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Effect of Antihypertensive Treatment on Cerebral Blood Flow in Older Adults: a Systematic Review and Meta-Analysis

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BACKGROUND: In older age, the benefits of antihypertensive treatment (AHT) become less evident, with greater associated risk. Of particular concern is compromising cerebral blood flow (CBF), especially in those with cognitive impairment.

METHODS: We created a synthesis of the published evidence by searching multiple electronic databases from 1970 to May 2021. Included studies had participants with mean age ≥50 years, hypertension or cognitive impairment, and assessed CBF before and after initiating AHT. Two authors independently determined eligibility and extracted data. Study quality was assessed using The Risk of Bias in Nonrandomized Studies of Interventions tool. We summarized study characteristics (qualitative synthesis) and performed random-effects meta-analyses (quantitative synthesis).

RESULTS: Thirty-two studies (total n=1306) were included, of which 23 were eligible for meta-analysis. In line with the qualitative synthesis, the meta-analysis indicated no effect of AHT initiation on CBF (standardized mean difference, 0.08 [95% CI, −0.07 to 0.22]; P=0.31, I^2=42%). This was consistent across subgroups of acute versus chronic AHT, drug class, study design, and CBF measurement. Subgroups by age demonstrated an increase in CBF after AHT in those aged >70 years (standardized mean difference, 4.15 [95% CI, 0.16–8.15]; P=0.04, I^2=42%), but not in those aged 50 to 65 and 65 to 70 years (standardized mean difference, 0.18 [95% CI,−2.02 to 2.38]; P=0.87, I^2=49%; standardized mean difference, 1.22 [95% CI, −0.45 to 2.88]; P=0.15, I^2=68%). Overall, risk of bias was moderate-to-high and quality of evidence (Grading of Recommendations Assessment, Development and Evaluation) was very low, reflecting the observational nature of the data.

CONCLUSIONS: Accepting the observed limitations, current evidence does not suggest a harmful effect of AHT on CBF. Concerns over CBF should not preclude treatment of hypertension. (***Hypertension**. 2022;79:1067–1078. DOI: 10.1161/ **HYPERTENSIONAHA.121.18255**.)* • **Supplemental Material**

The prevalence of hypertension increases with age to about 66% of older adults (aged ≥65 years).[1] With increasing age, the treatment goals, specifically the blood pressure (BP) targets, for hypertension become less evident, leading to uncertainty around treatment decisions.[1,2] Some of this uncertainty relates to the theoretical

risks associated with a too rapid or extreme reduction in BP from antihypertensive treatment (AHT). Studies in older adults have shown links between low BP or use of AHT and adverse health outcomes, including increased mortality[3] and various markers of cognitive impairment or dementia.[4–6] A frequently suggested underlying

NOVELTY AND RELEVANCE

What Is New?

Initiation of antihypertensive treatment in older adults does not result in changes in cerebral blood flow. However, quality of the current evidence is low and there is lack of high-quality studies.

What Is Relevant?

In older adults, there is an ongoing debate on the risks versus benefits of antihypertensive treatment.

This work indicates that concerns regarding compromised cerebral blood flow might be unfounded.

Clinical/Pathophysiological Implications?

Hypertension management in older adults should consider both the expected benefits and risks of treatment, taking into account that a reduction in CBF following treatment is not expected

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AHT	antihypertensive treatment
ARB	angiotensin receptor blocker
BP	blood pressure
CBF	cerebral blood flow
MCI	mild cognitive impairment
MD	mean difference
SBP	systolic blood pressure

mechanism for such associations is a reduction in cerebral blood flow (CBF), caused by the reduction in systemic BP.

In health, a stable level of CBF is ensured by cerebral autoregulation, a regulatory mechanism that counteracts fluctuations in systemic BP by adjusting the resistance of cerebral arteries and arterioles.[7] The arteriosclerosis associated with increasing age and prolonged hypertension could lead to dysfunctional cerebral autoregulation mechanisms.[8] In that case, a reduction in BP may no longer be fully compensated for, potentially resulting in cerebral hypoperfusion.[7–9]

Against the theoretical risk of reduced CBF are the proven benefits of BP reduction in terms of stroke, cardiovascular disease, and heart failure,[10] even in older adults.[11] Hypertension is associated with structural and functional changes in the cerebral circulation, some of which may reversible.[12,13] Thus, long-term BP reduction could improve, rather than worsen, CBF and its regulation. Indeed, in older adults, lowering BP could prevent or slow down cognitive decline while reversing the reduction in CBF.[12] As cognitive decline is associated with decreased CBF in older adults,[14] preventing this reduction in CBF by treating hypertension may preserve cognitive function.

The apparently conflicting evidence around AHT and CBF may represent differences in study methods or biases in the study design. Many studies of CBF in older adults have small sample sizes and thus, modest but important associations may be missed. In this situation a systematic review of the published literature, with critical appraisal of studies and quantitative meta-analysis can help make sense of the available data. Several factors contribute to the complexity of the effects of AHT on CBF. Any study of AHT and CBF should include assessment of the techniques used to quantify CBF, should account for varying CBF baseline levels with age[15] and describe potential differential class effects of AHT on CBF.[16]

Therefore, the aim of this systematic review and meta-analysis was to evaluate published evidence on the effects of AHT on CBF in hypertensive older adults and older adults with mild cognitive impairment (MCI) or dementia.

METHODS

The review protocol was preregistered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020193911). The meta-analysis was not preregistered but added later after the systematic search yielded sufficient studies to be included in a quantitative analysis. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline.[17] All aspects of title searching data extraction and risk of bias assessment were performed by 2 reviewers working independently (A.E. van Rijssel and B.C. Stins) with access to a third reviewer (R.A.A. de Heus and M.L. Sanders) to make final decisions in case of disagreement. The authors declare that all supporting data are available within the article and its online supplementary files.

