Q24 Classify antihypertensive agents by their mechanism of action, with a brief outline of each mechanism, and an example of a drug in each class (Sept 2010)

1. ADRENERGIC AGENTS
    - Alpha antagonists – prazosin is an alpha 1 antagonist which blocks the G_p protein, reducing phospholipase C, DAG, IP3 and intracellular calcium, causing vasodilatation and thus reducing TPR and BP.
    - Beta antagonists – metoprolol is a beta antagonist which blocks the G_s protein and thus reduces intracellular cAMP, causing a reduction in heart rate and cardiac output
    - Mixed alpha/beta antagonists – labetalol, carvedilol
    - Alpha-2 agonists – clonidine, methyldopa. Act on the alpha 2 receptor to reduce central sympathetic outflow

2. RAAS AGENTS
    - ACE's and ARBs block the effects of angiotensin II (namely, vasoconstriction, sympathetic stimulation, sodium and water retention via afferent/efferent arteriolar constriction and upregulation of sodium resorption along the length of the renal tubule, stimulation of aldosterone release and ADH). Examples include lisinopril (ACEI) and irbesartan or candesartan (ARB)

3. CA CHANNEL BLOCKERS
    - Specifically block the L type calcium channels to reduce cardiac contractility and heart rate. In vascular endothelial cells, calcium channel blockade reduces intracellular calcium and causes vasodilatation, reducing TPR and thus BP. Three classes:
        - Class 1 phenylalkylamines (verapamil) – reduces HR, contractility and causes vasodilatation
        - Class 2 dihydropyridines (amlodipine) – main effects are on vasodilatation
        - Class 3 benzothiazepines (diltiazem) – some reduction in HR and contractility, also causes vasodilatation

4. DIURETICS
    - There are multiple diuretics but in general they work by reducing renal sodium and hence water retention, thus reducing blood volume. Some (including frusemide) also have an effect on TPR prior to the diuretic effect occurs.
        - Acetazolamide works in the proximal tubule to inhibit carbonic anhydrase
        - Frusemide acts in the TAL of LOH inhibiting the triple symporter
        - Thiazides act in the early distal tubule inhibiting the Na/Cl symporter
        - Amiloride acts in the cortical collecting duct by blocking ENaC.

5. VASODILATORS
    - Nitrate drugs – eg, GTN. NO activates soluble guanylate cyclase to causes vasodilatation
    - Hydralazine – mechanism not entirely clear, possibly via guanylate cyclase, causes arteriolar vasodilatation
    - Minoxidil – direct arteriolar dilator, possibly via K channels
    - Nicorandil – K-ATP channel activator which also contains a nitrate moiety