ABSTRACT

Associations of hypertension with ischaemic stroke and intracerebral haemorrhage (ICH), particularly when attributed to cerebral small vessel disease (SVD), are well established. Whilst it seems plausible that treating hypertension should prevent SVD from developing or progressing, there is limited evidence demonstrating this. Here we critically appraise the existing evidence answering this clinical question. Hypertension is also closely associated with chronic kidney disease (CKD), 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, we also summarize data on prevention of CKD progression. The available evidence supports a target blood pressure of <130/80 mmHg to optimally prevent progression of both SVD and CKD. However, future studies are needed to determine long-term effects of more intensive blood pressure treatment targets on SVD progression and incident dementia.

Key words:

Cerebral small vessel disease (SVD); chronic kidney disease (CKD); hypertension; proteinuria; blood pressure targets

Key points:

As there are limited randomised studies of the effect hypertension treatment on the development and progression of cerebral small vessel disease, there is no consensus opinion on a target blood pressure. Recent randomised clinical trial evidence can help guide recommendations. Here we summarize and critically appraise the available

evidence and compare it to established guidance on blood pressure treatment targets for patients with chronic kidney disease. We recommend a treatment target of <130/80 mmHg.

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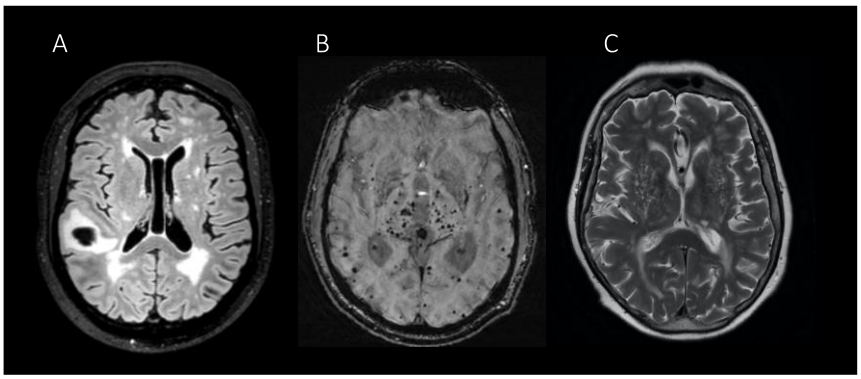
Background

Treatment of hypertension reduces the risk of ischaemic stroke and intracerebral haemorrhage (Turin et al. 2016). Cerebral small vessel disease (SVD) 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 non-traumatic intracerebral haemorrhage, it causes or contributes to nearly half of dementia cases. Clinical features also include gait dyspraxia and depression (Pantoni 2010). The most studied MRI neuroimaging features are white matter hyperintensities (WMH), lacunes of vascular origin, cerebral microbleeds (CMB) and visible peri-vascular spaces (PVS), illustrated in ***Figure 1***. There are many observational studies (Staals et al. 2014) showing a clear association of hypertension with these markers. Whether treating hypertension prevents the development of SVD or slows its progression is less well established. Mild SVD is rarely symptomatic, but as it progresses the correlation with cognitive impairment becomes much stronger (Kloppenborg et al. 2014). Therefore, it makes sense to try and stop the development or progression of SVD early. If any interventions are shown to clearly arrest or slow the progression of these abnormalities, there is potential to reduce the prevalence of dementia and mild cognitive impairment in the future, or at least slow its rate of progression.

Figure 1 Illustration of the different small vessel disease markers: A) white matter hyperintensities; B) cerebral microbleeds; C) enlarged peri-vascular spaces



Cerebral small vessel disease is very common

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

Table 1 Factors most commonly associated with SVD (Staals et al. 2014)

Variable	**OR (95% CI)**
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)

Hypertension is clearly associated with SVD

Of the modifiable risk factors in ***Table 1***, hypertension is by far the most common. Insight 46 (Lane et al. 2017) is a neuroscience sub-study 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. They underwent MRI brain aged 69-71. The investigators found a significant increase in total WMH volume and a significant decrease in whole brain volume in those participants who developed hypertension by the age of 53, as shown in ***Table 2***.

Table 2 Relative increase in WMH volume with the age of onset of hypertension (Lane et al. 2017)

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

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 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 SVD?

