Cardiovascular and renal pharmacology

Cardiovascular disease is the leading cause of death in the developed world.

Cardiac action potential

Many ion channels interact to generate a coordinated cardiac action potential.

- Depolarisation (0), rapid repolarisation (1), plateau (2), repolarisation (3), resting potential (4)
- Action potential differs in different parts of the heart e.g. in nodes membrane potential only reaches -60mV (c.f. -80 to -90mV)

Na channels

- Fast depolarising stage of action potential
- Transiently opened, becoming inactivated
- Activated by cardiac pacemaker cells (rather than neurotransmitter)
- 3 subunits: $\boldsymbol{\alpha}$, β_1, β_2
- α = 4 x 6 TMSD. S4 = voltage sensor, S6 lines pore (selectivity), S5-S6 loop outer entrance of pore; domain III-IV loop inactivation
- *Local anaesthetics* – alter form of action potential by stabilising channels in their inactivated state – antidysrhythmic

Ca channels

- 5 subunits $\boldsymbol{\alpha_1}$ α_2 β γ δ
- L-type: large depolarisation required (30mV) to open, found in most excitable cells, large single channel conductance, stay open long time, activity enhanced by phosphorylation $\boldsymbol{\alpha_1}$, responsible for plateau phase
- T-type: open transiently with rapid inactivation, low single channel conductance, small depolarisation required to open (10-20mV), present in pacemaker: trigger T-type may sufficiently depolarise cell to activate L-type.
- *Dihydropyridines – nifedipine*: S6 in domain III, S5-S6 loop in IV. Doesn't block T-type channels
- *Phenylalkylamines – verapamil*: S5-S6 loop in IV ? affecting selectivity and inactivation
- *Benzothiazepines – diltiazem*: block from outside (+ modulate nifedipine binding)

Potassium channels

- K conductance is complex with several channel types
- Mutations in VGKC can cause long QT syndrome and sudden adult death syndrome.
- Dual role: repolarisation at end of AP and stabilisation and modification of the resting cell membrane potential
- *Voltage gated*: 4 peptides make pore. Inactivation: 'N-type' ball and chain vs 'C-type' movement of residues at extracellular surface of pore - slower
- *Inward rectifying*: (the action of excitable membranes to allow electrical impulses to be conducted preferentially in one direction). Responsible for maintenance of resting membrane potential (I_{K1} current). If K channels open

all time then with cardiac plateau would lose massive amount of K. They conduct inward K current at hyperpolarised potentials, but close at depolarised potentials, preventing outward K current and K loss. They have 'valve-like' behaviour. Mg and polyamines such as spermine are implicated in rectification mechanism

- K_{ATP} channel – ATP sensitive (sulphonylurea sensitive - inhibition). Hypoxia → reduced ATP → channels open → hyperpolarisation → cardioprotection

Pacemaker

- No nervous input initiating each AP
- Intrinsic rhythm produced by spontaneous AP generated by nodal tissue.
- Nodal tissue doesn't have stable resting potential but gradually rises until gating potential of VGIC reached.
- I_f current is responsible 'hyperpolarisation activated cyclic nucleotide gated channels (HCN)– open on hyperpolarisation and close at depolarisation
- As permeable to Na as they are to K, but on hyperpolarisation Na enters.
- Activated directly by cAMP rather than through cAMP mediated PKA activity

Autonomic effects on cardiac physiology

- Sympathetic – β_1 adrenergic in nodal cells and ventricular muscle.
    - phosphorylation α_1 subunit L-type Ca channels increasing flux (via PKA activated by G_s – quite slow, takes ~30s to reach maximum current)
    - sensitise ryanodine receptors, increased Ca release → positive inotropic effect
    - potential at which I_f is activated is positively shifted → positive chronotropic effect (via cAMP)
    - Various delayed rectifier K channels enhanced leading to accelerated repolarisation and hence positive chronotropic effect

- Parasympathetic – M2 channels in nodes only (no inotropic effect)
    - ↓ PKA and βγ inhibit Ca current (but no effect on force)
    - potential at which I_f is activated is negatively shifted → negative chronotropic effect
    - I_{KACh} leads to hyperpolarisation

Dysrhythmia

- Conduction system of heart ensures organised and appropriate stimulation
- SA node initiates normal rhythm (~70min^{-1})
- SA node damage or increased excitability of another area can lead to ECTOPIC FOCI/PACEMAKER.
- Myocardium is a functional syncytium and can conduct in any direction
- AP's collide at common point: extinction patern
- VGIC inactivate upon activation which leads to refractory period preventing re-excitation inappropriately.

