JMCP

JOURNAL OF MANAGED CARE PHARMACY

Targeting Low HDL-Cholesterol to Decrease Residual Cardiovascular Risk in the Managed Care Setting

Mark J. Cziraky, PharmD, FAHA, CLS

Karol E. Watson, MD, PhD, FACC

Robert L. Talbert, PharmD, FCCP, BCPS, CLS

Supplement

October 2008

Vol. 14, No. 8-S

Continuing Education Activity

JMCP

Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
830.935.4319, fcurtiss@amcp.org

Associate Editor

Kathleen A. Fairman, MA
602.867.1343, kfairman@amcp.org

Peer Review Administrator

Jennifer A. Booker, 703.317.0725
jmcpreview@amcp.org

Graphic Designer

Leslie C. Goodwin, 703.845.5404
lgoodwin@amcp.org

October Supplement Editor

Peter Whittaker, PhD
pwhittak@med.wayne.edu

Account Manager

Peter Palmer, 800.486.5454, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; 703.683.8416; (fax) 703.683.8417.

Copyright © 2008, Academy of Managed Care Pharmacy.
All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without written permission from the Academy of Managed Care Pharmacy.

POSTMASTER: Send address changes to JMCP,
100 North Pitt St., Suite 400, Alexandria, VA 22314.

Supplement Policy Statement

Standards for Supplements to the Journal of Managed Care Pharmacy

Supplements to the *Journal of Managed Care Pharmacy* are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all JMCP supplements to ensure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.
2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.
3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.
4. Identify any off-label (unapproved) use by drug name and specific off-label indication.
5. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.
6. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.
7. Subject all supplements to expert peer review.

FACULTY

Mark J. Cziraky, PharmD, FAHA, CLS, is Vice President of Research Development and Operations at HealthCore Inc., Wilmington, Delaware; Adjunct Assistant Professor, Philadelphia College of Pharmacy, the University of the Sciences in Philadelphia; and Adjunct Associate Professor, the University of Delaware, Newark, Delaware. He received his BS and PharmD from the Philadelphia College of Pharmacy and Science, graduating summa cum laude. He also completed a residency in Ambulatory Care Pharmacy Practice through the Philadelphia College of Pharmacy and Science and Blue Cross Blue Shield of Delaware.

Dr. Cziraky is the author or coauthor of nearly 100 articles, abstracts, book chapters, and books, and is a frequent presenter at meetings and conferences nationwide. He serves as a reviewer for several journals and is a Fellow of the American Heart Association and a member of the American College of Clinical Pharmacy, the American Society of Hospital Pharmacists, and the American Pharmacists Association. Dr. Cziraky serves on the board of directors for the National Lipid Association, the Wellness Community of Delaware, the Northeast Lipid Association, and the Institute of Safe Medication Practice.

Karol E. Watson, MD, PhD, FACC, is Associate Professor of Medicine, Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles (UCLA). She is Director, UCLA Women's Cardiovascular Center; Codirector, UCLA Program in Preventative Cardiology; and Director, UCLA Center for Cholesterol and Hypertension Management. She obtained her medical degree from Harvard Medical School, Boston, followed by a residency in internal medicine and a fellowship in cardiovascular diseases at UCLA, where she also received her PhD in physiology.

Dr. Watson is a board member of the National Lipid Association, a steering committee member of the Internal Medicine Section, a cochair of the Cardiology Section of the National Medical Association, and a board member of the American Heart Association Western States Affiliate. She is the author or coauthor of more than 50 publications and serves on the editorial board of *Future Lipidology*, *Western Journal of Medicine*, and the *Journal of the National Medical Association*, among others.

Robert L. Talbert, PharmD, FCCP, BCPS, CLS, received his PharmD and BS from the University of Kentucky, Lexington. Dr. Talbert is SmithKline Professor of Pharmacy at The College of Pharmacy, University of Texas at Austin, and Professor of Medicine at The University of Texas Health Science Center at San Antonio.

Dr. Talbert has published more than 120 journal articles, books, book chapters, abstracts, and letters. He is an editor of *Pharmacotherapy: A Pathophysiologic Approach*, now in its seventh edition. Dr. Talbert is a reviewer for many journals, including the *American Journal of Cardiology*, *Diabetes Care*, *American Journal of Hospital Pharmacy*, *American Journal of Managed Care*, *Pharmacotherapy*, and *Journal of Pharmaceutical Sciences*.

Dr. Talbert is a Fellow of the American College of Clinical Pharmacy. He is a member of the American Society of Health-System Pharmacists, American Association of Colleges of Pharmacy, American Heart Association, American Pharmaceutical Association, Heart Failure Society of America, and National Lipid Association, among others. Dr. Talbert was named Preceptor of the Year (2005) by The University of Texas College of Pharmacy and received the Sustained Contributions to the Literature Award from the American Society of Health-System Pharmacists in 2005. In October 2007, he received the Russell Miller Award from the American College of Clinical Pharmacy for his contributions to the biomedical literature.

Table of Contents

Targeting Low HDL-Cholesterol to Decrease Residual Cardiovascular Risk in the Managed Care Setting

S4 Introduction

Mark J. Cziraky, PharmD, FAHA, CLS

S6 Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

Karol E. Watson, MD, PhD, FACC

S16 The Impact of Residual Cardiovascular Risk and Combination Lipid-Modifying Therapy in the Managed Care Setting

Robert L. Talbert, PharmD, FCCP, BCPS, CLS

S26 Conclusions

Mark J. Cziraky, PharmD, FAHA, CLS

S29 Continuing Education

CE Submission Instructions and Posttest Worksheet

Target Audience

This activity is intended for managed health care professionals, especially pharmacy directors and medical directors, and physicians interested in lipid management, pharmacoeconomics of lipid therapy, and health outcomes research.

Learning Objectives

After completing this activity, the participant will:

1. Describe the roles of low high-density lipoprotein cholesterol (HDL-C) and elevated triglycerides in the high residual cardiovascular risk remaining in statin-treated patients with diabetes or the metabolic syndrome
2. Evaluate the pharmacoeconomic impact of untreated residual cardiovascular risk in patients with suboptimal lipid values
3. Analyze health plan-level data to determine the appropriate patient types for treating beyond low-density lipoprotein cholesterol (LDL-C) as a way of improving disease management, leading to improved outcomes and cost savings
4. Compare the efficacy of various therapeutic modalities, including statin monotherapy and niacin/statin combination therapy, in treating beyond LDL-C to reduce residual cardiovascular disease risk

Funding and Original Presentation of This Learning Activity

This supplement was funded by an educational grant from Abbott Laboratories.

The content contained in this supplement was presented at the Academy of Managed Care Pharmacy 20th Annual Meeting, April 16-19, 2008, in San Francisco.

Sponsored by The Academy for
Continued Healthcare Learning

Abbott
A Promise for Life

Supported by an educational
grant from Abbott Laboratories

Release date: 10/01/08

Expiration date: 9/30/09

Faculty Disclosures

The Academy for Continued Healthcare Learning (ACHL) requires that the faculty participating in a continuing medical education (CME/CE) activity disclose any relevant affiliation or other financial relationship (1) with the manufacturers of any commercial product(s) and/or provider(s) of commercial services discussed in an educational presentation, and (2) with any commercial supporters of the activity. Conflict resolution must occur before the CME/CE activity. The ACHL also requires participating faculty to disclose when unapproved or unlabeled uses of a product are discussed in a CME/CE activity.

Faculty members have provided the following disclosure information:

Mark J. Cziraky, PharmD, FAHA, CLS, has received grant support, on behalf of HealthCore Inc, from Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Merck & Co. Inc., Novartis, and Pfizer.

Karol E. Watson, MD, PhD, FACC, has been a speaker, speakers' bureau participant, and advisor/consultant for Abbott Laboratories, Daiichi Sankyo, and Schering-Plough. She also has been a speaker for AstraZeneca and Merck & Co. Inc.

Robert L. Talbert, PharmD, FCCP, BCPS, CLS, has been an advisor/consultant for Abbott Laboratories and a speakers' bureau participant for Novartis.

Staff Disclosures

The ACHL staff members and others involved with the planning, development, and review of the content for this activity have no relevant affiliations or financial relationships to disclose.

Off-Label Use

The articles within this journal supplement include discussion of the unapproved or off-label use of niacin and fibrates in combination with statins.

Disclaimer

The content for this activity was developed independently of the commercial supporter. All materials are included with permission. The opinions expressed are those of the faculty and are not to be construed as those of the publisher or grantor.

This educational activity was planned and produced in accordance with the Accreditation Council for Continuing Medical Education *Essential Areas and Elements, Policies, and Standards for Commercial Support* as well as the ACPE *Criteria for Quality and Interpretive Guidelines*. Recommendations involving clinical medicine in a CME/CE activity must be based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. All scientific research referred to, reported or used in CME/CE in support or justification of a patient care recommendation must conform to the generally accepted standards of experimental design, data collection, and analysis.

Participants are advised that one or more presentations in this CME/CE activity may contain references to unapproved or unlabeled uses of drugs or devices. Participants should note that the use of these agents outside current approved labeling is considered investigational and are advised to consult current prescribing information for these products.

Targeting Low HDL-Cholesterol to Decrease Residual Cardiovascular Risk in the Managed Care Setting

Mark J. Cziraky, PharmD, FAHA, CLS; Karol E. Watson, MD, PhD, FACC;
and Robert L. Talbert, PharmD, FCCP, BCPS, CLS

ABSTRACT

BACKGROUND: Most clinicians recognize the importance of reducing low-density lipoprotein cholesterol (LDL-C) and, therefore, address this therapeutic need to decrease cardiovascular disease risk. In addition to the critical role that LDL-C plays, recent studies have shown the contribution of other lipid fractions, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), to overall cardiovascular health. Managed care initiatives to reduce cardiovascular risk typically focus on highly effective statin therapies, which are primarily LDL-C-lowering agents and have lesser TG-lowering and HDL-C-raising effects. However, clinical and epidemiologic data illustrate the need to expand the scope of therapies to reduce the residual cardiovascular risk associated with low HDL-C levels and elevated TG levels, even when LDL-C is managed successfully.

OBJECTIVE: To address the value of treating beyond LDL-C level to improve patient health outcomes and reduce health care-related costs.

SUMMARY: Several large trials and meta-analyses have investigated the effects of lipid-lowering statin therapy and have consistently demonstrated that statin therapy significantly reduces LDL-C levels and incidence of cardiovascular events. In spite of the efficacy of statin therapy in these studies, statins did not eliminate cardiovascular risk. Rather, significant residual cardiovascular risk remains after treatment with statins, especially in high-risk patients such as those with diabetes. Residual cardiovascular risk stems, at least partially, from low HDL-C and elevated TG. Low HDL-C levels have been identified as a significant, independent predictor of cardiovascular risk, and increases in HDL-C are associated with reductions in cardiovascular events. High TG levels are a significant risk factor for cardiovascular disease and are a marker for atherogenic remnant lipoproteins, such as very low-density lipoprotein cholesterol (VLDL-C). Additionally, with elevated TG levels, a combination of LDL-C with VLDL-C in the measure of non-HDL-C may be a better predictor of cardiovascular risk than LDL-C alone.

Recent national treatment guidelines suggest that combination therapy may be necessary to address multiple lipid targets (i.e., LDL-C, non-HDL-C, HDL-C, and TG); adding niacin or a fibrate to a statin is a therapeutic option that should be considered. As monotherapy agents, fibrates and niacin have been demonstrated to alter several lipid parameters and reduce cardiovascular events. Niacin appears to exert the greatest beneficial effects on the widest range of lipoprotein abnormalities, in addition to possessing an established safety profile. Moreover, niacin/statin combination therapy may provide greater benefits, as manifested through a correction of atherogenic lipid abnormalities, a slowing of atherosclerosis progression in coronary heart disease (CHD) patients, and a reduction of residual cardiovascular risk.

Pharmacoeconomic modeling studies have been used to describe the potential effects on both cardiovascular events and health care costs by the achievement of, or failure to achieve, combined optimal lipid values (OLVs). Achievement of OLVs is predicted to be associated with a reduced risk of cardiovascular events, in which greater magnitudes of risk reduction accompany the achievement of a greater number of lipid goals. Based on patient baseline lipid values and product labeling information, mathematical models estimate that OLVs are achieved more frequently with extended-release niacin (niacin ER)/simvastatin combination therapy than with other high-potency agents. These modeling estimates were maintained in different patient groups, including those with diabetes or the metabolic syndrome. Finally, these modeling studies estimated that a fixed-dose

niacin ER/simvastatin combination therapy would reduce direct medical costs of CHD events more effectively than would high-dose simvastatin monotherapy.

CONCLUSION: Statins are highly effective for lowering LDL-C levels and, consequently, cardiovascular event rates. However, statins do not eliminate cardiovascular risk. Even in the presence of tightly controlled LDL-C levels, evidence indicates that high TG and low HDL-C levels are independent cardiovascular risk factors. Treating lipid parameters beyond LDL-C may require the addition of niacin or a fibrate to statin therapy. Niacin is the most effective agent for raising HDL-C levels, and pharmacoeconomic modeling suggests that niacin ER/statin combination therapy may promote the cost-effective achievement of OLVs in several at-risk patient populations.

J Manag Care Pharm. 2008;14(8)(suppl):S1-S28

Copyright© 2008, Academy of Managed Care Pharmacy. All rights reserved.

Authors

MARK J. CZIRAKY, PharmD, FAHA, CLS, is Vice President, Research Development and Operations, HealthCore Inc., Wilmington, Delaware; and Adjunct Assistant Professor, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Pennsylvania. KAROL E. WATSON, MD, PhD, FACC, is Associate Professor of Medicine, Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles (UCLA); Director, UCLA Women's Cardiovascular Center; Codirector, UCLA Program in Preventative Cardiology; and Director, UCLA Center for Cholesterol and Hypertension Management. ROBERT L. TALBERT, PharmD, FCCP, BCPS, CLS, is Professor of Pharmacy, College of Pharmacy, University of Texas at Austin, and Professor of Medicine, School of Medicine, University of Texas Health Science Center at San Antonio.

