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Efficacy and Safety of Angiotensin-Based Pharmacotherapy versus Conventional Therapy for the Management of Isolated Systolic Hypertension: A Meta-Analysis of Randomized Controlled Trials

Research Article

TABLES.

Table 1. Characteristics of the Included Trials.

Bendersky 2002 [20]

Methods	Open-Label, Randomized, Parallel - Group Study.
Participants	Ambulatory patients ≥ 60 years of age with ISH (seated SBP >160 mm Hg and <220 mm Hg; diastolic blood pressure [DBP] <95 mm Hg) who had not been treated previously or who had stopped their medication at least 4 weeks before the study were enrolled. Patients taking concomitant drugs that could affect blood pressure were excluded.
Interventions	Patients were randomized to receive amlodipine 5 mg/d or enalapril 10 mg/d. After 4 weeks of treatment, the dose was doubled for those patients whose sitting SBP had not decreased to <150 mm Hg or by > 20 mm Hg, and treatment was continued for an additional 4 weeks.
Outcomes	Blood Pressure, Heart Rate, and Pulse Pressure. Efficacy evaluation by (1) the decrease in SBP at 4 and 8 weeks in both treatment arms; (2) the percentage of patients who had their SBP reduced to < 150 mm Hg or by > 20 mm Hg from baseline at 4 and 8 weeks; (3) the percentage of patients who required upward titration of the medication at the end of the first month because of inadequate SBP control; (4) the absolute and percentage reduction in SBP at 4 and 8 weeks; and (5) the changes in pulse pressure (PP) in both treatment arms at 4 and 8 weeks. Patients were also asked to report spontaneously any adverse event experienced over the previous month. Patients were then asked by the treating physician whether they had experienced any of the most frequent adverse reactions associated with both drugs. The assessments were performed at the end of the first and second month of active treatment.

Ekbom 2004 [21].

Methods	Randomized study subgroup analysis of Swedish Trial in Old Patients with Hypertension- 2 (STOP-Hypertension-2) trial
Participants	2280 patients (mean age 76.0 years, range 70–84 years at baseline) in STOP-2 that met the criteria of ISH defined as sBP at least 160 mmHg and dBP below 95 mmHg, in accordance with the Syst-Eur and Syst-China study criteria.
Interventions	Three treatment groups: "conventional" antihypertensive therapy with beta-blockers or diuretics (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed-ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily); ACE inhibitors (enalapril 10 mg or lisinopril 10 mg daily); or calcium antagonists (felodipine 2.5 mg or isradipine 2.5 mg daily). The mean follow-up time was 5.0 years and no patient was lost to follow-up.
Outcomes	Total mortality and cardiovascular specific mortality and morbidity including MI and stroke. Blood pressure reduction.

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Heesen 1998 [22].

Methods	Prospective double blind randomized study
Participants	Subjects with untreated ISH with a stratification for age: "younger" elderly, 60-64 years; and elderly, 65-74 years. The inclusion criterion was an untreated systolic BP >=160 mm Hg on three separate occasions, with a diastolic BP <95 mm Hg.
Interventions	ACE inhibitor quinapril (QUI) and triamterene/hydrochlorothiazide (THCT) treatment. Medication allocation was double blind, each capsule containing either 12.5/25 mg THCT or 10 mg QUI. Subjects started with one capsule a day (taken in the early morning). After 3 weeks, the dosage was doubled to two capsules once a day and continued until the end of the study (25/50 mg THCT or 20 mg QUI), except where orthostatic problems or other complaints had occurred. Follow-up examinations were done after 6 and 26 weeks of treatment.
Outcomes	Blood pressure and LV mass. At each study visit, including the initial visit, all subjects underwent the same measurements of BP and those of end-organ damage determination. BP measurements included standard supine (office) and 24-h ambulatory measurements. The end-organ damage measurements included echocardiographic LV mass and diastolic function determination. Office BP was determined by the average of three consecutive BP measurements, after 5 min rest. The 24-h ambulatory BP was measured with separate analysis of day-time and night-time measurements.

Leonetti 1997 [23].

Methods	Multicenter, double-blind, parallel group study.
Participants	312 elderly patients more than 60 years with ISH (sBP of 160-200 mmHg and seated diastolic of less than 95 mmHg). An orthostatic dBP>65 mm Hg was also required for admission. Patients were excluded if they had hypertensive retinopathy, clinical heart failure, recent MI or stroke, serum creatinine >1.5 mg/dL, proteinuria >500 mg/24 h, uncontrolled diabetes mellitus, or hepatic insufficiency
Interventions	Patients meeting all admission criteria with no exclusion criteria were randomized to 10 mg of fosinopril or 12.5 mg of chlorthalidone administered orally. After 4 weeks of active treatment, the doses of fosinopril or chlorthalidone were doubled if seated sBP was not <160 mm Hg or lowered by at least 20 mm Hg. The total period of active drug therapy was 9 weeks.
Outcomes	BP was measured 22 to 26 h after administration of placebo or active drug. A blood sample was taken for measurement of hemoglobin, white blood cells, platelets, total bilirubin, total cholesterol, serum transaminases, plasma sodium and potassium, serum creatinine, uric acid, and blood glucose levels. A urinalysis and electrocardiogram were performed also before and after treatment. The incidence of adverse events was estimated particularly for serum potassium and transaminase concentrations and cough.

Mackenzie 2009 [24]

Methods	Randomized placebo-controlled double-blinded study
Participants	Fifty-nine treatment-naïve patients over the age of 60 years with untreated ISH (sBP ≥140 mm Hg and dBP ≤90 mm Hg), Hg), confirmed on 3 occasions, were recruited from hypertension clinics and local general practices.
Interventions	Patients were randomly assigned to receive 1 of the following 4 antihypertensive agents for a 10-week period: perindopril 4.0 mg OD, atenolol 50.0 mg OD, lercanidipine 10.0 mg OD, or bendrofluazide 2.5 mg OD in a double-blinded manner. Drug doses were chosen as the midrange dose, according to standard clinical practice. Compliance was assessed by tablet counts at each visit.
Outcomes	Hemodynamic measurements of BP and aortic pulse wave velocity were measured at baseline, after 2 weeks of placebo therapy, and at the end of 10 weeks of active therapy.

Malacco 2003 [8].

Methods	Randomized, Double-Blind, Active-Controlled, Parallel-Group (The Val-Syst Study)
Participants	35 Italian outpatient center elderly (aged 60–80 years) patients with ISH (SBP 160–220 mm Hg and DBP <90 mm Hg after a 2-week placebo washout period) were eligible to participate. The main exclusion criteria were evidence of orthostatic hypotension (a decrease in sitting SBP of ≥20 mm Hg and/or a decrease in sitting DBP of ≥10 mm Hg on standing) or malignant hypertension; a history of transient ischemic attack or cerebrovascular accident within the preceding 6 months; evidence of a secondary type of hypertension; overt heart failure or a history of heart failure; a history of MI within the preceding 6 months; angina pectoris; clinically relevant arrhythmia; clinically significant valvular heart disease; evidence of hepatic disease; abnormal serum potassium level; evidence of renal impairment (serum creatinine level >1.5 times the upper limit of normal); type 1 diabetes mellitus; type 2 diabetes mellitus with poor glucose control (persistent fasting blood glucose >200 mg/dL) or peripheral neuropathy or autonomic neuropathy; and hypersensitivity to ARBs, ACEIs, thiazide diuretics, or dihydropyridine-type CCBs.
Interventions	Patients received oral treatment with valsartan 80-mg capsules or amlodipine 5-mg capsules once daily. After 8 weeks of treatment, the dose of the patients with poorly controlled SBP was titrated to 160 mg (valsartan) or 10 mg (amlodipine) once daily. At week 16, if trough SBP was still not adequately controlled, a low-dose diuretic (hydrochlorothiazide [HCTZ] 12.5 mg) was added to the treatment regimen for an additional 8 weeks.
Outcomes	Efficacy Assessment in visits scheduled at weeks 0, 4, 8, 12, 16, 20, and 24 of treatment. At each visit, participants underwent a complete physical examination and sitting BP was measured 3 times for the mean calculated. DBP and heart rate (HR) were also measured and the pulse pressure (SBP – DBP) was calculated. Tolerability was assessed at all study visits using physical examination and patient interview.

Mallion 2007 [25].