- Problems include SA damage, myocardium damage (slows conduction so pulse arrives late and can excite tissue that would have been refractory). Most often caused by MI → connective tissue low conductivity. E.g re-entrant dysrhythmias
- **Vaughan Williams classification of anti-dysrhythmics** (based on the effect of the drug on the action potential rather than the class of drug)

- ***Class I***
  Na channel block (LA)
  - ***IA*** *Quinidine* and *procainamide*– affinity for open state, drug lengthens refractory period preventing re-entrant behaviour – Intermediate kinetics
  - ***IB*** *Lignocaine* – (iv) binds during phase 0, and dissociates in time for next AP, but if AP arrives early, drug still associated and prevents excitation. Prevents premature beats. Rapid kinetics
  - ***IC*** – Flecainide – slow onset
- ***Class II***
  β adrenoreceptor antagonists
  - *β* blockers reduce sympathetic effects. Catecholamines can act on ischaemic myocardium which is already liable to inappropriate excitation, and exert inotropic and chronotropic effects which leads to susceptibility to dysrhythmias. E.g. *propranolol, atenolol*
- ***Class III***
  Sotalol and amiodarone – increase action potential duration possibly by inhibiting repolarising potassium currents
- ***Class IV***
  Ca channel blockers
  - *verapamil* and *diltiazem* Ca block – but not used when cardiac function is compromised as may inhibit contraction!

Congestive heart failure

Heart fails to maintain adequate circulation of the body. If the heart is unable to cope, more blood returns than can be pumped, and the venous circulation becomes congested. Although veins adaptable increased hydrostatic forces leads to oedema.

Can arise rapidly e.g. due to MI or streptococcal infection; but more normally develops gradually due to chronic excessive functional demands, e.g. dysrhythmias, diabetes. Severity of heart failure graded by the NYHA classification 1-4.

So to treat: increase contractile force of heart – positive inotropic effect, and reducing the load by reducing filling pressure.

- ***Cardiac glycosides*** – Digoxin and digitoxin. (also ouabain but too powerful) act by inhibiting the Na/K ATPase. This prevents 3Ca/1Na exchange due to raised intracellular Na. This leads to raised Ca. Also stimulates vagus – greater

time for ventricular filling. May also have deleterious effects on sympathetic transmission so often these are only used when there is also dysrhythmias.

- ***β_1 agonists*** – sympathetic stimulation leads to positive inotropic effect. BUT this leads to increased cardiac oxygen demand, increase heart rate – may precipitate dysrhythmias, may precipitate/potentiate hypertension. *Dobutamine* (β_1 block can make severe cardiac failure worse)
- ***β_1 antagonists –*** cardiac failure leads to chronic sympathetic stimulation, which can lead to desensitisation of receptors with β receptors disproportionately downregulated and α_1 upregulated. This leads to increased adrenergic output which can result in cardiomyocyte apoptosis. *Bisoprolol and carvedilol* limit damaging effects of chronic catecholamine stimulation and improve cardiac function.
- ***Inodilators*** – inotropic and vasodilatation. Phosphodiesterase inhibitors – raises cAMP mimicking β_1 stimulation. Type III phosphodiesterase inhibitors important here: *Amrinone (*short acting*), milrinone* (long acting). Dilatation… ? MLCK phosphorylation decreases action thus no contraction.
- ***Methylxanthines*** – *caffeine, theophtlline* – non selective phosphodiester inhibitors, but also adensosine A_2 antagonists leading to Ca release from stores
- ***Calcium sensitisers -*** *Pimobendan* – for canine dilated cardiomyopathy – calcium sensitiser, increase cardiac calcium binding efficiency to troponin without a requirement for more energy consumption. Also inhibit PDE III causing peripheral vasodilaition. In humans: *levosimendan*
- ***ACE inhibitors*** – see later. Reduce preload (decreasing body fluid volumes) and afterload (reducing peripheral vascular resistance)
- ***Diuretics*** – (decrease oedema) see later
- ***Drugs targeting excitation*-contraction coupling** – SERCA2 gene therapy – clinical trials in UK

