Estimating cardiovascular risk for primary prevention: outstanding questions for primary care

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Editorial by Jackson

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The recent joint British recommendations on the prevention of coronary heart disease,[1] the British Hypertension Society guidelines for the management of hypertension,[2] and comparable recommendations from the United States[3] all conclude that the decision to start drug treatment in people at high risk but without cardiovascular disease should be based on their risk of coronary heart disease as estimated by the Framingham risk equations. We review some implications of their use in primary care.

Summary points

- Prediction of coronary risk on the basis of multiple risk factors is more accurate than with any single factor alone
- People with a 30% or greater risk of a coronary heart disease event in 10 years should be considered for treatment with aspirin, antihypertensives, and statins
- Risk assessment for coronary heart disease should be routinely added to the existing screening programme for smoking and raised blood pressure
- The measurement of serum lipid concentrations in all adults is not necessary for the identification of people at high risk
- A national programme is required to support the identification and treatment of the 10% of the population who have coronary risks of 30% or more

What do the Framingham risk equations predict?

For 50 years the Framingham heart study has documented blood pressure, smoking, lipid concentrations, and other characteristics of 5300 white men and women, together with their causes of death and disease.[4] These data have been used to predict death or major vascular events.

It is important to be clear which outcome is being predicted and over what period. Expressed as risks at one, five, or 10 years the predicted outcomes include fatal and non-fatal coronary heart disease,[5] stroke,[6] and total cardiovascular disease including congestive cardiac failure and peripheral vascular disease.[7 8] The risk of a coronary heart disease event in 10 years (myocardial infarction deaths, non-fatal myocardial infarction, and angina) has been adopted as the standard in both Britain and the United States.[3]

The Framingham equations give an acceptable prediction of risk in northern European populations but overestimate risk compared with the British regional heart study.[9] The equations depend on prevalence and are more accurate at older than at younger ages. They are most accurate when using the ratio of concentrations of total cholesterol to high density lipoprotein cholesterol, and they correctly identify 85% of people who develop coronary heart disease, with a 30% false positive rate.[10] Based on multiple risk factors this prediction is significantly better than any single factor alone.

There was initial concern that to guide treatment of raised blood pressure the outcome of coronary heart disease events on its own might underestimate the need for treatment, particularly at older ages, compared with the combined outcome of coronary heart disease plus stroke events.[1] In practice the difference is negligible, and the equation predicting coronary heart disease events is a reasonable predictor of stroke ($r=0.64$)[7] and an accurate predictor of coronary heart disease plus stroke ($r=0.96$) (LE Ramsay, personal communication). The ease of using a single measure for all treatment decisions has led Britain and the United States to sacrifice a small amount of accuracy for a large amount of clarity and to adopt the risk of a coronary heart disease event in 10 years as a common currency to guide treatment for raised blood pressure as well as aspirin and statins.[2 3 11]

Pitfalls of risk predictions

The Framingham equations were not designed for people with pre-existing cardiovascular disease as these were excluded from the original study. People with hypertension and diabetes were included, and the estimates can be used in these groups. No direct evidence supports the view that the Framingham predictions underestimate risk in type 2 diabetes.[3] People with type 2 diabetes were as likely to have a myocardial infarction as people without diabetes who had already had one myocardial infarct.[12] For any given individual with diabetes, however, the multifactorial

Framingham equations are better predictors of risk than is diabetes alone.

When variables are at their extremes the equations may underestimate or overestimate risk. For example, a person with a systolic blood pressure of 280 mm Hg or a body mass index of over 35 is likely to have a higher risk than predicted. Family history is not considered in the equations, and in people with first degree relatives with ischaemic heart disease—below the age of 55 years in women and 50 years in men—risks are likely to be greater than predicted. Similar considerations apply to South Asians and those on the lowest incomes. Risk assessment aids rather than replaces clinical judgment, and individual factors should be considered alongside risk predictions. Relative risk rather than absolute risk remains a key factor in determining lifestyle advice, particularly in young people.

Calculating and displaying cardiovascular risk

Each group adopting absolute risk has attempted to make the Framingham estimates more accessible, resulting in a bewildering array of charts and tables that use categoric variables, as well as more accurate computer programs that use continuous data.[1 11 13] For general practitioners and nurses the most rapid estimate is likely to prove the most useful. The joint British recommendations include software to calculate coronary heart disease risk and also risk of stroke.[1] Software illustrating changes in risk factors is available,[14] and Framingham calculators abound on the world wide web. The Egton Medical Information Systems' clinical computer system, widely used in British general practice, integrates the Framingham equations with a clinical system, avoiding the need to open additional software or enter data twice.[15]

Screening, lipid measurement, and the lower limit

Should ascertainment of risk of coronary heart disease be a tool for occasional clinical assessment, or should it be a routine addition to screening for smoking and raised blood pressure that is already undertaken in general practice? The effectiveness of a programme can be improved in two ways. The intervention can be made more effective, and in this respect statins are a substantial advance. Alternatively, the population can be targeted more precisely, and the Framingham risk predictions do just this. The Oxford and collaborators health check study showed that the incremental addition of testing for serum cholesterol concentration to an existing programme, which included smoking and blood pressure, conferred additional benefit at reasonable cost.[16] That trial used a unifactorial model for risk prediction and was undertaken before the introduction of statins. Should a screening programme based on absolute risk derived from multiple risk factors be put to the test in a modern day multiple risk factor intervention trial, this time using statins, aspirin, and antihypertensives at a 30% threshold for a coronary event?[17]

Who should have serum cholesterol and high density lipoprotein cholesterol concentrations measured? Like previous recommendations the new guidelines fail to adequately address the service consequences of

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their policies[18] and leave primary care with an unresolved dilemma. Should lipid concentrations be measured in all adults, using the joint British tables, in 70% of the population, using the Sheffield tables, or in 15% of the population, using average lipid values rather than actual measured values?

The Sheffield tables now aim to identify everyone with a 15% risk of a coronary heart disease event in 10 years.[19] This would entail measurement of serum total cholesterol and high density serum cholesterol concentrations in 70% of the population aged 35-64 years, including all men over 42 years and all women over 50 years. The American and joint British tables require measurement of these lipid concentrations in all adults.[11]

The Egton Medical Information Systems' computer system uses initial default concentrations for serum total cholesterol of 6.4 mmol/l and high density lipoprotein cholesterol of 1.2 mmol/l in men and 1.4 mmol/l in women to give ratios of 5.3 and 4.6 respectively, representing average values in the age group 50-64 years derived from a national survey.[20] Serum lipid concentrations need only be measured in people whose initial coronary risk, based on average lipid values, is 15% or more. This would identify everyone whose risk of a coronary event is 30% or more in 10 years. It is not worth while measuring lipid concentrations in people whose risk is less than 15% because even if the ratio of total cholesterol to high density lipoprotein cholesterol concentration was three standard deviations above the average, the risk of a coronary event cannot reach 30%, the threshold at which treatment is advised.

This approach would entail measurement of lipid concentrations in 15% of people aged 30-74 years (almost no one under 50 and 40% of people aged 50-74 years) and can be used with any of the tables or computer programs. An even more conservative approach may be desirable. It may not be worth measuring lipid concentrations at all to estimate risk as they contribute so little in addition to age, sex, smoking, or blood pressure. Measurement of lipid concentrations could be limited to guide treatment among the 5% of the population whose risks, on the basis of these other factors, are 30% or more.

The cost effectiveness and advantages of these different strategies remain to be determined. The increased sensitivity and incremental cost effectiveness

would need to be considerable to justify the recommended increases in lipid measurement. The issue is not whether everyone above a given threshold is identified but whether their identification is worth the additional effort.

Threshold for treatment

A 30% risk of a coronary event in 10 years would identify 3.4% of the population aged 35-69 years for preventive drug treatment, to which a further 4.8% of the population with pre-existing coronary heart disease should be added to make a total of 8.2%. At this level of risk, evidence that benefits outweigh harm is substantial, national drug costs are around £900 million per annum, and there is a broad consensus, endorsed by the Department of Health, that this represents a reasonable policy objective.

Lowering the threshold to 15% would involve 25% of the population in treatment decisions for aspirin and statins, to which should be added people with blood pressures of 140-149/90-99 mm Hg requiring antihypertensives.[21] A national drug cost of £2,700 million per annum would put statins beyond the reach of NHS budgets. Although the costs of aspirin and thiazides are a fraction of this amount, more debate is required before any firm recommendation can be made to routinely treat half the population over 50 years of age.

The case for aspirin rests on trials that show a reduction in coronary events but no significant reduction in mortality. The trials yield increased but substantially different estimates of gastrointestinal haemorrhage. At the 15% coronary event threshold, 60 people would be exposed to these risks for five years to avert one coronary or stroke event.[22 23] Trials select populations to maximise benefits and minimise harm. Targeting older and less select populations may alter the ratio of harm to benefit. It may be prudent to adopt the higher 30% threshold until this question has been more fully reviewed.

The evidence of reduced mortality with thiazides and reduced cardiovascular events with β blockers in people with raised blood pressure is substantial. For mild hypertension at a 15% risk of a coronary event, 40 people would need to be treated with thiazides or β blockers for five years to avert one coronary or stroke event.[24] The question of reduced quality of life or harm has not been adequately set out in recent documents. The Medical Research Council's trial of mild hypertension continues to exert an unjustified influence over British general practice in this respect. This study found appreciable adverse effects from treatment, probably attributable to the single blind design. Several major double blind trials in the United States found that thiazides and β blockers were not associated with more adverse effects than placebo, and quality of life was enhanced in the treatment group.

The requirement for evidence and debate is greater where small effects are applied to such large populations. This debate on policy needs to include the public and primary care and should be considered together with national policy options to improve nutrition, increase physical activity, and reduce smoking in the general population. This discussion may help to clarify the difference between evidence of benefit and the political arithmetic of implementation, which is currently confused in the new guidelines. It would be unfortunate if concerns about treating 25% of the population at the 15% threshold should obscure the consensus for implementation in the top 10% of the population. The top 10% includes those who have cardiovascular disease as well as those who have a 30% risk of coronary heart disease in 10 years. How will a national programme of implementation to identify and treat these people be supported, and who will conduct a review of policy options below this level?

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