

Evidence based management of hypertension

Cardiovascular risk factors and their effects on the decision to treat hypertension: evidence based review

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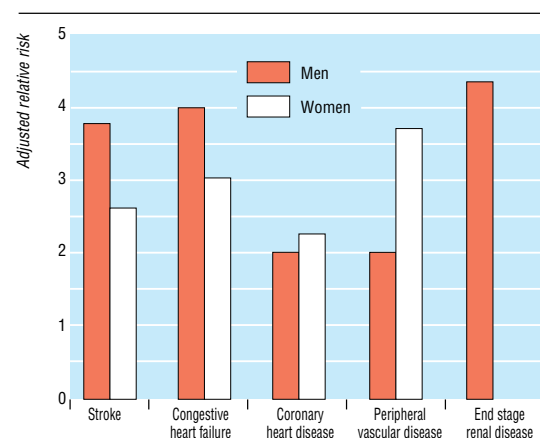
Blood pressure, like any physiological variable, is normally distributed in the population. Not surprisingly, expert bodies disagree substantially on the definition of hypertension—of the 27 national hypertension societies represented at the 17th world conference of the Hypertension League Council held in Montreal in 1997, 14 use 140/90 mm Hg to diagnose hypertension and 13 use 160/95 mm Hg.¹

Hypertension and cardiovascular risk

Relative risk

Most population based studies confirm that hypertension increases an individual's risk of various cardiovascular consequences approximately two to three times (figure). Large population based cohort studies consistently show continuous, strong, and graded relations between blood pressure (particularly systolic pressure) and the subsequent occurrence of various atherosclerotic events.²⁻³ The sizes of the relative risks reported in each study depend on the duration of follow up and the definition of hypertension in use.⁴ These relative risks are consistent across all settings⁵ and for all patient subgroups, including those with and without known atherosclerotic disease.⁶

Multiple high quality long term cohort studies and randomised clinical trials have shown that the risks from raised blood pressure can be partially reversed.⁶⁻⁷ Two important issues, however, remain unclear: the exact reduction in pressure that will achieve the greatest reduction in cardiovascular risk, and whether the benefits of treatment are specifically related to the extent the pressure is lowered (see next paper in this series). Hypertension is implicated in 35% of all atherosclerotic cardiovascular events,² including 49% of all cases of heart failure.⁸



Risk of atherosclerotic disease in people with hypertension

Summary points

There is a continuous, strong, and graded relation between blood pressure and cardiovascular disease, but no clear threshold value separates hypertensive patients who will experience future cardiovascular events from those who will not

Risk of cardiovascular disease depends on blood pressure, coexistent risk factors, and whether there is hypertensive damage to target organs

Numerous factors definitely increase cardiovascular risk, including age, male sex, family history, raised cholesterol, smoking, diabetes mellitus, obesity, sedentary lifestyle, and left ventricular hypertrophy

Models can be used to predict an individual's risk of cardiovascular disease to define the expected benefits and harms of treatment

Absolute risk

As hypertension is only one of the many risk factors for cardiovascular disease, a patient's prognosis depends more on the sum of their risk factors than on their blood pressure.²⁻⁵ Numerous methods to calculate a patient's absolute cardiovascular risk have been described (table 1).

Guidelines (for the management of both hypertension and hyperlipidaemia) generally now recommend the use of simplified versions of the Framingham risk equations for formal estimation of risk and specify absolute risk treatment thresholds.

Framingham risk equations—The Framingham risk equations were developed to predict coronary disease, heart failure, or stroke,⁹⁻¹¹ and they estimate the 10 year risk of each event and the average risk in controls matched for age and sex. Although the Framingham investigators have urged caution in extrapolating from their cohort of predominantly middle class white people, the risk equations have been shown to be reasonably accurate when applied to other populations in northern Europe and the United States (although they may overestimate risk elsewhere).¹² The equations have been criticised for not including several atherosclerosis risk factors (such as family history, sedentary lifestyle, and obesity).