Endothelin system

Endothelin-1 derived from vascular endothelium, potent vasoconstrictor, mitogenic and inotropic in myocardium. Larger peptide cleaved by 'endothelin converting enzyme'. Evidence for role of endothelin-1 in disease progression, plasma levels raised, can contribute to exercise intolerance. Two receptors: ET_A vascular smooth muscle – constriction; ET_B constriction at muscle, but also dilatation at endothelium. *Bosentan* non specific antagonist being used in trials.

Anticoagulant drugs

Fibrinolytic agents

MI emergency treatment with clot lysis can improve survival. Drugs aim to dissolve clots and limit necrosis.

- *Streptokinase* – binds plasminogen activator generating plasmin protease. This is antigenic so not suitable for chronic use
- *Anistreplase* – plasminogen and anisoylated streptokinase – more prolonged activity
- *Urokinase* – endogenous protein. Single chain secreted by kidney. Two chain plasminogen activator
- *Alteplase, duteplase, reteplase* – recombinant single/double chain human tissue plasminogen activators.

Note, *Tranexamic acid* can inhibit fibrinolysis, by competitively inhibiting plasminogen activation, and at higher concentrations, non-competitively inhibits plasmin.

Prevention of clot formation

Heparin – activates anti-thrombin III, which inactivates serine proteases of the coagulation cascade including Xa. Must be administered by injection.

Inhibitors of glycoprotein IIb/IIIa receptor – this receptor is involved in fibrinogen bridging between platelets causing aggregation. *Eptifibatide (peptide inhibitor), Tirofiban (non-peptide inhibitor)* and *Abciximab (monoclonal antibody against receptor)*

Aspirin – irreversible inhibitor of cyclooxygenase prevent platelet aggregation by altering balance of prostacyclin and thromboxane in favour of vasodilatory and anti-aggregative prostacyclin.

Clopidogrel – inhibits platelet aggregation by inhibiting binding of ADP to its receptors: $P2Y_1$ and $P2Y_{12}$.

Warfarin – oral anticoagulant. Blocks vitamin K epoxide reductase, an enzyme in a cycle that is required for gamma-carboxylation of clotting factors II, VII, IX and X as well as regulatory proteins C, S and Z. Problem is that many drugs interact (through activating or inhibiting warfarins metabolism and so regular blood tests required)

Dabigatran – a thrombin inhibitor used as prophylaxis in patients undergoing knee or hip surgery (DVT prophylaxis) and in patients with atrial fibrillation + 1 additional risk factor for stroke [shown to be 40% better than warfarin at reducing risk]

Rivaroxaban – first factor Xa inhibitor, similar uses as above.

Renal Pharmacology

DIURETICS

Diuretics cause an increased urine output – with increased Na excretion (*natriuresis*). Ie diuretics induce increased excretion of solutes and water.

Effect: reduces volume of extracellular fluid compartment.

Hence can reduce blood volume and so are useful in congestive heart failure and hypertension (as well as maintaining renal function in various renal diseases)

1. Loop diuretics

- Act on loop of henle
- 'high ceiling' – capacity to cause high diuresis (4 litres day^{-1}) can be dangerous if used inappropriately)
- *Frusemide, bumetanide, piretanide* – are sulphonamides
- Block Na-K-2Cl co-transporter in apical membrane of ascending limb
- Drugs actively secreted into proximal tubule – so concentration
- Weak inhibition of carbonic anhydrase
- Given iv, accelerated effect, putatively attributed to venodilatation role
- Can lead to hypokalaemia – can be reversed by use of slow release K compounds given in conjunction
- Also metabolic alkalosis – increased Na/H exchange leads to H loss
- Ca and Mg loss is increased
- Uric acid excretion decreased (*probenecid* given to reverse by blocking reabsorption)

2. Thiazide diuretics

- *Hydrochlorothiazide, bendrofluazide, xipamide*
- lesser effect than loop diuretics. Some inhibition of CA
- Action in cortical segment of thick ascending limb, or distal tubule, blocking the Na/Cl co-transporter (binding to Cl site)
- In later stages also have an effect on vasodilation
- Again hypokalaemia and metabolic acidosis problems (contraindication with cardiac glycosides, as with low K the action of glycosides is enhanced)
- Mg loss is increased, uric acid loss decreased.

