Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease

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Aims To estimate the potential effectiveness of different "high-risk" and "population" approaches to the primary prevention of cardiovascular disease (CVD) in middle-aged British men, after correction for regression dilution bias.

Methods and results We used a combination of cohort and randomised controlled trial evidence to estimate the effectiveness of high-risk strategies, based on the identification of high-risk factors or high absolute risk, and strategies based on population-wide reductions in cholesterol and blood pressure. High-risk strategies were potentially effective but would need to be used widely to have a substantial effect on CVD in the population. Aggressive pharmacological treatment (using statins, \(\beta\)-blockers, ACE-inhibitors and aspirin) in individuals with a 10-year Framingham event risk of \(P \geq 30\%\) (6\% of population) would have reduced major CVD by at most 11\%. This figure increased to 34\% at a \(P \geq 20\%\) treatment threshold (26\% of population). In contrast, modest downwards shifts in the population distributions of serum total cholesterol and systolic blood pressure led to marked expected reductions in major CVD. Taking regression dilution bias into account, 10\% reductions in long-term mean blood cholesterol and blood pressure could have reduced major CVD by 45\%.

Conclusions If high-risk strategies are to have a major impact on CVD in the population, they need to be more widely used than previously envisaged. Population-wide reduction of major risk factors is needed if CVD is to be substantially reduced.

Introduction

Two general strategies for the primary prevention of cardiovascular disease (CVD) are widely recognised — the "high-risk" approach, in which individuals at high risk of disease are identified and targeted for preventive treatment, and the "population" approach, in which population-wide changes in risk factors are made\textsuperscript{1}. The high-risk approach is the natural approach for medical practitioners who are concerned with the occurrence of disease in individuals. However, most CVD cases occur not amongst the small number of individuals at greatest risk, but amongst the much larger numbers of individuals.
Methods

We use a combination of data from a prospective observational study of cardiovascular disease (the British Regional Heart Study) and estimates of relative risk reduction from meta-analyses of randomised controlled trials (where possible) to examine the influence of population and high-risk strategies on first occurrences of major cardiovascular disease events (defined as fatal/non-fatal myocardial infarction (MI) and stroke) among middle-aged men with no previous diagnosis or symptoms of CVD.

Strategies for CVD prevention

A variety of high-risk prevention strategies were examined: (1) identification and management of individual risk factors: (a) set threshold for blood cholesterol and treat with a statin; (b) set threshold for blood pressure and treat with a β-blocker or diuretic and (2) identify threshold level of 10-year Framingham risk (as recommended in the UK at a ≥ 30% level and Europe at a ≥20% level) and treat with: (a) a statin; (b) a β-blocker or diuretic; and (c) a combination of treatment with aspirin, a β-blocker or diuretic, an ACE inhibitor and a statin. In a subsidiary analysis, the potential effects of a prevention approach based on age and the use of combination treatment with aspirin, a β-blocker or diuretic, an ACE inhibitor and a statin were examined. Though there is growing evidence that Framingham equations tend to overestimate true risk in European populations, the original equations are used throughout this paper to reflect current guidelines (note that correction for this overestimation would decrease the size of the high-risk group and hence decrease the estimated effectiveness of the high-risk approach). Using data from relevant trials or meta-analyses of trials, we assumed that blood cholesterol reduction with statins reduced the risk of MI by 31%,13 and stroke by 24%,14 and that blood pressure reduction with first line antihypertensive drugs (a diuretic or a β-blocker) reduced MI risk by 18% and stroke risk by 38%. Among individuals with a high Framingham risk score, we further assumed that aspirin reduced MI risk by 26% and stroke risk by 22%16 and ACE-inhibitors reduced MI risk by 20% and stroke risk by 32%.17 Assuming that the ratio of first episodes of MI to stroke during middle-age is 4:1 (the ratio observed in the first 10 years of our study), we estimated the relative risk reduction for the combined outcome of major CVD by calculating the weighted average of the two separate relative risk reductions (i.e., four-fifths of the relative risk reduction for MI plus one-fifth of the relative risk reduction for stroke). Treatment effects were assumed to be multiplicative so that the combined relative risk reduction from taking aspirin, statins, ACE-inhibitors and β-blockers/diuretics was 68% (1 – 0.75 (aspirin) × 0.70 (statins) × 0.78 (ACE inhibitors) × 0.78 (β-blockers/diuretics)).

