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A lipidologist perspective of global lipid guidelines and recommendations, part 2: Lipid treatment goals

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Abstract: Having knowledge of worldwide areas of harmonization and consensus regarding lipid guidelines and recommendations may provide clinicians a more global perspective on lipid management. This review examines 8 international scientific/medical organizations that have issued lipid guidelines, recommendations, and position papers: the National Lipid Association (2014), National Institute for Health and Care Excellence (2014), International Atherosclerosis Society (2013), American College of Cardiology/American Heart Association (2013), Canadian Cardiovascular Society (2013), Japan Atherosclerosis Society (2012), European Society of Cardiology/European Atherosclerosis Society (2012), and Adult Treatment Panel III (2001/2004). Part 1 of this perspective focused on sentinel components of these lipid guidelines and recommendations as applied to the role of atherogenic lipoprotein cholesterol levels, primary lipid target of therapy, other primary and secondary lipid treatment targets, and assessment of atherosclerotic cardiovascular disease (ASCVD) risk. This part 2 examines goals of lipid-altering therapy. While lipid guidelines and recommendations may differ regarding ASCVD risk assessment and lipid treatment goals, lipid guidelines and recommendations generally agree on the need to reduce atherogenic lipoprotein cholesterol levels, with statins being the first-line treatment of choice.

Introduction

A brief history of the emergence of lipid guidelines and recommendations was discussed in part 1 of this perspective, which examined the role of atherogenic lipoprotein cholesterol levels, primary lipid and lipoprotein targets of therapy, and other primary/secondary lipid treatment targets, as well as assessment of atherosclerotic cardiovascular disease (ASCVD) risk. The purpose of part 2 of this review was to summarize 8 worldwide lipid guidelines, recommendations, and position papers with respect to the goal of lipid-altering therapy in reducing ASCVD risk.

Does lowering atherogenic lipoprotein cholesterol levels reduce atherosclerotic cardiovascular disease risk?

According to most global lipid guidelines and recommendations, low-density lipoprotein cholesterol (LDL-C) levels are the primary lipid treatment target. The rationale for establishing LDL-C treatment goals is twofold: increased LDL-C levels are a strong and independent risk predictor of atherosclerotic coronary heart disease (CHD)

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and ASCVD,[1] and interventions that lower LDL-C levels often reduce CHD and ASCVD risk. Meta-analyses of randomized clinical trials of statins suggest that every 1.0-mmol/L (~40 mg/dL) reduction in LDL-C level is associated with an approximately 20% reduction in cardiovascular disease (CVD) mortality, nonfatal myocardial infarction (MI), and overall cardiovascular events.[2,3] In the Cochrane Database review of 56,934 individuals enrolled in 18 statin trials for primary prevention of CVD, statin therapy reduced the relative risk (RR) of all-cause mortality by 14% and of combined fatal and nonfatal CVD, CHD, and stroke by 25%, 27%, and 22%, respectively.[4] In an analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration of 27 randomized clinical trials of individuals grouped by predicted 5-year risk of a major vascular event and treated with statin therapy, the risk of a vascular event for patients without a history of vascular disease decreased by 15% (rate ratio per 1.0-mmol/L reduction in LDL-C) and all-cause mortality decreased by 9% (rate ratio per 1.0-mmol/L reduction in LDL-C).[3] The benefits of LDL-C lowering are generally consistent in both primary and secondary prevention and in different patient subpopulations.[2,3,5]

A question often arises about whether the ASCVD benefits noted in lipid-altering pharmacotherapy trials are due to cholesterol lowering or to some other "pleiotropic" properties of statins. However, non-statin, lipid-altering drug therapies that lower cholesterol are also associated with reduced ASCVD risk. When administered to patients without elevated triglyceride (TG) levels, fibrates can lower LDL-C levels. A number of outcomes clinical trials support fibrates as reducing ASCVD, although their benefit appears to be predominantly among patients with more elevated baseline TG levels.[6–10] Niacin is a lipid-altering agent that can lower LDL-C at higher doses. Recent ASCVD outcomes trials (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes [AIM-HIGH], Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]) have not supported niacin as reducing ASCVD risk in statin-treated patients with low baseline LDL-C levels.[11,12] However, when administered as monotherapy to patients with higher baseline LDL-C levels, data (eg, Coronary Drug Project trial) support niacin as reducing ASCVD events.[13] Bile acid sequestrants reduce cholesterol levels, and resin therapies such as cholestyramine and colestipol reduce ASCVD.[14] Finally, in patients at very high ASCVD risk with baseline LDL-C level of ~95 mg/dL, patients who attained an LDL-C level below 70 mg/dL (mean value ~53 mg/dL) with the addition of ezetimibe to simvastatin experienced significantly reduced ASCVD risk compared with patients who attained an LDL-C level of ~70 mg/dL with simvastatin alone.[15]

Thus, clinical trial evidence based on ASCVD outcomes trials supports the benefit of some non-statins in reducing ASCVD risk either as monotherapy or sometimes when combined with statins, depending on the patient population studied. In fact, a meta-analysis of non-statin therapies (ie, diet, bile acid sequestrants, ileal bypass surgery) demonstrated that the degree of LDL-C lowering correlates one-to-one with reduction of CHD risk over 5 years.[16]

Author perspective

The ASCVD benefits of LDL-C lowering are generally consistent in both primary and secondary prevention trials and in different patient subpopulations. However, therapeutic interventions that lower LDL-C levels do not always reduce ASCVD risk. Adding niacin does not seem to benefit statin-treated patients with low LDL-C levels. The ASCVD benefits of fibrates appear to be mostly among patients with baseline elevations in TG levels (and lower high-density lipoprotein cholesterol [HDL-C] levels), which is how fibrates are most often used in clinical practice. Estrogens lower LDL-C levels and increase HDL-C levels, and have a number of other cardiovascular effects that may reduce CVD risk.[17] However, the clinical trial evidence suggests when hormone therapy (including estrogen) is administered to some postmenopausal women, CHD and thromboembolic complications may be increased, not decreased.[18] Torcetrapib was an investigational cholesteryl ester transfer protein inhibitor that lowered LDL-C and substantially increased HDL-C levels,[19] but increased (not decreased) ASCVD risk, which may or may not have been due to agent-specific, off-target effects.[20] What has emerged from these experiences is that not all interventions that lower LDL-C levels will reduce ASCVD risk. Therapeutic agents that lower LDL-C levels are most likely to reduce ASCVD if the agent has the following: (1) natural genetic mutation support,[21] (2) a validated mechanism of action, (3) a lack of off-target harmful effects that might increase ASCVD risk, and (4) favorable signaling in pooled data during phase 2 and 3 clinical trial development.

What are the potential risks and benefits of lowering LDL-C levels below 70 mg/dL?

Although many guidelines recommend lipid treatment goals of LDL-C <70 mg/dL for patients who have the highest risk of ASCVD, the long-term clinical risks and benefits of achieving even lower levels of LDL-C <50 mg/dL (<1.3-1.8 mmol/L) are unknown. Data from aboriginal populations and patients with gene mutations having LDL-C levels between 30 and 70 mg/dL suggest ASCVD mortality is very low in these subpopulations.[22–24] In Treating to New Targets (TNT), patients with ASCVD were administered atorvastatin 10 or 80 mg per day. The lowest on-treatment LDL-C levels were associated with the lowest rate of death from any cause and the lowest rate of death from ASCVD. Achievement of the lowest LDL-C levels did not result in clinically important