Hypertension Part 3

Overview of Hypertension

http://www.geneactivatornrf2.org/wp-content/uploads/2012/09/hypertension.jpg

Drugs for Hypertension

Diuretics: Main classes are thiazide-type diuretics, loop diuretics, and K-sparing diuretics. Loop diuretics are used to treat hypertension only in patients who have lost > 50% of kidney function; these diuretics are given twice daily. Diuretics modestly reduce plasma volume and reduce vascular resistance, possibly via shifts in Na from intracellular to extracellular loci. These drugs are the least expensive initial therapy, and the dose needed is small, especially for the elderly (eg, for most people > 60 hydrochlorothiazide 12.5 mg is sufficient). Thiazide-type diuretics are most commonly used. In addition to other

antihypertensive effects, they cause vasodilation as long as intravascular volume is normal. All thiazides are equally effective in equivalent doses.

All diuretics except the K-sparing distal tubular diuretics cause significant K loss, so serum K is measured every 1 mo until the level stabilizes. Unless serum K is normalized, K channels in the arterial walls close and the resulting vasoconstriction makes achieving the BP goal difficult. Patients with K levels < 3.5 mEq/L are given K supplements. Supplements may be continued long-term at a lower dose, or a K-sparing diuretic (eg, daily spironolactone 25 to 100 mg, triamterene 50 to 150 mg, amiloride 5 to 10 mg) may be added. Supplements or addition of a K-sparing diuretic is also recommended for any patients who are also taking digitalis, have a known heart disorder, have an abnormal ECG, have **ectopy** or arrhythmias, or develop ectopy or arrhythmias while taking a diuretic. Although the K-sparing diuretics do not cause hypokalemia, **hyperuricemia**, or hyperglycemia, they are not as effective as thiazide-type diurectics in controlling hypertension and thus are not used for initial treatment. K-sparing diuretics or supplements are not needed when an ACE inhibitor or angiotensin II receptor blocker is used because these drugs increase serum K.

In most patients with diabetes, thiazide-type diuretics do not affect control of diabetes. Uncommonly, diuretics precipitate or worsen type 2 diabetes in patients with metabolic syndrome.

Thiazide-type diuretics can increase serum cholesterol slightly (mostly low-density **lipoprotein**) and also increase **triglyceride** levels, although these effects may not persist > 1 yr. Furthermore, levels seem to increase in only a few patients. The increase is apparent within 4 wk of treatment and can be **ameliorated** by a low-fat diet. The possibility of a slight increase in lipid levels does not **contraindicate** diuretics in hyperlipidemic patients.

A hereditary predisposition probably explains the few cases of gout due to diuretic-induced hyperuricemia. Diuretic-induced hyperuricemia without gout does not require treatment or discontinuation of the diuretic.

Table 5

Oral Diuretics for Hypertension		
Drug	**Usual Dose***	**Selected Adverse Effects**

	(mg)	
Thiazide type diuretics		
Bendroflumethiazide	2.5–5 once/day (maximum : 20)	Hypokalemia (which increases digitalis toxicity), hyperuricemia, glucose intolerance, hypercholesterolemia, hypertriglyceridemia, hypercalcemia, sexual dysfunction in men, weakness, rash; possibly increased blood levels of lithium
Chlorothiazide	62.5–500 bid (maximum : 1000)	
Chlorthalidone	12.5–50 once/day	
Hydrochlorothiazide	12.5–50 once/day	
Hydroflumethiazide	12.5–50 once/day	
Indapamide	1.25–5 once/day	
Methyclothiazide	2.5–5 once/day	
Metolazone	0.5–1	

	once/day	
(immediate-release)		
Metolazone	2.5–5 once/day	
(extended-release)		
K-sparing diuretics		
Amiloride	5–20 once/day	Hyperkalemia (particularly in patients with renal failure and in patients treated with an ACE inhibitor, angiotensin II receptor blocker, or NSAID), nausea, GI distress, gynecomastia, menstrual irregularities (withspironolactone); possibly increased blood levels of lithium
Eplerenone†	25–100 once/day	
Spironolactone†	25–100 once/day	
Triamterene	25–100 once/day	

- *Larger doses may be required in patients with renal failure.
- †Aldosterone receptor blockers.

β-Blockers: These drugs slow heart rate and reduce myocardial contractility, thus reducing BP. All β-blockers are similar in antihypertensive efficacy. In patients with diabetes, chronic peripheral arterial disease, or COPD, a cardioselective β-blocker (acebutolol, atenolol, betaxolol,

bisoprolol, metoprolol) may be preferable, although **cardioselectivity** is only relative and decreases as dose increases. Even cardioselective β-blockers are contraindicated in patients with asthma or in patients with COPD with a prominent **bronchospastic** component.

