Are pleiotropic effects of statins real?

Abstract: The clinical benefits of statins are strongly related to their low density lipoprotein-cholesterol (LDL-C) lowering properties. However, because mevalonic acid (MVA), the product of 3-hydroxy-3-methyl-3-glutaryl coenzyme A (HMG-CoA) reductase reaction, is the precursor not only of cholesterol but also of nonsteroidal isoprenoid compounds, the inhibition of HMG-CoA reductase may result in pleiotropic effects, independent of their hypocholesterolemic properties. The discrimination between the pleiotropic from LDL-C lowering effects may potentially be more evident during the early phase of treatment since plasma MVA levels drop up to 70% within 1–2 hours while a reduction of LDL-C, detectable after 24 hours, became significant after 6–7 days. Therefore, the deprivation of circulating MVA-derived isoprenoids in the early phase of treatment could be the main mechanism responsible for the atheroprotective effect of statins. This early window of protection in the absence of LDL-C lowering suggests that the anti-inflammatory and the pleiotropic properties of statins may have clinical importance. Therefore, acute coronary syndromes could represent a clinical condition for addressing the early benefits of statins therapy, ie, within 24 h of the event, independent of LDL-C lowering.

Keywords: anti-inflammatory effects of statins, mevalonate pathway, LDL lowering, acute coronary syndrome, prenylated proteins

The clinical benefits of 3-hydroxy-3-methyl-3-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are strongly related to their low density lipoprotein-cholesterol (LDL-C) lowering properties (Baigent et al 2005). However, because mevalonic acid (MVA), the product of HMG-CoA reductase reaction, is the precursor not only of cholesterol but also of nonsteroidal isoprenoid compounds, the inhibition of HMG-CoA reductase may result in pleiotropic effects (Liao and Laufs 2005). Indeed, a variety of experimental data indicates that statins can interfere with major events involved in the formation of atherosclerotic lesions, independent of their hypocholesterolemic properties, including improvement of eNOS activity and anti-inflammatory effects. However, the clinical evidence of these benefits still remain to be addressed (Liao and Laufs 2005).

Demonstrating the pharmacological properties of statins beyond LDL-C lowering

How can we demonstrate in a clinical setting the pharmacological properties of statins beyond LDL-C lowering? It is well established that the chronic use of statins, in coronary heart disease (CHD) patients, is strongly associated with LDL-C lowering (Baigent et al 2005). This includes most of the anti-inflammatory properties, such as C reactive protein (CRP) (Kinlay 2007). Therefore it fails to demonstrate the clinical relevance of nonLDL effects of statins. Thus, to date, what evidence do we have that supports the presence of pleiotropic effects?
Evidence of pleiotropic effects

The discrimination of the pleiotropic from LDL-C lowering effects may potentially be more evident during the early phase of treatment, as plasma MVA levels drop up to 70% within 1–2 hours after the first administration of statins (McTaggart et al 2001) due to a reduction in the liver synthesis of MVA, while a reduction of LDL-C, detectable after 24 hours (~10%), became significant after 6–7 days (Tober et al 1982; Pfohl et al 1998). Inhibition of MVA and isoprenoids production may then affect the function of intracellular proteins post-translationally modified by these isoprenoids, which have a half-life time of less than 20–30 hours (Holstein et al 2002). Among these prenylated proteins, we recall members of the Rho, Ras, and Rab families playing a key role in cell proliferation, cytoskeleton assembly, platelet activation and the generation of oxygen radicals (Corsini et al 2004; Endres and Laufs 2004). It should also be noted that mammalian cells do not usually have an intracellular pool of these isoprenoids that are synthesized only when requested (Corsini et al 1999). Indeed, a reduction of RhoA prenylation has been documented in peripheral blood mononuclear cells isolated from a healthy volunteer treated with 40 mg of simvastatin (Cich et al 2004). Therefore, the deprivation of circulating MVA-derived isoprenoids in the early phase of treatment could be the main mechanism responsible for the atheroprotective effect of statins. Indeed, the ARMYDA trial (Patti et al 2007) has shown that a 12 hour pretreatment with 40 mg of atorvastatin before percutaneous coronary intervention improves clinical outcomes in patients with acute coronary syndrome (ACS). This early window of protection, during which there is a lack of LDL-C lowering, suggests that the anti-inflammatory and pleiotropic properties of statins may be of clinical importance.