AUTHOR CORRESPONDENCE: Patti Stella, The Academy for Continued Healthcare Learning, 8725 West Higgins Road, Suite 910, Chicago, IL 60631-2716. Tel.: 773.714.0705, ext. 120; Fax: 773.714.0707; E-mail: pstella@achlcme.org

Introduction

Mark J. Cziraky, PharmD, FAHA, CLS

Statins changed the landscape of pharmaceutical interventions for the treatment of cardiovascular disease, primarily through their recognized efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels, as well as reducing cardiovascular events and mortality. Major statin trials have demonstrated that lowering LDL-C by 39 mg per dL (1 mmol per L) significantly reduces cardiovascular events,¹ and similar reductions in major vascular events (21%) are seen in high-risk patients with diabetes who receive statin therapy.²

Inclusion of statins in managed care formularies depends on comparisons of efficacy, adverse events, dosage, potential drug interactions, and cost.³ A survey of 12 health care plans revealed that simvastatin and atorvastatin had equal levels (75%) of preferred placement in formularies, whereas rosuvastatin and pravastatin had much less frequent preferred placement (25% and 17%, respectively).³ A cost-efficiency analysis in 2006 indicated that branded simvastatin and lovastatin provided moderate (<40%) reductions in LDL-C for the lowest cost per 1% decrease.⁴ This same analysis showed that branded rosuvastatin provided greater reductions in LDL-C levels (>40%) for the lowest cost per 1% reduction. Additionally, when considering statin use in the context of a cost-benefit analysis, it becomes clear that generic statins provide the most cost-effective choice for LDL-C reductions of <40%, especially when factoring in lowered wholesale prices charged by the manufacturers of generic medications in 2007.⁴ Because the clinical effect of statins is perceived to be a class effect, therapeutic interchange (TI) is fairly common within this class of drug, in which TI intervention is used to decrease cost while maintaining or improving therapeutic efficacy and safety.⁵ Meissner et al. reported that a significant cost savings can be achieved through this method.⁶ Patients were switched from atorvastatin to a different statin with a 12-month follow-up and, following the TI, pharmaceutical costs for statin therapy decreased by 12% and total cost (i.e., statin cost plus related medical costs) decreased by 10%.⁶ In addition to cost, therapeutic equivalence should be considered in a TI intervention, and the potential negative effect on patient outcomes due to switching from more potent statins to less potent statins is unknown, especially in an “uncontrolled” real-world setting.⁵

Statins are generally well tolerated and are the primary pharmaceutical intervention in patients with coronary heart disease (CHD).³ Over the past decade, statin therapy has increased dramatically in this population. In 2000, less than 50% of patients who had been hospitalized for CHD received a statin; in patients hospitalized for CHD in 2003 the chances of receiving statins after discharge were 80%-230% greater than that in 2000.⁷ Of course, in order for a statin, or any pharmaceutical agent for that matter, to exert a therapeutic effect, a patient must adhere to the treatment regimen. In the managed care setting, evidence indicates that education for patients can improve statin treatment

adherence and, in turn, increased medication adherence is associated with a greater likelihood of achieving LDL-C goals.^{8,9} Parris et al. showed that medication adherence did not significantly differ among patients receiving atorvastatin, pravastatin, or simvastatin, and no significant differences were seen in mean LDL-C levels.⁹ However, LDL-C goal attainment is of substantial concern in managed care and has been shown to be suboptimal, especially in high-risk patients.¹⁰ In patients who had been newly diagnosed with either CHD or diabetes in a managed care plan, an average of only 39% of patients achieved LDL-C goals within 6 months, and only 50% of patients achieved the goal within a year.¹¹ Additionally, in patients with diabetes and associated cardiometabolic risk factors, evidence indicates that such risk factors (i.e., obesity and dyslipidemia) should be reduced to improve medical care and control costs.¹²

Despite the benefits conferred by statin therapy across various patient populations, cardiovascular disease remains the leading cause of mortality worldwide and is present in at least 70 million people in the United States.³ The estimated economic costs associated with the disease were more than \$400 billion in 2006^{3,4} and, in 2008, had increased to \$448.5 billion.¹³ The articles in this supplement address two main issues surrounding the treatment of dyslipidemia and cardiovascular disease. In the first article, Dr. Karol Watson discusses current understanding of the involvement of various lipid parameters in cardiovascular risk, national guidelines for lipid values, and appropriate pharmacological interventions to target lipid abnormalities. It is apparent that a greater number of residual cardiovascular events occur than are prevented with statin therapy and, indeed, residual cardiovascular risk remains elevated even in clinical trials in which LDL-C levels have been aggressively reduced.¹⁴⁻¹⁶ Data indicate that high triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) levels are independent risk factors for CHD events, and the combination of both dramatically increases the risk of CHD.¹⁷ The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recognize HDL-C as a significant, independent risk factor for cardiovascular disease and state that elevated TG are a marker for increased cardiovascular risk.¹⁸ These lipid parameters are secondary therapeutic targets after LDL-C goals have been met, and a 2004 report from Grundy et al. recommended the possibility of adding a fibrate or niacin to LDL-lowering statin therapy.^{18,19}

Much of this supplement's second article, by Dr. Robert Talbert, discusses the achievement of optimal lipid values (OLVs), including LDL-C, HDL-C, TG, and non-HDL-C as well as the use of extended-release niacin (niacin ER)/statin combination therapy in the attainment of multiple lipid targets to decrease cardiovascular events. Several modeling studies based on patient information from managed care databases have shown both the potential therapeutic benefits of niacin ER/simvastatin combina-

tion therapy as well as the potential cost savings associated with this treatment.²⁰⁻²³ According to Grundy, the number of medications needed to control risk factors and disease complications is a limitation of combination therapies, both in terms of possible adverse effects and increased costs.²⁴ However, fixed-dose combination (FDC) therapies, in which 2 or more medications are combined in a single tablet or capsule, may provide one approach to managing these concerns. Recent reports from Ballantyne et al. have demonstrated the significant benefits of niacin ER/simvastatin FDC therapy for simultaneously modifying several abnormal lipid parameters.^{25,26}

This supplement seeks to outline the significant progress that has been made in the treatment of cardiovascular disease

and dyslipidemia, particularly through the use of lipid-lowering statin therapy. However, much can still be done to decrease the burden of cardiovascular disease as manifested through morbidity and mortality, as well as through the associated increasing health care costs. The goal of the information presented in the following articles is to promote understanding of lipid parameters beyond LDL-C in residual cardiovascular risk and appropriate interventions that can be used to target these parameters. By addressing multiple lipid values, including HDL-C, non-HDL-C, and TG through combination therapies, patient outcomes can be improved and potentially significant cost savings may be achieved.

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

Karol E. Watson, MD, PhD, FACC

One of the most effective classes of medications for preventing cardiovascular events is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, more commonly known as statins. Statin therapy has been shown to decrease cardiovascular morbidity and mortality rates in virtually every patient population studied and will likely continue to be a mainstay of cardiovascular risk prevention for years to come. However, close examination of statin clinical trial data reveals that, even though this class of drugs has been highly effective, an unacceptably large number of patients on statins still experience cardiovascular events. For example, in the Scandinavian Simvastatin Survival Study (4S) trial, which studied patients with very high levels of low-density lipoprotein cholesterol (LDL-C and known coronary heart disease (CHD), a significant risk reduction was observed with statin treatment. A greater percentage of patients on placebo (28%) experienced a major cardiovascular event than did patients on statin therapy (19%), and the relative risk of a major cardiovascular event in the statin-treated patients was 0.66.²⁷ On the other hand, those results from 4S also indicate that, over the 5 years of the study, almost 20% of statin-treated patients still had a cardiovascular event. In several major statin trials, significant residual cardiovascular risk remained even after significant reductions in LDL-C had been achieved.²⁷⁻³² Thus, despite the decrease in cardiovascular events due to statin treatment, two-thirds of the adverse cardiovascular events still occurred, which indicates that both patient lifestyle changes and new pharmacological strategies are necessary to address cardiovascular disease.³³

Additional trials have included high-risk patients with CHD or diabetes who were treated with intensive LDL-lowering statin therapy. In 3 of these trials, as shown in Figure 1, lowering LDL-C to approximately 100 mg per dL was compared with more intensive LDL-C lowering to approximately 70 mg per dL to investigate cardiovascular event reduction even in high-risk patient populations.^{14-16,34} In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study, 4,162 patients with acute coronary syndrome (ACS) were treated with either pravastatin 40 mg or atorvastatin 80 mg. Treatment with pravastatin reduced LDL-C to 95 mg per dL, whereas treatment with high-dose atorvastatin reduced LDL-C to 62 mg per dL.¹⁴ Clinical events were reduced in the high-dose atorvastatin group versus the pravastatin group; however, over the course of the 2-year trial, 22.4% of the individuals treated with intensive statin therapy (atorvastatin 80 mg) still suffered a major cardiovascular event.¹⁴ Similar results have been observed in the Incremental Decrease

in End Points Through Aggressive Lipid Lowering (IDEAL) study and the Treating to New Targets (TNT) study. After 4.8 years in the IDEAL study, 12.0% of patients experienced a major cardiovascular event even after intensive LDL-C lowering with 80 mg per day of atorvastatin.¹⁶ In the TNT trial, after 4.9 years of follow-up, 8.7% of patients receiving 80 mg per day of atorvastatin still suffered a major cardiovascular event.¹⁵ Thus, significant residual cardiovascular risk remains in patients even after intensive statin therapy that achieves LDL-C goals <100 mg per dL.^{14-16,34}

Patients with diabetes, another high-risk population, show significant cardiovascular risk reduction when treated with statins. A meta-analysis of 14 statin trials by the Cholesterol Treatment Trialists' Collaborators examined data of major vascular events in patients with diabetes.² A reduction in LDL-C in individuals with a prior history of CHD and either with or without diabetes was associated with a significant reduction in cardiovascular events. There was a 9% proportional reduction in all-cause mortality per 1 mmol per L (39 mg per dL) reduction in LDL-C in individuals with diabetes ($P=0.02$) and a 13% reduction in those without diabetes ($P<0.001$). Moreover, there was a significant 21% reduction in major vascular events per 1 mmol per L (39 mg per dL) reduction in LDL-C in people with diabetes ($P<0.001$) and those without diabetes ($P<0.001$).² Nonetheless, in patients with diabetes treated with statin therapy, the cardiovascular event rate (i.e., residual cardiovascular risk) remained unacceptably high, and was even higher than the cardiovascular event rate of those patients without diabetes who received placebo.² It is clear, then, that residual cardiovascular risk remains in all patients treated with statins, and that the residual cardiovascular risk is particularly high in patients with diabetes treated with statins.

Cardiovascular Risk and Lipid Parameters Beyond LDL-C

Residual cardiovascular risk is undoubtedly multifactorial, and likely due to a variety of both traditional and emerging risk factors. However, recent evidence suggests the important contribution to cardiovascular risk of lipid parameters beyond LDL-C, such as high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C). For example, Genest et al. reported that although 34% of patients with premature heart disease had LDL-C levels >160 mg per dL, more than half of the patients with premature heart disease (57%) had low HDL-C levels.³⁵ Additionally, it has been reported that, in both male and female patients with premature coronary artery disease (CAD), the greatest risk factor is actually low HDL-C levels, though these

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

individuals often possess high TG levels, as well.³⁶ Although this study had small sample sizes (n=87 men; n=15 women), men and women with premature CAD had LDL-C values of approximately 130 mg per dL, which is near the average LDL-C level in the United States today. Conversely, the study found that TG levels were significantly higher and HDL-C levels were significantly lower in men and women with premature CAD, compared with patients from the Framingham Offspring Study who were free of CHD at baseline.³⁶

In addition, a shift in the lipid parameters of patients with CHD has been observed. In past decades, the most frequently seen coronary care unit patient was probably a male cigarette smoker who suffered a myocardial infarction (MI) and who had an LDL-C level near 170 mg per dL. In more recent years, the profile of patients has changed; the average LDL-C level of an MI survivor today is 130 mg per dL, which is similar to the average LDL-C level in individuals without CHD. On the other hand, the average HDL-C level is much lower. According to the Third National Health and Nutrition Examination Survey, which provides a cross-sectional examination of the United States to determine lipid parameters across many different risk factors, more than one third of the adult population has low HDL-C levels.³⁷ About 35% of adult men were reported to have HDL-C levels <40 mg per dL, and about 39% of adult women were reported to have HDL-C levels <50 mg per dL.³⁷

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines report that low HDL-C is a significant, independent risk factor for CHD. This independent relationship is maintained between HDL-C and CHD even after correction for other risk variables, such as TG levels, obesity, and diabetes.¹⁸ In general, low HDL-C is correlated with elevations of serum TG and remnant lipoproteins and is strongly and inversely associated with CHD risk.¹⁸ There are a number of different mechanisms through which HDL-C may exert its antiatherogenic effects. It has been established, for example, that various atherogenic lipoproteins, including LDL-C and very low-density lipoprotein cholesterol (VLDL-C), can deposit cholesterol in the artery wall. In vitro studies have shown that HDL-C may promote the efflux of cholesterol from foam cells in atherosclerotic lesions through reverse cholesterol transport.³⁸ There are several other mechanisms, as well, as indicated by evidence demonstrating the inhibition of atherogenesis through antioxidant and anti-inflammatory properties.^{18,38,39} In addition, HDL-C is a component in a number of other basic physiologic processes, such as antithrombotic activity, antiapoptotic activity, vasodilatory activity, and endothelial repair.^{39,40}

A meta-analysis of 4 large prospective studies, considered classic trials in the field, revealed consistent effects of HDL-C levels. In an analysis of data from the Coronary Primary Prevention Trial, the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Prevalence Mortality Follow-up Study, and the Framingham Heart Study, for every 1 mg per dL (0.026 mmol

FIGURE 1 Residual Cardiovascular Risk After Intensive Statin Therapy

^aMean or median LDL-C after treatment

In the PROVE IT-TIMI 22 study, 22.4% of patients treated with intensive statin therapy (80 mg of atorvastatin) suffered a major cardiovascular event, compared with 26.3% of patients receiving low-dose statin (40 mg of pravastatin) therapy (P=0.005).¹⁴ In the IDEAL study, 12.0% of patients experienced a major cardiovascular event after intensive LDL-C lowering with statin therapy (80 mg of atorvastatin) after 4.8 years of follow-up, compared with 13.7% of patients receiving 20 mg of simvastatin (P=0.02).¹⁶ In the TNT study, a major cardiovascular event occurred in 8.7% of patients receiving intensive statin therapy (80 mg of atorvastatin) versus 10.9% of those receiving 10 mg of atorvastatin after 4.9 years (P<0.001).¹⁵

CVD=cardiovascular disease.

per L) increase in plasma level of HDL-C, there was a decrease in CHD risk of approximately 2% in men and 3% in women independent of other risk factors, including plasma LDL-C.⁴¹ In another analysis of Framingham Heart Study data, a significant increase in the number of cardiovascular events was observed in patients with low HDL-C levels (<34 mg per dL), especially women (P<0.01).^{42,43} Importantly, as shown by data from the Framingham Health Study, as HDL-C decreases, it contributes significantly to CHD risk at all LDL-C levels. Even when LDL-C levels are optimal (<100 mg per dL), the lower the HDL-C level, the higher the risk of CHD.⁴⁴

Figure 2 shows several scenarios in patients with differing levels of LDL-C and HDL-C and the resulting risk level for each individual. Patient 3, with very low HDL-C, has a very high risk of CHD that is equivalent to the risk level of a patient with very high LDL-C (220 mg per dL) and normal HDL-C. Therefore, in individuals who have near optimal LDL-C levels (100 mg per dL), the lower the HDL-C level, the higher the risk of CHD.⁴⁴ Even when LDL-C levels are well controlled with intensive statin

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

FIGURE 2 HDL-C Modifies Cardiovascular Risk

As shown in the patient scenarios on the left side of Figure 2, if all patients have near optimal levels of LDL-C (100 mg per dL), the lower the HDL-C level, the higher the risk of CHD. Also note that in a patient with an LDL-C level of 220 mg per dL and an HDL-C level of 45 mg per dL, the risk of CHD (1.2) is equivalent to that in a patient with optimal LDL-C and low HDL-C (1.2).⁴⁴

This information was originally published in *The Canadian Journal of Cardiology* 1988;4(Suppl. A):5A-10A.

therapy, the heightened risk of CHD conferred by low HDL-C remains. The TNT trial investigated the efficacy of high-dose statin therapy, compared with low-dose statin therapy in patients with stable CHD. Patients were randomized to receive either atorvastatin (80 mg), with a target LDL-C of 70 mg per dL, or atorvastatin (10 mg), with a target LDL-C of 100 mg per dL. Results from TNT showed that patients with lower LDL-C levels had an approximate 25% risk reduction of having a CHD event. However, as Figure 3 shows, even if individuals had low LDL-C levels, they still had a very high rate of CHD events if they also had low HDL-C levels. With higher HDL-C levels, the CHD rate decreased significantly. In particular, the TNT data revealed that, even for patients in the lowest stratum of LDL-C (≤ 70 mg per dL) after 3 months of statin treatment, there was an increased 5-year risk for major cardiovascular events if HDL-C levels also were low.⁴⁵ The risk for a major cardiovascular event differed significantly among quintiles of HDL-C levels ($P=0.03$) in which those patients in the highest HDL-C quintile (≥ 55 mg per dL) had a lower risk for major cardiovascular events than did patients in the lowest HDL-C quintile (Q1 <37 mg per dL; hazard ratio [HR] vs. Q5 = 0.61).⁴⁵

Although LDL is recognized as the most important atherogenic lipoprotein, elevations in TG levels can be considered a marker for atherogenic remnant lipoproteins. VLDL-C and other TG-rich lipoproteins are able to enter the artery wall and initiate atherosclerotic processes and aid in foam cell formation just as LDL can. Because VLDL-C is the most readily available measure

FIGURE 3 Low HDL-C Is Associated With High Cardiovascular Risk (TNT Study)

Hazard Ratio Versus Q1	0.85	0.57	0.55	0.61
------------------------	------	------	------	------

In the TNT study, patients with low LDL-C levels (≤ 70 mg per dL) after 3 months of statin treatment had an increased 5-year risk for major cardiovascular events if HDL-C levels were low. The risk for a major cardiovascular event differed significantly among quintiles of HDL-C levels (multivariate regression; $P=0.03$). Patients in the highest HDL-C quintile (≥ 55 mg per dL) had a lower risk for major cardiovascular events than did patients in the lowest quintile (<37 mg per dL). The mean LDL-C level in this group of patients ($n=2,661$, receiving statin therapy for 3 months) was 56 mg per dL; mean TG level was 126 mg per dL.⁴⁵

This information was originally published in Barter P, et al. *N Engl J Med*. 2007;357(13):1301-10. Copyright© 2007 Massachusetts Medical Society. All rights reserved.

