

DYSLIPIDEMIA: THE EVIDENCE FOR EARLY AGGRESSIVE THERAPY

Several seminal trials published within the past five years provide clear evidence for aggressively lowering LDL cholesterol. The 4S, CARE, and LIPID trials collectively enrolled over 17,500 patients with known coronary artery disease, and varying lipid profiles, demonstrating that lipid lowering management with statin medications was associated with highly statistically significant reductions in major coronary events. The WOSCOPS and AFCAPS/TEXCAPS studies showed similar reductions in primary end-points in patients with hypercholesterolemia and no evidence of clinical cardiac disease. Recent studies also demonstrated benefit in patients treated with elevated triglycerides and low HDL levels. Furthermore, in compilation, these studies suggest that aggressive measures to lower cholesterol are warranted. In the post-coronary artery bypass graft trial (CABG) trial, aggressive treatment to lower LDL cholesterol to less than 100 mg% slowed atherosclerotic progression in bypass grafts to a greater degree than less aggressive lipid lowering.^{1,2} While these studies have in general followed patients over a 5-6 year period, the Atorvastatin versus revascularization treatment trial (AVERT trial), in a small number of patients, found no statistical difference in ischemic events between patients with stable coronary artery disease randomized to angioplasty versus intense dyslipidemic therapy with 80 mg. of Atorvastatin over an 18 month period.³ Two recent studies further underscore the importance of early statin intervention in acute coronary syndromes. The Swedish Register of Cardiac Intensive Care (RIKS-HIA) evaluated the association between statin treatment initiated at or before the time of hospital discharge and one year mortality following acute myocardial infarction.⁴ Between 1995 and 1998, 5,528 patients

who received statins at or before hospital discharge were compared with 14,071 patients who did not receive reductase inhibitor therapy. At one year, unadjusted mortality was 9.3% in the group not receiving statin therapy compared with 4.0% in the statin treated group. While lipid measurements were not a part of the compulsory data, statin therapy was recommended in those who received this therapy with cholesterols of greater than 200 and LDL of greater than 115 mg%. The recently published MIRACL study further underscores the importance of early statin therapy in patients with acute coronary syndromes.⁵ A total of 3,086 adults with unstable angina or non Q wave myocardial infarction were randomized between May 1997 and September of 1999 to Atorvastatin 80 mg. per day, initiated between 24 and 96 hours following the acute coronary event, or matching placebo. Over the 16 week study period, treatment with Atorvastatin significantly reduced the risk of the primary combined end point of death, non fatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia requiring emergency re-hospitalization (14.8% in the Atorvastatin group and 17.4% in the placebo group $P = .048$). While this absolute reduction (2.6% or a 16% relative reduction) observed in the treated cohort over the 16 week period of the trial is less impressive than that observed in the other previous trials with longer followup in which risk reductions of from 24-37% were achieved, this early risk reduction in the MIRACL study is impressive since patients suffering an acute coronary syndrome often experience the highest rate of death and recurrent ischemic events during the early period following the acute episode. What might be the mechanisms for such an early benefit? A small study recently published from Madrid, Spain may lend some insight into the mechanism involved.⁶ Twenty patients with coronary artery disease and average LDL cholesterol levels and at least one reversible perfusion defect on Thallium SPECT study were randomized to either 20 mg. of Pravastatin or placebo for 16 weeks and then switched to the other treatment for 16 weeks. Treatment with Pravastatin was associated with a reduction in the magnitude of perfusion defects. It is known that lipid lowering

improves endothelial function which may lead to improved perfusion. Other recent studies have also suggested that statin therapy may have a greater impact on decreasing risk factors among patients with higher levels of inflammatory markers such as elevated levels of high sensitivity C-reactive protein. In addition to perhaps reducing calcium content and macrophage number in atherosclerotic lesions, thereby stabilizing the atherosclerotic plaque, lipid lowering may also “quiet” the active lesion and improve endothelial function.⁷⁻⁸

These emerging studies suggest that perhaps statin therapy should be initiated much earlier in patients recognized as having acute coronary syndromes than perhaps has been done in traditional practice. While there has been concern regarding the reliability of early lipid profiles in patients with acute coronary syndromes, the potential benefit of measuring inflammatory markers such as high sensitivity C-reactive protein and the knowledge that endothelial dysfunction may improve even in patients with lipid levels considered in the normal range, support aggressive therapy in lowering LDL cholesterol in patients with unstable coronary syndromes.⁹⁻¹¹