The reductions in major CVD following the various high-risk strategies were compared with those following three different population approaches: (a) population-wide reduction in mean cholesterol; (b) population-wide reduction in mean blood pressure; and (c) population-wide reductions in both mean cholesterol and mean blood pressure. For each of these approaches, the effects of various “downwards shifts” in the population distributions were assessed whereby each individual reduces his exposure level by the same absolute amount (for presentation purposes the size of these absolute reductions are expressed in terms of a percentage of the mean).

The British Regional Heart Study

The British Regional Heart Study (BRHS) is a prospective study of cardiovascular disease based in one General Practice in each of 24 British towns. Participants were enrolled in 1978–1980 aged 40–59 years and have been followed up for all-cause mortality and for cardiovascular morbidity, with fewer than 1% of participants being lost to follow-up. Details regarding baseline physical and biochemical measurements have been described previously. In two towns (one with high and one with low CHD mortality), men were re-examined after both 16 and 20 years of follow-up, at which blood pressure was measured and a blood sample was taken for measurement of blood lipids. These repeated measurements were used to provide estimates of the
effects of within-person variability (regression dilution ratios)\(^2\)\(^1\) for the current report.

Assessment of baseline risk

At the baseline assessment, participants were asked about recall of any doctor diagnosis of myocardial infarction, stroke or angina and whether they had ever had a history of severe chest pain lasting for half an hour or more that caused them to consult with a doctor. Participants also completed a WHO (Rose) angina questionnaire providing evidence of definite or possible angina. Individuals with recall of myocardial infarction, angina or stroke, history of severe chest pain or Rose angina questionnaire evidence of definite or possible angina were excluded from analyses.

Assessment of incident CVD

Information on date and cause of mortality was collected through the established "tagging" procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Fatal coronary events were defined as deaths with ischaemic heart disease as the underlying cause including sudden death of presumed cardiac origin (ICD-9 410–414) and fatal strokes were defined as deaths with an ICD-9 code of 430–438. Evidence of non-fatal heart attacks and strokes was obtained from general practitioner reports supplemented by systematic two-yearly reviews of the patients’ records, through to the end of the study period. Non-fatal heart attacks were diagnosed according to established World Health Organization criteria, whilst non-fatal strokes were defined as all cerebrovascular events which produced a neurological deficit present for more than 24 h. In this paper, major CVD events include death from coronary heart disease or stroke and non fatal myocardial infarction or stroke.

Statistical methods

The association between baseline risk exposures and 10-year major CVD risk was assessed using logistic regression; analyses were adjusted for age, blood cholesterol, blood pressure, cigarette smoking status (current, ex, never), body mass index, physical activity (none, occasional, light, moderate), diabetic status (yes/no) and area of residence (the South, Midlands & Wales, the North, Scotland). The relative abilities of different indices of blood cholesterol (total cholesterol and the ratio of total to HDL cholesterol) and blood pressure (systolic (SBP) and diastolic (DBP)) to predict major CVD risk were assessed through examination of its \(^2\) likelihood ratio statistic in the fully adjusted model (LDL cholesterol was not considered as it was only measured in 18 of the 24 towns studied). It was assumed that blood cholesterol and blood pressure were measured with error and subject to within-person variation over time. The effects of this variation were assessed over a four-year period (using the 16 and 20-year follow-up data) in order to estimate associations over the first 10 years of follow-up from observed "baseline" associations (regression calibration was used to estimate expected usual exposure levels and true regression coefficients).\(^2\)\(^1\)

Having determined the "most informative" blood cholesterol and blood pressure indices for CVD risk prediction purposes (and having corrected the regression coefficients for regression dilution bias), the potential effectiveness of each of the "high-risk" prevention strategies was assessed using logistic regression prediction (with the recalibrated blood pressure and blood cholesterol measurements). When predictions are made on the sample from which the prediction tool is derived, estimates of risk differences may be biased, often seriously. Therefore, predicted risks were obtained using the "jack-knife" technique which eliminates such bias from being introduced.\(^2\)\(^1\) The mean of these predicted risks provides an estimate of the expected 10-year absolute CVD risk in the population prior to implementation of the prevention strategy (which should be exactly the same as the observed CVD risk). Individuals whose observed risk exposure levels were sufficiently high to warrant preventive treatment (i.e., the high-risk group) subsequently had their predicted risks recalculated to take into account the effects of treatment. The mean predicted risk after implementation of the strategy was then calculated, allowing calculation of the expected reduction in major CVD risk due to the high-risk strategy. For the "population strategies", the expected reduction in major CVD over 10 years was estimated by comparing the predicted CVD risk in the observed sample with the predicted risks for the same sample following absolute reductions in each individual’s blood cholesterol and blood pressure level. For these approaches, the reductions in major CVD correspond to reductions that would be expected if the sample had had lifetime lower blood pressure and blood cholesterol levels.

