## Treating Individuals 5

# Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk

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**In this review, we outline the rationale for targeting blood pressure and blood cholesterol lowering drug treatments to patients at high absolute cardiovascular risk, irrespective of their blood pressure or blood cholesterol levels. Because the specific levels of blood pressure and cholesterol are of little clinical relevance when considered in isolation from other risk factors, terms such as hypertension or hypercholesterolaemia have limited value. Separate management guidelines for raised blood pressure and blood cholesterol need to be replaced by integrated cardiovascular risk management guidelines, and absolute cardiovascular risk prediction scores should be used routinely. Since cardiovascular risk factors interact with each other, moderate reductions in several risk factors can be more effective than major reductions in one. An affordable daily pill combining low doses of various drugs could be useful for the many individuals with slightly abnormal cardiovascular risk factors.**

Fifty years ago it was thought that people either had hypertension or not in the same way that a woman is pregnant or not. With the realisation that blood pressure is continuously related to cardiovascular risk, hypertension has more recently been defined as the blood pressure level above which there would be substantial (or clinically significant) benefits from lowering blood pressure;[1] the same idea has been applied to defining hyperlipidaemia. Most adults in developed countries and increasing numbers in developing countries would meet these so-called capacity to benefit[2–4] definitions. This fact has implications for governments since they are responsible for reducing major threats to health, and much greater investment is needed for population-based cardiovascular disease preventive strategies. In this review we focus on the clinical implications of these definitions, which are also relevant because almost every adult could be eligible for individualised treatment. We argue that treatment decisions should be based mainly on absolute estimates of cardiovascular risk. As a result, some patients with average or below average levels of blood pressure or blood cholesterol will be treated in preference to other patients with higher levels. Although this approach has been advocated for at least 10 years,[5,6] and is supported by both observational and clinical trial evidence, many clinicians still base treatment decisions mainly on blood pressure or cholesterol levels.

## Relative risk of cardiovascular diseases

Meta-analyses of individual patient data, from prospective observational studies covering both developed and developing populations, show the same general pattern of association between blood pressure or blood cholesterol levels and relative risk of cardiovascular disease.[4,7–9] As figure 1 shows, for a specific absolute change in blood pressure there is a constant relative change in cardiovascular risk between the blood pressure range of about 110/70 mm Hg and 170/105 mm Hg.[2–4,7–10] A difference in diastolic blood pressure of about 5 mm Hg is associated with about a 20% relative difference in coronary risk and about a 35% relative difference in stroke risk anywhere within this wide blood pressure range.[3] A 0·6 mmol/L difference in total blood cholesterol corresponds to about a 27% relative difference in coronary risk,[3] and this association is roughly constant anywhere in the total cholesterol range between about 4·0 mmol/L and 9·0 mmol/L.[7,10] The relation between blood cholesterol and ischaemic stroke is also positive but the relation with haemorrhagic stroke is uncertain.[11] Although observational studies show a stronger relation between these two risk factors and cardiovascular risk in younger than in older people, the relative association remains constant within any one age-group.[4,7,10]

Data from randomised trials of blood pressure or blood cholesterol lowering treatments are generally consistent with the observational evidence discussed above. Trials show that for a given absolute reduction in blood pressure or blood cholesterol, the cardiovascular risk reduction is similar to that predicted by observational studies.[3,12–15] Moreover, most of the predicted risk reduction seems to happen within about 5 years of treatment, which is the typical duration of trials. The relative risk reductions are also similar at different pretreatment levels of blood pressure and blood cholesterol. Several trials of blood pressure lowering drugs have been done without any blood pressure entry thresholds,[16,17] and these trials show similar relative risk reductions whatever the entry blood pressure. For example, figure 2 shows the constant relative reduction in stroke risk by tertile of entry blood pressure in PROGRESS,[17,18] a trial of blood pressure lowering in more than 6000 people with previous

cerebrovascular disease. The same pattern is seen with blood cholesterol lowering treatments and is best shown by the Heart Protection Study,[19] which randomly assigned more than 20 000 high-risk people to a statin or placebo if their total blood cholesterol concentration was greater than 3·5 mmol/L. About a quarter of the participants had entry total cholesterol concentrations less than 5·0 mmol/L or LDL cholesterol lower than 3·0 mmol/L, and no attenuation of relative cardiovascular risk reduction was noted across the tertiles of entry cholesterol concentrations (figure 3).

Although observational studies show an age-related attenuation of the relative association between blood pressure or blood cholesterol and cardiovascular risk,[4,20,21] randomised trials have not indicated a clear age-treatment interaction.[16,19,22,23] Whether this age-related attenuation in relative risk is real or an artifact is of little consequence because the absolute pretreatment risks (and therefore the absolute benefits of treatment) are generally much greater in elderly people than in younger patients.[16,17,19,22]

