HYPERTENSION

THERAPEUTICS

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CONTENTS

REFERENCES & INFORMATION RESOURCES

GENERAL

- Hypertension. Chapter 19. Clinical Pharmacy and Therapeutics (6th Edn) C.Whittlsea & K.Hodson 2019)

HYPERTENSION

Guidelines & standards

- Hypertension – Clinical management of primary hypertension in adults. NICE August 2019 (available at https://www.nice.org.uk/guidance/ng136 - accessed 12/10/21)
- Type 2 diabetes in adults: management. NICE Dec 2015 (available at https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-1837338615493 - accessed 12/10/21)
- Hypertension – Clinical Knowledge Summary (available at https://cks.nice.org.uk/topics/hypertension/ - accessed 12/10/21)

Websites

- British and Irish Hypertension Society https://bihsoc.org/ (accessed 12/10/21)
- British Heart Foundation https://www.bhf.org.uk/for-professionals/healthcare-professionals (accessed 12/10/21)
- British Cardiac Society https://www.britishcardiovascularsociety.org/ (accessed 12/10/21)
- European Society of Cardiology https://www.escardio.org/ (accessed 12/10/21)

DRUG GROUPS

CALCIUM CHANNEL BLOCKERS

Eg: **Dihydropyridines:**

Amlodipine
Felodipine
Isradipine
Lercanidipine
Nicardipine
Nifedipine
Nisoldipine

Non-dihydropyridines:

Diltiazem
Verapamil

Mechanism of action:

- Interfere with the inward displacement of calcium ions through the slow channels of active cell membranes in the peripheral blood vessels and/or heart
- ⇒ ↑ peripheral vasodilatation (dihydropyridines)
- ⇒ ↑ coronary vasodilatation (all but especially verapamil & diltiazem)
- ⇒ ↓ rate & force of cardiac contraction (verapamil & diltiazem)

Therapeutic use:

- **Dihydropyridines (E.g. Amlodipine) 1st line (step 1) choice in >55yrs or Black African or African Caribbean population of any age (non-diabetic)**
- VERAPAMIL must not be used in combination with a β-BLOCKER due to the risk of severe bradycardia and heart block

AMLODIPINE

Side-effects:

- Abdominal pain, nausea, palpitations, flushing, oedema, headache, dizziness, sleep disturbances, fatigue

Dose:

- **5mg daily increased according to response to 10mg daily**

NIFEDIPINE

Side-effects:

- Headache, flushing, dizziness, lethargy, tachycardia, ankle oedema

Dose:

- **10mg twice daily increased according to response up to 40mg twice daily (for twice daily M/R preparations eg Adalat® Retard)**
- **20-30mg once daily increased according to response up to 90mg once daily (for once daily long acting M/R preparations eg Adalat® LA)**

[NB: short acting Nifedipine is NOT recommended due to an association with ↑ risk of CV events]

DILTIAZEM

Contraindications:

- Severe bradycardia, heart block

Cautions:

- LVF

Side-effects:

- Bradycardia, heart block, palpitations, dizziness, hypotension, malaise, g.i., oedema

Dose:

- **90mg twice daily increased according to response up to 180mg twice daily (for twice daily M/R preparations eg Tildiem Retard®)**
- **200-240mg daily increased according to response – maximum depends on preparation (for once daily long acting M/R preparations eg Tildiem LA®)**

VERAPAMIL

Contraindications:

- Bradycardia, heart block, LVF

Side-effects:

- Constipation, bradycardia, heart block, g.i., flushing headache, dizziness, fatigue, ankle oedema

Dose:

- **240-480mg daily in 2-3 divided doses**

DIURETICS

THIAZIDES:

Eg: **Bendroflumethiazide**
Chlortalidone
Cyclopenthiazide
Indapamide
[Metolazone]
Xipamide

POTASSIUM-SPARING & ALDOSTERONE ANTAGONISTS:

Eg: **Amiloride**
Triamterene
Spironolactone

THIAZIDES

Bendroflumethiazide

Mechanism of action:

- Inhibit sodium reabsorption (inhibit Na^+/Cl^- co-transporter) at the beginning of the distal convoluted tubule
- $\Rightarrow$ diuresis $\Rightarrow \downarrow$ circulating volume $\Rightarrow \downarrow$ cardiac output
- Also have direct vasodilatory action
- Act within 1-2 hrs of oral administration, max effect 4-6hrs & duration of action of 8-12 hrs

Dose:

- **2.5mg in the morning**

- Maximal bp lowering occurs at 2.5mg dose and therefore higher doses are unnecessary when treating hypertension (and will $\uparrow$ risk of side-effects)

Side-effects:

- Postural hypotension
- Renal impairment
- Mild gastrointestinal effects
- Impotence
- Electrolyte disturbances:
    - Hypokalaemia
    - Hypomagnesaemia
    - Hyponatraemia
    - Hypercalcaemia
    - Hyperuricaemia & gout
    - Hyperglycaemia & impaired glucose tolerance
    - Altered lipid profile

Therapeutic use:

- Inexpensive
- Do not work if GFR<20ml/min
- Can be used in combination with other antihypertensive agents (step 2 of NICE guidelines)
- Use in combination with potassium-sparing diuretic if hypokalemia is a problem

POTASSIUM-SPARING DIURETICS

Amiloride

Mechanism of action:

- Inhibit the sodium-proton exchanger which affects sodium reabsorption in the distal tubule and collecting ducts
- Potassium loss is indirectly decreased

Dose:

- **5-10mg daily**

Side-effects:

- Hyperkalaemia
- Postural hypotension
- Mild gastrointestinal effects
- Dry mouth
- Rashes
- Confusion
- Hyponatraemia

Therapeutic use:

- Very weak diuretic on own
- **Almost always only used in combination with thiazides (or loop diuretics) to conserve potassium and prevent hypokalaemia**

ALDOSTERONE ANTAGONISTS

Spironolactone

Mechanism of action:

- Inhibits affect of aldosterone on distal renal tubule
- Results in decreased sodium absorption $\Rightarrow \downarrow$ circulating volume
- Also causes decreased potassium secretion (hence also potassium sparing)

Dose:

- **25mg daily**

Side-effects:

- Hyperkalaemia
- Hypotension
- Renal impairment
- Gynaecomastia

Therapeutic use:

- **Add-on for resistant hypertension**
- **Step 4 but only if K^+ <4.5mmol/L due to risk of hyperkalaemia**

ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIs)

Eg:

Captopril
Enalapril
Fosinopril
Imidapril
Lisinopril
Moexipril
Perindopril
Quinapril
Ramipril
Trandolapril

Mechanism of action:

- Block the action of Angiotensin converting enzyme (ACE) and thus prevent the conversion of Angiotensin I to Angiotensin II
- Prevents the vasoconstrictive effect of Angiotensin II and also prevents its stimulation of aldosterone

Contraindications:

- Hypersensitivity & angioedema
- Renal artery stenosis
- Pregnancy

Side-effects:

- Hypotension (especially first dose in patients on diuretics)
- Renal impairment
- Persistent dry cough (common) (due to blocking breakdown of bradykinins)
- Angioedema (rare but important – more common in people of Black African Caribbean origin)
- Hyperkalaemia
- Blood dyscrasias

Therapeutic use:

- **First line (step 1) therapy for younger patients (<55yrs) and patients with Diabetes (Type 1 and Type 2)**
- **Drug of choice to treat HT in patient who also has CCF or is post MI**

Dose:

Enalapril: **5mg daily increased as required to 20mg once daily maintenance**

Ramipril: **1.25mg daily increased as required at intervals of 1-2 weeks to 2.5-5mg daily maintenance**

Lisinopril: **Initially 10 mg once daily; usual maintenance 20 mg once daily; maximum 80 mg per day.**

Perindopril**:** **Erbumine** (more commonly prescribed salt): **Initially 4 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 8 mg per day**
Arginine: **Initially 5 mg once daily for 1 month, dose to be taken in the morning, then, adjusted according to response; maximum 10 mg per day**

ANGIOTENSIN-II RECEPTOR ANTAGONISTS/BLOCKERS (ARBs)

Eg: **Candesartan**
Eprosartan
Irbesartan
Losartan
Olmesartan
Telmisartan
Valsartan

