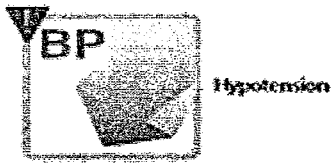
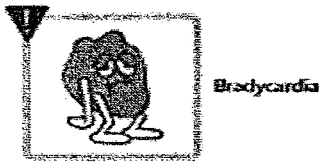
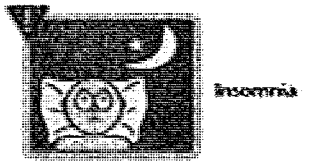
Drug	Selectivity	Partial agonist activity	Lipid solubility	Elimination half-life
Acebutolol	Beta 1	Yes	Low	3-4 hrs
Atenolol	Beta 1	No	Low	6-9 hrs
Betaxolol	Beta 1	No	Low	14-22 hrs
Bisoprolol	Beta 1	No	Low	9-12 hrs
Carteolol	None	Yes	Low	6 hrs
Carvedilol	None	No	High	7-10 hrs
Esmolol	Beta 1	No	Low	10 min
Labetalol	None	Yes	Moderate	5 hrs
Metoprolol	Beta 1	No	Moderate	3-4 hrs
Nadolol	None	No	Low	14-24 hrs
Penbutolol	None	Yes	High	5 hrs
Pindolol	None	Yes	Moderate	3-4 hrs
Propranolol	None	No	High	3.5-6 hrs
Sotalol	None	No	Low	12 hrs
Timolol	None	No	Moderate	4-5 hrs

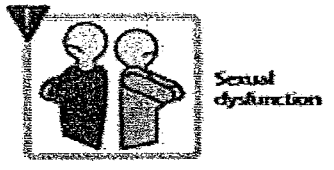
Beta blocker side effects

- Lipids decreased HDL, increase TG (β1)
- CNS depression (β2)
- Sexual dysfunction in men and women
- Occasional postural hypotension (β1)
- Bronchospasm (β2)
- Worsening of hypoglycemia (β1 and 2)
- Hyperkalemia during exercise (β2)
- Abrupt withdrawal may induce angina, myocardial infarction, or even sudden death









Beta Blockers: Treatment Strategy

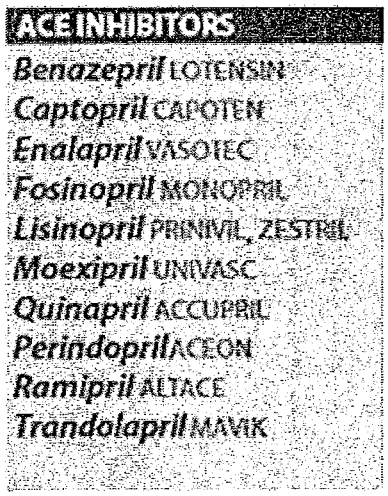
- Beta 1 selective (metoprolol) versus Non selective (propranol)
- More effective in hyperkinetic hypertension (tachycardia, excess sympathetic activity)
- Add to vasodilators to block reflex tachycardia
- Results in minimal fluid retention
- Takes 2 weeks to see dose effect
- Reduce mortality after myocardial infarction
- Use with caution in asthma, diabetes, COPD, PVD, depression

