Evaluation of Response—Treatment of Uncontrolled Hypertension in Adults Versus Pediatric Patients Across Age Spectrum

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Disclosures

- I have no financial relationships to disclose.

Objectives

- Review the nuance between uncontrolled and resistant hypertension
- Summarize efficacy of newer medications that are approved for uncontrolled hypertension
- Introduce adjunctive approaches to improve hypertension control

5.4. Plan of Care for Hypertension

Recommendations for Plan of Care for Hypertension Referenced studies that support the recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
Team-Based Care		
1	A	1. For adults with uncontrolled hypertension, a team-based care approach is recommended to achieve and maintain BP control.[1–4]
1	C-LD	2. For adults with uncontrolled hypertension, an evidence-based care plan utilizing HBPM, and team-based care that is responsive to addressing adverse SDOH, is recommended to achieve and maintain BP control.[5,6]
Framework in Clinical Practice to Improve Hypertension Control		
1	B-NR	3. For adults with uncontrolled hypertension, an integrated treatment model that includes accurate BP measurement, prompt treatment, patient engagement, and ongoing review of HBPM is recommended to improve BP control.[7–10]
Follow-Up After Initial BP Evaluation and Initiation of Antihypertensive Therapy		
1	B-R	4. Adults with uncontrolled hypertension placed on new or intensified medical therapy should have follow-up evaluations for medication adherence and response to treatment at monthly intervals until control is achieved.[11–13]
Health Information Technology		
1	B-R	5. For adults with uncontrolled hypertension, health information technology (HIT) by synchronous (eg, phone, video call) or asynchronous (eg, text, e-mail) communication is beneficial in improving BP control, access to care, and adherence to standards of care and should be incorporated in the management of hypertension, including the titration of BP medications.[14–17]
1	B-NR	6. In adults with undiagnosed or uncontrolled hypertension, use of the electronic health record (EHR) and patient registries is beneficial for screening and identification of hypertension to focus on those who need additional care.[15]
2a	B-R	7. In adults with uncontrolled hypertension, telehealth interventions can be useful to reduce BP[18–26] and improve office BP control.[19,21,23–26]

- No reference to "uncontrolled hypertension" in AAP CPG

Causes of Uncontrolled Hypertension

- **Nonadherence**
  - 50% of adult causes
- **White coat hypertension**
  - 37.5% of adult causes
- **Undiagnosed secondary hypertension (RAS, PHA)**
  - 5-25% of adult causes
- **Resistant hypertension**
  - ~10% of adult causes
  - Associated conditions: obesity, diabetes, CKD, OSA
  - Associated drugs: NSAIDs, antidepressants (SSRIs), illicit substances (cocaine)

How should true resistant hypertension be treated?

Management of true resistant hypertension includes lifestyle modifications (adherence to a low sodium diet [<1500 mg/d], reducing or avoiding alcohol, moderate-intensity exercise [≥150 min/wk of regular, moderate intensity aerobic exercise, and ≥2 d/wk of resistance exercise], and weight loss). For patients with resistant hypertension, the use of combinations pills, intensifying diuretic therapy by using preferably chlorthalidone (especially in patients with chronic kidney disease), and the addition of a mineralocorticoid receptor antagonist (eg, spironolactone) are recommended for patients with estimated glomerular filtration rate of 45 mL/min/1.73 m^2 or greater and serum potassium level of 4.5 mmol/L or less. Patients who experience adverse effects with spironolactone can be switched to amiloride or eplerenone. Other therapeutic options include β-blockers, α_1-adrenergic blockers, centrally acting antihypertensive agents, nondihydropyridine calcium channel blockers, direct vasodilators, or a dual endothelin receptor antagonist (eg, aprocitentan), which may be also used as alternatives to spironolactone in case of adverse events or contraindication or added sequentially to a regimen that includes spironolactone.

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Resistant HTN – Treatment in Adults

- Lifestyle
- Combination pills
- Intensified diuretics
  - Chlorthalidone
  - Spironolactone
  - Amiloride or Eplerenone
- 4th line agents:
  - Beta blockers, alpha blockers, nondihydropyridine CCBs, direct vasodilators
  - Dual endothelin receptor antagonist

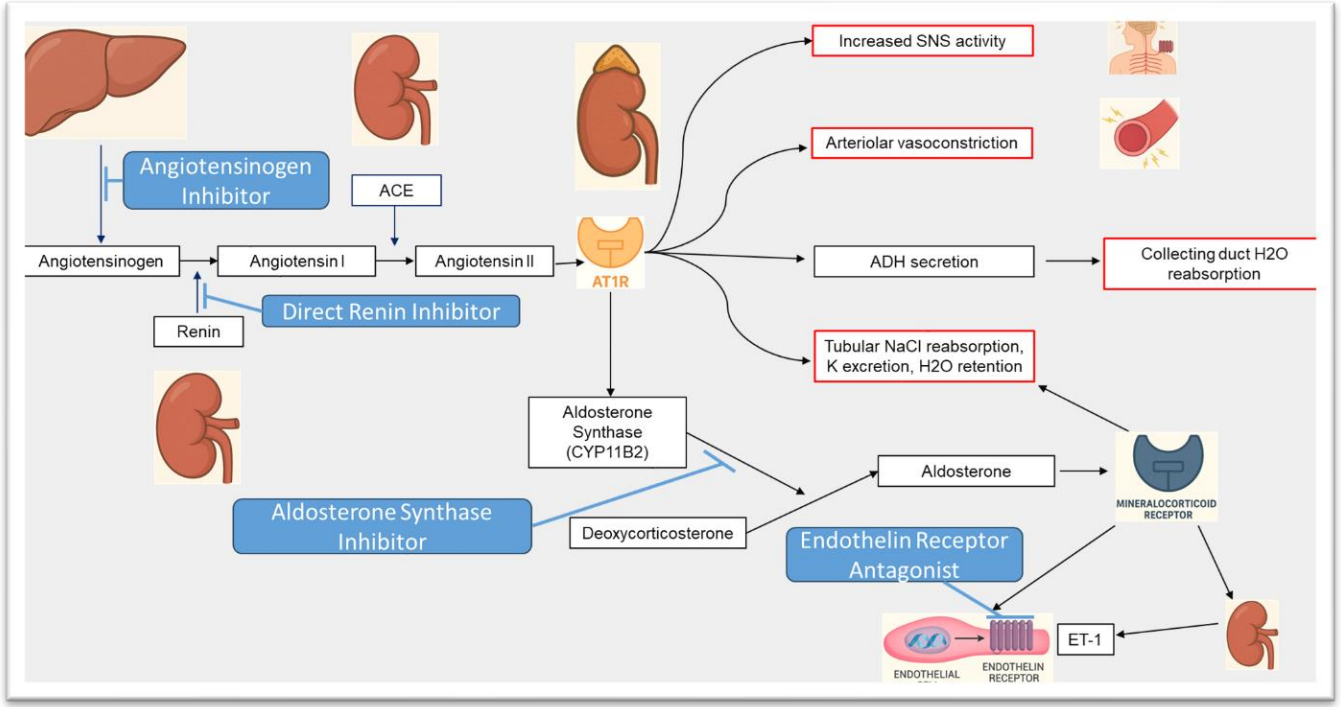
Table 3. Antihypertensive Medications for True Resistant Hypertension (Patient Receiving ≥3 Antihypertensive Medications)[a]

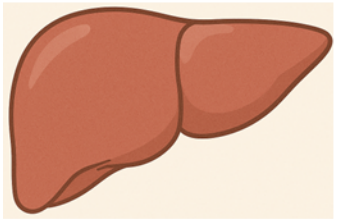
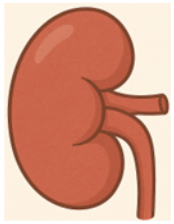
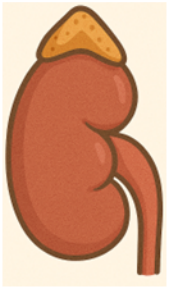
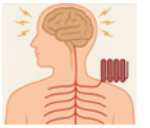
Medication (daily dose)	Mechanism of action	Efficacy (treatment vs control)	Adverse effects
Preferred medications[b]			
Spironolactone (25-50 mg)	Mineralocorticoid receptor antagonism	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −13.30 mm Hg (95% CI, −17.89 to −8.72) Mean difference in 24-h ambulatory SBP vs placebo: −8.46 mm Hg (95% CI, −12.54 to −4.38)	Hyperkalemia (≈3%-5%), acute kidney injury (relative risk, ≈2), sexual impotence (≈9%), gynecomastia (relative risk, ≈5), and menstrual irregularities compared with placebo or standard care
Eplerenone (50-100 mg) (in case of antiandrogenic or progestogenic adverse effects of spironolactone)	Mineralocorticoid receptor antagonism	Cochrane database[55] Eplerenone has only been evaluated in patients with uncontrolled hypertension Mean difference in office SBP vs placebo: −9.21 mm Hg (95% CI, −11.08 to −7.34) Comparative trial in primary hypertension[56] Eplerenone is less potent than spironolactone: mean changes in office SBP for eplerenone (50 mg and 100 mg) twice a day are approximately 50% to 75% of those observed with spironolactone (50 mg) twice a day	Risk of hyperkalemia and acute kidney injury compared with placebo or standard care No antiandrogenic or progestogenic effects
Alternative treatments[c]			
Amiloride (10-20 mg)[d]	Epithelial sodium channel blocker	Amiloride noninferior to spironolactone in patients with resistant hypertension[57,58]	Hyperkalemia
β-Blockers (eg, bisoprolol [5-10 mg])	Selective β1-receptor blockade	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −8.44 mm Hg (95% CI, −15.48 to −1.40) Mean difference in 24-h ambulatory SBP vs placebo: −7.10 mm Hg (95% CI, −18.12 to 3.92)	Fatigue, bradycardia, sexual impotence
α-1 Blockers (eg, doxazosin [4-8 mg])	α1-adrenergic blockade	Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −7.62 mm Hg (95% CI, −15.86 to 0.62)	Orthostatic hypotension, falls and fractures
Centrally acting sympatholytic medications (eg, clonidine [0.1-0.3 mg] twice daily)	Central α-2 receptor agonist	ReHOT study[59] Office blood pressure decreases from baseline to 3 mo: Clonidine: −13.7 mm Hg (95% CI, −18.4 to −9.0) vs spironolactone: −15.1 mm Hg (95% CI, −19.7 to 10.6) Network meta-analysis in resistant hypertension[54] Mean difference in office SBP vs placebo: −11.90 mm Hg (95% CI, −23.29 to −0.52) Mean difference in 24-h ambulatory SBP vs placebo: −4.26 mm Hg (95% CI, −12.10 to 3.59)	Somnolence, dry mouth, constipation, orthostatic hypotension, impotence, rebound hypertension[60]
Aprocitentan (12.5 mg)	Dual endothelin receptor antagonist	PRECISION trial[13] Mean difference in unattended office SBP vs placebo: −3.8 mm Hg (97.5% CI, −6.8 to −0.8) Mean difference in 24 h ambulatory SBP: −4.2 mm Hg (95% CI, −6.2 to −2.1)	Edema or fluid retention (9%)

