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REVIEW

Targeting blood pressure for stroke prevention: current evidence and unanswered questions

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Abstract

High blood pressure (BP) is the leading modifiable risk factor of stroke worldwide. Although randomized clinical trials have demonstrated the beneficial effect of BP reduction on stroke risk, there are still insufficiently explored issues concerning the optimal personalized management of BP in stroke patients in terms of thresholds to be achieved and drug classes to be prescribed. Few data are available about BP control in specific clinical contexts such as in older patients, in various stroke subtypes, or in association with co-morbidities such as diabetes. In addition, although drug trials based their conclusions on achieved mean BP values, recent findings indicate that aspects such as circadian variations of BP and BP variability should be taken into account as well. This article aims to highlight current knowledge about BP control in stroke prevention and to provide new perspectives to be addressed in future studies so as to guide clinicians in their day-to-day practice.

Keywords Stroke · Prevention · High blood pressure · Hypertension

Introduction

High blood pressure (BP) is a frequent condition worldwide and its prevalence is rising. A meta-analysis of 844 studies from 154 countries including a total of 8.7 million participants showed that the rate of systolic blood pressure (SBP) of at least 110–115 mmHg among adults aged ≥ 25 years dramatically increased between 1990 and 2015 (from 731 to 813 per 1000 persons), as did the rate of SBP of at least 140 mmHg (from 173 to 205 per 1000 persons), leading to an estimated total of 3.5 billion adults with SBP of at least 110–115 mmHg and 874 million with SBP ≥ 140 mmHg [1]. High BP has long been recognized as a major risk factor of stroke (the term "stroke" will refer to both ischemic stroke and intracerebral hemorrhage throughout this article), and substantial evidence has demonstrated the beneficial effect of BP control on the reduction of vascular risk, including stroke. However, there are still unanswered questions about the most appropriate BP thresholds to be achieved, the management of BP in specific conditions, and the importance of aspects other than mean BP in treatment strategies.

This article aims to highlight specific features of BP control in stroke prevention by reviewing current evidence and providing new perspectives.

The impact of high BP on stroke epidemiology

Population-based studies have shown that hypertension is one of the most prevalent risk factors in patients with first-ever stroke, ranging from 48 to 76% [2–7]. In the Dijon Stroke Registry, 59.9% of patients had known treated hypertension defined as BP > 140/90 mmHg, and 8% had known but untreated hypertension (Fig. 1). The prevalence of pre-stroke hypertension increased with age, affecting 78% of patients > 75 years. Because a non-negligible proportion of patients may have undiagnosed hypertension, these figures may be an underestimation of the true prevalence of hypertension in stroke patients.

There is a continuous relationship between BP and stroke risk. In the meta-analysis of epidemiological data from the

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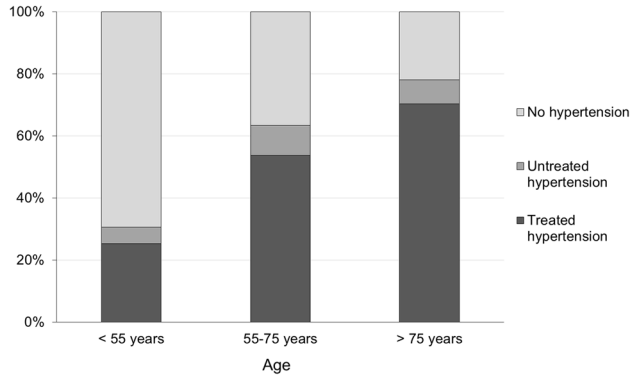

Fig. 1 Prevalence of treated and non-treated hypertension (defined as BP > 140/90 mmHg) in patients with first-ever stroke in the Dijon Stroke Registry, according to age (study period 2013–2015)

Prospective Studies Collaboration, each 20 mmHg increase in SBP or 10 mmHg increase in diastolic blood pressure (DBP) was associated with a two-fold increase in stroke mortality [8]. The increased risk was observed for values above 115 mmHg for SBP and 75 mmHg for DBP, and age-specific associations were similar for men and women, and for intracerebral hemorrhage and ischemic stroke.

