High-risk elderly patients PROSPER from cholesterol-lowering therapy

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Several large-scale statin trials have shown that cholesterol-lowering therapy produces substantial benefits for high-risk individuals, not just in middle age but also in old age, and the PROSPER trial reported in today's Lancet reinforces those findings for the elderly. Typically, in the previous trials, a 1 mmol/L reduction in plasma LDL cholesterol concentration maintained for about 5 years reduced the risks of coronary events, of strokes, and of revascularisation procedures by about one quarter (although the proportional reduction in risk appeared to be somewhat smaller during the first year after starting treatment). In PROSPER, 5804 high-risk individuals aged 70–82 (mean 75) years with mean LDL cholesterol of 3·8 mmol/L at entry were randomly allocated to receive 40 mg pravastatin daily or placebo for an average of 3·2 years. Despite a lowering of LDL cholesterol by an average of about 1·0 mmol/L during the study; however, allocation to pravastatin was associated with a proportional reduction of "only" 15% (SE 7, 95% CI 3–26) in the primary outcome of coronary death, non-fatal myocardial infarction, or stroke (408 [14·1%] pravastatin vs 473 [16·2%] placebo affected individuals, p=0·014). At least in part, this smaller than anticipated risk reduction may be due to chance, since the confidence interval around the estimate is wide and remains consistent with a reduction of one quarter. But it may also reflect the greater diluting effect on the overall risk reduction of a smaller reduction in risk during the first year after lowering LDL cholesterol in a trial involving 3 years of treatment (ie, 1 of 3 years) than in the previous statin trials that typically involved 5 years of treatment (ie, 1 of 5 years).

As PROSPER did not include patients aged less than 70, it cannot show whether the relatively short-term treatment studied would have produced similar proportional reductions in risk among younger individuals (and nor does the report provide separate analyses of the results above and below the mean entry age of 75 years). But some of the previous statin trials did involve large numbers of major vascular events among high-risk patients aged over and under 70, and their results indicate that a particular absolute LDL reduction produces similar proportional risk reductions in older and younger people. For example, among the 5806 patients aged 70 or over at entry to the Heart Protection Study (HPS), a 1 mmol/L reduction in LDL cholesterol maintained for an average of 5 years produced a substantial and definite 21% (SE 5, 95% CI 12–28) proportional reduction in the first-event rate of major vascular events (690 [23·6%] simvastatin vs 829 [28·7%] placebo, p=0·0001), which was about the same as the proportional reduction seen among younger participants. Similarly, in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial, an average LDL reduction of 1 mmol/L reduced the risk of vascular events by about one quarter irrespective of the age of the participants. Moreover, since older age is associated with higher risk, the absolute benefits during the 5-year treatment periods in those trials were somewhat larger among the older participants.

Although allocation to pravastatin in PROSPER was associated with a 19% (SE 8, 95% CI 6–31, p=0·006) proportional reduction in the rate of coronary death or non-fatal myocardial infarction, there was no apparent effect on strokes (hazard ratio 1·03, 95% CI 0·81–1·31, p=0·81). The investigators suggest that this may be because beneficial effects of statins on stroke do not begin to appear until after 3 years, whereas coronary risk reduction is an earlier phenomenon. But, with only 266 people having strokes during PROSPER (135 [4·7%] pravastatin vs 131 [4·5%] placebo), the statistical power of the study to detect a similar reduction in stroke to that observed for coronary events was very much lower than had been originally planned (see today’s report and reference 10). In such circumstances, when trying to determine whether the effects on the separate components of the primary outcome differ, it would be more appropriate to test for heterogeneity between the observed effects on coronary events and on strokes—and these do not appear to differ significantly. Moreover, there was a borderline significant 25% (SE 13) proportional reduction in the numbers who had transient ischaemic attacks (77 [2·7%] vs 102 [3·5%], p=0·051). By contrast, with more than 1000 participants having at least one stroke during HPS, separately significant reductions of about one quarter in strokes and in coronary events had already emerged within 3 years of starting statin therapy (each p<0·0001), and the 5-year stroke risk was significantly reduced both among younger and older participants (<70 years at entry: 274 [3·7%] simvastatin vs 349 [4·7%] placebo, p=0·002; 70–80 years: 170 [5·8%] vs 236 [8·2%], p=0·0003; data from HPS Collaborative Group). Despite these clear reductions in stroke, statin therapy did not appear to slow cognitive decline during 5 years of treatment in HPS, and this is now confirmed by PROSPER. Those findings suggest strongly that the lower rates of dementia found in observational studies among people taking statins were largely or wholly artefactual (ie, due to other differences that were actually responsible for the lower risks).