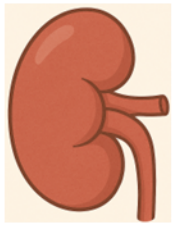
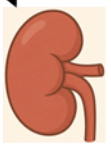
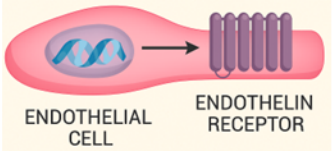
Medications

New(ish) BP Meds

- Direct Renin Inhibitors
- Aldosterone synthase inhibitors
- Endothelin receptor antagonists
- Angiotensinogen inhibitors



Increased SNS activity

Arteriolar vasoconstriction

ADH secretion

Collecting duct H2O reabsorption

Tubular NaCl reabsorption, K excretion, H2O retention

ACE

ACEi

Angiotensinogen

Angiotensin I

Angiotensin II

AT1R

Renin

ARB

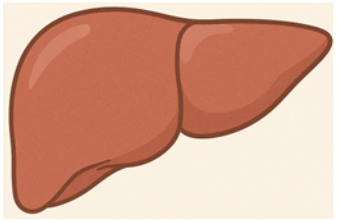
Aldosterone Synthase (CYP11B2)

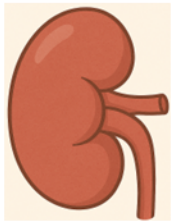
Deoxycorticosterone

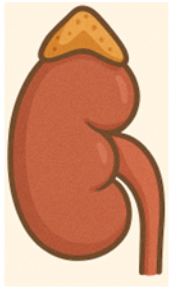
MR Antagonist

Aldosterone

ET-1







Angiotensinogen Inhibitor

ACE

Angiotensinogen → Angiotensin I → Angiotensin II → AT1R

Renin

Direct Renin Inhibitor

Increased SNS activity

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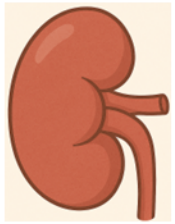
Tubular NaCl reabsorption, K excretion, H2O retention

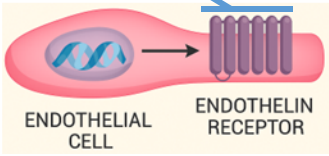


Aldosterone Synthase (CYP11B2)

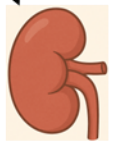
Aldosterone Synthase Inhibitor

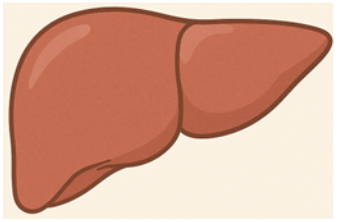
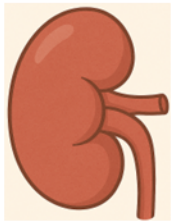
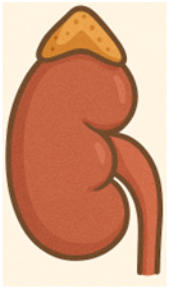
Deoxycorticosterone → Aldosterone

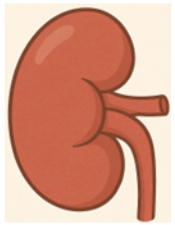
Endothelin Receptor Antagonist

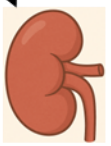
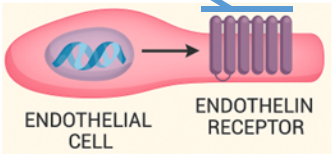


ET-1



Angiotensinogen Inhibitor

ACE

Angiotensinogen → Angiotensin I → Angiotensin II → AT1R

Renin

Direct Renin Inhibitor

Increased SNS activity

Arteriolar vasoconstriction

ADH secretion → Collecting duct H2O reabsorption

Tubular NaCl reabsorption, K excretion, H2O retention

Aldosterone Synthase (CYP11B2)

