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Review

An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia Executive summary

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1. Introduction

The International Atherosclerosis Society (IAS) here updates its recommendations on treatment of high level of blood cholesterol and dyslipidemia for the purpose of reducing risk for atherosclerotic cardiovascular disease (ASCVD). This summary highlights the major conclusions of the full report. The latter provides background rationale, panel deliberations, and IAS recommendations. The writing panel reviewed existing evidence-based recommendations and consolidated them into an overall set of recommendations. These recommendations are meant to inform clinical judgment and not to replace it. The report is divided into primary and secondary prevention. For secondary prevention, priority is given to randomized controlled clinical trials (RCTs) because of a wealth of data. For primary prevention, recommendations are based on many years of accumulated research in epidemiology, genetics, basic science, and clinical trials. RCT evidence for primary prevention is limited, both in number of trials and in world-wide RCTs. Moreover other lines of evidence relating cholesterol to ASCVD are strong.

The major innovations in this Position Paper are the following:

- International consensus guidelines based on multiple lines of evidence.
- Identification of non-HDL-cholesterol (non-HDL-C) as a major form of atherogenic cholesterol.
- Definition of atherogenic cholesterol as either LDL-cholesterol (LDL-C) or non-HDL-C.
- Definition of optimal levels of atherogenic cholesterol (both LDL-C and non-HDL-C) for primary and secondary prevention.
- Assigning priority to long-term risk categories over short-term risk.
- Adjustment of risk estimation according to baseline risk of different nations or regions.
- Primary emphasis on lifestyle intervention; secondary emphasis on drug therapy.

The IAS recognizes that many countries or regions have developed their own dyslipidemia guidelines. For those countries and regions that have their own guidelines, this IAS document is available to them should they choose to modify their own. For countries and regions that do not have their own current guidelines, the IAS document is available as an aid for them to develop their own guidelines (with help from the IAS if needed). The current document resembles other guidelines in many respects. One aim of the IAS effort is to harmonize existing guidelines such that they are applicable on a world-wide basis. Moreover they add perspective that may not be present in some of the guidelines. Because of advances in drug management of dyslipidemia, many guidelines over-emphasize drug therapy at the expense of lifestyle intervention. It is the view of the IAS that atherosclerotic disease is largely a disease of unhealthy life habits, except for genetic dyslipidemias. An important goal of the IAS recommendations is to reset the balance between lifestyle intervention and drug treatment.

2. Primary prevention

2.1. LDL cholesterol and Non-HDL cholesterol as targets of therapy

Many lines of evidence point to low density lipoprotein (LDL) as a major cause of ASCVD. Clinically, LDL is identified by LDL cholesterol (LDL-C). Over the past two decades RCTs have shown that LDL-lowering therapy reduces risk for ASCVD. The sum of accumulated evidence of multiple types supports the contention that elevated LDL-C is a major target of lipid-lowering therapy. But there is growing evidence that very low density lipoproteins (VLDL) likewise promote atherosclerosis. Thus VLDL cholesterol (VLDL-C) is another potential target of cholesterol-lowering therapy. VLDL-C is especially elevated in persons with hypertriglyceridemia. The sum of LDL-C and VLDL-C includes cholesterol in all atherogenic lipoproteins and is called non-high density lipoprotein cholesterol (non-HDL-C). Therefore non-HDL-C can be considered an alternative to LDL-C as target of therapy. Non-HDL-C is more reflective of atherogenicity in persons with elevated triglycerides. It also can be accurately measured in non-fasting serum whereas LDL-C cannot be. The IAS favors adoption of non-HDL-C as the major target of lipid-lowering therapy. But for those who favor use of LDL-C, the latter can be interchanged with non-HDL-C. In the foregoing, the term *atherogenic cholesterol* can be taken to be either LDL-C or non-HDL-C depending on clinical preference. It should be noted that total cholesterol (TC) is often used in risk assessment algorithms. TC is less reliable as a target of therapy, but it can be used if lipoprotein cholesterol values are not available.

2.2. Optimal levels of LDL-C and non-HDL-C for primary prevention

The IAS writing panel defines optimal levels for atherogenic cholesterol for primary prevention based three lines of evidence: RCTs, population epidemiology, and genetic epidemiology. An optimal LDL-C was identified as a level of $<$100 mg/dL (2.6 mmol/L). In accord, the optimal non-HDL-C for primary prevention is a level of $<$130 mg/dL (3.4 mmol/L). These levels are most apropos for high-risk populations. Low-populations may be able to tolerate somewhat higher levels without suffering much greater risk.

The IAS makes an important distinction between optimal levels of atherogenic lipoproteins and goals of therapy. The IAS does not specifically prescribe “treatment goals” for atherogenic lipoproteins for different circumstances. Instead it identifies optimal levels of atherogenic cholesterol and makes the general statement that the intensity of cholesterol-lowering therapy should be adjusted to long-term risk. Potency of cholesterol-lowering therapy relative to optimal levels must be left to clinical judgment.

