Lessons from Lipid-lowering Trials on the Prevention of Coronary Events

Professor of Clinical Pharmacology, Director University Center for Dyslipidemias, University of Milano and Niguarda Hospital, Milano, Italy

A number of large scale primary and secondary prevention trials have reported that cholesterol lowering therapies can reduce the rates of first occurrence or recurrence of coronary heart disease (CHD) by about 30-40%. In addition, some trials have specifically investigated whether raising the protective high density lipoprotein (HDL) associated cholesterol can also reduce cardiovascular risk. Such trials have been mainly carried out in male subjects in countries with a high incidence of CHD; recently, however, the MEGA trial of primary prevention in the Japanese population has also shown benefit from pravastatin treatment in a predominantly female population.

Results from the majority of the trials have been consistent with the idea that the degree of cholesterol reduction is associated with a higher vascular benefit. In primary prevention trials, however, where risk may not be high, extreme cholesterol reductions do not achieve a clinically significant higher benefit vs more moderate reductions. In contrast, in secondary prevention, the TNT and, more recently the IDEAL studies, appear to support the conclusion that higher doses of statins, resulting in more marked total and LDL-cholesterol reductions, may be more advantageous vs more ordinary statin doses, albeit at the expense of a frequently significantly higher incidence of side effects. These last findings have, however, found some inconsistencies when comparing patients from the US and from other countries; in these latter, in fact, there appears to be far less difference in clinical outcomes when patients are treated more aggressively (Wiviott et al, Circulation 113:1406-14, 2006). The reasons for these differences are, however, as yet, unexplained.

The concept of “the lower the better” is, at present, the mainstay of cholesterol management in, particularly, coronary patients. Objectives for LDL-reduction (down to < 70 mg/dl or even lower) are of course dependent on the type of patients and their overall management, since for some patients such objectives may turn out to be unrealistic. Thus, a reduction of at least 30% of total/LDL-cholesterolemia should be a reasonable target for high risk patients.

As far as HDL-C increases or at least beneficial changes, unquestionably direct infusion of HDL (HDL-therapy), treatment with statins increasing HDL-cholesterolemia (eg the case of rosuvastatin in the ASTEROID trial), or, finally, management with drugs effective on HDL-cholesterolemia (nicotinic acid, fibrates) may provide significant advantage in selected patients. These treatments may be given alone or in association. The case of direct HDL-therapy has been best exemplified by the use of the mutant apolipoprotein A-I_{Milano}, leading to direct coronary atheroma reduction when evaluated by intravascular ultrasound. Very recently a dose related activity in an animal model of focal arterial plaque has been reported.

The elevation of HDL-cholesterol levels has been attempted with inhibitors of the cholesterol ester transfer protein (CETP) system. Interestingly, contrasting data have been provided in studies with drugs inhibiting or activating CETP. Probucol, a CETP activator, reduces HDL-cholesterolemia by activating HDL turnover and may reduce cholesterol deposition and, in some studies, dramatically reduce coronary events. In contrast, CETP inhibitors (JTT-705 or torcetrapib) dramatically raise HDL-C levels, but their clinical benefit has not as yet been clearly shown.

The final lesson for the physician is that global baseline risk is probably the major determinant of the clinical outcome. A 30% event reduction, reported in most clinical trials, has certainly a far different clinical value for patient series with minimal risk (eg in the MEGA trial) or very high risk (4S or HPS trials). From the calculation of the absolute risk reduction one may draw the “number needed to treat” ie a figure allowing calculation of the potential benefit of treatment not only at the individual but also at the population level.