Hypertension

Hypertension

- Sustained systolic pressure of >140 mm Hg or sustained diastolic blood pressure >90 mm Hg

- Hypertension is caused by
  - Increased peripheral vascular arteriolar muscle tone which leads to increased arteriolar resistance
  - Reduced capacitance of the venous system

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Prehyper-tension	120–139	or	80–89
Stage I	140–159	or	90–99
Stage II	≥160	or	≥100

Figure 19.2
Classification of blood pressure, based on report of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

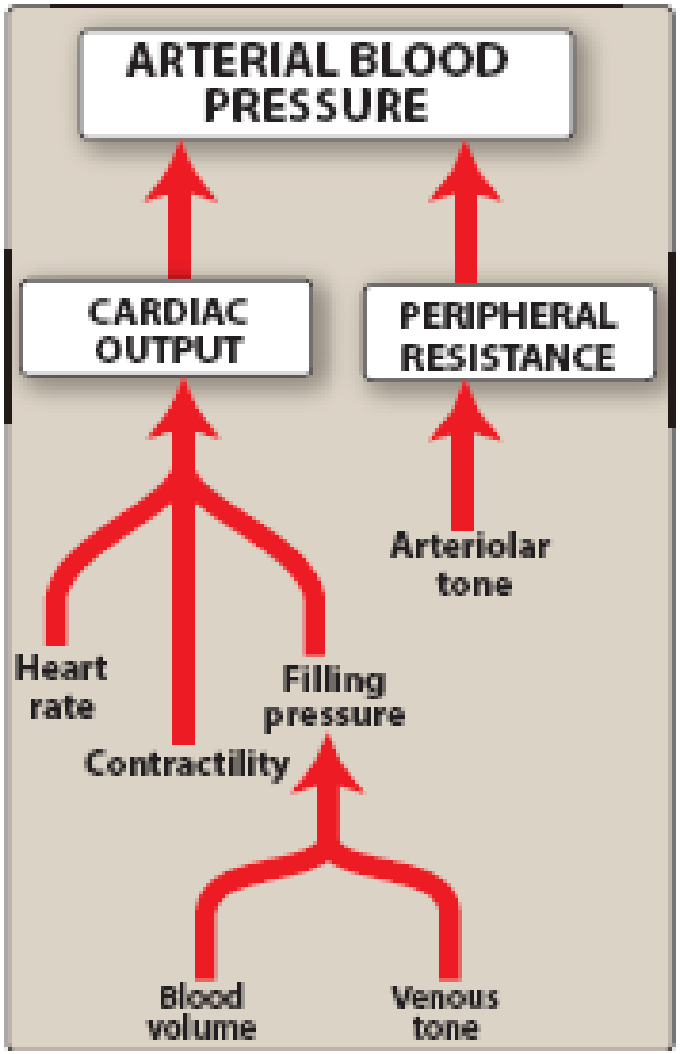
- Many people with hypertension are asymptomatic
- Chronic hypertension can lead to
  - Cerebrovascular accidents (strokes)
  - Congestive heart failure
  - Myocardial infarction
  - Renal damage
  - Retinal damage
- The incidence of morbidity and mortality decreases by early diagnosis and treatment of hypertension

- Causes of hypertension
  - 90% of the cases the cause is unknown, essential hypertension, primary hypertension (idiopathic)
  - Secondary Hypertension: caused by chronic renal disease (diabetic nephropathy), pheochromocytoma, stress, aortic coarctation
  - Family history
  - More common in middle aged males than females
  - Environmental factors such as stress, high sodium diet, and smoking

Risk Factors for Hypertension

- Blood relatives with hypertension
- Men over the age of 55
- Post-menopausal women
- Obesity
- Smoking
- Diabetes
- High blood cholesterol

- Arterial blood pressure is regulated within a narrow range to provide adequate tissue perfusion without damaging the vascular system
- Arterial blood pressure is directly proportional to cardiac output (CO) and peripheral resistance
- CO and peripheral resistance are controlled by:
  - Baroreflexes
  - Renin-angiotensin-aldosterone system

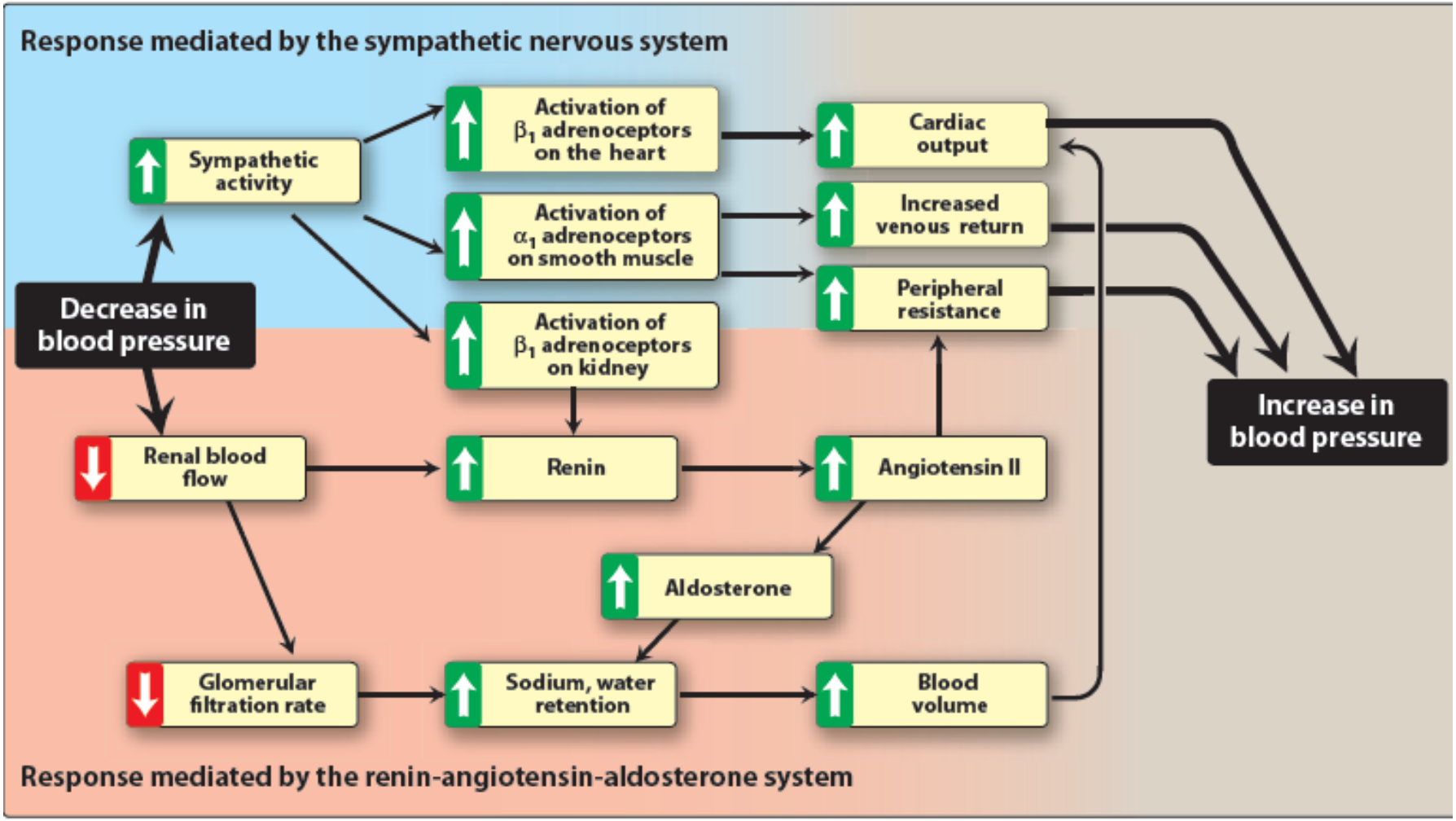

ARTERIAL BLOOD PRESSURE
CARDIAC OUTPUT
PERIPHERAL RESISTANCE
Arteriolar tone
Heart rate
Contractility
Filling pressure
Blood volume
Venous tone

Baroreceptors and sympathetic nervous system

- Baroreflexes change the activity of the sympathetic nervous system, altering blood pressure
- Low blood pressure causes baroreceptors to send fewer impulses to cardiovascular centers in the spinal cord
- This causes an increased sympathetic and decreased parasympathetic output to the heart and vasculature
- This causes vasoconstriction and increased cardiac output and increased blood pressure

Renin-angiotensin-aldosterone system

- Baroreceptors in the kidney respond to reduced blood arterial blood pressure and sympathetic activation of β1 receptors by releasing the enzyme renin
- Renin converts angiotensinogen to angiotensin I
- Angiotensin I is converted by ACE to angiotensin II which is a potent vasoconstrictor
- Angiotensin II stimulates aldosterone secretion which increases renal sodium reabsorption and blood volume and hence increases blood pressure


Response mediated by the sympathetic nervous system
Sympathetic activity
Activation of β_1 adrenoceptors on the heart
Activation of α_1 adrenoceptors on smooth muscle
Activation of β_1 adrenoceptors on kidney
Cardiac output
Increased venous return
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin-angiotensin-aldosterone system

Mechanisms for controlling blood pressure

- Most antihypertensive drugs lower blood pressure by:
  - Reducing cardiac output or/and
  - Lowering peripheral resistance

- The goal of hypertension treatment is to reduce cardiovascular and renal morbidity and mortality
- There is a strong relationship between blood pressure and cardiovascular risk, lowering even the moderately high blood pressure significantly reduces cardiovascular disease
- The new classification of “prehypertension” emphasizes the need for decreasing blood pressure by education and lifestyle modification

