Blood Pressure Reduction and Secondary Stroke Prevention

A Systematic Review and Metaregression Analysis of Randomized Clinical Trials

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Abstract—Current recommendations do not specifically address the optimal blood pressure (BP) reduction for secondary stroke prevention in patients with previous cerebrovascular events. We conducted a systematic review and metaregression analysis on the association of BP reduction with recurrent stroke and cardiovascular events using data from randomized controlled clinical trials of secondary stroke prevention. For all reported events during each eligible study period, we calculated the corresponding risk ratios to express the comparison of event occurrence risk between patients randomized to antihypertensive treatment and those randomized to placebo. On the basis of the reported BP values, we performed univariate metaregression analyses according to the achieved BP values under the random-effects model (Method of Moments) for those adverse events reported in ≥10 total subgroups of included randomized controlled clinical trials. In pairwise meta-analyses, antihypertensive treatment lowered the risk for recurrent stroke (risk ratio, 0.73; 95% confidence interval, 0.62–0.87; $P<0.001$), disabling or fatal stroke (risk ratio, 0.71; 95% confidence interval, 0.59–0.85; $P<0.001$), and cardiovascular death (risk ratio, 0.85; 95% confidence interval, 0.75–0.96; $P=0.01$). 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 ($P=0.009$). Funnel plot inspection and Egger statistical test revealed no evidence of publication bias. The extent of BP reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and cardiovascular events. Strict and aggressive BP control seems to be essential for effective secondary stroke prevention.
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Key Words: antihypertensive agents ■ blood pressure ■ meta-analysis ■ regression analysis ■ stroke

Evidence from randomized controlled trials (RCTs) supports the use of antihypertensive agents in the secondary prevention of patients with ischemic stroke (IS) or transient ischemic attack (TIA).[1,2] However, since heterogeneity is present for several outcomes among these trials, current recommendations do not specifically address the intensity of blood pressure (BP) lowering for secondary stroke prevention.[1,2] This heterogeneity has been attributed to both a potential class effect of antihypertensive drugs used (related also to the reduction of BP variability)[3] and differences in the degree of BP reduction using standard and aggressive antihypertensive strategies.[4] Moreover, the majority of RCTs of secondary stroke prevention did not specifically evaluate the association between the extent of BP reduction and long-term outcomes in patients with stroke or TIA, leading to increasing uncertainty about the optimal BP levels that should be aimed and achieved during secondary stroke prevention.[5,6]

In view of the former considerations, we conducted a systematic review and metaregression analysis on the association of BP reduction with recurrent stroke and cardiovascular events using available RCT data on secondary stroke prevention.

Methods

Trial Identification and Data Abstraction

This meta-analysis has adopted the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for systematic reviews and meta-analyses.[7] Eligible RCTs of all antihypertensive treatments used in the secondary prevention of IS/TIA

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patients were identified by searching MEDLINE, SCOPUS, and the CENTRAL Register of Controlled Trials. The combination of search strings that were used in all database searches included the terms: antihypertensive, blood pressure, ischemic stroke, transient ischemic attack, cerebral ischemia, and Clinical Trial. No language or other restrictions were imposed. Last literature search was conducted on July 4, 2016. Reference lists of all articles that met the criteria and of all relevant review articles were examined to identify studies that may have been missed by the database search.

All retrieved studies were scanned independently by 2 reviewers (A.H.K. and A.F.) to include only RCTs of antihypertensives for secondary stroke prevention patients that reported achieved BP values during the follow-up period. We excluded from the final analysis observational studies, case series, case reports, RCTs in non-IS/TIA population, and studies not reporting data on finally achieved BP values. In case of disagreement between the 2 coauthors about the literature search results, the senior coauthor (G.T.) was consulted, and disagreement was resolved with consensus.

For each study that met the inclusion criteria, a predefined 7-point quality control was used to address for biases. For each quality item, the corresponding risk of bias was categorized as low, high, or unclear according to the suggestions by Higgins et al.[8] Quality control and bias identification was performed by 2 independent reviewers (A.H.K. and G.T.), and all emerging conflicts were resolved with consensus.

Final, achieved systolic BP (SBP) and diastolic BP (DBP) and outcome events (recurrent strokes, ISs [defined as neurological deficits persisting for >24 hours confirmed by noninvestigational computed tomography or magnetic resonance imaging], hemorrhagic strokes, fatal or disabling strokes, myocardial infarction, death from any cause, and cardiovascular death) were extracted for the duration of follow-up in each study independently by 2 authors (A.H.K. and G.T.).