Previously there was a paucity of randomized control trial (RCT) evidence in this field, but recently several studies have been published. A meta-analysis of 4 RCTs found a

significantly lower white matter WMH volume in the intervention arms on follow up MRI scans (van Middelaar et al. 2018). The authors reported a pooled standardized mean difference of anti-hypertensive medication on WMH volume progression of -0.19 ml (95% confidence interval -0.32 to -.0.06). However, there was heterogeneity in both the trial 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) was a trial looking at the effects of hypertension treatment on cognition in older patients. The mean ages in each trial were 61.7 and 77 years respectively. Examining each trial individually, ACCORD-MIND was the only one to find a statistically significant difference in WMH volume progression. This trial also found a significant decrease in total brain volume (TBV) in the intensive BP-lowering arm of the trial, which is associated with poor outcomes (Hanning et al. 2016). In contrast SCOPE found that the intervention arm had the opposite association.

A significant problem with this meta-analysis is that each RCT included in the analysis was a sub-analysis of a larger trial with a different clinical question. SPRINT-MIND (Group et al. 2019b) was a large multi-centre RCT investigating the effect of intensive blood pressure management on the subsequent development of dementia or mild cognitive impairment. A subset of the participants had baseline and follow up MRI brain scans (Group et al. 2019a). These patients (n=449) were randomised either to intensive (SBP<120) versus standard (SBP<140) blood pressure management. The investigators did indeed find a smaller progression in total WMH volume in the intensive group (between-group difference in change -0.54 cm^2 95% CI -0.87 to -0.20).

Although this difference was relatively small, it was statistically significant despite the trial being stopped early in the context of the benefits for the intensive group seen in the cardiovascular outcomes of the trial. Owing to the early termination of the trial, a significant proportion of the participants (67%) did not have their follow up MRI so the observed difference may have been larger.

Subsequent to SPRINT-MIND, two more RCTs have been published which investigated the effect of blood pressure management on WMH volume progression. In 2019 Zhang *et al* (Zhang et al. 2019) reported an investigation into the effect of telmisartan versus placebo on WMH volume progression and cognitive decline. All trial participants were also taking hydrocholorothiazide. They found no difference in WMH volume progression (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 on any difference in volume change over time.

INFINITY (White et al. 2019), also published in 2019, was an RCT investigating the effect of intensive versus standard blood pressure control into WMH volume progression, gait speed and cognitive decline. The investigators found a significant blood pressure difference between the trial arms (16.3 mmHg). They found significantly less WMH volume progression in the intensive group than the control group (0.29% versus 0.48%).

The PRESERVE randomised controlled trial has recently been published (Markus et al. 2021), and this contributes to evidence guiding our management of SVD. The primary objective of the trial was to investigate whether intensive blood pressure lowering affects quantitative MRI findings using diffusion tensor imaging. Whilst this was not demonstrated, a secondary analysis showed a (nominally) statistically significant negative corelation between achieved SBP reduction and WMH volume progression. Importantly the authors demonstrated that there was no reduction in total brain volume for the participants in the intensive treatment group, and that cerebral blood flow was not reduced in that group. This helps to allay concerns from the results of the ACCORD-MIND study, mentioned previously, which found progression in brain atrophy in the intensively treated group.

A more recent systematic review and meta-analysis into this clinical question was published in 2020 (Lai et al. 2020). The authors included all the trials discussed in this article in the data synthesis, apart from PRESERVE. Like the previous meta-analysis, they found a modest overall beneficial effect on WMH volume progression in the intervention arms of the included trials, and moderately significant heterogeneity (SMD =-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 WMH volume progression, and no heterogeneity (SMD=-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 the WMH volume progression (β=-0.028, $p<0.001$). This systematic review supports employing an intensive blood pressure treatment target when trying to prevent SVD progression.

However, the specific target remains uncertain based on these results, as the three studies used different systolic blood pressure goals: <130 systolic for INFINITY; <120 for SPINT-MIND and ACCORD-MIND. Four of the trials contributing to this meta-analysis tested the effect of a specific class of antihypertensive on WMH volume progression: angiotensin-converting-enzyme (ACE) inhibitors (perindopril with or without the thiazide diuretic indapamide) in PROGRESS; and angiotensin receptor blockers (ARBs) in PRoFESS, SCOPE and Zhang *et al*. We 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 WMH volume progression between the study arms, while some other trials of intensive blood pressure lowering did show a reduction in WMH progression, suggesting that the magnitude of BP reduction might matter more than antihypertensive drug class. However, further data testing the effects of intensive treatment based on using specific drug classes (e.g. calcium channel blockers) are needed to resolve this question.

