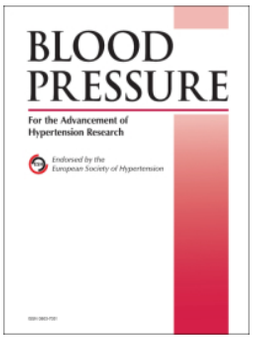

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Effect of antihypertensive treatment in isolated systolic hypertension (ISH) – systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

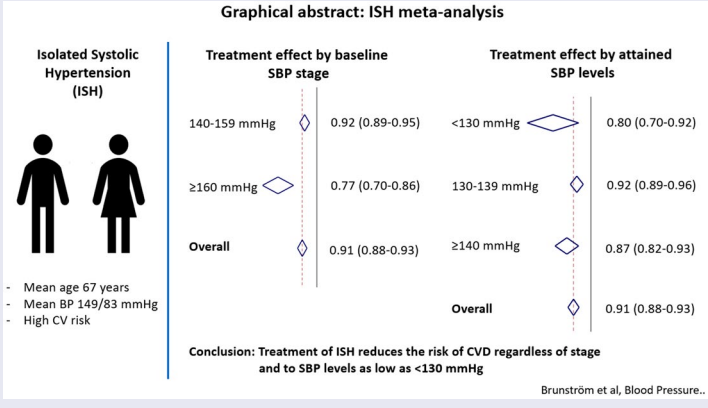
Background: Isolated systolic hypertension (ISH) in middle-aged and elderly is associated with high cardiovascular risk, but no randomised controlled trial has assessed the effect of antihypertensive treatment in ISH using today's definition, i.e. systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) <90 mmHg.

Methods: A systematic review and meta-analysis of randomised controlled trials was performed. Studies with ≥1000 patient-years of follow-up, comparing more intensive versus less intensive BP targets, or active drug versus placebo, were included if the mean baseline SBP was ≥140 mmHg and the mean baseline DBP was <90 mmHg. The primary outcome was major adverse cardiovascular events (MACE). Relative risks from each trial were pooled in random-effects meta-analyses, stratified by baseline and attained SBP level.

Results: Twenty-four trials, including 113,105 participants (mean age 67 years; mean blood pressure 149/83 mmHg) were included in the analysis. Overall, treatment reduced the risk of MACE by 9% (relative risk 0.91, 95% confidence interval 0.88–0.93). Treatment was more effective if baseline SBP was ≥160 mmHg (RR 0.77, 95% CIs 0.70–0.86) compared to 140–159 mmHg (RR 0.92, 95% CIs 0.89–0.95; $p=0.002$ for interaction), but provided equal additional benefit across all attained SBP levels (RR 0.80, 95% CIs 0.70–0.92 for <130 mmHg, RR 0.92, 95% CIs 0.89–0.96 for 130–139 mmHg, and RR 0.87, 95% CIs 0.82–0.93 for ≥140 mmHg; $p=0.070$ for interaction).

Conclusions: These findings support antihypertensive treatment of isolated systolic hypertension, regardless of baseline SBP, to target SBP <140 mmHg and even <130 mmHg if well tolerated.

GRAPHICAL ABSTRACT



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Introduction

Isolated systolic hypertension (ISH) in the most common form of hypertension in the elderly and it is an advanced form of hypertension, characterised by increased pulse pressure due to stiff arteries with reduced compliance [1–3]. The aetiology of ISH includes vascular remodelling and endothelial dysfunction and it commonly occurs in people with comorbidities affecting vascular structure and function, such as diabetes mellitus and chronic kidney disease (CKD) [1]. Although generally at an increased risk of cardiovascular events, treatment strategies for patients with ISH have been debated due to the fear of decreased coronary perfusion and myocardial oxygenation with lower diastolic pressure [3–5].

