Introduction

American hypertension guidelines have relaxed the long-established guidance to target lower blood pressure levels in patients with previous cardiovascular disease or diabetes. This has led to considerable discussion of the merits of this clinical approach.

A recent meta-analysis of randomised clinical trials conducted over the past 50 years thoroughly evaluated the benefits and risks of targeting lower blood pressure in patients at high cardiovascular risk and in patients with existing cardiovascular and renal disease. A summary of these results is presented, with discussion points from South African experts in this CPD-accredited review.

Big data study reveals benefits of lower blood pressure

Pharmacological blood pressure lowering to a mean baseline systolic blood pressure of 130mmHg resulted in a proportional reduction in the risk of cardiovascular disease and death in this meta-analysis of randomised clinical trials involving more than 600 000 patients.

One hundred and twenty-three trials were included in the study; 92 studies were blood pressure lowering trials, 43 studies compared different drug classes and 12 trials fell into both categories. All studies were required to have a minimum of 1 000 patient years of follow-up in each drug class to minimise the risk of small-study effects. Trials of antihypertensive drugs, such as the Blood Pressure Lowering Treatment Trialist Collaboration (BPLTTC), for indications other than hypertension were included. No trials were excluded because of co-morbidities. SPRINT, a trial with a substantial number of patients with low systolic blood pressure at baseline, was included. Analyses were conducted to establish:

- The effect of a 10mmHg blood pressure reduction on the relative risk of major cardiovascular disease, stroke, heart failure, renal failure and all-cause mortality
- The effect of a 10mmHg blood pressure reduction at different baseline blood pressure levels (<130, 130-139, 140-149, 150-159 and >160mmHg) on cardiovascular events
- The effect of a 10mmHg blood pressure reduction in the presence of baseline co-morbidities (cardiovascular disease, coronary heart disease, cerebrovascular accident, type 2 diabetes, heart failure and chronic kidney disease)
- The effects of different classes of blood pressure-lowering drugs: angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), β-blockers, diuretics and calcium channel blockers.
Standardised effect of lowering systolic blood pressure by 10mmHg

Overall, a 10mmHg reduction in systolic blood pressure reduced the risk of major cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28% and all-cause mortality by 13%. However, this occurred across several major high-risk groups of patients, suggesting that blood pressure lowering provides broadly generalisable benefits (Figure 1).

There was no strong evidence that proportional benefits were diminished in trials that included people with lower baseline systolic blood pressure (<130mmHg) or in patients with existing cardiovascular disease (Figure 2). The proportional reduction in stroke risk seemed to be larger in populations without a history of cerebrovascular disease than in populations with such a history. No significant trend towards increased risk was reported for any outcome – major cardiovascular events, coronary heart disease, stroke, heart failure, renal failure and all-cause mortality. Therefore a J-shaped relationship could not be substantiated.

When trials were stratified to populations with diabetes, the event reduction in respect of major cardiovascular disease was higher for populations without diabetes. The subgroup analysis based on the presence of heart failure suggested that a 10mmHg reduction might increase the risk of renal failure in these patients (rather few events were recorded in just two studies).

Patients with baseline chronic kidney disease

When trials were stratified by baseline chronic kidney disease, a significant interaction existed for major cardiovascular disease events (p_{interaction}=0.012), with larger proportional risk reductions for the populations without chronic kidney disease (0.68, 0.62-0.75) than in the populations with chronic kidney disease (0.84, 0.73-0.96). A significant interaction also existed for heart failure events, with a large and statistically significant risk reduction of 52% (0.48, 0.38-0.62) for every 10mmHg systolic blood pressure reduction in the subgroup without chronic kidney disease compared with a non-significant reduction for the subgroup with chronic kidney disease (0.95, 0.70-1.29; p_{interaction}=0.0008).

Effect of drug class on outcomes

This analysis also addressed whether some drug treatments achieved better results than others and showed that the various pharmacological classes of drugs achieved similar effectiveness in preventing cardiovascular outcomes. Some classes

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Figure 1: Standardised effects of a 10mmHg reduction in systolic blood pressure

RR–relative risk.
were more effective than others for specific outcomes: β-blockers seemed worse than other classes for the prevention of major cardiovascular disease, stroke and renal failure; calcium channel blockers seemed better than other classes for stroke; and diuretics were better than other classes for heart failure prevention. These findings support the results of previous studies and thus extend the evidence available for drugs to be used preferentially in specific conditions. However, as acknowledged by the authors, the present meta-analysis cannot determine the resulting effect of combinations of drug treatments that are increasingly prescribed in routine clinical practice today.

