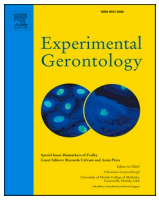
Experimental Gerontology 193 (2024) 112461

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero



Review article

The effect of a change in antihypertensive treatment on orthostatic hypotension in older adults: A systematic review and meta-analysis

Marjolein Klop [a,b], Andrea B. Maier [c,d,e], Carel G.M. Meskers [f], Julika M. Steiner [b], D. Odette Helsloot [b], Richard J.A. van Wezel [a,g,h], Jurgen A.H.R. Claassen [b,i], Rianne A.A. de Heus [b,j,*]

[a] Department of Neurobiology, Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands
[b] Department of Geriatric Medicine, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[d] Centre for Healthy Longevity, @AgeSingapore, National University Health System, Singapore
[e] Department of Human Movement Sciences, @AgeAmsterdam, Faculty of Behavioural and Movement Sciences, Amsterdam Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[f] Department of Rehabilitation Medicine, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, the Netherlands
[g] Department of Biomedical Signals and Systems, Technical Medical Centre, University of Twente, Enschede, the Netherlands
[h] OnePlanet Research Center, Radboud University, Nijmegen, the Netherlands
[i] Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom
[j] Department of Primary and Community Care, Radboud University Medical Center, Nijmegen, the Netherlands

ARTICLE INFO

Section Editor: Marzetti Emanuele

Keywords:
Hypertension
Antihypertensive medication
Blood pressure
Postural hypotension

ABSTRACT

Background: Orthostatic hypotension (OH) is common in older adults with hypertension. Antihypertensive treatment (AHT) prevents cardio- and cerebrovascular events. However, physicians are concerned to cause OH, making them hesitant to initiate or augment AHT in older adults with hypertension.
Methods: We systematically researched electronic databases for trials with older participants (≥65 years) with hypertension and OH assessment after initiating, discontinuing, or augmenting AHT. Study quality was assessed using the ROBINS-I tool. Meta-analyses on OH prevalence and postural blood pressure (BP) drop were performed.
Results: Twenty-five studies (26,695 participants) met inclusion criteria, of which fifteen could be included in the meta-analyses. OH prevalence decreased after AHT initiation or augmentation (risk ratio 0.39 (95 % CI = 0.21–0.72; $I^2 = 47$ %; $p < 0.01$), $n = 6$ studies), but also after AHT discontinuation (risk ratio 0.39 (95 % CI = 0.28–0.55; $I^2 = 0$ %; $p < 0.01$), $n = 2$ studies). Postural BP drop did not change after initiation or augmentation of AHT (mean difference 1.07 (95 % CI = -0.49–2.64; $I^2 = 92$ %; $p = 0.18$), $n = 11$ studies). The main reason for ten studies not to be included in the meta-analyses was absence of baseline OH data. Most of these studies reported OH incidences between 0 and 2 %. Studies were heterogeneous in OH assessment methods (postural change, timing of BP measurements, and OH definition). Risk of bias was moderate to serious in twenty studies.
Conclusion: Results suggest that AHT initiation or augmentation decreases OH prevalence, implying that the risk of inducing OH may be overestimated in current AHT decision-making in older adults. However, the overall low level of evidence and the finding that AHT discontinuation reduces OH prevalence limit firm conclusions at present and highlight an important research gap. Future AHT trials in older adults should measure OH in a standardized protocol, adhering to consensus guidelines to overcome these limitations.

1. Introduction

Orthostatic hypotension (OH) is classically defined as a sustained blood pressure (BP) drop upon standing of at least 20 mmHg systolic and/or 10 mmHg diastolic (Freeman et al., 2011; Brignole et al., 2018). OH is causally associated with immediate incidents, such as dizziness and falls (Mol et al., 2019), and is a marker for increased risk of functional decline (Mol et al., 2018), dementia (Iseli et al., 2019), and

* Corresponding author at: Department of Geriatric Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.
E-mail address: rianne.deheus@radboudumc.nl (R.A.A. de Heus).

https://doi.org/10.1016/j.exger.2024.112461
Received 21 March 2024; Received in revised form 7 May 2024; Accepted 15 May 2024
Available online 25 May 2024

mortality (Frith et al., 2015). Dizziness and falls can originate directly from temporarily reduced cerebral oxygenation (Mol et al., 2019; Finucane and Kenny, 2016). Longer-term adverse outcomes might also result from cerebral hypoperfusion due to inadequate BP regulation after postural change (Claassen et al., 2021). On the other hand, OH may be a manifestation of cardiovascular disease, which explains its association with poorer long-term outcomes (Juraschek et al., 2018). OH has a prevalence of 6 % in the general population (Joseph et al., 2017) up to 26 % in geriatric patients of 85 years or older (Low, 2008). It is common in adults with hypertension, which can be explained by overlap in underlying causes, such as impaired BP regulation caused by arterial stiffness (Mattace-Raso et al., 2006; Raber et al., 2022). In addition, antihypertensive drugs, prescribed to prevent cardio- and cerebrovascular events associated with hypertension, have been linked to OH and cerebral hypoperfusion, especially posing a risk to older adults (Veglio et al., 2009; Biaggioni, 2018).

A survey among US geriatric healthcare professionals showed they were less likely to initiate antihypertensive treatment (AHT) in older adults, especially those ≥85 years, and a recent study showed that the presence of OH leads primary care physicians to deprescribe AHT (Hajjar et al., 2002; Kaye et al., 2023). Recent, less conservative guidelines recommend AHT in older adults over 65 years at a systolic BP ≥ 130 mmHg (Whelton et al., 2018; Williams et al., 2018). However, these guidelines advise caution in frail older adults. Therefore, AHT in older adults is started at a higher threshold than in the adult population, as it is still unknown whether the benefits of treatment outweigh the risks (Fernandes and Olde Rikkert, 2019). The assumption that AHT causes or increases OH is, however, controversial. In a meta-analysis on drug-induced OH, of all commonly used types of AHT, only beta-blockers were associated with OH (Bhanu et al., 2021). In a randomized controlled trial (RCT) in community-dwelling older adults aged 75 years or older, discontinuing antihypertensives led to a lower incidence of OH (Moonen et al., 2016). On the other hand, a meta-analysis of clinical trials demonstrated that intensive AHT, i.e., treatment towards a lower target BP, reduced the risk of OH in adults (not necessarily older adults) with hypertension compared to standard treatment (Juraschek et al., 2021). In another meta-analysis, no cerebral hypoperfusion was found in older adults over 50 years undergoing AHT (van Rijssel et al., 2022). Differences in study design, OH assessment methods, and definitions of OH may partly explain these contrasting findings.

We aimed to investigate whether a change in AHT is associated with (changes in) OH prevalence and severity in older adults specifically. To do so, published trials that encompassed changes in antihypertensive drug use (either initiated, discontinued, or augmented) and measured OH solely at follow-up (qualitative synthesis) or at baseline and follow-up (meta-analyses) were systematically reviewed, including a critical review on the methods used to assess OH.

2. Methods

This systematic review was registered in PROSPERO under the number 'CRD42020191375'.

2.1. Study selection

Inclusion criteria were: 1) population with participants of 65 years or older, or subgroup analysis with participants of 65 years or older (Sabharwal et al., 2015); 2) study design was an RCT or uncontrolled trial during which AHT was initiated, discontinued, or augmented; 3) antihypertensives belonged to five major classes (Laurent, 2017): angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, calcium-channel blockers (CCBs), and diuretics (when studies investigated multiple types of AHT, only the analyses on these five types were considered in our synthesis); 4) AHT was prescribed for the indication 'hypertension'; 5) OH was reported after a change in AHT; 6) written in English. Exclusion criteria encompassed 1) study design of cross-sectional studies, case reports, letters to the editor, and review articles; 2) studies restricted to neurogenic OH, including only participants with Parkinson's disease, or related synucleopathies; 3) studies investigating an acute effect of AHT, for example in the postoperative setting.

2.2. Literature search

In consultation with a librarian, a search strategy was determined, using keywords and MeSH terms for 'antihypertensive drugs', 'orthostatic hypotension', and 'older adults', see Supplemental Material. Electronic databases that were searched were PubMed, Embase, Web of Science, and Cochrane Library. The search was performed from inception to 21 November 2023. Duplicate abstracts were removed using Endnote (version 20), and the remaining non-duplicate abstracts were imported into Rayyan QCRI software for title and abstract screening, performed independently by two reviewers (J.S., R.C., M.K., or R.d.H.). Full-text screening was independently performed by two reviewers (J.S., M.K., or R.d.H.). Discrepancies were solved by a third reviewer (R.d.H. or J.C.). Moreover, references of eligible studies were screened for additional studies meeting the inclusion criteria.

