CARDIOTONICS

Digoxin (Lanoxin) is most common agent - virtually the only one used
Monitor for digoxin toxicity - narrow therapeutic range (0.5-2.0 ng/ml)
Signs of toxicity

- Anorexia, nausea/vomiting, yellow vision, fatigue, weakness, arrhythmias
- Visual disturbance (esp blurred vision) halo vision (classic sign)

Elderly at risk for toxicity
Hold for bradycardia (HR >56) or tachycardia (HR >120) - sign of toxicity
Monitor electrolytes

Hypokalemia may potentiate toxicity
Overdose treated with digoxin immune Fab (antibody fractions specific for digitalis)
Antiarrhythmic Agents

Drugs that effect myocardial conduction

Classes: I, II, III, IV, misc unclassified agents

Etiology of arrhythmia determines choice of agent

Agents act to restore normal rhythm.

Many agents in this class are highly toxic - need to closely monitor patient

Fatal dysrhythmias can occur from pro-arrhythmic effects of most agents

“Cure may be worse than diseases”

Overall relatively dangerous agents

Monitor patient for arrhythmias

---

### COMMON ANTIARRHYTHMICS

**Class IA**

- **Quinidine (Quinaglute, Quinidex)**
  - PAC, VCs V tachycardias, PAC, maintain NSR after cardioversion
- **Procainamide (Procan SR, Pronestyl, Procanbid)**
  - Same as quinidine; also ventricular dysrhythmias, WPW
  - Associated with drug-induced lupus-like reaction with long-term use
  - Other hematological reaction: agranulocytosis, neutropenia, thrombocytopenia, eosinophilia
- **Disopyramide (Norpace):** PVCs, V-tachy, supraventricular tachycardia

**Class IB**

- **Lidocaine (Xylocaine)** - ventricular dysrhythmias - frequently given IV bolus
- **Mexiletine (Mexitil)** - toxic
- **Phenytoin (Dilantin)** - used also for seizure control
- **Tocainide (Tonocard)** - toxic

**Class IC - very toxic**

- **Flecainide (Tambocor)** - V-dysrhythmias (life threatening), paroxysmal a-fib, paroxysmal SVT
- **Propafenone (Rythmol)** - life threatening V-arrhythmias, persistent a-fib

**Class II - Beta-blockers (see separate section)**

**Class III - toxic, used as last resort - life-threatening arrhythmias** unresponsive to other agents

- **Amiodarone (Cordarone)** - very toxic; used where other drugs fail
  - Supraventricular-ventricular arrhythmias unresponsive to other drugs
- **Bretylium tosylate (Bretylol)** - life threatening ventricular arrhythmias (ICU/CCU)
  - Dofetilide (Tikosyn) - maintain NSR with a-fib or a-flutter

**Class IV - Calcium channel blockers (see separate section)**

Unclassified

- **Adenosine (Adenocard):** SVT, WPW
  - Short half-life - used IV emergency situations

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Agents for Hypotension (Low Blood Pressure)

**Adrenergic agonists** primary agents - stimulate **flight or flight** in autonomic nervous system

Work in same manner as epinephrine to raise BP

B-adrenergic agonists (stimulation) must be used with caution in cardiogenic shock

Increased heart rate and contractility may **increase O2 consumption**

May predispose to arrhythmias

If **volume depletion** causes shock must **replace fluid** (volume) to restore BP

Indications: treatment of **shock or resuscitation**

**Contraindicated hypovolemic shock** (low blood volume) until replace fluid

Side effects: potentially **fatal arrhythmias** (from increased O2 demand)

Monitor BP; check renal output; titrate up or down - do not abruptly stop; normally ICU/CCU

**Class members differ** with respect to indications and therapeutic actions

<table>
<thead>
<tr>
<th>COMMON ADRENERGIC AGONISTS</th>
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<tbody>
<tr>
<td>Epinephrine (Adrenalin)</td>
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<td>Norepinephrine (Levophed)</td>
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<tr>
<td>Isoproterenol (Isuprel)</td>
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<td>Dopamine (Intropin)</td>
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<tr>
<td>Dobutamine (Dobutrex)</td>
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</table>

**Epinephrine (Adrenalin)** - natural catecholamine; both alpha and beta activity

Increases HR, contractility, conduction speed

bronchodilation, gluconeogenesis

Used: cardiac arrest, anaphylaxis, status asthmaticus, bradycardia. (IV, IM, SQ)

**Norepinephrine (Levophed)** - naturally occurring catecholamine - primarily alpha

Intense vasoconstriction and PVR, increased contractility

Used only in shock refractory to other agents where need intense vasoconstriction

IV only - onset 1-2 minutes

**Isoproterenol (Isuprel)** - synthetic catecholamine; mostly B-adrenergic

Increases HR, contractility - stimulates more than epinephrine

Indications: bradycardia refractory to other agents

Contraindicated in routine treatment cardiac arrest; other agents used first

**Dopamine (Intropin)** - naturally occurring catecholamine - precursor to norepinephrine

Also functions as neurotransmitter

Increases force contraction, increase CO; minimal increase in HR - (less O2 demand)

**Low dose = renal dose** (1-2 ug/kg/min) - stimulates renal receptors

- Improves renal vasodilation

Intermediate dose 1 (2-10 ug/kg/min) stimulate B and dopaminergic receptors

  Enhanced cardiac output, modest increase SVR,

  Increased venous tone and central venous pressure
Intermediate dose 2 (10 ug/kg/min) predominately adrenergic activity
Renal, mesenteric, arterial and venous vasoconstriction
Marked increase in systemic SVR and pulmonary vascular resistance
High Doses (> 20 mg/kg/min) potent vasoconstriction similar to norepinephrine
Indications:

- increase in renal perfusion of low output states - **renal failure, CHF**
- Treatment of hypotension with bradycardia and no hypovolemia

**Causes** **tissue necrosis with extravasation**
- Avoid peripheral line (vs central line)
- Do NOT IV push

**Dobutamine (Dobutrex)** - synthetic catecholamine
- Dopamine derivative without vascular effects (does not bind to dopamine receptors)
- Potent inotropic effects (force) primarily beta receptors of myocardium
- Increases cardiac output; decreases PVR; increase HR (higher doses)
- **Indications**
  - Pulmonary congestion with low cardiac output, hypotension with LV dysfunction,
    septic shock (improve LVF), CHF (systolic), cardiogenic shock (with dopamine)
- Nurse: use **smallest effective dose** during titration
Calcium Channel Blockers

- Block entry of calcium into calcium selective channels in cellular membrane
- Clinical effects
  Vasodilation (reduces PVR thus reduces BP), bradycardia, decreased force of contraction, reduced AV node conduction
  Reduce oxygen consumption and myocardial energy demands

- Indications (clinical uses)
  Management of angina
  Mild to moderate hypertension
  Cardiac arrhythmias
  Cerebral arterial spasms, prevent coronary spasm
  Management of migraines
- Cautious use with beta-blockers
- Contraindications: LV dysfunction, heart block, cardiogenic shock

- Misc considerations
  Strongest chronotropic effect: verapamil
  Most potent smooth muscle (vaso)dilator: nifedipine
  Indicated for cerebral vasospasm: nimodipine
  Reduction in BP due to decreased PVR

Short acting agents are contraindicated - Do not administer (causes MI)
We used to commonly give Procardia 10 mg sl to acute HTN - this is now considered malpractice to order such and most nurses will not carry out this order even if written

<table>
<thead>
<tr>
<th>COMMON CALCULUM CHANNEL BLOCKERS</th>
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<tr>
<td><strong>Class:</strong> BENZOTHIAZEPINES</td>
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<tr>
<td>Diltiazem (Cardizem, Cardizem CD, Cardizem SR, Dilacor XR, Tiazac)</td>
</tr>
<tr>
<td><strong>Class:</strong> DIHYDROPYRIDINE</td>
</tr>
<tr>
<td>Nifedipine (Adalat CC, Procardia XL), amlodipine (Norvasc) felodipine (Plendil), nimodipine (Nimotop), nicardipine (Cardene, Cardene SR), nisoldipine (Sular) isradipine (DynaCirc, DynaCirc CR)</td>
</tr>
<tr>
<td><strong>Class:</strong> DIPHENYLAKYLAMINES</td>
</tr>
<tr>
<td>Verapamil (Calan, Calan SR, Isoptin SR, Covera HS, Verelan, Verelan PM)</td>
</tr>
</tbody>
</table>

COMBINATION PRODUCTS: ACE-inhibitor and calcium channel blocker
Tecezem (diltiazem and enalapril), Tarka (verapamil and trandolapril)
Lexxel (enalapril and felodipine) Lotrel (amlodipine and benazepril)
Beta Blockers

- **Blocks** action of catecholamines e.g. blocks adrenaline (epinephrine)
- **Blocks** “fight or flight” response
  Recall the “fight or flight” response = tachycardia, increased contractility, increased renin release (kidneys), bronchial dilation, K entry into cell

- **Indications**
  - Hypertension, (reduces myocardial O2 need)
  - Migraine prophylaxis,
  - Supraventricular/ventricular arrhythmias, reduces tachyarrhythmias
  - Glaucoma (reduce intraocular pressure)
  - Hyperthyroid crisis and thyroiditis symptom management
  - Acute MI and angina
  - Stage fright and public speaking anxiety (not for athletes or dancers)
  - Pheochromocytoma

- **Selective (B1)** vs **non-selective (B2)**
  - B1 = heart; B2 = lungs (hint to remember: you have “1 heart and 2 lungs”)
  - Selectivity lost at higher doses; prefer B1 if required use in asthmatic

- **Avoid** with bronchostenstion and asthma (further constricts bronchioles)
- **Masks** signs of hypoglycemia - cautious use with DM Type I (may mask insulin shock)
- Previously contraindicated in heart failure; some agents now indicated for heart failure
- Commonly causes impotence and fatigue/depression - leads to non-compliance
- Worsens PVD (peripheral constriction); unfavorable glucose-lipid profile (avoid in DM)
- **Hold** dose for bradycardia (usually held for HR below 56)
- **Never discontinue abruptly!** (Rebound hypertension)

### COMMON BETA BLOCKER AGENTS

#### NONSELECTIVE AGENTS - B2
- Nadolol (Corgard)
- Penbutolol (Levatol)
- Pindolol (Visken) B2
- Timolol (Blocadren, Timolide, Timoptic *)
- Labetalol (Normodyne, Trandate)
- Propranolol (Inderal, Inderal LA)
- Carvedilol (Coreg)
- Levobunolol (Betagan*)

#### SELECTIVE AGENTS - B1
- Acebutolol (Sectral) B1 selective
- Sotalol (Betapace) B1 selective
- Bisoprolol (Zebeta) B1 selective
- Betaxolol (Kerlone, Betoptic*) B1 selective
- Atenolol (Tenormin)- B1 - selective
- Metoprolol (Toprol, Toprol XL OptiPranolol*)

**AGENTS IN COMBO WITH DIURETIC HCTZ** Tenoretic, Ziac, Lopressor HCT, Inderide, Corzide - * OPTIC AGENTS for glaucoma
COMMENTS RE: INDIVIDUAL CLASS MEMBERS

**Propranolol (Inderal):**
Nonselective - commonly used in *stage fright, migraine, HTN, nightmares*

**Atenolol (Tenormin)** - selective agent, very commonly used

**Labetalol (Normodyne, Trandate)** B2 nonselective; both alpha1 and beta2 receptors
Used PO for routine HTN; also *IV for hypertensive crisis* (ICU/CCU)
Somewhat less impotence and other side effects

**Carvedilol (Coreg):** B2 nonselective used in heart failure and s/p MI
Previously BB were contraindicated in heart failure; thinking has changed and now they are not only used for pts with HF but mandated for use s/p MI. Contrary to previous thinking they causes reversal of neurohormonal stimulation which leads to LVF

**Esmolol (Brevibloc):** B1 selective and very short-acting (minutes)
Used IV only (ICU/CCU) for converting *a-fib*

**Metoprolol (Lopressor, Toprol)** selective agent - very commonly used

**Glaucoma Agents:**
- *Timolol (Timoptic)*, metoprolol (OptiPranolol), *levobunolol (Betagan)*, betaxolol (Betoptic)
Nitrates (Nitroglycerine)

Improve blood flow to heart
Work via direct relaxation of smooth muscle causing vasodilation
Vasodilation results in reduced preload
Indications: angina (acute or long-term)
Effects of reduced preload
  Reduces myocardial oxygen demand
  Reduces left ventricular (LV) end diastolic volume (EDV)
Relieves coronary artery spasm
High doses reduces system vascular resistance (SVR) - thus useful to treat CHF

SL route is very common route (dissolve tab under tongue; spray under tongue)
  SL results in rapid administration (1-2 minutes)
  Can also be give IV, PO, transdermal patch or ointment (30-60 minutes)

Transdermal patch or ointment
  Avoid contact with nurse’s hands - causes migraine-like headache
  Removed 8-10 hours qd (usually HS) to decrease toleration (decreased action)
Agents commonly cause vascular headache (similar to migraine)

IMPORTANT CONSIDERATIONS - NURSING IMPLICATIONS

- Results in hypotension (lowering BP) - monitor BP frequently
- Medicate prn for headache as ordered
- Never give to patient taking sildenafil (Viagra) - fatal interaction
- Cautious use with other drugs which can also lower BP:
  - Alcohol, CaCh blockers, B-blockers, phenothiazine (Thorazine), haloperidol (Haldol)
- SL NTG pills are very unstable - keep in dark bottle; replace q 30 days
  Patient should feel “tingling” under tongue

- Issues with topical administration (patch or ointment)
  - Rotate sites - remove previous patch
  - Avoid contact with hands of nurse (headache)
  - Do not rub-in
- Hypotension is very common following therapy - monitor BP
- Tolerance to nitrates - nitrate-free interval is needed - usually 8-10 hrs HS
COMMON NITRATE PREPARATIONS

SL PREPS (acute attacks, prophylaxis)
   Nitroglycerine SL tabs (1/150) Nitrostat (1/150)
   Nitroglycerine spray (Nitrolingual)
   Isosorbide dinitrate in SL tabs (Isordil)

IV PREPS: Nitroglycerine IV (Tridil, Nitro-Bid IV)

PO PREPS (prophylaxis only - not for acute attacks)
   Nitroglycerine sustained-release (Nitrobid, Nitrong, Nitrospan)
   Isosorbide mononitrate (Imdur, Ismo, Monoket, Tembids)
   Isosorbide dinitrate
      (Dilatrate-SR, Iso-Bid, Isonate, Isorbid, Isordil, Isotrate, Sorbitrate)

TRANSDERMAL (prophylaxis, not for acute attacks; remove HS to avoid tolerance)
   Nitroglycerine transdermal patches
      (Nitro-Dur, Nitro-bid, Transderm-Nitro, Nitro-Disc, Deponit, Minitran)
Angiotensin-Converting Enzyme (ACE) Inhibitors

Controls BP via preventing conversion of angiotensin I to angiotensin II
Kidney secretes renin -> angiotensin I -> angiotensin II
Angiotensin II is potent vasoconstrictor
Angiotensin II stimulates aldosterone release which retains sodium and water

Indications - HTN and CHF - Diabetic nephropathy
First line agent for CHF (previously diuretics and digoxin were first line agents)
Actually prevents and reverses left ventricular hypertrophy in CHF
One of most common agents for hypertension (low side effect profile)

Pharmacologic action

Prevents conversion angiotensin I to angiotensin II (inhibits needed enzyme)
Increases renal blood flow - promotes Na+/H2O excretion; reduces K+ excretion
Increases bradykinin release - vasodilation

IMPORTANT CONSIDERATIONS

Contraindicated for pregnancy - causes fetal death (renal agenesis)
Hypersensitivity is common esp angioedema mouth/lip and face
D/C if C/O tingling to lips - treatment is antihistamines and epinephrine
Bronchospasm, dyspnea
Dry cough is common annoying side effect for some people
DM - indicated for diabetics (renal blood flow) even if not hypertensive
CHF - first line therapy - "remodels" the failing ventricle
HTN - one of most commonly prescribed agents - "clean" side-effect profile
NSAIDs can decrease therapeutic effect
Retains potassium - avoid co-administration with K-sparing diuretics - monitor K+

ACE INHIBITOR PREPARATIONS

| Benazepril (Lotensin) |
| Captopril (Capoten) |
| Fosinopril (Monopril) |
| Quinapril (Accupril) |
| Lisinopril (Prinivil) |
| Ramipril (Altace) |
| Enalapril (Vasotec) |
| Perindopril (Aceon) |
| Moexipril (Univasc) |
| Trandolapril (Mavik) |

COMBINATION ACE-INHIBITOR PREPS

Combo with Diuretic (HCTZ)

Accuretic, Capozide, Lotensin HCT, Prinzide, Uniretic, Vaseretic, Zestoretic

Combo with Calcium Channel Blockers

Lexxel (enalapril and felodipine)
Lotrel (benazepril and amlodipine)
Tarka (trandolapril and verapamil)
Teczem (enalapril and diltiazem)
Angiotensin II Receptor Blocking Agents

- HTN also CHF (minor role used only where patient cannot take ACE)
- Action similar to ACE-inhibitors - blocks action of angiotensin II at tissue level
- Renin -> Angiotensin I -> Angiotensin II - X - blocks action at tissues
- Angiotensin II is potent vasoconstrictor - blocking it would relax vessels -> lower BP
- Effect on BP similar to ACE-inhibitors (lowers BP, treats HTN)
- Not usually associated with dry cough or angioedema
  Good choice for patients intolerant of these side-effects or allergic to ACE
  ACE is usually first choice due to somewhat better effectiveness
- Good second choice for CHF for patients who cannot take ACE
- Contraindicated in pregnancy (fetal death from renal agenesis)
- Widely prescribed for HTN - low incidence of side-effects - well tolerated
- Monitor for hyperkalemia

<table>
<thead>
<tr>
<th>ANGIOTENSIN II BLOCKING AGENTS</th>
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<tr>
<td>Losartan potassium (Cozaar)</td>
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<td>Valsartan (Diovan)</td>
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<td>Irbesartan (Avapro)</td>
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<td>Candesartan (Atacand)</td>
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<td>Telmisartan (Micardis)</td>
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<tr>
<th>COMBO ANGIOTENSIN II BLOCKING AGENTS</th>
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<tr>
<td>Irbesartan-HCTZ</td>
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<td>Valsartan-HCTZ</td>
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<tr>
<td>Losartan-HCTZ</td>
</tr>
<tr>
<td>Candesartan-HCTZ</td>
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<tr>
<td>Telmisartan-HCTZ</td>
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<tr>
<td>Avalide</td>
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<tr>
<td>Diovan-HCT</td>
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<tr>
<td>Hyzaar</td>
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<tr>
<td>Atacand HCT</td>
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<tr>
<td>Micardis-HCT</td>
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Alpha Adrenergic Blockers

Indication: HTN - some used also for BPH
Commonly used with diabetics: no unfavorable impact on CHO and lipid metabolism
    Actually has positive effect on lipids (decrease cholesterol/triglycerides; raise HDL
    No adverse effect on glucose, uric acid or potassium levels
First dose orthostatic hypotension
    - Common for patient to experience hypotension/syncope with first dosing
    - Usually administered HS
    - Use with caution in the elderly due to hypotension/syncope
    - Avoid use with diuretics (orthostatic hypotension)
Side effects: fatigue, weakness, nasal congestion, headache

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<thead>
<tr>
<th>ALPHA ADRENERGIC BLOCKERS</th>
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<tbody>
<tr>
<td>Doxazosin (Cardura)</td>
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<tr>
<td>Prazosin (Minipress)</td>
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<tr>
<td>Terazosin (Hytrin)</td>
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</tbody>
</table>
| Prazosin and polythiazide (Minizide) - combination product with diuretic
| Phenoxybenzamine (Dibenzyline) - nonselective - used for pheochromocytoma

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Central Alpha Agonists

Indication: **HTN**; clonidine also used for **drug withdrawal**
Mechanism:
- Reduce sympathetic vasoconstriction
- Reduce peripheral vascular resistance (PVR)

- Older agents which are used less frequently today
  Exception is **clonidine (Catapres)** - available as patch for HTN and drug withdrawal
  Exception: **methyldopa (Aldomet)** first choice for **pregnant patient with HTN**

- **Abrupt withdrawal** causes rebound hypertension
- Can cause **orthostatic hypotension** in elderly
- Common side effects are **dry mouth, sedation, bradycardia and withdrawal hypertension.**

---

**CENTRAL ALPHA AGONISTS**

**Clonidine (Catapres)** also available as transdermal patch (**Catapres TTS**)

Guanabenz acetate (**Wytsin**)

Guanfacine Hcl (**Tenex**)

**Methyldopa (Aldomet)** - hepatic and autoimmune-like disorders

**COMBINATION PRODUCTS WITH DIURETIC**

- Methyldopa and HCTZ (**Aldoril**)
- Clonidine and chlorthalidone (**Combipres**)

---

**Older - Infrequently Used Antihypertensive agents**

**PERIPHERAL ADRENERGIC INHIBITORS**

- Mechanism: prevents release or norepinephrine in response to sympathetic stimulation
- Interactions: displaced by indirect-acting sympathomimetics and tricyclic antidepressants
- Side effect profile: **orthostatic hypotension**, fluid retention, **diarrhea**, **bradycardia**

**PERIPHERAL ADRENERGIC BLOCKERS**

Guanadrel sulfate (**Hylorel**)

Guanethidine monosulfate (**Ismelin**)

Reserpine (**Serpasil**)

**DIRECT VASODILATORS**

Hydralazine (**Apresoline**)

Minoxidil (**Loniten**)

**DIRECT VASODILATORS**

- After load reducing agents
  - **Hydralazine (Apresoline)** - associated with **lupus-like syndrome**
  - **Minoxidil (Loniten)** - associated with hirsutism - also used to treat alopecia (baldness)
Cerebral and Peripheral Vascular Dilating Agents

Cause direct vasodilation of blood vessels
Therapeutic effect differs depending on tissue and actual vessels involved
  Artery (deliver oxygen) vs veins (remove unoxygenated blood)
  May differentially effect segments within same vascular bed
Indications:
  - HTN, atherosclerosis: coronary (angina) or cerebral (TIA)
  - Peripheral vascular constriction: intermittent claudication, severe ischemia
Action: relax smooth muscle; interfere with sympathetic-mediated vasoconstriction
Effect: improve blood flow in peripheral vascular tissue

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<tr>
<th>CEREBRAL AND PERIPHERAL VASODILATING AGENTS</th>
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<tr>
<td>Isoxsuprine (Vasodilan, Voxsuprine)</td>
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<td>Papaverine (Pavabid)</td>
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<tr>
<td>Dipyridamole (Persantine) - used to prevent TIA; also s/p valve replacement</td>
</tr>
<tr>
<td>Cyclandelate (Cyclen, Cyclospasmol)</td>
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<tr>
<td>Pentoxifylline (Trental)</td>
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</table>

Pentoxifylline (Trental) - xanthine derivative - affects blood viscosity
  - Increases microcirculation - enhances tissue oxygenation
  - Indication: intermittent claudication from occlusive arterial disease
  - Onset 2-4 wks; clinical manifestations: at least 8 wks
  - Contraindicated: cerebral or retinal hemorrhage
  - Side effects:
    - H/A, dizziness, blurred vision, n/v, dyspepsia, dyspnea, edema, hypotension,
      edema, epistaxis, flulike symptoms, belching/bloating
**Diuretics**

Promote *loss of body fluids* via increasing fluid lost through *renal system*

Classes of agents

- **Loop diuretics**: potent - act in distal Loop of Henle
- **Thiazide and thiazide-like**: act between ascending loop of Henle and early distal tubule
- **Potassium-sparing**: act on late portion of distal convoluted tubule and collecting duct
- **Carbonic anhydrase inhibitors**: proximal nephron
- **Osmotic agents**: proximal nephron

Action: alter *balance of sodium and water in renal tubules*

Sodium loss accompanied by osmotically equivalent amt water ("water follows sodium")

Increased electrolyte excretion - can result in hypokalemia (low potassium)

Indications: HTN, edema, CHF, intracranial or ocular pressure, electrolyte disorders

**IMPORTANT CONSIDERATIONS**

- **Fluid/electrolyte imbalances** - common sequelae
  - **Loop diuretics** greatest potential to *alter electrolyte esp K+*
  - **Elderly** particularly prone to imbalance and *hypokalemia*

Monitor *urine output*; daily *weights*; avoid HS administration

Reduce clearance of *lithium* - predisposes to *toxicity*

**Carbonic Anhydrase (CAH) Inhibitors**

- CAH (enzyme) found in brush border of proximal tubule epithelial cell
- CAH inhibitors derivatives of sulfonamide antibiotics
- **Limited usefulness**: tolerance develops as HCO₂ decline/metabolic acidosis development

Indications:

- Mountain sickness (rapid elevation), *glaucoma*, massive edema with metabolic acidosis (lowers bicarbonate level)

**Acetazolamide (Diamox)** - *glaucoma*, drug-induced edema (q other day)

**Osmotic Diuretics**

- **Mechanism**
  - Pull water into vascular space through high osmotic concentration
  - Water so pulled is then excreted via urine

- **Indication**
  - Reduce *cerebral* and *intraocular pressure* (esp acute *glaucoma emergency*)
  - Treat acute chemical poisoning - increased renal excretion toxins
  - Prevent oliguric renal failure
  - *Hemolytic transfusion reaction* (protect renal blood flow)

**Side effects**

H/A, blurred vision, confusion, convulsion, hypotension, angina-like pain, tachycardia, CHF, dermatologic rashes, n/v, diarrhea, marked diuresis, dry mouth, fever, chills, rhinitis, electrolyte imbalance, acidosis

**Mannitol (Osmitrol)**: *cerebral edema* - check syringes for crystallization
Loop Diuretics

**Potent** diuretics - considered high-ceiling diuretics (peak effect greater than other diuretics)

**Mechanism**
- Weak acids which bind to plasma proteins
- Blocks sodium-potassium-chloride cotransport in loop of Henle
  - Impairs sodium reabsorption
  - Decreased osmolarity of interstitial tubes surrounding collecting ducts
  - Impedes ability of kidneys to concentrate urine
  - Result is *excretion of large quantities of urine with high levels of sodium*
  - Increases potassium, magnesium, calcium excretion
- Increase blood flow to renal medulla - *increasing fluid through kidney* and urine flow
- Systemic hemodynamic effects
  - Increased venous capacitance which reduces left ventricular filling pressure
  - Relieves pulmonary edema

**Indications:**
- Severe edema with pulmonary edema, CHF, hepatic cirrhosis, renal disease
- Treatment of HTN
- Ascites from lymphedema, malignancy, idiopathic edema
- Acute hypercalcemia (furosemide)
- Severe symptomatic hyponatremia

**Side effects** (most important/common ones)

*Hearing loss/tinnitus*, visual disturbance, *orthostatic hypotension*, *ECG* changes, rashes, exfoliative dermatitis (rare), hepatic dysfunction/altered LFT, blood dyscrasias (rare), *fluid and electrolyte imbalance*, abnormal glucose tolerance (GTT), muscle cramping

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**Thiazide Diuretics - Thiazide-Like Diuretics**

- Possess weak CAH inhibitory activity
- Enhance action of antidiuretic hormone via sodium depletion - useful in *diabetes insipidus*

**Mechanism**
- Inhibit Na reabsorption in early distal tubules -> increase urinary excretion Na+
  - Water follows the excreted Na+
  - Also excreted is K+, magnesium, HCO₃⁻ (bicarbonate)
- Other actions
  - Augment calcium absorption in distal tubules
  - Relax arterial smooth muscle, reduce peripheral vascular resistance
  - Interfere with insulin release

**Indications**

*CHF* (mild to moderate), *HTN*, idiopathic hypercalcinuria (with renal calculi), nephrogenic diabetes insipidus, *edema* (hepatic cirrhosis, renal dysfunction, estrogen/steroid therapy)

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**LOOP DIURETICS**

- Furosemide (Lasix)
- Bumetanide (Bumex)
- Ethacrynic acid (Edecrin)
- Torsemide (Demadex)
Side effects (most important ones)

**Orthostatic hypotension**, light-headedness, **fatigue**, blurred vision, PVC, **rash**, photosensitivity, blood dyscrasias/marrow suppression (rare), muscle weakness, cramps, impotence, hyperglycemia, hyperuricemia, hypokalemia, increased BUN, unfavorable lipid-CHO effects

**THIAZIDE DIURETICS**

Chlorthalidone (Hygroton)
**Hydrochlorothiazide** (HydroDIURIL, Microzide, Esidrix)
Indapamide (Lozol)
Metolazone (Mykrox, Zaroxolyn)
Methyclothiazide (Enduron)
Chlorothiazide (Diumil)

ADDITIONAL CONSIDERATIONS

- Unfavorable lipid and CHO effects - caution with DM
- **Hydrochlorothiazide** most common combination agent in antihypertensive agents
  - Combination products with beta-blockers, ace-inhibitors, angiotensin II blockers
- Monitor for hypokalemia
- Less potent than loop diuretics; commonly used in out-patient setting

**Potassium-Sparing Diuretics**

Not potent diuretics when used alone - can result in hyperkalemia
- Sometimes used in combination preps with thiazide diuretics
- **Contraindicated with ace-inhibitor** therapy - predisposes to hyperkalemia

**Mechanism**
Act on distal nephron to inhibit sodium absorption and potassium secretion

**Indications**
- Adjuvant therapy with other diuretics - minimize K+ loss
- **Edema** (CHF, cirrhosis, nephrotic syndrome)

Side effects (most important ones)

**Photosensitivity/rash**, liver enzyme abnormalities, blood dyscrasia, azotemia, increased BUN/creatinine, electrolyte abnormalities

ADDITIONAL CONSIDERATIONS

Monitor for hyperkalemia
- Acute **renal failure** if triamterene is given with indomethacin
  - Increases serum digitalis levels; hyperkalemia with ACE-inhibitor therapy; lithium toxicity

**POTASSIUM-SPARING DIURETICS**

Amiloride (Midamor)
**Spirolactone (Aldactone)**
Triamterene (Dyrenium)

**DIURETIC COMBINATIONS**

**Triamterene/HCTZ** (Dyazide, Maxzide)
Amiloride/HCTZ (Moduretic)
Spirolactone/HCTZ (Aldactazide)
Lipid Lowering Agents

Goal lipid lowering agents - **change lipid profile** with minimal side effects
Many lipid-lowering agents are **hepatotoxic**
Lipid profile goals
  Lower: total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL)
  LDL: “bad cholesterol” - promotes atherosclerosis
  **LDL: most significant factor in disease development**
  Raise or maintain: high-density-lipoprotein (LDL) "good cholesterol"

**American Heart Association (AHA) goals re lipids**
- **LDL under 100 mg/dl** for cardiovascular disease or 2 or more risk factors ASHD
- **LDL under 130 mg/dl** for individuals without risk factors ASHD
- **TG** should be kept under **200 mg/dl**; **HDL** should be **over 35 mg/dl**

**Indications**
- Decision to initiate therapy based on lipid profile with consideration to risk factors
- Pharmacologic therapy to be used in conjunction with diet and life-style modification

**Monitor liver function testing (LFT) before and during therapy**
- Monitor q 6 wks x 3 months; q 8 weeks remainder of first year
- Check q 6 months after first year
- D/C medication if LFT elevated esp 3X normal

**Bile acid-sequestering resins**

**Mechanism**
- Decrease resorption of bile - > enhances oxidation of cholesterol to form bile
- Decrease serum TC and LDL
- Cholesterol required for formation of bile acids (secreted into intestines during digestion)
- Majority of bile acids secreted are reabsorbed from intestines (enterohepatic circulation)
- Resorption is prevented when bile-acids combine with sequestrants (insoluble complex)

**Indications**
- Reduction of elevated TC/LDL
- Only lipid-lowering agents **appropriate for individuals with active liver disease**

**Drug interactions**
- **Decrease absorption of other medications**

**Side effects (most important ones)**
- **Constipation, fecal impaction, abdominal discomfort, flatulence**, myalgia-arthritis, vitamin deficiency with long-term use (A, D, K)

**ADDITIONAL CONSIDERATIONS**
- Prevent constipation with fiber, etc.
- Life style issues with multiple dosing of unpalatable medications
- Scheduling other meds can be challenging (co-administration is contraindicated)
HMG-CoA Reductase inhibitors - “Statins”

Work on enzyme system - mainstay to lipid lowering therapy

**Contraindicated in liver disease** - caution with ETOH abuse or history of liver disease

Therapy requires **liver function monitoring**

**Rhabdomyolysis** can occur esp if used with other lipid lowering agents

CPK to monitor for rhabdo if suspicious

D/C therapy with complaints of muscle pain

Mechanism

- HMG-CoA reductase is required for cholesterol synthesis
- HMG-CoA reduces LDL and precursor VLDL (very low density lipoprotein)
- May contribute to LDL catabolism

Decrease serum TC and LDL via decreasing production and increasing catabolism

**Indications:**

- Reduction of elevated TC and LDL
- Reduction of elevated LDL in presence of hypertriglyceridemia

**Side effects:** (important ones)

- Elevated LFT esp transaminase levels, myalgia, myopathy, rhabdomyolysis, skin reactions

**Contraindicated for pregnancy** (category X)

### HMG COA REDUCTASE INHIBITORS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>Lovastatin</td>
<td>Mevacor</td>
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<tr>
<td>Pravastatin sodium</td>
<td>Pravachol</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Zocor</td>
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<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
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<tr>
<td>Fluvastatin</td>
<td>Lescol</td>
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Nicotinic Acid (Niacin)

**Mechanism:**

- Decreases synthesis of LDL via reducing hepatic synthesis of VLDL
- Increases synthesis of HDL, inhibiting lipolysis of adipose tissue; increases lipase

**Indications:**

- Good for low HDL; high triglycerides or both
- Most effective RX for raising HDL (15-30%)
- Indications: LDL 100-129 plus HDL less than 40

**Side effects are quite significant:** increase dose gradually to minimize

- Skin flushing/itching; GI disturbance, activation of peptic ulcer disease; induces GB disease (very common) - hepatotoxicity, hyperuricemia; glucose intolerance: avoid with DM, atrial fibrillation, hypotension, transient H/A

**OTHER CONSIDERATIONS**

- Causes marked skin flushing (transient) in 30 min
- Extended release has less flushing but higher incidence of hepatotoxicity
- ASA 325 30-40 min previous may minimize flushing; antihistamine decreases pruritus
- Contraindicated liver or GB disease; caution ETOHics, gout, diabetes, peptic ulcer
- Does not require RX - can purchase OTC and pt can thus induce gall bladder disease
Fibric Acid

Mechanism:
- Increase clearance of VDRL cholesterol via enhancing lipolysis
- Reduces hepatic cholesterol synthesis.

Effectiveness
- **Lowers triglyceride** 20-50%; raise HDL up to 20%; reduce LDL 5-15%*

Indications
- Severe hypertriglyceridemia (>150) - lowers 15-30%
- Increases HDL; **not effective for lowering LDL**
- Particularly useful for DM and familial beta-lipoproteinemia

Side Effects: can be quite significant

Nausea, bloating, flatulence, abdominal distress, liver-function abnormalities. **Myositis**, gallstones, elevation of LDL has been reported, malignancy with clofibrate, GB disease, hematologic abnormalities

In combo with “statin” there is greatly increased risk for myopathy
**Clofibrate** rarely if ever used - very toxic; risk of hepatic malignancy, serious GB disease
**Fenofibrate** (Tricor) newest agent - reportedly somewhat less toxic

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**FIBRIC ACID**

- Gemfibrozil (Lopid)
- Clofibrate (Atromid-5)
- Fenofibrate (Tricor)