Few trials have examined the effect of antihypertensive therapy in ISH patients specifically. In the Systolic Hypertension in the Elderly Program (SHEP), 4736 participants with baseline systolic blood pressure (SBP) higher than 160 mmHg and diastolic blood pressure (DBP) lower than 90 mmHg were randomly allocated to chlorthalidone-based antihypertensive treatment or placebo [6]. This resulted in a 36% relative risk reduction for stroke and a 27% relative risk reduction for coronary events. The benefits of drug treatment in ISH were confirmed in the Systolic Hypertension in Europe (Syst-Eur) trial, in which 4695 participants with similar BP inclusion criteria were randomised to nitrendipine-based antihypertensive treatment or placebo, resulting in 42% lower risk of stroke and 33% lower risk of coronary events [7].

No randomised clinical outcome trial has assessed the effect of antihypertensive treatment in patients recruited based on today's definition of ISH, i.e. SBP ≥140 mmHg and DBP <90 mmHg [8,9]. However, many trials, which were not designed to address treatment in ISH specifically, have included large portions of participants with ISH. Thus, the available evidence for the effect of antihypertensive treatment in people with ISH goes beyond that generated from trials designed to investigate outcomes by treating ISH specifically. In the present study we aimed to assess the effect of antihypertensive drug treatment in trials with, on average, ISH at baseline, i.e. trials with a mean baseline SBP ≥140 mmHg and a mean baseline DBP <90 mmHg.

Methods

We performed a systematic review and meta-analysis, including trials with at least 1000 patient-years of follow-up, which randomly compared more intensive versus less intensive BP targets, or an antihypertensive agent or combination of antihypertensive agents against placebo, in other words trials aiming for a BP difference between treatment arms. Trials comparing one agent against another were not included because such trials generally aim to assess BP independent effects, and a small difference in BP can then untoward be associated with a major difference in cardiovascular outcomes between different antihypertensive drugs [10,11]. Furthermore, trials in patients with overt heart failure, left ventricular dysfunction or acute myocardial infarction at baseline were excluded because several antihypertensive drug classes have possible BP independent effects on clinical outcomes in these conditions [12–14].

For the current analysis, we included trials with an average baseline SBP ≥140 mmHg and an average baseline DBP <90 mmHg, i.e. trials with on average ISH at baseline. Although such a selection will include participants with other BP phenotypes as well, our assumption was that a majority of participants in such trials would have ISH, and thus our findings may be applicable to this patient group.

Trial selection was based on a previous systematic review [15], in which PubMed, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews (DARE), and Cochrane Central Register for Controlled Trials (CENTRAL) were searched in 2017, using the search terms ('blood pressure lowering' OR 'blood-pressure lowering' OR 'blood pressure-lowering' OR antihypertensive) AND (mortality OR myocardial OR stroke). We performed a complementary search in PubMed with the same search terms from the date of the previous search until 23 May 2023, resulting in 586 titles and abstracts screened, and two additional trials to be included (Figure 1) [16,17].

Risk of bias was assessed using Cochrane's risk of bias assessment tool [18]. Trials at high risk of selection bias, performance bias or detection bias were excluded from all analyses. This led to the exclusion of one potentially eligible trial, where treatment was assigned in a non-random fashion [19]. Attrition bias was assessed on study level whereas selective reporting was assessed on outcome level. We systematically collected data on early termination, baseline imbalances and protocol changes as other potential sources of bias.