3. Potassium sparing diuretics

- *Amiloride, triamterene, spironolactone*
- Amiloride and triamterene: block the Endothelial Na channel in late distal tubule. Diuretic effect weak, but K loss reduced.
- Spironolactone: antagonises the action of aldosterone. Spironolactone is metabolised in liver to canrenone. Competes with aldosterone for binding to cytoplasmic receptor (hence reduced synthesis of Na channels and Na/K ATPase). Effect of drug is only significant when distal tubule under influence of aldosterone. Because requires turnover of channels, slow rate of onset.

4. Carbonic anhydrase inhibitors

- *Acetazolamide*.
- Inhibit $NaHCO_3$ reabsorption in proximal and distal tubules
- CAi reduce availability of H^+ and so urine pH rises as HCO_3^- increases

- BUT >99% enzyme must be blocked to achieve an appreciable effect
- Leads to K loss in distal tubule
- Only weak diuretics, but one important use is in glaucoma

5. Osmotic diuretics

- Simplest in action. Archetypal example is *mannitol*.
- Small molecular weight substance filtered but not reabsorbed, hence retaining osmotic equivalent of water and hence increasing urine volume
- Useful when urine flow is reduced due to excessive reabsorption, as maintains urine flow
- Can reduce rapidly intracranial and intraocular pressure so useful for cerebral oedema due to head injuries

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Blood pressure: hypertension

Renin angiotensin system

Decreased perfusion of renal vessels, and sympathetic stimulation, leads to release of rennin from juxtaglomerular apparatus. Renin cleaves angiotensinogen → angiotensin I converted to angiotensin II by ACE. Prevalent on endothelium of lung

Angiotensin II leads to increased ABP, via vasoconstriction, thirst, aldosterone…

- *ACE inhibitors: captopril, enalapril* (converted to active enalaprilat in liver) usually combined with diuretics. (hypotension is potentially dangerous as risk of renal failure is increased since glomerular efferent cant constrict (ang. II mediated)
- *Saralasin* – angiotensin II partial agonist – peptide so not good orally
- *Losartan* – non peptide angiotensin II antagonist

Renal kallikrein-kinin system

Bradykinin is a short peptide – potent natriuretic and renal vasodilator.

If high Na reaches distal tubule, then kallikrein released, catalyses kinninogen → bradykinin, and Na reabsorption inhibited

Atrial natriuretic peptide

Released from heart in response to atrial stretch. Acts via membrane bound guanylate cyclase receptor

Actions reduce blood pressure and volume: vasodilator, reduces Na reabsorption stimulatin natriuresis, inhibits rennin release.

MEDIC ONLY

Antihypertensive chemotherapy

Most cases are 'essential' hypertension with unknown aetiology.

Non pharmacological treatments: lose weight, sodium restriction, exercise etc.

Diuretics – as above

ACE inhibitors – captopril, enalapril. Decreased angiotensin II and aldosterone. Usually combined with diuretic. Decreased bradykinin metabolism may lead to dry cough

β adrenoreceptor antagonists – e.g. propranolol, or more specific atenolol (prevent bronchoconstriction) various suggested modes of action including decreased CO., decreased plasma renin.

α_1-adrenoceptor antagonists – prazosin. Arterioles tonically constricted via α_1 receptor. Non selective α block (phenoxybenzamine) gives vasodilatation AND reflex tachycardia due to increased sympathetic activity (***α_2*** normally inhibit NA release) With prazosin lack of reflex tachycardia. 'first-dose effect'

Calcium channel antagonist – act on L-type channels. May also have mild diuretic effects and may block aldosterone. Most commonly *nifedipine*.