Methods	Phase III, multinational, multicenter, randomized, double-blind, parallel-group study
Participants	Elderly (65–74 years) and very elderly (>= 75 years) male and female patients with ISH (SBP>160mmHg and DBP<90 mmHg) conducted in 33 investigational sites based in Europe. ISH that was either newly diagnosed and untreated or previously diagnosed but without treatment for at least 4 weeks prior to screening had to fulfil the inclusion criterion at screening. Patients with ISH who were receiving treatment at screening had to fulfil the ISH inclusion criterion at the end of the taper-off period (before entry into the placebo run-in phase). Major exclusion criteria included: any type of known secondary form of hypertension (e.g. renal, renovascular or adrenocortical disease, phaeochromocytoma, hyperthyroidism or iatrogenic); malignant hypertension or SBP>200 mmHg; clinically significant CVD; a history or clinical evidence of a clinically significant cerebrovascular, renal, gastrointestinal, respiratory, haematological or hepatic disease; biliary obstruction; known malabsorption syndromes; autoimmune diseases; poorly controlled diabetes; treatment for other indications with drugs that might affect BP; a history of a serious underlying disease that would prohibit patient participation. Patients with known hypersensitivity, lack of response or contraindication to ARBs, CCBs or HCTZ were excluded. Patients who had received an investigational drug within 30 days prior to entering the active treatment period were also excluded. The following concomitant medication was not permitted: antihypertensives other than the study medication; tricyclic antidepressants; neuroleptics; long-acting nitrates; potassium supplements; lithium; digoxin, cimetidine, intravenous calcium; rifampicin. Patients were instructed to maintain their dietary habits, including sodium intake, and not to deviate from this regimen for the duration of the study. Patients were instructed to avoid grapefruits/grapefruit juice.
Interventions	Patients were randomized to 24 weeks of treatment with either olmesartan medoxomil 20mg daily or nitrendipine 20mg twice daily in a double-dummy design, with possible dose increase (to 40mg daily) and addition of hydrochlorothiazide (HCTZ) 12.5 or 25mg daily if required.
Outcomes	The primary endpoint was the reduction in mean sitting SBP after 12 weeks of treatment. Tolerability was also assessed.

Manolis 2004 [26].

Methods	Multicentre, double-blind, parallel-group, randomized study (ARAMIS)
	Sponsorship: This study was funded by BoehringerIngelheim.
Participants	1039 patients (age 36–84 years) with ISH [seated SBP 150–179 mmHg and seated DBP < 90 mmHg]. Patients receiving antihypertensive therapy immediately before the study were only eligible if withdrawal of the medication and possible administration of placebo for 10 weeks would not jeopardize their health. Patients with secondary hypertension, hepatic and/or renal dysfunction, clinically relevant electrolyte imbalance, symptomatic cardiovascular or cerebrovascular disease, or inadequately controlled or recently stabilized diabetes mellitus, or gout were excluded. Pregnant or nursing women or of childbearing potential were excluded.
Interventions	Randomization to once-daily double-blind treatment with telmisartan 20, 40 or 80 mg, HCTZ 12.5 mg, or placebo.
Outcomes	The change in seated trough SBP after 6 weeks compared with baseline was the primary end point. Secondary end points were the percentage achieving the target fall in SBP and the change from baseline in seated trough DBP. Incidence and severity of adverse events and physical examination and laboratory parameters were monitored for the safety evaluation.

Palatini 2004 [27].

Methods	Randomised, active-controlled, parallel group, double blind trial (Sub-study of the Val-Syst trial that assessed the time-effect profiles of the two treatments in terms of ambulatory BP and heart rate using various parameters derived from 24-h BP monitoring data)
Participants	One hundred and sixty-four elderly outpatients aged 60–80 years with systolic hypertension (sitting office sBP of 160–220mmHg and a dBP of <90mmHg)
Interventions	Valsartan 80mg (n= 79) or amlodipine 5mg (n= 85) once daily for eight weeks, after which the patients with poorly controlled office BP were up-titrated to valsartan 160mg or amlodipine 10mg once daily. If their office sBP was still > 140mmHg after eight weeks at these doses, 12.5mg hydrochlorothiazide was added for a further eight weeks.
Outcomes	The hourly BP decreases in all of the patients were calculated on the basis of 24-h ambulatory recordings made after the placebo period and at the end of active treatment (24 weeks).

Papademetriou 2004 [28].

Methods	Subgroup analysis of the Study on Cognition and Prognosis in the Elderly (SCOPE) of outcome results in the ISH patients. Randomly assigned to double-blind treatment with open-label additional antihypertensive therapy.
Participants	1,518 ISH patients (sBP> 160 mm Hg and dBP<90 mm Hg) and age 70 to 89 years.
Interventions	Candesartan or placebo groups with open-label antihypertensive therapy (mostly thiazide diuretics) added as needed to control blood pressure. The average duration of follow-up in ISH patients was 3.6 years corresponding to 5,506 patient-years.
Outcomes	All-cause mortality and cardiovascular endpoints of mortality and morbidity including MI and stroke (fatal and non-fatal). Difference in blood pressure at end of study (Treatment - Control)

Pavlovic 2004 [29].

