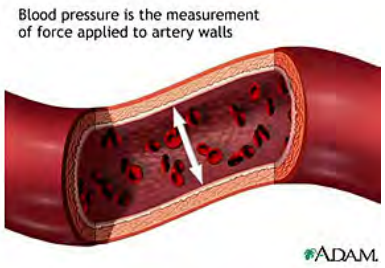
Hypertension

Dr K Outhoff



Some thoughts about high blood pressure

- Systemic arterial hypertension is one of the strongest known modifiable risk factors for ischaemic heart disease
- Also a risk factor for
  - Stroke
  - Heart failure
  - Chronic kidney disease
  - Cognitive decline
  - Premature death
- Under-diagnosed and under-treated
- Lower the *diastolic pressure*, the lower the incidence of complications

Background: High Blood Pressure:

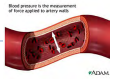
- Untreated hypertension can cause vascular and renal damage leading to a treatment-resistant state
- Each 2 mmHg rise in systolic blood pressure associated with increased risk of mortality:
  - 7% from heart disease
  - 10% from stroke.

Predisposing factors

1. Positive family history
2. Obesity
3. Insulin resistance
4. Salt intake
5. Stress
6. ? Low birth weight

Pathophysiology of essential hypertension

- Arterial BP determined by:
  - Cardiac output
    - Renal control of intravascular volume:
    - excretion of water and salt via RAAS
  - Peripheral vascular resistance (most NB)
    - Calibre of vessel
    - Total cross-sectional area of resistance vessels (small arteries and arterioles)



Increased Peripheral Resistance

- Structural abnormalities:
  - Reduction in vessel numbers
  - Vessel wall hypertrophy with encroachment on the lumen
- Functional abnormalities:
  - Increased vasoconstriction
    - Background Sympathetic tone
    - Endothelin (vasoconstrictor peptide)
  - Reduced vasodilation
    - decreased paracrine vasodilator, Nitric Oxide

Diagnosis in the ideal world (1)

If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) to confirm the diagnosis of hypertension.

Diagnosis in the ideal world (2)

When using the following to confirm diagnosis, ensure:
ABPM:
- at least two measurements per hour during the person's usual waking hours, average of at least 14 measurements to confirm diagnosis

HBPM:
- two consecutive seated measurements, at least 1 minute apart
- blood pressure is recorded twice a day for at least 4 days and preferably for a week
- measurements on the first day are discarded – average value of all remaining is used.

Definitions

Stage 1 hypertension:
- Clinic blood pressure (BP) is 140/90 mmHg or higher **and**
- ABPM or HBPM average is 135/85 mmHg or higher.

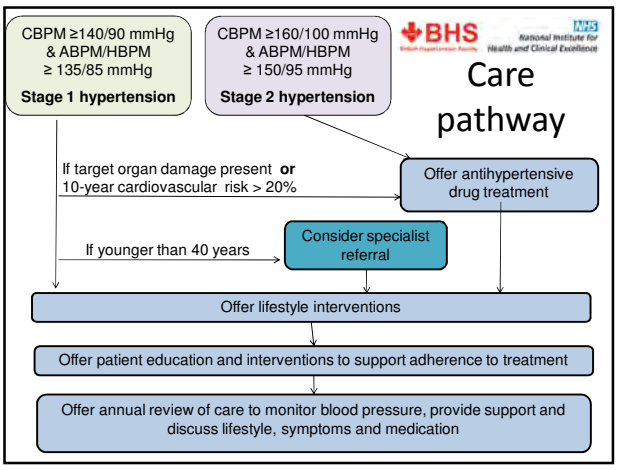
Stage 2 hypertension:
- Clinic BP 160/100 mmHg is or higher **and**
- ABPM or HBPM daytime average is 150/95 mmHg or higher.

Severe hypertension:
- Clinic BP is 180 mmHg or higher **or**
- Clinic diastolic BP is 110 mmHg or higher.

NICE guidelines for management of hypertension in primary care: 2011

- Measure blood pressure
  - >140/90
- Lifestyle advice
  - Initially, then periodically
- Cardiovascular risk
  - Diabetes,
  - Hypertensive damage to heart, kidneys
  - Secondary causes of hypertension
- Pharmacological interventions
- Continuing treatment
  - Annual review
  - If blood pressure well controlled and no other risk factors: give trial of reduction or withdrawal of therapy

Care pathway



Additional recommendations

Lifestyle interventions

Offer guidance and advice about:

- diet (including sodium and caffeine intake) and exercise
- alcohol consumption
- smoking.