2.3. Data extraction and risk of bias

Data were extracted from the original articles (M.K.), including age, study design, antihypertensive medication class, OH measurement characteristics (type of postural change, definition of OH used, timing of BP measurement), OH prevalence, and resting and standing BP. The consensus definition of OH as a '*sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60 degrees on a tilt table*' was used to retrieve OH prevalence, when more definitions were given (Freeman et al., 2011). When different standing BP values were given, the value between 1 and 3 min of standing was used rather than a value before 1 min or after 3 min. Resting and standing BP were derived from figures when not reported explicitly. When unreported, the difference between resting and standing BP (standing minus resting BP) was calculated, and standard deviations were imputed using a correlation coefficient calculated from a study in which these values were present, as explained in further detail in the Supplemental Material (Higgins et al., 2022). A sensitivity analysis was performed to determine the impact of imputation. Risk of bias was assessed by two authors independently (M.K. and O.H.) using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for uncontrolled trials, as we were interested in differences between pre- and post-treatment (Sterne et al., 2016; Higgins et al., 2022). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was performed to determine the overall level of evidence (Schunemann et al., 2013).

2.4. Meta-analysis

Meta-analyses were performed using Revman version 5.4.1, addressing two outcome values: prevalence of OH (after initiating AHT and after discontinuation of AHT) and rest-stand difference in BP as a measure for OH severity. Studies were included in the meta-analysis if they reported these outcomes before and after a change in AHT. These meta-analyses were repeated after exclusion of studies that were judged to have a serious or unknown risk of bias. For the OH prevalence analysis, the inverse variance method with a random effects model for dichotomous outcomes was used, reporting a risk ratio. For the rest-stand difference analysis, the inverse variance method with a random effects model for continuous variables was used, resulting in a reported mean difference. Heterogeneity was assessed using the I^2 statistic. *P*-values below 0.05 were considered statistically significant.

3. Results

3.1. Search

The literature search identified 2678 articles, 1905 of which were unique and screened. Eventually, twenty-five studies were included in this systematic review, see Fig. 1.

Included studies (26,695 individuals with a change in AHT) were performed between 1985 and 2023, see Table 1. Twelve RCTs, three cross-over trials, and ten uncontrolled trials were included. Four RCTs investigated drug versus placebo, one continuation versus discontinuation of AHT, six antihypertensive drug class 1 versus antihypertensive drug class 2, and one intensive (towards a lower BP target) versus standard AHT. Uncontrolled trials studied either the initiation or addition (nine studies) or discontinuation (one study) of a specific antihypertensive drug. All studies involved hypertensive community-dwelling older adults in age groups ranging to 80 years or older. Specific study samples included patients with mild cognitive impairment (one study (Moonen et al., 2016)) or Alzheimer's disease (one study (de Heus et al., 2019);). Restrictions on baseline OH were set in three studies, excluding all OH (Bravo et al., 1990), excluding only symptomatic OH (Lee et al., 2021) or excluding standing SBP values below 110 mmHg (Williamson et al., 2016). Five studies excluded people with (uncontrolled or insulin-dependent) diabetes mellitus (Lee et al., 2021; Williamson et al., 2016; Jansen et al., 1989; Masuo et al., 1996; Suzuki et al., 2015). Treatment duration varied between 6 weeks and 5 years. The postural change used to assess OH was sit-to-stand (ten studies), supine-to-stand (eight studies), or not reported (eight studies). Six studies adhered to the current consensus definition of OH (Freeman et al., 2011). Thirteen studies did not specify how they defined OH, three only investigated systolic OH, and three used supine-stand cut-off values for a sit-stand postural change.

3.2. Quality assessment

Three trials had a low risk, twelve moderate risk, and nine serious risk of bias; one was judged to no information (Table 2 and Supplementary Table S.1). Serious risk was mainly caused by inadequate control for potential confounders in an uncontrolled trial design (age, baseline BP). Moderate risk of bias in the selection domain was often due to the absence of an AHT washout period prior to a change in AHT. Unknown risk of bias in the domains 'deviation from intended interventions' and/or 'missing data' was due to unreported numbers of participants lost to follow-up and/or unreported numbers of participants with completed outcome assessment. Moderate risk of bias in the reporting domain was often judged because of the absence of a pre-published protocol.

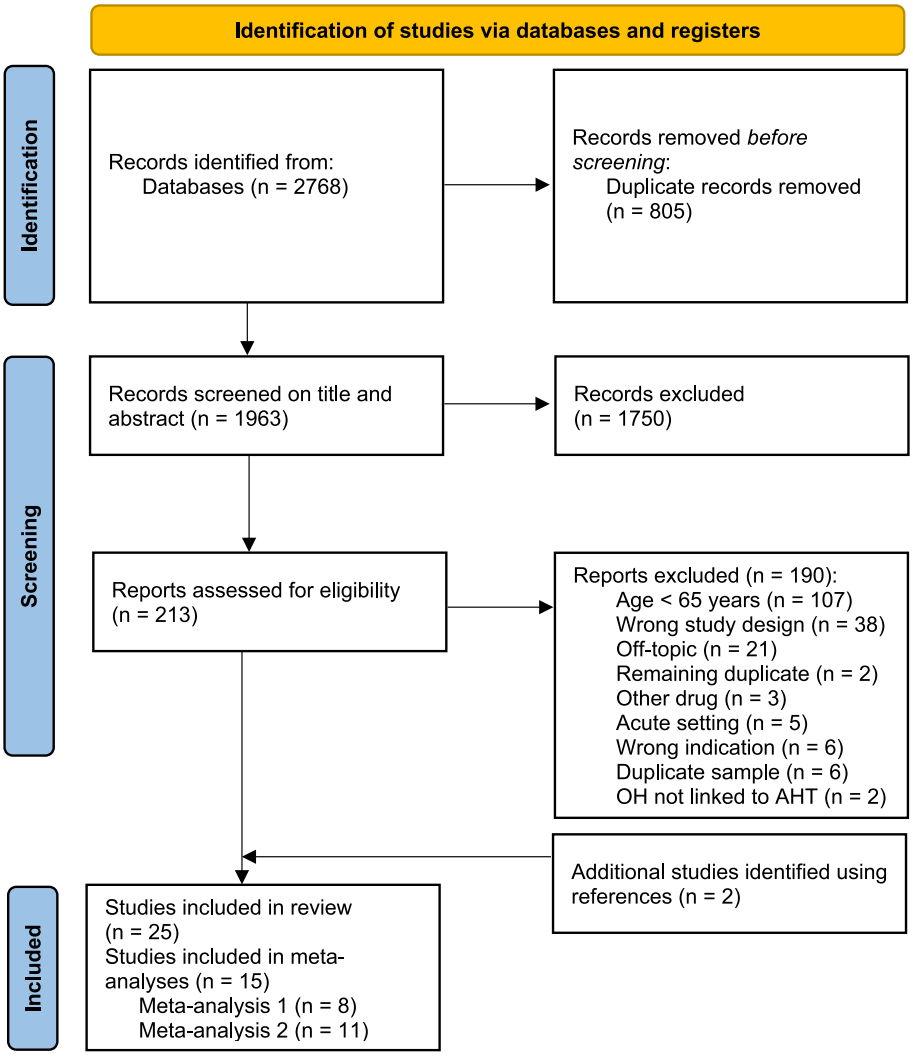


Fig. 1. PRISMA flow diagram of study selection and inclusion. Meta-analysis 1: meta-analysis on the OH prevalence before and after a change in AHT. Meta-analysis 2: meta-analysis on the rest-stand BP difference before and after a change in AHT.

Table 1
Characteristics of the included studies.

