Lipid lowering in patients with diabetes mellitus: what coronary heart disease risk threshold should be used?

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Objective: To examine the impact for the UK population of providing statin treatment for diabetic patients for the primary prevention of coronary heart disease at a coronary event risk lower than currently recommended by the National Service Framework (NSF) for coronary heart disease.

Design: Cross sectional survey.


Participants: Nationally representative sample of 6879 subjects aged 35–74 years living in private households.

Main outcome measures: The proportion of the UK population recommended for statin treatment according to the NSF for coronary heart disease, and the proportion of the population with diabetes at a coronary event risk of ≥15% over 10 years.

Results: Of the 6879 subjects with total cholesterol measurements, 218 (3.2%) had diabetes mellitus. In this nationally representative sample, 6.3% of the subjects (95% confidence interval [CI], 5.7% to 6.9%) were candidates for statin treatment for the secondary prevention of coronary heart disease, including 0.7% (95% CI 0.5% to 0.9%) with diabetes. A further 2.4% (95% CI 2.0% to 2.8%), including 0.4% (0.2% to 0.6%) with diabetes, were identified as candidates for primary prevention of coronary heart disease according to the NSF for coronary heart disease. Lowering the primary prevention threshold for statin treatment to a coronary event risk of ≥15% over 10 years in diabetic patients identified an additional 0.5% of the population.

Conclusions: Extending statin treatment to diabetic patients at a coronary heart disease risk of ≥15% over 10 years would have a relatively small numerical impact in the UK population. Thus patients with diabetes mellitus should, as a minimum, be targeted for statin treatment at this level of risk.

Current guidelines issued by the joint British societies and National Service Framework (NSF) for coronary heart disease recommend lipid lowering treatment with HMG-CoA reductase inhibitors (statins) for secondary prevention of coronary heart disease, and for primary prevention in patients estimated to be at a coronary event risk of at least 30% over 10 years. These recommendations, made largely on the basis of cost, apply to all subgroups of patients, including those with diabetes mellitus. Epidemiological studies have shown that coronary event rates in diabetic patients are approximately two- to threefold higher than in non-diabetic patients. After having a coronary event, diabetic patients are then at a two- to threefold higher risk of a second coronary event, and are much more likely to die after a myocardial infarct than non-diabetic individuals. Therefore, in addition to prioritising statin treatment for patients with cardiovascular disease and those at high risk of developing coronary heart disease, it may be equally important to target diabetic patients at a lower coronary event risk threshold than is currently recommended for primary prevention in the UK.

We have used data from the Health Survey for England 1998 to determine the proportion of adults in the UK population with diabetes mellitus who may require statin treatment according to national guidelines. We examined the impact for the UK population of extending statin treatment to diabetic patients for primary prevention at a coronary heart disease event risk of ≥15% over 10 years—the level of risk of subjects included in the west of Scotland coronary prevention study (WOSCOP).

METHODS

Health Survey for England 1998

The health survey examined a random stratified sample drawn from the Royal Mail’s postcode address file and is demographically representative of the English population aged two years and over living in private households. Each of the selected households was visited by a trained interviewer who elicited information on cardiovascular disease and associated risk factors. If subjects agreed, this was followed by a further visit from a nurse who obtained details of prescribed medicines, measured blood pressure, and collected a blood sample from those who consented.

Diabetes and stroke were defined as recall of a doctor’s diagnosis of these conditions. Subjects who reported a history of angina or myocardial infarction diagnosed by a doctor were classified as having coronary heart disease. As defined in the Framingham study, subjects were classified as smokers if they currently smoked cigarettes or had ceased smoking within the last year. Blood pressure was measured by a Dinamap 8100 monitor using an appropriate cuff size. Three blood pressure measurements were taken, and results were based on the mean of the second and third readings. Standard methods were used to measure concentrations of total and high density lipoprotein (HDL) cholesterol in a single, non-fasting blood sample at a central laboratory.