Table 3. Summary of available evidence from randomised controlled trials with neuroimaging and/or clinical endpoints.

Trial	Study design	Study population	Methods	N	Significant results
ACCORD-MIND (Williamson et al. 2014)	RCT	Diabetic patients	Randomised to target BP <120 or <140 Any medication Primary outcome measure was cognitive function at 40 months	314	Mean SBP reduction of 19.7 mmHg Significantly lower progression of WMH 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)	RCT	Individuals with recent ischaemic stroke	Telmisartan vs placebo Addition to BP treatment Primary outcome measure was recurrent stroke	771	Mean SBP reduction of 11.1 mmHg No significant difference in WMH volume progression in the intervention group No significant difference in the primary outcome measure
PROGRESS (Dufouil et al. 2005)	RCT	History of TIA, IS or ICH	Perindopril +/- indapamide vs placebo Addition to BP treatment Primary outcome measure was any stroke	192	Mean SBP reduction of 12.5 mmHg No significant difference in WMH volume progression in the intervention group Significantly fewer recurrent strokes in the intervention group, 307 vs. 420 (RR reduction 28%, 95% CI 17-38%, p<0.0001)
SCOPE (Firbank et al. 2007)	RCT	Patients aged 70 – 89	Randomised to candesartan or placebo	92	Mean SBP reduction of 26 mmHg No significant difference in WMH volume or atrophy progression in the intervention group

			Primary outcome was WMH volume progression		
Klijn *et al* (van Middelaar et al. 2018)	Meta-analysis	4 above RCTs	As above – primary endpoint was WMH progression	1369	Significant effect of anhihypertensive medication on WMH volume progression Pooled standardised mean difference of -0.19 (95% CI -0.32 to -0.06)
SPRINT – MIND (Group et al. 2019a)	RCT	Adults > 50 yrs with hypertension and increased cardiovascular risk	Randomised to SBP treatment target of <120 or <140 Primary outcome was incidence of probable dementia	449	Small but statistically significant difference in progression of WMH volume in the intensive group Between-group difference in change -0.54 cm^2 (95% CI -0.87 to -0.20) No significant difference in the primary outcome measure
PRESERVE (Markus et al. 2021)	RCT	Adults > 40 years with lacunar stroke and hypertension	Randomised to standard SBP target of <140 or intensive target of <125 Primary outcome was change in diffusion tensor imaging metrics: mean diffusivity and fractional anisotropy	90	No significant difference in WMH volume progression over 2 years follow up In secondary analysis a significant negative correlation found between magnitude of SBP reduction and WMH volume progression, showing that a greater achieved BP reduction led to less WMH volume progression No difference in the primary outcome measures
INFINITY (White et al. 2019)	RCT	Adults >75 years with no history of stroke or cognitive impairment	Randomised to standard SBP of <145 or intensive target of <130	199	Significant difference in WMH volume progression over 3 years of follow up, 0.19% WMH volume difference, p=0.03

			Primary clinical outcome was change in gait speed		Greater difference found in the per protocol population (n=52, 0.35% WMH volume difference, p=0.003) No significant difference in the primary outcome measure
Zhang-2019 (Zhang et al. 2019)	RCT	Adults >60 years with no history of stroke or cognitive impairment	1:1:1:1 randomisation to telmisartan, rosuvastatin, both or none (factorial design). Primary clinic outcome was the development of cognitive impairment	732	No significant difference in WMH progression between telmisartan and placebo arms However, they did not achieve a significant difference in BP between the arms They found a marginally and statistically significant lower incidence of cognitive impairment in the rosuvastatin group
Lai-2020 (Lai et al. 2020)	Meta-analysis	7 RCTs (all except PRESERVE)	As in each trial; primary outcome was WMH progression. Note moderately significant heterogeneity (I^2=63%)	2693	Small but significant difference in WMH volume progression SMD -0.22 (95% CI -0.35 to -0.09) When pooling results of trials with intensive BP targets only, a more significant difference was found; SMD -0.37 (95% CI -0.50 to -0.24) This is supported by meta-regression which found a significant association of the achieved difference in BP and the SMD (β=-0.028, p<0.001)

