Primary Agents for Patients Diagnosed with Hypertension

Executive summary: Select initial therapy based on patient's stage of hypertension, ASCVD risk, and comorbidities. Specific blood pressure goals and therapy should be based on patient specific comorbidities and risks. Initial therapy recommended with an ACE inhibitor/ARB, thiazide diuretic, and/or CCB. Once therapy is initiated, reassess blood pressure in 1 month; if not yet controlled, consider one dose increase or adding another agent. Once blood pressure is adequately controlled, reassess blood pressure every 3-6 months.

2017 ACC AHA Guidelines recommend the following treatment thresholds for hypertension

Stage 1 Hypertension BP 130-139/80-89 Clinical ASCVD Risk <10%	**Stage 1 Hypertension** BP 130-139/80-89 Clinical ASCVD >10%	**Stage 2 Hypertension** BP >140/90
Nonpharmacologic therapy	Nonpharmacologic and consider first line therapy	Consider 1-2 antihypertensive agents in addition to nonpharmacologic therapy
Reassess in 3-6 months*	Reassess in 1 month*	Reassess in 1 month*

*Advance therapy with pharmacologic treatment as necessary at each visit.

2017 ACC AHA Guidelines recommend initial antihypertensive therapy to include thiazide diuretics, calcium channel blockers (CCB), and ACE inhibitors or ARBs. In African American patients, initial therapy should include a thiazide diuretic or CCB, ACE inhibitors/ARBs are recommended as add-on therapy. Initial medication selection may change depending on the patient's comorbid conditions. If blood pressure is greater than 20/10 mmgHG over goal consider adding 2 antihypertensives with different mechanisms of action.

It is recommended that adults initiating a new or adjusted drug regimen should have a follow-up evaluation of adherence and response at monthly intervals until control is achieved. At follow-up, if BP goal is met, reassess in 3-6 months. If BP goal is not met, assess and optimize adherence to therapy and consider intensification of therapy.

The largest reduction in blood pressure is typically seen at moderate doses of any antihypertensive with only modestly greater reductions in blood pressure with standard/maximum or twice-standard doses. After initiating antihypertensives at a low or starting dose, going to higher doses produces relatively small further reductions in blood pressure, but does increase the rate of adverse effects. Since the steepest part of the dose-response curve is typically seen at lower doses, consider adding on an additional agent after initial medication selection or after one dose titration of initial medication even if the maximum dose has not been achieved yet.

It is important to note the differences between thiazide-like (Chlorthalidone, Indapamide) versus thiazide-type (Hydrochlorothiazide) diuretics. Thiazide-like diuretics are more potent, have a longer duration of action, fewer metabolic complications and proven reduction in cardiovascular events compared to thiazide-type diuretics.

Patients should monitor and document their blood pressure at home in between office visits to detect white coat hypertension and/or trends. To properly monitor blood pressure, the following should be ensured:

- Seated and resting in a chair with back supported for 5 minutes with arms supported when checking blood pressure
- Frequency of measurements to be individualized, determined by provider
- At least 2 measurements at each check
- Use automated upper arm blood pressure cuff, appropriately sized

Primary agents for hypertension treatment:

Class	Drug	Usual Dose, Range (mg per day)*	Daily Frequency	Comments
Primary Agents				
Thiazide or thiazide-type diuretics	**Chlorthalidone**	12.5–25	1	• Chlorthalidone preferred based on prolonged half-life and proven trial reduction of CVD • Monitor for hyponatremia and hypokalemia, uric acid and calcium levels. • Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy.
	Hydrochlorothiazide	25–50	1	
	Indapamide	1.25–2.5	1	
	Metolazone	2.5–5	1	
ACE Inhibitors	**Benazepril**	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor • Increased risk of hyperkalemia, especially in patients with CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ACE inhibitors. • Avoid in pregnancy
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
	Ramipril	2.5–20	1 or 2	
	Trandolapril	1–4	1	
ARBs	**Azilsartan**	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor • Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+-sparing drugs • May cause acute renal failure in patients with severe bilateral renal artery stenosis • Do not use if history of angioedema with ARBs. Patients with a history of angioedema with an ACEI can receive an ARB beginning 6 weeks after ACEI discontinued. • Avoid in pregnancy
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	
CCB—dihydropyridines	**Amlodipine**	2.5–10	1	• Avoid use in patients with HFrEF; amlodipine or felodipine may be used if required • Associated with dose-related pedal edema, which is more common in women than men
	Felodipine	2.5–10	1	
	Isradipine	5–10	2	
	Nicardipine SR	60–120	2	
	Nifedipine LA	30–90	1	
	Nisoldipine	17–34	1	
CCB—nondihydropyridines	**Diltiazem ER**	120–360	1	• Avoid routine use with beta blockers due to increased risk of bradycardia and heart block • Do not use in patients with HFrEF • Drug interactions with diltiazem and verapamil (CYP3A4 major substrate and moderate inhibitor)
	Verapamil IR	120–360	3	
	Verapamil SR	120–360	1 or 2	
	Verapamil-delayed onset ER	100–300	1 (in the evening)	

*Table from Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline

Considerations for individualizing antihypertensive therapy

Indication or contraindication	Antihypertensive drugs
Compelling indications (major improvement in outcome independent of blood pressure)	
Heart failure with reduced ejection fraction	ACE inhibitor or ARB, beta blocker, diuretic, aldosterone antagonist*
Postmyocardial infarction	ACE inhibitor or ARB, beta blocker, aldosterone antagonist
Proteinuric chronic kidney disease	ACE inhibitor or ARB
Angina pectoris	Beta blocker, calcium channel blocker
Atrial fibrillation rate control	Beta blocker, nondihydropyridine calcium channel blocker
Atrial flutter rate control	Beta blocker, nondihydropyridine calcium channel blocker
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hyperplasia	Alpha blocker
Essential tremor	Beta blocker (noncardioselective)
Hyperthyroidism	Beta blocker
Migraine	Beta blocker, calcium channel blocker
Osteoporosis	Thiazide diuretic
Raynaud phenomenon	Dihydropyridine calcium channel blocker
Contraindications	
Angioedema	Do not use an ACE inhibitor
Bronchospastic disease	Do not use a non-selective beta blocker
Liver disease	Do not use methyldopa
Pregnancy (or at risk for)	Do not use an ACE inhibitor, ARB, or renin inhibitor (eg, aliskiren)
Second- or third-degree heart block	Do not use a beta blocker, nondihydropyridine calcium channel blocker unless a functioning ventricular pacemaker
Drug classes that may have adverse effects on comorbid conditions	
Depression	Generally avoid beta blocker, central alpha-2 agonist
Gout	Generally avoid loop or thiazide diuretic
Hyperkalemia	Generally avoid aldosterone antagonist, ACE inhibitor, ARB, renin inhibitor
Hyponatremia	Generally avoid thiazide diuretic
Renovascular disease	Generally avoid ACE inhibitor, ARB, or renin inhibitor

*Table from UpToDate

Links to internal and/or external resources:

AMG Hypertension Guidelines

Sources:

1. J Am Coll Cardiol. Sep 2017, 23976; DOI: 10.1016/j.jacc.2017.07.745
2. Mann J. Choice of drug therapy in primary (essential) hypertension. UpToDate. Literature review current through: Jul 2021. Last updated Aug 5, 2021. Available at: https://www.uptodate.com/contents/choice-of-drug-therapy-in-primary-essential-hypertension?search=choice%20of%20drug%20therapy%20in%20primary%20essential%20hypertension&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Secondary Agents for Patients Diagnosed with Hypertension

Executive Summary: The guidelines concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in both younger and older patients with hypertension, not the choice of antihypertensive drug. Most secondary anti-hypertensives are used to treat other comorbidities and also provide the benefit of the reduction of blood pressure.

