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Aggressive Lipid Lowering: An Update

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Introduction

Placebo-Controlled trials have emphatically documented the incremental role of LDL-C lowering on cardiac event rates and LDL-C lowering has become the cornerstone of therapeutic guidelines for cardiovascular protection. Recent evidence of aggressive lipid-lowering in secondary prevention trials have strengthened the role of statin therapy in high risk patients.[1-3]

Declines in coronary and probably cerebrovascular events in patients with stable atherosclerosis result largely from declines in LDL levels. Whether the same might be said for raising high-density lipid protein, lowering triglyceride, diminishing inflammation, or altering vascular dysfunction independent of LDL lowering is not yet firmly established.[4]

Aggressive Lipid Lowering: Current Issues

It has been observed that the greatest impact of high-dose atorvastatin on both clinical events[5] and atheroma progression[6] is observed in patients who achieved substantial lowering of levels of both LDL-C and CRP, rather than just LDL-C alone. The anti-inflammatory properties of statins may be of potential significance in humans on the effect of plaque progression and cannot be completely accounted for by the effect of statins on LDL-C alone.[7]

The effect of statins on LDL-C and CRP levels has raised speculation about whether the CRP lowering effect is LDL-C lowering driven or an independent effect. Statins can diminish inflammation by decreasing plasma low-density lipoprotein (LDL) cholesterol and removing pro-inflammatory modified LDL from the artery wall. Statins also decrease cholesterol-independent isoprenoids and prevent activation of the proinflammatory rho kinase.[8,9]

In clinical studies, it is difficult to tease the known lipid effects of statins from their potential non-lipid effects. A systematic meta-analysis of 23 randomized placebo-controlled trials in stable patients reporting change in LDL and CRP, assessed the relationships between average mean differences in change in CRP and LDL with a variety of statins, nonstatin drugs, or other regimens.[10] Significantly greater CRP reduction occurred in statin and statin-ezetimibe interventions, interventions using 80 mg/day of statins, and with greater LDL lowering. In a multivariate model applied to a range of LDL reduction typically seen with statins, 89% to 98% of CRP change was related to LDL lowering and 2% to 11% was related to non-LDL effects of statins.

In clinical practice, most of the anti-inflammatory effect of LDL-lowering therapies is related to the

magnitude of change in LDL. The potential non-LDL effects of statins on inflammation are much smaller in magnitude. Histopathological studies in animals and humans using a variety of statin and nonstatin therapies have shown that LDL lowering dramatically reduces the content of oxidized LDL in plaque and inflammatory cell density and activity.[11-15]

Statins do have non-LDL effects that reduce inflammatory pathways in cell culture and animal experiments,[16,17] but may require high concentrations of statins that are several log concentrations higher than those achieved with their therapeutic use in humans. If these LDL-independent effects were clinically important (for example, the rho pathway, then statins should decrease CRP more than nonstatin therapies for a similar change in LDL. However, in this study, the effects of statin therapies and other LDL-lowering therapies were minimal and not statistically significant after accounting for the LDL-lowering effect. Across a range of LDL reduction typically seen with statin therapy, 90% or more of the change in CRP was related to LDL reduction and 10% or less was related to non-LDL effects of statins.

LDL lowering and inflammation are not separate entities. Rather, LDL lowering is likely a primary driver for the reduction in inflammation that contributes to lower cardiovascular risk.[18] Pleotropic effects of statins do not seem to contribute an additional cardiovascular risk reduction benefit beyond that expected from the degree of LDL-C lowering observed in other trials that primarily lowered LDL-C.[19]

Subtantial lowering of CRP, in addition to LDL-C, results in the greatest clinical benefit of high-dose atorvastatin in patients with an acute coronary syndrome.[20]

Comparison of the A to Z (Aggrastat to Zocor) and PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) studies provides preliminary evidence to suggest that anti-inflammatory properties of intensive statin therapy may be of clinical importance. The finding of an early separation in event curves only in PROVE IT was accompanied by a smaller difference in LDL-C but greater difference in CRP between the intensive and moderate statin arms.[21]

