Cardiovascular Drugs

Calcium Channel blockers

Phenylalkylamine	Verapamil	Binds to S5-S6 loop and S6 domain. ?Inactivation/selectivity interference
Dihydropyridines	Nifedipine	i) S5-S6 loop and S6 of domain III; S5-S6 loop domain IV. Don't bind to type T channel
Benzothiazepines	Diltiazem	Binds extracellularly, similar effect to phenylalkylamine; modulates dihydropyridine binding

Antidysrhythmics

Clonidine	Na channel block	Binds to open state of channel (only use dependent at high freq. – not attainable in heart)
Lignocaine	Na channel block	Binds to inactivatd channels – associates and dissociates in duration of normal heart beat – thus preventing premature beats. Also binds channels in partially depolarised cells (e.g ischaemia) – thus preventing ventricular dysrhythmia after MI
Propranolol et al	B blockers (useful where increased excitability due to tissue damage)	Reduce effect of catecholamines – negative inotropic and chronotropic effects. (note sensitisation of tissues to catecholamines after ischaemic damage can create ectopic foci)
Verapamil	Phenylalkylamine	Ca channel block
Diltiazem	Benzothiazepine	Ca channel block

Congestive heart failure

Digoxin, Digitoxin	Cardiac glycoside	Inhibits Na/K ATPase thus ^ [Na] reducing gradient for NCX so [Ca] ^ and has + inotropic effect. Also stimulated Vagus via CNS slowing I_f (hence its use for atrial dysrhythmia) Side effect = BIGEMINY due to $I_{Na\text{-}Ca}$.
Dobutamine	B_1 agonist	Positive inotropic effect > chronotropic effect. Used for congestive heart failure in absence of hypertension. (sympathomimetics will tend to increase oxygen demand of heart, heart rate (ppte/reveal dysrhythmia, as well as hypertension)
Xamoterol	Partial B_1 agonist	Positive inotropic effect but antagonises excessive symp.

		stimulation. Antagonistic action can reduce symp. activity and thus can make the congestive heart failure worse!
Amrinone	Type III Phosphodiesterase inhibitor	Short acting, acute cases, ^cAMP causing positive inotropic effect. Also causes dilatation of VSM – reducing afterload
Milrinone	Type III Phosphodiesterase inhibitor	Longer acting, may cause dysrhythmia. Same effects as above.
Caffeine, theophylline	Methylxanthines	Non selective phosphodiesterase inhibitor and adenosine A_1 and A_2 antagonists. = Positive inotropic and chronotropic effects. (but may give rise to dysrhythmia)
Bosentan	Endothelin ET_A and ET_B receptor antagonist	Endothelin mediates contraction by such receptors on VSM cells (although mediates dilatation via ET_B on endothelial cell)
ACE inhibitors	Reduce AT II	Prevent sodium, thus water, reabsorption in kidney.

Angina Pectoris

Glyceryl trinitrate	Nitrovasodilator	Must be taken sublingually (poor stomach absorption) Yields NO which can act via cGMP to vasodilate (not arterioles as already fully dilated) venous vessels and collateral vessels (primarily in ischaemic areas
Isosorbide dinitrate	Nitrovasodilator	Metabolised in stomach to form isosorbide mononitrate. Same mechanism as above
Dipyridamole	Blocks adenosine transporter	Acts to enhance adenosine action on A_2 receptors on VSM which elicit dilatation in all areas – ie results in diverting blood from ischaemic areas – coronary steal
Propranolol	B adrenoceptor antagonist	Reduces sympathetic effects on heart, thus reducing ABP (afterload). But can cause bronchoconstriction and cause vasoconstriction of coronary vessels (α_1 effect unmasked by blocking β_2)
Atenolol	B_1 antagonist	Reduces sympathetic effects on heart and reduces afterload
Alprenolol	Partial B agonist	Maintains sympathetic stimulation at low output, but blocks high sympathetic output (used in heart

		failure where sympathetic required to maintain heart function)
Nifedipine	Dihydropyridine Ca channel block	Reduces Ca entry into VSM cells – vasodilatation and reduced afterload (preferentially acts on VSM than cardiac since binds to inactivated form of channel. VSM resting potential more depolarised)
VEGF Gene transfer	Angiogenesis	Adenoviral or plasmid vector for transient expression; idea to create new blood flow to ischaemic areas. Still in clinical trial stages