Drugs used for Hypertension

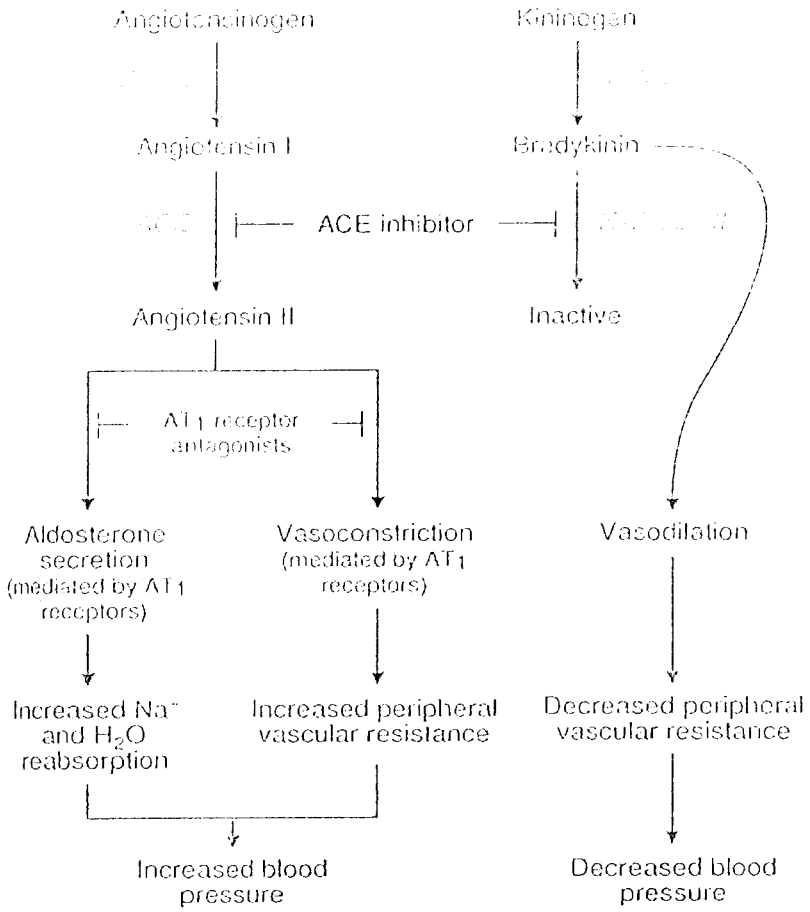
- Diuretics
- β-adrenergic receptor antagonists
- ACE inhibitors
- Angiotension II antagonists
- Ca^{2+} channel blockers
- α_1-adrenergic receptor antagonists
- Centrally acting drugs: α_2-adrenergic receptor agonists

ACE inhibitors

- first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease
- The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.



- ACE cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators.
- **ACE inhibitors decrease angiotensin II and increase bradykinin** levels. Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin). By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention. ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.



Pharmacokinetics

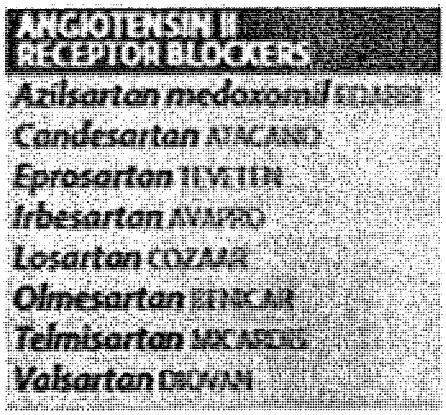
- ACE inhibitors are orally bioavailable.
- All but *captopril and lisinopril undergo hepatic conversion to* active metabolites, so these agents may be preferred in patients with severe hepatic impairment.
- *Fosinopril is the only ACE* inhibitor that is not eliminated primarily by the kidneys and does not require dose adjustment in patients with renal impairment.
- *Enalaprilat* is the only drug in this class available intravenously

Adverse effects

- Common side effects include dry cough, rash, fever, altered taste, hypotension, Angioedema and hyperkalemia.
- The dry cough, which occurs in up to 10% of patients, Angioedema, rare but potentially life-threatening reaction, are due to increased levels of bradykinin.
- ACE inhibitors and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalemia.
- ACE inhibitors can induce fetal malformations and should not be used by pregnant women.

ANGIOTENSIN II RECEPTOR BLOCKERS

- The ARBs, such as *losartan and irbesartan,* are alternatives to the ACE inhibitors. These drugs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors but ARBs do not increase bradykinin levels.
- Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.
- ARBs should not be combined with an ACE inhibitor
- These agents should not be used by pregnant.



Renin inhibitor

- *Aliskiren ,* selective renin inhibitor, *is available for the* treatment of hypertension.
- *Aliskiren should not be routinely* combined with an ACE inhibitor or ARB.
- *Aliskiren can cause diarrhea,* especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, *aliskiren is contraindicated during pregnancy.*
- *Aliskiren is metabolized* by CYP 3A4 and is subject to many drug interactions.

CALCIUM CHANNEL BLOCKERS

- Calcium channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective.
- Calcium channel blockers block the inward movement of calcium by binding to L-type calcium channels in the heart and in the smooth-muscle of the coronary and peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.
- Calcium channel blockers have an intrinsic natriuretic effect ; therefore, they do not usually require the addition of a diuretic.