Patient education and adherence

Provide:

- information about benefits of drugs and side effects
- details of patient organisations
- an annual review of care.

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Initiating drug treatment

Offer antihypertensive drug treatment to people:
– who have stage 1 hypertension, are aged under 80 and meet identified criteria
– who have stage 2 hypertension at any age.

If aged under 40 with stage 1 hypertension and without evidence of target organ damage, cardiovascular disease, renal disease or diabetes, consider:
– specialist evaluation of secondary causes of hypertension
– further assessment of potential target organ damage.

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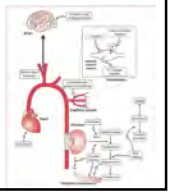
Drugs used to treat hypertension

1. ACE-I and ARB's
2. Calcium Channel Blockers (CCB)
3. Diuretics
   - Thiazide-like preferred
   - Or thiazide in some situations eg BP stable, well controlled
   - Or spironolactone for treatment resistant hypertension
4. Alpha-1 blockers
5. Beta blockers
6. Centrally acting



Which agent to be used first line?

- Usually 2 or more drugs required in most patients
- European and American guidelines suggest initiating Rx on 2 agents
- Traditionally these 2 agents have been:
  - B-blocker (atenolol) + diuretic (thiazide)
  - But this combination is associated with developing diabetes
- ASCOT-BPLA study suggests that:
  - Amlodipine (CCB) + Perindopril (ACE-I) is better in reducing cardiovascular events in hypertensive patients

NICE: pharmacological interventions 2011: choice of initial therapy

Younger than 55 years:

- ACE-inhibitor or ARB if not tolerated

Older than 55 years or Black patient of any age

Most likely to confer benefits:

- CCB or
- Thiazide-like diuretic (eg indapamide) if unable to tolerate CCB (heart failure, oedema, etc)

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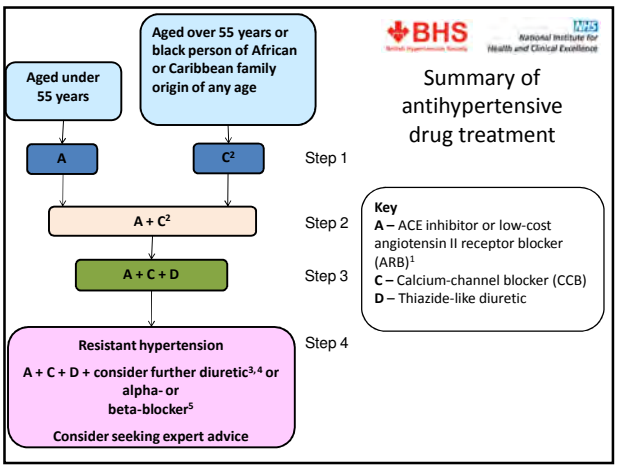
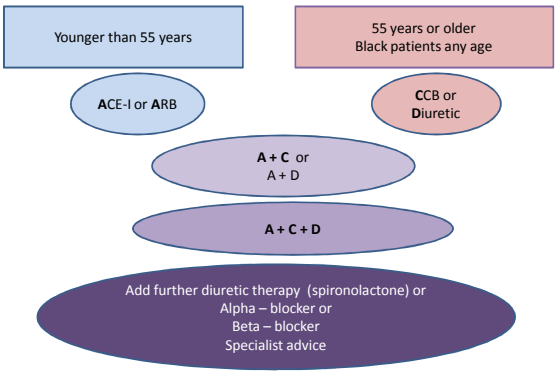


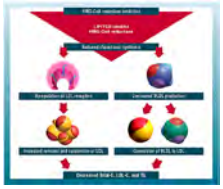
NICE: pharmacological interventions



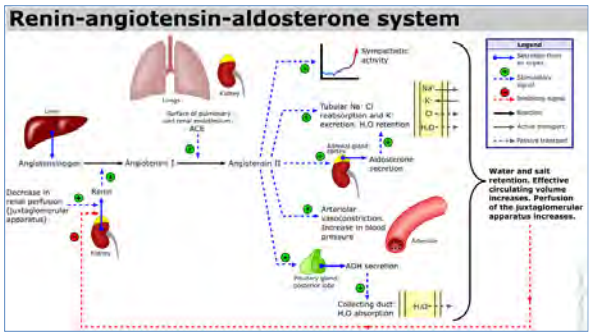
Statins

- In Hypertension with 3 other risk factors for cardiovascular disease, **but with a normal to low cholesterol**, adding a statin (Atorvastatin), decreases major cardiovascular events by 36%.