Since early statin treatment may significantly exacerbate the pleiotropic effect, which type of patients could achieve potential benefits from these pharmacological properties?

Potential benefits

Acute clinical conditions represent the potential target population for addressing the early benefits of statins therapy; ie, within 24 hours of the event. The acute presentation of coronary artery disease may involve a complex interaction between the vessel wall, inflammatory cells, and the coagulation cascade (Cannon et al 2005). Indeed, in the PROVE-IT trial high dosage of atorvastatin (80 mg) not only achieved a better LDL-C reduction as compared with 40 mg of pravastatin, but strongly lowered CRP: an effect that was associated with clinically significant benefits in acute coronary syndrome (ACS) patients (Cannon et al 2004). Nevertheless, the initiation of statin therapy in the major trials conducted (ie, PROVE-IT and A-to-Z, see Cannon et al 2004; de Lemos et al 2004; Wiviott et al 2006) occurred 4–7 days after the event (Wiviott et al 2006), thus leaving open the possibility for taking further advantage of the pleiotropic effects of statins at the early and critical stage in ACS patients. The only study addressing the early benefits of statin therapy in ACS patients was MIRACL (Schwartz et al 2001) where atorvastatin was initiated 24 to 96 hours after the event. The results show a reduction of recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring hospitalization.

Altogether, it is tempting to speculate that statins may indeed interfere with the prenylation process in vivo, leading to protective pleiotropic effects independent of LDL-C lowering, which may be more relevant after early and intensive statin therapy of acute coronary syndromes.

References


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Abstract: Despite numerous studies on women's cardiac health throughout the past decade, the number of female deaths caused by cardiovascular disease still rises and remains the leading cause of death in women in most areas of the world. Novel studies have demonstrated that cardiovascular disease, and more specifically coronary artery disease presentations in women, are different than those in men. In addition, pathology and pathophysiology of the disease present significant gender differences, which leads to difficulties concerning diagnosis, treatment and outcome of the female population. The reason for this disparity is all steps for female cardiovascular disease evaluation, treatment and prevention are not well elucidated; and an area for future research. This review brings together the most recent studies published in the field of coronary artery disease in women and points out new directions for future investigation on some of the important issues.

Keywords: coronary artery disease, women, risk factors, prevention, diagnosis, treatment.

Introduction
The first female-specific recommendations for preventive cardiology were published in 1999 (Mosca et al 1999). Even though research in the treatment of cardiovascular disease (CVD) had advanced in many areas, it remains the leading cause of death in women in most parts of the world. Studies have shown that 500 thousand women die of CVD every year in the United States, somewhat near one death every minute (American Heart Association 2003). Such index exceeds not only the number of deaths in men, but also the next seven causes of death in women combined, and more importantly, coronary artery disease (CAD) is believed to be the major cause responsible for these deaths (American Heart Association 2003). Over a quarter of a million deaths per year are attributed to CAD alone in the United States (Merz et al 2004). Although already high, these figures are expected to rise even more during the next decades, due to an increase of diabetes and obesity, as well as the aging of the world population (Merz et al 2004).

Even though women have a higher frequency of chest pain/angina than men, the incidence of obstructive CAD in the female population is lower when compared with men with similar symptoms (Kenedy et al 1982; Diamond et al 1983; Merz et al 1999). In addition, it would appear that young women with obstructive CAD have a worse prognosis after acute myocardial infarction (AMI), whereas older women in similar circumstances often present with larger number of comorbidities that adversely influence the outcome, when compared to men (Coronado et al 1997). Women with acute coronary syndromes (ACS) are also less likely to receive rapid effective diagnosis and treatment than are men (Ayanian and Epstein 1991; Maynard et al 1996; Pope et al 2000).

Regarding the North American population, the Women’s Ischemic Syndrome Evaluation (WISE) study workshop (Hayes et al 2004; Maseri 2004; Nabel et al 2004; Pepine et al 2004; Shaw et al 2004; Waters et al 2004) from the National Heart, Lung and Coronary artery disease in women: a review on prevention, pathophysiology, diagnosis, and treatment
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