

Statins at the Crossroads

Cardiovascular disease (CVD) is still unchallenged as the number one killer in the United States as it has been for virtually the entire past century, and the link between CVD and dyslipidemia is well established.¹ In particular, attention has focused on elevations in low-density lipoprotein cholesterol (LDL-C) as the lipid abnormality most directly implicated as a risk factor for CVD.

The most effective drugs for reducing LDL-C, and thereby reducing the risk of CVD, are the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), which act by blocking the hepatic synthesis of cholesterol. Accordingly, statins now comprise the largest drug category by dollar volume in the United States (\$16 billion in 2005) and the second largest category by number of dispensed prescriptions (144 million in 2005).²

The success of the statins has led to a reconsideration of therapeutic goals and means of achieving them, for the statins permit reduction of LDL-C to levels previously unattainable. In turn, this expanded vista of therapeutic possibilities has led to questions about the optimal utilization of statins. How should individual products of this class be selected for individual patients? What are the risks associated with statin therapy, and how do these risks differ among the individual statins? How should statins be used in patients at the highest risk of CVD? What is the most cost-effective means of using the statins?

With strategies for the management of CVD and optimal utilization of statins at a crossroads, this supplement to *The American Journal of Managed Care* brings together 3 special reports of timely interest. In "An Assessment of Statin Safety," **James M. McKenney, PharmD**, addresses the concerns about safety with statins. Since 2001, when cerivastatin was withdrawn from the market

for reasons of safety, some nonprofessional sources have called the statins "dangerous drugs." However, analysis of data from the professional literature and adverse event reports offer a different picture. Summarizing the findings of the National Lipid Association Statin Safety Assessment Task Force, Dr McKenney places the risk of myopathy in a realistic perspective. The risk varies among the statins and is clearly associated with dose and exposure. At approved dosages, the risk of serious myopathy (including rhabdomyolysis) is well under half of 1%; most cases of serious myopathy have been associated with pharmacokinetic interactions with drugs that retard statin metabolism. Among other perceived safety concerns, liver failure is considered a remote risk; proteinuria occurs with all statins but is not associated with any increased risk of renal failure; and there is no evidence to support concerns about neurotoxicity and cognitive impairment with statin therapy.

Robert M. Guthrie, MD, offers a cogent overview in "Rising to the Challenge of Treating High-risk Patients" of several important recent clinical trials involving aggressive statin therapy in patients at high risk of CVD. Several conditions place patients at high risk: diabetes, known coronary heart disease, noncardiac atherosclerosis, abdominal aneurysm, and the metabolic syndrome (a common condition in older patients, characterized by central obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia).³ Whereas the standard goal for LDL-C correction is 100 mg/dL or less, patients at very high risk for CVD may benefit from a more aggressive lipid-lowering regimen aimed at achieving LDL-C concentrations of 70 mg/dL or less. The conclusion from a number of important clinical trials utilizing high-dose statins is that the lower LDL-C goal is achievable and

is associated with significantly reduced risk of cardiovascular events and mortality.

Given the proven ability of statins to reduce CVD risk (and its estimated \$400-billion price tag in 2006¹), questions about cost-effectiveness involve the choice of statin rather than the rationale for statin therapy. As reviewed by **Terrance Killilea, PharmD**, and **Lori Funk, PharmD**, in “Cost Efficiency and Formulary Considerations for Statin Therapy,” cost analyses focus on achieving target LDL-C levels at the lowest medical and pharmaceutical costs. The overall cost of therapy is generally expected to become more affordable as older agents go off patent. However, differences in potency translate to different treatment costs associated with achieving moderate versus large reductions in LDL-C. For patients at moderate risk, for whom the target reduction in LDL-C concentration is up to 40%, any of the statins will be effective, and generic versions can be used. However, for patients at higher risk, who require greater reductions

in LDL-C, the greatest cost-effectiveness may be seen with rosuvastatin or with a fixed combination of simvastatin and the cholesterol-absorption blocker ezetimibe.

Questions still remain about individualization of statin therapy—which drug at what dosage? There is no question, however, that for now and the foreseeable future, statins will continue to play a key role in reducing the immense human and economic burden of CVD.

REFERENCES

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