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CARDIOLOGY BOARD REVIEW MANUAL

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Cholesterol and Cardiovascular Risk: Review and Case Studies

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Cover Illustration by Stacey Caiazzo

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Cholesterol and Cardiovascular Risk: Review and Case Studies

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I. INTRODUCTION

Coronary heart disease (CHD) was the leading cause of death of Americans in 2000, accounting for 1 in 5 deaths.¹ In the United States, the risk for developing CHD over a lifetime is 49% for men and 32% for women.² Data from the Framingham Heart Study, the Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics trial demonstrated a direct relationship between serum levels of low-density lipoprotein cholesterol (LDL-C) or total cholesterol and the rate of new-onset CHD in men and women who were initially free of CHD.³⁻⁵ There also was a direct relationship between serum cholesterol levels and recurrent coronary events in people with established CHD, although the event rate was higher in this group.³ After adjustment for other factors, approximately 27% of CHD events in men and 34% in women were attributable to elevated levels of total cholesterol (≥ 200 mg/dL), according to data from the Framingham Heart Study.⁶ A 10% decrease in total cholesterol levels may result in an estimated 30% reduction in the incidence of CHD.¹

The National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP-III) guidelines assert that LDL-C levels above 100 mg/dL are atherogenic and LDL-C levels between 100 and 129 mg/dL are above optimal.⁵ According to the third National Health and Nutrition Examination Survey, approximately 20% of adults over the age of 20 years have high cholesterol, defined as a total cholesterol level higher than 240 mg/dL (corresponding to a LDL-C level > 160 mg/dL).⁵ The mean LDL-C for men and women is 130 and 125 mg/dL, respectively, indicating that the average adult in the United States has an above optimal LDL-C level.⁵ This manual reviews the biochemistry of lipid metabolism and pharmacology of lipid-lowering agents and discusses the assessment and treatment of hyperlipidemia per the NCEP ATP-III guidelines.

II. BIOCHEMISTRY OF CHOLESTEROL

In humans, excess calories are ingested in the anabolic phase of the feeding cycle, which is followed by a period of negative caloric balance when the body draws upon its fat and carbohydrate stores. Lipoproteins mediate this cycle by transporting lipids from the intestine and the liver to most tissues for oxidation and to adipose tissue for storage (**Figure 1**). Lipoproteins are high-molecular-weight particles with a hydrophobic core consisting of varying amounts of triglycerides and/or cholesteryl esters and a hydrophilic phospholipid outer layer with varying amounts of free cholesterol, which permits water solubility and thus transport throughout the serum. Lipoproteins carry apolipoproteins (Apo), which mediate lipoprotein catabolism by binding with specific receptors or enzymes.⁵ In the fasting state, 3 major classes of lipoproteins are found in the serum: very-low-density lipoprotein (VLDL), LDL, and high-density lipoprotein (HDL), which contain 10% to 15%, 60% to 70%, and 20% to 30% of serum cholesterol, respectively.

Chylomicrons, the fourth major class of lipoproteins, are found in serum after a fat-containing meal. They transport dietary cholesterol and triglycerides to tissues after a meal. Chylomicrons are synthesized by the small intestine and are delivered to the circulation via the lymphatic system (**Figure 1**). They contain mostly triglycerides but also have a smaller amount of cholesteryl ester in their hydrophobic core. The nascent chylomicron contains Apo B-48, A-I, A-II, and A-IV in the phospholipid layer and obtains Apo C-II and E from HDL. Apo B-48 is necessary for the assembly and secretion of chylomicrons from the small intestine. Apo C-II is a cofactor that binds to and activates lipoprotein lipase, an enzyme found on the luminal surface of capillaries in muscle and fat. The activated lipoprotein lipase then liberates the triglycerides from the core of the chylomicrons by breaking them down into free fatty acids and