Preventing cardiovascular disease in hypertension: effects of lowering blood pressure and cholesterol

R. GREEN, S. KWOK and P.N. DURRINGTON

From the Department of Medicine, Manchester Royal Infirmary, Manchester, UK

Received 19 April 2002 and in revised form 13 September 2002

Summary

Background: In guidelines for the primary prevention of cardiovascular disease, systolic blood pressure (SBP) or diastolic blood pressure (DBP) is treated with medication at lower levels of risk than those at which statin treatment is recommended for cholesterol lowering.

Aim: To compare the potential benefits of antihypertensive medication and statin therapy in hypertensive patients, and examine whether this policy is rational.

Design: Retrospective cross-sectional survey.

Methods: We studied 146 men and 150 women aged 56 (54–58) (mean (95% CI)) years and 60 (58–62) years, respectively, who had commenced drug therapy for hypertension within 10 years in five general practices in Greater Manchester. Coronary heart disease (CHD) and stroke risk were calculated, and the potential benefit of blood pressure lowering treatment and statin therapy estimated using the results of published meta-analyses of clinical trials.

Results: Blood pressure before treatment was initiated was 176 (173–179)/102 (100–104) mmHg in men and 176 (172–179)/98 (96–100) mmHg in women. Serum cholesterol was 5.7 (5.5–5.9) mmol/l and high density lipoprotein (HDL) cholesterol 1.3 (1.2–1.4) mmol/l in men. The corresponding values in women were 6.3 (6.1–6.5) mmol/l and 1.5 (1.4–1.6) mmol/l. Of the men, 44% (36–52%) smoked and 23% (17–31%) had diabetes mellitus, whereas 27% (20–35%) of the women smoked and 26% (19–34%) had diabetes. These risk factors gave the combined group of men and women a CHD risk of 19.7% (12.0–28.0%) (median (IQR)) and a stroke risk of 8.8% (3.8–13.9%) over the next 10 years. All patients were prescribed antihypertensive medication and 15% subsequently received statin treatment.

The 10-year CHD risk would be expected to decrease to 16.5% (10.1–23.5%) on anti-hypertensive therapy. Had statin treatment been given instead, it would have been reduced to 13.2% (8.05–18.7%). For stroke, the 10-year risk on antihypertensive therapy was calculated as 5.5% (2.4–8.6%) and on statin 6.2% (2.7–9.9%). This meant that combined CHD and stroke risk would be reduced from 29.4% (17.5–41.5%) to 22.4% (17.5–41.5%) on antihypertensive therapy and to 20.1% (11.9–28.2%) on statins. The difference between statin and antihypertensive therapy was statistically significant (p<0.0001).

Discussion: Because the object of drug treatment in mild–moderate hypertension is to reduce cardiovascular disease risk and not simply to decrease blood pressure, current recommendations and practice should be revised so that more patients can benefit from evidence-based therapy favouring a more holistic approach, including cholesterol-lowering therapy.

Introduction

Two primary prevention trials of statin therapy have been published: the West of Scotland Coronary Prevention Study (WOSCOPS), in which the coronary heart disease (CHD) risk was equivalent to 15% over 10 years,1 and the Air Force/ Texas Coronary Atherosclerosis Prevention Study

Address correspondence to Professor P.N. Durrington, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL. e-mail: pdurrington@man.ac.uk

© Association of Physicians 2002
Hypertension Society (BHS) and the NSF on CHD line with both the Joint British recommendations for therapy in primary CHD prevention. However, in the NSF on CHD risk be 20 mmol/l and serum cholesterol levels must exceed 5 mmol/l when their 10-year CHD risk was as low as 15%. The intention was to limit the cost of statin therapy in primary CHD prevention. However, in line with both the Joint British recommendations (JBR) and the most recent guidance from the British Hypertension Society (BHS) the NSF on CHD recommended that blood-pressure-lowering drug therapy should be used in primary prevention if blood pressure is 160/100 mmHg or greater, regardless of CHD risk, and in the range 140–159/90–99 mmHg if the 10 year CHD risk exceeds 15%.

In the rest of Europe, treatment of blood pressure is recommended when it exceeds 140/90 mmHg, but serum cholesterol levels must exceed 5 mmol/l and the CHD risk be 20% or greater over the next 10 years for statin therapy. Even in the USA, where statin therapy advice has been more liberal, it is recommended that, whereas blood pressure levels that persist above 140/90 despite lifestyle advice require drug treatment, serum low-density lipoprotein (LDL) cholesterol in primary prevention must exceed 2.6 mmol/l and CHD risk be 20% or greater over the next 10 years for statin therapy. Higher levels of LDL cholesterol can be treated at lower levels of CHD risk (e.g. LDL cholesterol of ≥4.1 mmol/l at ≥10% risk) with levels exceeding 4.9 mmol/l receiving statin treatment regardless of CHD risk.