CVD=cardiovascular disease.

of atherogenic remnant lipoproteins, it is often combined with LDL-C to improve cardiovascular risk prediction (i.e., VLDL-C+LDL-C=non-HDL-C). When serum TG levels are elevated, the measure called non-HDL-C better represents the concentrations of all atherogenic lipoproteins than does LDL-C.¹⁸ Non-HDL-C incorporates all atherogenic lipoproteins, including LDL-C, VLDL-C, lipoprotein(a) (Lp[a]), and intermediate-density lipoprotein cholesterol (IDL-C). Non-HDL-C, according to the NCEP ATP III guidelines, is a secondary target of therapy after LDL-C goals have been reached and when TG levels are ≥ 200 mg per dL.¹⁸

Various studies have investigated the influence of the level of one or more of the components of atherogenic dyslipidemia on cardiovascular risk. A recent meta-analysis by Sarwar et al. included 29 prospective studies (262,525 participants; 10,158 CHD cases) to investigate the association between TG and CHD risk.⁴⁶ The meta-analysis showed an adjusted odds ratio (OR) of 1.72 (95% confidence interval [CI]=1.56-1.90) in patients

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

in the highest third versus those in the lowest third of TG values. A strong and statistically significant association was found between TG level and CHD risk, regardless of the duration of the follow-up, gender, fasting status, and adjustment for HDL-C, though adjusting for HDL-C attenuated the magnitude of the association between TG level and CHD risk.⁴⁶ The meta-analysis showed a strong and significant association between a high TG level and cardiovascular risk.

In the previously mentioned PROVE IT-TIMI 22 trial, intensive and normal statin therapy were compared to examine a combination of LDL-C and TG levels on cardiovascular risk in patients with ACS. Participants in the study were randomized to either atorvastatin (80 mg) or pravastatin (40 mg) within days of their cardiac event and then were followed for the next 2 years. The trial demonstrated that an LDL-C level <70 mg per dL was associated with a greater degree of CHD event reduction than was an LDL-C level <100 mg per dL. Further, the relationship between on-treatment levels of TG and LDL-C and the composite end point of CHD events (death, MI, and recurrent ACS) were assessed 30 days after initial presentation. Between the initial day 30 time point and the 2-year follow-up, significantly fewer CHD events occurred in patients who had an LDL-C level <70 mg per dL than in patients who had an LDL-C level ≥70 mg per dL (HR=0.81; $P=0.015$). Similarly, significantly fewer events occurred in patients with a TG level <150 mg per dL than in those patients with a TG level ≥150 mg per dL, as revealed through univariate analysis (HR=0.73; $P<0.001$). Even in multivariate analysis, after adjustment for age, gender, high LDL-C, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect, the HR associated with low on-treatment TG (<150 mg per dL) versus TG ≥150 mg per dL was 0.80 ($P=0.025$).³⁴ In univariate analysis, it appeared that for each 10 mg per dL reduction in on-treatment TG, the incidence of CHD events was reduced by 1.8% ($P<0.001$). In multivariate analysis, it also appeared that there was a significant effect of TG level on CHD event rate. After adjustment for LDL-C and other covariates, each 10 mg per dL reduction in on-treatment TG was associated with a 1.6% reduction in CHD events ($P<0.001$). Similarly, after adjustment for non-HDL-C and other covariates, each 10 mg per dL reduction in on-treatment TG was associated with a 1.4% reduction in CHD events ($P=0.01$).³⁴ On-treatment TG levels <150 mg per dL were independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG levels in patients after ACS may be an important consideration in addition to reducing LDL-C levels with statin therapy.³⁴

A Cox proportional hazards model was used to examine further the relationship between achieved LDL-C and TG at the initial day-30 time point and risk of recurrent CHD events in the PROVE IT-TIMI 22 trial, as shown in Figure 4. Compared with referent levels of LDL-C (≥70 mg per dL) and TG ≥150 mg

FIGURE 4 Triglyceride Levels and Risk of CHD Events (PROVE IT-TIMI 22)

A Cox proportional model was used to examine the relationship among low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and risk of recurrent coronary heart disease (CHD) events. Compared with LDL-C levels ≥70 mg per dL and TG levels ≥150 mg per dL (referent), lower CHD risk was observed with low on-treatment TG levels (<150 mg per dL) and LDL-C (<70 mg per dL) (hazard ratio [HR]=0.72; $P=0.017$), with a graded response for patients with LDL-C levels ≥70 mg per dL and TG levels <150 mg per dL (HR=0.85; $P=0.180$).³⁴ CHD events include death, myocardial infarction, and recurrent acute coronary syndrome (ACS); ACS patients treated with either 80 mg of atorvastatin or 40 mg of pravastatin; CHD event rate is adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment; lipid values are in mg per dL; n=4,162.

Reprinted from J Am Coll Cardiol, 2008;51(7):724-30: Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial.³⁴ (With permission from Elsevier.)

per dL), lower CHD risk was observed with low on-treatment TG (<150 mg per dL) and LDL-C (<70 mg per dL) (HR=0.72; $P=0.017$), with a graded trend observed among patients with LDL-C levels ≥70 mg per dL and TG <150 mg per dL (HR=0.85; $P=0.180$).³⁴ Patients with a TG level <150 mg per dL, even if they had LDL-C levels >70 mg per dL, experienced CHD event rates 15.0% lower than those patients who had low LDL-C but high TG. Additionally, when TG levels were <150 mg per dL, having a lower LDL-C was beneficial compared with higher LDL-C levels; however, in patients with TG levels <150 mg per dL LDL-C level did not appear to have as large an effect. The benefits conferred through reductions of LDL-C by statin therapy in the PROVE IT-TIMI 22 trial could be modulated by either having a TG level <150 mg per dL, or having a TG level >150 mg per dL. Thus, among patients receiving statin therapy after ACS, on-treatment TG level <150 mg per dL was associated with a lower risk of recurrent CHD events independent of the level of LDL-C. These data support the concept that achieving low levels of both LDL-C

FIGURE 5 Non-HDL-C Is a Significant Predictor of CHD Risk

Data from the Framingham Heart Study revealed no association between LDL-C and the risk for incident coronary heart disease (CHD) within non-HDL-C levels. Non-HDL-C was found to be strongly associated with CHD risk within every level of LDL-C.⁵¹

Reprinted from Am J Cardiol, 2006; 98(10):1363-68: Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease.⁵¹ (With permission from Elsevier.)

and TG may be an important therapeutic strategy in patients after an ACS.³⁴

When considering lipid parameters beyond LDL-C, non-HDL-C has been gaining recognition. However, clinicians have been somewhat slow to embrace it, possibly because non-HDL-C is defined by what it is not, rather than by what it is. To address this potential difficulty, one way to think about non-HDL-C is as the total atherogenic burden, which can be quickly calculated from nonfasting lipid profiles. Mathematically, non-HDL-C is equivalent to subtracting HDL-C from total cholesterol (i.e., non-HDL-C = total cholesterol - HDL-C).

Through this calculation, all atherogenic lipoproteins, such as LDL-C, VLDL-C, IDL-C, remnant lipoproteins and particles, and Lp(a), are captured by the non-HDL-C measure. Because VLDL-C is the most readily available measure of atherogenic remnant lipoproteins, it can be combined with LDL-C to improve cardiovascular risk prediction by calculating an approximate value of non-HDL-C.¹⁸ A normal VLDL-C level is defined as the value when the TG level is <150 mg per dL, which is typically ≤30 mg per dL.¹⁸ Thus, the goal for non-HDL-C is 30 mg per dL greater than the goal for LDL-C.¹⁸ If a patient's LDL-C goal is <100 mg per dL, then the non-HDL-C goal is <130 mg per dL.

Non-HDL-C is a significant predictor of CHD risk and is highly correlated with various lipid parameters that are associated with CHD risk. Non-HDL-C is correlated with apolipoprotein

B, which is the protein portion of every atherogenic lipoprotein, and with LDL particle number and size.⁴⁷⁻⁵⁰ Data from the Framingham Heart Study were analyzed to investigate the usefulness of non-HDL-C in predicting CHD risk. In this analysis (2,693 men; 3,101 women) non-HDL-C was compared with LDL-C as a predictor of CHD risk, and VLDL-C was assessed as an independent predictor of CHD risk. After multivariate adjustment, within non-HDL-C, no association was found between LDL-C and the risk for incident CHD, as shown in Figure 5. In contrast, a strong positive and graded association between non-HDL-C and risk for CHD was observed within every level of LDL-C. These results suggest that non-HDL-C is a stronger predictor of CHD risk than is LDL-C and that VLDL-C may play a critical role in the development of CHD.⁵¹ These data also were analyzed within TG levels <200 mg per dL and ≥200 mg per dL. Overall, the association with CHD incidence was stronger for non-HDL-C within every level of LDL-C than that for LDL-C within each level of non-HDL-C, regardless of whether TG levels were <200 mg per dL or ≥200 mg per dL.⁵¹

■ National Guidelines for Treating Beyond LDL-C

National guidelines address the treatment of atherogenic lipid parameters beyond LDL-C, such as high TG and non-HDL-C levels and low HDL-C. According to the NCEP ATP III guidelines, elevated LDL-C is the primary therapeutic target for interventions to decrease cardiovascular risk.¹⁸ However, as discussed previously, elevated TG and low HDL-C levels also make significant contributions to increased cardiovascular risk even after LDL-C treatment goals have been reached. The NCEP ATP III guidelines indicate that an elevated non-HDL-C level in patients with hypertriglyceridemia (i.e., TG ≥200 mg per dL) imparts an increased risk for cardiovascular events even after the LDL-C goal has been reached.^{19,52} For this reason, non-HDL-C is considered to be a secondary therapeutic target (after LDL-C) that may provide additional risk reduction.⁵² A 2004 update to the NCEP ATP III guidelines emphasized the increasing evidence for the benefits of combination therapy, compared with monotherapy, by recommending the possibility of adding a fibrate or niacin to LDL-lowering therapy in high-risk patients who have elevated TG or low HDL-C levels.¹⁹

In 2007, the American Diabetes Association (ADA) and the American Heart Association (AHA) collaborated on a joint statement outlining treatment guidelines in the Primary Prevention of Cardiovascular Disease in Patients with Diabetes.⁵³ This statement combines the recommendations of both organizations where possible and also recognizes areas in which ADA and AHA recommendations differ. The joint statement, like the NCEP ATP III guidelines, recommends that LDL-C should be the primary target of lipid-lowering therapy. The ADA/AHA guidelines further recommend an LDL-C goal level <100 mg per dL in patients with diabetes.⁵³ Also, because levels of TG-rich lipoproteins, especially VLDL-C, are often elevated in patients

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

with diabetes and appear to be atherogenic, they are identified as a secondary target of lipid-lowering therapy after the LDL-C goal level is achieved.⁵³

The ADA and AHA have also individually released guidelines for cardiovascular prevention that include therapies targeting multiple lipid parameters. According to the 2008 ADA guidelines, the primary goal is an LDL-C level <100 mg per dL in individuals without overt cardiovascular disease, although a lower LDL-C goal (<70 mg per dL) is an option in individuals with overt disease.⁵⁴ Additionally, the ADA recognizes serum TG concentration as a surrogate measure for atherogenic TG-rich lipoproteins and suggests a TG goal level <150 mg per dL.⁵⁴ Finally, the ADA standards suggest HDL-C goals of >40 mg per dL in men and >50 mg per dL in women.⁵⁴ The AHA suggests an alternative approach for patients who have elevated TG levels. For TG levels between 200 and 499 mg per dL, the AHA recommends that non-HDL-C should be calculated, and sets a non-HDL-C goal of <130 mg per dL.⁵³ This non-HDL-C target level is similar to that recommended by the NCEP ATP III guidelines.⁵³ Interestingly, the AHA advocates efforts to raise HDL-C levels but does not specifically designate therapeutic goals.

In addition to setting lipid goals, therapeutic recommendations have been advanced by the ADA and AHA. The 2008 ADA guidelines recommend that statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt cardiovascular disease and for diabetic patients who do not have cardiovascular disease but are older than 40 years of age and have one or more other cardiovascular risk factors.⁵⁴ One instance in which LDL-C is not the primary target of lipid-lowering therapy is in patients who have TG levels >500 mg per dL. If TG levels are >500 mg per dL, the AHA says that the greatest threat to life becomes pancreatitis; therefore, lowering TG levels to reduce the risk of pancreatitis is the primary goal. In this case, the AHA recommends that a TG-lowering therapy, such as a fibrate or niacin, is the first priority. After TG is sufficiently controlled, LDL-C and non-HDL-C levels need to be addressed through LDL-lowering therapy. Moreover, a non-HDL-C goal <130 mg per dL should be achieved in these patients, if possible.⁵³ Considering all of the lipid abnormalities, the ADA/AHA joint statement suggests that a combination of statins with fibrates or niacin may be necessary to achieve multiple lipid targets.⁵³

Similar guidelines for lipid levels and treatment recommendations were published in the 2006 AHA/American College of Cardiology Secondary Prevention Guidelines.⁵⁵ This update, related to secondary prevention for patients with known cardiovascular disease, provides target levels for TG and non-HDL-C. The guidelines recommend that if TG levels are between 200 and 499 mg per dL, the non-HDL-C goal level should be <130 mg per dL. Moreover, it is reasonable to consider reducing non-HDL-C levels to <100 mg per dL when a patient is at sufficiently high risk for cardiovascular events. The therapeutic options to reduce

non-HDL-C levels are more intensive LDL-C-lowering treatments, which will reduce LDL particle number, or the addition of niacin or a fibrate after LDL-lowering therapy has been initiated. As mentioned previously, when baseline TG levels are ≥500 mg per dL, the therapeutic intervention should be a TG-lowering treatment (i.e., a fibrate or niacin) to prevent pancreatitis before starting LDL-lowering therapy. Only after TG-lowering therapy has been initiated, and TG levels have been reduced, should efforts turn to treating LDL-C. For these patients, the non-HDL-C goal should be <130 mg per dL.⁵⁵