Eligibility Criteria

Studies included were interventional studies in which the effect of AHT on CBF was evaluated by measuring CBF pre-initiation and postinitiation of AHT, including: randomized controlled trials, nonrandomized controlled trials, and uncontrolled prestudies and poststudies. Populations of interest were older patients, (mean age ≥50 years), with hypertension (as defined by authors in the primary papers), dementia, or MCI as primary disease of interest. The following methods of measuring CBF were included: single photon emission computed tomography,

xenon-enhanced computed tomography, dynamic perfusion computed tomography, magnetic resonance imaging dynamic susceptibility contrast, arterial spin labeling, transcranial Doppler.[18] Articles with no full text available were excluded.

Sources and Search Strategy

A comprehensive search of PubMed (Medline), Embase (OVID), the Cochrane Library (CENTRAL), and Web of Science (Thomson Reuters) was performed. The articles were limited to humans and English language. The full search strategy is detailed in the data supplement.

Study Selection and Data Extraction

Study selection was performed using the Rayyan QCRI webtool.[19] Data on systolic BP (SBP) and CBF before and after AHT were extracted. When SBP was not reported we used mean arterial pressure. Our focus was global CBF (primary outcome), but CBF in cerebral regions was also extracted. If the study did not report global CBF, the average of the combined regions was calculated as a proxy for global CBF, and the SD's were pooled to give a summary estimate. When CBF values were only presented in a figure, the values were read from the figure by hand. Where necessary, we contacted authors of relevant articles to request additional data. All data are presented as value±SD, unless noted otherwise. SEM were converted to SD. We included CBF measurement using any metric but anticipated that the majority of data would be in the form CBF in mL/100 g/min, cerebral blood velocity in cm/s and Z scores. To ensure consistency of direction of effect, we multiplied data by minus one where necessary. For repeated measurements in an individual, a change in cerebral blood velocity measured with transcranial Doppler (eg, a 10% reduction) reflects a change in CBF of the same magnitude, under the assumption that the vessel diameter remained constant.[20]

Quality Assessment

Risk of bias for each study was assessed using the Risk of Bias in Nonrandomized Studies of Interventions tool.[21,22] For cross-over designs, a supplement was used to address some additional issues.[23] Discrepancies were resolved by an additional reviewer (R.A.A. de Heus or M.L. Sanders). In keeping with best practice guidance, any studies from our group were independently assessed by experienced reviewers who were not authors on the articles being assessed. The strength of evidence in this review was assessed using the Grading of Recommendations Assessment, Development and Evaluation criteria.[24]

Statistical Analysis

Revman Version 5.4 was used to conduct the quantitative meta-analysis. The inverse variance method[25] for continuous outcomes with a random effects model was used for all analyses. The primary analysis included all studies examining the chronic effects of AHT, using a standardized mean difference (MD) due to different outcome measures. We conducted the following sensitivity analyses: studies reporting (1) CBF in mL/100 g/min (to allow an analysis using MD, rather than a standardized effect), (2) acute (<24 hours) or chronic treatment (>2 weeks; standardized mean difference), (3) studies investigating chronic effects only: antihypertensive drug class, age, method of measuring CBF and study design (standardized mean difference). Forest plots with pooled estimates were created with 95% CI. The heterogeneity between studies was explored with the I^2 statistic[25] and publication bias using funnel plots.

RESULTS

Study Selection

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. After duplicate removal, 5020 records were screened for eligibility, of which 79 were assessed as full text. Thirty-two studies were included in the qualitative synthesis and 23 in the quantitative synthesis. Reasons for exclusion from this review after full-text review are presented in Table S1.

Study Characteristics

The study characteristics of the 32 included studies are presented in Table 1. Fourteen studies were randomized controlled trial's,[26–39] one was a nonrandomized trial (comparing hydrochlorothiazide with no medication without randomizing the groups)[40] and seventeen were prestudies and poststudies,[41–57] 6 of which used a cross-over design.[28,37–40,46] Twenty-three studies investigated chronic effects of AHT,[26–32,34–36,40–42,45–47,49–51,53,54] 5 investigated acute effects,[43,44,48,55] and 4 studies investigated both.[33,39,52,57] Sample sizes ranged from 6 to 673 participants with the mean age ranging from 50 to 79 years. Thirty studies included participants with hypertension.[27–54,56,57] Six studies included participants with dementia or MCI.[26,27,29,31,54,55] Fifteen studies used a calcium channel blocker,[26,29,31,32,34,36,38,39,43,44,47,48,52,55,57] but our data also included angiotensin receptor blockers,[27,31,36,49,50] diuretics,[27,28,36,38–40,42,51,52] angiotensin-converting enzyme inhibitors,[27,30,36,37,41,42,44,53,54,56] β blockers,[28,30,37,45,46,48] and α blockers.[36,44,48] Measurement techniques for CBF were 133-Xenon inhalation technique,[28,33,37–39,44–46,53,56] arterial spin labeling,[26,35,36] single photon emission computed tomography,[29,31,32,40,42,49,51,52,54] transcranial Doppler,[26,27,48,57] and PET.[30,50,55] The follow-up time ranged from 10 minutes to 1 year.

Quality Assessment and Grading of Recommendations Assessment, Development and Evaluation Rating