## Absolute risk of cardiovascular disease

Absolute cardiovascular disease risk (ie, the probability that a patient will have a cardiovascular event in a defined period) is determined by the synergistic effect of all cardiovascular risk factors present,[24] and absolute differences in risk can vary more than 20-fold in patients with the same blood pressure or cholesterol levels.[10] The most powerful risk predictors are age, previous symptomatic cardiovascular disease, and pathophysiological changes, such as left ventricular hypertrophy and renal impairment, but many factors, including increasing blood pressure and lipids, smoking, male sex, and others, interact to determine absolute risk.[25] Single risk factors such as blood pressure or cholesterol have a minor effect on a patient's absolute risk in the absence of other risk factors, but they can have a major effect in the presence of several risk factors.[26] For example, figure 4 shows the effect on absolute cardiovascular risk of successively adding risk factors in patients with different systolic blood pressure levels, and figure 5 shows the similar effects of additional risk factors in individuals with different blood cholesterol concentrations. A non-smoking non-diabetic 50-year-old woman with a total cholesterol of 4·0 mmol/L, an HDL cholesterol of 1·6 mmol/L, and a systolic blood pressure of 130 mm Hg, has a 5-year cardiovascular risk of about 1%. However, the same woman with the same blood pressure would have a 10% 5-year risk if she were a smoker with a total cholesterol of 7 mmol/L and an HDL of 1 mmol/L. If she also had diabetes her 5-year risk would be almost 20% despite an identical blood pressure. A similar range of predicted absolute cardiovascular risks would be recorded in women with identical total and HDL cholesterol levels but different patterns of other risk factors. As a result of this synergistic effect of risk factors, individuals with low blood pressure or blood cholesterol might have much higher absolute risks than others with high levels of one of these risk factors. These observations emphasise the clinical limitations of terms such as hypertension or hypercholesterolaemia.

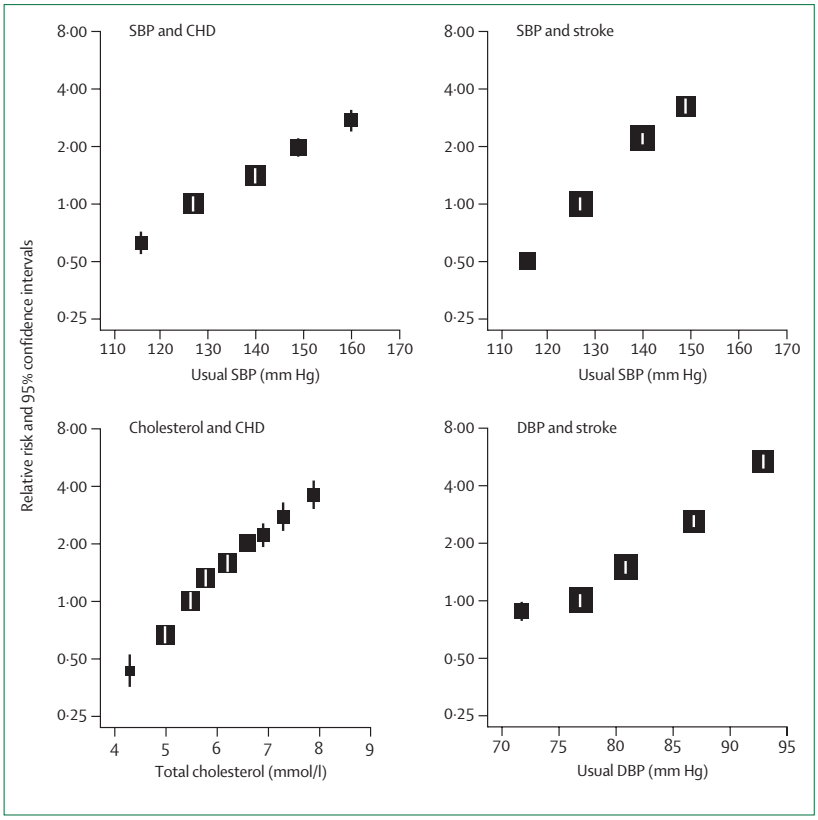


***Figure 1:*** **Relative risk of coronary heart disease and stroke by blood pressure[8] and cholesterol[10] concentration**
SBP=systolic blood pressure. CHD=coronary heart disease. DBP=diastolic blood pressure. Derived from data presented in the references cited.

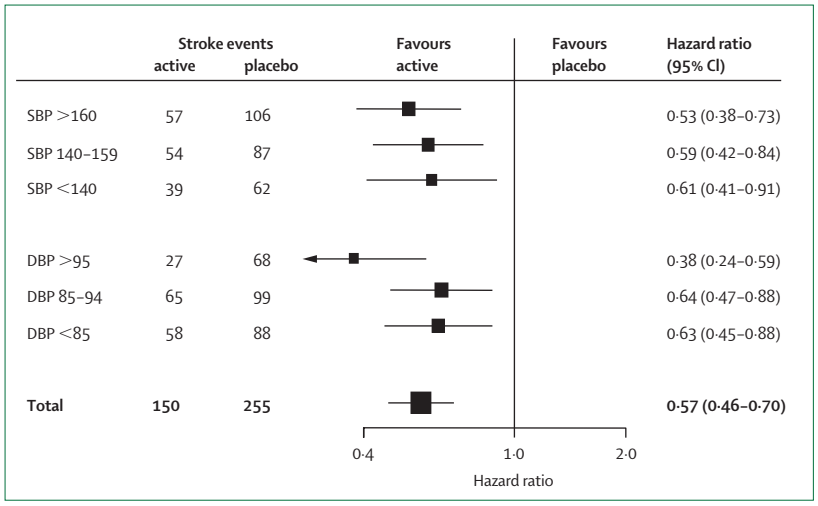


***Figure 2:*** **Relative risk reduction in stroke by baseline blood pressure level in PROGRESS[18]**
SBP=systolic blood pressure. DBP=diastolic blood pressure. Modified from reference 18 with permission of Elsevier.