Aldosterone Synthase Inhibitor

Deoxycorticosterone → Aldosterone → MINERALOCORTICOID RECEPTOR

Endothelin Receptor Antagonist

ENDOTHELIAL CELL

ENDOTHELIN RECEPTOR

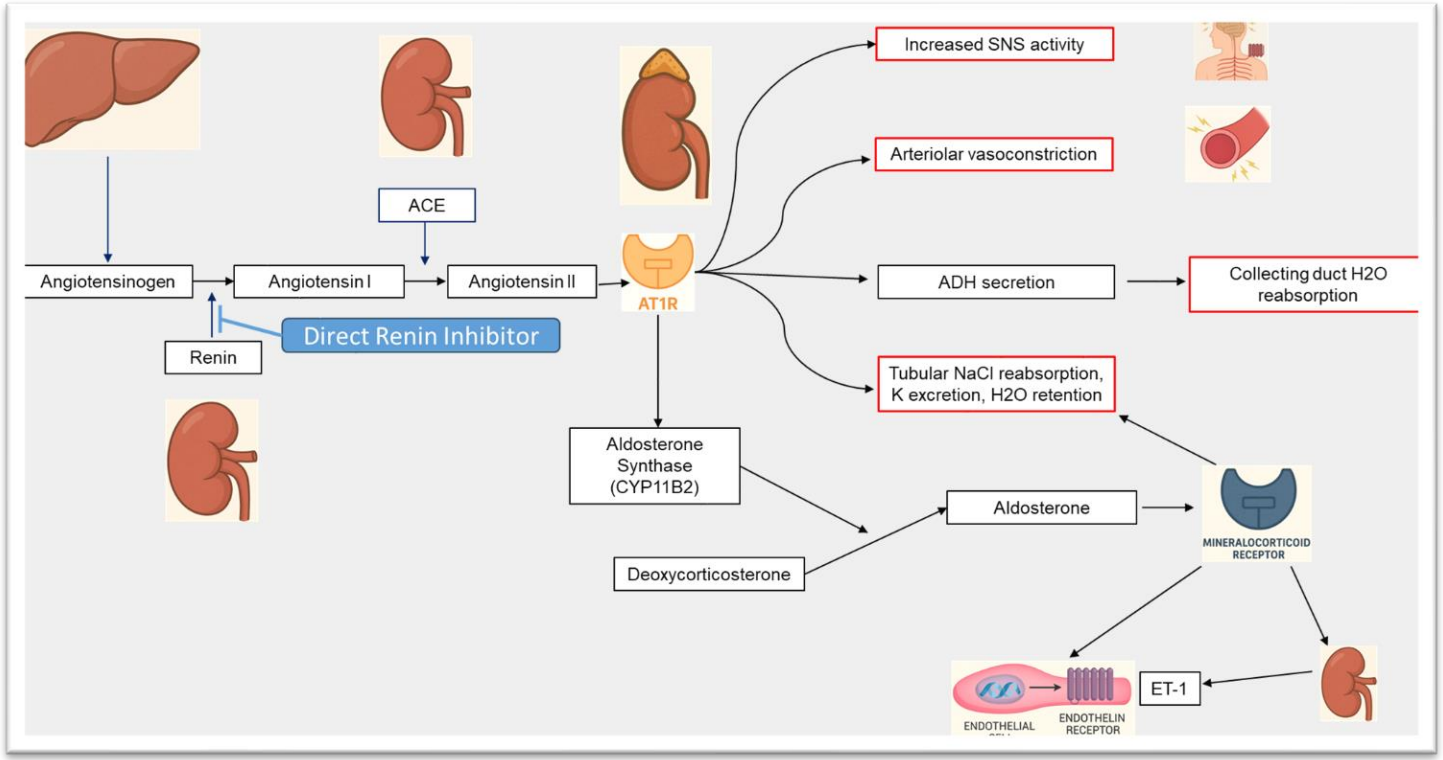
ET-1

FDA approved for hypertension

FDA approved for uncontrolled hypertension

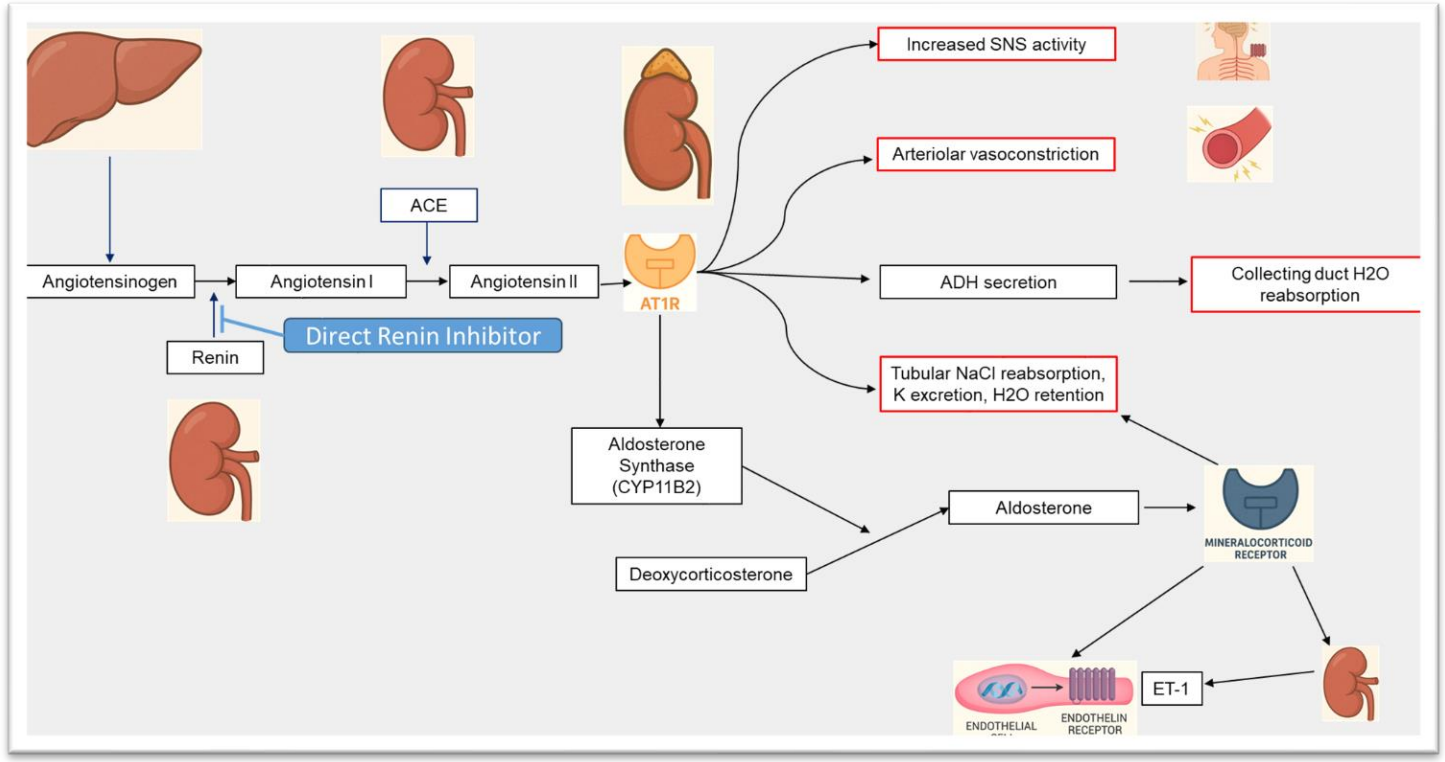
Not FDA approved

Direct Renin Inhibitors (DRI)



- Aliskiren is the only orally active DRI approved for clinical use
- Long duration of action
  - Half-life elimination: ~24 hours (range: 16 to 32 hours)

Direct Renin Inhibitors (DRI)

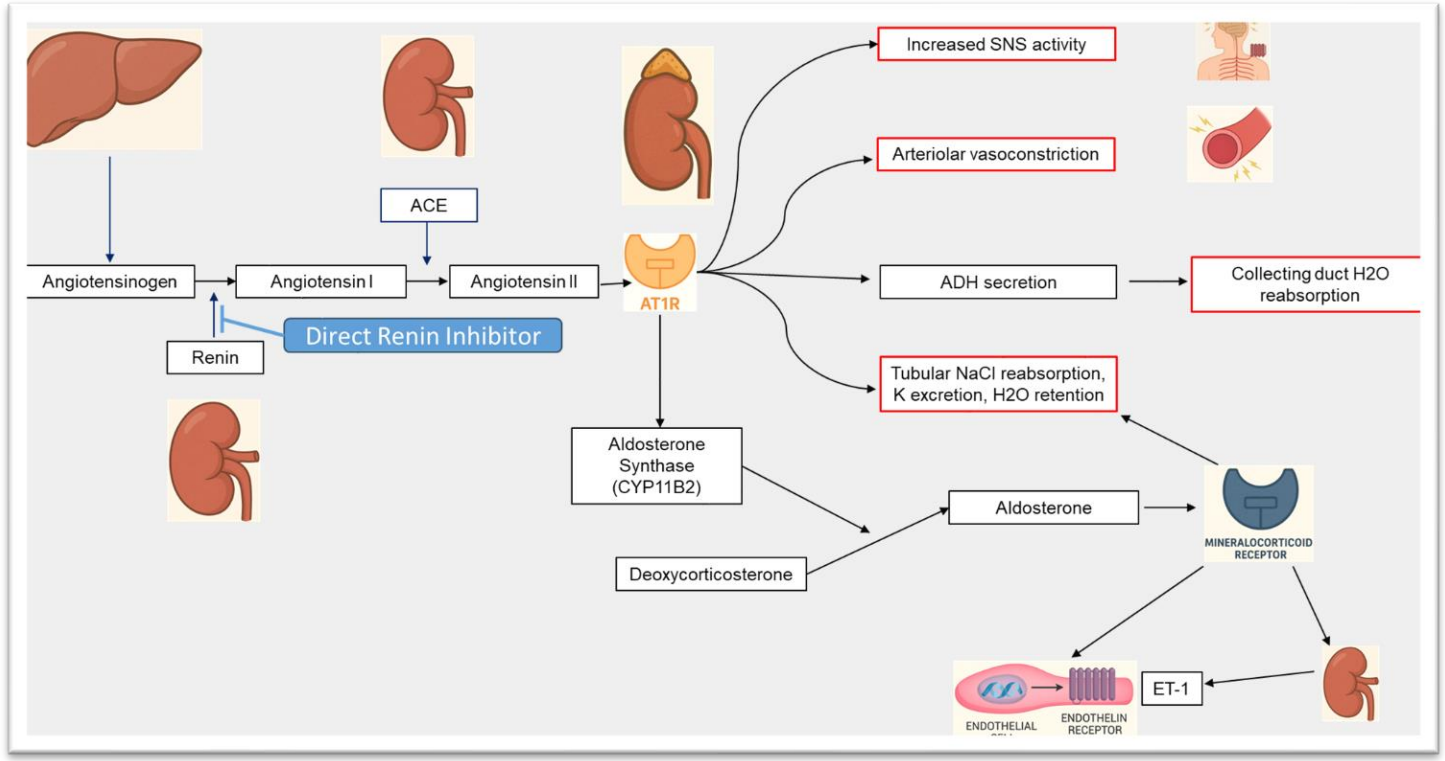


- Aliskiren
  - Similar BP lowering as ACEi and ARBs
  - Meta-analyses of RCTs (Aliskiren vs. placebo):

Aliskiren Dose	SBP reduction	DBP reduction
150 mg daily	6 mmHg	3 mmHg
300 mg daily	8 mmHg	4.5 mmHg
600 mg daily	11 mmHg	6 mmHg

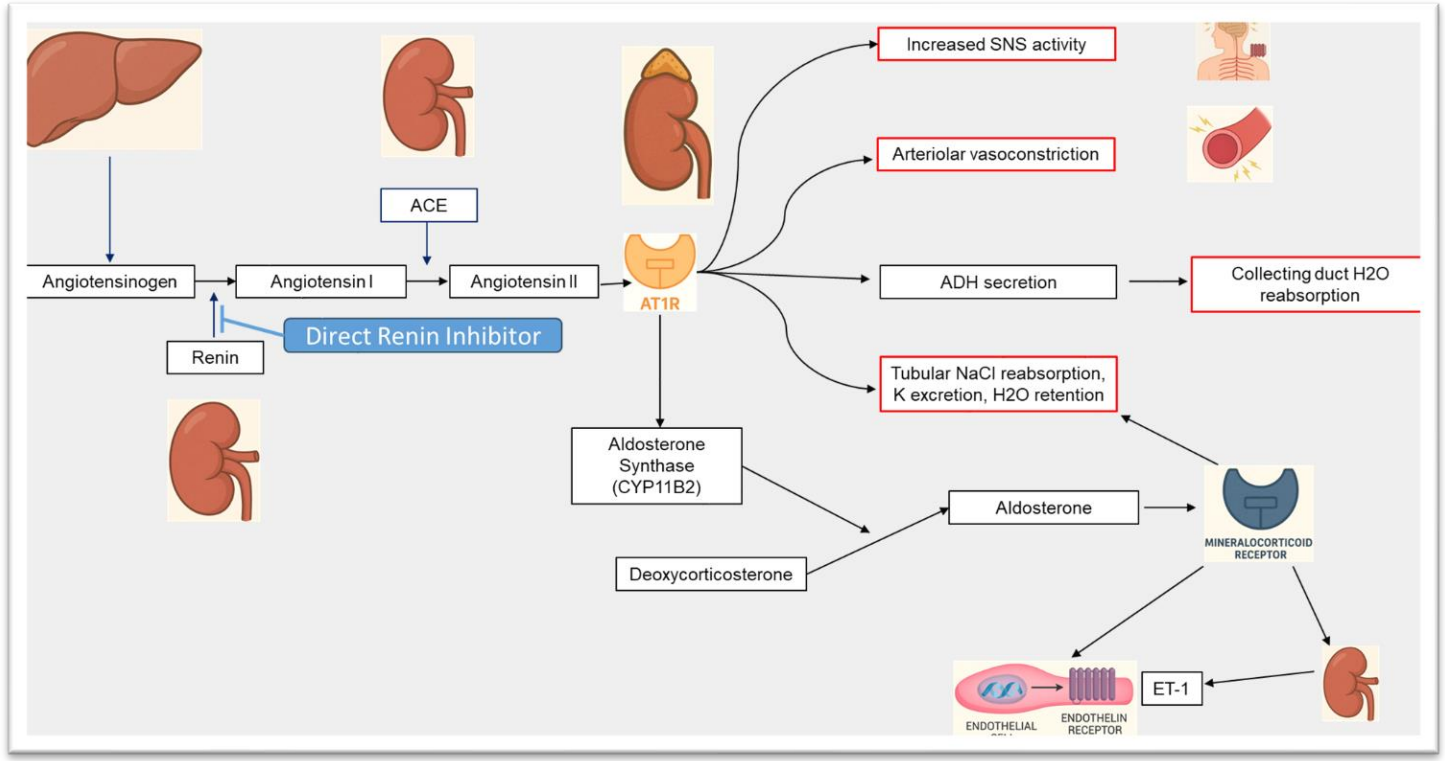
Musini VM et al, The Cochrane Database of Systematic Reviews, 2017
Wang GM et al, The Cochrane Database of Systematic Reviews, 2020
Wang GM et al, The Cochrane Database of Systematic Reviews, 2025

Direct Renin Inhibitors – Pediatric Evidence?



