The future of coronary heart disease prevention

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Clin Med 2007;7:392–6

Coronary heart disease (CHD) causes death or serious disability in about one-third of people in Western societies and is now the leading cause of death worldwide. There are about 120,000 deaths each year in the UK, a rate that has remained constant despite a substantial decline in age-specific mortality over the past 25 years.[1] Smoking cessation and interventions such as aspirin, thrombolysis and, more recently, statins and blood pressure (BP) lowering drugs have been largely responsible for this decline, but have only shifted the number of CHD deaths from a younger age group (50–59 years) to an older one, leaving the absolute number of deaths unchanged.

A large reduction in CHD mortality will require prevention strategies combining lifestyle measures (such as weight and salt reduction) with pharmacological initiatives that widen the use of effective preventive medications.

Risk factor thresholds

Prevention strategies based on the existence of risk factor thresholds limit the efficacy of interventions to lower risk factors by restricting them to people with high levels of risk factor and lowering them to arbitrary target levels rather than to the lowest practical level. Cohort (prospective) studies provide evidence that for all the major cardiovascular risk factors there are continuous proportionate relationships with disease risk without 'threshold' – that is, without a point below which the risk of CHD ceases to decline with further reductions in the risk factor.[2]

This is illustrated in Fig 1(a) which summarises the results from a meta-analysis of cohort studies (diastolic BP plotted against risk of CHD).[3] The notion of thresholds arose as a result of plotting disease risk on arithmetic rather than proportionate (or logarithmic) scales – a plotting error that gives the illusion of a threshold when there is none (Fig 1(b)). Such plots conceal the fact that there is a constant proportional change in disease risk for a given change in risk factor. This is an important observation indicating benefit in reducing risk factors, regardless of the level of the risk factor, in all people at risk of cardiovascular disease.[4]

Consideration should be given to abandoning the notion of thresholds and targets. This would allow more people who would benefit from preventive medications (those at high risk for any reason) to receive them. It would also enable those who receive them to achieve the full potential preventive benefit.

Risk factors as screening tests

Measurement of risk factors such as BP and serum cholesterol is widely practiced because of a perception that known causes of CHD will be an effective means of screening to identify people who will not develop a CHD event.[4] It has been assumed that an important cause of CHD must be a useful screening test for CHD. However, the strength of association needed between a risk factor and a disease for that risk factor to discriminate usefully between those who will and those who will not develop CHD is much larger than for any of its known causes. Relative risks of about 100 (comparing those in the top and bottom fifths of the risk factor distribution) would be needed and those for serum cholesterol or BP are no more than about 5.[3–5]

Cholesterol

Figure 2 shows the distribution of total cholesterol in people who did and did not die from CHD in the BUPA cohort study.[6] There is substantial overlap between the two distributions, such that it is not possible to select a cholesterol level (or cut-off) which adequately includes most of those who develop CHD and excludes those who do not. At a cholesterol cut-off of 6 mmol/l (the approximate level recommended for treatment with statins in recent national guidelines)[7,8] about 70% of people who develop CHD would be identified (the detection rate), however, so too would 56% of the population who do not (the false-positive rate). Cholesterol measurement is therefore a poor screening test. Moreover, the 30% in the shaded area who would be classified as low risk will develop CHD but are excluded from

Key Points

- **Risk factors like serum cholesterol and blood pressure while important in causing coronary heart disease (CHD) are poor predictors of who will and will not suffer a CHD event. Combining them does not overcome this problem, so screening for risk by measuring risk factors is not worthwhile**
- **The best predictors of risk are a history of vascular disease or those risk factors which can not be changed (age and sex)**
- **The dose-response relations between risk factors and CHD show benefit in modifying risk factors in people at high risk, regardless of the level of the risk factor and whatever the reason for the high risk**
- **Coronary heart disease is largely preventable; a simple strategy of combination therapy to simultaneously reduce all major risk factors in everyone above a specified age (say 55) and younger people who already have vascular disease would reduce risk by over 80%**

KEY WORDS: blood pressure, cholesterol, coronary heart disease, homocysteine, Polypill

