Increasing the impact of cardiological treatments

How best to reduce deaths

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Aims To determine the extent to which increases in the uptake of effective treatments could further reduce coronary heart disease mortality in Scotland.

Methods and Results A cohort-based mortality model combining effectiveness data from published meta-analyses with available information on uptake of all coronary heart disease treatments in all patient categories in Scotland (population 5·1 million).

In 1994, medical and surgical coronary disease treatments prevented or postponed an estimated 2722 deaths (minimum estimate 1373, maximum estimate 5986). Increasing treatment uptake to 100% of all eligible patients was considered unrealistic. Increasing uptake to 80% would have prevented or postponed a further 4078 deaths (39% from increases in secondary prevention therapies, 29%, 13%, 10% and 9% from the treatments of heart failure, acute myocardial infarction, hypertension and angina respectively).

Conclusions Many eligible patients are currently not receiving treatment that is effective in reducing coronary heart disease mortality. Increasing treatment uptake could prevent or postpone a further 4080 deaths each year in Scotland, approximately, more than doubling the present benefit from treatment. By implication, about 30 000 additional deaths could be prevented, annually, in the U.K. Comparable symptom and morbidity benefits might also be expected. Future clinical audit activities should focus particularly on secondary prevention and heart failure treatments.

Key Words: Mortality, cardiology, treatment, audit, coronary heart disease.

See page 1376 for the Editorial comment on this article

Introduction

Coronary heart disease is the largest cause of mortality in the United Kingdom, accounting for some 150 000 deaths annually of which half occur prematurely[1]. Coronary heart disease also causes considerable distress and disability. It accounts for over 800 000 hospital admissions annually and National Health Service costs exceeding one billion pounds[3]. A number of cardiological interventions have been demonstrated to be effective in reducing coronary deaths and morbidity[2–10]. The treatment of coronary heart disease is thus an important area for clinical audit. Clinical audit aims to systematically review and improve care[11]. However, given the scale of activities and the scarcity of resources, it is clearly important to focus audit activities on those interventions likely to produce the greatest benefit[11,12].

Recent clinical audits, particularly ASPIRE (Action on Secondary Prevention through Intervention to Reduce Events), and EURO-ASPIRE, show that treatment uptake rates remain disappointingly low for many categories. For instance, only about 30% of eligible patients receive thrombolysis[12–14], only 20% are prescribed beta-blockers after infarction[13,15–17], only one third of angina patients in the community are taking aspirin[18] and only 40% of hospital patients with heart failure receive ACE inhibitors[19,20]. Clearly, there is scope for considerable improvement in treatment uptake and thereby reductions in morbidity and mortality. However, tackling all these areas would require substantial effort, and prioritization is essential. This study was therefore undertaken to determine the magnitude of coronary heart disease mortality reduction achievable through increased uptake of specific treatments, in order to identify those likely to contribute most to this reduction.
Methods

The cell-based mortality model has been described in detail elsewhere[21]. In brief, the number of coronary heart disease deaths prevented or postponed in Scotland in 1994 was calculated for specific interventions, such as thrombolysis, coronary artery bypass grafting aspirin and so on. This mortality reduction was based on the absolute mortality reduction reported in published trials and meta-analyses and applied to the appropriate patient group in Scotland for the year 1994[2–10]. Survival benefit over a 1-year time interval was used for all treatments.

In each treatment category, the best maximum and minimum estimates of deaths prevented or postponed were calculated by multiplying the numbers of eligible patients by treatment uptake, treatment adherence and absolute risk reduction per 100 patients treated. ‘Eligible’ was defined as those patients meriting treatment on the basis of the relevant clinical guideline.

Specific treatments evaluated and the calculation of treatment effectiveness

The interventions considered were:

(a) Initial treatments for acute myocardial infarction: prehospital cardiopulmonary resuscitation, in-hospital resuscitation, aspirin[6], thrombolytic therapy, intravenous beta-blockers and ACE inhibitors[4,5,7,14,27]
(b) Secondary prevention following myocardial infarction: treatment with aspirin, beta-blockers, warfarin, comprehensive rehabilitation (for which all patients are potentially eligible), ACE inhibitors and HMG CoA reductase inhibitor therapy (where selected patients are eligible[1,3,5–7]). The effects of these treatments were evaluated for all patients alive in 1994 who had been discharged from hospital after an acute myocardial infarction during the previous 5 years, 1989–1994. This total was adjusted for (i) a subsequent re-admission rate of 20%, and (ii) an annual mortality loss of 5%.
(c) Secondary prevention following angioplasty or cardiac surgery, using the same medications.
(d) Treatment of angina in hospital: aspirin, heparin[8], CABG surgery and coronary angioplasty[9,9a]. Angioplasty was assumed to have a maximum mortality benefit equal to CABG surgery for one- and two-vessel disease and a minimum effect of zero[9,9a]. Because revascularization benefit may continue for at least 10 years, all angina patients alive in 1994 following admission to hospital within the past 10 years for CABG surgery (13 384) or for angioplasty (6114) were considered[9]
(e) Angina patients in the community given aspirin[3]; beta-blockers were assumed to have no mortality benefit in the absence of a previous infarct[7]. The prevalence of angina in Scotland is approximately 11% in both men and women aged 45–64 years and 18% in those aged 65 years or older[23]. This produced a total of some 260 982 angina subjects. To prevent double counting, this total was reduced to 156 751 after adjusting for two potential overlaps:
(i) The hospital angina categories above and
(ii) the 39% of angina patients with a history of myocardial infarction (included in the secondary prevention categories above[23]).

On the basis of ASPIRE, EUROASPIRE and local audits, it was estimated that some 33% of these patients were treated with aspirin[12,13,15,17,18].
(f) Treatment of heart failure with ACE inhibitor therapy[8]; both patients admitted to hospital and those managed in primary care were considered.

Three-quarters of the 9526 patients admitted to hospital in 1994 were assumed to have severe heart failure and to obtain the mortality reduction demonstrated in the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study I) trial[5]. The remaining quarter, and patients treated in the community, were assumed to have mild to moderately severe heart failure and to obtain a smaller absolute benefit from treatment[5]. Local and national audits indicated that in 1994 in Scotland some 40% of hospital patients and 20% of community patients received ACE inhibitor treatment[19,20]. To adjust for overlap, it was assumed that half the community patients had received in-patient treatment.

(g) Treatment of hypertension: this was estimated as treatment of individuals[5]. In 1994, the prevalence of hypertension (defined as a diastolic blood pressure > 95 mmHg, or a systolic blood pressure > 160 mmHg or treatment with anti-hypertensive medication) was approximately 5% in men and 50% in women aged over 45 years[12,23]. It was estimated that, overall, some 62% of patients were treated, and that half of these patients complied sufficiently to achieve an effective diastolic blood pressure reduction of 6 mmHg or more[5,21].

Patient groups considered for treatment

The numbers of individual coronary heart disease patients eligible for, and given, specific treatments were identified using a variety of sources detailed in an Appendix 2.

Adjustment for patient overlap

Adjustments for potential overlaps between patient groups, such as hypertension and heart failure, or angina and secondary prevention post-infarction, were made using data from the third MONICA (Monitoring trends and determinants in Cardiovascular disease) risk factor survey, and local audits[21].

Combination therapy

In conditions where combination therapy is common, such as acute myocardial infarction and secondary treatment of ongoing angina and primary prevention post-infarction, was made using data from the third MONICA (Monitoring trends and determinants in Cardiovascular disease) risk factor survey, and local audits[21].

Combination therapy

In conditions where combination therapy is common, such as acute myocardial infarction and secondary
prevention, clinical trial evidence is sparse, but suggests that the same relative benefit from each treatment may operate cumulatively\cite{31}. Cumulative benefit was therefore estimated using the formula \( \text{relative benefit} = \frac{1}{1 - (1 - \text{treatment a}) \times (1 - \text{treatment b}) \times \ldots} \) etc\cite{21,31}.

### Treatment adherence (compliance)

Adherence (compliance) was defined as the proportion of patients taking therapeutically effective levels of treatment. Overall compliance was assumed to be 100% in hospital inpatients, 70% in symptomatic patients with angina or heart failure and 50% in patients with hypertension. A modest age-gradient was assumed\cite{21,32}. An example is given in Appendix 1.

### Effects of increasing treatment uptake

In this study, the mortality model was used to examine the consequences of increasing uptake of specific treatments in each category of patients. All existing figures for the year 1994 contained within the model were left unchanged (eligible patients, treatment compliance and absolute effectiveness\cite{21}). The best available data on uptake of specific treatments in each category of patients was used as a baseline\cite{12,13,15–22}. In order to ascertain the potential for increasing benefit above current levels, two uptake increases were compared: firstly a ‘modest’ increase of one tenth above current levels, and secondly, a ‘maximum feasible’ increase to 80%. Coverage of all eligible patients; 100% was considered unrealistic\cite{11,23}.