2017 ACC AHA Guidelines recommend the following treatment thresholds for hypertension

Stage 1 Hypertension BP 130-139/80-89 Clinical ASCVD Risk <10%	**Stage 1 Hypertension** BP 130-139/80-89 Clinical ASCVD >10%	**Stage 2 Hypertension** BP >140/90
Nonpharmacologic therapy	Nonpharmacologic and consider first line therapy	Consider 1-2 antihypertensive agents in addition to nonpharmacologic therapy
Reassess in 3-6 months	Reassess in 1 month	Reassess in 1 month

*Advance therapy with pharmacologic treatment as necessary at each visit.

Treatment Pearls:

- Initial hypertensive treatment will bring down the blood pressure in 30 to 50 percent of patients. In those patients who don't respond, try to limit dose titration to one step with each new anti-hypertensive drug and start at the lowest possible dose to lessen adverse effects.
- Secondary agents may be used as initial treatment depending on patient's comorbidities
    - If no comorbidities exist, secondary agents are reserved for treatment if not controlled on combination of primary agents, or if primary agents are contraindicated
    - Spironolactone is generally the preferred add-on agent
    - If spironolactone is contraindicated or not tolerated, consider adding on one of the following: amiloride, doxazosin, eplerenone, clonidine, or a beta-blocker
- Diuretics are typically added on as a third or fourth line agent for volume control in patients with heart failure or chronic kidney disease. Additionally, a mineralocorticoid receptor agonist (spironolactone/eplerenone) is indicated in patients with heart failure that have preserved heart function and may be hypokalemic.
- Beta blockers without intrinsic sympathomimetic activity (all except for acebutolol, penbutolol, and pindolol) should be given after an acute myocardial infarction and to stable patients with asymptomatic left ventricular dysfunction or stable heart failure.
- Alpha blockers are used for treatment of Benign Prostatic Hyperplasia in men as long as they do not have a high cardiovascular risk. The ALLHAT trial included a doxazosin arm in which they noticed significantly increased risk of heart failure compared to chlorthalidone.

Monitoring Response:

- Encourage home blood pressure monitoring of patients
  - Reasons:
    - Diagnosing white-coat hypertension and masked hypertension
    - Identifying white-coat effect and masked uncontrolled hypertension
    - Evaluating BP in response to treatment
    - Confirming the diagnosis of resistant hypertension
    - Detecting morning hypertension
  - Patient Advantages:
    - Blood pressure readings are more reproducible than office readings
    - Greater patient acceptance
    - Cost effective
    - Less side effects or complications from overtreatment

Class	Drug	Usual Dose Range	Daily Frequency	Comments
Diuretics – loop	Bumetanide	0.5-2 mg	2	Preferred diuretics in patients with symptomatic HF. Preferred over thiazide in patient with moderate to severe CKD (GFR < 30mL/min).
	Furosemide	20-80 mg	2	
	Torsemide	5-10 mg	1	
Diuretics – potassium sparing	Amiloride	5-10 mg	1 or 2	Monotherapy agents minimally effective antihypertensives. Combination therapy of potassium sparing diuretic with a thiazide can be considered in patients with hypokalemia on thiazide monotherapy. Avoid in patients with significant CKD (GFR< 45mL/min).
	Triamterene	50-100 mg	1 or 2	
Diuretics – aldosterone antagonists	Eplerenone	50-100 mg	1 or 2	Preferred agents in primary aldosteronism and resistant hypertension. Spironolactone associated with greater risk of gynecomastia and impotence compared to eplerenone. Common add-on therapy in resistant hypertension.
	Spironolactone	25-100 mg	2	

