Question 38 evidence tables

# Question 38: What is the best blood pressure treatment target for vascular prevention after stroke?

*NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting*

BP = blood pressure, SBP = systolic blood pressure, CVD = cardiovascular disease, CV = cardiovascular, MI = myocardial infarction, SAE = severe adverse events, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
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| 619 | K. Kitagawa et al (2022). Intensive or standard blood pressure control in patients with a history of ischemic stroke: RESPECT post hoc analysis. Hypertension research : official journal of the Japanese Society of Hypertension. 45: 4. 591-601. | Post hoc analysis of the RESPECT trial- standard BP (140/90) v intensive (120/80). This analysis included patients with prior cerebral infarction only. | BP lowering standard (140/90) vs intensive (120/80) | Recurrent stroke | After 3.9 years, 78 recurrent strokes occurred.<br><br>Intensive BP lowering trended to reduce overall annual stroke recurrence (1.74% in intensive vs. 2.17% in standard; p = 0.351) and did not change the risk of ischaemic stroke (1.74% vs. 1.75%, p = 0.999) but markedly reduced the risk of haemorrhagic stroke (0.00% vs. 0.39%, P = 0.005) | ++ |
| 619 | K. Kitagawa et al (2022). Intensive or standard blood pressure control in patients with a history of ischemic | Post hoc analysis of trial standard (140/90) v intensive (120/80). This analysis on patients with prior cerebral infarction only. | BP lowering standard (140/90) v intensive (120/80). | Recurrent stroke. | At 3.9 years mean follow up, 78 recurrent strokes occurred.<br><br>Intensive treatment tended to reduce overall annual stroke recurrence (1.74% in intensive vs. 2.17% in standard; P = | +<br><br>Post hoc analysis of randomised data |

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| | stroke: RESPECT post hoc analysis. Hypertension research : official journal of the Japanese Society of Hypertension. 45: 4. 591-601. | | | | 0.351 by log-rank test) and did not change the risk of ischaemic stroke (1.74% vs. 1.75%, P = 0.999) but markedly reduced the risk of haemorrhagic stroke (0.00% vs. 0.39%, P = 0.005). | |
| 620 | H. S. Markus et al (2021). PRESERVE: Randomized Trial of Intensive Versus Standard Blood Pressure Control in Small Vessel Disease. Stroke. 2484-2493. | RCT- parallel group, multicentre, blinded-outcomes. One hundred eleven participants with magnetic resonance imaging confirmed symptomatic lacunar infarct and confluent white matter hyperintensities randomised to standard (systolic=130–140 mmHg) (N=56) or intensive (systolic<125 mmHg) (N=55) BP target | SBP lowering 130–140 mmHg (n=56) vs intensive SBP target, i.e. <125 mmHg (N=55) | Diffusion tensor imaging white matter mean diffusivity peak height between baseline and 24 months. | No difference between treatment groups for the primary end point: standard, adjusted mean (SE)=12.5×10−3 (0.2×10−3); intensive, 12.5×10−3 (0.2×10−3), P=0.92. In the whole population over 24 months follow-up, there was a significant deterioration in white matter microstructure but no detectable decrease in cognition. | ++ |
| 620 | H. S. Markus et al (2021). PRESERVE: Randomized Trial of Intensive Versus Standard Blood Pressure Control in Small Vessel Disease. Stroke. 2484-2493. | Randomized, parallel, multicenter controlled, blinded-outcomes clinical trial. One hundred eleven participants with magnetic resonance imaging confirmed symptomatic lacunar infarct and confluent white matter hyperintensities and were recruited and randomized to standard (systolic=130–140 mmHg) (N=56) or intensive (systolic<125 mmHg) (N=55) blood pressure targets. | BP lowering (systolic=130–140 mmHg) (N=56) or intensive (systolic<125 mmHg) (N=55) blood pressure targets. | The primary end point was change in diffusion tensor imaging white matter mean diffusivity peak height between baseline and 24 months. | There was no difference between treatment groups for the primary end point: standard, adjusted mean (SE)=12.5×10−3 (0.2×10−3); intensive, 12.5×10−3 (0.2×10−3), P=0.92. In the whole population over 24 months follow-up, there was a significant deterioration in white matter microstructure but no detectable decrease in cognition. | ++ |

