Pharmacological Therapy for Cardiovascular Disease
Current and Emerging Therapies

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INTRODUCTION

The morbidity and mortality associated with coronary heart disease (CHD) are significant, with CHD accounting for 37.3% of all deaths in 2003 (or 1 of every 2.7 deaths) in the United States \(1\). Current estimates indicate that more than 13,200,000 Americans have CHD \(1\). As a result, lipid-lowering drugs are the most prescribed medications in the world with more than 20 million people being prescribed this pharmacological class of drug. Despite increasing evidence for the benefits of lipid-lowering therapy on patient outcomes, recent surveys demonstrate that only 18% of very high risk patients are at the optimal low-density lipoprotein (LDL) goal of less than 70 mg/dL \(2\). As pharmacological options for CHD treatment are increasing, awareness of the benefits of single-agent as well as combination therapies is essential for ensuring the achievement of LDL goal. This chapter discusses current and emerging agents targeting pharmacological regulation of lipid metabolism in patients with dyslipidemia.

STATINS

Cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been established as an effective method of reducing death and myocardial infarction (MI) among patients with CHD. Numerous
clinical trials have demonstrated that statins can improve the lipid profile of patients with dyslipidemia, bring large numbers of these patients within treatment guidelines, and lower their risk of cardiovascular-related morbidity and mortality (3). In fact, all of the major statin trials have had a consistent linear correlation between cholesterol lowering and cardiovascular risk reduction (Fig. 1).

Statin outcome trials have proven conclusively that lowering LDL-C results in significant improvement in cardiovascular morbidity or mortality (Table 1). Additionally, primary and secondary prevention studies using statins have established the safety and efficacy of this class of pharmacological agents.

**Mechanism**

Statins are structural inhibitors of HMG-CoA reductase, the rate-limiting enzyme for hepatic cholesterol biosynthesis resulting in the upregulation of the LDL receptor and the lowering of serum LDL-C (Fig. 2). All statins share a similar structure (the *pharmaphore*) that inhibits HMG-CoA reductase. The fungally derived statins (lovastatin, simvastatin, and pravastatin) have other structural similarities, whereas the synthetic statins (cerivastatin, fluvasatin, atorvasatin, rosvastatin, and pravastatin) also have common clinical structures. As a result, classifying statins as fungal metabolites (natural statins) or synthetic statins is an acknowledged way to differentiate the two types. Another classification scheme involves identifying statins by their solubility in octanol (lipophilicity) or water (hydrophilicity). Pravastatin, rosvastatin, and, to a much lesser degree, fluvasatin are considered hydrophilic statins, whereas the other statins are considered lipophilic (Fig. 3).

Statins have clinically relevant differences in efficacy, pharmacokinetics, and safety profiles, yet differences in the statin class of drugs have focused on the pleiotropic or nonlipid-mediated effects. Almost all cells possess the mevalonate pathway that

![Fig. 1. Meta-regression analysis CHD (nonfatal MI and CHD death). Relation of total cholesterol differential in active treatment versus control group to % change in CV events versus placebo. CHD, coronary heart disease; CTL, control group; CV, cardiovascular; MI, myocardial infarction; TC, total cholesterol; TRT: treatment group. Reprinted with permission from Davidson and Robinson (83).](image-url)