Quality assessment of studies included in the review is presented in Table 2. Risk of bias was judged to be low in only one trial, moderate in 11 trials, serious in 19 trials, and no information in 1 trial. The large number of trials rated at serious risk was mainly due to lack of adequate control for potential confounding factors (age, duration
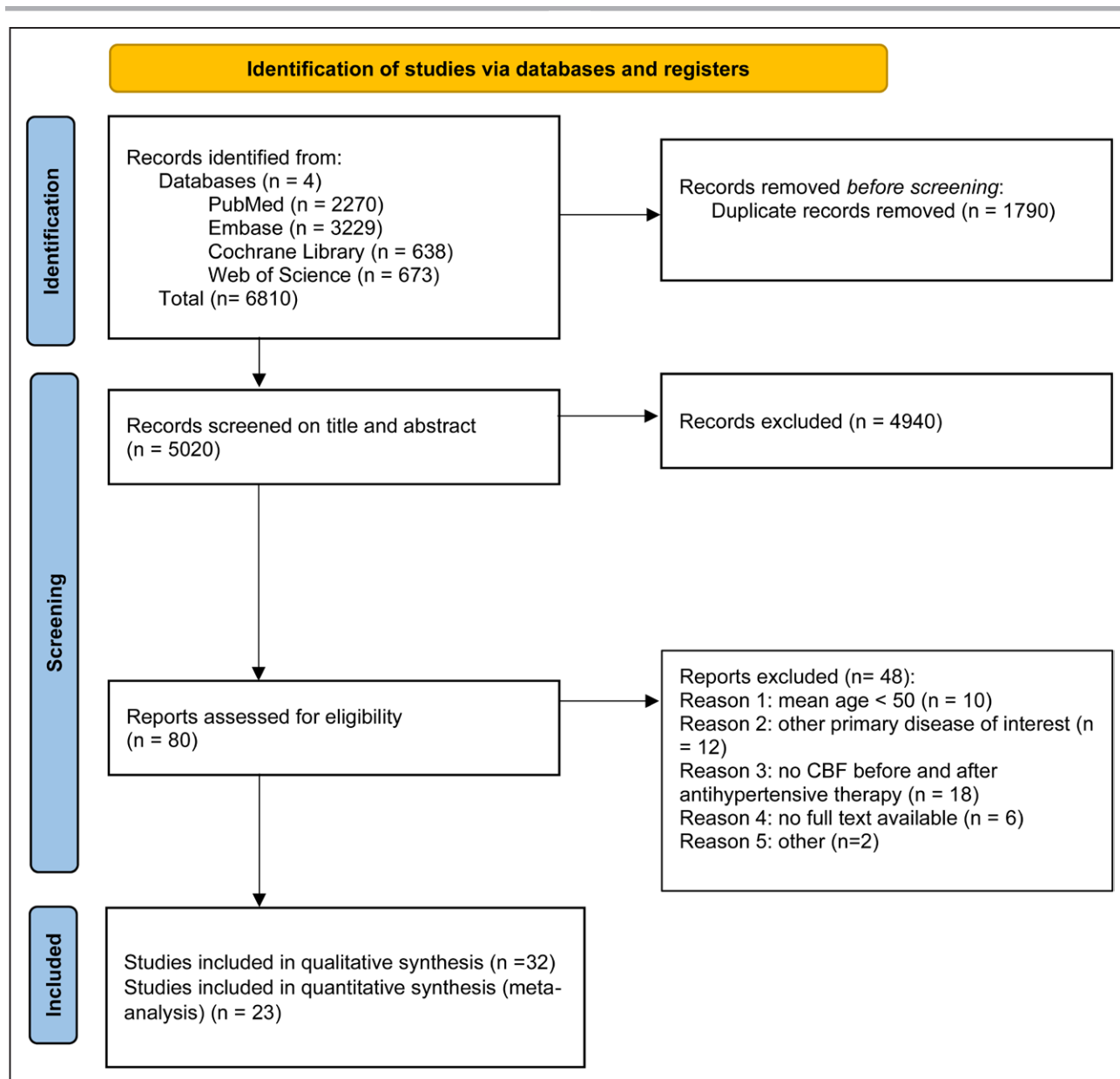
ORIGINAL ARTICLE

Figure 1. Study flow diagram.
N indicates number.

of follow-up). Risk of bias was judged to be moderate in the reporting bias domain for most studies as few pre-published an adequate trial protocol. Grading of Recommendations Assessment, Development and Evaluation rating of the quality of evidence was very low (Table S2). The funnel plot asymmetry suggests publication bias towards studies demonstrating a reduction in CBF (Figures S1 and S3).

Qualitative Synthesis

All studies showed a significant decrease in SBP or mean arterial pressure following AHT, expect for Globus et al.[45] The fall in SBP ranged between −3.9 and −39.4 mm Hg. Five studies did not report the change in BP.

Global CBF

None of the 9 studies assessing the acute effect of AHT demonstrated a significant effect on global CBF. Eighteen studies investigating the chronic effect of AHT equally showed no significant change in global CBF. Only one study showed a significant decrease in global CBF after treatment with ceronapril for 9 weeks.[41] In contrast, 5 studies showed a significant increase in global CBF with chronic AHT.[34,35,42,45,49] Of these, 3 studies investigated the effect of AHT over time in one intervention group.[42,45,49] One study compared the effects of nifedipine and nilvadipine, demonstrating a significant increase in global CBF in the nilvadipine group.[34] Another study compared the effect of intensive BP lowering (target <120 mm Hg SBP) with usual BP lowering (target <140