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| 621 | A.Adler et al (2021). Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis | 50 410 (35·8%) of 157728 had prior stroke.<br>IPDMA of BP lowering trials – drug v placebo.<br>Prior CVD vs no CVD | Pharmacological BP lowering | Primary: major cardiovascular event (defined as a composite of fatal and non-fatal stroke, fatal or non-fatal MI or IHD, or heart failure causing death or requiring admission to hospital), analysed as per intention to treat. | 0·89, 0·86–0·92, for those with previous cardiovascular disease with pharmacological BP lowering vs placebo. | ++ |
| 621 | A.Adler et al (2021). Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis | 50 410 (35·8%) of 157728 had prior stroke.<br>IPDMA of BP lowering trials – drug v placebo.<br>Prior CVD vs non. CVD | Pharmacological BP lowering. | The primary outcome was a major cardiovascular event (defined as a composite of fatal and non-fatal stroke, fatal or non-fatal myocardial infarction or ischaemic heart disease, or heart failure causing death or requiring admission to hospital), analysed as per intention to treat. | 0·89, 0·86–0·92, for those with previous cardiovascular disease with pharmacological BP lowering v placebo. | ++ |
| 622 | M. Bohm et al (2017). Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials.<br>The Lancet.<br>389.<br>2226-2237. | High-risk patients aged 55 years or older with a history of cardiovascular disease, 70% of whom had hypertension, from the ONTARGET and TRANSCEND trials investigating ramipril, telmisartan, and their combination, with a median follow-up of 56 months | Intensive versus guideline BP lowering | All cause and CV mortality | Baseline systolic<br>SBP 140 mm Hg or higher was associated with greater incidence of all outcomes compared with<br>120 mm Hg to less than 140 mm Hg.<br>In 4052 patients with SBP less than 120 mm Hg on treatment, the risk of the composite cardiovascular outcome<br>(Adjusted hazard ratio [HR] 1·14, 95% CI 1·03–1·26), | ++ |

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| | | | | | cardiovascular death (1·29, 1·12–1·49), and all deaths (1·28, 1·15–1·42) were increased compared with those in whom SBP was 120–140 mm Hg during treatment (HR 1 for all outcomes, n=16 099). No harm or benefit was observed for myocardial infarction, stroke, or hospital admission for heart failure. Mean achieved SBP more accurately predicted outcomes than baseline or time-updated SBP, and was associated with the lowest risk at approximately 130 mm Hg, and at 110–120 mm Hg risk increased for the combined outcome, cardiovascular death, and all-cause death except stroke. | |
| 622 | M. Bohm et al (2017). Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. The Lancet. 389. 2226-2237. | In this analysis, assessment of previously reported outcome data from high-risk patients aged 55 years or older with a history of cardiovascular disease, 70% of whom had hypertension, from the ONTARGET and TRANSCEND trials investigating ramipril, telmisartan, and their combination, with a median follow-up of 56 months. | BP lowering (intensive v guideline) | All cause and CV mortality | Baseline systolic blood pressure (SBP) 140 mm Hg or higher was associated with greater incidence of all outcomes compared with 120 mm Hg to less than 140 mm Hg. In 4052 patients with SBP less than 120 mm Hg on treatment, the risk of the composite cardiovascular outcome (adjusted hazard ratio [HR] 1·14, 95% CI 1·03–1·26), cardiovascular death (1·29, 1·12–1·49), and all | + |

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|---|---|---|---|---|---|---|
| | | | | | deaths (1·28, 1·15–1·42) were increased compared with those in whom SBP was 120–140 mm Hg during treatment (HR 1 for all outcomes, n=16 099). No harm or benefit was observed for myocardial infarction, stroke, or hospital admission for heart failure. Mean achieved SBP more accurately predicted outcomes than baseline or time-updated SBP, and was associated with the lowest risk at approximately 130 mm Hg, and at 110–120 mm Hg risk increased for the combined outcome, cardiovascular death, and all-cause death except stroke. | |
| 623 | X. Xie et al (2016). Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis. The Lancet. 387. 435-443. | SRMA<br>19 RCTs; 44 989 patients with mean 3.8 years of follow-up (range 1.0–8.4 years). Included trials that had patients with previous stroke and no previous stroke. | Intensive versus less intensive BP lowering; different targets or BP change from Baseline. | Major cardiovascular events (myocardial infarction, stroke, heart failure, or cardiovascular death, separately and combined), and non-vascular and all-cause mortality, end-stage kidney disease, and adverse events, as well as albuminuria and progression of retinopathy in trials done in patients with diabetes | More intensive mean BP133/76 mm Hg vs less intensive mean BP 140/81 mm Hg.<br>RR reduction with intensive BP lowering for stroke was 22%, 95%CI [10–32].<br>No separate analyses for previous stroke vs no previous stroke | ++ |
| 623 | X. Xie et al (2016). Effects of intensive blood pressure | Systematic review/meta-analysis of 19 RCTs up till 3.11.2015. | More intensive versus less intensive | Major cardiovascular events (myocardial infarction, stroke, heart | More intensive mean BP133/76 mm Hg vs less intensive mean BP 140/81 mm | ++ |

