Lipid and Non-lipid Effects of Statins

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1 Introduction ........................................ 366

2 Statins and Cardiovascular Disease: LDL Lowering and Beyond ........ 368

3 Effects of Statins on Lipid Classes Other Than LDL-C ............... 369
3.1 HDL Levels ....................................... 369
3.2 HDL Subclass Profile ................................ 371
3.3 Small Dense LDL .................................. 372
3.4 Lipoprotein(a) ................................... 373

4 Non-lipid Effects of Statins ................................ 373
4.1 Endothelial Function ................................ 374
4.2 Inflammation ..................................... 376
4.3 LDL Oxidation .................................... 377
4.4 Athero-thrombotic Tendency ......................... 377
4.5 Plaque Stabilization ................................ 378
4.6 Lipid or Non-lipid: Is That the Question? ............... 379

5 Future Directions of Statin Therapy ................................ 380

6 Conclusion ........................................ 381

References ........................................ 381

Abstract Long- and short-term trials with the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have demonstrated significant reductions in cardiovascular events in patients with and without history of coronary heart disease. Statins are well-established low-density lipoprotein (LDL)-lowering agents, but their clinical benefit is believed to result from a number of lipid and non-lipid effects beyond LDL lowering, including a rise in plasma high-density lipoprotein levels. Beyond improving the lipid profile, statins have additional non-lipid effects including benefit on endothelial function, inflammatory mediators, intima-media thickening, prothombotic factors that ultimately result in plaque stabilization. These effects arise through the inhibition of several mevalonate-derived metabolites other than cholesterol itself, which are involved in the control of different cellular functions. Although statins represent the gold standard in the prevention and treatment of coronary heart disease, combination therapy with other lipid-lowering drugs, as well as novel therapeutic indications, may increase their therapeutic potential.
Keywords Statins · Coronary heart disease · LDL cholesterol · Pleiotropic effects · Plaque stabilization

1 Introduction

The direct correlation between plasma levels of low-density lipoprotein (LDL)-cholesterol (C) and the development of atherosclerosis is well established. Pharmacological lipid-lowering therapy is therefore a rational approach towards reduction of cardiovascular risk. The most significant achievements in this field came with the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). By inhibiting the committed step in its biosynthetic pathway, statins prevent the intracellular synthesis of cholesterol and increase expression of LDL receptors particularly in the liver, whereby the plasma concentration of LDL particles is reduced. Several statins are currently available. All share an HMG-like moiety, which may be inactive in lacton form, to be hydrolysed in vivo, or in active hydroxyl-acid form. Lovastatin has been the first statin available for clinical use since 1987; thereafter simvastatin, pravastatin, fluvastatin and atorvastatin were introduced. Rosuvastatin and pitavastatin are the most recent additions to the group (Fig. 1; Bolego et al. 2002). Another compound, cerivastatin, was withdrawn from the market in August 2001 because of serious adverse effects arising especially when combined with gemfibrozil. This occurred because gemfibrozil (but not other fibrates) impairs the biotransformation of cerivastatin, in particular its glucuronidation (Thompson et al. 2003).

Fig. 1 The chemical structure of the newly introduced statins rosvastatin and pitavastatin