose ranging study with administration of the drug once a week, for 12 weeks. IONIS-APO(a)-LRx reduced Lp(a) by 66% to 92%, with no serious side effects. The study also showed a significant reduction in LDL-C, apo B and oxidised phospholipids (OxPL) associated with

apoB and apo(a). The lowering of Lp(a) and associated OxPL led to reduced monocyte inflammatory activation supporting the hypothesis that Lp(a) is proinflammatory.

A double-blind, placebo-controlled, dose-ranging trial randomized 286 patients with established CV disease and lipoprotein(a) levels of ≥60 mg/dL to the hepatocyte-directed antisense oligonucleotide APO(a)-LRx, in 5 different dosing regimens (20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week), or saline placebo subcutaneously for 6 to 12 months.[32] The primary end point was the percent change in isoform-independent assay measured lipoprotein(a) level from baseline to sixth month of exposure. The median baseline Lp(a) levels in the six groups ranged from 81.8 to 98.6 mg/dL. Administration of APO(a)-LRx resulted in dose-dependent decreases in lipoprotein(a) levels, with mean percent decreases of 35% at a dose of 20 mg every 4 weeks, 56% at 40 mg every 4 weeks, 58% at 20 mg every 2 weeks, 72% at 60 mg every 4 weeks, and 80% at 20 mg every week, as compared with 6% with placebo (P values 0.003 to <0.001). There were no significant differences between any APO(a)-LRx dose and placebo with respect to platelet counts, liver and renal measures, or influenza-like symptoms. The most common adverse events were injection-site reactions.[32]

Plasma Lp(a) Apheresis

There are no drugs available now for clinical use to lower Lp(a) effectively, and thus lipid apheresis has an important role to play. Lipoprotein apheresis decreases LDL-C and Lp(a) by about 60-70%. There is a rebound, necessitating weekly apheresis. Apheresis has shown to improve endothelial function and myocardial perfusion in patients with high Lp(a).

The German Lipoprotein Apheresis Registry (GLAR) data showed that ASCVD events were reduced significantly.[33] A significant regression of coronary atherosclerosis by angiography was seen with in the selective Lp(a) apheresis group compared to atorvastatin in an open label prospective study of 18 months.[34] Shettler et al from Germany report that relative to the two years before initiating LA, incidence of MACEs has decreased by 78% during two years of LA treatment.[35]

Lipoprotein apheresis is generally well tolerated and safe, but cost and accessibility are the constraints. An interesting clinical point is that ACE-inhibitors are contraindicated in patients undergoing apheresis, since they could cause a bradykinin reaction.

Lp(a) lowering vs LDL-C lowering

A Mendelian randomization analysis[36] compared Lp(a) and LDL-C in >62,000 patients with CHD and >127,000 controls. The conclusion was that for each 10 mg/dL reduction in Lp(a), the CHD risk decreased by 5.8%. In contrast, a 10 mg/dL reduction in LDL-C would reduce the CHD risk by 14.5%. Thus, for CHD risk reduction equivalent to reducing LDL-C by 38.67 mg/dL is 101.5 mg/dL for Lp(a), which is a daunting task. However, it is likely that it is an overestimation, as Lp(a) also has proinflammatory and prothrombotic actions.

Laboratory estimation of Lp(a)

Lp(a) particle sizes differ and has more than 40 isoforms. Small isoforms of Lp(a) are associated with high Lp(a) levels and high risk of ASCVD while large isoforms are associated with low Lp(a) levels and low ASCVD risk. An isoform-insensitive enzyme-linked immunosorbent assay (ELISA) is the reference standard for measuring Lp(a) levels. As small Lp(a) isoforms deteriorate significantly than larger isoforms in specimens stored over a period of time. Lp(a), should be measured in fresh plasma.[37] Measures of Lp(a) in nmols/l can be roughly translated into mg/dL using the conversion factor of 2.4.[38]

Guidelines and Recommendations:

The LAI in 2016 recommended[40] estimation of Lp(a) levels by isoform insensitive assay 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, Lipoprotein (a) ≥50 mg/dL is a high-risk feature. Lipoprotein (a) 20-49 mg/dL is a moderate risk nonconventional risk factor. ACC/AHA 2018 guidelines[41] consider an elevation of Lp(a) as a risk-enhancing factor, when Lp(a) is >50 mg/dl or125 nmol/L. The recommendations for measuring Lp(a) are:

1. Family history of premature ASCVD , or

2. Personal history of ASCVD not explained by major risk factors

They recommend it to be considered in women only in the presence of hypercholesterolemia since improvement in risk prediction in adult women was minimal.

European Society of cardiology (ESC)/European Atherosclerosis Society (EAS)[42] recommend that Lp(a) measurement should be done at least once in each adult's lifetime to identify those with very high Lp(a) levels, especially in patients with family history of premature CVD. Lp(a) >180 mg/dL has a lifetime risk of ASCVD equivalent to the risk associated with HeFH.[42]

Enas et al[43] have suggested that Lp(a) can be measured any time beyond age of 2 years after which the levels do not change, and recommended Lp(a) estimation in subjects with a) personal history of premature CVD, b) family history of premature CVD and/or elevated lipoprotein(a) levels c) familial hypercholesterolemia d) recurrent CVD events despite high-intensity statin treatment e) statin resistance (<50% reduction in LDL-C, in spite of high intensity statin therapy) and f) unclear about indications and/or intensity of statin therapy. Mora[44] recommends that it is preferable to do one-time measurement of Lp(a) in patients after ACS. This would be useful for risk stratification, in selecting higher risk patients for novel therapies, including PCSK9 inhibitors, and for cascade screening of families with inherited Lp(a) disorders. Treatment with a PCSK9 inhibitor antibody may be considered in FH patients with CVD or with other factors putting them at very high risk for CHD, such as other CV risk factors, family history, and high Lp(a).[39] However, neither PCSK9 inhibitors or any other therapies are currently indicated for lowering Lp(a) for the purposes of reducing CVD risk.

A recent international consensus statement[45] recommended that Lp(a)-corrected LDL-C should be assessed at

least once in patients with high Lp(a) or if the patient shows a poor response to LDL-lowering therapy. Peter Libby once commented "Lp(a)– a frustrating final frontier in lipid management?"[46] However, with vigorous research activities being witnessed in the field currently, it may not remain so for long.

LAI Recommendations - 2020

1. Use an assay for Lp(a) measurement that is unaffected by the isoform size.

2. Lp(a) multiples the risk of other ASCVD risk factors like high LDL-C, low HDL-C, systemic hypertension, diabetes and hyperhomocysteinemia. With only PCSK9 inhibitors being available as effective pharmacotherapy at present, other risk factors must be treated optimally to counter multiplicative risk of raised Lp(a).

3. Lp(a) ≥20 mg/dL indicates increased ASCVD risk in Indians. Lp(a) 20-49 mg/dL is a moderate risk non-conventional risk factor, whereas Lp(a) ≥50 mg/dL is a high-risk feature.

4. In view of the high prevalence of raised Lp(a) in Indian population its routine assessment will help in detecting high risk individuals (Lp(a) ≥50 mg/dL) and as non-conventional risk marker for further risk stratification in low and moderate-risk individuals (Lp(a) 20-49 mg/dL).

