VASODILATORS:

Drugs may cause vasodilation by opening potassium channels, by releasing nitric oxide, by blocking calcium channels or by acting as agonists of dopamine receptors. These drugs may be mainly arteriolar dilators (hydralazine, minoxidil, calcium channel blockers, diazoxide, fenoldopam), mainly venodilators (nitrates) or may dilate both arterioles and venules (sodium nitroprusside, ACE inhibitors, ARBs, α-blockers). All vasodilators can lead to reflex tachycardia due to vasodilation and sodium and fluid retention due to compensatory mechanisms; therefore these are best utilized in combination with diuretics and beta blockers

Sodium nitroprusside and hydralazine act by releasing nitric oxide from the endothelium, which in turn increases intracellular cGMP by stimulation of guanylyl cyclase leading to vasodilation. Nitroprusside, in addition can directly stimulate guanylyl cyclase to cause increase in cGMP. Nitroprusside is a very short acting drug; therefore has to be administered by constant i.v. infusion for the treatment of hypertensive emergencies. Its solution should be freshly prepared because it is unstable and sensitive to light. Prolonged administration of this drug can result in accumulation of cyanide leading to toxicity particularly in patients with renal disease. It can also result in hypothyroidism due to the accumulation of thiocyanate (antithyroid compound). It is contra-indicated in pregnancy

HYDRALAZINE: Hydralazine acts mainly by relaxing arteries and arterioles, causing a fall in blood pressure accompanied by reflex tachycardia and increased cardiac output. It interferes with the action of inositol trisphosphate on Ca^{2+} release from the sarcoplasmic reticulum. Its original clinical use was in hypertension, and is still used for short-term treatment of severe hypertension in pregnancy but it can cause an immune disorder resembling systemic lupus erythematosus (SLE), so alternative agents are now preferred for long-term treatment of hypertension. It has a place in treating heart failure in patients of African origin in combination with a long-acting organic nitrate

Minoxidil: Minoxidil is a vasodilator drug that was originally developed for treating hypertension (acting through an active sulfate metabolite) is an especially potent and long-acting vasodilator, used as a drug of last resort in treating severe hypertension unresponsive to other drugs. It causes hirsutism (the active metabolite is actually used as a rub-on cream to treat baldness. It is usually prescribed with a loop diuretic. It causes reflex tachycardia, and a β-adrenoceptor antagonist is used to prevent this.

Minoxidil, when applied topically, it is converted in hair follicles to a more potent metabolite (or some preparations contain this salt - minoxidil sulfate). Perhaps because of its ability to increase blood supply to hair follicles, it stimulates growth of new hair and the progression of the new follicle.

NITROPRUSSIDE (nitroferricyanide): is a powerful vasodilator which acts by releasing NO. Unlike the organic nitrates, *it acts equally on arterial and venous smooth muscle*. Its clinical usefulness is limited because it must be given intravenously. In solution, particularly when exposed to light, nitroprusside hydrolyses with formation of cyanide. The intravenous solution must therefore be made up freshly from dry powder and protected from light (LIGHT SENSITIVE). Nitroprusside is rapidly converted to thiocyanate in the body, its plasma half-life being only a few minutes, so it must be given as a continuous infusion with careful monitoring to avoid hypotension. Prolonged use causes thiocyanate accumulation and toxicity (weakness, nausea and inhibition of thyroid function); consequently, nitroprusside is useful only for short-term treatment (usually up to 72 h maximum). It is used in ICUs for hypertensive emergencies, to produce controlled hypotension during surgery, and to reduce cardiac work during the reversible cardiac dysfunction that occurs after cardiopulmonary bypass surgery.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)

Captopril, enalapril, lisinopril, ramipril, perindopril, trandolapril, fosinopril and moexipril etc are the compounds in this group.

• The first ACEI to be marketed was captopril. Captopril is less potent, has fast onset and short duration of action and less absorption in presence of food in GIT. Because of short and fast action, it can cause postural hypotension which is not seen with other ACEI. Captopril has a short plasma half-life (about 2 h) and must be given 2 or 3 times daily

• **All are prodrugs except captopril and lisinopril**. Other drugs like enalapril are converted to its active metabolite (enalaprilat) and thus are slow acting.

• **ACEI are used for** the treatment of hypertension, CHF (Cardiac failure), Following myocardial infarction (especially when there is ventricular dysfunction) i.e. evolving MI, In people at high risk of ischaemic heart disease, Diabetic nephropathy, Diabetic retinopathy, non-diabetic renal disease or Chronic renal insufficiency to prevent progression and also in scleroderma crisis. These drugs reduce proteinuria in diabetic as well as non-diabetic renal disease and also prevent the manifestations of scleroderma crisis which are mediated by angiotensin II.

• Most frequent adverse effect associated with these agents is dry cough. It can be reduced by iron supplements and asprin. ACEI can also cause angioedema. Both cough and angioedema is due to elevated levels of bradykinin.

• These can cause hyperkalemia if used along with other agents causing elevation of serum potassium (like potassium sparing diuretics).

• Other adverse effects include rashes, dysguesia (altered taste sensation), and acute renal failure (if used in bilateral renal artery stenosis). It is important to distinguish between acute renal failure and a normal predictable rise in serum creatinine secondary to ACE inhibitor therapy. An increase in serum creatinine upto 30% within 2-5 days can be expected in most patients started on ACE inhibitors. It stabilizes in 2-3 weeks and is reversible on stopping drug therapy.

These drugs are contra-indicated in pregnancy (teratogenic in second half of pregnancy) and when serum creatinine is high.

Class	Drug[a]	Pharmacokinetics	Adverse effects[b]	Uses	Notes
ACE inhibitors	Captopril	Short acting $t_{1/2}$ ~2 h Dose 2–3 times daily	Cough Hypotension Proteinuria Taste disturbance	Hypertension Heart failure After MI	ACEIs are cleared mainly by renal excretion
	Enalapril	Prodrug – active metabolite enalaprilat $t_{1/2}$ ~11 h Dose 1–2 times daily	Cough Hypotension Reversible renal impairment (in patients with renal artery stenosis)	As captopril	Lisinopril, perindopril, ramipril, trandolapril are similar Some are licensed for distinct uses (e.g. stroke, left ventricular hypertrophy)