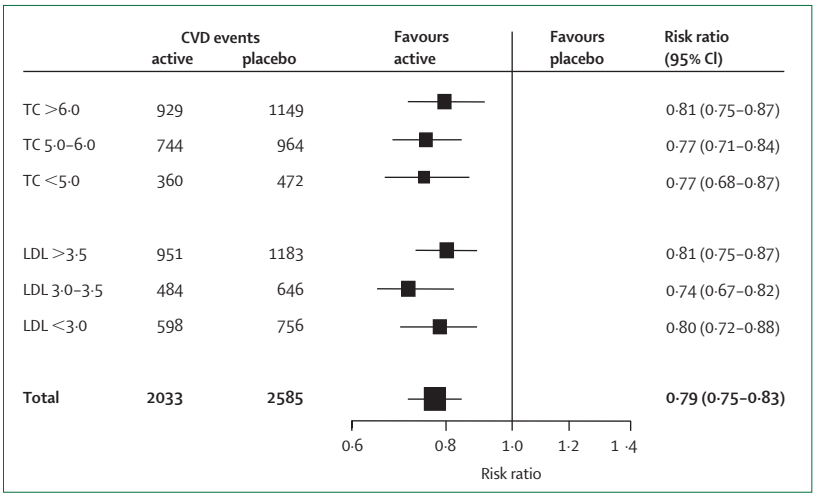


***Figure 3:*** **Relative risk reduction in cardiovascular disease by baseline blood cholesterol concentration in the Heart Protection Study[19]**

CVD=cardiovascular disease. TC=total cholesterol. Derived from data presented in the reference cited.

As with relative differences in risk, the absolute cardiovascular risk reductions shown in clinical trials of blood pressure or cholesterol lowering are consistent with the absolute benefits predicted from prospective observational studies. For a specific reduction in either blood pressure or blood cholesterol, randomised trials show that the absolute cardiovascular treatment benefit is directly proportional to the pretreatment absolute risk (figures 6 and 7).[22,27–29] These figures show similar relative reductions in risk whether or not the trials included individuals with previous stroke or vascular disease. By contrast, the absolute differences in benefit vary about two-fold to three-fold with a greater absolute benefit in patients with previous cardiovascular disease.

## Estimating absolute cardiovascular risk

In view of the wide range of possible absolute cardiovascular risks in patients with similar blood pressure or blood cholesterol concentrations, accurate risk assessment is fundamental to effective clinical risk management. Results from a North American study examining clinicians' ability to quantify cardiovascular risk and treatment benefits suggests that knowledge of risk is poor in both generalists and specialists.[30] Clinicians had inflated perceptions of cardiovascular risk and benefits of treatment. When given a hypothetical case of a patient with raised cholesterol, family doctors and general internists overestimated 5-year risk of myocardial infarction by more than three-fold and absolute treatment benefits by a greater margin, and specialists overestimated risk by two-fold and benefits by three-fold.

A range of paper-based and electronic cardiovascular risk prediction scores is now readily available (table 1). Although the degree of uptake is uncertain, a growing body of research has shown that risk prediction scores are usable in routine clinical practice[39,40] and lead to