Clot Lysis

Streptokinase	Activates plasminogen activator	Plasmin yielded from plasminogen = protease degrading fibrin …. In clots.
Anistreplase	Activates plasminogen activator	Combination of plasminogen and anisoylated streptokinase. Anisoyl group must be removed in blood (long $t_{1/2}$) more prolonged effect than above.
Urokinase	Endogenous plasminogen activator	Single chain scu-PA released from kidney and hydrolysed to two chain enzymatic tcu-PA form. Both given clinically
Alteplase; Duteplase	Human tissue plasminogen activators	Single and double chain; act preferentially on plasminogen bound to fibrin in clots (localising action)
Asprin	COX inhibitor	Prophylaxis for thrombosis
Clopidogrel	Anti coagulant	Inhibits binding of ATP to platelets. Shown that use with asprin improves morbidity and mortality
Aminocaproic acid; tranexamic acid	Inhibits clot lysis	Prevent excessive clot lysis which can lead to severe bleeding.

Hypolipidaemic agents

Lovastatin; Simvastatin	HMG CoA Reductase inhibitor	Causes liver to increase expression of LDL receptors to scavenge cholesterol from blood for hepatic requirements
Cholestyramine	Bile acid reuptake inhibitor	Anion resin. Liver must uptake more cholesterol from blood to metabolise new bile acids
Clofibrate	Lipoprotein lipase activator	Releases lipids from VLDL > LDL, and they are then stored in fat or metabolised in skeletal muscle

Nicotinic acid		Inhibits triglyceride production and VLDL secretion from liver; increases levels of tcu-PA
Fish oil		Reduces hypertriglyceridaemia and increased unsaturated FA reduce thrombosis risk (via production of less effective thromboxane)

Diuretics

Frusemide; bumetanide; piretanide	Loop diuretics	Inhibit Na/K/2Cl cotransporter in thick ascending limb. Also mild inhibition of CA and a vasodilatory effect (piretanide shows vasodilatation at sub-diuretic levels). High ceiling diuretic (15-25%) BUT – hypokalaemia, metabolic alkalosis, uric acid excretion decrease (gout) Ca and Mg loss ^
Probenecid		Competes for reabsorption with uric acid, thus reducing its reabsorption
Hydrochlorothiazide bendrofluazide xipamide	Thiazide diuretics	Inhibit Na/Cl cotransport in early distal tubule, have a mild inhibitory effect on CA, and a vasodilatory effect proceeding the diuresis (accompanied by ^ blood glucose level). BUT – metabolic alkalosis, hypokalaemia (significant decrease may cause problems if given with cardiac glycosides for congestive heart failure – potentiates effect) ^Mg excretion ^Ca reabsorption ^uric acid reabsorption
Diazoxide	Thiazide	Non diuretic thiazide – produces vasodilatory effect – via opening K_{ATP}. – Hence ^ blood glucose levels.
Triamterene	K Sparing diuretics	Block ENaC with mild diuresis – but reduced K loss
Amiloride	K Sparing diuretics	Can only Block ENaC from apical side - with mild diuresis – but reduced K loss.
Spironolactone	K Sparing diuretics	Competes for aldosterones intracellular binding site, preventing its action. Spironolactone metabolised in liver to canrenone (both involved) Effect only significant when under influence of aldosterone, and due to involving gene expression, long rate of onset.
Acetazolamide	Carbonic anhydrase inhibitor	Prevents reabsorption of $NaHCO_3$. in proximal and late distal tubule. Urine pH rises as consequence. BUT must block >99% enzyme to have appreciable effect. Only use now really is glaucoma
Mannitol	Osmotic	Small molecule, filtered but not

	diuretic	reabsorbed. Retains its equivalent of water so increased urine volume with decreased Na reabsorption. Maintains urine flow so good when reduced GFR. Used acutely to reduce cerebral oedema.

