

- **Second-line agents:** If high LDL despite maximal statin therapy, consider statin + bile resin or niacin or ezetimibe; statin + ER niacin may ↓ risk of CV events in pts w/ CAD compared to ezetimibe combination (*NEJM* 2009;361:2113)

Secondary Lipid Lowering Drugs					
Drug	Dosing	S/e & notes	LDL (%)	HDL (%)	TG (%)
Gemfibrozil	600 mg BID	↑ INR on warfarin; ↑ gallstones, ↑ rhabdo w/ statins	↓ 10–15	↑ 5–20	↓ 35–50
Fenofibrate	145 mg/d nanocrystal 160–200 mg/d micronized	Rash, GI upset, myalgia, ↑ LFTs, ↑ CsA, avoid if CrCl <30; ↑ gallstones; use cautiously w/ statin	↓ 6–20	↑ 5–20	↓ 41–53
Niacin <i>Regular more effective than timed-release</i>	1–4.5 g/d Start at 100 mg AC & ↑ or use ER	Flushing, HA, pruritus, GI upset; avoid in gout, PUD, liver disease; may worsen DM; pre-Tx w/ NSAIDs/ASA ↓ flushing	↓ 5–25	↑ 15–35	↓ 20–50
Bile sequestrants Cholestyramine Colestipol Colesevelam	Take w/ meals 2–24 g/d 5–30 g/d 1.5–4.5 g/d	GI upset, ↓ drug absorption; avoid in biliary/bowel obstruction; effect additive to statins	↓ 15–30	No Δ	No Δ
Ezetimibe (inhibits absorption)	10 mg QD	↑ LFTs w/ statins	↓ 17	No Δ	No Δ
Fish oil (Ω3-acid ethyl esters)	4 g QD or 2 g BID	GI upset; useful in CAD pts intolerant of statins	May ↑	No Δ	↓ 20–50

- **Hypertriglyceridemia (mg/dL)** (*NEJM* 2007;357:1009; *J Fam Pract* 2006;55:S1; *AFP* 2007;75:1365):
Screen pts w/ ↑ TG for metabolic syndrome; blood glucose control key to ↓ TG in diabetics
150–199: Diet (fat <15% total cal, low sugar, ↓ EtOH), exercise (↓ TG up to 25%)
200–499: Consider Rx ↑ risk pts (CAD or equiv); non-HDL cholesterol (TC – HDL) is a 2° target w/ a goal 30 mg/dL higher than LDL goal; statins ↓ TG 5–33%
≥500: Ω3-acid ethyl esters (fish oil), fibrate, nicotinic acid to avoid pancreatitis
- **Complimentary and alternative therapies:**
Plant sterols (i.e., Benecol, Promise active): ↓ LDL 8–20%; consider in pts w/ CAD or equiv; use in general population not recommended pending long-term studies
Soy: Low in saturated fat, useful in substitution for animal protein, ↓ LDL
Other: Fiber (psyllium, oatmeal), nuts, green tea, DASH, & Mediterranean diets
- **Patient information:** *JAMA* 2001;285:2536; 2004;291:2276; 2013;309:1419; *AFP* 2003;67:1775; 2005;71:1147; 2010;81:1103

HYPERTENSION

Background (*JAMA* 2010;303:2043; *NEJM* 2010;362:2102)

- **Definition:** Elevated BP on ≥2 separate visits spaced >1 wk apart unless signs of end-organ damage or stage II HTN (below)
- **Epidemiology:** HTN affects ~50% pts >60 y; only ~50% pts w/ HTN at BP goal
- BP control ↓ risk of stroke by 35–40%, MI by 20–25%, CHF by 50%; to prevent 1 death/y from stage I HTN, NNT = 11
- Each 20 mmHg ↑ in SBP over 115/75 doubles risk of CV complications (stroke, MI, heart/renal failure, PVD) (*Lancet* 2002;360:1903)

Evaluation (*Ann Intern Med* 2011;154:781; *NEJM* 2003;348:610; 2006;355:385)

- **History:** Duration of HTN, comorbid conditions (CAD, CKD, stroke, DM, OSA, PAD, thyroid), evidence of end-organ damage, FHx, medication use, lifestyle
- **Adherence:** Ask pts not at goal BP: "Did you take your meds today, & at what time? Thinking over the past 2 weeks, were there any days when you did not take your blood pressure medicine?"
- **Exam:** Cardiac exam (LVH, murmurs, volume status), fundoscopic, neuro, thyroid, BMI, auscultation for bruits (carotid, renal); average several BP measurements;
- **BP measurement:** Pt seated, arm supported & level to heart, measured in both arms unless contraindicated (i.e., HD fistula, axillary LN dissection in breast CA); proper cuff size key: Improperly small cuffs overestimate SBP by up to 10 mmHg; check supine + standing BP in elderly, fall risk, or diabetics to detect/avoid orthostatic HoTN w/ tx (difference in SBP >20 mmHg, HR >20, or sx such as dizziness); check leg BP in young (eval for coarctation)
- **Home BP monitors:** Should be calibrated in office; pts may keep daily log
- **Initial workup:** CBC, Chem-12, lipids, TSH, U/A w/ protein:Cr ratio, ECG, HbA1c

Treatment

Treatment of Hypertension by Stage	
Definition	Treatment (see below for compelling indications)
Normal	Encourage healthy lifestyle
Pre-HTN: SBP 120–139 or DBP 80–89	Lifestyle modification for 3 mos (<i>NEJM</i> 2010;362:2102): <ul style="list-style-type: none"> • Wt loss (SBP ↓ 0.5–2 mmHg/kg lost) • DASH diet rich in fruits, vegetables, low fat (SBP ↓ 8–14 mmHg) (http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf) • Na⁺ reduction <2.4 g/d (SBP ↓ 2–8 mmHg), avoid canned, packaged, processed foods as high in Na • Aerobic exercise >30 mins/d, minimum 5 d/wk; intensity more effective than freq (SBP ↓ 4–9 mmHg) • Mod EtOH consumption <2 drinks/d men, <1 drink/d women (SBP ↓ 2–4 mmHg)
Stage I: SBP 140–159 or DBP 90–99	Lifestyle modification & in pts w/o compelling indication: Hydrochlorothiazide 12.5 mg PO QD
Stage II: SBP >160 or DBP >100	Lifestyle modification & in pts w/o compelling indication: ACEI + CCB (ACCOMPLISH, <i>NEJM</i> 2008;359:2417)
HTN urgency: >180/>120	Tx for stage II plus close f/u (1–3 d); consider home BP monitoring
Hypertensive emergency (e/o end-organ damage)	HA, CP, visual changes, altered mental status, stroke, neuro sx, pulm edema, bleeding, aortic dissection, renal failure, CHF, pre-eclampsia/eclampsia; requires ED referral for IV agents

(Adapted from JNC VII; *JAMA* 2003;289:2560)

- **General principles:** 1st-line drugs (ACEI, thiazides, CCB, β B) have equal efficacy (*BMJ* 2009;338:b1665; *JAMA* 1993;270:713); degree of CV benefit related to how well BP is controlled & compelling indication (below table) (*Arch Intern Med* 2005;165:1410)
- **Treatment failure:** 50–60% of pts w/ HTN will achieve BP control w/ a single agent; 50–80% of pts who fail a 1st agent will achieve BP control by switching to a different agent in a different class, ∴ a sequential single agent approach may be preferable to initial combination Rx (*Arch Intern Med* 1995;155:1757); may consider switching to a stronger drug within class if applicable; (e.g., not at goal on HCTZ → switch to chlorthalidone, which is a longer-acting and more potent thiazide)
- **Secondary causes:** ~2–5% pts, esp in pts w/ refractory HTN, or onset <20 y (*NEJM* 2006;355:385)
 - **CKD:** Proteinuria, elevated Cr, volume overload
 - **Renal artery stenosis:** Carotid/abdominal bruits; ↑ Cr w/ ACEI/ARB; resistant HTN in young (fibromuscular dysplasia); renal artery U/S, CT angio, or MRA
 - **Sleep apnea:** "Do you snore, wake up tired, fall asleep during the day?" (see "Obstructive Sleep Apnea")
 - **White coat HTN:** Seen in 10–20% of patients; consider in refractory HTN; ✓ home BP log (*NEJM* 2006;354:2368)

Medications: Antidepressants, NSAIDs, celecoxib, estrogen-OCPs, steroids, decongestants, diet pills, CsA, tacrolimus, herbal medications (ephedra, ginseng)

Endocrine: Cushing syndrome, hypercalcemia, hyperthyroidism, hyperparathyroidism

Hyperaldosteronism: ↓ K suggestive, but >50% pts normokalemic; ratio of plasma aldosterone:renin activity >20; confirm w/ saline infusion test; eval for adrenal adenomas or bilateral adrenal hyperplasia w/ CT (see "Adrenal Nodules"); Rx aldosterone antagonist

Pheochromocytoma: Palpitations, diaphoresis, pounding HA, episodic HTN; 24 h urine fractionated metanephrines, catecholamines

Pseudo-HTN: Inability to compress stiff brachial artery; assoc w/ orthostatic sx

Aortic coarctation: Discrepancy in BP btw arms/legs, ↓ femoral pulses

Compelling Indications (NEJM 2006;355:385)
AF: βB or CCB (i.e., diltiazem) for rate control
DM2: ACEI (renoprotective) or ARB; ACEI + CCB for combined therapy (ACCOMPLISH, NEJM 2008;359:2417). Goal BP <140/90 in absence of nephropathy/CKD (ACCORD, NEJM 2010; 362:1575)
High CAD risk: βB (1st line), ACEI, CCB, thiazide
Hx MI: ACEI, βB, ± aldosterone antagonist
CKD: ACEI/ARB plus a loop diuretic
CHF: ACEI or ARB, βB, diuretics, aldosterone antagonist, avoid CCB in pts w/ ↓ EF
Hx stroke: Thiazide, ACEI
Hx thoracic aortic aneurysm: βB or losartan
Special Populations
African ancestry: Response rate by agent: diltiazem (64%), HCTZ (58%), clonidine (45%), prazosin (38%) (NEJM 1993;328:914)
Angina: βB (1st line) or CCB
BPH: αB
Elderly: Thiazide or CCB (JACC 2011;57:2037; NEJM 2007;357:789); tx of HTN in pts >80 y resulted in ↓ stroke & CHF, ↓ in death from CV, stroke, & any cause (HYVET, NEJM 2008;358:1887)
Migraines, essential tremor, significant anxiety/phobia, hyperthyroid: βB (i.e., propranolol)
Nephrolithiasis or osteoporosis: Thiazide (↓ renal Ca clearance)
Pregnancy: Methyldopa (Pregnancy risk factor B), hydralazine or nifedipine sustained release (Pregnancy risk factor C), βB used in some situations
Younger pts (<50 y): ACEI or ARB

- **Refractory hypertension:** Persistent HTN despite 3 meds; discuss adherence, titrate meds to max dose, & consider w/u of secondary causes + home BP monitoring before moving onto 2° agents (below)
- **Second-line agents:**
 - Aliskiren:** Oral renin inhibitor; assoc w/ diarrhea; limited outcomes data
 - αB:** Doxazosin, prazosin
 - Aldosterone antagonists:** Spironolactone, eplerenone (↓ gynecomastia)
 - Clonidine:** Available in transdermal dosing; anxiolytic; taper if discontinuing
 - Combined αB & βB:** Carvedilol, labetalol
 - Combinations:** (Diltiazem/verapamil + amlodipine) or (ARB + ACEI) w/ careful K/Cr monitoring; avoid in HF due to ⊖ inotropy
 - Hydralazine:** TID or preferably QID dosing; may cause rebound tachycardia
 - Loop diuretics:** Furosemide, bumetanide, torsemide; useful in refractory HTN w/ CKD (Cr >1.5/CrCl <30)
 - Triamterene:** Na⁺ channel antagonist; available in combo pill w/ HCTZ for 1° tx
- **Medication side-effects:**
 - αB:** ↑ risk of CHF (doxazosin), postural HoTN
 - ACEI:** Cough (~15% pts); ↑ K in CKD; angioedema, contraindicated in pregnancy
 - Aldosterone antagonists:** Hyperkalemia, esp w/ ACEI, DM, renal insufficiency; Gynecomastia & breast pain (less so w/ eplerenone)
 - ARB:** Contraindicated in pregnancy
 - βB:** Angina/rebound HTN on abrupt discontinuation; may mask hypoglycemic sx in DM; may exacerbate asthma, COPD, impotence; caution in pts w/ conduction disease (heart block), pheo (unopposed α-stimulation); can → nightmares, fatigue, ↓ exercise tolerance

CCB: Peripheral edema (esp amlodipine); verapamil/diltiazem are nodal agents & \ominus inotropes & contraindicated if low EF or heart block

Clonidine: Rebound HTN on discontinuation

Thiazides: Hypokalemia, most common in 1st wks of tx, prevent by dietary salt restriction; hyperglycemia, esp in diabetics; hyponatremia; may exacerbate gout & erectile dysfunction; ineffective in pts w/ CrCl <30

- **Patient handouts:** www.nlm.nih.gov/medlineplus/highbloodpressure.html

LOWER EXTREMITY EDEMA & ULCERS

LOWER EXTREMITY EDEMA

Background (AFP 2005;71:2111)

- **Causes:** Δ in hydrostatic or oncotic pressure, \downarrow lymph drainage, \uparrow capillary permeability
- **Unilateral/asymmetric Ddx:** DVT, cellulitis, lymphedema, venous insufficiency, popliteal (Baker) cyst, ruptured muscle/tendon
- **Bilateral/symmetric Ddx:** CHF/RHF, nephrotic syndrome, cirrhosis, venous insufficiency, malnutrition, hypothyroidism, lymphatic disease, IVC thrombosis, lipedema, pregnancy/premenstrual or idiopathic, vasculitis (rare)
- **Meds:** CCB (amlodipine), steroids, estrogens, hydralazine, thiazolidinediones, diazoxide, pramipexole, minoxidil, NSAIDs (in CHF or cirrhosis)

Evaluation

- **History:** Onset (acute vs. chronic), location, assoc sx (dyspnea, orthopnea, pain, urinary), hx CAD/CHF/HTN/DM/EtOH/clotting, medications; hx immobility, malignancy, surgery (i.e., LN dissection venous harvest for CABG), radiation or cath, filariasis (where endemic), recurrent cellulitis/lymphangitis, prior DVT; consider OSA \rightarrow pHTN
- **Exam:** HEENT (periorbital edema), lungs (crackles), CV (JVP, S₃/S₄), abdominal (HSM, ascites); lower extremities (\checkmark limb circumference, \checkmark peripheral pulses, e/o venous insufficiency); pattern of edema involving dorsal foot & toes (Stemmer sign) suggests lymphedema; sharp demarcation at ankle, sparing the foot suggests lipedema
- **Diagnosics:** As dictated by hx; consider BUN/Cr, LFTs including albumin, U/A for protein, blood, D-dimer or venous duplex U/S for unilateral/bilateral disease; TTE, CXR, BNP, D-dimer, TFTs, CBC, per clinical suspicion

Treatment

- **General measures:** Treat underlying etiology; low salt diet (<2 g/d), properly fitted compression stockings (>20 mmHg), fluid restriction limb elevation (30 mins QID)
- **For hypervolemic states:** Loop diuretics (+ spironolactone in cirrhosis)
- **Diuretics:** Not effective in venous insufficiency; benefit limited to hypervolemic states; 1st line is loop diuretic (+ spironolactone in cirrhosis); monitor for \downarrow K, AKI, dehydration
- **Patient information:** AFP 2005;71:2118

Lymphedema (BMJ 2000;320:1527; Am J Med 2001;110:288)

- **Causes:** \downarrow Lymphatic flow due to LN dissection, XRT, malignancy, filariasis, recurrent cellulitis, obesity, congenital, RA, psoriasis
- **Diagnosis:** Localized, *nonpitting*, gradual swelling/heaviness of limb, including involvement on the dorsum of the foot, worse at day's end; does not improve w/ recumbency; cutaneous fibrosis, dry/scaly skin, peau d'orange, \oplus Stemmer sign (unable to lift skin at base of upper surface of 2nd digits); edema may be monitored by measuring limb circumference at set points (i.e., wrists); MRI or CT helpful if dx unclear; consider malignant lymphatic obstruction in new or worsening lymphedema
- **Complications:** Discomfort > cellulitis >> lymphangiosarcoma (particularly in LE)
- **Prevention:** Skin/nail care to prevent infection; avoid tight clothing, dependent positioning for long periods; avoid phlebotomy, vaccination, IVs in affected limb; Hot climates, baths, & saunas may exacerbate; wt loss; ROM & wt exercises
- **Treatment:** Manual lymph drainage/compression (bandages, hose, intermittent pneumatic compression); for severe cases, surgery & cold laser tx (data unclear); **Diuretics not beneficial**