Hypertension in adults: intensive or standard blood-pressure control?

The SPRINT study found that in people with an increased risk of cardiovascular events, but without diabetes, treating to a systolic blood pressure target of 120 mmHg lowered the incidence of adverse cardiovascular events and mortality compared with a target of 140 mmHg. People receiving the more intensive blood pressure lowering treatment took more medication and experienced higher rates of serious adverse events of hypotension, syncope, electrolyte abnormalities and acute kidney injury or failure but there was no increase in injurious falls. Healthcare professionals should continue to follow NICE guidance on blood pressure targets; decisions about adopting lower targets for an individual should follow an informed discussion about the potential benefits and risks that takes into account the individual person's clinical circumstances, values and preferences. The Cates Plots included in this commentary may help facilitate shared decision-making.

Overview and current advice

Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. The NICE guideline on hypertension in adults recommends the following blood pressure targets for people with treated hypertension:

- a target clinic blood pressure below 140/90 mmHg in people aged under 80 years
- a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over

For people using ambulatory or home blood pressure monitoring targets 5/5 mmHg lower than these (during the person's usual waking hours) are recommended.

Other NICE guidelines recommend different blood pressure targets in specific situations:

- The NICE guidance on chronic kidney disease (CKD) in adults recommends a target systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and a target diastolic blood pressure below 90 mmHg for most people with CKD. People who have CKD and diabetes, and people with an albumin:creatinine ratio of 70 mg/mmol or more should aim for a systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and a diastolic blood pressure below 80 mmHg.
- The NICE guidance on type 2 diabetes in adults recommends a target blood pressure below 140/80 mmHg for most people with type 2 diabetes. People with type 2 diabetes and kidney, eye or cerebrovascular damage should aim for blood pressure below 130/80 mmHg.
- The NICE guidance on hypertension in pregnancy recommends a target blood pressure below 150/100 mmHg for pregnant women with uncomplicated chronic hypertension. A lower target of 140/90 mmHg is recommended for pregnant women with target-organ damage secondary to chronic hypertension (for example, kidney disease).
The full NICE guideline on hypertension (published in 2011) states that most clinical trials adopted a treatment target below 140/90 mmHg and there was no convincing evidence supporting a lower target. However, the full guideline notes the evidence specifically examining optimal treatment targets for hypertension is inadequate and consequently the optimal treatment target could not be clearly defined with certainty. The guideline also recommends the need for further studies prospectively randomising people to more versus less systolic blood pressure lowering to determine the optimal systolic pressure treatment target for people with treated hypertension.

The NICE Pathways on hypertension, chronic kidney disease, type 2 diabetes in adults and hypertension in pregnancy bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams.

New evidence

A meta-analysis of 19 open label randomised controlled trials (RCTs, total n=44,989) by Xie et al. (2016) found benefits from more intensive blood pressure control. Over a mean follow-up of 3.8 years (range 1.0–8.4 years), people treated with an intensive blood pressure lowering regimen (mean attained blood pressure 133/76 mmHg) had a 14% lower risk of major cardiovascular events compared with those people treated with a less intensive regimen (mean attained blood pressure 140/81 mmHg), including reductions in risk of stroke and myocardial infarction. There was no statistically significant difference in risk of death overall or death from cardiovascular causes. However, the blood pressure targets varied across the trials, and some trials had change in blood pressure as the target endpoint, whereas others had a mixture of target level and change in blood pressure. Importantly, adverse events were inconsistently reported in the included studies, making it difficult to assess the risk-benefit of the more intensive regimen.

The Systolic Blood Pressure Intervention Trial (SPRINT) was an open-label, multi-centre RCT conducted across 102 centres in the USA. The study enrolled 9,361 people aged 50 years or older (mean age 68 years; 28% aged 75 years or older) with a systolic blood pressure between 130 and 180 mmHg (mean 139.7 mmHg at baseline) and an increased risk of cardiovascular events, although people with diabetes or previous stroke were excluded. Increased cardiovascular risk was defined as the presence of one or more of the following: clinical or subclinical cardiovascular disease other than stroke; chronic kidney disease, excluding polycystic kidney disease, with an estimated glomerular filtration rate (eGFR) of 20–60 ml/min/1.73 m²; a 10 year risk of cardiovascular disease of 15% or greater on the basis of the Framingham risk score; or an age of 75 years or older. The mean number of antihypertensive drugs per person at baseline was 1.8 (standard deviation [SD] 1.0), with approximately 9.4% of participants not taking any antihypertensive medication at baseline.

Participants were randomised to intensive treatment, defined as a target systolic blood pressure less than 120 mmHg; or standard treatment, defined as a target systolic blood pressure of less than 140 mmHg (target range 135–139 mmHg). After randomisation, participants were seen monthly for the first 3 months and every 3 months thereafter. Their baseline antihypertensive medication was adjusted to achieve the target blood pressure using predefined study algorithms: in the standard treatment group, the medication dose was reduced if clinic systolic blood pressure was less than 130 mm Hg on a single visit or less than 135 mm Hg on 2 consecutive visits.

The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. Secondary outcomes included the individual components of the primary composite outcome and all-cause mortality. Renal outcomes were also assessed. For people with CKD at baseline (eGFR less than 60 ml/min/1.73m²) the outcome was a composite of a decrease in eGFR of 50% or more or the development of end stage renal disease. For people without CKD at baseline the renal outcome was a decrease in eGFR of 30% or more to a value of less than 60 ml/min/1.73m².
The planned average follow-up was 5 years but the study was stopped early after a median follow-up of 3.26 years. This was because of the observed differences in outcomes in interim data monitoring and safety analyses. Over the 3.26 year follow-up the mean systolic blood pressure was 121.5 mmHg in the intensive group and 134.6 mmHg in the standard group, an average difference in systolic blood pressure of 13.1 mmHg. People in the intensive group were taking on average 1 more antihypertensive drug compared with the standard group (2.8 and 1.8 medications respectively).

A primary composite outcome occurred more frequently in the standard group (319/4683 people, 2.19% per year) compared with the intensive group (243/4678 people, 1.65% per year; hazard ratio [HR] with intensive treatment 0.75, 95% confidence interval [CI] 0.64 to 0.89, p<0.001). A between-group difference in the primary composite outcome was observed from 1 year. All-cause mortality was lower for intensive therapy (3.3%, 155/4678) compared with standard therapy (4.5%, 210/4683, HR 0.73, 95% CI 0.60 to 0.90, p=0.003), with a difference between groups observed at 2 years. The risk of death from cardiovascular causes was lower for people in the intensive group compared with the standard group (HR 0.57, 95% CI 0.38 to 0.85, p<0.003). The individual parts of the composite primary endpoint were examined as secondary outcomes, but no statistically significant difference between intensive and standard treatment was found for myocardial infarction (p=0.19), acute coronary syndrome (p=0.99) or stroke (p=0.50). People treated with intensive therapy were at lower risk of acute decompensating heart failure compared with those on standard therapy (HR 0.62, 95% CI 0.45 to 0.84).

There was no statistically significant difference in the risk of serious adverse events overall (38.3% group in the intensive group and 37.1% in the standard group, p=0.25). However, events judged serious or which led to an emergency department visit were statistically significantly more common in the intensive group than in the standard group: hypotension (3.4% compared with 2.0% respectively, HR 1.70, p<0.001), syncope (3.5% compared with 2.4% respectively, HR 1.44, p=0.003), electrolyte abnormalities (3.8% compared with 2.8% respectively, HR 1.38, p=0.006). The between-group differences in rates of injurious falls or bradycardia judged serious or which led to an emergency department visit were not statistically significant.

Relatively few renal events occurred during the 3.26 year follow-up, which may have been because of the early termination of the trial. Among participants who had chronic kidney disease at baseline, the number of participants with a decrease in the eGFR of 50% or more or reaching end-stage renal disease over the course of the trial did not differ significantly between the two groups (1.1% in both groups, p=0.76). Among participants who did not have chronic kidney disease at baseline, a decrease in the eGFR of 30% or more to a value of less than 60 ml/min/1.73m² occurred more frequently in the intensive group (1.21% per year) compared with the standard group (0.35% per year, HR 3.49; 95% CI 2.44 to 5.10; p<0.001). Incidences of acute kidney injury or failure judged serious or which led to an emergency department visit were statistically significantly more common in the intensive group than in the standard group (4.4% compared with 2.6% respectively, HR 1.71, p<0.001).

