An unresolved problem

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The impact of hypertension as a risk factor on the occurrence of cardiovascular disease clinical events should not be underestimated.

Increased blood pressure is the leading risk factor for death and disability in the world. Increased blood pressure is the cause of about 50% of heart disease, stroke and heart failure (HF). It is responsible for 18% of all global deaths and more than 40% of deaths in people with diabetes.

In addition, increased blood pressure is an important risk for foetal and maternal death in pregnancy and a leading risk factor for the development of dementia and renal failure. Furthermore, it is currently estimated that four in 10 adults older than 25 years have hypertension. About two thirds of people with hypertension are found in economically developing countries and in these countries heart disease and stroke occur in younger people due to hypertension than elsewhere in the world.

STUDIES

Much information on hypertension came from epidemiological studies. In nine major prospective observational studies on 418 343 people aged 25 years and older that was followed for an average of 10 years, the relationship between the level of diastolic blood pressure and the risk of coronary heart disease (CHD) and stroke was log-linear with the slope of the association for CHD only about two thirds as steep as for stroke.

A much larger meta-analysis of approximately one million people from 61 prospective observational studies showed a similar log-linear relationship between the risk of hypertension and the risk for stroke and CHD.

For every increase in blood pressure of 20 mm/Hg systolic pressure and 10 mm/Hg diastolic pressure the risk of CHD is increased four-fold and the risk of stroke is more than two-fold. This is much the same conclusion that was reached from observational results 10 years earlier.

What also became clear from longitudinal observational studies such as the Framingham Heart Study is that more than 80% of people with elevated blood pressure levels and hypertension also have other independent cardiovascular (CV) risk factors such as dyslipidaemia, smoking, elevated blood glucose and physical inactivity and an increased body mass index.

50%
of heart disease, stroke and heart failure is caused by increased blood pressure

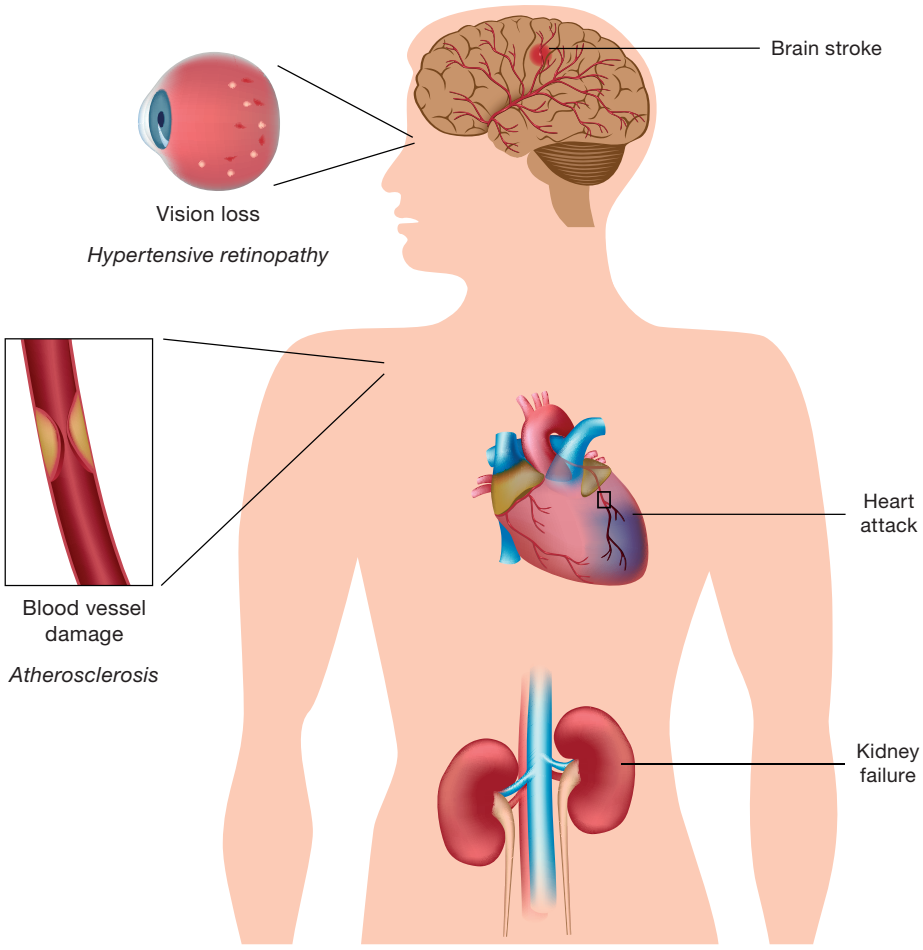
Although treatment has been shown to reduce CV risk, the risk of treated hypertensive patients remains higher than that of the general population of the same age. Hypertension is currently probably best viewed as one component of a CV risk profile.

