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A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials

Stuart J Pocock, Valerie McCormack, François Gueyffier, Florent Boutitie, Robert H Fagard, Jean-Pierre Boissel on behalf of the INDANA project steering committee

Abstract

Objective To create a risk score for death from cardiovascular disease that can be easily used.

Design Data from eight randomised controlled trials of antihypertensive treatment.

Setting Europe and North America.

Participants 47 088 men and women from trials that had differing age ranges and differing eligibility criteria for blood pressure.

Main outcome measure 1639 deaths from cardiovascular causes during a mean 5.2 years of follow up.

Results Baseline factors were related to risk of death from cardiovascular disease using a multivariate Cox model, adjusting for trial and treatment group (active versus control). A risk score was developed from 11 factors: age, sex, systolic blood pressure, serum total cholesterol concentration, height, serum creatinine concentration, cigarette smoking, diabetes, left ventricular hypertrophy, history of stroke, and history of myocardial infarction. The risk score is an integer, with points added for each factor according to its estimated contribution to cardiovascular risk. Other scoring methods already exist for assessing patient’s overall cardiovascular risk. Our score is more useful for predicting risk of death from cardiovascular disease.

Conclusion The risk score is an objective aid to assessing an individual’s risk of cardiovascular disease, including stroke and coronary heart disease. It is useful for physicians when determining an individual’s need for antihypertensive treatment and other management strategies for cardiovascular risk.
literature searches and personal inquiries we are confident that all such major trials are included. Here we assess data from all eight trials with results on mortality by intention to treat, totalling 47 008 participants of whom 3001 died (1639 from cardiovascular causes) during a mean 5.2 years of follow up (table 1).† The trials had differing eligibility criteria, and for the multiple risk factor intervention trial we focus only on the subset of participants with raised blood pressure.

Sixteen baseline factors were available in all datasets and had a priori plausibility as risk factors: age, sex, height, body mass index, current cigarette smoking, systolic and diastolic blood pressure, heart rate, concentrations of serum total cholesterol, serum creatinine and serum uric acid, previous myocardial infarction, previous stroke, diabetes, left ventricular hypertrophy detected by electrocardiography, and treatment group.

We fitted a multivariate Cox proportional hazards model, stratified by trial, for all 16 risk factors simultaneously, with cardiovascular death as outcome. We excluded body mass index, diastolic blood pressure, heart rate, and uric acid concentration, which were non-significant predictors. Systolic blood pressure was a stronger predictor than pulse pressure. For the remaining 12 factors we investigated possible statistical interactions in risk prediction. Thus we determined a final Cox model based on 1639 cardiovascular deaths in 47 088 participants with 12 risk factors and five interactions. No interactions with treatment group were strong enough to merit inclusion, and separate analyses for each trial broadly agreed with the overall model. We found no departures from linearity for quantitative risk factors.

We converted the Cox model predictor to an integer to age is slightly less noticeable for men—those aged 60–64 have 18 extra points (18 + 12 = 30 points). Cigarette smoking scores more points in women and at younger ages—for example, a female smoker aged 35-39 has 13 extra points compared with just 4 extra points for a male smoker aged 70-74.

Systolic blood pressure has a sliding scale: 5 extra points for moderate hypertension (160-169 mm Hg) and 11 extra points for severe hypertension (>210 mm Hg), the same for both sexes and all ages. For serum total cholesterol concentration the sliding scale is steeper for men than it is for women because cholesterol is not related to stroke, and the proportion of cardiovascular deaths due to stroke is higher in women—for a cholesterol concentration of 0.6-0.9 mmol/l women should be given 1 extra point and men 4 extra points. Short stature and a raised serum creatinine concentration also contribute to the score. With a history of myocardial infarction, history of stroke, and left ventricular hypertrophy 8, 8, and 3 points should be added, respectively. Diabetes contributes more to risk in women than it does in men: 9 points should be added for women and 2 points for men.