Hypertension treatment

- Mild hypertension can be controlled with one drug but most patients require more than one drug
- Currently therapy is started with a thiazide diuretic with other drugs added if needed
- The selection of added drugs is based on minimizing side effects of the combined regimen and achieving goal blood pressure
- A beta blocker can be added as a second drug, and a vasodilator as a third drug for patients who still have high blood pressure
- If an ACE inhibitor is the first drug, a diuretic is the most common second drug
- The choice of drugs also should consider benefits for concomitant diseases

Hypertension treatment

- Noncompliance to treatment is the most common reason for failure of antihypertensive treatment
- Usually the hypertensive patient is asymptomatic, and is diagnosed by routine checkups before organ damage
- Hypertension therapy is initiated to prevent future diseases rather than to relieve current symptoms
- Side effects of antihypertensive drugs might affect compliance

Antihypertensive drugs

- Diuretics
- β-blockers
- ACE inhibitors
- Angiotensin II receptor blockers
- Renin inhibitors
- Calcium channel blockers
- α-blockers
- Other

Diuretics

- First line therapy for hypertension
- Helps prevent stroke, myocardial infarction and congestive heart failure
- Diuretics classes used for HTN
  - Thiazide diuretics
  - Loop diuretics
  - Potassium sparing diuretics

Thiazide diuretics

- Hydrochlorothiazide
- Chlorthalidone

- MOA:
  - Decrease Na^+ reabsorption by inhibiting Na^+/Cl^- co-transporter
  - Lower blood pressure by increasing sodium and water excretion
  - This decreases extracellular volume resulting in lower cardiac output and renal blood flow
  - With long term use peripheral resistance decreases

Thiazide diuretics

- Useful alone or can be used in combination with β-blockers, ACE inhibitors, angiotensin receptor blockers and K^+ sparing diuretics if needed
- Adverse effects
  - Hypokalemia (K^+ levels should be monitored in patients predisposed to cardiac arrhythmias)
  - Hyperuricemia (thiazide diuretics compete with uric acid for excretion from the organic acid secretory system of the nephron)
  - Hyperglycemia (in 10% of patients)
  - Hypomagnesemia

Loop diuretics

- Furosemide
- Bumetanide
- Torsemide

- MOA:
  - Inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the loop of Henle
  - Decrease renal vascular resistance and increase renal blood flow

Loop diuretics

- Adverse effects
  - Hyperuricemia
  - Hypokalemia
  - Ototoxicity (damage to the ear)
  - Acute hypovolemia, severe and rapid reduction in blood volume with the possibility of hypotension, shock and cardiac arrhythmias

Potassium sparing diuretics

- Amiloride and triamterene
  - Block Na^+ transport channels resulting in a decrease in Na^+/K^+ exchange
  - Inhibit sodium reabsorption in collecting duct
- Spironolactone and eplerenone are aldosterone receptor antagonists
  - Spironolactone is useful in patients with congestive heart failure
- Adverse effects
  - Hyperkalemia

β-Blockers

- First line therapy for HTN when concomitant disease is present like heart failure, angina, post MI patients
- Reduce blood pressure by decreasing cardiac output
- Block sympathetic activity and decrease renin release and angiotensin II formation and aldosterone secretion thereby decreasing peripheral resistance and blood volume

β-Blockers

- Antihypertensive β-blockers
  - Propranolol: β1, β2 blocker
  - Metoprolol: β1 blocker
  - Atenolol: β1 blocker
  - Nebivolol: β1 blocker, vasodilator due to increase in nitric oxide production
- Propranolol is contraindicated in asthma because it block β2 receptors causing bronchoconstriction
- β-blockers may take several weeks to develop their full effects

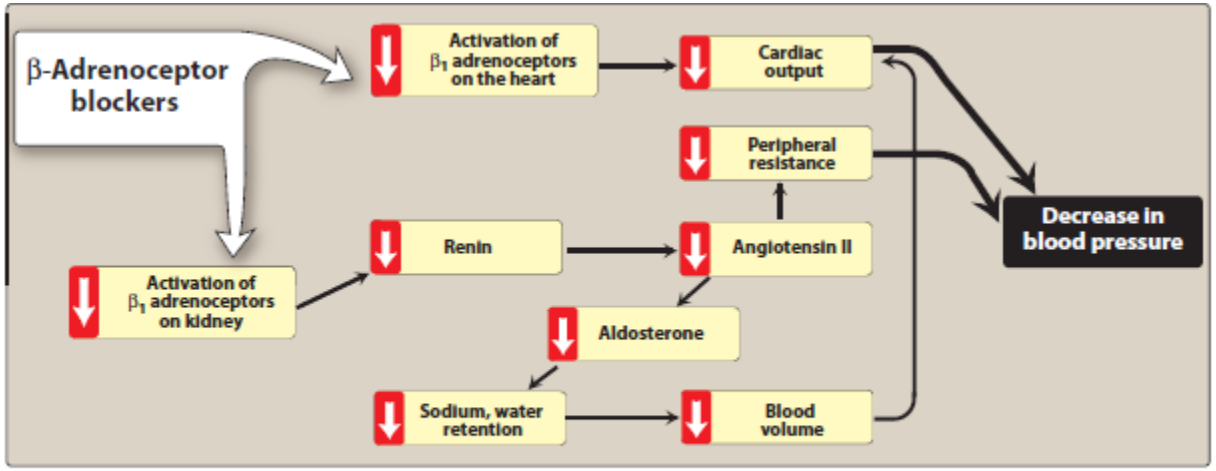
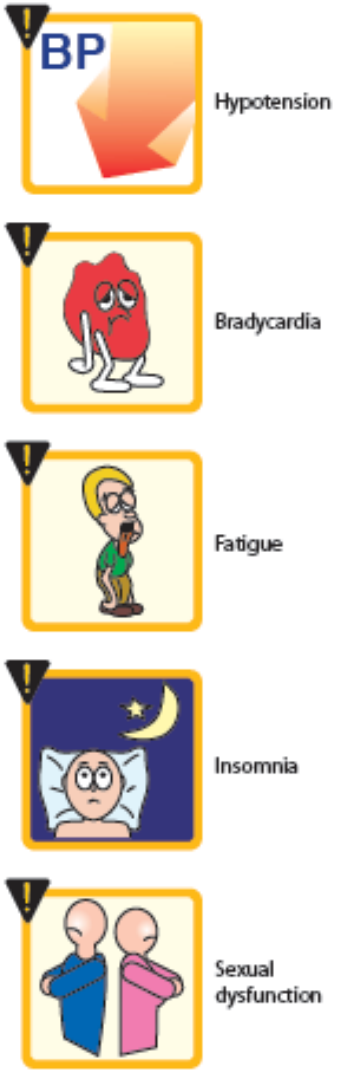


Figure 17.8
Actions of β-adrenoceptor–blocking agents.

β-Blockers

- Adverse effects
  - Bradycardia
  - Hypotension
  - CNS effects: fatigue, insomnia, lethargy
  - Decrease libido
  - Sudden withdrawal can cause myocardial infarction



ACE inhibitors

- Benazepril
- Captopril
- Enalapril
- Fosinopril
- Lisinopril
- Quinapril
- Ramipril

- Used when diuretics and β-blockers are ineffective or contraindicated

- Can be used in combination with a diuretic

ACE inhibitors

- MOA
  - Lower blood pressure by inhibiting ACE and reducing peripheral resistance
  - Inhibit the breakdown of bradykinin which increases production of the potent vasodilators nitric oxide and prostacyclin by blood vessels
  - Reduce secretion of aldosterone, decreasing sodium and water retention
  - Reduce cardiac preload and afterload, decreasing cardiac work

ACE inhibitors

- Used in hypertensive patients with CHF, and patients with chronic renal disease and hypertension and patients with high risk for CAD
- Slow the progression of diabetic nephropathy
- Benefits on renal function are due to decreased intraglomerular pressure because of efferent arteriolar vasodilation
- Used for patients with previous MI, prevent ventricular remodeling after MI

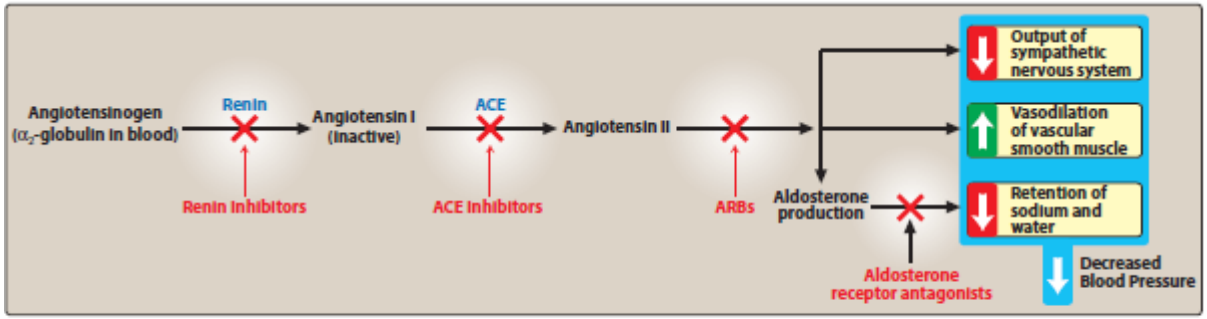


Figure 17.10
Effects of various drug classes on the renin–angiotensin–aldosterone system. Blue = drug target enzymes; red = drug class.

