# MANAGEMENT OF LIPID DISORDERS



by

David A. Leaf, M.D., M.P.H.

## TABLE OF CONTENTS

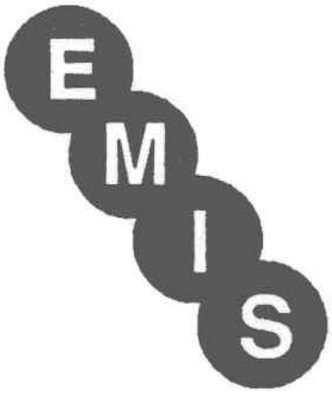
## TABLES

# MANAGEMENT OF LIPID DISORDERS

*by*

DAVID A. LEAF, M.D., M.P.H.

Assistant Professor
Division of Nutrition
Department of Medicine
University of California
Los Angeles, California






Essential Medical
Information Systems, Inc.
Dallas, TX

*Direct Mail Orders*
**Essential Medical**
**Information Systems, Inc.**
P.O. Box 811247
Dallas, TX 75381

*Telephone Orders*
1-800-225-0694

*FAX Your Order*
(405) 924-9414

ISBN: 0-929240-23-5



Printed in the United States of America

## Center Index Texts Published by

*Essential Medical Information Systems, Inc.:*

---

**Emergency Cardiac Maneuvers** — Bartecchi

**Management of Hypertension-3rd Ed.** — Kaplan

**Estrogen Replacement Therapy-2nd Ed.** — Gambrell

**Contraceptive Sterilization** — Moss

**Hormonal Contraception: Pills, Injections & Implants** — Goldzieher

**Breastfeeding: A Problem-Solving Manual-2nd Ed.** — Johnson, Carroll & Saunders

**Diagnosing and Managing Chemical Dependency** — Beasley

**Menopause: Clinical Concepts** — London & Chihal

**Premenstrual Syndrome-2nd Ed.** — Chihal

**Management of Diabetes Mellitus** — Schwartz

**Children With Special Needs-2nd Ed.** — Bradway & Block

**Assessment and Management of the Suicidal Adolescent** — Clayton

**Management of Heart Failure** — Cohn & Kubo

**Infertility: A Clinician's Manual** — Cohen

**Anesthesia Guide** — Jerome

**Mid-Life Sexuality: Enrichment and Problem Solving** — Semmens

**Estrogen Replacement Therapy User Guide** — Gambrell

**Hypertension Treatment: User Guide** — Kaplan

---

*Request Catalog for complete list of center index texts.*

# DEDICATION

This book is dedicated to my wife, Leslee, and our little daughter, Chanel, for the joy and warmth they give to my life; to Mr. Ronald James Padovana for providing a special and personal source of inspiration for the majority of my life; for my friend and colleague, Dr. Stephen Inkeles, for his critical review of my manuscript; and, for the dedicated scientists whose career devotion to this important aspect of disease prevention continues to provide insights and direction in this field and contributes to our quality of living.

## TABLE OF CONTENTS

## TABLES

## FIGURES



## Center Index Systems

The purpose of the center index system is to enable readers to immediately locate all the information contained in the book. Tabs are provided with each center index so there is a direct connection between the center index and text. The text is organized in a sequential format to enable the reader to proceed to any area of the text without having to read through information not relevant to the situation.

1.

# #1 Cholesterol and Coronary Artery Disease

## The Cholesterol Hypothesis

Although the cholesterol hypothesis has been subjected to longstanding debate, recent research has provided strong evidence in support of this position and has served to stimulate the formation of national guidelines aimed at lowering plasma cholesterol levels.

According to the cholesterol hypothesis, elevated levels of plasma cholesterol directly contribute to the pathogenesis of atherosclerotic disease, which ultimately causes coronary artery disease (CAD). CAD is the result of both thrombogenic and progressive atherogenic occlusion of the arterial blood vessel lumen.