5. Lp(a) measurement is strongly recommended:

i. At the time of initial screening of all subjects (18 years of age in adults and at the age of 2 years in subjects with family history of FH and premature ASCVD)

ii. In patients with:

a. Premature ASCVD (<55 years in men, <65 years in women)

b. Familial hypercholesterolemia

c. A family history of premature CVD and/or elevated Lp(a)

d. Recurrent ASCVD despite optimal lipid lowering treatment

iii. In patients after an ACS: This helps in risk stratification, selection of higher risk patients for novel therapies and for cascade screening of families.

iv. In patients showing poor response to maximum lipid lowering therapy (and Lp(a) corrected LDL-C could be assessed in such patients). If LDL-C is at goal and Lp(a) is high, PCSK9 inhibitors may be used.

v. It is preferable to estimate in patients

a. Who sustain ischemic stroke of uncertain etiology

b. Who have calcific aortic valve stenosis

c. Who are undergoing transcatheter aortic valve replacement (TAVR)

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High Sensitivity C-Reactive Protein

In many patients ASCVD events occur in individuals with none or only one risk factor. Hence newer biomarkers are needed to identify individuals at risk of future adverse CV events especially in those individuals who have no or minimal conventional risk factors.[1]

Biomarkers are naturally occurring molecules, genes, or characteristics by which a particular pathological or physiological process, disease, etc. can be identified. There are three types of biomarkers for ASCVD, the genetic biomarkers, serum circulating biomarkers and the imaging biomarkers. The genetic biomarkers may be useful in predicting genetic susceptibility to disease and for detecting subclinical disease. Serum circulating biomarkers may be most informative in detecting earlier stages of disease, whereas imaging biomarkers directly detect subclinical disease.

Inflammation is an integral component of atherosclerosis and acute coronary syndromes, being involved in initiation, development and progression of atherosclerosis. High sensitivity C-reactive protein (hsCRP) is one of the serum circulating biomarkers that has been shown to predict ASCVD in patients.[2] It has the most clinical evidence as a marker of cardiovascular risk, and recently evidence of its reduction (and other inflammatory measures) linked to reductions in cardiovascular disease risk.

C-reactive protein (CRP) is an acute phase reactant and nonspecific marker of inflammation. It is mainly produced in the hepatocytes as a pentamer of identical subunits.[3] One of the most potent drivers of production of CRP is interleuin-6 which is released from activated leukocytes. The leukocytes are activated in response to trauma, infection or cytokines released from vascular smooth muscle cells in response to atherosclerosis. CRP binds to oxidized LDL which is atherogenic.[4] Persistent low-grade inflammation in atherosclerosis is detected during health as low levels of hsCRP (levels <10 mg/L). A serum hsCRP >2 mg/L is considered elevated, in the absence of infection, arthritis, chronic inflammatory disorders or recent trauma. hsCRP levels increase with age and are also elevated in metabolic syndrome, mediated by inflammatory cytokines released from visceral fat. Women compared to men have higher levels of hsCRP and certain ethnic groups such as African-Americans have lower levels. There are several studies correlating the role of hsCRP with CV events. They support a role of hsCRP as a risk marker and not as a risk factor.[5]

Clinical evidence of utility of CRP

Primary prevention

The inclusion criteria of LDL-C level of <130 mg/dL with hsCRP level ≥2.0 mg/L in healthy men and women was used in the primary prevention JUPITER trial in which rosuvastatin 20 mg/d reduced LDL cholesterol levels by 50% and hsCRP levels by 37%. This resulted in 44% relative risk reduction in CV events (P <0.00001) and 20% relative risk reduction in all-cause mortality (P =0.02).[6] Lowest event rates were seen in individuals with both low achieved LDL-C (<70 mg/dl) and low achieved hs-CRP levels (<2 mg/L).[7] It should be noted that hsCRP is related to event rates rather than atherosclerosis. Since hsCRP levels increase with age, the JUPITER study data may be applicable to primary prevention in adults as studied in JUPITER trial i.e. men ≥50 years and women ≥60 years. In the Framingham Heart study 3006 subjects free of CV disease were followed up for 12 years.[8] The net reclassification improvement (NRI) with hsCRP in the Framingham Heart study was 11.8% for CHD and 5.6% for CVD.[8] The above studies suggest that the circulating levels of CRP are helpful in estimating the risk of first adverse CV event and that this risk can be mitigated by statin therapy initiated on the basis of elevated CRP levels in select group of patients. However, since statins lower both hsCRP as well as LDL-C, whether the reduction in CVD risk was due mainly or exclusively to LDL-C reduction or partly from reductions in hs-CRP is not clear, and the actual contribution of reductions in hsCRP to the observed reduction in CVD risk in JUPITER was not described. Hence, the JUPITER trial did not provide conclusive evidence for the inflammatory hypothesis.

Secondary prevention

The data regarding the role of CRP in patients with risk factors for CVD and those with established CVD is divisive. In the PROVE IT-TIMI 22 trial[9] and REVERSAL trial[10], greater reduction in LDL-C and hsCRP levels together was associated with a greater reduction in the number of clinical events and progression of the plaque. In contrast, in the HPS trial, simvastatin 40 mg resulted in CV risk reduction in proportion to LDL-C lowering, irrespective of hsCRP levels.[11] In this study the patients (n=20,536) were divided into six groups based on baseline CRP levels and the proportional reduction in primary endpoint was similar regardless of the baseline CRP levels.[11] The authors concluded that baseline CRP levels had no bearing on the magnitude of vascular benefit with statins. Similarly, in the ASCOT trial, atorvastatin decreased CRP levels by 27.4%.[12] Although baseline CRP levels correlated with baseline LDL-C levels and showed a direct linear association with the risk of CHD, the statin effect did not differ according to the tertile of baseline CRP levels. Further, there was no significant difference in the area under ROC curve in the modified Framingham model after addition of CRP.[12]

In the in the Multi-Ethnic Study of Atherosclerosis (MESA) 1330 intermediate risk participants (median Framingham Risk Score 8.8%) without diabetes mellitus were followed up for a median of 7.6 years. The prevalence of hypertension was 38.2% and 14.1% patients were taking statins. For prediction of CHD/CVD events, the addition of 6 risk markers to the baseline model improved the AUC significantly. Of these, coronary artery calcium showed the highest increment for incident CHD and CVD whereas high-sensitivity CRP showed modest improvement for incident CHD and brachial flow mediated dilation showed the least increment for incident CVD. The NRI was 7.9% for CHD for hsCRP, whereas the corresponding NRI values for coronary artery calcium (CAC) score was 65.9%, suggesting small but significant incremental value of hsCRP in risk prediction in intermediate risk individuals.[13] Significantly, in persons

who had low 10-year risk, an elevated hsCRP did not significantly increase the CV risk above that predicted by conventional risk factors. Conversely, a low hsCRP in high risk individuals did not significantly reduce the risk.[14] This leaves us with the intermediate risk patients (Framingham Risk Score >5% to <20%) only in whom hsCRP may have clinical utility.[14] In the WOSCOPS Heart Study, 26% men with metabolic syndrome had high CRP levels as compared to those without metabolic syndrome despite similar LDL-C levels. The elevated CRP increased the risk of future CHD events and had similar predictive value as presence of metabolic syndrome for CHD events (HR=1.6) with risk increasing markedly with both high CRP levels and metabolic syndrome being present (HR=2.75) compared to both low CRP levels and absence of metabolic syndrome.[15]

