# Are pleiotropic effects of statins real?

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**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?

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## 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 (Tobert et al 1982; Pfohl et al 1998). Inhibition of MVA and isoprenoids production may then affect the function of intracellular proteins post-traslationally 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 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 (Cicha 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.

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