Table 6

Oral β -Blockers for Hypertension

Drug	Daily Dose (mg)	Selected Adverse Effects	Comments
Acebutolol *,†	200–800 once/day	Bronchospasm, fatigue, insomnia, sexual dysfunction, exacerbation of heart failure, masking of symptoms of hypoglycemia, triglyceridemia, increased total cholesterol and decreased high density lipoprotein cholesterol (except for pindolol ,acebutolol ,penbutolol	Contraindicated in patients with asthma, greater than 1st-degree atrioventricular block, or sick sinus syndrome
Atenolol *	25–100 once/day		Should be used cautiously in patients with heart failure or insulin-treated diabetes
Betaxolol *	5–20 once/day		Should not be stopped abruptly in patients with coronary artery disease
Bisoprolol *	2.5–20 once/day		Carvedilol approved for treating heart failure
Carteolol †	2.5–10 once/day		
Carvedilol	6.25–25		

	bid	,carteolol
‡		
Carvedilol	20–80 mg once/day	, andlabetalol
(controlled-release)‡		)
Labetalol	100–900 bid	
‡		
Metoprolol	25–150 bid	
*		
Metoprolol	50– 400 once/day	
(extended-release)		
Nadolol	40–320 once/day	
Penbutolol	10–20 once/day	
†		

Pindolol	5–30 bid
†	
Propranolol	20–160 bid
Propranolol, long-acting	60–320 once/day
Timolol	10–30 bid

- *Cardioselective.
- †With intrinsic sympathomimetic activity.
- ‡ α-β-Blockers. Labetalol

can also be given IV for hypertensive emergencies. For IV administration, it is started as 20 mg up to a maximum 300 mg.

β-Blockers are particularly useful in patients who have angina, who have had an MI, or who have HF, although atenolol may worsen prognosis in patients with CAD. These drugs are no longer considered problematic for the elderly.

β-Blockers with intrinsic sympathomimetic activity (eg, acebutolol, carteolol, penbutolol, pindolol) do not adversely affect serum lipids; they are less likely to cause severe bradycardia.

β-Blockers have CNS adverse effects (sleep disturbances, fatigue, lethargy) and exacerbate depression. Nadolol affects the CNS the least and may be best when CNS effects must be avoided. β-Blockers are contraindicated in patients with 2nd- or 3rd-degree **atrioventricular block**, asthma, or sick sinus syndrome.

Ca channel blockers: **Dihydropyridines** are potent peripheral vasodilators and reduce BP by decreasing TPR; they sometimes cause reflexive tachycardia. The nondihydropyridines verapamil anddiltiazem slow the heart rate, decrease atrioventricular conduction, and decrease myocardial contractility. These drugs should not be prescribed for patients with 2nd- or 3rd-degree atrioventricular block or with left ventricular failure.

Table 7

Oral Calcium Channel Blockers for Hypertension

Drug	Usual Dose (mg)	Selected Adverse Effects	Comments
Benzothiazepine derivatives			
Diltiazem, sustained-release	60–180 bid	Headache, dizziness, asthenia, flushing, edema, negative inotropic effect; possibly liver dysfunction	Contraindicated in heart failure due to systolic dysfunction, in sick sinus syndrome, or in greater than 1st-degree atrioventricular block
Diltiazem, extended-release	120–360 once/day		
Diphenylalkylamine derivatives			
Verapamil	40–120 tid	Same as for benzothiazepine derivatives, plus constipation	Same as for benzothiazepine derivatives
Verapamil, sustained-	120–480 once/da		

release	y		
Dihydropyridines			
Amlodipine	2.5–10 once/day	Dizziness, flushing, headache, weakness, nausea, heartburn, pedal edema, tachycardia	Contraindicated in heart failure, possibly except for amlodipine
Felodipine	2.5–20 once/day		Use of short-actingnifedipine
Isradipine	2.5–10 bid		possibly associated with higher MI rate
Nicardipine	20–40 tid		
Nicardipine, sustained-release	30–60 bid		
Nifedipine, extended-release	30–90 once/day		
Nisoldipine	10–60 once/day		

Long-acting nifedipine, verapamil, or diltiazem is used to treat hypertension, but short-acting nifedipine and diltiazem are associated with a high rate of MI and are not recommended.

