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

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Abstract: An international panel of the International Atherosclerosis Society has developed a new set of recommendations for management of dyslipidemia. The panel identifies non-high density lipoprotein cholesterol (non-HDL-C) as the major atherogenic lipoprotein. Primary and secondary prevention are considered separately. Optimal levels for atherogenic lipoproteins are derived for the two forms of prevention. For primary prevention, the recommendations emphasize lifestyle therapies to reduce atherogenic lipoproteins; drug therapy is reserved for higher risk subjects. Risk assessment is based on estimation of lifetime risk according to differences in baseline population risk in different nations or regions. Secondary prevention emphasizes use of cholesterol-lowering drugs to attain optimal levels of atherogenic lipoproteins.
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The International Atherosclerosis Society (IAS) updates its recommendations on the treatment of high levels of blood cholesterol and dyslipidemia for the purpose of reducing risk of atherosclerotic cardiovascular disease (ASCVD). This summary highlights the major conclusions of the full report. The full report 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 preventions. 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 the number of trials and in worldwide 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 are based on multiple lines of evidence.
- Non–high-density lipoprotein cholesterol (non–HDL-C) is identified as a major form of atherogenic cholesterol.
- Atherogenic cholesterol is defined as either low-density lipoprotein cholesterol (LDL-C) or non–HDL-C.
- Optimal levels of atherogenic cholesterol (both LDL-C and non–HDL-C) are defined for primary and secondary prevention.
- Priority is assigned to long-term risk categories over short-term risk.
- Risk estimation is adjusted according to baseline risk of different nations or regions.

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- Primary emphasis is on lifestyle intervention; secondary emphasis is 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 guidelines. For countries and regions that do not have their own current guidelines, the IAS document is available as an aid to develop their own guidelines (with help from the IAS if needed). The present 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 worldwide basis. Moreover, these recommendations add perspective that may not be present in some of the guidelines. Because of advances in drug management of dyslipidemia, many guidelines overemphasize 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.

Primary prevention

LDL-C and non–HDL-C as targets of therapy

Many lines of evidence point to LDL as a major cause of ASCVD. Clinically, LDL is identified by LDL-C. Over the past 2 decades RCTs have shown that LDL-lowering therapy reduces risk of ASCVD. The sum of accumulated evidence of multiple types supports the contention that elevated LDL-C is a major target of lipid-lowering therapy. However, evidence is growing that very low density lipoproteins (VLDLs) 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–HDL-C. Therefore, non–HDL-C can be considered an alternative to LDL-C as a target of therapy. Non–HDL-C is more reflective of atherogenicity in persons with elevated triglycerides. It also can be accurately measured in nonfasting serum, whereas LDL-C cannot be. The IAS favors adoption of non–HDL-C as the major target of lipid-lowering therapy. However, for those who favor use of LDL-C, the LDL-C 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 is often used in risk assessment algorithms. Total cholesterol is less reliable as a target of therapy, but it can be used if lipoprotein cholesterol values are not available.

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 according to 3 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-risk populations may be able to tolerate somewhat higher levels without experiencing 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.

Identifying persons at long-term risk of 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 of ASCVD should be determined by absolute, total risk. This precept applies to the management of atherogenic lipoproteins; that is. the greater the risk, the more intense should be cholesterol-lowering therapy. Most previous guidelines have used 10-year risk algorithms that are based on major risk factors to define absolute risk. Guidelines that incorporate emerging risk factors and atherosclerosis imaging are promising, but they 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. Two risk assessment tools are available for estimating lifetime (long-term) risk of ASCVD morbidity: Framingham risk score and QRISK. Framingham risk scoring is based on 4 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 (BMI; calculated as weight divided by height squared; kg/m^2). QRISK has the advantage of allowing estimates for different ethnic groups, at least in the United Kingdom and likely much of Western Europe. Its applicability to other nations is uncertain. A