Data were extracted by two reviewers independently (MB and BC) with any discrepancies resolved by discussion and re-evaluation of original publications. Participant characteristics at baseline and design features were collected on study level, whereas follow-up BP levels and outcomes were collected on treatment arm-level. The primary outcome was major adverse

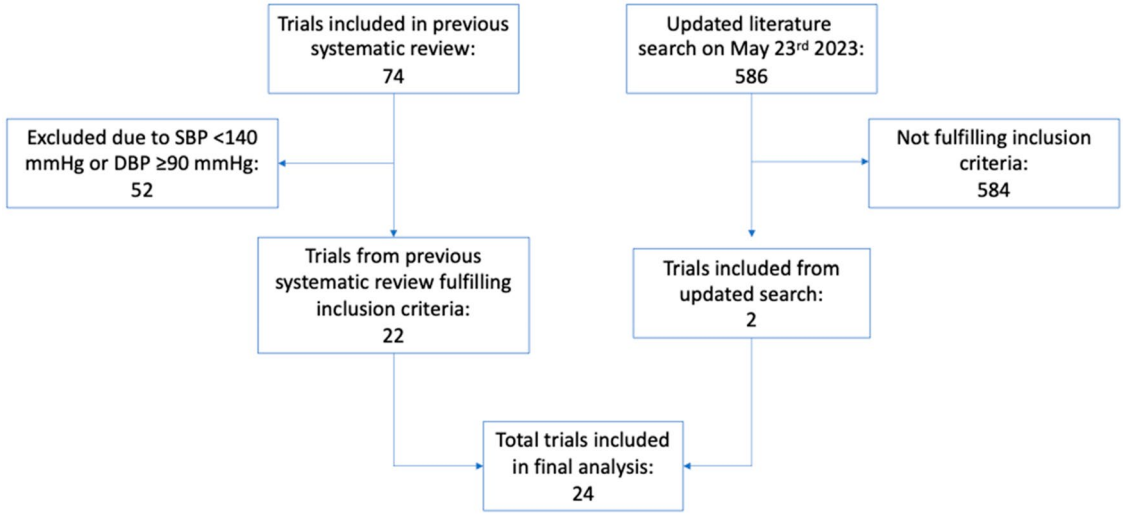

Figure 1. PRISMA flowchart. Study selection process. SBP: systolic blood pressure.

cardiovascular events (MACE), defined as a composite of stroke, myocardial infarction, heart failure and cardiovascular death. For several trials, we had to accept slightly different definitions, most often either excluding heart failure or including revascularization, as defined by trial investigators. Secondary outcomes were stroke, myocardial infarction, heart failure, and all-cause and cardiovascular mortality.

We performed random-effects meta-analyses, pooling non-standardized relative risks (RR) from included trials to generate an average effect estimate with 95% confidence intervals (95% CIs) [20]. Analyses were stratified according to baseline SBP level 140–159 mmHg versus ≥160 mmHg to explore potential differences in treatment effect between ISH stage 1 and stage 2. Additionally, analyses were stratified according to attained SBP level <130 mmHg, 130–139 mmHg and ≥140 mmHg to assess the potential effect of different guideline-defined SBP targets. Heterogeneity was assessed using the *I*-squared statistic and sources for heterogeneity explored in meta-regression analyses.

Sensitivity analyses were performed for the primary outcome MACE, using random-effects meta-regression analysis to assess the association between treatment effect and SBP measured as a continuous variable at baseline and during follow-up, respectively, and attained DBP to explore potentially detrimental effects of low DBP levels. Furthermore, we assessed the impact of type-2 diabetes and CKD on treatment effect using Cochrans Q to test for interaction, and by performing separate random-effects meta-analyses when trials in patients with type-2 diabetes and CKD were removed.

All analyses were performed using Stata/MP version 16.1 for Mac.

Results

Twenty-four trials [6,7,16,17,21–40], including 113,105 participants, fulfilled our inclusion criteria. The mean age at baseline was 67 years and 45,140 participants (40%) were women. Mean baseline blood pressure was 149/83 mmHg. Eight trials, including 21,711 participants were restricted to people with type-2 diabetes, seven trials, including 9950 participants had chronic kidney disease (CKD) as an inclusion criterion, and five trials, including 31,440 participants, were performed post stroke (Table 1).