A systematic review and meta-analysis by Ettehad et al. (2015) examined the effect of blood pressure lowering on the risk of cardiovascular disease and mortality. The review included 123 RCTs (total n=613,815) on blood pressure lowering treatment, including the SPRINT trial. The review estimated that a 10 mmHg reduction in systolic blood pressure statistically significantly reduced the relative risk of a major cardiovascular disease event by 20% (95% CI 17% to 23%), coronary heart disease by 17% (95% CI 12% to 22%), stroke by 27% (95% CI 23% to 32%) and heart failure by 28% (95% CI 22% to 33%), with a 13% (95% CI 9% to 16%) reduction in all-cause mortality. There was no statistically significant change in risk of renal failure (relative risk reduction 5%, 95% CI 16% reduction to 7% increase in risk). The investigators comparing the effects of a 10 mmHg systolic blood pressure by baseline level, finding similar proportional risk reductions in trials with higher mean baseline systolic blood pressure compared with trials with a lower mean baseline systolic blood pressure. The authors state that these results are consistent with and extend the findings of the SPRINT trial. The rates of adverse events associated with more intensive blood pressure reductions are not reported.
Commentary

Commentary provided by the Medicines and Prescribing Programme, NICE

The SPRINT study\(^2\) found that people with an increased risk of cardiovascular events and who did not have diabetes benefitted from more aggressive blood pressure lowering, with a target systolic blood pressure of 120 mmHg. However people treated to lower blood pressure targets experienced more serious adverse events.

It should be remembered that the SPRINT study recruited a selective group of participants and the results may not be applicable to the general population of people with hypertension. SPRINT did not include people with diabetes, with a history of stroke, aged less than 50 years, people who do not have an increased risk of cardiovascular disease and older people living in nursing homes or assisted living facilities. The benefits of more using lower blood pressure targets in these groups, and the risks of adverse events, are not known.

Trials stopped early because of an observed benefit are, generally speaking, more likely to overestimate that benefit\(^4\). This is a particular risk with small studies; in trials with more than 500 primary events, like SPRINT, any overestimates are likely to be small\(^4\). However, stopping a trial early may mean that certain adverse effects that might otherwise have emerged over time are not fully identified. The increases in risk of hypotension and syncope associated with more intensive blood pressure control are probably not surprising, although the absence of an increased risk of injurious falls, even in this older population, may be. The observed 71% relative increase in the risk of acute kidney injury or failure judged serious or which led to an emergency department visit, and the 3.49-fold increase in risk of clinically significant reduction in renal function in people without CKD at baseline suggest that a strategy of intensive blood pressure control is not without its problems. A longer-term study might allow these to be better elucidated. The composite renal outcome of a decrease in the eGFR of 50% or more or reaching end-stage renal disease in people with CKD occurred in only 29 of the 2646 people with CKD; SPRINT may well have lacked sufficient power to compare the risk in the 2 study groups in the time it lasted.

Conflicting results were observed in the 2010 ACCORD trial\(^5\), in which 4,733 people with type 2 diabetes were randomised to intensive (target systolic blood pressure 120 mm Hg or less) or standard blood pressure-lowering therapy (target systolic blood pressure 140 mm Hg or less). After 1 year, the mean systolic blood pressure was 119.3 mmHg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. However, over a mean 4.7 year follow-up, there was no statistically significant difference in the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) or all-cause mortality. Serious adverse events attributed to antihypertensive treatment occurred statistically significantly more often in the intensive-therapy group (3.3%) than the standard-therapy group (1.3%, p<0.001).