Early evidence in support of the cholesterol hypothesis was derived from plaque studies and feeding experiments in primate models. Similarly, epidemiological evidence supports the direct relationship between plasma cholesterol levels and CAD risk.

In spite of these findings, only recently has more conclusive evidence been available to support the cholesterol hypothesis and prospective, randomized, double-blind, control intervention trials been completed. These indicate that lowering of plasma cholesterol levels can reduce CAD risk and cause disease regression.

It should be recognized that "plasma cholesterol" from the perspective of the cholesterol hypothesis refers to total plasma cholesterol levels as a reflection of plasma LDL-C, the atherogenic plasma lipoprotein. Thus, plasma choles-

terol values as a predictor of CAD risk are a surrogate, reflecting plasma LDL-C levels.

## Recent Prospective Trials

### The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)

This double-blind, placebo-controlled trial, randomized 3,806 asymptomatic hypercholesterolemic (Type IIa) men to receive diet (low fat, low cholesterol) intervention plus one of the following:

- Cholestyramine (Questran®)
- Placebo

After seven years of intervention, the experiments resulted in:

- The incidence of CAD events in seven percent of the cholestyramine group
- The incidence of CAD events in 8.6 percent of the placebo group
- A 19 percent reduction in CAD events in the treated group associated with the reduction in total cholesterol (13.4 percent) and LDL cholesterol (20.3 percent)
- An eight percent reduction in total cholesterol associated with a 19 percent reduction in CAD risk (one to two ratio)
- A 25 percent reduction in total plasma cholesterol levels in the men who took the full therapeutic medication dose, corresponding with a 49 percent reduction in fatal and nonfatal CAD events

## The Helsinki Heart Study (THHS)

This randomized, double-blind, prospective primary prevention trial compared:

- The effects of gemfibrozil placebo on plasma lipids and lipoproteins
- Incidence of CAD events in 4,081 Finnish men (Types IIa, IIb and IV)

After five years, this study resulted in:

- A 34 percent total reduction of CAD events in the gemfibrozil group (most evident in the subgroups of men with elevated plasma triglyceride levels, Types IIb and IV)
- Reduction of CAD risk by three to five percent associated with a one percent increase in plasma HDL-C levels

## The Cholesterol-Lowering Atherosclerosis Study (CLAS)

This secondary prevention, placebo-controlled study involved men who had undergone coronary artery bypass graft surgery. It was designed to assess the effect of plasma cholesterol lowering using a combination therapy of colestipol (Colestid®) and niacin with dietary intervention on angiographic findings.

Compared with the placebo group, the men receiving medication therapy experienced:

- Plasma LDL-C reduction of 43 percent
- Plasma triglyceride reduction of 22 percent
- Increase in plasma HDL-C of 37 percent
- A regression of lesions of 16 percent

These changes in plasma lipids and lipoproteins were also associated with a decrease in the number of new lesions noted in both native arteries and vein grafts. In addition, less disease progression was evident in the native vessels of the treated group.

## Relationship Between Plasma Cholesterol Level and CAD Risk

Although the presence of a continuous relationship between plasma cholesterol levels and CAD has been suggested, findings from the Multiple Risk Factor Intervention Trial (MRFIT) recently confirmed the existence of this relationship. Figure 3.1 (see Section #3) shows the relationship between serum cholesterol levels in the group of 325,348 men during screening and the age-adjusted incidence of CAD-related mortality during a five-year period of subsequent follow-up.

Despite the definite direct relationship between serum cholesterol levels and CAD risk shown in these findings, this relationship is notably curvilinear. This indicates that, although lower plasma cholesterol levels represent a lower CAD risk, there appears to be an aspect of diminishing returns.

Clearly, plasma cholesterol lowering in the hypercholesterolemic is important for CAD risk reduction. This is especially exemplified by the previous clinical intervention trials, which involved hypercholesterolemic men. Similar trials have not been conducted in women and normocholesterolemics. Additionally, in terms of population attributable risk, nearly half of CAD-related mortality occurs between the plasma cholesterol range of

190 to 249 mg% (4.9 to 6.4 mmol/L). Although from the individual patient's standpoint, high plasma cholesterol levels bear an increased risk for CAD.

