Therapeutic Class Overview
Angiotensin II Receptor Blockers (ARBs)-Combination Products

Therapeutic Class

- **Overview/Summary:** The angiotensin II receptor blocker (ARB) combination products are Food and Drug Administration (FDA) approved for the treatment of hypertension. Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. Recently, the combination of azilsartan/chlorthalidone (Edarbyclor®) was approved by the FDA, and is the only chlorthalidone-containing product in the class. The other available products in this class include various combinations of an ARB with a calcium channel blocker (amlodipine), a thiazide diuretic (hydrochlorothiazide [HCTZ]) or both. The losartan/HCTZ combination product is available generically and is currently the only generic product in the class. The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including ventricular hypertrophy and cardiac remodeling.[1,2] The RAAS plays an important role in the development and progression of heart failure.[2] The ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[1-4] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (e.g., chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[1,2] The ARBs block the angiotensin II receptor subtype AT_1, preventing the negative effects of angiotensin II, regardless of its origin. The ARBs do not appear to affect bradykinin.

Table 1. Current Medications Available in Therapeutic Class[5-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Azilsartan/ chlorthalidone (Edarbyclor®)	Hypertension*	Tablet: 40/ 12.5 mg 40/ 25 mg	-
Candesartan/HCTZ (Atacand HCT®)	Hypertension†	Tablet: 16/12.5 mg 32/12.5 mg 32/25 mg	-
Eprosartan/HCTZ (Teveten HCT®)	Hypertension†	Tablet: 600/12.5 mg 600/25 mg	-
Irbesartan/HCTZ (Avalide®)	Hypertension*	Tablet: 150/12.5 mg 300/12.5 mg 300/25 mg	-
Losartan/HCTZ (Hyzaar®)	Hypertension‡, reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy§	Tablet: 50/12.5 mg 100/12.5 mg 100/25 mg	✔
Olmesartan/HCTZ (Benicar HCT®)	Hypertension†	Tablet: 20/12.5 mg 40/12.5 mg 40/25 mg	-
Telmisartan/HCTZ	Hypertension†	Tablet:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Micardis HCT®)		40/12.5 mg 80/12.5 mg 80/25 mg	
Valsartan/HCTZ (Diovan HCT®)	Hypertension*	Tablet: 80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg	-
Olmesartan/ amlodipine (Azor®)	Hypertension*	Tablet: 20/5 mg 40/5 mg 20/10 mg 40/10 mg	-
Olmesartan/ amlodipine/HCTZ (Tribenzor®)	Hypertension†	Tablet: 20/5/12.5 mg 40/5/25 mg 40/10/12.5 mg 40/10/25 mg	-
Telmisartan/ amlodipine (Twynsta®)	Hypertension*	Tablet: 40/5 mg 40/10 mg 80/5 mg 80/10 mg	-
Valsartan/ amlodipine (Exforge®)	Hypertension*	Tablet: 160/5 mg 160/10 mg 320/5 mg 320/10 mg	-
Valsartan/ amlodipine/HCTZ (Exforge® HCT)	Hypertension†	Tablet: 160/5/12.5 mg 160/10/12.5 mg 160/5/25 mg 160/10/25 mg 320/10/25 mg	-

HCTZ=hydrochlorothiazide
*Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
†This fixed-dose combination is not indicated for initial therapy.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

Evidence-based Medicine

- Clinical trials assessing the combination angiotensin II receptor blockers (ARBs) in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either hydrochlorothiazide (HCTZ) or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or HCTZ.[18-29]
- A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy.[30]
- Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy.[31-33]

Head-to-head trials have not consistently demonstrated "superiority" of one combination product over another within the class.[34-40]

- Results from the LIFE trial demonstrated that therapy with losartan plus HCTZ was associated with a lower risk of the composite endpoint of cardiovascular death, myocardial infarction and stroke compared to atenolol plus HCTZ (RR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.021). There was no difference in the incidence of cardiovascular mortality (*P*=0.206) and MI (*P*=0.491), but losartan treatment resulted in a 24.9% reduction in the risk of stroke compared to atenolol (*P*=0.001).[41]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current treatment guidelines indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade 2 hypertension may require initial therapy with medications from two different drug classes.[42,43]
  - Angiotensin II receptor blockers (ARBs) are recommended in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[42-44]
  - If more than one drug is needed to effectively control blood pressure, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure recommends that one agent be a thiazide diuretic.[42]
  - According to the European Society of Hypertension/European Society of Cardiology, combinations that can be recommended based on clinical trial evidence include a diuretic with an angiotensin converting enzyme (ACE) inhibitor, an ARB or a calcium channel blocker or a combination of an ACE inhibitor with a calcium channel blocker.[43] If triple therapy is needed, a blocker of the renin-angiotensin system, a calcium channel blocker and a diuretic are recommended.[43]
- Other Key Facts:
  - To date, no studies have been published evaluating the antihypertensive effects of azilsartan/chlorthalidone.
  - Clinical trials have demonstrated the safety and efficacy of the angiotensin II receptor blockers (ARBs) in combination with hydrochlorothiazide (HCTZ) and/or amlodipine in patients with hypertension.
  - Losartan/HCTZ is the only ARB in the class that carries an additional indication for the reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy.[9]
  - Losartan/HCTZ is the only generic ARB combination product available.

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Therapeutic Class Review
Angiotensin II Receptor Blockers (ARBs)-
Combination Products

Overview/Summary

The angiotensin II receptor blocker (ARB) combination products are Food and Drug Administration (FDA) approved for the treatment of hypertension. Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. Recently, the combination of azilsartan/chlorthalidone (Edarbyclor®) was approved by the FDA, and is the only chlorthalidone-containing product in the class. The other products available in this class include various combinations of an ARB with a calcium channel blocker (amlodipine), a thiazide diuretic (HCTZ) or both. The only available generic within the class is losartan/HCTZ.

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[1,2] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[3] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[1,3] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy and remodeling.[1,2] The RAAS plays an important role in the development and progression of heart failure.[2]

ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[1-4] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (e.g., chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[1,2] The ARBs block the angiotensin II receptor subtype AT1, preventing the negative effects of angiotensin II, regardless of its origin. ARBs do not appear to affect bradykinin.

Amlodipine, a nondihydropyridine calcium channel blocker, inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Cardiac and vascular smooth muscle contraction depends on the movement of extracellular calcium ions into cells through specific ion channels. Amlodipine inhibits calcium ion influx and exerts a greater effect on vascular smooth muscle cells compared to cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator, which results in a reduction in peripheral vascular resistance and reduction in blood pressure.[5]

HCTZ, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney. Indirectly, the diuretic action of HCTZ reduces plasma volume, which increases plasma renin activity, aldosterone secretion and subsequently potassium excretion in the urine. The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor.[5]

Current treatment guidelines indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade 2 hypertension may require initial therapy with medications from two different drug classes.[6,7] ARBs are recommended in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[6-8] If more than one drug is needed to effectively control blood pressure, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure recommends that one agent be a thiazide diuretic.[6] According to the European Society of Hypertension/European Society of Cardiology, combinations that can be recommended based on clinical trial evidence include a diuretic with an ACE inhibitor, an ARB or a calcium channel blocker or a combination of an ACE inhibitor with a calcium channel blocker.[7] If triple therapy is needed, the European

Society of Hypertension/European Society of Cardiology recommends a blocker of the renin-angiotensin system, a calcium channel blocker and a diuretic.[7]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Azilsartan/chlorthalidone (Edarbyclor®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Candesartan/hydrochlorothiazide (Atacand HCT®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Eprosartan/hydrochlorothiazide (Teveten HCT®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Irbesartan/hydrochlorothiazide (Avalide®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Losartan/hydrochlorothiazide (Hyzaar®)	Angiotensin II receptor blocker/ thiazide diuretic	✔
Olmesartan/hydrochlorothiazide (Benicar HCT®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Telmisartan/hydrochlorothiazide (Micardis HCT®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Valsartan/hydrochlorothiazide (Diovan HCT®)	Angiotensin II receptor blocker/ thiazide diuretic	-
Olmesartan/amlodipine (Azor®)	Angiotensin II receptor blocker/ calcium channel blocker	-
Olmesartan/amlodipine/ hydrochlorothiazide (Tribenzor®)	Angiotensin II receptor blocker/calcium channel blocker/thiazide diuretic	-
Telmisartan/amlodipine (Twynsta®)	Angiotensin II receptor blocker/ calcium channel blocker	-
Valsartan/amlodipine (Exforge®)	Angiotensin II receptor blocker/ calcium channel blocker	-
Valsartan/amlodipine/ hydrochlorothiazide (Exforge® HCT)	Angiotensin II receptor blocker/calcium channel blocker/thiazide diuretic	-

Indications

Table 2. Food and Drug Administration Approved Indications[9-21]

Generic Name	Hypertension	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
Azilsartan/chlorthalidone	✔ *	
Candesartan/HCTZ	✔ †	
Eprosartan/HCTZ	✔ †	
Irbesartan/HCTZ	✔ *	
Losartan/HCTZ	✔ ‡	✔ §
Olmesartan/HCTZ	✔ †	
Telmisartan/HCTZ	✔ †	
Valsartan/HCTZ	✔ *	
Olmesartan/amlodipine	✔ *	
Olmesartan/amlodipine/HCTZ	✔ †	
Telmisartan/amlodipine	✔ *	
Valsartan/amlodipine	✔ *	
Valsartan/amlodipine/HCTZ	✔ †	

HCTZ=hydrochlorothiazide

*Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
†This fixed-dose combination is not indicated for initial therapy.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

Pharmacokinetics

Table 3. Pharmacokinetics[5,9-21]

Generic Name	Bioavailability (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Angiotensin II Receptor Antagonists					
Azilsartan	60	CYP2C9	No	Feces (55); renal (42)	11
Candesartan	15	CYP2C9	None	Feces (67); renal (33)	9
Eprosartan	13	Glucuronidation	None	Feces (90); renal (7)	6
Irbesartan	60 to 80	CYP2C9	None	Feces (80); renal (20)	11 to 15
Losartan	33	CYP2C9; CYP3A4	Yes; 5-carboxylic acid (E-3174)	Feces (60); renal (35)	2 (6 to 9)
Olmesartan	26	Deesterification	None	Feces (50 to 65); renal (35 to 50)	13
Telmisartan	42 to 58	Conjugation	None	Feces (>97)	24
Valsartan	25	Minimal; enzyme unknown	None	Feces (83); renal (13)	6
Calcium Channel Blockers					
Amlodipine	64 to 90	Liver	None	Renal (70)	30 to 60
Thiazide Diuretics					
Hydrochloro-thiazide	~50 to 75	Not appreciably metabolized	Not reported	Renal (50 to 70)	6 to 15
Chlorthalidone	65	Not reported	None	Renal (96*)	40 to 89

*Intravenous administration.