Results

Of the 7735 men recruited at the baseline screening, 1186 (15.3%) had baseline evidence of CVD and a further 210 were receiving blood pressure lowering or lipid-lowering drugs at baseline. Of the remaining men, 5997 (94.6%) had complete risk factor data. The baseline characteristics of these men are displayed in Table 1. Repeat blood pressure and blood cholesterol measurements over four years (between 16 and 20 years) were available for 165 men with no previous evidence of CVD and not receiving blood pressure lowering or lipid-lowering drugs at either the 16- or 20-year examinations. Regression dilution ratio estimates of 0.79 for total cholesterol, 0.88 for the logarithm of total:HDL cholesterol, 0.75 for systolic blood

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of 5997 men with no baseline evidence of CVD and not receiving blood pressure lowering or lipid-lowering drugs at baseline</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline risk factor</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
</tr>
<tr>
<td>Total:HDL cholesterol</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
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<tr>
<td>Body mass index (kg/m(^2))</td>
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<tr>
<td>Proportion current cigarette smokers (%)</td>
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<tr>
<td>Proportion moderately active in leisure time (%)</td>
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<tr>
<td>Proportion diabetic (%)</td>
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</table>

Data correspond to mean (SD) unless otherwise stated. \(^a\) Geometric mean presented (IQR).
pressure and 0.65 for diastolic blood pressure were obtained.

Over the first 10 years of follow-up, 450 men (7.5%) had a major CVD event. The "relative informativeness" of different blood cholesterol and blood pressure indices at predicting CVD risk was assessed by examining the likelihood ratio $\chi^2$ statistics in the fully adjusted logistic regression model. Compared with serum total cholesterol, the ratio of total cholesterol to HDL cholesterol was 55% as informative, whilst compared with systolic blood pressure, diastolic pressure was 67% as informative. For CVD risk prediction purposes, total cholesterol and systolic blood pressure were therefore selected as the "most informative" indices of blood cholesterol and blood pressure.

Effectiveness of high-risk strategies for prevention

Table 2 shows the estimated effectiveness of each of the high-risk policies at specific "treatment thresholds" and Fig. 1 the relations between the thresholds, effectiveness and the proportion of the population treated under the strategy. As the threshold for treatment reduces (i.e., as the proportion of the population treated increases) the estimated reductions in CVD events in the population increase. For a given intervention, the effectiveness of identification based on overall risk (through the calculation of a Framingham risk score) is generally greater than that based on identification of single risk factors, and becomes more so as thresholds fall. Multiple interventions have considerably greater benefits in terms of prevention than intervention based only on blood cholesterol or blood pressure. However, even with multiple drug treatment, the predicted reduction in first occurrences of major CVD following preventive treatment at a threshold based on a Framingham risk of $\geq 30\%$ (as is currently recommended in the UK) was only 11%. This increased to 34% when the Framingham threshold was reduced to a 10-year risk of $\geq 20\%$ (as recommended by the European Joint Task Force on Coronary Prevention) and 49% when the threshold was reduced to $\geq 15\%$. At these thresholds, respectively, one-quarter and one-half of the population without symptomatic CVD would be receiving multiple preventive treatment.