2.3. Identifying persons at long-term risk for ASCVD

Although atherogenic lipoproteins are primarily responsible for development of atherosclerosis, other risk factors accelerate atherogenesis once lipoproteins are high enough to initiate and

support atherosclerosis. These other risk factors include cigarette smoking, hypertension, diabetes, low levels of HDL, and a positive family history for ASCVD. The sum of these risk factors adjusted for age accounts for *total risk*. A widely accepted therapeutic strategy holds that the intensity of management of persons at risk for ASCVD should be determined by absolute, total risk. This precept applies to the management of atherogenic lipoproteins, i.e. the greater the risk; the more intense should be cholesterol-lowering therapy. Most previous guidelines have used 10-year risk algorithms based on major risk factors to define absolute risk. Guidelines incorporating emerging risk factors and atherosclerosis imaging are promising, but have not been widely accepted. In recent years emphasis has been shifting to lifetime risk or long-term risk. This is appropriate because management of risk is a lifetime process. There are two risk assessment tools for estimating lifetime (long-term) risk for ASCVD morbidity: Framingham and QRISK. Framingham scoring is based on four risk factors: hypercholesterolemia, hypertension, smoking, and diabetes (see Full Report for details). QRISK is an on-line calculator that includes standard risk factors, family history of ASCVD, and body mass index. QRISK has the advantage of allowing estimates for different ethnic groups, at least in the UK and likely much of Western Europe. Its applicability to other nations is uncertain. A major advantage of Framingham data is that its estimates have been compared to risk in many different countries or regions. Thus it is possible to recalibrate risk estimates based on Framingham scoring. Therefore, for different countries, the IAS recommends using Framingham as the core estimate followed by re-calibration for individual countries (see Full Report for recalibration coefficients).

The IAS identifies four levels of risk for total ASCVD up to age 80: high (≥45%), moderately high (30–44%), moderate (15–29%), and low (<15%).

Many guidelines identify familial hypercholesterolemia, diabetes + other risk factors and chronic kidney disease as high risk conditions. Depending on the population and gender, they are either high-risk or moderately high risk conditions. Regardless, each requires active intervention, often with cholesterol-lowering drugs.

2.4. Adjusting intensity of lipid-lowering therapy to long-term risk

Because of the great variety of circumstances affecting use of cholesterol-lowering therapy, these guidelines leave to clinical judgment and national recommendations the intensities of therapies (or specific goals of therapy). Several factors must be kept in mind when deciding how low to drive the atherogenic lipoproteins. Lifestyle therapies are first-line intervention; but depending on risk status, drug therapies may be necessary. The Table 1 gives a general prescription for adjusting intensity of therapy to long-term risk.

For high-risk subjects, many will require cholesterol-lowering drugs (e.g. statins) in addition to lifestyle therapies. Most high-risk persons in this risk category should be treated to an LDL-C level of <100 mg/dL (2.6 mmol/L) (or non-HDL-C < 130 mg/dL [3.4 mmol/L]). In many countries, but not all, persons at moderately high risk also are candidates for drug therapy. In this category, an LDL-C level near 100 mg/dL (2.6 mmol/L) is recommended in national guidelines. Neither women nor older persons should be excluded from cholesterol-lowering drugs if they fall into high or moderately high risk categories. If a younger person has a higher long-term risk based on non-lipid risk factors (e.g. smoking and hypertension), this does not necessarily mean that primary prevention calls for an LDL-lowering drug. In such people, more attention should be given to the risk factors than to the estimated risk. For those at moderate risk, lifestyle therapies alone should be adequate to achieve an acceptable risk reduction. However, at this risk level, a high LDL-C level, and especially a very high level, deserves consideration for a cholesterol-lowering drug.

2.5. Lifestyle therapies

The primary goal of lifestyle intervention is to reduce LDL-C and non-HDL-C. A secondary aim is to reduce other risk factors. Healthy lifestyle behaviors including a recommended dietary pattern are cornerstones for the prevention and treatment of ASCVD. Globally, many healthy dietary patterns are cardioprotective; they achieve a low LDL-C and improve other established and novel risk factors.

The IAS panel made the following lifestyle recommendations for primary prevention.

LDL-raising lipids. Reduce intake of saturated fatty acids to <7% of total calories, and at least to <10%. Lower intake of *trans* fatty acids to <1% of total calories and of dietary cholesterol to <200 mg/day.

Other dietary factors: Maintain relatively high intakes of fruits, vegetables, and fiber. Replace excess saturated fatty acids with either complex, fiber-rich carbohydrates (with emphasis on whole grains) or monounsaturated/polyunsaturated fatty acids. Consume some fish rich in n-3 fatty acids. Other cardioprotective foods include nuts, seeds, and vegetable oils. Eat foods low in sodium and high in potassium. Dietary sodium should be less than 2 g per day and <1500 mg for individuals at risk. For individuals who choose to consume alcohol, not more than 2 servings daily for men and 1 serving daily for women is advised. Consider using plant sterols/stanols (2 g/day) and soluble/viscous fiber (10–25 g/day) as a dietary adjunct to further lower LDL-C levels.