- Limited but emerging evidence
- Need for close monitoring of labs (K, Cr)
- Not 1st line
- Should be reserved for cases where standard therapies are ineffective or not tolerated

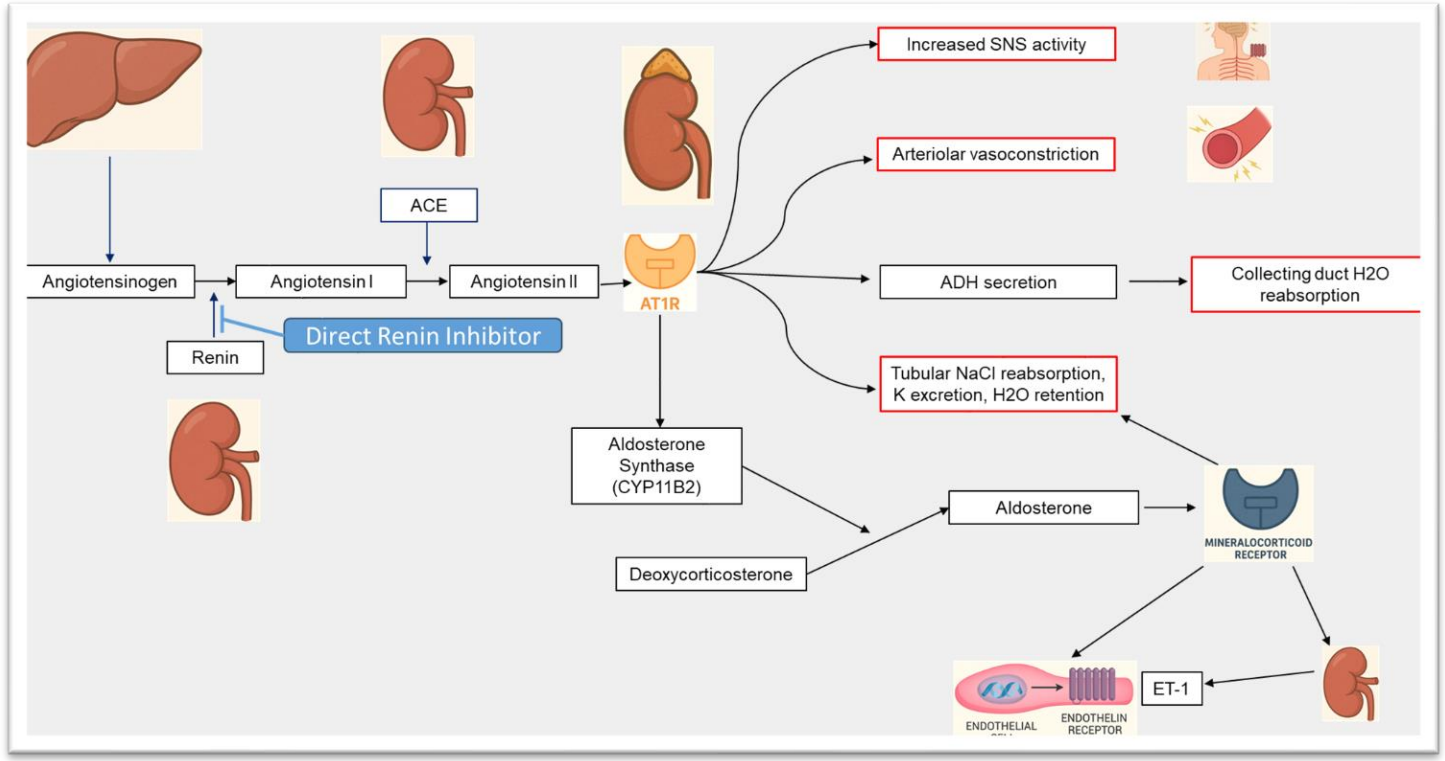
Direct Renin Inhibitors – Pediatric Dosing



Children ≥6 years and Adolescents:

- 20 to 50 kg
  - Initial: 75 mg once daily
  - May increase to 150 mg once daily
  - Maximum daily dose: 150 mg/day.
- ≥50 kg
  - Initial: 150 mg once daily
  - May increase to 300 mg once daily
  - Maximum daily dose: 300 mg/day.

Direct Renin Inhibitors – Pediatric Evidence

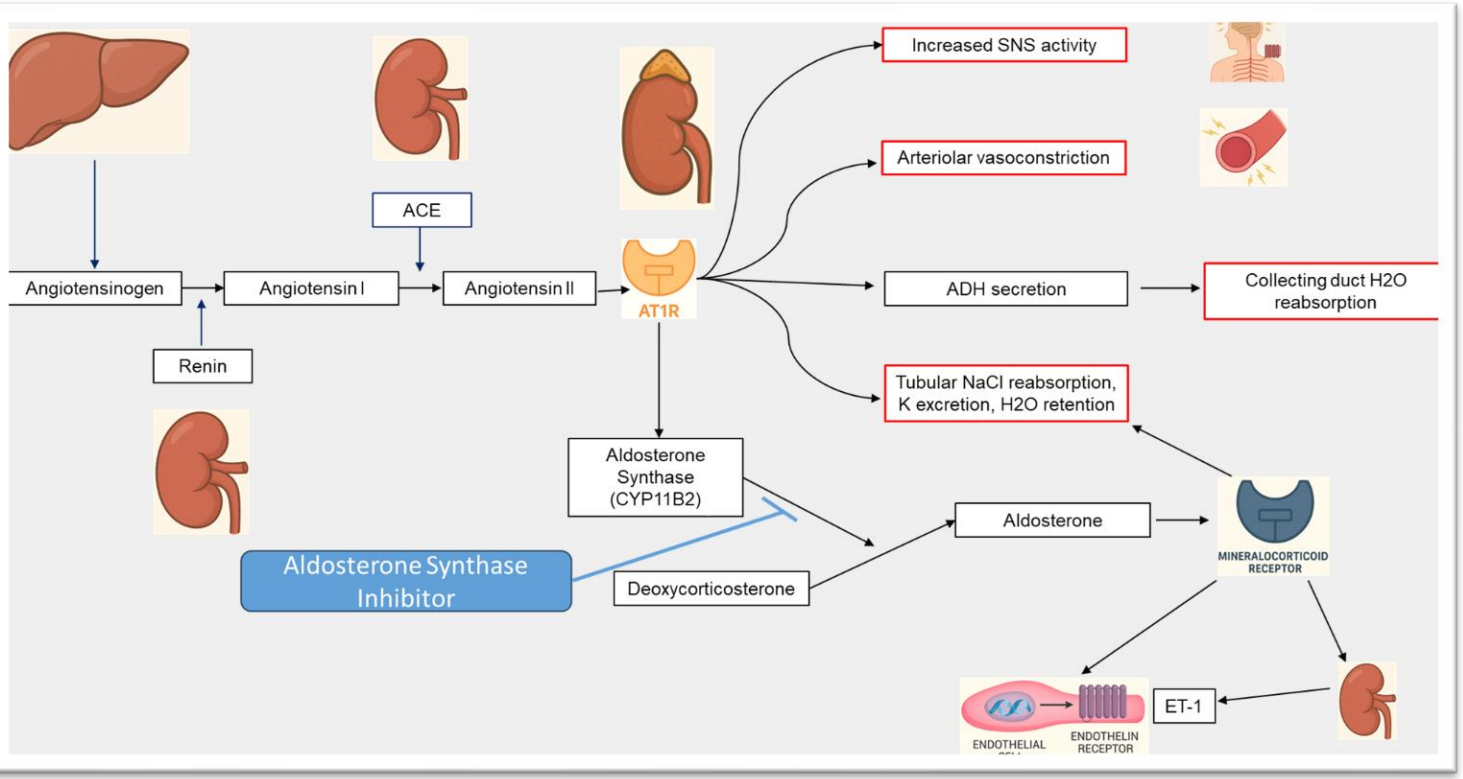


8 week randomized, double-blind trial in 267 pediatric patients 6-17 years, compared to placebo, aliskiren decreased SBP by:

- Low dose: 4.8 mmHg
- Mid dose: 5.6 mmHg
- High dose: 8.7 mmHg

NCT01150357

Aldosterone synthase inhibitors (ASI)



- Orally active, once daily
- Newer agents (lorundrostat and baxdrostat):
  - Highly selective for AS
    - CYP11B2 > CYP11B1
  - Minimal effect on cortisol
    - Earlier agents (osilodrostat) also inhibited cortisol synthesis
  - Decreased risk of adrenal insufficiency

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QUESTION Is the aldosterone synthase inhibitor lorundrostat more effective than placebo in reducing blood pressure in participants with uncontrolled hypertension, including treatment-resistant hypertension, taking 2 to 5 prescribed antihypertensive medications?

CONCLUSION These data support use of lorundrostat as a treatment option for patients with uncontrolled hypertension, including treatment-resistant hypertension.