First author	Sample size	Study sample	Age[a]	Baseline SBP/DBP[b]	BP target	Class of AHT	Medication at start[c]	Design	Comparison	OH definition[d]	Baseline position	Timing BP measurement[e]	Follow-up duration
Acanfora (Acanfora et al., 1997)*	28		69 (1)	156 (1.5) / 101 (1.0)	Not reported	ACE + Diu	Washout	Uncontrolled trial	Drug use	Not reported	Sit	Not reported	24 weeks
Beckett (Beckett et al., 2008)*	1933		84 (3)	173.0 (8.4) / 90.8 (8.5)	< 150/ 80 mmHg	Diu (+ ACE)	Washout	RCT	Drug	≥ 20/10 mmHg at 2	Sit	2	1.8 years (median)
	1912			173.0 (8.6) / 90.8 (8.5)					Placebo				2.1 years (mean)
Bravo (Bravo et al., 1990)*	214	No OH	70 (4)	164 (18) / 100 (4)	DBP < 90 mmHg	CCB	Washout	Uncontrolled trial	Drug use	Not reported	Sit	Mean 1;3;5	12+ weeks
Bursztyn (Bursztyn et al., 1993)*	23		68 (1)	163 (4) / 97 (1)	DBP < 90 mmHg	CCB	Washout	RCT (cross-over)	Drug 1	≥ 10 mmHg SBP or DBP	Sit	Not reported	6 weeks
				163 (4) / 97 (2)		ACE			Drug 2				
De Heus (de Heus et al., 2019)*	112	AD	76 (5)	148.2 (6.3) / 78.8 (8.4)	Not reported	CCB	AHT	RCT	Drug	≥ 15/7 mmHg at 1	Sit	1;5	78 weeks
	103		75 (6)	149.3 (6.8) / 80.5 (8.9)					Placebo				
Fogari (Fogari et al., 2009)*	47		82 (4)	178.9 (13.8) / 98.6 (5.2)	DBP < 90 mmHg	ARB + CCB	Washout	RCT	Drug 1	≥ 20/10 mmHg at 2	Supine	2	24 weeks
	47		83 (5)	178.7 (14.1) / 97.7 (4.9)		ARB + Diu			Drug 2				
Fotherby (Fotherby and Potter, 1994)*	47		76 (range 65–84)	151 (19) / 81 (11)	Not reported	62 % Diu, 47 % CCB, 43 % β	AHT	Uncontrolled trial	Drug discontinuation	≥20 mmHg SBP at 1–3	Supine	Mean 1;2;3	12 months
Germino (Germino et al., 2012)	176		72 (5)	165.5 (11.9) / 87.7 (9.6)	< 130/ 80 mmHg	ARB (+ Diu)	Washout	Uncontrolled trial	Drug use	Not reported	Not reported	Not reported	12 weeks
Jansen (Jansen et al., 1989)*	15	No insulin-dependent DM	72 (2)	190 (6) / 104 (1)	Not reported	CCB	Washout	RCT	Drug 1	≥ 20 mmHg SBP	Supine	2	12 weeks
	16		75 (4)	186 (4) / 103 (2)		Diu			Drug 2				
Juraschek (Juraschek et al., 2019)	2552		≥ 65[f]	146.6 (15.7) / 83.1 (10.1)	< 140/ 90 mmHg	Diu (+ β)	AHT	RCT	Drug 1	≥ 20/10 mmHg <3	Not reported	Not reported	5 years
	1552			146.5 (15.6) / 82.9 (10.1)		CCB (+ β)			Drug 2				
	1559			146.8 (15.6) / 83.0 (10.0)		ACE (+ β)			Drug 3				
Krakoff (Krakoff, 1989)	57		78 (7)	Range DBP	DBP < 95 mmHg	CCB	Washout	RCT	Drug	Not reported	Supine	5	8 weeks
	32		78 (8)	95–114					Placebo				
Laher (Laher et al., 1988)*	60		75 (range 65–85)	190 (6.3) / 106 (1.3)	<160/90 mmHg	ACE (+ Diu)	Washout	Uncontrolled trial	Drug use	Not reported	Sit	Not reported	12 weeks
Landmark (Landmark and Dale, 1985)*	10		73 (range 65–83)	193 (29) / 104 (12)	Not reported	CCB	Washout	RCT (cross-over)	Drug 1	Not reported	Supine	2	8 weeks
				193 (30) / 106 (11)					Placebo				

(*continued on next page*)

Table 1 (*continued*)

First author	Sample size	Study sample	Age[a]	Baseline SBP/DBP[b]	BP target	Class of AHT	Medication at start[c]	Design	Comparison	OH definition[d]	Baseline position	Timing BP measurement[e]	Follow-up duration
Langdon (Langdon, 2000)	1507		≥ 65[f]	181.3/ 104.2	DBP < 90 mmHg	CCB	AHT	Uncontrolled trial	Drug use	Not reported	Not reported	Not reported	10 weeks
Lee (Lee et al., 2021)	238	No symptomatic OH and insulin-dependent or uncontrolled DM	74 (3)	156.6 (9.9) / 83.7 (8.9)	< 140/ 90 mmHg	ARB (+Diu)	Washout	RCT	Drug 1	Not reported	Sit	Not reported	16 weeks
	120		74 (4)	156.5 (9.9) / 83.7 (8.9)		ACE (+ Diu)			Drug 2				
Masuo (Masuo et al., 1996)*	50	No DM	73 (6)	SBP 170	SBP < 140 mmHg	CCB	No AHT	RCT	Drug 1	≥10 % SBP or ≥ 20/10 mmHg at 2	Supine	2	2 years
	50		74 (7)			β			Drug 2				
	50		74 (5)			ACE			Drug 3				
	50		78 (8)			Diu			Drug 4				
Moonen (Moonen et al., 2016)*	86	MCI	80 (4)	155.6 (21.6) / 84.7 (11.0)	Not reported	β/Diu/ ARB/ACE /CCB	AHT	RCT	Discontinuation	≥ 20/10 mmHg <3	Sit	Immediately; 2× within 3	4 months
	76		82 (3)	149.5 (23.8) / 82.1 (11.3)					Continuation				
Neutel (Neutel et al., 2004)	3010		74 (6)	162.2 (14.6) / 88.9 (10.4)	< 140/ 90 mmHg	ACE	AHT	Uncontrolled trial	Drug use	Not reported	Not reported	Not reported	12 weeks
Sato (Sato et al., 2015)	62		74 (7)	156.0 (14.0) / 82.9 (10.5)	< 140/ 90 mmHg	ARB + Diu	AHT	RCT	Drug 1	Not reported	Not reported	Not reported	1 year
	58		75 (6)	156.1 (11.6) / 82.7 (9.5)		ARB + CCB			Drug 2				
Silveira (Silveira et al., 2004)*	400		> 80[f]	SBP 181.5 (11.3)	Not reported	Diu	Washout	RCT	Drug 1	≥ 20/10 mmHg	Sit	Not reported	6 months
	400			182.2 (11.3)		ACE			Drug 2				
	400			180.9 (11.5)					Placebo				
Slavachevsky (Slavachevsky et al., 2000)*	39		70 (4)	158.8 (8.7) / 97.1 (5.9)	> 6 mmHg SBP decrease	ACE	Washout	RCT (cross-over)	Drug 1	≥ 20 mmHg SBP	Supine	Immediately;1;5	8 weeks
				160.3 (9.1) / 96.3 (5.7)		CCB			Drug 2				
Suzuki (Suzuki et al., 2015)	9255	No DM	≥ 65[f]	SBP 157 (15)	SBP < 140 mmHg	ARB + Diu	AHT	Uncontrolled trial	Drug use	Not reported	Not reported	Not reported	6 months
Weijs (Weijs et al., 2023)*[g]	14	Frail (CFS 4–7)	80 (5)	164 (10) / 87 (11)	SBP ≤ 140 mmHg	ACE/ARB/ CCB/Diu (+β/Diu)	AHT	Uncontrolled trial	Drug use	≥ 20/10 mmHg <5	Supine/ sit	1;3;5	7 weeks (median)
Weir (Weir et al., 2013)	228		70 (4)	155.1 (9.3) / 85.4 (8.9)	SBP < 140 mmHg	CCB/ARB (+ Diu)	AHT	Uncontrolled trial	Drug use	Not reported	Not reported	Not reported	20 weeks
Williamson (Williamson et al., 2016)	1317	No type 2 DM and standing DBP < 110 mmHg	80 (4)	141.6 (15.7) / 71.3 (11.0)	SBP < 120 mmHg	#AHT	AHT	RCT	Intensive	Not reported	Not reported	Not reported	3.14 years (median)
	1319		80 (4)	141.6 (15.8) / 70.9 (11.0)	SBP < 140 mmHg				Standard				

OH: orthostatic hypotension, DM: diabetes mellitus, CFS: clinical frailty scale, RCT: randomized controlled trial, AHT: antihypertensive treatment, ARB: angiotensin receptor blocker, ACE: angiotensin-converting enzyme inhibitor, CCB: calcium channel blocker, Diu: diuretic, β: beta blocker, #AHT: number of antihypertensive drugs, BP: blood pressure. <3: within three minutes. SBP: systolic blood pressure, DBP: diastolic blood pressure,

AD: Alzheimer's Disease, MCI: mild cognitive impairment. Study sample: all studies included community-dwelling older adults, specific characteristics of the sample are reported, as well as relevant exclusion criteria that might have influenced study results regarding OH. If nothing reported, there were no particularities.

* In meta-analysis.

[a] Reported as mean (SD) or mean (range minimum-maximum).

[b] Reported as SBP/DBP mean (SD) or range minimum-maximum, in mmHg.

[c] Medication at start: AHT means that AHT was still used, no AHT means that as an inclusion criterium, participants did not use AHT, and washout means there was a washout period before the intervention.

[d] Reported as systolic/diastolic blood pressure drop (resting-standing value).

[e] Reported in minutes after postural change. Mean before the number of minutes means that the mean of different measurements was taken as the standing blood pressure value.

[f] Mean (SD) or range of age not reported, only age group.

[g] Only available in pre-print (not yet peer-reviewed).

3.3. Qualitative synthesis

3.3.1. AHT efficacy

All studies showed AHT to reduce resting BP (not reported by five studies). The SBP decrease after initiating AHT ranged from 6.8 to 33 mmHg, while the SBP increase after antihypertensive discontinuation was 6 mmHg (Moonen et al., 2016).

3.3.2. OH prevalence before and after a change in AHT

Twenty-three studies investigated the effect of AHT use on OH prevalence (Moonen et al., 2016; de Heus et al., 2019; Bravo et al., 1990; Lee et al., 2021; Williamson et al., 2016; Jansen et al., 1989; Masuo et al., 1996; Suzuki et al., 2015; Acanfora et al., 1997; Bursztyn et al., 1993; Fogari et al., 2009; Fotherby and Potter, 1994; Germino et al., 2012; Krakoff, 1989; Laher et al., 1988; Landmark and Dale, 1985; Langdon, 2000; Neutel et al., 2004; Sato et al., 2015; Silveira et al., 2004; Slavachevsky et al., 2000; Weir et al., 2013). Before treatment, OH prevalence, reported by seven of these studies, ranged from 0 to 33 % (de Heus et al., 2019; Williamson et al., 2016; Jansen et al., 1989; Masuo et al., 1996; Silveira et al., 2004; Slavachevsky et al., 2000). After treatment, twenty-one studies reported OH prevalence (de Heus et al., 2019; Bravo et al., 1990; Lee et al., 2021; Williamson et al., 2016; Jansen et al., 1989; Masuo et al., 1996; Suzuki et al., 2015; Acanfora et al., 1997; Bursztyn et al., 1993; Fogari et al., 2009; Germino et al., 2012; Krakoff, 1989; Laher et al., 1988; Landmark and Dale, 1985; Langdon, 2000; Neutel et al., 2004; Sato et al., 2015; Silveira et al., 2004; Slavachevsky et al., 2000; Weir et al., 2013), of which nine reported no OH events (Bravo et al., 1990; Jansen et al., 1989; Acanfora et al., 1997; Bursztyn et al., 1993; Krakoff, 1989; Laher et al., 1988; Landmark and Dale, 1985; Sato et al., 2015; Weir et al., 2013), six had an on-AHT prevalence between 0 and 2 % (Lee et al., 2021; Masuo et al., 1996; Suzuki et al., 2015; Germino et al., 2012; Langdon, 2000; Neutel et al., 2004), and six between 2 and 22 % (de Heus et al., 2019; Williamson et al., 2016; Fotherby and Potter, 1994; Silveira et al., 2004; Slavachevsky et al., 2000). Two RCTs reported a decrease in OH on both AHT and placebo but no significant differences between AHT and placebo (de Heus et al., 2019; Silveira et al., 2004). Both studies measured OH using a sit-stand transition, for which one study used supine-stand cut-off values. AHT initiation led to a significant decrease in OH events in one uncontrolled trial, measured according to the consensus definition of OH (Masuo et al., 1996), and no significant change in two, considering only systolic OH (Jansen et al., 1989; Slavachevsky et al., 2000). One RCT showed that augmenting AHT did not lead to a higher OH incidence in the intensive compared to the standard treatment group (Williamson et al., 2016). In this study population, OH was present at baseline in almost 10 % of the samples, but people with a baseline standing SBP below 110 mmHg were excluded while having a resting SBP above 130 mmHg (inclusion criterion) (Williamson et al., 2016). Discontinuation of AHT, as assessed by two studies, led to a significantly decreased OH prevalence at follow-up for the discontinuation compared to the continuation group, assessed by a supine-stand or sit-stand transition (Moonen et al., 2016; Fotherby and Potter, 1994).

3.3.3. Classes of antihypertensives

Ten included studies compared different antihypertensive classes (Lee et al., 2021; Jansen et al., 1989; Masuo et al., 1996; Bursztyn et al., 1993; Fogari et al., 2009; Juraschek et al., 2019; Landmark and Dale, 1985; Sato et al., 2015; Silveira et al., 2004; Slavachevsky et al., 2000). A combination of different antihypertensive drug classes was frequently initiated, either immediately or when a participant was not responsive to monotherapy. The most used antihypertensive drugs were CCBs (63 %), diuretics (44 %), ACE inhibitors (41 %), ARBs (30 %), and beta blockers (11 %). One RCT compared the use of enalapril (ACE inhibitor), nifedipine (CCB), metoprolol (beta blocker), and thiazide (diuretic) and showed a significant decrease in OH prevalence for all drugs, from approximately 20 % to 0 % for all classes except thiazide (Masuo et al.,

Table 2
Quality assessment.

First author	Year	D1	D2	D3	D4	D5	D6	D7	Overall
Acanfora	1997	x	+	+	?	?	+	−	x
Beckett	2008	+	+	+	+	+	+	+	+
Bravo	1990	x	+	+	?	+	+	+	x
Bursztyn	1992	+	+	+	+	+	+	−	−
De Heus	2019	+	−	+	+	+	+	+	−
Fogari	2008	+	+	+	+	?	+	−	−
Fotherby	1994	x	+	+	?	+	+	−	x
Germino	2012	x	+	+	+	+	+	+	x
Jansen	1988	+	+	+	+	+	+	−	−
Juraschek	2019	+	−	+	?	?	+	+	−
Krakoff	1989	+	+	+	x	+	+	−	x
Laher	1988	x	+	+	+	+	+	−	x
Landmark	1985	+	+	+	+	+	+	−	−
Langdon	2000	x	−	+	+	+	+	−	x
Lee	2021	+	+	+	+	+	+	+	+
Masuo	1996	+	+	+	?	?	+	−	−
Moonen	2016	+	+	+	+	+	+	+	+
Neutel	2004	x	−	+	−	−	+	−	x
Sato	2014	+	+	+	?	−	+	+	−
Silveira	2004	+	+	+	?	?	+	?	?
Slavachevsky	2000	+	+	+	+	+	+	−	−
Suzuki	2015	x	−	+	+	+	+	−	x
Weijs	2023	−	−	+	+	+	+	+	−
Weir	2013	−	−	+	+	?	+	+	−
Williamson	2016	+	−	+	+	+	+	+	−

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: x: serious risk of bias, −: moderate risk of bias, +: low risk of bias,?: no information.

1996). A randomized cross-over trial showed a significant decrease for enalapril but not for nifedipine (Slavachevsky et al., 2000), while an RCT showed no significant differences for both nitrendipine (CCB) and hydrochlorothiazide (diuretic) (Jansen et al., 1989). The stratification for AHT class by one RCT showed that discontinuing ARBs had the highest probability of recovery from OH, but most participants used multiple antihypertensives at baseline (Moonen et al., 2016). Another RCT showed that long-term OH risk did not significantly differ between

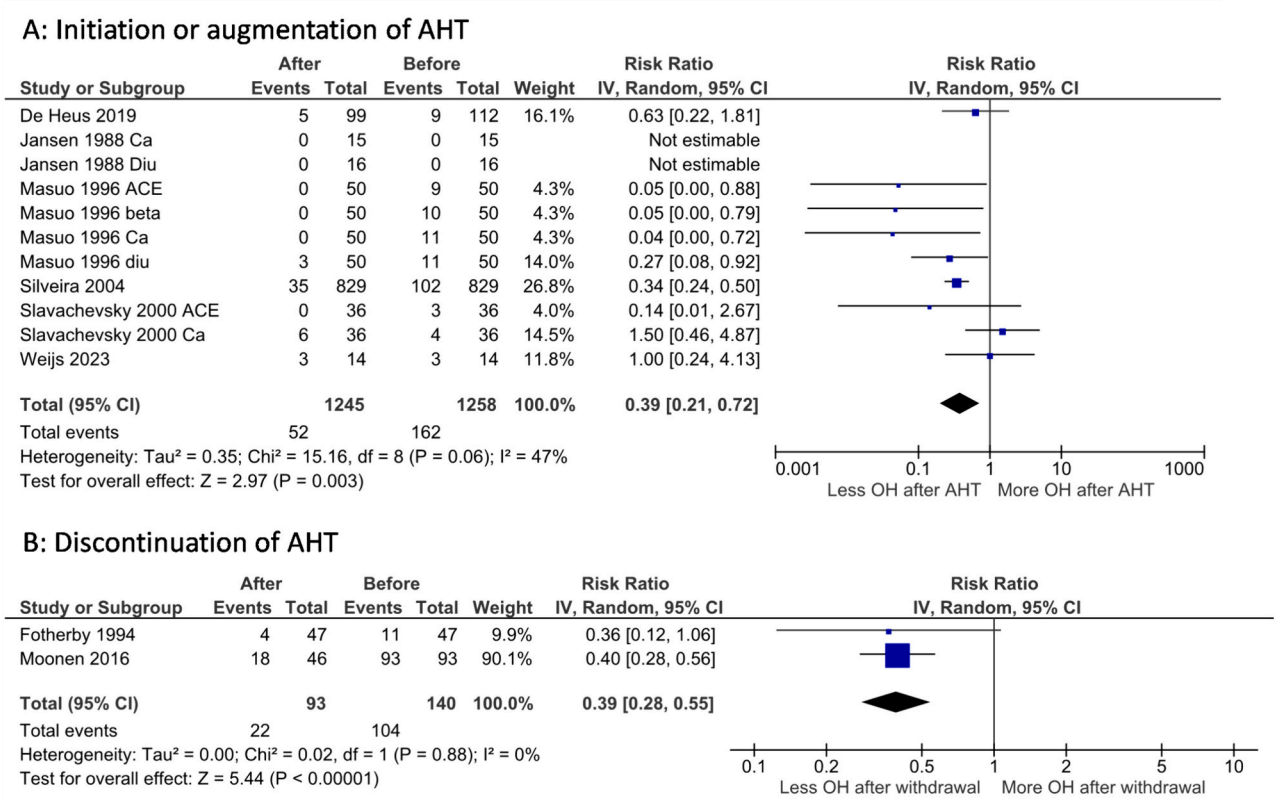


Fig. 2. Forest plot of orthostatic hypotension (OH) prevalence after and before initiation, augmentation (A) or discontinuation (B) of antihypertensive treatment (AHT). ACE: ACE inhibitor, Ca: calcium channel blocker, Diu: diuretic, beta: beta-blocker.

different classes of antihypertensive drugs. Within the first year after the initiation of AHT, amlodipine, a CCB, showed a significantly higher risk of OH than lisinopril (ACE inhibitor) or chlorthalidone (diuretic) (Juraschek et al., 2019).

3.4. Meta-analysis

Six studies (1258 individuals) could be included in the meta-analysis on OH prevalence before and after initiation of AHT (de Heus et al., 2019; Jansen et al., 1989; Masuo et al., 1996; Silveira et al., 2004; Slavachevsky et al., 2000), and two (140 individuals) on OH prevalence before and after discontinuation of antihypertensives (Moonen et al., 2016; Fotherby and Potter, 1994). Eleven studies (3406 individuals) were suitable for the meta-analysis on BP difference between resting and standing before and after treatment (de Heus et al., 2019; Bravo et al., 1990; Jansen et al., 1989; Acanfora et al., 1997; Beckett et al., 2008; Bursztyn et al., 1993; Fogari et al., 2009; Laher et al., 1988; Landmark and Dale, 1985; Silveira et al., 2004; Slavachevsky et al., 2000). Meta-analyses showed that OH prevalence decreased after the initiation of AHT, with a risk ratio of 0.39 (95 % confidence interval (CI) 0.21–0.72; $I^2 = 47$ %; $p < 0.01$) after treatment compared to before treatment (Fig. 2A). OH prevalence decreased after AHT discontinuation with a risk ratio of 0.39 (95 % CI 0.28–0.55; $I^2 = 0$ %; $p < 0.01$) after compared to before discontinuation of AHT (Fig. 2B). The difference between resting and standing BP did not change significantly after AHT initiation with a mean difference of 1.07 (95 % CI -0.49-2.64; I (Brignole et al., 2018) = 92 %; $p = 0.18$) (Fig. 3). A sensitivity analysis revealed no significant impact of imputation of standard deviations on the results of the meta-analysis (eFigure 1 in the Supplement). Funnel plots showed publication bias towards a decrease in OH after initiating AHT, and publication bias towards a decrease in OH after AHT discontinuation (see eFigure 4 and 5 in the Supplement). The overall level of evidence was graded as very low (GRADE assessment, eFigure 3 in the Supplement). A sensitivity analysis presented that omitting all studies with serious or unknown risk of bias did not significantly alter the results of the meta-analysis (eFigure 2 and 3 in the Supplement).

4. Discussion

4.1. Main findings

This systematic review and meta-analysis focused on the effects of AHT on postural BP, especially on the prevalence of OH, in older adults with hypertension. Our meta-analyses showed a reduction in the prevalence of OH and no significant change in the magnitude of the drop in BP upon standing after initiation or augmentation of AHT. Contrarily, the two studies on AHT discontinuation also showed a decrease in the prevalence of OH. Studies were heterogeneous concerning antihypertensive classes, trial designs, and methods to assess and define OH; very often, such methods were not reported. In line with this, quality of evidence, as assessed by GRADE, was very low.

4.2. Mechanisms behind a possible association between AHT and OH

Initiation of AHT most often decreased or did not change OH prevalence. Similarly, there were no differences in OH prevalence between initiating intensive versus standard AHT in one large RCT. However, patients with severe systolic OH at baseline were excluded from this study, limiting the generalizability (Williamson et al., 2016). Our findings on AHT initiation in older adults are consistent with previous research that did not specifically focus on older adults. A recent meta-analysis showed that adults (≥18 years) treated towards a lower BP target (intensive treatment) had lower odds of OH compared to those receiving standard treatment (Juraschek et al., 2021). Age did not alter this result. Moreover, the Syst-Eur trial, including 4695 adults aged 60 years and older, observed no effect of an ARB, ACE inhibitor, or diuretic on the prevalence of OH, regardless of the type of postural change used to assess OH (Grobman et al., 2023). A study that was excluded from this review for wrong prescription indication (not all participants had hypertension) investigated the effect of AHT versus placebo on OH in people who had experienced at least one fall in the last year. There was no significant difference between AHT and placebo on either the magnitude of the postural BP drop or the prevalence of OH (Sumukadas et al., 2018). In older adults with a lacunar stroke, of whom 78 % were hypertensive, a higher OH prevalence after standard treatment (towards a higher BP goal) compared to intensive treatment (towards a lower BP goal) was found (White et al., 2015). Shared mechanisms between OH and hypertension could explain the improvement of OH after AHT initiation. Examples are autonomic dysfunction and decreased baroreflex sensitivity in hypertension, causing increased BP variability and, thus, a higher risk of OH (Raber et al., 2022). Reducing hypertension could restore baroreflex function and improve postural BP regulation.

On the other hand, AHT can theoretically have a negative effect on the stability of postural BP by inhibiting vasoconstriction or reducing intravascular volume (Rivasi et al., 2020). In addition to the rise in heart rate, which is limited by beta-blockers, vasoconstriction is a compensatory mechanism to maintain BP after postural change via the baroreflex, failure of which leads to OH. Moreover, a reduced intravascular

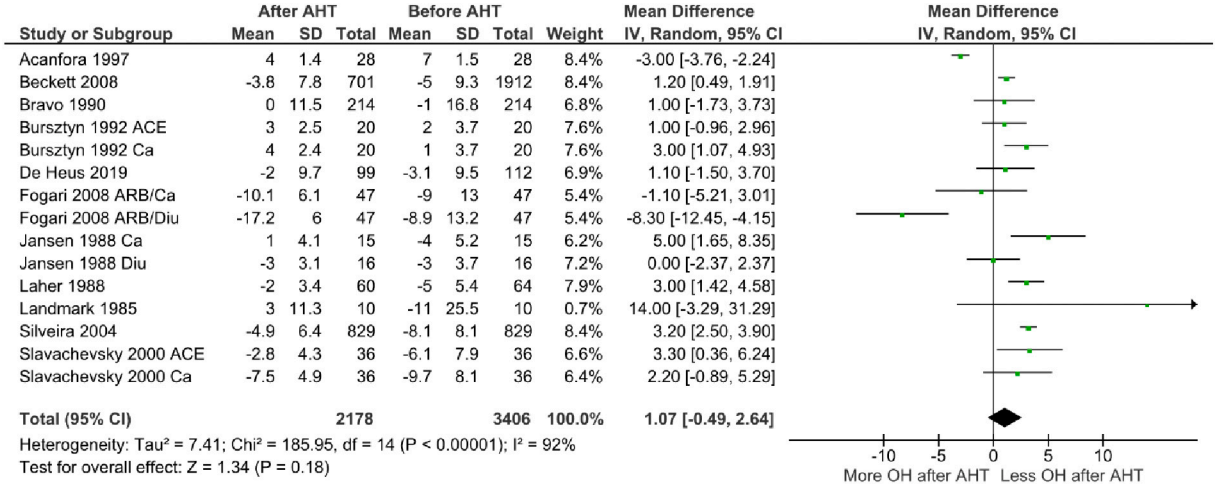


Fig. 3. Forest plot of systolic blood pressure (BP) rest-stand difference after and before initiation of antihypertensive treatment (AHT). ACE: ACE inhibitor, Ca: calcium channel blocker, Diu: diuretic.

volume worsens OH (Rivasi et al., 2020). Accordingly, two studies that investigated the discontinuation of AHT reported a reduction in OH (Moonen et al., 2016; Fotherby and Potter, 1994). However, these studies have important drawbacks. One used the consensus OH definition for systolic BP (Fotherby and Potter, 1994), while the other assessed OH through a sit-stand transition (Moonen et al., 2016). In the latter study, BP was measured three times successively immediately after standing, of which at least one measurement should meet the criteria for OH. The first measurement was taken immediately after standing (much earlier than after 1 min of standing) and, therefore, will have reflected initial OH. Applying the consensus definition of OH to such early measurements, rather than the appropriate criteria of initial OH (i.e., a BP drop of >40 mmHg systolic and/or 20 mmHg diastolic within the first 15 s after standing (Wieling et al., 2007)) will overestimate the prevalence of OH. The time needed to complete a measurement immediately after postural change depends on the height of BP, with shorter cuff inflation and deflation times for lower BP values and longer times for higher BP values. This may have caused a bias towards finding less OH after discontinuation of AHT. Another large AHT discontinuation trial, the TONE trial, which did not meet our inclusion criterium for age and, therefore, was not included in our analyses, did not support the finding of reduced OH after AHT discontinuation. In 975 older adults (60 years and older), AHT discontinuation increased orthostatic symptoms and related events such as falls (Juraschek et al., 2022a).