Cardiovascular disease life expectancy model—The cardiovascular disease life expectancy model is a Markov model developed using data from the Lipid Research Clinics Follow-up Cohort, the Canadian Heart Health survey, and Canadian life tables.¹³ It has two key advantages over the Framingham risk equations. Firstly, it provides a single estimate for the

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Table 1 Tools for determining cardiovascular prognosis in individual patients

Risk prediction model	Population derived in	Variables incorporated	Validated in other data sets?
Framingham (USA)	5300 men and women aged 30-74 (original and offspring Framingham studies)	Age; sex; systolic and diastolic blood pressure; total, LDL, and HDL cholesterol; diabetes mellitus; smoking.	Yes
Cardiovascular disease life expectancy model (USA and Canada)	3700 men and women aged 35-74 (lipid research clinics follow-up cohort)	Age; sex; mean blood pressure; total and HDL cholesterol; diabetes mellitus; smoking; cardiovascular disease	Yes
Dundee coronary risk disk (UK)	5203 men aged 40-59 (UK heart disease prevention project)	Total cholesterol; systolic blood pressure; smoking	Not in women
PROCAM risk function (Germany)	4400 men and women aged 40-65 (workplace study)	Age; systolic blood pressure; total and HDL cholesterol; diabetes mellitus; smoking; family history; anginal symptoms	Not in women
British regional heart study risk function (UK)	7735 men aged 40-59 (from general practitioner practices)	Mean blood pressure; total cholesterol; diabetes mellitus; smoking; family history; anginal symptoms	No

LDL=low density lipoprotein; HDL=high density lipoprotein.

risk of non-fatal or fatal coronary events and strokes in any one person (the Framingham equations for coronary events and for strokes are different, and there is no way of combining them). Secondly, this model was derived from a cohort of patients with and without overt coronary heart disease and thus can be used to predict the potential benefits (and cost effectiveness) of modifying risk factors both before and after the development of overt atherosclerotic disease (the Framingham equations were derived only from people without coronary disease). The major disadvantage of this model is that it requires access to the original formulas and is not yet available in a simple form.

Dundee coronary risk disk—The Dundee coronary risk disk provides an estimate of a patient's relative risk for coronary mortality matched for age and sex.¹⁴ It was derived solely in men and has not been independently validated in women; there is no information on its generalisability to other populations; and its predictions correlate only moderately well with the Framingham estimates.¹²

PROCAM risk function—Estimates derived from the PROCAM risk function¹⁵ correlate reasonably well with those derived from the Framingham equation, but it cannot be used to predict coronary risk in women and, again, its generalisability to other populations is unknown.¹²

British regional heart study risk function—The British regional heart study function¹⁶ has never been validated in an independent test set, cannot be used to predict coronary risk in women, and has been found to systematically underestimate risk when compared with all other risk functions.¹⁷

Other risk factors affecting cardiovascular prognosis

Unmodifiable risk factors for cardiovascular disease include age, male sex, and family history. The effect of race is unclear, although most high quality evidence that adjusts for differences in baseline risk factors suggests that cardiovascular mortality, and the relative risks from modifiable risk factors, are similar across ethnic groups.¹⁷ A number of potentially modifiable risk factors have been reported, and those for which strong evidence supports an independent causal effect are described in table 2. Wherever possible, we have summarised relative risks for cardiovascular morbidity and mortality (the potential effects of therapy on these factors are described in the next paper in this series).

Cholesterol

A strong, graded relation between raised serum cholesterol and coronary artery disease is seen with total cholesterol values above 4.65 mmol/l.¹⁸ The protective effect of high density lipoprotein cholesterol seems to be at least as strong as the atherogenic effect of the low density fraction, particularly in women.¹⁸

Smoking

The risk of cardiovascular disease in smokers is proportional to the number of cigarettes smoked and how deeply the smoker inhales, and it is apparently greater for women than men.^{18 19} The risks of pipe and cigar smokers seem to fall between those of non-smokers and cigarette smokers (relative risk 1.3 (95% confidence interval 1.1 to 1.5)) for ischaemic heart disease, with a dose-response relation.²⁰