Statistical Analyses

For all reported events during each eligible study period, we calculated the corresponding risk ratios (RRs) to express the comparison of event occurrence risk between patients randomized to antihypertensive treatment and those randomized to placebo. In all pairwise meta-analyses, RR values lower than 1 denote that antihypertensive treatment has a favorable effect on the prevention of adverse events. A random-effects model (DerSimonian and Laird) was used to calculate the pooled RRs. The equivalent z test was performed for each pooled RR, and if $P<0.05$ it was considered statistically significant.[9]

Heterogeneity between studies was assessed with the Cochran Q and I^2 statistics. For the qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity, as per the Cochrane Handbook.[10] Publication bias (ie, assessment of bias across studies) was evaluated both graphically using a funnel plot[11] and with the Egger statistical test for funnel plot asymmetry.[12]

After the overall analyses, we performed additional sensitivity analyses: (1) for all reported outcomes according to the reported achieved SBP (<130, 130–140, and >140 mm Hg) and DBP (<85, 85–90, and >90 mm Hg) in each subgroup of the included RCTs,[13] (2) for the risk of stroke recurrence according to the class of the antihypertensive agent that was used in each placebo-controlled RCT, and (3) for the risk of stroke recurrence according to the definition of stroke that was used in each placebo-controlled RCT. The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates. According to the mixed-effects model, we used a random-effects model (DerSimonian Laird) to combine studies within each subgroup and a fixed-effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the study-to-study variance (T^2) to be the same for all subgroups. T^2 was first computed within subgroups and then pooled across subgroups.[14]

Additional univariate metaregression analyses according to both achieved SBP and DBP values under the random-effects model (Method of Moments) were performed for those adverse events reported in ≥10 total subgroups of included RCTs, according to the rule of thumb for metaregression analysis,[15] to evaluate a possible moderating effect of finally achieved BP values (during the follow-up period) on the aforementioned events. Final, an additional univariate

Table 1. Baseline Characteristics of Included Studies

Study Name	Country	Year	Antihypertensive Treatment	Stroke Definition	Patients, n	ICH as Index Event, %
Carter[16]	United Kingdom	1970	Guanethidine	>48 h	97	0
Dutch TIA[17]	Netherlands	1993	Atenolol	>24 h	1473	0
TEST[18]	Sweden	1995	Atenolol	>24 h	720	6.1
HOPE[19]	Multicenter	2000	Ramipril	>24 h	1013	0
HSCSG[20]	United States	1974	Deserpidine/methyclothiazide	>24 h	452	0
Liu et al[21]	China	2005	Perindopril/indapamide	>24 h	1520	17.7
Martí Massó and Lozano[22]	Spain	1990	Nicardipine	>24 h	264	0
MOSES[23]	Germany/Austria	2005	Eprosartan vs nitrendipine	>24 h/+neuroimaging	1352	5.4
PAST-BP[24]	United Kingdom	2016	NR	>24 h/+neuroimaging	529	0
PATS[25]	China	1995	Indapamide	+neuroimaging	5665	15.8
PRoFESS[26]	Multicenter	2008	Telmisartan	>24 h+neuroimaging	20 332	0
PROGRESS[27]	Multicenter	2001	Perindopril/indapamide	>24 h	6105	11
SCOPE[28]	Multicenter	1999	Candesartan	…	194	…
SPS3[29]	Multicenter	2013	NR	+neuroimaging	3020	0

(*Continued*)

metaregression analysis on the RRs of stroke recurrence between treatment and placebo groups reported in placebo-controlled RCTs according to their publication year was performed to investigate publication year as a possible confounder on the aforementioned association of BP with cardiovascular outcomes.

Statistical analyses were conducted using Review Manager (RevMan) version 5.2 software (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012) and Comprehensive Meta-analysis version 2 software (Borenstein M, Hedges L, Higgins J, Rothstein H, Biostat, Englewood NJ, 2005).

Results

Study Selection and Study Characteristics

Systematic search of MEDLINE and SCOPUS databases yielded 340 and 553 results, respectively. Subsequent search in the CENTRAL Register of Controlled Trials retrieved no additional RCTs. After removing duplicates, the titles and abstracts from the remaining 872 studies were screened, and 21 potentially eligible studies for the meta-analysis were retained. After retrieving the full-text version of the aforementioned 21 studies, 1 study was excluded because it did not report data on achieved BP, as well as 6 more studies that included non-IS/TIA population (Table S1 in the online-only Data Supplement). In the final presentation of the literature search results, there was no conflict or disagreement between the 2 reviewers, and the 14 studies that met the study protocol's inclusion criteria[16–29] were included both in the qualitative and quantitative synthesis (Figure S1). The characteristics of the included studies, comprising a total of 42 736 patients (63.9% men), are summarized in Table 1. Included studies consisted of 11 placebo-controlled RCTs,[16–22,25–28] 2 RCTs that randomized stroke patients according to the BP reduction intensity (intensive [SBP<130 mm Hg] versus conservative [SBP=130–149 mm Hg] BP reduction),[24,29] and 1 RCT that randomized stroke patients to 2 different antihypertensive agents (eprosartan versus nitrendipine).[23] In most studies, stroke was defined according to the still used WHO definition[30,31] as a focal neurological deficit of cardiovascular origin persisting for >24 hours.[17–22,27] In 5 of the studies, positive neuroimaging was either sufficient by itself[25,26,29] or additional[23,24] to the clinical presentation above for the final definition of stroke. Final, 1 study reported a duration of focal neurological >48 hours for the definition of stroke,[16] whereas another study provided no definition for stroke.[28]