Because this score is derived from controlled trials of hypertension, the effect of treatment can be

### Table 1 Eight randomised controlled trials of antihypertensive treatment

<table>
<thead>
<tr>
<th>Trial and Warrender11</th>
<th>Blood pressure inclusion criteria (mm Hg)</th>
<th>Age range (years)</th>
<th>No of participants</th>
<th>Mean follow up (years)</th>
<th>All cardiovascular</th>
<th>Coronary heart disease</th>
<th>Stroke</th>
<th>All causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic 170-280 or diastolic 195-120</td>
<td>60-80</td>
<td>884 856</td>
<td>3.5</td>
<td>84 52 18</td>
<td>127</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EWPHE</td>
<td>Systolic 160-239 and diastolic 90-119</td>
<td>&gt;60</td>
<td>840 779</td>
<td>4.4</td>
<td>153 49 50</td>
<td>266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDFP</td>
<td>Diastolic &gt;90</td>
<td>30-69</td>
<td>10 940 10 529</td>
<td>5.0</td>
<td>396 257 73</td>
<td>706</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRFIT</td>
<td>Systolic &lt;200 and diastolic 90-109</td>
<td>35-64</td>
<td>17 354 16 851</td>
<td>5.3</td>
<td>262 196 43</td>
<td>480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC2</td>
<td>Systolic 160-209</td>
<td>65-74</td>
<td>4 396 4 090</td>
<td>6.1</td>
<td>313 179 71</td>
<td>571</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIRFIT</td>
<td>Diastolic &gt;90 or previous treatment</td>
<td>35-58</td>
<td>8 012† 8 006</td>
<td>6.9</td>
<td>193 151 20</td>
<td>343</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNEP</td>
<td>Systolic 160-209 and diastolic &lt;90</td>
<td>&gt;60</td>
<td>4 738 4 472</td>
<td>4.5</td>
<td>192 126 23</td>
<td>430</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP</td>
<td>Systolic 180-229 and diastolic &lt;230</td>
<td>70-84</td>
<td>1 027 1 505</td>
<td>2.0</td>
<td>46 22 16</td>
<td>78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All trials 48 789 47 008 1639 1031 314 3001

* Only 47 088 participants used in development of final model for cardiovascular mortality are included. † Men.

### Results

#### The risk score

Figure 1 presents the risk score for both men and women. Age is a particularly strong risk factor—a woman aged 60–64 has 23 extra points compared with a woman aged 35–39. Sex is also important, with men having 12 extra points. The gradient for risk according to age is slightly less noticeable for men—those aged 60-64 have 18 extra points (18 + 12 = 30 points). Cigarette smoking scores more points in women and at younger ages—for example, a female smoker aged 35-39 has 13 extra points compared with just 4 extra points for a male smoker aged 70-74.

Systolic blood pressure has a sliding scale: 5 extra points for moderate hypertension (160-169 mm Hg) and 11 extra points for severe hypertension (>210 mm Hg), the same for both sexes and all ages. For serum total cholesterol concentration the sliding scale is steeper for men than it is for women because cholesterol is not related to stroke, and the proportion of cardiovascular deaths due to stroke is higher in women—for a cholesterol concentration of 0.6-0.9 mmol/l women should be given 1 extra point and men 4 extra points. Short stature and a raised serum creatinine concentration also contribute to the score. With a history of myocardial infarction, history of stroke, and left ventricular hypertrophy 8, 8, and 3 points should be added, respectively. Diabetes contributes more to risk in women than it does in men: 9 points should be added for women and 2 points for men.

Because this score is derived from controlled trials of hypertension, the effect of treatment can be
measured: a reduction of 2 points if antihypertensive drugs are started. For any individual, points scored for each risk factor are added together to produce the total risk score.

**The chance of dying from cardiovascular disease**

Figure 2 shows the exponential relation between the risk score and the probability of dying from cardiovascular disease in five years. Rates of cardiovascular death vary between trials and between communities in ways not fully explained by known risk factors. The curve in figure 2 relates to a British population, being based on cardiovascular death rates for participants in the two MRC trials. The risk score itself, however, is derived from data on all participants in all eight trials.