Total fat. The IAS recommends flexibility in the intake of total fat depending on cultural preferences; alternatives are lower fat intakes of 20–25% of calories or even lower (as is typical in Pacific-rim countries), or higher fat intakes of 30–35% of calories or even higher (as is typical in Mediterranean countries). Any fat intake above the recommended for saturated and *trans* fatty acids should be in the form of unsaturated fatty acids. In addition, irrespective of the total fat content of the diet, nutrient needs must be met and

Table 1
IAS recommendations for cholesterol-lowering therapy at different risk levels.

Risk level to age 80 yrs	Low (<15%)	Moderate (15–29%)	Moderately high (30–44%)	High (>45%)
Therapeutic intensity		Moderate	Moderately high	High
Specific therapy	Public health recommendation[a]	MLT[b] + CLD[c] optional[d]	MLT[b] + CLD[c] consideration[e]	MLT[b] + CLD[c] indicated[f]

[a] Persons at low risk for ASCVD should be treated according to national recommendation for the general public. These recommendations should accord with IAS recommendations for lifestyle therapies.
[b] MLT = maximal lifestyle therapies.
[c] CLD = cholesterol-lowering drug, usually a statin.
[d] Cholesterol-lowering drug therapy usually reserved for patients with high levels of atherogenic cholesterol.
[e] Statin therapy is widely recommended for this risk category, although it is not accepted in many countries because of cost considerations. If drugs are employed, the dose should be adequate to achieve optimal atherogenic-cholesterol levels.
[f] Cholesterol-lowering drug therapy is usually indicated in this category. The dose should be adequate to achieve optimal atherogenic-cholesterol levels.

Table 2
Criteria for clinical diagnosis of the metabolic syndrome.

Measure	Categorical cut points
Elevated waist circumference[a]	Population- and country-specific definitions See Full Report
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator[b])	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator[b])	<40 mg/dL (1.0 mmol/L) in males <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose[c] (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.
[a] It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.
[b] The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presumes high triglycerides.
[c] Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

energy intake should be appropriate for maintenance of a healthy body weight.

Total calories. Body mass index (BMI) should be measured in all patients. Control intake of total calories to achieve and maintain a desirable weight. If desirable weight is defined by BMI, employ national standards for BMI.

Physical activity. Engage in approximately 30 min of moderate intensity physical activity daily. The activity should be aerobic, 40–75% of aerobic capacity, for 5–7 days a week, for 30–60 min per day. For individuals trying to lose weight it is recommended that these individuals eventually progress to higher amounts of exercise (e.g. 250–300 min/week or > 2000 kcal/week of leisure-time physical activity).

Metabolic syndrome. The metabolic syndrome is a multiplex risk factor for ASCVD. Obesity and physical inactivity contribute importantly to development of the metabolic syndrome. For patients with this syndrome, weight reduction and increased physical activity can reduce metabolic risk factors. The metabolic syndrome is defined by the characteristics shown in Table 2.

2.6. Drug therapies

Statins are first line therapy for achieving the optimal levels of atherogenic cholesterol in higher risk persons. In those who are statin intolerant, several options are available: switching statins, reducing statin dose, every other day statins, use of alternate drugs (*ezetimibe, bile acid resins, niacin*) alone or in combination, and maximizing lifestyle intervention. For high-risk patients, addition of ezetimibe or bile acid resins to statin therapy may be useful for achieving an optimal atherogenic cholesterol. In patients with severe hypertriglyceridemia, fibrates or niacin can be used to prevent acute pancreatitis.

3. Secondary prevention

The optimal LDL-C in patients with established ASCVD is < 70 mg/dL (1.8 mmol/L) (or non-HDL-C of <100 mg/dL [2.6 mmol/L]). Most patients with ASCVD deserve maximal statin therapy when it is tolerated. To achieve an LDL-C <70 mg/dL (1.8 mmol/L) some patients will require add-on drugs to statins (i.e. ezetimibe and/or bile acid resins). In patients who cannot tolerate high-dose statins, an alternative is to combine a moderate dose of statin with either ezetimibe or bile acid resin. For those with high triglycerides, nicotinic acid or a fibrate are alternative add-on drugs. However, risk reduction with combined drug therapy comparable to that with high-dose statins has not been documented in RCTs. Subgroup analysis of RCTs and atherosclerosis imaging provides some evidence of benefit of combined drug therapy. Even in patients who are treated with maximal cholesterol-lowering drugs, lifestyle therapies should be continued and emphasized. They have the potential to give additional risk reduction. Finally, all other ASCVD risk factors must be appropriately managed.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2013.11.031