ISCHAEMIC HEART DISEASE (IHD) TREATMENT
RISK FACTORS

• a) risk factors atherogenesis
  • (ED, lipidic nucleus, proliferation)

• b) risk factors thrombotic arterial occlusion
  • (plaque destabilization, thrombotická occlusion, fibrinolysis)
- organic stenosis
  - stable AP

- vasospastic stenosis
  - vasospastic AP

- Stenosis and thrombus
- nonstable AP, MI
For LV coronary perfusion is diastolic interval decisive

- ml/min
- systole
- diastole
- LV coronary perfusion
Increased coronary perfusion during decreased heart frequency

- systole
- diastole

LV coronary perfusion

ml/min
COMPLEX TREATMENT IHD:

- a) stop atherogenic progression – plaque stabilization – elimination of endotelial dysfunction
- b) avoid arterial thrombotic occlusion (or rapid restoration of perfusion)
- c) decrease of myocardial ischemia
  - improvement of flow through ischemic myocardium
  - decrease myocardial metabolic requirements
  - optimalization of metabolic energy utilization
- d) prevention of arrythmia
- e) prevention of myocardial remodeling and development of heart failure
Atherosclerotic plaque stabilization

• a) endothelial dysfunction adjustment
  – (hypolipidemics, ACEI, estrogens, prostanoids, arginine supplementation, calcium channel blockers)

• b) atherosclerotic plaque stabilization
  – soft nucleus (diet, hypolipidemics - statins)
Effect of antioxidants on plaque

• Clinical studies
  – Secondary prevention > 20 000 patients
  – vit. C, vit. E, β-karoten, 5 year treatment

• No any effect on cardiovascular mortality and morbidity

• Study HOPE (vitamine E)
  – Secundary prevention 9 500 patients, 4-5 year
  – No any effect on cardiovascular mortality and morbidity

• Scavangeres have no effect
COMPLEX TREATMENT IHD:

- a) stop atherogenic progression – plaque stabilization – elimination of endothelial dysfunction
- b) avoid arterial thrombotic occlusion (ev. rapid restoration of perfusion)
- c) decrease of myocardial ischemia
  - improvement of flow through ischemic myocard
  - decrease myocardial metabolic requirements
  - optimization of metabolic energy utilization
- d) prevention of arrhythmia
- e) prevention of myocardial remodeling and development of heart failure
<table>
<thead>
<tr>
<th>studies</th>
<th>příhody</th>
<th>populace</th>
<th>RRR ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>primární</td>
<td>1176</td>
<td>27210</td>
<td>12 ± 6 %</td>
</tr>
<tr>
<td>prev. cerebrální</td>
<td>1916</td>
<td>9530</td>
<td>24 ± 5 %</td>
</tr>
<tr>
<td>po IM</td>
<td>2270</td>
<td>15529</td>
<td>24 ± 4 %</td>
</tr>
<tr>
<td>AIM</td>
<td>2783</td>
<td>18126</td>
<td>26 ± 4 %</td>
</tr>
<tr>
<td>AP</td>
<td>398</td>
<td>3450</td>
<td>39 ± 9 %</td>
</tr>
<tr>
<td>CABG/P</td>
<td>245</td>
<td>3057</td>
<td>33 ± 13 %</td>
</tr>
<tr>
<td>TCA</td>
<td>444</td>
<td>3864</td>
<td>25 ± 10 %</td>
</tr>
<tr>
<td>ICHDK</td>
<td>67</td>
<td>4771</td>
<td>42 ± 19 %</td>
</tr>
<tr>
<td>po DVT</td>
<td>283</td>
<td>3948</td>
<td>44 ± 10 %</td>
</tr>
<tr>
<td>ostatní</td>
<td>9789</td>
<td>90297</td>
<td>25 ± 2 %</td>
</tr>
</tbody>
</table>

