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REVIEW

Hypertension and small vessel disease: do the drugs work?

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Abstract

Associations of hypertension with ischaemic stroke and intracerebral haemorrhage, particularly when attributed to cerebral small vessel disease, are well established. While it seems plausible that treating hypertension should prevent small vessel disease from developing or progressing, there is limited evidence demonstrating this. This article critically appraises the evidence answering this clinical question. Hypertension is also closely associated with chronic kidney disease, with anatomical and functional similarities between the vasculature of the brain and kidneys leading to the hypothesis that shared multi-system pathophysiological processes may be involved. Therefore, the article also summarises data on prevention of progression of chronic kidney disease. Evidence supports a target blood pressure of <130/80 mmHg to optimally prevent progression of both small vessel disease and chronic kidney disease. However, future studies are needed to determine long-term effects of more intensive blood pressure treatment targets on small vessel disease progression and incident dementia.

Key words: Blood pressure; Cerebral small vessel disease; Chronic kidney disease; Hypertension; Proteinuria

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Background

Treatment of hypertension reduces the risk of ischaemic stroke and intracerebral haemorrhage (Turin et al, 2016). Cerebral small vessel disease is a group of pathologies affecting small perforating cerebral arterioles, capillaries and venules, associated with a characteristic spectrum of clinical and imaging findings. In addition to causing about a quarter of ischaemic strokes and 80% of cases of non-traumatic intracerebral haemorrhage, it causes or contributes to nearly half of cases of dementia. Clinical features also include gait dyspraxia and depression (Pantoni, 2010). The most studied magnetic resonance imaging features are white matter hyperintensities, lacunes of vascular origin, cerebral microbleeds and visible perivascular spaces (Figure 1). Observational studies, such as Staals et al (2014), show a clear association of hypertension with these markers. Whether treating hypertension prevents the development of small vessel disease or slows its progression is less well established. Mild small vessel disease is rarely symptomatic, but as it progresses the correlation with cognitive impairment becomes much stronger (Kloppenborg et al, 2014). Therefore, it

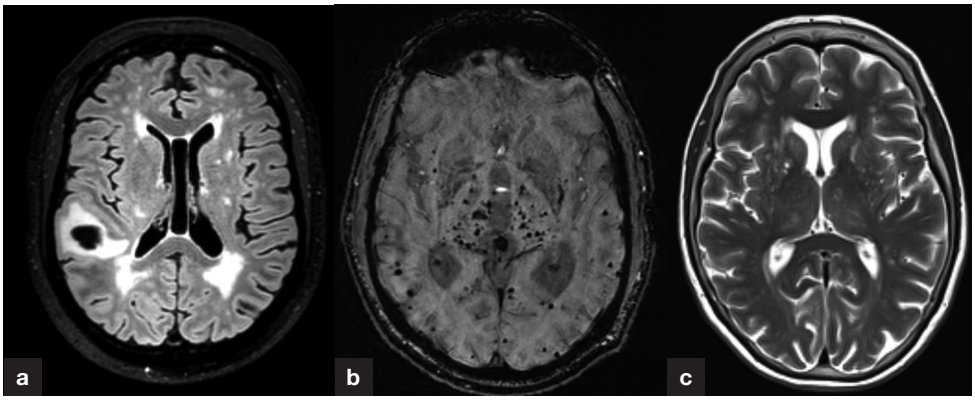

Figure 1. Different markers of small vessel disease: (a) white matter hyperintensities; (b) cerebral microbleeds; (c) enlarged peri-vascular spaces.

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makes sense to try and stop the development or progression of small vessel disease early. Any intervention that clearly arrests or slows the progression of these abnormalities has the potential to reduce the prevalence of dementia and mild cognitive impairment in the future, or at least slow its rate of progression.