The INTERSTROKE study, which enrolled 13,447 stroke patients (10,388 cases of ischemic stroke and 3059 of intracerebral hemorrhage) and 13,472 controls in 32 countries worldwide, concluded that ten potentially modifiable risk factors were associated with about 90% of the population attributable risks (PARs) of stroke [9]. Among these factors, self-reported history of hypertension or BP of ≥ 140/90 mmHg was associated with an increased risk of both ischemic stroke (OR = 2.78, 95% CI: 2.50–3.10) and intracerebral hemorrhage (OR = 4.09, 95% CI: 3.51–4.77). The corresponding PARs were 45.7% and 56.4%, respectively. Similarly, the Global Burden of Disease Study reported that high SBP was the leading risk factor for disability-adjusted life years (DALYs) attributable to stroke in all regions around the world. In addition, stroke-related DALYs associated with high SBP increased by 39% between 1990 and 2013 [10].

Impact of BP reduction on cerebrovascular risk

General data from primary and secondary prevention drug trials

A recent meta-analysis identified 123 BP-lowering trials that included 613,815 participants in a context of either primary or secondary vascular prevention [11]. Every 10 mmHg reduction in SBP was associated with a reduction in the risk of major cardiovascular disease events (defined by a composite outcome including fatal and non-fatal myocardial infarction, sudden cardiac death, revascularization, fatal and non-fatal stroke, and fatal and non-fatal heart failure) (RR = 0.80, 95% CI: 0.77–0.83). A decrease in risk was also observed for coronary heart disease (RR = 0.83, 95% CI: 0.78–0.88), stroke (RR = 0.73, 95% CI: 0.68–0.77), and heart failure (RR = 0.72, 0.67–0.78), but not for chronic kidney disease (RR = 0.95, 95% CI: 0.84–1.07). All-cause mortality was reduced by 13% (RR = 0.87, 95% CI: 0.84–0.91). Interestingly, the benefit was observed in patients with and without a history of stroke for all outcomes. In addition, when trials were stratified by mean baseline systolic blood pressure and the effect of a 10 mmHg reduction in SBP was compared between strata, no significant trends for any outcomes were observed, thus suggesting that the favorable effects were also observed in people with lower baseline SBP (< 130 mmHg).

Data from drug trials focusing on secondary prevention in stroke patients

Only a few trials have focused on BP lowering in secondary prevention of stroke. Table 1 presents the characteristics of the main trials in which only stroke patients were specifically included [12–18].

The Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial included 6105 patients (mean age 64 ± 10 years) with a history of stroke or TIA < 5 years (mean time between cerebrovascular event and inclusion: 8 months) who were assigned to receive active treatment that comprised a flexible regimen based on perindopril (4 mg daily) with the addition of indapamide (2.5 mg daily, except in Japan, where the dose was 2 mg daily) in patients for whom the attending physician judged there to be no specific indication for or contraindication to treatment with a diuretic, or placebo [12]. The mean baseline BP of 147/86 mmHg was reduced by an overall average of 9/4 mmHg (SE 0.3/0.2) among those assigned active treatment compared with those assigned a placebo. In addition, those treated with combination therapy (12.3/5.0 mmHg) saw their BP reduced by about twice as much as participants treated with single-drug therapy (4.9/2.8 mmHg). After a mean follow-up of 3.9 years, a significant 28% reduction in the primary outcome (fatal and non-fatal stroke) was observed in the active-treatment group. A significant 38% reduction of myocardial infarction was also reported, but the beneficial impact on vascular death and total mortality was not demonstrated. Interestingly, in subgroup analyses, the benefit was observed in patients with combined treatment (risk reduction: 43%, 95% CI: 30–54) but not in those taking a single drug (risk reduction: 5%, 95% CI: − 19 to 23). In PROGRESS, the index

Table 1 Characteristics of the main clinical trials on BP reduction for secondary prevention of stroke

Study	Year	Total number of patients	Stroke types	Mean age (SD)	Intervention	Primary outcome	Mean follow-up duration	Baseline and achieved BP	Main selected results
PROGRESS [12]	2001	6105	IS: 71% ICH: 11% UNK: 5% TIA/amaurosis fugax: 23%[$]	64 (10)	A: perindopril ± indapamide C: placebo	Fatal or non-fatal stroke	3.9 years	Mean baseline BP: 147/86 mmHg Average reduction of 9/4 mmHg (SE 0.3/0.2) among A versus C	Fatal/non-fatal stroke: A: 10% versus C: 14%; HR 0.72 (0.64–0.84), $p < 0.001$ In hypertensive: HR 0.68 (0.56–0.83) In normotensive: HR 0.73 (0.58–0.92) In baseline IS: HR 0.74 (0.62–0.88) In baseline ICH: HR 0.51 (0.32–0.82) In baseline TIA/amaurosis fugax: HR 0.77 (0.32–1.23) In baseline UNK: HR 0.51 (0.32–0.82) Non-fatal stroke: HR 0.71 (0.61–0.83) IS: HR 0.76 (0.66–0.90) Lacunar: HR 0.71 (0.56–1.07) LAA: HR 0.61 (0.39–0.95) Cardio: HR 0.77 (0.43–1.38) Undetermined: HR 0.81 (0.65–1.00) ICH: HR 0.50 (0.33–0.74) Major vascular events: HR 0.74 (0.66–0.84) All deaths: HR 0.96 (0.83–1.11) Vascular deaths: HR 0.92 (0.75–1.11) Stroke in perindopril versus C: HR 0.95 (0.77–1.19) Stroke in combination versus C: HR 0.57 (0.46–0.70) Myocardial infarction: HR 0.62 (0.45–0.86)