ACE inhibitors

- Adverse effects
  - Dry cough
    (reversible upon discontinuation of the drug)
  - Hyperkalemia
  - Rash
  - Hypotension
  - Angioedema

- Contraindicated in pregnancy

Angiotensin II receptor blockers (ARB)

- Losartan
- Valsartan
- Candesartan
- Eprosartan
- Irbesartan
- Olmesartan
- Telmisartan

ARBs

- Block angiotensin II binding to its AT1 receptor
- Mechanism: Lower BP by causing arteriolar and venous dilation and block aldosterone secretion decreasing Na and H_2O retention
- ARBs do not lower bradykinin levels
- Decrease nephrotoxicity of diabetes
- Adverse effects: similar to ACE inhibitors with less chance of dry cough and angioedema
- Contraindicated in pregnancy

Renin inhibitor

- Aliskiren
  - Lowers blood pressure by inhibiting renin
  - As effective in lowering blood pressure as ACE inhibitors and ARBs
  - Can be combined with other antihypertensive drugs
  - Metabolized by CYP 3A4, subject to drug interactions
  - Adverse effects
    - Diarrhea
    - Dry cough and angioedema

    (less common than with ACE inhibitors)
    - Hyperkalemia

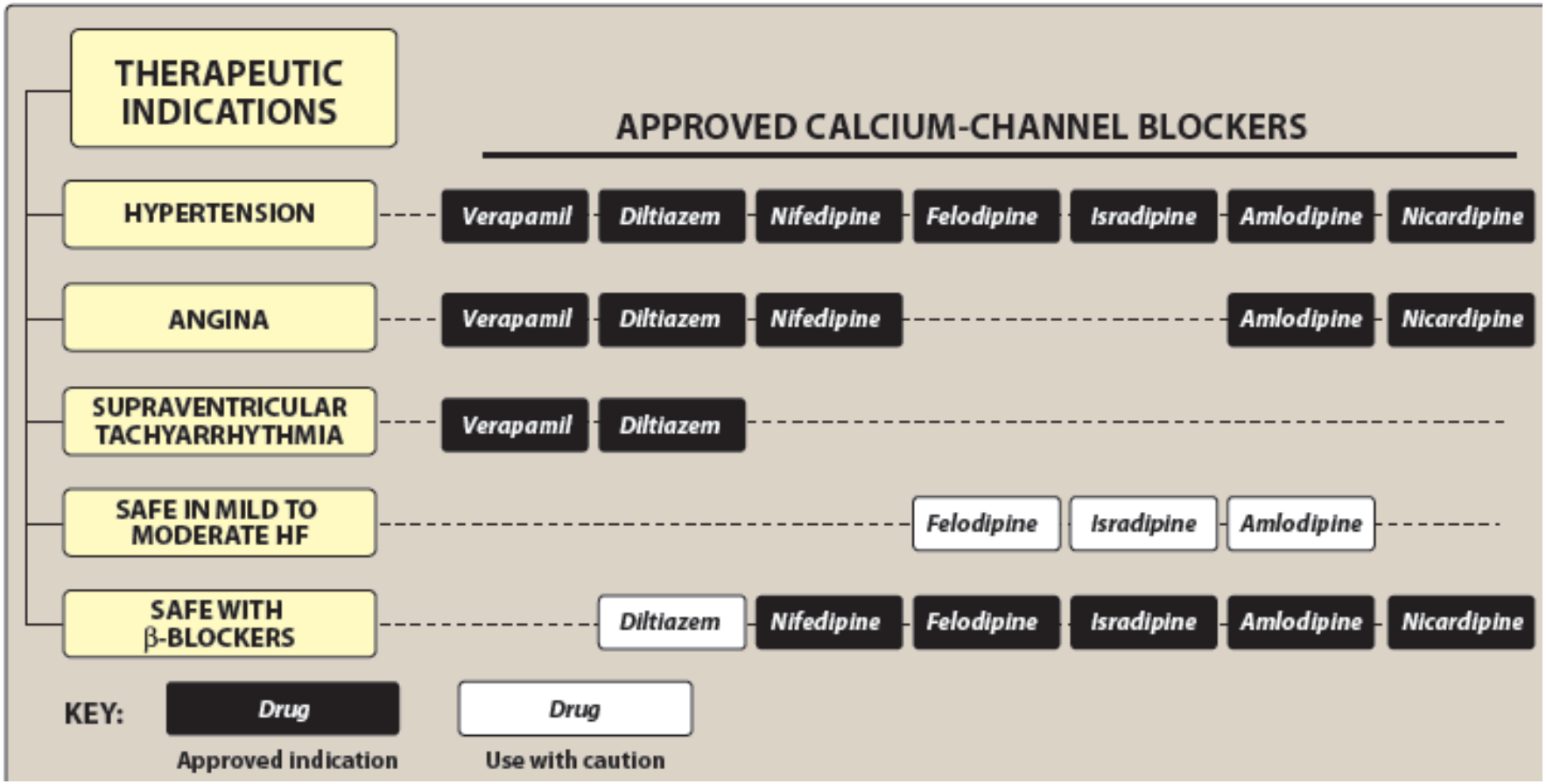
Calcium channel blockers

3 Classes

- Diphenylalkylamines
  - Verapamil
- Benzothiazepines
  - Diltiazem
- Dihydropyridines
  - First generation
    - Nifedipine
  - Second generation
    - Amlodipine
    - Felodipine
    - Isradipine
    - Nicardipine
    - Nisoldipine

Calcium channel blockers

- MOA: Bind to calcium channels in the heart and smooth muscle of coronary and peripheral arteriolar vasculature blocking calcium entry to cells, causing smooth muscles to relax and dilating the arterioles and decreasing blood pressure
- Used when preferred first line agents are contraindicated or ineffective like in patients with asthma
- Effective in hypertension with angina or diabetes
- Dihydropyridines have a greater affinity for vascular calcium channels than cardiac calcium channels and show little interaction with other cardiovascular drugs like digoxin or warfarin


THERAPEUTIC INDICATIONS
APPROVED CALCIUM-CHANNEL BLOCKERS
HYPERTENSION
Verapamil
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
ANGINA
Verapamil
Diltiazem
Nifedipine
Amlodipine
Nicardipine
SUPRAVENTRICULAR TACHYARRHYTHMIA
Verapamil
Diltiazem
SAFE IN MILD TO MODERATE HF
Felodipine
Isradipine
Amlodipine
SAFE WITH β-BLOCKERS
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
KEY:
Drug
Approved indication
Drug
Use with caution

Calcium channel blockers

- Adverse effects
  - Hypotension
  - Constipation (verapamil)
  - Fatigue, headache (dihydropyridines)
  - Flushing
  - Verapamil should be avoided in patients with chronic heart failure or atrioventricular block due to its negative inotropic (force of contraction) and dromotropic (velocity of conduction) effect
  - Verapamil can cause atrioventricular block
  - Diltiazem causes less negative inotropic effect and a better side effect profile than verapamil
  - Nifedipine causes gingival enlargement

α-Blockers

- Prazosin
- Doxazosin
- Terazosin

- Block α_1 receptors decreasing peripheral resistance and blood pressure by relaxing the arterial and venous smooth muscle
- Cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate
- Adverse effects
  - First dose syncope
  - Short term reflex tachycardia (can be controlled with the use of a β-blocker like propranolol)

α-/β- Blockers

- Labetalol
- Carvedilol

- Block α1, β1 and β2 receptors

- Carvedilol is mainly used for heart failure

α_2-Agonists (Centrally acting adrenergic drugs)

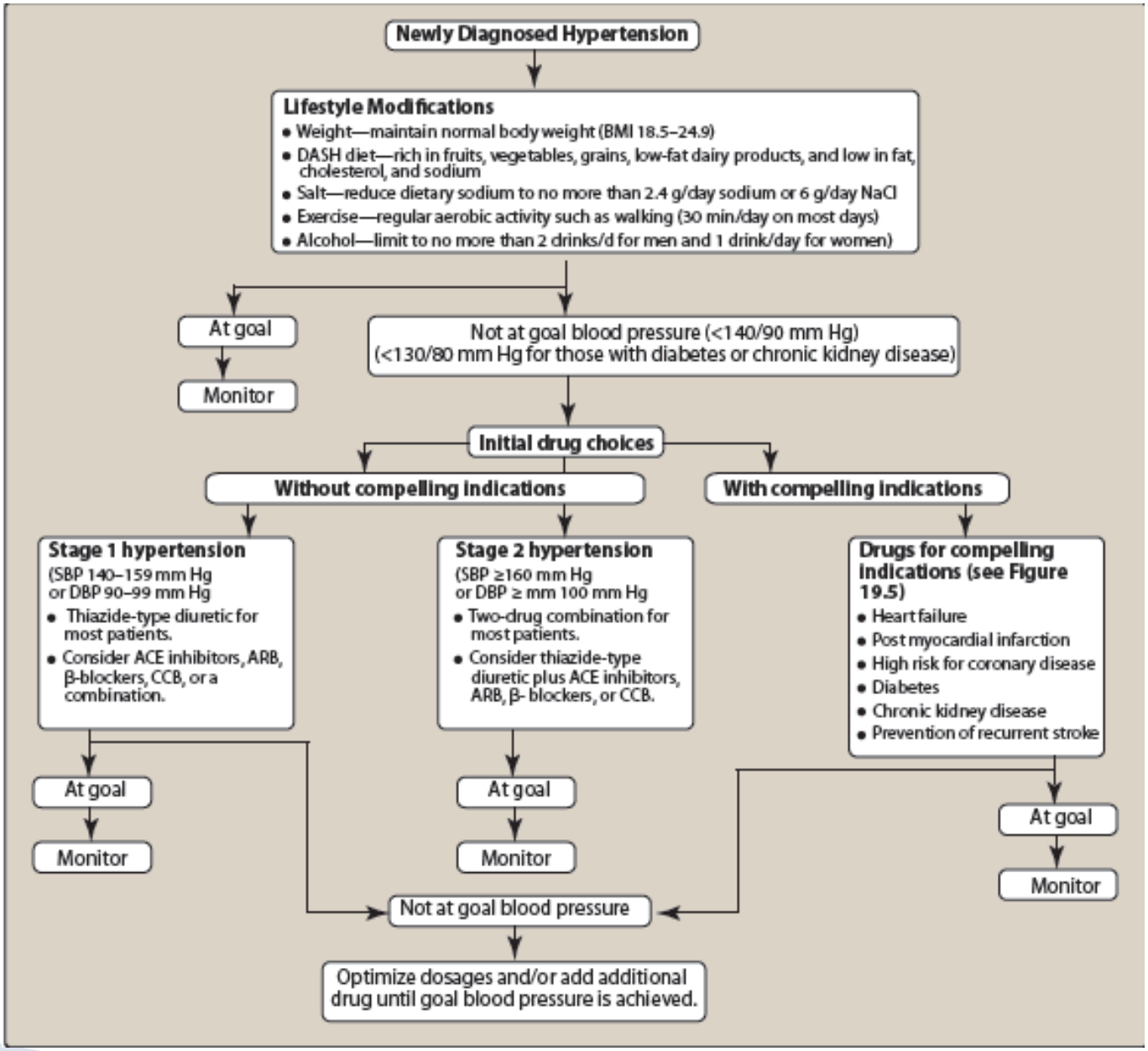
- Decrease the sympathetic nervous system activity and epinephrine release
- Decrease total peripheral resistance and blood pressure
  - Clonidine