Cerebral small vessel disease is very common

Large population-based studies of ageing have shown that at least 66% of the population aged between 55 and 64 years will have some white matter hyperintensities on magnetic resonance imaging, regardless of symptoms or past medical history (Smith et al, 2017). These data also show that 97% of individuals over the age of 75 years will have subcortical white matter hyperintensities.

Hypertension is clearly associated with small vessel disease

Of the modifiable risk factors in Table 1, hypertension is by far the most common. Insight 46 (Lane et al, 2017) is a neuroscience substudy of a large longitudinal MRC survey of health and development (Wadsworth et al, 2006). All participants were born in the UK in the same week in 1946 and underwent magnetic resonance imaging scans of the brain between the ages of 69 and 71 years. The investigators found a significant increase in total volume of white matter hyperintensities and a significant decrease in whole brain volume in participants who developed hypertension by the age of 53 years (Table 2).

Another longitudinal study (McGrath et al, 2017) examining cognitive outcomes and hypertension found a significant interaction between hypertension and the development of dementia. The cohort study followed 1440 participants for >40 years. Defining midlife hypertension as a blood pressure of >140/90 mmHg with a median age of 55 years, the authors found a hazard ratio of 1.70 (95% confidence interval 1.14–2.53) for developing dementia.

Is treating hypertension effective in halting or slowing the progression of small vessel disease?

Previously there was a paucity of randomised controlled trial evidence in this field, but a meta-analysis of four randomised controlled trials found a significantly lower volume of white matter hyperintensities in the intervention arms on follow-up magnetic resonance imaging scans (van Middelaar et al, 2018). The authors reported a pooled standardised mean difference of antihypertensive medication on progression of white matter hyperintensities volume of -0.19 ml (95% confidence interval -0.32 to -0.06). However, there was heterogeneity in the populations and methodology used in each trial (I^2=20%). For example all participants in the ACCORD-MIND (Williamson et al, 2014) study had diabetes mellitus, whereas SCOPE (Firbank et al, 2007) looked at the effects of hypertension treatment on cognition in older patients. The mean ages in these trials were 61.7 and 77 years respectively. Examining

Table 1. Factors most commonly associated with small vessel disease

Variable	Odds ratio (95% confidence interval)
Age (per year)	1.10 (1.08–1.12)
Male sex	1.58 (1.10–2.29)
Diabetes mellitus	0.98 (0.57–1.67)
Hypertension	1.50 (1.02–2.20)
Smoking	2.81 (1.59–3.63)
Peripheral vascular disease	1.64 (0.75–3.61)
Lacunar stroke	2.45 (1.70–3.54)

From Staals et al (2014)

Table 2. Relative increase in volume of white matter hyperintensities with the age of onset of hypertension

Variable	Age of onset of hypertension (years)	*n*	Relative increase in volume of white matter hyperintensity (95% confidence interval)	*P* value
Systolic blood pressure	36	413	1.02 (0.94–1.10)	0.64
	43	430	1.05 (0.98–1.14)	0.17
	53	441	1.10 (1.04–1.16)	0.001*
	60–64	452	1.05 (0.99–1.12)	0.094
	69	447	1.07 (1.00–1.25)	0.047
Diastolic blood pressure	36	413	1.08 (0.97–1.19)	0.16
	43	430	1.06 (0.95–1.19)	0.28
	53	441	1.17 (1.07–1.28)	0.0006*
	60–64	452	1.12 (1.00–1.25)	0.054
	69	447	1.07 (0.97–1.18)	0.20

**statistically significant associations. From Lane et al (2017)*

each trial individually, ACCORD-MIND was the only one to find a statistically significant difference in progression of white matter hyperintensities volume. This trial also found a significant decrease in total brain volume in the intensive blood pressure-lowering arm of the trial, which is associated with poor outcomes (Hanning et al, 2016), whereas SCOPE found the opposite association with the intervention arm.