				Avoid use with K+ supplements, other K+ sparing diuretics or significant renal dysfunction. Eplerenone often requires twice daily dosing for adequate BP lowering.
Beta blockers – Cardioselective	Atenolol	25-100 mg	2	Beta blockers are not recommended as first-line agents unless the patient has IHD or HF. Preferred in patients with bronchospastic airway disease requiring a beta blocker. Bisoprolol and metoprolol succinate preferred in patients with HFrEF. Avoid abrupt cessation.
	Betaxolol	5-20 mg	1	
	Bisoprolol	2.5-10 mg	1	
	Metoprolol tartrate	100-200 mg	2	
	Metoprolol Succinate	50-200 mg	1	
Beta-Blockers – Cardioselective and vasodilatory	Nebivolol	5-40 mg	1	Induces nitric oxide-induced vasodilation. Avoid abrupt cessation.
Beta-Blockers – Noncardioselective	Nadolol	40-120 mg	1	Avoid in patients with reactive airways disease. Avoid abrupt cessation.
	Propranolol IR	80-160 mg	2	
	Propranolol LA	80-160 mg	1	
Beta Blockers – Intrinsic sympathomimetic activity	Acebutolol	200-800 mg	2	Generally avoid, especially in patients with IHD or HF. Avoid abrupt cessation.
	Penbutolol	10-40 mg	1	
	Pindolol	10-60 mg	2	
Beta Blockers – combined alpha- and beta-receptor	Carvedilol	12.5-50 mg	2	Carvedilol preferred in patients with HFrEF. Avoid abrupt cessation.
	Carvedilol phosphate	20-80 mg	1	
	Labetalol	200-800 mg	2	
Direct renin inhibitor	Aliskiren	150-300 mg	1	Do not use in combination with ACE inhibitors or ARBs. Aliskiren is very long acting. Increased risk of hyperkalemia in CKD or in those on K+ supplements or K+ sparing diuretics. May cause acute renal failure in patients with severe bilateral renal artery stenosis.

				Avoid in pregnancy.
Alpha-1 blockers	Doxazosin	1-16 mg	1	Associated with orthostatic hypotension, especially in older adults. May consider as second-line agent in patients with concomitant BPH.
	Prazosin	2-20 mg	2 or 3	
	Terazosin	1-20 mg	1 or 2	
Central Alpha2-agonists and other centrally acting drugs	Clonidine oral	0.1-0.8 mg	2	Generally reserved as last-line due to significant CNS adverse effects, especially in older adults. Avoid abrupt discontinuation of clonidine, which may induce hypertensive crisis; clonidine must be tapered to avoid rebound hypertension.
	Clonidine patch	0.1-0.3 mg	Weekly	
	Methyldopa	250-1000 mg	2	
	Guanfacine	0.5-2 mg	1	
Direct Vasodilators	Hydralazine	100-200 mg	2 or 3	Associated with sodium and water retention and reflex tachycardia; use with a diuretic and beta blocker. Hydralazine associated with drug-induced lupus-like syndrome at higher doses. Minoxidil associated with hirsutism and requires a loop diuretic. Can induce pericardial effusion.
	Minoxidil	5-100 mg	1 to 3	

*Table from Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Synopsis of the 2017 American College of Cardiology/American Heart Association Hypertension Guideline

Abbreviations: IHD – Ischemic Heart Disease, HF – Heart Failure, CKD – Chronic Kidney Disease, HFrEF – Heart Failure with reduced Ejection Fraction, BPH – Benign Prostatic Hyperplasia

Links to internal and/or external resources:
Avera Hypertension Guidelines (2020)

Sources:

1. J Am Coll Cardiol. Sep 2017, 23976; DOI: 10.1016/j.jacc.2017.07.745
2. Mann J. Choice of drug therapy in primary (essential) hypertension. UpToDate. Literature review current through: Jul 2021. Last updated Aug 5, 2021. Available at: https://www.uptodate.com/contents/choice-of-drug-therapy-in-primary-essential-hypertension?search=choice%20of%20drug%20therapy%20in%20primary%20essential%20hypertension&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

