PHARMACOLOGY TEAM 432

Diuretics

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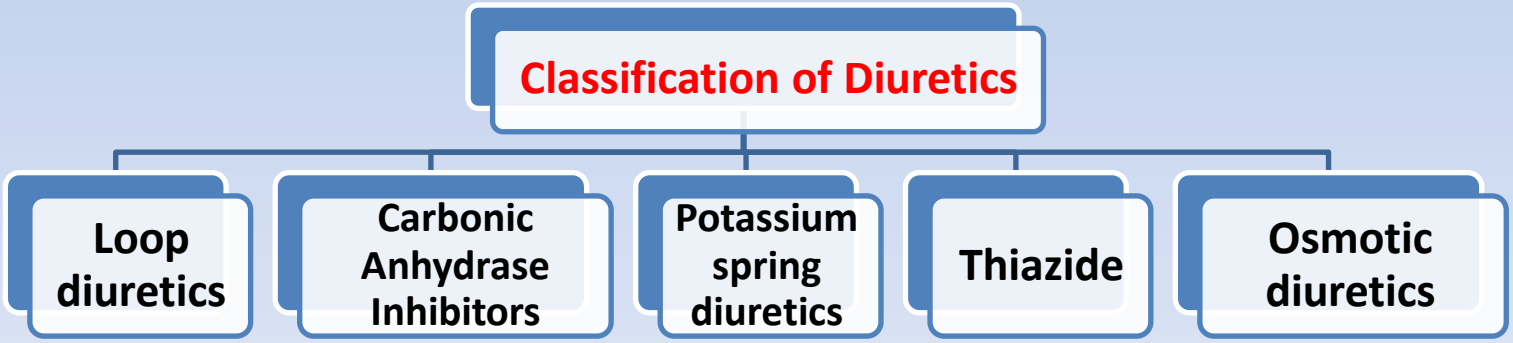
RED: IMPORTANT
PURPLE :EXTRA NOTES

MIND MAP :

Depending upon the site where the drug is acting we have 5 classes of diuretics



Nephron Segment	Na^+ Transporter	Diuretics
Proximal convoluted tubules	Na+/H+ transporter Carbonic anhydrase	Carbonic anhydrase inhibitors
Ascending Loop of Henle	Na+/K+/Cl- cotransporter	Loop diuretics
Distal convoluted tubules	Na+/Cl- transporter	Thiazide diuretics
Cortical Collecting Tubules	Na+ channel Aldosterone	K-sparing diuretics

DIURETICS :

* Most diuretics act by interfering with the normal sodium reabsorption by the kidney.

* Are drugs that increase renal excretion of sodium and water resulting in increase in urine volume.

***Aldosterone** and **ADH** Normally work in **Cortical collecting tubule** to reabsorb **NA** OR To reabsorb **Water** (H_2O) respectably.

***We can Increase Urine Output (Decrease Reabsorption) either By :**

* The Heart has a limited action
* In case of Heart Diseases like Heart Failure (It can be Fatal)

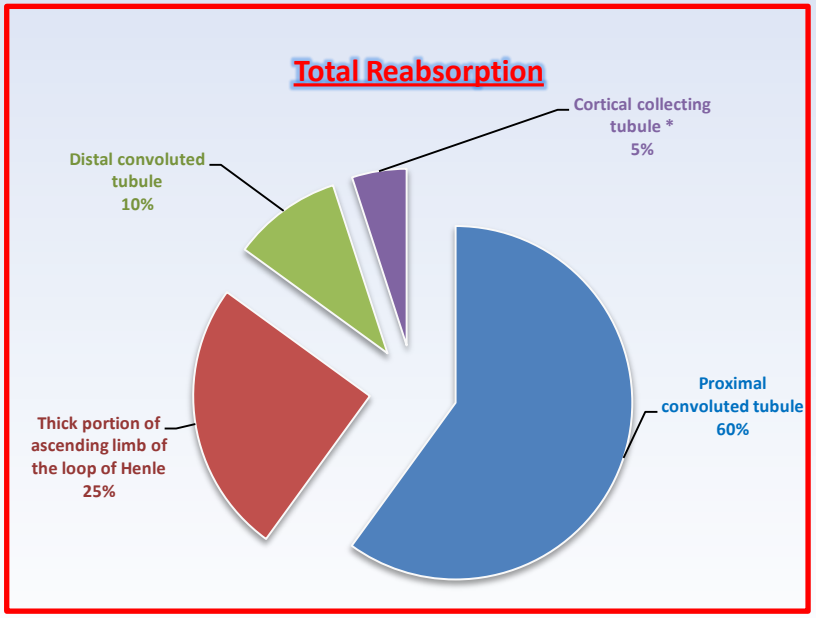
I. Increase Glomerular filtration (But We don't use it) **WHY**???
II. Decrease tubular Reabsorption (And this what Diuretics DO)