### Table 2  A comparison of approaches to the primary prevention of major CVD

<table>
<thead>
<tr>
<th>Prevention approach</th>
<th>Management</th>
<th>RRR</th>
<th>Predicted reduction in major CVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top 10% Top 20% Top 30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'High-risk' approach</td>
<td>Statin</td>
<td>30%</td>
<td>6% 9% 12%</td>
</tr>
<tr>
<td>Treatment decision based on total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment decision based on blood pressure</td>
<td>β-blocker/diuretic</td>
<td>22%</td>
<td>6% 8% 10%</td>
</tr>
<tr>
<td>Treatment decision based on total cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment decision based on blood pressure</td>
<td>Aspirin, statin, ACE inhibitor and β-blocker/diuretic</td>
<td>68%</td>
<td>13% 21% 28%</td>
</tr>
<tr>
<td>Treatment decision based on overall absolute risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment decision based on overall absolute risk</td>
<td>Statin</td>
<td>30%</td>
<td>5% 15% 21%</td>
</tr>
<tr>
<td>β-blocker/diuretic</td>
<td>22%</td>
<td>4% 11% 16%</td>
<td></td>
</tr>
<tr>
<td>Aspirin, statin, ACE inhibitor and β-blocker/diuretic</td>
<td>68%</td>
<td>11% 34% 49%</td>
<td></td>
</tr>
<tr>
<td>Framingham 10-year CHD event risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 30%$ $\geq 20%$ $\geq 15%$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce mean total cholesterol in the population</td>
<td>–</td>
<td>12% 22% 32%</td>
<td></td>
</tr>
<tr>
<td>Reduce systolic blood pressure</td>
<td>–</td>
<td>16% 29% 40%</td>
<td></td>
</tr>
<tr>
<td>Reduce both mean total cholesterol and mean systolic blood pressure</td>
<td>–</td>
<td>26% 45% 59%</td>
<td></td>
</tr>
</tbody>
</table>

RRR: relative risk reduction (high-risk approach).
*Everyone reduces their total cholesterol blood pressure level by the same absolute amount.*
been prevented. Therefore, approximately 45% of all first major CVD events over the following 10 years (201/450) may have been prevented through implementation of this particular high-risk policy (assuming 100% prescription rates and adherence levels as high as those observed in the clinical trials). Reducing the age threshold to 50 would have increased this proportion to 60% ((399 × 0.68)/450).

Effectiveness of population strategies for prevention

Fig. 2 (see also Table 2) shows the predicted effectiveness of each of the “population” approaches. Long-term reductions in the population distributions of both serum total cholesterol and systolic blood pressure of 5% (corresponding to an absolute reduction of 0.3 mmol/L in total cholesterol and 7 mmHg in systolic blood pressure) would have led to a 26% reduction in first occurrences of major CVD over the following 10 years, whilst a shift of 10% would have resulted in a 45% reduction in major CVD.

Effects of regression dilution bias

Regression dilution bias had no effect on the estimated effectiveness of the high-risk approach. In comparison, the effects of regression dilution bias on the effectiveness of the population approach were marked. The corrected estimates presented in Table 2 and Fig. 2 were between 20 and 30% greater than the uncorrected estimates.

Discussion

Taking measurement imprecision and within-person variability (regression dilution bias) of blood cholesterol and blood pressure into account, we considered the potential effectiveness of a variety of high-risk and population strategies for the primary prevention of CVD. Our results indicate that in order to have a substantial effect on CVD rates, high-risk multiple-intervention primary prevention policies would need to be used widely – at a level below the 3% predicted risk per annum recommended in the UK,7 and possibly even below the 2% predicted risk per annum recommended by the European Joint Task Force on Coronary Prevention.8 In comparison, relatively small reductions in the population levels of two key risk factors (blood cholesterol and blood pressure) would potentially lead to large reductions in major CVD.

Assumptions in the analyses

The validity of our estimates for the high-risk approaches depends on the treatment effects assumed and the appropriateness of the strategies. The effects of statins, aspirin and first line blood pressure lowering drugs were taken from meta-analyses of randomised controlled trials,13–16 whilst the effects of ACE inhibitors were estimated from a large randomised controlled trial of these agents.17 These estimates were used in preference to estimates from cohort studies,10 because whilst cohort studies allow estimation of the effects of differences in risk due to long-term differences in risk exposure levels,
clinical trials show the extent to which these epidemiological associations are reversible though treatment. The clinical trial estimates also take non-adherence into account as they are obtained from “intention-to-treat” analyses, though they may still overestimate the true efficacy of the drugs in routine practice, as trials often exclude those with poor adherence in “run-in” phases and supervision is often more systematic than in usual care. In addition, since the treatment effects were generally obtained from studies of “high-risk” men (including men with previous CVD), by applying the results to men without previous CVD, the effectiveness of the high-risk approach may have been overestimated. This may be particularly true for ACE inhibitors, for which evidence of effectiveness is substantially based on subjects with established CHD.\textsuperscript{17} For statins and aspirin, this assumption is more clearly valid, as relative risk reductions are reasonably stable across a wide range of risk groups.\textsuperscript{16,27} Furthermore, by assuming that the treatment effects were multiplicative, the combined effects of taking all four drugs may have been overestimated (for example ACE inhibitors may be less effective when used in combination with aspirin).\textsuperscript{28} However, by combining different combinations of drugs (including multiple low dose drugs), greater reductions in CVD risk may be possible than assumed in this paper,\textsuperscript{29} though even if this were the case, it is unlikely that our estimates would be greatly affected (if the true relative risk reduction of the combined pill was 85%, for instance, treatment of individuals with a $\geq 30\%$ Framingham risk would reduce major CVD by 14\%, compared with 11\% shown in Table 2).