Table 1. Study Characteristics

Study ID	Study design	Mean/median age (SD)	No. participants	Study population	Antihypertensive class	Acute/chronic	Change in SBP/MAP, mm Hg	Method measuring CBF	Follow-up†	CBF unit
Conen 1988[39]‡	RCT (Crossover)	50	5	Uncomplicated hypertensives	Calcium blocker	Acute	22	Xenon-133 infusion technique	2 h	mL/100 g/min
		61	21		Calcium blocker	Chronic	20		4 wk	
					Diuretic		15			
Cutler 1996[41]	Prepost	52 (8)	12	Essential hypertension	ACE inhibitor	Chronic	−12*	133-Xe with scintillation probes	9 wk	mL/100 g/min
De Jong 2019[26]	RCT	72.8 (6.2)	22 nilvadipine	Mild to moderate Alzheimer disease aged 50+	Calcium blocker	Chronic	−6.1	ASL MRI, TCD	6 mo	mL/100 g/min
			22 placebo				1.4			
Efimova 2008[42]	Prepost	53.0 (5.7)	15	Untreated or ineffectively treated essential hypertension	ACE inhibitor, diuretic	Chronic	−14.1	SPECT with 99 m Tc-HMPAO	24 wk	mL/100 g/min
Fagan 1992[43] ‡	Prepost	69	6	Hypertension for at least 5 y and receiving nifedipine	Calcium blocker	Acute	Unknown	MCA TCD	7 h	cm/s
Fagan 1995[44]‡	Prepost	66.9	15	Chronic hypertension, age range 53–85 y	ACE inhibitor, calcium blocker, vasodilator, α blocker	Acute	−3.9	133-Xe inhalation technique	60 min	mL/100 g/min
Globus 1983[45]‡	Prepost	59.2	6	Essential hypertension	Beta blocker	Chronic	−3.89	133-Xe inhalation technique	1 mo	mL/100 g/min
Griffith 1979[46]	Prepost (crossover)	56.8	33	Newly diagnosed essential hypertension	β blocker	Chronic	−23.3*	133-Xe inhalation technique	3 wk	mL/100 g/min
							−21.67*			
							−21*			
							−20.33*			
Hajjar 2013[27]	RCT	72	17 lisinopril	Hypertension and executive dysfunction, aged 60+	ACE inhibitor	Chronic	−19	MCA TCD	6 and 12 mo	cm/s
			17 candesartan		ARB		−16.67			
			13 hydrochlorothiazide		Diuretic		−14.33			
Hamdy 1984[28]	RCT (crossover)	69–91	9 dyazide	Hypertension above 170/100 mm Hg, age range 69–91	Diuretic	Chronic	−19.81	133-Xe	12 wk	mL/100 g/min
			14 propranolol		β blocker		−16.5			
Hanyu 2007[29]	RCT	76.4	6 nilvadipine	Essential hypertension, MCI	Calcium blocker	Chronic	−21	SPECT with I-123 IMP	12–16 wk	Z score
			6 amlodipine				−18			
James 1988[56]	Prepost	59.1 (11.9)	12	Essential hypertension	ACE inhibitor	Chronic	−19.7	133-Xenon inhalation technique	2 mo	mL/100 g/min
Jennings 2008[30]	RCT	52.6	12 lisinopril	Untreated mild to moderate hypertension	ACE inhibitor	Chronic	−16.56	PET with O15 labeled water	1 y	mL/100g/min (posterior parietal)
			16 atenolol		β blocker		−19.5			
Kamlow 1990[37]‡	RCT (crossover)	55.4	10	Hypertension, male treated with a diuretic	β blocker	Acute	−22	133-Xenon inhalation technique	3 h	mL/100 g/min
					ACE inhibitor		−21			
Kashiwagi 1998[47]	Prepost	69 (4)	10	Mild to moderate chronic hypertension, age range 61–75	Calcium blocker	Chronic	−13.67	Xenon computed tomography scans	12 wk	mL/100 g/min
Kume 2012[31]	RCT	78.8 (5.1)	10 telmisartan	Mild Alzheimer disease, essential hypertension	ARB	Chronic	−10.7	SPECT with I-123 IMP	6 mo	Z score
			10 amlodipine		Calcium blocker		−11.7			
Landmark 1995[38]	RCT (crossover)	70	22	Hypertension	Calcium blocker	Chronic	−16	133-Xenon inhalation technique	8 wk	mL/100 g/min
					Diuretic		−23			
Miller 2019[48]‡	Prepost	50 (12)	39	Severely elevated blood pressure SBP >180 mm Hg, history of poorly controlled chronic hypertension	Beta blocker, alpha blocker, calcium blocker	Acute	−34.7	TCD	60 min	cm/s

(Continued)

Table 1. Continued

Study ID	Study design	Mean/median age (SD)	No. participants	Study population	Antihypertensive class	Acute/chronic	Change in SBP/MAP, mmHg	Method measuring CBF	Follow-up†	CBF unit
Miyamori 1987[57]	Prepost	56 (6)	22	Essential hypertension	Calcium blocker	Acute	−29	Transcutaneous doppler	60 min	cm/s
			14			Chronic	Unknown		8 wk	
Nagata 2010[49]	Prepost	70.5 (5.7)	10	First- or second-degree essential hypertension	ARB	Chronic	−15.9	SPECT with 99 m Tc-HMPAO	24 wk	mL/100g/min
Nasrallah 2021[36]	RCT	67.3 (8.2)	356 intensive	>50 y, SBP 130–180 mm Hg and increased vascular risk (having clinical or subclinical cardiovascular disease, chronic kidney disease (estimated glomerular filtration rate of <60 mL/min/1.73 m²), a 10-year Framingham cardiovascular disease risk 15% or higher, or age 75 y and older	Diuretic, ACE inhibitor, ARB, calcium blocker, alpha blocker	Chronic	Unknown	Pseudo ASL	4 y	mL/100 g/min (frontal gray matter)
			317 standard							
Oku 2005[50]	Prepost	60.8 (3.4)	10	Essential hypertension	ARB	Chronic	−15.1	PET with O¹⁵ labeled water	8–23 wk	mL/100 g/min
Pandita-Gunawardena 1999[32]‡	RCT	79.0	13 amlodipine	Mild to moderate hypertension DBP ≥95 mm Hg, aged 65+	Calcium blocker	Chronic	−10	SPECT with 99 m Tc-HMPAO SPECT	8 wk	mL/100 g/min
			13 placebo				−2			
Pandita-Gunawardena 1989[33]	RCT	75	15 once daily	Mild to moderate essential hypertension SBP >170, DBP >100—130 mm Hg, aged 65+	Calcium blocker	Acute, chronic	−16	133-Xe inhalation technique with SPECT	2 h and 6 wk	mL/100 g/min
			15 divided daily dose				−36			
Ram 1987[51]	Prepost	67 (6)	8	Chronic stable uncomplicated hypertension, aged 60+	Diuretic	Chronic	−19.6	133-Xe with SPECT	6 wk	mL/100 g/min
Shimamoto 1995[34] ‡	RCT	68.8 (7.1)	13 nifedipine	Essential hypertension	Calcium blocker	Chronic	−16*	Carotid and vertebral artery	8 wk	mL/min
			12 nilvadipine				−15.4*	Doppler flowmetry		
Thulin 1993[52]	Prepost	50	12	Severe hypertension DBP >120 mm Hg	Calcium blocker	Acute, chronic	−33.4	133-Xe with SPECT	60 min and 3 wk	mL/100 g/min
					Diuretic		−39.4			
Traub 1982[40]	Non-RCT (cross-over)	61—76	8 HCTZ	Hypertension SBP >170 and DBP <100 mm Hg, only men, age range 61—76	Diuretic	Chronic	−10	133-Xe with SPECT	15 wk	mL/100 g/min
			12 no medication				Unknown			
Tryambake 2013[35]	RCT	75 (4)	20 intensive	Uncontrolled hypertension SBP >150 mm Hg, aged 70+	Intensive therapy	Chronic	−20	3T ASL MRI	12 wk	mL/100 g/min
			17 normal		Normal therapy		−4			
Waldemar 1990[53]	Prepost	55 (9)	8	Moderate essential hypertension	ACE inhibitor	Chronic	−14	133-Xe inhalation technique with SPECT	4–12 wk	mL/100 g/min
Weiner 1992[54]‡	Prepost	74.4 (4.4)	11	Alzheimer disease	ACE inhibitor	Chronic	Unknown	133-Xe with SPECT	4 wk	mL/100 g/min
Zazulia 2010[55]	Prepost	75 (6)	20	Very mild or mild symptomatic Alzheimer disease, hypertension, aged 60+	Calcium blocker	Acute	−14.7*	PET with O15 labeled water	10 min	mL/100 g/min