Table 1 (continued)

Study	Year	Total number of patients	Stroke types	Mean age (SD)	Intervention	Primary outcome	Mean follow-up duration	Baseline and achieved BP	Main selected results
PRoFESS [13]	2008	20,332	IS only lacunar: 52% LAA: 29% Cardio: 2% Other: 18%	66 (8.6)	A: telmisartan C: placebo	All strokes (IS + ICH)	2.5 years	Mean baseline BP: 144/84 mmHg Mean BP at 1 year: A: 136/80 mmHg C: 140/82 mmHg	All strokes: A: 8.7% versus C: 9.2%; HR 0.95 (0.86–1.04) IS: A: 7.6% versus C: 8.0% ICH: A: 0.6% versus C: 0.7% UNK: A: 0.5% versus C: 0.5% All deaths: HR 1.03 (0.93–1.14) Death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure: HR 0.94 (0.87–1.01) Myocardial infarction: HR 1.00 (0.81–1.23) New or worsening heart failure A: 1.2% versus C: 1.1% New-onset diabetes: HR 0.82 (0.65–1.04)
SPS3 [14]	2013	3020	Lacunar ischemic strokes only proven by MRI	63 (10.7)	A: lower target (< 130 mmHg) of SBP C: higher target (130–149 mmHg)	All strokes (IS + ICH)	3.7 years	Mean baseline BP: 144/79 mmHg Mean SBP at 1 year: A: 127 mmHg C: 138 mmHg	All strokes (% per patient-year): A: 2.25% versus C: 2.77%; HR 0.81 (0.64–1.03) IS or UNK: HR 0.84 (0.66–1.09) ICH: HR 0.37 (0.66–1.09) Major vascular events: HR 0.84 (0.68–1.04) All deaths: HR 1.03 (0.79–1.35) Vascular deaths: HR 0.86 (0.55–1.35)
Dutch TIA [15]	1993	1473	Nondisabling IS: 66% TIA: 34%	N/A 52% of patient > 65 yo	A: atenolol C: placebo	Death from vascular causes, non-fatal stroke, or Non-fatal myocardial infarction	2.6 years	Mean baseline BP: 157/91 mmHg Mean BP at 1 year: A: 146/86 mmHg C: 152/91 mmHg	Death from vascular causes, non-fatal stroke, non-fatal myocardial infarction: A: 5.3% versus C: 5.1%; HR 1.00 (0.76–1.33) Fatal and non-fatal stroke: HR 0.82 (0.57–1.19) All deaths: HR 0.82 (0.57–1.19) Vascular deaths: HR 1.29 (0.81–2.04)

Table 1 (continued)

Study	Year	Total number of patients	Stroke types	Mean age (SD)	Intervention	Primary outcome	Mean follow-up duration	Baseline and achieved BP	Main selected results
PATS [16]	1995	5665	IS/TIA: 84% ICH: 16%	60	A: indapamide C: placebo	Fatal and non-fatal stroke	2 years	Mean baseline BP: 154/93 mmHg Mean BP during follow-up: A: 144/87 mmHg C: 149/89 mmHg	Recurrent stroke: A: 5.6% versus C: 7.7%; %; HR 0.73 (0.60–0.89) All deaths: HR 0.92 (0.74–1.14) Vascular deaths: HR 0.86 (0.65–1.14)
TEST [17]	1995	720	IS: 86% TIA: 8% ICH: 6%	71	A: atenolol C: placebo	Death, stroke and myocardial infarction	2.3 years	N/A	Recurrent stroke: A: 19.9% versus C: 19.8%; %; HR 1.00 (0.75–1.35) All deaths: HR 0.82 (0.53–1.26) Vascular deaths: HR 0.82 (0.53–1.26) Myocardial infarction: HR 0.87 (0.41–1.82)
Liu et al. [18]	2005	1520	IS/TIA: 82% ICH: 18%	64 (7.6)	A: perindopril + Indapamide C: placebo	All strokes	4 years	Mean baseline BP: 145/87 mmHg BP reduced on average 14/6 mmHg more in A versus C at 4 years	Recurrent stroke: A: 8.8% versus C: 19.4%; %; HR 0.45 (0.35–0.59) All deaths: HR 0.80 (0.56–1.12) Vascular deaths: HR 0.54 (0.34–0.85) Myocardial infarction: HR 0.52 (0.25–1.07)