The effectiveness of the population approach to prevention depends critically on the size of population-wide changes that could realistically be achieved in practice. The population-wide reductions in mean total cholesterol and blood pressure of between 5\% and 15\% assumed in this paper (Table 2) are relatively modest and are consistent with reductions that may be achievable through changes in diet.\textsuperscript{30–33} In the case of total cholesterol, a study in Mauritius, for example, found that population levels of total cholesterol fell by 15\% over 5 years following a change in the island’s supply of cooking oil from palm to soy bean oil and the implementation of an intervention programme aimed at the promotion of a healthy lifestyle.\textsuperscript{32} In Western countries, meta-analysis of metabolic ward studies has shown that the same sized reduction could be achieved if 60\% of saturated fats could be replaced by other fats and 60\% of dietary cholesterol could be avoided.\textsuperscript{33} Similarly, reduction in the amount of salt added to processed foods could lower population blood pressure by about 10\%,\textsuperscript{34} though clinical advice to restrict salt intake is less effective.\textsuperscript{35} Even these population wide reductions are small, however, when compared with the differences in cholesterol and blood pressure that exist between different populations,\textsuperscript{36,37} suggesting that our estimates of the potential effect of population approaches are conservative. Secular trends in blood pressure have also shown large falls over relatively short periods of time; among Glasgow students mean systolic blood pressure fell by 9 mmHg between 1948 and 1968,\textsuperscript{38} whilst trends of a similar size, independent of antihypertensive treatment, have been reported from the Health Survey for England.\textsuperscript{39} Furthermore, approaches directed towards lowering blood pressure and blood cholesterol in the population are likely to have additional favourable benefits on other cardiovascular risk factors such as body mass index and physical activity.

In this report we have focussed on cholesterol, blood pressure and pharmacological interventions and have not addressed the additional contribution made to CHD risk by cigarette smoking. Taking account of cigarette smoking is likely to make an additional contribution to
the effectiveness of both population and high-risk approaches (for instance, approximately one-third of the falls in CHD mortality in Scotland over the last two decades has been estimated to be due to reductions in cigarette smoking), however, the balance of potential effectiveness of the two strategies is unlikely to be affected by taking cigarette smoking into account.

**Effects of regression dilution bias**

In our analyses we have corrected for regression dilution bias (the underestimation of relationships between usual risk factor levels and disease risk caused by within-person variability). Though the high-risk approaches were robust to these effects (as treatment effects were taken from trials), the effects of regression dilution bias on the estimated effectiveness of the population approaches were marked. This is because the true size of the shift in the exposure distribution relative to the exposure variance is greater than would be estimated if within-person variability were not taken into account. It is therefore crucially important to take regression dilution bias into account when assessing population approaches, as failure to do so results in substantial underestimation of the likely effects.

**Implications of the findings**

The results illustrate the limited potential of single risk factor management on the occurrence of CVD in the population. In agreement with a recent review of interventions to lower blood pressure and cholesterol and their effects on CVD risk, we found that by taking multiple risk factors into account, predicted Framingham risks generally provide a more effective measure on which to base treatment decisions than single risk factor measurements such as total cholesterol or blood pressure (though the differences only become marked when an appreciable proportion is selected for treatment; see Table 2). However, even when combinations of drug treatment are used to reduce CVD risk, the impact of “high-risk” pharmacological primary prevention methods is likely to be limited unless used very much more widely than is currently recommended (particularly as recommended in the UK). Over one-third of the middle-aged male population without pre-existing CVD would need to be treated with all four drugs to obtain benefits comparable with those following population-wide reductions in blood cholesterol and blood pressure of 10%. This scale of prescribing would ensure a steady supply of middle-aged people requiring drug treatment.

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**References**

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