3. Unger T, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75:1334-1357. https://doi.org/10.1161/HYPERTENSIONAHA.120.15026
4. Townsend RR, Cohen J. Out-of-office blood pressure measurement: Ambulatory and self-measure blood pressure monitoring. UpToDate. Literature review current through: Jul 2021. Last updated May 18, 2020. Available at: https://www.uptodate.com/contents/out-of-office-blood-pressure-measurement-ambulatory-and-self-measured-blood-pressure-monitoring?csi=79066a5a-0310-4fa0-bb72-164810e8cd34&source=contentShare

Resistant Hypertension

Executive Summary: Resistant hypertension is defined as blood pressure not at goal in patients on 3 or more antihypertensives at optimal (or maximally tolerated) doses, one of which is a diuretic. Confirm medication adherence, consider screening for causes of secondary hypertension, and optimize the current hypertensive regimen. If blood pressure remains uncontrolled, recommend adding a mineralocorticoid receptor antagonist (spironolactone or eplerenone).

Uncontrolled vs. controlled resistant hypertension (RH)

- Uncontrolled: elevated blood pressure (BP) on 3 or more antihypertensives, commonly a calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and diuretic
- Controlled: BP at goal on 4 or more antihypertensives

Low Risk No CVD risk factors and 10 year CVD risk <10%	**Intermediate – High Risk** 10 year CVD risk >10%, or 1 or more CVD risk factors	**Frail, orthostatic, increased risk of adverse drug effects**
<140/90	<130/80	<150/90

Considerations for treatment of resistant hypertension

- Choosing a diuretic: switching patients from hydrochlorothiazide to chlorthalidone may result in an additional 7-8 point lowering of SBP
  - Chlorthalidone 12.5 mg = hydrochlorothiazide 25 mg
- Spironolactone is effective in many patients with RH as a 4th agent (monitor for hyperkalemia)
- Consider dosing one antihypertensive agent at night to improve BP control

Monitoring Response:

- Encourage home blood pressure monitoring of patients
  - Reasons:
    - Evaluating BP in response to treatment
    - Confirming the diagnosis of resistant hypertension
    - Detecting morning hypertension
  - Patient advantages:
    - Blood pressure readings are more reproducible than office readings
    - Greater patient acceptance
    - Cost effective
    - Fewer side effects or complications from overtreatment

The following algorithm can be used in the evaluation of resistant hypertension:

Evaluation of Resistant Hypertension

Confirm Treatment of Resistance

Clinic BP uncontrolled to individualized BP goal and patient taking 3 or more antihypertensive agents (including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system [ACEI or ARB] and a diuretic) at maximal or maximally tolerate doses

↓

Review and Implement Lifestyle Interventions

- Weight loss if overweight or obese
- DASH diet
- Sodium restriction
- Dietary potassium supplementation
- Exercise
- Alcohol moderation (≤1 per day for women, ≤2 per day for men)

↓

Exclude Pseudoresistance

- Confirm adherence to antihypertensive therapy (review side effects and adequate dosing)
- Perform 24-hour ambulatory BP monitoring (if unavailable, use home BP) to exclude white-coat effect
- Review for recreational drug use and other medications that raise BP

↓

Assess for Secondary Hypertension

- Primary aldosteronism
- Renal parenchymal disease
- Renal artery stenosis
- Pheochromocytoma/paraganglioma
- Cushing syndrome
- Obstructive sleep apnea
- Coarctation of the aorta
- Hyperthyroidism and other endocrine causes

↓

Assess for Target Organ Damage

Ocular: funduscopic exam
Cardiac: left ventricular hypertrophy, coronary artery disease
Renal: proteinuria, reduced glomerular filtration rate
Peripheral arterial disease: ankle/brachial index

Management of Resistant Hypertension

Step 1

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence

+

Ensure low sodium diet (<2400 mg/d)
Maximize lifestyle interventions:
- ≥6 hours uninterrupted sleep
- Overall dietary pattern
- Weight loss
- Exercise

+

Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function.

BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

BP not at target

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.

Step 4

Check heart rate: unless <70 beats/min, **add β-blocker** (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

BP still not at target

Step 5

Add hydralazine*** 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).

BP still not at target

Step 6

Substitute minoxidil****** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies—www.clinicaltrials.gov.

Sources

Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR et al. Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association. Hypertension 2018;72:e53-e90.

Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International society of hypertension global hypertension practice guidelines. Hypertension 2020;75:1334-57.

Considerations for Administering Hypertension Medication at Bedtime Improving CVD Risk Reduction

Executive Summary: Blood pressure is not constant throughout the day, following a predictable circadian pattern in most patients. Blood pressure begins to increase slowly between 3:00 and 6:00 in the morning, then increases rapidly upon awakening in response to increased cortisol, plasma renin and catecholamine secretion. Data from Framingham studies show cardiovascular event risk is highest during early waking hours. Also, patients whose blood pressure does not decrease during the night (non-dipper) tend to have higher cardiovascular risk. Interest has been generated with these observations in targeting morning blood pressure reduction with nighttime dosing of anti-hypertensives.

The Hygia Chronotherapy trial sought to determine if bedtime hypertension therapy in comparison to usual upon awakening hypertension therapy further reduces risk of cardiovascular disease. Chronotherapeutics is defined as the purposeful timing of medications, whether or not they utilize special drug release technology, to proportion serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of enhancing beneficial outcomes and/or attenuating or averting adverse effects.[4]

This multicenter, prospective endpoint trial involving 19,084 Caucasian patients with hypertension and a median age of 60.5 was conducted in Spain. Patients excluded from the trial included night or shift work, cardiovascular disease, heart failure, renal failure and secondary hypertension.

Initially and with every scheduled visit throughout follow up, ambulatory blood pressure monitoring was performed for 48 hours. During the study, 1,752 patients experienced a primary CVD outcome, with patients in the bedtime administration arm showing significantly lower hazard ratio than the morning administration arm. Patients who routinely administered hypertensive medications at bedtime had improved ambulatory blood pressure control after following these patients for a median of 6.3 years. The hazard ratio for overall mortality was 0.55 (95% CI 0.50-0.63), $P < 0.001$ and each of its single components, i.e., CVD death [0.44 (0.34-0.56)], myocardial infarction [0.66 (0.52-0.84)], coronary revascularization [0.60 (0.47-0.75)], heart failure [0.58 (0.49-0.70)], and stroke [0.51 (0.41-0.63)].

Information available shows dosing ACEI and ARBs at bedtime improves blood pressure control, and CCBs are more effective when dosed at bedtime.[2] Dosing valsartan at bedtime significantly reduces albumin excretion compared to morning dose.[3] The HOPE study dosed ramipril at bedtime, but did not have a comparative morning dose arm.

Routine ingestion of BP lowering medications at bedtime appears to result in ambulatory blood pressure control and diminished occurrence of major CVD events. There were no significant differences in overall adverse events and withdrawals due to adverse events among the evening versus morning dosing regimens.[4] It is speculated that patients should take their diuretics early in the day, since poor sleep contributes to adverse cardiovascular outcomes. The

biggest factor to preventing cardiovascular outcomes is adherence to blood pressure medications.

Sources:
1. Hermida RC, Crespo JJ, Dominguez-Sardina M, et al. Bedtime hypertension treatment improved cardiovascular risk reduction: the Hygia Chronotherapy Trial. *Eur Heart J* 2019 Oct 22. doi: 10.1093/eurheartj/ehz754.
2. Smolensky MH, Hermida RC, Ayala DE, et al. Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. *Blood Press Monit* 2010;15:173-80
3. Hermida RC, Calvo C, Ayala DE, et al. Treatment of non-dipper hypertension with bedtime administration of valsartan. *J Hypertens* 2005;23:1913-22.
4. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev 2011:CD004184