Calcium channel blockers

- Useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike β-blockers, they do not have the potential to adversely affect these conditions.
- All CCBs are useful in the treatment of angina.
- High doses of short-acting calcium CCB should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.
- Short half-lives (3 to 8 hours) , except *Amlodipine,* following an oral dose.

CCB are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications

1. **Diphenylalkylamines:**
   Verapamil
2. **Benzothiazepines:**
   Diltiazem is the only member

3. **Dihydropyridines:**

nifedipine (the prototype), amlodipine, felodipine , isradipine, nicardipine, and nisoldipine.

have a much greater affinity for vascular calcium channels than for calcium channels in the heart.

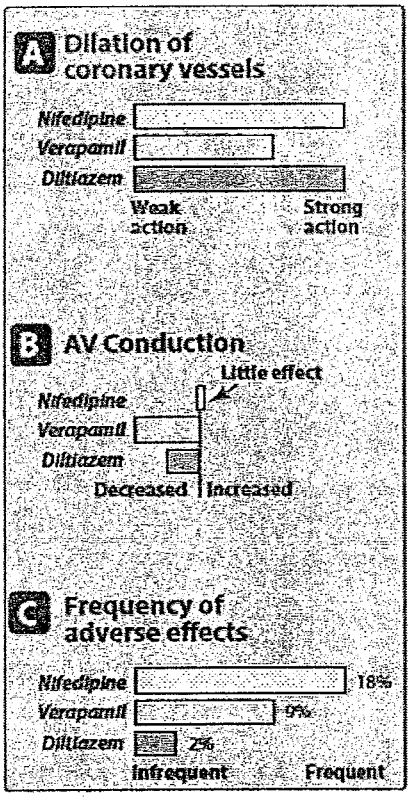
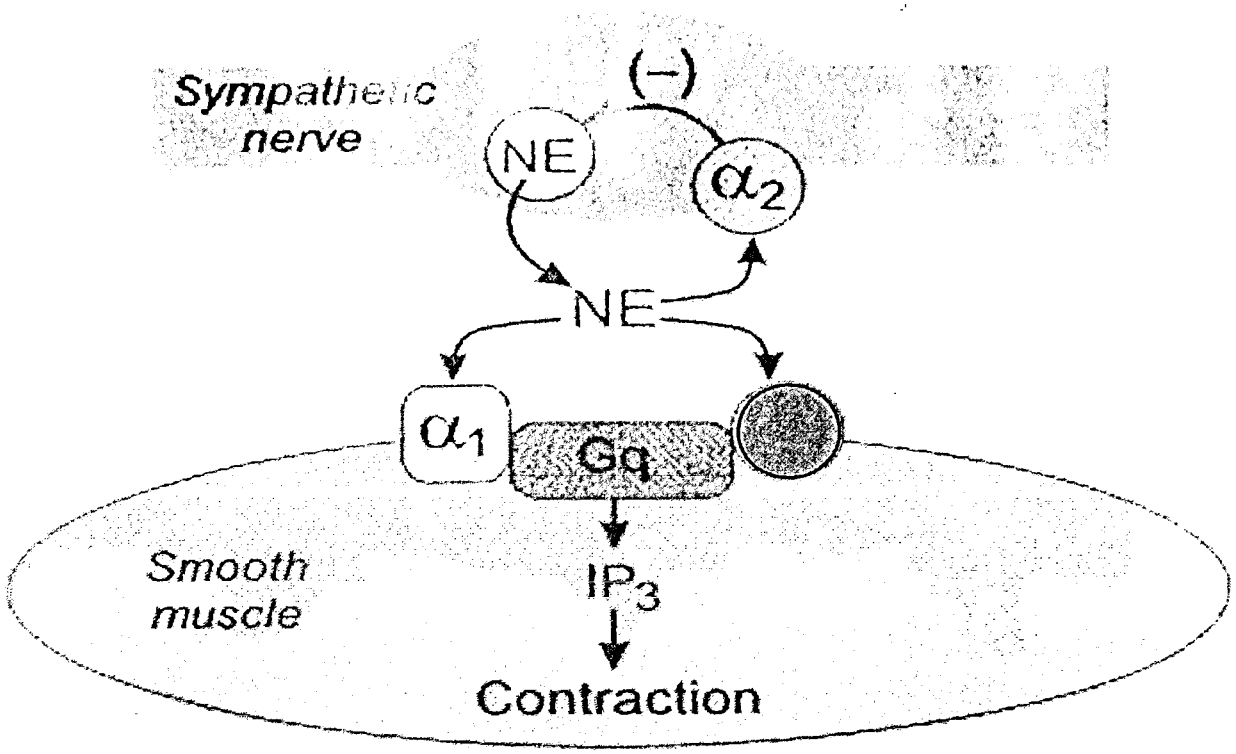


Figure 17.12
Actions of calcium channel blockers.
AV = atrioventricular.