RCT randomised controlled trial, *SBP* systolic blood pressure, *WMH* white matter hyperintensities, *RR* relative risk, *SMD* standardised mean difference

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. 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 (HR 0.83, 95% CI 0.67-1.04). The secondary cognitive outcomes included adjudicated mild cognitive impairment (MCI) and a composite outcome of MCI and probable dementia. Both of these secondary outcomes 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 (HR 0.81, 95% 0.69-0.95). These findings are potentially important since MCI is a risk factor for the development of dementia and can itself 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* (Zhang et al. 2019), which found no difference between telmisartan and placebo. However, as mentioned previously, the BP difference achieved was not statistically significant (138/67 for telmisartan and 144/68 for placebo at final follow-up, p=0.612 for the difference in systolic BP), which may partly explain these results.

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Some of the trials investigated non-cognitive clinical outcomes. The PROGRESS investigators found significantly fewer strokes in the intervention arm of the trial (Dufouilet al. 2005), 307 vs. 420 (RR reduction 28%, 95% CI 17-38%, p<0.0001). 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 BP treatment targets. There was no difference between the groups.

A meta-analysis (Peters et al. 2019) of randomised controlled trials which achieved a difference in systolic BP of 10 mmHg or more between the treatment arms did show 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 that further dedicated work to assess the impact of hypertension treatment on dementia is required.

Hypertension treatment in chronic kidney disease

The vascular beds of the brain and kidneys are structurally and physiologically very similar. They are both 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 3***), 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 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). In particular arteriolosclerosis, as shown in ***Figure 4*** (and, in severe cases, fibrinoid necrosis), is thought to be implicated in the pathogenesis of lacunar stroke and intracerebral haemorrhage.

Figure 3 Hyaline arteriolosclerosis (blue arrows) of renal interlobular artery vessel walls caused by hypertension (Bonert 2011)

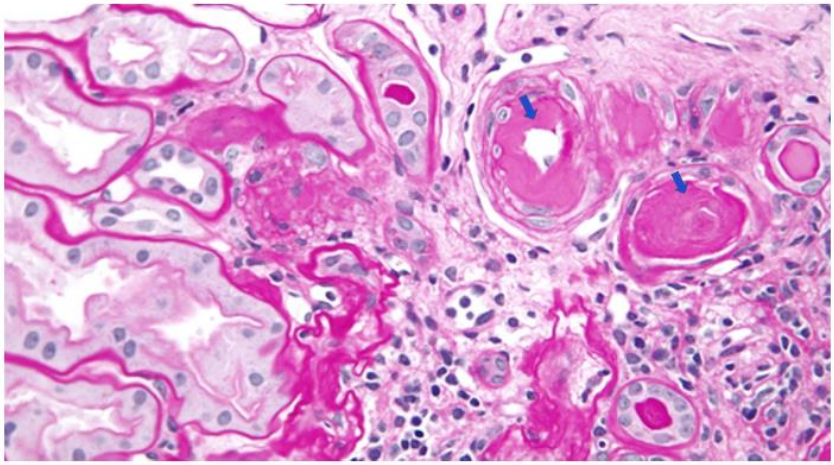
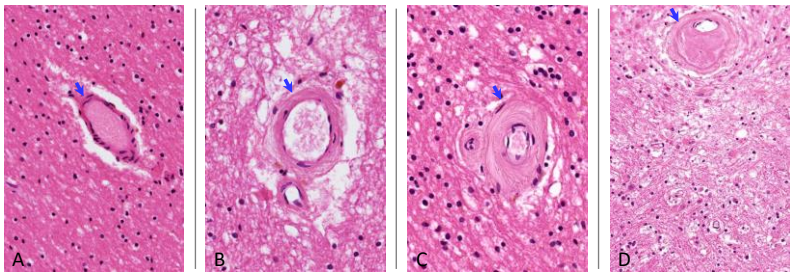


Figure 4. Hyaline arteriosclerosis of varying severity in the subcortical cerebral white matter(Rosenblum 2008)



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

For many years it has been the standard practice of nephrologists to rigorously manage high blood pressure to prevent the progression of Chronic Kidney Disease (CKD), particularly proteinuric CKD, defined as a twenty-four hour urinary protein quantification of >1 gram. This definition is equivalent to a spot urine protein creatinine ratio (UPCR) of >100 mg/g. This common practice became international guidance when KDIGO published their recommendations on hypertension in CKD in 2012, recommending a target BP of <130/80 for patients with proteinuric CKD (KDIGO 2012). This target was also adopted by NICE in 2014 (NICE 2014).