Clinical Trials

Clinical trials assessing the combination angiotensin II receptor blockers (ARBs) in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either a thiazide diuretic or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or a thiazide diuretic.[22-34] A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy.[35] Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy.[36-38] Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class.[39-45]

There are no published studies evaluating the antihypertensive effects of azilsartan/chlorthalidone. In an eight-week, randomized, double blind trial in patients with moderate to severe hypertension, all strengths of azilsartan/chlorthalidone were associated with significant reductions in systolic and diastolic blood pressure compared with their individual components, as determined by ambulatory blood pressure monitoring (*P* values not reported). In a 12-week, double blind trial, azilsartan/chlorthalidone 40/25 mg demonstrated a significantly greater improvement in systolic blood pressure compared to olmesartan/HCTZ 40/25 mg in patients with moderate to severe hypertension ($P<0.001$).[9]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
McInnes et al[46] Candesartan/HCTZ 8/12.5 mg QD vs lisinopril/HCTZ 10/12.5 mg QD	DB, DD, MC, PG, RCT Patients 20 to 80 years of age with mild-to-moderate HTN on prior antihypertensive monotherapy	N=355 26 weeks	Primary: Mean changes in DBP Secondary: Mean changes in SBP and heart rate, proportion of responders and controlled patients, safety	Primary: Changes in mean sitting DBP did not differ significantly between the groups (mean difference, 0.5 mm Hg; *P*=0.20). Secondary: No significant differences between the groups were reported for mean sitting SBP, heart rate, proportion of responders and controlled patients. Both drugs were well tolerated but a greater percentage of those in the lisinopril group (80 vs 69%) had a least one side effect (*P*=0.020). The proportion of patients spontaneously reporting cough (23.1 vs 4.6%) and discontinuing therapy due to adverse events (12.0 vs 5.9%) was also higher in the lisinopril group compared to the candesartan group.
Ohma et al[39] Candesartan/HCTZ 16/12.5 mg QD vs losartan/HCTZ 50/12.5 mg QD	DB, MC, RCT Patients 20 to 80 years of age with mild- to moderate uncontrolled HTN while on monotherapy (any kind of medication)	N=340 12 weeks	Primary: Change in sitting DBP Secondary: SBP, proportion of responders, safety and tolerability	Primary: Greater reductions in DBP were reported with candesartan/HCTZ vs losartan/HCTZ (-10.4 vs -7.8 mm Hg; *P*=0.016). Secondary: Greater decreases in SBP were reported with candesartan/HCTZ (-19.4 mm Hg) vs losartan/HCTZ (-13.7 mm Hg; *P*=0.004). The proportion of patients achieving a DBP ≤90 mm Hg was greater with candesartan/HCTZ (60.9 vs 49.3%; *P*=0.044). There were eight withdrawals due to adverse effects in the candesartan/HCTZ group and 12 in the losartan/HCTZ group. The most common adverse effects were headache, tachycardia/palpitations, dizziness and fatigue.
Sachse et al[22] Eprosartan 600 mg plus HCTZ 12.5 mg QD	DB, MC, PG, PRO, RCT Patients 18 years of age and older	N=309 8 weeks	Primary: Trough sitting DBP Secondary: Trough sitting SBP	Primary: Significantly greater reductions in sitting DBP were observed at study endpoint in the eprosartan plus HCTZ group compared to the eprosartan monotherapy group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs eprosartan 600 mg QD	with mild- to moderate HTN		and heart rate, proportion of patients whose sitting DBP had normalized, proportion of responders (defined as normal sitting DBP or sitting DBP ≤100 mm Hg and decreased from baseline by at least 10 mm Hg)	Secondary: Significantly greater reductions in sitting SBP were observed at study endpoint in the eprosartan plus HCTZ group compared to the eprosartan monotherapy group (*P*=0.001). No significant difference was observed between groups in the proportion of patients whose sitting DBP had normalized (*P*=0.10). The response rate was significantly higher in the eprosartan plus HCTZ group compared to the eprosartan monotherapy group (*P*=0.004).
Ambrosioni et al[40] (INSIST) Eprosartan/HCTZ 600/12.5 mg QD vs losartan/HCTZ 50/12.5 mg QD	DB, DD, MC, PG, PC, RCT Patients 60 years of age and older meeting the World Health Organization criteria for grade 2 systolic HTN	N=155 6 weeks	Primary: Mean change from end of wash-out period to the end of combination therapy in ABPM SBP Secondary: Pulse pressure, SBP at daytime, SBP at nighttime, SBP in the last four hours before taking study medication, hourly SBP, response rate	Primary: No significant difference was observed between the eprosartan and losartan groups in mean change in ABPM SBP (*P*≥0.075). Secondary: No significant differences were observed between groups in any secondary endpoints.
Neutel et al[23] Irbesartan 150 mg for 1 week with forced titration to 300 mg monotherapy for 6 weeks vs	AC, DB, MC, PRO, RCT Patients 18 years of age and older with severe HTN who were untreated (seated DBP ≥110	N=737 7 weeks	Primary: Proportion of patients with DBP <90 mm Hg at week five Secondary: Proportion of patients who achieved seated	Primary: Significantly more patients on combination therapy achieved seated DBP <90 mm Hg at week five compared to monotherapy (47.2 vs 33.2%; *P*=0.0005). Secondary: Significantly more patients attained SBP/DBP <140/90 mm Hg at week five (34.6 vs 19.2%, respectively; *P*<0.0001), while the mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
irbesartan/HCTZ 150/12.5 mg for 1 week then forced titration to irbesartan/HCTZ 300/25 mg for 6 weeks	mm Hg) or currently receiving antihypertensive monotherapy with DBP ≥100 mm Hg		SBP/DBP <140/90 mm Hg	difference between combination and monotherapy in seated DBP and SBP was 4.7 and 9.7 mm Hg, respectively (*P*<0.0001). Greater and more rapid BP reduction with irbesartan/HCTZ was achieved without additional side effects.
Neutel[24] Irbesartan/HCTZ 300/25 mg QD vs irbesartan 300 mg QD vs HCTZ 25 mg QD	AC, DB, PG, PRO, RCT Patients (mean age 55 years) with moderate HTN (seated SBP 160 to 179 mm Hg when DBP <110 mm Hg; or DBP 100 to 109 mm Hg when SBP <180 mm Hg)	N=538 12 weeks	Primary: Change in SBP after week eight Secondary: Change from baseline in DBP at weeks eight and 12, SBP at week 12, proportion of responders (SBP <140 mm Hg and DBP <90 mm Hg) at weeks eight and 12	Primary: At week eight, there was a reduction in SBP of 27.1 mm Hg with irbesartan/HCTZ compared to 22.1 mm Hg with irbesartan monotherapy (*P*=0.0016) and 15.7 mm Hg with HCTZ (*P*<0.0001). Secondary: At week eight, there was a reduction in DBP of 14.6 mm Hg with irbesartan/HCTZ compared to 11.6 mm Hg with irbesartan monotherapy (*P*=0.0013) and 7.3 mm Hg with HCTZ (*P*<0.0001). A significantly greater percentage of patients reached a treatment goal of SBP <140 mm Hg and DBP <90 mm Hg by week eight with irbesartan/HCTZ (53.4%) compared to irbesartan (40.6%; *P*=0.0254) and HCTZ (20.2%; *P*<0.0001) alone. Treatment was well tolerated in all three treatment groups with a slight increase in adverse events in the combination therapy group.
Weir et al[47] Irbesartan/HCTZ 300/25 mg QD Post hoc pooled analysis of 2 RCTs.	AC, DB, MC, RCT Patients with stage 1 or 2 HTN Patients were evaluated according to age presence or absence of obesity, type 2 diabetes, and high World Health Organization-	N=796 7 to 8 weeks	Primary: Antihypertensive efficacy, tolerability Secondary: Not reported	Primary: SBP/DBP reductions (27 to 31/16 to 22 mm Hg) were similar regardless of age, obesity and type 2 diabetes status and were greater in high- vs low-risk patients. Dizziness (2.0 to 3.7%), hypotension (0 to 0.7%), and syncope (0%) were rare and not centered in any subgroup. There was no hypotension in the elderly or in patients with type 2 diabetes. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	defined cardiovascular risk			
Bobrie et al[41] Irbesartan/HCTZ 150/12.5 mg QD vs valsartan/HCTZ 80/12.5 mg QD	OL, PRO, RCT, blinded-end point Patients whose BP remained uncontrolled after 5 weeks of HCTZ 12.5 mg QD	N=464 8 weeks	Primary: BP reductions, safety Secondary: Not reported	Primary: Irbesartan/HCTZ produced greater reductions in average SBP and DBP measured by home BP monitoring than valsartan/HCTZ (SBP, -13.0 vs -10.6 mm Hg; *P*=0.0094; DBP, -9.5 vs -7.4 mm Hg; *P*=0.0007). These differences were more pronounced in the morning than in the evening. Normalization rates observed with home BP monitoring (SBP <135 mm Hg and DBP <85 mm Hg) were significantly greater with irbesartan/HCTZ than with valsartan/HCTZ (50.2 vs 33.2%; *P*=0.0003). The overall safety was similar in the two groups. Secondary: Not reported
Salerno et al[25] Losartan/HCTZ 50/12.5 mg to 100/25 mg/day vs losartan 50 to 100 mg/day Doses were titrated as needed at 2-week intervals to reach goal BP (<90 mm Hg).	DB, RCT Patients with severe HTN	N=585 6 weeks	Primary: Proportion of patients achieving goal BP Secondary: Adverse events	Primary: Almost twice as many patients achieved goal BP at four weeks on losartan/HCTZ 50/12.5 mg vs losartan 50 to 100 mg monotherapy (*P*=0.002). Almost three times as many patients achieved goal BP at six weeks with losartan/HCTZ vs losartan monotherapy (*P*<0.001). Secondary: Adverse experiences on losartan/HCTZ (43%) were significantly less than with losartan monotherapy (53%).
Minami et al[48] Losartan 50 mg plus HCTZ 12.5 mg QD	OL Japanese outpatients with essential HTN	N=15 12 months	Primary: Changes in BP Secondary: Not reported	Primary: In patients who had previously received candesartan, 24-hour BP decreased significantly from 137/89 to 126/81 mm Hg after three months (*P*<0.05/*P*<0.001) and to 123/81 mm Hg after 12 months (*P*<0.01/*P*<0.001) of treatment with losartan plus HCTZ.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Candesartan 8 mg QD (n=10) or amlodipine 5 mg QD (n=5) administered to all patients for 2 months prior to switch to losartan plus HCTZ.	treated for at least 2 months with either candesartan or amlodipine and 24-hour ambulatory BP ≥135/80 mm Hg			In patients who had previously received amlodipine, 24-hour BP decreased significantly from 137/81 to 125/75 mm Hg after three months (*P*<0.05/*P*<0.05) and to 124/77 mm Hg after 12 months (*P*<0.05/*P* value not significant) of treatment with losartan plus HCTZ. There were significant decreases in SBP during the daytime, nighttime and early morning after 12 months in both groups. No adverse changes in the indices of glucose or lipid metabolism were observed in either group. Secondary: Not reported
Lacourcière et al[42] Losartan/HCTZ 50/12.5 mg QD vs telmisartan/HCTZ 40/12.5 mg QD vs telmisartan/HCTZ 80/12.5 mg QD	DB, MC, OL, RCT, blinded-end point trial Patients 18 years of age and older with mild-to-moderate essential HTN	N=597 6 weeks	Primary: Mean changes in ambulatory DBP Secondary: Mean changes in ambulatory SBP, 24-hour DBP, safety	Primary: During the last six hours of the dosing interval, telmisartan/HCTZ 40/12.5 and 80/12.5 mg reduced mean DBP to a greater extent vs losartan/HCTZ 50/12.5 mg. Treatment differences between the groups were 1.8 (*P*<0.05) and 2.5 mm Hg (*P*<0.001) lower, respectively, with the telmisartan/HCTZ arms. Secondary: Telmisartan/HCTZ 40/12.5 and 80/12.5 mg produced greater reductions in ambulatory SBP vs losartan/HCTZ 50/12.5 mg of 2.5 and 3.4 mm Hg, respectively, during the last six hours of the dosing interval (*P*<0.05), and of 2.1 and 3.4 mm Hg, respectively, over the entire 24-hour dosing interval (*P*<0.05). Telmisartan/HCTZ 80/12.5 mg also lowered mean 24-hour DBP by 2.3 mm Hg more than losartan/HCTZ 50/12.5 mg (*P*<0.001). All treatments were well tolerated.
Chrysant et al[26] Olmesartan 10, 20 or 40 mg QD	DB, RCT Patients with a baseline mean	N=502 8 weeks	Primary: Change in DBP at week eight	Primary: Olmesartan/HCTZ produced greater reductions in seated DBP at week eight than did monotherapy with either component.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs HCTZ 12.5 or 25 mg QD vs olmesartan/HCTZ (all possible combinations of doses used in monotherapy) vs placebo	seated DBP of 110 to 115 mm Hg		Secondary: Change in SBP at week eight	All olmesartan/HCTZ combinations significantly reduced DBP compared to placebo in a dose-dependent manner. Reductions in mean trough DBP were 8.2, 16.4 and 21.9 mm Hg with placebo, olmesartan/HCTZ 20/12.5 mg and olmesartan/HCTZ 40/25 mg, respectively. Secondary: Olmesartan/HCTZ produced greater reductions in seated SBP at week eight than did monotherapy with either component. All olmesartan/HCTZ combinations significantly reduced DBP compared to placebo in a dose-dependent manner. Reductions in mean trough SBP were 3.3, 20.1 and 26.8 mm Hg with placebo, olmesartan/HCTZ 20/12.5 mg and olmesartan/HCTZ 40/25 mg, respectively. All treatments were well tolerated.
Kereiakes et al[49] Olmesartan 20 mg/day for 2 weeks, followed by 40 mg/day for 2 weeks, followed by olmesartan/HCTZ 40/12.5 mg/day for 4 weeks; increased to 40/25 mg for 4 weeks vs benazepril 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks, followed by benazepril 20 mg/day plus amlodipine 5	DB, DD, MC, PG, RCT Patients with stage 2 HTN	N=190 12 weeks	Primary: Change in mean seated SBP at the end of week 12 Secondary: DBP at the end of week 12, percent of patients attaining BP goals of <140/90, <130/85 and <130/80 mm Hg	Primary: Patients treated with olmesartan/HCTZ experienced significantly greater reductions in mean seated SBP at week 12 than patients treated with benazepril plus amlodipine (least square mean change, -32.5 vs -26.5 mm Hg; *P*=0.024; least square mean treatment difference, -6.0 mm Hg; 95% CI, -11.1 to -0.8). Secondary: The least square mean change for reduction in DBP approached statistical significance with olmesartan/HCTZ compared to benazepril plus amlodipine at week 12 (*P*=0.056). The percentage of patients achieving goal rates at the end of the study for olmesartan/HCTZ and benazepril plus amlodipine were 66.3 and 44.7% (*P*=0.006) for <140/90 mm Hg, 44.9 and 21.2% (*P*=0.001) for <130/85 mm Hg and 32.6 and 14.1% (*P*=0.006) for <130/80 mm Hg. Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day for 4 weeks, followed by benazepril 20 mg/day plus amlodipine 10 mg/day for 4 weeks				
Braun et al[50] Olmesartan 20 mg plus amlodipine 10 mg QD If patients were uncontrolled after 4 weeks, they were changed to valsartan/amlodipine 160/10 mg QD.	OL, PRO Patients with DBP 100 to 109 mm Hg	N=257 8 weeks	Primary: Reduction in SBP and DBP Secondary: Adverse events	Primary: Following treatment with olmesartan plus amlodipine, SBP/DBP decreased by 19.2±12.4/14.4±7.4 mm Hg. The number of patients who progressed to treatment with valsartan/amlodipine was 175. Additional reductions in SBP and DBP of 7.9 and 3.9 mm Hg were seen (*P*<0.0001 for both). Secondary: Both treatments were well tolerated and reported adverse events were consistent with drug profiles.
Chrysant et al (COACH)[27] Olmesartan 10, 20 or 40 mg QD vs amlodipine 5 or 10 mg QD vs olmesartan 10 to 40 mg plus amlodipine 5 to 10 mg QD (all possible combinations) vs placebo	DB, MC, PC, RCT Patients 18 years of age and older with seated DBP 95 to 120 mm Hg	N=1,940 8 weeks	Primary: Change from baseline in seated DBP at week eight Secondary: Change from baseline in seated SBP at week eight; mean change from baseline in seated DBP and SBP at weeks two, four, six and eight without last observation carried forward; proportion of patients achieving BP goal (<140/90 or <130/80 mm Hg), safety	Primary: All active treatments and placebo resulted in significant decreases in seated DBP at week eight (*P*<0.001). Reductions in seated DBP with monotherapy treatment ranged from -8.3 to -12.7 mm Hg; reductions with combination therapy ranged from -13.8 to -19.0 mm Hg. All combinations reduced seated DBP significantly greater than either component as monotherapy at the same dosage (*P*<0.001). Secondary: All active treatments and placebo resulted in significant decreases in seated SBP at week eight (*P*<0.001 for treatment, *P*=0.024 for placebo). All combinations reduced seated SBP significantly greater than either component as monotherapy at the same dosage (*P*<0.001). The proportion of patients achieving goal BP were 20.0 to 36.3% of patients receiving olmesartan monotherapy, 21.1 to 32.5% of patients receiving amlodipine monotherapy, 35.0 to 53.2% of patients receiving combination therapy and 8.8% of patients receiving placebo. Combination therapy resulted in significantly greater achievement of goal BP than monotherapy (*P*<0.005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No difference in overall rates of adverse events across the different treatment groups was seen. The proportion of patients who experienced a drug-related adverse event was 26.9%. Changes in laboratory values were not considered clinically significant nor followed a consistent pattern with treatment. Platelet counts increased significantly from baseline for patients receiving amlodipine, however; the increase was <10% and not deemed clinically relevant (*P* value not reported).
Oparil et al (COACH secondary analysis)[51] Olmesartan 10, 20 or 40 mg QD vs amlodipine 5 or 10 mg QD vs olmesartan 10 to 40 mg plus amlodipine 5 to 10 mg QD (all possible combinations) vs placebo	DB, factorial, MC, PC, RCT Patients 18 years of age and older with seated DBP 95 to 120 mm Hg, with a subgroup analysis based on HTN (stage 1: SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; stage 2: SBP ≥160 mm Hg or DBP ≥100 mm Hg) and no prior antihypertensive medication	N=1,940 8 weeks	Primary: Mean change in DBP and SBP at week eight for each subgroup Secondary: Proportion of patients achieving BP goal (<140/90 or <130/80 mm Hg)	Primary: Reductions in mean DBP as a result of combination treatment were similar between subgroups. Patients with stage 1 HTN achieved reductions of 14.8 to 15.8 mm Hg and patients with stage 2 HTN achieved reductions of 13.6 to 19.8 mm Hg. Reductions in mean SBP as a result of combination treatment resulted in greater reductions in patients with stage 2 HTN (25.1 to 32.7 mm Hg) compared to stage 1 HTN (17.7 to 23.7 mm Hg) (*P* values not reported). Reductions in mean DBP and SBP were similar between those with no prior antihypertensive treatment and those with prior hypertensive treatment. Secondary: The proportion of patients with stage 1 HTN who received combination treatment and achieved BP goal was 65.6 to 80.0%, compared to 40.5 to 66.7% of those who received monotherapy (*P*<0.0001 across treatments). The proportion of patients with stage 2 HTN who received combination treatment and achieved BP goal was 40.5 to 49.2%, compared to 13.1 to 29.2% of those who received monotherapy (*P*<0.0001). Results of patients with baseline SBP ≥180 mm Hg were similar to other subgroups.
Littlejohn et al[52]	DB, DD, MC, PC,	N=1,461	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Telmisartan 20 to 80 mg or placebo plus amlodipine 2.5 to 10 mg or placebo (all possible combinations)	PG, RCT Patients 18 years of age and older with stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg)	8 weeks	Change in DBP Secondary: Change in SBP, percent of patients achieving DBP response (DBP <90 mm Hg or decrease in DBP of ≥10 mm Hg), percent of patients achieving SBP response (SBP <140 mm Hg or decrease in SBP of ≥15 mm Hg), percent of patients achieving BP control (<140/<90 mm Hg), percent of patients achieving DBP control (<90 mm Hg), adverse events/safety	All doses of telmisartan, regardless of amlodipine dose and all doses of amlodipine, regardless of telmisartan dose, significantly lowered DBP (*P*<0.0001 for all). Secondary: Amlodipine 10 mg plus telmisartan 80 mg resulted in the greatest reduction in BP, 26.4/20.1 mm Hg (*P*<0.005 vs both monotherapy). The proportion of patients receiving combination therapy who achieved a DBP response was 80.0 to 92.5%. Additionally, 52.1 to 85.5% of patients receiving monotherapy achieved a DBP response (*P* values not reported). The proportion of patients receiving combination therapy who achieved a SBP response was 76.1 to 91.9%. Additionally, 47.9 to 82.3% of patients receiving monotherapy achieved a SBP response (*P* values not reported). The proportion of patients receiving combination therapy who achieved BP control was 51.1 to 76.5%. Additionally, 25.0 to 62.9% of patients receiving monotherapy achieved BP control (*P* values not reported). The proportion of patients receiving combination therapy who achieved DBP control was 64.4 to 85.3%. Additionally, 33.3 to 73.4% of patients receiving monotherapy achieved DBP control (*P* values not reported). The percent of patients reporting adverse events were similar between treatment groups and placebo (*P* values not reported). The most commonly reported adverse events were headache and peripheral edema. The highest incidence of peripheral edema occurred in patients treated with amlodipine 10 mg; this rate decreased when amlodipine was used in combination with telmisartan.
Littlejohn et al[28]	DB, DD, MC, PC, PG, RCT	N=1,078	Primary: Change in DBP from	Primary: Significant reductions in DBP were seen from baseline to study end for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Telmisartan 40 mg plus amlodipine 5 mg, dosing frequency not specified vs telmisartan 40 mg plus amlodipine 10 mg, dosing frequency not specified vs telmisartan 80 mg plus amlodipine 5 mg, dosing frequency not specified vs telmisartan 80 mg plus amlodipine 10 mg, dosing frequency not specified vs respective monotherapies, dosing frequency not specified	Patients 18 years of age and older with stage 1 or 2 HTN (DBP ≥95 and ≤119 mm Hg), with a subgroup analysis including patients with DBP ≥100 mm Hg at baseline	8 weeks	baseline to study end point Secondary: Change from baseline to study end in SBP; percent of patients achieving a DBP response (DBP <90 mm Hg) and SBP response (SBP <140 mm Hg or reduction from baseline ≥15 mm Hg); percent of patients achieving BP control (SBP/DBP <140/<90 mm Hg) and DBP control (<90 mm Hg), safety	both dual therapy and monotherapy (*P* values not reported). Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced DBP compared to respective monotherapies (*P* values not reported). Secondary: Amlodipine 5 and 10 mg with telmisartan 40 and 80 mg significantly reduced SBP compared to respective monotherapies (*P* values not reported). Combination therapy resulted in a greater DBP and SBP response than monotherapy (*P* values not reported). The highest rate of BP control was achieved with amlodipine 10 mg plus telmisartan 80 mg. Rates of adverse events were similar between dual therapy and monotherapy. Incidences of adverse events were 4.40% with telmisartan monotherapy, 11.00% with amlodipine monotherapy and 11.75% with combination therapy. The most commonly reported events were headache and peripheral edema. Patients receiving amlodipine 10 mg had the highest incidence of peripheral edema; however, rates were lower when amlodipine was used in combination with telmisartan.
Sharma et al[29] Telmisartan/amlodipine 40/5 mg QD vs amlodipine 5 mg QD	DB, MC, PRO, RCT Patients 18 to 65 years of age with stage 2 HTN (SBP/DBP 160 to 179/100 to 109 mm	N=210 12 week	Primary: Reduction in SBP/DBP from baseline to study end and number of responders (SBP/ DBP <130/<80 mm Hg) at end of the	Primary: Significant reductions from baseline in SBP were found in both groups. Combination treatment reductions were 176.3 to 128.0 mm Hg, and amlodipine reductions were 171.8 to 143.4 mm Hg (*P*<0.05 for both treatments from baseline). At week 12, the mean percent reduction in SBP from baseline was significantly greater for the combination treatment (27.4%) than