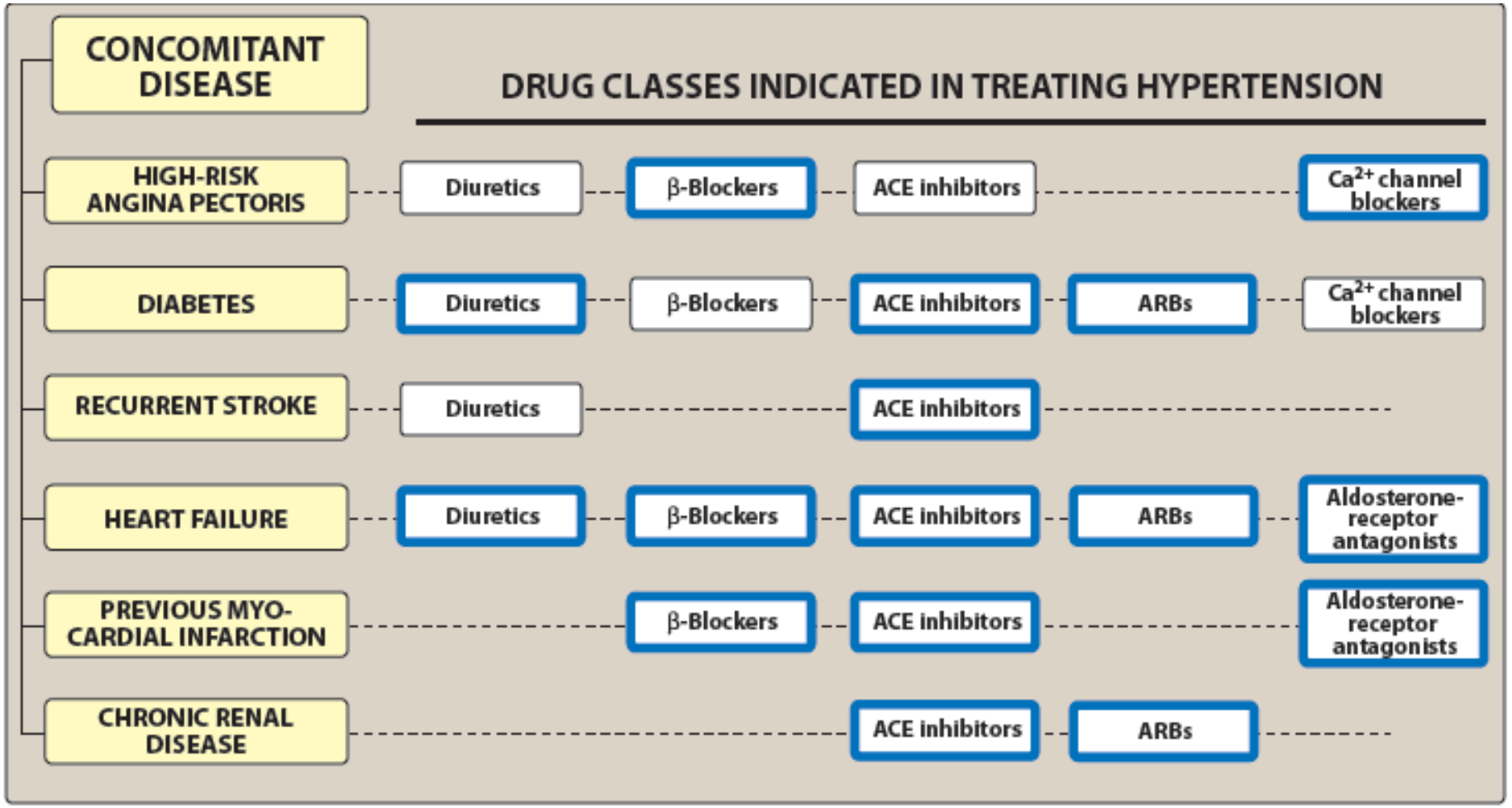
  (Rebound hypertension occurs if the drug is abruptly withdrawn)

  - Methyldopa (can be used in pregnant patients)

Vasodilators

- Hydralazine
- Minoxidil
- MOA: Activate potassium channels increasing potassium efflux and inducing hyperpolarization of smooth muscle membrane leading to inhibition of calcium influx and arteriolar smooth muscle relaxation and vasodilation, decreasing peripheral resistance
- Cause reflex elevation in heart rate and cardiac output
- Used for moderate to sever hypertension
- Hydralazine can be used in pregnant hypertensive patients
- Minoxidil is used for severe to malignant hypertension
- Minoxidil causes hypertrichosis (the growth of body hair) and is used topically to treat male baldness


Newly Diagnosed Hypertension
Lifestyle Modifications
• Weight—maintain normal body weight (BMI 18.5–24.9)
• DASH diet—rich in fruits, vegetables, grains, low-fat dairy products, and low in fat, cholesterol, and sodium
• Salt—reduce dietary sodium to no more than 2.4 g/day sodium or 6 g/day NaCl
• Exercise—regular aerobic activity such as walking (30 min/day on most days)
• Alcohol—limit to no more than 2 drinks/d for men and 1 drink/day for women)
At goal
Monitor
Not at goal blood pressure (<140/90 mm Hg)
(<130/80 mm Hg for those with diabetes or chronic kidney disease)
Initial drug choices
Without compelling indications
With compelling indications
Stage 1 hypertension
(SBP 140–159 mm Hg
or DBP 90–99 mm Hg
• Thiazide-type diuretic for most patients.
• Consider ACE inhibitors, ARB, β-blockers, CCB, or a combination.
Stage 2 hypertension
(SBP ≥160 mm Hg
or DBP ≥ mm 100 mm Hg
• Two-drug combination for most patients.
• Consider thiazide-type diuretic plus ACE inhibitors, ARB, β- blockers, or CCB.
Drugs for compelling indications (see Figure 19.5)
• Heart failure
• Post myocardial infarction
• High risk for coronary disease
• Diabetes
• Chronic kidney disease
• Prevention of recurrent stroke
At goal
Monitor
At goal
Monitor
At goal
Monitor
Not at goal blood pressure
Optimize dosages and/or add additional drug until goal blood pressure is achieved.


CONCOMITANT DISEASE
DRUG CLASSES INDICATED IN TREATING HYPERTENSION
HIGH-RISK ANGINA PECTORIS
Diuretics
β-Blockers
ACE inhibitors
Ca2+ channel blockers
DIABETES
Diuretics
β-Blockers
ACE inhibitors
ARBs
Ca2+ channel blockers
RECURRENT STROKE
Diuretics
ACE inhibitors
HEART FAILURE
Diuretics
β-Blockers
ACE inhibitors
ARBs
Aldosterone-receptor antagonists
PREVIOUS MYO-CARDIAL INFARCTION
β-Blockers
ACE inhibitors
Aldosterone-receptor antagonists
CHRONIC RENAL DISEASE
ACE inhibitors
ARBs

β-BLOCKER-DIURETIC COMBINATIONS

Atenolol + chlorthalidone TENORETIC

Bisoprolol + hydrochlorothiazide ZIAC

Metoprolol + hydrochlorothiazide LOPRESSOR HCT

Nadolol + bendroflumethiazide CORZIDE

Propranolol + hydrochlorothiazide INDERIDE

ACEI-DIURETIC COMBINATIONS

Benazepril + hydrochlorothiazide LOTENSIN HCT

Captopril + hydrochlorothiazide CAPOZIDE

Enalapril + hydrochlorothiazide VASERETIC

Fosinopril + hydrochlorothiazide MONOPRIL HCT

Moexipril + hydrochlorothiazide UNIRETIC

Lisinopril + hydrochlorothiazide PRINZIDE, ZESTORETIC

Quinapril + hydrochlorothiazide ACCURETIC, QUINARETIC

ARB-DIURETIC COMBINATIONS

Candesartan + hydrochlorothiazide ATACAND HCT

Eprosartan + hydrochlorothiazide TEVETEN HCT

Irbesartan + hydrochlorothiazide AVALIDE

Losartan + hydrochlorothiazide HYZAAR HCT

Olmesartan + hydrochlorothiazide BENICAR HCT

Telmisartan + hydrochlorothiazide MICARDIS HCT

Valsartan + hydrochlorothiazide DIOVAN HCT

Resistant hypertension

- High BP that does not respond to treatment
- BP that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic
- Causes of resistant hypertension:
  - Poor compliance
  - Excessive ethanol intake
  - Concomitant conditions (diabetes, obesity, sleep apnea, high salt intake)
  - Use of sympathomimetics or antidepressants
  - Insufficient dose, drugs
  - Use of drugs with similar mechanisms of action

Hypertensive emergency

- BP> 210/150 in a healthy individual

- IV administration of antihypertensive drugs

- Example:
  - Labetalol (α-/β- blocker)
  - Sodium nitroprusside (vasodilator)
  - Nicardipine (Ca channel blocker)

Diuretics

Diuretics

- Drugs inducing a state of increased urine flow
- Act by inhibition of renal ion transporters that decrease the reabsorption of Na^+ at different sites of the nephron
- This causes Na^+ and other ions to enter the urine along with water in a greater amount than normal

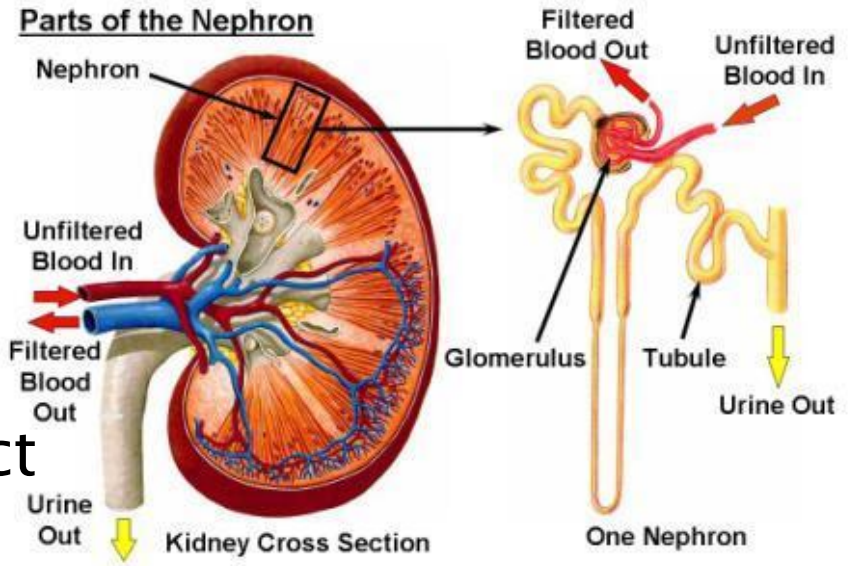
Diuretics

- Used for
  - Edema
  - Heart failure
  - Hypertension

Normal regulation of fluid and electrolytes by the kidney

Five functional zones

1. PCT
2. The descending LH
3. The ascending LH
4. DCT
5. The collecting tubule and duct

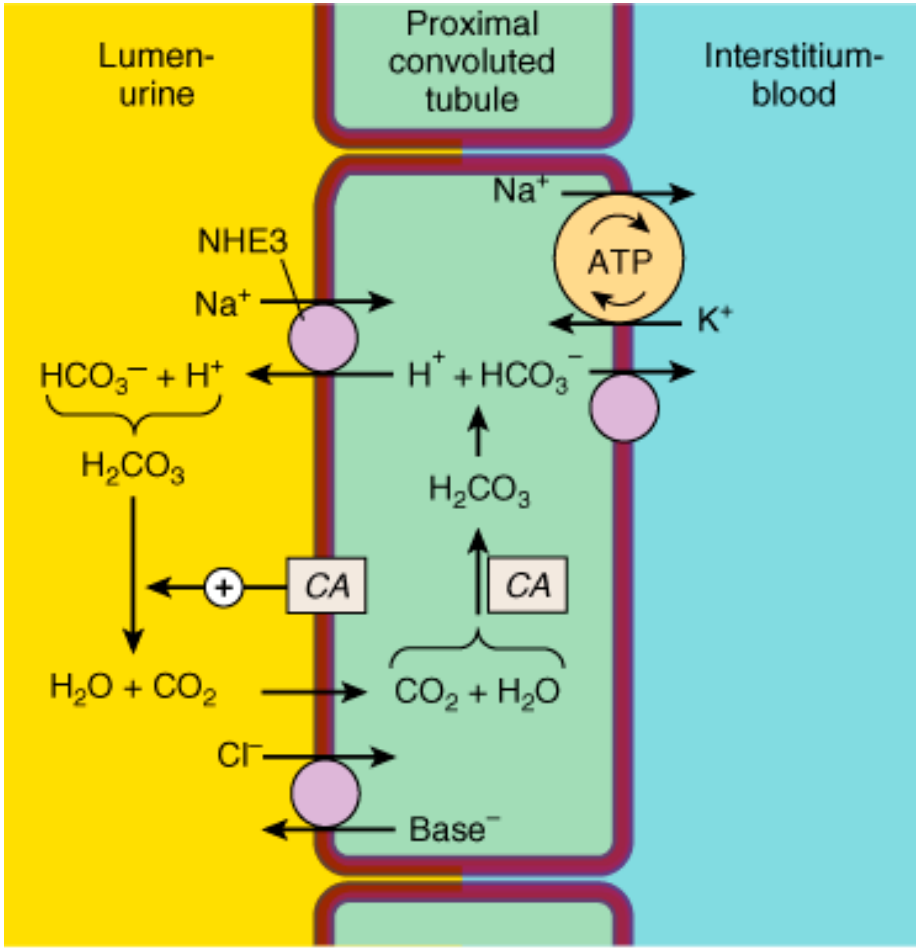


Proximal convoluted tubule

- Located in the cortex of the kidney
- Almost all glucose, bicarbonate, amino acids and other metabolites are reabsorbed
- About two thirds of Na is reabsorbed
- Cl^- enters the lumen in exchange of an anion such as oxalate
- Water moves passively from the lumen to the blood to maintain osmolar equality
- Maintain normal osmolarity through sodium and water reabsorption
- The reabsorbed sodium is pumped to the interstitium by Na/K ATPase maintaining normal levels of and Na

Proximal convoluted tubule

- Carbonic anhydrase modulates the reabsorption of bicarbonate
- Site of the acid and base secretory systems
  - The organic acid secretory system secretes a variety of organic acids: uric acid, some antibiotics and diuretics
  - The organic secretory system is saturable and the diuretic drugs in the bloodstream compete for transfer with endogenous organic acids
  - The organic base secretory system is responsible for the secretion of creatinine and choline



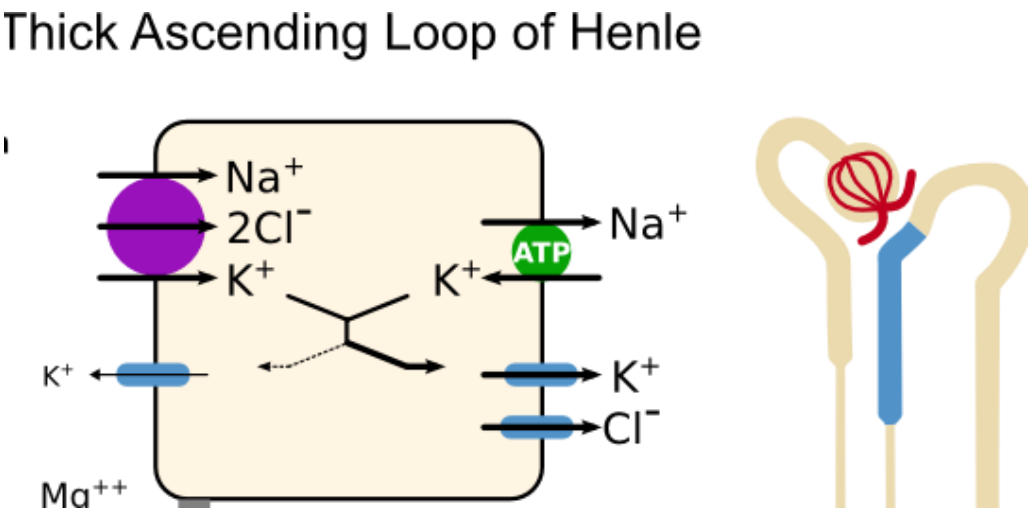
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharm*

Descending loop of Henle

- Passes through the kidney medulla
- The osmolarity of the urine increase due to water reabsorption mechanisms
- The result is tubular fluid with a threefold increase in salt concentration

