Treatment of Dyslipidemia in Elderly Patients With Coronary Heart Disease

There Are Miles to Go Before We Sleep*

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The treatment of dyslipidemia with statin therapy is a cornerstone in the management of patients in both the primary and secondary prevention settings. Dyslipidemia is widely prevalent in its various forms (1). The lowering of low-density lipoprotein cholesterol (LDL-C) with a statin in patients with established coronary heart disease (CHD) has shown unequivocal capacity to safely reduce risk for clinical sequelae such as nonfatal myocardial infarction, ischemic stroke, cardiovascular and all-cause mortality, as well as the need for revascularization (2,3). The American College of Cardiology/American Heart Association Guideline for the Treatment of Blood Cholesterol continues to place primary emphasis on cardiovascular (CV) risk reduction by lowering LDL-C by a specific percentage according to estimated level of risk for sustaining an acute CV event (4).

Statin therapy generally lowers risk for an acute CV event by 25% to 45% over 5 years of follow-up, depending upon the magnitude of LDL-C reduction, specific patient characteristics, and the intensity of statin therapy used. Consistent with these findings, the “residual risk” for a CV event is estimated as being 55% to 75%. Clearly, not all of the residual risk is attributable to dyslipidemia. Persistent cigarette smoking, inadequately controlled hypertension, obesity, insulin resistance, and other risk factors all contribute. However, because elevated triglycerides and non-high-density lipoprotein cholesterol (HDL-C) and low HDL-C have also been shown to be independent risk factors for CV events, there has been understandable motivation to address this residual risk with use of adjuvant lipid-modifying therapies that provide incremental LDL-C lowering, triglycerides and non-HDL-C reduction, and HDL-C elevation.

The treatment of elderly patients (≥65 years of age) is an issue that is often met with some trepidation. Questions arise as to the strength of evidence supporting lipid lowering in older patients. The decision to treat may also be influenced by age-related impairments in renal and hepatic function, reduced muscle mass and frailty, risk of drug interactions secondary to substantial polypharmacy, and neurocognitive integrity. Contrapuntal to these concerns is the fact that elderly patients are at highest CV risk and hence are among the most vulnerable for sustaining both primary and secondary coronary and cerebrovascular events. The HPS (Heart Protection Study) (5) and the PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) (6) studies randomized 10,697 patients ≥65 years of age and 5,804 patients who are 70 to 82 years of age, respectively, to treatment with either statin or placebo. In HPS, the elderly patients derived as much CV benefit from simvastatin therapy as their younger counterparts. In PROSPER, pravastatin significantly reduced the risk for the primary composite endpoint as well as for multiple individual endpoints including a 24% decrease in cardiovascular mortality. An important meta-analysis which included elderly patients from 9 large prospective randomized controlled trials showed that statin therapy for an average of 5 years was associated with the following reductions in CV

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intensity statin therapy (3). The current guideline elaborates that the increase in event rates better than lower intensity of a statin. High-intensity statin therapy is associated with significant increases in survival among those 78 to 85 years of age (74.7% vs. 64.3%, log-rank p = 0.07) and 85 to 90 years of age (76.2% vs. 67.4%; p = 0.01) (9). Both of these studies were observational and nonrandomized and must, therefore, be interpreted with caution. However, they clearly emphasize the benefit of statin therapy in elderly patients.

More recently, other studies lend further support to the use of statins in elderly patients. The Age, Gene/Environment Susceptibility-Reykjavik Study included 5,152 men and women with a mean age of 77 years (range 66 to 96 years) and compared CV and all-cause mortality among patients who did and did not receive statin treatment over a median follow-up period of 5.3 years (8). Among persons with diabetes mellitus (DM), statin therapy reduced CV and all-cause mortality by 50% and 53%, respectively. For persons without DM, statin therapy reduced CV and all-cause mortality by 16% and 30%, respectively. In the Jerusalem Longitudinal Cohort Study compared to no treatment, statin therapy was associated with significant increases in survival among those 78 to 85 years of age (74.7% vs. 64.3%, log-rank p = 0.07) and 85 to 90 years of age (76.2% vs. 67.4%; p = 0.01) (9). Both of these studies were observational and nonrandomized and must, therefore, be interpreted with caution. However, they clearly emphasize the benefit of statin therapy in elderly patients.