A Ca channel blocker is preferred to a β-blocker in patients with angina pectoris and a bronchospastic disorder, with coronary spasms, or with Raynaud's syndrome.

ACE inhibitors: These drugs reduce BP by interfering with the conversion of angiotensin I to angiotensin II and by inhibiting the **degradation** of **bradykinin**, thereby decreasing peripheral vascular resistance without causing reflex tachycardia. These drugs reduce BP in many hypertensive patients, regardless of plasma renin activity. Because these drugs provide renal protection, they are the drugs of choice for patients with diabetes and may be preferred for blacks.

Table 8

Oral ACE Inhibitors and Angiotensin II Receptor Blockers for Hypertension

Drug	Usual Dose (mg)	Selected Adverse Effects
ACE inhibitors*		
Benazepril	5–40 once/day	Rash, cough, angioedema, hyperkalemia (particularly in patients with renal insufficiency or taking NSAIDs, K-sparing diuretics, or K supplements), dysgeusia, reversible acute renal failure if stenosis affecting one or both kidneys threatens renal function, proteinuria (rare at recommended doses), neutropenia (rarely), hypotension with initiation of treatment (particularly in patients with high plasma renin activity or with hypovolemia due to diuretics or other conditions)
Captopril	12.5–150 bid	
Enalapril	2.5–40 once/day	
Fosinopril	10–80 once/day	

Lisinopril	5–40 once/day	
Moexipril	7.5–60 once/day	
Quinapril	5–80 once/day	
Ramipril	1.25–20 once/day	
Trandolapril	1–4 once/day	
Angiotensin II receptor blockers		
Candesartan	8–32 once/day	Dizziness, angioedema (very rare); theoretically, same adverse effects as ACE inhibitors on renal function (except proteinuria and neutropenia), serum K, and BP
Eprosartan	400–1200 once/day	
Irbesartan	75–300	

	once/day
Losartan	25–100 once/day
Olmesartan	20–40 once/day
Telmisartan	20–80 once/day
Valsartan	80–320 once/day

- *All ACE inhibitors and angiotensin II receptor blockers are contraindicated in pregnancy (category C during 1st trimester; category D during 2nd and 3rd trimesters).

A dry, irritating cough is the most common adverse effect, but **angioedema** is the most serious and, if it affects the **oropharynx**, can be fatal. Angioedema is most common among blacks and smokers. ACE inhibitors may increase serum K and creatinine levels, especially in patients with chronic renal failure and those taking K-sparing diuretics, K supplements, or NSAIDs. ACE inhibitors are the least likely of the antihypertensives to cause erectile dysfunction. ACE inhibitors are contraindicated during pregnancy. In patients with a renal disorder, serum creatinine and K levels are monitored at least every 3 mo. Patients who have stage 3 nephropathy (estimated GFR of < 60 mL/min to > 30 mL/min) and are given ACE inhibitors can usually tolerate up to a 30 to 35% increase in serum creatinine above baseline. ACE inhibitors can cause acute

renal failure in patients who are hypovolemic or who have severe HF, severe bilateral renal artery stenosis, or severe stenosis in the artery to a solitary kidney.

Thiazide-type diuretics enhance the antihypertensive activity of ACE inhibitors more than that of other classes of antihypertensives.

Spironolactone and eplerenone also appear to enhance the effect of ACE inhibitors.

Angiotensin II receptor blockers: These drugs block angiotensin II receptors and therefore interfere with the renin-angiotensin system. Angiotensin II receptor blockers and ACE inhibitors are equally effective as antihypertensives. Angiotensin II receptor blockers may provide added benefits via tissue ACE blockade. The 2 classes have the same beneficial effects in patients with left ventricular failure or with nephropathy due to type 1 diabetes. An angiotensin II receptor blocker used with an ACE inhibitor or a β-blocker reduces the hospitalization rate for patients with HF. Angiotensin II receptor blockers may be safely started in people < 60 with initial serum creatinine of ≤ 3 mg/dL.

Incidence of adverse events is low; angioedema occurs but much less frequently than with ACE inhibitors. Precautions for use of angiotensin II receptor blockers in patients with renovascular hypertension, hypovolemia, and severe HF are the same as those for ACE inhibitors. Angiotensin II receptor blockers are contraindicated during pregnancy.

Direct renin inhibitor: Aliskiren, a direct renin inhibitor, is used in the management of hypertension. Dosage is 150 to 300 mg po once/day, with a starting dose of 150 mg. Clinical trials are ongoing to assess its efficacy for slowing diabetic nephropathy and reducing mortality in HF.