ASCOT-LLA



ACE-inhibitors

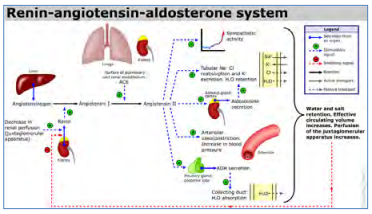


ACE inhibitors

- Some licensed for use in as single agents in mild hypertension
- Others licensed for add-on therapy with diuretics in moderate to severe hypertension
- Beneficial in patients with heart failure – reduce mortality
- ? favourable for slowing diabetic nephropathy
- Initiate treatment with small dose, given last thing at night – first dose hypotension
- Increase dose gradually

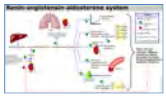
ACE inhibitors

- Captopril
- Enalopril
- Lisinopril
- Quinapril
- Perindopril
- Ramipril
- Trandolapril



ACE inhibitors mechanism of action

- Inhibit production of Angiotensin II (a potent vasoconstrictor and growth promoter)
- Increase the levels of the vasodilator bradykinin by inhibiting its degradation
- Bradykinin associated with release of vasodilators
  - NO
  - Prostacyclin
- Bradykinin also responsible for some adverse effects:
  - Dry cough from stimulating cough afferents
  - Hypotension
  - Angio-oedema

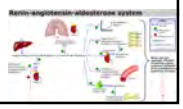


ACE inhibitors

- Reduce the activity of the sympathetic nervous system as angiotensin II promotes
  - Release of noradrenaline from sympathetic nerve terminals
  - Inhibits NA re-uptake
  - Therefore use not associated with reflex tachycardia despite arteriolar and veno-dilatation
- Reduce aldosterone secretion from zona glomerulosa
  - Reduced Na and H20 retention
- Improve:
  - beta receptor density (causing up-regulation)
  - Variation in heart rate
  - Baroreceptor function
  - Autonomic function (incl. Vagal tone)

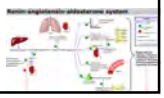
ACE inhibitors clinical uses

- Hypertension
- Symptomatic left ventricular dysfunction:
  - When added to diuretics, improve symptoms, exercise tolerance, survival in chronic heart failure
- Asymptomatic left ventricular dysfunction:
  - Enalapril has been shown to reduce the development of heart failure
- Left ventricular dysfunction after myocardial infarction:
  - Lower mortality in patients with impaired systolic function, irrespective of symptoms
- Slowing disease progression:
  - From mild to severe heart failure



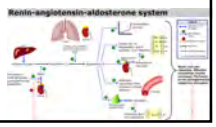
ACE inhibitors Adverse Effects

- First dose hypotension
- Dry cough
- Functional renal failure
  - Occurs predictably in bilateral renal artery stenosis
  - renal failure in foetus with oligohydramnios
- Rare urticaria and angio-oedema, but esp in Afro-Caribbean
- Modest hyperkalaemia (reduced aldosterone)
  - Caution with K sparing diuretics, K supplements, renal impairment



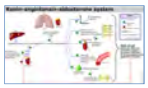
ACE-I pharmacokinetics

- Oral absorption
- Highly polar
- Eliminated in urine
- Some are pro-drugs requiring conversion to active metabolites:
  - Enalapril
  - Quinapril
- Do not penetrate CNS well

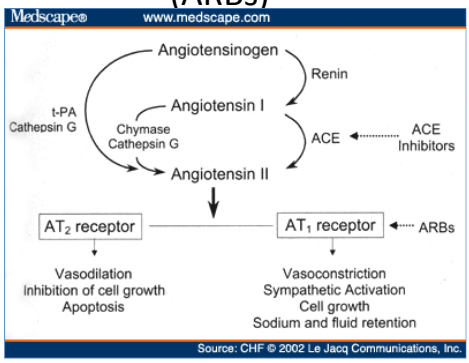


Drug interactions

- Useful interaction with loop and thiazide diuretics
  - Diuretics increase renin which limits their efficacy
  - ACE-inhibitors interrupt this loop and confer greater diuretic efficacy
- Life-threatening hyperkalaemia
  - K sparing diuretics
  - K supplements
  - Renal failure
  - NSAIDs contra-indicated in heart failure and may cause severe hyperkalaemia and fluid retention in patients receiving ACE-I