Ascending loop of Henle

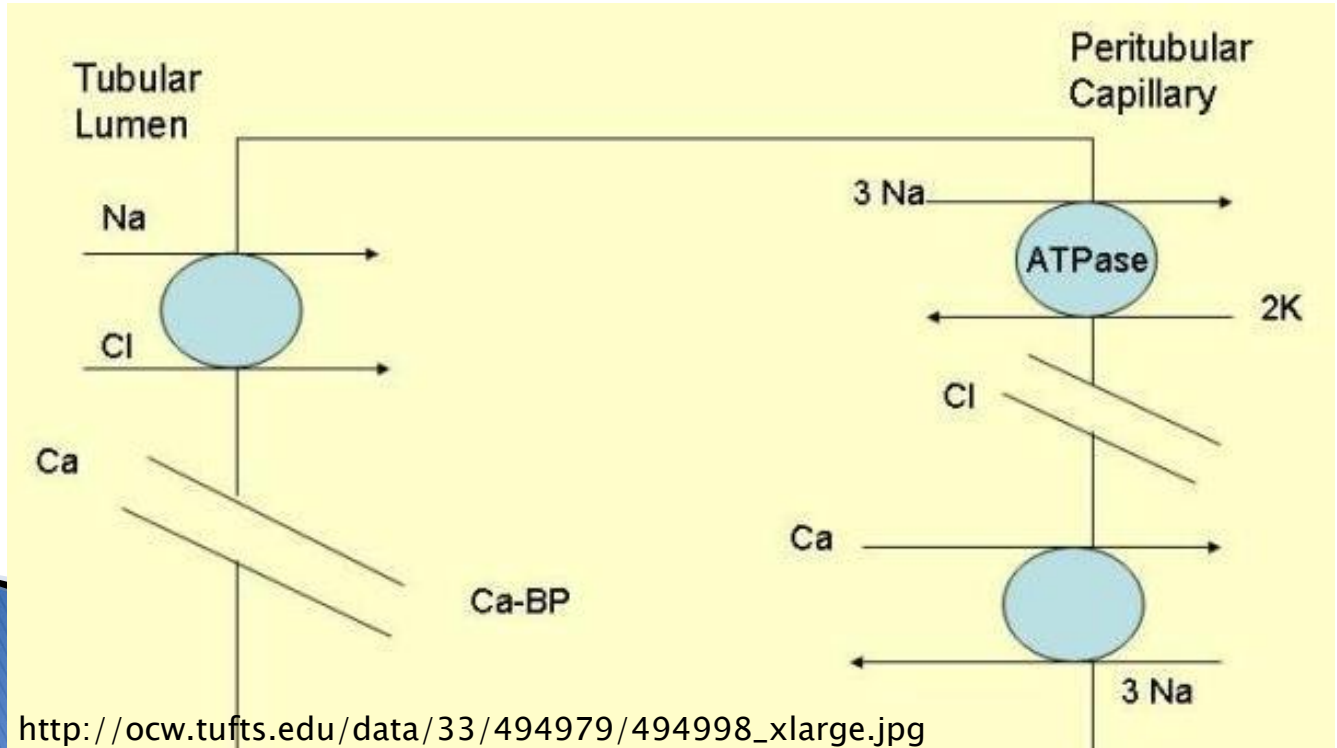
- A major site of salt reabsorption
- Drugs affecting this site such as loop diuretics are the most efficacious of all diuretics
- Active reabsorption of Na^+, K^+ and Cl^- occurs by a $Na^+/K^+/2Cl^-$ cotransporter
- Mg^{2+} and Ca^{2+} enter the interstitial fluid



syncytiabeta.org/syncytiafigures/Thick_Ascending_Loop_of_Henle_Transport

Distal convoluted tubule

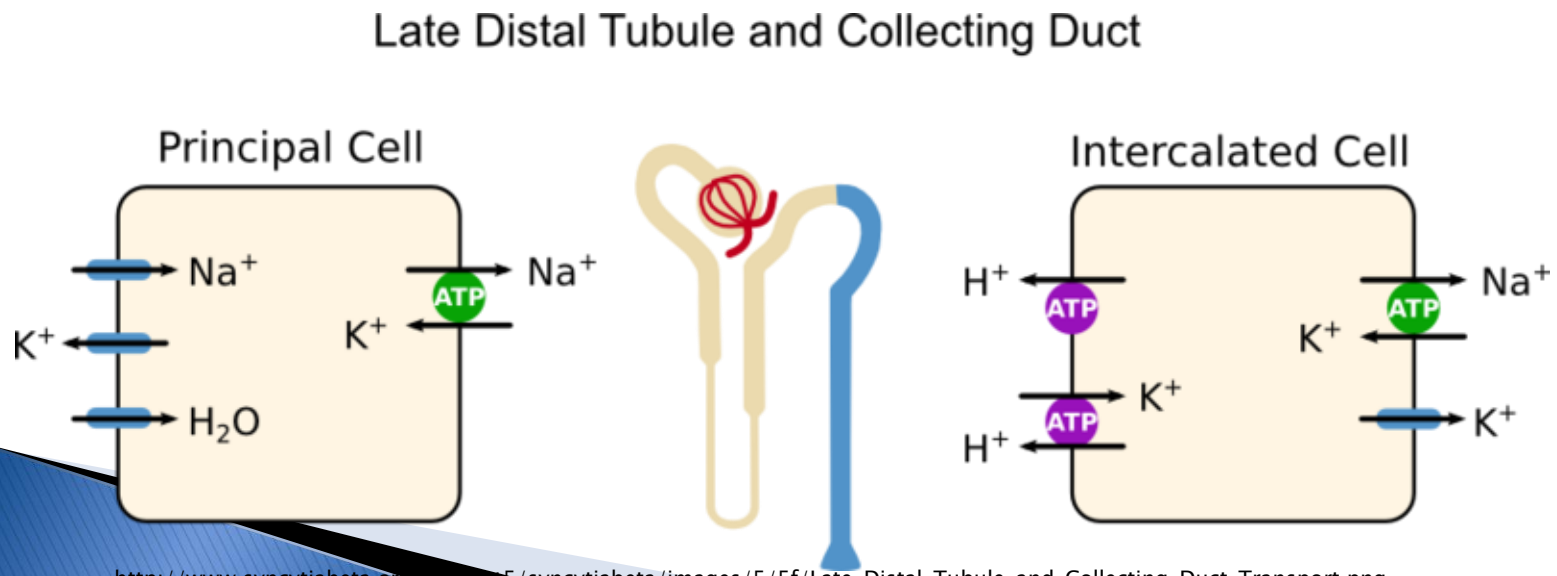
- NaCl is reabsorbed via the Na^+/Cl^- transporter
- Ca^{2+} reabsorption occurs through a channel and then Ca^{2+} is transported by a Na^+/Ca^{2+} exchanger into the interstitial fluid



http://ocw.tufts.edu/data/33/494979/494998_xlarge.jpg

Collecting tubule and duct

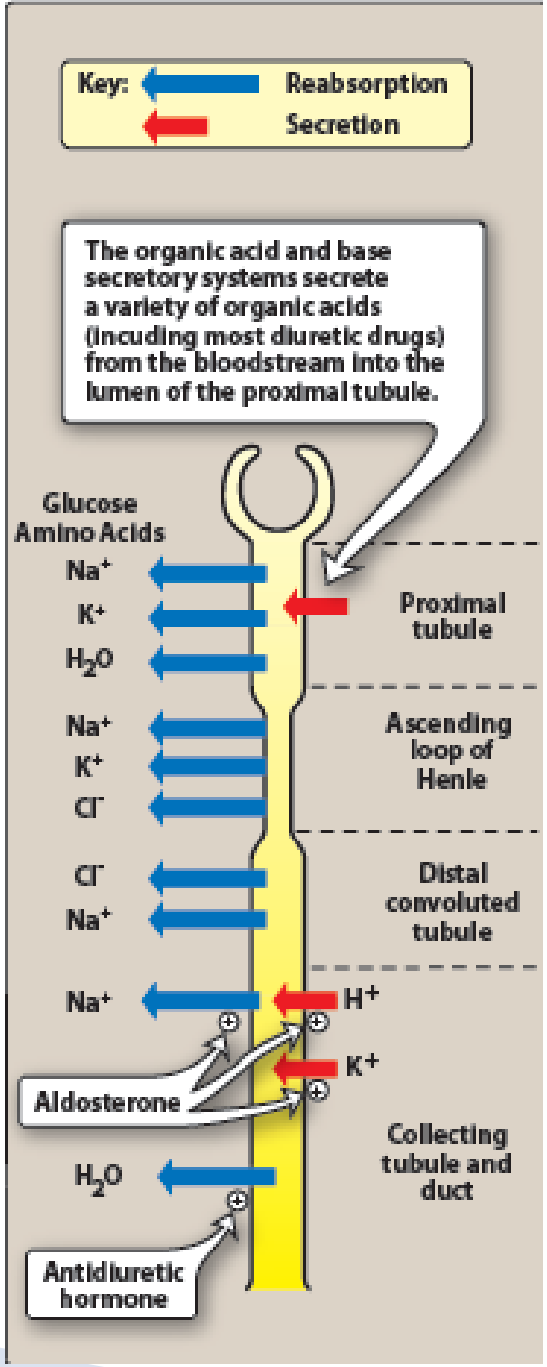
- Principal cells are responsible for Na^+, K^+ and water transport
- Sodium reabsorption relies on Na^+/K^+ ATPase to be transported into blood
- Intercalated cells affect H^+ secretion