Risk of Bias for Independent Studies

Risk of bias in the included studies is summarized in Figures S2 and S3. Overall, the risks of attrition and detection bias were considered unclear because of the absence of adequate report in the methods of many included trials. More specifically, the risk of both performance bias and detection bias was considered high in 2 studies that reported open-label design with lack of any blinding method[22,24] and partially high in a study protocol reporting blinding only in end point evaluation (PROBE design).[23] The risk for reporting bias was judged to be low because study protocols were available in most cases, although published reports from all trials included all expected outcomes. Similarly, the overall risk of selection bias was considered to be low. Final, the risk of other bias was considered as unclear in 3 study protocols that reported involvement of a study sponsor with a clear conflict of interest on the topic.[18,26,28]

Table 1. Continued

Mean Age, y	Males, %	Previous MI, %	AF, %	CHF, %	DM, %	HTN, %	HCL, %	AP, %	AC, %	Statins, %	Study Duration, mo
…	57	…	…	…	…	100	…	…	…	…	48
…	64	5.5	…	…	…	28.8	…	100	…	…	31.2
70	60	10	9.8	4.2	12.5	…	…	…	…	…	30.7
…	…	…	…	…	…	…	…	…	…	…	60
59	60	…	…	…	36	100	21.5	…	…	…	27.4
63.8	70.6	3.2	…	…	10.5	63.1	…	…	…	…	48
61.4	71.2	3.4	…	…	19.9	35.2	…	100	…	…	12
68	54.2	8.1	…	…	36.8	83.9	53.1	78	…	16.6	48
71.8	59		10.5	2	10		…	…	…	…	12
60	72	…	…	…	…	…	…	…	…	…	24
66.1	64.1	6.7	2.6	2.6	28	74	46.7	100	…	47.3	30
64	70	7	8	…	12.5	48	…	72	9	8	46.8
…	…	…	…	…	…	…	…	…	…	…	44.6
63	63	…	…	0	37	75	49	100	…	69	44.4

AC indicates anticoagulant treatment; AF, atrial fibrillation; AP, antiplatelet treatment; CHF, congestive heart failure; CT, computed tomography; DM, diabetes mellitus; HCL, hypercholesterolemia; HOPE, Heart Outcomes Prevention Evaluation Study; HSCSG, Hypertension-Stroke Cooperative Study Group; HTN, hypertension; ICH, intracranial hemorrhage; MI, myocardial infarction; MOSES, Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention; MRI, magnetic resonance imaging; PAST-BP, Prevention After Stroke–Blood Pressure; NR, not reported; PATS, Post-Stroke Antihypertensive Treatment Study; PROBE, Prospective Randomized Open Blinded End Point; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition Prognosis in the Elderly SPS3, Secondary Prevention of Small Subcortical Stroke; TEST, Tenormin After Stroke and TIA; and TIA, transient ischemic attack.

Table 2. Overview of All Pairwise Meta-Analyses of Included Placebo-Controlled Randomized Clinical Trials

Outcome	No. of Studies	RR (95% CI)	*P* Value	I^2, %	*P* for Cochran *Q*
Recurrent stroke	11	0.73 (0.62–0.87)	<0.001	75	<0.001
Ischemic stroke	2	0.87 (0.70–1.07)	0.19	81	0.02
Hemorrhagic stroke	2	0.65 (0.41–1.05)	0.08	76	0.04
Disabling or fatal stroke	7	0.71 (0.59–0.85)	<0.001	0	0.57
Myocardial infarction	5	0.77 (0.57–1.03)	0.08	48	0.10
Death from any cause	8	0.92 (0.82–1.03)	0.16	41	0.10
Cardiovascular death	8	0.85 (0.75–0.96)	0.01	17	0.29

CI indicates confidence interval; and RR, risk ratio.

Overall Meta-Analyses of Reported Study Outcomes

The findings of pairwise meta-analyses of placebo-controlled RCTs are summarized in Table 2. Antihypertensive treatment was associated with a lower risk for recurrent stroke (RR, 0.73; 95% confidence interval [CI], 0.62–0.87; *P*<0.001; Figure 1A), disabling or fatal stroke (RR, 0.71; 95% CI, 0.59–0.85; *P*<0.001; Figure S7), and cardiovascular death (RR, 0.85; 95% CI, 0.75–0.96; *P*=0.01; Figure S1B). Antihypertensive treatment was not associated with the risk of recurrent IS (RR, 0.87; 95% CI, 0.70–1.07; *P*=0.19; Figure S5), hemorrhagic stroke (RR, 0.65; 95% CI, 0.41–1.05; *P*=0.08; Figure S6), myocardial infarction (RR, 0.77; 95% CI, 0.57–1.03; *P*=0.08; Figure S8), and the risk of death from any cause (RR, 0.92; 95% CI, 0.82–1.03; *P*=0.16; Figure S9) during the follow-up period of each study protocol. Evidence of considerable heterogeneity was present in the analyses of recurrent strokes (I^2=75%, *P* for Cochran *Q*<0.001), recurrent IS (I^2=81%, *P* for Cochran *Q*=0.02), and hemorrhagic strokes (I^2=76%, *P* for Cochran *Q*=0.04). Final, no evidence of publication bias was present in both the funnel plot inspection (Figure S4) and the Egger statistical test (*P*=0.083).

