CARDIOVASCULAR DISEASE

A dual target

During a time in which public awareness of harmful off-target adverse effects of drugs is heightening, two studies on statins in atherosclerosis published in the *New England Journal of Medicine* serve as a timely reminder for how these often unpredictable effects can also be beneficial.

At first the role of statins in atherosclerosis seemed straightforward: statins inhibit synthesis of the serum low-density lipoprotein (LDL)-cholesterol that contributes to the formation of plaques in atherosclerosis, and less cholesterol means fewer plaques.

But evidence has been building up that atherosclerosis involves inflammation in blood vessels, and that the inflammatory biomarker C-reactive protein (CRP) is a strong predictor of cardiovascular risk. Almost concurrently, studies have indicated that statins work more broadly than first anticipated and seem to have anti-inflammatory effects, as well as lowering CRP levels.

Two trials tie both of these strands of evidence together by providing hard clinical endpoint data for statin-mediated CRP reduction. The PROVE-IT–TIMI 22 and REVERSAL trials, which had shown that an aggressive LDL-lowering regimen of atorvastatin (Lipitor; Pfizer) provided superior clinical benefits to a moderate LDL-lowering regimen of pravastatin (Pravachol; Bristol-Myers Squibb), had hinted at possible anti-inflammatory effects. A follow-up analysis of each study has found that reduced CRP levels from statins is associated with fewer cardiovascular events, independent of LDL-lowering effects.

Among the wealth of data obtained in each trial, Paul Ridker and colleagues showed in the PROVE-IT–TIMI 22 trial that a post-treatment reduction in CRP levels to below 2 mg per litre is associated with a similar event-free survival rate to the post-treatment reduction in LDL levels advocated by current evidence-based guidelines on cholesterol management of acute coronary syndromes (below 70 mg per dl).

Using intravascular ultrasound (IVUS) imaging of vessel walls in the REVERSAL trial, Steven Nissen and colleagues showed that both CRP and LDL levels were influential in determining the progression of atherosclerosis. The results also indicate that statin-mediated reduction in CRP seems unlikely to be a secondary consequence of a reduction in LDL cholesterol.

Both teams say that strategies to lower cardiovascular risk with statins should now include monitoring CRP as well as cholesterol levels. And an editorial accompanying both studies says that the inflammatory contribution in atherosclerosis means that it should be deemed an organ-specific autoimmune disease. The findings that anti-inflammatory effects of statins independently reduce cardiovascular disease risk suggests that it should be possible to create other anti-inflammatory agents specifically tailored to the immunological abnormalities in atherosclerotic plaques.

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References and links

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FURTHER READING Ehrenstein, M. R., Jury, E. C. & Mauri, C. Statins for atherosclerosis — as good as it gets? *N. Engl. J. Med.* **352**, 73–75 (2005) | Frantz, S. Cardiovascular disease: Intensive care. *Nature Rev. Drug Discov.* **3**, 297 (2004)