Mechanisms of Blood Pressure Regulation

Blood Pressure

Cardiac Output
- Heart Rate
  - Myocardial contractility
- Stroke volume
  - Blood volume

Peripheral Resistance
- Vascular tone
- Vessel elasticity

Parasympathetic
Sympathetic
RAAS
Local Factors
- **Parasympathetic:**
  - Heart rate ↓ → Cardiac output ↓ → BP ↓

- **Sympathetic:**
  - Heart rate ↑
  - Contractility ↑
  - Vascular tone ↑

  → BP ↑

- **RAAS:**
  - Vascular tone ↑
  - Blood volume ↑

  → BP ↑

- **Local factors:**
  - Vasodilators: EDRF, Prostacylin (PGI2) → BP ↓
  - Vasocostrictors: Ang. II, Endothelin → BP ↑
## Blood Pressure Classification (JNC VI, 1997)

<table>
<thead>
<tr>
<th>Category</th>
<th>DBP</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 80</td>
<td>&lt; 120</td>
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<tr>
<td>Normal</td>
<td>&lt; 85</td>
<td>&lt; 130</td>
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<tr>
<td>High normal</td>
<td>85-89</td>
<td>130-139</td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>90-99</td>
<td>140-159</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>100-109</td>
<td>160-179</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>&gt; 110</td>
<td>&gt; 180</td>
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<tr>
<td>Isolated systolic HT</td>
<td>&lt; 90</td>
<td>&gt; 140</td>
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</table>
# Blood Pressure Classification (JNC VII, 2003)

<table>
<thead>
<tr>
<th>BP classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>\leq 120</td>
<td>&lt; 80</td>
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<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
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<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>\geq 160</td>
<td>\geq 100</td>
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</tbody>
</table>
Cardiovascular Risk Factors

- Hypertension
- Cigarette smoking
- Obesity (BMI $\geq 30$ kg/m$^2$)
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or estimated GFR < 60 ml/min.
- Age (>55 yrs for men, > 65 yrs for women)
- Family history of premature CV disease (men under age 55 or women under age 65)
Target Organ Damage

- Heart: left ventricular hypertrophy, heart failure, angina, myocardial infarction
- Brain: stroke
- Kidney: hypertensive nephropathy
- Vessel: atherosclerosis
- Eye: hypertensive retinopathy
# Treatment Strategy

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Lifestyle Modification</th>
<th>Initial Drug Therapy Without Compelling Indication</th>
<th>Initial Drug Therapy With Compelling Indications (See Table 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Encourage</td>
<td>No antihypertensive drug indicated.</td>
<td>Drug(s) for compelling indications.†</td>
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<tr>
<td>Prehypertension</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.</td>
<td>Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>Yes</td>
<td>Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).</td>
<td></td>
</tr>
</tbody>
</table>
Non Pharmacologic Treatment

- **Lifestyle modification**
  - Weight reduction (if overweight/obese)
  - Adopt DASH eating plan (rich in fruit and vegetables, and low fat diet)
  - Dietary sodium reduction
  - Moderation of alcohol consumption
  - Stop smoking
  - Regular physical activity
  - Stress avoidance
Sites of action of major classes of antihypertensive drugs.
Pharmacologic Treatment

- First line: 6 groups
  - Diuretics
  - Beta blockers
  - ACE-inhibitors
  - Ang II receptor blockers (ARB)
  - Ca antagonists
  - Alpha blockers* (considered first line in JNC VI but not in JNC VII)

- Second line: 3 groups
  - Adrenergic neuron inhibitors
  - Central $\alpha_2$- agonist
  - Direct vasodilators
I. DIURETICS

- Mechanisms of action:
  - Diuresis, natriuresis $\rightarrow$ blood volume $\downarrow$
    $\rightarrow$ cardiac output $\downarrow$ $\rightarrow$ BP $\downarrow$
  - Na$^+$ in serum & vascular smooth muscle $\downarrow$
    $\rightarrow$ vascular resistance $\downarrow$ $\rightarrow$ BP $\downarrow$

- 3 groups of diuretics:
  - I.a. Thiazides
  - I.b. Loop diuretics
  - I.c. Potassium sparing diuretics
I.a. THIAZIDE DIURETICS

Hydrochlorthiazide (HCT), Bendroflumethiazide, Chlortalidone, Indapamid

- Onset of anti hypertensive effect: 2-3 days
- Maximum effects: 2-4 weeks
- Drug of choice for mild to moderate HT, and HT with low renin activity (elderly)
- Much less effective in renal insufficiency
- Frequently used in combination with other anti HT drugs:
  - Prevents water retention by other anti HT drugs
  - Potentiation with other anti HT drugs
Adverse effects

- Hypokalemia $\rightarrow$ digitalis toxicity $\uparrow$
- Hyponatremia, hypomagnesemia
- Hyperuricemia $\rightarrow$ precaution in gout arthritis
- Hyperglycemia, hypercholesterolemia $\rightarrow$ precaution for DM and dyslipidemia
- Hypercalcemia (rare) $\rightarrow$ might be beneficial in retarding osteoporosis
- Sexual dysfunction
- Caution: not effective in renal failure
- Interaction: NSAIDs reduce anti HT effects of diuretics
I.b. Loop Diuretics (high ceiling diuretics)

- FUROSEMIDE
  - Strong and rapid diuretic effects
  - Effective for HT with renal failure
  - First line drug for heart failure
  - Side effects:
    - $\approx$ Thiazide
    - Except Hypocalcemia
I.c. Potassium Sparing Diuretics

Spironolactone, Triamterene, Amiloride

- Weak diuretics
- Generally used in combination with other diuretic
- Reduces the risk of hypokalemia by other diuretic
- May risk hyperkalemia:
  - In renal failure
  - In combination with ACE-Inhibitor/ARB, NSAID
- Spironolactone is an aldosteron antagonist
  → Drug of choice for hyper aldosteronism
II. Beta-Blockers

- Mechanism: inhibition of b1 receptors
  - Heart $\rightarrow$ decreases cardiac output $\downarrow$
  - Juxtaglomerular cells $\rightarrow$ renin secretion $\downarrow$

- Clinical use:
  - Mild to moderate HT
  - HT with coronary artery disease
  - HT with supraventricular arrhythmia
  - HT with tachycardia
• **Adverse effects**
  • Bronchospasm
  • Bradycardia
  • Impotency
  • Peripheral vascular disturbances
  • Unfavourable effect on lipid profile
  • Masking hypoglycemic symptoms
  • Decrease renal function

• **Contraindications**
  • Asthma, COPD
  • Peripheral vascular disease
  • AV block grade 2-3
  • Sick sinus syndrome
III. ACE-inhibitor dan ARB

- Angiotensinogen
  - Angiotensin I
    - Angiotensin II
      - AT1 receptor
        - Vasoconstriction
        - Aldosterone secretion
        - Vascular/cardiac remodelling
        - Sympathetic stimulation
      - AT2 receptor
        - Vasodilatation
        - Nitric oxide secretion
        - Anti remodelling
  - ACE
    - Bradykinin
      - Inactive peptide
  - ACE-inhibitor
  - ARB
- **ACE-Inhibition:**
  - AngII ↓: vasodilatation → BP ↓
    : aldosterone ↓ → Na⁺ and water retention ↓
  - Bradykinin ↑ → vasodilatation
- **Clinical use:**
  - First line drug for mild, moderate and severe HT
  - HT with heart failure
  - Hypertensive crisis
  - HT in diabetes, dyslipidemia, and DM nephropathy
  - Longterm use: cardioprotective, vasculoprotective
Adverse effects:
- Dry cough (10-20%)
- Angioedema, skin rash, dysgeusia
- Hypotension (first dose phenomenon)
- Risk of hyperkalemia:
  - In renal failure
  - If combination with K⁺ sparing Diuretics or NSAID
- Embryotoxic