Again, consider the NCEP ATP III guidelines and the ADA and AHA national guidelines, all of which addressed various lipid parameters as well as therapeutic agents for achieving multiple lipid values. These national guidelines all support raising HDL-C to reduce cardiovascular risk, and they specifically mention fibrates or niacin as a therapeutic option to do so.^{18,53,54} The NCEP ATP III guidelines state: “Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.”¹⁸ Similarly, the 2007 ADA/AHA joint scientific statement reports that “the most effective available drug for raising HDL-C levels is nicotinic acid.”^{53,56} Because there is an extensive constellation of lipid parameters that should be addressed, there is a promising future for HDL-C-raising therapies, particularly in combination with LDL-C-lowering therapies.^{57,58} The key is to increase HDL-C in a productive and nondetrimental way. Niacin safely raises HDL-C and has a completely different mechanism of action than torcetrapib, which also increases HDL-C but has been reported to also increase cardiovascular risk.⁵⁹ Niacin is the most effective currently available agent for raising HDL-C and has been in clinical use for more than 5 decades with an established safety profile.⁵⁷ Niacin can also be used safely in combination with statins and in patients with diabetes.⁵⁸

Therapeutic Options for Reducing Cardiovascular Risk

A large amount of evidence has been presented to show the efficacy of statin therapy for the reduction of both LDL-C levels and cardiovascular risk,^{2,27-32} and niacin has been investigated for its lipid-lowering effects for several decades. The first large trial that established the benefit of niacin was the Coronary Drug Project (CDP), which was a randomized, double-blind, placebo-controlled trial with a primary end point of total mortality.⁶⁰ This trial, conducted between 1966 and 1974 and published in 1975, enrolled 8,341 men with a history of prior MI to 6 treatment arms, including treatments with 5 different lipid-lowering agents. The trial's groups were: placebo, low-dose estrogen, high-dose estrogen, clofibrate, dextrothyroxine, and niacin. Both estrogen treatment groups and the dextrothyroxine group were discontinued before the scheduled completion of the study due to increased cardiovascular event rates. The clofibrate and niacin groups completed the study (follow-up ranged from 5 to 8.5 years per patient; mean 6.2 years); at the conclusion of the trial,

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

the only treatment arm that showed any benefit was the niacin therapy group.⁶⁰ Total mortality tended to be lower in the niacin group (24.4%; $n=1,119$) than in the placebo group (25.4%; $n=2,789$) by the end of the study, although this difference was not statistically significant. Participants in the niacin treatment arm did have a significant reduction in the combined outcome of CHD death and nonfatal MI (15% reduction; $P<0.05$), nonfatal MI (26% reduction; $P<0.05$), and cerebrovascular events categorized as stroke or transient ischemic attack (24% reduction; $P<0.05$) during the follow-up.⁶⁰ Niacin monotherapy also provided a significant reduction in the number of patients having any cardiovascular surgery from the time of trial entry to a follow-up of 5 years (47% reduction; $P<0.05$).⁶⁰

Although the CDP demonstrated the benefits of niacin on cardiovascular risk, one of the lingering questions about niacin has been whether it promotes an increase in insulin resistance. Therefore, there has been some concern surrounding the use of niacin in patients with abnormal glucose metabolism or with diabetes. These concerns were addressed in a 2005 post-hoc analysis of CDP data that evaluated rates of nonfatal MI in patient subgroups defined by baseline fasting plasma glucose (FPG) levels.⁶¹ This additional analysis of CDP data showed that patients with diabetes appear to benefit as much, if not more, from niacin therapy than do nondiabetic patients. Compared with placebo, niacin reduced the risk of 6-year recurrent MI similarly (interactive P value is ≥ 0.05 or nonsignificant) in patients at all levels of baseline FPG.⁶¹ Individuals with a baseline FPG level <95 mg per dL had a 30% risk reduction with niacin; patients with an FPG level between 95 and 125 mg per dL showed an approximate 25% risk reduction with niacin. Perhaps most importantly, patients with FPG levels ≥ 126 mg per dL, which is the current ADA definition of diabetes, had a 57% risk reduction with niacin.^{54,61} Compared with placebo, niacin treatment tended to reduce the 6-year risk of the combined end point of CHD death or nonfatal MI similarly (interactive P value nonsignificant) in patients at all baseline FPG levels. The beneficial effect of niacin on reducing recurrent nonfatal MI and CHD events was not associated with increased baseline FPG levels, even in those patients with the highest baseline FPG levels.⁶¹ Therefore, any increase in FPG levels with niacin did not translate into any disadvantage with respect to CHD events.⁶¹

Based on the evidence that indicates the importance of lowering LDL-C and raising HDL-C as well as the efficacy of statin monotherapy or niacin monotherapy for reducing cardiovascular risk, an obvious question follows: if lowering LDL-C with statins is beneficial and raising HDL-C with niacin is also beneficial, should a combination therapy that includes both treatments be even better? Trials studying combination therapy have, in fact, shown remarkable cardiovascular risk reductions that various monotherapies—whether a statin, a high-dose statin, a fibrate, or niacin—cannot duplicate. As Figure 6 shows, significant residual cardiovascular risk remains after reducing LDL-C levels in the

major statin trials.^{27-29,32} Even with high-dose statin therapy (80 mg vs. 10 mg of atorvastatin in TNT), significant residual risk remains, even though the LDL-C level is reduced to approximately 77 mg per dL.¹⁵ As with statin monotherapy, fibrate and niacin monotherapies also are effective in reducing cardiovascular risk (Veterans Affairs HDL Cholesterol Intervention Trial [VA-HIT] and CDP); however, residual cardiovascular risk was still observed to exist in patients in those trials.^{60,62} The Familial Atherosclerosis Treatment Study (FATS) and HDL-Atherosclerosis Treatment Study (HATS) trials, although small, showed dramatic CHD event reduction with the use of combination therapies.^{63,64} In the FATS trial, a combination therapy of niacin plus a bile acid sequestrant was used, and in the HATS trial, niacin plus simvastatin was used. The striking benefits observed in both trials suggest that combination therapy may be most effective for optimally reducing CHD risk—simultaneously lowering LDL-C levels, predominantly with statins, while raising HDL-C levels yields what appears to be the most cardiovascular event reduction.^{63,64}

A meta-analysis of 23 different lipid trials investigated the cardiovascular event rate reductions associated with decreases in LDL-C levels and increases in HDL-C levels and revealed that the 2 components were statistically independent.⁶⁵ Therefore, the benefits accrued from an increase in HDL-C would be additive to those benefits conferred by a decrease in LDL-C, and the combined cardiovascular benefits would be greater than that from altering any single lipid parameter alone. The meta-analysis, in fact, demonstrated that the sum of the percent reduction in LDL-C and the percent increase in HDL-C predicts cardiovascular benefits much more effectively than either lipoprotein component alone. If this simple algorithm is proven accurate, a readily attainable 40% reduction in LDL-C and a 30% elevation in HDL-C will result in a 70% CHD risk reduction and a revolution in cardiovascular disease prevention.⁶⁵ The meta-analysis revealed a strong linear association between the composite lipoprotein variable (i.e., the sum of the HDL-C percent increase and LDL-C percent reduction, placebo adjusted) and the therapeutic reduction in the predefined primary clinical study end point rate relative to the placebo rate.⁶⁵ Importantly, combination therapy trials, including a statin-plus-resin trial and niacin-plus-statin trials, showed the largest reductions in LDL-C levels and largest increases in HDL-C levels, leading to the largest reduction in cardiovascular events. This meta-analysis supports the hypothesis that patients with vascular disease gain additive benefits from LDL-C reduction and HDL-C elevation.⁶⁵

The HATS trial enrolled 160 patients with CAD in a 3-year, double-blind, placebo-controlled study that evaluated slow-release niacin therapy. The patient population had low HDL-C levels (≤ 35 mg per dL in men or ≤ 40 mg per dL in women) and acceptable LDL-C levels (≤ 145 mg per dL). An angiogram was performed on patients at baseline and after a 2-year follow-up; the end points were angiographic evidence of a change in coronary stenosis and the occurrence of a first cardiovascular event, such

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

FIGURE 6 Comparing Monotherapies With Combination Therapies

Residual cardiovascular risk remains after reducing LDL-C, even with high-dose statin therapy (80 mg of atorvastatin vs. 10 mg of atorvastatin in Treating to New Targets [TNT]). Monotherapy with fibrates or niacin is also effective in reducing cardiovascular risk, although residual cardiovascular risk remains in these patients, too. Dramatic coronary heart disease (CHD) event reduction has been observed in trials of combination therapies (niacin plus a bile acid sequestrant (BAS) or niacin plus a statin). In TNT, the control condition was 10 mg of atorvastatin; in the other trials, the control condition is placebo. In the Scandinavian Simvastatin Survival Study (4S), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), Heart Protection Study (HPS), and West of Scotland (WOS), the treatment condition is statin therapy.

The references for these data are: 4S, LIPID, HPS, WOS, TNT, Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT), Coronary Drug Project (CDP), Familial Atherosclerosis Treatment Study (FATS), and HDL-Atherosclerosis Treatment Study (HATS).^{15,27-29,32,60,63}

as death, MI, stroke, or cardiac revascularization.⁶⁴ Study participants received either active niacin plus active simvastatin or placebo niacin plus placebo simvastatin, with or without active antioxidant vitamins or placebo antioxidant vitamins. The angiographic results of the trial indicated that patients in the placebo group experienced an increase in percent stenosis, as could be expected through the natural progression of atherosclerosis. The group that received the niacin/simvastatin combination exhibited the greatest benefit. For the angiographic primary end point, which was the change in severity of the most severe stenosis in 9 proximal coronary segments, regression in stenosis was observed in patients receiving niacin/simvastatin treatment (−0.4% stenosis change) versus patients receiving placebo (+3.9% stenosis change; $P < 0.005$).⁶⁴ Interestingly, some of that benefit in stenosis regression was lost in the patients who received

antioxidant vitamins in addition to the niacin/simvastatin combination (+0.7% stenosis change), though the change was still significantly different from the placebo group ($P < 0.005$).⁶⁴ The clinical results from HATS exactly mirrored the changes observed through angiography. That is, the worst clinical results occurred in the placebo arm, the best clinical results occurred in the niacin/simvastatin combination therapy arm, and some of the benefit conferred by the niacin/simvastatin combination therapy was lost by adding antioxidant vitamins to the treatment regimen. The composite clinical end point of death from coronary causes, confirmed MI or stroke, or revascularization was reduced by 90% in patients treated with niacin/simvastatin versus placebo ($P = 0.03$).⁶⁴ Patients who also received antioxidant vitamins showed no significant change in clinical endpoints.⁶⁴ The authors concluded that the addition of niacin to simvastatin

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

therapy in CAD patients with low HDL-C levels and normal LDL-C levels resulted in slight coronary atherosclerosis regression and a significant reduction (90%) in clinical coronary events over 3 years.⁶⁴ Interestingly, more in-depth analyses of the data from HATS revealed that patients receiving antioxidant vitamins in addition to niacin/simvastatin therapy had a blunted HDL-C increase.⁶⁶ Therefore, those patients did not have as large an increase in HDL-C as did those patients who received only niacin/simvastatin, which provides further evidence of the importance of HDL-C in reducing cardiovascular events and its antiatherogenic properties. Several studies have reported similar effects of antioxidant vitamins on HDL-C.^{67,68}

Although the HATS study provided noteworthy data, the study did not use a statin monotherapy group with which a niacin/statin combination therapy could be compared. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trials sought to fill this gap. These trials were based on carotid intima-medial thickness (CIMT) as the surrogate marker of atherosclerosis, which involved an examination of the thickness of the innermost lining of the carotid artery. ARBITER 2 was a double-blind, randomized, placebo-controlled study of once-daily 1,000 mg of extended-release (ER) niacin added to background statin therapy in 167 patients with known CHD and low levels of HDL-C (<45 mg per dL).⁶⁹ The background statin in the study was at the discretion of each patient's primary care physician. Thus, the 2 groups in the trial were placebo/statin and niacin ER/statin. Trial participants were then followed for 12 months, after which time the primary end point of CIMT change (in mm) was assessed. The change in CIMT during the 12 months of the trial was 0.044 mm in the placebo/statin group ($P<0.001$) and 0.014 mm in the niacin ER/statin group ($P=0.23$), though the overall difference in CIMT progression between the placebo/statin group and niacin ER/statin group was not statistically significant ($P=0.08$). Clinical cardiovascular events, defined as a composite of hospitalization for an ACS, stroke, an arterial revascularization procedure, or sudden cardiac death, occurred in 3 patients treated with niacin ER/statin combination therapy and in 7 patients treated only with a statin ($P=0.20$).⁶⁹ In both therapeutic conditions, either placebo/statin or niacin ER/statin, an increase in CIMT was observed, but the increase in CIMT tended to be greater in the placebo/statin group than in the niacin ER/statin group.

At the conclusion of the ARBITER 2 trial, the investigators continued the trial with ARBITER 3, which was a prespecified 12-month extension study of ARBITER 2 that included 130 patients who had completed the blinded 12-month end point CIMT assessment. Participants in ARBITER 3 were placed on open-label niacin ER, such that patients initially randomized to the niacin ER/statin group continued on this combination therapy and received niacin ER/statin for the entire 2-year duration of the studies. Similarly, those patients who were initially randomized to the placebo/statin group were switched to niacin ER/statin

combination therapy. In ARBITER 3 a prespecified end point was the within group changes in mean CIMT across 3 different treatment groups. The groups included patients receiving placebo/statin for 12 months ($n=61$), niacin ER/statin for 12 months ($n=78$ subjects from ARBITER 2 and 47 subjects crossing over from placebo in ARBITER 2 to niacin ER in ARBITER 3), and niacin ER/statin for 24 months ($n=57$ subjects spanning both ARBITER 2 and ARBITER 3). Among the 125 patients treated with niacin ER/statin for 12 months, there was a significant regression in CIMT (-0.027 mm; $P<0.001$ vs. placebo/statin), shown in Figure 7. Similarly, among the 57 patients treated with niacin ER/statin for 24 months, there was a significant regression in CIMT (-0.041 mm; $P<0.001$ vs. placebo/statin). Thus, when niacin ER was added to statin therapy, there was a significant regression in atherosclerosis as measured by CIMT after both 12 and 24 months of treatment.⁷⁰ In patients with diabetes or the metabolic syndrome ($n=62$), there was also a significant regression in CIMT (-0.046 mm; $P<0.001$ vs. placebo/statin) with niacin ER/statin after 12-24 months of treatment versus statin monotherapy.⁷⁰ Therefore, the ARBITER trials provide additional evidence to support the promise of long-term combination therapy in reducing cardiovascular risk. Overall, in terms of niacin/statin combination therapy safety, the National Lipid Association (NLA) Safety Task Force concluded that the 2 decades of clinical evidence since the introduction of statins do not support a general myopathic effect of niacin either alone or in combination with statins. In fact, no major clinical trial has suggested a potential drug interaction between statins and niacin, and there is no proposed theoretical mechanistic reason to expect a drug interaction.⁵⁸

When all of the evidence addressing various lipid parameters and cardiovascular risk is considered, it is clear that lipid management should not be limited to statin monotherapy. Rather, achieving multiple lipid targets and reducing cardiovascular risk should be about statins and additional therapeutic agents to further reduce cardiovascular risk by targeting lipid parameters beyond LDL-C. Current, ongoing clinical trials will augment the already substantial catalog of knowledge about atherogenic lipid species and treatments thereof. The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High TG and Impact on Global Health Outcomes (AIM-HIGH) study has enrolled approximately 3,300 men and women with vascular disease (CHD, cardiovascular disease, peripheral artery disease [PAD]) and atherogenic dyslipidemia (TG level >150 mg per dL and HDL-C level <40 mg per dL).⁷¹ A 4-year median follow-up is planned for this trial that started in September 2005. Patients enrolled in AIM-HIGH will be treated either with a combination therapy of niacin ER (2,000 mg) and simvastatin (40 mg) or simvastatin monotherapy. As a therapeutic target, the LDL-C goal level is <80 mg per dL, and the primary outcome is the first major cardiovascular event.⁷¹ The Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) has enrolled approximately 20,000 patients with preexisting ath-

Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

erosclerotic vascular disease (cardiovascular disease, CHD, PAD) and began in January 2007. Patients in this trial, which includes a planned 4-year follow-up, will be assigned to combination therapy with niacin ER/laropiprant (2,000 mg) and simvastatin (40 mg) or simvastatin monotherapy. Some patients may also receive ezetimibe (10 mg) to reach optimal LDL-C levels. The LDL-C target level for all groups is <77 mg per dL. The primary outcome in HPS2-THRIVE is the first major vascular event.^{72,73} The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol-HDL and LDL Treatment Strategies (ARBITER 6-HALTS) trial, which began enrolling participants in November 2006, involves approximately 400 patients with CHD or CHD equivalents who have achieved an LDL-C goal <100 mg per dL and who have a reduced HDL-C level (<50 mg per dL for men and <55 mg per dL for women). Patients on statin monotherapy will be assigned to either intensified LDL-C-lowering therapy with ezetimibe (10 mg per day) or HDL-C-raising therapy with niacin ER (≥1,000 mg per day, titrated to maximum tolerable dose up to 2,000 mg per day). The primary end point is mean CIMT change after 14 months.⁷⁴

Summary

Several lipid parameters, such as LDL-C, TG, HDL-C, and atherogenic remnant lipoproteins, are strongly associated with atherosclerosis and heightened cardiovascular risk. The primary therapeutic target is LDL-C, and lipid-lowering therapy with statins has proved to be highly beneficial for reducing cardiovascular event rates. However, a substantial amount of residual cardiovascular risk remains in patients treated with statins, even intensive statin therapy, to reduce LDL-C levels. As a result, there has been an increased focus on elevated TG levels and low HDL-C levels and their significant contributions to residual cardiovascular risk even when LDL-C levels are well controlled. In response to the increasing importance of an array of lipid parameters, several noteworthy sets of national guidelines have been published. All of the guidelines report that elevated LDL-C is the primary therapeutic target. However, these guidelines also recommend that combination therapy may be necessary to achieve multiple lipid targets, including LDL-C, non-HDL-C, HDL-C, and TG. Niacin has been demonstrated to exert beneficial effects in this regard; niacin promotes significant increases in antiatherogenic HDL-C and, consequently, reduces cardiovascular risk. Significantly, the benefits conferred by statins through the reduc-

FIGURE 7 Carotid Intima-Medial Thickness With Statin Monotherapy and Combination Therapy

In 125 patients treated with extended-release niacin (niacin ER) for 12 months, analysis of variance (ANOVA) revealed a significant regression of carotid intima-medial thickness (CIMT; -0.027 ; $P<0.001$ vs. statin monotherapy). In 57 patients treated with niacin ER for 24 months, ANOVA revealed a significant regression of CIMT (-0.041 ; $P<0.001$ vs. statin monotherapy). In patients with the metabolic syndrome (Met-S) or diabetes ($n=62$), ANOVA revealed a significant regression of CIMT (-0.046 ; $P<0.001$) in statin plus niacin ER versus statin monotherapy after 12-24 months of treatment.⁷⁰

^a $P<0.001$ versus statin monotherapy; 92.3% of patients were on simvastatin; mean dose was 36 mg per day of simvastatin, and all patients received 1,000 mg of niacin ER.

tion of LDL-C levels are additive to the benefits of raising HDL-C levels with niacin. By combining niacin with the LDL-lowering therapy of statins, several atherogenic lipid abnormalities are addressed, the progression of atherosclerosis in CHD patients is slowed, and residual cardiovascular risk is reduced. Moreover, niacin/statin combination therapy appears to be safe and may be necessary to optimally reduce cardiovascular risk in high-risk patients. The completion of several ongoing clinical outcome trials, such as AIM-HIGH, HPS2-THRIVE, and ARBITER 6-HALTS, will provide important data that should continue to expand and refine therapeutic strategies targeting dyslipidemia and cardiovascular disease.

The Impact of Residual Cardiovascular Risk in Combination Lipid-Modifying Therapy in the Managed Care Setting

Robert L. Talbert, PharmD, FCCP, BCPS, CLS

When considering combination lipid-modifying therapy in the managed care setting, the focus is somewhat different than an academic discussion of clinical trials and national treatment guidelines; there should be a greater emphasis on economic considerations involved with the management of cardiovascular risk. Rather than an examination of the efficacy of statins in reducing low-density lipoprotein cholesterol (LDL-C), for example, the issue becomes one of improving the cost-effectiveness of statin therapy. Taking into account both long-term medical costs and short-term pharmaceutical costs may be a difficult balancing act, but it is one that concerns managed care professionals on a daily basis. One way in which long-term medical costs could be better controlled is through the targeted use of appropriate therapeutic agents in high-risk populations. As a part of a medication therapy management program (MTMP), a medical provider statin initiation program began with the goal of investigating whether the providers, when supplied with educational materials, would prescribe statins to their untreated, high-risk patients.⁷⁵ The providers for the patients included in the intervention group (n=1,144) were sent educational materials and a list of their patients with coronary artery disease (CAD) or diabetes, who were not receiving statins. A control group (n=700) consisted of people who did not meet MTMP criteria. During the 4-month intervention period, 138 patients (12.1%) in the intervention group started treatment with a statin versus 51 patients (7.3%) in the control group ($P=0.001$). Patients in the intervention group were 65% more likely (odds ratio [OR]=1.65; $P=0.006$) to start statin therapy than were patients in the control group.⁷⁵ This study demonstrated that medical providers can be educated to consider initiating therapy. In this instance, there was an increase in the number of high-risk individuals treated with statins, which may, in the long-term, decrease incidence of costly cardiovascular events.

Treatment adherence addresses similar issues, though from a different point of view. One measure of treatment adherence is medication possession ratio (MPR), which assesses the percentage of days during which a patient has the medication. The relationship between adherence to statin therapy (MPR during a 9-month period) and achievement of LDL-C goal levels (≤ 100 mg per dL) was studied in patients with diabetes or atherogenic dyslipidemia (n=653) in a managed care program.⁹ The average MPR was significantly higher for men than for women (0.75 vs. 0.66; $P<0.05$) and, overall, 44% (n=290) of the patients achieved an LDL-C level <100 mg per dL (52% of men and 37% of women; $P<0.05$). A significant correlation emerged between statin MPR and plasma LDL-C ($P<0.001$), and the MPR was significantly higher in patients who achieved the LDL-C target level than in those who did not (0.82 vs. 0.61; $P<0.05$).⁹ Adherence to statin therapy, as reflected by MPR, is closely related to LDL-C goal level attainment

in patients with diabetes and dyslipidemia. The probability of goal level achievement appears to increase substantially when the MPR is 0.80 (i.e., 80%) and so that is a potentially important MPR target in managed care. Because outcomes are directly related to patients' medication-taking behavior, when clinical goals such as serum cholesterol levels are not being reached, adherence should be assessed.⁹

Nevertheless, even when patients adhere to statin therapy, a substantial amount of residual cardiovascular risk remains. Additionally, the residual cardiovascular risk is associated with the magnitude of LDL-C reduction. The Cholesterol Treatment Trialists' (CTT) Collaborators reported on a prospective meta-analysis of data from 90,056 individuals in 14 randomized statin trials, as described previously. In a separate analysis of the CTT data, weighted estimates of effects on different clinical outcomes per 1 mmol per L (39 mg per dL) reduction in LDL-C were obtained.¹ During a mean follow-up of 5 years, 8,186 deaths were recorded and 14,348 individuals experienced major vascular events. There was a significant 23% proportional reduction in the incidence of first major coronary heart disease (CHD) events per 1 mmol per L (39 mg per dL) LDL-C reduction, in which 3,337 events occurred in patients receiving statins (7.4% CHD event rate) and 4,420 events occurred in patients receiving placebo (9.8% CHD event rate).¹ However, significant residual cardiovascular risk remained for patients treated with statins. Addressing this residual risk, which means addressing lipid parameters beyond LDL-C, should be the new target of lipid-modifying therapy. By achieving multiple lipid levels, thereby reducing residual cardiovascular risk, a long-term reduction in cardiovascular events, and the attendant costs, may be possible.

A recent study by Alsheikh-Ali et al. examined lipid levels and the use of lipid-altering drugs in a contemporary general medical population in which patients did not have documented CHD but had CHD risk equivalents, defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines as diabetes, peripheral artery disease (PAD), abdominal aortic aneurysm, or carotid artery disease complicated by a stroke or a transient ischemic attack (n=877).⁷⁶ Patients with documented CHD (n=635) were also included in the study. On the basis of the present national guidelines, the following lipid values were considered optimal for the patients with CHD risk equivalents: LDL-C level <100 mg per dL; high-density lipoprotein cholesterol (HDL-C) level ≥ 40 mg per dL (men) and ≥ 50 mg per dL (women); and non-HDL-C level <130 mg per dL when triglyceride (TG) levels are ≥ 200 mg per dL.¹⁸ Of the study participants with CHD risk equivalents, most did not meet optimal lipid targets for LDL-C (67%), HDL-C (66%), and non-HDL-C (71%), as shown in Figure 8. In fact, 88% of patients with CHD risk equivalents did not meet 1 or more of the guideline-established

lipid goals.⁷⁶ Statins were used by 57% of the patients, and lipid-altering drugs other than statins were rarely used in patients with CHD risk equivalents (4.7% used niacin, 5.7% used fibrates, and 2.2% used ezetimibe).⁷⁶ Specifically, in patients with low HDL-C levels (n=577), only 4.7% were taking niacin, 4.9% were taking a fibrate, and 0.9% were taking niacin and a fibrate. In patients with TG levels ≥ 200 mg per dL, only 9.5% were taking a fibrate, 8.2% were taking niacin, and 1.9% were taking niacin and a fibrate. This analysis highlights the dramatic need to further improve preventive measures in a substantial proportion of high-risk patients with CHD risk equivalents even though national guidelines urge the addition of niacin or fibrates to statins to achieve multiple lipid goals.^{18,76} Interestingly, the characteristics of individuals prescribed fibrates or extended-release niacin (niacin ER) differ significantly. Patients receiving initial niacin ER prescriptions were significantly older and more frequently male, had greater odds of a previous myocardial infarction (MI) diagnosis, and had greater previous use of beta-blockers and statins than did patients receiving initial fenofibrate prescriptions.⁷⁷

Consequences of Failing to Achieve Lipid Goals

A significant percentage of patients do not achieve their goal levels for LDL-C or other lipid parameters. Even though the primary focus of lipid-lowering therapy should be LDL-C, approximately 50% of those patients with known CHD do not achieve their LDL-C goal level.¹⁸ Among those with the metabolic syndrome, the percentage of patients who fail to achieve lipid goals increases to approximately 67%. To address the percentage of patients who fail to achieve lipid goals, as well as the potential outcomes from this failure, longitudinal, retrospective analyses of administrative claims data and laboratory results from a U.S. managed care organization were performed in 3 patient cohorts.⁷⁸ In cohort 1, LDL-C was not optimal at baseline. In cohort 2, LDL-C plus HDL-C or TG were not optimal at baseline. In cohort 3, LDL-C, HDL-C, and TG (i.e., all 3 lipid parameters) were not optimal at baseline. The analyses revealed that there was a difference in cardiovascular event-free survival between patients who achieved optimal lipid values (OLVs) for LDL-C and those who did not (hazard ratio [HR]=0.75; $P<0.001$) in patient cohort 1.⁷⁸ For patients in cohort 2, there was a large difference in cardiovascular event-free survival in patients who achieved OLVs for 2 lipid parameters (LDL-C and HDL-C or TG) versus those patients who did not (HR=0.54; $P<0.001$).⁷⁸ Patients in cohort 3 who achieved OLVs for all 3 lipid parameters (LDL-C, HDL-C, and TG), compared with those who did not (HR=0.54; $P=0.001$), showed the most striking difference in cardiovascular event-free survival.⁷⁸ These data emphasize the importance of achieving OLVs for all 3 lipid parameters (LDL-C, HDL-C, and TG) to maximize the reduction in cardiovascular events.⁷⁸

In a similar study, evaluating the risk of cardiovascular events, a retrospective cohort analysis was conducted using a 1.1-million-member managed care database.⁷⁹ In this analysis, the risk of

FIGURE 8 Significant Numbers of Patients Do Not Achieve Lipid Goals

Of the 877 patients with coronary heart disease (CHD) risk equivalents (96% had diabetes), most patients did not meet optimal lipid targets for low-density lipoprotein cholesterol (LDL-C) (67%), high-density lipoprotein cholesterol (HDL-C) (66%), and non-HDL-C (71%). Overall, 88% of patients did not meet ≥ 1 lipid goal (combined lipid goal).⁷⁶

Lipid goals: <100 mg per dL LDL-C; ≥ 40 mg per dL HDL-C (men); ≥ 50 mg per dL HDL-C (women); <130 mg per dL non-HDL-C (in patients with TG ≥ 200 mg per dL)

Reprinted from Am J Cardiol, 2006; 98(9):1231-33: Alsheikh-Ali AA, Lin JL, Abourjaily P, Ahearn D, Kuvlin JT, Karas RH. Extent to which accepted serum lipid goals are achieved in a contemporary general medical population with coronary heart disease risk equivalents.⁷⁶ (with permission from Elsevier)

experiencing cardiovascular events was compared between patients who attained combined OLVs (LDL-C, HDL-C, and TG) and patients who did not attain the OLVs. The patients in the study cohort (N=30,348) were naïve to lipid therapy, had been in the plan at least 12 months, and had a mean follow-up of 27 plus or minus 8 months. The OLVs for LDL-C, HDL-C, and TG in this study were established using the NCEP ATP III guidelines, and patients were placed into 1 of 4 groups: all 3 lipid parameters optimal, only 2 optimal, only 1 optimal, and none optimal at baseline.^{18,79} Although the baseline lipid values (LDL-C, HDL-C, TG, and total cholesterol) did not significantly differ among groups, patients who had experienced a cardiovascular event had a greater number of abnormal lipid values. During the follow-up period, there appeared to be only moderate improvement in lipid values and, therefore, achievement of OLVs. Stanek et al. demonstrated that the TG target was achieved most frequently and was stable over time at approximately 75%.⁷⁹ Achievement of HDL-C goal levels was also frequent and stable at approximately 65%. Thus, although TG and HDL-C targets were attained with regularity, the rate did not improve during

FIGURE 9 Optimal Lipid Values and Cardiovascular Event Rate

The presence of a single nonoptimal lipid value slightly increased cardiovascular (CV) event risk (odds ratio [OR]=1.06; 95% confidence interval [CI]=0.95-1.18), whereas 2 or all 3 nonoptimal lipid values significantly increased the risk of a CV event (OR=1.22; 95% CI=1.08-1.37; and OR=1.45; 95% CI=1.24-1.68, respectively; $P<0.05$ vs. all 3 optimal lipids using multivariate logistic regression).⁷⁹

Optimal lipid values: low-density lipoprotein cholesterol level <130 mg per dL (elevated risk primary prevention) or <100 mg per dL (CHD), high-density lipoprotein cholesterol level >40 mg per dL, and triglyceride level <200 mg per dL; $n=30,348$.

follow-up. In terms of LDL-C, goal level achievement improved from approximately 30% of patients to close to 40% of patients during follow-up. Even lower than LDL-C goal achievement was attainment of combined lipid targets; during the follow-up, achievement of combined OLVs occurred in approximately 13% of patients and increased to only approximately 20%. It is apparent from these results that management of all three major lipid levels remains a challenge.⁷⁹