In addition to using hsCRP for ASCVD risk prediction, inflammation has been explored as a direct therapeutic target also.[16] Interleukin-1β is a cytokine that drives the interleukin-6 signalling pathway and is pivotal to the inflammatory response. In the CANTOS trial, canakinumab, a high-affinity fully human monoclonal antibody against interleukin-1β (IL-1β) was used to address residual inflammatory risk in a secondary prevention setting.[17] The study enrolled 10061 patients with history of myocardial infarction and elevated hsCRP >2 mg/L. Canakinumab (150 mg administered subcutaneously every 3 months) decreased hsCRP levels by 37% and showed a significant 15% reduction in the primary outcome of nonfatal MI, nonfatal stroke and CV death (P =0.02) at 48 months. The key secondary endpoint which included the components of primary endpoint plus hospitalization for unstable angina that led to urgent revascularization was significantly decreased in canakinumab 150 mg dose group, HR =0.83, P =0.005). There was nominally significant reduction in MI and hospitalization for unstable angina that led to urgent revascularization in canakinumab 150 mg dose group. However, when the persons who achieved hsCRP <2.0 mg/L were compared to those who did not, a significant reduction in CV mortality was found (HR 0.69, p=0.004) without any significant reduction in LDL-C. This shows that a specific group of responders can be identified by checking hsCRP levels one month following initiation of canakinumab. Canakinumab was associated with a higher incidence neutropenia, thrombocytopenia and fatal infections than was placebo. There was no significant difference in all-cause mortality (HR for all canakinumab doses vs. placebo, 0.94; P =0.31).[17] In a subgroup analysis of CANTOS study, subjects with on-treatment hsCRP levels <2 mg/L had a 25% reduction in primary endpoint (P <0.0001) compared to only 5% among those with on-treatment hsCRP levels ≥2 mg/L. Similarly, reduction in hsCRP <2 mg/L also led to a 31% reduction in CV death (P =0.0004) and all-cause mortality (P <0.0001) compared to non-significant reductions with achieved hsCRP levels ≥2 mg/L.[18] While these adverse effects were in part responsible for the drug not being approved in the US for CVD event reduction, the CANTOS trial is the first clear proof of the inflammatory hypothesis demonstrating reduction of inflammation to reduce CVD events.

To pursue this inflammatory theory further and to find a less expensive alternative to canakinumab, the US National Institutes of Health sponsored CIRT trial was performed with methotrexate at multiple sites throughout the US and Canada. Methotrexate produces adenosine mediated anti-inflammatory effect and is used for the treatment of rheumatoid arthritis. However, in 2018 the trial was terminated prematurely due to futility. There was no significant reduction in MACE (HR 0.96, 95% CI, 0.79-1.16, P =0.67) and neither LDL-C, nor hsCRP or IL-1β showed any significant reduction with methotrexate. The probable reason for the failure of methotrexate is that adenosine mediated anti-inflammatory effects are not beneficial in CV risk reduction, and only the IL-1 blocking drugs are effective.[19]

In another study of 17,464 patients, when hsCRP was studied among MI survivors (>30 days after MI), previous percutaneous coronary intervention, ongoing renin angiotensin receptor blockade and statin therapy were associated with low hsCRP. High values of hsCRP ≥2 mg/L seen in 66% of patients were associated with major adverse coronary events (HR 1.28; 95% CI, 1.18-1.38) and death (HR 1.42; 95% CI, 1.31-1.53) during a median follow up of 3.2 years. The relationship between the hsCRP and outcomes was linear until hsCRP >5 mg/L.[20]

Colchicine is an oral drug which has potent anti-inflammatory effects and is an accepted treatment for pericarditis. In the COLCOT study, 4745 post myocardial infarction patients were randomized to low dose colchicine (0.5 mg daily) or placebo within 30 days of index event. The primary endpoint occurred in 5.5% of patients in the colchicine group as compared to 7.1% in the placebo group (P =0.02) over a median follow up of 22.6 months.[21] When colchicine (0.5 mg) was administered in the chronic coronary artery disease patients in the LODOCO2 trial, primary endpoint occurred in 6.8% compared to 9.6% in the placebo group (P <0.001). However an increase in the incidence of non-cardiovascular deaths with colchicine (0.7 vs 0.5 events per 100 patient years, hazard ratio, 1.51; 95% CI, 0.99 to 2.31) was an area of concern.[22]

In a recent review, Indian data from various published studies on hsCRP was analysed. Multiple techniques were used for estimation of hsCRP (33% ELISA, 25% nephelometry, 29% turbidimetry, 8.3% chemiluminescence, and one study with latex agglutination test) which could have contributed to varying values across the studies. The basal concentration of hsCRP in Indians was high with a mean hsCRP of 1.88 mg/L in the control arm and 2.46-9.3 mg/L in patients having established CVD. The high prevalence of obesity and metabolic syndrome in India could be one of the contributors of high basal hsCRP in India. This increased basal inflammation among Indians, in turn, could be the reason for the higher prevalence of premature CHD disease in India. The hsCRP was found to be an independent predictor of diverse end points ranging from obesity, type 2 diabetes mellitus, metabolic syndrome, increased carotid intima-media thickness, stable CAD, first acute coronary event, and recurrent CVD events among Indian patients.[23]

LAI 2019 Recommendations

1. HsCRP is not directly involved in atherosclerosis but is a risk marker for adverse cardiac events. It is not a replacement for conventional risk factors like serum LDL-C levels but may

be used as an adjunct to further risk stratify select individuals. However, lower levels (hsCRP <2 mg/L) are associated with improved CVD-event free prognosis and there is now clinical trial evidence that lowering the levels of hsCRP lowers CVD events.

2. For using hsCRP as a risk stratification tool, at least 2 readings 2-3 weeks apart must be obtained. If the second reading is also ≥2 mg/L then it can be used for risk stratification. If readings are very high, i.e. >10 mg/L, they may suggest acute phase response to underlying subclinical or clinical infection or other inflammatory disorder. They should be repeated after 4 weeks and the initial strategy of 2 consecutive readings must be fulfilled.

3. The hsCRP has modest benefits in reclassifying moderate risk persons in primary prevention, whereas its utility in low- and high-risk individuals is limited. Therefore, hsCRP may be used as a marker for further risk stratification in intermediate-risk individuals, provided there is no alternate cause for elevated hsCRP.

4. In the post-ACS setting, hsCRP may be useful in identifying patients at high risk for future adverse cardiac events who may warrant more aggressive management of risk factors. For this purpose, hsCRP readings at least 4 weeks after ACS should be considered.

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Apolipoprotein B as a Predictor of CVD

"Apolipoprotein B unifies, amplifies, and simplifies the information from the conventional lipid markers as to the atherogenic risk attributable to the apo B lipoproteins".

-Sniderman et al[1]

Apolipoproteins, the protein components of lipoproteins have the following functions:[2,3]

1. They modulate the enzymatic activity on lipoproteins,

2. They are responsible for maintaining the structural integrity of the lipoproteins, and,

3. They facilitate the uptake of lipoproteins through a receptor mediated mechanism.

Apolipoprotein B (Apo B) is the carrier for chylomicrons, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and lipoprotein (a). There are two circulating forms of apo B: apo B48 (from the small intestine) and apo B100 (from the liver). Intestinal Apo B present in chylomicrons has a molecular mass 48% of that of hepatic apo B. The same gene codes for both apo B48 and apo B 100. A genetic mutation in apo B that prevents binding of the defective apo B to the LDL receptor is an autosomal dominant disorder and leads to classical familial hypercholesterolemia.

Apo B-100 is necessary for assembling VLDL in the liver and also serves as a ligand for LDL receptor-mediated clearance. Apo B-48 is essential for the formation of chylomicrons and serves in the absorption of dietary fats from the intestine.[4]

One molecule of apo B48 is found in each chylomicron and chylomicron remnant. One molecule of apo B100 is found in each LDL, IDL and VLDL and Lp(a) particle. However, 85-90% of apo B100 is found in LDL-C. Many methods for apo B measure total apo B or apo B100.

Apo B envelops the surface of atherogenic lipoproteins as a macromolecular scaffold and provides structural integrity.[5]

Total apo B concentration = apo B in chylomicron + apo B in VLDL + apo B in VLDL remnant + apo in IDL + apo in LDL + apo B in Lp(a).