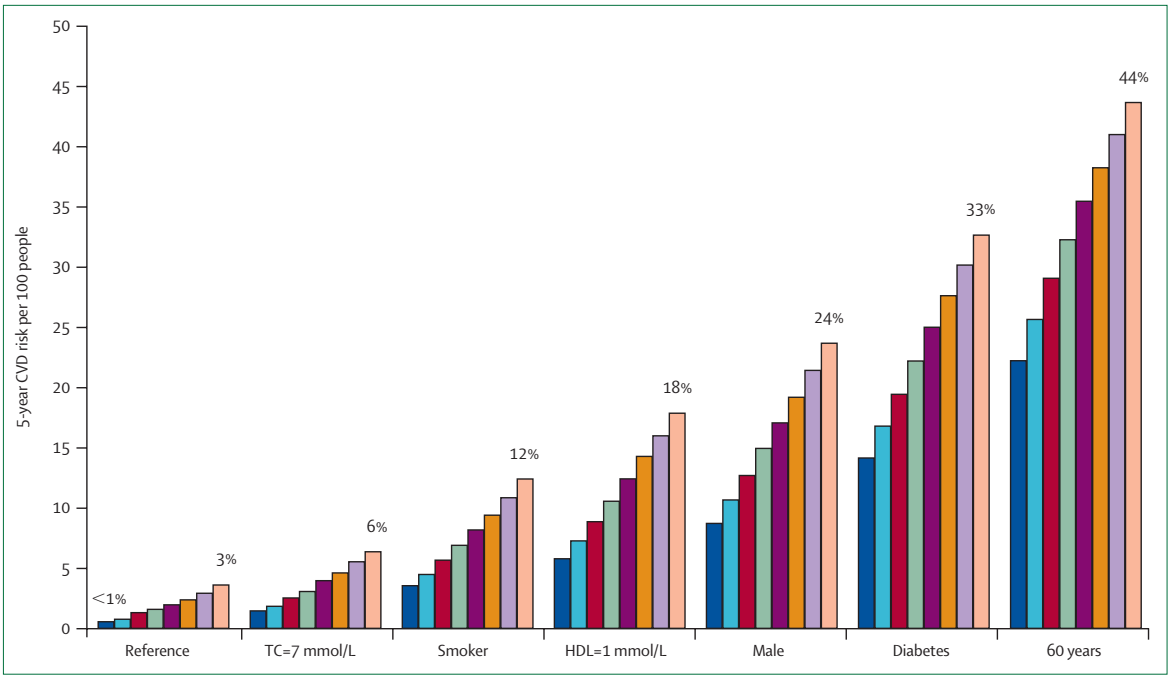


***Figure 4:*** **Absolute risk of cardiovascular disease over 5 years in patients by systolic blood pressure at specified levels of other risk factors[26]**

Reference category is a non-diabetic, non-smoker female aged 50 years with total cholesterol of 4·0 mmol/L and HDL of 1·6 mmol/L. Risks are given for systolic blood pressure levels of 110, 120, 130, 140, 150, 160, 170, and 180 mm Hg. In the other categories additional risk factors are added consecutively, for example, the diabetes category is a diabetic 50-year-old male cigarette smoker, with a total cholesterol of 7 mmol/L and HDL of 1 mmol/L. TC=total cholesterol. Derived from data presented in the references cited.

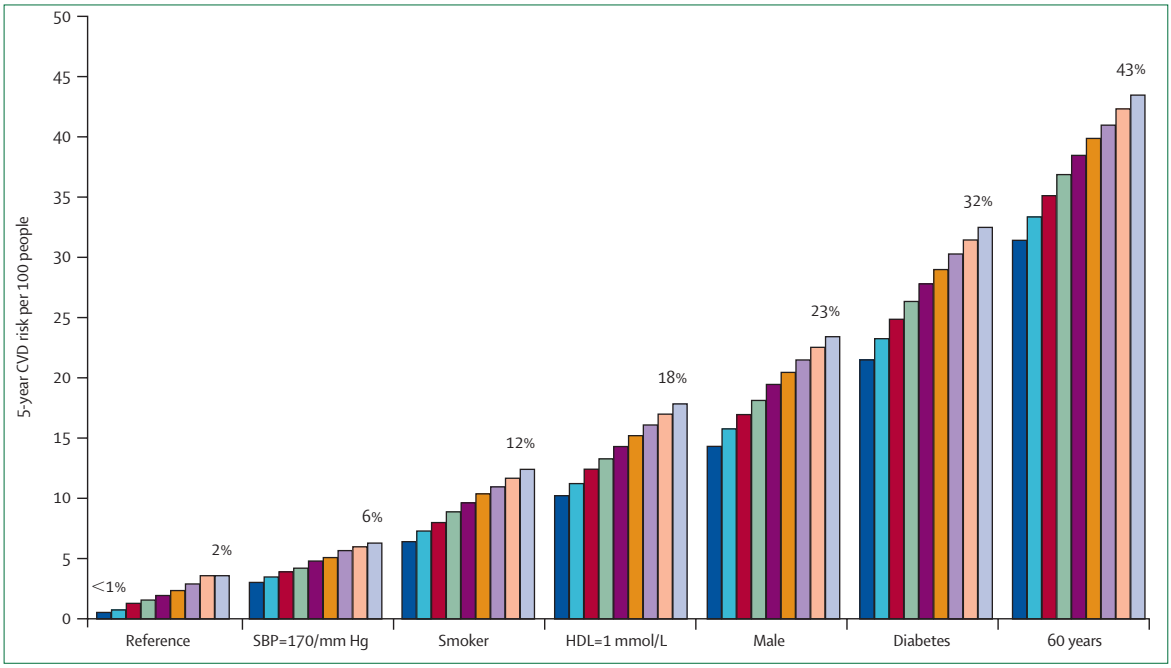


***Figure 5:*** **Absolute risk of cardiovascular disease over 5 years in patients by blood total cholesterol at specified levels of other risk factors[26]**
Reference category is a 50-year-old non-smoker, non-diabetic female with systolic blood pressure of 110 mm Hg, HDL of 1·6 mmol/L. Risks are given for total cholesterol concentrations of 4·0, 4·5, 5·0, 5·5, 6·0, 6·5, 7·0, 7·5, and 8·0 mmol/L. In each of the other categories additional risk factors are added consecutively, for example the HDL=1 mmol/L category is a 50-year-old, female cigarette smoker with systolic blood pressure of 170 mm Hg and HDL of 1 mmol/L. Derived from data presented in the references cited. SBP=systolic blood pressure.

improved risk management.[41,42] Many scores have been derived from the Framingham Heart Study, a cohort study of about 5000 white Americans, established more than 50 years ago and replenished by offspring of the original cohort.[43] Scores have also been based on the Prospective Cardiovascular Munster (PROCAM) Study, a working population of about 20 000 people in northern Germany, initiated in 1979,[44] and another score is based on about 5000 people with diabetes from the UK Prospective Diabetes Study.[35] Several other cardiovascular mortality scores have been published, one based on 47 088 adults with raised blood pressure from eight European and North American trials,[37] and the European SCORE project's high risk and low risk region charts based on 12 European cohorts representing 2·7 million person-years of follow-up.[38]

Most of the scores have been generated with regression models, although the PROCAM investigators have developed a neural network-based score that they believe will improve prediction.[36] Their neural network model predicted about 75% of all cohort events over 10 years within a high-risk subgroup including only 7·9% of the cohort, whereas a regression model predicted only 46% of events in 8·4% of the cohort. However, the investigators have yet to validate their models in independent populations and neural network models are typically less generalisable than regression models.