In another analysis of these data, as shown in Figure 9, patients were placed into 1 of 4 groups at baseline: all 3 lipid parameters optimal, 2 lipid parameters optimal, 1 lipid parameter optimal, or no optimal lipid parameters.⁷⁹ The definition of a cardiovascular event included diagnosis of ischemic heart disease, PAD, stroke/transient ischemic attack, or a revascularization procedure. Odds ratios (ORs) for a cardiovascular event associated with attainment of each optimal lipid parameter were determined from 5,955 cardiovascular events that occurred in 4,059 (13%) study patients. The presence of a single nonoptimal lipid value slightly increased cardiovascular event risk (OR=1.06; 95% confidence interval [CI]=0.95-1.18), whereas 2 or all 3 nonoptimal lipid values significantly increased the risk of a cardiovascular event (OR=1.22; 95% CI=1.08-1.37; and OR=1.45; 95% CI=1.24-1.68, respectively; $P<0.05$ vs. all 3 optimal lipid values). By not attaining combined OLVs, the risk of cardiovascular events was independently and significantly increased in this large at-risk

population during approximately 68,283 patient-years of follow-up. The combination of failing to achieve optimal LDL-C with failing to achieve optimal HDL-C or TG values, or both, increased the adjusted risk of cardiovascular events by 22%-45%. These data provide evidence for focusing therapeutic strategies on assessment and management of multiple lipid abnormalities, rather than on a single lipid abnormality.⁷⁹

According to the 2008 ADA guidelines, the primary goal is an LDL-C level <100 mg per dL in individuals without overt cardiovascular disease, though a lower LDL-C goal (<70 mg per dL) is an option in individuals with overt cardiovascular disease.⁵⁴ Additionally, the ADA recognizes serum TG concentration as a surrogate measure for atherogenic TG-rich lipoproteins and suggests a TG goal level of <150 mg per dL.⁵⁴ Finally, the ADA standards suggest an HDL-C goal levels of >40 mg per dL in men and >50 mg per dL in women. Based on these guidelines, it is apparent that achieving multiple lipid targets in patients with type 2 diabetes is of great importance. In association with type 2 diabetes, medical costs increase as a function of disease severity. Patients with diabetes followed in a diabetes clinic under a managed care plan ($n=697$) were grouped according to severity of illness and care requirements.⁸⁰ Severity of illness correlated with total medical and pharmaceutical costs. Patients were grouped according to severity of illness in 6 areas: glycemic control, cardiovascular disease, peripheral vascular disease/peripheral neuropathy, retinopathy, renal disease, and autonomic neuropathy. Patients in high- and very high-risk categories for cardiovascular disease, among other diabetes-related disease states, had markedly increased medical costs versus those patients in low-risk categories.⁸⁰ Additionally, although the magnitude of the increase was much smaller and pharmaceutical costs remained reasonably similar across groups, drug costs were also significantly greater for patients in the very high-risk category. Patients who were in multiple high- and very high-risk categories had dramatically increased medical costs, as much as 10 times greater than those for patients who were in none of these categories.⁸⁰ These findings indicate that people are having costly cardiovascular-related procedures, which drive the overall cost of treatment. The pharmaceutical costs, according to this study, do not increase dramatically across risk groups, and considerations beyond drug cost should be taken into account.

Studies by Cziraky et al. and Simko et al. further address attainment of lipid goals and their relationship with cardiovascular events and costs through longitudinal, retrospective analyses conducted using administrative claims data and laboratory results.^{81,82} Target lipid levels were established according to the NCEP ATP III guidelines, lipid goal attainment was determined in patients with and without diabetes, and the effects of lipid goal attainment on cardiovascular events and cost were determined.^{18,81,82} In the first analysis, a total of 10,303 patients with type 2 diabetes and 42,475 patients without type 2 diabetes were evaluated for lipid goal attainment over a mean follow-up

of 27 plus or minus 10 months. The baseline characteristics indicated that patients with diabetes had more severe cardiovascular disease and more comorbidities, whereas patients without diabetes had a lower incidence of hypertension and CHD.⁸¹ Achievement of OLVs was analyzed during the follow-up period, which showed a fairly large difference between patients with diabetes and those without diabetes. Over the follow-up, patients with diabetes were less likely to reach combined OLVs at 12 months (OR=0.76; 95% CI=0.71-0.82), 24 months (OR=0.80; 95% CI=0.75-0.85), 36 months (OR=0.82; 95% CI=0.74-0.90), and 48 months (OR=0.77; 95% CI=0.64-0.92) postindex event, compared with patients without diabetes.⁸¹ Thus, this retrospective analysis revealed that achievement of combined OLVs in patients with diabetes is suboptimal, which may be related to the undertreatment of all components of the lipid panel in such patients.⁸¹

Further analysis of the same database evaluated the effects of attaining multiple lipid values on cardiovascular event rates and costs. In this study, the population (n=52,778) included both the diabetic and nondiabetic patients who were previously assessed separately.⁸² There was a significant difference in the proportion of patients who experienced ischemic heart disease or any cardiovascular event between those who achieved combined OLVs (n=10,645) for LDL-C, HDL-C, and TG and those who did not (n=42,133; $P<0.05$, Figure 10).⁸² The observed incidence of PAD and stroke between groups was not significantly different. The differences between those patients who achieve OLVs and those who do not are also reflected in medical costs. As Figure 11 shows, patients achieving combined OLVs (n=10,645) for LDL-C, HDL-C, and TG showed a 9% reduction in annual cardiovascular-related costs per patient per year, compared with patients not achieving all 3 goals (n=42,133) (OR=0.91; 95% CI=0.85-0.95; $P<0.05$). In conclusion, achieving multiple OLVs was associated with a reduced risk of cardiovascular events as well as lower associated health care costs. Adherence to lipid treatment guidelines to reduce residual risk benefits patients by reducing the risks of cardiovascular events and the health care system by lowering the overall cost.⁸²

Model-Based Analyses of Pharmacotherapy

In these analyses, presented at various conferences, mathematical models were used to predict the effects of niacin ER in combination with simvastatin on lipid parameters in patients enrolled in managed care plans. The estimates of patients achieving lipid goals were modeled according to individual patient baseline lipid values, as determined by a full lipid panel and the current product labeling, assuming additive effects of niacin ER and simvastatin on lipid values. Therefore, the results obtained through these models express the average change that would be expected to occur. These modeling analyses were conducted on information gathered from patients selected from a 2.1-million-patient managed care database. From these records, OLV attainment

FIGURE 10 Predicted Cardiovascular Events as a Function of Optimal Lipid Values

Between patients achieving combined optimal lipid values (OLVs) for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (n=10,645) and those who did not achieve all 3 combined OLVs (n=42,133), there was a significant difference in the proportion of patients experiencing ischemic heart disease (IHD) and any cardiovascular (CV) event (multivariate analysis; $P<0.05$).⁸²

n=52,778.

PAD=peripheral artery disease.

FIGURE 11 Predicted Annual Cardiovascular Costs

Patients achieving combined optimal lipid values (OLVs) for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (n=10,645) had a 9% reduction in annual cardiovascular-related costs per patient per year, compared with patients not achieving all 3 goals (n=42,133) (odds ratio=0.91; 95% confidence interval=0.85-0.95; $P<0.05$ by logistic regression).⁸²

CVD=cardiovascular disease.

TABLE 1 Baseline Lipid Values and OLVs in Population Modeling Studies

Lipid Parameter	OLVs ^a	Met Syn ^b	DM ^c	Cardiovascular Events ^d
LDL-C	<130/<100 ^e	131	125	131
HDL-C	>40/>50	43	47	48
Triglycerides	<150	188	160	159
Non-HDL-C	<160/<130	169	157	163
Total cholesterol		212	204	211

^aThird Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-21.¹⁸

^bStanek EJ, Quimbo RA, Cziraky MJ, Weathermon RA, Charland SL. Population-based response estimates for extended-release niacin/simvastatin versus other high-potency dyslipidemia therapy in patients with the metabolic syndrome. (poster) Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference. Chicago, IL; 2007. Abstract P438.²²

^cStanek EJ, Charland SL, Weathermon RA, Quimbo RA, Cziraky MJ. Diabetes mellitus population modeling of lipid goal achievement with extended-release niacin/simvastatin versus other high-potency agents. (poster) American Diabetes Association 67th Scientific Sessions. Chicago, IL; 2007. Abstract 2445-PO.²¹

^dCharland SL, Quimbo R, Cziraky MJ, Weathermon RA, Stanek EJ. Modeled achievement of optimal lipid values and associated cardiovascular event rates with extended-release niacin/simvastatin, ezetimibe/simvastatin, and individual agents in a managed care population. (poster) *Value Health*. 2007;10:A56.²⁰

^eAn LDL-C level ≤ 70 mg per dL may be a desirable goal in patients with known coronary artery disease and multiple poorly controlled risk factors.

Lipid values are expressed in mg per dL.

DM=diabetes mellitus; Met Syn=metabolic syndrome; OLV=optimal lipid value.

models were constructed for patients with metabolic syndrome or diabetes, and for the effects of OLV achievement on cardiovascular event rates.²⁰⁻²²

In the population modeling study of lipid goal achievement in metabolic syndrome patients (n=23,773), effects were simulated for various lipid-modifying therapies.²² The pharmaceutical treatments compared were niacin ER/simvastatin (2,000 mg/40 mg) combination therapy, atorvastatin (80 mg), simvastatin (80 mg), simvastatin/ezetimibe (80 mg/10 mg) combination therapy, and rosuvastatin (40 mg). Table 1 shows the baseline lipid values for the patients included in the metabolic syndrome study, and the defined OLVs.¹⁸ The model revealed that, under baseline conditions (i.e., no pharmaceutical therapy), only 4% of people could be expected to achieve OLVs.²² The model further showed that atorvastatin (80 mg; 30.9%), simvastatin (80 mg; 31.1%), simvastatin/ezetimibe (80mg/10mg; 32.1%), and rosuvastatin (40 mg; 39.6%) would produce comparable effects on OLV achievement. However, when considering the niacin ER/simvastatin combination therapy, the model showed that 55.2% of patients would be expected to achieve the OLVs. The percentage with niacin ER/simvastatin was found to be significantly greater than those percentages calculated for atorvastatin, simvastatin, simvastatin/ezetimibe, and rosuvastatin (all $P<0.05$).²² According to these results, even the most potent statin produces a more than 15%

lower OLV achievement than that with niacin ER/simvastatin combination therapy.

Somewhat similar results were seen in a modeling study of patients with diabetes (n=8,164). Table 1 shows the baseline lipid values for the patients included in this model. As in the metabolic syndrome model, the model treatments were niacin ER/simvastatin (2,000 mg/40 mg) combination therapy, atorvastatin (80 mg), simvastatin (80 mg), simvastatin/ezetimibe (80 mg/10 mg) combination therapy, and rosuvastatin (40 mg).²¹ The model showed that, at baseline (no pharmacological therapy), only 7.4% of patients with diabetes would be expected to meet all OLVs. In this patient population, all of the potential drug treatments were found to be more effective in attaining OLVs than in metabolic syndrome patients. Again, the modeled percentage of patients achieving OLVs with niacin ER/simvastatin combination therapy (62.8%) was significantly greater ($P<0.05$ for all between treatment comparisons) than the percentages calculated with atorvastatin (45.4%), simvastatin (41.9%), simvastatin/ezetimibe (45.9%), or rosuvastatin (52.3%). In patients with type 2 diabetes, the niacin ER/simvastatin combination therapy was projected to result in 10% more patients attaining OLVs than with rosuvastatin.²¹

The final population modeling study of interest in this discussion examined the achievement of OLVs and cardiovascular event reduction as a consequence of various pharmacologic interventions, including niacin ER/simvastatin and simvastatin/ezetimibe, as well as niacin ER, simvastatin, and ezetimibe monotherapies.²⁰ In this model, cardiovascular risk and cardiovascular events were identified for each patient (n=44,351) and the population cardiovascular event rate during the follow-up (30 plus or minus 12 months) was calculated to be 15.2% (OR=0.69; CI=0.61-0.81), which places these patients at high risk according to Framingham score prediction. Achievement of OLVs (18% of patients) versus nonachievement of OLVs (82%) was used to estimate the cardiovascular event rates associated with OLV achievement.²⁰ Table 1 shows baseline lipid values and OLVs.²⁰ Figures 12 and 13 show the results from these models. Figure 12 shows the hypothetical achievement of OLVs with the different treatments. In this model, as in the models described previously, niacin ER/simvastatin combination therapy yielded a significantly greater percentage of patients (66.2%) who could be expected to achieve OLVs, compared with other treatments in the model ($P<0.05$ compared with simvastatin/ezetimibe, niacin ER, and simvastatin) due to the additive beneficial effects expected with the combination of niacin with the statin.²⁰ Additionally, ezetimibe monotherapy was expected to result in a much lower percentage of patients achieving OLVs than the other treatments. In several trials, ezetimibe has been demonstrated to reduce LDL-C levels by approximately 18%. Compared with statins, ezetimibe is less potent and has little or no effect on either TG or HDL-C levels, so it is not surprising that OLV attainment is likely to be lower under this therapeutic condition.²⁰ Figure 13 shows the relative risk reductions associated with the different therapies.

Under baseline conditions the cardiovascular event rate is estimated to be 15.2%, whereas a relative risk reduction is observed across all of the interventions studied. The largest risk reduction (38%) occurred under the niacin ER/simvastatin treatment condition, in which the 15.2% baseline cardiovascular event rate was reduced to 9.4%, which was significantly different from the cardiovascular event reductions calculated for the other treatment conditions ($P < 0.05$ vs. simvastatin/ezetimibe, niacin ER, and simvastatin).

A separate modeling study examined the effects of niacin ER/simvastatin combination therapy on the medical costs of CHD events. These medical costs during a 5-year period were projected based on data gathered from clinical trials, national databases, and published literature, and took into account emergency, inpatient, and outpatient costs.²³ These models were based on hypothetical cohorts of 10,000 patients with CHD who had any abnormal lipid values for LDL-C, HDL-C, TG, and non-HDL-C. Therapeutic agents in the models included simvastatin monotherapy at various doses or fixed-dose combination (FDC) niacin ER/simvastatin. Direct medical costs were expressed in dollars with an annual discount rate of 3%.²³ The modeled medical costs are shown in Table 2. Compared with simvastatin monotherapy (20 mg), the low-dose niacin ER/simvastatin combination therapy (1,000 mg/20 mg) yields an 8.8% reduction in costs. At the highest dose of niacin ER/simvastatin (2,000 mg/40 mg) combination therapy, an 11% reduction in cost was calculated compared with simvastatin monotherapy (80 mg). Therefore, in terms of pharmaceutical costs, niacin ER/simvastatin FDC results in a noteworthy cost savings.²³

Fixed-Dose Niacin ER/Simvastatin Combination Therapy

For many chronic conditions, such as hypertension, dyslipidemia, and diabetes, adequate therapy is typically not achieved through the use of just one drug. Instead, multiple drug therapies must often be used to target multiple risk factors or disease-associated complications. For example, patients with diabetes must often be managed through a combination of lipid-lowering therapies, anti-hypertensives, and hypoglycemic medications; as the number of drugs required increases, so does the treatment cost.²⁴ Therefore, potentially beneficial methods to address drug number include the combination of 2 or more drugs in a single capsule or tablet and the development of individual drugs that address multiple risk factors. Both of these approaches should reduce pharmaceutical costs.²⁴ Using FDC therapy reduces the number of pills (i.e., pill burden), simplifies the dosing regimen, and ensures that the correct dosage of each component is taken.^{83,84} FDC therapy also improves medication compliance, which is often associated with enhanced outcomes.^{83,84}

Evidence for benefits conferred by a FDC therapy has been reported from a prescription database analysis that examined patients (n=6,206) taking the same 2 antihypertensive drugs

FIGURE 12 Modeled Achievement of OLVs

Optimal lipid values (OLVs) are defined as low-density lipoprotein cholesterol level <130/100 mg per dL per risk level, high-density lipoprotein cholesterol >40 mg per dL in men (50 mg per dL in women), triglyceride level <150 mg per dL, and non-HDL-C level <160/130 mg per dL per risk level. The percentage of patients predicted to achieve OLVs with extended-release niacin (NER)/simvastatin (S) combination therapy was significantly greater than those percentages for other treatments.