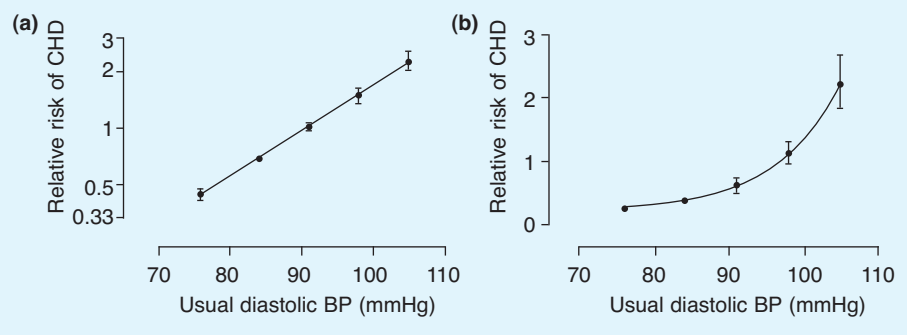

Fig 1. Dose-response relationship between diastolic blood pressure (BP) and risk of coronary heart disease (CHD) in a meta-analysis of cohort studies with risk plotted on (a) a proportionate scale and (b) an arithmetic scale. Data sourced from Reference 3.

cholesterol-lowering treatment. The same limitations apply using systolic or diastolic BP as the screening test.[4]

Combining coronary risk factors for screening

It is often assumed that combining information on several coronary risk factors will overcome the problem that individually they are poor screening tests.[9] But this is not the case. An analysis of the BUPA cohort[10] showed that using either systolic BP or apoprotein B alone, the detection rate was 17% for a false-positive rate of 5%. Using both together, the detection rate increased to 22% (keeping the false-positive rate fixed at 5%). Using six risk factors in combination gave a detection rate of only 28% for the same false-positive rate. The improvement in screening performance from combining several risk factors, including more recently investigated factors such as C-reactive protein and serum homocysteine,[11] is marginal and can be achieved only by identifying a large proportion who will not develop clinical CHD.

Simpler and more discriminatory means of identifying people in the population at highest risk of a CHD event are needed and are available. In people who have survived a myocardial infarction (MI) the risk of death from CHD in the absence of treatment is about 5% per year regardless of age or risk factor levels.[12] This is an extremely high risk group in whom all interventions known to reduce reversible risk factors can reasonably be offered. Adults with diabetes mellitus have a similarly high risk of CHD and are justifiably treated by multiple risk factor reduction regardless of risk factor levels.[13]

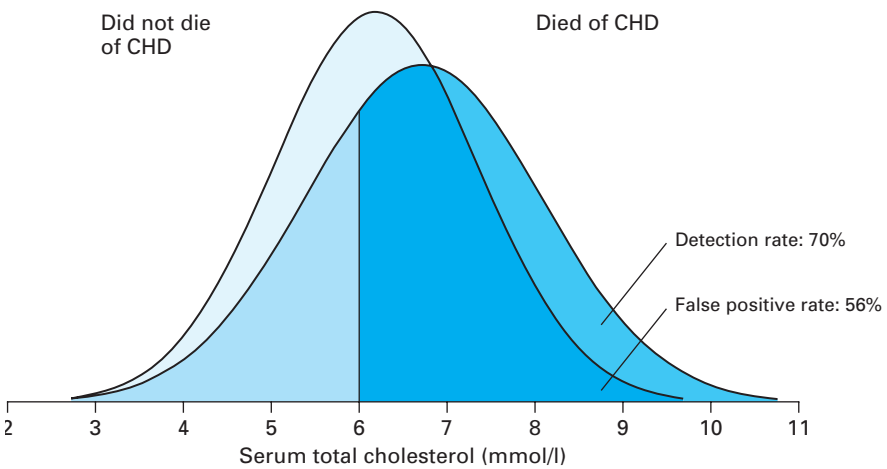

Fig 2. Overlapping distributions of serum total cholesterol in people who did and did not die of coronary heart disease (CHD) in the BUPA cohort study. The shaded area indicates the proportion of people (30%) who will die of CHD but would be excluded from treatment if a serum cholesterol cut-off of 6 mmol/l were used to screen for CHD risk. Data sourced from Reference 6.