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Hg)		study Secondary: Tolerability	amlodipine (16.6%) (*P*<0.005 between and within groups). At week 12, the mean percent reduction in DBP from baseline was significantly greater for the combination treatment (20.2%) than amlodipine (12.7%) (*P*<0.005 between and within groups). Significantly more patients receiving combination treatment were qualified as responders (87.3% for combination treatment vs 69.3% for amlodipine treatment; *P*<0.05). Secondary: All adverse events were mild to moderate in severity and rates did not differ between treatment groups. The most commonly reported adverse events in the amlodipine/telmisartan group were peripheral edema (nine/106), headache (six/106), dizziness and cough (four/106 each) and diarrhea (two/106) (*P* values not reported). The most commonly reported adverse events in the amlodipine group were peripheral edema (14/104), headache (five/104), dizziness and diarrhea (three/104 each) (*P* values not reported).
Fogari et al[53] Telmisartan/amlodipine 80 to 160/2.5 mg, dosing frequency not specified vs telmisartan/amlodipine 40/2.5 to 10 mg, dosing frequency not specified Patients added clonidine 0.1 mg/day if BP >130/>80 mm Hg after 16 weeks.	PRO, dose titration study Patients 35 to 70 years of age with essential HTN, controlled type 2 diabetes and microalbuminuria (>30 and <300 mg/24 hours)	N=210 48 weeks	Primary: Changes in proteinuria and BP Secondary: Not reported	Primary: Microalbuminuria was significantly reduced from baseline as a result of both combination therapies, with reductions significantly more marked in patients receiving fixed-dose amlodipine with increasing doses of telmisartan. Patients treated with telmisartan 80, 120 and 160 mg plus fixed-dose amlodipine 2.5 mg achieved significantly greater reductions in microalbuminuria (62.9, 86.5 and 102.0 mg/day, respectively) compared to those receiving fixed-dose telmisartan 40 mg plus amlodipine dose ranging therapy (*P*<0.05, *P*<0.01 and *P*<0.001, respectively). Patients treated with amlodipine 2.5, 5, 7.5 and 10 mg plus telmisartan 40 mg had reductions in microalbuminuria of 35.1, 46.2, 50.0 and 45.0 mg/day (*P*<0.05, *P*<0.03, *P*<0.03 and *P*<0.03, respectively from baseline). Low dose amlodipine/high dose telmisartan and high dose amlodipine/