4.3. OH assessment

In some trials we included in this review, OH prevalence and incidence were extremely low, leading to concerns regarding the reliability of the OH measurement. For example, a trial including >1000 older participants that reports an OH incidence of almost zero during a 6- to 16-week trial is unlikely, with a reported prevalence in community-dwelling older adults around 30 % (Low, 2008; Hiitola et al., 2009). We suspect these trials specifically investigated side effects and were only warned of the presence of OH when a participant reported OH-related symptoms. However, OH symptoms and OH do not overlap (Freeman et al., 2020; Claffey et al., 2022). Therefore, results of studies reporting only OH incidence and not prevalence at baseline should be interpreted with caution.

Our review highlighted a significant issue regarding the lack of consistency in OH assessment. We observed variations in the time points for BP assessment (directly upon standing, after 1, 2, 3, or 5 min of standing), the type of postural change (supine-stand or sit-stand), which requires different cut-off values (Shaw et al., 2017), and the definition of OH that was used (depending on the year of publication and the presence of a consensus definition). The 2011 consensus definition of OH is most often used in recent literature (Freeman et al., 2011). This definition is still vague regarding two important aspects. First, the term *within 3 min* may still include a measurement taken before 1 min, overlapping with initial OH. Second, the term *sustained* is not defined. In addition, this consensus definition suggests to use a different cut-off value (SBP reduction of 30 mmHg) for patients with supine hypertension. However, no study included in this review has used this definition, although all studies included older adults with hypertension. A sit-stand postural change, especially when using supine-stand cut-off values, may underestimate the presence of OH (Juraschek et al., 2022b), which could partly explain the very low prevalence rates found in some studies.

4.4. Strengths and limitations

An important strength of this systematic review is the focus on older adults since this group is at greater risk of OH, and we lack understanding of the balance between harms and benefits of AHT. Furthermore, we provide a critical and comprehensive review of OH assessment methods used in all the included studies. In the meta-analysis, we pooled results regarding OH prevalence and compared the BP drop after standing before and after treatment. While the first approach is more sensitive to individual differences in response to treatment, the second approach can capture small postural BP changes after treatment.

This systematic review also had some limitations. First, different classes of AHT have different mechanisms of action: some have been linked to an increased risk of OH (beta-blockers) (Bhanu et al., 2021), and others to a reduced risk of OH (ARBs, ACE inhibitors) (Yee and Struthers, 1998). As many studies investigated antihypertensive combination therapy instead of monotherapy, we could not stratify the meta-analyses for AHT class and specifically could not separate beta-blockers from other classes. While most guidelines do not recommend beta-blockers as a first-line treatment option in older patients to reduce the risk of OH, in clinical practice, many older patients still use beta-blockers for reasons other than hypertension. Because guidelines now also advise to use combination therapy rather than monotherapy, separating effects of individual drug classes may clinically be less relevant. Second, we included differences between resting and standing BP, for which standard deviations were often unknown and imputed from a study with known standard deviations. Third, cross-over trials were treated as parallel-group instead of paired-group designs in the meta-analyses, as no individual patient data were reported, making imputation of treatment effects impossible. A carryover effect was not expected in any of these trials since these used a washout period between two AHT classes, making inclusion of only the first treatment regimen undesirable. The result might be a higher reported standard deviation and, therefore, lower weight in the meta-analysis, possibly underestimating the contribution of the cross-over trials (Elbourne et al., 2002). Fourth, our meta-analyses should be interpreted with caution as many studies had a moderate to serious risk of bias, often due to the lack of a per-protocol analysis or the lack of reporting the participants lost to follow-up. Therefore, participants who changed from treatment to no-treatment group were part of the analysis, underestimating the effect of AHT to either reduce or aggravate OH. Fifth, many included studies were designed to investigate AHT effectiveness and/or safety instead of studying OH, which was only a secondary outcome. Therefore, the generalizability of the meta-analysis is reduced, for example illustrated by the exclusion criteria. Two studies excluded diabetes mellitus (either only insulin-dependent or all cases) (Jansen et al., 1989; Masuo et al., 1996), excluding a large proportion of the older population. One study excluded participants with OH at baseline (Bravo et al., 1990). Nonetheless, for that study, we could still determine whether AHT induced a reduction in standing BP. As a previous systematic review and meta-analysis showed no significant influence of exclusion of baseline OH in studies on falls incidence after AHT (Reddin et al., 2023), we also expect no significant bias here. Sixth, besides AHT, other drugs can influence postural BP. In three studies, use of alpha-blockers (although excluded when prescribed for hypertension) (Weijs et al., 2023), antipsychotics (Moonen et al., 2016; de Heus et al., 2019), antidepressants (Moonen et al., 2016; de Heus et al., 2019; Weijs et al., 2023), benzodiazepines (Moonen et al., 2016; de Heus et al., 2019; Weijs et al., 2023) and dopaminergic agents (de Heus et al., 2019) was reported at baseline. Use of this medication may have confounded the effect of AHT on OH, in the sense that the combination of AHT with this medication could increase the risk of OH. Seventh, we did not limit our search to only recent studies, as most AHT efficacy trials have been performed in the 1980s and 1990s. Different BP targets were strived for at that time (systolic BP <140–160 mmHg, diastolic BP <90 mmHg) compared to more recent studies (systolic BP <130 mmHg, diastolic BP <80 mmHg). However, all studies show a decrease in BP, making it still possible to research the effects of BP lowering on OH prevalence and severity.

4.5. Perspectives

Age influences the balance between hypertension, OH, and AHT (Hajjar, 2005). Older adults are more susceptible to BP dysregulation, and thus hypertension and OH, since they often have diminished

baroreceptor function and vascular compliance due to arterial stiffness (Lipsitz, 1989). As OH is related to falls, this poses a high risk of fractures and hospitalization in older adults. In addition, the absolute risk of hypertension-related cardio- and cerebrovascular events is highest in older adults (Izzo et al., 2018). Moreover, the combination of uncontrolled hypertension and OH has been shown to pose a greater risk of falling than OH without concomitant hypertension (Gangavati et al., 2011; Donoghue et al., 2021). The results of this systematic review suggest that evidence is lacking for the widespread concern that initiating or augmenting AHT in older adults causes OH. Even in a small study in frail older adults the prevalence of OH did not increase after augmentation of AHT (Weijs et al., 2023). However, heterogeneity in studies, especially in the assessment of OH, and few studies performed in frail older adults (e.g. those who are more susceptible to hypotension or syncope) limit firm conclusions about AHT not being a possible predisposing or exacerbating factor for OH. The use of intermittent BP measurements, although simple and cheap, is problematic, as timing is crucial for OH cut-off values. Including continuous BP measurements could provide a solution in future AHT trials (Finucane et al., 2019; Breeuwsma et al., 2018). The cost and complexity of these devices may limit widespread use, although having these measurements, at least in a well-defined subgroup, may help address the raised issues.

5. Conclusion

This systematic review and meta-analysis identifies an important research gap in the effect of AHT on OH in older adults. Current, albeit limited, evidence suggests that AHT initiation and augmentation do not increase OH prevalence or severity in older adults with hypertension, confirming previous reviews in adults. In contrast, two trials of discontinuation of AHT found a reduced prevalence of OH; however, in one of those, we identified important methodological flaws. We found that the overall quality of evidence is low, limiting firm conclusions to be drawn. A notable finding is that studies were heterogeneous in their methods to assess OH, their definition of OH, and the classes of AHT investigated. Therefore, in future AHT trials that include older adults, the use of an OH measurement protocol according to current consensus guidelines is recommended, if possible, using continuous BP measurements, to allow for in-depth analysis of the effect of AHT on OH.

Abbreviations

ACE	angiotensin-converting enzyme
AHT	antihypertensive treatment
ARB	angiotensin receptor blocker
BP	blood pressure
CCB	calcium channel blocker
OH	orthostatic hypotension
RCT	randomized controlled trial

Sources of funding

None.

CRediT authorship contribution statement

Marjolein Klop: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Andrea B. Maier:** Writing – review & editing, Supervision. **Carel G.M. Meskers:** Writing – review & editing, Supervision. **Julika M. Steiner:** Writing – review & editing, Methodology, Formal analysis. **D. Odette Helsloot:** Writing – review & editing, Formal analysis. **Richard J.A. van Wezel:** Writing – review & editing, Supervision. **Jurgen A.H.R. Claassen:** Writing – review & editing, Supervision, Conceptualization. **Rianne A.A. de Heus:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

Acknowledgment

We would like to thank Renate Claassen for her support in the title/abstract screening for this systematic review.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2024.112461.