Subgroup Analyses of Reported Study Outcomes

In the subgroup analyses of reported outcomes according to the mean level of achieved SBP (Figure 2A), subgroups of patients reported to achieve mean SBP <130 mm Hg had lower prevalence (*P*=0.048) of recurrent strokes (8.3%; 95% CI, 7.0–9.8%) compared with the subgroups with SBP ranging between 130 and 140 mm Hg (9.2%; 95% CI, 6.9–12.1%) and SBP >140 mm Hg (11.7%; 95% CI, 9.4–14.3%; Figure S10). SBP reduction to mean values lower than 130 mm Hg was also related (*P*=0.049) to a lower prevalence of cardiovascular death during follow-up (0.8%; 95% CI, 0.1–4.3%), when compared with achieved SBP values of 130–140 mm Hg (3.3%; 95% CI, 1.6–6.7%) and >140 mm Hg (5.5%; 95% CI,

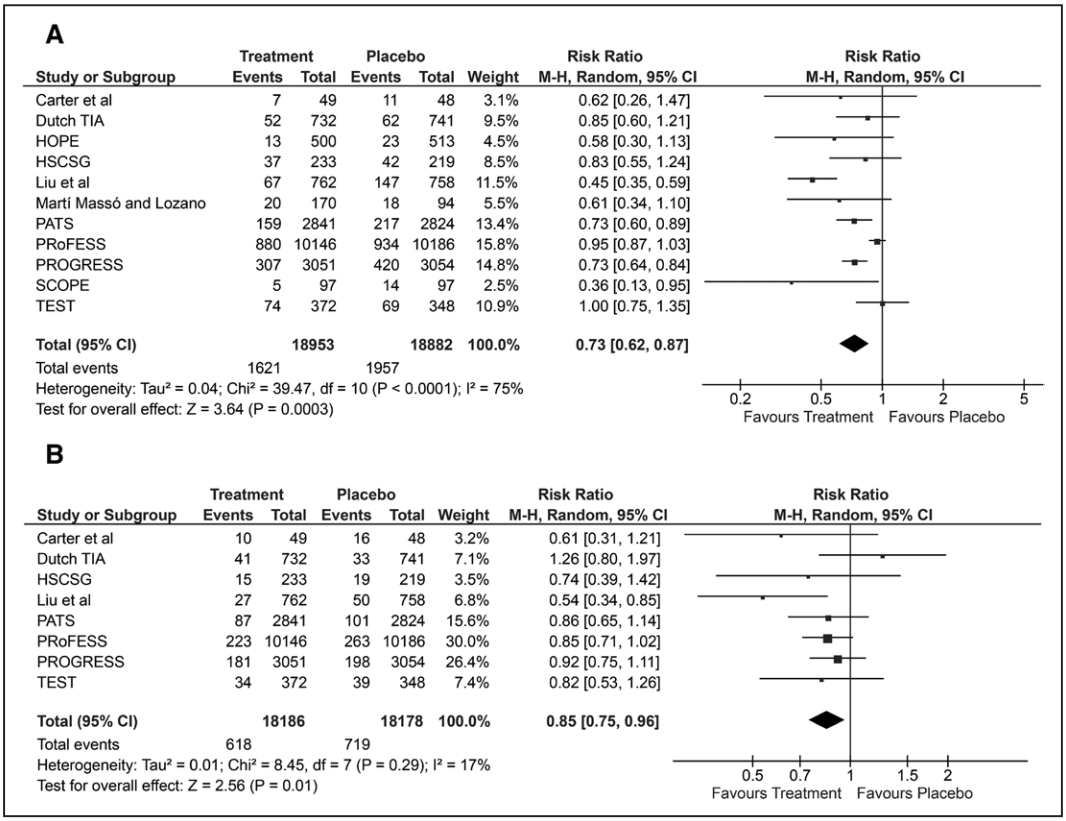

Figure 1. Forest plot on the risk of (**A**) recurrent stroke and (**B**) cardiovascular death between stroke patients randomized to antihypertensive treatment or placebo. CI indicates confidence interval.