Method of analysis

The analysis, as outlined in fig 1, was restricted to the 9590 subjects aged 35–74 years—the target population of the NSF for coronary heart disease. Of the 9590 subjects, 2711 had no serum total cholesterol data. The remaining 6879 had a valid

Abbreviations: AFCAPS/TexCAPS, Airforce/Texas coronary atherosclerosis prevention study; NSF, National Service Framework; WOSCOP, west of Scotland coronary prevention study.
measurement of serum total cholesterol and complete data on myocardial infarction, angina, and stroke. Among these, 218 subjects with diabetes mellitus were identified.

Secondary prevention
Current guidelines recommend statin treatment up to the age of 75 years when serum total cholesterol is > 5.0 mmol/l. For the 218 diabetic and 6661 non-diabetic subjects, we identified those with a history of cardiovascular disease and total cholesterol > 5.0 mmol/l. To estimate the proportion of subjects that were candidates for secondary prevention, we included those who were already taking lipid lowering treatment. The denominator used for estimates of prevalence in the population was 6879.

Primary prevention
Statin treatment is recommended up to the age of 70 in patients whose serum total cholesterol is ≥ 5.0 mmol/l and whose coronary heart disease event risk is ≥ 30% over 10 years. We used these guidelines to identify potential subjects for primary prevention with complete data for coronary heart disease risk assessment (fig 1). We applied the Framingham equation to estimate the 10 year coronary event risk for each individual. This required the following variables: age, sex, systolic blood pressure, smoking habit, diabetes status, total cholesterol, HDL cholesterol, and assessment for left ventricular hypertrophy. In practice, we assumed absence of left ventricular hypertrophy for all individuals. Subjects who were already on lipid lowering treatment were excluded from the analysis, as it was not possible to calculate their baseline coronary disease risk.

We determined the proportion of diabetic and non-diabetic patients at a coronary event risk of ≥ 30% over 10 years. In addition, two further levels of coronary event risk were examined for primary prevention, as follows:

- **Coronary event risk ≥ 15% over 10 years**—the level of risk of subjects included in the WOSCOP study and also the third priority in the joint British societies guidelines.
- **Coronary event risk ≥ 6% over 10 years**—the level of risk of subjects enrolled in AFCAPS/TexCAPS (Airforce/Texas coronary atherosclerosis prevention study); this is the lowest level of coronary event risk at which patients have been shown to derive significant benefit from statin treatment.

Statistical analysis
Differences in baseline characteristics between diabetic and non-diabetic subjects were tested for significance using the Student t test. Comparisons of the prevalence of smoking, cardiovascular disease, and high coronary heart disease risk among diabetic and non-diabetic subjects were examined using the \( \chi^2 \) test.

RESULTS
Baseline characteristics
Of the 6879 subjects aged 35–74 years with total cholesterol measurements, 218 (3.2%) had diabetes mellitus. Table 1 shows mean baseline characteristics of the 218 diabetic subjects and the 6661 subjects without diabetes. With the exception of total cholesterol, the mean baseline physiological characteristics of the diabetic subjects were significantly different from those of the non-diabetic subjects (table 1). The proportions of smokers did not differ between the groups. For both men and women, the prevalence of a history of myocardial infarction, stroke, or angina was approximately fourfold higher in diabetic than in non-diabetic subjects (table 1). The overall burden of established cardiovascular disease was significantly higher in diabetic patients (27.1% vs 6.7%; difference 20.4%, 95% confidence interval (CI), 14.5% to 26.3%; \( \chi^2 \), 130; p < 0.0001).
Lipid lowering in patients with diabetes mellitus