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				low dose telmisartan produced similar reductions in SBP and DBP. Low dose amlodipine/high dose telmisartan and high dose amlodipine/low dose telmisartan, for all dose ranges, significantly reduced BP compared to baseline (*P*<0.01 from baseline). Changes in weight, creatinine clearance, plasma potassium, fasting glycemia and HbA_{1c} were not significantly influenced (*P* values not reported). Secondary: Not reported
Destro et al[30] (abstract- EX-EFFeCTS) Valsartan/amlodipine 160/5 mg QD for 2 weeks, followed by force titration to 160/10 mg QD for 6 additional weeks vs amlodipine 5 mg QD for 2 weeks, followed by force titrated to 10 mg QD for 6 additional weeks HCTZ was added on at week 4 if mean sitting SBP was ≥130 mm Hg.	DB, MC, RCT Patients 18 years of age and older with stage 2 HTN	N=646 8 week	Primary: Mean sitting SBP Secondary: Mean sitting SBP in patients with baseline mean sitting SBP ≥180 mm Hg, BP control	Primary: At week four, significantly greater reductions in mean sitting SBP were observed in the valsartan/amlodipine group compared to the amlodipine monotherapy group (*P*<0.0001). Secondary: For patients with baseline mean sitting SBP ≥180 mm Hg, significantly greater reductions in mean sitting SBP were observed in the valsartan/amlodipine group compared to the amlodipine monotherapy group (*P*=0.0018). Differences favoring valsartan/amlodipine were observed for BP control (*P* value not reported).
Destro et al[36] Valsartan/amlodipine 160/5 mg QD for 2 weeks, followed by force titration to 160/10	Post-hoc analysis of EX-EFFeCTS[30] Patients 18 years of age and older	N=646 8 week	Primary: Mean sitting SBP and mean sitting DBP from baseline to week eight and week	Primary: At each post-baseline measurement, patients in the valsartan/amlodipine plus HCTZ triple therapy group achieved significantly greater BP reduction compared to the amlodipine plus HCTZ group (*P*≤0.0012).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD for 6 additional weeks vs amlodipine 5 mg QD for 2 weeks, followed by force titrated to 10 mg QD for 6 additional weeks HCTZ was added on at week 4 if mean sitting SBP was ≥130 mm Hg.	with stage 2 HTN who required HCTZ therapy at week 4		four to week eight, BP control rate at week eight Secondary: Not reported	A higher proportion of patients in the initial valsartan/amlodipine group achieved BP control with the addition of HCTZ compared to those in the initial amlodipine monotherapy group (37.7 and 15.4% respectively; *P* value not reported). Secondary: Not reported
Philipp et al[31] Valsartan 40 to 320 mg QD vs amlodipine 2.5 to 5 mg QD vs valsartan 40 to 320 mg plus amlodipine 2.5 to 5 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 18 years of age and older with HTN (mean sitting DBP ≥95 and <110 mm Hg)	N=1,911 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events	Primary: All treatments significantly decreased mean sitting DBP from baseline (*P*<0.05). Combination treatment resulted in significantly greater BP reduction than either monotherapy (*P*<0.05 for all combinations compared to respective doses of monotherapy except amlodipine 2.5 mg and valsartan 40 mg). Secondary: All treatments significantly decreased mean sitting SBP from baseline (*P*<0.05). Combination treatment resulted in a significantly greater BP reduction than either monotherapy (*P*<0.05 for all combinations compared to respective doses of monotherapy). Response rates were significantly different from placebo for all treatment groups (*P*<0.05). Response rates for combination products were significantly different than each monotherapy for the following combinations: amlodipine 5 mg plus valsartan 80 mg, amlodipine 5 mg plus valsartan 40 mg and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				amlodipine 2.5 mg plus valsartan 80 mg (*P*<0.05 for each combination compared to both monotherapies). Response rates for all combinations produced significant improvement compared to either one of the monotherapies except amlodipine 2.5 mg plus valsartan 40 mg (*P*<0.05 for each combination compared to one of the respective monotherapies). Control rates with therapy were significantly better than placebo, with the highest control rate achieved with amlodipine 5 mg plus valsartan 320 mg (*P*<0.05 compared to placebo, *P* value not reported for others). Adverse event rates were not significantly different among combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between amlodipine plus valsartan and valsartan monotherapy (*P*<0.05). The most commonly reported adverse events for combination treatment were: peripheral edema, headache, nasopharyngitis, upper respiratory tract infection and dizziness. Peripheral edema occurred significantly less frequently in the combination treatment group than the amlodipine monotherapy group (5.4 vs 8.7%; *P*=0.014) and significantly more frequently than in the valsartan monotherapy group (5.4 vs 2.1%; *P*<0.001). Peripheral edema occurrence in the valsartan group was similar to the rate in the placebo group.
Philipp et al[32] Valsartan 160 to 320 mg QD vs amlodipine 10 mg QD	DB, MC, PC, PG, RCT Patients 18 years of age and older with HTN (mean sitting DBP ≥95 and <110 mm Hg)	N=1,250 8 weeks	Primary: Mean sitting DBP Secondary: Change in mean sitting SBP, response rate (proportion of patients with mean	Primary: Mean sitting DBP was significantly reduced for both combinations as compared to the individual components and to placebo (*P*<0.05). Secondary: Response rates and control rates for combination treatments were significantly greater than valsartan monotherapy therapy and placebo therapy (*P*<0.05), but not different from amlodipine monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs valsartan 160 or 320 mg plus amlodipine 10 mg QD vs placebo			sitting DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline), control rate (proportion of patients with mean sitting DBP <90 mm Hg), adverse events	Adverse event rates were not significantly different between combination treatment, amlodipine treatment and placebo. Adverse event rates were significantly different between combination treatment and valsartan treatment (*P*<0.05).
Flack et al[33] Valsartan/amlodipine 160 to 320/5 to 10 mg QD vs amlodipine 5 to 10 mg QD HCTZ 12.5 mg was added at week 8, to either group, if SBP ≥130 mm Hg.	DB, PG, PRO, RCT African American patients with stage 2 HTN (SBP ≥160 and <200 mm Hg)	N=572 12 weeks	Primary: Change in SBP Secondary: Change in SBP for subgroups	Primary: At week eight, combination treatment reduced SBP significantly more than monotherapy (33.3 vs 26.6 mm Hg; *P*<0.0001). Secondary: Combination treatment reduced SBP significantly more than monotherapy in the following subgroups: patients ≥65 years, isolated systolic hypertension, BMI ≥30kg/m^2 (*P*=0.002, *P*=0.01 and *P*<0.0001, respectively). More patients receiving combination therapy than monotherapy achieved BP control, <140/<90 mm Hg, at weeks eight and 12 (49.8 vs 30.2%; *P*<0.0001and 57.2 vs 35.9%; *P*<0.001).
Poldermans et al[54] Valsartan 160 mg plus amlodipine 5 to 10 mg QD vs lisinopril 10 to 20 mg plus HCTZ 12.5 mg QD	AC, DB, MC, PG, RCT Patients 18 years of age and older with HTN (mean DBP ≥110 and <120 mm Hg)	N=130 6 weeks	Primary: Safety/adverse events, vital signs, hematology, biochemistry variables Secondary: Efficacy (mean DBP, response rate, proportion of patients with mean DBP <90 mm Hg or a ≥10 mm Hg reduction from baseline)	Primary: Both treatments were well tolerated, 26 (40.6%) patients receiving valsartan plus amlodipine and 21 (31.8%) patients receiving lisinopril plus HCTZ reported an adverse event and most were not considered drug related (*P* value not reported). Peripheral edema was reported more often in the valsartan plus amlodipine group than the lisinopril plus HCTZ group (7.7 vs 1.5%) and cough was reported less often in the valsartan plus amlodipine group than the lisinopril plus HCTZ group (1.6 vs 3.0%) (*P* values not reported). No difference was found between the treatments in changes in laboratory values or biochemistry variables.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Both treatments resulted in significant reductions from baseline in mean SBP and DBP (*P*<0.0001 for both from baseline), but were not significantly different from each other (*P* value not reported). The mean BP for each group at study end was 135.0/83.6 mm Hg for valsartan plus amlodipine 138.7/85.2 mmHg for lisinopril plus HCTZ. The response rate was similar between the groups (100 vs 95.5%; *P* value not significant).
Fogari et al[55] Valsartan/amlodipine 160/5 to 10 mg, dosing frequency not specified vs irbesartan/HCTZ 300/12.5 to 25 mg, dosing frequency not specified	Blind end endpoint, OL, PG, PRO, RCT Patients 75 to 89 years of age with moderate essential HTN (SBP ≥160, DBP>95 to <110 mm Hg)	N=94 24 weeks	Primary: Proportion of patients achieving DBP <90 mm Hg Secondary: Changes in ambulatory BP, lying and standing changes in BP, safety	Primary: The proportion of patients receiving valsartan/amlodipine and irbesartan/HCTZ who achieved BP <140/<90 mm Hg was 82.9 and 85.1% (*P* value not significant between groups). Secondary: Both treatment combinations resulted in a significant decrease in ambulatory BP without any differences between treatment groups (*P*<0.001 from baseline, *P*>0.05 between groups). Results were similar between groups for lying SBP/DBP but patients receiving irbesartan/HCTZ experienced greater changes in ambulatory BP than those receiving valsartan/amlodipine (17.2/9.0 vs 10.1/1.9 mm Hg; *P*<0.05 for SBP and *P*<0.01 for DBP). Changes from baseline in serum potassium (decrease) and uric acid (increase) were significant for those receiving irbesartan/HCTZ, but not valsartan/amlodipine (*P*<0.05 for irbesartan/HCTZ).
Calhoun et al[37] Valsartan 320 mg QD plus amlodipine 10 mg QD plus HCTZ 25 mg QD vs	DB, MC (multinational), PG, RCT Patients 18 to 85 years of age with moderate to severe HTN (mean	N=2,271 8 weeks	Primary: Change from baseline to end point in mean SBP and DBP Secondary: Change from	Primary: Reductions in mean SBP and DBP were greatest for triple therapy-treated patients (39.68 and 24.74 mm Hg) and were significantly greater than dual therapy-treated patients (*P*<0.0001 for all comparisons). Dual therapy-treated patients achieved BP reductions of 32.0/19.7 for valsartan plus HCTZ- (*P*<0.0001 for both SBP and DBP); 33.5/21.5 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
valsartan 320 mg plus HCTZ 25 mg QD vs valsartan 320 mg QD plus amlodipine 10 mg QD vs amlodipine 10 mg plus HCTZ 25 mg QD	SBP/DBP 145 to 200/100 to 120 mm Hg)		baseline to weeks five, seven and nine in mean SBP and DBP, DBP control (<90 mm Hg), overall BP control (mean <140/<90 mm Hg) rates at endpoint and at weeks five, seven and nine, safety	amlodipine plus valsartan- (*P*<0.0001 for both SBP and DBP) and 31.5/19.5 mm Hg for amlodipine plus HCTZ-treated patients (*P*<0.0001 for both SBP and DBP). Secondary: Reductions in mean SBP and DBP were greatest for triple therapy-treated patients and were significantly greater compared to dual therapy-treated patients at weeks five, seven and nine (*P*<0.0001 for all comparisons). Triple therapy-treated patients achieved significantly greater DBP control compared to dual therapy-treated patients (*P*≤0.0002). After week three, significantly more triple therapy-treated patients achieved overall control (<140/90 mm Hg) compared to dual therapy-treated patients (*P*<0.0001 for all comparisons). Rates of control at trial endpoint were: 70.8, 48.3, 54.1 and 44.8% in triple therapy-, valsartan plus HCTZ-, amlodipine plus valsartan- and amlodipine plus HCTZ-treated patients (*P* values not reported). Most frequently reported adverse events were peripheral edema, dizziness and headache. Peripheral edema occurred more frequently in amlodipine plus HCTZ- (8.9%) and amlodipine plus valsartan-treated patients (8.5%) compared to triple therapy- (4.5%) or valsartan plus HCTZ-treated patients (0.9%). Dizziness occurred more frequently in triple therapy- (7.7%) and valsartan plus HCTZ-treated patients (7.0%) compared to amlodipine plus valsartan- (2.3%) or amlodipine plus HCTZ-treated patients (3.9%) (*P* values not reported).
Calhoun et al[38] Valsartan/amlodipine/HCTZ 320/10/25 mg QD vs	Secondary analysis of Calhoun et al[37] Patients 18 to 85 years of age with moderate to severe HTN (mean	N=2,271 8 weeks	Primary: Proportion and mean SBP of patients with mean SBP reductions ≥60, ≥50, ≥40, ≥30 and ≥20 mm Hg at week three and at the	Primary: The proportion of patients with mean SBP reductions ≥20 mm Hg was greater with triple therapy than dual therapy at week three (74.5 vs 58.8 to 65.5%) and at study endpoint (87.6 vs 75.8 to 81.5%). More patients who received triple therapy, as compared to dual therapy, achieved mean SBP reductions of ≥30, ≥40, ≥50 and ≥60 mm