Renin – Angiotensin system

Captopril	ACE Inhibitor	Blocks production of angiotensin II thus leading to a reduction in pre and afterload. Most benefit in congestive heart failure associated with raised renin levels. BUT in hypotensive state can lead to renal failure because no constriction of glomerular efferent arteriole usually mediated by angiotensin II. ALSO bradykinin metabolism dependent on ACE, so ACEi prevent breakdown, so accumulates, some in brain stem and irritates cough reflex area – hence 'dry cough' also since Bradykinin is potent vasodilator and induces natriuresis, may add effect.
Enalapril	ACE Inhibitor	As above. However drug is inactive, must be metabolised in liver to enalaprilat
Saralasin	Partial AT_1 agonist	Inhibits the action of angiotensin II, similar effects as above. BUT peptide so cannot be used via oral administration. Not used
Losartan	AT_1 antagonist	Non peptide so doesn't have the problem as above. Has similar effects to above

Antihypertensive drugs

Thiazides, loop, K^+ sparing, CA inhibitors, osmotic	Diuretics	Act to reduce blood volume by inducing a natriuresis (thiazides/loop also cause a vasodilatation)
Captopril enalapril(at)	ACE Inhibitors	Reduce angiotensin II, aldosterone; ^ Na excretion. Decreased bradykinin metabolism may have an effect. BUT dry cough. Often used in combination with a diuretic for ^ effect
Propranolol	B non slelctive antagonist	^ TPR (B_2) decrease CO (B_1) so ABP~ over time ABP decreases. BUT bronchoconstriction and coronary constriction. Also depression and insomnia
Atenolol	B_1 specific antagonist	Decreased CO and rennin release. Fewer side effects
Pindolol	Partial B agonist	No effect on rennin; reduced effect on CO. (note xamoterol has no hypertensive effect)
Phenoxybenzamine phentolamine	Non selective α antagonist	Vasodilatation but with reflex tachycardia and ^ rennin release (α_2 block)

Prazosin	α_1 specific antagonist	Veno/vasodilatation, lack of reflex tachycardia (blockade CNS α_1 reduces sympathetic discharge) 'First dose effect' – postural hypotension (probably due to venodilatation)
Labetolol	α_1 β_1 β_2 antagonist	Used in pregnancy because reduced transmission across placenta
Nifedipine	L-type Ca channel block	Cardiovascular effects and mild diuretic effect (? Reduce aldosterone release) also antagonise baroreceptor reflexes. Usually combined with β blocker to combat reflex tachycardia (decrease TPR)
Minoxidil diazoxide (pinacidil, cromakalim, lemakalim)	K channel openers	Opens ATP dependent K channels (ATP closes) = hyperpolarisation and relaxation. Side effect minoxidil = hirtuism! Note often combined with β blocker and diuretic to combat reflex tachycardia and any increase in blood volume
Clonidine	α_2/I_1 agonists	Vasoconstriction topically, vasodilatation systemically; thought to be via imidazoline receptors. Rapid withdrawal may cause problems
Guanficine	α_2/I_1 agonists	More potent α_2 agonist so > topical vasoconstriction but not very potent antihypertensive (showing dilatation is not α_2 mediated)
Moxonidine Rilmenidine	I_1 agonists	Centrally acting antihypertensives with fewer side effects. Avoid rapid withdrawal
α-methyldopa	α_2 agonist	Converted to α-methynoradrenaline which is released as false transmitter. More potent on α_2 receptors and acts as partial agonist at $\alpha_1$receptors. Thus reducing central sympathetic release. Used in pregnancy.
Guanethidine		Depletes NA stores and reduces release. BUT postural hypotension
Reserpine	Inhibits uptake into vesicles	Initial hypertension but consequent depletion of vesicle store BUT severe depression
Hexamethionium trimetaphan	Ganglion block	First used. Block all ganglion transmission so many side effects. Hexamethonium used for malignant hypertension.
Sodium nitroprusside	Vasodilator	Metabolised to NO – used IV in hypertensive emergencies. BUT in solution yields CN so must be stored as powder.
Hydralazine	Vasodilator	Arteriolar vasodilatation.