Mechanism of action:

- Block the action of Angiotensin II at the $AT2_1$ receptor and thus have similar effect to ACEIs

Side-effects:

- Hypotension (especially first dose in patients on diuretics)
- Renal impairment
- Angioedema (rare)
- Hyperkalaemia
- Blood dyscrasias (anaemia)

Therapeutic use:

- **Low cost agents first line (step 1) therapy for younger patients (<55yrs)**
- **Useful alternative when ACEIs not tolerated due to cough** (do not block breakdown of bradykinins and therefore do not cause cough)
- **Consider ARB instead of ACEIs in Black African or African Caribbean population (due to greater risk of angioedema with ACEIs)**

Dose:

Losartan: **50mg daily, increased if required over several weeks to 100mg daily**

NB: Avoid combined use of ACEIs and ARBs due to increased risk of hyperkalaemia, hypotension and impaired renal function especially in patients with diabetic nephropathy

RENIN INHIBITORS

Eg: **Aliskiren**

Mechanism of action:

- Inhibits renin directly and therefore prevents the conversion of angiotensinogen to angiotensin I.

- Contraindications:

- Hypersensitivity & angioedema
- Renal artery stenosis
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2)
- Pregnancy
- **Combination with ARBs or ACEIs is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) and is not recommended in other patients**

Side-effects:

- Hypotension (especially first dose in patients on diuretics)
- Renal impairment
- Angioedema (rare but important)
- Hyperkalaemia
- Blood dyscrasias

Therapeutic use:

- Expensive
- Evidence is limited (no recommended in NICE guidelines) and is reserved for resistant hypertension

Dose:

- **150mg once daily, increased if necessary to 300mg once daily**

ALPHA-BLOCKERS

Eg: **Doxazosin**
Indoramin
Prazosin
Terazosin

Mechanism of action:

- Selectively block α_1 receptors responsible for noradrenaline (norepinephrine) mediated vasoconstriction $\Rightarrow \downarrow$ peripheral resistance

DOXAZOSIN

Side-effects:

- Postural hypotension (especially first dose), dizziness, vertigo, headache, fatigue, asthenia, oedema, sleep disturbance, nausea, rhinitis

Therapeutic use:

- Appropriate add-on therapy (step 4) for patients uncontrolled by other agents
- Not for monotherapy (ALLHAT trial demonstrated increased heart failure and stroke compared to thiazide)
- Appropriate first line for patients with prostatism
- Useful for hypertension associated with CKD

Dose:

- **1mg daily increased every 1-2 weeks according to response up to 16mg daily**

BETA-BLOCKERS

Eg: **Propranolol**
Acebutolol
Atenolol
Bisoprolol
Carvedilol
Celiprolol
Labetolol
Metoprolol
Nadolol
Nebivolol
Oxprenolol
Pindolol
Timolol

Mechanism of action:

- Block beta-1 adrenoreceptors in the heart and beta-2 adrenoreceptors in the peripheral vasculature, bronchi, pancreas and liver
- Exact mechanism of action in HT unknown, although known to ↓ CO

Side-effects:

- Bradycardia
- Heart failure
- Hypotension
- Arrhythmias
- Bronchospasm
- Peripheral vasoconstriction (⇒ cold extremities)
- Gastrointestinal disturbances
- Fatigue
- Sleep disturbance
- Sexual dysfunction
- Exacerbation of psoriasis

Contraindications:

- Asthma
- Uncontrolled heart failure
- Bradycardia
- Heart block
- Severe peripheral vascular disease

Cautions:

- Diabetes – may cause deterioration in glucose tolerance and mask the symptoms of hypoglycaemia
- If no alternative in asthma, use cardioselective β-blocker (see below)

Therapeutic use:

- Appropriate add-on therapy (step 4) for patients uncontrolled by other agents
- Drug of choice to treat HT in patient who also has CCF or is post MI
- Choice of β-blocker will depend on their relative characteristics:

Cardioselectivity:

- **Eg Atenolol, bisoprolol, metoprolol**
- Tendency to block β_1 receptors in heart rather than β_2 receptors in lungs (but NOT cardiospecific and still have potential to block β_2 receptors in lungs therefore caution required)
- Can be used with caution in asthmatics if no other option available
- Also less likely to be a problem in diabetics