During an average of 3.6 years follow-up, 14,228 participants experienced a MACE and 9657 participants died, reflecting a mean 10-year risk for cardiovascular events of 35%, and a 10-year mortality of 23%. The risk of bias was judged as low or unclear for most included trials and outcomes (Figure 2). However, the ADVANCE trial failed to report heart failure, and the DEMAND trial failed to report stroke and myocardial infarction, as intended, which may represent selective reporting [21,26].

Overall, treatment reduced the risk of MACE by 9% (RR 0.91, 95% CIs 0.88–0.93) across all included trials (Figure 3). When trials were stratified according to baseline SBP, the effect was significantly greater in trials with baseline SBP ≥160 mmHg (RR 0.77, 95% CIs 0.70–0.86) compared to the 140–159 mmHg range (RR 0.92, 95% CIs 0.89–0.95; $p = 0.002$ for interaction). However, when analyses were stratified based on attained SBP in the intervention arm, we found no

Table 1. Study characteristics.

Study acronym	Total pts (*n*)	Mean age (years)	Sex (% female)	Inclusion criteria	Mean baseline blood pressure (mmHg)	Intervention vs. control
ADVANCE	11,140	66	43	Type 2 diabetes, ≥55 years with CVD risk factor	145/81	Perindopril + indapamide vs. placebo
AIPRI	583	51	28	Mild to moderate renal insufficiency	143/87	Benazepril vs. placebo
BENEDICT	1204	62	47	Type 2 diabetes	150.4/87.5	Trandolapril, verapamil or both vs. placebo
BENEDICT-B	281	62	26	Type 2 diabetes with micro-albuminuria	149.5/86.3	Trandolapril + verapamil vs. trandolapril
CARDIO-SIS	1111	67	59	SBP ≥150 mmHg, ≥55 years with CVD risk factor	163.3/89.6	Target SBP <130 vs. <140 mmHg
DEMAND	380	61	35	Type 2 diabetes with or without microalbuminuria	147.5/87.1	Manidipine + delapril vs. placebo
DIABHYCAR	4912	65	30	Type 2 diabetes with micro- or macroalbumniuria	145.4/82.3	Ramipril vs placebo
IDNT	1715	59	34	Type 2 diabetes with macro-albumniuria	159/87	Irbesartan or amlodipin vs. placebo
JATOS	4418	74	61	65–85 years old with SBP ≥160 mmHg	171.6/89.1	Target SBP <140 vs 140–160 mmHg
ONTARGET	25 620	66	27	Previous CVD or type 2 diabetes with end-organ damage	141.8/82.1	Ramipril vs telmisartan vs combination of both
ORIENT	566	59	31	Type 2 diabetes with overt nephropathy	141/77.5	Olmesartan vs. placebo
PROGRESS	6105	64	30	Previous stroke or transient ischaemic attack	147/86	Perindopril +/− indapamide vs placebo
PRoFESS	20 332	66	36	Recent ischaemic stroke	144.1/83.8	Telmisartan vs. placebo
RENAAL	1513	60	37	Type 2 diabetes with overt nephropathy	152.5/82	Losartan vs. placebo
RESPECT	1263	67	31	50–85 years old with previous stroke	145.4/83.6	Target SBP <120 vs <140 mmHg
SHEP	4736	72	57	Isolated systolic hypertension ≥60 years old	170.3/76.6	Chlorthalidone +/− atenolol vs. placebo
SHEP pilot	551	72	63	Isolated systolic hypertension ≥60 years old	172/75	Chlorthalidone vs. placebo
SPS3	3020	63	37	Recent lacunar stroke	143/78.5	Target SBP <130 vs 130–150 mmHg
STEP	8511	66	53	60–80 years old with SBP 140–190 mmHg	146/82.5	Target SBP 110–130 vs 130–150 mmHg
Syst-Eur	4695	70	67	≥60 years old with SBP 160–219 and DBP <95 mmHg	173.8/85.5	Nitrendipine +/− enalapril +/− HCTZ vs placebo
TEST	720	70	40	Recent stroke or transient ischaemic attack	161/88.5	Atenolol vs placebo
TRANSCEND	5926	67	43	Previous CVD or type 2 diabetes with end-organ damage	141/81.9	Telmisartan vs. placebo
VALISH	3079	76	62	70–84 years old with isolated systolic hypertension	169.5/81.5	Target SBP <140 vs 140–150 mmHg
Wei −13	724	77	34	≥70 years old	159.5/84.2	Target SBP <140 vs <150 mmHg

CVD: cardiovascular disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HCTZ: hydrochlorothiazide.