Secondary prevention

Of the 59 diabetic subjects with cardiovascular disease, 19 were already on lipid lowering treatment and six of these (31.6%) had their cholesterol controlled. Including those on lipid lowering treatment and the 28 subjects with a total cholesterol value of ≥ 5.0 mmol/l (fig 1), 47 of the 218 diabetic subjects (21.6%, 95% CI 16.1% to 27.0%)—comprising 15 women (6.9%) and 32 men (14.7%)—were candidates for secondary prevention of coronary heart disease. Among the 6661 non-diabetic subjects, there were 159 women (2.4%) and 226 men (3.4%) with a history of cardiovascular disease who had either a total cholesterol value of ≥ 5.0 mmol/l or who were already taking lipid lowering treatment. Of the 106 on treatment, 47 (44.3%) had their cholesterol concentration controlled to < 5.0 mmol/l. The percentage of non-diabetic subjects identified for secondary prevention (5.8%, 95% CI 5.2% to 6.3%) was three- to fourfold lower than observed for subjects identified for secondary prevention (5.8%, 95% CI 4.4% to 7.1%). The proportion of smokers was not significantly different between the two groups. The mean predicted coronary heart disease event risks over 10 years in men and women, respectively, were 25% and 17% for diabetic subjects, and 12% and 6% for non-diabetic subjects. Taking men and women together, the mean coronary heart disease risk for the 101 diabetic subjects was 21%, more than twice that for the non-diabetic subjects (9%).

The frequencies in men and women of subjects with a total cholesterol value of ≥ 5.0 mmol/l and 10 year coronary heart disease risk levels of ≥ 30%, ≥ 15%, and ≥ 6% are shown in table 3. Excluding subjects with cardiovascular disease, 27 of the 218 diabetic subjects (12.4%, 95% CI 8.0% to 16.8%) were at a 10 year coronary heart disease risk of ≥ 30%, 64 (29.4%, 95% CI 23.3% to 35.4%) at ≥ 15%, and 91 (41.7%, 95% CI 34.7% to 47.8%) at ≥ 6%. Corresponding figures for the 6661 non-diabetic subjects were 138 (2.1%, 95% CI 1.7% to 2.4%), 803 (12.1%, 95% CI 11.3% to 12.8%), and 2290 (34.4%, 95% CI 33.2% to 35.5%). The proportion of diabetic subjects identified for primary prevention of coronary heart disease (12.4%) was approximately sixfold higher than observed for non-diabetic subjects (difference 10.3%, 95% CI 5.9% to 14.7%; χ²(1) = 96; p < 0.0001). Of the denominator population, 0.4% and 2.0% of the diabetic and non-diabetic subjects, respectively, were at a coronary risk of ≥ 30% over 10 years, 0.9% and 11.7% at a coronary risk of ≥ 15% over 10 years, and 1.3% and 33.7% at a coronary risk of ≥ 6% over 10 years. According to current national guidelines, 2.4% of the subjects (95% CI 2.0% to

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic</th>
<th>Non-diabetic</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Men (n=129)</td>
<td>Women (n=89)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.9 (9.7)</td>
<td>60.0 (10.4)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>145 (21)</td>
<td>149 (26)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>80 (12)</td>
<td>78 (14)</td>
</tr>
<tr>
<td>Serum TC (mmol/l)</td>
<td>5.4 (0.9)</td>
<td>6.0 (1.2)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.1 (0.5)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Smokers</td>
<td>31 (24.0%)</td>
<td>18 (20.2%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>40 (31.0%)</td>
<td>19 (21.3%)</td>
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</tbody>
</table>

Values are mean (SD) or n (%). All subjects had total cholesterol measurements. The prevalence of cardiovascular disease is greater than the sum of the prevalence of myocardial infarction, stroke, and angina because some subjects had more than one condition.

***p<0.001, **p<0.01 v non-diabetic subjects.

BP, blood pressure; HDL, high density lipoprotein; TC, total cholesterol.

### Table 2

<table>
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<tr>
<th>Variable</th>
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<th>Non-diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Men (n=52)</td>
<td>Women (n=49)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.2 (9.6)</td>
<td>57.0 (10.5)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>143 (20)</td>
<td>150 (27)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82 (11)</td>
<td>80 (14)</td>
</tr>
<tr>
<td>Serum TC (mmol/l)</td>
<td>6.0 (0.7)</td>
<td>6.3 (1.0)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.1 (0.4)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Smokers</td>
<td>18 (34.6%)</td>
<td>10 (20.4%)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or n (%). All subjects had total cholesterol measurements ≥ 5.0 mmol/l and complete data for coronary heart disease risk assessment.