Figure 2: Standardised effects of a 10mmHg reduction in systolic blood pressure stratified by history of cardiovascular disease

Data are stratified by subgroups in which all (cardiovascular disease) or none (no cardiovascular disease) of the participants had a history of cardiovascular disease at baseline. A cardiovascular disease subgroup is not shown for renal failure because no trial that reported renal failure as an outcome reported an analysis stratified by the presence of cardiovascular disease. RR—relative risk.
Hypertension

Issues in clinical practice – what should we do in everyday practice for our hypertensive patients?

Uncontrolled blood pressure or hypertension remains one of the leading causes of death and cardiovascular morbidity worldwide. Blood pressure still seems to be poorly controlled, irrespective of guidelines, with adherence or treatment-to-goal of blood pressure still less than 50% in first-world countries. Data from the ONTARGET trial indicated that hypotension also increases the risk of cardiovascular mortality, syncope and renal failure. This was described as ‘the J-curve phenomenon’, where high blood pressure on the one hand and hypotension on the other both increase cardiovascular morbidity and mortality.

At the European Hypertension Society meeting in Milan 2013, hypertension guidelines were adjusted to set new goals of therapy at 140/90mmHg, even in the higher-risk population of diabetics and renal failure patients. For the elderly, a systolic blood pressure of 150mmHg would be acceptable and for the very frail an even higher systolic blood pressure would be acceptable.

The results of the new meta-analysis published in The Lancet indicate that stricter control to lower targets with safer drugs seems to have a better outcome with fewer side-effects. The 2013 European hypertension guidelines are currently under advisement and will probably be adjusted at the next European Hypertension Society meeting.

There is no question that the optimal treatment of hypertension is still the most cost-effective way of prolonging life. Even a small reduction in blood pressure reduces the risk of cardiovascular events. Meta-analyses of 61 prospective observation trials showed that a 2mmHg decrease in mean systolic blood pressure leads to a 7% reduction in ischaemic heart disease mortality and a 10% risk reduction in stroke.

Remember that beta-blockers are not considered first-line therapy for hypertension anymore, but play a role in patients with hypertension and ischaemic heart disease or hypertension and congestive heart failure.

The British Hypertension Society Guideline9 is still a very practical and applicable way to approach the treatment of hypertension in everyday clinical practice (Figure 3).

“There is still no question that the optimal treatment of hypertension is the most cost-effective way of prolonging life,”
Dr Rust Theron

Figure 3. Summary of antihypertensive drug treatment
Managing hypertension to lower targets – what are the clinical issues?

**Question:** What is your view of the overall approach of targeting systolic blood pressure control to 130mmHg, regardless of the presence of co-morbidities?

**Answer:** In my view, we should strive for the lower targets but this must come with more attention to detail to avoid the increased adverse events seen in the SPRINT\(^9\) study, which were mainly due to overtreatment of blood pressure. Physicians must make greater use of home and ambulatory blood pressure monitoring in conjunction with office measurements, increase patient visits and monitor electrolytes and renal function more regularly.

**Question:** The reduced benefit in patients with kidney disease; is this expected?

**Answer:** I am not surprised by this finding. Firstly, one of the problems of lower targets, as illustrated in both the SPRINT\(^9\) and ACCORD\(^11\) studies, was the increased risk of acute kidney injury due to overtreatment of blood pressure that may mask the long-term benefits. Secondly, renal end-points in trials, especially where kidney function is normal, take many years to develop and are frequently beyond the time scope of most clinical trials.

**Question:** No substantiation was found for a J-curve below 130mmHg; what are your views on this?

**Answer:** In my view a J-curve has never been demonstrated for systolic blood pressure. *Post hoc* analyses of studies have suggested a possible J-curve for diastolic pressure. Coronary perfusion occurs in diastole and may be a potential issue in patients with coronary disease. This is especially applicable to elderly patients with a high pulse pressure and low diastolic pressures. Just from a common sense point of view, there must be a J-curve as adequate perfusion is essential for survival but this is not defined for systolic blood pressure and for diastolic it is suggested to be approximately 60-64mmHg.
References


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