BP blodd pressure, *SBP* systolic blood pressure, *A* active group, *C* control group, *N/A* not available, *Cardio* cardioembolism, *LAA* large artery atheroma ischemic stroke, *UNK* unknown stroke, *HR* hazard ratios. Presented as adjusted HR when available

[$]Some patients had several previous cerebrovascular events, thus explaining that total is > 100%

stroke was hemorrhagic in 11% of cases. In this group, the effect of treatment was the most remarkable, with a 49% (95% CI: 18–68%) reduction in the risk of recurrent stroke, whereas risk reduction was 26% (95% CI: 12–38%) among patients with baseline ischemic stroke, 23% (95% CI: − 23 to 52%) among patients with a baseline TIA/amaurosis fugax, and 33% (95% CI: − 36 to 67%) among patients with a baseline stroke of unknown type, with no evidence of differences between these subgroups ($p = 0.65$ for homogeneity) [19]. No information about baseline etiological subtype of ischemic stroke was available; therefore, treatment effect by subtype categories was not analyzed. However, the authors reported no interaction between the effect of the treatment and the etiological subtype of recurrent ischemic stroke subtypes. In detail, risk reduction for recurrent ischemic stroke in the active group was 23% for lacunar stroke (95% CI: − 7 to 44%), 39% (95% CI: 5–61%) for large artery atheroma stroke, 23% (95% CI: − 38 to 57%) for patients with cardioembolic stroke, and 19% (95% CI: 0–35%) for patients with ischemic stroke of undetermined origin.

Two other large international trials found contrasting results. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study included 20,332 patients > 50 years old (mean age: 66 ± 10 years) who had recently had an ischemic stroke [13]. The etiological subtype was lacunar in half of patients, whereas 29% had large artery atheroma ischemic stroke, 2% had cardioembolic stroke, and 18% had other ischemic stroke. A two-by-two factorial design was used to compare four regimens: a combination of acetylsalicylic acid (aspirin) and extended-release dipyridamole, or clopidogrel, or telmisartan (an angiotensin-receptor blocker), or placebo. Mean blood pressure at inclusion was 144/84 mmHg. Average SBP was reduced by 8.3 mmHg with telmisartan at 1 month compared with 2.9 mmHg in the placebo group (difference of − 5.4 mmHg). However, after 1 year the difference had narrowed (− 4.0 mmHg), and the average difference in SBP between the two groups was only − 3.8 mmHg over the entire study. After a mean follow-up of 30 months, there was no significant difference in recurrent stroke reduction (RR = 0.95, 95% CI: 0.86–1.04). Similar rates were observed in the two regimen groups regarding the occurrence of ischemic stroke, intracerebral hemorrhage, or unknown stroke. The occurrence of secondary outcomes (including death from cardiovascular causes, myocardial infarction, new or worsening heart failure, or new-onset diabetes) was also similar. In post-hoc analysis, the authors found that at follow-up, compared with patients with achieved mean SBP levels of between 130 and 140 mmHg, SBP in the very low–normal (< 120 mmHg), high (140–150 mmHg), or very high (> 150 mmHg) range were associated with increased risk of recurrent stroke, thus suggesting a J-shaped relationship [20]. Treatment effect according to baseline etiological subtypes of ischemic stroke was available.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial included 3020 patients with MRI-confirmed lacunar ischemic stroke < 6 months (mean age: 63 ± 10.7 years) to compare two therapeutic strategies for BP management: SBP target of 130–149 mmHg versus SBP < 130 mmHg [14]. After a mean follow-up of 44 months, there was a non-statistically significant difference in the primary outcome (all strokes) in favor of the intensive regimen (HR = 0.81, 95% CI: 0.64–1.03). The intensive SBP reduction strategy was associated with a reduction in hemorrhagic stroke (HR = 0.37, 95% CI: 0.15–0.85), and no impact was observed on the other secondary outcomes. In post-hoc analyses, the authors confirmed a J-shaped association between achieved BP and outcomes, with the lowest risk obtained at SBP 124 mmHg and DBP 67 mmHg [21].

Four other multicenter trials were conducted in The Netherlands [15], Sweden [17], and China [16, 18]. The Dutch TIA trial that included 1473 patients with nondisabling ischemic stroke (66%) or TIA (34%) [15], and the Tenormin after Stroke and TIA (TEST) trial that enrolled 720 patients with ischemic stroke (86%), TIA (8%), or intracerebral hemorrhage (6%) [17] failed to demonstrate any reduction in stroke recurrence, vascular deaths, or deaths from all causes in patients assigned atenolol versus patients receiving placebo. In contrast, the Chinese trial Post-stroke Antihypertensive Treatment Study (PATS, 5665 patients, 84% with ischemic stroke/TIA and 16% with intracerebral hemorrhage) [16], and the trial conducted by Liu et al. [18] (1520 patients, 82% with ischemic stroke/TIA and 18% with intracerebral hemorrhage) demonstrated a significant reduction of stroke recurrence in the active group (indapamide, and perindopril + indapamide, respectively) compared with placebo.

A recent meta-analysis identified seven additional studies that focused on BP management after stroke [22–29]. Most of them included a limited number of patients [23, 25, 26, 28, 29], and two studies were conducted during the 70 s [23, 25]. Only a few proportion of stroke patients were included in the Heart Outcomes Prevention Evaluation (HOPE) trials (10.9% of the total cohort of the trial) [24], and in the Study on Cognition and Prognosis in the Elderly (SCOPE) trials (3.9%) [29]. Finally, the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) trial compared two regimens (eprosartan versus nitrendipine) in 1405 stroke patients, with a reduction in stroke recurrence in the eprosartan group (incidence density ratio: 0.75; 95% CI: 0.58–0.97) after a mean follow-up of 2.5 years [27].

The meta-analysis of the 14 clinical trials totalized 42,736 patients [22]; two thirds were part of the PROGRESS, PRoFESS or SPS3 trials. Pairwise meta-analyses of placebo-controlled randomized clinical trials showed that

antihypertensive treatment was associated with a reduced risk of recurrent stroke (RR = 0.73; 95% CI: 0.62–0.87), disabling or fatal stroke (RR = 0.70, 95% CI: 0.59–0.85), and cardiovascular death (RR = 0.85, 95% CI: 0.75–0.96). Although favorable trends were observed, the association was not statistically significant for ischemic stroke (RR = 0.87; 95% CI: 0.70–1.07), hemorrhagic stroke (RR = 0.65; 95% CI: 0.41–1.05), myocardial infarction (RR = 0.77; 95% CI: 0.57–1.03), or death from any cause (RR = 0.92; 95% CI: 0.82–1.03). Of note, the subgroups of patients who achieved a mean SBP < 130 mmHg had a significantly lower prevalence of recurrent stroke (8.3%) compared with the subgroups whose SBP ranged between 130 and 140 mmHg (9.2%) and SBP > 140 mmHg (11.7%). Finally, meta-regression analyses demonstrated that SBP reduction was linearly related to a lower risk of recurrent stroke, myocardial infarction, death from any cause, and cardiovascular death.

Specific situations

Intracranial artery stenosis

BP reduction in patients with intracranial artery stenosis is controversial, because it may theoretically compromise cerebral blood flow and favor the occurrence of hemodynamic ischemic stroke. However, the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial provided interesting data on this subject [30]. In this study, 451 patients with recent TIA or ischemic stroke associated with 70–99% stenosis of a major intracranial artery were assigned to receive either only aggressive medical management (dual antiplatelet therapy for 3 months followed by monotherapy, antihypertensive treatment to achieve a target of SBP < 140 mmHg or < 130 mmHg in diabetic patients, and statin therapy to achieve a target of LDL-cholesterol < 1.81 mmol/L) or aggressive medical management plus arterial stenting with the Wingspan stent. After a mean follow-up of 32 months, aggressive medical management was only found to be more beneficial than stenting, with a reduced risk of the primary endpoint (stroke or death within 30 days after enrolment, ischemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up). Interestingly, a sub-analysis of this trial showed that 75% of enrolled patients achieved the SBP target during follow-up, primarily after the first 4 months [31]. The patients who did not achieve the target SBP had greater risk of ischemic stroke at 3 years: each 10 mmHg increase was associated with a 20% increase in recurrent ischemic stroke. However, this result needs to be nuanced: further studies are needed to define strategies with regard to the time needed before antihypertensive treatment is initiated in patients with symptomatic intracranial artery stenosis and to confirm whether BP management should differ according to the origin of the index ischemic stroke (watershed infarct versus embolic mechanism).