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
valsartan 320 mg plus HCTZ 25 mg QD vs valsartan/amlodipine 320/10 mg QD vs amlodipine 10 mg plus HCTZ 25 mg QD	SBP/DBP ≥145/≥100 mm Hg)		end of the study Secondary: Changes from baseline in mean SBP based upon baseline severity, SBP control rates, safety	Hg at week three and at study endpoint (*P* value not reported). In patients with severe SBP (≥180 mm Hg), triple therapy resulted in significantly greater reductions than those for each dual therapy at week three (*P*<0.01), except for amlodipine/valsartan (*P*=0.11). Secondary: Patients with higher baseline mean SBP had greater reductions in mean SBP than those with lower baseline mean SBP. Changes in mean SBP were significantly greater for triple therapy than dual therapy for all baseline SBP (*P*<0.05), except for valsartan plus HCTZ and amlodipine plus HCTZ in patients with baseline mean SBP 150 to <160 mm Hg (*P* value not reported). Significantly more patients (91.8%) receiving triple therapy achieved SBP control (≥20 mm Hg reduction or mean SBP <140 mm Hg) compared to those receiving amlodipine plus HCTZ (80.1%), valsartan plus HCTZ (80.8%) or valsartan/amlodipine (85.7%) (*P*<0.01 for all). The overall incidence of adverse events was comparable across treatments, regardless of baseline BP severity.
Waeber et al[34] Valsartan 80 mg/day switched to valsartan/HCTZ 80/12.5 mg/day, or combination of valsartan 80 mg plus benazepril 10 mg/day	OL, RCT Patients with mild-to-moderate uncontrolled HTN (DBP ≥90) while on valsartan monotherapy	N=327 4 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The two combinations produced an additional BP reduction compared to monotherapy (both *P*<0.001), with similar DBP reductions reported for the two combination groups (-4.5 mm Hg with valsartan/HCTZ and -3.3 mm Hg with valsartan/benazepril; *P* value not reported). SBP reductions of -6.7 and -3.2 mm Hg with valsartan/HCTZ and valsartan/benazepril, respectively, were reported (*P*=0.1). At the end of the trial, the BP of the responders to valsartan monotherapy was lower than that of patients requiring combination therapy. Valsartan given alone or in association with HCTZ or benazepril was well tolerated. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Schweizer et al[56] Valsartan/HCTZ 160/25 mg QD vs candesartan 32 mg plus HCTZ 25 mg QD	OL Hypertensive patients not adequately controlled by free combination of candesartan and HCTZ for 4 weeks	N=197 8 weeks	Primary: Reduction in mean sitting DBP between week four and eight Secondary: Reduction in mean sitting SBP between week four and eight	Primary: At baseline, DBP was 103.0 mm Hg. After four weeks of candesartan plus HCTZ, DBP decreased to 93.8 mm Hg (n=197). Subsequent treatment with valsartan/HCTZ for four additional weeks reduced DBP to 88.7 mm Hg (n=138). This represented an additional decrease in DBP of 5.1 mm Hg (*P*<0.0001). Secondary: The valsartan/HCTZ fixed-dose combination reduced SBP by 3.4 mm Hg (*P*=0.0029).
Fogari et al[57] Valsartan 160 mg plus amlodipine 5 mg QD vs losartan 100 mg plus amlodipine 5 mg QD	Blinded endpoint, PRO, RCT, XO Patients 35 to 75 years of age with sitting DBP ≥99 and <110 mm Hg	N=185 12 weeks	Primary: Average 24-hour, daytime and nighttime ambulatory SBP and DBP, averaged hourly SBP and DBP Secondary: Not reported	Primary: Significantly greater reductions in 24-hour, daytime and nighttime SBP and DBP were observed in the valsartan plus amlodipine group compared to the losartan plus amlodipine group (*P*<0.01). Hourly averaged SBP and DBP showed that BP reduction in both combination groups was more consistent than that observed with amlodipine monotherapy. Secondary: Not reported
Fogari et al[43] Valsartan 160 mg plus HCTZ 12.5 mg QD vs olmesartan 20 mg plus HCTZ 12.5 mg QD	PG, PRO, RCT Hypertensive patients 35 to 75 years of age with DBP 90 to 110 mm Hg after 4 weeks of monotherapy on either valsartan or olmesartan	N=130 8 weeks	Primary: Changes in BP Secondary: Not reported	Primary: Both combinations induced a greater ambulatory BP reduction than monotherapy. However, mean reduction from baseline in the valsartan plus HCTZ-treated patients (-21.5/-14.6 mm Hg for 24 hours, -21.8/-14.9 mm Hg for daytime and -20.4/-13.7 mm Hg for nighttime SBP/DBP) was greater than in the olmesartan plus HCTZ-treated patients (-18.8/-12.3 mm Hg for 24 hours, -19.3/-12.8 mm Hg for daytime and -17.4/-10.6 mm Hg for nighttime SBP/DBP). The difference between the effects of the two treatments was significant (*P*<0.01). Plasma concentrations of HCTZ were significantly greater with valsartan than with olmesartan at each determination time (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
White et al[44] Valsartan 160 mg plus HCTZ 25 mg QD vs telmisartan 80 mg plus HCTZ 25 mg QD vs placebo	DB, PC, RCT Hypertensive patients	N=1,181 8 weeks	Primary: Changes in DBP and SBP at eight weeks Secondary: Safety	Primary: Changes from baseline in BP following telmisartan plus HCTZ (-24.6/-18.2 mm Hg) were significantly greater than both valsartan plus HCTZ (-22.5/-17.0 mm Hg; *P*=0.017 for SBP and *P*=0.025 for DBP) and placebo (-4.1/-6.1 mm Hg; *P*<0.0001). Secondary: The total number of patients with at least one adverse event reported was similar among the three treatment groups and was 37% for valsartan plus HCTZ, 36% for telmisartan plus HCTZ and 42% for placebo.
Sharma et al[45] (SMOOTH) Valsartan 160 mg for 4 weeks plus HCTZ 12.5 mg for 6 weeks vs telmisartan 80 mg for 4 weeks plus HCTZ 12.5 mg for 6 weeks	MC, PRO, OL, RCT, blinded-end point Patients 30 years of age and older with mild-to-moderate HTN (mean seated SBP 140 to 179 mm Hg and/or DBP 95 to 109 mm Hg), with type 2 diabetes and BMI >27 kg/m2	N=840 10 weeks	Primary: Change in mean ambulatory SBP and DBP Secondary: Not reported	Primary: At 10 weeks, telmisartan plus HCTZ provided significantly greater reductions in the last six hours of mean ambulatory BP (differences in SBP were 3.9 mm Hg; *P*<0.0001 and differences in DBP were 2.0 mm Hg; *P*=0.0007). Telmisartan plus HCTZ also produced significantly greater reductions than valsartan plus HCTZ in 24-hour mean ambulatory BP (differences in SBP were 3.0 mm Hg; *P*=0.0002 and differences in DBP were 1.6 mm Hg; *P*=0.0006) and during morning, daytime and nighttime periods (*P*<0.003). Both treatments were well tolerated. Secondary: Not reported
Conlin et al[35] (PREVAIL) Candesartan 8 to 16 mg/day, irbesartan 150 to	MA Patients with HTN	N=11,281 Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs (*P* value not reported). Responder rates for ARB monotherapy were 48% to 55%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
300 mg/day, losartan 50 to 100 mg/day and valsartan 80 to 160 mg/day vs another ARB vs ARB plus low-dose HCTZ			titration and with the addition of low-dose HCTZ were calculated; responder rates Secondary: Not reported	Dose titration resulted in slightly greater BP reduction and an increase in responder rates of 53 to 63% (*P* value not reported). ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy (*P* value not reported). Responder rates for ARB and HCTZ combinations were 56 to 70% (*P* value not reported). The authors concluded that candesartan, irbesartan, losartan and valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported
Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy				
Dahlöf et al[58] (LIFE) Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed for BP control vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revasculari-zation procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference; *P*=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference; *P*=0.37). Mean arterial pressure was 102.2 and 102.4 mm Hg, respectively (*P* value not significant). Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 vs -1.8 bpm, respectively; *P*<0.0001). Compared to atenolol, the primary composite endpoint occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.021). While there was no difference in the incidence of cardiovascular mortality (*P*=0.206) and MI (*P*=0.491), losartan treatment resulted in a 24.9% RRR in stroke compared to atenolol (*P*=0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (*P*=0.001). There was no significant difference among the other secondary end points between the two treatment groups. Note: At end point or end of follow-up, 18 and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16 and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al[59] Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years of age with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=523 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: Not reported	Primary: Compared to atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; *P*=0.033). Hazard ratios favored atenolol across all parameters (*P*=0.246 for cardiovascular mortality, *P*=0.140 for MI and *P*=0.030 for stroke). In African American patients, BP reduction was similar in both groups, and regression of electrocardiographic-LVH was greater with losartan. Secondary: Not reported
Lindholm et al[60] Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years of age with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (*P*=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (*P*=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (*P*=0.002). Mean BP fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; *P*=0.002).
Kjeldsen et al[61] Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years of age with isolated systolic HTN (SBP of 160 to 200 mm Hg and DBP <90 mm Hg) and LVH	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (*P*=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (*P*=0.01) and 40% risk reduction in stroke compared to atenolol (*P*=0.02). There was no difference in the incidence of MI. BP was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; *P*<0.046).
Fossum et al[62] Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed for BP control vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=81 3 years	Primary: Amount and density of atherosclerotic lesions in the common carotid arteries and carotid bulb Secondary: Not reported	Primary: The amount of plaque decreased in the losartan group and increased in the atenolol group, though the difference between groups was not statistically significant (*P*=0.471). Patients in the atenolol group had a greater increase in plaque index compared to the losartan group, though the difference between groups was not statistically significant (*P*=0.742). Secondary: Not reported
Kizer et al[63] Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years old with essential HTN (sitting SBP/DBP	N=9,193 ≥4 years	Primary: Reduction in the risk of different stroke subtypes and neurological deficits Secondary:	Primary: The risk of fatal stroke was significantly decreased in the losartan group compared to the atenolol group (*P*=0.032). The risk of atherothrombotic stroke was significantly decreased in the losartan group compared to the atenolol group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	160 to 200/95 to 115 mm Hg) and LVH		Not reported	Comparable risk reductions were observed for hemorrhagic and embolic stroke but did not reach statistical significance. The risk of recurrent stroke was significantly reduced in the losartan arm compared to the atenolol arm (*P*=0.017). The number of neurological deficits per stroke was similar (*P*=0.68), but there were fewer strokes in the losartan group for nearly every level of stroke severity. Secondary: Not reported
Wachtell et al[64] Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed BP control vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=8,851 (patients in LIFE with no baseline history of AF but at risk for AF) ≥4 years	Primary: Incidence of new-onset AF and outcome Secondary: Not reported	Primary: Significantly fewer patients in the losartan group experienced new-onset AF compared to the atenolol group (*P*<0.001). Randomization to losartan treatment was associated with a 33% lower rate of new onset AF independent of other risk factors (*P*<0.001). Patients in the losartan group had a 40% lower rate of composite events consisting of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI (*P*=0.03). Significantly fewer strokes occurred in the losartan group compared to the atenolol group (*P*=0.01), and there was a trend toward fewer MIs in the losartan group (*P*=0.16). There was no significant difference in cardiovascular mortality between groups. In contrast, the atenolol group experienced significantly fewer hospitalizations for heart failure (*P*=0.004) and a trend toward fewer sudden cardiac deaths (*P*=0.07). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wachtell et al[65] Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed for BP control vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	Substudy of LIFE trial[58] Patients 55 to 80 years old with essential HTN(sitting SBP/DBP 160 to 200/95 to115 mm Hg) and LVH	N=342 (LIFE patients with AF at the start of the LIFE study) ≥4 years	Primary: Cardiovascular morbidity and mortality Secondary: Not reported	Primary: Patients with a history of AF had significantly higher rates of cardiovascular and all-cause mortality, fatal and non-fatal stroke, heart failure, revascularization and sudden cardiac death compared to patients without AF (*P*<0.001). Patients with a history of AF had similar rates of MI and hospitalization for angina pectoris (*P*≥0.209). The primary composite endpoint of cardiovascular mortality, stroke and MI occurred in significantly fewer patients in the losartan group compared to the atenolol group (*P*=0.009). The difference in MI between groups was not significant. Treatment with losartan trended toward lower all-cause mortality (*P*=0.09) and fewer pacemaker implantations (*P*=0.065). Secondary: Not reported