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
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| | lowering on cardiovascular and renal outcomes: Updated systematic review and meta-analysis.<br>The Lancet.<br>387.<br>435-443. | 44,989 patients with mean 3.8 years of follow-up (range 1.0–8.4 years). Included trials that had patients with previous stroke and no previous stroke. | blood pressure-lowering treatment, with different blood pressure targets or different blood pressure changes from baseline. | failure, or cardiovascular death, separately and combined), and non-vascular and all-cause mortality, end-stage kidney disease, and adverse events, as well as albuminuria and progression of retinopathy in trials done in patients with diabetes | Hg. RR reductions with intensive BP lowering for stroke was 22%, 95%CI [10–32]. No separate analyses for previous stroke vs no previous stroke | High quality. However, the meta-analysis is done > 5 years ago. |
| 624 | K. Kitagawa et al (2019).<br>Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis.<br>JAMA Neurology.<br>76: 11.<br>1309-1318. | Multicentre RCT; 1,280 patients with stroke | < 140/90 < 120/80mmHg | Recurrent stroke | Non-significant reduction | ++ |
| 624 | K. Kitagawa et al (2019).<br>Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis.<br>JAMA Neurology.<br>76: 11.<br>1309-1318. | Multicentre RCT included 1280 patients in 140 centres in Japan. Included patients with previous stroke. A meta-analysis was included as well. | less than 140/90 mmHg (standard treatment) (n = 640) or to less than 120/80mmHg (intensive treatment) (n=640) | Stroke recurrences | Nonsignificant rate reductions were seen for recurrent stroke in the intensive group compared with the standard group.<br>When this finding was pooled in 3 previous relevant RCTs in a meta-analysis, the risk ratio favored intensive BP control (relative risk, 0.78; 95%CI, 0.64-0.96; P =0.02; absolute risk difference, −1.5%; 95%CI, −2.6%to −0.4%) | ++<br><br>High quality for both RCT and meta-analysis |

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| 625 | L. Li (2019). Intensive versus usual control of hypertension in the prevention of cardiovascular and renal outcomes: A cumulative meta-analysis of randomized controlled trials. Kidney and Blood Pressure Research. 44: 3. 384-395. | SRMA 20 trials, 56,687 patients. Included patients with previous stroke and no previous stroke. F/U >1 year | Intensive vs standard BP | Major cardiovascular events, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, end-stage renal disease, retinopathy, albuminuria | Intensive BP lowering reduced the risk of major cardiovascular events (RR: 0.85; 95% CI: 0.77–0.94; p = 0.001), MI (RR: 0.87; 95% CI: 0.76–1.00; p = 0.044), stroke (RR: 0.77; 95% CI: 0.66–0.89; p < 0.001), and albuminuria (RR: 0.90; 95% CI: 0.84–0.97; p = 0.007). | ++ |
| 625 | L. Li (2019). Intensive versus usual control of hypertension in the prevention of cardiovascular and renal outcomes: A cumulative meta-analysis of randomized controlled trials. Kidney and Blood Pressure Research. 44: 3. 384-395. | Systematic review/meta-analysis of 20 RCTs up till Oct 2017. 56,687 patients. Included trials that had patients with previous stroke and no previous stroke. duration of follow-up period was greater than one year. | Intensive vs standard BP control | MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, retinopathy, or albuminuria | Intensive control achieved SBP of 118 to 144 mmHg vs standard control SBP 124 to 154 mmHg. Intensive blood pressure lowering reduced the risk of major cardiovascular events (RR: 0.85; 95% CI: 0.77–0.94; p = 0.001), including myocardial infarction (RR: 0.87; 95% CI: 0.76–1.00; p = 0.044), stroke (RR: 0.77; 95% CI: 0.66–0.89; p < 0.001), and albuminuria (RR: 0.90; 95% CI: 0.84–0.97; p = 0.007). | ++ High quality. The meta-analysis however did not provide a pooled mean achieved BP or BP targets for intensive vs standard arm. |
| 626 | R. Aggarwal et al (2018). Intensive blood pressure targets for diabetic and other high-risk populations: A pooled individual patient data analysis. | Pooled individual patient data analysis; 2 RCT's 14 094 patients No patients with previous stroke | Intensive BP target < 120 mmHg vs standard SBP <140 mmHg | A composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular death. Secondary outcomes included nonfatal MI, | Intensive management significantly lowered primary outcome rate (hazard ratio, 0.83; 95% confidence interval, 0.74–0.92; P<0.001). Significantly reduced | ++ |