VLDL to LDL conversion takes six hours, and LDL remains in the circulation for 48 hours. Thus apo B spends 90% of its lifespan as an LDL.[6]

The principal event in the pathogenesis of atherosclerotic disease is the retention of apo B containing particles within the arterial vessel wall. Most Apo B containing lipoproteins (up to 70 nm in diameter), except for fully formed chylomicrons and large VLDL promote plaque formation.[7] The concentration of apo B containing particles in the blood, the permeability of the vascular endothelium and the binding affinity of the apo B particles to the collagen and elastin of the arterial wall determine the rate and extent of this retention of apo B in the vessel wall.[5]

Plasma LDL-C is a measure of the cholesterol mass carried by LDL particles, by far the most numerous of the Apo B-containing lipoproteins, and is an estimate of the concentration of circulating LDL. In general, LDL-C, non-HDL-C, and apo B concentrations are very highly correlated. As a result, under most circumstances, they provide very similar information about ASCVD risk.[8] However, under certain circumstances—including among people with elevated TG levels, DM, obesity, or very low achieved LDL-C levels—the calculated or directly measured LDL-C level may underestimate both the total concentration of cholesterol carried by LDL and, more importantly, underestimate the total concentration of apo B containing lipoproteins, thus underestimating the risk of ASCVD. In around 20% of patients there may be discordance between measured LDL-C and Apo B levels. Considering these potential inaccuracies in measuring LDL-C in dyslipidemia among patients with DM or high TG levels, and in patients with very low LDL-C levels, measurement of both Apo B and non-HDL-C is recommended as part of a routine lipid panel for risk evaluation in patients with elevated plasma TGs. When there is high non-HDL-C due to high VLDL-C and high buoyant LDL-C, the small dense LDL particles may be low in numbers, indicating comparatively low numbers of apo B particles. These larger cholesterol containing VLDL and IDL particles, though rich in cholesterol can not penetrate into the arterial subintimal space.[16,17,21] Because Apo B provides an accurate estimate of the total concentration of atherogenic particles under all circumstances, it is the preferred measurement to further refine the estimate of ASCVD risk.

LDL-C is the predominant cholesterol carrying apo B among the non-HDL-C particles and has 70% of cholesterol. The remaining 25% is present in TG-rich VLDL, IDL, Chylomicrons and their remnants as well as Lp(a). Most of the clinical laboratories calculate LDL-C using the Friedewald equation (LDL-C = Total Cholesterol–HDL-C–VLDL-C), VLDL-C being calculated as triglycerides/5 in mg/dl, as long as the triglyceride value is <400 mg/dl. This calculated value includes the LDL-C as well as the IDL-C and the cholesterol carried by Lp(a).[9]

LDL-C measures the cholesterol content of LDL. Non-HDL-C measures the cholesterol content of all atherogenic lipoprotein particles. Apo B concentration measures the number of all atherogenic particles.[10]

Statin therapy reduces the LDL-C more than apo B. The decrease in LDL-C is greater than the apo B lowering by 15%.[11] Hence on-treatment apo B is a more reliable index of the residual risk. The 4S, LIPID, AFCAPS/TexCAPS, and the Leiden Heart Study showed that apo B was more predictive of the residual risk of vascular events.[10] The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), is a primary prevention study of 6605 asymptomatic individuals with average LDL-C and below-average HDL-C. The levels of LDL-C, HDL-C and apo B were significant predictors of a first acute coronary event; however, only on-treatment apo B and apo B/apo A-I ratio was predictive of subsequent risk.[12]

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial studied 9014 CHD patients with pravastatin for 1 year. Baseline apo B and apo A-I were stronger predictors of CHD events than LDL-C and HDL-C. The unadjusted on treatment apo B and apo A-I levels were predictive of a subsequent coronary event,

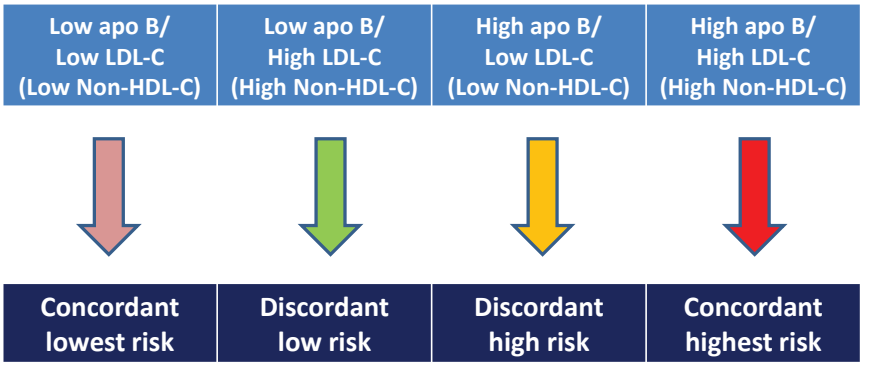

Fig. 1: Apo B, LDL-C Discordance/Concordance and risk of subclinical atherosclerosis

whereas on-treatment concentrations of LDL-C or HDL-C were not.[13] The Scandinavian Simvastatin Survival Study (4S) included 4444 CHD patients randomized to receive simvastatin or placebo and were followed up for 5 years. Baseline apo B was significant predictor of CHD for patients in the placebo and treatment groups, but LDL-C only predicted CHD risk for patients in the placebo group.[14] The Leiden Heart Study had 848 patients (675 men, 173 women) with proven CAD who received effective statin treatment. The study found that apo B and apo A-I were superior to LDL-C for predicting vascular events. In multivariate analysis, on-treatment apo B and apo A-I were the only significant predictors for subsequent MI and all-cause mortality, after adjusting for total cholesterol, triglycerides, gender, diabetes, age and smoking. In a meta-analysis of prospective studies of apo B,[15] it was seen that apo B was a significant predictor of CHD, with an overall relative risk of about 2.0 for the upper versus the lower tertile.

In the AMORIS (Apolipoprotein-Related Mortality Risk Study) study,[16] >1,75,000 men and women over the age of 60 were followed for about 5 years. After adjusting for age and traditional lipid risk factors, including LDL-C, apo B remained a significant predictor of MI for both men and women. From the INTERHEART study, a case control study of myocardial infarction in 52 countries (15152 cases and 14820 controls), blood samples of 9345 cases and 12,120 controls were tested for discordance analysis of non-HDL-C and apo B. Discordance analysis showed that apo B was a more accurate marker of cardiovascular risk than non-HDL-C.[17] The Framingham Heart Study[18] showed that apo B had a greater predictive ability for CHD events than LDL-C and non-HDL-C. In the Women's Health Study, non-HDL-C, apo B, and LDL particle number had greater predictive value than LDL-C for CHD events.[19]

Although of apparently similar significance, measurement of the number of atherogenic particles may be more meaningful than the measurement of the cholesterol content alone. Calculation of non-HDL-C and apo B are highly correlated but only moderately concordant.[20]

In a meta-analysis[21] based on all the published epidemiological studies that contained estimates of the relative risks of non-HDL-C and apo B of fatal or nonfatal ischemic CV events, there were 233,455 subjects and 22,950 events. Apo B was the most potent marker of CV risk. The authors calculated the number of clinical events prevented. Over a 10-year period, a non-HDL-C strategy would prevent 3,00,000 more events than a LDL-C strategy, whereas an apo B strategy would prevent 5,00,000 more events than a non-HDL-C strategy. These results further strengthen the value of apo B in clinical care.