Contraindication
- Pregnancy
- Lactation \(\rightarrow\) risk of renal failure in the fetus
- Bilateral stenosis of renal artery or unilateral stenosis in single kidney
<table>
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<tr>
<th>Drugs</th>
<th>Prodrug /active</th>
<th>Active form</th>
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<th>Daily Dosing</th>
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<td>-</td>
<td>-</td>
<td>Kidney</td>
<td>OD</td>
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<td>+</td>
<td>Kidney</td>
<td>OD</td>
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<td>OD/ 2x</td>
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<tr>
<td>Quinapril</td>
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<tr>
<td>Fosinopril</td>
<td>Prodrug</td>
<td>Fosinoprilat</td>
<td>+</td>
<td>Kidney + bilier</td>
<td>OD</td>
</tr>
</tbody>
</table>
IV. Angiotensin Receptor Blockers (ARB)

Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan

Mechanism of action:
- Blockade of Ang II (AT1) receptor.
- → Vasodilatation
- → Aldosterone ↓
- → Decreasing Ang II-mediated sympathetic activation
- → Prevents vascular and cardiac hypertrophy (vasculo- and cardio protective)
Angiotensin Receptor Blocker (ARB)

- Side effects ≈ ACE-I, except:
  - No dry cough
  - No angio-edema
- Indications and contraindications = ACE-I
V. Calcium Channel Blockers

Inhibition of Ca\(^{++}\) influx
- Blood vessels $\rightarrow$ vasodilatation
- Heart $\rightarrow$ negative inotropism, negative dromotropism
- $\rightarrow$ not recommended in the presence of heart failure
Three groups of CCB

1. Dihydropyridine (DHP):
   - (nifedipine, amlodipine, nicardipine, felodipine, lasidipine, nitrendipine, …)
   - Vasculo selective:
     → Predominant vasodilatory effect
     → Minimal cardiac effects

2. Diphenylalkilamine: - verapamil
   - More cardioselective:
     → Decreases myocardial contractility and conduction

3. Benzothiazepine: - diltiazem
   - Cardioselective
   → Decreases myocardial contractility and conduction
Pharmacokinetics:

- **Nifedipine:**
  - Rapid oral absorption $\rightarrow$ rapid BP ↓
  - Short T1/2 $\rightarrow$ needs 3-4 x daily dosing

- **Amlodipine:**
  - Slow absorption
  - Long T1/2 $\rightarrow$ once daily

- First pass metabolism (all CCB)
- Extensive hepatic metabolism (>90%): all CCB $\rightarrow$ precaution in liver failure
- Minimal renal excretion $\rightarrow$ relatively save for renal failure
INDICATIONS

- Hypertension: dihydropiridin, verapamil, (diltiazem: rare)
- Hypertensive crisis: nifedipine (sublingual), nicardipine iv
- Angina pectoris: verapamil, diltiazem, nifedipine (short acting)
- Arrhythmia: verapamil, diltiazem

Note: Short acting nifedipine is not recommended for maintenance therapy of HT
Adverse effects

- Nifedipine:
  - Hipotension → risk of myocardial and cerebral ischemia
  - Tachycardia
  - Headache, flushing, peripheral edema
- Verapamil, diltiazem:
  - Bradycardia, constipation

Contraindication

- Heart failure (except amlodipine)
- Precaution in liver cirrhosis
VI. Alpha-blocker

Prazosin, terazosin, bunazosin, doxazosin

- Blockade of a-1 $\rightarrow$ vasodilatation
- Positive effect on lipid profile (LDL $\downarrow$, HDL $\uparrow$)
- Decreases insulin resistance

CLINICAL USE

- Mild to moderate HT
- Benign prostatic hypertrophy (HT or not)
- HT with DM /dyslipidemia
- HT with peripheral vascular disease
• ADVERSE EFFECTS
  • Orthostatic hypotension (first dose phenomenon: often w/ prazosin)
    → Start low dose, before bed time
  • Tachycardia
  • Headache
  • Peripheral edema
  • Prazosin, terazosin, bunazosin: short halflife → 2-3 x daily
  • Doxazosin: longer half life → once daily
Second line drugs

- I. ADRENERGIC BLOCKING AGENTS
  (Reserpine, Guanethidine)

- Mechanism:
  - Reserpine: inhibits NE transport into nerve vesicles
  - Guanethidine: releases NE out of vesicles
    - \(\rightarrow\) depletion of NE vesicles
  - Low dose reserpine + HCT: effective and very cheap

- Side effects:
  - Sedation, depression
  - Nasal congestion
  - Peptic ulcer
II. Central $\alpha$-agonist
(Clonidine, methyldopa, guanfacine)

$\rightarrow$ Sympathetic outflow ↓ $\rightarrow$ cardiac output ↓

- Methyldopa: D.O.C for pregnant women
- Side effects:
  - Dry mouth, sedation, dizziness
  - Sexual dysfunction
  - Fluid retention $\rightarrow$ decreased effects
  - Withdrawal effect can lead to hypertensive crisis
- Interaction: tricyclic antidepressants, sympathomimetic drugs $\rightarrow$ reduces effects
III. DIRECT VASODILATORS

- **Hydralazine**: Mechanism?
  - Indications: - HT emergency
    - HT in glomerulonephritis
    - HT in eclampsia

- **Minoxidil & Diazoxide**: Potassium channel opener
  - Malignant HT
  - HT in glomerulonephritis
  - Hypertensive encephalopathy

**Adverse effects**

- Hydralazine: *lupus like syndrome*, tachycardia, fluid retention, angina pectoris
- Minoxidil: hirsutism
- Diazoxide: hyperglycemia → for insulinoma
Antihypertensive in special conditions

Pregnancy

- Methyldopa: drug of choice
- Beta blockers: atenolol, metoprolol, labetalol (relatively safe)
- CCB: widely used in preeclampsia/eclampsia, synergism with MgSO$_4$
- Hydralazin: preeclampsia/eclampsia
- ACE-I and ARB: contraindication
Antihypertensive in special conditions

Hypertensive emergency
- Oral drugs: captopril, nifedipine
- Parenteral drugs: clonidin, nitroglycerin, hydralazin, furosemide

Renal failure
- CCB, furosemide, clonidine, alpha blockers, hydralazine, NTG → safe
- ACE-I /ARB → CI if hyperkalemia, stop if creatinine increases
- B-blocker → tends to reduce renal function
Antihypertensive in special conditions

Liver cirrhosis
- CCB: not recommended

Asthma
- Beta-blockers: contraindicated

DM/dyslipidemia
- Choice: ACE-I /ARB
- B-blockers, thiazides: not recommended
- CCB, a-blockers, clonidine: safe
Thank You
DRUGS FOR HEART FAILURE

Nafrialdi
Definition

- Complex syndrome characterised by inability of the heart to pump sufficient quantity of blood to satisfy tissue perfusion.
- All kind of heart disease can lead to heart failure.
ETIOLOGY

1. Myocardial abnormality:
   - Cardiac ischemia
   - Myocardial infarction
   - Cardiomyopathy

2. Hemodynamic burden
   - Severe hypertension
   - Thyrotoxicosis
   - Severe anemia
   - Fluid overload

3. Valve/septum abnormalities

4. Filling defects
   - Pericardial effusion/tamponade
   - Constrictive pericarditis
   - Endomyocardial fibrosis
Pathophysiology

Lung edema → dyspnea

Cardiac load ↑

V. Cava

Water/Na+ retention

Leg edema

RAAS

CO ↑

Vasoconstriction

CO ↑

Afterload ↑

Cardiac output ↓

HR ↑

Sympathetic

Cardiac output ↓

Afterload ↑
Principals of HF Management

1. Non Pharmacologic
   - Rest
   - Limitation of fluid and salt intake

2. Pharmacologic
   - Preload reduction: Diuretics
   - Afterload reduction
     - ACE-inhibitors / Vasodilators
   - Inotropic drugs
   - $\beta$-blocker