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| | Hypertension.<br>71: 5.<br>833-839. | | | stroke, heart failure, cardiovascular death, and overall mortality. | secondary outcomes including stroke (hazard ratio, 0.75; P=0.033. | |
| 626 | R. Aggarwal et al (2018).<br>Intensive blood pressure targets for diabetic and other high-risk populations: A pooled individual patient data analysis.<br>Hypertension.<br>71: 5.<br>833-839. | Pooled individual patient data analysis, 14,094 patients from 2 RCTs | Intensive SBP < 120 mmHg (n=7040) vs standard SBP <140 mmHg (n=7054), no patients with previous stroke | A composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, and cardiovascular mortality. Secondary outcomes included nonfatal myocardial infarction, stroke, heart failure, cardiovascular mortality, and overall mortality. | Intensive management significantly lowered primary outcome rate (hazard ratio, 0.83; 95% confidence interval, 0.74–0.92; P<0.001). Significantly reduced secondary outcomes included stroke (hazard ratio, 0.75; P=0.033) and heart failure (hazard ratio, 0.76; P=0.014). | **++**<br><br>Indirectness as the patients in this study did not have prior stroke |
| 627 | T. P. Zonneveld et al (2018).<br>Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack.<br>Cochrane Database of Systematic Reviews.<br>2018: 7.<br>CD007858. | SRMA<br>11 studies 38742 participants: 8 studies (35110 participants) compared BP lowering drugs vs placebo or no treatment; 3 studies (3632 participants) compared different systolic BP targets | BP lowering drugs vs placebo vs no treatment | Primary: Recurrent stroke<br><br>Secondary:<br>Time to recurrent stroke<br>Major vascular event<br>MI<br>Vascular death<br>Death any cause<br>Dementia<br>Ischaemic stroke<br>Haemorrhagic stroke | BP lowering reduced recurrent stroke (RR 0.81, 95%CI 0.70 to 0.93) and vascular death (RR0.85, 95%CI 0.76 to 0.95) | **+** |
| 627 | T. P. Zonneveld et al (2018).<br>Blood pressure-lowering treatment for preventing recurrent stroke, major vascular | Cochrane systematic review and meta-analysis of RCTs testing blood pressure lowering drugs started at least 48hrs after stroke or TIA | Blood pressure lowering drugs vs placebo or no treatment | Primary outcome:<br>Recurrent stroke<br><br>Secondary outcomes:<br>Time to recurrent stroke;<br>Major vascular event; | BP lowering drugs reduced recurrent stroke (RR 0.81, 95%CI 0.70 to 0.93) and vascular death (RR0.85, 95%CI 0.76 to 0.95) | **++** |

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| | events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database of Systematic Reviews. 2018: 7. CD007858. | 11 studies with 38742 participants: 8 studies (35110 participants) compared BP lowering drugs vs placebo or no treatment; 3 studies (3632 participants) compared different systolic BP targets<br><br>Not IPD | | MI;<br>Vascular death;<br>Death by any cause;<br>Dementia;<br>Ischaemic stroke;<br>Haemorrhagic stroke | Only limited data comparing different BP targets available. | |
| 628 | L. C. Saiz et al (2017). Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database of Systematic Reviews. 2017: 10. CD010315. | CDSR Six RCTs including 9795 participants.<br>Five RCTs with IPD; n=6775 participants | Lower target (<=135/85) vs standard target (<=140-160/90-100) | Primary:<br>1. Total mortality<br>2. Total SAEs<br>3. Total cardiovascular events including MI, stroke, sudden death, hospitalisation or death from CCF and other significant vascular events<br>4. Cardiovascular mortality<br><br>Secondary:<br>1. Participant withdrawals due to adverse effects.<br>2. Systolic blood pressure and the difference from baseline at one year, or both.<br>3. Diastolic blood pressure and the difference from baseline at one year, or both.<br>4. Proportion of participants reaching the target blood pressure level. | No reduction in mortality of cardiovascular death<br>Reduction in fatal and non-fatal CV events with lower BP target: RR 0.87, 95%CI 0.78-0.98 | ++ |

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| | | | | 5. Number of antihypertensive drugs that each participant needed at the end of the study. | | |
| 628 | L. C. Saiz et al (2017). Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database of Systematic Reviews. 2017: 10. CD010315. | Cochrane systematic review and meta-analysis of RCTs testing BP targets in adults with documented HTN or receiving treatment for HTN and a history of MI, stroke, PVD, or angina.<br><br>Six RCTs including 9795 participants. Five RCTs provided IPD (6775 participants) | Lower target (<=135/85) vs standard target (<=140-160/90-100) | Primary:<br>1. Total mortality<br>2. Total SAEs<br>3. Total cardiovascular events including MI, stroke, sudden death, hospitalisation or death from CCF and other significant vascular events<br>4. Cardiovascular mortality<br><br>Secondary:<br>1. Participant withdrawals due to adverse effects.<br>2. Systolic blood pressure and the difference from baseline at one year, or both.<br>3. Diastolic blood pressure and the difference from baseline at one year, or both.<br>4. Proportion of participants reaching the target blood pressure level.<br>5. Number of antihypertensive drugs that each participant needed at the end of the study. | No difference in mortality or CV mortality.<br>Reduction in fatal and non-fatal CV events with lower BP target: RR 0.87, 95%CI 0.78-0.98 | ++ |