POPULATION

575 Men
508 Women

Adults with uncontrolled or treatment-resistant hypertension

Median age: **61.6** years

LOCATIONS

159
Clinic sites worldwide

INTERVENTION

1083 Participants randomized
1078 Participants analyzed

808
Lorundrostat
50 mg/d for 12 weeks;
50 mg/d for 6 weeks and escalated to 100 mg/d for 6 weeks if met prespecified criteria

270
Placebo
Placebo once/d for 12 weeks

PRIMARY OUTCOME

The primary efficacy outcome was the least-squares mean change in automated office systolic blood pressure at week 6

FINDINGS

Mean change in systolic blood pressure at week 6

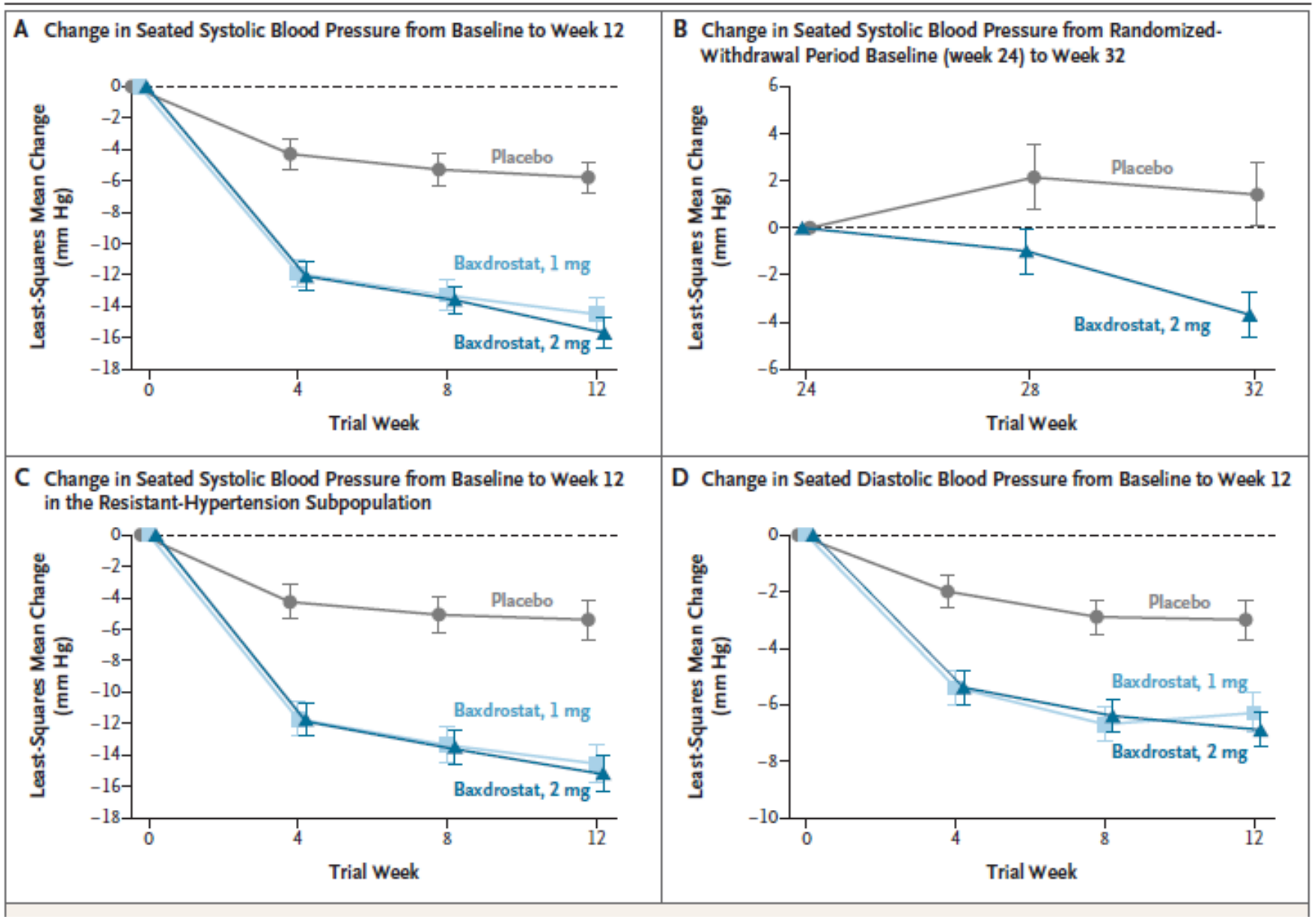
Lorundrostat
−16.9 (95% CI, −19.0 to −14.9) mm Hg

Placebo
−7.9 (95% CI, −11.5 to −4.2) mm Hg

Lorundrostat demonstrated blood-pressure lowering efficacy:

Least-squares between-group difference,
−9.1 (95% CI, −13.3 to −4.9) mm Hg; *P* < .001

Saxena M, Laffin L, Borghi C, et al; Launch-HTN Investigators. Lorundrostat in participants with uncontrolled hypertension and treatment-resistant hypertension: the Launch-HTN randomized clinical trial. *JAMA*. Published online June 30, 2025. doi:10.1001/jama.2025.9413



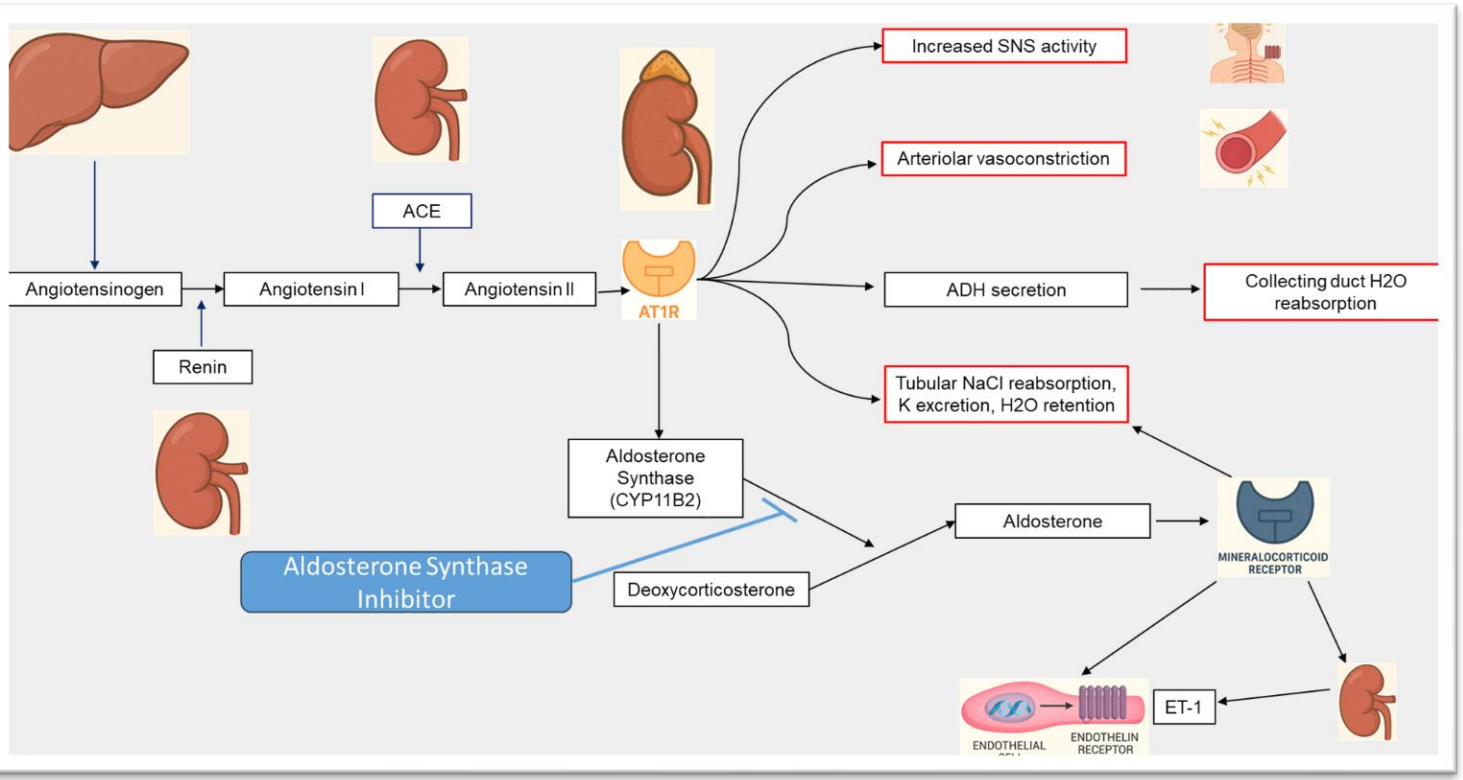
Baxdrostat

Least squares mean difference:

1mg:
–8.7 (–11.5 to –5.8) mmHg

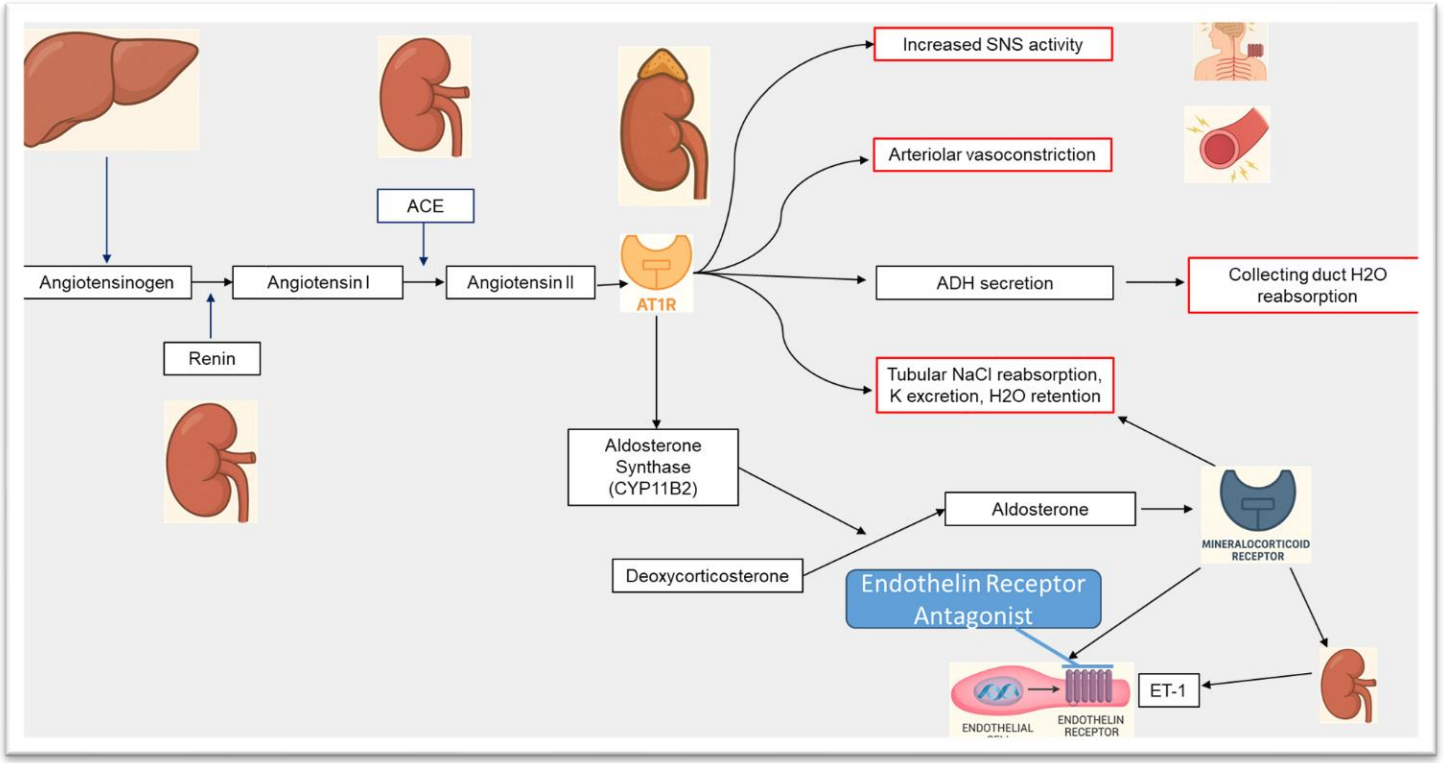
2mg:
–9.8 (–12.6 to –7.0) mmHg

Aldosterone synthase inhibitors (ASI) – Pediatric Evidence?