'Global' cardiovascular risk

Cardiovascular screening is sometimes used to compute 'global' cardiovascular risk in people without a history of CHD or diabetes, based on age, sex and the level of combinations of the causal cardiovascular risk factors. The risk estimate itself has become the screening variable and treatment is offered to all those whose 10-year risk exceeds a specified cut-off level (eg 20%, as advocated in recent British guidelines).[7] However, because the risk factors are poor screening tests this does not overcome the inclusion of almost as many people who will not develop CHD as those who will.

Age dominates over other risk factors, so adding the latter to age adds little further precision and is not worth the considerable cost and complexity. The most effective approach would be to select an age above which most CHD events occur and treat all above this age. Since 96% of all fatal CHD and stroke events occur over age 55 this has been proposed as a reasonable age cut-off.[14]

Medical interventions to prevent coronary heart disease (Table 1)

Cholesterol reduction: statins

Statins are the most effective drugs available for lowering serum cholesterol and reducing the risk of CHD. The maximum effect was initially underestimated in randomised trials because events in the first two years (before the full effect is attained) were not removed from the analysis and no adjustment was made for non-adherence. A meta-analysis of 58 trials of the effect of serum cholesterol reduction on disease events allowed for these effects. It

showed that a reduction in low-density lipoprotein (LDL) cholesterol of 1.8 mmol/l (from a starting level of 4.8 mmol/l) reduced the risk of CHD events by about 60% and was achieved with moderate doses of statins (such as simvastatin 40 mg or atorvastatin 10 mg).[15]

Some statins achieve larger reductions, but that does not mean they are preferred. The choice of statin depends on the balance between efficacy, side effects and cost. Both simvastatin 40 mg and atorvastatin 10 mg are safe and well tolerated and equivalent in efficacy, but simvastatin is preferred because it is less expensive. Atorvastatin 80 mg and rosuvastatin 40 mg reduce LDL cholesterol by as much as 2.6 mmol/l,[15] but the risk of side effects (which are strongly dose related) and the increased expense mean that they would probably not be sensible choices for routine use.

Table 1. Effect of combination medical intervention (pills) on coronary heart disease (CHD) risk. Data sourced from Reference 14.

Risk factor	Intervention	Approximate risk factor reduction	CHD risk reduction (%)	Ref
LDL cholesterol	Statin	1.8 mmol/l	61	15
Blood pressure	Half standard dose of 3 from: • thiazide • β-blocker • ACEI or ARB • calcium-channel blocker	10.7 mm Hg diastolic*	46	16
Serum homocysteine	Folic acid	3 μmol/l	16	24
Platelet aggregation	Aspirin	–	32	14
Combined**	Polypill	–	88	14

* starting blood pressure 150/90 mmHg
**calculated by multiplying the relative risks for each risk factor, taking the complement and expressing as a percentage, ie 0.39 x 0.54 x 0.84 x 0.68 = 0.12, the complement of which is 0.88 or 88%.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LDL = low-density lipoprotein.

Blood pressure reduction

Lowering systolic or diastolic BP by 10 mmHg or 5 mmHg, respectively, reduces the risk of CHD by about 25% at age 65.[2,3,17] This applies to people with and without CHD and across all levels of BP in Western populations, not simply in those with so-called 'hypertension'. Over time, trials have been reported claiming superiority of one class of BP lowering drug over another or one combination of drugs over another.[18,19] Such comparisons can be misleading unless the differences in risk of CHD are measured against the BP reductions achieved in the trials. When this is done, the differences in preventive effect are shown to relate largely to the differences in BP reductions observed rather than to pleotropic effects of the individual drugs.[20]

A meta-analysis of 354 randomised trials showed that any of the five main classes of BP lowering drugs, given in its usual maintenance dose (as recommended in the British National Formulary) achieved about a 5 mmHg diastolic BP reduction. There was no material difference between any of the classes (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers and calcium-channel blockers) in terms of their BP lowering effect.[16] The meta-analysis also showed that halving the dose did not halve the effect, but decreased it by only about 20%. In contrast, side effects from these drugs (with the exception of the cough due to ACEIs) were strongly dose related. Since the efficacy of drugs from different classes in combination are additive, these observations provide a rationale for using combinations of low-dose BP lowering drugs as first-line therapy in the treatment of BP – an approach that will maximise efficacy and minimise side effects.

