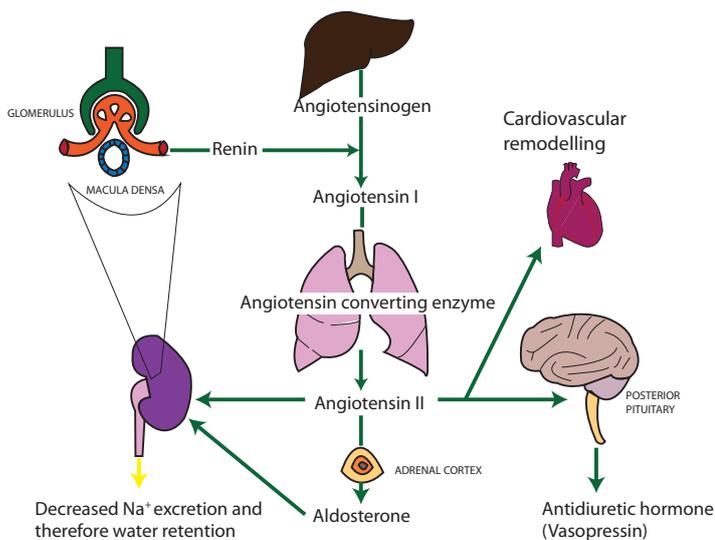


ANTIHYPERTENSIVE MEDICATIONS 1

Antihypertensive Classification The main determinants of mean arterial pressure are cardiac output and total peripheral resistance. Anything that increases CO (increased preload, decreased afterload, increased contractility or HR) or decreases peripheral resistance (increased arteriole resistance) or total circulating volume (without any compensation) will increase MAP. There are a range of different drug agents used to decrease MAP. The following is one scheme to classify anti-hypertensive medications. Following this explanation there will be a detailed explanation of each of the classes. Some of the material overlaps with other sections such as diuretics, adrenergic blockers and anti arrhythmics. Also see associated drug description cards.

Renin Angiotensin Aldosterone System	Angiotensin Converting Enzyme (ACE) Inhibitors Angiotensin Receptor Blockers Aldosterone Antagonists
Sympathetic Nervous System	Peripheral adrenergic blockers (Alpha blockers, Beta Blockers) Central adrenergic agonists (Alpha agonists)
Vasodilators	Calcium channel antagonists Potassium channel activators Nitrogen related agents Direct vasodilators
Diuretics	Thiazides Loop diuretics Potassium sparing Aldosterone antagonists Osmotic Carbonic anhydrase inhibitors

Renin Angiotensin Aldosterone System is a critical part of the neuroendocrine response to **regulate Na⁺ and K⁺ homeostasis and blood pressure** and is subsequently a target for blood pressure control. **Renin is the rate limiting step** in the RAAS. Renin is released from the granular cells of the juxtaglomerular apparatus in response to **three main triggers**. Firstly, activation of the **sympathetic nervous system** via the medulla as a result of carotid and aortic baroreceptor sensing of a decrease in blood pressure. Secondly, in response to **decreased renal perfusion pressures noted by intrarenal baroreceptors** and finally in response to **reduced delivery of NaCl** by the macula densa. Renin is a catalyst for the proteolysis of hepatic protein angiotensinogen into angiotensin I. This is further converted into angiotensin II by angiotensin converting enzyme (ACE) mostly in the lungs. **Angiotensin II has many functions**, directly causing **vasoconstriction** and acting on tubules to **increase Na⁺ reabsorption**. Long term it effects cardiovascular remodelling. It also acts on the posterior pituitary to **secrete antidiuretic hormone (vasopressin)**. ADH increases the water permeability of the collecting duct luminal membrane which **increases water reabsorption**. Angiotensin II the adrenal cortex to **secrete aldosterone**. Aldosterone is the main determinant of tubular sodium reabsorption and stimulates potassium secretion.



ACE Inhibitors The **essential effect of these agents on the renin-angiotensin system is to inhibit the conversion of Angiotensin I to the active Angiotensin II**. Thus, ACE inhibitors attenuate or abolish responses to AngI but not to AngII. They do not interact directly with other components of the renin-angiotensin system, and their principal pharmacological and clinical effects all apparently arise from suppression of AngII synthesis. Nevertheless, ACE is an enzyme with many substrates, and inhibition of ACE may induce effects unrelated to reducing the levels of AngII. Since ACE inhibitors **increase bradykinin levels** and bradykinin stimulates prostaglandin biosynthesis, bradykinin and/or prostaglandins may contribute to the pharmacological effects of ACE inhibitors. In a healthy, **Na⁺ replete person**, a single oral dose of an ACE inhibitor has **little effect** on blood pressure, but repeated doses over several days cause a small reduction in blood pressure. By contrast, even a single dose of these inhibitors **lowers blood pressure substantially** in normal subjects when they have been **depleted of Na⁺**. In general, **ACE inhibitors differ with regard to three properties**: (1) **potency** (ramipril > lisinopril > captopril), (2) **whether ACE inhibition is primarily a direct effect of the drug itself or the effect of an active metabolite** (captopril has active metabolites, ramipril is a prodrug and lisinopril itself is active), and (3) **pharmacokinetics** (i.e., extent of absorption, effect of food on absorption, plasma t_{1/2}, tissue distribution, and mechanisms of elimination) Captopril has a much shorter half life and duration of action compared to ramipril and lisinopril.

Angiotensin receptor blockers Angiotensin II receptor blockers (ARBs) interfere with the renin-angiotensin system by impairing the binding of angiotensin II to the **AT1 receptor on the cell membrane**, thereby inhibiting the action of angiotensin II. Blockade of the action of angiotensin II leads to elevations in plasma levels of renin, angiotensin I, and angiotensin II. However, this build-up of precursors does not overwhelm the receptor blockade, as evidenced by a persistent fall in both blood pressure and plasma aldosterone levels with treatment. In comparison to the ACE Inhibitors, the bradykinin levels are not elevated, this may prevent the cough associated with ACE but removes the vasodilatory benefit provided by bradykinin. ACE inhibitors also block both AT1 and AT2, however ARBs only block AT1, it has been postulated that AT2 stimulation is renal protective. Angiotensin I may also be converted by enzymes other than ACE therefore ARBs may block more completely.

Aldosterone antagonists These agents are also placed in the diuretic category. Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in patients with low-renin essential hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACE inhibitors, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist.

Sympathetic Nervous System antihypertensives included in this classification system are the peripheral acting adrenergic blockers and the central acting alpha 2 agonists. Other agents which are not commonly used but would be considered to fall within this classification are the ganglion blockers such as trimetaphan, the noradrenaline depleters such as reserpine and guanethidine and false neurotransmitters such as methyl dopa.

Peripheral adrenergic blockers including the beta blockers, the selective alpha blocker prazosin and the non selective alpha blocker phenoxybenzamine. This were covered in the previous page.

Central Alpha₂ Agonists which include clonidine and dexmetomidine. Central pathways in the hypothalamus, the nucleus tractus solitarius, locus ceruleus and the cardioaccelerator and vasomotor centres in the medulla are under the modulatory control of alpha₂-adrenoceptors, increased agonism of these pathways by clonidine and dexmetomidine results in a negative feedback and decreased activity. This leads to the main effects seen by the centrally acting agents such as sympatholysis (a drop in peripheral noradrenaline) causing decreased TPR and MAP, decreased HR and CO, analgesia, and sedation. The sedation specifically is caused by depression of the locus ceruleus due to alpha₂ stimulation and is opposed by alpha₁ stimulation, this explains why clonidine does not achieve full anesthesia. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal.