

## CLINICAL STRATEGIES FOR REACHING CURRENT NCEP III GUIDELINES

Since the publication of the Scandinavian Simvastatin Survival Study (4S)<sup>1</sup>, a secondary prevention study in patients with established coronary artery disease published in 1994, it has become clear that aggressive management of dyslipidemia may have a profound effect on clinical outcomes. Further studies have shown that even patients with less elevated cholesterol levels may achieve significant benefit with aggressive dyslipidemic therapy. In addition, it appears that even patients with risk factors for vascular disease may benefit from statin therapy, even in the absence of traditionally defined hypercholesterolemia. The Heart Protection Study (HPS)<sup>2</sup> is the largest clinical trial evaluating statin therapy and enrolled 20,536 adults with coronary artery disease, but also those with peripheral vascular disease and diabetes mellitus. Patients received either 40 mg. of Simvastatin or placebo, and there was a 25% reduction in the incidence of cardiac events (nonfatal MI or CHD death) and those with LDL levels below 100 mg% received as much benefit as those with higher LDL levels, raising the issue of the “pleiotropic” effects of statins. Although at odds with the ALLHAT-LLT study, in the somewhat better designed Anglo-Scandinavian cardiac outcomes trial (ASCOT)<sup>3</sup>, 19,342 hypertensive subjects were randomized to two anti-hypertensive strategies and also randomized to receive either placebo or 10 mg. of the Atorvastatin. At a median followup of 3.3 years, there was a 36% relative reduction in the primary end-point of non-fatal myocardial infarction and fatal coronary heart disease favoring Atorvastatin. These recent studies have clearly indicated that even patients at high risk for the development of vascular disease, i.e., those with hypertension, diabetes or the metabolic syndrome, and peripheral vascular disease, should be aggressively treated with statin therapy even in the absence of established traditionally defined hypercholesterolemia. The recently published Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL)<sup>4</sup> trial and the PROVE-IT trial<sup>5</sup>, further challenges our ability to achieve goals even more stringent than the traditional LDL cholesterol lowered to less than 100 mg%. Both trials used the same statin regimen, randomizing patients either to Pravastatin 40 mg. daily or Atorvastatin 80 mg. daily. The REVERSAL trial was an intravascular ultrasound study that compared the coronary atheroma burden over an eighteen

month period in each of the randomized arms. The LDL levels in the Pravastatin group were 110 mg% compared with 79 mg% in the Atorvastatin group. There was no difference in adverse effects of either liver or muscle enzyme elevations between the two groups. The PROVE-IT study, using the same doses of Pravastatin and Atorvastatin, was a clinical events trial in 4,162 post acute coronary syndrome (ACS) patients. After two years of therapy, the Atorvastatin regimen reached an LDL cholesterol level of 62 mg% compared with the Pravastatin group of 95 mg%. There was a reduction in the risk of the combined incidence of major cardiovascular events and death by 16% in the Atorvastatin group and the curves began to diverge as early as 30 days into the study. Although in the REVERSAL trial there was a 36.4% decrease in C-reactive protein levels in the Atorvastatin group compared with 5.2% decrease in the Pravastatin arm, it is unclear whether this pleiotropic effect contributed to what most feel was a lower LDL cholesterol as the explanation for the reduction in cardiac events. The PROVE-IT study also confirms the findings of the MIRACL<sup>6</sup> study in patients with acute coronary syndromes in demonstrating not only a benefit with prescribing statin therapy, literally within days of a cardiac event, but that the benefit appears to occur within the first month of therapy. This does suggest that potent anti-inflammatory effects and improvement in endothelial function may be additional important actions of statins in patients with established coronary disease or simply in high risk patient subsets.

In view of this information, how it is possible to achieve yet even more stringent goals of LDL cholesterols of 70 mg% or less? Fortunately, several medications and combinations have become available that may help to achieve these new goals established by the studies discussed above. First, there is a considerable difference in the efficacy of various HMG Co-A reductase inhibitors as noted in figure 1. In addition, most of the effect of LDL reduction of a statin occurs with entry level doses as noted in figure 2. Doubling the dose of these agents increases their effectiveness by only approximately 6% each time the dose is doubled. This observation has also led to the development of some new recent combination drugs that may be helpful in certain patient subsets. Advicor, a combination of Lovastatin and extended release niacin (figure 3) is one such combination that may offer particular benefit in those with particularly depressed HDL cholesterol. Often using small doses of nicotinic acid can give considerable additional benefit in reducing LDL cholesterol or even improving HDL cholesterol. This is important in considering that epidemiologic data indicate a 2-3% reduction in cardiovascular disease risk for each 1% increase in HDL cholesterol. The use of niacin, however, is frequently limited by several side

effects. Although statins and bile acids sequestrants may also be combined, the new combination medication of Simvastatin and Ezetimibe (Vytorin - figure 4) seems particularly intriguing in that an entry level dose of 10-20 may lower LDL cholesterol up to 50%. This medication is also similarly priced across all dosage levels. Diabetic patients who often have the “metabolic syndrome” lipid profile of low HDL, elevated triglycerides, and elevated LDL, will often respond to a fibric acid drug, especially in those individuals with higher triglyceride levels (over 350 mg%). Fibric acid derivative drugs (gemfibrozil, Fenofibrate), like the Thiazolidinedione class of diabetic agents (Actos, Avandia) activate peroxisome proliferator-activated alpha receptors (PPAR alpha). This activation increases the synthesis of lipoprotein lipase and increases the synthesis of APO AI and APO AII, which are the major proteins of HDL cholesterol. In addition, fenofibrate, unlike gemfibrozil, does not appear to be involved in the glucuronidation pathway of degradation that has been responsible for the myositis seen when gemfibrozil and statins are combined as was seen in particular with Cerivastatin and gemfibrozil before the former drug was removed from the market. For this reason, fenofibrate is a better choice when combined with a statin. Finally, it is also important to consider the use of fish oil (2-6 grams tid) in patients with severe hypertriglyceridemia, which can cause a marked fall in the VLDL plasma level due to increased intercellular degradation of APO B100. Although not FDA approved, a combination of Ezetimibe (Zetia) with a bile acid sequestrant or nicotinic acid could certainly be considered in individuals who have not been able to tolerate statin therapy and whose risks of developing or worsening vascular disease outweigh the risk of less established regimens.

In conclusion, recent information suggests that an aggressive therapeutic approach be applied certainly to patients with established vascular disease or high risk cohorts, such as patients with diabetes mellitus, metabolic syndrome, hypertension, or peripheral vascular disease. Clearly, recent studies, such as PROVE-IT and REVERSAL, indicate that, for LDL, lower is better especially in high risk patients discussed above. Newer combination medication hopefully should allow such goals to be reached in a growing number of patient subset (figure 5).

## REFERENCES

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