

Statins, Inflammation and Atherosclerosis: Past, Present and Future

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Results from multiple clinical trials show that reductions in LDL-C are associated with reduced risk of coronary heart disease. After the results of the Coronary Primary Prevention Trial were released in 1984, the development of the statins helped to conclusively establish the link between blood cholesterol levels and coronary heart disease. The first statin, or HMG-CoA reductase inhibitor, was discovered by Akira Endo in 1976. The first marketed statin, lovastatin, was introduced in 1987. Subsequently, a series of large-scale clinical trials confirmed the efficacy and safety of statins in reducing the risk for coronary heart disease in both primary and secondary prevention. Later clinical trials, including the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), extended these initial findings to show that statins provided clinical benefit in women, the elderly, and patients with lower cholesterol levels.

No lower threshold beyond which LDL-C reduction ceases to be beneficial has yet been identified. Beginning at the turn of the millennium, studies comparing intensive versus standard-dose statin therapy in secondary prevention provided support for the hypothesis that “lower is better.” A meta-analysis by the Cholesterol Treatment Trialists’ Collaboration confirmed that clinical benefit was proportional to LDL-C reduction across all patient subgroups and that statin therapy was associated with low risk of side effects.

A growing body of evidence suggests that measures of inflammation may further enhance cardiovascular risk assessment and help guide clinical decision-making. The results of the recent Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating

Rosuvastatin (JUPITER), which demonstrated significant reductions in cardiovascular events and mortality in healthy individuals with low LDL-C but elevated levels of the inflammatory marker C-reactive protein, suggest that statins may confer additional benefit when reductions in LDL-C are coupled with reductions in markers of inflammation.

While LDL-C is the primary target of cardiovascular prevention, increasing attention has focused on HDL-C as a secondary target. Epidemiologic evidence demonstrates that HDL-C is an independent predictor of CHD risk even at low levels of LDL-C, and HDL is believed to be the key mediator in reverse cholesterol transport. Intensive statin therapy that substantially increases HDL-C levels and reduces LDL-C can induce atherosclerotic regression. Nicotinic acid has the greatest effect on HDL-C levels, but often induces a flushing response in patients. The development of new therapies to increase HDL-C and the refinement of existing therapies have the potential to reduce significantly the incidence of cardiovascular events.

Finally, with the sequencing of the human genome, it has become possible to identify genetic variants that might affect cardiovascular risk and hypothetically serve as new biomarkers. Future research can help clarify how targeting biomarkers and lipid fractions other than LDL-C may enhance cardiovascular prevention, diagnosis, and treatment.