Adverse effects

- First-degree atrioventricular block and constipation are common dose dependent side effects of *verapamil.*
- *Verapamil and diltiazem should* be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic.
- Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure and Peripheral edema are more frequent with dihydropyridines.

Alpha adrenoreceptor effects



α-ADRENOCEPTOR–BLOCKING AGENTS

- *Prazosin, doxazosin and terazosin* produce a competitive block of α1-adrenoceptors.
- They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses (could be blunt by beta blocker).
- α-blockers are no longer recommended as initial treatment for hypertension, but may be used for refractory cases.

α-/β-ADRENOCEPTOR–BLOCKING AGENTS

- *Labetalol and carvedilol block α1, β1, and β2* receptors.
- *Carvedilol, although an effective antihypertensive, is mainly* used in the treatment of heart failure.
- *Labetalol is used in the management* of gestational hypertension and hypertensive emergencies

Centrally Acting Sympathoplegic Drugs

Clonidine

- *Clonidine , α2 agonist,* inhibits the sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.
- *Clonidine is used primarily for* the treatment of hypertension that has not responded adequately to treatment with two or more drugs.
- *Clonidine does not decrease* renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.
- *Clonidine is* absorbed well after oral administration and is excreted by the kidney.
- It is also available in a transdermal patch.
- Adverse effects include sedation, dry mouth, and constipation. Rebound hypertension occurs following abrupt withdrawal of *clonidine. The drug should, therefore,* be withdrawn slowly if discontinuation is required.

Methyldopa

- Analog of L-dopa
- Converted to alpha methyldopamine and alpha methylnorepinephrine thus producing false neurotransmitters
- Anti hypertensive action due to stimulation of central alpha adrenoceptors by the above metabolites
- Lowers peripheral vascular resistance with some reduction in heart rate and cardiac output
- Reduces renal vascular resistance

Methyldopa

- *Methyldopa is an α2 agonist that is converted to* methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.
- The most common side effects of *methyldopa are sedation* and drowsiness. Its use is limited due to adverse effects and the need for multiple daily doses.
- It is mainly used for management of hypertension in pregnancy, where it has a record of safety

Vasodilators

- Hydralazine and minoxidil (oral)
- Nitroprusside, diazoxide, and fenoldopam (IV)
- Calcium Channel Blockers (oral and IV)
- Vasodilators relax smooth muscles of arterioles and decrease peripheral vascular resistance
- Sodium Niroprusside also relaxes veins
- Compensatory responses mediated by baroreceptors and the sympathetic nervous system and renin-angiotensin-aldosterone system cause tachycardian and salt/water retention

- The direct-acting smooth muscle relaxants, such as *hydralazine* and *minoxidil, are not used as primary* drugs to treat hypertension.
- Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.
- These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker. For example, *hydralazine is almost always* administered in combination with a β-blocker, such as *propranolol, metoprolol,* or *atenolol (to balance the reflex tachycardia) and a diuretic (to* decrease sodium retention).
- *Hydralazine* is an accepted medication for controlling blood pressure in pregnancy induced hypertension.
- Adverse effects of *hydralazine include headache,* tachycardia, nausea, sweating, arrhythmia, and precipitation of angina.
- *Minoxidil treatment causes hypertrichosis* (the growth of body hair). This drug is used topically to treat male pattern baldness.

