Introduction

All agree that the introduction of the 3-hydroxy 3-methylglutaryl coenzyme A inhibitors (HMG-CoA reductase inhibitors, statins) has revolutionized the practice of cardiovascular medicine. A series of well-known, well-designed, conclusive, and concordant studies has shown that statin therapy can reduce “hard” end points, including myocardial infarction, stroke, and cardiovascular, and all-cause mortality in a broad variety of populations. This victory of therapeutics has raised questions about the mechanisms by which this class of drugs produces these profound clinical benefits. Designed as interventions to reduce low-density lipoprotein (LDL), the statins certainly provide at least some of their benefit by targeting this trigger of lipid overload and altering arterial biology at the heart of atherosclerosis.

However, the statins have a panoply of effects unrelated to their LDL-lowering ability. Indeed, the biosynthetic pathway of cholesterol is a long one, encompassing more than 20 steps on the way from mevalonate to cholesterol. Many of the smaller lipid intermediates play important roles in biologic control, as explained in detail in the various contributions to this supplement. Yet the clinical relevance of many of these effects, often referred to as pleiotropic, remains uncertain.

In view of the central role of the statin class of drugs in contemporary cardiovascular therapeutics and the controversial nature of their pleiotropic effects, we believed that it was timely to gather a panel of experts to explore these mechanisms and weigh the evidence favoring their operation in the clinic. This exercise has clear scholarly and intellectual interest, but it may also have practical implications. Insight gained into the mechanisms of action of the statin drugs may help us make further inroads into the residual burden of morbidity and mortality due to atherosclerosis by identifying new therapeutic targets.

Moreover, statins may exert a number of modulatory effects on chronic diseases ranging from multiple sclerosis to osteoporosis. Understanding the non–LDL-dependent mechanisms of action of this class of drugs, therefore, has broader clinical implications that extend beyond the cardiovascular realm. We are pleased to provide this authoritative compilation of expert discussions to explore these issues in depth. We hope that the papers assembled in this supplement will prove useful in understanding the proven benefits of the statin class of medications today and pave the way to further advances that will promote even greater reductions in morbidity and mortality due to cardiovascular and other diseases.

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