3. Surgery / Intervention
Pharmacologic Treatments

1. Diuretics
   - Furosemide
   - Thiazides
   - Aldosterone antagonists

2. ACE-inhibitors and other vasodilators

3. Inotropic agents:
   - Digitalis
   - β1 Agonists
   - Phosphodiesterase inhibitors

1. β-blockers
DIURETICS
(First line drug for CHF)

- (See also diuretics and antihyperensive agents)
- **Furosemide:**
  - Strong diuretic with rapid onset
  - For acute (and chronic) CHF
  - Mechanism of action: reducing preload
- **Thiazides:** HCT, indapamid
  - For chronic CHF
- **Aldosteron Antagonists:** spironolaktone
  - Reduces the risk of furosemide-induced hypokalemia
  - Use in longterm treatment
  - Prevent myocardial fibrosis
ACE-inhibitor

- The second most important drug after diuretics
- Short term benefit:
  - Decreasing RAS activity
    → decrease afterload / peripheral resistance
    → reduces cardiac work
- Long term benefit:
  - Prevention of myocardial remodelling → prevention of hypertrophy
β-blockers

- Change of paradigm about β-blockers on CHF
  - Old paradigm: β-blocker was contraindicated for CHF
  - New paradigm: β-blocker is indicated for CHF
    → Former indication: chronic CHF
    → Newer indication: “Stable” acute and chronic CHF
  - Mechanism of action: reducing sympathetic stimulation on the heart
- Recommended drugs: carvedilol (α,β blocker), selective β-blockers (bisoprolol, metoprolol)
DIGITALIS

- **Source:**
  - *Digitalis purpureae* → digitalis (digoxin, digitoxin)
  - *Strophanthus gratus* → ouabain

- **Prototype:** Digoxin

- **Pharmacodynamic:**
  - Positive Inotropic effect
  - Negative Chronotropic effect
  - Negative Dromotropic effect
  - Arrhythmogenic effect
Mechanisms of Action of Digitalis

Digitalis Works by Inhibiting Na/K-ATPase
Mechanisms of Action of Digitalis

Inhibition of Na/K-ATPase

Membrane Depolarization

Ca++ channel opening

Na+ int ↑

Na+/Ca++ exchanger

CONTRACTILITY ↑

Ca intracell ↑

Sarcoplasmic reticulum

Ca++-induced Ca++ release
Electrophysiologic effects of Digitalis

- Lowers resting potential (phase 4 becomes less negative)
- Increases the slope of phase 4 → automaticity ↑
- Produces delayed after depolarization
- Shortening of potential action duration
- → Arrhythmogenic
**Direct effects on the heart**

- Increases automaticity in the atria, ventricles and Purkinje fibres → *arrhythmogenic*
- Delays conductivity (AV node, Purkinje) → *dromotropic* (-)
- Shortens refractory periods in the atrium and ventricle → *arrhythmogenic*
- Prolongs refractory period in AV node → *chronotropic* (-)

<table>
<thead>
<tr>
<th></th>
<th>Atrium</th>
<th>AV node</th>
<th>Ventricle/Purkinje</th>
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</thead>
<tbody>
<tr>
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<td>↑</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Conductivity</td>
<td>--</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Refractory period</td>
<td>↓</td>
<td>↑↑</td>
<td>-- / ↓</td>
</tr>
</tbody>
</table>
Indirect effects

- Vagal effect: In SA and AV nodes
  - Vagal tone $\uparrow$
  - Increases sensitivity of heart to acetylcholine
  $\Rightarrow$ Negative chronotropic

- Sympathetic effects:
  - Decreases sympathetic tone
  - Decreases sensitivity of heart to NE
  - Decreases sympathetic flow
  $\Rightarrow$ Negative chronotropic effect

- At high/toxic dose: sympathetic flow $\uparrow$
  $\Rightarrow$ arrhythmogenic
<table>
<thead>
<tr>
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<tr>
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<td>↓</td>
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<td><strong>Toxic dose</strong></td>
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<td>AV block grade 2-3</td>
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<td>ST elevation</td>
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<td></td>
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<td>T-inversion</td>
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</tbody>
</table>
Pharmacodynamic effects

1. Direct effects:
   - Positive inotropism
     - Improved contractility
     - Improved cardiac output
     - Decreased pulmonary congestion
     \rightarrow Relieved dyspnoe

2. Indirect effects
   - Sympathetic tone ↓
     - Decreased heart rate
     - Decreased peripheral resistance \rightarrow afterload ↓
   - Improved renal circulation
     - SRA activity ↓ \rightarrow peripheral resistance ↓
     - Aldosterone ↓ \rightarrow salt /water retention ↓ \rightarrow edema ↓
   \rightarrow IMPROVE CARDIAC PERFORMANCE
Digitalis in Atrial Flutter / Fibrillation

- Digitalis prolongs refractory period in AV node
  - some impulses from atrium are retained in AV node
  and not transmitted to ventricle

In other words:

Digitalis prevent the transmission of fibrillation from atrium to ventricle

(Not directly eliminate AF)

(Although spontaneous conversion to sinus rhythm frequently occur)
INTOXICATION

- Digitalis has a low margin of safety → risk of intoxication with increasing dose
- Potassium depletion due to diuretics facilitates intoxication
- Symptoms of intoxication sometimes resembles cardiac worsening.

CAUSES OF INTOXICATION

- Doses too high
- Hypokalemia/hyperkalemia
- Hypercalcemia
- Hypomagnesemia
- Myocardial ischemia
Symptoms of Intoxication
- GI symptoms (nausea, vomiting, abdominal pain)
- Neurologic symptoms (dizziness, restlessness, confusion)
- Visual disturbances (blurred, yellow vision)
- Cardiac: arrhythmia, AV-block

Treatment
- Stop digitalis and diuretics
- Electrolyte correction
- Management of arrhythmia: lidocain, phenytoin
- Antidigoxin-Antibody
• **Indications**
  - Atrial fibrillation/flutter
  - Paroxysmal supraventricular tachycardia
  - Heart failure (especially with tachycardia)

• **Contraindications**
  - AV-block
  - Bradycardia
  - Wolff-Parkinson-White (WPW) syndrome
  - Ventricular tachycardia, ventricular fibrillation
  - Obstructive hypertrophic cardiomyopathy
  - Renal failure (needs dose adjustment)
  - Hypothyroidism
Drug Interactions

- Quinidine
- Verapamil
- Diltiazem
- Amiodarone
- Phenobarbital
- Phenytoin
- Phenylbutazone
- Rifampicin
- Amphotericin

Quinidine, Verapamil, Diltiazem, Amiodarone, and Phenobarbital increase plasma digoxin.

Phenytoin, Phenylbutazone, Rifampicin, and Amphotericin lead to enzyme inducers → metabolism ↑.

Phenytoin and Phenylbutazone decrease plasma digoxin.

Amphotericin → hypokalemia → digitalis toxicity ↑
## Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th><strong>Digoxin</strong></th>
<th><strong>Digitoxin</strong></th>
<th><strong>Ouabain</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral absorption</strong></td>
<td>40-90%</td>
<td>90-100%</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Influenced by food</td>
<td>Not influenced by food</td>
<td>Influenced by food</td>
</tr>
<tr>
<td><strong>Onset of action</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>1,5 - 6 hrs</td>
<td>3 - 6 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 - 30 min.</td>
<td>0,5 - 3 hrs</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>4 - 6 hrs</td>
<td>6 - 12 hrs</td>
<td>0,5 - 2 hrs</td>
</tr>
<tr>
<td></td>
<td>1,5 - 3 hrs</td>
<td>4 - 6 hrs</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Halflife</strong></td>
<td>1,5 day</td>
<td>4-7 days</td>
<td>&lt; 1 day</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>Kidney</td>
<td>Liver</td>
<td>Kidney</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>1,25 – 1,50 mg</td>
<td>0,7 – 1,2 mg</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0,7 – 1 mg</td>
<td>1 mg</td>
<td>0,3 – 0,5 mg</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>0,125 – 0,5 mg</td>
<td>0.1 mg</td>
<td>-</td>
</tr>
</tbody>
</table>
I. β1-adrenergic agonists

- **DOPAMINE**
  - All β1 → inotropic (+), tachycardia
  - Low dose: D1-receptors in kidney and mesenterium → vasodilatation
  - High dose:
    - α-receptor → vasoconstriction
    - Synthesis of NE ↑ → vasoconstriction
  - Indication: cardiogenic shock, refractory heart failure

- **DOBUTAMINE**
  - β1 receptor → inotropic (+)
  - Less tachycardia than dopamine
  - Indication = Dopamin
II. Phosphodiesterase (PDE) inhibitors
(Amrinone, Milrinone, Enoximone, Pimobendan)

- cAMP / cGMP $\rightarrow$ 5-AMP / 5-GMP
  PDE

- Prevents degradation of cAMP $\rightarrow$ Ca$^{++}$ influx $\uparrow$
- Prevents degradation of cGMP $\rightarrow$ vasodilatation

=======
DRUG USE IN CORONARY ARTERY DISEASE

Dr. Frans Suyatna
Angina Pectoris

- Sign of myocardial ischemia
- Causes: - Coronary obstruction (atherosclerosis)
  - Vasospasm
- Pathophysiology: Imbalance between supply (S) vs demand (D) of oxygen
Determinant of S and D

Determinant of D
- Heart rate
- Ventricular contractility
- Myocardial wall tension
  - Preload
  - Afterload
  - Wall thickness
  - Metabolic factors

Determinant of S
- Blood flow: - Pressure, - Resistance
- Blood O₂ content and delivery
Pathophysiology

Coronary circulation ↓

$O_2$ ↓

↓

Aerobic metab. ↓

Anaerobic metab. ↑

↓

ATP ↓

↓

Biochemical changes
(acidosis, electrolyte homeostasis)

↓

Physiological changes
(contractility, electrophysiology)

↓

Structural damage (infarction)
Types of angina

- Stable angina (atherosclerotic plaque, exercise, emotional stress)
- Variant angina (Prinzmetal angina: vaso-spasm, rest)
- Unstable angina (atherosclerotic plaque rupture, platelet adhesion/aggregation)
- Silent (no symptom, EKG-echocardiography-radionuclid exams)
- Other (autonomic dysfunction, orthostatic hypotension)
Therapeutic strategy

- Prevention of CAD
- Treatment of acute and life-threatening symptoms
- Delay or prevent disease progression
Prevention

I. Primary
   Risk factors modification / amelioration
   * Hypertension
   * Cigarette smoking
   * Dyslipidemia
   * Diabetes mellitus
   * Etc

II. Secondary
   * Drugs (antianginal, hypolipidemic drugs)
   * PTCA (Percutaneaus Transluminal Coronary Angioplasty)
   * CABG (Coronary Artery Bypass Grafting Surgery)
   * Gene therapy
Antianginal agents:

- Organic nitrates
- Calcium channel blocking agents
- β-adrenergic receptor antagonists
ORGANIC NITRATES

- Amylnitrites: volatile liquid
- Nitroglycerin: liquid
- Isosorbid dinitrate
- Erythrityl tetranitrate
- Pentaerythritol tetranitrate

solid
Mechanism of action

1. NO release

Nitrovasodilators ↓

NO ↓

Guanlylate cyclase ↓

c GMP ↑

c GMP protein kinase ↓

Myosin dephosphorylation ↓

Relaxation
Mechanism of action

2. Hemodynamic (smooth muscle relaxation a & v)
   - Vasodilation of vein
   - Vasodilation of artery
Haemodynamic effects

1. Low dose
   Vein dilation (> arteriole)
   L & R - VEDP ↓
   • HR remains
   • Pulmonary resistency ↓
   • CO ↓

2. High dose
   Veins & systemic arteries dilation
   • BP ↓ (systole & diastole)
   • CO ↓
   • Transiently increased coronary blood flow
   • Compensatory tachycardia
Antianginal mechanisms

- Peripheral venodilation $\rightarrow$ preload ↓
- Peripheral arteriolar dilation $\rightarrow$ afterload ↓
- Ejection time ↓
- Epicardial coronary dilation
- Collateral flow $\uparrow$
- LVDP ↓
- Inhibition of platelet aggregation (moderate)
  Interferes heparin pharmacokinetic $\rightarrow$ antiplatelet effect of heparin ↓
Other effects

- Relaxation of bronchus, GI tract, urinary tract, uterine muscle, biliary tract, oesophagus
Pharmacokinetics

- Mucosal surfaces and skin: well absorbed
- Metabolism: liver
  - glutathione-organic
  - **nitrate reductase**
  - Organic nitrates (lipid soluble) → denitrated metabolites (water sol.) + inorganic nitrites
- Bioavailability depends on preparation
Use of organic nitrates

1. Acute treatment
2. Chronic treatment (→ tolerance !)

Stable angina
Unstable angina
Vasospastic angina
Side effects

- Headache, dizziness, weakness, etc. due to postural hypotension
- Palpitation, tachycardia
- Skin rash (esp. PETN)
- Tolerance (oral, patch, prolonged IV, not sublingual)
  - SH depletion
  - Neurohumoral → biogenic amine release → vasoconstriction
Side effects

- Volume expansion → nitrate hemodilution
  → Interrupt therapy 8-12 h (night)
  Change of interval or dose
  Eccentric dosing (7 or 8 a.m. and 2 or 3 p.m.)

- Rebound phenomenon (during nitrate - free) esp. in unstable angina in CCU
  → Increase gradually IV nitroglycerin
  Troublesome

- Met. Hb (nitrate + Hb)
Precaution

- Intracranial pressure ↑
- Hypotension, hypovolemia
- Hypertrophic cardiomyopathy
- Stenotic aorta
- Tachyarrhythmias
- Use in combination with other vasodilators
Contraindication

Hypersensitivity

Other indication

- Myocardial infarction
- Congestive heart failure (nitrates + hydralazine)
CALCIUM CHANNEL BLOCKING AGENTS

- Definition
- Chemistry
  1*. Phenylalkylamines : verapamil
  2*. Dihydropyridines : nifedipine, nicardipine, nimodipide
  3*. Benzothiazepines : diltiazem
  4. Diphenylpiperazines : sinarizin
  5. Others : prenylamine

* Specific and non specific
Ca\textsuperscript{++} ion : heart $\rightarrow$ contraction

vascular system $\rightarrow$ constriction
Myocardium

↓

Ca$_0$$^{++}$

↓

Ca$_i$$^{++}$

↓

Ca$^{++}$ - troponin C

↓ stimulates

Actin – myosin interaction

↓

Contraction

\[ \text{cAMP - } \beta \text{ stimulation} \]
Smooth muscle

\[ \text{Ca}^{++} \]
\[ \downarrow \]
\[ \text{Ca}^{++} - \text{calmodulin} \]
\[ \downarrow \text{stimulates} \]
\[ \text{cAMP} \rightarrow \text{myosin light chain-kinase (MLCK)} \]
\[ \text{X} \]
\[ \downarrow \text{phosphorylates} \]
\[ \text{Myosin light chain} \]
\[ \downarrow \]
\[ \text{Contraction} \]

\( \beta \) Blockade → cAMP ↓ → removes inhibition of MLCK
→ contraction (e.g. asthmatic attack, vasoconstriction)
Vascular system