A significant problem with this meta-analysis is that each randomised controlled trial included was a sub-analysis of a larger trial with a different clinical question. SPRINT-MIND (Williamson et al, 2019) was a large multicentre randomised controlled trial investigating the effect of intensive blood pressure management on the subsequent development of dementia or mild cognitive impairment. A subset of participants (n=449) had baseline and follow-up magnetic resonance imaging brain scans (Nasrallah et al, 2019) and were randomised either to intensive (systolic blood pressure <120 mmHg) or standard (systolic blood pressure <140 mmHg) blood pressure management. The investigators found a smaller progression in total white matter hyperintensities volume in the intensive group (between-group difference in change -0.54 cm^2; 95% confidence interval -0.87 to -0.20 cm^2). Although this difference was relatively small, it was statistically significant despite the trial being stopped early because of the benefits for cardiovascular outcomes in the intensive group. A significant proportion of participants (67%) did not have their follow-up magnetic resonance imaging because of the early termination of the trial so the observed difference may have been larger.

After SPRINT-MIND, two more randomised controlled trials investigated the effect of blood pressure management on progression of white matter hyperintensities volume. Zhang et al (2019) looked at the effect of telmisartan vs placebo on progression of white matter hyperintensities volume and cognitive decline. All trial participants were also taking hydrochlorothiazide. They found no difference in progression of white matter hyperintensities volume (P=0.236). However, they also did not achieve a statistically significant difference in the blood pressures of the trial groups (systolic mean difference 5 mmHg, P=0.612) and did not report any difference in volume change over time.

INFINITY (White et al, 2019) was a randomised controlled trial investigating the effect of intensive vs standard blood pressure control into progression of white matter hyperintensities volume, gait speed and cognitive decline. The investigators found a significant blood pressure difference between the trial arms (16.3 mmHg). They found significantly less progression of white matter hyperintensities volume in the intensive group than the control group (0.29% vs 0.48% of baseline volume).

The PRESERVE randomised controlled trial (Markus et al, 2021) contributes to evidence guiding the management of small vessel disease. The primary objective was to investigate whether intensive blood-pressure lowering affects quantitative magnetic resonance imaging

findings using diffusion tensor imaging. While this was not demonstrated, a secondary analysis showed a (nominally) statistically significant negative correlation between achieved systolic blood pressure reduction and progression of white matter hyperintensities volume. Importantly, the authors demonstrated that there was no reduction in total brain volume or cerebral blood flow for participants in the intensive treatment group. This helps to allay concerns from the ACCORD-MIND study results, which found progression in brain atrophy in the intensively treated group.

A more recent systematic review and meta-analysis into this clinical question (Lai et al, 2020) included all the trials discussed above in the data synthesis, apart from PRESERVE. Like the previous meta-analysis, they found a modest overall beneficial effect on progression of white matter hyperintensities volume in the intervention arms of the included trials, and moderately significant heterogeneity (standardised mean difference=-0.22, I^2=63%). However, when pooling the results of trials with intensive blood-pressure lowering as the intervention group, they found a larger net effect on progression of white matter hyperintensities volume and no heterogeneity (standardised mean difference=-0.37, I^2=0%). These results were supported by an additional meta-regression which showed a significant negative correlation of the magnitude of the blood pressure reduction achieved with progression of white matter hyperintensities volume (β=-0.028, P<0.001). Lai et al (2020) support use of an intensive blood pressure treatment target when trying to prevent progression of small vessel disease.

However, the specific target remains uncertain based on these results, as the studies used different systolic blood pressure goals: <130 mmHg for INFINITY, and <120 mmHg for SPRINT-MIND and ACCORD-MIND. Four of the trials contributing to the meta-analysis tested the effect of a specific class of antihypertensive on progression of white matter hyperintensities volume: angiotensin-converting enzyme inhibitors (perindopril with or without indapamide) in PROGRESS, and angiotensin-receptor blockers in PRoFESS, SCOPE and Zhang et al (2019). The authors are not aware of any studies testing the specific effects of other classes of antihypertensives, such as calcium-channel blockers or beta blockers. None of these trials found a statistically significant difference in progression of white matter hyperintensities volume between the study arms, suggesting that the magnitude of blood pressure reduction might matter more than antihypertensive drug class. However, further data testing the effects of intensive treatment using specific drug classes (eg calcium-channel blockers) are needed to resolve this question. These results are summarised in Table 3.