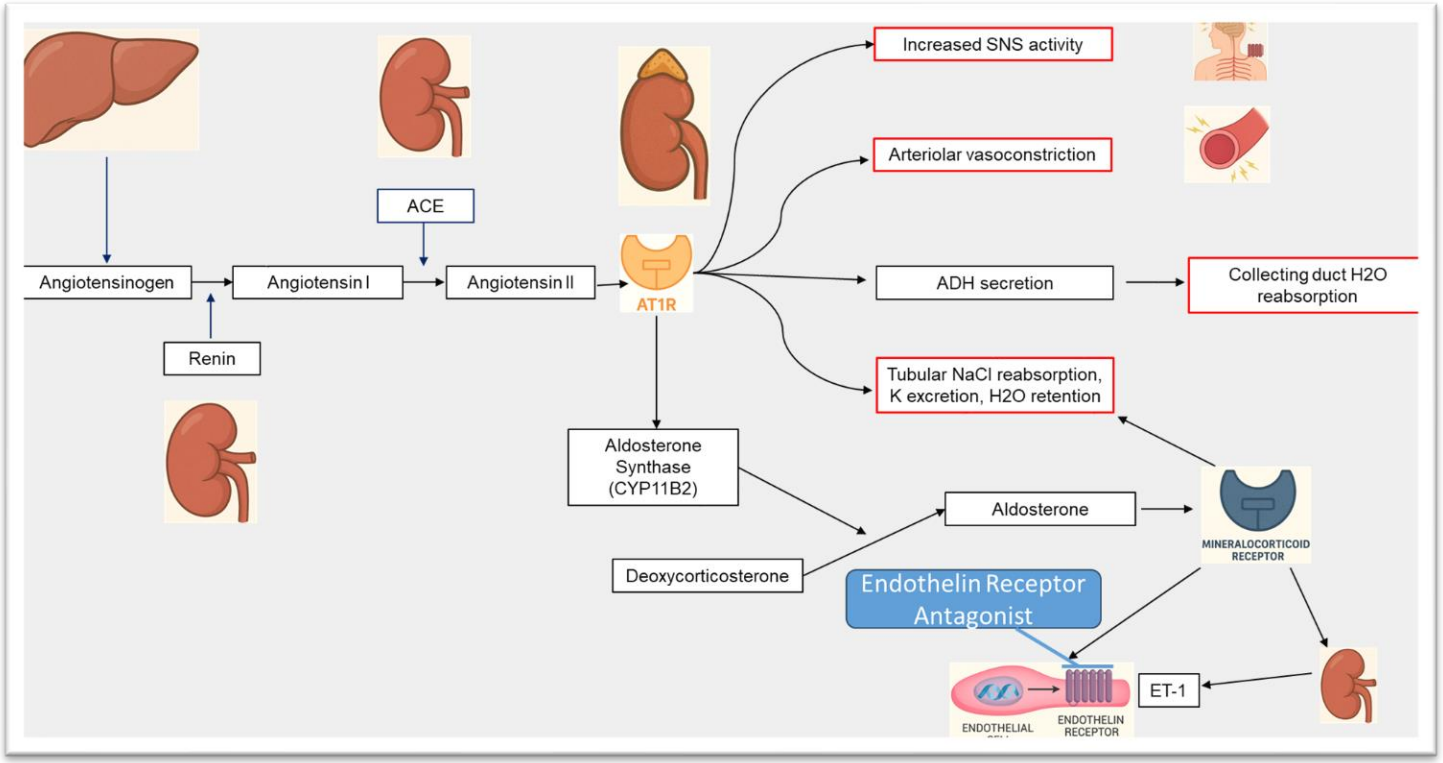
- Not studied in children
- Not recommended for use

Endothelin receptor antagonists (ERA)



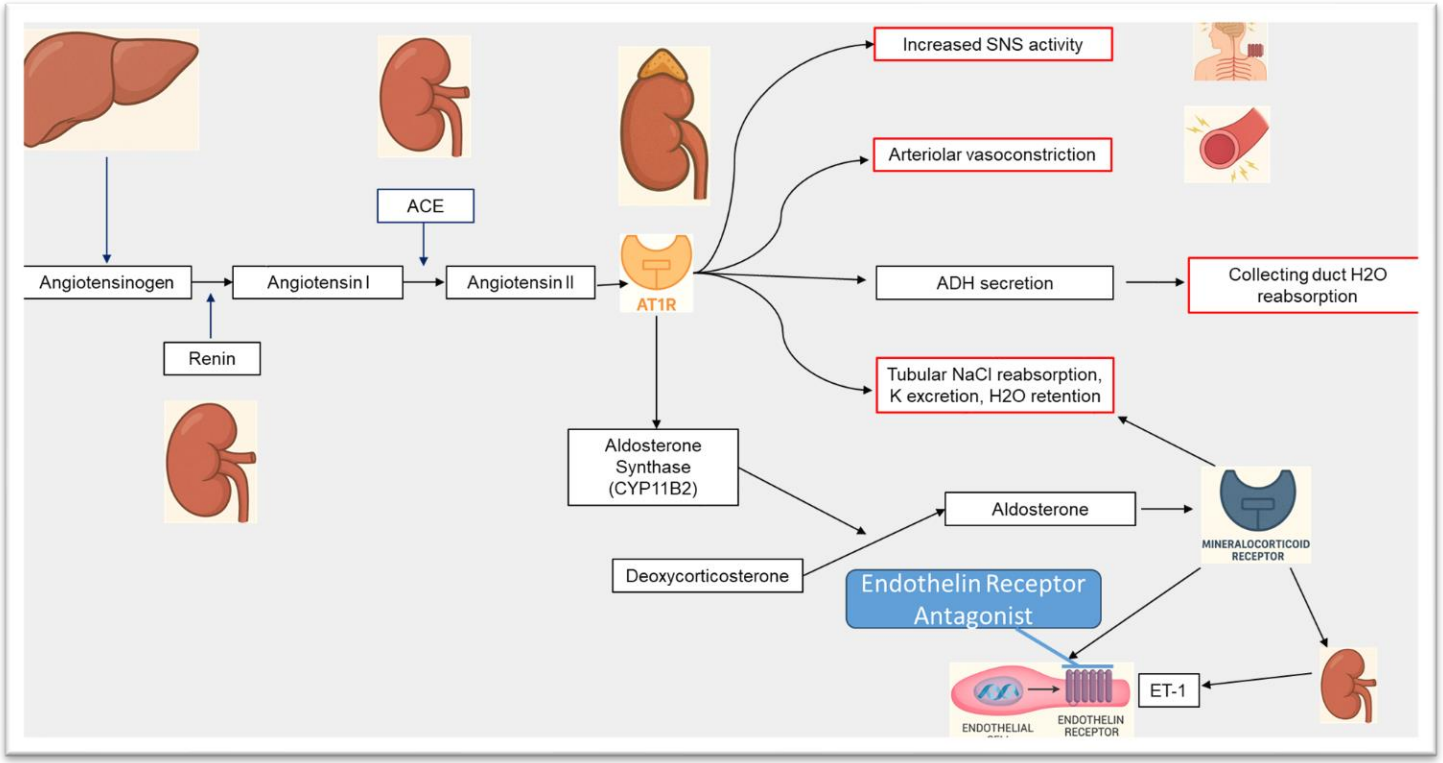
- Endothelin-1 (ET-1) is a vasoconstrictive peptide
  - Upregulated in resistant HTN
  - Receptors are on vascular smooth muscle and endothelial cells
- ETA receptor: vasoconstriction, proliferative effects
- ETB receptor: vasodilatation via release of NO and prostacyclin
- Dual antagonists (e.g., bosentan) inhibit ETA and ETB
- ETA receptor antagonists (e.g., ambrisentan, macitentan)
  - Selectively block the vasoconstrictive and proliferative effects of ET-1
  - Preserves beneficial ETB-mediated effects

Endothelin receptor antagonists (ERA)



- Not 1st line
- Adjunctive therapy for adults with **resistant HTN** who are not adequately controlled on 3+ BP meds
  - RAAS inhibitor, calcium channel blocker, and diuretic
- Do not increase HR or activate RAAS or SNS

Endothelin receptor antagonists (ERA) – Pediatric Evidence?