Age and BP reduction

The issue of BP targets for secondary prevention of stroke in the elderly has not been clearly investigated. The mean age of patients in secondary prevention trials ranges from 59 to 72 years old. This raises the question of whether the findings of these trials can be directly applied to day-to-day practice when, in real life, mean age at first-ever stroke onset is about 75 years old [32]. Currently, the proportion of patients aged > 75 years is 60%, and 45% of patients are > 80 years old [33]. The ageing of the population is also expected to dramatically increase the number of elderly stroke patients in the coming years, highlighting the importance of specific guidelines for this age group. Indeed, recent estimates indicate that 70% of stroke patients will be 75 years old or more by 2030 [33].

A post-hoc analysis of the SPS3 study revealed that there was no statistical interaction between age (older/younger than 75 years old) and the effect of treatment, except for vascular death, which was significantly reduced in the intensive BP group in patients > 75 years old [34].

Other interesting data originate from trials not specifically conducted in stroke patients. In the Hypertension in the Very Elderly Trial (HYVET), 3845 patients ≥ 80 years old with SBP ≥ 160 mmHg were assigned to receive either indapamide or placebo (and if necessary perindopril 2 or 4 mg or placebo) to achieve a target BP of 150/80 mmHg [35]. Median follow-up was 1.8 years. Active treatment was associated with a 30% reduction in the occurrence of the primary outcome of fatal or non-fatal stroke. In addition, the rate of death from stroke was reduced by 21% and that of death from cardiovascular causes by 23%, and fewer serious adverse events were reported in the active-treatment group. However, at inclusion, less than 7% of patients had a history of stroke and 3% had previous myocardial infarction, so this study should be regarded as a primary prevention trial. The Systolic Blood-Pressure Intervention Trial (SPRINT) randomized high cardiovascular risk patients with a SBP of 130 to 180 mmHg (but no diabetes or stroke), to two therapeutic strategies: target SBP of < 120 mmHg versus target SBP of < 140 mmHg [36]. A sub-analysis performed on 2636 participants ≥ 75 years old (mean age 79.9 ± 4 years; 37.9% women) found a reduction in the occurrence of the primary endpoint (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) in the intensive regimen group (achieved

SBP: 123.4 mmHg) versus the control group (achieved SBP: 134.8 mmHg) after a median follow-up of 3.1 years (HR = 0.66, 95% CI: 0.51–0.85, $p = 0.01$) [37]. A non-significant reduction in the occurrence of stroke was observed as well (HR = 0.72, 95% CI: 0.43–1.21, $p = 0.22$). All-cause mortality was significantly reduced by 33%. Although high-risk patients were enrolled, stroke patients were excluded, making direct application to secondary prevention difficult.

BP reduction in diabetic patients

Although most clinical practice guidelines recommend a target SBP of < 130 mmHg in patients with diabetes, this recommendation was called into question by the publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial (ACCORD-BP) in 2010 [38]. In this trial, 4733 patients with type 2 diabetes and hypertension were assigned to either intensive antihypertensive therapy (target SBP < 120 mmHg) or standard therapy (target SBP < 140 mmHg). At 1 year, mean SBP was 119.3 mmHg in the intensive-therapy group and 133.5 mmHg in the standard therapy group. After a mean follow-up of 4.7 years, there was no significant difference in the occurrence of the primary outcome (a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death): 1.87%/year for the intensive versus 2.09%/year for the standard group (HR = 0.88; 95% CI: 0.73–1.06; $p = 0.20$). Concerning the secondary endpoints, there was no significant difference in the rates of non-fatal myocardial infarction, major coronary disease, heart failure, or death. However, patients in the intensive-therapy group had a lower risk of any stroke (0.32%/year versus 0.53%/year, HR = 0.59; 95% CI: 0.39–0.89; $p = 0.01$), and non-fatal stroke (0.30%/year versus 0.47%/year, HR = 0.63; 95% CI: 0.41–0.96; $p = 0.03$). In this trial, one third of patients had a cardiovascular history, but there was no significant interaction for primary outcome. Interestingly, the intensive-therapy group experienced more serious adverse events attributed to antihypertensive treatment (3.3% versus 1.3%, $p < 0.001$), which contributed to the reexamination of the most relevant BP target in diabetic patients.