Mechanism of action of diuretics

Most diuretics act by **inhibiting carriers (transporters)** That are required for sodium tubular reabsorption from filtrate back into blood.

Purpose of Using Diuretics:

1)- To maintain urine volume (e.g.: renal failure)
2)- To mobilize edema fluid (e.g.: heart failure, liver failure; nephrotic syndrome)
3)- To control high blood pressure.



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1 Loop Diuretics:

The most efficacious diuretics. Because:
*It acts on the segment where the most (25%- 30%) Nacl reabsorbed opposite to thiazide which work on DCT just 5%
*It has a limited compensatory mechanism.

Furosemide, Torsemide, Bumetanide, Ethcrynic acid

MOA

Inhibits Na+/K+/2 Cl- Co-transporter (NKCC2) in the luminal membrane of the thick ascending loop of Henle (TAL).
Inhibit Ca++ and Mg ++ paracellular reabsorption.

1-The driving force is: Difference in potential
2- By inhibiting the co-transporter > Back diffusion of K is inhibited > Potential is inhibited.

Also, they have potent pulmonary vasodilating effects (via Prostaglandins).

Pharmacokinetics

Given orally or I. V.
Has fast onset of action. (Suitable for emergency)
Have short duration of action.
Bumetanide is the most potent.
Excreted by active tubular secretion of weak acids into urine. (Competes with uric acid for renal secretory system)
Interfere with uric acid secretion.

Both Loop and Thiazide diuretics are acidic in nature (their structure is related to Sulfonamide) so, they are excreted by active tubular secretion of weak acids (requires a carrier and energy). Uric acid is also acidic and requires the **same carrier** to be excreted in urine.
So if a patient with Gout (Hyperuricemia) takes Loop or Thiazide diuretics, they will compete with Uric acid for the same carrier resulting in: secretion of Loop/Thiazide and retaining uric acid > increase gouty attacks.
Therefore, a patient with Gout SHOULD **NOT** be given Loop or Thiazide diuretics.

Pharmacological actions:

↑ Urinary excretion of Na+ , K,+ Ca++ and Mg ++ (In other words: Hyponatremia, Hypokalemia , Hypomagnesemia.) *If electrolytes are high in the urine, they will be low in the serum)
↑ Urine volume.
↑ Renal blood flow. By increase prostaglandin synthesis

Compensatory mechanisms:

• **Inhibiting salt reabsorption in the thick ascending loop > increases delivery of (Na) to the collecting duct > Aldosterone release > (Na) reabsorption in-exchange secretion of (K) and (H) > hypokalemic metabolic alkalosis.**

Therapeutic Uses:

Acute pulmonary edema. (Because they have potent pulmonary vasodilating effects)
Congestive heart failure. (Edema associated with heart failure)
Edema due to nephrotic syndrome
Acute hyperkalaemia.
Acute hypercalcemia.
Acute renal failure. (Given IV)
Not used in regular hypertension ,because it has short duration of action.

While thiazide diuretics are more effective in patients with normal kidney function, loop diuretics are more effective in patients with impaired kidney function (Acute renal failure)

Adverse Effects:

- **Hypokalemia. (Treated by: dietary K supplementation or in combination with K-sparing diuretics, to avoid cardiac arrhythmias)**

- **Metabolic alkalosis. (As a result of K secretion in urine which leads to secretion of H) .**
- **Acute Hypovolemia (volume depletion), postural hypotension with chronic use . (As a result of Hyponatremia)**

- **Hyponatremia.**
- **Hypomagnesaemia**
- **Hyperuricemia. (Increase gouty attack).**