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASL, arterial spin labeling; CBF, cerebral blood flow; DBP, diastolic blood pressure; HMPAO, hexamethylprolyleneamine oxime; IMP, iodoamphetamine; MAP, mean arterial pressure; MCA, middle cerebral artery; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; RCT, randomized controlled trial; SBP, systolic blood pressure; SPECT, single photon emission computed tomography; Tc, technetium; TCD, transcranial Doppler; and Xe, xenon.

*MAP is presented instead of SBP.

†Time between the pre- and post-measurement of CBF.

‡Study was not included in meta-analysis.

Table 2. Quality Assessment

	D1	D2	D3	D4	D5	D6	D7	Overall
Conen et al[39]	?	?	+	+	+	+	?	?
Cutler et al[41]	−	+	+	+	+	+	−	−
De Jong et al[26]	+	+	+	+	+	+	+	+
Efimova et al[42]	×	+	+	+	+	+	−	×
Fagan et al[43]	×	−	+	+	+	+	×	×
Fagan et al[44]	−	+	+	+	+	+	−	−
Globus et al[45]	×	×	+	?	+	+	?	×
Griffith et al[46]	×	+	×	?	?	+	?	×
Hajjar et al[27]	+	+	+	?	?	+	−	−
Hamdy et al[28]	+	+	+	?	×	+	×	×
Hanyu et al[29]	+	+	+	+	+	+	−	−
James et al[56]	×	+	+	+	−	+	−	×
Jennings et al[30]	+	+	+	+	+	+	×	×
Kamlow et al[37]	+	+	+	+	+	+	−	−
Kashiwagi et al[47]	×	+	+	+	?	+	−	×
Kume et al[31]	+	+	+	+	+	+	−	−
Landmark et al[38]	+	+	+	+	−	+	−	−
Miller et al[48]	×	+	−	−	+	+	−	×
Miyamori et al[57]	×	+	+	+	+	+	−	×
Nagata et al[49]	×	+	+	+	+	+	−	×
Nasrallah et al[36]	+	+	+	?	×	+	+	×
Oku et al[50]	×	+	+	+	+	+	−	×
Pandita-Gunawardena et al[32]	+	+	+	×	×	+	−	×
Pandita-Gunawardena et al[33]	+	+	+	+	+	+	×	×
Ram et al[51]	−	+	+	+	+	+	−	−
Shimamoto et al[34]	+	+	+	?	?	+	−	−
Thulin et al[52]	−	+	+	+	+	+	−	−
Traub et al[40]	×	?	?	+	?	+	−	×
Tryambake et al[35]	+	+	+	+	+	+	−	−
Waldemar et al[53]	×	+	+	+	+	+	−	×
Weiner et al[54]	×	+	+	?	×	+	×	×
Zazulia et al[55]	×	+	+	+	−	+	−	×

Domains: D1: bias due to confounding; D2: bias due to selection of participants; D3: bias in classification of interventions; D4: bias due to deviations from intended interventions; D5: bias due to missing data; D6: bias in measurement of outcomes; and D7: bias in selection of the reported result. Judgement: ×, serious; −, moderate; +, low; and ?, no information.

mm Hg), with a significant increase in global CBF after intensive BP lowering.[35]

Regional CBF

Thirteen studies investigated regional CBF.[26,28,29,31,32,34,36,42,47,49,50,52,54] Only 5 studies showed significant changes (mostly increases) in CBF in specific brain regions.[26,29,31,52,54] However, these regions were not consistent across the 5 studies. One study showed a significant increase in CBF in the left hippocampal region after treatment with nilvadipine.[26] Another study showed a significant increase in CBF in the left frontal region after treatment with nilvadipine and a significant decrease in the left temporal region after treatment with amlodipine.[29] One study investigated the effect of telmisartan and amlodipine,[31] with a significant increase in CBF in the right subcallosal gyrus, right superior parietal lobe, right cuneus, and right lingual gyrus with telmisartan. Whereas, with amlodipine, a significant increase was only found in the right cingulate gyrus. Another study showed a significant increase in CBF in the left temporal region after treatment with ceronapril.[54] Finally, a significant increase in CBF was found in the left cortex after acute treatment with felodipine.[52]

CBF in Patients With Cognitive Impairment or Dementia

Six studies included participants with dementia or MCI. These studies showed results consistent with those that had included cognitively intact participants with hypertension. None found significant changes in global CBF. Four studies demonstrated a significant change (mostly increases) in specific cerebral regions: left hippocampus, left frontal, left temporal, right subcallosal gyrus, right superior parietal lobe, right cuneus, right lingual gyrus, right cingulate gyrus.[26,29,31,54]

Meta-Analysis

The results of the primary analysis are presented in Figure 2. Twenty-two studies were included in the primary analysis. The number of participants was 1107 before therapy and 888 after therapy. There was no significant effect of AHT on global CBF on pooled analyses across all studies (standardized mean difference, 0.08 [95% CI, −0.07 to 0.22]; P=0.31, I^2=42%).