The levels of LDL-C and apo B can be used to reclassify risk as elegantly described by Wilkins et al.[22] They also suggest a dose–response association between apo B in young adults and the presence of midlife CAC independent of baseline traditional CVD risk factors.[22] This study demonstrates a strong association between plasma levels of apo B in young adulthood (mean: 25 years) and coronary calcification in middle age (mean: 50 years). In the big contest between non-HDL-C which measures the cholesterol payload and apo B measuring the number of atherogenic particles, apo B is superior to LDL-C.[22]

The risk of coronary artery calcification was more influenced by apo B than by LDL-C and non–HDL-C in early adulthood. The subjects with the high LDL-C or non–HDL-C and high apo B had the highest risks for subclinical atherosclerosis (coronary artery calcification) in midlife. In fact, Apo B is also recommended to assess CV risk, particularly in patients with hypertriglyceridemia, diabetes, obesity, metabolic syndrome and very low LDL-C levels, and it can be used as an alternative to LDL-c for screening, diagnosis and management.[9,23]

It has been demonstrated that in metabolic syndrome patients or in those with evidence of insulin resistance, a discordance between apo B and LDL-C is more evident and apo B appears to be superior to LDL-C in predicting CV risk (Figure 1).[24]

Type III hyperlipoproteinemia (remnant lipoprotein disorder or familial dysbetalipoproteinemia), a highly atherogenic dyslipidemic disorder is common and is a less recognised entity. Measurement of apo B makes possible the diagnosis of all the atherogenic apo B dyslipoproteinemias, including type III hyperlipoproteinemia.[25] This is another strong justification to include apo B in the assessment of dyslipoproteintemia. Otherwise, the diagnosis may be missed in routine clinical care. In fact, Sniderman et al state emphatically that "Indeed, except for Lp(a), diagnosis of all the apo B atherogenic dyslipoproteinemias is possible based on the plasma levels of triglyceride, cholesterol, and apo B.[26]

Statin therapy usually increases discordance between apo B and the cholesterol markers as LDL-C and non-HDL-C are lowered more than apo B.[27] Thus apo B is a more accurate measure of the response to statin therapy and benefit due to statin therapy than either LDL-C or non-HDL-C.[27] Two transformational studies by Ference et al clearly showed that clinical benefit correlated with apo B, not LDL-C and measuring apo B

Table 1: Effectiveness of statin treatment at reducing LDL-C, non–HDL-C, apo B in Apo B studies of 17,035 participants[26]

	Reduction on therapy	Mean on-treatment concentration
LDL-C	42.1 %	99.2 mg/dL
Non–HDL-C	39.6 %	127.0 mg/dL
Apo B	33.1 %	101.6 mg/dL

provides all the information necessary to assess the adequacy of a lipid-lowering therapy.[28,29]

Multiple discordance analyses have shown that when non–HDL-C was high but apo B was normal, cardiovascular risk was not high, whereas when non–HDL-C was normal but apo B was high, cardiovascular risk was high.[6] Apo B, therefore, is superior to non–HDL-C as a marker of cardiovascular risk.[30]

Apo B and CKD : Serum Apo B, ApoA1, conventional lipid parameters and lipid subfractions were analyzed in 9403 subjects and were followed up for 10 years. Even after adjusting for other risk factors, high Apo B concentrations had an association with the risk of end stage renal disease (ESRD). Apo B levels may be helpful for the predicting the risk of ESRD. Probably glomerular endothelial cells and kidney vessels can become sites of oxidation and inflammation secondary to high Apo B concentrations, leading to progression of CKD.[31]

Apo B or LDL-P measurement to assess CHD risk is becoming increasingly important in the present scenario of a rapidly growing subset of the population with prediabetes, diabetes and metabolic syndrome. Individuals with metabolic syndrome or diabetes tend to have an increased number of small, dense LDL particles but relatively normal LDL-C concentrations. Because statin therapy reduces LDL-C to a greater extent than they do LDL particles,[26] apo B or LDL-particles (LDL-P) appear to provide a better assessment of on-treatment residual risk than LDL-C measurement.[32]

The reduction in serum apo B or LDL-P concentration is not as dramatic as the reduction in LDL-C or non-HDL-C (Table 1). So, the patients treated to goal for LDL-C may not have achieved optimal LDL particle concentrations or apo B levels, leaving them with residual risk.[26,32]

Table 2: The treatment goal of apo B and their corresponding LDL-C and non-HDL-C goal in the AACE guidelines[35]

Risk category	Goal LDL-C (mg/dL)	Goal Non-HDL-C (mg/dL)	Goal Apo B (mg/dL)
High Risk	<100	<130	<90
Very high risk	<70	<100	<80
Extreme risk	<55	<80	<70

From all the studies available, it may be surmised that at a population level, apo B is a superior analytic tool to LDL-C or non-HDL-C. In patients in whom LDL composition is normal, the cholesterol markers and apo B are equivalent markers of risk. But, when the markers are discordant, that is, when LDL-C is normal but LDL-P is high or, alternatively, when LDL-C is high but LDL-P is normal, there is evidence that risk follows apo B and LDL-P, not LDL-C.[33]

Once apo B gets into the sub endothelial space in the vessel wall, smaller cholesterol-depleted apo B particles get trapped more avidly than larger cholesterol-enriched apo B particles to the glycosaminoglycans. Cholesterol-enriched particle would contribute more cholesterol than a cholesterol-depleted apo B particle. Thus, all apo B particles are equally atherogenic.[1]

ApoB Measurement

Measurement of apo B can be done directly from the non-fasting serum. Measurements of apolipoproteins are internationally standardized (Table 2), automated, cost-effective in many areas and more convenient and precise than those for LDL cholesterol.[34]

The goal Apo B is <80/dL in very high-risk individuals whereas the LDL-C goal is <70 mg/dL and non-HDL-C is <100 mg/dl. The AACE guidelines equate an LDL-C <55 mg/dl to an Apo B <70 mg/dl.

The 2018 ACC/AHA guidelines mention apo B, stating that an apo B greater than 130 mg/dl is a risk-enhancing factor and requires measurement in primary prevention treatment protocols and this is an essential step towards the analysis of apo B for cardiovascular risk.[36]

In 2019, the ESC/EAS Guidelines[37] recommended that when evaluating patients with diabetes, metabolic syndrome, obesity, high triglyceride

Table 3: The treatment goals of Apo B and their corresponding LDL-C and non-HDL-C goals recommended by Lipid Association of India

Risk category	Goal LDL-C (mg/dL)	Goal Non-HDL-C (mg/dL)	Goal Apo B (mg/dL)
High Risk group	<70	<100	<80
Very high risk group	<50	<80	<65
Extreme risk group-Category A	<50	<80	<65
Extreme risk group-Category B	≤30	<60	<50

concentration or very low LDL-C levels, non-HDL-C and apo B could be preferred in order to estimate CV risk. The LAI recommended apo B goals for Indians in high risk, very high risk and extreme risk groups are listed in Table 3.

The use of LDL-C to assess cardiovascular risk and guide therapy is firmly established and entrenched in the minds of clinicians and in routine practice. Replacing LDL-C with apo B is likely to take time and is not easy, since physicians and patients are accustomed to LDL-C. Efforts should be made to change perceptions and practice gradually.[33]

LAI Recommendations

1. Apo B is moderate non-conventional risk factor (a level ≥110 mg/dl of apo B corresponds to an LDL-C ≥130 mg/dl) in low and moderate risk groups

2. To assess ASCVD risk, It is preferable to estimate serum apo B in patients with

i. diabetes,

ii. metabolic syndrome,

iii. obesity,

iv. high triglyceride concentration or

v. very low LDL-C levels

3. Apo B measurement is recommended in high-risk subjects, after LDL-C and non-HDL-C goals have been achieved. Discordant elevated apo B levels may identify individuals who have high residual cholesterol risk. This may warrant intensive statin therapy and use of non-statin drugs.

4. Recommended for diagnosis of Type III hyperlipoproteinemia.

5. Efforts should be made to bring in gradual change in perception of the importance of apo B amongst

physicians, patients and laboratories. Laboratories should standardise their methods.

6. Apo B estimation should be included in the standard lipid panel, initial and follow up. Where its measurement is not possible, non-HDL-C at a minimum should be assessed and utilized as a co-primary treatment target.

7. An ideal detailed lipid panel for screening, diagnosis should include total cholesterol, HDL-C, triglycerides, apo B and Lp(a).