- **Ca**^{++} function >> **Na**^{+}
- **Ca**^{++} channels:
  - voltage-sensitive channel (VSC, PDC)
  - receptor-operated channel (ROC)
  - stretch-operated channel
- **PDC:** Depolarization-induced or increased **K**_{o}^{+}
  - Influx **Ca**_{o}^{++} → **Ca**_{i}^{++}
  - T,N,L (sensitive against Ca^{++} blockers)
  - Vascular smooth muscle (artery) and heart
Vascular system

- ROC: receptor occupancy
  - influx $\text{Ca}_o^{++} \rightarrow \text{Ca}_i^{++}$
  - Vascular smooth muscle ($\alpha$) and heart ( $\beta_1$)

Receptor-mediated Ca$^{++}$ release

- Hydrolysis of PPI
- Release $\text{Ca}_i^{++}$, from SR $\rightarrow$ cytosol
Heart

- Ca\(^{++}\), Na\(^{+}\) function
- Ca\(^{++}\) → conduction system
Ca$^{++}$ ion and contraction (heart and vascular system)
# Pharmacodynamic

<table>
<thead>
<tr>
<th></th>
<th>D</th>
<th>N</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation (coronary)</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Inotropic (-)</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Chronotropic (-) (SA)</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Dromotropic (-) (AV)</td>
<td>4</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

N: does not influence channel recovery, is not affected by frequency of stimulation

V: slows channel recovery, is affected by frequency of stimulation
Antianginal mechanism

- Contractility ↓ (V > D)
- HR ↓ (D > V)
- Systemic arteriolar resistency N > V > D)
- Dilation of epicardial artery (N > D > V)
- BP ↓ (N > V = D)
- HR ↓ (D > V)

→ Use of Ca++ blockers : stable and variant angina
Other use

- Hypertension (esp. N)
  - Mild to moderately severe hypertension
  - ~ beta blocking agents, diuretics
- Arrhythmia
  V to SA and AV nodes
  - Supraventricular tachycardia
  - Atrial fibrillation
  - Atrial flutter
- Hypertrophic cardiomyopathy
  V improves LV outflow obstruction
- Raynaud’s disease (esp. N)
Pharmacokinetics

- Absorption: oral, sublingual
- Bound to plasma protein (80-90%)
- Metabolism: liver (esp. V,D)

Repeated administration → increase bio availability
Side effects

- Headache
- Hypotension, paradoxical anginal attack (N)
- Tachycardia
- AV block
BETA ADRENERGIC RECEPTOR ANTAGONIST

Antianginal mechanisms
- Heart rate ↓
- Contractility ↓
- Blood pressure ↓
- Ventricular wall stress during systole ↓ (afterload ↓)
- Heart rate ↓

Use of beta adrenergic receptor antagonists:
- stable angina pectoris
  → mortality ↓ after myocardial infarction
Pharmacologic properties

- Cardioselectivity
  - Presents at low dose, disappears at high dose
  - Bronchospasm ↓
  - E.g.: acebutolol, atenolol, metoprolol
Pharmacologic properties

- Intrinsic sympathomimetic activity (ISA)
  - Less bradicardia
  - Less depression of contractility
  - Maybe less effective in ameliorating anginal attack
  - Less affecting lipid abnormality (HDL ↓, TG ↓)
  - Useful for patients with peripheral vascular disorders

Cardioprotection due to: *cardioselectivity*? *ISA*?

- Membrane stabilizing activity (MSA)
  - Anesthetic local effect
  - Clinically not important
Side effects

- Bradicardia
- AV block
- Heart failure
- Bronchospasm
- Others: GI tract, CNS, allergic reaction
Contraindications

- Hypotension
- Symptomatic bradicardia
- AV block 2nd - 3rd degree
- Congestive heart failure
- Asthmatic attack exacerbation
- Diabetes mellitus with hypoglicemic episodes
Precaution

- Stable diabetes mellitus
- *Rebound phenomenon*
  Discontinue drug gradually
Monotherapy

- Acute episodes: short acting nitrates
- Chronic attack: - long acting nitrates
  - $\beta$ blockers (exertional angina, arhythmia)
  - Ca++ antagonist
    (if $\beta$ blockers are contraindicated, mostly diltiazem)
Combination therapy

- Lower individual doses, effectiveness ↑
- Goal of therapy: ? serious side effects!

1. Nitrates + beta blockers
   - Exertional angina
   - Beta blockers block rf. tachycardia, & inotropic (+) by nitrates
     Nitrates ↑ LVED volume & decrease coronary resistance by beta blockers
2. Beta blockers + Ca++ antagonists
   - Beta blockers block rf. tachycardia & BP ↑ in exercise by Ca++ antagonists
   - Ca++ antagonists relieve coronary vasospasm
Combination therapy

3. Ca\(^{++}\) antagonist + nitrates
   - Severe exertional or vasospastic angina
   - preload ↓ by nitrates
     afterload ↓ by Ca\(^{++}\) antagonists

   Additive, but excessive vasodilation and hypotension!

4. Combination of 3 drugs
   Only if angina can not be alleviated by one or two drugs
HYPOLIPIDEMIC AGENTS

TG
esterified cholesterol
Free cholesterol
Phospholipid
Apolipoprotein
# Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Density</th>
<th>Electrophoretic mobility</th>
<th>Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>&lt; 0.94</td>
<td>origin</td>
<td>70-120</td>
</tr>
<tr>
<td>Very low density LP (VLDL)</td>
<td>&lt; 1.006</td>
<td>pre-β</td>
<td>30-70</td>
</tr>
<tr>
<td>Intermediate-density LP (IDL)</td>
<td>= 1.006-1.019</td>
<td>β</td>
<td>23-30</td>
</tr>
<tr>
<td>Low-density LP (LDL)</td>
<td>= 1.019-1.063</td>
<td>β</td>
<td>18-23</td>
</tr>
<tr>
<td>High density LP (HDL)</td>
<td>= 1.063-1.215</td>
<td>α</td>
<td>5-12</td>
</tr>
<tr>
<td>* Lipoprotein (a)</td>
<td></td>
<td>pre-β</td>
<td>23-26</td>
</tr>
</tbody>
</table>
## Composition

<table>
<thead>
<tr>
<th>Lipo-protein</th>
<th>Chylomicrons (%)</th>
<th>VLDL (%)</th>
<th>LDL (%)</th>
<th>HDL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride</td>
<td>80-90</td>
<td>45-65</td>
<td>4-8</td>
<td>2-7</td>
</tr>
<tr>
<td>Cholesteryl esters</td>
<td>2-4</td>
<td>16-22</td>
<td>45-50</td>
<td>15-20</td>
</tr>
<tr>
<td>Free cholesterol</td>
<td>1-3</td>
<td>4-8</td>
<td>6-8</td>
<td>3-5</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>3-6</td>
<td>15-20</td>
<td>18-24</td>
<td>26-32</td>
</tr>
<tr>
<td>Protein</td>
<td>1-2</td>
<td>6-10</td>
<td>18-22</td>
<td>45-55</td>
</tr>
<tr>
<td>Apolipoprotein species</td>
<td>B-48, Al, AlIV, CI, CII, CIII, E</td>
<td>B-100, C1, CII, CIII, E</td>
<td>B-100</td>
<td>Al, All, Cl, CII, CIII, D, E</td>
</tr>
</tbody>
</table>
## Treatment goals

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Target Concentration of LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong></td>
<td></td>
</tr>
<tr>
<td>Men &lt; 35 years and premenopausal women</td>
<td>&lt; 190 mg/dl</td>
</tr>
<tr>
<td>Men &gt; 35 years and women &gt; 45 years</td>
<td>&lt; 160 mg/dl</td>
</tr>
<tr>
<td>with &lt; 2 other CV risk factor</td>
<td></td>
</tr>
<tr>
<td>Adults with ≥ 2 other CV risk factor</td>
<td>&lt; 130 mg/dl</td>
</tr>
<tr>
<td>Adults with diabetes mellitus or a strongly family history of early CV disease</td>
<td>≤ 100 mg/dl</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td>100 mg/dl</td>
</tr>
</tbody>
</table>
Treatment goals