Clinical endpoints of trial interventions

These are also shown in Table 3. The primary outcome of SPRINT-MIND was the occurrence of probable dementia, with the hypothesis that the incidence would be lower in the intensive blood pressure management group. A total of 9361 patients were randomised and 8563 had at least one cognitive assessment. The study did not find a lower incidence of probable dementia in the intensive group, perhaps because the early termination meant the results were not powered to detect a difference. There were 149 cases in the intensive group and 176 in the standard group (hazard ratio 0.83, 95% confidence interval 0.67–1.04). Secondary cognitive outcomes included adjudicated mild cognitive impairment and a composite outcome of mild cognitive impairment and probable dementia, both of which were significantly less frequent in the intensive treatment group. There were 287 cases of the composite outcome in the intensive group and 353 in the standard group (hazard ratio 0.81, 95% confidence interval 0.69–0.95). These findings are potentially important since mild cognitive impairment is a risk factor for the development of dementia and can worsen an individual's quality of life. The only trial which tested the effect of a specific antihypertensive class on cognitive outcomes was Zhang et al (2019), and found no difference between telmisartan and placebo. However, as mentioned, the difference in blood pressure achieved was not statistically significant (138/67 mmHg for telmisartan and 144/68 mmHg for placebo at final follow up, P=0.612 for the difference in systolic blood pressure), which may partly explain these results.

Some trials investigated non-cognitive clinical outcomes. The PROGRESS investigators found significantly fewer strokes in the intervention arm of the trial (Dufouil et al, 2005): 307 vs 420 (relative risk reduction 28%, 95% confidence interval 17–38%, P<0.0001).

Table 3. Evidence from randomised controlled trials investigating the effects of hypertension treatment on small vessel disease neuroimaging biomarkers and/or clinical endpoints

Trial and reference	Study design	Study population	Methods	No of patients	Significant results
ACCORD-MIND (Williamson et al, 2014)	Randomised controlled trial	Diabetic patients	Randomised to target blood pressure <120 mmHg or <140 mmHg Any medication Primary outcome measure was cognitive function at 40 months	314	Mean systolic blood pressure reduction of 19.7 mmHg Significantly lower progression of white matter hyperintensities volume in intensive group Significantly more progression in brain atrophy in intensive group No significant difference in the primary outcome measure
PRoFESS (Weber et al, 2012)	Randomised controlled trial	Individuals with recent ischaemic stroke	Telmisartan vs placebo Addition to blood pressure treatment Primary outcome measure was recurrent stroke	771	Mean systolic blood pressure reduction of 11.1 mmHg No significant difference in white matter hyperintensities volume progression in the intervention group No significant difference in the primary outcome measure
PROGRESS (Dufouil et al, 2005)	Randomised controlled trial	History of transient ischaemic attack, ischaemic stroke or intracerebral haemorrhage	Perindopril +/- indapamide vs placebo Addition to blood pressure treatment Primary outcome measure was any stroke	192	Mean systolic blood pressure reduction of 12.5 mmHg No significant difference in white matter hyperintensities volume progression in the intervention group Significantly fewer recurrent strokes in the intervention group, 307 vs 420 (relative risk reduction 28%, 95% confidence interval 17–38%, $P<0.0001$)
SCOPE (Firbank et al, 2007)	Randomised controlled trial	Patients aged 70–89 years	Randomised to candesartan or placebo Primary outcome was progression of white matter hyperintensities volume	92	Mean systolic blood pressure reduction of 26 mmHg No significant difference in progression of white matter hyperintensities volume or atrophy in the intervention group
van Middelaar et al (2018)	Meta-analysis	The four randomised controlled trials listed above	As above – primary endpoint was progression of white matter hyperintensities	1369	Significant effect of antihypertensive medication on progression of white matter hyperintensities volume Pooled standardised mean difference of -0.19 (95% confidence interval -0.32 to -0.06)
SPRINT – MIND (Nasrallah et al, 2019)	Randomised controlled trial	Adults >50 years with hypertension and increased cardiovascular risk	Randomised to systolic blood pressure treatment target of <120 mmHg or <140 mmHg Primary outcome was incidence of probable dementia (Williamson et al, 2019)	449	Small but statistically significant difference in progression of white matter hyperintensities volume in the intensive group Between-group difference in change -0.54 cm^2 (95% confidence interval -0.87 to -0.20) No significant difference in the primary outcome measure