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In this issue of the Journal, Bittner et al. (10) explore the use of lipid-lowering medications in more than 300,000 elderly patients with established CHD using a cohort from a Medicare database. Over the 5-year period of surveillance, statin usage among these patients increased from 53.1% to 58.8%. This is a positive finding, but it still constitutes inadequate treatment. Approximately 40% of elderly patients with CHD are not receiving a therapy known to reduce recurrent CV events, disability, and death. Certainly some patients do not tolerate statins because of myalgia and other side effects (11). But such a high prevalence of high-risk patients not being treated with a statin is puzzling. There was also a small increase in the percentage of these patients treated with high-intensity statin, having increased from 11.1% to 14.2%. This too is inadequate. Age alone should not determine treatment with, or intensity of, a statin. High-intensity statin therapy is known to reduce event rates better than lower intensity statin therapy (3). The current guideline encourages the use of high-intensity statin therapy in elderly patients unless the treating physician ascertains they are not an appropriate candidate in which case they are encouraged to treat with moderate-intensity statin therapy (4).

These investigators also explored the usage patterns of nonstatin lipid-modifying medications. The findings are of great interest. Subsequent to publication of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial, there was a steep reduction in the prescribing of ezetimibe of two-thirds in patients on statin therapy and approximately 50% among patients not taking a statin (12). ENHANCE evaluated the efficacy of adding ezetimibe to statin therapy in patients with heterozygous familial hypercholesterolemia. Given flaws in the design of the study and the thin carotid intima media thickness at baseline (0.69 mm), the result was predictable (13). There was no apparent increase in prescribing when the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial suggested that ezetimibe used in combination with a statin had a positive impact on rates of carotid intima media thickness progression (14). The prescribing of ezetimibe likely declined further when the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial suggested an increased signal for malignancy (15), despite a subsequent meta-analysis which suggested no such relationship existed (16). With publication of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), we now have evidence that the addition of ezetimibe to statin therapy is safe and provides a degree of risk reduction that is commensurate with the magnitude of LDL-C reduction in patients who have sustained an acute coronary syndrome (17). Understandably, it is anticipated that the use of ezetimibe will gradually increase in response to these findings. A very interesting finding is that, despite having evidence for reducing cardiovascular events (18), bile acid binding resin therapy did not increase as ezetimibe use decreased.

In contrast to prescribing patterns with ezetimibe, publication of the negative ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial had little to no effect on the prescribing of fenofibrate (19). The reason for this is not immediately obvious especially because the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial was also negative (20). When the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial was discontinued due to futility (21), there was an apparent small decrease in the prescribing of niacin, a finding that is more intuitively obvious. This will likely trend further down because publication of HPS-2 THRIVE (Heart Protection Study-2: Treatment of HDL to Reduce the Incidence of Vascular Events)
also showed no efficacy attributable to niacin adjuvant therapy (22).

These authors found additional important relationships. Male sex and Caucasian race compared to female sex and other racial groups were associated with a higher likelihood of being prescribed nonstatin adjuvant therapy, possibly signaling a disparity in care. Having DM increases risk for mixed forms of dyslipidemia, and diabetic patients had a higher rate of being prescribed adjuvant therapy.

There is much yet to be learned about residual risk and the role of adjuvant lipid-lowering therapy. However, as this study makes clear, the prescribing of lipid-lowering medication by health care providers and its responsiveness to clinical trials is an issue that warrants much careful additional study. In the meantime, it is crucial that statins and adjuvant therapies with demonstrable efficacy be used appropriately to help more patients achieve guideline-determined goals for LDL-C reduction, especially among elderly patients.

**REFERENCES**


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