References

Acanfora, D., et al., 1997. The effects of delapril in combination with indapamide on glomerular filtration rate in elderly hypertensive patients. Am. J. Ther. 4, 405–408. https://doi.org/10.1097/00045391-199711000-00011.

Beckett, N.S., et al., 2008. Treatment of hypertension in patients 80 years of age or older. N. Engl. J. Med. 358, 1887–1898. https://doi.org/10.1056/NEJMoa0801369.

Bhanu, C., et al., 2021. Drug-induced orthostatic hypotension: a systematic review and meta-analysis of randomised controlled trials. PLoS Med. 18, e1003821 https://doi.org/10.1371/journal.pmed.1003821.

Biaggioni, I., 2018. Orthostatic hypotension in the hypertensive patient. Am. J. Hypertens. 31, 1255–1259. https://doi.org/10.1093/ajh/hpy089.

Bravo, E.L., Krakoff, L.R., Tuck, M.L., Friedman, C.P., 1990. Antihypertensive effectiveness of nifedipine gastrointestinal therapeutic system in the elderly. The Modern Approach to the Treatment of Hypertension (MATH) study group. Am. J. Hypertens. 3, 326s–332s.

Breeuwsma, A.C., et al., 2018. Diagnosing orthostatic hypotension with continuous and interval blood pressure measurement devices. J. Hum. Hypertens. 32, 831–837. https://doi.org/10.1038/s41371-018-0091-9.

Brignole, M., et al., 2018. Practical instructions for the 2018 ESC guidelines for the diagnosis and management of syncope. Eur. Heart J. 39, e43–e80. https://doi.org/10.1093/eurheartj/ehy071.

Bursztyn, M., Ghanem, J., Kobrin, I., Fidel, J., Ben-Ishay, D., 1993. Comparison of verapamil and captopril in elderly hypertensive subjects: results of a randomized, double-blind, crossover study. J. Cardiovasc. Pharmacol. 21, 84–88. https://doi.org/10.1097/00005344-199301000-00012.

Claassen, J.A.H.R., Thijssen, D.H.J., Panerai, R.B., Faraci, F.M., 2021. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol. Rev. 101, 1487–1559. https://doi.org/10.1152/physrev.00022.2020.

Claffey, P., et al., 2022. Asymptomatic orthostatic hypotension and risk of falls in community-dwelling older people. Age Ageing 51. https://doi.org/10.1093/ageing/afac295.

Donoghue, O.A., O'Connell, M.D.L., Bourke, R., Kenny, R.A., 2021. Is orthostatic hypotension and co-existing supine and seated hypertension associated with future falls in community-dwelling older adults? Results from The Irish Longitudinal Study on Ageing (TILDA). PLoS One 16, e0252212. https://doi.org/10.1371/journal.pone.0252212.

Elbourne, D.R., et al., 2002. Meta-analyses involving cross-over trials: methodological issues. Int. J. Epidemiol. 31, 140–149. https://doi.org/10.1093/ije/31.1.140.

Fernandes, M., Olde Rikkert, M.G.M., 2019. The new US and European guidelines in hypertension: a multi-dimensional analysis. Contemp. Clin. Trials 81, 44–54. https://doi.org/10.1016/j.cct.2019.04.008.

Finucane, C., Kenny, R.A., 2016. Falls risk, orthostatic hypotension, and optimum blood pressure management: is it all in our heads? Am. J. Hypertens. 30, 115–117. https://doi.org/10.1093/ajh/hpw129.

Finucane, C., et al., 2019. A practical guide to active stand testing and analysis using continuous beat-to-beat non-invasive blood pressure monitoring. Clin. Auton. Res. 29, 427–441. https://doi.org/10.1007/s10286-019-00606-y.

Fogari, R., et al., 2009. Efficacy and safety of two treatment combinations of hypertension in very elderly patients. Arch. Gerontol. Geriatr. 48, 401–405. https://doi.org/10.1016/j.archger.2008.03.012.

Fotherby, M.D., Potter, J.F., 1994. Orthostatic hypotension and anti-hypertensive therapy in the elderly. Postgrad. Med. J. 70, 878–881. https://doi.org/10.1136/pgmj.70.830.878.

Freeman, R., et al., 2011. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin. Auton. Res. 21, 69–72. https://doi.org/10.1007/s10286-011-0119-5.

Freeman, R., et al., 2020. Symptom recognition is impaired in patients with orthostatic hypotension. Hypertension 75, 1325–1332. https://doi.org/10.1161/hypertensionaha.119.13619.

Frith, J., Bashir, A.S., Newton, J.L., 2015. The duration of the orthostatic blood pressure drop is predictive of death. QJM: An International Journal of Medicine 109, 231–235. https://doi.org/10.1093/qjmed/hcv126.

Gangavati, A., et al., 2011. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent

living, intellect, and zest in the elderly of Boston study. J. Am. Geriatr. Soc. 59, 383–389. https://doi.org/10.1111/j.1532-5415.2011.03317.x.
Germino, F.W., Neutel, J.M., Dubiel, R., Maa, J.-F., Chavanu, K.J., 2012. Efficacy of olmesartan medoxomil and hydrochlorothiazide fixed-dose combination therapy in patients aged 65 years and older with stage 1 and 2 hypertension or isolated systolic hypertension. Am. J. Cardiovasc. Drugs 12, 325–333. https://doi.org/10.1007/BF03261841.
Grobman, B., et al., 2023. Body position and orthostatic hypotension in hypertensive adults: results from the Syst-Eur trial. Hypertension 80, 820–827. https://doi.org/10.1161/HYPERTENSIONAHA.122.20602.
Hajjar, I., 2005. Postural blood pressure changes and orthostatic hypotension in the elderly patient. Drugs Aging 22, 55–68. https://doi.org/10.2165/00002512-200522010-00004.
Hajjar, I., Miller, K., Hirth, V., 2002. Age-related bias in the management of hypertension: a national survey of physicians' opinions on hypertension in elderly adults. The Journals of Gerontology: Series A 57, M487–M491. https://doi.org/10.1093/gerona/57.8.M487.
de Heus, R.A.A., et al., 2019. Blood pressure lowering with Nilvadipine in patients with mild-to-moderate Alzheimer disease does not increase the prevalence of orthostatic hypotension. J. Am. Heart Assoc. 8, e011938 https://doi.org/10.1161/JAHA.119.011938.
Higgins, J.P.T., Li, T., Deeks, J.J., 2022. In: Higgins, J.P.T., et al. (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* Vol. Version 6.3 (Updated February 2022). Cochrane.
Higgins, J., Eldridge, S., Li, T., 2022. In: Higgins, J.P.T., et al. (Eds.), In *Cochrane Handbook for Systematic Reviews of Interventions* Vol. version 6.3 (updated February 2022) (Cochrane, 2022).
Hiitola, P., Enlund, H., Kettunen, R., Sulkava, R., Hartikainen, S., 2009. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. J. Hum. Hypertens. 23, 33–39. https://doi.org/10.1038/jhh.2008.81.
Iseli, R., et al., 2019. Orthostatic hypotension and cognition in older adults: a systematic review and meta-analysis. Exp. Gerontol. 120, 40–49. https://doi.org/10.1016/j.exger.2019.02.017.
Izzo, C., et al., 2018. The impact of aging on cardio and cerebrovascular diseases. Int. J. Mol. Sci. 19 https://doi.org/10.3390/ijms19020481.
Jansen, R.W., Van Lier, H.J., Hoefnagels, W.H., 1989. Nitrendipine versus hydrochlorothiazide in hypertensive patients over 70 years of age. Clin. Pharmacol. Ther. 45, 291–298. https://doi.org/10.1038/clpt.1989.31.
Joseph, A., Wanono, R., Flamant, M., Vidal-Petiot, E., 2017. Orthostatic hypotension: a review. Nephrol. Ther. 13, S55–S67. https://doi.org/10.1016/j.nephro.2017.01.003.
Juraschek, S.P., et al., 2018. Orthostatic hypotension and risk of clinical and subclinical cardiovascular disease in middle-aged adults. J. Am. Heart Assoc. 7 https://doi.org/10.1161/jaha.118.008884.
Juraschek, S.P., et al., 2019. Effects of antihypertensive class on falls, Syncope, and orthostatic hypotension in older adults: the ALLHAT trial. Hypertension 74, 1033–1040. https://doi.org/10.1161/HYPERTENSIONAHA.119.13445.
Juraschek, S.P., et al., 2021. Effects of intensive blood pressure treatment on orthostatic hypotension : a systematic review and individual participant-based meta-analysis. Ann. Intern. Med. 174, 58–68. https://doi.org/10.7326/m20-4298.
Juraschek, S.P., et al., 2022a. Effects of antihypertensive deprescribing strategies on blood pressure, adverse events, and orthostatic symptoms in older adults: results from TONE. Am. J. Hypertens. 35, 337–346. https://doi.org/10.1093/ajh/hpab171.
Juraschek, S.P., et al., 2022b. Comparison of supine and seated orthostatic hypotension assessments and their association with falls and orthostatic symptoms. J. Am. Geriatr. Soc. 70, 2310–2319. https://doi.org/10.1111/jgs.17804.
Kaye, M.G., et al., 2023. Screening for orthostatic hypotension in the geriatric population in a real-world primary care setting reduces prescribed antihypertensive medications. Blood Press. Monit. 28, 338–342. https://doi.org/10.1097/mbp.0000000000000673.
Krakoff, L.R., 1989. Nicardipine monotherapy in ambulatory elderly patients with hypertension. Am. Heart J. 117, 250–255. https://doi.org/10.1016/0002-8703(89)90692-3.
Laher, M.S., Donohoe, J.F., Kelly, J.G., Doyle, G.D., 1988. Antihypertensive and renal effects of lisinopril in older patients with hypertension. Am. J. Med. 85, 38–43. https://doi.org/10.1016/0002-9343(88)90349-x.
Landmark, K., Dale, J., 1985. Antihypertensive, haemodynamic and metabolic effects of nifedipine slow-release tablets in elderly patients. Acta Med. Scand. 218, 389–396. https://doi.org/10.1111/j.0954-6820.1985.tb08863.x.
Langdon, C., 2000. Treatment of hypertension in patients > or =65 years of age: experience with amlodipine. Clin. Ther. 22, 1473–1482. https://doi.org/10.1016/s0149-2918(00)83045-3.
Laurent, S., 2017. Antihypertensive drugs. Pharmacol. Res. 124, 116–125. https://doi.org/10.1016/j.phrs.2017.07.026.
Lee, H.Y., et al., 2021. A randomized, double-blind, active-controlled, two parallel-group, optional titration, multicenter, phase IIIb study to evaluate the efficacy and safety of Fimasartan versus perindopril monotherapy with and without a diuretic combination in elderly patients with essential hypertension. Clin. Ther. 43, 1746–1756. https://doi.org/10.1016/j.clinthera.2021.08.003.
Lipsitz, L.A., 1989. Orthostatic hypotension in the elderly. N. Engl. J. Med. 321, 952–957. https://doi.org/10.1056/nejm198910053211407.
Low, P.A., 2008. Prevalence of orthostatic hypotension. Clin. Auton. Res. 18, 8–13. https://doi.org/10.1007/s10286-007-1001-3.
Masuo, K., Mikami, H., Ogihara, T., Tuck, M.L., 1996. Changes in frequency of orthostatic hypotension in elderly hypertensive patients under medications. Am. J. Hypertens. 9, 263–268. https://doi.org/10.1016/0895-7061(95)00348-7.
Mattace-Raso, F.U., et al., 2006. Arterial stiffness as the candidate underlying mechanism for postural blood pressure changes and orthostatic hypotension in older adults: the Rotterdam study. J. Hypertens. 24, 339–344. https://doi.org/10.1097/01.hjh.0000202816.25706.64.
Mol, A., et al., 2018. Orthostatic hypotension and physical functioning in older adults: a systematic review and meta-analysis. Ageing Res. Rev. 48, 122–144. https://doi.org/10.1016/j.arr.2018.10.007.
Mol, A., et al., 2019. Orthostatic hypotension and falls in older adults: a systematic review and meta-analysis. J. Am. Med. Dir. Assoc. 20, 589–597.e585. https://doi.org/10.1016/j.jamda.2018.11.003.
Moonen, J.E., et al., 2016. Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE study Leiden. Age Ageing 45, 249–255. https://doi.org/10.1093/ageing/afv199.
Neutel, J.M., et al., 2004. Clinical experience with perindopril in elderly hypertensive patients: a subgroup analysis of a large community trial. Am. J. Cardiovasc. Drugs 4, 335–341. https://doi.org/10.2165/00129784-200404050-00006.
Raber, I., et al., 2022. Orthostatic hypotension in hypertensive adults: Harry Goldblatt award for early career investigators 2021. Hypertension 79, 2388–2396. https://doi.org/10.1161/HYPERTENSIONAHA.122.18557.
Reddin, C., et al., 2023. Randomised controlled trials of antihypertensive therapy: does exclusion of orthostatic hypotension alter treatment effect? A systematic review and meta-analysis. Age Ageing 52. https://doi.org/10.1093/ageing/afad044.
van Rijssel, A.E., et al., 2022. Effect of antihypertensive treatment on cerebral blood flow in older adults: a systematic review and meta-analysis. Hypertension 79, 1067–1078. https://doi.org/10.1161/hypertensionaha.121.18255.
Rivasi, G., Rafanelli, M., Mossello, E., Brignole, M., Ungar, A., 2020. Drug-related orthostatic hypotension: beyond anti-hypertensive medications. Drugs Aging 37, 725–738. https://doi.org/10.1007/s40266-020-00796-5.
Sabharwal, S., Wilson, H., Reilly, P., Gupte, C.M., 2015. Heterogeneity of the definition of elderly age in current orthopaedic research. Springerplus 4, 516. https://doi.org/10.1186/s40064-015-1307-x.
Sato, N., et al., 2015. Visit-to-visit variability and seasonal variation in blood pressure: combination of antihypertensive therapy in the elderly, multicenter investigation (CAMUI) trial subanalysis. Clin. Exp. Hypertens. 37, 411–419. https://doi.org/10.3109/10641963.2014.995802.
Schunemann, H., Brozek, J., Guyatt, G., Oxman, A., 2013. GRADE Handbook. https://gdt.gradepro.org/app/handbook/handbook.html>.
Shaw, B.H., et al., 2017. Optimal diagnostic thresholds for diagnosis of orthostatic hypotension with a 'sit-to-stand test'. J. Hypertens. 35, 1019–1025. https://doi.org/10.1097/hjh.0000000000001265.
Silveira, E., et al., 2004. Anti-hypertensive treatment does not lead to an increase in postural hypotension in most very elderly patients - results from the HYVET pilot study. J. Hypertens. 22.
Slavachevsky, I., et al., 2000. Effect of enalapril and nifedipine on orthostatic hypotension in older hypertensive patients. J. Am. Geriatr. Soc. 48, 807–810. https://doi.org/10.1111/j.1532-5415.2000.tb04757.x.
Sterne, J.A.C., et al., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919. https://doi.org/10.1136/bmj.i4919.
Sumukadas, D., et al., 2018. The effect of perindopril on postural instability in older people with a history of falls-a randomised controlled trial. Age Ageing 47, 75–81. https://doi.org/10.1093/ageing/afx127.
Suzuki, H., Shimada, K., Fujiwara, K., 2015. Antihypertensive effectiveness of combination therapy with losartan/hydrochlorothiazide for 'real world' management of isolated systolic hypertension. Ther. Adv. Cardiovasc. Dis. 9, 10–18. https://doi.org/10.1177/1753944714558244.
Veglio, F., et al., 2009. Hypertension and cerebrovascular damage. Atherosclerosis 205, 331–341. https://doi.org/10.1016/j.atherosclerosis.2008.10.028.
Weijs, R.W.J., de Roos, B.M., Thijssen, D.H.J., Claassen, J.A.H.R., 2023. The Effects of Intensive Antihypertensive Treatment Targets on Cerebral Blood Flow and Orthostatic Hypotension in Frail Older Adults. medRxiv. https://doi.org/10.1101/2023.10.05.23296632.
Weir, M.R., Shojaee, A., Maa, J.F., 2013. Efficacy of amlodipine/olmesartan medoxomil ± hydrochlorothiazide in patients aged ≥ 65 or < 65 years with uncontrolled hypertension on prior monotherapy. Postgrad. Med. 125, 124–134. https://doi.org/10.3810/pgm.2013.03.2646.
Whelton, P.K., et al., 2018. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 71, e13–e115. https://doi.org/10.1161/HYP.0000000000000065.
White, C.L., et al., 2015. Can blood pressure be lowered safely in older adults with lacunar stroke? The secondary prevention of small subcortical strokes study experience. J. Am. Geriatr. Soc. 63, 722–729. https://doi.org/10.1111/jgs.13349.
Wieling, W., Krediet, C.T., van Dijk, N., Linzer, M., Tschakovsky, M.E., 2007. Initial orthostatic hypotension: review of a forgotten condition. Clin. Sci. (Lond.) 112, 157–165. https://doi.org/10.1042/cs20060091.
Williams, B., et al., 2018. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the

European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur. Heart J. 39, 3021–3104. https://doi.org/10.1093/eurheartj/ehy339.
Williamson, J.D., et al., 2016. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. Jama 315, 2673–2682. https://doi.org/10.1001/jama.2016.7050.
Yee, K.M., Struthers, A.D., 1998. Endogenous angiotensin II and baroreceptor dysfunction: a comparative study of losartan and enalapril in man. Br. J. Clin. Pharmacol. 46, 583–588. https://doi.org/10.1046/j.1365-2125.1998.00832.x.