Potassium channel openers – *lemakalim, pinacidil, minoxidil, diazoxide, cromakalim*. Act on ATP-sensitive K channels in vascular smooth muscle – hyperpolarising. Drugs antagonise the activity of ATP and sulphonylureas

Centrally acting α_2/I_1 agonist – *clonidine, guanfacine.* Vasoconstriction if given topically, vasodilator systemically. Originally thought to be due to decreasing NA. However effect now seems to be via imidazoline receptor I_1. circumstantial evidence: guanficine more potent α_2 agonist but low efficacy as antihypertensive.

Alpha-methyldopa – centrally acting. Converted to 'false transmitter' reducing NA release.

Sympatholytics

- *Guanethidine –*
- *Reserpine –*

Ganglion blockers

- *Hexamethonium –*
- *Trimetaphan*

Sodium nitroprusside – metabolised to NO. in solution hydrolyses to HCN so stored as powder in dark

Hydralazine – arteriolar vasodilator mechanism unknown.

Hypolipidaemic drugs

Reducing plasma lipids beneficial for reducing effects downstream of atherosclerosis.

- *Statins, e.g. lovastatin* – inhibits HMG-CoA reductase (rate limiting step in cholesterol synthesis), hence liver scavenges from blood
- *Cholestyramine* – anion exchange resin, prevents reuptake of bile acids from intestine – hence liver increases cholesterol metabolism to generate bile acids
- *Clofibrate* – stimulates lipoprotein lipase releasing triglycerides from VLDL which can then be taken up for metabolism or storage
- *Nicotinic acid* – inhibits triglyceride production in liver
- *Fish oil* – reduces hypertriglyceridaemia, and eicosapentanoic acid contained substitutes for arachidonic acid in production of Pg and Tx which are less effective at causing platelet aggregation.

Angina Pectoris

Commonest manifestation of ischaemic heart disease – inadequate blood flow to the myocardium. Can lead to dysrhythmias or congestive heart failure.

Variant angina – coronary artery spasms spontaneously

In systole myocardium receives little blood. Sympathetic stimulation causes angina pt to suffer pain:

- Increased heart rate (less time in diastole),
- increased force of contraction (O_2 demand),
- decreased cardiac efficiency

Sympathetic stimulation can also cause dilatation via β_2 receptors. However in angina pt resting oxygen demand is achieved by full dilatation and so no additional capacity.

Collateral circulation develops – form of adaptation

- *Nitrovasodilators – glyceryl trinitrate* (poor absorption so sublingual)*, isosorbide dinitrate, amyl nitrite*. They are converted to NO in smooth muscle cells by modulation of Ca sensitive eNOS. NO → cGMP → MLCK. As coronary vessels fully dilated, believed main effect is on VENOUS dilatation as well as collaterals.

- *Dipyridamole* – another vasodilator stimulates adenosine receptors – opens all vessels leading to coronary steal.
- *β antagonists – propranolol, atenolol*… reduce sympathetic stimulation. BUT non selective have disadvantage by revealing α_1 mediated vasoconstriction by removing β_2 dilatation. In heart failure, sympathetic stimulation must be maintained for adequate CO, and so partial agonists can be used: *alprenolol*
- *Ca channel block – nifedipine* – acts on vascular smooth muscle > myocardium, leading to vasodilatation. Nifedipine binds inactivated state (more at -60 of muscle, than -90 myocardium)
- *Angiogenesis* – promising recent development. Most work using VEGF. Must limit duration of exposure, so use adenoviral or plasmid.

VETS ONLY

Anthelmintics

Helminths: malnutrition, tissue damage, anaemia, luminal obstruction, migratory damage, carriers of other pathogens, hypersensitivity.

Need to subvert unique and novel characteristics of helminths. However often precise MODA isn't known for sure.