Br Med J 1994
DECREASE OF MYOCARDIAL ISCHEMIA
NITRATES
and
NO DONORS
NITRATES

• **Mechanism of action**
  - metabolized in vessel wall (enzymes or nitrosothiol) to NO (identical with EDRF), stimulation cGMP
  - smooth muscle dillatation (arteries, veins, but arterioles very small)

• **Clinical effectivity**
  - dilatation of eccentric stenosis in epicardial arteries
  - prophylaxis and treatment of coronary spasm
  - (increased tolerance, decreased number of angina, no evidence for better prognosis)
  - veins dilatation (only short term effect)
  - high doses arteriolodilatation (hypotension)
# NITRATES

<table>
<thead>
<tr>
<th>Generick names</th>
<th>Admin.</th>
<th>dose</th>
<th>onset</th>
<th>duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin (NTG, GTN)</td>
<td>subling.</td>
<td>0,3 – 0,6 mg</td>
<td>30 s</td>
<td>15 – 20 min</td>
</tr>
<tr>
<td></td>
<td>transderm.</td>
<td>-</td>
<td>1 h</td>
<td>6 – 14 h</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>2,5 – 19,5 mg</td>
<td>1 h</td>
<td>2 – 4 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,5 – 10 mg</td>
<td>5 min</td>
<td>1 – 2 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0,3 – 0,6 mg</td>
<td>30 min</td>
<td>4 – 6 h</td>
</tr>
<tr>
<td>Isosorbidinitrate (ISDN)</td>
<td>subling.</td>
<td>2,5 – 10 mg</td>
<td>5 min</td>
<td>1 – 2 h</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>20 – 120 mg</td>
<td>30 min</td>
<td>4 – 6 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 – 100 mg</td>
<td>30 min</td>
<td>8 – 12 h</td>
</tr>
<tr>
<td>Isosorbid 5 mono-nitrate (ISMN)</td>
<td>p.o.</td>
<td>20 – 100 mg</td>
<td>30 min</td>
<td>8 – 12 h</td>
</tr>
</tbody>
</table>
NITRATES

treatment of myocardial ischemia –
equivalent to calcium channel blockers

Usually underdosed – not properly used high
dose galenic forms ISDN a ISMN

ISMN or ISDN – first line
GTN (nitroglycerine) – only exceptionally
NITRATES

Adverse reactions:
• - headache (frequently limits use)
• - hypotension (rarely)
• - suspicion for increased oxidation stress in vessel wall

Nitrates tolerance:
• - decreased vasodilatation after long lasting treatment
• - SH group depletion, decreased cGMP, activation of contra-regulation
• - intermittent treatment (nitrate-free interval)
MOLSIDOMINE

- Syndonimine group – NO donors
- Same mechanism as nitrates – NO release
- Prodrug
- No need for SH-group, without tolerance
- Onset: 20 – 40 min
- Lasting: 4 – 6 h
  - 8 – 12 h retard form
- Dilatation smooth muscle in stenotic region
- Fibrinolysis activation (not clear effect)
- Indication: prophylaxis AP combination with nitrates
CALCIUM CHANNELS
BLOCKERS
CCB
Calcium channel blockers

- effective for myocardial ischemia (better quality of live)
- short acting (nifedipine) worsening patients prognosis
- long lasting – slow down atherogenesis and probably better prognosis

- antihypertensive effect and antiarythmic effect
CCB groups

• I. generation: low vascular selectivity
  short time effect
  • (nifedipine, verapamile, diltiazem)

• II. generation: high vascular selectivity
  long lasting effect
  (felo-, isra-, niso-, nitre-, nilva-, nimodipin)

• III. generation:
  high affinity to cell membranes
  slow onset, long lasting effect
  antiatherogenic effect
  (amlo-, barni-, laci-, lercainidipin)
Pharmacodynamic effect of CCB

**Dihydropyridines**
- Selective vasodilatation
  - Peripheral vasodilatation
  - Coronary vasodilatation

**Non-dihydropyridines**
- Myocardial depresion
  - Peripheral
  - Vasodilatación
  - Heart rate↓
  - Impulse propagation↓
  - Myocardial contractility↓
Dihydropyridine
Diltiazem

