A viewpoint on statin effects – benefits and problems

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Perhaps acetylsalicylic acid was the first blockbuster medication, but in the modern era of cardiovascular (CV) medicine, statins are the major blockbuster medical treatment. The practice of state-of-the-art cardiology and other types of CV medicine depends on these incredible compounds with many intriguing effects. Five key placebo-controlled trials proved the benefit of statins in reducing myocardial infarctions, coronary artery disease (CAD) mortality and, to some extent, overall mortality (1-5). Nevertheless, much is left to be understood and accomplished because approximately 60% of patients treated with statins did not have a beneficial reduction in CV events. This 60% deficit of reduction in CV events and CAD complications may involve noted favourable risk modifiers such as high-density lipoprotein (HDL).

LOW-DENSITY LIPOPROTEIN, STATIN PLEIOTROPIC EFFECTS AND INFLAMMATORY RISK

Without question, the gold standard of statin benefit is the resultant reduction of plasma low-density lipoprotein (LDL) (6,7). This clinical benefit is uncontested. In addition, the apparently beneficial pleiotropic effects of statins provoke much interest (8). The study of these pleiotropic properties, such as anti-inflammatory effects, inhibition of thrombosis, inhibition of enzymes related to atherogenesis, favourable modulation of immune function, increased fibrinolysis, improved endothelial motor dysfunction and increased nitric oxide, appears to be of clinical interest. However, clinical assessment of these beneficial effects is limited, and only high-sensitivity C-reactive protein (9,10) and phospholipase A2 (11) measurements currently have value for the practicing clinician as inflammatory risk factors.

Statin have also been postulated to help control arrhythmias, especially the recurrence of atrial fibrillation (12). They may also help control hypertension and improve congestive heart failure through favourable modulation of neurohormonal mechanisms, as well as antioxidant effects and effects on endothelial function, angiogenesis, cardiac hypertrophy and left ventricular remodelling (13).

Ideal LDL level in the patient with high CV risk

Prescribing a statin may now be considered semiurgent for acute clinical coronary artery events. Acute coronary syndrome is a good example of a condition in which failure to continue a statin has been established as detrimental (14) to the patient. There is valuable evidence of benefit from starting a statin early in the clinical course of a patient not taking one. The goal for any high-risk CV patient is to attain an LDL level of less than 70 mg/dL (15); statin use offers the best chance of achieving

this goal. A high-risk patient can be defined as anyone who has sustained previous CV events (either peripheral vascular or CAD in origin), anyone with multiple CV risk factors and any patient with diabetes mellitus. Although atherosclerotic plaque regression has been shown to be possible with aggressive LDL reduction, the major benefit of achieving marked reduction of LDL appears to be atherosclerotic plaque stabilization so that plaque rupture is avoided (16). Plaque rupture is the major cause of acute intravascular thrombosis, resultant artery obstruction and thereby the cause of severe or fatal clinical events.

PROBLEMS WITH STATINS

Although statins have been billed as perfectly safe wonder drugs by their pharmaceutical company manufacturers, there are problems with their usage that are not accurately covered in promotional literature and some sponsored clinical studies. There are even a few physicians and pharmaceutical companies who would like to promote the availability of statins over the counter (OTC). This appears to be a bad idea and one that would be dangerous to patients who are undereducated about their medication, because even patients with prescriptions fail to take their medications exactly as directed in a high percentage of documented cases (17). Various studies have shown statin-related myopathy incidence of up to 9% (18). For severe resultant rhabdomyolysis, an assessment from 2002 showed an incidence of 0.15 deaths from rhabdomyolysis per 1.0 million statin prescriptions (19). Furthermore, this rhabdomyolysis can develop very rapidly – within a very few weeks or less. One pharmaceutical company has even claimed that the highest approved dose of their statin has no more complications than the lowest recommended dose, a claim not substantiated by data submitted for United States Food and Drug Administration (FDA) approval of any statin or by clinical studies with more than short-term follow-up (18).

USE OF STATINS WITH OTHER MEDICATIONS – THE CLINICAL ISSUES

The additional use of ezetimibe allows a statin to remain at a safer lower dose while still achieving marked reduction of LDL. This lowering of LDL is presently the gold standard of CAD reduction. The benefit of statins to high-risk CV patients far outweighs any risk; however, such potent medications must be respected and used with great care, and patients with symptoms and laboratory results that indicate possible complications must receive attention. Although there is currently much interest in high-sensitivity C-reactive protein, only LDL has solid, universally accepted evidence-based medicine supporting the fact that its reduction promotes an associated decrease in the incidence of acute and chronic CV

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events. Despite a major push for high-dose statins by many physicians, the majority of LDL reduction with statin monotherapy is seen with the initial dose. Thereafter, each doubling of the dose, on average, reduces the LDL by only another 6% (20). Furthermore, higher statin doses cause more problems, especially myopathy, as reported in the data initially submitted to the FDA for each statin. As already noted, a review of various studies showed a possible incidence of statin-related myopathy of up to 9% (18) despite some statements from short-term studies that there is no increase in myopathy with a high-dose statin (15,21). Therefore, if LDL lowering is the gold standard, a medication such as ezetimibe that can lower LDL another 25% while keeping the statin at a safer, lower, long-term dose with the majority of statin benefit and pleiotropic effects warrants further consideration (22). High-dose statin therapy appears established in selected situations, such as in immediate association with acute coronary syndrome (21). However, high-dose statin therapy cannot claim specific long-term benefit versus a lower statin dose plus other medication as long as an LDL level of less than 70 mg/dL is achieved – the new standard for high-risk CV patients (15).

All statins increase HDL with the initial statin dosing but after one year there is a decrease from the initial HDL elevations achieved. However, in the case of atorvastatin, the increase achieved with the HDL at week 12 is abolished and, in contrast to other statins, the HDL level at 52 weeks can actually be below the starting baseline (23).

The issue of statins OTC has already been mentioned. Fortunately, this has been denied a second time by the FDA

even though the stated goals are good and the cited risk appears small. OTC statin availability to patients at high risk for adherence problems and who do not have regular medical care may result in significant harm, especially from rhabdomyolysis that may remain undetected until appropriate management can no longer help (24,25).

Coenzyme Q10 may help to prevent statin-related myopathy, or at least decrease symptoms and allow continuation of these vital CV medications (26). Coenzyme Q10 is a functional element in cell membranes that has antioxidant action and regenerates redox capacity. It provides important control of membrane channels, and its biosynthesis in mitochondria and endoplasmic reticulum is inhibited by statins (27).

CONCLUSION

The statin class of medications is essential to the modern practice of CV prevention and intervention. The marked LDL reduction and beneficial pleiotropic effects achieved with statins are spectacular and essential. However, as in all of medicine, every medical treatment and surgical procedure, despite incredible contributions to the well-being of mankind, has problems, drawbacks and complications. Despite the realities of statins that have to be managed and handled with care, the equation is balanced in favour of their aggressive use in high-risk CV patients. This awareness and skillful use by physicians is making a major difference in the lives of many CV patients while we gain the knowledge to favourably alter the parts of the equation not altered by these fabulous medications.

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