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HMG-CoA Reductase Inhibitors

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Contents

List of contributors VII

Preface IX

Stefano Bellosta, Rodolfo Paoletti and Alberto Corsini
History and development of HMG-CoA reductase inhibitors 1

Margaret E. Brousseau and Ernst J. Schaefer
Structure and mechanisms of action of HMG-CoA reductase inhibitors 19

Jörg Kotzka, Wilhelm Krone and Dirk Müller-Wieland
Sterol-regulatory element binding proteins (SREBPs): gene-regulatory target of statin action 35

Gerd Schmitz and Michael Torzewski
Cellular effects of HMG-CoA reductase inhibitors on blood cells (monocytes, macrophages, platelets) 55

Koichi Node and James K. Liao
Pleiotropic effects of HMG-CoA reductase inhibitors on cells of the vascular wall 81

Hans-P. Thomas and Elisabeth Steinhagen-Thiessen
Indications and contra-indications for statin treatment (primary and secondary prevention of hypercholesterolemia) 99

Helena K. Gylling and Tatu A. Miettinen
Clinical experience: studies with HMG-CoA reductase inhibitors 121

Colin Berry, Andrew Davie and John McMurray
Cost-effectiveness of statins in primary and secondary prevention of coronary heart disease 135

Index 149

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Preface

The discovery of drugs is still an unpredictable process. Breakthroughs are often the result of a combination of factors, including serendipidity, rational strategies and a few individuals with novel ideas. An encouraging development in the treatment of hypercholesterolemia has been the introduction of a new class of fungal-derived compounds that are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in the biosynthetic pathway for cholesterol. HMG-CoA reductase (HMGR) inhibitors (statins) are established drugs for the treatment of hypercholesterolemia, and have been shown to induce regression of vascular atherosclerosis as well as reduction of cardiovascular-related morbidity and death in patients with and without coronary artery disease.

This book deals with statins which have substantially altered the approach to therapy of atherosclerosis and its sequelae. Emphasis is placed on the scientific background to the discoveries and the development of the therapy, with an overview of the current state of knowledge of the drugs by experts in the field. We are happy to say that invitations to these authors were gratefully accepted and each contribution constitutes an important part of this book. Each of the chapters has been designed in such a way that it can be read independently of the others, but has been written with a uniformity of theme and style that should allow smooth transitions. In the first chapter, an overview of the history and development of HMG-CoA reductase inhibitors is provided by *Stefano Bellosta*, *Rodolpho Paoletti* and *Alberto Corsini*. Although the cholesterol-lowering ability of this class of drugs is irrefutable, the mechanisms responsible for their hypocholesterolemic effects are yet to be completely defined. The goal of the following chapter written by *Margaret E. Brousseau* and *Ernst J. Schaefer* is to review the results of recent *in vitro* and *in vivo* studies that have investigated the mechanisms by which statins reduce plasma LDL concentrations, with particular emphasis on the metabolism of apoB-containing lipoproteins in humans.

Inhibition of the HMG-CoA reductase and therefore of cholesterol biosynthesis leads to an alteration of intracellular signaling cascades by modifying subcellular localisation of small G-proteins via prenylation. Other mechanisms involve the regulation of cholesterol-regulated transcription factors, as described in the third chapter (*Jörg Kotzka*, *Wilhelm Krone* and *Dirk Müller-Wieland*).

Independent of their ability to reduce plasma cholesterol, several other potential targets for statins are emerging. These targets comprise blood cells

(*Gerd Schmitz* and *Michael Torzewski*) as well as cells of the vascular wall (*Koichi Node* and *James K. Liao*). Indications and contraindications for statin treatment (primary and secondary prevention of hypercholesterolemia) are then described by *Hans-P. Thomas* and *Elisabeth Steinhagen-Thiessen*. An overview of the five large clinical trials of the beneficial effect of statins on coronary disease, which have been published since 1994, is given in the following chapter by *Helena K. Gylling* and *Tatu A. Miettinen*. The final chapter written by *Colin Berry*, *Andrew Davie* and *John McMurray* deals with the economic impact of statin therapies.

It is our hope that this book provides the reader not only with information but also stimulates further research into the pathogenesis of atherosclerosis and the mechanisms behind the action of effective statins.

Gerd Schmitz and Michael Torzewski
Regensburg, February 2002