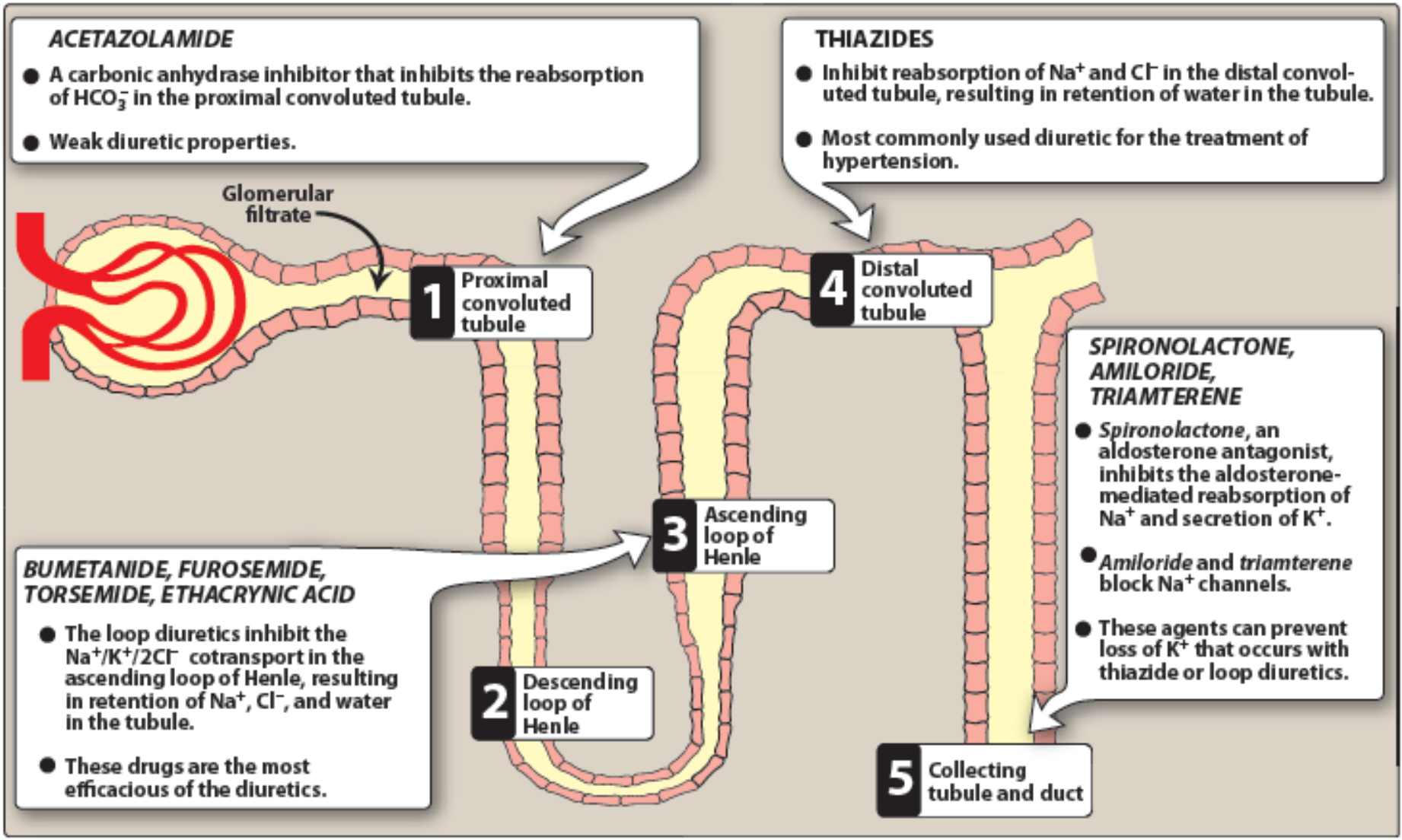


http://www.syncytiabeta.org/[illegible]5/syncytiabeta/images/5/5f/Late_Distal_Tubule_and_Collecting_Duct_Transport.png

Collecting tubule and duct

- Aldosterone receptors in the principle cells influence Na^+ reabsorption and K^+ secretion
- Aldosterone increases the synthesis of Na^+ channels and of Na^+/K^+ ATPase which when combined increase sodium reabsorption
- Antidiuretic hormone (ADH) receptors promote the reabsorption of water from the collecting tubules and ducts, an action mediated by cAMP


Key:
Reabsorption
Secretion
The organic acid and base secretory systems secrete a variety of organic acids (including most diuretic drugs) from the bloodstream into the lumen of the proximal tubule.
Glucose
Amino Acids
Na+
K+
H2O
Proximal tubule
Na+
K+
Cl-
Ascending loop of Henle
Cl-
Na+
Distal convoluted tubule
Na+
H+
K+
Aldosterone
Collecting tubule and duct
H2O
Antidiuretic hormone


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

Kidney function in disease

- Edematous states:
  - Edema of tissues because of expansion of extravascular fluid compartment caused by water retention and increase in blood volume due to abnormally higher amounts of sodium reabsorbed by the kidney tubules
  - Examples
    - Heart failure
    - Hepatic ascites
    - Nephrotic syndrome
    - Premenstrual edema

- Heart failure:
  - The decreased ability of the failing heart to sustain adequate cardiac output caused the kidney to respond as if there is a decrease in blood volume increasing sodium and water retention, and venous return
  - The failing heart can not increase cardiac output and edema occurs
  - Loop diuretics are common for treatment of heart failure

- Hepatic ascites
  - Accumulation of fluids in abdominal cavity,
  - A common complication of liver cirrhosis
  - Caused by
    - Increased portal BP and impaired ability of the liver to synthesize plasma protein lead to decreased osmolarity of the blood and collection of fluids in the abdominal cavity
    - Secondary hyperaldosteronism due to decreased ability of the liver to inactivate aldosterone, spironolactone is effective for treatment of this condition

- Nephrotic syndrome: glomerular membranes allow plasma proteins to enter the filtrate which reduces osmotic pressure resulting in edema

- Premenstrual edema: edema associated with menstruation due to imbalance of hormones such as estrogen excess which facilitates the loss of fluid into the extracellular space

Kidney function in disease

- Nonedematous states
  - Hypertension:
    - Thiazide diuretics are widely used for treatment of hypertension
  - Hypercalcemia
    - Loop diuretics are used as they promote calcium excretion
  - Diabetes insipidus
    - Polyuria and polydipsia
    - Problems in ADH
    - Patients respond to thiazide diuretics, as hypovolemia causes a drop in the GFR and promotes reabsorption of Na^+ and water, reducing the volume of urine and urine flow

Thiazide and thiazide related agents

- Most commonly used diuretics
- Affect the distal tubule
- Sulfonamide derivatives
- Called ceiling diuretics because increasing the dose above normal does not increase diuresis

Thiazide and thiazide related agents

- Thiazides
  - Chlorothiazide
  - Hydrochlorothiazide

- Thiazide like diuretics (contain sulfonamide and have similar MOA as thiazides)
  - Chlorthalidone
  - Metolazone
  - Indapamide

Thiazide diuretics

- MOA: Decrease Na^+ reabsorption by inhibiting Na^+/Cl^- co-transporter
- Effects
  - Increase excretion of Na^+ and Cl^-
  - Loss of K^+ : Require monitoring
  - Loss of Mg^{2+}: Mechanism is not known, require supplementation
  - Decrease urinary calcium excretion: Thiazide diuretics promote Ca^{2+} reabsorption
  - Reduce peripheral vascular resistance

Thiazide diuretics

- Therapeutic uses
  - Hypertension
    - Reduce systolic and diastolic blood pressure
    - Reduce peripheral resistance
  - Heart failure
  - Hypercalciuria: thiazides inhibit urinary Ca excretion, they are beneficial in patients with calcium oxalate stones in the urinary tract
  - Diabetes insipidus
- Most thiazide diuretics take 1–3 weeks to produce a stable reduction in blood pressure
- All thiazide diuretics are excreted by the organic secretory system of the kidney
- Indapamide is excreted by the GIT, and so is less likely to accumulate in patients with renal failure

Thiazide diuretics

- Adverse effects
  - Hypokalemia (K^+ supplements can be added)
  - Volume depletion, can cause orthostatic hypotension
  - Hyponatremia
  - Hyperuricemia
  - Hypercalcemia
  - Hyperglycemia
  - Hyperlipidemia
  - Hypersensitivity (in people hypersensitive to sulfa drugs)

Loop diuretics

- Furosemide
- Torsemide
- Bumetanide
- Ethacrynic acid
  - Shows greater side effects than other loop diuretics

- Major site of action is the ascending limb of the loop of Henle

Loop diuretics

- MOA: inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the loop of Henle decreasing their reabsorption
- High ceiling diuretics
- Loop diuretics are the most efficacious of all diuretics because 25-30% of NaCl is reabsorbed in the ascending limb of LH
- Act well even among patients with poor renal functions or unresponsive to thiazides or other diuretics

Loop diuretics

- Increase PG synthesis which has a role in their diuretic action, NSAIDs interfere with PG synthesis and can reduce the diuretic action of loop diuretics
- Increase Ca^{2+} excretion
- Decrease vascular resistance and increase renal blood flow

Loop diuretics

- Therapeutic Uses
  - Drug of choice for reducing pulmonary edema in HF
  - Useful in emergency situations like acute pulmonary edema
  - Useful for treatment of hypercalcemia and hyperkalemia
  - Treatment of hypertension

Loop diuretics

- Adverse effects
  - Ototoxicity (damage to the ear). Hearing can be affected.
    - (Particularly with ethacrynic acid)
  - Acute hypovolemia, severe and rapid reduction in blood volume with the possibility of hypotension, shock and cardiac arrhythmias
  - Hyperuricemia: furosemide and ethacrynic acid compete with uric acid for renal and biliary secretory system blocking its secretion.
  - Hypokalemia
  - Hypomagnesemia

Potassium sparing diuretics

- Act in the collecting tubules to inhibit Na^+ reabsorption and K^+ excretion
- Their major use is treatment of hypertension, often in combination with a thiazide
- Less efficacious in diuresis
- Used in combination with other diuretics
- Potassium levels should be monitored

Potassium sparing diuretics

- Aldosterone receptor antagonitsts
- Spironolactone
- Eplerenone
  - newer, similar action but has less endocrine effects
- MOA of spironolactone:
  - Aldosterone receptor antagonist.
  - The spironolactone-receptor complex is inactive.
  - It inhibits the translocation of the receptor into the nucleus, so it does not bind to DNA and fail to produce the mediator proteins that stimulate Na/K exchange.
  - Na reabsorption is inhibited and therefore K and H secretion are also inhibited

Spironolactone

- Therapeutic uses:
  - Diuretic
  - Secondary hyperaldosteronism
  - Heart failure: Spironolactone prevents the remodeling that occurs as compensation for the progressive failure of the heart

- Adverse effects:
  - Nausea
  - Gastric upsets, can cause peptic ulcer
  - Gynecomastia in male patients
  - Menstrual irregularities in female patients
  - Hyperkalemia

Potassium sparing diuretics

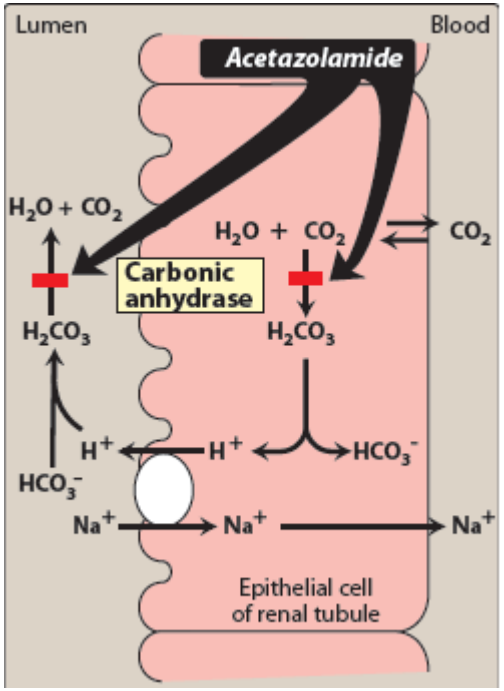
Amiloride

Triamterene

- Mechanism: Block Na^+ transport channels resulting in a decrease in Na^+/K^+ exchange
- Not very efficacious diuretics, used in combination with other diuretics for their K^+ sparing properties
- Example: Amiloride + hydrochlorothiazide
- Adverse effects
  - Hyperkalemia
  - Hyperuricemia

Carbonic anhydrase inhibitor

- Acetazolamide
- Much less efficacious than thiazide or loop diuretics
- MOA: inhibit carbonic anhydrase enzyme in the proximal tubular epithelium. This decreases the ability to exchange Na^+ for H^+ due to decreased H_2CO_3 production by the enzyme, causing mild diuresis



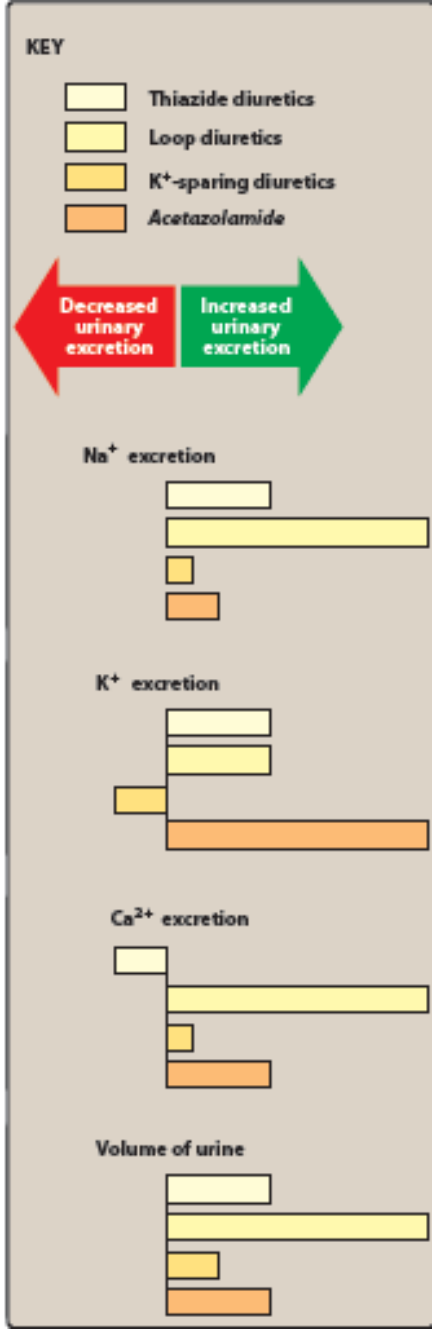
Carbonic anhydrase inhibitor

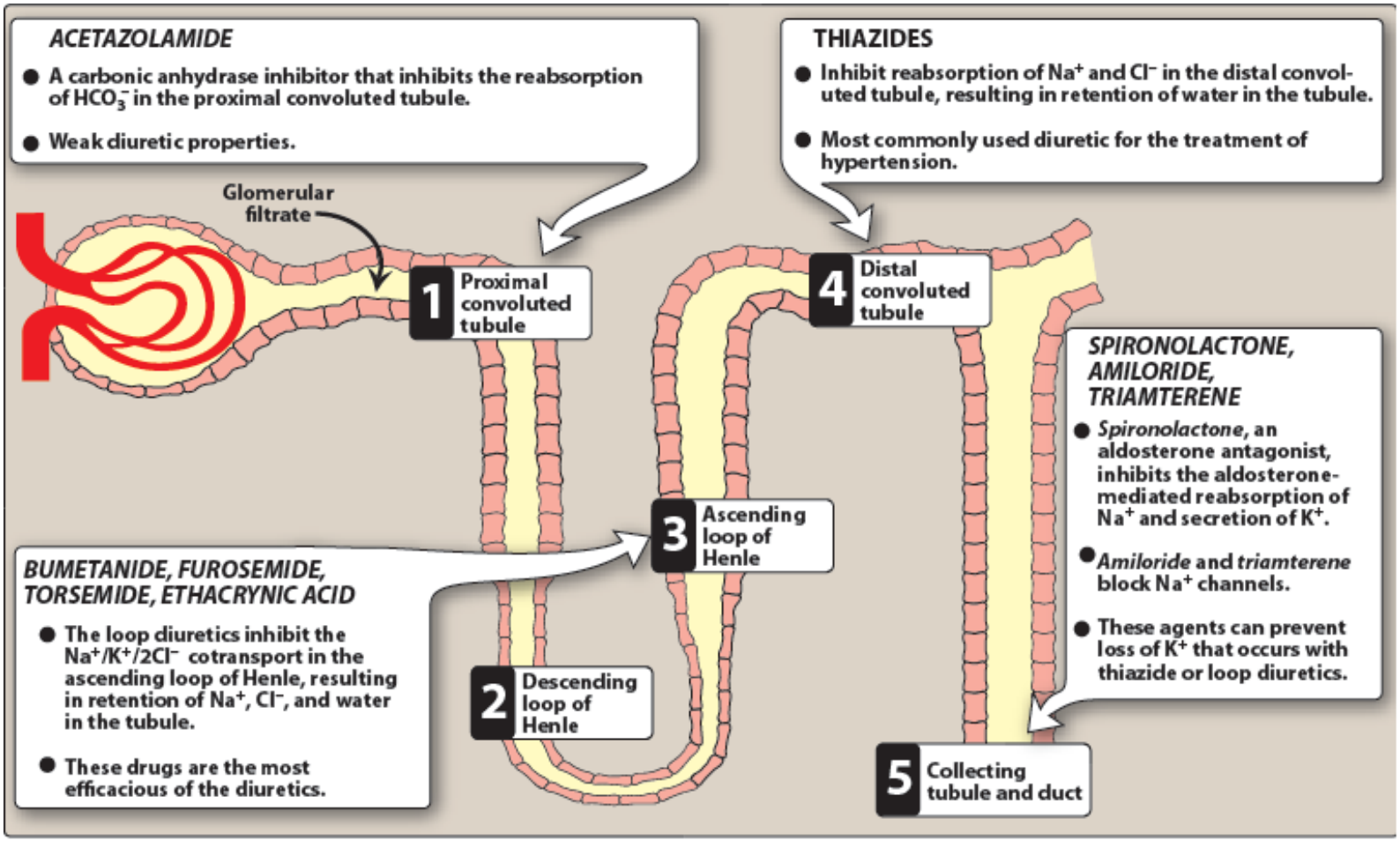
- Therapeutic uses
  - Acetazolamide is used for treatment of glaucoma, it decreases IOP by reducing the production of aqueous humor by blocking CA in the ciliary body of the eye
  - Acetazolamide is used prophylactically for mountain sickness, it prevents weakness, breathlessness, dizziness, nausea and cerebral and pulmonary edema
- Side effects:
  - Potassium depletion
  - Renal stone formation

Osmotic diuretics

Mannitol

- Osmotic diuretics are filtered through the glomerulus and can carry water with them into the tubular fluid causing diuresis
- Used in patients with increased intracranial pressure or acute renal failure due to shock, drug toxicity and trauma.
- Maintaining urine flow preserves long term kidney function and may save the patient from dialysis
- Mannitol is given IV
- Adverse effects
  - Dehydration


KEY
Thiazide diuretics
Loop diuretics
K+-sparing diuretics
Acetazolamide
Decreased urinary excretion
Increased urinary excretion
Na+ excretion
K+ excretion
Ca2+ excretion
Volume of urine


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
4 Distal convoluted tubule
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.
3 Ascending loop of Henle
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
2 Descending loop of Henle
5 Collecting tubule and duct