Younger women have a lower death rate from cardiovascular disease: for instance a score of 10 points—typical for a woman aged 35-59—has a five year risk of 0.11%; a score of 25, typical for men aged 35-59, 0.51%; and a score of 35, not unusual for aged 60-64 or men aged 50-54, 1.4%. A typical score for 10 years older is 45, with a five year risk of 3.7%. A score of 55 indicates a 10% risk of cardiovascular death in five years, not uncommon for men aged 70-74, and a score of 65 indicates a 25% risk, achieved in a few elderly men only.

**Risk score by age and sex**

Figure 3 shows the noticeable influence of age and sex on the risk score for the 20,941 participants in the two MRC trials. In general, the median age specific score for a man is similar to the median score for a woman 10 years older. Age affects risk: the median age specific score for a man corresponds to the score of a man at high risk who is 10 years younger and the score of a man at very low risk who is 10 years older. A score of 45, typical for a man aged 60-64, is achieved or exceeded by only 6% of men aged 50-54 but is exceeded by virtually all men aged 70-74; 45 is also the upper 90% point for women aged 60-64 and is achieved by no woman aged 50-54.

Thus when assessing individual risk, comparisons should be made with others of the same age and sex. For example, a 66 year old male smoker (22, 12, and 4 points) has a systolic blood pressure of 150 mm Hg (4 points), a total cholesterol concentration of 6.5 mmol/l (4 points), a serum creatinine concentration of 125 μmol/l (3 points), a previous myocardial infarction (8 points), and is 1.64 metres tall (4 points). His risk score is 61 points. His risk of cardiovascular death in five years is 17% (fig 1). For his age he has an unusually high cardiovascular risk (fig 3), although his systolic blood pressure is not particularly high. His risk score emphasises the importance of tackling his overall risk of cardiovascular disease in several ways—for example, lipid lowering, smoking cessation, continued monitoring, or lowering of blood pressure.

A female non-smoker aged 52 (0, 0, and 14 points) has a systolic blood pressure of 165 mm Hg (3 points), a total cholesterol concentration of 5.2 mmol/l (0 points), a creatinine concentration of 85 μmol/l (2 points), no history of disease (0 points), and is 1.63 metres tall (3 points). Her risk score is 24 points. Her risk of cardiovascular death in five years is 0.5% (fig 2), low for her age (around the 20% point in figure 3). Despite her moderately raised blood pressure the risk score identifies her overall cardiovascular risk as low.

This helps to balance the benefit of continued blood pressure monitoring against that of starting antihypertensive drugs.

**The risk factors**

The list of risk factors chosen is not surprising, although their distributions vary between populations. Table 2 shows the distributions of risk factors for our subjects. Eligibility criteria differed between trials: one studied isolated systolic hypertension, whereas others primarily had an inclusion criterion for diastolic pressure. Hence the distribution of systolic blood pressure covers a wide range. The MRC trials excluded patients with previous stroke. Five trials were in elderly patients. The distributions of cholesterol and
creatinine concentrations and height are representative of developed countries in the West. The prevalence of diabetes is low, and it is an exclusion criterion in the MRC trials.

**Stroke, coronary heart disease, and all cause mortality**

Separate predictions of stroke, coronary heart disease, and death from any cause are also relevant. Table 3 presents the results from the Cox model that led to the risk score for cardiovascular death, and also corresponding results for fatal coronary disease, fatal stroke, and all cause mortality.

For fatal coronary disease (1031 deaths) all risk factors remain significant predictors. For fatal stroke (317 deaths) the influences of systolic blood pressure and antihypertensive treatment are more noticeable, whereas sex, cholesterol concentration, height, and a history of myocardial infarction do not predict risk. For all cause mortality all factors except cholesterol concentration are significant predictors.