In this study we examined whether in patients receiving treatment for hypertension in general practice, these recommendations best serve their interests in terms of potential reductions in CHD and stroke risk, and make the best use of the scientific evidence.

Methods

The study was carried out in five general practices in Manchester and Salford. Practice records were examined in alphabetical order, with the aim of finding up to 30 men and 30 women who had commenced antihypertensive treatment between 1991 and 2001 in each practice. All practices had computerized records. Hypertensive patients were identified by a search based on the Read code G2 (hypertensive disease) followed by a search of patients receiving bendrofluazide to identify any additional patients who were receiving this medication for hypertension but were not coded for hypertension. Exclusions were: patients aged <18 years; patients known to have CHD or other atherosclerotic disease at the time antihypertensive therapy was commenced; accelerated hypertension (in the opinion of the general practitioner); familial hypercholesterolaemia; secondary hypertension; or pregnancy-related hypertension. The inclusion criteria for the study were that the following information was recorded: age when antihypertensive medication was initiated, gender, systolic and diastolic blood pressure on date treatment was started, smoking status (non-smoker/smoker), values of serum cholesterol and HDL cholesterol concentration on first occasion measured and whether diabetes was present (defined as receiving hypoglycaemic treatment or random glucose ≥11.1 mmol/l or fasting glucose ≥7 mmol/l). Patients without a resting electrocardiogram were not excluded.

The inclusion criteria were not met by 365 patients whose notes were examined because there was no cholesterol value (n = 193), no HDL cholesterol value (n = 153), no blood pressure recorded on day treatment commenced (n = 18) and one patient had undergone gender reassignment therapy. Each of the five practices yielded 30 women. Three each provided the full complement of 30 men. In another, only 29 men were eligible and in the fifth, only 27 men. There were thus 296 patients (150 women and 146 men) included in the study after examining 661 sets of notes. Whether the patients were receiving statin as well as antihypertensive medication on 1 May 2001 was recorded.

The study was performed according to the criteria of the Manchester Research Ethics Committees for student research projects. Patients’ names or other information by which they could be identified...
were not recorded. It was for this reason that alphabetical order was used for recruitment rather than a randomized sampling frame. No exclusion was made on ethnic grounds.

CHD and stroke risk for each patient were calculated as percentage risk over the next 10 years from the time antihypertensive treatment was initiated using the risk equation derived from the Framingham study (the Joint British Societies Cardiac Risk Assessor programme for Windows Excel). The expected reduction in stroke and CHD risk from a meta-analysis of blood-pressure-lowering agents in clinical trials was calculated as a 16% decrease in CHD risk and a 38% decrease in stroke risk. The reduction in stroke and CHD risk that would have been anticipated had statin treatment been instituted was calculated from the results of a meta-analysis as a 33% reduction in CHD risk and a 29% decrease in stroke risk.

**Statistics**

Variables with a normal distribution are presented as means with 95% CIs. CHD and stroke risk, which were non-Gaussian, are presented as medians with interquartile ranges. The differences between risks on antihypertensive medication and on statin medication were distributed normally, and a two-tailed Student’s paired t test was used to compare them.

**Results**

The risk factors and the calculated risks for the men and women studied are shown in Table 1. All of the patients had been prescribed antihypertensive medication, and 43 (15%, 95% CI 11–19%) had been prescribed a statin. UK guidelines are identical for the management of hypertension, and only 14 patients (5%, 95% CI 3–8%) had received antihypertensive medication unnecessarily according to UK guidelines, although they all should have received antihypertensive medication if they lived in the USA or elsewhere in Europe. In every instance, these patients had blood pressure in the range 140–159/90–99 mmHg, but had a CHD risk of <15% over 10 years. In the great majority (93, 90–96%) receiving antihypertensive therapy, the indication was that the blood pressure exceeded 160/100 mmHg. In 34% (30–39%) of the whole group, who were treated for hypertension quite correctly according to UK guidelines, on the grounds that their blood pressure exceeded 160/100 mmHg, their CHD risk was <15% over 10 years.

CHD risk over 10 years was ≥10% in 241 patients (81%, 76–84%), ≥15% in 189 patients (64%, 58–69%), ≥20% in 139 (47%, 41–53%) and ≥30% over 10 years in 59 (20%, 16–25%). There were 239 patients whose serum cholesterol was ≥5 mmol/l. Of these, CHD risk over 10 years was ≥10% in 201 (68%, 61–72% of the whole study group), ≥15% in 152 (51%, 46–58%), ≥20% in 14 (39%, 32–44%) and ≥30% in 47 (16%, 12–21%). Only the last group could be recommended for statin therapy according to the British NSF guidelines. In reality, a total of 43 (15%, 11–20%) patients received statin therapy, 20 (7% 4–11%) of whom had a CHD risk ≥30% over 10 years.