Several validation studies have been done with the Framingham prediction scores but findings are conflicting. Framingham investigators report that their risk scores are reasonably generalisable across populations with coronary rates similar to North American rates and that the scores can be recalibrated for other populations.[45] Other investigators report less favourable results for both the discriminatory power and generalisability of Framingham predictive functions.[46,47] Most validation studies report relative measures of validity, such as similarities in relative risks or areas under receiver-operator characteristic curves. However, such measures do not capture the more clinically relevant absolute predictive validity of the approach, such as the proportion of all events predicted in a small, definable, and treatable high-risk group. Models that include a

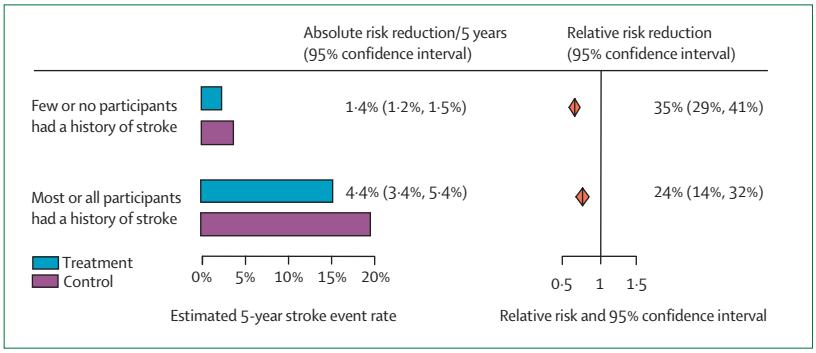


***Figure 6:*** **Absolute and relative treatment effects on stroke in blood pressure lowering trials, by prior history of stroke[15]**
Derived from data presented in the references cited.

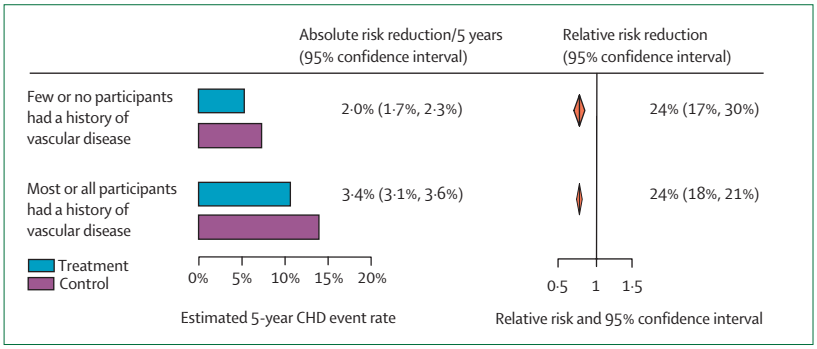


***Figure 7*: Absolute and relative treatment effects on coronary heart disease in cholesterol lowering trials, by history of vascular disease[29]**
CHD=coronary heart disease. Derived from data presented in the references cited.

greater range of risk factors[35,36] tend to be more predictive than do those with fewer factors,[26] suggesting that there is potential to improve on the models in use and that the usefulness of predictive factors such as C-reactive protein[48] should be investigated further.

As a minimum requirement, risk prediction scores should be based on populations with reasonably similar risk profiles and event rates to those to which they are applied, or the scores should be calibrated to fit the target population.[45] The proportions of patients likely to be classified at different absolute risk levels should be estimated so that practical and economically sustainable treatment thresholds can be set. Although, ideally, prediction models should be developed locally, they should at least be validated in local populations.[49] With the increasing use of electronic medical records, it is now theoretically possible to link risk factor profiles with disease event data in large patient populations.[50,51] These developments in information technology will enable cardiovascular risk prediction scores to be generated rapidly for specific populations as part of routine clinical practice.

## Unresolved issues

### Potential life years gained from preventing a cardiovascular event

There is much confusion about the relation between short-term absolute risk (eg, 5-year risk of a cardiovascular event) and the long-term absolute benefits of treatment (eg, life-years gained from prevention of a cardiovascular event). Short-term absolute risk and therefore short-term absolute treatment benefit increase exponentially with age, favouring treatment in older patients, but it has been argued that younger people have more to gain than do older people from preventive therapies because of their greater life-expectancy.[52] Although the number of potential life-years lost after a cardiovascular event in younger people is greater than in older people, the differences are surprisingly small after adjustment for discounting of life expectancy and case fatality.[53] A description is given below and is shown in table 2.