Sensitivity Analysis

The results of the analysis by treatment type (acute/chronic) are presented in Figure S2. There was no significant effect of AHT on global CBF in either the acute or chronic treatment groups (MD, −0.67 [95% CI, −4.70 to 3.36]; P=0.75, I^2=0%; MD, 0.82 [95% CI, −0.41 to 2.05]; P=0.19, I^2=59%, respectively). Results of the subgroup analyses by study characteristics are presented in Table 3. The forest plot of the subgroup analysis age is presented in Figure 3. There was a significant increase in CBF with AHT in the study populations with a mean age of >70 years (n=126; MD, 4.15 [95% CI, 0.16–8.14]); P=0.04, I^2=42%). The majority of subgroup analyses showed high heterogeneity (I^2 >50%), except the calcium blocker and mean age >70 years subgroups (I^2=30% and 42%, respectively), and the acute, diuretic, 133-Xe inhalation technique, and 133-XE single photon emission computed tomography subgroups (I^2=0%). The forest plots of the other subgroup analyses are presented in Figures S4 through S6.
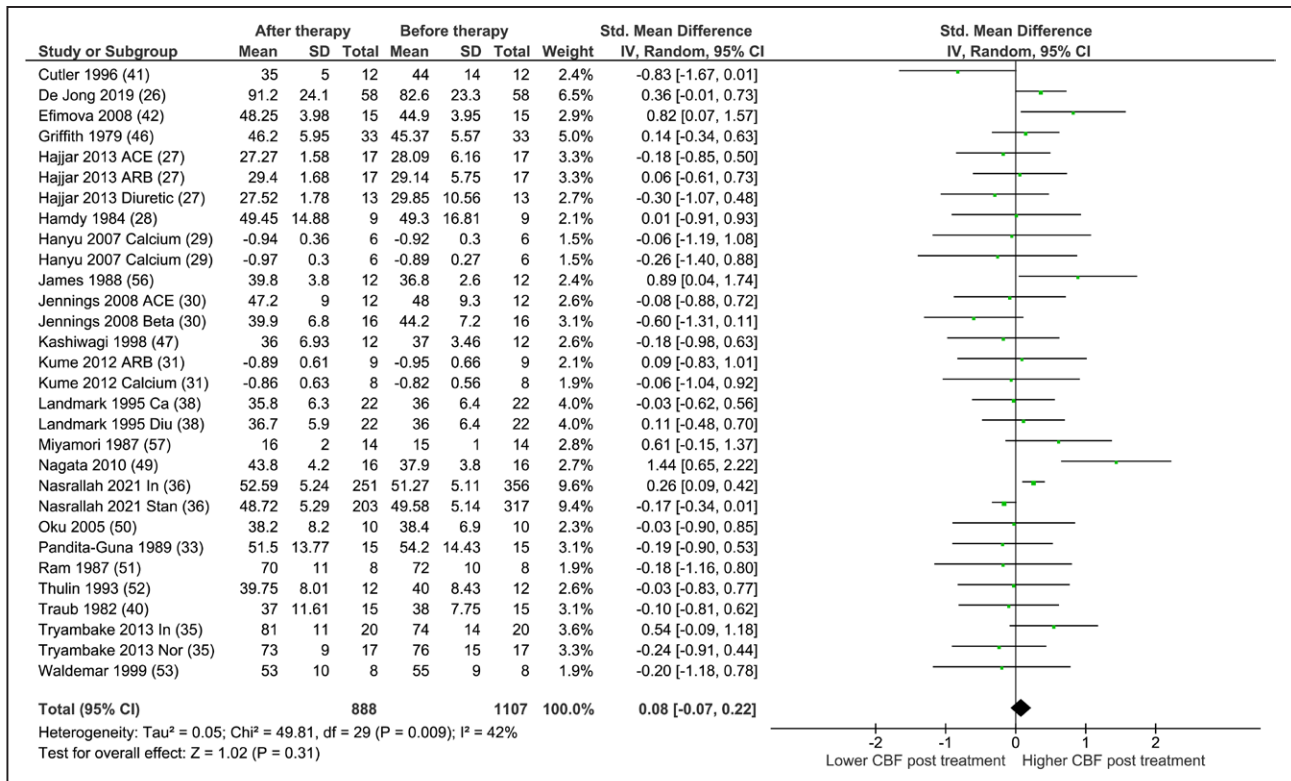
Figure 2. Standardized mean difference (SMD) in cerebral blood flow before and after chronic antihypertensive treatment.
Total indicates number of participants. Some randomized controlled trials investigated the effect of 2 different therapies, these have been added to the analysis separately. Most studies expressed cerebral blood flow (CBF) in mL/100 g/min, except for Fagan 1992 (cm/s), Hajjar 2013 (cm/s), Hanyu 2007 (Z score), Kume 2012 (Z score), Miller 2019 (cm/s), Miyamori 1987 (cm/s), and Shimamoto 1995 (mL/min). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; Ca, calcium blocker; Diu, diuretic; IV, inverse variance; In, intensive; Nor, normal; and Stan, standard.