In a large prospective observational study of 1.25 million people followed for a number of years it was shown that the life-time risk for CV disease (CVD) of hypertension at the age of 30 years was 63.3% (95% confidence interval [CI]: 62.9-63.8%) as compared to the life-time risk of CVD in similar normotensive people of 46.1% (95%CI: 45.5 -46.8%).

The life-time risk for myocardial infarction (MI), for instance, was 8.0% (95%CI:7.8-8.3%) as compared to the life-time risk of MI in normotensive people with a life-time risk of 5.5% (95%CI: 5.3-5.8%).With CIs not overlapping, this significant increased life-time risk of MI occurred despite modern treatment of hypertension.

The reduction of CHD, although significant is not proportional to the reduction in blood pressure. This discrepancy currently does not have an adequate explanation, but could

Main complications of hypertension



imply that to reduce CHD sufficiently in hypertension other treatment modalities are probably needed such as adding a statin for instance.

TREATMENT OF HYPERTENSION

The first meta-analysis on the treatment effects of hypertension was published in 1994 by Collins *et al* and evaluated the benefit of the treatment of hypertension using older type of drugs: Diuretics with and without beta-blockers.

Treating hypertension for an average of 4.9 years reduced the risk of cardiovascular events: relative risk reduction (RRR) in stroke was 38% (95% CI: 31%-45%) and prevented 13 strokes for every 1000 patients treated for 4.9 years. The RRR for CHD was 16% (95% CI: 8%-23%) and seven CHD events were prevented for every 1000 patients treated for 4.9 years.

> For every increase in blood pressure of 20 mm/Hg systolic pressure and 10 mm/Hg diastolic pressure the risk of CHD is increased four-fold and the risk of stroke is more than two-fold

A recent meta-analysis, 20 years later, of 68 randomised clinical trials including 245 885 individuals, evaluated the effect of treatment of hypertension demonstrating the RRRs but also, uniquely, absolute risk reduction numbers and numbers needed to treat (NNT) to prevent one event.

In the intentional blood pressure lowering clinical trials, active treatment as compared to placebo or no treatment, was evaluated in 33 of the 68 trials. In standardised blood pressure lowering of 10 mm/Hg systolic blood pressure and 5 mm/Hg diastolic pressure, the RRR of different CV outcomes were: RRR in stroke: 33% (95% CI: 27%-39%); RRR in CHD 16% (95% CI:9%-21%); RRR in HF 48% (95% CI:31-61%), RRR in CV death 18% (95%CI:11%-25%).

These results were much the same as the results from the Collins meta-analysis in the 1990s. The absolute risk reductions in the new meta-analysis were expressed as the number of patients prevented from an event per 1000 patients treated over five years.

The absolute risk reductions were: Stroke - 17 strokes prevented per 1000 patients treated for five years (95% CI:13-20) and NNT 59 (95% CI:50-72), seven CHD events (95% CI:4-10) prevented per 1000 patients treated for five years and NNT 138 (95% CI:105-244), HF 16 (95% CI:10-19) and NNT 63 (95% CI:51-94) and CHD mortality nine (95% CI:5-12) NNT 115 (95% CI:86-192).

The value of this meta-analysis is the provision of absolute risk reduction and NNT values, which is much more understandable and valuable for practising clinicians. There is a greater risk reduction of strokes than CHD demonstrated in this meta-analysis which is in keeping with the observations in epidemiological observational studies on hypertension. The reasons why CHD events, although it is significantly reduced by hypertension treatment, are not reduced in proportion to the blood pressure reduction remain unclear.

Compare these data on outcome with old data on the treatment of severe hypertension with diastolic blood pressure of 115-129mm/Hg, a combination of CV death and stroke and MI treated for five years, the NNT to prevent one event is only three. The higher the baseline risk, the better the outcome in the treatment of hypertension.

A recent meta-analysis of 14 randomised clinical trials and 67475 people with hypertension, evaluated blood pressure lowering treatment based on absolute CV risk calculated with a risk engine (risk chart) similar to the Framingham risk chart.

The NNT in low risk people was 71 (95% CI:49-130), in medium risk the NNT was 51 (95% CI:32-122) and in a high risk patient the NNT was 26 (95%CI:17-62). Absolute risk reductions were greater with higher baseline risk.

CONCLUSION

The debate on goal blood pressure is also not at the end as currently a universal goal for all is hotly debated. For now, a goal of <140/90 mm/Hg for all below 60 years is accepted, but many are of the opinion this goal should be for all below the age of 80 years. What is not clear is what about high risk patients such as diabetics for instance, should the goal not be lower?

The debate on which single drug as monotherapy is the best seems fruitless when recent combination randomised clinical trials have shown better outcomes with even further risk reductions.

Combination trials such as the Losartan Intervention For Endpoint Reduction (LIFE) in Hypertension Study, the Anglo-Scandinavian Cardiac Outcomes Trial and the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension Trial, may have shown the future of therapy. We need more such trials maybe even combining a statin with the antihypertensive drugs - the polypill?

> Hypertension is currently probably best viewed as one component of a CV risk profile

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