First, most people value time in the distant future less than in the near future.[54] Therefore, meaningful comparisons of potential life-years lost from a cardiovascular event at different ages need a weighting (ie, discounting) that gives less value to years in the distant future than in the near future. With the conservative discount rate of 3% that has been recommended by a US panel on cost-effectiveness[55] (ie, every future year is valued at about 3% less than the previous one), the average life expectancy of a 40-year-old man falls from 37 actual years to about 22 discounted years and the average life expectancy of a 70-year-old man falls from 12 actual years to about 10 discounted years. Second, case fatality after a cardiovascular event is much higher in older than in younger people. Norris[56] reported 30-day case fatality after acute coronary events of more than 50% in people aged 65–74 years but less than 25% in those younger than 50 years. Therefore people older than 65 years who have a major

| Risk prediction method | Data from which approach derived | Outcomes predicted | Target population | Available formats |
|---|---|---|---|---|
| NZ chart[31,32] | Framingham Heart Study, USA | Non-fatal and fatal CVD | 35–75 year olds without CVD | Colour charts and electronic calculator |
| Sheffield table[33] | Framingham Heart Study, USA | Non-fatal and fatal CHD | 28–70 year olds without CVD | Colour charts |
| Joint British Societies chart[34] | Framingham Heart Study, USA | Non-fatal and fatal CHD | 35–75 year olds without CVD | Colour charts and electronic calculator |
| UKPDS risk engine[35] | UKPDS, UK | Non-fatal and fatal CHD or Stroke | People with diabetes without CVD | Online and electronic calculators |
| PROCAM Neural Network Calculator[36] | PROCAM, Germany | Non-fatal and fatal myocardial infarction | Men aged 40–65 years with or without CVD | Web-based calculator |
| Pocock Risk Score[37] | Eight randomised controlled trials of antihypertensive treatment in North America and Europe | Fatal CVD | 35–74 year olds with or without CVD | Paper-based and online calculators |
| Framingham subsequent CHD score[25] | Framingham Heart Study, USA | Non-fatal and fatal CHD | 35–74 year olds with CVD | Paper-based calculator |
| The SCORE charts for low and high risk European regions[38] | 12 European cohort studies | Fatal CVD | 40–65 year olds | Colour charts |

CVD=cardiovascular diseases. CHD=coronary heart disease. UKPDS=United Kingdom Prospective Diabetes Study.

***Table 1*: Examples of absolute cardiovascular risk prediction scores**

cardiovascular event will lose more than half their potential remaining life expectancy through death in the first 30 days whereas those younger than 50 years will lose only a quarter of their remaining life expectancy.

The approximate halving of the difference in life expectancy between 40-year-olds and 70-year-olds through slight discounting, and the doubling of case-fatality in 70-year-olds compared with 40-year-olds, results in a similar number of discounted life-years lost after a cardiovascular event in the two age-groups (table 2). This finding suggests that any additional long-term benefits from prevention of an event in a 40-year-old compared with a 70-year-old might be smaller than one would intuitively expect. These calculations do not take into account the morbidity or disability attributable to a cardiovascular event or other comorbidities, and young people who have a non-fatal event could lose more disability-free years than older individuals. While elderly people are more likely to be physically disabled as a result of a non-fatal cardiovascular event than younger people, they are also more likely to have other health-related disabilities. However, the psychological effect of a cardiovascular event in younger people might be greater than in elderly individuals. Therefore, the effect of disability that can be attributed to a cardiovascular event in different age-groups, including both physical and psychological effects, is difficult to quantify.

Data shown in table 2 suggest that individuals aged about 80 years lose fewer potential discounted life years after a cardiovascular event than do younger people, principally because of their much shorter life expectancy. It might therefore be reasonable to make some adjustment to absolute risk-based risk prediction scores for any individual with a short life expectancy. Age-specific disability weights might be deemed appropriate in future.

| Age (years) | Average life expectancy (years) | Average life expectancy discounted at 3% per year (years) | 30-day case fatality after a major CVD event* (%) | Average discounted life-years lost after a CVD event, attributable to 30-day case fatality (years) |
|---|---|---|---|---|
| 80 | 6·8 | 6·2 | 60 | 3·7 |
| 70 | 12·2 | 10·3 | 50 | 5·2 |
| 60 | 19·2 | 14·8 | 40 | 5·9 |
| 50 | 27·6 | 18·9 | 30 | 5·7 |
| 40 | 36·8 | 22·4 | 25 | 5·6 |

*Coronary heart disease case fatality used as a proxy for cardiovascular disease case fatality[56] (note that the model does not account for morbidity after a cardiovascular disease event).

*Table 2:* **Effect of discounting and 30 day case fatality on life years lost after a cardiovascular disease event in men**

## Treatment targets

Few trials assessing cardiovascular outcomes have randomly assigned patients to standard versus intensive blood pressure lowering. An overview of three trials of intensive compared with less intensive blood pressure lowering showed a greater reduction in cardiovascular events with intensive treatment; the difference in stroke risk was 20% (95% CI 2–35), coronary risk was 19% (2–33), and major cardiovascular disease risk was 15% (4–24).[14,59] A recent trial has shown that intensive lipid-lowering treatment with statins provides greater cardiovascular protection than do standard statin treatment regimens,[58] and overviews of cholesterol lowering trials show a dose-response relation with cardiovascular outcomes.[3,59] Individual patients are therefore likely to achieve the greatest benefit from the maximum tolerated reductions in blood pressure or cholesterol. Since side-effects of drug treatment are typically dose-related, and because cardiovascular risk factors act synergistically, the most effective strategy for lowering cardiovascular risk might be one that targets moderate reductions in multiple risk factors rather than large reductions in single factors; however, no trials have compared these two strategies. Although cost and complexity of management is one barrier to multiple interventions, development of one tablet combining different drugs, such as the proposed polypill,[59] could be of substantial merit. For high-risk patients with only slightly raised levels of different risk factors, a low-dose combination tablet might be especially appropriate. A low-dose multidrug approach would also be consistent with the absolute risk-based treatment strategy that lessens the importance of any one risk factor in the decision to treat or in setting treatment goals.