- **Hypocalcaemia. it is not sever enough to cause osteoporosis ,because the reabsorption of Ca will occur again in the distal convoluted ("Hypercalciuria" > Stones).**
- **Hyperglycemia. because they interfere with the secretion of insulin**

- **Ototoxicity. (Loss of hearing, Risk increased if combined with aminoglycosides)**

- **Allergic reactions. (Except for Ethcrynic acid, the loop diuretics are sulfonamides that may lead to hypersensitivity)**

Extra Notes

- Why furosemide is a better diuretic than acetazolamide despite the fact that only 25% of the reabsorption occurs at the ascending loop of Henle?
- A: Because the compensatory mechanisms after ascending loop of Henle will be limited.

- What are the differences between furosemide and torsemide?
- A: Simply oral torsemide considers as effective as I.V of furosemide.

- What are the advantages of bumetanide over that of furosemide?
- A: Potent (40 times) with very fast onset and short duration.

- Why can't we use Fuosemide with Hypertensive patients?
- ".1- it is effective in excreting water "high urine volume" > Hypovolemia > postural hypotension.2-short action

2 Carbonic Anhydrase Inhibitors :

Diuretics that inhibit transporter in the Proximal Convoluted Tubule ,
They have weak diutetic action (: المجموعة الغريبة

Acetazolamide (Oral)
Others :(**Dorsolamide --- Brinzolamide) (Topical)

MOA	They inhibit reabsorption of sodium* and bicarbonate by inhibiting carbonic anhydrase ⟶ more bicarbonate will be lost in urine (Alkaline urine) and acidic blood. carbonic anhydrase enzyme is required for reversible reaction and inter-conversion of co2 and water into carbonic acid which gives H and HCO3 and stimulate reabsorption of bicarbonate .. For illustration\ https://www.youtube.com/watch?v=FmKv2qPuB4k *(little amount Na reabsorbed in PCT but high amount reabsorbed in loop)
Pharmacokinetics	*given orally once a day. *Onset of action is rapid (30 min). *Duration of action (12 h). (long Action but not strong diuretic) *Excreted by active secretion in proximal convoluted tubules forming alkaline urine
Pharmacological actions:	1)- ↑ urine volume (not like loop diuretic). 2)- ↑ urinary excretion of sodium, potassium , bicarbonate (alkaline urine). 3)- Metabolic acidosis. In blood. 4)-↑ urinary phosphate excretion. (for unknown mechanism) 5)- Weak diuretic properties. (decreases after several days ; self-limiting as the blood bicarbonate falls).
NOT used in treatment of HTN , edema !! **Clinical Uses**	**1)-** Glaucoma (by reducing the intraocular pressure) HOW??? ↓ IOP by reducing aqueous humor formation via blocking carbonic anhydrase in ciliary body of eye). 2)-As prophylactic therapy, in acute mountain sickness . (to decrease CSF and pH of brain). (By increasing the amount of bicarbonate excreted in the urine, the blood becomes more acidic., artificially acidifying the blood fools the body into thinking it has an excess of CO2, and it excretes this imaginary excess CO2 by deeper and faster breathing, which in turn increases the amount of oxygen in the blood) 3)-Epilepsy (Benign intracranial hypertension) by reducing the intracranial pressure HOW ??? Excretion of HCO3- withdraws Na+ out fro the brain; water follows by osmosis and pressure decreases 4)-Alkalization of urine and metabolic alkalosis. 5)- Hyperphosphatemia.

Side Effects	**1)-Metabolic Acidosis (because it preserve Cl into the body and Cl is has an acidic effect) They inhibit reabsorption of bicarbonate** 2)-**Hypokalemia & Hyponatremia (Due to elimination of Na & K) 3)-Renal Stone formation** (calcium phsphate stones) **4)-Hypersensitivity reaction**
Contraindication	Hepatic failure due to decrease elimination of ammonium

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**Dorsolamide used topically for treatment of ↑IOP in Glaucoma and NO diuretic or systemic side effects

3 Potassium sparing Diuretics:

Diuretics that inhibit transport in the Cortical Collecting Tubule

Corticosteroids

Mineralocorticoid

Any of a group of steroid hormones that are secreted by the adrenal cortex and regulate the balance of water and electrolytes in the body. (E.g. Aldosterone)