Adrenergic modifiers: This class includes central α_2-agonists, postsynaptic α_1-blockers, and peripheral-acting adrenergic blockers.

Table 9

Adrenergic Modifiers for Hypertension

Drug	Usual Dose	Selected Adverse Effects	Comments

	(mg)		
α $_2$-Agonists (central acting)			
Clonidine	0.05–0.3 bid	Drowsiness, sedation, dry mouth, fatigue, sexual dysfunction, rebound hypertension with abrupt discontinuance (particularly if doses are high or concomitant β-blockers are continued), localized skin reaction toclonidine	Should be used cautiously in elderly patients because of orthostatic hypotension Interferes with measurements of urinary catecholamine levels by fluorometric methods
Clonidine TTS (patch)	0.1–0.3 once/wk		
Guanabenz	2–16 bid		
Guanfacine	0.5–3 once/day		
Methyldopa	250–1000 bid	patch; possibly liver damage, Coombs'-positive hemolytic anemia withmethyldopa	
α-Blockers			
Doxazosin	1–16 once/day	First-dose syncope, orthostatic hypotension, weakness,	Should be used cautiously in elderly patients because of

Prazosin	1–10 bid	palpitations, headache	orthostatic hypotension
Terazosin	1–20 once/day		Relieves symptoms of benign prostatic hyperplasia
Peripheral-acting adrenergic blockers			
Guanadrel sulfate	5–50 bid	Diarrhea, sexual dysfunction, orthostatic hypotension with guanadrel sulfate or guanethidine, lethargy, nasal congestion, depression, activation of peptic ulcer with rauwolfia alkaloids orreserpine	For guanadrel sulfate or guanethidine, should be used cautiously because orthostatic hypotension is a risk
Guanethidine	10–50 once/day		
Rauwolfia alkaloids	50–100 once/day		
Reserpine	0.05–0.25 once/day		For reserpine , contraindicated in patients with history of depression and

			should be used cautiously in patients with history of peptic ulcer

 TTS = transdermal therapeutic system.

α $_2$-Agonists (eg, methyldopa, clonidine, guanabenz, guanfacine) stimulate α_2-adrenergic receptors in the brain stem and reduce sympathetic nervous activity, lowering BP. Because they have a central action, they are more likely than other antihypertensives to cause drowsiness, lethargy, and depression; they are no longer widely used. Clonidine can be applied **transdermally** once/wk as a patch; thus, it may be useful for nonadherent patients (eg, those with dementia).

Postsynaptic α_1-blockers (eg, prazosin, terazosin, doxazosin) are no longer used for primary treatment of hypertension because evidence suggests no reduction in mortality. Also,doxazosin used alone or with antihypertensives other than diuretics increases risk of HF.

Peripheral-acting adrenergic blockers (eg, reserpine, guanethidine, guanadrel) deplete tissue stores of norepinephrine. Reserpine also depletes the brain of norepinephrine and serotonin. Guanethidine and guanadrel block sympathetic transmission at the neuroeffector junction. Guanethidine, in particular, is potent but difficult to titrate, so it is rarely used. Guanadrel is shorter acting and has fewer adverse effects. These 3 adrenergic blockers are not routinely recommended for initial therapy; they are used as 3rd or 4th drugs if required.

Direct vasodilators: These drugs (including minoxidil and hydralazine) work directly on vessels, independently of the autonomic nervous system. Minoxidil is more potent than hydralazine but has more adverse effects, including Na and water retention and hypertrichosis, which is poorly tolerated by women. Minoxidil should be reserved for severe, refractory hypertension. Hydralazineis used during pregnancy (eg, for preeclampsia) and as an adjunct antihypertensive. Long-term, high-dose (> 300 mg/day) hydralazine has been associated with a drug-induced lupus syndrome, which resolves when the drug is stopped.

Table 10

Direct Vasodilators for Hypertension

Drug	Usual Dose (mg)	Selected Adverse Effects*	Comments
Hydralazine	10–50 qid	Positive antinuclear antibody test, drug-induced lupus (rare at recommended doses)	Augments vasodilating effects of other vasodilating drugs
Minoxidil	1.25–40 bid	Na and water retention, hypertrichosis; possibly new or worsening pleural and pericardial effusions	Reserved for severe, refractory hypertension

*Both drugs may cause headache, tachycardia, and fluid retention and may precipitate angina in patients with coronary artery disease.

Reference: http://www.merckmanuals.com