^a $P < 0.05$ versus S/E, NER, and S by chi-square; N=44,351.

E=ezetimibe.

FIGURE 13 Modeled Cardiovascular Event Rate Reduction^a

The relative risk reduction with extended-release niacin (NER)/simvastatin (S) combination therapy was predicted to be significantly greater than for other treatments.

^aCharland SL, Quimbo R, Cziraky MJ, Weathermon RA, Stanek EJ. Modeled achievement of optimal lipid values and associated cardiovascular event rates with extended-release niacin/simvastatin, ezetimibe/simvastatin, and individual agents in a managed care population. (poster) Value Health. 2007;10:A56.²⁰

^b $P < 0.05$, compared with S/ezetimibe (E), NER, and S by chi-square; n=44,351.

CVD=cardiovascular disease; RRR=relative risk reduction versus baseline CVD event rate.

TABLE 2 Reduced Costs With Niacin ER/Simvastatin^a

Treatment Comparisons	Cost Reduction With NER/S
S20 vs. NER/S (1,000 mg/20 mg)	8.8%
S40 vs. NER/S (1,000 mg/40 mg)	9.1%
S80 vs. NER/S (2,000 mg/40 mg)	11.2%

^aDirect medical costs of coronary heart disease events, expressed in \$U.S. 2006, over 5 years.

ER=extended release; NER=niacin ER; S=simvastatin.

FIGURE 14 Fixed-Dose Combination Therapy Improves Adherence Rates

As shown on the left, in the patients receiving monotherapy ($n=1,815$) who required the addition of the alternative agent, resulting in combination therapy with 2 separate drugs, adherence rates were significantly lower (54.0%) than in the patients receiving monotherapy ($n=105$) who were switched to fixed-dose combination (FDC) therapy (77.0%; $P<0.001$ vs. combination therapy with 2 separate drugs by analysis of covariance [ANCOVA]).⁸⁶ As shown on the right, patients receiving combination therapy as 2 separate drugs who were switched to FDC therapy ($n=59$) had a significant improvement in adherence after the switch (71.0% vs. 87.0%; $P<0.001$ by ANCOVA).

^a $P<0.001$ versus 2 separate drugs.

individually or as a FDC. Adherence patterns of patients were studied through a retrospective analysis of pharmacy claims from a managed care organization in the northeastern United States.⁸⁵ Overall, MPRs were significantly higher for the FDC than for the 2 separate drugs (88% vs. 69%, $P<0.001$), regardless of the number of concomitant drugs prescribed.⁸⁵ In addition, adherence rates were significantly higher in the FDC group during all 3-month assessment periods ($P<0.001$ for all comparisons). At 3 months, MPR was increased by approximately 10%; at 12 months, there was an MPR difference of approximately 20%. Thus, patients prescribed a FDC drug had possession of their medication for a significantly greater percentage of time over the 1-year follow-up period than did patients prescribed 2 drugs

taken separately. As the number of concomitant drugs increased, the difference in the MPR between the 2 treatment groups increased in favor of the FDC drug, which suggests that it would be advantageous to use FDCs more frequently.⁸⁵

A similar study analyzed the effect of switching between separate drug therapies and FDC therapies on medication adherence among patients with diabetes in a managed care organization. Medication adherence, defined as the sum of the days' supply of medication obtained by the patient during the follow-up period divided by the total number of days in the designated follow-up period (180 days), was evaluated through a retrospective database analysis of pharmacy claims. After adjustment for potential confounding factors, including overall medication burden at index, there were no significant differences in adherence rates in 6,502 newly treated patients receiving monotherapy, combination therapy, or FDC therapy.⁸⁶ However, as shown in Figure 14 (left panel), among the 1,815 previously treated patients receiving monotherapy who required the addition of the alternative agent, resulting in combination therapy with 2 separate drugs, adherence rates were significantly lower (54.0%) than in the 105 patients receiving monotherapy who were switched to FDC therapy (77.0%; $P<0.001$ vs. combination therapy with 2 separate drugs). As shown in Figure 14 (right panel), the 59 previously treated patients receiving combination therapy as 2 separate drugs who were switched to FDC therapy showed a significant improvement in adherence after the switch (71.0% vs. 87.0%; $P<0.001$).⁸⁶ Thus, previously treated patients receiving monotherapy who then required additional therapy showed significantly greater adherence when they were switched to FDC therapy, compared with combination therapy with 2 separate drugs. Furthermore, patients receiving combination therapy with 2 separate drugs who were switched to FDC therapy showed significantly greater medication adherence after the switch.⁸⁶

The Safety and Efficacy of Fixed Dose Niacin ER and Simvastatin Combination Therapy (SEACOAST) trial, which investigated niacin ER/simvastatin FDC therapy, has been recently published.^{25,26} This 24-week randomized clinical trial compared simvastatin monotherapy with a novel combination of niacin ER/simvastatin in patients with mixed dyslipidemia, as identified by elevated levels of non-HDL-C.^{25,26} After a simvastatin run-in phase during which patients received either 20 mg or 40 mg of simvastatin for at least 2 weeks, patients were assigned to either simvastatin low-dose groups (SEACOAST I) or simvastatin high-dose groups (SEACOAST II), which were determined by the final run-in simvastatin dose. Patients were then randomized to 1 of 3 treatment groups in each half of the study. In SEACOAST I, the treatment groups were simvastatin (20 mg), niacin ER/simvastatin (1,000 mg/20 mg), and niacin ER/simvastatin (2,000 mg/20 mg).²⁶ In SEACOAST II, which included more intensive lipid-modifying therapy during both the run-in phase and the 24-week trial phase, the treatment groups were simvastatin (80 mg), niacin ER/simvastatin (1,000 mg/

FIGURE 15

SEACOAST I: Efficacy of Niacin ER/Simvastatin Combination Therapy

Extended-release niacin (niacin ER)/simvastatin (1,000 mg/20 mg and 2,000 mg/20 mg) fixed-dose combination (FDC) therapies demonstrated significant, dose-related improvements in non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and lipoprotein A (Lp[a]), compared with simvastatin (20 mg) monotherapy, as revealed by nonparametric analyses.²⁶

^aP<0.05 versus simvastatin (20 mg).

^bP<0.001 versus simvastatin (20 mg).

40 mg), and niacin ER/simvastatin (2,000 mg/40 mg). The primary end point in SEACOAST was the median percent change in non-HDL-C during the period from baseline to week 24, beginning from the end of the simvastatin run-in.^{25,26}

In SEACOAST I, the niacin ER/simvastatin (1,000 mg/20 mg and 2,000 mg/20 mg) FDC therapies produced significant, dose-related improvements in non-HDL-C, HDL-C, TG, and lipoprotein A (Lp[a]), compared with simvastatin (20 mg) monotherapy.²⁶ Figure 15 shows a 22.5% reduction in non-HDL-C levels with high-dose niacin ER/simvastatin versus a 7.4% reduction with simvastatin monotherapy. Although there was a dose-related response in LDL-C level reduction, there were no significant differences between groups in this lipid parameter; simvastatin alone resulted in a 7.1% decrease in LDL-C levels, whereas high-dose niacin ER/simvastatin FDC therapy produced a 14.2% reduction. Perhaps the most interesting result was the 24.9% increase in HDL-C associated with high-dose niacin ER/

simvastatin. The FDC therapy would appear to confer a much greater benefit than most statin monotherapies, which provides further support for considering combination therapy to achieve multiple lipid targets. The results of SEACOAST I also showed substantial reduction of TG that, because of the niacin component of the FDC therapy, reached 38% in the high-dose group. Statins tend to have a TG-lowering effect, but this effect is generally proportional to the size of LDL-C reduction and depends on the baseline TG concentration and the dose or potency of the statin used. Finally, a substantial 25.0% reduction in Lp(a) was observed with the high-dose niacin ER/simvastatin treatment, whereas little change in Lp(a) was observed with simvastatin monotherapy, which is consistent with previous reports in the literature. Lp(a) is a lipoprotein particle that is not routinely measured, but is considered by many to be as atherogenic as LDL-C.

A similar pattern of results was seen in SEACOAST II, in which the primary end point was the median percent change from

FIGURE 16

SEACOAST II: Efficacy of Niacin ER/Simvastatin Combination Therapy

Extended-release niacin (niacin ER)/simvastatin (1,000 mg/40 mg and 2,000 mg/40 mg) fixed-dose combination (FDC) therapies were comparable to simvastatin (80 mg) monotherapy (double the simvastatin dose) in reduction of non-high-density lipoprotein cholesterol (non-HDL-C) levels. Both niacin ER/simvastatin (1,000 mg/40 mg and 2,000 mg/40 mg) FDC therapies resulted in significant, dose-related improvements in HDL-C, lipoprotein A (Lp[a]), and triglycerides (TG), compared with simvastatin (80 mg) therapy (double the simvastatin dose), as revealed by nonparametric analyses.²⁵ Simvastatin 40 mg at baseline.

^aComparable to simvastatin (80 mg).

^bP<0.01 versus simvastatin (80 mg).

^cP<0.001 versus simvastatin (80 mg).

baseline to week 24 in non-HDL-C (from a simvastatin [40 mg] run-in baseline). Figure 16 shows that the changes may appear to be somewhat more modest than those in SEACOAST I; however, the patients in SEACOAST II received more intensive statin therapy during the run-in phase of the study. A 17.1% reduction in the primary end point of non-HDL-C was seen with the high-dose niacin ER/simvastatin (2,000 mg/40 mg) FDC therapy versus a 10.1% reduction with simvastatin (80 mg) monotherapy, although this difference was not statistically significant. Decreases in levels of LDL-C were observed to be comparable across all treatment groups. Both fixed-dose niacin ER/simvastatin (1,000 mg/40 mg and 2,000 mg/40 mg) combination therapies resulted in significant, dose-related improvements in HDL-C, Lp(a), and TG levels, compared with simvastatin (80 mg) therapy.²⁵ Across these lipid parameters, simvastatin 80 mg monotherapy had essentially no

effect beyond that conferred by the 40 mg dose of simvastatin administered during the run-in phase.

To summarize the SEACOAST trial, niacin ER/simvastatin FDC therapy yielded significant improvements in levels of atherogenic (non-HDL-C, TG, and Lp[a]) and antiatherogenic (HDL-C) particles, compared with simvastatin monotherapy over a 24-week period. Treatment with niacin ER/simvastatin for 24 weeks was well tolerated with no unanticipated adverse effects. Only flushing/pruritus was significantly more frequent with niacin ER/simvastatin FDC therapy, compared with simvastatin monotherapy. There was no evidence of increased risk of hepatotoxicity or myopathy with niacin ER/simvastatin therapy. Overall, these data support the safe and efficacious use of niacin ER/simvastatin FDC therapy in a broad population of dyslipidemic patients to help them reach and maintain multiple OLVs.^{25,26}

■ Summary

Statins are often the initial pharmaceutical intervention for reducing LDL-C levels and cardiovascular event risk, and usage of statins in managed care populations may help to reduce the long-term costs associated with cardiovascular events. However, as demonstrated in the first article, residual cardiovascular risk remains after statin therapy, which can be linked to elevated levels of TG and non-HDL-C as well as low HDL-C. Studies modeling attainment of multiple lipid targets in managed care populations have demonstrated that the achievement of combined OLVs, rather than simply achieving a goal for LDL-C reduction, is predicted to be associated with a reduced risk of cardiovascular events and lower associated health care costs. Modeling studies also estimated that OLVs would be more

frequently achieved in managed care organization populations with niacin ER/simvastatin FDC therapy than with other high-potency agents and, subsequently, would provide significant reductions in projected cardiovascular event rates. Moreover, models indicated that lipid-modifying therapy with a niacin ER/simvastatin combination would be expected to reduce direct medical costs of CHD events more effectively than high-dose simvastatin monotherapy. Because one of the important factors in any treatment is medication adherence, FDC therapy may prove to be highly beneficial in treating multiple lipid abnormalities. Indeed, the SEACOAST clinical trial showed that a niacin ER/simvastatin FDC therapy produced significantly greater effects on various lipid parameters than did simvastatin monotherapy.

Conclusions

Mark J. Cziraky, PharmD, FAHA, CLS

Lipid-lowering treatment with statins has proven effective for reducing LDL-C levels and cardiovascular event risk, yet much more remains to be achieved in addressing the cardiovascular risk associated with other lipid fractions, including low HDL-C, high TG, and high non-HDL-C levels. Even with the advances in treating cardiovascular and atherogenic dyslipidemia, it is clear that further research is needed to determine the contributions to residual cardiovascular disease risk of these fractions and the mechanisms through which they exert their atherogenic effects or, in the case of HDL-C, antiatherogenic effects. In high-risk populations, such as patients with diabetes or the metabolic syndrome, it is especially important to reach treatment goals for multiple lipid parameters. Analyses of managed care databases suggest that attainment of OLVs across various patient groups is associated with lower cardiovascular event rates and significant cost savings. To achieve multiple lipid targets beyond LDL-C goals, national guidelines suggest adding niacin or a fibrate to a statin. Such therapy holds great promise for reducing the residual cardiovascular risk that remains even after intensive statin therapy due to the additive effects of niacin or a fibrate when combined with a statin. Investigations that have modeled the efficacy of a niacin ER/statin combination therapy have indicated increased achievement of OLVs and decreased cardiovascular risk, compared with other treatments, such as statin or niacin monotherapy. Additionally, models have suggested that a niacin ER/simvastatin combination therapy would result in a cost savings versus simvastatin monotherapy.

Concerns about combination therapies that have been raised include increased pill burden and increased cost as a consequence of multiple medications, which, in turn, may reduce treatment adherence. One method that can be used to avoid this issue is to include 2 or more medications in a single FDC therapy, and evidence indicates that adherence increases with such a combination. Therapeutically, clinical trial results have demonstrated the safety and efficacy of a niacin ER/simvastatin FDC therapy in addressing multiple lipid parameters; the SEACOAST trial showed that a niacin ER/simvastatin FDC decreased LDL-C, TG, non-HDL-C, and Lp(a) levels while simultaneously raising HDL-C levels. Taken together, it is possible that FDC therapies of this type could enhance treatment of dyslipidemia by addressing multiple lipid parameters in a cost-effective manner that promotes medication adherence through decreased pill burden. Additionally, the growing medical and pharmaceutical costs associated with cardiovascular disease and cardiovascular risk factors such as diabetes and metabolic syndrome lend an increased sense of urgency to managing the clinical and economic burden related to these diseases.

REFERENCES

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-78.
2. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371(9607):117-25.
3. Davidson MH. Overview of prevention and treatment of atherosclerosis with lipid-altering therapy for pharmacy directors. *Am J Manag Care*. 2007;13(Suppl 10):S260-69.
4. Killilea T, Funk L. Cost efficiency and formulary considerations for statin therapy. *Am J Manag Care*. 2006;12(Suppl 11):S325-31.
5. Hess G, Sanders KN, Hill J, Liu LZ. Therapeutic dose assessment of patient switching from atorvastatin to simvastatin. *Am J Manag Care*. 2007;13(Suppl 3):S80-85.
6. Meissner B, Dickson M, Shinogle J, Reeder CE, Belazi D, Senevirante V. Drug and medical cost effects of a drug formulary change with therapeutic interchange for statin drugs in a multistate managed Medicaid organization. *J Manag Care Pharm*. 2006;12(4):331-40. Available at: www.amcp.org/data/jmcp/formulary_management_331-340.pdf.
7. Ye X, Gross CR, Schommer J, Cline R, Xuan J, St Peter WL. Initiation of statins after hospitalization for coronary heart disease. *J Manag Care Pharm*. 2007;13(5):385-96. Available at: www.amcp.org/data/jmcp/JMCPMaga_June%2007_p385-396.pdf.
8. Gazmararian JA, Kripalani S, Miller MJ, Echt KV, Ren J, Rask K. Factors associated with medication refill adherence in cardiovascular-related diseases: a focus on health literacy. *J Gen Intern Med*. 2006;21(12):1215-21.
9. Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care*. 2005;28(3):595-99.
10. Insull W, Jr., Ghali JK, Hassman DR, JW YA, Gandhi SK, Miller E. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. *Mayo Clin Proc*. 2007;82(5):543-50.
11. Nag SS, Daniel GW, Bullano MF, et al. LDL-C goal attainment among patients newly diagnosed with coronary heart disease or diabetes in a commercial HMO. *J Manag Care Pharm*. 2007;13(8):652-63. Available at: www.amcp.org/data/jmcp/JMCPMaga_652-663.pdf.
12. Hoerger TJ, Ahmann AJ. The impact of diabetes and associated cardiometabolic risk factors on members: strategies for optimizing outcomes. *J Manag Care Pharm*. 2008;14(1 Suppl C):S2-18. Available at: www.amcp.org/data/jmcp/JMCPSuppC_Feb08.pdf.
13. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2008;117(4):e25-146.
14. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350(15):1495-04.
15. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425-35.
16. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294(19):2437-45.
17. Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. *Am J Cardiol*. 1996;77(14):1179-84.