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| 629 | S. Bangalore et al (2017). Optimal Systolic Blood Pressure Target After SPRINT: Insights from a Network Meta-Analysis of Randomized Trials. American Journal of Medicine. 130: 6. 707. | Network MA 17 RCTs including 55163 patients with 204103 patient-years follow-up | Grouped into different systolic BP targets: <160mmHg; <150mmHg; <140mmHg;<130mmHg;<120mmHg | Stroke, MI, death, cardiovascular death, heart failure, SAEs | Significant reduction in stroke with <120mmHg vs <160mmHg target (RR 0.54, 95%CI 0.29-1.00), and MI (RR 0.68, 95%CI 0.47-1.00) | ++ |
| 629 | S. Bangalore et al (2017). Optimal Systolic Blood Pressure Target After SPRINT: Insights from a Network Meta-Analysis of Randomized Trials. American Journal of Medicine. 130: 6. 707. | Network meta-analysis of 17 RCTs including 55163 patients with 204103 patient-years of follow-up.<br><br>Unclear how many participants with prior stroke included | Trial arms grouped into different systolic BP target categories: <160mmHg; <150mmHg; <140mmHg;<130mmHg;<120mmHg | Stroke, MI, death, cardiovascular death, heart failure, SAEs | Significant reduction in stroke with <120mmHg vs <160mmHg target (RR 0.54, 95%CI 0.29-1.00), and MI (RR 0.68, 95%CI 0.47-1.00)<br><br>No difference in death, CV death, or heart failure when comparing any BP targets. | ++ |
| 630 | A. H. Katsanos et al (2017). Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. Hypertension (Dallas, Tex. : 1979). | Systematic review and meta-regression on the association of BP reduction with recurrent stroke and cardiovascular events from RCTs of secondary stroke prevention.<br><br>14 studies including 42.736 patients | 11 placebo-controlled trials; 2 intensity trials (<130 systolic vs 130-149); 1 RCT of eprosartan vs nitrendipine | Recurrent stroke, ischaemic strokes, haemorrhagic stroke, fatal or disabling stroke, myocardial infarction, death from any cause, and cardiovascular death | In meta-analyses, antihypertensive treatment lowered the risk for recurrent stroke (RR 0.73; 95% CI 0.62–0.87), disabling or fatal stroke (RR 0.71; 95% CI 0.59–0.85), and cardiovascular death (RR 0.85, 95% CI 0.75–0.96.<br><br>In meta-regression, systolic BP lowering was linearly related to lower risk of recurrent | ++ |

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| | 69: 1.<br>171-179. | | | | stroke (P =0.049), MI (P =0.024), death from any cause (P =0.001), and cardiovascular death (P <0.001). Similarly, diastolic BP reduction was linearly related to a lower risk of recurrent stroke (P =0.026) and all-cause mortality (P =0.009). | |
| 630 | A. H. Katsanos et al (2017).<br>Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials.<br>Hypertension (Dallas, Tex. : 1979).<br>69: 1.<br>171-179. | Systematic review and meta-regression on the association of BP reduction with recurrent stroke and cardiovascular events from RCTs of secondary stroke prevention.<br><br>14 RCTs involving 42736 patients. | 11 placebo-controlled trials; 2 intensity trials (<130 systolic vs 130-149); 1 RCT comparing eprosartan vs nitrendipine | Recurrent strokes, ischaemic strokes (defined as neurological deficits persisting for >24 hours confirmed by imaging), haemorrhagic strokes, fatal or disabling strokes, myocardial infarction, death from any cause, and cardiovascular death | In pairwise meta-analyses, antihypertensive treatment lowered the risk for recurrent stroke (RR 0.73; 95% CI 0.62–0.87), disabling or fatal stroke (RR 0.71; 95% CI 0.59–0.85), and cardiovascular death (RR 0.85, 95% CI 0.75–0.96.<br>In metaregression analyses, systolic BP reduction was linearly related to the lower risk of recurrent stroke (P =0.049), myocardial infarction (P =0.024), death from any cause (P =0.001), and cardiovascular death (P <0.001). Similarly, diastolic BP reduction was linearly related to a lower risk of recurrent stroke (P =0.026) and all-cause mortality (P =0.009). | ++ |
| 631 | C. Thomopoulos et al (2016).<br>Effects of blood pressure lowering on outcome incidence in | SRMA in patients with High BP | Intensive versus less intensive BP lowering | N/A | N/A | + |