Table 3. Evidence from randomised controlled trials investigating the effects of hypertension treatment on small vessel disease neuroimaging biomarkers and/or clinical endpoints (continued)

Trial and reference	Study design	Study population	Methods	No of patients	Significant results
PRESERVE (Markus et al, 2021)	Randomised controlled trial	Adults >40 years with lacunar stroke and hypertension	Randomised to standard systolic blood pressure target of <140 mmHg or intensive target of <125 mmHg Primary outcome was change in diffusion tensor imaging metrics: mean diffusivity and fractional anisotropy	90	No significant difference in progression of white matter hyperintensities volume over 2 years follow up In secondary analysis a significant negative correlation was found between magnitude of reduction in systolic blood pressure and progression of white matter hyperintensities volume, showing that a greater blood pressure reduction led to less progression of white matter hyperintensities volume No difference in the primary outcome measures
INFINITY (White et al, 2019)	Randomised controlled trial	Adults >75 years of age with no history of stroke or cognitive impairment	Randomised to standard systolic blood pressure of <145 mmHg or intensive target of <130 mmHg Primary clinical outcome was change in gait speed	199	Significant difference in progression of white matter hyperintensities volume over 3 years of follow up, 0.19% white matter hyperintensities volume difference, *P*=0.03 Greater difference found in the per protocol population (*n*=52, 0.35% white matter hyperintensities volume difference, *P*=0.003) No significant difference in the primary outcome measure
Zhang et al (2019)	Randomised controlled trial	Adults >60 years of age with no history of stroke or cognitive impairment	1:1:1:1 randomisation to telmisartan, rosuvastatin, both or none (factorial design) Primary clinical outcome was the development of cognitive impairment	732	No significant difference in progression of white matter hyperintensities volume between telmisartan and placebo arms, although there was no significant difference in blood pressure between the arms They found a marginally and statistically significant lower incidence of cognitive impairment in the rosuvastatin group
Lai et al (2020)	Meta-analysis	Seven randomised controlled trials (all except PRESERVE)	As in each trial, primary outcome was progression of white matter hyperintensities volume Note moderately significant heterogeneity (I^2=63%)	2693	Small but significant difference in progression of white matter hyperintensities volume Standardised mean difference -0.22 (95% confidence interval -0.35 to -0.09) When pooling results of trials with intensive blood pressure targets only, a more significant difference was found; standardised mean difference -0.37 (95% confidence interval -0.50 to -0.24) This is supported by meta-regression which found a significant association of the achieved difference in blood pressure and the standardised mean difference (β=-0.028, *P*<0.001)

The PRoFESS investigators used the same outcome measure and found no association between additional telmisartan treatment and recurrent stroke (Weber et al, 2012). The primary outcome measure of INFINITY (White et al, 2019) was a difference in gait speed between the groups with intensive and standard blood pressure treatment targets, but no difference was seen between groups.