Table 2 Established risk factors for cardiovascular disease

Risk factor	Range of relative risks in highest quality studies*	Level of evidence	Reference
Cholesterol	1.01 for each 1% increase in total or LDL cholesterol or 1% reduction in HDL cholesterol	1	Neaton and Wentworth ¹⁸
Smoking	1.4 (men) to 2.2 (women)	1	Prescott et al ¹⁹
Diabetes mellitus	2.2 (men) to 3.7 (women)	1	Wilson et al ⁹
Obesity	1.2 (men over 50) to 2.1 (women under 50)	1	Hubert et al ²²
Sedentary lifestyle	2.4 (men)	1	Sandvik et al ²¹
LVH on electrocardiogram	2.0 (women) to 2.7 (men)	1	Dunn et al ²⁵
LVH with strain on electrocardiogram	2.5 (women) to 5.8 (men)	1	Levy et al ²⁶

LDL=low density lipoprotein; HDL=high density lipoprotein; LVH=left vessel hypertrophy.

*For cardiovascular disease, including coronary events or stroke, or both.

Diabetes mellitus

Diabetes is one of the strongest modifiable risk factors for cardiovascular disease, and its effect in women is relatively greater than in men for all cardiovascular events except congestive heart failure.⁹ Diabetes often coexists with obesity, dyslipidaemia, hypertension, and hyperuricaemia ("syndrome X"); these patients are particularly predisposed to atherosclerotic disease.

Sedentary lifestyle

A high quality cohort study in middle aged men followed for 16 years showed that physical fitness is a graded and independent predictor of cardiovascular mortality: after adjustment for baseline risk factors, the relative risks were 0.41 (0.20 to 0.84) in the fittest fourth, 0.45 (0.22 to 0.92) in the second fittest group, and 0.59 (0.28 to 1.22) in next fourth, compared with the group with the lowest fitness ratings.²¹

Body weight and obesity

Body weight and incidence of cardiovascular disease are positively associated in both sexes after adjustment for other risk factors, but obesity is a more potent risk factor in women than men and in younger than older people.²²

The waist:hip ratio is the most widely used measure of central adiposity. Although multiple studies have suggested that it is a better predictor of cardiovascular disease than measures of overall adiposity such as the body mass index, this association may not be as strong as first thought, as other atherosclerotic risk factors often coexist as well. For example, a nested case-control study of a cohort of almost 42 000 older women showed that although the waist:hip ratio was associated with the incidence of stroke, this association became much weaker after adjustment for hypertension and diabetes mellitus (adjusted relative risk 1.3 (0.8 to 2.1)).²³

Alcohol

Observational studies consistently show inverse (or U shaped) relations between alcohol intake and death from coronary heart disease.²⁴ While mild to moderate consumption seems to be protective, taking more than two drinks a day is associated with increased mortality, primarily from cancer, trauma, and cirrhosis.

Left ventricular hypertrophy

Left ventricular hypertrophy is a common effect of hypertension and a strong independent predictor of future cardiovascular events.^{25–26} Left ventricular hypertrophy with repolarisation changes on the electrocardiogram carries a higher risk than hypertrophy diagnosed solely on voltage criteria.²⁶

Risk factors of uncertain significance

The evidence supporting independent causal effects for other potentially modifiable cardiovascular risk factors is conflicting and weak (because the epidemiological studies have been done in highly selected populations, often with many confounding factors, or no randomised trials to evaluate the effects of modifying these factors have been carried out). Furthermore, there is no evidence that measuring these newer risk factors improves our prognostic ability beyond that provided by the established risk factors discussed above. These factors are briefly reviewed here, but a

more complete discussion is contained in *Evidence-Based Hypertension*.²⁷

Triglycerides—Analysis of data from three large prospective studies (almost 16 000 subjects) found that measuring serum triglycerides for estimation of cardiovascular risk had no advantage over using measurements of cholesterol alone.²⁸ In view of the skewed distribution of fasting triglyceride concentrations in the population, their high intraindividual variability, their high degree of correlation with cholesterol subfractions (particularly HDL-C), and the lack of trial evidence that lowering triglyceride levels reduces coronary events, their value in screening for high risk patients is debatable.²⁹

Lipoprotein(a)—Evidence of an association of lipoprotein(a) with cardiovascular disease is conflicting: two of the four largest cohort studies reported no independent association.³⁰ No trials have investigated the effects of treatment for excess lipoprotein(a).

