

Hypertension: how low to go?

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SYNOPSIS

As blood pressure rises the risk of dying of cardiovascular disease increases. Lowering blood pressure aims to reduce the risk, but it is not certain that a low target for blood pressure will improve survival. An important consideration is the presence of other risk factors such as diabetes. Reducing the diastolic blood pressure, of a patient with hypertension but no other risk factors, to below 90 mmHg may cause more harm than benefit.

Index words: blood pressure, antihypertensives, cardiovascular disease.

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Introduction

Epidemiological studies have established that systolic and diastolic blood pressures have a strong, continuous, graded and aetiologically significant positive association with cardiovascular disease outcomes. Treatment of hypertension reduces cardiovascular risk, and this has been a major focus of campaigns aimed at reducing cardiovascular mortality and morbidity.¹

We now have many effective treatments for hypertension. In recent studies the questions about treatment have generally addressed the refinement and comparison of treatment regimens. The questions of which type of drug should be first-line treatment, which type of drug is best for what type of patients, and what should be the target blood pressure have all been considered.

A number of international guidelines (WHO/ISH, JNC-VI) suggest that blood pressure should be reduced at least to below 160/90 mmHg to normalise cardiovascular risk in patients with hypertension. In patients at higher baseline risk of cardiovascular disease, for example those with diabetes², the recommendations in JNC-VI are that the target blood pressure should be substantially lower: 130/85 mmHg. This recommendation is based on the view that the absolute risk of a cardiovascular event in these patients is much greater, and therefore the absolute benefit of treatment is larger. The question is, how good is the evidence for these recommendations?

Research evidence

Several randomised controlled trials published in the last 3–4 years are used to support proposals for lower target blood pressures in hypertension.^{3,4} In addition, there are two cohort studies that provide important information about the likely risk of heart disease in patients with blood pressures that are lower than those previously considered to be a problem.^{5,6}

One analysis examined the outcomes for participants in the Framingham study according to their baseline blood pressure.⁶ It had a particular focus on the group who started the study with a 'high-normal' blood pressure (defined as systolic pressures of 130–139 mmHg and/or diastolic pressures of 85–89 mmHg). This group did not have cardiovascular disease at the outset of the study, but they were older, had a higher body mass index and higher cholesterol concentrations than completely normotensive participants. After 10 years, the cumulative age-adjusted incidence of cardiovascular disease in people with 'high-normal' blood pressure was 4.4% (95% CI* 3.2–5.5%) in women and 10.1% (95% CI 8.1–12.1%) in men, compared with 1.9% (95% CI 1.1–2.7%) and 5.8% (95% CI 4.2–7.4%) in the participants with optimal blood pressure. The 'high-normal' blood pressure appeared to be associated with an increased risk of cardiovascular disease, even after adjustment for other coexisting risk factors.

An analysis of blood pressure in six different populations (USA, northern Europe, Mediterranean southern Europe, inland southern Europe, Serbia and Japan) examined the relationship between deaths from coronary heart disease and blood pressure.⁵ After 25 years of follow-up, for an increase of 5 mmHg in diastolic blood pressure the **relative** risk of mortality ranged from 1.06 (in inland southern Europe) to 1.19 (in Mediterranean southern Europe). The differences in these risks between populations for a given level of change in blood pressure were not statistically significant – that is, the relative risk of death remained constant. The **absolute** risk of death, however, was clearly different among the six populations, varying from 44 per 10 000 person years (Japan) to 153 per 10 000 person years (northern Europe).

These two cohort studies suggest that elevated blood pressure – according to whatever definition – alone does not predict risk of the final event (death) and that not all populations are equal. Although the risk goes up with increasing blood pressure very consistently, the studies do not tell us if the risk comes down with decreasing blood pressure.

HOT study

Only one intervention study has examined the effect of lowering blood pressure to different targets in patients with or without the other major cardiovascular risk factor of diabetes. The Hypertension Optimal Treatment (HOT) study randomised 18 790 patients aged 50–80 years from 26 countries to one of three groups, each defined by a target diastolic blood pressure. The targets were ≤ 90 mmHg, ≤ 85 mmHg and ≤ 80 mmHg.

* CI confidence interval

These targets were to be achieved by treatment with a series of drugs starting with long-acting felodipine 5 mg per day, followed if necessary by stepwise addition of ACE inhibitors or beta blockers, increasing doses of felodipine, and then finally addition of a diuretic. All patients were also randomised to receive low-dose aspirin (75 mg per day) or placebo. Follow-up was for up to five years (mean actual follow-up 3.8 years), and the main end-points were cardiovascular events, cardiovascular mortality and total mortality.