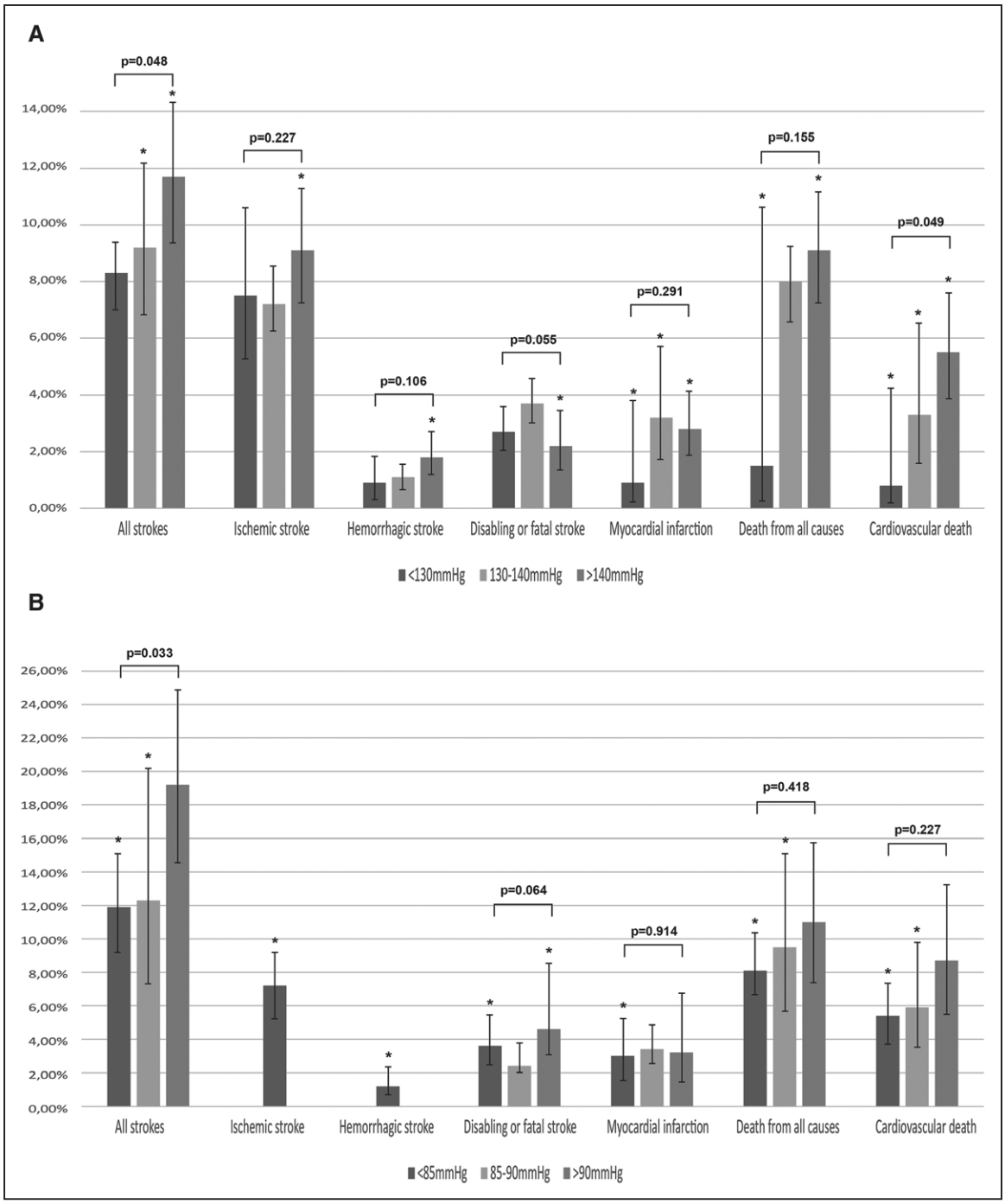

Figure 2. Overview of the subgroup analyses on the reported outcomes during follow-up according to the reported (**A**) achieved mean systolic blood pressure and (**B**) achieved mean diastolic blood pressure in the patients' subgroups of included trials (*considerable heterogeneity present defined as $I^2 \geq 75\%$).

3.9–7.6%; Figure S16). Even though no significant differences between the aforementioned subgroups were detected about the prevalence of IS (P=0.227; Figure S11), hemorrhagic stroke (P=0.106; Figure S12), disabling/fatal stroke (P=0.055; Figure S13), myocardial infarction (P=0.291; Figure S14), and death from all causes (P=0.155; Figure S15), a gradual increase in the risk of outcome events was observed in the 2 subgroups with higher SBP levels (130–140 and >140 mm Hg) in comparison to the reference subgroup of SBP <130 mm Hg (Figure 2A).

Similarly, in the subgroup analyses of reported outcomes according to the mean level of achieved DBP (Figure 2B), subgroups of patients reported to achieve mean DBP <85 mm Hg had a significantly lower prevalence (P=0.033) of recurrent strokes (11.9%; 95% CI, 9.2–15.1%) compared with the subgroups reporting achieved DBP ranging between 85 and 90 mm Hg (12.3%; 95% CI, 7.3–20.1%) and >90 mm Hg (19.2%; 95% CI, 14.5–24.9%; Figure S17). No significant differences between the aforementioned subgroups were detected about the prevalence of disabling/fatal stroke (P=0.064; Figure

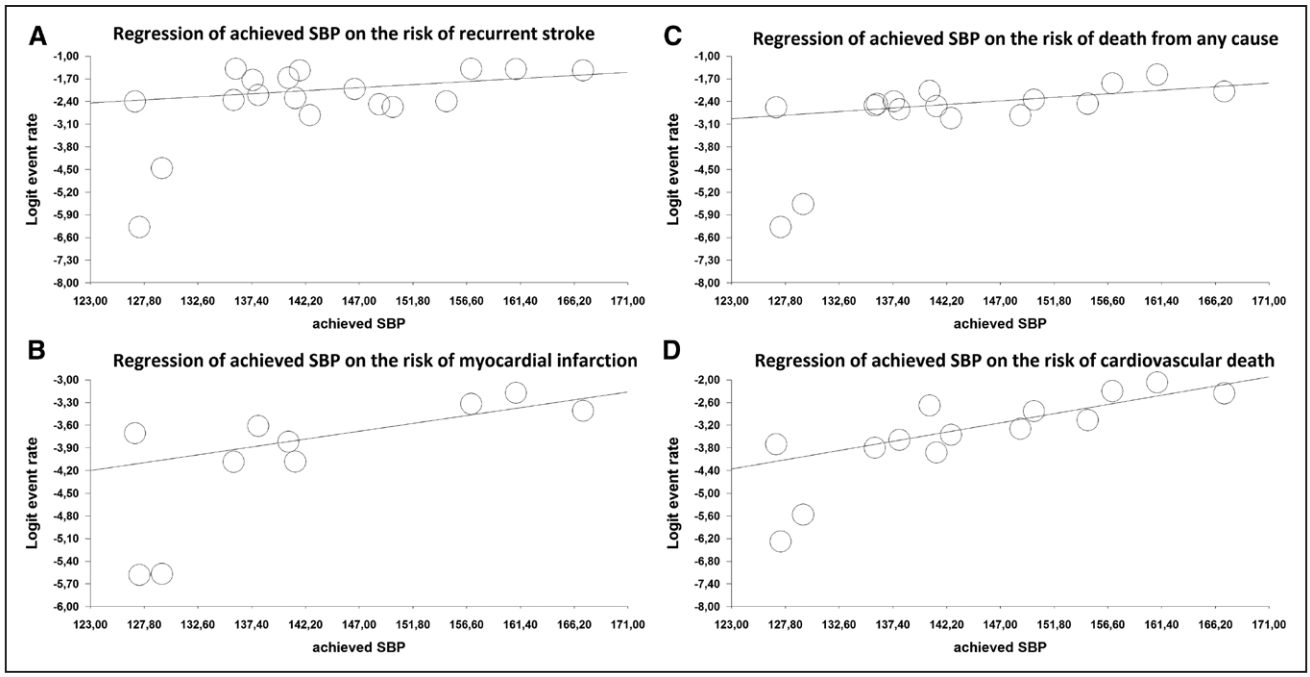

Figure 3. Metaregression analysis on the association between the achieved systolic blood pressure (SBP) values and (**A**) the risk of recurrent stroke, (**B**) the risk of myocardial infarction, (**C**) the risk of death from any cause, and (**D**) the risk of cardiovascular death during follow-up.

S20), myocardial infarction (*P*=0.914; Figure S21), death from all causes (*P*=0.418; Figure S22), and cardiovascular death (*P*=0.227; Figure S23). However, a gradual increase in the risk of outcome events was observed in the 2 subgroups with higher DBP levels (85–90 and >90 mm Hg) in comparison to the reference subgroup of DBP <85 mm Hg (Figure 3B). Final, for the outcomes of IS and hemorrhagic stroke, only data from subgroups reporting intensive BP reduction with achieved mean DBP values of <85 mm Hg were available (Figures S18 and S19), and thus no subgroup analysis was feasible (Figure 3B).

Sensitivity Analyses

Additional sensitivity analyses were performed evaluating recurrent stroke reduction in relation to antihypertensive agent class in placebo-controlled RCTs. Even though RCTs reporting the use of thiazide diuretics as monotherapy (RR, 0.73; 95% CI, 0.60–0.89; *P*=0.002) or in combination with other antihypertensive agent (RR, 0.64; 95% CI, 0.46–0.91; *P*=0.010) presented a more pronounced magnitude of risk reduction compared with other RCTs reporting the use of antiadrenergic drugs (RR, 0.62; 95% CI, 0.26–1.47; *P*=0.280), β-blockers (RR, 0.73; 95% CI, 0.60–0.89; *P*=0.570), calcium channel blockers (RR, 0.61; 95% CI, 0.34–1.10; *P*=0.100), or renin–angiotensin system blockers (RR, 0.68; 95% CI, 0.39–1.17; *P*=0.160), no significant differences were found in the subgroup analyses of secondary stroke prevention according to the class of the antihypertensive agent used (*P* for subgroup differences=0.390; Figure S24). In addition, even though the use of thiazide diuretics in monotherapy or in combination therapy seemed to be related with a lower risk of stroke recurrence compared with other antihypertensive regimens, this difference was marginally not significant (RR [thiazide diuretics as monotherapy or combination therapy], 0.67; 95% CI, 0.54–0.83; *P*<0.001 versus RR [other antihypertensive regimens], 0.85; 95% CI, 0.71–1.01; *P*=0.06; *P* for subgroup differences=0.09; Figure S25]).