Allocation to pravastatin in PROSPER was associated with marginally significantly more participants having cancer diagnosed during the scheduled treatment period (245 [8·5%] pravastatin vs 199 [6·8%] placebo, p=0·02). Table 4 in the report indicates that much of this slight excess occurred early after the start of therapy and that it was not confined to any particular site, which suggests it may have been due to chance. This conclusion is supported by the lack of any overall excess of cancer among patients of all ages allocated pravastatin or other statins in the meta-analysis of previous large-scale trials.
provided by the PROSPER investigators. A non-
significant trend towards more cancers among patients
aged over 65 years who were allocated statin therapy has
been reported from the LIPID trial, but again no
particular site predominated. More, however, among more
than 1600 people with cancers recorded during HPS,
there was no significant excess either among younger or
older participants (570 years at entry: 460 [6.4%] simvastatin
vs 474 [6.4%] placebo, p=0.8; 70–80 years: 345 [11.8%]
vs 329 [11.4%], p=0.8; data from HPS Collaborative
Group) or at any particular site (eg, gastrointestinal
cancer: 228 [2.2%] vs 223 [2.2%]). The Cholesterol Treatment Trials’ prospectively
planned meta-analyses of the results of all large-scale
randomised trials of cholesterol-lowering therapy should
provide even more reliable assessment of any effects on
the main types of cancer, as well as of the effects on
vascular events in different circumstances (eg, with
respect to entry age and lipid concentrations, and time
from start of treatment).

Given that the overall reduction in vascular events in
PROSPER is not highly statistically significant, selective
emphasis on the results observed in some particular
subgroup may well not be reliable. So, even though there
was little apparent risk reduction among those
participants who presented with HDL concentrations
of 1·1 mmol/L or greater, this subgroup analysis should be
interpreted with caution—especially since it is not
confirmed by the much larger numbers in the previous trials.

For example, among the 7694 participants in HPS with HDL concentrations of 1·1 mmol/L or
greater, there was a substantial and definite 21% (SE 5, 95% CI 12–28) proportional reduction in
the rate of major vascular events (655 [17.0%] simvastatin vs 801 [20.9%] placebo, p<0.001).
Nor do other aspects of the pretreatment lipid-profile appear to influence materially the
proportional risk reductions with statin therapy. Most notably, reducing LDL cholesterol from
about 4 to 3 mmol/L in HPS reduced risk by about one quarter, and reducing it from about 3 to 2 mmol/L,
also reduced risk by about one quarter. Those findings indicate that any thresholds below which lowering LDL
cholesterol does not safely reduce risk are at much lower concentrations (eg, below 2 mmol/L) than are typically
seen in Western populations.

In conclusion, PROSPER and the other large-scale
trials have now collectively shown that cholesterol-
lowering statin therapy rapidly reduces the risks of major
vascular events not only in middle age but also in older
age, and the benefits are substantial among patients who
are at high risk because of pre-existing occlusive artery
disease, diabetes, or other factors (including age). These
studies have also shown that such treatment is well-
tolerated and safe, even among older patients, with no
good evidence of any increase in cancer or other non-
vascular morbidity or mortality. Hence, long-term statin
therapy should now be considered routinely for all such
high-risk patients largely irrespective of whether their
presenting lipid concentrations or their age.

The Clinical Trial Service Unit has a staff policy of not accepting
honouraria or other payments directly or indirectly from the
pharmaceutical industry, except for reimbursement of costs
to participate in scientific meetings. HPS was coordinated by the unit
independently of all funding sources (Medical Research Council, British
Heart Foundation, Merck & Co, and Roche Vitamins Ltd).

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**Childhood adversity still matters for adult health outcomes**

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That conditions experienced early in life have a long-lasting
influence on adult health is not a new idea. But only
d Recently has the entire lifecycle become a major focus of
epidemiological research, with the objective of under-
standing when as well as how particular exposures act on
health outcomes.

One approach to yield valuable clues as to when influences might be acting has been to
evaluate associations with socioeconomic circumstances earlier in life on adult health
outcomes, with the objective of understating when and how particular exposures act on
health outcomes. Clues as to when influences might be acting have been provided by
epidemiological research, with the objective of understating when and how particular exposures act on
health outcomes.