Cholesterol: - vitamin D
   - steroid hormones
   - bile acid

Therapy:
1. Secondary cause (hypothyroidism, DM)
2. Dietary modification 3-6 months
3. Hypolipidemic agents

Choice: Hypercholesterolemia: Bile acid sequestrants-niacin-
        statins-gemfibrozil

Hypertriglyceridemia: Gemfibrozil-niacin-statins
Treatment goals

Hypolipidemic agents:
1. Fibric acids
2. Bile acid sequestrants
3. HMG-CoA reductase inhibitors (statins)
4. Probucol
5. Nicotinic acid
FIBRIC ACIDS

- M.A: - ligand for peroxisomal proliferator activated receptor (PPAR)
  - LP lipase $\uparrow \rightarrow$ VLDL catabolism $\uparrow$
  - VLDL $\downarrow$, IDL $\downarrow$, LDL $\uparrow$ (in primary hypertriglyceridemia, type IV) or $\downarrow$ (in hypercholesterolemia, type II), HDL $\uparrow$
Kinetics

- Oral
- Highly bound to protein (90-95%)
- Enterohepatic circulation
- Elimination: kidney
  * Fenofibrate: prodrug
  * Gemfibrozil: homolog of clofibrate

→ 22% reduction in death from CHD or non-fatal MCI
→ 1st line treatment of hypertriglyceridemia
  2nd line treatment other hyperlipidemias
S.E.

- GI tract
- Rash, alopecia
- Myositis (bezafibrate), CPK ↑, SGOT ↑
- Lithogenicity index ↑
Indication

- Hypertriglyceridemia
  - FA : - TG ↓ (25-60%)
    - Cholesterol ↓ (5-25%)
    - HDL ↑ (10-20%)
    - LDL ↓ (10-20%) or ↑ (5-20%)

- Hypercholesterolemia (type II b) DM, nephrotic syndrome
- Dysbetalipoproteinemia (type III)
Contraindication

- Pregnancy, lactation
- Liver, kidney diseases
- Anticoagulants
BILE ACID SEQUESTRANTS (RESINS)

Cholestyramine, colestipol

M.A

Liver

Cholesterol pool

↓

cholesterol-7 hydroxylase

Bile acids

(cholic, chenodeoxycholic acid)

secreted by liver

Bile

unesterified cholesterol

intestine

faecal sterol

Resins

Reabsorbed by ileum

Pl, bile acids,
Results

Cholesterol content ↓

↓

HMG-CoA reductase inhibition

↓

Cholesterol synthesis ↑

LDL receptors ↑

Net results:
- LDL catabolism ↑ in liver → plasma cholesterol ↓
- Compensatory increases in cholesterol and TG synthesis
Results

Lipid Research Clinic Primary Prevention Trial (1984) cholestyramine monotherapy: 12% reduction of LDL and 19% reduction in CAD. However, total mortality was unchanged.
S.E.

- Constipation, flatulence, nausea, vomiting, poor palatability
- SGOT ↑, AP ↑, hyperchloremic acidosis, hypoprothrombinemia
- Impair absorption of drugs: digoxin, furosemide, gemfibrozil, niacin, thiazides, warfarin, NSAIDs, aspirin, vitamins A,D,E,K etc. → give other drugs 1 h before or 4 hs after resins. Resins administration with meals.
**Indication**

- Hyperlipoproteinemia (type II)
- **X** Homozygous familial hypercholesterolemia
- **X** Hypertriglyceridemia
- Probably safe for pregnant and lactating women, children (but pay attention to fat sol. vitamins availability)
- Reduce pruritus in partial biliary obstruction.
STATINS (HMG-CoA reductase inhibitors)

M.A.:

Acetyl - CoA
↓
HMG - CoA
↓ HMG - CoA reductase
Mevalonate

Farnesyl pyrophosphate
↓
Squalene
↓
Ubiquinone

\[\text{Cholesterol} \]

\[\text{Dolichol} \]

\[\text{Farnesylated proteins} \]
STATINS (HMG-CoA reductase inhibitors)

Statins (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin)

- Competitive inhibitors of HMG-CoA reductase
  → cholesterol synthesis ↓ (modest)
  → LDL receptors ↑
45 study (Scandinavian Simvastatin Survival Study Group, 1994)

- Total cholesterol ↓ 25%
- LDL ↓ 35%
- TG ↓ 10%
- HDL ↑ 8%

42% reduction in mortality from CHD
30% reduction in mortality from all causes
Kinetics

- Oral: absorption varies, 12% (atorvastatin), > 90% (fluvasatin)
- All except cerivastatin undergo extensive first pass metab. → target: liver
- Lovastatin & simvastatin: prodrug
Indications

- Hypercholesterolemia (heterozygous familial hypercholesterolemia / type II hyperlipoproteine-mia and polygenic forms)
S.E.

- Liver function ↓, SGPT ↑ > 3x → stop therapy
  Liver function monitoring 4-6 weeks (1 1/2 years)
- Myositis, rhabdomyolisis → CPK ↑ >10 x normal
  X combination with cyclosporine, gemfibrozil, niacin, erythromycin, imidazole antifungals
- Skin rash, GI complaints
Contraindication

- Premenopausal women, nursing
NIACIN (nicotinic acid)

M.A.:

- In adipose tissue: hormone sensitive
  - TG lipase
  - hepatic TG synthesis ↓
  - transport FFA to liver
  - niacin

- In liver: inhibits FFA synthesis & esterification → TG synthesis ↓
  - → VLDL ↓ → LDL-C ↓
- Enhances LPL activity → chylomicrons & VLDL triglyceride clearance ↑
- Increases HDL
Kinetics

- Oral: rapid & complete
- First-pass metabolism
- $t^{1/2} : 45 \text{ min.}$
- Distribution: all tissues
- Excretion: kidney
Indications:

- 1st line agent for hypertriglyceridemia and hypercholesterolemia
- Type III, IV, & V hyperlipoproteinemia
S.E.

- Flushing, pruritus, dryness, hyperpigmentation
- Liver dysfunction: AP ↑, SGPT ↑, SGOT ↑
- GI complaints
- Atrial fibrillation, ventricular ectopy
- Glucose intolerance, uric acid ↑
Contraindications:

- Peptic ulcer
PROBUCOL

• M.A. : LDL ↓ (not TG), antioxidant
  HDL ↓ ↓

• Indication : type IIA hypercholesterolemia

• Side effects : - GI complaints
  - Odorous perspiration
  - Blood abnormality
  - Liver dysfunction
Dietary and biliary cholesterol absorption inhibitor

Ezetimibe (azetidione-based cholesterol absorption inhibitor)

M.A.: block intestinal absorption of chol. → total cholesterol ↓ and LDL-C ↓

Kinetics: glucuronidation in intestine → active metabolic → bile (enterohepatic circulation) t ½ : 22 h
Studies:
- 10 mg daily → LDL-C ↓ 19%
- 20 mg simvastatin + 10 mg ezetimibe → LDL-C ↓ 52%
  ~ 80 mg simvastatin
  margin of safety ↑

Indications:
- Primary hypercholesterolemia
- Homozygous familial hypercholesterolemia
Others

- Neomycin, activated charcoal, psyllium hydrophilic muciloid, β-sitosterol, D-thyroxin
Ezetimibe

MA:
- Inhibits absorption of phytosterols and cholesterol
- Effective even in the absence of dietary cholesterol
Kinetics:

- Well absorbed, conjugated in intestine to active glucuronide
- Undergoes enterohepatic circulation
- $T_{\frac{1}{2}} : 22$ h, 80% excreted in faeces
- Plasma conc $\uparrow +$ fibrates
  $\downarrow +$ cholestyramine
- No significant interaction with warfarin, digoxin
Indication:
- 10 mg single dose
- LDL in primary cholesterolemia ↓ 18%
- HDL slightly ↑
- Synergistic + statin (↓ 25%)
S.E.:
- Not a substrate for cytochrome P450
- Reversibly impaired hepatic function
- Liver function test every 2-4 mo.
THANK YOU
Antiarrythmias

Frans D. Suyatna

Departemen Farmakologi & Terapeutik FKUI
Cardiac action potential (AP)

1. Ion movement across cell membrane
   - electrical gradient
   - concentration gradient

1. Normal AP at rest: - 90 mV
   - Na/K- ATPase
   - fixed anion charges in the cells

1. $Na^+_{o} \rightarrow Na^+_{i}$; but Na channels are closed (in resting membrane)

$K^+_{o} \leftrightarrow K^+_{i}$; inward rectifier channels open
Cardiac action potential (AP)

4. Nernst equation
   \[ E_x = -61 \log \left( \frac{[x]_i}{[x]_o} \right) \]

   for \( K^+ \), \([K]_o = 4 \text{ mM}, [K]_i = 140 \text{ mM}\)
   \[ E_K = -94 \text{ mM} \sim \text{resting AP} \]
   Hyperkalemia: \( E_K \) rises to more positive
   \( K^+ \) enters cell
   \( E_K \) changes \( \sim [K]_o \) changes, \([K]_o \) major determinant
   of resting potential
Na$^+$ current
\[ \text{Ca}^{2+} \text{ current} \{ \begin{array}{ll}
\text{L-type} \\
\text{T-type} \\
\text{transient outward current} \{ \begin{array}{ll}
I_{T01} & (4-\text{AP-sensitive}) \\
I_{T02} & (\text{Ca}^{2+}\text{-activated}) \\
\text{delayed rectifiers} (I_K) \{ \begin{array}{ll}
I_{KS} \\
I_{KR} \\
I_{Kur} \\
I_{Cl} \text{ or } I_{KP} \\
inward \text{ rectifier, } I_{K1} \\
pacemaker \text{ current, } I_f & (\ldots, \text{see above}) \\
\text{Na}^+-\text{Ca}^{2+} \text{ exchange} \\
\text{Na}^+, \text{K}^+-\text{ATPase}
\end{array} \}
\end{array} \}
\end{array} \]
**Fast response**

- $\text{Na}^+$ channel dependent
- Fast conduction
  - "All or none"
- Recovery of excitability
  - Voltage-dependent
  - (in the absence of drugs)
- Atria, ventricles, His-Purkinje system

**Slow response**

- $\text{Ca}^{2+}$ channel dependent
- Slow conduction
  - Decremental
- Time-dependent
- Sinus, AV nodes, depolarized tissue
Mechanisms of cardiac arrhythmias

1. Disturbances in impulse formation
   - Failure of impulse formation
     * vagal discharge $\rightarrow$ more negative max. diastolic potential reducing phase 4 slope
     * $\beta$ receptor-blocking drugs $\rightarrow$ reducing phase 4 slope
   - Acceleration of impulse formation (enhanced automatically)
     * Hypokalemia, $\beta$ adrenoreceptor stimulation, fiber stretch, acidosis, partial depolarization by currents of injury $\rightarrow$ increasing phase 4 slope
Mechanisms of cardiac arrhythmias

2. Disturbances in impulse conduction
   - Failure of impulse propagation (A $\rightarrow$ V) $\rightarrow$ heart block
   - Reentry
     * presence of an anatomically defined circuit
     * unidirectional block
     * slow conduction in one part of the circuit
B. Normal conduction

Twig

Ventricular wall
E. Reentry circuit established

Depressed region
Afterdepolarizations & triggered automatically

1. Delayed afterdepolarizations (DAD), (in rapid HR) $\text{Ca}^{++} \uparrow$ (myoc. ischemia, adrenergic stress, digitalis intoxication)

2. Early afterdepolarization (EAD), (in slow HR), $K^{+} \downarrow$, certain antiarrhythmic drugs
   eg. torsades de pointes
   long QT syndrome
Mechanism of action

1. Alter automatic rhythm
   - max. diastolic potential ...... adenosine, Ach
   - phase 4 slope .................. \( \beta \)-blockers
   - threshold potential ............ blocking of Na\(^+\)
     Ca\(^{2+}\) channels
   - AP duration .................... blocking of K\(^+\)
     channels
A

Na⁺ Channel Blockers

B

Action Potential-Prolonging Drug

25% of Na⁺ channels recovered from inactivation

● no drug    ● drug

ΔERP

ΔERP
Mechanism of action

2. DAD & EAD

- inhibition of development of afterdepolarization
- interfere inward current (Na$^+$, Ca$^{2+}$ channels)
  eg. verapamil for digitalis-induced DAD
  quinidine for digitalis-induced DAD
  (blocks Na$^+$ channels $\rightarrow$ threshold $\uparrow$)
  isoproterenol shortens AP duration in EAD
  Mg$^{2+}$ inhibits triggered beats from EAD
  $\beta$ blocker for prevention of torsades de pointes in cong. prolonged QT interval
Anatomically determined reentry
Ca\textsuperscript{++} blocking agents, β blockers, digitalis prolong AV nodal refractoriness & slow AV nodal conduction $\rightarrow$ block propagation of AP

Functionally determined reentry
Na\textsuperscript{+} channel blocking agents shift voltage dependent of recovery from block $\rightarrow$ prolong refractororiness
Also blocking delayed rectifier currents, Ca\textsuperscript{++} channels $\rightarrow$ prolong refractororiness
Antiarrhythmic drugs

Classification

I. Na\(^+\) channel blocker (local anesthetic of action)
   I.a. Quinidine, procainamide, disopyramide
       lengthen AP duration
   I.b. Lidocaine, mexiletine, flecainide, phenytoin, shorten AP duration
   I.c. Flecainide
       no effect on or slightly lengthen AP duration

II. Sympathoplegic, beta-blocker
Antiarrhythmic drugs

III. Prolong effective refractory period by prolonging AP duration
   Blocking K+ channels or enhancing inward current through Na+ or Ca++ channels

IV. Calcium channel blocking drugs
Class I.a
Quinidine
1. Mechanism of action

- Blocks Na\(^+\) current (open state blocker) $\rightarrow$ threshold of excitability $\uparrow$, automaticity $\downarrow$
- Blocks multiple K\(^+\) currents $\rightarrow$ prolongs APD
  - ! At slow HR $\rightarrow$ EAD produced, esp. when $[K]_o \sim$ low
- Prolongs refractoriness due to Na\(^+\) channel blocking and prolongation of APD
- Additional effect: $\alpha$-adrenergic receptor blockade vagal inhibition
  - $\rightarrow$ hypotension & tachycardia
- Use of: atrial fibrill./flutter
  - prevention of VT or VF
2. Adverse effects
- Non cardiac: diarrhea (30-50%, be aware of hypokalemia \(\rightarrow\) torsades de pointes \(\uparrow\))
- Others (non dose dependent, immunologic): thrombocytopenia, hepatitis, bone marrow depression, LE cinchonism (dose dependent)
- Cardiac: QT prolongation, torsade de pointes (2-8%) ventricular tachycardia, may exacerbate heart failure

3. Pharmacokinetics
- Well absorbed, 80% bound to plasma proteins
- Extensive hepatic oxidative metabolism, 20% excreted unchanged by kidney
- 3-OH quinidine ~ quinidine as Na\(^+\) channel blocker
4. Drug interactions