### Statistical and sensitivity analyses

Mortality effects were analysed by age and sex. The key parameters were all subject to uncertainty, with a potential for over-estimation or under-estimation of mortality benefit. Multi-way sensitivity analyses were therefore performed using the analysis of extremes method\cite{24}. Minimum and maximum mortality reductions were generated using the minimum and maximum plausible values for the main parameters: patient numbers, treatment effectiveness and adherence\cite{24}.

### Results

Coronary heart disease mortality in Scotland in 1975 and 1994

There were 18 251 coronary heart disease deaths in Scotland in 1975 (ICD codes 410–414). If the 1975

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Patients eligible</th>
<th>Treatment uptake in 1994</th>
<th>Absolute risk reduction</th>
<th>Deaths prevented or postponed (minimum and maximum estimates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1994</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community CPR</td>
<td>3189</td>
<td>0.5</td>
<td>0.112</td>
<td>694</td>
</tr>
<tr>
<td>Hospital CPR</td>
<td>1355</td>
<td>0.95</td>
<td>0.15</td>
<td>179</td>
</tr>
<tr>
<td>Aspirin and thrombolysis</td>
<td>12 181</td>
<td>0.3</td>
<td>0.052</td>
<td>193</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>12 181</td>
<td>0.29</td>
<td>0.024</td>
<td>190</td>
</tr>
<tr>
<td>Thrombolysis alone</td>
<td>12 181</td>
<td>0.01</td>
<td>0.03</td>
<td>85</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>12 181</td>
<td>0.2</td>
<td>0.013</td>
<td>4</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>12 181</td>
<td>0.16</td>
<td>0.0065</td>
<td>32</td>
</tr>
<tr>
<td>Secondary prevention post AMI</td>
<td></td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Aspirin alone</td>
<td>36 196</td>
<td>0.55</td>
<td>0.007</td>
<td>105</td>
</tr>
<tr>
<td>Beta-blocker alone</td>
<td>36 196</td>
<td>0.15</td>
<td>0.023</td>
<td>94</td>
</tr>
<tr>
<td>Aspirin and beta-blocker</td>
<td>36 196</td>
<td>0.05</td>
<td>0.029</td>
<td>39</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>36 196</td>
<td>0.1</td>
<td>0.023</td>
<td>62</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>36 196</td>
<td>0.1</td>
<td>0.0066</td>
<td>16</td>
</tr>
<tr>
<td>Warfarin</td>
<td>36 196</td>
<td>0.05</td>
<td>0.01</td>
<td>15</td>
</tr>
<tr>
<td>Rehabilitation including</td>
<td>36 196</td>
<td>0.19</td>
<td>0.02</td>
<td>117</td>
</tr>
<tr>
<td>Exercise</td>
<td>36 196</td>
<td>0.05</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>No treatment</td>
<td>36 196</td>
<td>0.05</td>
<td>0</td>
<td>136</td>
</tr>
<tr>
<td>Secondary prevention post-bypass surgery or angioplasty</td>
<td>11 267</td>
<td>0.75</td>
<td>0.019</td>
<td>(52,245)</td>
</tr>
<tr>
<td>Sub total</td>
<td>1279</td>
<td>117</td>
<td>2149</td>
<td></td>
</tr>
</tbody>
</table>
| CPR=cardio-pulmonary resuscitation; AMI=acute myocardial infarction; ACE=angiotensin converting enzyme.
age-specific mortality rates had continued unchanged, and adjusting for changes in the population age structure, 21,439 deaths would have been expected in 1994. In fact, only 15,234 deaths occurred in 1994, 6205 fewer deaths than expected[21,23].

The estimated effects from medical and surgical treatments accounted for 2722 of the deaths prevented or postponed in 1994 (minimum estimate 1373, maximum estimate 5986[21] (Tables 1 and 2).

### Model estimation: total deaths prevented or postponed by all interventions in 1994

Using the spreadsheet model, all risk factor changes between 1975–1994 accounted for 4025 deaths prevented or postponed (minimum 3417, maximum 4679)[21].