Nevertheless, there are several potential explanations for the lack of beneficial effect observed for the primary outcome of ACCORD-BP. First, the event rate was 50% lower than expected among patients assigned to the standard treatment, leading to a lack of power in the analysis of the outcome. In addition, ACCORD-BP was part of the larger ACCORD trial in which diabetic patients were assigned to intensive or standard glucose lowering, and a post-hoc analysis of ACCORD-BP showed a reduced risk of the primary composite outcome with intensive BP/intensive glycemic control, intensive BP/standard glycemic control, and standard BP/intensive glycemic control compared with standard BP/standard glycemic control [39].

Several meta-analyses were published after the ACCORD trial [40, 41]. In a meta-analysis of 13 randomized clinical trials that enrolled 37,736 participants with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance and followed-up on them for 4.8 years, intensive BP control (achieved SBP < 135 mmHg) was associated with a reduction in the rates of stroke (OR = 0.83; 95% CI: 0.73–0.95) and all-cause mortality (OR = 0.90; 95% CI: 0.83–0.98), but not with a reduction in cardiovascular mortality (OR = 0.93; 95% CI: 0.82–1.02) or myocardial infarction (OR = 0.92; 95% CI: 0.80–1.06) [40]. In addition, the intensive regimen was associated with a 20% increase in serious adverse effects. For patients with more intensive BP reduction (achieved SBP < 130 mmHg), the reduction in stroke occurrence was more pronounced (OR = 0.53; 95% CI: 0.38–0.75) though there was no difference in other outcomes. However, this result was offset by a 40% increase in serious adverse effects. Finally, this meta-analysis failed to demonstrate that intensive BP reduction had any beneficial effect on the microvascular complications of diabetes including nephropathy, retinopathy, or neuropathy.

A more recent meta-analysis of data from 49 randomized trials, including 73,738 participants with diabetes mellitus, analyzed each outcome according to baseline SBP and attained SBP [41]. It was found that, although the interactions were not statistically significant, the risk of stroke was reduced if baseline SBP was > 140 mmHg and attained SBP was < 140 mmHg. For myocardial infarction, a beneficial effect of treatment was observed if baseline SBP was > 140 mmHg (p for interaction = 0.017), and attained SBP was > 130 mmHg (p for interaction = 0.48). Finally, a reduction in all-cause mortality was observed only in patients with baseline SBP > 140 mmHg who attained SBP between 130 and 140 mmHg.

Based on these results, the optimal target of BP in diabetic patients remains to be confirmed. Although intensive SBP reduction seems to be relevant for reducing stroke risk, this result is counterbalanced by an increase in serious side-effects, and no improvement in the risk of other macrovascular events. Furthermore, whether diabetic patients with a history of stroke could benefit more from intensive SBP reduction is unclear, particularly because such patients are older and more vulnerable to side-effects.

Circadian BP variations and BP variability: new targets of stroke prevention?

The conclusions of previous randomized clinical trials were based on mean BP values obtained at follow-up visits, meaning that aspects such as circadian variations of BP and BP variability were not taken into consideration.

BP variability is defined as the overall variability during a period of time (standard deviation SD or coefficient of variation), with or without adjustment for time trends in underlying mean blood pressure (residual SD), or the average absolute difference between adjacent readings (successive variation) [42]. Post-hoc analyses of the UK-TIA aspirin trial, the European Stroke Prevention Study (ESPS-1), the Dutch TIA trial, and the Anglo-Scandinavian Cardiac Outcomes Trial Blood-Pressure-Lowering Arm (ASCOT-BPLA) revealed that visit-to-visit variability in SBP was strongly predictive of subsequent stroke and coronary events independent of mean SBP and independent of any time trend in SBP during follow-up [43]. Moreover, maximum SBP measured either during 24-h ambulatory blood-pressure monitoring (ABPM) or on clinic readings was more predictive of these events than mean SBP. In the ASCOT-BPLA trial in which 19,257 patients were randomly assigned to receive either amlodipine-based regimens or atenolol-based regimens, group SBP SD was lower in the amlodipine group than in the atenolol group at all follow-up visits, mainly because of lower within-individual visit-to-visit variability [44]. Interestingly, variability decreased over time in the amlodipine group, while it increased in the atenolol group. In addition, the lower risk of stroke in the amlodipine was partly attenuated after adjustment for mean SBP during follow-up and was abolished by further adjustment on within-individual SD of clinic SBP, thus suggesting a class effect. In line with this result, in a meta-analysis in which authors used effect of treatment on inter-individual variance in SBP as a surrogate for within-individual variability, calcium-channel blockers and non-loop diuretic drugs appeared to reduce inter-individual variation in SBP compared with other drugs [45]. Conversely, ACE inhibitors, angiotensin-2-receptor blockers, and β-blockers increased SBP variation. More recently, analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial that compared valsartan to amlodipine in 13,803 patients with hypertension also showed that that visit-to-visit SBP variability was associated with a greater risk of cardiovascular events, including ischemic stroke and death [46]. This association was observed irrespective of individual level of risk.