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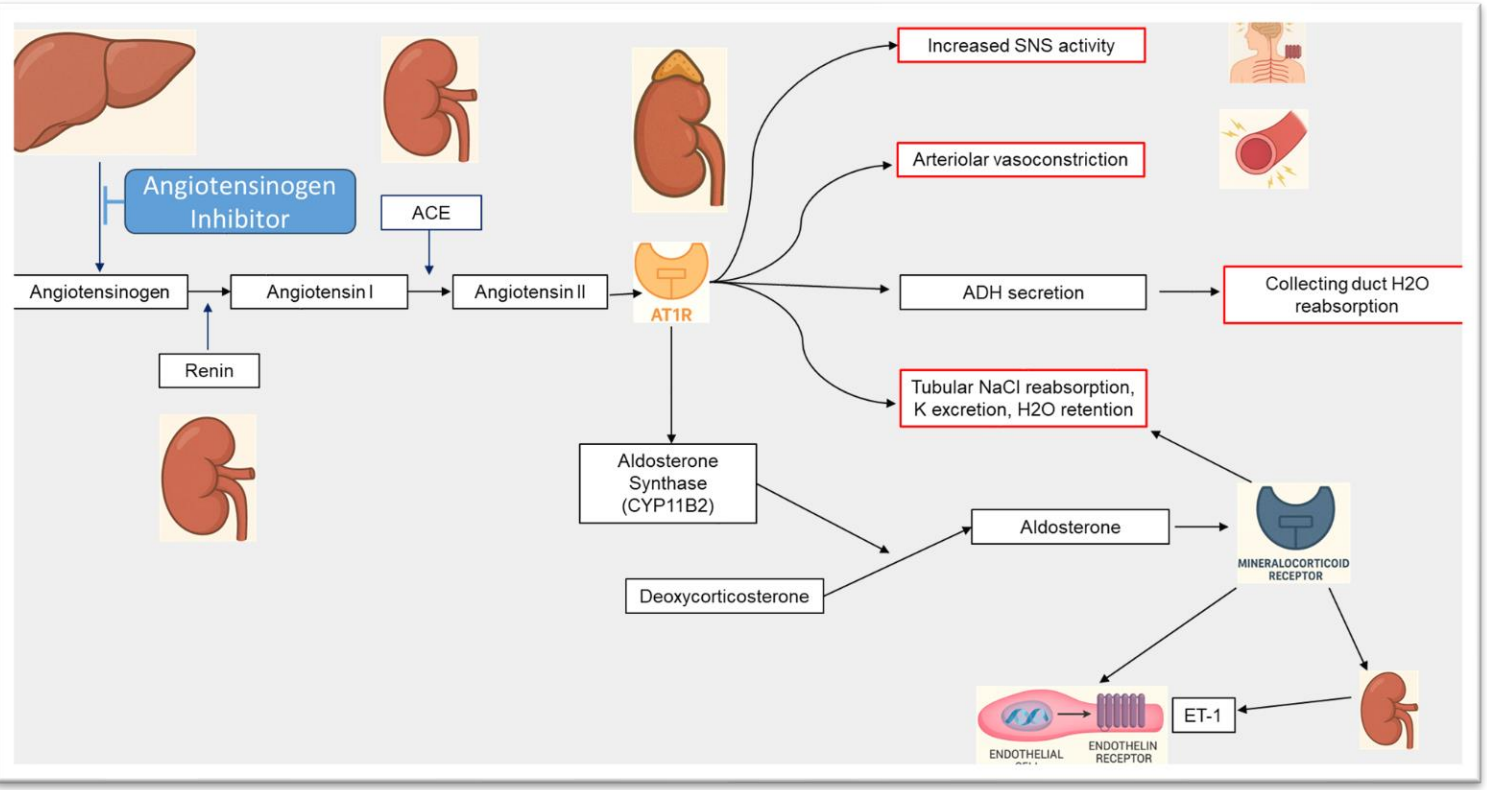
RNA based angiotensinogen inhibitors*



- Use small interfering RNA (siRNA) technology to silence hepatic angiotensinogen synthesis
- Administered SQ
- Effects can last up to 6 months

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QUESTION Does targeting hepatic angiotensinogen synthesis with the RNA interference therapeutic zilebesiran reduce blood pressure in adults with mild to moderate hypertension?

CONCLUSION In adults with mild to moderate hypertension, treatment with zilebesiran across a range of doses at 3-month or 6-month intervals significantly reduced 24-hour mean ambulatory systolic blood pressure (SBP) at 3 months.

POPULATION

210 Male
167 Female

Adults aged 18 to 75 years with hypertension

Mean age: **57** years

LOCATION

78
Medical sites in Canada, Ukraine, the UK, and the US

INTERVENTION

394 Patients randomized
377 Patients analyzed

78
Zilebesiran, 150 mg
Subcutaneous zilebesiran, 150 mg, every 6 months

148
Zilebesiran, 300 mg
Subcutaneous zilebesiran, 300 mg, every 3 months or every 6 months

76
Zilebesiran, 600 mg
Subcutaneous zilebesiran, 600 mg, every 6 months

75
Placebo
Subcutaneous placebo every 3 months

PRIMARY OUTCOME

Between-group difference in least-squares mean (LSM) change from baseline to month 3 in 24-hour mean ambulatory SBP

FINDINGS

Change from baseline to 3 months in SBP

Zilebesiran, 150 mg	**−7.3 mm Hg** (95% CI, −10.3 to −4.4)
Zilebesiran, 300 mg	**−10.0 mm Hg** (95% CI, −12.0 to −7.9)
Zilebesiran, 600 mg	**−8.9 mm Hg** (95% CI, −11.9 to −6.0)
Placebo	**6.8 mm Hg** (95% CI, 3.6 to 9.9)

LSM difference vs placebo in change ($P < .001$ for all):

zilebesiran, 150 mg, **−14.1 mm Hg** (95% CI, −19.2 to −9.0)
zilebesiran, 300 mg, **−16.7 mm Hg** (95% CI, −21.2 to −12.3)
zilebesiran, 600 mg, **−15.7 mm Hg** (95% CI, −20.8 to −10.6)

Bakris GL, Saxena M, Gupta A, et al; KARDIA-1 Study Group. RNA interference with zilebesiran for mild to moderate hypertension: the KARDIA-1 randomized clinical trial. *JAMA*. Published February 16, 2024. doi:10.1001/jama.2024.0728

KARDIA-2: Add-On Treatment With Zilebesiran for Inadequately Controlled Hypertension

- Open-label run-in treatment >=4 weeks with once daily indapamide 2.5 mg, amlodipine 5 mg, or olmesartan 40 mg
- Adherent patients with 24-hour mean ambulatory SBP of 130 mm Hg to 160 mm Hg were subsequently randomized (1:1) to:
  - Zilebesiran 600 mg
  - placebo

KARDIA-2: Add-On Treatment With Zilebesiran for Inadequately Controlled Hypertension

- Change in 24-hr ABPM from baseline to 3 months (SBP):
  - Indipamide: −12.1 mm Hg (95% CI, −16.5 to −7.6; *P* < .001)
  - Amlodipine: −9.7 mm Hg (95% CI, −12.9 to −6.6; *P* < .001)
  - Olmesartan: −4.5 mm Hg (95% CI, −8.2 to −0.8; *P* = .02)

New(ish) adjunctive meds for children

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Pediatric Indications:

- Glycemic control, T2DM, ≥10yrs

Glucagon-like peptide-1 (GLP-1) receptor agonists

Pediatric Indications:

- Glycemic control, T2DM, ≥10yrs
- Obesity (≥12 yrs) with lifestyle

New(ish) adjunctive meds for children

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

- Adult data, mechanistic studies:
  - Lower SBP by 2-5 mmHg
  - Lower DBP by 1-2 mmHg
- Mechanism of BP lowering likely:
  - Weight loss
  - Natriuresis
  - Osmotic diuresis
  - Reduced arterial stiffness

*Pediatric RCT have focused on DM outcomes, not BP or HTN; no studies have evaluated SGLT2 inhibitors as antihypertensive monotherapy in children without diabetes.

Glucagon-like peptide-1 (GLP-1) receptor agonists

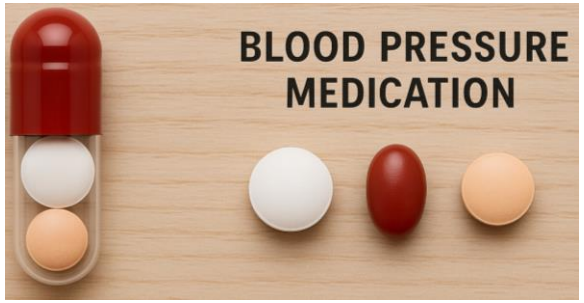
- Pediatric studies:
  - Lower SBP by 2-3 mmHg in youth with obesity or T2DM (obesity>T2DM)
  - Minimal to no effect on DBP
- Mechanism of BP lowering likely:
  - Weight loss
  - Natriuresis
  - Improved endothelial function
  - Reduced SNS activity

*The antihypertensive effect is smaller than that of traditional agents but may provide additive benefit in children with obesity-related hypertension.

*Not currently indicated as primary antihypertensive therapy in pediatric hypertension.

Sternlicht and Bakris, Curr Hyp Rep, 2019

Old(ish) meds, new(ish) strategy



5.2.4. Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy
Referenced studies that support the recommendations are summarized in the Evidence Table.

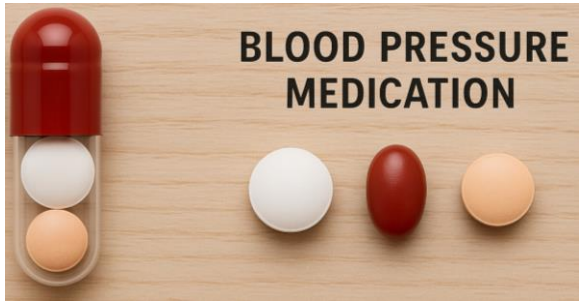
COR	LOE	Recommendations
1	B-R	1. In adults with stage 2 hypertension (SBP ≥ 140 mm Hg and DBP ≥90 mm Hg), initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination (SPC), is recommended to improve BP control and adherence.[1–6]
2a	C-EO	2. In adults with stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control.
3: Harm	A	3. In adults with hypertension, simultaneous use of an ACEi, ARB, and/or renin inhibitor in combination is not recommended due to the potential for harm.[7–9]