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Non-HDL Cholesterol and Atherosclerotic Cardiovascular Disease

Low density lipoprotein cholesterol (LDL-C) plays a key role in atherogenesis from initiation (e.g. endothelial dysfunction) to eventual clinically evident atherosclerotic cardiovascular disease (ASCVD).[1] Hence, lowering LDL-C levels results in substantial reduction of ASCVD risk.[1] Large scale randomized clinical trials of statins support this conclusion. Numerous primary and secondary prevention trials, especially trials conducted in high risk populations, have clearly proven the benefit of statins in decreasing ASCVD risk by reducing LDL-C levels.[2-6] The dominant role of LDL-C is further exemplified by people with familial hypercholesterolemia (FH), who commonly develop premature atherosclerosis and clinical ASCVD even in the absence of other risk factors.[7] Based on these evidences, the prime focus for prevention of ASCVD has been on lowering LDL-C levels and maintaining this throughout life.

However, 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%.[8-12] Further with the advent of newer lipid lowering therapies, that help to achieve very low LDL- C levels, focus on other lipoproteins to reduce the residual risk has gained recognition. There are several other atherogenic lipoproteins in the circulation that contribute to ASCVD risk including triglyceride (TG)-rich lipoprotein remnants [very low-density lipoprotein (VLDL) and intermediate density lipoprotein (IDL)] and lipoprotein (a) [Lp(a)]. These lipoproteins may account for a significant proportion of ASCVD risk, particularly in those with elevated TG levels or where LDL-C has already been lowered with statins.[8] It seems prudent that in order to reduce ASCVD risk effectively, all atherogenic lipoproteins should be targeted and not just LDL-C alone. While the clinical trial evidenced has focused on LDL-C as the target of therapy, meta-analyses[13] show non-HDL-C to be at least as strong if not a strong predictor of CHD risk than LDL-C, suggesting the appropriateness of non-high density lipoprotein-cholesterol (non-HDL-C) as a co-primary or secondary target of therapy. Importantly, non-HDL-C can be estimated in the non-fasting state, eliminating the necessity of patients to return on a separate fasting visit for assessment of calculated LDL-C. Non-high density lipoprotein-cholesterol (non-HDL-C) has already been included as a co-primary target in the previous Expert Consensus of the LAI.

Calculated LDL-C: Almost all laboratories report a calculated LDL-C based on the Friedewald equation. There are several issues with using this equation, especially in patients with combined hyperlipidemia which is not uncommon in patients with diabetes mellitus (DM) or those with insulin resistance. When the TG concentration is >400 mg/dl, calculating the LDL-C concentration using Friedewald equation becomes invalid. Even at TG levels of 200-400 mg/dl, there are data showing LDL-C is underestimated when the Friedewald equation is used, hence questioning the validity of calculated LDL-C even in this ranges of TGs. In an Indian population, such moderately elevated TG levels are highly prevalent and pose challenge in using and achieving target LDL-C levels. Further, when the calculated LDL-C levels are low (<70 mg/dl), this may often be a result of underestimation by the Friedewald equation.[14]

Direct LDL-C (D-LDL-C): Clinical laboratories are increasingly able to provide a direct LDL-C estimation method, because it offers the advantage that fasting may not be required to obtain a valid sample. There is also evidence showing that D-LDL-C correlates well with beta quantification of LDL-C. Although in the original paper by Friedewald, calculated LDL-C was shown to correlate with beta quantification, in patients with moderate increase in TG levels it showed discordant calculated LDL-C compared with beta quantification even between TG concentration 200 and 499 mg/dl. Here apolipoprotein B (apo B) or non-HDL-C and perhaps D-LDL-C, if available, are superior to calculated LDL-C. The lack of standardization of D-LDL-C continues to be an issue.[15]

Non HDL-C and ASCVD risk

Non-HDL-C is calculated as total cholesterol minus HDL-C. Since HDL-C is the only anti-atherogenic lipoprotein, non-HDL-C effectively measures all atherogenic (apo B carrying) lipoproteins in the circulation, including LDL, VLDL, IDL and Lp(a) (Figure 1). Hence, non-HDL-C is accepted as a more accurate predictor of ASCVD risk compared with LDL-C. Several large scale studies have proven this hypothesis[5-9], showing that non-HDL-C levels are stronger predictors of all-cause and ASCVD mortality when compared with LDL-C levels. For example, in the Lipid Research Clinics Program, 4462 middle aged individuals, free from ASCVD, were followed up for an average

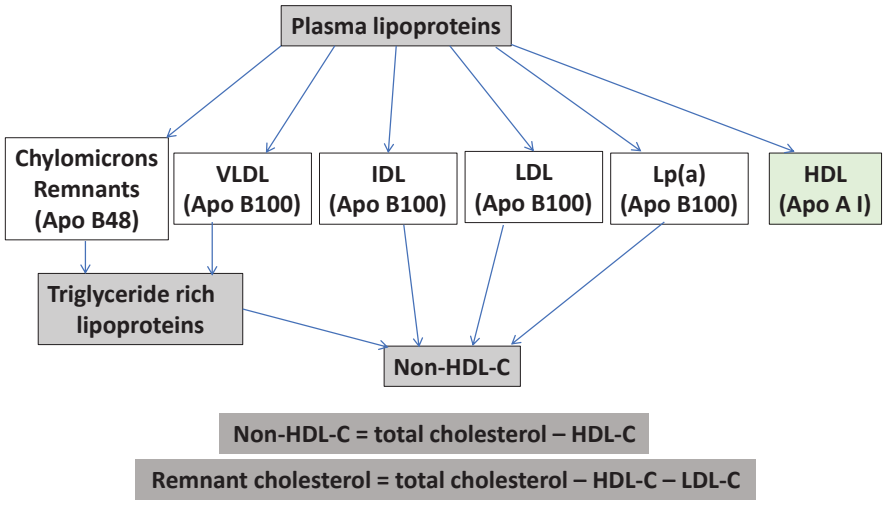

Fig. 1: Plasma lipoproteins and non-HDL-C. CM- chylomicrons, VLDL- very low density lipoprotein, IDL- intermediate density lipoprotein, LDL- low density lipoprotein, HDL- high density lipoprotein, Lp(a)- lipoprotein(a), Apo B- apolipoprotein B, Apo A1- apolipoprotein A1

of 19 years.[5] Non-HDL-C was a stronger predictor of ASCVD outcomes compared with LDL-C. A 30 mg/dl (0.78 mmol/l) increase in non-HDL-C resulted in a 19% increase in CV mortality in men and 11% increase in women compared with 15% and 8%, respectively for LDL-C concentration.[5] In other studies, non-HDL-C has correlated well with subclinical atherosclerosis assessed either by imaging studies[10,11] or at autopsy.[12]

Non-HDL-C levels predict ASCVD risk irrespective of TG concentration. Thus, while EPIC-Norfolk (European Prospective Investigation into Cancer and nutrition- Norfolk) study[16] confirmed predictive accuracy of non-HDL-C in patients with relatively low TG (<200 mg/dl), the SHEP (Systolic Hypertension in the Elderly Program) study[17] documented that non-HDL-C predicted ASCVD risk in those with elevated TG (>400 mg/dl). In the SHEP study, LDL-C lost its predictive value when TG levels exceeded 400 mg/dl.

