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Overcoming toxicity and side-effects of lipid-lowering therapies

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Lowering serum lipid levels is part of the foundation of treating and preventing clinically significant cardiovascular disease. Recently, the American Heart Association/American College of Cardiology released cholesterol guidelines which advocate for high efficacy statins rather than LDL-c goals for five patient subgroups at high risk for cardiovascular disease. Therefore, it is critical that clinicians have an approach for managing side-effects of statin therapy. Statins are associated with myopathy, transaminase elevations, and an increased risk of incident diabetes mellitus among some patients; connections between statins and other processes, such as renal and neurologic function, have also been studied with mixed results. Statin-related adverse effects might be minimized by careful assessment of patient risk factors. Strategies to continue statin therapy despite adverse effects include switching to another statin at a lower dose and titrating up, giving intermittent doses of statins, and adding non-statin agents. Non-statin lipid-lowering drugs have their own unique limitations. Management strategies and algorithms for statin-associated toxicities are available to help guide clinicians. Clinical practice should emphasize tailoring therapy to address each individual's cholesterol goals and risk of developing adverse effects on lipid-lowering drugs.

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Introduction

Lipid altering drugs, especially statins, are among the most widely prescribed drugs in the world. Clinical trials over the past 25 years demonstrate that statins are well tolerated and prevent cardiovascular (CV) deaths, major CV events (stroke, myocardial infarction), and total mortality in high risk patients [1]. Although a significant decline in cardiovascular mortality began prior to the regulatory approval of statins in 1987, cholesterol lowering to prevent coronary heart disease (CHD) has been credited with much of the marked reduction of CHD incidence worldwide [2]. Little controversy remains regarding the clinical benefits of statins in high risk patients, and increasingly data and guidelines support more widespread statin use and more intensive statin therapy [1]. However, a significant number of patients (perhaps 10% or more) [3] develop intolerant symptoms to statins, and another 1–2% develop serious side-effects such as myositis or liver enzyme elevations [4]. The growing number of patients receiving these drugs, and the recent recommendations for higher intensity therapy [1], creates a significant absolute number of people intolerant of statin therapy or who suffer side-effects. Many primary care physicians face the challenge of identifying a therapeutic regimen that achieves desired lipid goals, but also is well tolerated by the patient. Consequently, a leading reason for a referral to a lipid clinic is statin intolerance. The purpose of this review is to identify risk factors for statin-induced side-effects, strategies to overcome true or perceived intolerance, and alternative approaches to treat elevated low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) if statins cannot be utilized. In addition, safety issues related to non-statin lipid altering therapy will also be addressed. An enhanced understanding regarding the risk factors for statin-induced toxicity and deploying successful approaches to overcome statin intolerance will hopefully avoid unnecessary ancillary tests or referrals which ultimately could reduce health costs with improved patient outcomes.

Adverse effects of statins

Myopathy

Among the symptoms associated with statins, muscle-related complaints are common and frequently limit the use of statins [5,6]. The term myopathy has been used to describe muscle-related symptoms that occur with evidence of muscle injury (serum creatine kinase (CK) $>$10 times the upper limit of normal (ULN)) [5]. This definition of myopathy is used by the National Lipid Association. However, the term myopathy may also be used more broadly; for example, the American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) defines myopathy as any disease of muscles. In the latter case, myalgia, myositis, and rhabdomyolysis may be thought of as representing a spectrum of myopathy, or muscle-related side-effects, ranging from symptoms without CK elevation (myalgia), to myositis (CK elevated above the ULN, but $\leq$10 times the ULN), to rhabdomyolysis. The definition of rhabdomyolysis, typically includes CK elevation $>$10 times ULN and an elevation in serum creatinine [6].

Symptoms of statin myopathy include muscle cramps, stiffness, and weakness. Statin-associated myalgia typically affects the proximal muscles and tends to occur within the first 6 months of starting a statin. However, the onset of symptoms may occur later. Myalgia tends to resolve within 2 months of discontinuing a statin [6].

The incidence of statin-associated myopathy varies depending on the source of the estimate, specifically whether data are derived from randomized clinical trials, cohort studies, or reported adverse events (such as through the Food and Drug Administration (FDA)). However, in the United States the proportion of patients (including those on combined therapy) affected by significant statin-associated myopathy (CK $>$10 times ULN), is likely between 0.2 and 0.5% [6].

Another estimate of the incidence of statin-associated myopathy (derived from 21 clinical trials with 180,000 person-years of follow-up data), found that myopathy (defined as muscle symptoms with CK $>$10 times ULN) occurred in 5 patients per 100,000 person-years. Rhabdomyolysis, as may be expected, was even rarer, occurring in only 1.6 patients per 100,000 person-years [5]. Authors from the FDA performed a review of reports of fatal rhabdomyolysis by accessing the Adverse Event Reporting