Study acronym	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
ADVANCE						HF	
AIPRI							
BENEDICT							
BENEDICT-B							
CARDIO-SIS							
DEMAND						MI + stroke	
DIABHYCAR							
IDNT							
JATOS							
ONTARGET							
ORIENT							
PROGRESS							
PRoFESS							
RENAAL							
RESPECT							
SHEP							
SHEP pilot							
SPS3							
STEP							
Syst-Eur							
TEST							
TRANSCEND							
VALISH							
Wei -13							

Figure 2. Risk of bias assessment. Green marks low risk of bias, yellow marks unclear risk of bias, and red marks high risk of bias. The large portion of unclear risk of bias for the domain 'blinding of participants and personnel' comes from prospective randomised open-label blinded endpoint (PROBE) trials or target trials, which can never be blinded. Because we only assess objective cardiovascular outcomes, the impact of blinding in this meta-analysis is unclear. Under other sources of bias, trials are marked as unclear risk if they were stopped preterm as this may increase the risk of chance findings. HF: heart failure; MI: myocardial infarction.

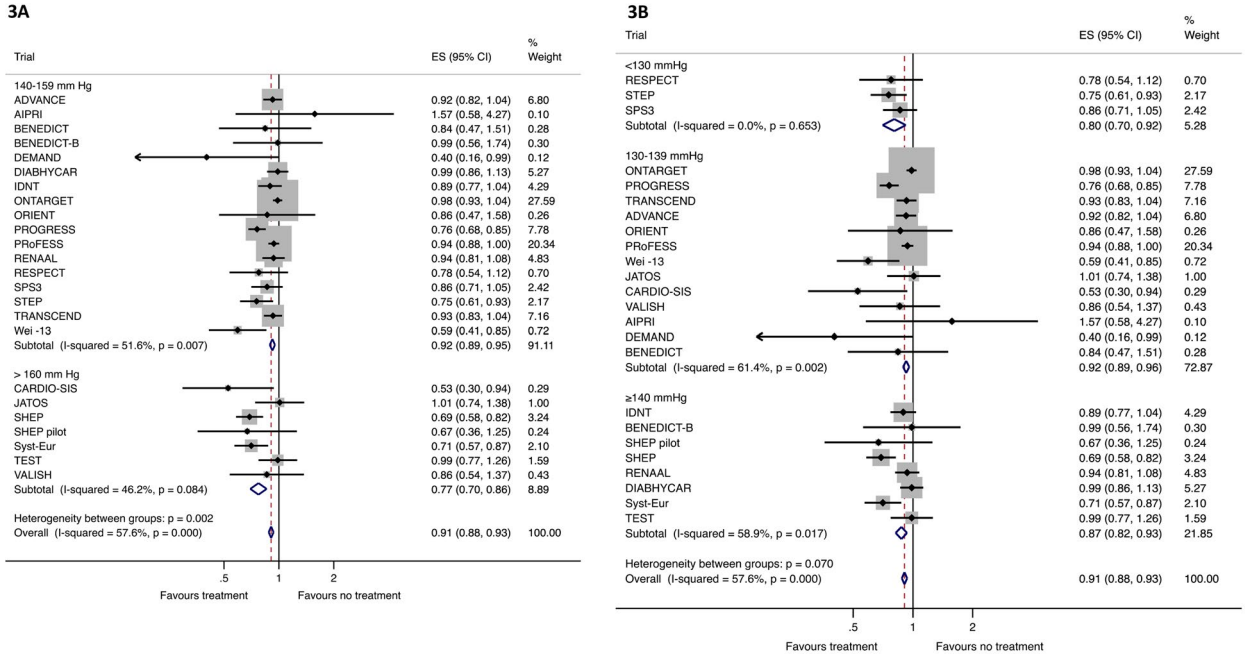

Figure 3. Effect of antihypertensive treatment on MACE. (A) Analysis of MACE based on baseline BP 140–159 mmHg (upper part) and SBP ≥160 mmHg (lower part). (B) Analysis of MACE based on achieved SBP <140 mmHg (upper part) and achieved SBP ≥140 mmHg (lower part). MACE: major adverse cardiovascular event; ES: effect size reported as relative risk; CI: confidence interval.

difference in treatment effect between trials with an average in-treatment SBP <130 mmHg (RR 0.80, 95% CIs 0.70–0.92), 130–139 mmHg (RR 0.92, 95% CIs 0.89–0.96) and ≥140 mmHg (RR 0.87, 95% CIs 0.82–0.93; $p = 0.070$ for interaction).