DISCUSSION

Summary of Evidence

This systematic review assessed the effects of AHT on CBF in older adults with hypertension, as well as in people with cognitive impairment. Overall, we identified no significant effect of AHT on global CBF. This finding did not vary by class of antihypertensive drug used, method of measuring CBF, and study design. Five studies showed significant changes (mostly increases) in CBF in specific brain regions, but these regions were not consistent. Studies including participants with dementia or MCI demonstrated similar findings to cognitively normal participants with hypertension. However, the quantitative synthesis was limited by significant heterogeneity and moderate-to-serious risk of bias.

Results in Context

This review focused on older patients (mean age in our included studies ranged from 50 to 79 years) with hypertension, including patients with cognitive impairment and dementia, due to clinical concerns around BP lowering in these groups. Chronic hypertension is highly prevalent in older adults.[2] Longstanding hypertension causes

remodeling of cerebral blood vessels, leading to higher vascular resistance due to thicker walls and smaller lumens.[58] Moreover, there is a higher risk of developing stenotic atherosclerotic plaques with chronic hypertension.[59] In theory, increased cerebrovascular resistance and cerebrovascular stenosis could require higher BP to maintain CBF. Indeed, a rightward shift of the autoregulation curve has been demonstrated in older adults with chronic hypertension, where CBF is maintained at high levels of BP.[60,61] It is often suggested that this phenomenon implies an impairment in cerebral autoregulation, where CBF would no longer be maintained if BP were reduced, due to irreversible remodeling and stenosis.[60,61] Finally, the selfish brain hypothesis suggests that the brain drives hypertension to ensure adequate CBF.[62] All these theories suggest that the brain and its vasculature have adapted to the chronic hypertension state and that consequently, lowering BP might disrupt CBF and cause deterioration of brain function.

However, the findings of this review do not support this notion. In contrast, we found that BP reduction in hypertension, even in patients with MCI and dementia, does not reduce CBF. Recent studies in older adults with hypertension and common comorbidities have demonstrated consistent findings with those reported here. In

Table 3. Subgroup analyses MD in Cerebral Blood Flow After Chronic Antihypertensive Treatment

Characteristics		No. participants before therapy	No. participants after therapy	Mean difference (95% CI)	P value	I²	Included studies
Acute/chronic treatment	Acute	62	62	−0.67 (−4.70 to 3.36)	0.75	0	33,52,55
	Chronic	1017	798	0.82 (−0.41 to 2.05)	0.19	59	26,28,30,33,35,36,38,40–42,46,47,49–53,56
Antihypertensive class	Calcium blocker	119	119	0.14 (−2.46 to 2.71)	0.91	8	26,33,38,47,52
	Beta blocker	49	49	−1.33 (−6.30 to 3.63)	0.60	69	30,46
	ACE inhibitor/ARB	70	70	0.90 (−2.70 to 4.50)	0.63	67	30,41,49,50,53,56
	Diuretic	54	54	0.28 (−2.72 to 3.29)	0.85	0	28,38,40,51
Age	<65 y	130	130	−0.18 (−2.02 to 2.38)	0.87	49	30,41,42,46,50,52,53,56
	>65 y	872	653	1.22 (−0.45 to 2.88)	0.15	68	26,28,33,35,36,38,47,49,51
	>70 y	126	126	4.15 (0.16 to 8.14)	0.04	42	26,33,35,49
Method measuring CBF	ASL MRI	549	768	0.78 (−1.37 to 2.93)	0.48	79	26,35,36
	133-Xe inhalation technique	124	124	0.98 (−0.44 to 2.40)	0.18	0	33,38,46,47,53,56
	133-Xe SPECT	35	35	−0.85 (−5.21 to 3.51)	0.70	0	40,51,52
Study design	RCT	645	864	0.17 (−1.35 to 1.69)	0.83	56	26,28,30,33,35,36,38
	Prepost/non-RCT	153	153	1.23 (−0.76 to 3.22)	0.23	52	40–42,46,47,49–53,56

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASL, arterial spin labeling; CBF, cerebral blood flow; MD, mean difference; MRI, magnetic resonance imaging; Xe, xenon; SPECT, single photon emission computed tomography; and RCT, randomized controlled trial.

patients with small vessel disease and carotid artery occlusive disease, there was no significant change in CBF with AHT.[63,64] Similarly, in patients with type 2 diabetes, a progressive reduction in CBF was only seen with BP lowering in patients with microvascular complications.[65] In contrast, in patients with metabolic syndrome, CBF increased following BP reduction.[66] Similarly, studies in younger populations (mean age <50 years) demonstrated comparable findings of stable CBF after BP lowering with AHT.[13,67,68]

Different classes of AHT could differ in their effects on CBF due to their varying mechanisms of action. Angiotensin converting enzyme inhibitors are known to successfully reverse hypertensive vascular hypertrophy and remodeling.[69] Angiotensin receptor blockers reverse the cerebrovascular pathological growth and inflammation and can improve vessel compliance.[68,70] Lastly, calcium antagonists may have a neuroprotective effect on cerebral ischemia through inhibition of intracellular calcium accumulation which may serve as a trigger for irreversible cellular injury. In particular, nilvadipine can reach higher concentrations in the brain than other calcium blockers, as a result of the high brain blood ratio and longer half-life in the brain compared with blood.[34] Despite these different theoretical benefits, this review did not demonstrate different effects between different AHT classes. The effect of specific AHT classes on the risk of dementia has also been studied in a meta-analysis, again finding no evidence for class effects.[71]

We observed a significant increase in CBF with BP reduction in studies with participants with a mean age >70 years, but not in studies with a lower age cut off. While this should be interpreted with caution, given the small number of studies and the risk for multiplicity, and

ecological bias in subgroup analyses, this is an interesting finding. Previous studies have shown that hypertension may reduce CBF, and this finding suggests this could be partially reversible. Mechanistically, antihypertensive drugs might be involved in remodeling of cerebral arteries, although direct evidence is lacking.[13,26,72,73]

Strengths and Limitations

This review had some limitations. First, a large number of trials were rated as moderate or serious risk of bias, mainly due to confounding and reporting bias. Reporting bias was high because many studies (published before 2000) did not prepublish their protocol. However, this was not standard practice before 2000 and, therefore, the risk of bias may be inflated. Second, not all studies presented exact values of BP and CBF. As a result, the values were derived from a figure or global CBF was calculated from the average of specific regions, potentially reducing the reliability of these estimates.