### The mortality benefit of increasing treatment uptake

Initial treatment of acute myocardial infarction

In 1994, pre-hospital cardiopulmonary resuscitation, in-hospital cardiopulmonary resuscitation, treatment

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**Table 2** Treatment of angina, heart failure and hypertension in 1994: estimated mortality reduction at different treatment uptake levels

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Patients eligible</th>
<th>Treatment uptake in 1994</th>
<th>Absolute risk reduction</th>
<th>Deaths prevented or postponed (minimum and maximum estimates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In 1994                                              If 10% extra uptake</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
<td>327                                                  (36,866)           134 (4,69)            107</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>13,384</td>
<td>1</td>
<td>0.01</td>
<td>327                                                  (36,866)           134 (4,69)            107</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>6114</td>
<td>1</td>
<td>0.002</td>
<td>134                                                  (36,866)           134 (4,69)            107</td>
</tr>
<tr>
<td>Hospitalized unstable angina</td>
<td>6450</td>
<td>1</td>
<td>0.005</td>
<td>134                                                  (36,866)           134 (4,69)            107</td>
</tr>
<tr>
<td>Aspirin for community angina</td>
<td>156,751</td>
<td>0.33</td>
<td>0.004</td>
<td>134                                                  (36,866)           134 (4,69)            107</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td>523                                                  (309,1117)         54 (31,112)          1190</td>
</tr>
<tr>
<td>Severe heart failure in hospital</td>
<td>9526</td>
<td>0.4</td>
<td>0.125</td>
<td>523                                                  (309,1117)         54 (31,112)          1190</td>
</tr>
<tr>
<td>Community treatment</td>
<td>76,978</td>
<td>0.2</td>
<td>0.03</td>
<td>333                                                  (309,1117)         33 (31,112)          333</td>
</tr>
<tr>
<td>Hypertension</td>
<td>822,460</td>
<td>0.62</td>
<td>0.003</td>
<td>323                                                  (309,1117)         32 (31,112)          970</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2722                                                 (150,1132)         263 (15,114)         4078</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td></td>
<td></td>
<td>1373,5986                                            (138,597)           139,1022 (1886,6702)</td>
</tr>
</tbody>
</table>

**Figure 1** Estimated coronary heart disease mortality reduction as a result of increasing levels of treatment uptake.
with aspirin, thrombolysis, intravenous beta-blockers and early ACE inhibition were estimated to have prevented or postponed a total of 694 deaths (minimum estimate 366, maximum 1083) (Table 1). Increasing treatment uptake by one tenth would have prevented or postponed a further 58 deaths. Increasing uptake to at least 80% of eligible patients would have prevented or postponed a further 544 deaths (minimum 344, maximum 980) (Table 1).

The mortality benefits of increasing treatment uptake rates (a) by 10% and (b) for 80% of eligible patients, for treatments for secondary prevention, angina, heart failure, and hypertension, are detailed in Tables 1 and 2.

**Total mortality reductions**

Increasing all treatment uptakes by one tenth would have prevented or postponed an additional 263 deaths in total (minimum estimate 138, maximum 597) (Tables 1 and 2).

Achieving uptake rates of at least 80% across all patient categories would have prevented or postponed approximately 4078 additional deaths (minimum 1886, maximum 6702, Table 2). Of these 4078 fewer deaths, 1605 (39%) would have resulted from increases in secondary prevention treatments, 1190 (29%) from heart failure treatments, 544 (13%) from initial treatment for acute myocardial infarction, 390 (10%) from hypertension treatment, and 349 (8%) from treatments for angina (Fig. 1).

**Discussion**

About 40% of the fall in coronary heart disease deaths in Scotland since 1975 can be attributed to medical and surgical treatments\[21]. Substantial survival benefits have accrued from individual treatments, particularly those for acute myocardial infarction, secondary prevention, hypertension and heart failure. Recent data show, however, that treatment uptake rates are variable and often low. In general, less than one third of eligible patients received appropriate therapy\[21]. This suggests that increasing the uptake of such therapies might produce large additional benefits.

We estimated that some 260 fewer deaths annually could be achieved by very small increases in treatment uptake. This has almost certainly been exceeded by now, in 1999. If 80% of eligible patients received appropriate treatment, a further 4078 deaths could probably be prevented or postponed in Scotland and, by implication, some 30 000 fewer deaths in England and Wales. This would double the reduction in mortality currently achieved by treatment. This potential gain may not, however, be realizable in all areas, for instance acute myocardial infarction. Less than 80% of patients may be eligible for thrombolytic or ACE inhibitor treatment. By concentrating on secondary prevention and heart failure only, an 80% treatment uptake might achieve 2800 fewer deaths in Scotland. How can this be achieved? Focused clinical audit has substantially increased treatment uptake rates for thrombolysis\[25,26], and also for secondary prevention therapies including aspirin and beta-blockers\[17,23]. Appropriate clinical guidelines now exist and strategies to achieve this level of treatment uptake have been published and disseminated\[23,27,28]. The emphasis on secondary prevention and heart failure therapy will mean focusing on treatment in the community.