Non-HDL-C has also been compared with apo B for its ability to predict ASCVD risk. Since all the atherogenic lipoproteins, whether LDL, VLDL or Lp(a), contain one apo B molecule, apo B may be a more accurate predictor of ASCVD risk. This was indeed confirmed by the INTERHEART case-control study of acute myocardial infarction (MI) in 52 countries in which 15,152 cases and 14,820 controls were enrolled. It showed that the ratio of apo B to apo A-I was the strongest determinant of myocardial infarction risk with population attributable risk of 49·2% for top four quintiles versus lowest quintile.[18] Since non-HDL-C measures all the apo B containing lipoproteins, it also correlates withthe circulating levels of apo B. In the Women's Heart Study, the highest quintile of non-HDL-C had similar relative risk for major ASCVD events as the highest quintile of apo–B.[9] However, in the Health Professionals Follow-up study, non-HDL-C was found to be an inferior predictor of CV events compared with apo B.[19] Nevertheless, it is important to note that in both these studies, non-HDL-C was a better predictor of ASCVD risk than LDL-C. A meta-analysis of 25 trials (1,31,134 participants) on lipid lowering therapy concluded that non-HDL-C outperforms apo B for prediction of CVD.[20]

A number of studies have found that non-HDL-C and apo B are better than LDL-C in CVD risk prediction. A meta-analysis of LDL-C, non-HDL-C and apo B as markers of CV risk including 233,455 subjects and 22,950 events, was carried out. It showed that a reduction in non-HDL-C strategy are likely to avoid 300,000 events more than an LDL-C strategy, while an apo B strategy is likely to avoid 500,000 events more than a non- HDL-C strategy.[21] This study concluded that apo B was superior in clinical care. However, the performance of non-HDL-C compared with apo B, continues to be a point of on-going debate. Non-HDL-C is more a practical marker of choice due to ease of calculation and no added cost.[22] The calculation uses parameters such as total cholesterol and HDL-C measurements which have already been standardized. An elevation in non-HDL-C, apo B100 or LDL particle concentrations puts a patient at an increased risk and aggressive lipid lowering is recommended in this case.[23]

A large multinational cardiovascular risk consortium data from 19 countries involving 524,444 individuals with a median follow up of 13.5 years showed a progressively higher CV event rates with increasing non-HDL-C levels from <2.6 mmol/L to ≥5.7 mmol/L (7.7% to 33.7% in women and from 12.8% to 43.6% in men; P <0.0001). The multivariable adjusted Cox models showed an increase in association between non-HDL-C and cardiovascular risk with HR 1.1 to 1.9 in women and 1.1 to 2.3 in men with increasing non-HDL-C lvevls.[24] Hence, it is pertinent that all laboratories should report non-HDL-C levels in addition to conventional reporting of LDL-C and TG for better characterization of residual ASCVD risk and treatment targets.

Non HDL-C and statin treatment

There is reasonable evidence in favour of non-HDL-C for an accurate prediction of residual ASCVD risk in patients on statin therapy. A meta-analysis of 62,154 statin-treated patients in 8 trials (4S, AFCAPS, LIPID, CARDS, TNT, IDEAL, SPARCL, JUPITER) published between 1994 and 2008 revealed that 1 SD 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 apo B.[25] 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 >130 mg/dl but low LDL-C levels <100 mg/dL the hazard ratio (HR) was 1.32 indicating 32% excess ASCVD. In contrast, the HR 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. A meta-analysis of 8 statin trials which focused on LDL-C and non-HDL-C levels, the HR for major CV events revealed continuous and progressive reduction in HR for MACE with lower achieved levels of LDL-C and non-HDL-C. The HR for LDL-C was 0.44 and for non- HDL-C 0.57 for achieved LDL-C levels <50 mg/dl (achieved by 4375 patients of 38,153 patients) and achieved non-HDL-C levels <75 mg/dl, respectively. There was large inter-individual variation in achieved LDL-C and non-HDL-C levels with only 13.8% patients on statins achieving non-HDL-C of <75 mg/dl.[26]

A retrospective study attempted to predict the association of attaining non-HDL-C goals as compared to attaining LDL-C goals with long-term major adverse CV events (MACE) in patients who presented with acute MI (AMI). Patients (n=868) were followed post- AMI for 2.6 years. Of these, 34.4% reached non-HDL-C target <100 mg/dl while 23.7% reached LDL-C target <70 mg/dl and 21.2% experienced MACE. The incidence of MACE was higher in patients with non-HDL-C of >130 mg/dl compared with non-HDL-C <100 mg/dl. The conclusion was that if non-HDL-C goals were not achieved, the risk at long-term follow up for MACE after AMI was higher while not attaining the LDL-C goal was not associated with a similar increased risk. Hence, non-HDL-C may be considered a better target for treatment than LDL-C in post-AMI patients.[27]

The Very Large Database of Lipids (VLDL-2) examined patient-level discordance between population percentiles of LDL-C and non-HDL-C in 1,310,440 adults. LDL-C cut offs of 70, 100, 130, 160, and 190 mg/dl were in the same population percentiles as non–HDL-C values of 93, 125, 157, 190, and 223 mg/dl, respectively. Among those with LDL-C <70 mg/dl, 15% had a non-HDL-C level of ≥100 mg/dl (guideline-based cut point) and 25% had a non-HDL-C value of 93 mg/dl (percentile-based cut point). However concurrent higher TG levels of 150 to 199 mg/dl altered these values to 22% and 50%, respectively meaning that discordance between LDL-C and non-HDL-C increased with higher TG levels. This has implications in the treatment of high-risk individuals as there is significant patient-level discordance between non-HDL-C and LDL-C percentiles at lower LDL-C and higher triglyceride levels. The recommended non-HDL-C cut points for

high risk patients need to be lowered to match percentiles of LDL-C cut points. Small absolute changes in non-HDL-C cut offs will result in substantial reclassification of patients to higher risk categories with potential implications for risk assessment and treatment.[28]

Data of 4957 patients with coronary heart disease (CHD) from 9 clinical trials who underwent serial intravascular ultrasonography to assess changes in percent atheroma volume (ΔPAV) was evaluated against on-treatment non-HDL-C levels (<100 mg/dl/≥100 mg/dl) and TG levels (<200 mg/dl/≥200 mg/dl). This evaluation was carried out in patients with variable on-treatment LDL-C </≥70 mg/dl, C-reactive protein </≥2 mg/l and in those with or without diabetes mellitus (DM).[27] Coronary atheroma progression was found to have stronger association with achieved non-HDL-C than LDL- C in this analysis. TG values >200 mg/dl were associated with plaque progression.[29] This strengthens the fact that non-HDL-C (and possibly TG) lowering is essential to reduce residual CV risk.

Although most patients with non-HDL-C ≥160 mg/dl show elevations in LDL-C and/or TG, a disproportionate elevation in non-HDL-C that coincides with low to normal levels of LDL-C (<100 mg/dl) may occur in some patients. Familial dysbetalipoproteinemia is characterized by elevation in remnant particles (i.e. IDL) due to mutation(s) in the apoE gene that encodes a defective apoE ligand (i.e. E2/E2 rather than the normal E3/E3 isoform), resulting in impaired hepatic clearance of TG rich remnants, elevated TG levels and premature CVD.[30] High non-HDL-C can also result from elevations in Lp(a).[30]

Non-HDL-C in DM

Non-HDL-C is particularly informative in diabetic patients who tend to have higher TG levels, and thus a greater difference is observed between LDL-C and non-HDL-C. A *post-hoc* analysis of 4 large prospective studies- The Lipid Research Clinics Program follow up study, Multiple Risk factor intervention trial, The Framingham Cohort Study and The Framingham offspring study included 19381 participants and demonstrated that diabetic patients had significantly higher non-HDL-C levels compared with non-diabetic patients (194.1 and 176.7 mg/dl, respectively) but almost identical LDL-C levels (148.6 and 148.0 mg/dl, respectively). The CV risk in diabetics increased with increase in non-HDL-C but not LDL-C on multivariate analysis.[7] In fact, the calculated LDL-C excludes the cholesterol of triglyceride-rich lipoproteins (TGRLs) which are proatherogenic. Thus, for diabetic patients with the combined dyslipidemia, calculated LDL-C fails to be an adequate index of overall lipid-associated risk.