Table 3. Overview of Metaregression Analyses on the Effect of Achieved SBP and DBP Values on the Reported Study Outcomes

	Metaregression Analysis for SBP Reduction			Metaregression Analysis for DBP Reduction		
Outcome	No. of Subgroups	Point Estimate (95% CI)	*P* Value	No. of subgroups	Point Estimate (95% CI)	*P* Value
Recurrent stroke	18	0.02 (0.01 to 0.04)	0.049	12	0.08 (0.01 to 0.15)	0.026
Ischemic stroke	6	…	…	0	…	…
Hemorrhagic stroke	6	…	…	0	…	…
Disabling or fatal stroke	10	0.001 (−0.024 to 0.022)	0.944	6	…	…
Myocardial infarction	10	0.022 (0.002 to 0.041)	0.024	6	…	…
Death from any cause	16	0.02 (0.01 to 0.03)	0.001	10	0.08 (0.02 to 0.13)	0.009
Cardiovascular death	14	0.05 (0.03 to 0.07)	<0.001	8	…	…

CI indicates confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Final, no significant differences (*P*=0.560) were detected in the subgroup analysis according to the definition of stroke that was used in included placebo-controlled RCTs (Figure S26).

Metaregression Analyses

The findings of metaregression analyses evaluating the association of SBP and DBP reduction with cerebrovascular and cardiovascular outcomes are presented in Table 3. SBP reduction was linearly related to lower risk of recurrent stroke (regression slope, 0.02; 95% CI, 0.01–0.04; *P*=0.049; Figure 3A), myocardial infarction (regression slope, 0.022; 95% CI, 0.002–0.041; *P*=0.024; Figure 3B), death from any cause (regression slope, 0.02; 95% CI, 0.01–0.03; *P*=0.001; Figure 3C), and cardiovascular death (regression slope, 0.05; 95% CI, 0.03–0.07; *P*<0.001; Figure 3D). However, no association was observed between the degree of SBP reduction and the risk of disabling or fatal stroke (regression slope, 0.001; 95% CI, −0.024 to 0.022; *P*=0.944; Figure S27). The association of SBP reduction with IS or hemorrhagic stroke was not evaluated because of the small number of studies with available data (<10). Similarly, DBP reduction was also linearly related to a lower risk of recurrent stroke (regression slope, 0.08; 95% CI, 0.01–0.15; *P*=0.026; Figure S28A) and death from any cause (regression slope, 0.08; 95% CI, 0.02–0.13; *P*=0.009; Figure S28B). The association of DBP reduction with other outcomes was not evaluated because of the small number of studies with available data (<10).

In the metaregression analysis on stroke recurrence risk between treatment and placebo groups reported in placebo-controlled RCTs, we detected no evidence of association with the publication year (regression slope, −0.002; 95% CI, −0.023 to 0.018; *P*=0.823; Figure S29).

Discussion

Our systematic review and metaregression analysis showed that the extent of both SBP and DBP reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and cardiovascular events. These findings underscore the importance of strict and aggressive BP control, which is increasingly being considered as the most essential therapeutic strategy for effective secondary stroke prevention and suggest that intensive SBP reduction to a target of <130 mm Hg seems to be effective for the secondary stroke prevention of patients with cerebrovascular events.

Our findings are in accordance with another recent systematic review and meta-analysis on intense BP reduction in high-risk patients, suggesting a pronounced benefit of intensive BP lowering, with a target of SBP <140 mm Hg, on all cardiovascular outcomes for high-risk individuals.[32] Interestingly, we documented an independent relationship between the degree of SBP decline and risk reduction in cardiovascular and all-cause mortality that was not detected in the meta-analysis of Xie et al,[32] including both RCTs of primary and secondary stroke prevention. This observation lends support to the assumption that the benefit of effective BP control may be even greater in secondary than in primary stroke prevention.[6]

In addition, our results lend support to current recommendations of the European Society of Hypertension and the European Society of Cardiology of SBP goal of <140 mm Hg for patients with a history of stroke or TIA, irrespective of the drug regimen being used.[33] Furthermore, current American Heart Association and American Stroke Association recommendations on secondary stroke prevention suggest an even more aggressive SBP reduction with a goal of <130 mm Hg in patients with lacunar stroke (Class IIb; Level of Evidence B).[2] The linear association between the degree of BP reduction and the magnitude of risk reduction in recurrent stroke and cardiovascular death that we documented in our metaregression analyses supports this more aggressive threshold and provides reassurance that SBP may be actually lowered below the cut-off of 140 mm Hg in the setting of secondary stroke prevention. Our findings may also be interpreted as confirmatory of the recent Eighth Joint National Committee recommendation, suggesting that in patients older than 60 years of age and with a positive history of IS or TIA the SBP goal of 150 mm Hg should not be considered, and thus more intensive BP control should be targeted.[34] Our findings are also in accordance with the recent hypertension guidelines from the American Heart Association, American College of Cardiology, and American Society of Hypertension, which suggest that even though a BP target of 140/90 mm Hg is reasonable for the secondary prevention of cardiovascular events in patients with hypertension and coronary artery disease, more intensive BP reduction (<130/80 mm Hg) could be more appropriate in patients with coronary artery disease and a history of stroke or TIA.[35]