Microalbuminuria—Other risk factors (such as hyperlipidaemia, obesity, and smoking) may increase urinary albumin excretion, and microalbuminuria is commoner in patients with severe hypertension, advanced target organ damage, high renin or insulin concentrations, or a non-dipping profile on ambulatory monitoring.³¹ It is unclear whether microalbuminuria is an independent cardiovascular risk factor or even if it predicts renal failure in hypertensive patients, and additional data are needed from larger numbers of patient numbers followed for a longer period.

Uric acid—Hyperuricaemia is commonly associated with other coronary risk factors and may complicate treatment with β blockers or diuretics, so it is still not clear whether it will remain an independent cardiovascular risk factor after adjustment for other risk factors.^{32–33}

Plasma renin—A cohort study of 2902 treated hypertensive patients reported that raised plasma renin increased the relative risks for myocardial infarction (3.8 (1.7 to 8.4)), total cardiovascular disease (2.4 (1.3 to 4.5)), and mortality from all causes (2.8 (1.2 to 6.8)) in those patients with elevated renin concentrations.³⁴ These results need to be confirmed in larger studies, however, and trials to establish whether treatment of high renin levels reduces cardiovascular risk are needed before high renin can be accepted as an independent risk factor.

Fibrinogen—Although increased fibrinogen often coexists with other cardiovascular risk factors, there is substantial interindividual variability and no standardised assay, and a meta-analysis of six studies reported an odds ratio of 2.3 (1.9 to 2.8) for coronary disease for the highest compared with the lowest third of fibrinogen levels.³⁵ Subsequent subgroup analyses (without adjustment for treatment allocation or differences in lipid profiles) suggest that treatment of raised fibrinogen levels (in association with abnormal lipid findings) may help secondary prevention of cardiovascular disease, but further studies are needed to confirm these results.³⁶

Homocysteine—While a meta-analysis of 27 observational studies reported that 5 $\mu\text{mol/l}$ increases in serum homocysteine were associated with 1.6 to 1.8-fold increases in coronary disease,³⁷ a more recent systematic review of the five highest quality studies found substantial variations between them, and after

adjustment for differences in other risk factors a less convincing association (odds ratio 1.3 (1.1 to 1.5)) for each 5 $\mu\text{mol/l}$ increase in homocysteine concentrations.³⁸ Until trials currently under way show that reducing raised homocysteine levels reduces cardiovascular disease, the role of this risk factor remains uncertain.

Chlamydia pneumoniae—A meta-analysis of all 15 prospective studies evaluating serological evidence of *Chlamydia pneumoniae* infection excluded any strong association between titres of *C pneumoniae* IgG and incidence of coronary heart disease.³⁹

Inflammatory markers—A meta-analysis of 14 prospective studies found that people in the highest third of levels of C-reactive protein had more coronary heart disease than those in the lowest third (relative risk 1.9 (1.5 to 2.3)).⁴⁰ However, it is still unclear whether C-reactive protein is an independent risk factor for atherosclerotic disease, since there is no direct evidence that it contributes to vascular damage, and adjustment for baseline confounders markedly reduces the size of the putative effect.⁴⁰

Conclusion

Raised blood pressure is only one of many risk factors for atherosclerosis. The decision to treat it should rest on careful consideration of the absolute cardiovascular risk. A number of equations to predict risk are available to clinicians; those most frequently used are the Framingham equations. A number of potential risk factors additional to the established atherosclerotic risk factors have recently been described, but further research is needed to determine their exact role.

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