Methods	Prospective, randomized, open-label and placebo-controlled
Participants	Sixty patients > 60 years of age with ISH (mean seated SBP 140 and DBP 90mmHg).
Interventions	Fosinopril or amlodipine for 3 months after a week of wash-out placebo run-in period.
Outcomes	Twenty four h ambulatory BP, clinical and echocardiographic examination. Safety assessment for incidence of any side effects.

Vogt 2005 [30].

Methods	Prospective parallel-group sub-study of a large, multicentre, double-blind, placebo-controlled, randomized study (ARAMIS).
Participants	ARAMIS patients (n= 1039, aged 35–84 years) with ISH (seated BP 150–179/< 90 mmHg) and with urinary albumin excretion (UAE) of any degree (including below the threshold for microalbuminuria)
Interventions	Once-daily fixed doses of telmisartan 20, 40 or 80 mg versus hydrochlorothiazide 12.5 mg or placebo for 6 weeks.
Outcomes	Antihypertensive efficacy. UAE using spot morning samples. Safety by incidences of all-cause adverse events and most frequently reported adverse events after 6 weeks' treatment.

Volpe 2003 [31].

Methods	Multicenter, prospective, randomized, double-blind, parallel-group study (CDSP-944)
Participants	Adult men and women having a mean age of 67.6 years with a documented history of ISH were eligible for entry into the study if, at visit 3, they had a mean sitting SBP of 160 to 200 mm Hg and a mean sitting DBP of >65 but <90 mm Hg.
Interventions	Patients were randomized into 2 groups in a 1: 1 ratio according to a computer-generated allocation schedule. One group received a losartan-based regimen, and the other received an amlodipine-based regimen, both for 18 weeks. Losartan was initiated at 50 mg; the regimen could be increased to losartan 50 mg/hydrochlorothiazide (HCTZ) 12.5 mg at week 6 and to losartan 100 mg/HCTZ 25 mg at week 12 as needed to achieve the target SBP of <140 mm Hg. Amlodipine was initiated at 5 mg; the regimen could be increased to amlodipine 10 mg at week 6 and to amlodipine 10 mg/HCTZ 25 mg at week 12 as needed to achieve the SBP target. Each group received placebo tablets to match the medication in the other treatment group. Medication was taken as in the placebo period.
Outcomes	The primary efficacy measure was change in SBP from baseline to week 18. Tolerability of study treatments was collected at each visit, including the investigators and patients' observations of clinical adverse experiences, laboratory adverse experiences, and responses to a symptom questionnaire.

Wing 2003 [32].

Methods	Double-blind, randomized, placebo-controlled, crossover design
Participants	Twenty-eight patients aged 55–84 years were recruited into the run-in phase of the study with sitting SBP 160–210 mmHg and DBP <95 mmHg. Seventeen patients (nine male and eight female, median age 68 years, range 61–81 years) completed all the randomized treatment phases.
Interventions	Four active treatment phases were each of 6 weeks duration with no washout period between phases. The treatments in each of the four randomized phases were placebo, candesartan, hydrochlorothiazide and the combination of candesartan and hydrochlorothiazide. The comparisons between these treatments represented a within-patient 2 x 2 factorial experiment, i.e. analysis of the effect of each treatment (candesartan or hydrochlorothiazide) in the presence and in the absence of the other treatment. Blinding was achieved with the "double-dummy" technique as follows: candesartan monotherapy phase (C) (active candesartan and placebo for hydrochlorothiazide); hydrochlorothiazide monotherapy phase (H) (active hydrochlorothiazide and placebo for candesartan); "combination therapy" phase (C-H) (active candesartan and active hydrochlorothiazide); placebo phase (P) (placebo for candesartan and placebo for hydrochlorothiazide). All medications were dispensed every 6 weeks in two separate bottles containing candesartan 8 mg or "candesartan placebo" tablets, and hydrochlorothiazide 12.5 mg or "hydrochlorothiazide placebo" capsules.
Outcomes	Average 24-h, daytime and night-time SBP, DBP and mean arterial pressure. Safety evaluations and adverse events.