A number of NICE guidelines make recommendations on target blood pressure; these are guided by age, co-morbidities and, in women, pregnancy status. Different health professionals will have different views on the merits or disadvantages of adopting a more intensive approach to blood pressure control for an individual person, as a case study published alongside SPRINT shows. Following the principles discussed in the NICE guidelines on medicines optimisation and on patient experience in adult NHS services it is important that health professionals adopt a shared decision-making approach when considering how to manage a person’s blood pressure. Multiple factors may need to be considered, including the person’s age, co-morbidities, other medications, renal function, risk of cardiovascular events and risk of falls, as well as the person’s views on the implications for them if they occurred. Healthcare professionals should make clear that they accept that the person may have different views from them about the balance of risks, benefits and consequences of treatments, and that they have the right to decide not to have a treatment (as long as they have the capacity to make an informed decision and have been given and understand the information needed to do this).
The Cates plots below illustrate the results of SPRINT over the mean 3.26 year follow up in terms of the absolute reduction in risk of the primary composite outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) and the absolute increase in risk of syncope, and of acute kidney injury or failure, rated serious (fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalisation, or that were judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention) or which led to an emergency department visit. The Cates Plots may help facilitate shared decision-making.

As part of the discussion with the person, a healthcare professional might use a form of words similar to the following: ‘Imagine there were 1000 people like you. If all 1000 people kept to a systolic blood pressure of 135 mmHg, over the next 3¼ years, and on average, 68 people would have a heart attack or stroke, develop heart failure or die from heart problems, but that means that 932 people would not. If all 1000 people kept to a lower systolic blood pressure of 122 mmHg for the next 3¼ years, over that time 932 of them would not develop those problems, just as if they had kept to the higher blood pressure. Fifty-two people would still develop those problems, even though they kept to the lower blood pressure. However, 16 people would be saved from developing those problems, because they kept to the lower blood pressure. We can’t say if you would be 1 of the 16 people who benefit from keeping to the lower blood pressure, or 1 of the 984 people for whom doing so makes no difference to what would have happened if they had kept to the higher blood pressure’.

Similar wording could be used for the potential harms. These numbers will need to be adjusted to take account of the person’s baseline risk: For an individual person, the higher their individual baseline the greater their absolute difference in risk.

**Benefits: primary composite outcome: having a heart attack or stroke, develop heart failure or dying from heart problems**

In 1000 people like those in SPRINT who maintained a systolic blood pressure of 122 mmHg instead of 135 mmHg, over 3¼ years and on average:

- 932 people did not have a heart attack or stroke, develop heart failure or die from heart problems and would not have done whichever of the 2 blood pressure levels they maintained (the green faces)
- 52 people had have a heart attack or stroke, develop heart failure or died from heart problems and would have done whichever of the 2 blood pressure levels they maintained (the red faces)
• 16 people were saved from having a heart attack or stroke, develop heart failure or dying from heart problems because they maintained the lower blood pressure level (the yellow faces)

**Harms: syncope (blackout)**

In 1000 people like those in SPRINT who maintained a systolic blood pressure of 122 mmHg instead of 135 mmHg, over 3½ years and on average:

• 965 people did not have a blackout that was judged serious or led to an emergency department visit and would not have done whichever of the 2 blood pressure levels they maintained (the green faces)

• 24 people had a blackout that was judged serious or led to an emergency department visit and would have done whichever of the 2 blood pressure levels they maintained (the red faces)

• 11 people had a blackout that was judged serious or led to an emergency department visit because they maintained the lower blood pressure level (the green faces with the red cross)

**Harms: acute kidney injury or failure**
In 1000 people like those in SPRINT who maintained a systolic blood pressure of 122 mmHg instead of 135 mmHg, over 3½ years and on average:

- 956 people did not have acute kidney injury or failure that was judged serious or led to an emergency department visit and would not have done whichever of the 2 blood pressure levels they maintained (the green faces).
- 26 people had acute kidney injury or failure that was judged serious or led to an emergency department visit and would have done whichever of the 2 blood pressure levels they maintained (the red faces).
- 18 people had acute kidney injury or failure that was judged serious or led to an emergency department visit because they maintained the lower blood pressure level (the green faces with the red cross).

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**References**

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