Table 2 shows the CHD, stroke and combined CHD and stroke risk before treatment, and what it would be on treatment with drugs to lower blood pressure or with statin therapy in the men and women studied, if the results of published

**Table 1** The risk factors for cardiovascular disease in 296 patients with mild-moderate hypertension and their absolute coronary heart disease (CHD), stroke and combined CHD and stroke risk, calculated from the Joint British Societies Cardiac Risk Assessor programme

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>146</td>
<td>150</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (54–58)</td>
<td>60 (58–62)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>176 (173–179)</td>
<td>176 (172–179)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102 (100–104)</td>
<td>98 (96–100)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>44 (36–52)</td>
<td>27 (20–35)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>23 (17–31)</td>
<td>26 (19–34)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.7 (5.5–5.9)</td>
<td>6.3 (6.1–6.5)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.3 (1.2–1.4)</td>
<td>1.5 (1.4–1.6)</td>
</tr>
<tr>
<td>CHD risk (%/10 years)*</td>
<td>24.4 (15.4–31.3)</td>
<td>15.3 (10.2–23.0)</td>
</tr>
<tr>
<td>Stroke risk (%/10 years)*</td>
<td>9.1 (4.0–14.7)</td>
<td>8.4 (3.4–13.2)</td>
</tr>
<tr>
<td>Combined CHD and stroke risk (%/10 years)*</td>
<td>33.2 (20.1–45.1)</td>
<td>24.7 (14.6–34.7)</td>
</tr>
</tbody>
</table>

Results are mean with 95% CIs in parentheses except for risk, which has a non-Gaussian distribution, for which the median (interquartile range) is provided. *Events per 100 men or women (%) over the next 10 years.
meta-analyses of clinical trials were realised in practice. The reduction on stroke risk is greater with antihypertensive therapy, whereas the decrease in CHD risk is greater with statins. However, because the likelihood of a CHD event is greater than that of a stroke, the statins have a significantly greater benefit on overall cardiovascular risk.

Discussion

The majority of patients considered to have hypertension by their general practitioners were receiving medication to lower blood pressure appropriately according to the British recommendations. Most did so on the criterion that their blood pressure was >160/100 mmHg, so patients whose blood pressure was in the range 140–159/90–99 mmHg combined with a CHD risk exceeding 15% over 10 years may have gone untreated. In the USA and the rest of Europe, these patients would have received antihypertensive therapy regardless of their cardiovascular risk. The reasons for this are likely to be manifold, but the complexity of the guidelines and whether they make sense are likely to be important. Indeed, the most important finding from our study concerns the logic of the guidelines themselves, not only in Britain, but also in the rest of Europe and the USA. Meta-analyses of statin and blood-pressure-lowering drug trials show that the reduction in CHD risk with statin treatment is greater than that for antihypertensive therapy. Even in the hypertensive patients studied here, CHD risk greatly exceeded stroke risk. Thus although blood pressure lowering is more effective than statin therapy in decreasing stroke risk, because stroke occurs less frequently than CHD, antihypertensive therapy at least in these ‘common or garden’ hypertensive patients has less benefit in reducing cardiovascular risk (combined CHD and stroke risk) than statin therapy. It could be argued that the evidence that statins reduce stroke risk cannot be applied in primary prevention of stroke because most of the cases of stroke in the studies included in meta-analyses have been in patients who have CHD. The findings of the Heart Protection Study, however, suggest that this is untrue. Furthermore, even if we totally discount any potential for statins to decrease stroke risk in primary prevention, the greater reduction in CHD risk with statins and the higher incidence of CHD still means that they offer at least as much, if not more, benefit in terms of reducing overall cardiovascular risk. It could be argued that the figure of 16% for the reduction in CHD risk with blood-pressure-lowering therapy, which we have used in this study, is an underestimate, and that greater benefit may accrue from some antihypertensive agents such as ACE inhibitors. Some studies have suggested that this may be as high as a 20% reduction in CHD risk. However, even if we were to use this value to calculate overall benefit from blood pressure reduction, the effect would still be less than the 33% decrease in risk from statin trials, and that this figure is relevant to primary prevention is amply supported in primary prevention trials.