**Discussion**

The risk score developed by us is unique in being based on a large cohort of adults with moderately raised blood pressure, both treated and not treated with antihypertensive drugs, including both European and North American populations, and covering a wide age range. Thus the score has wide applicability in general practices and hypertension clinics, providing a simple means of quantifying a patient’s risk of cardiovascular disease based on what should be routinely available information. The focus on overall cardiovascular risk, both of stroke and of coronary disease, ensures that a patient’s overall wellbeing, including management of other cardiovascular risk factors such as smoking and lipid lowering, gets sufficient attention, keeping control of blood pressure and antihypertensive drug treatment in proper perspective.

The score is derived from people with blood pressure sufficiently raised to be included in a trial. However, the trials’ differing eligibility criteria result in...
a wide spread of baseline blood pressures. Thus the score may be used in the general population, not just in people meeting specific criteria for hypertension. The score takes into account systolic but not diastolic blood pressure, because diastolic blood pressure does not independently predict cardiovascular risk.21 22

Mortality from cardiovascular disease varies between countries,23 which affects the generalisability of any risk score internationally. Although our data cover many developed countries, the problem remains of how to make a risk score specific to a country. Our solution has been to first obtain the most precisely estimated risk score from the whole sample of trials, but then focus on mortality in two UK trials when calculating the risk of cardiovascular disease for any individual.24 25 Because the relative importance of risk factors remains similar in most developed countries, the main complication concerns differences in mortality from cardiovascular disease between countries. For instance, the United States and United Kingdom have rather similar death rates for cardiovascular disease, making the score readily applicable to the United States. In France the rates are much lower, so if the man in the example above were French his risk of cardiovascular death within five years would be substantially less than the calculated 19%. Also, within countries there are social and geographical inequalities and secular trends in cardiovascular disease, so any assessment of risk should take account of these less quantifiable influences on health.

Assessing individual risk

Individual risk assessment should be age and sex specific (fig 3). Risk of death from cardiovascular disease varies noticeably by age and sex (for example, the man aged 65 at lowest risk is at higher risk than the woman aged 50 at highest risk), and risk management strategies need to recognise this. It would be useful to obtain age and sex specific distributions of our risk score for representative samples of individuals from other countries.

The computation of risk should be kept simple, and an integer score seemed our best approach. Sometimes not all 11 items will be known for a patient, but that is easily solved by inserting scores that are middle of the range for quantitative missing items—for example, an extra 2 points for creatinine concentration—and optimistically scoring 0 for any binary factor. However, effective health screening should avoid having data missing.

The integer score simplifies the precise Cox model for death from cardiovascular disease in table 2 although the correlation between the integer score and the Cox model linear predictor is high (r = 0.98). Routine use of the risk score by busy physicians and others may be done by accessing www.riskscore.org.uk. Keying in the 11 items provides the score, the probability of death from cardiovascular disease within five years, and the individual’s risk level compared with others of the same age and sex.

Components of risk score

The risk score includes 11 risk factors for coronary heart disease and stroke. Age, sex, and cigarette smoking are the strongest predictors. The sex difference narrows with age, and the impact of smoking is more noticeable in women and at younger ages. Serum total cholesterol concentration and systolic blood pressure have similar predictive strength in men, but cholesterol
concentration is less important for women because their risk of coronary disease is much lower. Raised creatinine concentration and short stature are both established highly significant risk factors for coronary disease and stroke, and although not present in previous risk scores should be included here. Diabetes is a more noticeable predictor of cardiovascular disease in women than it is in men, and history of stroke, myocardial infarction, and left ventricular hypertrophy are obvious factors to include. Other risk factors, such as more detailed assessment of blood lipids (for example, high density lipoprotein cholesterol and triglycerides) or presence of angina or intermittent claudication, could in principle be included but were not available in all our trials, and there is a danger of making risk scores too detailed and complicated.

Of interest is the limited impact of antihypertensive treatment on overall cardiovascular risk. According to these randomised trials, antihypertensive treatment reduces the risk score by 2—that is, in a meta-analysis the treatment on overall cardiovascular risk. According to scores too detailed and complicated.