Glucocorticoid

Such as: cortisol, cortisone

Aldosterone mechanism → Reabsorption of Na^+ and Eliminate (K^++Acid)
Which lead to **(Hypokalemia, Alkalosis, increase Blood pressure)**

MOA

1) They work by inhibiting the passage of sodium from the luminal fluid into the principal cells of the late distal convoluted tubule and cortical collecting tubule. Subsequently, this prevents the movement of K from these cells into the luminal fluid, thus will lead to Na loss in urine and (K+ H) reabsorption "Hyperkalemia and acidosis"
Opposite Aldosterone mechanism = antagonist for aldosterone : SPIRONOLACTONE

2)Inhibition of Na influx through Na channel at the luminal membrane **AMILORIDE & TRIAMETRENE**
the *natriuretic activity of this group has limited range (less than 5%), Although its very important clinically. Because it's the only diuretic that produce hyperkalemia.
*Natriuretic: A chemical compound that may be used to inhibit the tubular reabsorption of ions from glomerular filtrate, especially sodium ions, thereby resulting in greater amounts of that ion in the urine.

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Classification

1)-Direct

E.g. Spironolactone (Aldactone)
This drug is the synthetic steroid that is a competitive antagonist for the mineralocorticoid aldosterone. It's binds to aldosterone receptor sites and prevent the formation of mediator protein that stimulate the Na/K pump

2)-Indirect

E.g. Amiloride and Triamterene work independently of aldosterone by directly blocking the Na channels; therefor, these agents can be used even in cases of hypoaldosteronism.
But Spironolactone requires elevated levels of aldosterone to have an effect

Net result is same in both mechanisms ☺

Indication

- ✧ Primary hyperaldosteronism (Conn's syndrome, Ectopic **ACTH**[1] production)
- ✧ Edematous states caused by secondary aldosteronism, especially (cirrhosis, nephrotic syndrome and congestive heart failure).
- ✧ For **Hypokalemic**[2] action of diuretics such Thiazide.
- ✧ Hirsutism
- ✧ Drug of choice in Liver cirrosis

What stimulate aldosterone hypersecretion?
Any case of HYPOVOLEMIA "CHF" will stimulate Renin Angiotensin Aldosterone System.

Side effects

- ✧ **Hyperkalemia**[2]
- ✧ Metabolic acidosis – because of an intracellular shift of H^+ ions.
- ✧ **Antiandrognic**[3] effects "with **spironolactone**" (e.g. gynecomastia, impotence)

>> because Testosterone is a steroidal enzyme, so it might antagonize its action

- ✧ Rarely, **triamterene** form renal stones.

Contraindication

- ➢ **Hyperkalaemi a** "Chronic renal failure, K supplementation, B-blockers or ACE-inhibitors"
- ✧ **Liver disease** (dose adjustment is needed**)**

Diuretics Combination preparations

Examples:

Dyazide^R = Triametrene 50 mg + Hydrochlorothiazide HCT 25 mg
Aldactazide^R= Spironolactone 25 mg + HCT 25 mg
Moduretic^R = Amiloride 5 mg + HCT 50 mg

Thiazide should always be combined with Potassium sparing diuretics.
To make balance in the K^+

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[1]**ACTH**:Adrenocorticotropic hormone that stimulates the secretion of aldosterone.
[2] the benefit of **hyperkalemic** effect to over come **Hypokalemic**
[3]**Antiandrognic** A substance that blocks the action of androgens, the hormones responsible for male characteristics.

4 Thiazide diuretics :

Efficacy: It acts on the segment where 5% of Nacl reabsorbed.

Hydrochlorothiazide, indapamide, metolazone.