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
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| | hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - Updated overview and meta-analyses of randomized trials. Journal of Hypertension. 34: 4. 613-622. | | | | | |
| 632 | M. C. Penaloza-Ramos et al (2016). Cost-effectiveness analysis of different systolic blood pressure targets for people with a history of stroke or transient ischaemic attack: Economic analysis of the PAST-BP study. European Journal of Preventive Cardiology. 23: 15. 1590-1598. | Secondary analysis of PAST-BP to determine the cost-effectiveness of systolic <130 or lower vs <140mmHg target using model based cost-utility analysis in a primary care population after stroke/TIA. | SBP < 130 vs <140 mm Hg | A Markov model with a one-year time cycle and a 30-year time horizon was used to estimate the cost per quality-adjusted life year of an intensive target versus a standard target. Individual patient level data were used from the PAST-BP trial with regard to change in blood pressure and numbers of primary care consultations over a 12-month period. Published sources were used to estimate life expectancy and risks of cardiovascular events and their associated costs and utilities. | In the base-case results, intensive blood pressure target was dominant, with the incremental lifetime costs £169 lower per patient than for the standard blood pressure target with a 0.08 quality-adjusted life year gain. This was robust to sensitivity analyses, unless intensive blood pressure lowering reduced quality of life by 2% or more. | ++ |
| 632 | M. C. Penaloza-Ramos et al (2016). | Secondary analysis of PAST-BP trial to determine the cost-effectiveness of systolic <130 or | Systolic <130 or lower vs <140mmHg | A Markov model with a one-year time cycle and a 30-year time horizon was | In the base-case results, aiming for an intensive blood | ++ |

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| | Cost-effectiveness analysis of different systolic blood pressure targets for people with a history of stroke or transient ischaemic attack: Economic analysis of the PAST-BP study.<br>European Journal of Preventive Cardiology.<br>23: 15.<br>1590-1598. | lower vs <140mmHg target using model based cost-utility analysis in a primary care population after stroke/TIA. | | used to estimate the cost per<br>quality-adjusted life year of an intensive target versus a standard target. Individual patient level data were used from the PAST-BP trial with regard to change in blood pressure and numbers of primary care consultations over a 12-month<br>period. Published sources were used to estimate life expectancy and risks of cardiovascular events and their associated<br>costs and utilities. | pressure target was dominant, with the incremental<br>lifetime costs being £169 lower per patient than for the standard blood pressure target with a 0.08 quality-adjusted life<br>year gain. This was robust to sensitivity analyses, unless intensive blood pressure lowering reduced quality of life by 2% or<br>more. | |
| 633 | M. C. Odden et al (2016).<br>Achieved Blood Pressure and Outcomes in the Secondary Prevention of Small Subcortical Strokes Trial.<br>Hypertension.<br>67: 1.<br>63-69. | Post-hoc analysis of Secondary Prevention of Small Subcortical Strokes Trial; 2747 participants<br>Assessed achieved BP | Higher (130–149 mm Hg) vs lower (<130 mm Hg) systolic BP target in lacunar infarcts<br><br>This post hoc analysis compared high achieved SBP ≥124 mmHg vs low achieved SBP <124 mmHg | Primary: All recurrent stroke<br>Secondary: major cardiovascular events | Lowest risk of recurrent stroke was ~124/67 mm Hg.<br>The lowest risk of all events occurred at a nadir of systolic ≈120 to 128 mm Hg systolic BP and 65 to 70 mm Hg diastolic BP | ++ |
| 633 | M. C. Odden et al (2016).<br>Achieved Blood Pressure and Outcomes in the Secondary Prevention of Small Subcortical Strokes Trial. | SPS3 RCT, 2747 patients with recent lacunar infarcts.<br>mean follow up of 3.7 years.<br>This is a post-hoc analysis of SPS3 looking at achieved SBP rather than assigned SBP target | Higher (130–149 mm Hg) versus<br>lower (<130 mm Hg) systolic blood pressure targets in participants with recent lacunar infarcts. | Primary: All recurrent stroke. Secondary outcome: major CV events | There was a J-shaped association between achieved blood pressure and outcomes: the lowest risk was at ≈124 and 67 mm Hg systolic and diastolic blood pressure,<br>The lowest risk of all events occurred at a nadir of | ++<br>Indirectness as this is post hoc analysis, looking at achieved BP. |

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|---|---|---|---|---|---|---|
| | Hypertension.<br>67: 1.<br>63-69. | | This post hoc analysis compared high achieved SBP ≥124 mmHg vs low achieved SBP <124 mmHg | | ≈120 to 128 mm Hg systolic blood pressure and 65 to 70 mm Hg diastolic blood pressure. | |
| 634 | C. L. White et al (2015).<br>Can blood pressure be lowered safely in older adults with lacunar stroke? the secondary prevention of small subcortical strokes study experience.<br>Journal of the American Geriatrics Society.<br>63: 4.<br>722-729. | Cohort study from the Secondary Prevention of Small Subcortical Strokes (SPS3) Trial, which compared the efficacy of two systolic blood pressure (SBP) targets (<130 mmHg and 130–149 mmHg) for secondary stroke prevention. | Efficacy of two systolic blood pressure (SBP) targets (<130 mmHg and 130–149 mmHg) for secondary stroke prevention. | Recurrent stroke | Lower SBP target was associated with a significant reduction in vascular death in older participants (HR = 0.42, 95% CI = 0.18–0.98) | +<br><br>(non-randomised study) |
| 634 | C. L. White et al (2015).<br>Can blood pressure be lowered safely in older adults with lacunar stroke? The secondary prevention of small subcortical strokes study experience.<br>Journal of the American Geriatrics Society.<br>63: 4.<br>722-729. | Cohort study. The Secondary Prevention of Small Subcortical Strokes (SPS3) Trial, which compared the efficacy of two systolic blood pressure (SBP) targets (<130 mmHg and 130–149 mmHg) for secondary stroke prevention. | BP lowering | Recurrent stroke after initial lacunar event. | Lower SBP target was not associated with lower likelihood of recurrent stroke | +<br><br>Non randomised cohort study |
| 635 | P. M. Okin et al (2015). Systolic Blood Pressure Control and Mortality | Post-hoc analysis of the Losartan Intervention For Endpoint | Losartan vs Atenolol groups | All cause death<br>Cardiovascular death | During 2.02±1.65 years mean follow-up after incident stroke, 170 patients (31.4%) | +<br><br>Post-hoc analysis |

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
|---|---|---|---|---|---|---|
| | After Stroke in Hypertensive Patients. Stroke; a journal of cerebral circulation. 46: 8. 2113-2118. | reduction (LIFE) study to assess the relationship of average on-treatment SBP after incident stroke to subsequent all cause and cardiovascular mortality in hypertensive patients with LVH on ECG, and determine whether lower achieved average SBP (<144mm Hg) and higher achieved SBP (>157 mm Hg) are associated with higher short-term mortality compared with an average SBP between 144 and 157 mm Hg after adjusting for other predictors of mortality Losartan vs Atenolol in 9193 patients overall. 541 had incident stroke during follow-up. | | | died, 135 (25.0%) from cardiovascular causes. In multivariate Cox analyses, adjusting for significant univariate predictors of mortality, compared with average SBP between 144 and 157, an average SBP<144 was a significant predictor of all-cause (HR 1.81; 95% CI 1.20–2.73) and cardiovascular mortality (HR 1.60; 95% CI 1.02–2.54). | Selection bias and observational data with the context of a RCT. |
| 635 | P. M. Okin et al (2015). Systolic Blood Pressure Control and Mortality After Stroke in Hypertensive Patients. Stroke; a journal of cerebral circulation. 46: 8. 2113-2118. | Post-hoc analysis of the Losartan Intervention For Endpoint reduction (LIFE) study to assess the relationship of average on-treatment SBP after incident stroke to subsequent all cause and cardiovascular mortality in hypertensive patients with LVH on ECG, and determine whether lower achieved average SBP (<144mm Hg) and higher achieved SBP (>157 mm Hg) are associated with higher short-term mortality compared with an average SBP between 144 and 157 mm Hg after adjusting for other predictors of mortality in this population. | Losartan vs Atenolol Randomised groups pooled for this analysis | All-cause mortality; Cardiovascular mortality | During 2.02±1.65 years mean follow-up after incident stroke, 170 patients (31.4%) died, 135 (25.0%) from cardiovascular causes. In multivariate Cox analyses, adjusting for significant univariate predictors of mortality, compared with average SBP between 144 and 157, an average SBP<144 was a significant predictor of all-cause (HR 1.81; 95% CI 1.20–2.73) and cardiovascular mortality (HR 1.60; 95% CI 1.02–2.54). | **+**<br><br>Post-hoc analysis – unclear if pre-specified. Selection bias and observational data with the context of a RCT. |

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
|---|---|---|---|---|---|---|
| | | Losartan vs Atenolol in 9193 patients overall. 541 had incident stroke during follow-up. | | | | |

**Table 1. Trials of blood pressure lowering for prevention of stroke**

| Characteristic | Participants (N) | Mean age (years) | Follow-up (years) | Primary outcome | Intensive treatment | | Strokes (n/N) | Standard treatment | | Strokes (n/N) | Results as Relative Risk/Hazard ratio (95% CI)as reported for stroke* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Target BP (mm Hg) | Achieved BP (mm Hg) | | Target BP (mm Hg) | Achieved BP (mm Hg) | | |
| ***Trials which included stroke patients*** | | | | | | | | | | | |
| SPS3, 2013 | 3020 | 62 | 3.7 | Stroke | <130 | 12/7 | 118/1501 | 130-149 | 138 | 147/1519 | 0.81 (0.64-1.02) |
| RESPECT, 2019 | 1263 | 67 | 3.9 | Stroke | <120/80 | 127/77 | 39/633 | <140/90 | 133/78 | 52/630 | 0.75 (0.50-1.11) |
| PAST-BP, 2016 | 83 | 72 | 1.0 | BP | <130 | 127/72 | 0/266 | <140 | 129/74 | 3/263 | 0.14 (0.01-2.72) |
| PODCAST, 2017 | 83 | 74 | 2/0 | Cognition | <125 | 130/73 | 1/41 | <140 | 140/77 | 3/42 | 0.34 (0.04-3.15) |
| ***Trials which did not include stroke patients*** | | | | | | | 165 | | | 210 | 0.78(0.64-0.96) |
| PROGRESS, 2001 | 6105 | 64 | 4.0 | Total stroke, fatal or non-fatal stroke | 8-9/4-5 | 12/5* | 307/3051 | * | * | 420/3054 | 42% reduction in recurrent stroke and 35% coronary events |
| ACCORD, 2010 | 4733 | 62 | 4.7 | Non-fatal MI, non-fatal stroke, cardiovascular death | <120 | 119/64 | 36/2363 | <140 | 133/71 | 62/2371 | 0.59 (0.39-0.89) in favour of SBP<120 mm Hg; Total stroke (p=0.01) and non-fatal stroke (p=0.03) reduced |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | in intensive group |
| SPRINT, 2015 | 9361 | 68 | 3.2 | Composite of MI, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular cause | <120 | 121/69 | | <140 | 136/76 | | Event rate: 1.65% vs 2.19% HR (0.75 (0.64-0.89) |

* reference: intensive versus standard

**Table 2. Meta-analyses of blood pressure lowering including intensive BP lowering for reducing risk of stroke and major vascular events**

| Author, year | Number of studies | Participants (N) | Follow-up (mean or median as reported) | Result/key finding |
|---|---|---|---|---|
| Ettehad et al, 2019 | 123 | 613,815 | - | 10 mm Hg SBP reduction significantly decreased stroke risk [OR 0.73(0.68-0.77)] |
| Xie et al, 2016 | 19* | 44,989 | 3.8 years | 22% risk reduction for stroke and 13% reduction in MI |
| Thomopolous et al, 2015 | 16 | 195,267 | upto 8.4 years | BP lowering (12/5 mm Hg) by any class of antihypertensives reduced stroke, heart failure and major cardiovascular events |
| Verdecchia et al, 2016 | 18** | 53,405 | 3.98 years | Intensive 'lower' BP target associated with reduction in cumulative risk of stroke [OR 0.80(0.67-0.95)] |
| Bangalore et al, 2017 | 17 | 55,163 | 3.7 years | Significant reduction in risk of stroke with lower BP target. SBP 120 mm Hg vs 160 mm Hg [(RR 0.54; 0.29-1.00)]; favoured SBP <120 mm Hg <130 mm Hg.<br>SBP<130 mm Hg found to be best balance between safety and treatment efficacy |
| Bundy et al, 2017 | 44 | 144,220 | - | Reduced risk in major cardiovascular events, stroke and death at lower levels of achieved SBP; 120-124 mm Hg better than 125-129 mm Hg |
| Bath, 2014 | 26 | 17,011 | upto 90 days | BP lowering did not reduce death or dependency by drug class, stroke type or time to treatment; treatment in those who continued**** in the immediate period had worse outcome [OR 1.06 (0.91-1.240] and disability (Barthel Index, MD -3.2, -5.8, 0.6) than those randomised to continue treatment |
| Blood pressure lowering treatment trialists collaboration, 2014 | 11 | 67,475 | 4 years | 4,167 participants (8%) had cardiovascular event during follow-up. BP reduction produced similar relative protection at all levels, but greater absolute risk reduction as baseline risk increased |

| | | | | |
|---|---|---|---|---|
| Katsanos et al, 2017 | 14 | 42,736 | upto 4 years | Antihypertensive treatment significantly reduced the risk of recurrent stroke (RR 0.73 (0.62-0.87); disabling or fatal stroke (RR 0.71 (0.59-0.85) and cardiovascular death (RR 0.85; 0.75-0.96) |
| Zonneveld et al, 2018 | 11 | 38,742 | upto 3.9 years | BP lowering reduced risk of recurrent stroke (RR 0.81; 0.70-0.93) and major vascular events 0.90 (0.78-1.04). Insufficient evidence on best target after stroke or TIA. |
| Aggarwal et al, 2018 | 2 | 14094 | | Intensive treatment significantly reduced the primary outcome (composite of MI, ACS, stroke, heart failure and cardiovascular mortality) (HR 0.83; 0.74-0.92]; stroke (HR 0.75]<br>Intensive group had increased risk of adverse outcomes (3.97% vs 1.53%) |

BP: blood pressure; MD: mean difference; MI: myocardial infarction; SBP: systolic blood pressure; OR: Odds ratio; RR: relative risk

* not including SPRINT trial; **including SPRINT trial; *** patients treatted within one week of stroke; **** two trials contributed to the continue versus stop question; treatment in one trial was for two weeks in one and one week in the other