Drug regimen abbreviations: QD=once daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: ABPM=ambulatory blood pressure monitoring, AF=atrial fibrillation, ARB=angiotensin II receptor antagonist, BP=blood pressure, bpm=beats per minute, DBP=diastolic blood pressure, HbA_{1C}=hemoglobin A1C, HCTZ=hydrochlorothiazide, HTN=hypertension, LVH=left ventricular hypertrophy, MI=myocardial infarction, SBP=systolic blood pressure

Special Populations

Table 5. Special Populations[9-21]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Azilsartan/ chlorthalidone	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate hepatic impairment.	D	Unknown
Candesartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Consider lower starting dose of 8 mg in patients with moderate hepatic impairment.	C (first trimester) D (second and third trimester)	Unknown
Eprosartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Irbesartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	D	Unknown
Losartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not recommended in hepatic impairment.	C (first trimester) D (second and third trimester)	Unknown
Olmesartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Telmisartan/HCTZ	No dosage	No dosage	Not	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	adjustment required in the elderly population. Safety and efficacy in children have not been established.	adjustment required.	recommended in severe hepatic impairment.	(first trimester) D (second and third trimester)	
Valsartan/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	D	Unknown
Olmesartan/ amlodipine	No dosage adjustment required in the elderly population. Initial therapy is not recommended in patients ≥75 years of age. Safety and efficacy in children have not been established.	No dosage adjustment required.	Use caution in patients with severe hepatic impairment. Initial therapy is not recommended in hepatically impaired patients.	C (first trimester) D (second and third trimester)	Unknown
Olmesartan/ amlodipine/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate starting dose of amlodipine at 2.5 mg in patients with severe hepatic impairment. Initial therapy is not recommended in hepatically impaired patients.	C (first trimester) D (second and third trimester)	Unknown
Telmisartan/ amlodipine	No dosage adjustment required in the elderly population. Initial therapy is not recommended in patients ≥75 years of age.	No dosage adjustment required.	Initiate starting dose of amlodipine at 2.5 mg in patients with severe hepatic impairment. Initial therapy is not recommended	C (first trimester) D (second and third trimester)	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.		in hepatically impaired patients.		
Valsartan/ amlodipine	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Lower starting doses of amlodipine may be required in patients with hepatic insufficiency.	D	Unknown
Valsartan/ amlodipine/HCTZ	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	No dosage adjustment required.	Lower starting doses of amlodipine may be required in patients with hepatic insufficiency.	D	Unknown

HCTZ=hydrochlorothiazide

Adverse Drug Events

Adverse effects presented in Table 6 are those reported in the prescribing information for the combination products. These reported adverse effects may differ from those reported for each individual agent, which are covered in the respective single entity product reviews.

Table 6. Adverse Drug Events[9-21]

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Cardiovascular													
Abnormal electrocardiogram	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Angina	-	<0.5	-	-	-	-	-	-	-	-	-	-	-
Bradycardia	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	≥0.5	-	2	-	>1	-	>0.2	-	-	-	≥0.2	-
Extrasystoles	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Hypotension	1.7	-	-	0.6 to 0.9	0.6	-	<2	>0.2 to 1.0	✔	-	<2	<1	0.5
Myocardial infarction	-	<0.5	-	-	-	-	-	-	-	-	-	-	-
Palpitations	-	≥0.5	-	-	1.4	-	-	>0.2	✔	-	-	≥0.2	-
Syncope	0.3	-	-	-	-	-	-	✔	-	1	<2	✔	>0.2
Tachycardia	-	≥0.5	-	1	-	-	<2	>0.2	-	-	-	≥0.2	>0.2
Central Nervous System													
Anxiety	-	≥0.5	-	≥1	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Asthenia	✔	≥0.5	-	-	≥1	-	-	>0.2	-	-	-	≥0.2	>0.2
Depression	-	≥0.5	-	-	-	-	-	✔	-	-	-	≥0.2	>0.2
Dizziness	8.9	2.9	4.1	1 to 8	5.7	9	1 to 7	>0.2 to 6.0	-	5.8 to 8.9	3	2.1	8.2
Headache	✔	2.9	3.4	1.0 to 5.5	≥1	>2	≥2	-	-	6.4	-	≥0.2	5.2
Hypesthesia	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Hypoaesthesia	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Insomnia	-	≥0.5	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Nervousness	-	-	-	≥1	-	-	-	-	-	-	-	-	-
Paresthesia	-	≥0.5	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Somnolence	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Tremor	-	-	-	-	-	-	-	-	-	-	-	-	>0.2

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Vertigo	-	≥0.5	-	-	-	>1	-	>0.2	-	-	-	-	>0.2
Dermatological													
Alopecia	-	-	-	-	-	✔	-	✔	-	-	-	-	-
Dermatitis	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Eczema	-	≥0.5	-	-	-	-	-	-	-	-	-	≥0.2	-
Erythema	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Exanthema	-	-	-	-	-	-	-	-	-	-	-	✔	-
Night sweats	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Pruritus	-	≥0.5	-	-	-	✔	-	✔	✔	-	-	≥0.2	>0.2
Rash	✔	≥0.5	-	≥1	1.4	>1	<2	>0.2	✔	-	-	≥0.2	>0.2
Sweating	-	≥0.5	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Urticaria	-	-	-	✔	-	✔	-	-	-	-	-	-	-
Gastrointestinal													
Abdominal discomfort	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Abdominal distension	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Abdominal pain	-	≥0.5	-	2	1.2	>1	<2	>0.2	-	-	-	≥0.2	>0.2
Anorexia	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Colitis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Constipation	-	-	-	-	-	-	-	✔	-	-	-	≥0.2	>0.2
Diarrhea	✔	≥0.5	-	≥1	≥1	>1	3	>0.2	-	2.6	-	≥0.2	>0.2
Dry mouth	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Dyspepsia	-	≥0.5	-	2	-	>1	<2	>0.2	-	-	-	≥0.2	2.2
Flatulence	-	-	-	-	-	-	-	>0.2	-	-	-	-	-
Gastritis	-	≥0.5	-	-	-	-	-	-	-	-	-	≥0.2	>0.2
Gastroenteritis	-	≥0.5	-	-	-	>1	-	>0.2	-	-	-	≥0.2	>0.2
Hemorrhoids	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Hepatic function abnormal	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Hepatitis	-	-	-	✔	-	-	-	✔	-	-	-	-	-
Nausea	✔	≥0.5	-	3	≥1	3	2	>0.2	-	3	-	≥0.2	2.1
Taste disturbance	-	-	-	-	-	-	-	-	-	-	-	-	>0.2

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Toothache	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Vomiting	-	≥0.5	-	3	-	✔	<2	>0.2	-	-	-	≥0.2	>0.2
Laboratory Test Abnormalities													
Bilirubin increased	-	✔	-	-	✔	-	✔	-	-	-	-	-	-
BUN increased	✔	≥0.5	-	-	0.6	1.3	2.8	>0.2	-	-	-	-	-
Creatine phosphokinase increased	-	≥0.5	-	-	-	>1	-	-	-	-	-	-	>0.2
Hematocrit decreased	-	✔	-	-	✔	0.4	0.6	-	-	-	-	-	-
Hemoglobin decreased	-	✔	-	-	✔	-	1.2	-	-	-	-	-	-
Hyper-cholesterolemia	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Hyperglycemia	-	≥0.5	-	-	-	>1	-	-	-	-	-	-	-
Hyperkalemia	-	-	-	0.2 to 1.2	-	✔	-	✔	-	-	-	-	-
Hyperlipemia	-	-	-	-	-	>1	-	-	-	-	-	-	-
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Hyperuricemia	✔	≥0.5	-	-	-	4	-	-	-	-	-	-	>0.2
Hypokalemia	1.7	≥0.5	-	0.6 to 0.9	-	-	<2	-	-	-	-	-	>0.2
Hyponatremia	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Serum creatinine increased	2.0	✔	-	-	0.8	-	1.4	-	-	-	-	-	-
Thrombocytopenia	-	-	-	-	✔	-	-	-	-	-	-	-	-
Transaminase levels increased	-	≥0.5	-	-	✔	>1	✔	✔	-	-	-	-	-
Musculoskeletal													
Arthralgia	-	≥0.5	-	-	-	>1	-	>0.2	-	-	-	≥0.2	>0.2
Arthritis	-	≥0.5	-	-	-	>1	-	-	-	-	-	-	-
Arthrosis	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Attention disturbance	-	-	-	-	-	-	-	-	-	-	-	-	>0.2

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Back injury	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Back pain	-	3.3	2.6	-	2.1	>1	<2	>0.2	-	-	2.2	≥0.2	2.1
Contusion	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Epicondylitis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Joint sprain	-	-	-	-	-	-	-	-	-	-	-	≥0.2	>0.2
Joint swelling	-	-	-	-	-	-	-	-	-	2.1	-	≥0.2	>0.2
Leg cramps	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Muscle cramps	-	-	-	≥1	-	-	-	>0.2	-	-	-	-	-
Muscle spasms	✔	-	-	-	-	-	-	-	-	3.1	-	≥0.2	2.2
Muscle weakness	-	-	-	-	-	-	-	✔	-	-	-	-	>0.2
Musculoskeletal chest pain	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Musculoskeletal pain	-	-	-	6	-	-	-	-	-	-	-	-	>0.2
Musculoskeletal stiffness	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Myalgia	-	≥0.5	0.4	-	-	>1	-	>0.2	-	-	-	≥0.2	-
Neck pain	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Procedural pain	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Osteoarthritis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	>0.2
Pain in extremity	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>.2
Rhabdomyolysis	-	-	-	✔	-	✔	-	✔	-	-	-	-	-
Sciatica	-	≥0.5	-	-	-	-	-	-	-	-	-	≥0.2	-
Tendonitis	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Respiratory													
Bronchitis	-	≥0.5	-	-	≥1	-	<2	>0.2	-	-	-	≥0.2	>0.2
Bronchospasm	-	-	-	-	-	-	-	✔	-	-	-	-	-
Cough	✔	≥0.5	-	≥1	2.6	>1	≥2	>0.2	-	-	-	≥0.2	>0.2
Dysphonia	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Dyspnea	-	≥0.5	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Epistaxis	-	≥0.5	-	-	-	-	-	✔	-	-	-	≥0.2	-
Nasal congestion	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Nasopharyngitis	-	-	-	-	-	-	2.4	-	-	3.5	-	4.3	2.1

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Pharyngitis	-	≥0.5	-	≥1	≥1	-	<2	✔	-	-	-	≥0.2	>0.2
Pharyngolaryngeal pain	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Pharyngotonsillitis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Rhinitis	-	≥0.5	-	≥1	-	-	-	-	-	-	-	-	>0.2
Seasonal allergies	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Sinus abnormality	-	-	-	≥1	-	-	-	-	-	-	-	-	-
Sinus congestion	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	-
Sinus headache	-	-	-	-	-	-	-	-	-	-	-	≥0.2	>0.2
Sinusitis	-	≥0.5	-	-	1.2	-	4	>0.2	-	-	-	≥0.2	-
Tonsillitis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Upper respiratory tract infection	-	3.6	0.4	≥1	6.1	7	8	>0.2	-	2.8	-	2.9	>0.2
Miscellaneous													
Abnormal vision	-	-	-	-	-	-	-	✔	-	-	-	-	>0.2
Acute renal failure	-	-	-	-	-	✔	-	-	-	-	-	-	-
Allergy	-	-	-	1	-	-	-	-	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-	-	✔	-	-	-	-	-
Angioedema	-	<0.5	-	✔	✔	✔	-	✔	-	-	-	-	-
Appetite increased	-	-	-	-	-	-	-	✔	-	-	-	-	>0.2
Carpal tunnel	-	-	-	-	-	-	-	-	-	-	-	≥0.2	>0.2
Cerviocobrachial syndrome	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Chest pain, non-cardiac	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Chills	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Conjunctivitis	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Cystitis	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Dehydration	-	-	-	-	-	-	-	✔	-	-	-	-	>0.2
Diabetes mellitus	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Diabetes mellitus, type 2	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Dysuria	-	-	-	-	-	-	-	✔	-	-	-	-	>0.2

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Ear pain	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Edema	-	-	-	3	1.3	-	-	-	5.7 to 11.2	-	<2	≥0.2	6.5
Edema, pitting	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Erectile dysfunction	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Facial edema	-	-	-	-	-	✔	-	-	-	-	-	-	-
Fatigue	2	≥0.5	1.9	6	≥1		3	>0.2		4.2		≥0.2	2.2
Fever	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	-
Flushing	-	-	-	-	-	-	-	✔	-	-	-	≥0.2	-
Gout	-	-	-	-	-	-	-	✔	-	-	-	≥0.2	-
Head discomfort	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Hematuria	-	≥0.5	-	-	-	>1	-	-	-	-	-	≥0.2	-
Hot flush	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Hypersensitivity	-	-	-	-	-	-	-	-	-	-	-	-	-
Inflicted injury	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Influenza-like symptoms	-	2.5	-	3	-	-	2	>0.2	-	-	-	-	-
Influenza	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Infection	-	≥0.5	-	-	-	-	-	-	-	-	-	-	-
Lethargy	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Libido decreased	-	-	-	-	-	-	-	✔	-	-	-	-	-
Limb injury	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Lymphadenopathy	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Malaise	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Nephrolithiasis	-	-	-	-	-	-	-	-	-	-	-	≥0.2	-
Nocturia	-	-	-	-	-	-	-	-	✔	-	-	-	-
Pain	-	≥0.5	-	-	-	-	≥2	-	-	-	-	-	-
Peripheral edema	-	≥0.5	-	-	-	>1	-	>0.2	-	7.7	1.4 to 11.3	5.4	-
Pollakiuria	-	-	-	-	-	-	-	>0.2	-	-	-	≥0.2	>0.2
Renal impairment	-	-	-	-	-	-	-	✔	-	-	-	-	-
Sunburn	-	-	-	-	-	-	-	✔	-	-	-	-	-
Tinnitus	-	≥0.5	-	-	-	-	-	>0.2	-	-	-	✔	>0.2

Adverse Event	Azil-sartan/ chlorth-alidone	Cande-sartan/ HCTZ	Epro-sartan/ HCTZ	Irbe-sartan/ HCTZ	Lo-sartan/ HCTZ	Olme-sartan/ HCTZ	Telmi-sartan/ HCTZ	Val-sartan/ HCTZ	Olme-sartan/ Amlod-ipine	Olme-sartan/ Amlod-ipine/ HCTZ	Telmi-sartan/ Amlod-ipine	Val-sartan/ Amlod-ipine	Valsartan/ Amlod-ipine/ HCTZ
Tooth abscess	-	-	-	-	-	-	-	-	-	-	-	-	>0.2
Urinary frequency	-	-	-	-	-	-	-	-	✔	-	-	-	-
Urinary tract infection	-	≥0.5	-	≥1	-	>2	≥2	-	-	2.4	-	-	>0.2
Urination abnormal	-	-	-	2	-	-	-	>0.2	-	-	-	-	-
Vasculitis	-	-	-	-	-	-	-	✔	-	-	-	-	-
Viral infection	-	≥0.5	-	-	-	-	-	✔	-	-	-	-	>0.5
Visual disturbance	-	-	-	-	-	-	-	-	-	-	-	✔	-
Weight loss	-	-	-	-	-	-	-	-	-	-	-	-	>0.2

BUN=blood urea nitrogen, HCTZ=hydrochlorothiazide
- Event not reported.
✔ Percent not specified.

Contraindications/Precautions

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women during the second and third trimester. When pregnancy is detected, angiotensin II receptor blockers (ARBs) should be discontinued as soon as possible.[9-21]

Drugs that act directly on the renin-angiotensin system have been associated with fetal and neonatal injury when used during the second and third trimesters, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, possibly resulting from decreased renal function in the fetus. Oligohydramnios has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Rarely, no alternative to an ARB may be found. In these cases, the mother should be informed of the potential risk and serial ultrasound examinations should be performed. If oligohydramnios is observed, the ARB should be discontinued unless considered life saving for the mother. Oligohydramnios may not be detected until after the fetus has sustained irreversible injury.[9-21]

Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported though their association to exposure to drugs is unclear. Infants with a history of in utero exposure to ARBs should be closely monitored for hypotension, oliguria and hyperkalemia.[9-21]

Symptomatic hypotension may occur after initiation of an ARB in patients with an activated renin-angiotensin system, such as those who are volume- and/or salt-depleted (i.e., patients on high doses of diuretics). Volume and salt depletion should be corrected before administration of an ARB. If an excessive fall in blood pressure occurs, the patients should be placed in the supine position and given an intravenous infusion of normal saline if necessary. A transient hypotensive response does not contraindicate further treatment once blood pressure has been stabilized.[9-21]

Changes in renal function may be anticipated in patients being treated with medications which inhibit the renin-angiotensin system. Patients whose renal function may depend on the renin-angiotensin system (i.e., patients with severe congestive heart failure, renal artery stenosis, volume depletion), treatment with ARBs may be associated with oliguria or progressive azotemia, acute renal failure and death.[9-21]

Studies with angiotensin converting enzyme inhibitors in patients with unilateral of bilateral renal artery stenosis have shown increases in serum creatinine and/or blood urea nitrogen. Similar effects have been reported with angiotensin receptor blockers.[9-21]

Hypotension may occur during major surgery and anesthesia in patients treated with angiotensin receptor blockers due to the blockade of the renin-agniotensin system. Very rarely, hypotension may be severe enough to warrant the use of intravenous fluids and/or vasopressors.[9-21]

Telmisartan and valsartan are mainly eliminated by biliary excretion and reduced clearance may be expected in patients with biliary obstructive disorders or hepatic insufficiency.[14,15,18-20]

Due to vasodilatory effects, caution is recommended when administering amlodipine, especially in patients with severe aortic stenosis. Amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic function. Caution is recommended when administering to patients with severe hepatic impairment. Patients, specifically those with severe obstructive coronary artery disease, may develop increased frequency, duration or severity of angina or acute myocardial infarction on starting therapy with a calcium channel blocker or during dosage increase. In general, calcium channel blockers should be used in caution in patients with congestive heart failure.[16-20]

Thiazide diuretics cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia and possible other adverse reactions that have occurred in adults.[9-15,17,21]

Hydrochlorothiazide (HCTZ) can cause an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. HCTZ should be discontinued immediately. Prompt medical or surgical treatments may be needed.[9-15,17,20]

Loop diuretics are preferred over thiazide diuretics in patients with severe renal impairment.[9-15,17,21]

Thiazide diuretics should be uptitrated slowly in patients with hepatic impairment. Minor alterations in fluid and electrolyte balance may precipitate hepatic coma.[9-15,17,21]

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide diuretics.

Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma but are more likely in patients with such a history.[9-15,17,20]

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.[9-15,17,21]

Lithium should generally not be given with thiazide diuretics.[9-15,17,21]

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.[9-15,17,21]

Thiazide diuretics should be used with caution in patients with severe renal disease. Thiazide diuretics may precipitate azotemia in these patients. Cumulative effects of the drug may develop.[9-15,17,21]

In diabetic patients, dosage adjustment of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Latent diabetes may become manifest during thiazide diuretic therapy.[9-15,17,21]

Black Box Warning for angiotensin II receptor antagonists combination products[9-21]

WARNING
When pregnancy is detected, discontinue the combination angiotensin II receptor antagonist as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Drug Interactions

Table 7. Drug Interactions[5]

Drug(s)	Interaction	Mechanism
Angiotensin II receptor blockers (all)	Lithium	Angiotensin II receptor blockers may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium. Monitor patients for lithium toxicity and adjust dose as needed.
Angiotensin II receptor blockers (all)	Potassium sparing diuretics	Angiotensin II receptor blockers and potassium sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects. Regularly monitor serum potassium concentrations and renal function in patients receiving these agents concurrently. Consider estimating creatinine clearance in elderly patients and high risk patients.
Angiotensin II receptor blockers	Nonsteroidal anti-inflammatory	Concurrent use of angiotensin II receptor blockers and nonsteroidal anti-inflammatory agents may result in

Drug(s)	Interaction	Mechanism
	agents	decreased antihypertensive effects and an increased risk of renal impairment.
Thiazide diuretics (all)	Digitalis glycosides	Thiazide diuretics may induce electrolyte disturbances which may predispose patients to digitalis-induced arrhythmias. Measure plasma levels of potassium and magnesium, supplement low levels, and use dietary sodium restriction or potassium sparing diuretics to prevent further losses.
Thiazide diuretics (all)	Dofetilide	Thiazide diuretics may induce hypokalemia which may increase the risk of torsades de pointes. The coadministration of dofetilide with a thiazide diuretic is contraindicated.
Thiazide diuretics (all)	Lithium	Decreased lithium clearance may occur with thiazide use. This may lead to increased serum lithium levels and possibly lithium toxicity. Monitor plasma lithium levels and symptoms of toxicity, and adjust the dose as needed.
Thiazide diuretics (HCTZ)	Cisapride	Cisapride is contraindicated in patients receiving thiazide diuretics. Thiazide diuretics may lead to a rapid reduction in plasma potassium. This electrolyte loss may lead to additive prolongation of the QT interval, increasing the risk of life-threatening arrhythmias.
Thiazide diuretics (HCTZ)	Diazoxide	Hyperglycemia and symptoms similar to frank diabetes may occur. The effect appears to return to pre-treatment values approximately two weeks after discontinuation of the medications. Decreased dose of one or both medications may be indicated. Avoidance of concurrent use is recommended with close monitoring of blood and urine glucose levels if concurrent use is necessary.
Thiazide diuretics (HCTZ)	Loop diuretics	Coadministration may lead to greater sodium, potassium and chloride excretion and dieresis. Careful titration with small or intermittent doses is recommended. Monitor for dehydration and electrolyte abnormalities during concurrent use.
Thiazide diuretics (HCTZ)	Sulfonylureas	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion, and increase potassium loss. This may lead to hyperglycemia, decreasing the hypoglycemic effects of the sulfonylureas. Blood glucose levels should be closely monitored, and an increase of the sulfonylurea dose may be needed.

HCTZ=hydrochlorothiazide

Dosage and Administration

Table 8. Dosing and Administration[9-21]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Azilsartan/ chlorthalidone	Hypertension*: Tablet: initial, 40/12.5 mg QD; maximum, 40/25 mg; initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 40/ 12.5 mg 40/ 25 mg
Candesartan/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; patients not controlled or	Safety and efficacy in children have not been established.	Tablet: 16/12.5 mg 32/12.5 mg 32/25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	experiencing hypokalemia on HCTZ 25 mg can expect an incremental effect from 16/12.5 mg; patients not controlled on candesartan 32 mg can expect incremental blood pressure effects from 32/12.5 mg and then 32/25 mg		
Eprosartan/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maintenance, 600/12.5 mg QD when used in patients who are not volume-depleted; patients may be titrated to 600/25 mg QD	Safety and efficacy in children have not been established.	Tablet: 600/12.5 mg 600/25 mg
Irbesartan/ HCTZ	Hypertension*: Tablet: initial, 150/12.5 mg QD; maintenance, in patients not controlled on monotherapy with irbesartan or HCTZ, the recommended dose, in order of increasing mean effect are, 150/12.5, 300/12.5 and 300/25 mg; combination may be substituted for the titrated individual components; maximum, 300/25 mg QD	Safety and efficacy in children have not been established.	Tablet: 150/12.5 mg 300/12.5 mg 300/25 mg
Losartan/ HCTZ	Hypertension‡: Tablet: initial, 50/12.5 mg QD; maintenance, if blood pressure remains uncontrolled, the dose may be increased to 2 tablets of 50/12.5 mg QD or 1 tablet of 100/25 mg QD; maximum, 100/25 mg/day Left ventricular hypertrophy in hypertensive patients§: Tablet: initial, losartan 50 mg QD; HCTZ 12.5 mg QD should be added or 50/12.5 mg substituted if blood pressure reduction is inadequate; maintenance, if additional blood pressure reduction is needed, losartan 100 mg and HCTZ 12.5 mg or 100/12.5 mg may be substituted, followed by losartan 100 mg and HCTZ 25 mg or 100/25 mg	Safety and efficacy in children have not been established.	Tablet: 50/12.5 mg 100/12.5 mg 100/25 mg
Olmesartan/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maintenance, in patients not controlled on olmesartan, HCTZ may be added starting with a dose of 12.5 mg and later titrated to 25 mg QD; if patient is taking HCTZ, olmesartan may be added starting with a dose of 20 mg QD and titrated to 40 mg	Safety and efficacy in children have not been established.	Tablet: 20/12.5 mg 40/12.5 mg 40/25 mg
Telmisartan/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual	Safety and efficacy in children have not been established.	Tablet: 40/12.5 mg 80/12.5 mg 80/25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	components; maintenance, patients not controlled on telmisartan 80 mg monotherapy may be switched to 80/12.5 mg QD and titrated up to 160/25 mg if necessary; patients not controlled on HCTZ 25 mg may be switched to 80/12.5 or 80/25 mg QD		
Valsartan/ HCTZ	Hypertension*: Tablet: initial, 160/25 mg QD; maximum, 320/25 mg QD; patients not controlled on valsartan or HCTZ monotherapy may switch to combination therapy	Safety and efficacy in children have not been established.	Tablet: 80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg
Olmesartan/ amlodipine	Hypertension*: Tablet: initial, 20/5 mg QD; maximum, 40/10 mg QD; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 20/5 mg 40/5 mg 20/10 mg 40/10 mg
Olmesartan/ amlodipine/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 40/10/25 mg	Safety and efficacy in children have not been established.	Tablet: 20/5/12.5 mg 40/5/25 mg 40/10/12.5 mg 40/10/25 mg
Telmisartan/ amlodipine	Hypertension*: Tablet: initial, 40/5 mg QD, patients requiring larger blood pressure reductions may be started at 80/10 mg QD; combination may be substituted for the titrated individual components; maximum, 80/10 mg QD	Safety and efficacy in children have not been established.	Tablet: 40/5 mg 40/10 mg 80/5 mg 80/10 mg
Valsartan/ amlodipine	Hypertension*: Tablet: initial, 160/5 mg QD; maximum, 320/10 mg QD; combination may be substituted for the titrated individual components	Safety and efficacy in children have not been established.	Tablet: 160/5 mg 160/10 mg 320/5 mg 320/10 mg
Valsartan/ amlodipine/ HCTZ	Hypertension†: Tablet: initial, initiate combination therapy after failure on monotherapy; combination may be substituted for the titrated individual components; maximum, 320/10/25 mg QD	Safety and efficacy in children have not been established.	Tablet: 160/5/12.5 mg 160/10/12.5 mg 160/5/25 mg 160/10/25 mg 320/10/25 mg

HCTZ=hydrochlorothiazide, QD=once daily
*Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
†This fixed-dose combination is not indicated for initial therapy.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Heart, Lung, and Blood Institute:	• Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class

Clinical Guideline	Recommendations
The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)[6]	(angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], β-adrenergic blockers [β-blockers], calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. • Certain high risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. • Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. • When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal. However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. • High risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). • The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. • For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. • Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria. • Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. • African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. • Calcium channel blockers may be useful in Raynaud's syndrome and

Clinical Guideline	Recommendations
	certain arrhythmias. • ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
World Health Organization/ International Society of Hypertension: **2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)**[8]	• When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. • Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension/ European Society of Cardiology: **2007 Guidelines for the Management of Hypertension (2007)**[66], **Reappraisal of Guidelines on Hypertension Management (2009)**[7]	• In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. • In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. • There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). • Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. • Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. • Fixed combination medications can favor compliance and simplify regimens. • When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. • Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor

Clinical Guideline	Recommendations
	with a calcium channel blocker. • Avoid β-blocker/diuretic combination unless required for other reasons. • If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. • A β- or α-blocker may be included in triple therapy approach depending on clinical circumstances. • Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. • Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. • Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. • Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. • The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. • In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
National Institute for Health and Clinical Excellence/British Hypertension Society: **Hypertension: Clinical Management of Primary Hypertension in Adults: (2011)**[67]	• Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. • Do not combine an ACE inhibitor with an ARB to treat hypertension. • Initial therapy in patients ≥55 years of age should be a calcium channel blocker or for black people of African or Caribbean family origin of any age. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. • If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlorthalidone (12.5 to 25.0 mg daily) or indapamide (1.5 mg modified-release daily or 2.5 mg once) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. • Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly those with an intolerance or contraindication to ACE inhibitors and ARBs, women of child-bearing potential those with an increased sympathetic drive. • If a second medication is required treatment with a calcium channel blocker in combination with an ACE inhibitor or an ARB should be added. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, a thiazide-like diuretic is recommended.

Clinical Guideline	Recommendations
	• If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. • If clinic blood pressure remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. • For resistant hypertension, consider further diuretic therapy with low dose spironolactone (25 mg daily) if the blood potassium level is less than 4.5 mmol/L. Consider a higher-dose thiazide-like diuretic if the blood potassium level is greater than 4.5 mmol/L.

Conclusions

The angiotensin II receptor blocker (ARB) combination products are Food and Drug Administration (FDA) approved for the treatment of hypertension. Losartan/hydrochlorothiazide (HCTZ) carries the additional indication of reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. Recently, the combination of azilsartan/chlorthalidone (Edarbyclor®) was approved by the FDA and is the only chlorthalidone-containing product in the class. The other available products in this class include various combinations of an ARB with a calcium channel blocker (amlodipine), a thiazide diuretic (HCTZ) or both. Losartan/HCTZ is the only generic product available within the class.

Current treatment guidelines indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade 2 hypertension may require initial therapy with medications from two different drug classes.[6,7] ARBs are recommended in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[6-8] If more than one drug is needed to effectively control blood pressure, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure recommends that one agent be a thiazide diuretic.[6] According to the European Society of Hypertension/European Society of Cardiology, combinations that can be recommended based on clinical trial evidence include a diuretic with an ACE inhibitor, an ARB or a calcium channel blocker or a combination of an ACE inhibitor with a calcium channel blocker.[7] If triple therapy is needed, the European Society of Hypertension/European Society of Cardiology recommends a blocker of the renin-angiotensin system, a calcium channel blocker and a diuretic.[7]

Clinical trials assessing the ARB combination products in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or HCTZ.[22-34] A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy.[35] Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy.[36-38] Head-to-head trials have not consistently demonstrated superiority of one combination product over another within the class.[39-45]

Losartan/HCTZ is the only combination agent in the class which carries an additional indication for reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy. The efficacy of losartan in preventing stroke in this population was demonstrated in the Losartan Intervention for Endpoint trial and its corresponding substudies. Losartan was compared to therapy with atenolol (HCTZ could be added to primary regimens if needed for blood pressure control). Results demonstrate a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as compared to atenolol-based regimens.[58]

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