Taken together, these findings may be relevant for clinical practice, but further dedicated work is needed to confirm the effects of antihypertensive drugs on BP variability, the consequences in terms of risk of recurrence in secondary prevention of stroke, and to determine the best approach for evaluating BP variability in routine practice.

Another insufficiently explored consideration is the impact of circadian BP variation on stroke risk. Firstly, nocturnal BP dipping patterns may influence the occurrence of vascular events. In normal conditions, nocturnal BP decreases by 10% to 20% compared with daytime values; individuals with this pattern are known as dippers. Three other profiles have been defined: non-dippers ($>0\%$ to $\leq 10\%$ nocturnal BP dipping), extreme dippers ($>20\%$ nocturnal BP dipping), and risers, also called reverse dippers ($\leq 0\%$ nocturnal BP dipping). Though the data is conflicting, it has been shown that reduced nocturnal BP dipping could be associated with stroke in both general and hypertensive populations [47]. Similarly, the extreme dipper pattern may confer a greater risk of cerebrovascular events. The JMU–ABPM study reported a J-shaped relationship between dipping status and stroke incidence in 575 older Japanese patients with sustained hypertension (determined by ABPM) after a mean follow-up of 41 months (extreme dippers 12%, risers 22%, non-dippers 7.6%, dippers 6.1%), and the associations remained significant after adjustment on confounding variables [48]. In addition, silent cerebral infarcts were significantly more frequent in extreme dippers and risers (extreme dippers 53%, risers 49%, non-dippers 41%, and dippers 29%).

Secondly, morning BP may also be considered in the evaluation of the risk of cerebrovascular events. The morning BP surge is an increase in BP values that occurs just after wakening, and it is defined by two parameters: the sleep-trough morning surge (average morning BP value minus lowest moving nocturnal BP value), and the pre-wakening morning surge (average morning BP value minus pre-wakening morning BP value). In the JMU–ABPM study, the morning surge in SBP based on ABPM was associated with an increased risk of both stroke events and silent cerebral infarcts on MRI, independently of 24-h SBP and nocturnal BP dipping status [49]. In the Japan Morning Surge Home Blood-Pressure (J-HOP) Study, in which self-measurement of BP was performed by 4310 hypertensive Japanese patients, increased SBP in the morning was more predictive of stroke events than evening SBP [50]. Finally, in the Olmesartan Naive patients to Establish Standard Target blood-pressure (HONEST) Study that enrolled 21,591 hypertensive patients with home BP monitoring followed for >2 years, on-treatment morning SBP ≥ 145 mmHg was associated with an increased risk of stroke, even in patients who had office SBP <130 mmHg (HR $=2.47$, $p=0.014$) [51]. This result was consistent with other studies that demonstrated that masked hypertension is associated with a greater risk of cardiovascular events [52, 53].

These data indicate that clinicians should consider 24-h control of BP when aiming to reduce the risk of stroke recurrence. In practice, home BP monitoring should be encouraged, and ABPM should be used to detect masked hypertension, abnormal circadian variations of BP, and excessive BP variability. The impact of different treatment strategies on these parameters needs to be evaluated in future dedicated trials.

Conclusion

BP control is a major challenge for stroke prevention. Randomized clinical trials have underscored the beneficial impact of BP reduction in decreasing stroke risk, but personalized management can still be improved. Several questions remain to be answered. Since etiological mechanisms of ischemic stroke are multiple, BP targets according to baseline ischemic stroke subtypes need to be refined given the current lack of convincing data. Moreover, whether specific conditions such as age and patient's comorbidities may have an impact on BP management strategies remains to be elucidated. Finally, beyond mean BP, circadian BP variations and BP variability have to be considered, and the impact of drug classes on these variables to be investigated more precisely. Future studies should specifically address these issues so as to guide clinicians in their day-to-day practice.

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Compliance with ethical standards

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