A meta-analysis (Peters et al, 2019) of randomised controlled trials which achieved a difference in systolic blood pressure of 10 mmHg or more between the treatment arms showed a significantly lower incidence of dementia in the intensive group. The authors acknowledged significant heterogeneity of the trial populations of the studies contributing to the meta-analysis and recommended further dedicated work to assess the impact of hypertension treatment on dementia.

Treatment of hypertension in people with chronic kidney disease

The vascular beds of the brain and kidneys are structurally and physiologically very similar. They are high volume, low resistance circuits providing continuous high flow during systole and diastole. As a result, the small arteries and arterioles of both organs are particularly susceptible to hypertensive damage. Hyaline arteriosclerosis (Figure 2), arteriolar intimal thickening and intimal fibrosis are ubiquitous findings in the renal biopsies of patients with a long history of hypertension (Liang et al, 2016). More acute and severe hypertension can cause thrombotic microangiopathy and fibrinoid necrosis. Similar findings are present at post-mortem in the perforating arteries supplying the cerebral white matter of patients who have died as a consequence of acute ischaemic stroke or intracerebral haemorrhage (Lammie, 2002). Arteriolosclerosis in particular (Figure 3) (and, in severe cases, fibrinoid necrosis) is thought to be implicated in the pathogenesis of lacunar stroke and intracerebral haemorrhage.

For many years the standard practice of nephrologists has been rigorous management of high blood pressure to prevent the progression of chronic kidney disease, particularly proteinuric chronic kidney disease (24-hour urinary protein quantification >1 g). This definition is equivalent to a spot urine protein:creatinine ratio of >100 mg/g. This became international guidance when Kidney Disease, Improving Global Outcomes (2012) recommended a target blood pressure of <130/80 mmHg for patients with proteinuric chronic kidney disease. This target was also adopted by National Institute for Health and Care Excellence (2014).

The evidence underpinning these recommendations was derived from a few small randomised controlled trials, a meta-analysis, post-hoc analyses of randomised controlled trials and some observational data. Among the most compelling was a meta-analysis of 11 randomised controlled trials examining outcomes in intensive vs standard blood pressure management in patients with

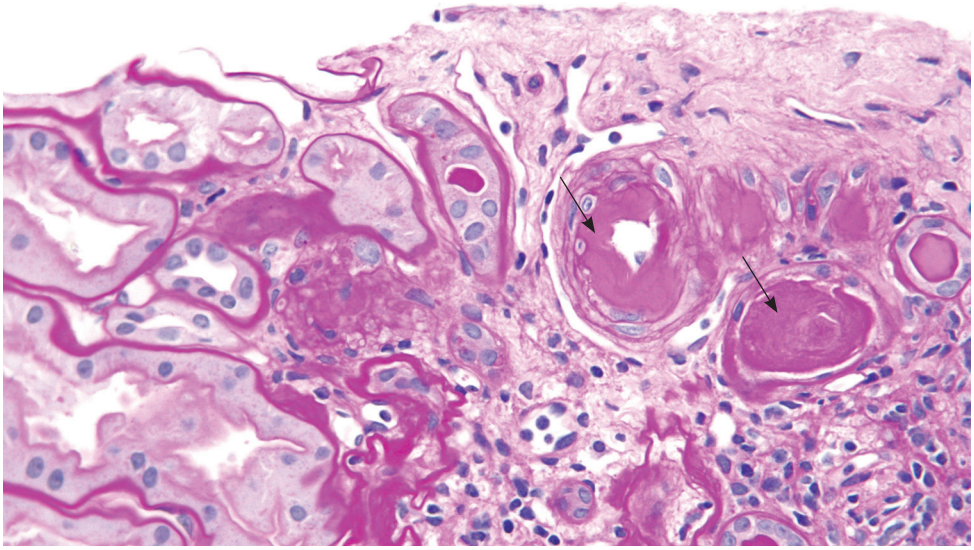

Figure 2. Hyaline arteriolosclerosis (arrows) of renal interlobular artery vessel walls caused by hypertension (Bonert, 2011).