HYPERTENSIVE EMERGENCY

- Hypertensive emergency is a rare but life-threatening (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, myocardial infarction).
- A severe elevation in blood pressure without evidence of target organ damage is considered a hypertensive urgency.
- Hypertensive emergencies require timely blood pressure reduction with treatment administered intravenously to prevent or limit target organ damage.
- A variety of medications are used, including calcium channel blockers (*nicardipine and clevidipine), nitric oxide vasodilators (nitroprusside* and *nitroglycerin), adrenergic receptor antagonists (phentolamine, esmolol, and labetalol), the vasodilator hydralazine, and the dopamine* agonist *fenoldopam.*

concomitant disease among the hypertensive patient

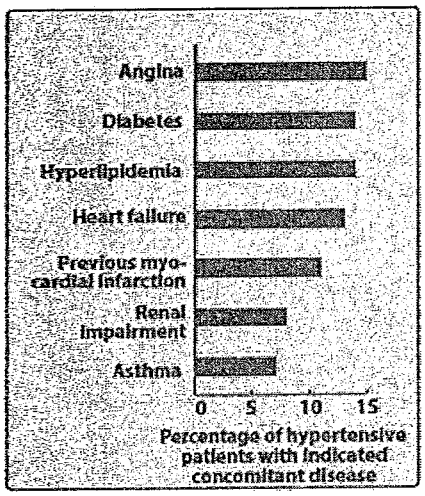


Figure 17.6
Frequency of occurrence of concomitant disease among the hypertensive patient population.

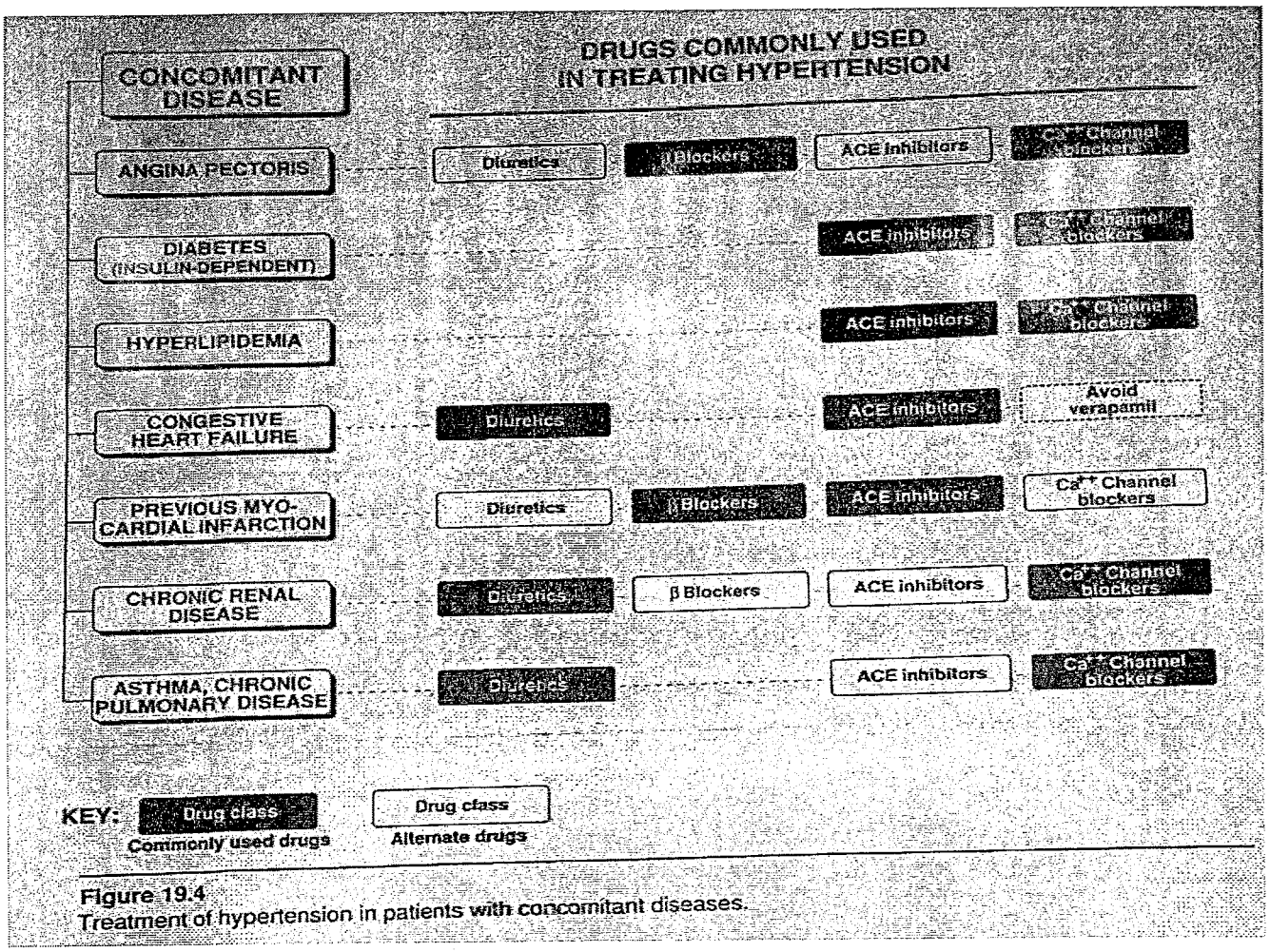


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.