However, it should be highlighted that even though intensive BP reduction seems to be associated with a lower risk of cardiovascular events and mortality, both the optimal BP target (below 140 mm Hg for SBP and below 90 mm Hg for DBP) and the most favorable timing for achieving this goal after the index event still remain unknown. These specific knowledge gaps need to be addressed in future RCTs in view of the recent evidence underscoring that intensive and acute BP control have also been associated with a higher risk for adverse events.[36,37] More specifically, SBP reduction with a target of <120 mm Hg in nondiabetic patients at high risk for cardiovascular events was related with significantly higher rates of hypotension, syncope, electrolyte abnormalities, and renal failure in SPRINT (Systolic Blood Pressure Intervention Trial).[36] Similarly, acute BP reduction to a target SBP between 110 and 139 mm Hg right during the first hours after intracranial hemorrhage onset was also related with a higher risk for serious adverse events at 3 months and specifically significantly higher renal adverse events within 7 days after randomization in ATTACH II trial (Antihypertensive Treatment for Acute Cerebral Hemorrhage).[37]

Our observations also challenge the findings of a recent network meta-analysis on the use of antihypertensives in secondary stroke prevention, suggesting that the disparities of treatment effect in available RCTs can be attributed to the class of the antihypertensive treatment and not in the magnitude of BP reductions.[38] In a subgroup analysis, the authors found no effect of achieved SBP on total cerebrovascular events, using a cut-off value of 140 mm Hg.[38] However, in our metaregression analysis the achieved SBP/DBP values were significantly related with the risk of recurrent stroke, rendering this way both SBP and DBP reduction as a potential moderator for the aforementioned relationship. Even though no significant differences in the risk of stroke recurrence according to the class

of antihypertensive used among included RCTs were found, we detected a nonsignificant trend for lower risk of stroke recurrence in RCTs reporting the use of thiazide diuretics as monotherapy or in combination therapy for secondary stroke prevention. Our observation is consistent with previously published recommendations focusing on treatment intensity with a goal of SBP <140 mm Hg and expressing uncertainty about the potential disparities between different antihypertensive regimens,[33–35] suggesting thus that the degree of BP reduction may be more important than the class of the agent used to achieve it.

To the best of our knowledge, our meta-analysis is the first to date that documents a linear association between SBP and DBP reduction and decrease in the risk of recurrent stroke and cardiovascular events in patients with previous stroke. Nevertheless, certain limitations need to be taken also into consideration when interpreting our findings. First, in our analysis, we could not assess for potential disparities about the stroke subtypes as these data were not available in the included studies. Second, sufficient information on baseline patient characteristics (Table 1) and study protocol methods to permit bias assessment (Figure S2) were not available for most study protocols. Third, as the publication of included studies expands for a period of over 45 years (1970–2016), neither the definition of both stroke, incorporating the advances in neuroimaging,[31] nor the definition and treatment of cardiovascular risk factors (eg, hypertension, diabetes mellitus, dyslipidemia, etc) can be considered to be univocal among trials. However, significant differences were detected neither in the subgroup analysis according to the definition of stroke that was used (Figure S26) nor in the metaregression analysis according to the publication year (Figure S29). Fourth, the adverse events in the different studies were not reported in relation to the achieved BP levels, and thus, we were unable to evaluate the potential relationship between the degree of BP reduction and the risk of potential adverse events, including hypotension and impairment of renal function. Moreover, metaregression analysis could not be performed for some of the study outcomes, because of the low number of total subgroups, and thus the association of achieved SBP/DBP with these outcomes remains uncertain. Final, even though the relationship of achieved BP with cardiovascular outcomes was confirmed in subgroup and metaregression analyses, the substantial heterogeneity that was documented in both of these analyses may indicate the presence of other effect modifiers in addition to the level of BP reduction. Consequently, this heterogeneity should be considered as a potential source of bias and a point that needs to be taken into consideration for the correct interpretation of the findings of our meta-analysis. Nevertheless, our sensitivity analyses (Figure 2) underline that the differences in the achieved BP levels across the included RCTs may account partly for this observed heterogeneity.

Perspectives

The degree of BP reduction is linearly and positively associated with the risk reduction in recurrent stroke and cardiovascular events. Although optimal BP cut-offs and goals in different patient groups may still be debated, strict and aggressive BP control toward normotension in patients with IS/TIA is essential for secondary stroke prevention. Further research is required to determine both the lower optimal BP limits and appropriate timing of treatment initiation for effective secondary stroke prevention separately for IS and hemorrhagic stroke subgroups.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The majority of randomized clinical trials did not specifically evaluate the association between blood pressure (BP) reduction and long-term outcomes in patients with cerebrovascular events.
- Current recommendations still do not address the intensity of BP lowering for secondary stroke prevention

What Is Relevant?

- We show that the extent of both systolic and diastolic BP reduction is linearly associated with the magnitude of risk reduction in both cerebrovascular and cardiovascular event recurrence.
- Intensive systolic BP reduction below 130 mm Hg seems to be effective for secondary stroke prevention in patients with history of cerebrovascular diseases.

Summary

The degree of BP reduction is linearly and positively associated with the risk reduction in patients with a history of cerebrovascular event. Strict and aggressive BP control toward normotension seems to be essential for effective secondary stroke prevention.