The evidence underpinning these recommendations was derived from a number of small RCTs, a meta-analysis, post-hoc analyses of RCTs and some observational data. Among the most compelling was a meta-analysis of 11 RCTs examining outcomes in intensive versus standard blood pressure management in patients with 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 or initiation of dialysis in trial participants with systolic blood pressure (SBP) in the range 130-139 compared to those with SBP in the range 110-119.

There is good RCT evidence that intensive BP management can cause proteinuria to regress. The AASK trial (Wright et al. 2002) randomised 1094 participants to a target mean arterial pressure (Sturt, #165) of either 107 (standard) or 92 (intensive). The mean blood pressures in the two groups were 141/85 and 128/78 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 CKD so these data add support to current practice.

Since SPRINT was published a comprehensive review of optimal BP targets for patients with CKD was undertaken by NICE in 2021 (NICE 2021). This was a large piece of work the results of which are beyond the scope of this review. In summary they did not find sufficient evidence to change the existing guidance mentioned already (target 130/80 mmHg) (NICE 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

Whilst the results of SPRINT were impressive for cardiovascular outcomes, all-cause mortality and prevention of SVD progression, differences between the trial methods of measuring blood pressure and standard clinical practice have meant that the evidence for a BP treatment target of <120 systolic has not been widely followed. Measurement of blood pressure in the SPRINT trial was standardised. The trial participants were seated alone in a room and after 5 minutes of quiet rest three automated blood pressure readings were taken, leading some commentators 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 NICE hypertension guidance (NICE 2019) have taken this viewpoint, as have the authors of the joint European Society of Cardiology / European Society of Hypertension guidelines (ESC/ESH 2019). In addition, the intensive treatment arm of SPRINT had a higher rate of adverse events, mostly attributable to hypotension. Renal function also declined more quickly in the intensive treatment group. Interestingly, despite these adverse renal outcomes, KDIGO is one of the few advisory bodies to adopt its findings, recommending the intensive target (120/70 mmHg) assuming that blood pressure measurement is standardised (as in the trial) (KDIGO 2021). This is based on the benefits in terms of cardiovascular and all-cause death.

A meta-analysis published in 2017 included 17 RCTs and data from over 55,000 participants (Bangalore et al. 2017). The results were grouped into 5 systolic BP treatment targets: <160, <150, <140, <130 and <120 mmHg. 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, treatment targets <120 and <130 showed the lowest risk. There was a significant increase in serious adverse events for the <120 group when compared to both the <150 and <140 groups. The authors designed cluster plots for combined efficacy and safety and suggested that the systolic BP target of <130 provided optimal balance for net benefit.

In agreement with this meta-analysis and the other RCT data summarized, we support a target BP of <130/80 for hypertensive patients with SVD. This is likely to help prevent the development of progressive SVD and CKD, and reduce the risk of dementia, cardiovascular death, and all-cause death. It may be that for selected highly motivated patients who regularly monitor their BP at home and titrate their medications accordingly, the more ambitious target proposed by the SPRINT investigators can be followed.

Conclusion

The available evidence from randomised controlled trials suggests that treatment of hypertension is likely to help to prevent cerebral SVD progression, particularly when treating to an intensive target BP. 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 SVD, for example people with previous stroke due to SVD-associated ischaemia or haemorrhage or with neuroimaging evidence of SVD. 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 (e.g. calcium channel blockers) might provide maximal benefit. Although SPRINT-MIND had a reasonably long median follow-up period of 5.1 years, the other RCTs had much shorter follow up periods. Given the slow rate of progression of SVD over years, more long-term studies are therefore needed. Longer periods of untreated hypertension in early mid-life result in more severe WMH years later, likely because of altered cerebral autoregulation. Therefore, earlier initiation of hypertension treatment should prevent WMH progression, 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 SVD. Promising options include multidomain strategies (Meng, 2022) (e.g. modification of lifestyle, diet, exercise (Bolandzadeh, 2015), cognitive training, overall vascular care) and treatments targeting endothelial function (Wardlaw, 2020 #540).

So, the answer to the question posed in our title as 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 don't need to look for improved treatments".

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