Among secondary outcomes, treatment reduced the risk of stroke, myocardial infarction and heart failure, with a borderline trend towards reduced risk for cardiovascular mortality, but no significant effect on all-cause mortality, in the overall analyses (Table 2).

Table 2. Effect of antihypertensive treatment on secondary outcomes.

		Relative risk (95% confidence intervals) Heterogeneity, *I*-squared						
		Baseline SBP			Attained SBP			
Endpoint	Overall	140–159	≥160	P_{int}	<130	130–139	≥140	P_{int}
Stroke	0.88 (0.84–0.92) 45%	0.89 (0.85–0.94) 33%	0.76 (0.66–0.88) 54%	0.035	0.78 (0.66–0.93) 0%	0.90 (0.85–0.95) 47%	0.82 (0.73–0.93) 53%	0.160
Myocardial infarction	0.89 (0.83–0.95) 11%	0.91 (0.85–0.97) 26%	0.75 (0.62–0.91) 0%	0.061	0.77 (0.59–1.001) 0%	0.94 (0.88–1.02) 13%	0.75 (0.65–0.86) 0%	0.009
Heart failure	0.88 (0.82–0.94) 50%	0.91 (0.85–0.97) 28%	0.58 (0.45–0.74) 11%	0.001	0.27 (0.08–0.98) *	0.92 (0.85–0.99) 0%	0.77 (0.67–0.88) 66%	0.013
All-cause mortality	0.99 (0.96–1.03) 41%	1.01 (0.97–1.05) 49%	0.89 (0.79–1.01) 0%	0.067	1.01 (0.84–1.22) 0%	1.01 (0.96–1.05) 58%	0.95 (0.88–1.03) 3%	0.409
Cardiovascular Mortality	0.95 (0.90–1.004) 43%	0.97 (0.91–1.02) 54%	0.80 (0.67–0.96) 0%	0.046	0.94 (0.70–1.25) 0%	0.96 (0.90–1.02) 61%	0.93 (0.83–1.05) 16%	0.933

SBP: systolic blood pressure; P_{int}: *p*-value for interaction assessed using Cochran's Q.
*Only one trial, heterogeneity not applicable.

As for the primary outcome, there was a significant interaction between baseline SBP and treatment effect, with more pronounced effect if baseline SBP was ≥160 mmHg for stroke, heart failure and cardiovascular mortality ($p < 0.05$), and borderline significant interactions for myocardial infarction ($p = 0.062$) and all-cause mortality ($p = 0.063$). Importantly, treatment reduced the risk of stroke, myocardial infarction and heart failure also in ISH stage 1.