Aggressive Lipid Lowering in ACS

The effect of atorvastatin compared with placebo among patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) has been evaluated in the ARMADA ACS study.[22] Patients were randomized in a double-blind manner to pretreatment with atorvastatin (80 mg 12 hours prior to PCI and 40 mg immediately pre-PCI) or matching placebo. After the procedure, all patients were treated with atorvastatin 40 mg indefinitely. The primary endpoint of death, MI, or unplanned revascularization was lower in the atorvastatin group compared with the placebo group (5% vs. 17%, $p = 0.01$). The anti-inflammatory effect of statins may have contributed to the reduction. The relative lower increase in CRP post-PCI in the atorvastatin arm supports this potential mechanism of action. A recent study has proposed that the total cholesterol content of erythrocyte membranes is increased in patients with acute coronary syndrome.[23]

The IMPROVE IT study compromising 10,000 subjects will address the important issue of whether a ezetemibe 10 mg combination with various doses of simvastatin versus 80 mg dose will effectively lower the cardiovascular morbidity and mortality end-points in patients with acute coronary syndrome over a period of 2.5 years. The results are expected in 2010.

Safety of Aggressive Lipid management

A recent review of all papers published between 1985 and 2006 on the safety, efficacy, and side effects of statins by Armitage J. in the June 7, 2007 issue of Lancet has shown that myopathy occurs in fewer than one in 10000 patients at standard doses of statins and is very low with atorvastatin 80 mg. Unlike with myopathy, the effects might be because

of a greater fall in LDL cholesterol. Even at high doses, these liver-enzyme increases have not been associated with hepatitis or liver failure. Aggressive lipid management in high-risk subjects is safe.[24]

In the context of mixed dyslipidemia in Indian subjects with elevated LDL-C and triglycerides, combination of statin and fibrates are more often used. This will raise concerns about the safety of using both the group of drugs together.

Low-dose statin with fenofibrate has been reasonably safe as shown in the FIELD study. Safety of moderate dose of statin and fenofibrate will be highlighted in the ACCORD study. However, extreme caution need to be exercised when combining high dose statin and fenofibrate as no studies are available to date on this aspect.

The role of coenzyme Q10 in statin-associated myopathy has recently been evaluated in a systematic review by Leo Marcoff.[25] There is insufficient evidence to prove the etiologic role of CoQ10 deficiency in statin-associated myopathy. Routine use of CoQ10 cannot be recommended in statin-treated patients. However, CoQ10 can be tested in patients requiring statin treatment, who develop statin myalgia, and who cannot be satisfactorily treated with other agents. No known risks to this supplement and there is some anecdotal and preliminary trial evidence of its effectiveness.

Recommendations From the National Lipid Association Statin Safety Task Force for Muscle Issues

For patients with muscle symptoms and/or an asymptomatic CK elevation or both:

1. First, rule out other etiologies (including increased physical activity, trauma, falls, accidents, seizure, hypothyroidism, infections, alcohol or drug abuse, and rheumatologic or other muscle disorders)
2. CK monitoring
   a. Obtain CK for unexplained muscle symptoms
   b. May obtain baseline CK in high-risk patients, optional for others
   c. No need to routinely monitor CK levels during therapy
3. Discontinue the statin if intolerable muscle symptoms occur, with or without CK increase

a. Rechallenge with same or lower dose of same or different statin once symptoms resolve

4. If tolerable muscle symptoms with CK < 10x ULN, continue statin at same or lower dose until symptoms dictate otherwise
5. Discontinue the statin and reconsider risk/benefit if:
   a. CK > 10x ULN even with tolerable muscle symptoms
   b. CK > 10,000 IU/l
   c. Worsening serum creatinine and/or need for intravenous hydration therapy

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