The most important treatment goal might be keeping the patient on a one tablet drug cocktail rather than achieving best possible individual risk factor levels. In usual practice, the magnitude of a patient's response to treatment is difficult to determine accurately anyway, even with multiple measurements of one risk factor. Irwig and colleagues[60] used data for within individual and population variance of blood cholesterol to investigate the number of tests needed to accurately estimate an individual's cholesterol concentration and response to treatment. They concluded that even with several measurements the confidence interval around the recorded estimate is wide. The same measurement difficulties have been shown for blood pressure.[61] For these reasons, less emphasis should be placed on reaching treatment targets for specific risk factors and more on identifying high-risk patients and targeting multiple risk factors. Shepherd[62] describes a so-called "fire and forget" approach in which a small standard dose of statin is given to many people without considering the target blood cholesterol concentration. Perhaps this approach could be modified to aim (at high-risk patients), fire (with a multidrug low dose tablet), and forget (the individual risk factors—but not adherence to treatment).

## Patients' expectations of treatment benefits

Little research has been done on patients' expectations of preventive interventions, but perceptions of cardiovascular risk and treatment benefits are probably as inflated

as doctors' perceptions.[30] Investigators have examined the threshold of benefit for a hypothetical cholesterol-lowering drug below which participants would not be prepared to take the drug.[63] The study included 307 people who: had been discharged from a coronary care unit; were taking cardioprotective drugs but had no recent history of myocardial infarction; or were neither on drugs nor had a history of myocardial infarction. Median absolute benefit thresholds were 20% over 5 years in the first two groups and 30% in the third group. These values are well above the probable benefits of most standard treatments, which are seldom greater than 10–15% in absolute terms. Research on patients' knowledge of risk and their expectations of treatment benefits should be a major priority in view of the apparent discrepancy between their expectations and the actual benefits of treatment. This difference in expectations of patients and those inferred from clinical recommendations might account for the poor uptake of many preventive interventions.

## Conclusions

Individualised management of cardiovascular risk should be informed mainly by the probable size of absolute treatment benefits. Neither doctors nor their patients are well informed about the importance of these benefits. Attention should be moved from knowing one's blood pressure and cholesterol concentrations to knowing one's absolute cardiovascular risk and its determinants. Most cardiovascular risk factors cannot be divided into present or absent categories and, in view of the synergistic effects of these factors, risk cannot be easily estimated in one's head. A quantitative cardiovascular risk/benefit assessment should be a routine component of quality clinical practice in middle aged and older adults. It is timely for terms such as hypertension and hypercholesterolaemia to be removed from our clinical vocabulary and the next generation of clinicians should treat risk not risk factors.

**Conflict of interest statement**

R Jackson and A Rodgers are planning research to investigate the potential of a single multidrug tablet for management of cardiovascular disease risk but do not stand to gain financially from this development. The remaining authors declare that they have no conflict of interest.

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**References**

1 Rose G. Sick individuals and sick populations. *Int J Epidemiol* 2001; **30:** 427–32.

2 Rodgers A. Quantifying selected major risks to health. In: Murray CJL, Lopez AD, eds. The world health report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization, 2002: 47–92.

3 Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002; **324:** 1570–76.

4 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:** 1903–13.

5 Alderman MH. Blood pressure management: individualised treatment based on absolute risk and the potential for benefit. *Ann Intern Med* 1993; **119:** 329–35.

6 Jackson R, Barham P, Maling T, et al. The management of raised blood pressure in New Zealand. *BMJ* 1993; **307:** 107–10.

7 Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease and stroke in the Asia Pacific Region. *Int J Epidemiol* 2003; **32:** 563–72.

8 Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific Region. *J Hypertens* 2003; **21:** 707–16.

9 Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998; **352:** 1801–07.

10 Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992; **152:** 56–64.

11 Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke:13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995; **346:** 1647–53.

12 Lawes C, Bennett D, Lewington S, Rodgers A. Blood pressure and coronary heart disease: a review of the evidence. *Seminars Vasc Med* 2002; **2:**355–68.

13 MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. *Lancet* 1990; **335:** 765–74.

14 Turnbull F, for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362:** 1527–35.

15 Lawes CMM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke* 2004; **35:** 776–85.

16 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, Ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **342:** 145–53.

17 Progress Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358:** 1033–41.

18 Cruikshank J. The lowering of blood pressure after stroke (authors' reply). *Lancet* 2001; **358:** 1994–95.

19 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360:** 7–22.

20 Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? *JAMA* 1986; **256:** 2823–28.

21 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994; **308:** 367–62.

22 Mulrow CD, Cornell JA, Herrera CR, Kadri A, Farnett L, Aguilar C. Hypertension in the elderly. Implications and generalizability of randomised trials. *JAMA* 1994; **272:** 1932–38.

23 LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease. Meta-analysis of randomized controlled trials. *JAMA* 1999; **282:** 2340–46.