The strength of this review is that the article selection, data extraction and risk of bias assessment were performed independently by 2 reviewers, ensuring reliability. In addition, a comprehensive search strategy was conducted to detect as many studies as possible, with a quantitative synthesis of the available evidence.

Perspectives

There is clear evidence of a beneficial effect of BP reduction on stroke, cardiovascular disease, and heart failure,[10] even in older adults.[11] However, concerns that BP reduction may reduce CBF in older adults with longstanding hypertension may deter physicians
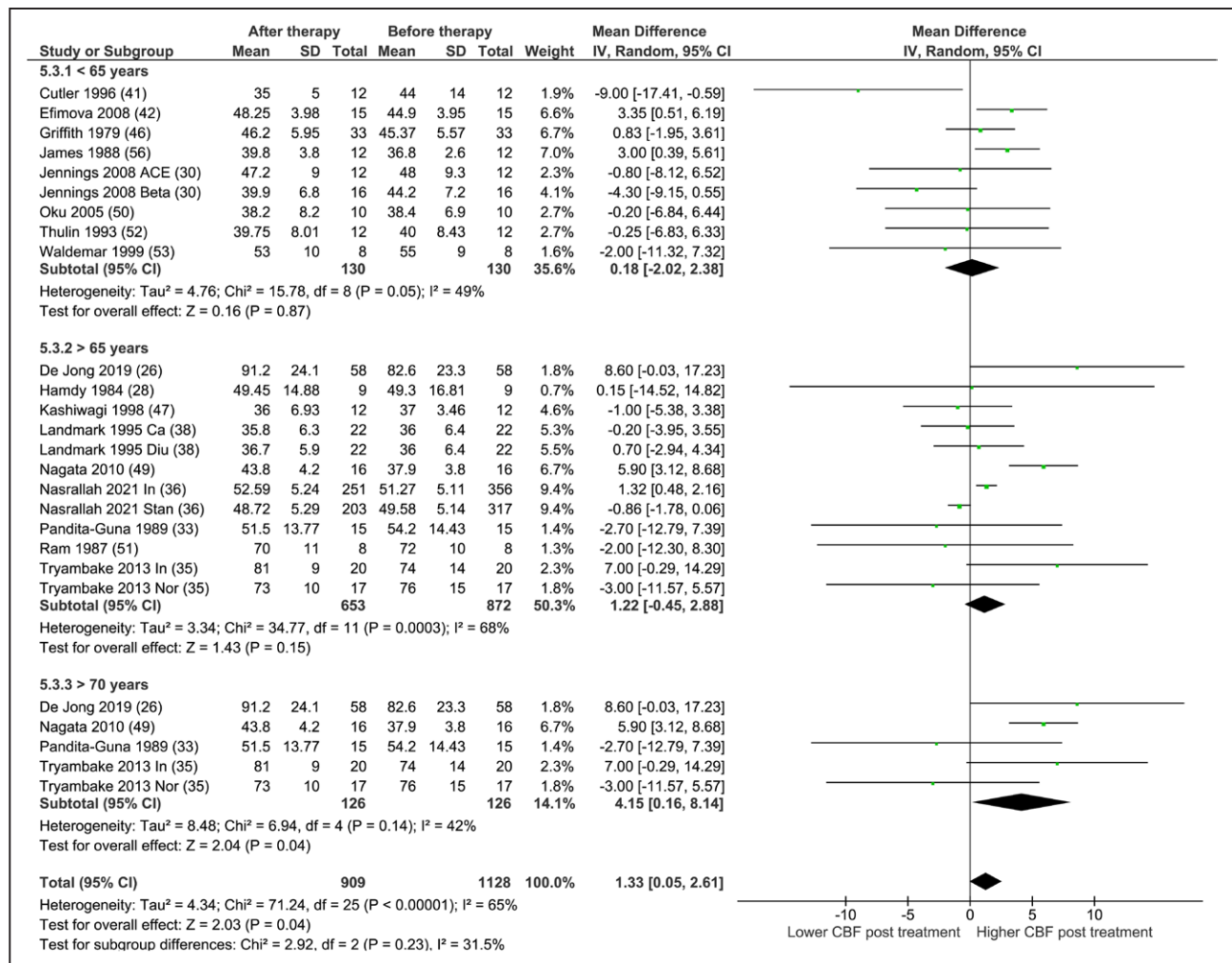
ORIGINAL ARTICLE

Figure 3. Subgroup analysis age in mean difference.
Total indicates number of participants. Some randomized controlled trials investigated the effect of 2 different therapies. ACE indicates angiotensin-converting enzyme; Ca, calcium blocker; CBF, cerebral blood flow; Diu, diuretic; In, intensive; IV, inverse variance; Nor, normal; and Stand, standard.

or patients from adequately treating hypertension. The results from this systematic review and meta-analysis support treatment of hypertension in older adults, given that there was no evidence for a reduction in CBF. However, there were too few studies to draw definitive conclusions on the effects of AHT in older adults with cognitive impairment. Further research is needed to understand if AHT is equally beneficial and safe in this population.

Conclusions

With the best current available evidence this review does not suggest a reduction in CBF following treatment with AHT in older patients, although quality of evidence is low, and heterogeneity was high. Despite these limitations, it seems warranted to conclude no harmful effects on CBF occur in the populations studied. A well-designed follow-up study is needed to confirm this in (very) frail older adults (eg, >75 years,

clinical frailty scale >4 or with dementia/MCI), using treatment algorithms used in clinical practice for a reasonable duration (eg, at least 3 months). Preliminary power calculations suggest that such a trial would need about 50 patients.

Supplemental Materials

Methods 1
References[1–81]
Tables S1–S4
Figures S1–S6

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