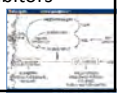


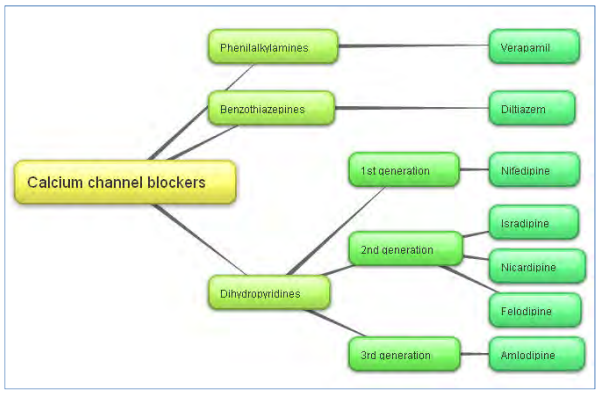
Angiotensin Receptor Blockers (ARBs)



ARBs - angiotensin receptor (AT-1) blockers
LOSARTAN, valsartan, olmesartan

- Newer class of agents
- Orally active angiotensin II type 1 receptor antagonist
- Alternative for blocking renin-angiotensin system
- Improved tolerability – no bradykinin, no cough
- Some develop angioedema
- Acceptable alternative in patients who develop intolerable side effects from ACE-inhibitors
- Also appear more effective than ACE-inhibitors in black patients and should be the preferred second line agent (in combination with CCBs)
- Should not be used in combination with ACE-inhibitors



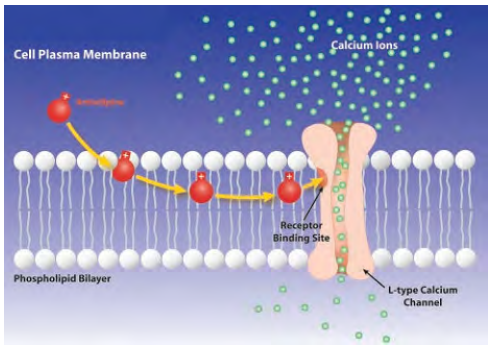


Calcium channel blockers (CCBs)

Indicated for:
- Hypertension
- Angina
- Supraventricular tachy-arrhythmias

Three chemically distinct classes:
1. Dihydropyridines: (Nifedipine, Amlodipine, Nimodipine)
2. Benzothiazepines: (Diltiazem)
3. Phenylalkylamines: (Verapamil)

CCBs

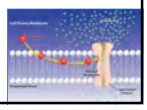


Calcium channel blockers mechanism of action

- Calcium entry through L-type channels in vascular smooth muscle controls the contractile state of actomyosin
- CCBs inhibit the influx of Ca through voltage dependent L-type calcium channels
- Therefore, relax arteriolar smooth muscle → vasodilation
- Reduce peripheral vascular resistance
- Lower arterial blood pressure
- Useful for hypertension, coronary artery spasm, cerebral vasospasm following subarachnoid haemorrhage, Raynaud's phenomenon

- In black patients, more effective than ACE-I or ARBs

Drugs and therapeutics 2007



CCBs

Nifedipine, Amlodipine (Dihydropyridines) :

- Lower BP
- Licensed for monotherapy in mild hypertension
- Adverse effects:
  - **Headache and flushing due to vasodilation**
  - Reflex tachycardia via activation of baroreceptors and sympathetic nervous system
  - Related to peak plasma concentrations; more marked with short-acting drugs
  - **Ankle swelling due to increased pedal capillary pressure**
  - ? increased risk of GIT bleeding in elderly
  - Relative negative inotropic – exacerbation of heart failure

CCBs

Diltiazem (Benzothiazepines)
- Prophylaxis of angina
- Hypertension
- Little effect on the heart rate
- Adverse effects generally mild

Verapamil (Phenylalkylamines) :
- Slow release preparation for hypertension
- Angina
- Arrhythmias
- Adverse effects:
  - Negative inotrope – avoid in heart block
  - Constipation from relaxation of GIT smooth muscle

CCBs Pharmacokinetics

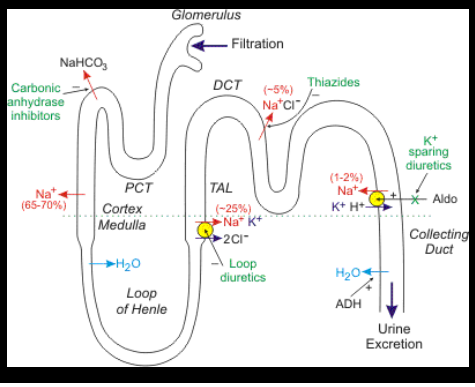
- Well absorbed
- Nifedipine has short half life
  - Adverse effects relate to peak plasma concentrations
  - Slow-release preparations improve its tolerability
- Amlodipine has a half life of 2-3 days
  - Produces smooth effect
  - Requires once daily administration only

CCBs Drug interactions

Favourable: dihydropyridines (nifedipine, amlodipine)
- With beta blockers in moderate to severe hypertension uncomplicated by cardiac failure

Unfavourable: intravenous Verapamil:
- Potentially fatal with beta blockers in the treatment of tachy-arrhythmias

Thiazide and Thiazide-like diuretics



Diuretics

Thiazide: :
- Stage 1 hypertension where CCBs contra-indicated
- Or in combination for severe hypertension
- Given by mouth as single morning dose
  - Hydrochlorothiazide
  - Bendroflumethiazide

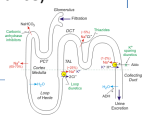
Thiazide-like:
- Preferred to thiazide diuretics for hypertension
  - Chlortalidone (12.5-25mg once daily), long acting
  - Indapamide (1.5mg modified release or 2.5mg once daily) shorter acting

Thiazide and thiazide-like diuretics

- Act on cortical segment of nephron
- Inhibit re-absorption of Na+ and Cl- in early distal convoluted tubule resulting in natriuresis
- Also have direct vasodilatory effects on resistance vessels
- Often ineffective in elderly
  - Age related heart failure and low GFR
- Hyponatraemia and hypokalaemia associated with high doses
- K supplements / K sparing agents

Thiazide and thiazide-like diuretics Adverse effects

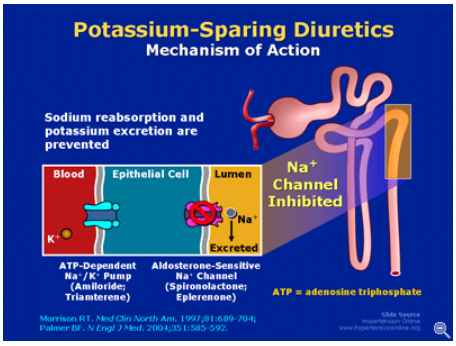
- Impotence
  - Increased plasma renin due to contraction of plasma volume
- Electrolyte changes
  - hypoNa
  - hypoK (increased Na delivery to distal nephron, Na and K ions exchanged
  - hypoMg
- Metabolic changes
  - Hyperuricaemia (↓urate clearance)
  - Hyperglycaemia in NIDDM (reduced glucose tolerance)
  - Hypercalcaemia (↓calcium clearance)
  - Hypercholesterolaemia (transient, insignificant)



Thiazide and thiazide-like diuretics: Drug-drug interactions

1. Other potassium depleting agents (corticosteroids, amphotericin B)
2. NSAIDs reduce efficacy of diuretics by inhibiting PGE and prostacyclin synthesis (Na, water retention)
3. Lithium toxicity (Increased absorption from PCT)
4. Digoxin toxicity (hypokalaemia and hypomagnasaemia)
5. CCB (↓ efficacy when used with diuretics)

Aldosterone antagonists: Spironolactone and Eplerenone

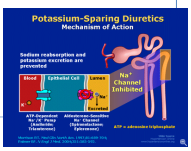


Spironolactone

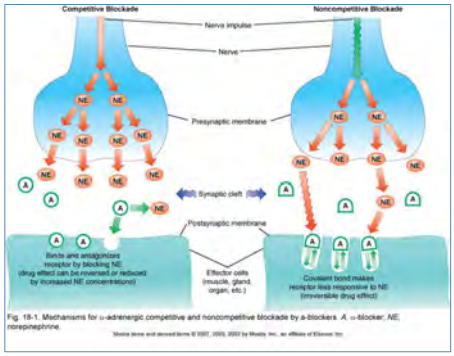
- Competitive aldosterone antagonist
- Competes for aldosterone receptors in distal tubule
- Aldosterone promotes Na retention, K loss
- Therefore spironolactone promotes Na, water loss and conserves K
- Particularly in hyperaldosteronism
  - Conn's
  - Cirrhosis
  - Heart failure

Spironolactone

- Structure related to oestrogen
- Onset of action 2-3 days
- Main metabolite: canrenone has half life 16hrs
- Interferes with tubular secretion of digoxin
- Adverse effects:
  - Gynaecomastia
  - Menstrual irregularities



Peripheral alpha-1 blockers



Alpha-1 blockers

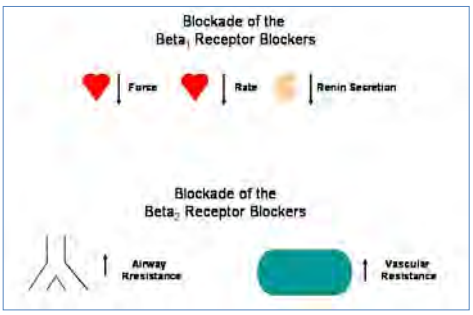
Prazosin and others

- Useful additional agents in patients who are poorly controlled on three or four drugs
- Cause peripheral vasodilation in venous and arterial systems
- Long acting drugs are preferred as less hypotension:
  - Doxazosin
  - Terazosin
- Reflex tachycardia not problematic as α-2 receptors are not blocked
- They improve the lipid profile
- Useful in hypertension associated with cardiac failure:
  - Reduce cardiac afterload
  - No direct negative chronotropic effect

Alpha-1 blockers
Adverse effects

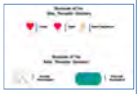
- First dose hypotension
- Postural hypotension, dizziness, vertigo, headache, fatigue
- Nasal stuffiness / rhinitis
- Urinary incontinence

Beta blockers

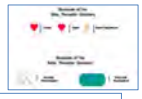


Beta Blockers

- May lower blood pressure and reduce the risk of stroke in hypertension
- Most sensitive to effects:
  - Ethnic Chinese
  - Whites less so
  - Afro-Caribbean even less so.
- Appropriate add-on drug, 4th line option
- Particularly useful:
  - HT + Ischaemic Heart Disease (Angina, MI)
  - Stabilising patients with dissecting aortic aneurysms (given iv)



NICE: Beta blockers



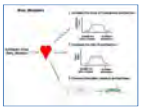
- 'In head to head trials, beta blockers were usually <u>less effective</u> than comparator drugs at <u>reducing major cardiovascular events,</u> particularly stroke.
- Beta blockers were also <u>less effective</u> than an ACE-I or CCB at <u>reducing the risk of diabetes</u>, particularly in patients taking the combination of a beta blocker + thiazide diuretic

Beta blockers mechanism of action

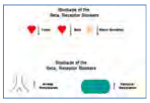
- Speculative
- Actually increase peripheral vascular resistance in acute dose studies!
- Reduce renin-secretion
- Propranolol has central effects, reducing sympathetic output from CNS
- Hypotensive action possibly related to effects on the heart (decreased cardiac output and changes in baroreceptors)

Classification of Beta blockers

- Cardio-selective (beta -1 receptors):
  - **Atenolol** (convenient once daily dose)
  - Metoprolol
  - Bisoprolol
  - Esmolol (v. Short duration, given iv)
  - Celiprolol
  - Nebivolol

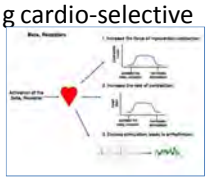


- Non-selective (beta-1 and beta-2 receptors):
  - **Propranolol**
  - Sotalol
  - Labetalol
  - Oxprenolol



Cardio-selective Beta blockers

- *Relative* selectivity for cardiac beta-1 receptors
- Thus, remain hazardous for asthma + COAD
- Should still be avoided in IDDM
- Metabolic differences unremarkable
- (Little to be gained by prescribing cardio-selective beta-blocker)



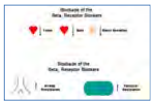
Beta blockers cont...