A new score uses 11 risk factors to quantify an adult’s risk of death from cardiovascular disease, including stroke and coronary heart disease. The score is based on a large cohort of participants in controlled trials of antihypertensive drugs. An individual’s risk can be readily assessed as high or low compared with others of the same age and sex. The website www.riskscore.org.uk is available for users of the risk score.

What is already known on this topic

Many other factors are known to affect the risk of cardiovascular disease in patients with raised blood pressure

A patient’s overall risk should be taken into account when determining their need for antihypertensive drugs and other strategies for improving cardiovascular health

What this study adds

A new score uses 11 risk factors to quantify an adult’s risk of death from cardiovascular disease, including stroke and coronary heart disease. The score is based on a large cohort of participants in controlled trials of antihypertensive drugs. An individual’s risk can be readily assessed as high or low compared with others of the same age and sex. The website www.riskscore.org.uk is available for users of the risk score.

...
Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review

Seokyung Hahn, YaeJean Kim, Paul Garner

Abstract

Objectives To compare reduced osmolarity oral rehydration solution with standard World Health Organization oral rehydration solution in children with acute diarrhoea.

Design Systematic review of randomised controlled trials.

Studies 15 randomised controlled trials including 2397 randomised patients.

Outcomes The primary outcome was unscheduled intravenous infusion; secondary outcomes were stool output, vomiting, and hyponatraemia.

Results In a meta-analysis of nine trials for the primary outcome, reduced osmolarity rehydration solution was associated with fewer unscheduled intravenous infusions compared with standard WHO rehydration solution (odds ratio 0.61, 95% confidence interval 0.47 to 0.81). Three trials reported that no patients required unscheduled intravenous infusion. Trials reporting secondary outcomes suggested that in the reduced osmolarity rehydration solution group, stool output was lower (standardised mean difference in the log scale −0.214 (95% confidence interval −0.305 to −0.123; 13 trials) and vomiting was less frequent (odds ratio 0.71, 0.55 to 0.92; six trials). Six trials sought presence of hyponatraemia, with events in three studies, but no significant difference between the two arms.

Conclusion In children admitted to hospital with dehydration associated with diarrhoea, reduced osmolarity rehydration solution is associated with reduced need for unscheduled intravenous infusions, lower stool volume, and less vomiting compared with standard WHO rehydration solution.

Introduction

Diarrhoea remains a leading cause of childhood death in developing countries. The main complication is dehydration, which until the early 1960s was treated with intravenous infusion. Solutions of oral rehydration salts are now the main treatment and are particularly useful when intravenous fluids are in short supply, health services are basic, and there is a shortage of skilled staff. The combination of salt and sugar probably enhances absorption of fluid because sodium and glucose transport in the small intestine are coupled; glucose promotes absorption of both sodium ions and water. Oral rehydration solutions have proved both safe and effective worldwide in hospital settings and are now widely used in the home to prevent dehydration.

For more than two decades, the World Health Organization has recommended a standard formula of glucose based oral rehydration solution with 90 mmol/L of sodium and 110 mmol/L of glucose and a total osmolarity of 311 mmol/L. It remains unclear however, whether this is the optimum sodium concentration. Some studies have found patients with blood sodium concentrations above the normal level of 150 mmol/L laboratory work suggests that lower concentrations of sodium and glucose enhance solute induced water absorption.

We conducted a systematic review of all relevant randomised controlled trials comparing the effects of reduced osmolarity and standard WHO oral rehydration solutions. We confined the review to children, as they are most vulnerable to dehydration and electrolyte imbalance from diarrhoea.

Methods

Study inclusion and characteristics

We included only randomised controlled trials, defined as a trial in which the subjects were assigned prospectively to one of two or more interventions by random allocation. This excludes quasirandomised designs. Patients included were children with acute diarrhoea for less than 5 days who were treated either by reduced hypotension: final results of the systolic hypertension in the elderly program (SHEP). JAMA 1991;265:325-64.


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