Levamisole and pyrantel – cholinergic agonists

- Agonists at synaptic and extrasynaptic nicotinic receptors. Channel permeable to both K and Na.
- Open channel blockade – self antagonism by drug entering channel
- Channel pentameric – variation of subunits can lead to resistance

Aldicarb and dichloros – anticholinesterases

- ACh builds up causing contractions and paralysis.
- Drugs carbamylate or phosphorylate the AChE
- Helminths have multiple isoforms with different distributions

Paraherquamide – nicotinic antagonist

- Causes flaccid paralysis by inhibiting depolarisation
- Also inhibit motility of worms
- Show selectivity for parasite nAChR

Piperazine – GABA agonist

- Ligand gated Cl channels – causing hyperpolarisation and flaccid paralysis
- High [CO_2] is required – as found in gut – less active against free living worms
- Distinct worm isoforms of receptor: $GABA_n$ (insensitive to mammalian $GABA_a$ antagonist bicuculine

Avermectins and milbemycin – glutamate gated Cl channel

- Increases muscle Cl permeability – hyperpolarisation and flaccid paralysis
- Novel receptor appears to be invertebrate specific
- Two subunit types: α and β forming pentamers. Drug binds to α unit whilst glutamate binds β units.
- Targets pharyngeal muscles preventing feeding, also egg laying and motile musculature
- Low [drug] potentiates glutamate; high [ ] directly opens

Praziquantel – Ca permeability

- Believed to increase Ca permeability but the precise channel involved is unknown
- Rapid muscle contraction and thus spastic paralysis
- Also damages tegument revealing antigens allowing immune response
- Schisto β subunit decreases peak Ca current but also confers sensitivity to praziquantel when coexpressed with mammalian α.

Benzimidazoles – microtubule formation

- Vesicle trafficking, structural integrity, cell division, glucose uptake
- Drugs bind β tubulin and act as 'cap' preventing further polymerisation
- 'dynamic instability' leads to disappearance of microtubules
- leads to a slow starvation
- resistance can be generated by mutation in tubulin: Y200F

Nitroxynil and closantel – proton ionophores

- dissociateable H^+ and lipophilic, allows proton gradient to be dissipated across mitochondrial membranes
- also fall in pH gradient across tegument

MCQ – True/False – Negatively marked

1. Ion channels and the cardiac AP

a) Phase 2 of the cardiac AP is rapid repolarisation
b) Fast depolarising phase is attributed to Na channels
c) L-type Ca channels require only low depolarisation to become active
d) T-type Ca channels have a low single channel conductance
e) VG K^+ channel comprises single peptide with 4 domains (each with 6 TMSD)
f) I_f is the current responsible for initiating the activity of the SA node

2. Autonomic effects

a) Sympathetic stimulation shifts I_f to more depolarising potentials
b) Parasympathetic system has both negative inotropic and chronotropic effects

3. Dysrhythmias

a) Cardiac muscle can conduct in any direction
b) Ectopic pacemaker is when the SA node increases its frequency
c) Local anaesthetics can be used to treat dysrhythmias
d) β_1 agonists may be used to treat dysrhythmias

4. Congestive heart failure

a) If the left side of the hear fails there is pulmonary oedema
b) Chronic excessive functional demands lead to rapid development of CHF
c) Type V phosphodiesterase inhibitors can be used to treat CHF
d) Reduced endothelin is associated with CHF

5. Angina pectoris

a) Dilatation of coronary arteries is a plausible means of treatment
b) β_1 antagonists are better than β non selective for angina treatment

6. Clot lysis and hyperlipidaemia

a) several drugs target the activation of plasmin to degrade clots
b) statins target the rate limiting step of cholesterol synthesis

MCQ – True/False – Negatively marked

1. Ion channels and the cardiac AP

g) Phase 2 of the cardiac AP is rapid repolarisation **F PHASE 1**
h) Fast depolarising phase is attributed to Na channels **T**
i) L-type Ca channels require only low depolarisation to become active **F LARGE**
j) T-type Ca channels have a low single channel conductance **T**
k) VG K^+ channel comprises single peptide with 4 domains (each with 6 TMSD) **F 4 PEPTIDES**
l) I_f is the current responsible for initiating the activity of the SA node **T**

2. Autonomic effects

c) Sympathetic stimulation shifts I_f to more depolarising potentials **T**
d) Parasympathetic system has both negative inotropic and chronotropic effects **F NO INOTROPIC BECAUSE NO RECEPTORS IN MUSCLE**