References

18. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106(25):3143-21.
19. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-39.
20. Charland SL, Quimbo R, Cziraky MJ, Weathermon RA, Stanek EJ. Modeled achievement of optimal lipid values and associated cardiovascular event rates with extended-release niacin/simvastatin, ezetimibe/simvastatin, and individual agents in a managed care population. (poster) *Value Health*. 2007;10:A56.
21. Stanek EJ, Charland SL, Weathermon RA, Quimbo RA, Cziraky MJ. Diabetes mellitus population modeling of lipid goal achievement with extended-release niacin/simvastatin versus other high-potency agents. (poster) *American Diabetes Association 67th Scientific Sessions*. Chicago, IL; 2007. Abstract 2445-PO. Available at: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=55899.
22. Stanek EJ, Quimbo RA, Cziraky MJ, Weathermon RA, Charland SL. Population-based response estimates for extended-release niacin/simvastatin versus other high-potency dyslipidemia therapy in patients with the metabolic syndrome. (poster) *Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference*. Chicago, IL; 2007. Abstract P438. *Arterioscler Thromb Vasc Biol*. 2007;27(6):e114.
23. Zhang B, Friedman M, Charland SL, Burge RT, Simko RJ, Menzin J. A model-based analysis of the effects of intensifying lipid-altering therapy on direct medical costs of coronary heart disease events in a secondary prevention population in the United States. (poster) *Value Health*. 2007;10:A411.
24. Grundy SM. Drug therapy of the metabolic syndrome: minimizing the emerging crisis in polypharmacy. *Nat Rev Drug Discov*. 2006;5(4):295-309.
25. Ballantyne CM, Davidson MH, McKenney J, Keller LH, Bajorunas DR, Karas RH. Comparison of the efficacy and safety of a combination tablet of niacin extended-release and simvastatin with simvastatin 80 mg monotherapy: the SEACOAST II (high-dose) study. *J Clin Lipidol*. 2008;2:79-90.
26. Ballantyne CM, Davidson MH, McKenney J, Keller LH, Bajorunas DR, Karas RH. Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs. simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). *Am J Cardiol*. 2008;101:1428-36.
27. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-89.
28. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med*. 1998;339(19):1349-57.
29. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):7-22.
30. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615-22.
31. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*. 1996;335(14):1001-1009.
32. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301-07.
33. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46(7):1225-28.
34. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51(7):724-30.
35. Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. *Am J Cardiol*. 1991;67(15):1185-89.
36. Genest JJ, Jr., Martin-Munley SS, McNamara JR, et al. Familial lipoprotein disorders in patients with premature coronary artery disease. *Circulation*. 1992;85(6):2025-2033.
37. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among U.S. adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA*. 2002;287(3):356-59.
38. Berliner JA, Navab M, Fogelman AM, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation*. 1995;91(9):2488-96.
39. Assmann G, Nofer JR. Atheroprotective effects of high-density lipoproteins. *Annu Rev Med*. 2003;54:321-41.
40. Chapman MJ, Assmann G, Fruchart JC, Shepherd J, Sirtori C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid—a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin*. 2004;20(8):1253-68.
41. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;79(1):8-15.
42. Kannel WB. High-density lipoproteins: epidemiologic profile and risks of coronary artery disease. *Am J Cardiol*. 1983;52:9B-12B.
43. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837-47.
44. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease—the Framingham Heart Study. *Can J Cardiol*. 1988;4(Suppl A):5A-10A.
45. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357(13):1301-10.
46. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 western prospective studies. *Circulation*. 2007;115(4):450-58.
47. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161(11):1413-19.
48. Jiang R, Schulze MB, Li T, et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care*. 2004;27(8):1991-97.
49. Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, Grundy SM. Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. *Diabetes Care*. 2005;28(8):1916-21.
50. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294(3):326-33.
51. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98(10):1363-68.
52. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation*. 2002;106(20):2526-29.

References

53. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care*. 2007;30(1):162-72.
54. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(Suppl 1):S12-54.
55. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113(19):2363-72.
56. American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care*. 2007;30(Suppl 1):S4-41.
57. Brown WV. Expert commentary: the safety of fibrates in lipid-lowering therapy. *Am J Cardiol*. 2007;99(6A):19C-21C.
58. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol*. 2007;99(6A):22C-31C.
59. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357(21):2109-22.
60. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231(4):360-81.
61. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2005;95:254-57.
62. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med*. 1999;341(6):410-18.
63. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323(19):1289-98.
64. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345(22):1583-92.
65. Brown BG, Stukovsky KH, Zhao XQ. Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr Opin Lipidol*. 2006;17(6):631-36.
66. Zhao XQ, Morse JS, Dowdy AA, et al. Safety and tolerability of simvastatin plus niacin in patients with coronary artery disease and low high-density lipoprotein cholesterol (The HDL Atherosclerosis Treatment Study). *Am J Cardiol*. 2004;93(3):307-12.
67. Brown BG, Cheung MC, Lee AC, Zhao XQ, Chait A. Antioxidant vitamins and lipid therapy: end of a long romance? *Arterioscler Thromb Vasc Biol*. 2002;22(10):1535-46.
68. Cheung MC, Zhao XQ, Chait A, Albers JJ, Brown BG. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler Thromb Vasc Biol*. 2001;21(8):1320-26.
69. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation*. 2004;110:3512-17.
70. Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr Med Res Opin*. 2006;22(11):2243-50.
71. Cannon CP. Combination therapy in the management of mixed dyslipidaemia. *J Intern Med*. 2008;263(4):353-365.
72. HPS2-THRIVE: Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events. Available at: <http://controlled-trials.com/isrctn/pf/29503772>.
73. ClinicalTrials.gov. Treatment of HDL to Reduce the Incidence of Vascular Events HPS2-THRIVE. Available at: www.clinicaltrials.gov/ct2/show/NCT00461630.
74. Devine PJ, Turco MA, Taylor AJ. Design and Rationale of the ARBITER 6 Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol)-6-HDL and LDL Treatment Strategies in Atherosclerosis (HALTS). *Cardiovasc Drugs Ther*. 2007;21(3):221-25.
75. Stockl K, Tjioe D, Gong S, Stroup J, Harada A, Zhang S. Increased statin use in MTMP members with diabetes or coronary artery disease following implementation of a provider-based statin initiation intervention. (poster) *J Manag Care Pharm*. 2008;14(2):252. Available at: www.amcp.org/data/jmcp/JMCPMaga_March%2008_205-252.pdf.
76. Alsheikh-Ali AA, Lin JL, Abourjaily P, Ahearn D, Kuvlin JT, Karas RH. Extent to which accepted serum lipid goals are achieved in a contemporary general medical population with coronary heart disease risk equivalents. *Am J Cardiol*. 2006;98(9):1231-33.
77. Zachry W, Martin E, Hume A. Contrasting case-mix characteristics of patients treated with niacin extended release and fenofibrate in a large managed care dataset. *ASHP Midyear Clinical Meeting*. Las Vegas, NV; 2007.
78. Charland SL, Cziraky MJ, Quimbo R, et al. Achieving optimal lipid values in patients with dyslipidemia is associated with reduced risk of cardiovascular events. *J Clin Lipidol*. In press.
79. Stanek EJ, Sarawate C, Willey VJ, Charland SL, Cziraky MJ. Risk of cardiovascular events in patients at optimal values for combined lipid parameters. *Curr Med Res Opin*. 2007;23(3):553-63.
80. Rosenzweig JL, Weinger K, Poirier-Solomon L, Rushton M. Use of a disease severity index for evaluation of healthcare costs and management of comorbidities of patients with diabetes mellitus. *Am J Manag Care*. 2002;8(11):950-58.
81. Cziraky MJ, Quimbo R, Sarawate C, Burge RT, Simko RJ. Simultaneous attainment of multiple lipid fraction target levels in 10,303 patients with type-2 diabetes mellitus (DM). (poster) *American Diabetes Association 67th Annual Scientific Sessions*. Chicago, IL; 2007. Abstract 0908-P. Available at: http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=55008.
82. Simko RJ, Cziraky MJ, Quimbo R, Sarawate C, Burge RT. The effects of multiple lipid goal attainment on cardiovascular events and costs. (poster) *National Lipid Association Annual Meeting*. Scottsdale, AZ; 2007. Abstract 406.
83. Bangalore S, Shahane A, Parkar S, Messerli FH. Compliance and fixed-dose combination therapy. *Curr Hypertens Rep*. 2007;9(3):184-89.
84. Valenti WM. Expanding role of formulations in the treatment of HIV infection: impact of fixed-dose combinations. *AIDS Read*. 2004;14(10):541-43, 547-50.
85. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm*. 2007;64(12):1279-83.
86. Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clin Ther*. 2002;24(3):460-67.

Targeting Low HDL-Cholesterol to Decrease Residual Cardiovascular Risk in the Managed Care Setting

Intended Audience

This activity is intended for managed health care professionals, especially pharmacy directors and medical directors, and physicians interested in lipid management, pharmacoeconomics of lipid therapy, and health outcomes research.

Activity Purpose

This activity offers educational information to advance the clinician's knowledge about methods used for achieving optimal lipid outcomes in patients with atherogenic dyslipidemia who have residual cardiovascular disease risk. Recent health economics and outcomes research data on the impact of residual risk on health care costs will be presented along with a discussion of which lipid-modifying therapies are best suited for raising high-density lipoprotein cholesterol, reducing triglycerides, and reducing residual risk.

Method of Participation

It has been determined that this activity can be completed in 1 hour(s). The participant should review the learning objectives and faculty disclosures, review the materials, reflect on the content, answer the posttest questions, and complete the enrollment/evaluation forms. To earn credit, a minimum score of 70% must be achieved on the posttest. There is no fee to participate in the program or for the generation of the certificate.

Release date: 10/01/08

Expiration date: 9/30/09

Accreditation

Accreditation is provided by The Academy for Continued Healthcare Learning.

Pharmacists

The Academy for Continued Healthcare Learning is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. In order to receive credit, pharmacists must complete the activity requirements and evaluation at the conclusion of the program. This activity has been approved for a maximum of **0.1 Continuing Education Unit**. ACPE Universal Program Number: **396-000-08-027-H01-P**

Initial Release Date: 10/01/08

Expiration Date: 9/30/09

To complete the activity online, go to www.amcp.org (CE/CME Center), where you will access the posttest and evaluation form.

The Posttest Answers and Evaluation Form may be faxed or mailed to:
Postgraduate Institute for Medicine, 367 Inverness Pkwy., Suite 215, Englewood, CO 80112; Fax: 303.790.4876

Posttest Worksheet: Targeting Low HDL-C to Decrease Residual Cardiovascular Risk in the Managed Care Setting

1. In the meta-analysis of statin trials by the Cholesterol Treatment Trialists' Collaborators, patients with diabetes who were treated with statins experienced which of the following?
 - a. A 13% reduction in all-cause mortality
 - b. A 21% reduction in major vascular events
 - c. 8.7% of patients experienced a major cardiovascular event
 - d. Low-density lipoprotein cholesterol (LDL-C) level reduction to an average of 95 mg per dL
2. According to the Third National Health and Nutrition Examination Survey, what percentage of adult women have suboptimal high-density lipoprotein cholesterol (HDL-C) values (<50 mg per dL)?
 - a. 35%
 - b. 3%
 - c. 39%
 - d. 57%
3. Which of the following trials revealed a significantly increased risk for major cardiovascular events associated with low HDL-C even with an LDL-C level <70 mg per dL?
 - a. Framingham Heart Study
 - b. Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)
 - c. Safety and Efficacy of Fixed Dose Niacin ER and Simvastatin Combination Therapy (SEACOAST)
 - d. Treating to New Targets (TNT)
4. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial, which of the following was associated with risk of coronary heart disease (CHD) events?
 - a. Triglyceride (TG) level <150 mg per dL and LDL-C level <70 mg per dL
 - b. LDL-C level >70 mg per dL and TG level <150 mg per dL
 - c. HDL-C level >40 mg per dL and TG level <70 mg per dL
 - d. TG level <150 mg per dL and HDL-C level <70 mg per dL
5. The American Diabetes Association treatment guidelines suggest HDL-C goal levels of:
 - a. >50 mg per dL in men and >40 mg per dL in women
 - b. >40 mg per dL in men and <70 mg per dL in women
 - c. >40 mg per dL in men and >50 mg per dL in women
 - d. <70 mg per dL in men and <100 mg per dL in women
6. Which of the following therapies was associated with a regression in stenosis in the HDL-Atherosclerosis Treatment Study (HATS) trial?
 - a. Niacin/simvastatin
 - b. Niacin/fenofibrate
 - c. Fenofibrate/simvastatin
 - d. Simvastatin monotherapy
7. Adherence to statin therapy, as measured by medication possession ratio (MPR), is associated with LDL-C goal attainment. A potentially important MPR target to increase goal achievement in managed care appears to be:
 - a. 0.80
 - b. 0.52
 - c. 0.37
 - d. 0.61
8. Which of the following guideline-established lipid goals is achieved by the smallest percentage of people with CHD risk equivalents?
 - a. LDL-C
 - b. HDL-C
 - c. Non-HDL-C
 - d. One or more lipid goals
9. Retrospective analyses of managed care databases indicate that the achievement of optimal lipid values (OLVs) for LDL-C, HDL-C, and TG is associated with a reduced risk of cardiovascular events and a:
 - a. 10-fold increase in medical costs
 - b. Greater incidence of comorbidities
 - c. 9% decrease of cardiovascular-related cost
 - d. 25% reduction all-cause mortality
10. In a population modeling study based on a managed care database of metabolic syndrome patients, the greatest percentage of patients was predicted to achieve OLVs with which therapeutic intervention?
 - a. Simvastatin/ezetimibe
 - b. Atorvastatin
 - c. Rosuvastatin
 - d. Extended-release niacin (niacin ER)/simvastatin

Posttest Worksheet: Targeting Low HDL-C to Decrease Residual Cardiovascular Risk in the Managed Care Setting

11. In a population modeling study based on clinical trials and national databases, the direct medical costs of CHD events were estimated for simvastatin monotherapy and for various doses of niacin ER/simvastatin combination therapy. An 11% reduction in cost was associated with:
 - a. Simvastatin (40 mg)
 - b. Niacin ER/simvastatin (2,000 mg/40 mg)
 - c. Niacin ER/simvastatin (1,000 mg/20 mg)
 - d. Niacin ER/simvastatin (1,000 mg/40 mg)
12. What is an advantage of fixed-dose combination therapy?
 - a. Increased pill burden
 - b. Increased costs
 - c. Improved compliance
 - d. All of the above

NOTES

[illegible]

NOTES

[illegible]

Supplement