A recent observational study in India of 808 patients with DM showed that elevated non- HDL-C was the second commonest lipid abnormality after low HDL-C levels among type 2 DM patients. The prevalence of elevated non-HDL-C was 21.6% among patients who were on statin therapy with optimal LDL-C levels although the authors did not define optimal LDL-C levels. Also, 47% of the T2DM patients with CV events had elevated non-HDL-C levels.[31]

Non-HDL-C is probably a stronger predictor of CV disease than LDL-C or TGs as it represents the majority of all circulating atherogenic lipoproteins. Under-treatment of patients may arise as a result of not considering the significance of non-HDL-C among people with diabetes.[32] The use of non-HDL-C as a screening tool to identify individuals with clustering metabolic abnormalities and increased predisposition to coronary artery disease has been highlighted in a study conducted in a North Indian population with and without CAD.[33]

Non-HDL-C as a predictor of future risk

In the Framingham Offspring study of 2,516 subjects aged 25-40 years, free of CVD and DM were divided into 2 groups based on non-HDL-C levels: non-HDL-C ≥160 mg/dl ("high") and <130 mg/dl ("low") at the first 2 examinations. The mean non-HDL-C levels measured in young adulthood were highly predictive of levels later in life at a mean follow-up of 32.6 years, with later values remaining close to initial values in most subjects. Those with high non-HDL-C in young adulthood had a 22.6% risk of CVD in the next 25 years compared with a 6.4% risk in those with low non-HDL-C. Thus, non- HDL-C levels in younger healthy individuals may identify those at increased risk of future adverse CV events.[35] This may even be more important for the Indian population who develop vascular disease 10 years earlier than their western counterparts and have a high prevalence of DM.[33]

Also, it is recently observed that the ratio of non-HDL-C to TC significantly predicts the severity of coronary lesion in statin treated patients and the occurrence of MACE [RR 1.9 (95% CI; 1.2-3.4)].[34]

Practical advantages of non-HDL-C

Besides being an important ASCVD risk marker, non-HDL-C offers several other advantages that are relevant to clinical practice:

- Estimation of non-HDL-C adds no extra cost; it can be easily calculated by subtracting HDL-C from total cholesterol.
- Calculation of non-HDL-C includes total cholesterol and HDL-C measurements that are standardized. Therefore, it is considered superior to D-LDL-C or apo B since both these measurements have not undergone the rigorous standardization.
- Measurement of non-HDL-C does not require a fasting blood sample because both total cholesterol and HDL-C are unaffected by feeding. Calculated LDL-C cannot be obtained and is inappropriate at TG level is >400 mg/dl.
- Non-HDL-C measures all the atherogenic lipoproteins including LDL-C and the TG-rich lipoprotein remnants. Furthermore, as LDL-C is the major component of non-HDL-C, non-HDL-C maintains focus on LDL-C, currently the primary target for ASCVD risk reduction.
- Non-HDL-C also equates to the excess ASCVD risk imparted by the small dense form of LDL that is more atherogenic than the normal large buoyant particles. Small dense LDL is the dominant form of LDL particles in patients with elevated TG levels.[23,35-37] An elevated non-HDL-C, being a surrogate for elevated TG, indirectly represents the presence of greater proportion of small, dense LDL particles in contrast to LDL-C levels that fail to provide any information about LDL particle size.

International guidelines and non-HDL-C

Based on accumulated evidence, non-HDL-C is being increasingly recognized by most experts worldwide to be a better target for lipid lowering therapy than LDL- C alone. Most of the current guidelines have incorporated non-HDL-C in their recommendations.

The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) recommended the use of non-HDL-C as a secondary target of lipid lowering, after achieving adequate control of LDL-C and if TGs are elevated (≥200 mg/dl).

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.[38] In 2014, the National Institute for Health and Care Executive (NICE) lipid management guidelines recommended the measurement of total cholesterol, HDL-C, non-HDL-C, and TG concentrations. It also recommended to lower non-HDL-C by 40% in patients on lipid lowering drugs for secondary prevention.[39] Similarly, the U.S. National Lipid Association guidelines have placed a greater emphasis on non-HDL-C than LDL-C.[40] The International Atherosclerosis Society has recommended non-HDL-C alongside LDL-C as a target for therapy.[41] The European Society of Cardiology(ESC)/ European Atherosclerosis Society (EAS) guidelines for dyslipidemia management[42] in 2019 recommended LDL-C reduction of >50% from baseline and a target of <55 mg/dl for very high risk individuals not very different from the LAI target of <50 mg/dl published in 2016 as part of their guideline. However, they defined non-HDL-C levels as a secondary target but they did not reflect the differential importance of non-HDL-C especially those with high TG. The levels recommended were 30 mg/dl higher for each risk group as <85, 100 and 135 mg/dl of non-HDL-C and these levels are more conservative for population that have a very high risk.

In view of high prevalence of atherogenic dyslipidaemia in Indians, LAI recommends non-HDL-C as a co-primary target which is as important as LDL-C target. It can be concluded that non-HDL-C is a metric of good quality of care for CVD prevention.[43] However, reaching to non-HDL-C goals has been inadequate. Various reasons can explain this: (1) Lack of knowledge among practitioners of the importance of non-HDL- C, (2) Laboratories not providing automatically calculated non-HDL-C levels. Ignorance regarding the simple math required to calculate non-HDL-C, (3) Unawareness about the treatment goals for non-HDL-C, (4) Patients related issues like intolerance to statins or lack of adherence to statin or non-statin treatment which are required to achieve non- HDL-C goals.

Providing non-HDL-C as part of a routine lipid profile from laboratories may improve the existing lack of awareness among practitioners. Goal attainment for non-HDL-C will probably require interventions that incorporate measures geared towards better dissemination of cholesterol-management guidelines to the providers, together with continual feedback on their performance.[43]

What should be recommended for Indians?

Several studies have shown that Indians have high prevalence of T2DM, 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 dyslipidaemia. Accordingly, as discussed in relevant sections in this document, a high prevalence of elevated TG and low HDL-C has been highlighted 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. Accordingly, the LAI recommends non-HDL-C as a co-primary target, as important as LDL-C, for lipid lowering therapy in Indians. In all individuals, the non-HDL-C level should be kept not any higher than 30 mg/dl of LDL-C goals.

Summary and recommendations:

- Non-HDL-C, which is equal to total cholesterol minus HDL-C, includes all circulating atherogenic lipoproteins and is therefore a more accurate predictor of ASCVD risk, particularly in patients who have elevated TG (e.g. diabetics, obese persons, those with metabolic syndrome) and those already on statin therapy.
- The LAI 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 ezetimibe should be considered when the above measures prove inadequate. Icosapent ethyl, once available in India, may also be a useful alternative as in higher doses of 4 g/day, it lowers triglycerides. It also reduces ASCVD risk beyond statin therapy in persons with LDL-C 41-100 mg/dl and known ASCVD or diabetes and multiple risk factors.[44]

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CONFLICT OF INTEREST

The following authors declare conflict of interest

Raman Puri	:	Boehringer Ingelheim, Novartis
Vimal Mehta	:	Participated as principal investigator from GIPMER in FOURIER, Evolocumab in Homozygous Hypercholesterolemia, THEMIS, DAPA-HF and EMPEROR studies
SS Iyengar	:	Reddy's Lab, Amgen, Emcure, Glenmark, Boehringer Ingelheim, Pfizer, Mankind
P Barton Duell	:	Esperion, Regeneron, Regenxbio, Retrophin
Krishnaswami Vijayaraghavan	:	Amgen, Amarin, Esperion
SN Narasingan	:	USV, Novo Nordisk, ERIS, Glenmark, Torrent, Boehringer Ingelheim, J.B. chemicals and Pharmaceuticals
Devaki Nair:	:	Abbott Diagnostics
Nathan D Wong	:	Research funding through institution from Amgen and Amarin, Speakers bureau for Esperion and Amarin, Research funding through institution from Novo Nordisk, Boehringer-Ingelheim, and Novartis, Consultant, Novartis and I-Health

Other authors have no conflict of interest.