Introduction

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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.