HOW I TREAT: CORONARY HEART DISEASE: THE PLEIOTROPIC EFFECTS OF STATINS

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Cardiovascular (CV) diseases currently represent the first cause of death in industrialised countries with coronary heart disease (CHD) corresponding to the zenith of the phenomenon being responsible either for acute CV events or chronic heart failure (HF). Over 7 million people every year die from CHD, accounting for 12.8% of all deaths. Dyslipidaemias undeniably play a pivotal role in the pathogenesis and progression of atherosclerosis, and lipid lowering with statins is an essential and integral part of CHD prevention and management. Statins are the most widely prescribed drugs worldwide for lowering blood cholesterol levels. They have been used for over 20 years, and have been found to be effective, safe, and well tolerated over a broad range of patients.

Statins reduce synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. A number of large-scale clinical trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention. Statins at doses that effectively reduce low-density lipoprotein cholesterol (LDL-C) by 50% also slow progression or even promote the regression of coronary atherosclerosis. Current available evidence suggests that the clinical benefit is largely independent of the type of statin while it is reliant on the extent of LDL-C lowering; therefore, the type of statin used should reflect the degree of LDL-C reduction that is required to reach the target LDL-C in a given patient.

Besides the reduction of LDL, statins have been demonstrated to accomplish a number of other effects, known as 'pleiotropic effects'. These effects are due to cholesterol-independent mechanisms and include improvement of endothelial dysfunction, inhibition of inflammatory responses, decreased oxidative stress, stabilisation of atherosclerotic plaque, modulation of platelet function, and smooth muscle cell proliferation. Statins exert their effect by upregulating the expression of endothelial nitric oxide synthase, increasing the expression of tissue-type plasminogen activator, decreasing the expression of endothelin-1, reducing the production of thromboxane A2 and high-sensitivity C-reactive protein levels, inhibiting the lymphocyte function-associated antigen 1/intercellular adhesion molecule 1 interaction. Furthermore, statins are able to inhibit the expression of metalloproteinases and tissue factor with cholesterol-dependent and independent mechanisms, and to induce angiogenesis by promoting proliferation, migration, and survival of circulating endothelial progenitor cells. Many of these pleiotropic effects are mediated by inhibition of isoprenoids, which serve as lipid attachments for intracellular signalling molecules.

The benefits in terms of primary and secondary prevention of acute CV events are highlighted by more than 27 trials. Statin therapy reduces the 5-year incidence of major CV events by 20% per mmol/L reduction in LDL-C regardless of initial LDL-C or other baseline characteristics. Specific trials have demonstrated the benefit of early and intensive statin therapy in patients with acute coronary syndromes in terms of reduction of the risk of CV death, non-fatal myocardial infarction (MI), and coronary revascularisation.[1] Moreover, a meta-analysis performed on 13 randomised clinical trials with 3,341 patients with high-dose statin pre-treatment showed a significant reduction in periprocedural MI and 30-day adverse events in patients undergoing percutaneous coronary intervention (PCI).[2]

Furthermore, numerous large observational studies demonstrated that statin therapy was associated with decreased development of HF after MI and improved outcomes in patients with HF. A meta-analysis with data from 10 randomised trials (10,192 patients with HF) compared statins to placebo showing that statins did not affect CV mortality but significantly decreased hospitalisation rate for HF worsening, with a significant 4.2% increase in left ventricular ejection fraction.[3] These clinical benefits may be related to pleiotropic effects of statins such as a beneficial modulation of endothelial function as well as a reduction of oxidative stress and inflammation. On this basis, the pleiotropic effects of statins may also reduce the risk of iodinated contrast-induced nephropathy (CIN), which is an important cause of hospital-acquired acute renal injury in patients undergoing PCI.

The pathophysiological mechanism responsible for CIN may be related to direct renal tubular toxicity, vasoconstriction, and high levels of oxidative stress. A recent meta-analysis compared the effects of statins to placebo or standard therapies for the prevention of CIN, showing that atorvastatin and rosuvastatin administered at high doses before iodinated contrast administration have a consistent and beneficial preventive effect on CIN, with no difference between these two agents.[4] All these current evidences show that statins exert multiple nonlipid lowering (i.e. pleiotropic) effects including several mechanisms involving the positive modulation of inflammation and endothelial function, and the reduction of oxidative stress and of apoptopic pathways. These new emerging data have obvious and non-negligible theoretical and applicative implications. Taken together, the key effects of statins are significant at different levels, and implications identifying novel potential therapeutic mechanisms or suggesting new clinical indications for statin therapy broadening in this way underline the drug's range of action as the term pleiotropy refers to.

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