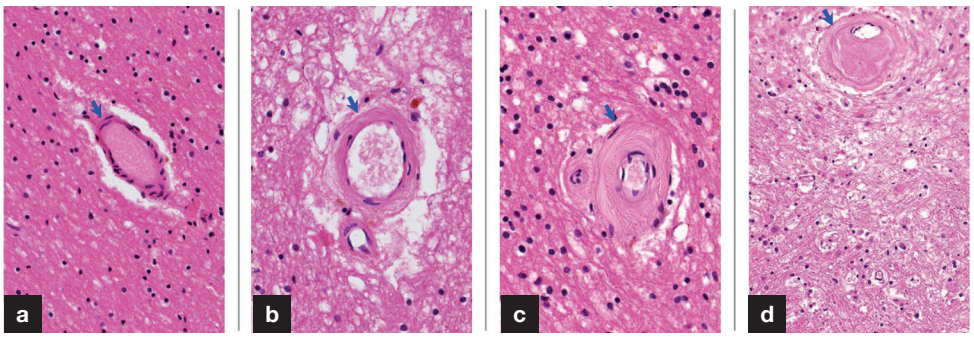

Figure 3. Hyaline arteriosclerosis of varying severity in the subcortical cerebral white matter. a. Normal blood vessel in cerebral white matter. b. Mild hyaline mural thickening, with partial loss of smooth muscle cells in the wall. c. Severe hyaline arteriolosclerosis with much more prominent depletion of smooth muscle cells in the wall and narrowing of the lumen. d. Very severe hyaline arteriolosclerosis with particularly narrow lumen.

non-diabetic kidney disease (Jafar et al, 2003). For the subgroup of patients with proteinuria >1 g/day, the investigators found a significantly increased risk of doubling of serum creatinine levels or initiation of dialysis in trial participants with systolic blood pressure in the range 130–139 mmHg compared to those with systolic blood pressure in the range 110–119 mmHg.

There is good randomised controlled trial evidence that intensive blood pressure management can cause proteinuria to regress. The AASK trial (Wright et al, 2002) randomised 1094 participants to a target mean arterial pressure of either 107 mmHg (standard) or 92 mmHg (intensive). The mean blood pressures in the two groups were 141/85 mmHg and 128/78 mmHg respectively. The investigators found a mean decrease in proteinuria of 17% in the intensive group and a mean increase of 7% in the standard group (P<0.001). Uncontrolled proteinuria is an established risk factor for progressive chronic kidney disease, so these data support current practice.

Since SPRINT was published, the National Institute for Health and Care Excellence (2021) undertook a comprehensive review of optimal blood pressure targets for patients with chronic kidney disease which did not find sufficient evidence to change the existing guidance (target 130/80 mmHg) (National Institute for Health and Care Excellence, 2014). However, the working group acknowledged the strong evidence of reduced cardiovascular death and all-cause death in the intensive treatment arm of SPRINT.

Recommendations for hypertension treatment target

While the results of SPRINT were impressive for cardiovascular outcomes, all-cause mortality and prevention of small vessel disease progression, differences between the trial methods of measuring blood pressure and standard clinical practice have meant that the evidence for a blood pressure treatment target of <120 mmHg systolic has not been widely followed. Measurement of blood pressure in the SPRINT trial was standardised. Trial participants were seated alone in a room and after 5 minutes of quiet rest three automated blood pressure readings were taken, leading some to judge that results of the trial might not be generalisable to standard practice and must be interpreted with caution. The authors of the most recent National Institute for Health and Care Excellence (2019) hypertension guidance have taken this view, as have the authors of the joint European Society of Cardiology/European Society of Hypertension (Williams et al, 2018) guidelines. The intensive treatment arm of SPRINT also had a higher rate of adverse events, mostly attributable to hypotension, and renal function declined more quickly in this group. Interestingly, despite these adverse renal outcomes, Kidney Disease, Improving Global Outcomes is one of the few advisory bodies to adopt SPRINT's findings, recommending the intensive target (120/70 mmHg) assuming that blood pressure measurement is standardised (as in the trial) (Kidney Disease, Improving Global Outcomes, 2021). This is based on the benefits in terms of cardiovascular and all-cause death.

