**PHAR3816 Notes – Cardiovascular and Respiratory**

**Evidence-based medicine**

- Conscientious, explicit and judicious use of *current best* evidence in making decisions about the care of *individual* patients
- Integrates best research evidence with clinical expertise and patient values
    - Evidence incorporates drug efficacy, observational studies, safety issues
    - Primary evidence = original research
    - Secondary evidence = interpretation of original research
    - Tertiary evidence = use of secondary evidence to make clinical recommendations
- Systematic review/meta-analyses of RCT > cohort studies > case-control > case-series > expert opinion
    - Case series and expert opinion – help identify rare cases/side effects of the drug
- Generalisability of trial data to whole pop$^{n}$ – consider comorbidities, recruitment bias/criteria, age

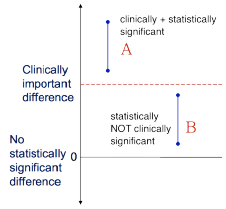
1. Ask a *focused* question, e.g. is the current treatment of hypertension the best one we have?
2. Find evidence in literature, and perform a critical appraisal of evidence for validity/applicability
3. Make a decision – apply the results to patient or clinical practice – then evaluate the outcomes
4. Evaluate the outcomes of the applied evidence in patient/practice

| Significance | Definition | Parameters |
|---|---|---|
| Statistical | Probability that outcome occurred due to chance | P<0.05, confidence interval |
| Clinical | Does the difference in effect translate to a *meaningful* difference in outcome? | Quality of life, symptomatic changes |

| | | |
|---|---|---|
| **Relative risk (RR)** | Ratio of probability of outcome occurring in exposed vs. unexposed | $RR = \frac{Incidence\ in\ exposed\ group}{Incidence\ in\ unexposed\ group}$ |
| **Absolute relative risk (ARR) = risk difference (RD)** | How many extra outcomes/events are due to the exposure | ARR = difference in risk (control – intervention) |
| **Numbers needed to treat (NNT)** | Number of people to receive intervention for 1 to benefit | NNT = 1/ARR |

| | ≥20mmHG change in BP | <20mmHG change in BP | Total |
|---|---|---|---|
| Wonderdrug | 8(a) | 92 (b) | 100 (a+b) |
| Placebo | 2 (c) | 98 (d) | 100 (c+d) |
| Total | | | 200 |

**Wonderdrug** = 8/100 = 0.08 = 8% (incidence)
**Placebo** = 2/100 = 0.02 = 2%
**ARR** = 0.08 - 0.02 = 0.06 = 6%
**NNT=1/ARR** = 1/0.06 = 16.6




**Hypertension treatment**

- Primary prevention – treatment of patients who have *not yet* developed clinical CVD
- Secondary prevention – avoid *recurrent* events in those who already have CVD
- Aims – reduce CVD morbidity/mortality, and microvascular diseases (brain/kidney/retina)
    - Reduce *risk* of CVD events – myocardial infarction, stroke, heart failure
- Risk assessment for CVD – blood pressure (BP), age, gender, lipids, smoking status, diabetes
    - Control a combination of risk factors for synergistic results
- Current blood pressure targets ~140/90mmHg
    - May be higher for elderly (hypotension may cause falls)
    - <65yo/diabetes/renal insufficiency/CHD – 130/80mmHg

| Blood pressure category | Systolic (mmHg) | Diastolic (mmHg) |
|---|---|---|
| Optimal | <120 | <80 |
| Normal | <130 | <85 |
| Prehypertension | 130-139 | 85-89 |
| Stage 1 hypertension (mild) | 140-159 | 90-99 |
| Stage 2 hypertension (mod) | 160-179 | 100-109 |
| Stage 3 hypertension (severe) | >180 | >110 |

| Non-pharmacological | Recommendation | BP reduction |
|---|---|---|
| Reduce weight | BMI <25, waist <94/80cm (male/female) | 1mmHg per 1% ↓weight |
| Reduce salt intake | <4g/day | 4-5mmHg |
| Regular physical activity | >30min most days of the week | 4-9mmHg |
| Modify diet | >400g fruit and veg/day, ↓saturated fats and LDL-c | 8-14mmHg |
| Reduce alcohol intake | <2 standard drinks/day | 2-4mmHg |
| Other | Smoking cessation, diabetes control | |

Antihypertensive treatment

- Start treatment with a *single* drug at lowest recommended dose – reduces BP in 25-50% patients
    - Add second antihypertensive rather than increasing dose of the first
- Uncomplicated hypertension – begin monotherapy with ACEI/ARA/dihydro-CCB/thiazide (>65yo)
    - ACEI – suitable for kidney disease, diabetes, micro/macro-albuminuria, heart failure
    - Non-dihydro-CCBs – *contraindicated* in heart failure
    - Thiazide diuretics – well-tolerated, avoid if <65yo (↑diabetes risk)
- Beta-blockers – no longer recommended as first-line therapy in uncomplicated HBP
    - Increased risk of diabetes onset, reduced stroke-protection
    - Suitable for hypertension + angina

ACE inhibitors (-pril)

- Inhibit angiotensin converting enzyme to inhibit ANGII production
    - ↓Aldosterone/$Na^+$/water retention, ↓BP, ↓thirst, vasodilation
- Side effects – dizziness, orthostatic hypotension, angioedema, renal artery stenosis (narrowing)
    - Hyperkalaemia – stop potassium supplements (aldosterone ↑$K^+$ excretion)
- Persistent dry cough due to bradykinin build-up
- Pregnancy category D, triple whammy

ANGII receptor antagonists (-sartan)

