HMG Coenzyme A Reductase Inhibitors

Good News and Bad News

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly called statins, are one of the success stories of modern medicine. Before their introduction and evaluation, the efficacy of lipid-lowering therapy in the prevention of coronary heart disease was controversial. Meta-analyses of clinical trials of bile acid resins, fibric acid derivatives, and other agents demonstrated a reduction in coronary heart disease incidence but not a corresponding fall in overall mortality. These medications did not lower patients' serum cholesterol levels to as marked a degree, had to be taken more frequently, and were much more likely to produce adverse effects compared with statins. In sharp contrast to the preexisting situation, therapy with statins reduces total mortality in men with hypercholesterolemia when used for both primary and secondary prevention of coronary artery disease. In fact, the impressive efficacy of these medications led Brown and Goldstein, winners of the Nobel Prize in medicine, to predict that their availability would lead to the disappearance of coronary artery disease as a public health problem.¹ Although a debate of the population-based versus the individual approach to disease prevention is beyond the bounds of this discussion, fulfillment of such an optimistic prediction would be the case only if treatment were applied uniformly to everyone at risk.²

Two articles in this issue of the *Journal* highlight the current state of lipid-lowering therapy. The good news is that statins have beneficial effects on stroke incidence that were unsuspected until relatively recently. The bad news is that, despite a very favorable risk-benefit profile, lipid-lowering therapy is underprescribed even in high-risk populations likely to benefit most from treatment.

In a carefully done quantitative summary of clinical trials of HMG CoA reductase inhibitors, Warshafsky et al. demonstrate that treatment with statins reduces overall stroke incidence by 30%, owing to a reduction in nonfatal stroke.³ The risk of fatal stroke, however, is greater in the active treatment groups. As the authors point out, these results are consistent with large observational studies that demonstrate a direct relation between serum cholesterol level and ischemic stroke but an inverse relation with hemorrhagic stroke.⁴ Previous quantitative summaries have yielded similar results. This situation is analogous to that for antiplatelet therapy, which lowers the incidence of ischemic stroke while increasing the risk of hemorrhagic stroke.⁵ In populations like that of the United States, where the risk of ischemic stroke is greater

than the risk of hemorrhagic stroke, there is a net gain in prevention of stroke. Moreover, it is important to emphasize that in such populations the benefit of lipid-lowering therapy in prevention of coronary artery disease greatly outweighs the increased risk of fatal stroke.

Also in this issue, Majumdar et al. report that only 37% of patients with coronary artery disease and hyperlipidemia admitted with an acute myocardial infarction to 37 hospitals in Minnesota were receiving lipid-lowering therapy on admission.⁶ Patients less likely to be treated were older than 74 years, had fee-for-service insurance, were not taking aspirin, were taking fewer medications, and had severe comorbidity. Perhaps more disturbing is that only 11% of those not treated on admission were prescribed a lipid-lowering medication at discharge. Sadly, lipid-lowering therapy joins a long list of other life-saving preventive interventions, such as use of β -blockers and angiotensin-converting enzyme inhibitors, that often are not prescribed for persons with clinically evident coronary artery disease.

Any therapy, no matter how efficacious, will benefit our patients only if we use it. The research agenda is to identify the important barriers—whether related to patients, providers, or health systems—to the use of effective therapy and design interventions to overcome them. In the interim, we need to examine our individual practice patterns and improve our efforts to give patients the highest-quality care.—**MICHAEL J. KLAG, MD**, *Johns Hopkins University, Baltimore, Md.*

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