A meta-analysis including 17 randomised controlled trials and data from over 55 000 participants grouped results into five systolic blood pressure treatment targets: <160 mmHg,

<150 mmHg, <140 mmHg, <130 mmHg and <120 mmHg (Bangalore et al, 2017). Although there were no differences between any of the targets when comparing death, cardiovascular death or heart failure, when assessing for stroke and myocardial infarction as individual outcomes, the treatment targets of <120 mmHg and <130 mmHg showed the lowest risk. There was a significant increase in serious adverse events for the <120 mmHg group compared to both the <150 mmHg and <140 mmHg groups. The authors designed cluster plots for combined efficacy and safety and suggested that the systolic blood pressure target of <130 mmHg provided optimal balance for net benefit.

In agreement with this meta-analysis and the other data summarised, the authors support a target blood pressure of <130/80 mmHg for hypertensive patients with small vessel disease. This is likely to help prevent the development of progressive small vessel disease and chronic kidney disease, and reduce the risk of dementia, cardiovascular death and all-cause death. Selected highly motivated patients, who regularly monitor their blood pressure at home and titrate their medications accordingly, could follow the more ambitious target proposed by the SPRINT investigators.

Conclusions

Evidence from randomised controlled trials suggests that treatment of hypertension is likely to help to prevent progression of cerebral small vessel disease, particularly when treating to an intensive target blood pressure. However, the results are heterogeneous and the effect sizes for both neuroimaging and clinical outcomes appear to be small. Further studies are needed, ideally in well-phenotyped populations of patients with evidence of small vessel disease, for example people with previous stroke caused by small vessel disease-associated ischaemia or haemorrhage. More data are also needed to clarify what the intensive treatment target should be, and whether blood pressure regimens based on individual antihypertensive drug classes (eg calcium-channel blockers) might provide maximal benefit. Given the slow rate of progression of small vessel disease over years, more long-term studies are needed. Longer periods of untreated hypertension in early mid-life result in more severe white matter hyperintensities years later, likely because of altered cerebral autoregulation. Therefore, earlier initiation of hypertension treatment should prevent progression of white matter hyperintensities, and longer-term follow-up studies will test this hypothesis.

Most importantly, additional interventions beyond blood-pressure lowering are urgently needed to mitigate the effects of progressive small vessel disease. Promising options include

Key points

- Cerebral small vessel disease is very common, and clinically important, causing a quarter of ischaemic strokes, 80% of non-traumatic intracerebral haemorrhage, and causing or contributing to almost half of dementia cases.
- Hypertension is the most important modifiable risk factor for small vessel disease.
- As there are limited randomised studies of the effect of treatment of hypertension on the development and progression of cerebral small vessel disease, there is no consensus opinion on a target blood pressure.
- The trials showing the most benefit for prevention of progression of small vessel disease used an intensive blood pressure target rather than testing specific drug classes, but different trials used different targets.
- Nephrologists have recommended for many years that those with chronic kidney disease and proteinuria should have an intensive blood pressure treatment target of <130/80 mmHg.
- Summarising and critically appraising the available evidence and comparing it to established guidance on blood pressure treatment targets for patients with chronic kidney disease leads to a recommended treatment target of <130/80 mmHg for those with cerebral small vessel disease, proteinuric chronic kidney disease, or both.

multidomain strategies (eg modification of lifestyle, diet, exercise, cognitive training, overall vascular care) and treatments targeting endothelial function.

So, the answer to whether antihypertensive drugs work in small vessel disease might best be expressed as 'yes, they probably do work on some neuroimaging and clinical outcomes, but not so well that we do not need to look for improved treatments'.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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