- Competitive antagonist of ANGII at $AT_1$ receptors
    - ↓Vasoconstriction and aldosterone release, ↓TPR/EDV, no effect on bradykinin (no cough)
- Side effects – hyperkalaemia, decreased renal function, same as ACEI

β-adrenoceptor antagonists (-olol)

- Non-selective ($B_1R/B_2R$ – propranolol) or cardio-selective blockers ($B_1R$ – atenolol)
    - ↓Renin and cardiac output (↓arterial BP and workload of heart)
- Treat hypertension, angina, cardiac dysrhythmias, heart failure, tremor, migraine
- Side effects – bradycardia, fatigue, reduced exercise tolerance, sleep disturbances, impotence
    - Possible wheezing and acute asthma attacks in asthmatics (bronchoconstriction)

Calcium-channel blockers

- Bind L-type $Ca^{2+}$ channels to block entry of calcium – vasodilation, ↓cardiac contraction force/HR
- Dihydropyridines – amlodipine, felodipine, lercanidipine, nifedipine
    - Primarily inhibit calcium entry into arterioles – treat hypertension and angina
- Non-dihydropyridines – diltiazem, verapamil
    - Inhibit calcium entry into arterioles *and* cells in heart and GI tract
    - Treat hypertension, angina, some cardiac dysrhythmias
- Side effects – hypotension, headache, flushes, gut reflux
    - Peripheral oedema (ankle) – arteriole dilation and increased permeability of venules
        - Does not respond to diuretics – reduce dose or change drug
    - Non-dihydropyridines – bradycardia, constipation (blocks L-channels/peristalsis in gut)

Thiazide diuretics

- Inhibit $Na^+/Cl^-$ reabsorption in early distal tubule of nephron – ↑$Na^+$/water loss, vasodilation
- Side effects – dizziness, postural hypotension, impotence, photosensitivity
    - Hy*po*kalaemia, hy*po*magnesaemia, hy*per*uricaemia (gout), hy*per*glycaemia (diabetes)
- Enhance BP-lowering of all other classes *except* CCBs

Recommended combination therapies

- ACEI/ARA + CCB/low-dose thiazide
- CCB + thiazide
- Other possible combinations – BB + ACE/ARA/dihydro-CCB or thiazide (↑diabetes risk)
- Contraindications – non-dihydropyridines + beta-blockers (bradycardia)

| Comorbidity | Suitable drug | Contraindicated drug |
|---|---|---|
| Angina | Beta-blockers | |
| Asthma/COPD | | Beta-blockers |
| Atrial fibrillation | ACEI, ARA, beta-blockers | |
| Bradycardia | | Beta-blockers, non-dihydro-CCBs |
| Diabetes with proteinuria | ACEI, ARA, CCBs | Beta-blockers, thiazide diuretics |
| Gout | | Thiazide diuretics |
| Heart failure | ACEI, ARA, beta-blockers, thiazides | Non-dihydro-CCBs |
| Post myocardial infarction | ACEI, ARA, beta-blockers | |

**Lipidemics and cholesterol**

Cardiovascular disease

- Coronary heart disease, heart attack, angina, ischaemic disease
    - Risk factors – age (male >45yo, female >55yo), elevated/modified LDL, low HDL, smoking, hypertension, genetics, diabetes, triglycerides, obesity, high homocysteine levels
- Stroke and peripheral vascular disease
- Atherosclerosis – lipid deposits build up on inner arterial walls
    - Reduced blood flow → clogging of arteries (via thrombotic events) → heart attack/stroke
    - Lipid-rich diet can increase blood lipids (cholesterol and triglycerides)
- 10%↓ in plasma cholesterol = 15%↓ CHD mortality, 11%↓ total mortality

Functions of lipids

- Membrane components and compartmentalisation
- Energy storage and transport
- Cell recognition and signalling
- Major plasma lipids – fatty acids, triglycerides, phospholipids, cholesterol (-esters)

Fatty acids

- More than 100 types, C14-C22 and C16-C18 are most common, includes TGs and phospholipids
    - Trans fatty acids – increases risk of CHD, ↑LDL, ↓HDL
    - Polyunsaturated fatty acids – protect against CHD
- Mostly unsaturated – double bond generally between C9-C10
- Only small amounts of free fatty acids – FFAs are toxic
- Essential fatty acids – cannot be synthesised, e.g. cis-linoleic acid
    - EFAs and their metabolites have anti-hypertensive and anti-atherosclerotic properties
        - ACEI, HMG-CoA reductase inhibitors, activation of PPARs
    - Altered EFA metabolism in obesity, hypertension, diabetes, CHD, cancer, schizophrenia
- Triglycerides – neutral storage lipids to provide energy in adipocytes and muscle cells
    - Structure – three fatty acids per glycerol backbone
    - Plasma TGs are highly elevated in diabetes and obesity – increased risk of CHD
- Phospholipids – polar membrane lipids; glycerol (hydrophilic) + two fatty acids (hydrophobic)

Cholesterol

- Important component of cellular membranes
- Precursor of steroid hormones, bile acids, vitamin D and oxysterols (regulate cholesterol synthesis)
- Enzymatic degradation of cholesterol produces:
    - Prenenolone for synthesis of endogenous steroids
    - Bile acids and bile salts
- De novo cholesterol synthesis 70%, diet intake 30%
- HMG CoA → mevalonate → isopentenyl pyrophosphate → farnesyl pyrophosphate → cholesterol
- Cholesterol synthesis is regulated by:
    - HMG-CoA reductase – converts HMG-CoA to mevalonate
    - Hormones – e.g. insulin (stimulates), glucagon (inhibits)
    - Metabolites – high cholesterol → ↑ oxysterols → transcriptional repression of HMGCR