5.2.5. Antihypertensive Medication Adherence Strategies

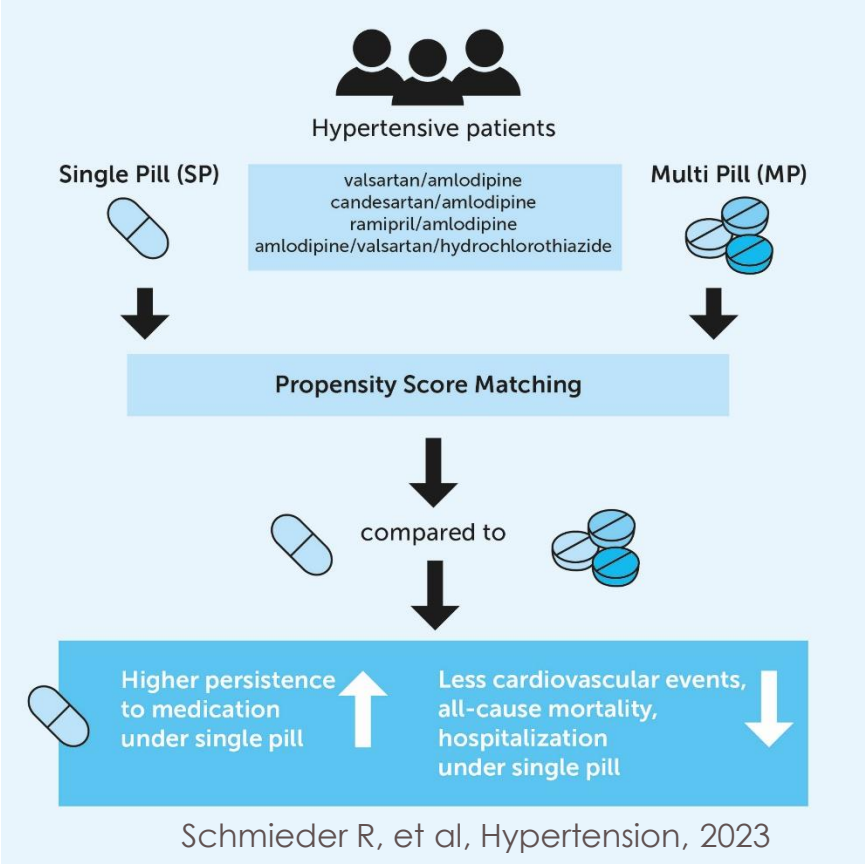
Recommendations for Antihypertensive Medication Adherence Strategies
Referenced studies that support the recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	B-R	1. In adults with hypertension, antihypertensive medication dosing once daily rather than multiple times daily is beneficial to improve medication adherence.[1–3]
1	B-R	2. In adults with hypertension, the use of a SPC to reduce pill burden rather than taking separate pills is effective to improve medication adherence.[4–9]
2a	B-R	3. In adults with hypertension, use of medication reminder aids and educational or self-management interventions can be useful to improve medication adherence.[10–16]

Old(ish) meds, new(ish) strategy



- Better medication adherence
- Greater reductions in SBP, DBP
- Higher rates of BP goal achievement (vs. single pill)



Schmieder R, et al, Hypertension, 2023

Table 2. Commonly Used Antihypertensive Medications in Fixed-Dose Combination Available in the US[a]

Antihypertensive class	Medication combination	Dose range
ACE inhibitor in dual combination		
With thiazide-type diuretic	Benazepril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
	Captopril + hydrochlorothiazide	25 mg/15 mg to 50 mg/25 mg
	Enalapril + hydrochlorothiazide	5 mg/12.5 mg to 10 mg/25 mg
	Fosinopril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/12.5 mg
	Lisinopril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
	Moexipril + hydrochlorothiazide	7.5 mg/12.5 mg to 15 mg/25 mg
	Quinapril + hydrochlorothiazide	10 mg/12.5 mg to 20 mg/25 mg
With calcium channel blocker	Benazepril + amlodipine	10 mg/2.5 mg to 40 mg/10 mg
	Perindopril + amlodipine	3.5 mg/2.5 mg to 14 mg/10 mg
	Trandolapril + verapamil	1 mg/240 mg to 4 mg/240 mg
Angiotensin receptor blocker in dual combination		
With thiazide-type diuretic	Azilsartan + chlorthalidone	40 mg/12.5 mg to 40 mg/25 mg
	Candesartan + hydrochlorothiazide	16 mg/12.5 mg to 32 mg/25 mg
	Irbesartan + hydrochlorothiazide	150 mg/12.5 mg to 300 mg/25 mg
	Losartan + hydrochlorothiazide	50 mg/12.5 mg to 100 mg/25 mg
	Olmesartan + hydrochlorothiazide	20 mg/12.5 mg to 40 mg/25 mg
	Telmisartan + hydrochlorothiazide	40 mg/12.5 mg to 80 mg/25 mg
	Valsartan + hydrochlorothiazide	80 mg/12.5 mg to 320 mg/25 mg
With calcium channel blocker	Olmesartan + amlodipine	20 mg/5 mg to 40 mg/10 mg
	Telmisartan + amlodipine	40 mg/5 mg to 80 mg/10 mg
	Valsartan + amlodipine	160 mg/5 mg/12.5 mg to 320 mg/10 mg/25 mg
With β-blocker	Valsartan + nebivolol	80 mg/5 mg
Angiotensin receptor blocker in triple combination		
With calcium channel blocker + thiazide-type diuretic	Olmesartan + amlodipine + hydrochlorothiazide	20 mg/5 mg/12.5 mg to 40 mg/10 mg/25 mg
	Valsartan + amlodipine + hydrochlorothiazide	160 mg/5 mg/12.5 mg to 320 mg/10 mg/25 mg
	Telmisartan + amlodipine + indapamide	10/1.25/0.625 mg; 20/2.5/1.25 mg; and 40/5/2.5 mg
β-Blocker in dual combination		
With thiazide-type diuretic	Atenolol + chlorthalidone	50 mg/25 mg to 100 mg/25 mg
	Bisoprolol + hydrochlorothiazide	2.5 mg/6.25 mg to 10 mg/6.25 mg
	Metoprolol tartrate + hydrochlorothiazide	50 mg/25 mg to 100 mg/50 mg
Thiazide-type diuretics in dual combination		
With potassium-sparing diuretic	Hydrochlorothiazide + amiloride	50 mg/5 mg
	Hydrochlorothiazide + triamterene	25 mg/37.5 mg to 50 mg/75 mg
With mineralocorticoid receptor antagonist	Hydrochlorothiazide + spironolactone	25 mg/25 mg

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a] Adapted from the 2025 American Heart Association/American College of Cardiology guidelines[3]; see also https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed September 3, 2025) for more information.

		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

Figure 4: **Predicted reductions in systolic blood pressure for different combinations of five antihypertensives at different doses as single, dual, or triple therapy for a baseline systolic blood pressure of 154 mm Hg**

Mean (95% prediction intervals) systolic blood pressure reduction was estimated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second or third components. Different colours indicate efficacy intensity: low (red), moderate (yellow), and high (green) correspond to systolic blood pressure reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg, with darker shades corresponding to greater reductions. Mean reductions are larger for higher baseline blood pressures and smaller for lower baseline blood pressures.

		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

Figure 4: **Predicted reductions in systolic blood pressure for different combinations of five antihypertensives at different doses as single, dual, or triple therapy for a baseline systolic blood pressure of 154 mm Hg**

Mean (95% prediction intervals) systolic blood pressure reduction was estimated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second or third components. Different colours indicate efficacy intensity: low (red), moderate (yellow), and high (green) correspond to systolic blood pressure reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg, with darker shades corresponding to greater reductions. Mean reductions are larger for higher baseline blood pressures and smaller for lower baseline blood pressures.

		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

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		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	Amlodipine	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
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		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
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0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

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		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	**Amlodipine**	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

Figure 4: **Predicted reductions in systolic blood pressure for different combinations of five antihypertensives at different doses as single, dual, or triple therapy for a baseline systolic blood pressure of 154 mm Hg**

Mean (95% prediction intervals) systolic blood pressure reduction was estimated by adding the expected blood pressure reduction from derived meta-regression equations for the respective monotherapy components, accounting for a lower baseline blood pressure for the second or third components. Different colours indicate efficacy intensity: low (red), moderate (yellow), and high (green) correspond to systolic blood pressure reductions of <10 mm Hg, 10–19·9 mm Hg, and ≥20 mm Hg, respectively, from a baseline of 154 mm Hg, with darker shades corresponding to greater reductions. Mean reductions are larger for higher baseline blood pressures and smaller for lower baseline blood pressures.

		None	Losartan		Lisinopril		Metoprolol	
Hydrochlorothiazide	Amlodipine	0 mg	50 mg	100 mg	10 mg	20 mg	50 mg	100 mg
0 mg	0 mg		7 (6–8)	8 (7–9)	7 (6–8)	10 (7–11)	7 (5–8)	7 (6–8)
0 mg	5 mg	9 (8–10)	15 (13–16)	16 (14–17)	15 (13–16)	18 (15–19)	15 (13–16)	15 (14–17)
0 mg	10 mg	12 (10–15)	18 (15–19)	19 (16–21)	18 (16–20)	21 (17–22)	18 (16–20)	18 (16–21)
12·5 mg	0 mg	6 (5–7)	12 (11–13)	13 (12–14)	12 (11–13)	15 (13–16)	12 (11–13)	12 (11–14)
12·5 mg	5 mg	14 (13–15)	19 (17–20)	20 (18–21)	20 (18–21)	22 (19–24)	19 (17–21)	20 (17–21)
12·5 mg	10 mg	17 (15–19)	22 (19–24)	23 (20–25)	22 (20–24)	25 (21–27)	22 (19–24)	22 (19–24)
25 mg	0 mg	8 (7–9)	14 (12–15)	15 (13–16)	14 (12–15)	17 (15–18)	14 (12–15)	14 (12–15)
25 mg	5 mg	16 (14–17)	21 (19–22)	22 (19–23)	21 (19–22)	24 (21–25)	21 (19–22)	21 (18–23)
25 mg	10 mg	19 (17–21)	23 (20–25)	24 (21–26)	24 (21–25)	26 (22–28)	23 (20–25)	23 (20–25)

Efficacy

Low intensity Moderate intensity High intensity

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Summary

- Uncontrolled hypertension encompasses a variety of conditions including WCH, nonadherence, secondary hypertension
- Resistant hypertension needs a multifaceted approach to treatment
  - Combo pills
  - Enhanced lifestyle (role for combo GLP-1?)
  - Treatment of comorbidities (role for combo SGLT2i?)
  - New agents, including those with longer duration of action (SQ)