Pleiotropic Effects of Statin Drugs: Clinical Paradigm or Research Fiction?

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We enjoyed the review by Dr. Ito and his colleagues detailing the evidence that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) possess ancillary plaque-stabilizing properties independent of cholesterol reducing; so called pleiotropic effects.[1]

Although experimental data support these properties, it is often clinically difficult to separate lipid and non-lipid effects (e.g., reduction in inflammation) of statins since both occur rapidly and concurrently.[2] Dr. Ito and his colleagues suggest that statins have been demonstrated to possess pleiotropic properties in clinical trials across the broad coronary artery disease (CAD) continuum both stable and unstable.

While we agree that the early event rate reductions seen within months in acute coronary syndrome (ACS) trials are difficult to explain through lipid-effects alone, this premise seems less applicable to trials of stable CAD. In particular, one trial the authors did not mention in their review is the Heart Protection Study.[3] This is the largest randomized placebo-controlled statin trial ever published, involving over 20,0000 patients with stable atherosclerosis. In HPS, there was no evidence of early separation of the cardiovascular (CV) event curves (Figure 1), which from a temporal perspective argues against meaningful non-lipid benefits of statins. Moreover, in order to posit pleiotropic properties of statins one would expect statin-treated patients to have a lower CV event rate at any given low density lipoprotein (LDL)-cholesterol level. To the contrary, in HPS, statin allocated or placebo allocated patient tertiles with the same LDL-cholesterol level were indistinguishable in terms of CV event rate (Figure 2). One wonders if CV events reduction is really all about the cholesterol level.

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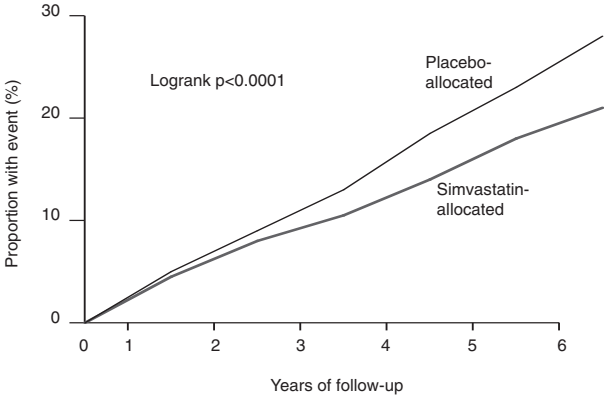

Figure 1. Cardiovascular event curves.

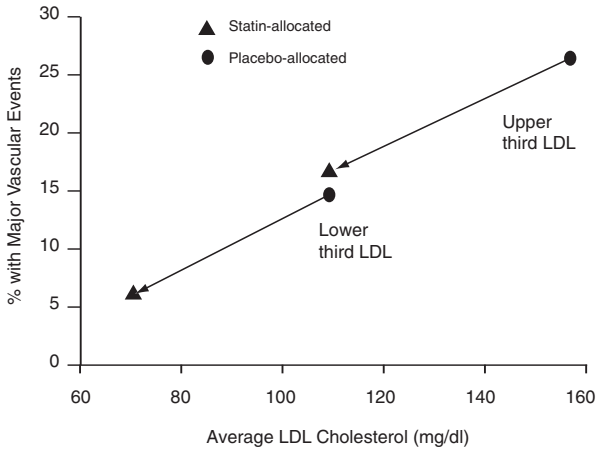

Figure 2 CV event rate and LDL-cholesterol levels. (Adapted from Heart Protection Study Collaborative Group. Lancet 2002;360:7–22.)
Legend: Statin-treated cohort (▲) placebo patients (●).

Authors' Reply

Dr. Ito and his colleagues declined the opportunity to reply.