Statins in the Management of LDL-C

Written by **Brian Hoyle**

Peter Libby, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, provided an overview of the present and prospective roles of statins in the management of low-density lipoprotein (LDL).

Multiple studies have found an association between physical activity, a healthy diet, and moderate consumption of alcohol with a lower risk of cardiovascular disease (CVD). Yet, few randomized trials have shown that incorporating these lifestyle modifications reduce CV events. Indeed, the Look AHEAD study explored the influence of an intensive lifestyle intervention involving weight loss on CVD risk in 5145 overweight and obese patients with type 2 diabetes (T2DM). This trial was stopped early and did not show a difference between the control and intervention arms for the primary composite endpoint of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, and hospitalization for angina after an average of 9.6 years of follow-up (HR, 0.95; 95% CI, 0.80 to 1.09; p=0.51) [The Look AHEAD Research Group. *N Engl J Med* 2013]. Although the lifestyle intervention did result in beneficial changes to biomarkers and other important endpoints, Look AHEAD illustrates that lifestyle changes alone may not be able to produce the magnitude of changes necessary to improve outcomes and treat patients at increased risk of CV events such as those with established T2DM.

Statin medications provide another opportunity to reduce the risk of CV events. In the randomized, double-blind Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, 4162 patients who had a recent acute coronary syndrome were randomized to standard statin therapy (pravastatin 40 mg) or intensive statin therapy (atorvastatin 80 mg). All-cause death or major cardiac events in the mean 2-year follow-up was reduced more by intensive statin therapy (22.4% vs 26.3; p=0.005) than the standard statin arm [Cannon CP et al. *N Engl J Med* 2004].

The mechanisms by which statins reduce cardiovascular events may include both the direct effects of a reduction in LDL as well as indirect, so-called pleiotropic effects, that do not depend on LDL lowering [Libby P, Aikawa M. *Nature Med* 2002]. The effects of statins on atherosclerosis beyond LDL lowering may involve reduced thrombogenicity, opposing action on vasospasm, decreased inflammation, and plaque stabilization. All statins tested yield reductions in the biomarker of inflammation C-reactive protein (CRP.) The reductions of CRP and LDL in statin-treated individuals do not correlate well [Blake GJ, Ridker PM. *J Am Coll Cardiol* 2003; Ridker PM et al. *N Engl J Med* 2005].

Indeed, inflammatory status can effectively target statin treatment in individuals with below median LDL. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER] was a multinational, randomized, double-blind, placebo-controlled trial that tested the ability of rosuvastatin to prevent CV events in individuals with low LDL and elevated high sensitivity CRP (hsCRP) [Ridker PM et al. *N Engl J Med* 2008]. Patients without diabetes and prior CVD (men aged ≥50 years and women aged ≥60 years), LDL <130 mg/dL, and hsCRP >2 mg/L were randomized to receive rosuvastatin 20 mg or placebo (n=8901 per arm). Primary outcomes of MI, stroke, unstable angina, and CVD-related death occurred in 251 patients in the placebo arm and 142 patients in the treatment arm (HR, 0.56; 95% CI, 0.46 to 0.69; p<0.00001).

Lipid reduction may prevent CV events by stabilizing the fibrous cap of atherosclerotic plaques. Plaques with a thick fibrous cap may be less apt to rupture and cause thrombosis. In rabbit models, reduced lipid levels appear to aid in stabilizing plaques by reducing the expression of collagenase and increasing collagen accumulation, and reducing plaque tissue factor expression [Aikawa M et al. *Circulation* 1998, 1999, 2001]. Magnetic resonance imaging of human carotid plaque composition during lipid-lowering therapy showed 3 years of lipid therapy decreased the lipid-rich necrotic core of carotid plaques and increased the amount of fibrous tissue. These data indicate that the findings seen in rabbit models mirror that which is found in humans [Zhao XQ et al. *J Am Coll Cardiol Cardiovasc Imaging* 2011].

The transcription regulator Kruppel-like Factor-2 (KLF-2) may mediate the diverse effects produced by statins through mechanisms which are independent of LDL lowering. KLF-2 antagonizes cytokine-induced endothelial activation and promotes vasculoprotective gene expression. Statins have been shown to raise levels of KLF-2.

Some have questioned the efficacy of statins in women, and have claimed that these agents raise the risk of serious side effects without providing protection from CV events, especially in primary prevention. Yet, currently available trial data does not support this view. For example, statins were found to improve outcomes in at-risk women without established CVD in both the JUPITER trial and a meta-analysis of the JUPITER, Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), and management of elevated cholesterol in the primary prevention of adult Japanese (MEGA) trials [Mora S et al. *Circulation* 2010].

The JUPITER trial also called attention to a potential link between statin use and diabetes. The rosuvastatin and placebo arms displayed insignificant differences in median values of fasting glucose at 24 months (98 mg/dL, range 91 to 107 mg/dL; 98 mg/dL, range 98 to 106 mg/dL, respectively; p=0.12), glycated hemoglobin percentage at 24 months (HbA1C 5.9%, range 5.7% to 6.1%; 5.8%, range 5.6 % to 6.1%, respectively; p=0.01), and glycosuria at 12 months (36 mg/dL and 32 mg/dL respectively; p=0.64). This finding rapidly led to meta-analyses that showed that statins were associated with a slightly increased risk of incident diabetes. These findings led many to conclude that statins are associated with the development of diabetes, and that this concern should limit their use. Another analysis of the JUPITER data established that development of diabetes occurred in only those with risk factors for this condition and that in comparison with placebo, statins did indeed accelerate the average time to diagnosis of diabetes by 5.4 weeks. The outcomes data from JUPITER however showed that the CV reduction produced by statin therapy was similar in patients who were at high risk of developing diabetes and those without prior risk of this condition [Ridker PM et al. *Lancet* 2012]. Thus, despite hastening crossing of the biochemical threshold use to define diabetes in those already at risk for this disease, the data do not support withholding statin treatment due to this concern, as a chief goal in managing diabetes is to lower risk of CV events.

Similarly, careful scrutiny of the available relevant data has led to the conclusion that statin use does not increase the risks of cognitive decline or cancer [Jukema JW et al. *J Am Coll Cardiol* 2012]. The authors further opined that the informational warnings issued by the United States Food and Drug Administration regarding diabetes and statins should be rescinded.

The available data support a number of conclusions for statins, stated Dr. Libby:

- Statins have direct anti-inflammatory effects that extend beyond the lowering of LDL
- Statins lower CV risk in both women and men
- While statins may hasten the diagnosis of diabetes in those already at risk, they confer compelling CV benefit in this population
- Statins are key in the pharmacotherapy for lipid management and CV risk reduction