MOA	Acts via inhibition of Na/Cl Co-transporter on the luminal membrane of distal convoluted tubules.
Pharmacokinetics	***Given orally, slow of onset. Long duration of action. (40 h)** ***Are secreted by active tubular secretory system of the kidney may interfere with uric acid secretion and cause hyperuricemia. (Just like Loop diuretics).**
Pharmacological actions:	• ↓ Urinary calcium excretion. Good for treating calcium stones. • ↑ Calcium reabsorption. (Hypercalcemia) *Ca is reabsorbed in Loop of Henle and Distal Convoluted Tubules through Ca channels and under the effect of Parathyroid hormone (PTH) Thiazide produces Hypercalcemia by 2 mechanisms: 1) Stimulate NA/Ca ATPase > reabsorption of Ca through the Ca channels & extrusion of Na in tubular cells. 2) Stimulation of PTH > Stimulation of Ca channels > Stimulation of Ca reabsorption. • ↑ Urinary Na excretion. "More than water" • ↑ Urinary K excretion. (Hypokalemia and alkalosis "by compensatory mechanism") • ↑ Urinary magnesium excretion. • ↑ Uric acid in blood. (Hyperuricemia) "Competitive excretion" • ↑ Glucose in blood. (Hyperglycemia: As a result of reduction in releases of Insulin "thiazides inhibit insulin release". It is more noticed in diabetic patients).
Compensatory mechanisms:	*** Since they increase NA excretion at the DCT > Aldosterone release in collecting duct > more (K+) and (H) are going to be exchanged with NA+ > hypokalemic metabolic alkalosis.**

Therapeutic Uses:

- **Treatment of essential (primary) hypertension**. (Hydrochlorothiazide; Indapamide "natriuretics") "Because thiazides excrete more sodium than water and they have long duration of action also they are cheap. If there is no response we will combine them with ACEI and k sparing.

- Refractory Edema together with the Loop diuretics (e.g Metolazone "more of a diuretic than a natriuretic)

When we give a patient furosemide and we didn't get an effect "still low urine volume". We add metolazone > it will give potent diuretic actions. Because metolazone acts on both proximal and distal convoluted tubules.

- Treatment of mild heart failure *(to reduce extracellular volume).*

*Nephrolithiasis due to hypercalciuria. (Due to increase calcium reabsorption and decrease renal calcium stones).

*Nephrogenic diabetes insipidus.

In diabetes insipidus, the patient's kidney tubules do not respond to antidiuretic hormone "ADH" > polyuria + hypernatremia.
So we give thiazides "because it excretes more sodium than water" and make a balance. "Also we should advise the patient to drink fluids".
*It decrease GF

Adverse effects:

- ✧ Hyponatremia. "More than loop diuretics"
- ✧ Hypovolemia (volume depletion). It is not so severe as loop diuretics
- ✧ Hypokalemia. We have to correct
- ✧ Metabolic alkalosis.
- ✧ Hyperuricaemia (gout).
- ✧ Hypercalcemia. "Due to increased PTH reabsorption of Ca"
- ✧ Hyperglycemia.
- ✧ Hyperlipidemia. By ↑ LDH and ↓ HDL

Thiazide diuretics don't cause ototoxicity

5 Osmotic diuretics :

Diuretics that inhibit transport in the Proximal Convoluted Tubule & descending loop of Henle by osmotic effect.

Mannitol

(((Last line drugs)))

MOA	* Retain water within tobules (water diuresis) * Has a secondary effect on reducing Na re-absorption. (Its action mainly on the water) Hydrophilic compounds that are easily filtered through the glomerulus with little re-absorption Thus : increase urinary output via Osmosis* *They are low-molecular-weight substances that can remain in high concentrations in renal tubules, thus contributing to osmolality of glomerular filtrate.
Pharmacokinetics	• Poorly absorbed • Given intravenously. • Not metabolized (just excreted) • Excreted by glomerular filtration without being re-absorbed or secreted within 30-60 min.
Therapeutic Uses:	• Cerebral edema (Increase intracranial pressure)in neurological condition • Glaucoma (Increase intraocular pressure in acute) • Maintain high urine flow in acute renal failure during shock, trauma and drug toxicities
Adverse effects	• Extracellular water expansion (تضخم) (extracts water from cells) • Dehydration • Hypernatremia • Headache, nausea, vomiting • Adequate water replacement is required. **They Are not considered as good diuretics** In Fact : They Are the last line Drugs

* Osmosis : the movement of a pure solvent such as water through a differentially permeable membrane from a solution that has a lower solute concentration to one that has a higher solute concentration

** Osmolality :the concentration of a solution

SUMMARY :