Therefore, regarding public health, all efforts aimed at lowering the population's mean plasma cholesterol level from its current value of approximately 210 mg% are beneficial measures for society as a whole.

## The Importance of Plasma HDL-C Level in CAD Risk

Although international correlates of plasma HDL-C levels with CAD risk are not as predictive as is plasma LDL-C, plasma HDL-C levels show a well-established inverse relationship to CAD risk in Western cultures. The current recommendation for the treatment of hypercholesterolemia focuses on reduction of atherogenic LDL-C levels.

Although few animal studies are available involving plasma HDL-C and CAD risk, plasma HDL-C levels may explain the gender differences in CAD risk. Similarly, postmenopausal estrogen use raises plasma HDL-C levels and lowers CAD risk. Certainly, there is an appropriate pathophysiological model of the mechanism by which HDL-C can reduce atherosclerosis.

The exclusion of HDL-C from current formally-sanctioned treatment schemes also stems from the difficulty in interpretation of research studies assessing the effects of plasma HDL-C changes. Plasma HDL-C alterations do not occur in isolation and are confounded by concomitant changes in other plasma lipoprotein levels. Thus, it remains difficult to decipher the interactive effects of plasma HDL-C and LDL-C changes. Also, certain genetic

disorders with low plasma HDL-C levels do not appear to cause increased CAD risk.

In addition, from the clinical standpoint, the measurement of plasma HDL-C levels is problematic. This is because lab variability in the measurement of plasma HDL-C can have a proportionately greater influence on the smaller plasma HDL levels than is the case of plasma total cholesterol. Similarly, current laboratory standardization is not available for plasma HDL-C, as it is for total cholesterol, which means HDL-C measurements are less accurate in the clinical setting than are plasma LDL-C measurements.

Furthermore, few clinical measures are available that can safely promote plasma HDL-C increases. In our cost-minded health care system, the added cost/benefit ratio of plasma HDL-C levels remains to be shown.

In contrast, a growing body of epidemiological evidence continues to identify the powerful inverse relationship between plasma HDL-C levels and CAD risk. Therefore, this issue remains to be settled.

Recent findings based on the combined evaluation of four major prospective American studies indicate that a one percent increase in plasma HDL-C level is associated with a reduction in CAD risk of:

- Two percent for men
- Three percent for women

Using a proportional hazards model, the LRC-CPPT study indicated a small, but significant, CAD-lowering effect of increasing plasma HDL-C levels.

The Helsinki Heart Study found that the best benefit in CAD risk reduction occurred for the men with plasma HDL-C levels below 35 mg%. Also, in the study population with the highest baseline levels of plasma LDL-C, the plasma HDL-C lipoprotein fraction provided the greatest predictive value for CAD risk. The severity of LDL-C elevation did not provide any predictive value of CAD risk.

Conversely, the Framingham Study showed that even at lower cholesterol levels (below 200 mg), lower plasma HDL-C levels are associated with increased rates of CAD in both men and women.

Certainly the current guidelines are no replacement for clinical judgment. Hopefully, continued research findings will help to clarify the HDL-C issue and provide directives for more concrete clinical guidelines which incorporate HDL-C directly in the management strategies.

## The Total-Cholesterol/HDL-C Ratio and CAD Risk

The concept of combining the CAD predictive capacity of plasma total cholesterol (LDL-C) and plasma HDL-C levels was initially suggested by findings from the Framingham Study, which provided evidence that the total-cholesterol/HDL-C ratio was predictive of CAD risk. Although not utilized by current guidelines, the concept of this ratio should not be ignored, especially when individual CAD risk-factor management is involved.

In view of Framingham Study findings indicating that HDL-C is predictive of CAD risk in individuals with total plasma cholesterol levels below 200 mg%, a resurgence in the use of this index may