Partial agonists:
- have intrinsic sympathomimetic activity; antagonise full agonists by occupying the receptor.
- In theory, less likely to induce cardiac failure, peripheral vasoconstriction, depressed A-V conduction, bradycardia
  - Oxprenolol
  - Pindolol

Vasodilating beta blockers:
- Additional alpha-blocking activity:
  - Labetalol
  - Carvedilol (increases insulin sensitivity)
- Relatively selective beta 1 blocking with additional agonist activity at beta-2 receptors.
  - Celiprolol
- Most potent cardio-selective beta-1 antagonist with additional release of endothelium derived NO
  - Nebivolol

Adverse effects of beta blockers

- Intolerance:
  fatigue, cold extremities, sexual dysfunction, hallucinations, vivid dreams, depression
- Airways obstruction
  avoid in asthmatics and COAD
- Heart Failure
  Most beta blockers, due to negative inotrope action
- Peripheral vascular disease and vasospasm
- Hypoglycaemia
  mask symptoms of hypoglycaemia, slow rate of recovery
- Heart block
- Metabolic disturbances
  Small increase TG
  Small fall in HDL
  Small increase in K+ (inhibit renin release)



Beta blockers pharmacokinetics

Polarity important

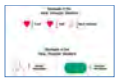
Polar drugs:
- Excreted unchanged by kidneys
- Longer half-lives
- Accumulate in renal failure
  - Atenolol
  - Sotolol

Non-polar (lipophilic):
- More extensive and rapid absorption from gut
- Higher pre-systemic metabolism in gut wall + liver
- Enter brain more readily – more CNS adverse effects
- Highly protein bound
  - Propranolol
  - Oxprenolol
  - Metoprolol

Beta-blockers drug interactions

Pharmacokinetic:
- Inhibit drug metabolism by reducing hepatic blood flow (decreased cardiac output)
  - Accumulation of drugs with high hepatic extraction ratio eg lignocaine
- Cimetidine causes accumulation of propranolol by inhibiting CYP450 oxidation

Pharmacodynamic:
- Exaggerated negative inotrope and AV nodal effects with
  - Verapamil
  - Lignocaine
- Exaggerated hypoglycaemia with
  - Insulin
  - Oral hypoglycaemics
- Antihypertensive effects opposed by NSAIDs

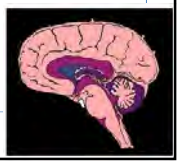


Centrally acting alpha blockers

Also reserved for fourth line use.

Occasionally used.

- Reserpine
- Methyldopa
- Moxonidine (related to clonidine)



Additional antihypertensives used in special situations

Minoxidil: K channel activator:

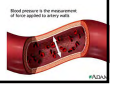
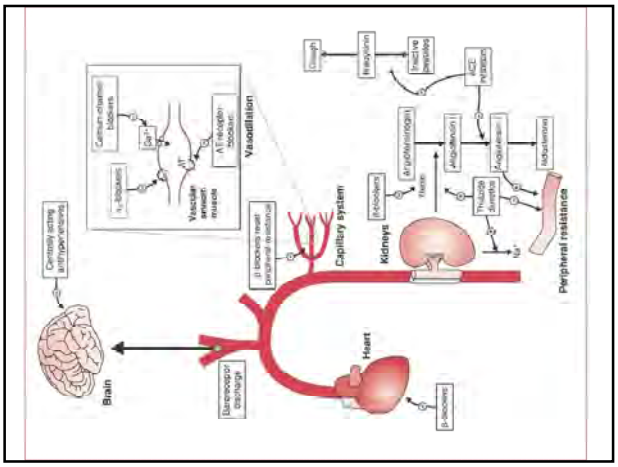
- For severe, resistant hypertension
- Fluid retention, reflex tachycardia, hirsutism, coarsening facial features

Nitroprusside: breaks down to vasodilator, NO:

- For malignant hypertension via iv infusion in ICU
- Cyanide toxicity, light sensitivity,

Alpha-methyldopa: false NA transmitter, alpha-2 agonist

- For hypertension in pregnancy
- Drowsiness, depression, hepatitis, haemolytic anaemia, drug fever

Hydralazine: direct action on vascular smooth muscle:

- For severe hypertension in pregnancy
- Headache, flushing, tachycardia, lupus-like syndrome