In analyses stratified by attained SBP, treatment reduced the risk of stroke and heart failure across all SBP strata, with a 22% relative risk reduction for stroke if attained SBP was below 130 mmHg (RR 0.78, 95% CIs 0.66–0.93). For myocardial infarction, there was a non-significant trend towards benefit with attained SBP below 130 mmHg, virtually excluding potential harm (RR 0.77, 95% CIs 0.59-1.001). The effect on mortality outcomes was neutral across all attained SBP strata.

Overall, there was low to moderate statistical heterogeneity across primary and secondary outcome analyses (Figure 3 and Table 2). There was a significant interaction between baseline SBP as a continuous variable and treatment effect on MACE, with more pronounced effect in trials with higher baseline SBP ($p = 0.021$). Importantly, inclusion of baseline SBP as a covariate reduced statistical heterogeneity for all outcomes (from 58% to 41% for MACE), indicating that differences in treatment effect between trials could be partly explained by differences in baseline SBP level. Contrary to baseline levels, treatment was equally effective across attained SBP levels when assessed as a continuous variable ($p = 0.996$), indicating no threshold under which treatment was not beneficial within the attained SBP range studied (127–157 mmHg). Furthermore, there was no sign of harm in meta-regression analyses of treatment effect in relation to attained DBP ($p = 0.16$ for MACE; range 68 to 86 mmHg).

There was no interaction between diabetes status ($p = 0.42$) or CKD status ($p = 0.39$) and treatment effect, with a beneficial treatment effect in sensitivity analyses excluding trials in people with diabetes (RR 0.90, 95% CIs 0.87–0.93) as well as trials in people with CKD (RR 0.90, 95% CIs 0.87–0.93).

Discussion

With ISH being the most common form of hypertension in people older than 65 years, the effect of antihypertensive treatment on clinical cardiovascular outcomes in this patient group is of great interest to clinical practice. Whereas no RCT have addressed this question specifically using the current definition of ISH, this analysis summarises the findings from 24 trials, including more than 100,000 participants, with baseline ISH on average. Importantly, our findings confirm the protective effect of antihypertensive treatment on cardiovascular outcomes in this patient group, including those with ISH stage 1, i.e. baseline SBP 140–159 mmHg. Furthermore, analyses stratified by attained SBP found a significant benefit on MACE, as well as stroke and heart failure, in trials with average attained SBP down to below 130 mmHg, with no sign of harm at low BP levels in meta-regression analyses exploring the association between treatment effect and attained SBP and DBP, respectively .

These findings have important clinical implications as they provide evidence for a beneficial effect of

antihypertensive treatment which goes beyond that of designated ISH RCTs. Firstly, all designated ISH trials have had average baseline SBP values >170 mmHg, thus representing ISH stage 2 [6,7,35,39]. Here, we include data from 17 trials with an average baseline SBP 140–159 mmHg (ISH stage 1), showing a beneficial effect on several clinically important cardiovascular outcomes, thereby supporting initiation of antihypertensive treatment in people with ISH stage 1. Secondly, the average attained SBP in the intensive treatment group in designated ISH RCTs have been in the 140–150 mmHg range, giving the impression that current evidence does not support antihypertensive treatment to below 140 mmHg in this group. Our findings clearly demonstrate that BP lowering treatment to below 140 mmHg, and possibly even to below 130 mmHg, reduces the risk of MACE, stroke and heart failure in trials with baseline ISH on average.

