Statins and mortality

See page 207, doi:10.1053/euhj.2001.2775 for the article to which this Editorial refers

In this issue Simes et al. present pooled estimates for mortality from the Pravastatin Pooling Project (PPP)[1]. The two secondary prevention studies[2-3] and the primary prevention trial[4] included in the PPP enrolled together about 20 000 men and women aged 45–75 years with or without established coronary artery disease and a wide range of baseline lipid levels. As compared to placebo, in those allocated to pravastatin, LDL cholesterol was lowered by 24% and triglycerides by 9%, whereas HDL cholesterol increased by 5%. After a follow-up period of about 5 years, in the pravastatin arm, there was a relative risk reduction of 20% for total mortality, and 24% for coronary heart disease mortality. Moreover, non-cardiovascular mortality was non-significantly reduced by 12%, with no evidence for an increase in specific deaths. There was no statistical evidence for differences in the relative risk reduction between primary and secondary prevention, different age strata, or sex. Among cardiovascular disease endpoints, the risk reduction was most impressive for fatal definite MI, with a risk reduction of 50%. Because of the similar relative risk reduction across different strata, the absolute risk reduction of pravastatin use was largely driven by the underlying mortality risk.

These results corroborate findings of single statin trials[2-6] and results of pooled combined cardiovascular end-points[7]. Compared to other interventions and medications after myocardial infarction[8], statins are among the most effective therapies in the reduction of subsequent cardiovascular events and mortality. Moreover, the results confirm that the relative risk reduction for different end-points is quite stable across different strata of baseline risk. As is known from many previous studies, the risk of mortality is several-fold increased among patients with established coronary heart disease[9], and accordingly, these patients derive the greatest benefit from statins with respect to absolute risk reduction. Despite the known large benefits, many patients with established coronary heart disease still do not receive lipid-lowering drugs as recently demonstrated in the EUROASPIRE II study[10] which surveyed patients up to 70 years of age after a hospital stay for coronary heart disease. In the PPP, the observed benefit was reached with a pravastatin dose of 40 mg per day, lowering cholesterol in a large proportion of participants to <5 mmol. l⁻¹. In daily practice, many treated patients do not reach this therapeutic goal[10], frequently due to underdosage of lipid-lowering drugs. The current study, together with previous reports of statin trials, support the broad use of statins in appropriate doses for secondary prevention of coronary heart disease.

Among patients without coronary heart disease, the relative risk reduction for cardiovascular and total mortality did not significantly differ from those with a history of myocardial infarction. The primary prevention subjects included in this quantitative overview were all male with moderate to high cardiovascular risk, and therefore do not represent a typical sample of primary prevention subjects. Nevertheless, the relative risk reduction for combined end-points and mortality was also similar among subjects in the AFCAPS/TEXCAPS trial[6] that enrolled men and women with a far lower average risk. Among subjects without coronary heart disease in the PPP, the coronary mortality risk was about one third of that of patients with coronary heart disease, and in the AFCAPS/TEXCAPS study the coronary mortality risk was about 15 times lower than in the secondary prevention subjects of the PPP. Because of the wide range of cardiovascular and total mortality risk in primary prevention, decisions regarding statin therapy have to be tailored to the individual patient according to his/her risk for subsequent cardiovascular events, as proposed in recent European[11] and US[12] guidelines.

Despite the growing body of evidence regarding the benefits of lipid lowering drugs, there are several issues that have to be clarified in further studies. First, the current analysis did not provide mortality results according to baseline lipid readings. These numbers would have been of interest because it is still not entirely clear whether there is a lower cut-off of LDL cholesterol for a benefit of lipid lowering drugs.
Despite the high number of subjects included in the PPP, the number of women enrolled was low, and no female subjects were included in primary prevention. Although there is no clear evidence that the mortality reduction by statin use differs among women and men, the small number of female subjects does not permit the drawing of clear conclusions, in particular with respect to total mortality. However, in secondary prevention, the risk reduction for combined fatal and non-fatal end-points was similar among both genders[7]. Although the included secondary prevention studies enrolled patients up to a relatively high age of 75 years, it would be important to have more data on patients at a more advanced age, particularly whether they benefit from statin therapy with respect to quality of life.

An additional point is the duration of drug treatment. The majority of patients receiving statins for secondary prevention are older than 50 or 60 years of age, and have a particularly high cardiovascular mortality risk. Therefore, it is not likely that with increased follow-up the benefits for cardiovascular risk reduction could be offset by any long-term harm from treatment. In primary prevention, however, the question of whether to treat or not to treat more frequently rises in subjects at younger age, with the consequence that lipid lowering therapy would have to be taken potentially for decades. So far, there is no evidence that statins increase the rate of non-cardiovascular disease incidence or mortality, and in the current pooled estimates the risk tended to be decreased. Although this is reassuring, certain diseases like cancer have a long latent period before clinical manifestations become apparent. Therefore, more data are needed regarding potential harm in the very long-term. Thus, the ongoing follow-up of the WOSCOP and LIPID population will provide important additional information with respect to this issue.

In summary, the accrued evidence clearly indicates a large benefit of lipid lowering drugs in most subjects at high risk for cardiovascular events. Moreover, the results demonstrate a similar relative risk reduction among groups irrespective of baseline risk, with an absolute risk reduction proportional to the underlying baseline risk. Despite the convincing results so far published, additional data would be very helpful to optimize treatment decisions, such as results from primary prevention trials including subjects with an intermediate risk, data on long-term use, as well as more study results on treatment effects among women and among patients at very advanced age.

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References