- Potent inhibitor of CYP 2D6 (reduced analgetic effect of codein, increased plasma propafenone & β adrenergic blockade)
- Reduces clearance of digoxin & digitoxin
- Phenobarbital increases metabolism of quinidine
- Cimetidine & verapamil increases plasma quinidine (modest)
Procainamide (1)

1. Mechanism of action

- ~ quinidine, but vagolytic activity (-) & α-adrenergic blocking activity (-)
- Use of: acute therapy (i.v.) in supraventricular and ventricular arrhythmias
- N-acetyl procainamide (metabolite) lacks Na\(^+\) channel blocking activity
Procainamide (2)

2. Adverse effects

- Hypotension, marked slowing of conduction (i.v.)
- Nausea (oral), bone marrow aplasia, lupus syndrome (parent drug)
- Torsade de pointes

3. Pharmacokinetics

- $t \frac{1}{2}: 3-4$ h, renal & hepatic
- Lupus develops often in slow acetylators
Disopyramide

Mechanism of action ~ quinidine
- $\alpha$-adrenergic blocking activity (-), vagolytic action (+)
- Use of : atrial flutter, fibrillation, prevention of recurrence of VT or VF
- Side effects: glaucoma, constipation, dry mouth, urinary retention, torsade de pointes
- Oral administration (well absorbed)
Amiodarone

1. Mechanism of action

- Analog of thyroid hormone
- Blocks inactivated Na\(^+\) channels, ↓ Ca\(^++\) currents, ↓ transient outward, delayed rectifier & inward rectifier K\(^+\) currents, non competitive β adrenergic blocking effect
- Potent inhibitor of abnormal automaticity, prolongs AP
- Use of: recurrent VT or VF resistant to other drugs, atrial fibrillation
2. Pharmacokinetics

- Poorly absorbed per oral (bioavail. ~ 30%), highly lipophilic – distributed in lipid >> plasma
- Slowly accumulated in tissue (needs high-dose oral loading for several weeks)
- Metabolized by CYP3A4 to desethyl-amiodarone (effect ~ parent drug)
- Inhibitor of CYP3A4, CYP2C9 and P-glycoprotein
- Reduce dosage of warfarin, flecanide, procainamide, quinidine, digoxin when used together
2. Pharmacokinetics
   - $t_{1/2}$ : long
   - Elimination : ?

3. Adverse effects
   - Hypotension, nausea
   - Pulmonary fibrosis, corneal microdeposits, hepatic dysfunction, hypo-hyperthyroidism, neuromuscular symptoms, photosensitivity
   - Prolong QT interval and marked bradycardia, but torsade de pointes is rare
Lidocaine

1. Mechanism of action

- Local anesthetic (i.v.)
- Blocks open & inactivated Na\(^+\) channels
- Reduces slope of phase 4 & threshold for excitability, AP duration is unaffected
- Use of: drug of choice for VT & VF after cardioversion ↓ incidence of VF in acute myocardial infarction but routine prophylactic use in myocardial infarction is no longer practiced, because of lidocaine-exacerbated heart block or congestive heart failure

Not for: atrial arrhythmias
2. Adverse effect

- Seizures (rapid & large iv dose)
- Tremor, dysarthria, altered level of consciousness, nystagmus (early sign)

3. Pharmacokinetics

- $t_{\frac{1}{2}} : 2 \text{ h}$
  - therapeutics plasma level : 2-4 $\mu$g/ml
- Decrease doses (loading & maintenance) when volume of distribution and total body clearance are decreased (congestive heart failure)
Tocainide and mexiletine

- Analogs of lidocaine for oral chronic administration
- Tocainide is rarely used, it can cause fatal bone marrow aplasia and pulmonary fibrosis
- Metabolism: tocainide $\rightarrow$ renal excretion
  mexiletine $\rightarrow$ hepatic metabolism
- Use of: ventricular arrhythmias
Flecainide

1. Mechanism of action
   - Blocks Na\(^+\) current & delayed rectifier K\(^+\) current
   - Very long T recovery from Na\(^+\) channel block
   - Use of: supraventricular arrhythmias (incl. atrial fibrillation)

2. Adverse effects
   - Exacerbate congestive heart failure, lethal arrhythmias (increase ventricular rate in atrial flutter, frequency of reentrant ventricular tachycardia, mortality in myocardial infarction)
   - Subjected, dose-related blurred vision
Flecainide

3. Pharmacokinetics
   - Well absorbed
   - Metabolized by CYP2D6
Propafenone

1. Mechanism of action

- $\text{Na}^+$ channel blocker with slow $T$ recovery
  Also blocks $\text{K}^+$ channels $\sim$ quinidine
  $S\ (+)$ propafenone has $\beta$ adrenergic receptor blocker activity
- Use of: supraventricular tachycardia
  modestly effective in ventricular arrhythmias
Propafenone

2. Adverse effects
   - Arrhythmias exacerbation, metallic taste, constipation

3. Pharmacokinetics
   - $t_{1/2}: 5\ h$
   - metabolized by CYP2D6
Moricizine

- Phenothiazine analog
- Chronic therapy for ventricular arrhythmias
- Undergoes extensive hepatic metabolism
Phenytoin

- Used for acute and chronic ventricular arrhythmias and in digitalis intoxication
Class II

Beta adrenergic blocking drugs

- Beta adrenergic blocking & membrane stabilizing effects
- Suppressive effect on ventricular arrhythmias is lower than class I

Prevent recurrent infarction & sudden death in myocardial infarction

- Sotalol: non selective $\beta$-adrenergic receptor antagonist used for ventricular tachyarrhythmias and atrial flutter or fibrillation
- Causes EAD, torsade de pointes
Class III
Bretylium

1. Mechanism of action
   - Prolongs AP in Purkinje cells
     - Interferes with reuptake of NE by sympathetic nerves
   - Use of: VF (when lidocaine & cardioversion have failed)

2. Adverse effect
   - Transient hypertension and increased arrhythmias (e.g. digitalis intoxication)
   - Hypotension (can be inhibited when coadministered with protryptiline)

3. Pharmacokinetics
   - Excreted in unchanged form by kidneys
Class IV

Calcium channel blocking agents - (verapamil, diltiazem, bepridil)

Verapamil

- Blocks activated and inactivated Ca^{++} channels
  Marked effect on tissues that fire frequently, depolarized, SA & AV nodes
- Use of: reentrant supraventricular tachycardia (verapamil & adenosine are more preferred to propranolol, digoxin, edrophonium, vasoconstrictor agents & cardioversion)
Class IV

- Reduce ventricular rate in atrial fibrillation and flutter
- Misuse of verapamil in patients with VT mistakenly diagnosed as SVT → hypotension and cardiac arrest
1. Adenosine
   - Naturally occurring nucleoside
   - Use of: acute termination of reentrant SVT
     VT of DAD – mediated
     Produces controlled hypotension during surgical procedure in the diagnosis of CAD
   - Effects are mediated by interaction with G protein-coupled adenosine receptors
     Enhances $K^+$ conductance
     Inhibits cAMP-induced $Ca^{++}$ influx
     AP shortening, hyperpolarization, slowing automaticity
- $t_{1/2} : < 10 \text{ secs}$

  **Administration**: rapid bolus IV

  **Effects**: is potentiated in patients receiving dipyridamole (adenosine-uptake inhibitor) and patients with cardiac transplants (due to denervation hypersensitivity)

  **Xanthine drinks** block adenosine receptors

- **Adverse effects**: short-lived, transient asystole (< 5sec), chest fullness & dyspnea, sometimes atrial fibrillation
2. Magnesium

- Used in digitalis – induces arrhythmias in hypomagnesemic patients
- Mechanism of action: ? through Na/K ATPase, Na\(^+\)-channel, Ca\(^{++}\) channels
- Has been used in preventing torsade de pointes, chronic therapy, antiarrhythmic effects