The effect of drug treatment in ISH stage 1 appears similar to that of stage 1 hypertension in general [15]. Furthermore, the present analysis suggests that treatment targets recommended for the general hypertensive population [8,9] are also beneficial and safe in people with ISH. Thus, it simplifies hypertension guidelines in the sense that we may generalise and recommend therapeutic treatment target below 140/90 mmHg for all patients with Stage I hypertension if drug treatment is indicated, and even target SBP below 130 mmHg, if well-tolerated. Importantly, the studies that have been included in the present analysis included middle-aged and older patients [41]. ISH is the dominant form of hypertension also in adolescence, with different risk factor profile compared to diastolic or combined hypertension [42]. For young people with ISH, data on treatment effect are lacking and other considerations beyond the scope of the present meta-analysis may be relevant, like weighing lifelong treatment against low short-term risk. Likewise, several trials included here had an upper age limit of 80 years, making the applicability of our findings to very elderly ISH patients uncertain as well. In this patient group, the absolute risk of cardiovascular events is always very high, but at the same time arterial stiffens have progressed further, with increased risk of hypotension-related side effects, like dizziness, syncope and falls.

ISH represents an advanced form of hypertension with stiff arteries and high pulse pressure. Thus, ISH patients are already characterised by hypertensive mediated organ damage (HMOD) in the form of arterial stiffness. Stiff arteries in these patients are general and affect all large and to a certain degree medium sized arteries; the condition is characterised by deposition of collagen and general fibrotic tissue throughout the vessel walls, in contrast to atherosclerotic disease of the major and large arteries which are characterised by endothelial patchy plaques in certain areas of the vascular system. These pathophysiological aspects are important to understand the difference between stiff arteries, representing HMOD, in many ways similar to left ventricular hypertrophy of the heart and increased urinary albumin excretion from the kidneys, and atherosclerotic arterial disease for which the relationship to hypertension is different and far more complex, and other risk factors, like dyslipidaemia, play an important role.

Considering coexisting HMOD, patients with left ventricular hypertrophy (LVH) may be an exception from where target SBP <130 mmHg is beneficial. Patients with LVH have poor myocardial microcirculation [43] and they may need a certain arterial-venous perfusion pressure to maintain tissue blood flow and avoid myocardial ischaemia, arrhythmias and sudden cardiac death [44]. In the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE), all 9193 patients had LVH diagnosed by ECG [45]. The target SBP in LIFE was below 140 mmHg, but on average this target was not achieved and few patients attained a SBP below 130 mmHg. In line with common practice in hypertension outcome trials, patients attaining low BP levels were not back-titrated, however, and subsequent analyses have found increased all-cause mortality in these patients [45]. These findings were confirmed in a pre-specified and similar analysis of patients in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, who had qualified for participation in the study by having LVH on ECG, showing increased cardiac and all-cause mortality if averaged achieved SBP came below 130 mmHg [46]. In the present analysis certainly some fractions of patients had LVH and their inclusion in the analysis may potentially have masked a larger benefit of SBP target below 130 mmHg in non-LVH patients with ISH.

This analysis has some limitations. Firstly, trials were included based on mean BP values at baseline; only four trials were strictly limited to ISH patients (stage 2), and none included participants based on the current definition of ISH (stage 1). Although this means that individuals with other blood pressure phenotypes contribute to the analyses, the majority of patients had ISH, and our findings are likely to be generalisable to both ISH stage 1 and 2. Secondly, the finding that treatment reduced the risk of MACE, stroke and heart failure when attained SBP was below 130 mmHg should be

interpreted with some caution. This analysis included only three trials, all of which assessed the effect of intensive treatment targets post stroke. Whether our findings also apply to ISH patients without previous stroke is unknown, although we have no reason to suspect that the effect on MACE and heart failure should differ by cerebrovascular disease status.

In summary, this meta-analysis, including 24 randomised controlled outcome studies with more than 100,000 participants, of whom most had ISH at baseline, strongly suggests that patients with ISH stage 1 and 2 should be treated. Treatment seems effective and safe down to target SBP levels below 140 mmHg, and possibly even below 130 mmHg, supporting the general recommendation to get all hypertensive patients to a SBP <140 mmHg, and further below 130 mmHg if tolerated.

Disclosure statement

MB and BC report no conflict. SEK has in the past 3 years received lecture honoraria from Getz, Vector-Intas, Merck Healthcare KGaA, and Sanofi Aventis.

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