Common Examples of Drug Classes and Naming Conventions

Drug Class	Common suffix	Common Examples
ACE Inhibitors	-pril	Lisinopril, benazepril, fosinopril, enalapril
Thiazide diuretics	None	Hydrochlorothiazide (HCTZ), chlorthiazide, chlorthalidone
Loop diuretics	None	Furosemide, bumetanide, torsemide
Dihydropyridine calcium channel blockers	-dipine	Amlodipine, felodipine, nicardipine, nifedipine
Non-dihydropyridine calcium channel blockers	None	Diltiazem, verapamil
ARBs	-sartan	Losartan, valsartan, irbesartan
Beta blockers	-olol	Metoprolol, carvedilol, labetalol, propranolol, esmolol
Alpha blockers	-osin	Terazosin, prazosin, doxazosin

Medication Selection for Initial Monotherapy

General Treatment Principles

Primary benefit from antihypertensive therapy is more associated with the degree of improvement in the blood pressure, and not associated with the use of any one specific drug.

Therefore, selection of initial monotherapy is largely driven by side effect profile and patient preference.

If SBP > 20mmHg above target or DBP > 10mmHg above target, one should consider that monotherapy will not be sufficient.

Medication Selection for Initial Monotherapy

Eric's Recommendations

(Assumes no compelling secondary indications or specific contraindications)

Non-Elderly, Non-Black

- ACE Inhibitor

  (twice daily lisinopril preferred)

- Thiazide diuretic

  (chlorthalidone preferred)

Non-Elderly, Black

- Thiazide diuretic

  (chlorthalidone preferred)

- Dihydropyridine calcium channel blocker

Elderly

- Dihydropyridine calcium channel blocker

Compelling Secondary Indications for Antihypertensives

	CAD: Stable Angina	CAD: Post-MI	Heart Failure	A-fib	CKD	DM	BPH
Diuretic			✓				
ACE-I / ARB		✓	✓		✓	✓	
Non-dihydropyridine CCB				✓			
Beta blocker	✓	✓	✓	✓			
Nitrates	✓		✓				
Hydralazine			✓				
Aldosterone antagonist			✓				
Alpha blocker							✓

Contraindications to Antihypertensives

	CAD: Stable Angina	CAD: Post-MI	Heart Failure	A-fib	CKD	DM	COPD
Diuretic						X (thiazides)	
ACE-I / ARB							
Non-dihydropyridine CCB			X				
Beta blocker						X ?	X
Nitrates							
Hydralazine	X						
Aldosterone antagonist					X		
Alpha blocker			X				

What To Do If Initial Therapy Is Insufficient

In general, either switching to a different monotherapy or adding a second drug is more effective in controlling hypertension than escalating doses of the first drug.

Risk of side effects may be increased by either adding a second drug, or escalating doses of the first drug, depending upon patient and situation.

Adding a second drug may result in decreased compliance, unless a combination pill is used.

What To Do If Initial Therapy Is Insufficient

First line combination therapy is generally considered to be an ACE-I/ARB + a dihydropyridine calcium channel blocker.

(e.g. benazepril + amlodipine)

Final Pearls About Antihypertensive Medications

ARBs have virtually identical indications and contraindications to ACE-Is, but due to increased cost, should generally be reserved for patients intolerant to ACE-Is due to cough.

Remember to monitor electrolytes and renal function after initiation and any dose increase of an ACE-I, ARB, or diuretic.

When using combination therapy, if poor compliance is not a concern, it is preferable to give at least one medication at bedtime.

Twice daily dosing of lisinopril may be more effective than once daily.

There is both theoretical and empirical evidence to favor using chlorthalidone over hydrochlorothiazide (although the latter is heavily favored in the US).

Atenolol should never be used for hypertension, ever.