The patients in each group were similar in terms of the presence of other risk factors. At the start of the study 8% of patients had diabetes, and approximately 15% were smokers. By the end of the study, approximately 80% of the patients were still taking felodipine, usually with an ACE inhibitor (41%) or a beta blocker (28%). The reason why 20% had stopped felodipine by the end of the study is not stated in the main report of the study.⁴

The key results of the study are summarised in Table 1. The majority of patients achieved their target blood pressure and the authors concluded that the intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events and that the study showed the benefits of lowering the diastolic blood pressure down to 82.6 mmHg. The implication was therefore that targets for the treatment of hypertension should be lower, than the previously accepted 90 mmHg, to maximise the reduction in cardiovascular risk. This was the recommendation in much of the correspondence which followed the publication of the study, but is this recommendation reasonable?

Questions about the HOT study

In the lengthy correspondence about the HOT study, it was pointed out that:

- using an intention to treat analysis, there was no difference in results between treatment groups⁷

- the method of blood pressure measurement was not optimal⁸
- the data, excluding patients with diabetes, suggested an **increase** in mortality with lower blood pressures⁹
- the results did not take into account the potential increase in adverse effects and costs of medications that might be required to achieve lower blood pressures.¹⁰

This list of problems is not comprehensive. There was also debate about the potential influence of the pharmaceutical company sponsoring the trial and the promotion of calcium channel blockers as first-line treatment.

On reviewing the data in the original publication, the argument that there is no significant difference in the results for mortality or cardiovascular events between treatment groups (arguably the primary analysis for the primary outcomes) appears to be correct. The confidence intervals for the relative risks for the comparisons between groups all include 1.00 (see the last column in Table 1). The data for cardiovascular event rates actually appear to show an increase in mortality with lower blood pressure, although given the relatively small total number of deaths (approximately 600 out of nearly 19 000 patients), the increase is not statistically significant.

There have been several subsequent analyses of the data from the HOT study.^{11,12} The most comprehensive analysis examined the data set using a 'risk stratification' approach. Patients were grouped according to the presence or absence of other cardiovascular risk factors, and the frequency of events in each risk group was considered. The analysis suggested that the higher the risk group, the more likely the chance of cardiovascular events. Unfortunately, the analysis did not compare the outcomes in the risk strata according to the blood pressure target – hence it is not helpful in assessing the value of intensive treatment. A second analysis examined the impact of the presence of other risk factors on the outcomes and concluded that blood pressure alone did not predict the risk of cardiovascular events.

Table 1

Summary of key outcomes from HOT study⁴

Event	Target blood pressure	Total number of events	Events per 1000 patient years	Comparison between target groups *	Relative risk (95% confidence interval)
<i>Major cardiovascular events</i>					
	≤ 90 mmHg	232	9.9	90 vs 85	0.99% (0.83–1.19%)
	≤ 85 mmHg	234	10.0	85 vs 80	1.08% (0.89–1.29%)
	≤ 80 mmHg	217	9.3	90 vs 80	1.07% (0.89–1.28%)
<i>Cardiovascular mortality</i>					
	≤ 90 mmHg	87	3.7	90 vs 85	0.97% (0.72–1.30%)
	≤ 85 mmHg	90	3.8	85 vs 80	0.93% (0.70–1.24%)
	≤ 80 mmHg	96	4.1	90 vs 80	0.90% (0.68–1.21%)
<i>Total mortality</i>					
	≤ 90 mmHg	188	7.9	90 vs 85	0.97% (0.79–1.19%)
	≤ 85 mmHg	194	8.2	85 vs 80	0.93% (0.77–1.14%)
	≤ 80 mmHg	207	8.8	90 vs 80	0.91% (0.74–1.10%)

Adapted from Table 4, reference 4

* This represents the comparison between the groups of target blood pressures (mmHg)

Conclusion

The HOT study does not provide sufficient evidence of the benefits of intensive treatment of blood pressure (that is, reducing diastolic pressures below 90 mmHg) in patients with hypertension. However, in the original sub-group analysis of the HOT study, which looked at the results in patients with diabetes, there **are** differences in the outcomes between treatment groups. Patients with diabetes in the lowest target blood pressure group had significantly lower rates of cardiovascular events. Total mortality was also decreased.

This difference in the results, depending on the presence of other risk factors, highlights the need to consider hypertension in the context of the other risk factors that an individual patient possesses. It is not sufficient to assess and manage blood pressure alone and indeed, we may be doing our patients a disservice if we do so. As with all treatment decisions, the question of overall benefits and harms (including the cost of medication and medical care, and the impact of taking the treatment on quality of life) need to be discussed with the patient. Just lowering blood pressure to an arbitrary target – particularly in a low-risk patient – may not provide benefits and may cause harm.

In patients with multiple risk factors for cardiovascular disease, for example diabetes, we need to be more aggressive in our approach. Trials in high-risk patients support the argument for more aggressive interventions to reduce the risk of adverse cardiovascular outcomes.³ One size rarely fits all – and a single target blood pressure for the treatment of hypertension across all patient groups is clearly not justified.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 71)

- The target blood pressure for patients with hypertension and diabetes is 130/85 mmHg.
- To reduce the morbidity and mortality of hypertension, the target diastolic blood pressure should be less than 80 mmHg.

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