24 Kannel WB. Some lessons in cardiovascular epidemiology from Framingham. *Am J Cardiol* 1976; **37:** 269–82.

25 D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. *Am Heart J* 2000; **139:** 272–81.

26 Anderson KV, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; **121:** 293–98.

27 West of Scotland Coronary Prevention Group. West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* 1996; **348:** 1339–42.

28 Rodgers A, Neal B, MacMahon S. The effects of blood pressure lowering in cerebrovascular disease. *Neurol Rev Int* 1997; **2:** 12–15.

29 Law MR, Wald NJ, Rudnicka AR. Quantifying effects of statins on low density lipoprotein cholestrol, ischaemic heart disease and stroke: systematic review and meta-analysis. *BMJ* 2003; **326:** 1423.

30 Friedmann PD, Brett AS, Mayo-Smith MF. Differences in generalists' and cardiologists' perceptions of cardiovascular risk and the outcomes of preventive therapy in cardiovascular disease. *Ann Intern Med* 1996; **124:** 414–21.

31 Jackson R. Updated New Zealand cardiovascular disease risk-benefit prediction guide. *BMJ* 2000; **320:** 709–10.

32 New Zealand Guideline Group. Management of mildly raised blood pressure in New Zealand: http://www.nzgg.org.nz/guidelines/dsp_guideline_popup.cfm?&guidelineID=35.

33 Wallis EJ, Ramsay LE, Haq IU, et al. Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish Health Survey population. *BMJ* 2000; **320:** 671–76.

34 Wood D. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ* 2000; **320:** 705–08.

35 Stevens RJ, Kothari V, Adler AI, Stratton IR, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci* 2001; **101:** 671–79.

36 Voss R, Cullen P, Schulte H, Assmann G. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Munster Study (PROCAM) using neural networks. *Int J Epidemiol* 2002; **31:** 1253–62.

37 Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. 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. *BMJ* 2001; **323:** 75–81.

38 Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24:** 987–1003.

39 Montgomery AA, Fahey T, Peters TJ, MacIntosh C, Sharp DJ. Evaluation of computer based clinical decision support system and risk chart for management of hypertension in primary care: randomised controlled trial. *BMJ* 2000; **320:** 686–89.

40 Isles CG, Ritchie LD, Murchie P, Norrie J. Risk assessment in primary prevention of coronary heart disease: randomised comparison of three scoring methods. *BMJ* 2000; **320:** 690–91.

41 Lowensteyn I, Joseph L, Levinton C, Abrahamowicz M, Steinert Y, Grover S. Can computerized risk profiles help patients improve their coronary risk? The results of the Coronary Health Assessment Study (CHAS). *Prev Med* 1998; **27:** 730–37.

42 Hall LML, Jung RT, Leese GP. Controlled trial of effect of documented cardiovascular risk scores on prescribing. *BMJ* 2003; **326:** 251–52.

43 Kannel WB. The Framingham study: its 50-year legacy and future promise. *J Atheroscler Thromb* 2000; **6:** 60–66.

44 Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation* 2002; **105:** 310–15.

45 D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001; **286:** 180–87.

46 Diverse Populations Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? *Heart* 2002; **88:** 222–28.

47 Brindle P, Emberson J, Lampe F, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ* 2003; **327:** 1267.

48 Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107:** 499–511.

49 Milne R, Gamble G, Whitlock G, Jackson R. Framingham Heart study risk equation predicts first cardiovascular event rates in New Zealanders at the population level. *NZ Med J* 2003; **116:** U662.

50 Black N. Using clinical databases in practice. *BMJ* 2003; **326:** 2–3.

51 Lundin J, Lundin M, Isola J, Joensuu H. A web-based system for individualised survival estimation in breast cancer. *BMJ* 2003; **326:** 29.

52 Ulrich S, Hingorani AD, Martin J, Vallance P. What is the optimal age for starting lipid lowering treatment? A mathematical model. *BMJ* 2000; **320:** 1134–40.

53 Marshall T. Optimal age for starting lipid lowering treatment. It is more efficient to screen and treat elderly people. *BMJ* 2000; **321:** 637.

54 Gold M, Siegel J, Russell L, Weinstein M. Cost effectiveness in health and medicine. Oxford: Oxford University Press, 1996.

55 Weinstein MC, Seigel JE, Gold MR, Kamlet MS, Russel LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996; **276:** 1253–58.

56 Norris RM. Fatality outside hospital from acute coronary events in three British health districts, 1994–5. United Kingdom Heart Attack Study Collaborative Group. *BMJ* 1998; **316:** 1065–70.

57 Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000; **356:** 1955–64.

58 Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350:** 1495–504.

59 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326:** 1419.

60 Irwig L, Glasziou P, Wilson A, Macaskill P. Estimating an individual's true cholesterol level and response to intervention. *JAMA* 1991; **266:** 1678–85.

61 Jones DW, Appel LJ, Sheps SG, Roccella EJ, Lenfant C. Measuring blood pressure accurately: new and persistent challenges. *JAMA* 2003; **289:** 1027–30.

62 Shepherd J. Resource management in prevention of coronary heart disease: optimising prescription of lipid-lowering drugs. *Lancet* 2002; **359:** 2271–73.

63 Trewby PN, Reddy AV, Trewby CS, Ashton VJ, Brennan G, Inglis J. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. *Clin Med* 2002; **2:** 527–33.