Lipid lowering drugs for patients who continue to smoke?

For many of us, the issues raised by the prescription of lipid lowering drugs to patients who continue to smoke are perplexing. In particular there is the concern that the benefits of lowering serum cholesterol may be offset by the harmful effects of nicotine; and that general practitioners and hospital doctors who advise on one aspect of a patient’s care to the exclusion of another may somehow be construed as approving, or at least accepting of, the fact that their patient continues to smoke.

Risks of smoking

Some smokers still cling to the belief, reinforced by the tobacco companies, that nicotine is not harmful. A sympathetic but firm explanation of the risks may therefore be helpful. The study of 35,000 British doctors followed from 1951 to 1991 showed that 50% of habitual smokers die of diseases that have nothing to do with smoking, 25% of smokers die of smoking related diseases in old age, but that 25% of smokers die of smoking related disease in middle age, so denying themselves 20–25 years of a non-smoker’s life expectancy. This explanation acknowledges the fact that everyone knows at least someone who smoked happily until the age of 90 years before being run over by a bus, while at the same time puts the risk of premature death into chilling perspective: who among us would willingly hold a gun to his or her head with one of four barrels loaded and then pull the trigger?

Results of the statin trials

The results of the five statins trials are illuminating. These show that the event rate among current smokers on active treatment is nearly identical in each trial to the event rate among never and ex-smokers on placebo (table 1, last column). This implies there may be as much to be gained by stopping smoking as there is by taking a statin. Also given are the odds ratios for the highest risk group (placebo smokers) against the lowest risk (statin non-smokers), and the placebo against statin comparisons for the smokers and the non-smokers. Because proportionate risk reduction was similar across all five trials, those at highest risk initially had most to benefit by treatment, particularly those with established vascular disease and patients who smoked cigarettes. The irony therefore is that while stopping smoking is likely to be as effective as statin treatment, smokers may have more to gain than never and ex-smokers by taking statins. Where does this leave the clinician?

Secondary prevention

We consider primary and secondary prevention separately. Patients who have been admitted to hospital and survived a myocardial infarction (MI) are usually highly motivated to reduce their risk of a further heart attack. Smokers who quit after their MI halve their risk of a further event, and fortunately at least 50% of smokers who have had an MI can be persuaded to do so. Patients who are struggling to quit should try nicotine replacement therapy, behavioural techniques, hypnosis or acupuncture. Nicotine replacement therapy has been shown to be safe in cardiac disease, although patients should be warned against smoking while wearing a patch in order to avoid a potentially harmful additional dose of nicotine.

This will leave up to 50% of all MI survivors who used to smoke before their MI, still smoking because they are either unable or unwilling to quit. Up to 85% of these will have serum total cholesterol > 5 mmol/l and so will qualify for a statin. Given the substantial benefits to be gained by statin treatment in this group, we imagine few would wish to deny smokers this particular form of treatment.

### Table 1 Event rates and odds ratios by smoking habit and treatment status in the five statin trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Statin</th>
<th>Placebo</th>
<th>Statin</th>
<th>Odds ratio with approximate 85% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>193/996</td>
<td>127/542</td>
<td>429/1627</td>
<td>304/1679</td>
<td>2.17 (1.75 to 2.68) 1.57 (1.20 to 2.04) 1.62 (1.37 to 1.910 1.17 (0.93 to 1.477)</td>
</tr>
<tr>
<td>LIPID</td>
<td>92/444</td>
<td>66/425</td>
<td>623/4058</td>
<td>491/4087</td>
<td>1.91 (1.49 to 2.45) 1.42 (1.00 to 2.02) 1.33 (1.17 to 1.51) 0.99 (0.75 to 1.30)</td>
</tr>
<tr>
<td>CARE</td>
<td>111/334</td>
<td>81/337</td>
<td>437/1744</td>
<td>349/1744</td>
<td>1.99 (1.54 to 2.57) 1.57 (1.12 to 2.21) 1.34 (1.14 to 1.57) 1.06 (0.81 to 1.39)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>144/1460</td>
<td>100/1445</td>
<td>104/1832</td>
<td>74/1855</td>
<td>2.63 (1.97 to 3.52) 1.47 (1.13 to 1.92) 1.45 (1.07 to 1.97) 0.81 (0.61 to 1.08)</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>36/389</td>
<td>17/429</td>
<td>147/2012</td>
<td>99/2875</td>
<td>2.86 (1.92 to 4.25) 2.47 (1.37 to 4.48) 1.49 (1.15 to 1.93) 1.29 (0.77 to 2.15)</td>
</tr>
</tbody>
</table>

The study primary end points considered were CHD death and non-fatal myocardial infarction (NFMI) (4S, LIPID, WOSCOPS), CHD death or NFMI or coronary revascularisation (CARE), and fatal or non-fatal MI, unstable angina or sudden cardiac death in AFCAPS. Within each study, subjects were followed up for differing lengths of time; our analyses ignore this feature and report odds ratios based on events and subjects implicitly assumed to have the same follow up. The studies reported data on smoking status differently: our analyses contrast current smokers with never and ex-smokers, at the time of the baseline visit. Smoking in WOSCOPS meant cigarettes, pipes or cigars, whereas in the other studies it appeared to relate only to cigarettes. 4S, Scandinavian Simvastatin Survival Study; LIPID, Longterm Intervention with Pravastatin in Ischaemic Disease; CARE, Cholesterol And Current Events; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS, Airforce Coronary Atherosclerotic Prevention Study.
Primary prevention
The position in primary prevention is likely to be different. By virtue of the very much larger numbers involved, primary prevention must necessarily rely more on lifestyle measures than pharmacological intervention. To do otherwise would be undesirable, unaffordable, and unachievable. Pharmacological intervention in primary prevention, whether by antihypertensive drugs, aspirin or statins, is therefore likely to be limited to those individuals at high risk of coronary heart disease (CHD). CHD risk may be estimated by an individual's age, sex, smoking habit, glucose tolerance, blood pressure, and total cholesterol/high density lipoprotein (HDL) cholesterol ratio using validated risk scores, of which the Joint British Chart is probably the most helpful. The currently recommended threshold for intervention with a statin in primary prevention is 3% per year which is approximately equivalent to the risk experienced by subjects who were included in the low risk secondary prevention studies LIPID and CARE.

The difficulty for the clinician is that lifestyle measures tend to be ineffective in primary prevention, particularly among poorly motivated socioeconomically deprived populations, whereas the benefits of pharmacological intervention are well established. This does not alter the fact that a 60 year old non-diabetic male with systolic pressure 150 mm Hg and total cholesterol/HDL cholesterol ratio of 7 has a CHD risk greater than 30% over 10 years if he smokes, and nearer 20% over 10 years if he does not, it just means that it is sometimes more realistic to prescribe a statin.

Smoking cessation
Before prescribing a statin, the trial results described earlier make a strong case for ensuring that all opportunities for smoking cessation have been explored. Most smokers must have thought at some stage in their lives that they would be undesirable, unaffordable, and unachievable. Pharmacological intervention in primary prevention, whether by antihypertensive drugs, aspirin or statins, is therefore likely to be limited to those individuals at high risk of coronary heart disease (CHD). CHD risk may be estimated by an individual's age, sex, smoking habit, glucose tolerance, blood pressure, and total cholesterol/high density lipoprotein (HDL) cholesterol ratio using validated risk scores, of which the Joint British Chart is probably the most helpful. The currently recommended threshold for intervention with a statin in primary prevention is 3% per year which is approximately equivalent to the risk experienced by subjects who were included in the low risk secondary prevention studies LIPID and CARE.

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