Diuretics	Mechanism of action	Effects
CA inhibitors Acetohexamide Dorzolamide	Inhibition of NaHCO3 reabsorption in PCT	– Urinary Na HCO3, K Urinary alkalosis Metabolic acidosis
Osmotic diuretic Mannitol	Osmotic effect in PCT & DLH	–Urine excretion – Little Na
Loop diuretics Furosemide	Na/K/2Cl transporter in TAL the most effective	–Urinary Na, K, Ca, Mg
Thiazide diuretics hydrochlorothiazide	Na and Cl cotransporter in DCT	–Urinary Na, K, Mg BUT↓ urinary Ca (hypercalcemia) Metabolic alkalosis
K-sparing diuretic Spironolactone.	competitive antagonist of aldosterone in CCT	↑ Urinary Na ↓ K, H secretion Metabolic acidosis

Diuretics	Uses
CA inhibitors Acetohexamide Dorzolamide (topically) for glaucoma	Glaucoma, epilepsy Mountain sickness
Osmotic diuretic Mannitol	• Cerebral edema • Acute renal failure
Loop diuretics Furosemide	Acute pulmonary edema (Drug of choice) Heart failure Hyperkalemia, Hypercalcemia
Thiazide diuretics hydrochlorothiazide	Commonly used Hypertension, heart failure, hypercalciuria, kidney stones, diabetes inspidus
K-sparing diuretic Spironolactone.	Hepatic cirrhosis (Drug of choice)

Diuretics	Side effects
CA inhibitors **Acetohexamide** **Dorzolamide**	**Metabolic acidosis , Urinary alkalosis** **Hypokalemia**
Osmotic diuretic **Mannitol**	**Extracellular water expansion** **Dehydration** **Hypernatremia**
Loop diuretics **Furosemide**	**Hypokalemia,** **hypovolemia, hyponatremia, hypomagnesemia, hypocalcemia** **Precipitate gout, alkalosis**
Thiazide diuretics **hydrochlorothiazide**	**Hypokalemia, hyponatremia, hypovolemia, hypomagnesemia, hypercalcemia** **Alkalosis, precipitate gout** **Hyperlipidemia, hyperglycemia**
K-sparing diuretic **Spironolactone.**	**Gynaecomastia** **Hyperkalaemia, Metabolic acidosis.** **GIT upset and peptic ulcer**

MCQS from:Lippincott's Illustrated Reviews: **Pharmacology**

1)- An elderly patient with a history of heart disease and who is having difficulty breathing is brought into the ER . examination reveals that she has pulmonary edema. Which of the following treatments is indicated ?

A.Spironolactone . B.Furosemide. C.Acetazolamide D.Chlorthalidone. E.Hydrochlorothiazide.

2)- A group of college students is planning a mountain climbing trip to the Andes. Which of the following drugs would be appropriate for them to take to prevent mountain sickness ?

A. A thiazide diuretic. B. An anticholinergic. C. A carbonic anhydrase inhibitor. D.Loop diuretic. E.A b-blocker.

3)- An alcoholic male has developed hepatic cirrhosis. To control the ascites and edema, he is prescribed which one of the following ?

A. Hydrochlorothiazide. B.Acetazolamide. C. Spironolactone. D.Furosemide. E.Chlorthalidone

4)- A 55-year-old man with kidney stones has been placed on a diuretic to decrease calcium excretion. However, after a few weeks he develops an attack of gout. Whic diuretic was he taking ?

A.Furosemide. B.Hydrochlorothiazide. C.Spironolactone. D.Triamterene. E.Urea.

5)- A 75-year-old woman with hypertension is being treated with a thiazide. Her BP responds and reads at 120/76 mm Hg. After several months on the medication, she complains of being tired and weak. An analysis of the blood indicates low values for which of the following ?

A.Cacium. B.Uric Acid. C.potassium .DGlucose.

6)- Which of the following drugs is contraindicated in patient with hyper kalmia ?

A.Acetazolamide. B.Chlorothiazide. C.Ethacrynic Acid. D.Chlorthalidone. E.Spironolactone

7)- Which would be the initial treatment choice to manage the hypertension in an African American woman with a post medical history of gout and severe hypokalemia ?

A.Hydrochlorothiazide. B.Spironolactone. C.Valartan. D.Atenolol. E.Enalapril.

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B, C, C, B, C, E, B

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