### Table 2

The CHD, stroke and CVD (CHD + stroke) risk calculated using the Joint British Societies Cardiac Risk Assessor programme in 296 men and women considered to have hypertension by their general practitioners and the hypothetical reduction in these risks which would be achieved either by antihypertensive or statin therapy from the results of published meta-analyses

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>After antihypertensive</th>
<th>After statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD risk (%/10 year)*</td>
<td>19.7 (12.0–28.0)**</td>
<td>16.5 (10.1–23.5)</td>
<td>13.2 (8.05–18.7)***</td>
</tr>
<tr>
<td>Stroke risk (%/10 year)*</td>
<td>8.8 (3.8–13.9)***</td>
<td>5.5 (2.4–8.6)</td>
<td>6.2 (2.7–9.9)***</td>
</tr>
<tr>
<td>Combined CHD and stroke risk (%/10 year)*</td>
<td>29.4 (17.5–41.5)***</td>
<td>22.4 (13.6–31.6)</td>
<td>20.1 (11.9–28.2)***</td>
</tr>
</tbody>
</table>

Values are median (IQRs). *Events per 100 people (%) over the next 10 years. **Significantly different from risk on antihypertensive and statin, p<0.0001. ***Significantly different from risk on antihypertensive, p<0.0001.
The proportion of diabetic patients (25%) included in the hypertensive population studied here is relatively high, probably because general practitioners are more likely to measure serum lipid levels in diabetic patients. Both the JBR and NSF guidelines recommend treatment of blood pressure in diabetes mellitus when it exceeds 130/80 mmHg without CHD risk calculation, although both unlike those in the USA, they recommend risk calculation for statin therapy in diabetes as in non-diabetic patients. Nonetheless, the inclusion of patients with diabetes in our population does not affect our conclusions, as the findings were similar when they were excluded from the calculations. It could also be argued that the meta-analyses of clinical trials of statins and antihypertensive agents will not accurately reflect the benefit from these agents in clinical practice, because of the vicissitudes of patient compliance, the greater heterogeneity of patients treated, and the degree of determination on the part of physicians and nurses. It is beyond the scope of the present study to answer such questions, but this does not render our findings invalid, because the guidelines themselves are based whenever possible on the outcome of meta-analyses, which are regarded as the highest form of evidence. It is within that convention that we have found them to be irrational. Our cardiovascular risk assessments were made over 10 years exactly in accordance with the guidelines, whereas most of the clinical trial evidence upon which the meta-analyses are based was obtained over shorter periods, usually 5 years. A greater relative reduction in risk for both statin and hypertensive agents would be expected over a longer period. However, adjusting the period of risk calculation to the duration of the trials makes no difference to our conclusions, and we have chosen to present the simpler analysis, which is closer to the guidelines themselves.

We would not wish to conclude from these results that lowering blood pressure should be abandoned in favour of statin therapy. Both should be used more effectively. Indeed, if the relative reduction in cardiovascular risk with statins in patients on treatment for high blood pressure are the same as in patients not receiving antihypertensive medication (which appears to be the case), the overall cardiovascular risk in the patients in this study would have decreased from 29% to 15% over the next 10 years on a combination of statin and antihypertensive medication. There is clearly evidence that both the guidelines themselves and current medical practice do not take full advantage of abundant clinical trial evidence. In particular, there is no argument, based on scientific evidence, for retaining a higher level of CHD or cardiovascular risk as an indication for statin as opposed to antihypertensive therapy. There is agreement between Britain and the rest of Europe and the USA that statin therapy should be used in the secondary prevention of CHD. However, the European and US recommendation that in primary prevention patients at >20% rather than >30% risk of CHD over the next 10 years should receive statin therapy makes better use of evidence than the British guidelines. The advice from the US that all diabetic patients with LDL cholesterol >2.6 mmol/l, and all people with LDL cholesterol >4.9 mmol/l, should receive lipid-lowering therapy in primary prevention, goes further still. The American guidelines also permit intervention with medication at progressively lower levels of CHD risk than 20% over 10 years as LDL cholesterol rises from 2.6 to 4.9 mmol/l. Even so, many Americans will receive treatment for blood pressure at lower levels of risk than those in whom statin therapy is indicated. The reason for retaining a higher cardiovascular risk for the institution of statin therapy than for antihypertensive therapy in primary prevention, which is general internationally, but most extreme in Britain, would appear to be challenged by our findings.

Acknowledgements
We are grateful for statistical advice to Drs S. St Leger and A. Vail of the Biostatistics Group, University of Manchester School of Biological Sciences, and to Drs I. Bennett, L. Brosnan, I. Burton, S. Haber, J. Rowan and K. Shearer for allowing us access to practice records. We thank Ms C. Price for expert manuscript preparation. Support was received from the NHS R&D Levy. Professor Durrington conceived the study. All three authors contributed to the design. SG obtained the data and carried out the statistical analysis. All three of us contributed to the manuscript. Interests declared: none.

References
3. Hiebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and
18. Waters D. Cholesterol-lowering: should it continue to be the last thing we do? Circulation 1999; 99:3215–17.