We have previously emphasized the limitations of this type of analytical model\[23]. The model assumes that the mortality benefits reported in randomized control trials of selected young patients can be uncritically generalized to unselected groups in clinical practice. For instance, older patients may obtain greater benefits. A consistent treatment effect independent of level of risk is seen with some 85% of cardiovascular treatments, but not 100%\[30]. Various explicit assumptions were needed to cover gaps and deficiencies in information. Sensitivity analyses are therefore clearly essential to examine the effect of varying these underlying assumptions and hence test the robustness of the model\[24]. Although the estimation of each individual intervention was surrounded by uncertainty, their relative contributions remained remarkably consistent when subjected to a robust sensitivity analysis\[21]. Future research is indicated, firstly, to compare the different coronary heart disease mortality models now available,\[21,33] secondly, to translate the deaths prevented or postponed into more useful measures such as added years of life\[21]. This would also resolve the potential problems associated with estimating the mortality benefits of treating incident conditions, such as myocardial infarction, vs the treatment of prevalent conditions such as hypertension. The study focused entirely on mortality reduction, ignoring quality of life, and symptom relief. Serious morbidity, such as myocardial infarction and repeated hospitalization may also be reduced, potentially offsetting costs. Morbidity benefits comparable to those seen for mortality might be expected. Indeed, many of these treatments are given principally for symptomatic improvement, such as angioplasty and beta blockers for angina, and ACE inhibitors for heart failure\[29].

In conclusion, modern treatments have already contributed substantially to the observed reduction in coronary mortality. However, a more systematic and widespread application of proven medical therapies, reaching 80% of eligible patients, would probably double the number of deaths prevented or postponed in Scotland and, by implication, in the United Kingdom, and Europe\[13]. Audit resources are limited, and prioritization is essential. Future local audit activity should therefore initially focus on secondary prevention and heart failure.

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Sharpe, Hugh Tunstall-Pedoe, Andrew Walker, Harvey White, Bob Wilcox and David Wood.
Population and mortality data was provided by courtesy of The Registrar General for Scotland.

References


Appendix 1

Calculation example

e.g. Males aged 45–64 with acute myocardial infarction, given aspirin PLUS thrombolysis.

(a) Actual mortality reduction in 1994, and (source of information):

<table>
<thead>
<tr>
<th>Patients eligible (ISD data)</th>
<th>Absolute risk reduction (ISIS 2)</th>
<th>Treatment uptake (Local audits)</th>
<th>Deaths prevented or postponed</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>b</td>
<td>c</td>
<td>=a × b × c</td>
</tr>
<tr>
<td>4482</td>
<td>0·052</td>
<td>30%</td>
<td>69·9</td>
</tr>
</tbody>
</table>

Eur Heart J, Vol. 20, issue 19, October 1999
(b) Mortality gain if treatment uptake was 10% higher:

<table>
<thead>
<tr>
<th>Patients eligible</th>
<th>Absolute risk reduction</th>
<th>Treatment uptake</th>
<th>Deaths prevented or postponed</th>
</tr>
</thead>
<tbody>
<tr>
<td>4482</td>
<td>0.052</td>
<td>30%</td>
<td>69.9</td>
</tr>
<tr>
<td>4482</td>
<td>0.052</td>
<td>33%</td>
<td>69.9</td>
</tr>
</tbody>
</table>

Therefore seven additional deaths prevented or postponed (76.9 minus 69.9).

(c) Mortality gain if 80% eligible patients were given this treatment:

<table>
<thead>
<tr>
<th>Patients eligible</th>
<th>Absolute risk reduction</th>
<th>Treatment uptake</th>
<th>Deaths prevented or postponed</th>
</tr>
</thead>
<tbody>
<tr>
<td>4482</td>
<td>0.052</td>
<td>30%</td>
<td>69.9</td>
</tr>
<tr>
<td>4482</td>
<td>0.052</td>
<td>80%</td>
<td>186.4</td>
</tr>
</tbody>
</table>

Therefore 116.5 additional deaths prevented or postponed (186.4 minus 69.9).

This process was then repeated for: men and women, all age groups, all treatments.

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**Appendix 2**

**Epidemiological and audit studies used in this analysis**