3. Dysrhythmias

e) Cardiac muscle can conduct in any direction **T**
f) Ectopic pacemaker is when the SA node increases its frequency **F WHEN OTHER PACEMAKER (IE NOT SA)**
g) Local anaesthetics can be used to treat dysrhythmias **T**
h) β_1 agonists may be used to treat dysrhythmias **F ANTAGONISTS**

4. Congestive heart failure

e) If the left side of the hear fails there is pulmonary oedema **F SYSTEMIC E.G. ABDOMINAL ASCITES**
f) Chronic excessive functional demands lead to rapid development of CHF **F GRADUAL DEVELOPMENT**
g) Type V phosphodiesterase inhibitors can be used to treat CHF **F TYPE III**
h) Reduced endothelin is associated with CHF **F RAISED**

5. Angina pectoris

c) Dilatation of coronary arteries is a plausible means of treatment **F THEY ARE ALREADY DILATED AT REST**
d) β_1 antagonists are better than β non selective for angina treatment **T**

6. Clot lysis and hyperlipidaemia

c) several drugs target the activation of plasmin to degrade clots **T**
d) statins target the rate limiting step of cholesterol synthesis **T**

MCQ – True/False – Negatively marked

1. Diuretics

a) Loop diuretics block Na/Cl co-transporter
b) Loop diuretics induce hypokalaemia and metabolic acidosis
c) Thiazide diuretics demonstrate greater diuresis than loop diuretics
d) >99% carbonic anhydrase must be blocked for efficacy
e) osmotic diuretics can be filtered but not reabsorbed

2. Renal system

a) Renin is induced by raised renal perfusion pressure
b) Renin converts angiotensin I to angiotensin II
c) ACE inhibitors are used as antihypertensives
d) Bradykinin reduces the reabsorption of Na
e) ANP responses aim to reduce the ABP

3. Antihypertensives

a) α_1 agonists can be used to treat hypertension
b) Calcium channel blockers can be used to treat hypertension
c) Drugs can be used to antagonise the effect of ATP on the K_{ATP} channels to treat hypertension.
d) β_1 selective agonists are preferred as antihypertensives
e) central α_2 receptors are targeted by antihypertensives

4. Anthelmintics

a) Nicotinic agonists and antagonists are useful as anthelmintics
b) GABA agonists induce a flaccid paralysis
c) Glutamate gated Ca^{2+} channels are targeted by anthelmintics
d) Resistance to microtubule disrupting drugs has not been recognised yet
e) Microtubule disrupting drugs kill worms by starving them

MCQ – True/False – Negatively marked

1. Diuretics

a) Loop diuretics block Na/Cl co-transporter **F Na/K/2Cl**
b) Loop diuretics induce hypokalaemia and metabolic acidosis **F ALKALOSIS**
c) Thiazide diuretics demonstrate greater diuresis than loop diuretics **F**
d) >99% carbonic anhydrase must be blocked for efficacy **T**
e) osmotic diuretics can be filtered but not reabsorbed **T**

2. Renal system

a) Renin is induced by raised renal perfusion pressure **F - LOWERED**
b) Renin converts angiotensin I to angiotensin II **F (ACE)**
c) ACE inhibitors are used as antihypertensives **T**
d) Bradykinin reduces the reabsorption of Na **T**
e) ANP responses aim to reduce the ABP **T**

3. antihypertensives

a) α_1 agonists can be used to treat hypertension **F - ANTAGONISTS**
b) Calcium channel blockers can be used to treat hypertension **T**
c) Drugs can be used to antagonise the effect of ATP on the K_{ATP} channels to treat hypertension **T**
d) β_1 selective agonists are preferred as antihypertensives **F ANTAGONISTS**
e) central α_2 receptors are targeted by antihypertensives **T**

4. Anthelmintics

a) Nicotinic agonists and antagonists are useful as anthelmintics **T**
b) GABA agonists induce a flaccid paralysis **T**
c) Glutamate gated Ca^{2+} channels are targeted by anthelmintics **F Cl**
d) Resistance to microtubule disrupting drugs has not been recognised yet **F**
e) Microtubule disrupting drugs kill worms by starving them **T**