Antiplatelet therapy

The value of aspirin in the secondary prevention of cardiovascular disease is well established: there is about a 30% reduction in risk of MI, stroke or vascular death using low-dose (75 mg) aspirin.[14] In contrast, its value in people without prior cardiovascular disease is less certain because of the increased risk of cerebral haemorrhage and gastrointestinal bleeding which tends to diminish the mortality benefit.[21]

Combinations of antiplatelet drugs are used in secondary prevention. The addition of clopidogrel (75 mg per day) to aspirin resulted in a 20% relative reduction in risk of vascular death, MI and stroke following a non-ST elevation MI in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study (with about a 38% increased risk of major bleeding complications).[22] Current recommendations are to continue treatment for one year following an MI.

Homocysteine reduction

Increasing the consumption of B vitamins reduces blood levels of homocysteine. An additional 0.8 mg folic acid per day is the minimum fully effective dose that maximally reduces serum homocysteine (by about 3 μmol/l).[23] This is expected to reduce the risk of CHD by 10–15%,[24,25] but randomised controlled trials on the effect of homocysteine reduction on CHD events and stroke have been inconclusive. The modest expected effects and the small number of events recorded in the randomised trials mean that they lack statistical power. Despite this, the reports from individual trials tend inappropriately to interpret statistically non-significant effects as evidence of no effect.[26]

If the trials were the only source of evidence, it would not be known whether homocysteine reduction is useful in preventing CHD. However, other evidence is available from studies of people with and without a common homocysteine-raising mutation (the MTHFR 677C→T polymorphism). The presence of this mutation in the population is, in effect, a natural randomised trial. The popula-

tion has been randomly allocated to two groups, one with a higher homocysteine (TT) than the other (CC), where there is no reason to expect any other systematic difference between the two groups (so-called Mendelian randomisation).

A meta-analysis of studies assessing the risk of CHD events in 57,000 people with and without the mutation found a 14% higher risk in TT than in CC homozygotes for an observed 2.2 μmol/l homocysteine difference.[27] This is equivalent to a 16% lower risk for a 3 μmol/l lower homocysteine (achievable with folic acid), similar to the result from cohort studies even though the two types of study do not share the same potential sources of error. A recent meta-analysis of randomised trial has shown that folic acid, taken for at least three years, reduces the risk of stroke by 20–30%.[28] Comparable trial evidence on CHD is lacking. The large number of trial participants needed to show a 10% reduction in CHD events and the uncertainty over the time needed to achieve this means that trials may not show the expected effects. The balance of evidence points towards a favourable, albeit modest, effect of folic acid in preventing CHD.

Combination multiple risk factor reduction: the Polypill

It is expected that a Polypill will be available within a few years for use in people with and without cardiovascular disease to reduce their risk of CHD and stroke by over 80%.[14] Proposed in 2003, the Polypill is a combination of three low-dose BP lowering drugs – a statin, aspirin and folic acid – in fixed dose as a single daily pill that simultaneously reduces four separate cardiovascular risk factors. It is advocated for all people aged 55 and over, for diabetics from age 35 and people with known coronary artery disease or cerebrovascular disease at any age.

Lowering all risk factors simultaneously has a multiplicative effect in reducing risk because the risk factors act independently in causing disease. This has been shown in cohort studies. More recently, randomised trials have shown that treatment to reduce one risk factor (eg serum cholesterol with statins) reduces risk by the same percentage in people taking and not taking BP lowering drugs or whether or not they are taking aspirin.[29,30]

The Polypill strategy is based on the principles set out above, that:

- combinations of low-dose BP lowering drugs offer greater efficacy and safety than higher doses of single drugs
- thresholds, targets and screening needlessly limit the efficacy of preventive treatments and should be abandoned.

The strategy is not intended to replace exercise, a sensible diet and smoking cessation. It would complement these activities, recognising the difficulties of adopting such lifestyle changes in modern society.

Conclusions

Drug treatments to prevent CHD have generally been limited to treating single risk factors, to targeting the minority of people with values in the upper tails of the risk factor distributions (in whom relatively few CHD events occur) and to reducing risk factors to arbitrary target levels judged to be 'normal'. This approach can achieve only a modest reduction in disease. A large preventive effect would require intervention in everyone at increased risk, irrespective of risk factor levels, with simultaneous intervention on all causal risk factors in people at high risk and reducing risk factors as low as possible. Widespread adoption of these three principles has the potential to make rare what is currently the most common cause of death and disability in the world.

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