Intrinsic sympathomimetic activity (ISA):

- **Eg Oxprenolol, pindolol, acebutolol, celiprolol**
- Capacity to stimulate as well as block adrenergic receptors
- Less bradycardia & cold extremities than other β-blockers

Lipid / Water solubility:

- **Eg Water soluble: Atenolol, celiprolol**
  Lipid soluble: Propranolol
- Water soluble less likely to cross blood brain barrier and therefore may cause less sleep disturbance & nightmares
- Water soluble excreted by the kidneys and may accumulate in renal impairment therefore dose reduction maybe necessary

Dose:

Bisoprolol: **5-10mg daily (max 20mg daily)**

Propranolol: **80mg twice daily increased at weekly intervals if required to maintenance of 160-320mg daily**

CENTRALLY ACTING AGENTS

Eg: **Methyldopa**
Clonidine
Moxonidine

Mechanism of action:

- Methyldopa and Clonidine act at presynaptic α_2 receptors to $\downarrow$ sympathetic outflow $\Rightarrow$ vasodilatation
- Moxonidine selectively blocks imidazole receptors and has less action on α_2 receptors resulting in less central adverse effects

Therapeutic use:

- Due to adverse effects, methyldopa and clonidine are reserved for resistant hypertension (not in NICE guidelines)
- Methyldopa is the drug of choice in hypertension of pregnancy due to its proven safety record
- Moxonidine evidence is limited (not in NICE guidelines) and is reserved for resistant hypertension

METHYLDOPA

Contraindications:

- Include depression

Side-effects:

- G.I., dry mouth, mouth ulcers, inflammation of salivary glands, bradycardia, exacerbation of angina, postural hypotension, oedema, sedation, nightmares, depression and other central effects (caution with driving) + others

Dose:

- **250mg 2-3 times daily increased according to response up to a maximum of 3g daily**

CLONIDINE

Cautions:

- Include withdrawing therapy slowly to avoid hypertensive crisis

Side-effects:

- Dry mouth, sedation (caution with driving), depression, fluid retention, bradycardia, Raynaud's phenomenon + others

Dose:

- **50-100mcg 3 times daily increased according to response up to maximum of 1.2mg daily**

MOXONIDINE

Cautions:

- Include withdrawing therapy slowly

Contra-indications:

- Include cardiac arrythmias

Side-effects:

- Dry mouth, headache, fatigue, nausea, sleep disturbance + others

Dose:

- **200mcg daily increased after 3 weeks according to response up to a maximum of 600mcg in 2 divided doses**

OTHER VASODILATORS

Eg: **Hydralazine**
Monoxidil

Mechanism of action:

- Directly relax smooth muscle ⇒ vasodilatation

Therapeutic use:

- Reserved for add on therapy in resistant hypertension due to severe side-efects

HYDRALAZINE

Side-effects:

- Tachycardia, palpitations, flushing, hypotension, fluid retention, GI + others

Dose:

- **25mg twice daily increased according to response to a maximum of 50mg twice daily**

MINOXIDIL

Side-effects:

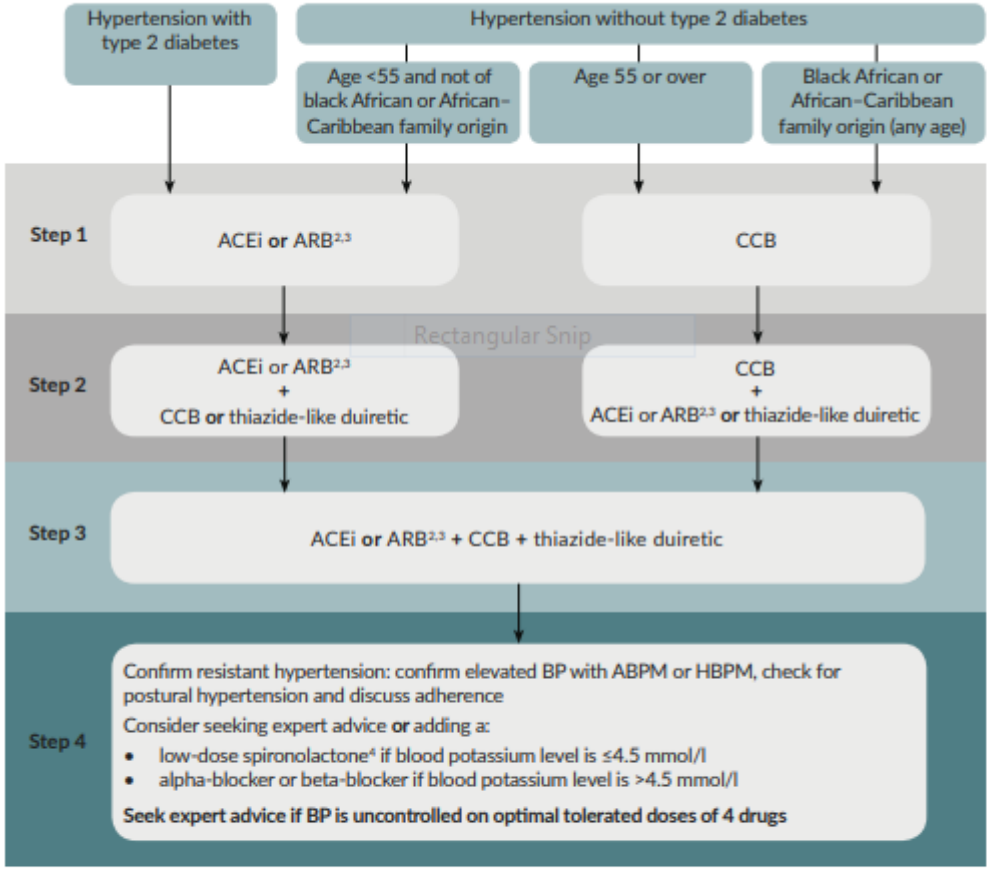
- Sodium & water retention, weight gain, peripheral oedema (use in combination with diuretic), tachycardia (use in combination with β-blocker), hirsuitsim + others

Dose:

- **5mg daily in 1-2 doses increased according to response up to a maximum 50mg daily in divided doses**

DRUG CHOICE IN HYPERTENSION
NICE 2019

Choice of antihypertensive drug[1], monitoring treatment and BP targets



Monitoring treatment

Use clinic BP to monitor treatment.

Measure standing and sitting BP in people with:

- type 2 diabetes **or**
- symptoms of postural hypotension **or**
- aged 80 and over.

Advise people who want to self-monitor to use HBPM. Provide training and advice.

Consider ABPM or HBPM, in addition to clinic BP, for people with white-coat effect or masked hypertension.

BP targets

Reduce and maintain BP to the following targets:

Age <80 years:

- Clinic BP <140/90 mmHg
- ABPM/HBPM <135/85 mmHg

Age ≥80 years:

- Clinic BP <150/90 mmHg
- ABPM/HBPM <145/85 mmHg

Postural hypotension:

- Base target on standing BP

Frailty or multimorbidity:

- Use clinical judgement

[1] For women considering pregnancy or who are pregnant or breastfeeding, see NICE's guideline on hypertension in pregnancy. For people with chronic kidney disease, see NICE's guideline on chronic kidney disease. For people with heart failure, see NICE's guideline on chronic heart failure

[2] See MHRA drug safety updates on ACE inhibitors and angiotensin-II receptor antagonists: not for use in pregnancy, which states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed', ACE inhibitors and angiotensin II receptor antagonists: use during breastfeeding and clarification: ACE inhibitors and angiotensin II receptor antagonists. See also NICE's guideline on hypertension in pregnancy.

[3] Consider an ARB, in preference to an ACE inhibitor in adults of African and Caribbean family origin.

[4] At the time of publication (August 2019), not all preparations of spironolactone have a UK marketing authorisation for this indication.

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, ACE inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; HBPM, home blood pressure monitoring.

BIHS
British and Irish Hypertension Society
Committed to preventing cardiovascular disease

This visual summary builds on and updates previous work on treatment published by the BIHS (formerly BHS)

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