***p<0.001, **p<0.01 v non-diabetic subjects.

BP, blood pressure; HDL, high density lipoprotein; TC, total cholesterol.
previously diagnosed by a physician, was 2.3%. Diabetes in a UK white population aged 25–74 years, of a recent study which showed that the prevalence of recall of a doctor's diagnosis. This is consistent with the finding that subjects aged 35–74 years were identified as diabetic, based on screening for diabetes. When all subjects were formally diagnosed with diabetes Association criteria when all subjects were formally screened for diabetes. However, the prevalence of diabetes increased to 4.8% and 7.1%, respectively, based on the World Health Organization and American Diabetes Association criteria when all subjects were formally screened for diabetes. When population screening for diabetes is implemented for all subjects aged 35–74 years as part of the population, and the prevalence of diabetes in the UK population will increase two-fold.

One possible source of bias in the analysis could have been the exclusion of 2711 subjects with no data on total cholesterol. Ninety-four (3.5%) of these subjects had diabetes, with a mean age of 59.5 years. Among these, there were 49 women (52.1%), 29 smokers (30.9%), and 24 (25.5%) had a history of cardiovascular disease. Of the 2617 subjects without diabetes, 1520 (58.1%) were women, 727 (27.8%) were smokers, and 211 (8.1%) had cardiovascular disease. Their mean age was 52.3 years. Characteristics of the 94 diabetic and 2617 non-diabetic subjects are similar to those of the respective groups included in the analysis (table 1), and therefore exclusion of subjects with no total cholesterol measurements did not appear to introduce bias.

There was a significant age difference of 4.8 years between diabetic and non-diabetic subjects assessed for coronary heart disease risk (table 2), and comparisons between these groups may have been influenced by age. We do not believe that this is important, as the health survey reflects a representative sample of the population, and the prevalence of diabetes increases with age. However, critics may argue that the very high risk in diabetic patients is simply a reflection of age. We have therefore examined the effect of matching the two groups for age. The coronary heart disease risk increased from 9% to 11% over 10 years for the non-diabetic subjects, a value that was still approximately twofold lower than that estimated for diabetic individuals. The higher coronary heart disease risk associated with diabetic populations is likely to reflect a clustering of risk factors.

Estimates of the proportion of subjects identified for secondary prevention are probably conservative, as information on peripheral vascular disease was not included in the Health Survey for England 1998 questionnaire. Data from the 1995 Scottish health survey suggest that approximately 1.3% of the population aged between 35–64 years with a total cholesterol of ≥ 5.0 mmol/l suffer from peripheral vascular disease alone. This may mean that a disease register for secondary prevention of coronary heart disease in patients with a total cholesterol of ≥ 5.0 mmol/l would include about 8.0% of the age group targeted by the NSF. For primary prevention, we excluded 95 patients (1.4% of the cohort) already on lipid lowering drugs because we could not assess their baseline coronary heart disease risk. However, using on-treatment total cholesterol values, four and 10 of the 14 diabetic subjects had a coronary heart disease risk of ≥ 30% and ≥ 15%, respectively, over 10 years. Among the 81 non-diabetic subjects, only four had a coronary risk of ≥ 30% over 10 years. Thus, excluding subjects on lipid lowering treatment does not have a significant effect on the overall proportion of subjects who are candidates for treatment for primary prevention.

Another limitation of the study is that absence of left ventricular hypertrophy was assumed for all patients, and this may have underestimated coronary heart disease risk in the population. However, this effect is likely to be small as the incidence of left ventricular hypertrophy in the Framingham cohort was 0.5% in women and 1.0% in men. Assuming the absence of left ventricular hypertrophy may also influence comparisons between diabetic and non-diabetic populations, as left ventricular hypertrophy is more common in diabetic patients, especially in women. However, it should be noted that the majority of diabetic patients had a high coronary disease risk despite the fact that left ventricular hypertrophy was not included as a risk factor.

### Implications of the findings
In the Health Survey for England 1998, the prevalence of existing cardiovascular disease was fourfold higher for subjects with diabetes mellitus than for those without (27.1% vs 6.7%). This result supports the findings of other studies showing that diabetic patients have two- to fourfold higher coronary event rates than the non-diabetic population. Patients with diabetes who have sustained a coronary event are also much more likely to die after a myocardial infarct. Therefore, to offer diabetic patients the same level of protection against coronary heart disease it is important to consider targeting them at a lower coronary risk threshold than is currently recommended for primary prevention in the UK. According to current UK guidelines, 6.3% of subjects aged 35–74 years in this nationally representative sample (0.7% diabetic and 5.6% non-diabetic) were identified for statin treatment for secondary prevention of coronary heart disease, and a further 2.4% (0.4% diabetic and 2.0% non-diabetic) for primary prevention. Lowering the primary prevention threshold for treatment to a coronary event risk of ≥ 15% or ≥ 6% over 10 years in diabetic patients would include only an additional 0.5% or 0.9% of the population, respectively. Targeting all diabetic patients with a total cholesterol of ≥ 5.0 mmol/l—that is, essentially treating diabetes as secondary prevention—would involve extending treatment to an additional 1.1% of the population over and above that recommended by the NSF for coronary heart disease.

On the basis of the scientific evidence there seems little doubt that targeting diabetic patients for secondary and

### Table 3 Proportion of diabetic and non-diabetic subjects aged 35–70 years free of cardiovascular disease with total cholesterol ≥5.0 mmol/l and predicted coronary heart disease event risks of ≥30%, ≥15%, and ≥6% over 10 years

<table>
<thead>
<tr>
<th>Diabetic</th>
<th>Non-diabetic</th>
</tr>
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<tbody>
<tr>
<td>CHD risk</td>
<td>Men (n=129)</td>
</tr>
<tr>
<td>≥30% over 10 years</td>
<td>19 (14.7%)</td>
</tr>
<tr>
<td>≥15% over 10 years</td>
<td>35 (27.1%)</td>
</tr>
<tr>
<td>≥6% over 10 years</td>
<td>50 (38.8%)</td>
</tr>
</tbody>
</table>

Values are n (%).

CHD, coronary heart disease.
primary prevention of coronary heart disease is worthwhile. Factors such as the relatively high cost of statins and the high prevalence or risk of coronary heart disease in the UK population have tempered guidelines for lipid lowering treatment. The mean annual cost per patient when trying to achieve a cholesterol target of <5.0 mmol/l ranges from £374 to £439, depending on the statin used. The annual cost of statin prescribing when implementing the NSF for coronary heart disease for an average primary care group with 100,000 patients ranges from £1.59 million to £1.86 million. The extra annual cost of treating diabetic patients at coronary heart disease risk thresholds of >15% and >6% over 10 years may range from £91,000 to £107,000 and from £164,000 to £193,000, respectively. Extending treatment to all diabetic patients with a total cholesterol of >5.0 mmol/l would cost an extra £200,000 to £240,000 per annum.

Recommendations

The Framingham equation is the most accurate method for estimating risk in population data that include men and women, and is recommended by the joint British societies and NSF for coronary heart disease. However, the accuracy of predicting coronary risk in patients with diabetes has been questioned, mainly because of the relatively small numbers of diabetic patients in the Framingham study. When values for risk factors are close to the population mean, the predicted 10 year coronary disease risks are fairly accurate, with confidence intervals ranging from ±2.8% to 4.4%. However, with less frequent covariates the confidence intervals are as wide as ±14%. For diabetes, the error is likely to be in the range of ±5% to 10%, and to ensure that we do not miss diabetic patients at high risk they should be targeted at a lower level than is currently recommended.

Emerging evidence from epidemiological and outcome studies shows that diabetic patients are at very high risk of coronary heart disease and have much to gain from statin treatment. We suggest that diabetes should be regarded as a special case in the fight against coronary heart disease. Diabetic patients should either be targeted for statin treatment at a coronary event risk of >15% over 10 years, or be treated as “secondary prevention” cases—a view recently endorsed by the National Cholesterol Education Program Adult Treatment Panel III.

ACKNOWLEDGEMENT

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