Verapamil

Ca\textsuperscript{2+}

Varadi (1995)

Ca\textsuperscript{2+}

cAMP

H\textsubscript{3}N

α\textsubscript{1}

β

γ

δ

δ
Bioavailability CCB

- **amlodipin**: 60-65%
- **lacidipin**: 9-15%
- **isradipin SR**: 17-33%
- **nitrendipin**: 10-20%
- **nilvadipin**: 10-19%
- **nicardipin**: 7-30%
- **nisoldipin**: 4-8%
- **nifedipin SR**: 45-68%
- **verapamil SR**: 12-48%
- **felodipin SR**: 12-16%
- **diltiazem SR**: 30-40%
Maximal plasma levels CCB

- **amlodipin**: 1-2
- **barnidipin**: 1-2
- **lacidipin**: 1-2
- **isradipin SR**: 1-2
- **nitrendipin**: 1-2
- **nilvadipin**: 1-2
- **nicardipin**: 1-2
- **nisoldipin**: 1-2
- **nifedipin SR**: 0.2-0.6
- **verapamil SR**: 1-2
- **felodipin SR**: 2-4
- **diltiazem SR**: 1-2

$t_{max}$ h

$
\begin{array}{c|c|c}
\text{Drug} & \text{t}_{max} \text{ h} & \text{t}_{max} \text{ h} \\
\hline
\text{amlodipin} & 1-2 & 12-12 \\
\text{barnidipin} & 1-2 & 12-12 \\
\text{lacidipin} & 1-2 & 12-12 \\
\text{isradipin SR} & 1-2 & 12-12 \\
\text{nitrendipin} & 1-2 & 12-12 \\
\text{nilvadipin} & 1-2 & 12-12 \\
\text{nicardipin} & 1-2 & 12-12 \\
\text{nisoldipin} & 1-2 & 12-12 \\
\text{nifedipin SR} & 0.2-0.6 & 12-12 \\
\text{verapamil SR} & 1-2 & 12-12 \\
\text{felodipin SR} & 2-4 & 12-12 \\
\text{diltiazem SR} & 1-2 & 12-12 \\
\end{array}
$
Slow onset mechanism for CCB III generation

- Lipophilic compound
- Terminal aminogroup
- Hydrophilic combination hydro- and lipophilic terminal allowed interaction with phospholipids layer of sarcolemma (binding to membranes)

amlodipin
Slow onset mechanism for CCB III generation

- slow and stable decrease of BP, no activation of contra-regulation

1) no limited antihypertensive effect
   (no vasoconstriction and fluid retention)
2) no proarythmogenic effect and tachycardia
3) no metabolic effect
Plasma halflife CCB

- **amlodipin**: 35-50 hours
- **lacidipin**: 1-4 hours, 15-20 hours
- **isradipin SR**: 9 hours
- **nitrendipin**: 8 hours
- **nilvadipin**: 15-20 hours
- **nicardipin**: 1-4 hours
- **nisoldipin**: 6-19 hours
- **nifedipin SR**: 3-6 hours
- **verapamil SR**: 5-12 hours
- **felodipin SR**: 20-25 hours
- **diltiazem SR**: 4-9 hours
ADVANTAGES OF AMLODIPINE
LONG HALFLIFE

• minimal plasma level fluctuations during day

• T/P index – ratio between minimal and maximal blood level
  - FDA requirements: effect "trough" 2/3 of "peak"
    - amlodipin T/P index 68%,
    - lacidipin, felodipin ER, verapamil SR and nifedipin GITS index 37-66%

safety limits for missing dose
FARMACODYNAMIC PROPERTIES OF CCB

- ANTIISCHEMIC EFFECT
  - direct vasodilatation
  - endothelial function improvement

• ANTIATHEROGENIC EFFECT
Prophylactic effect of CCB

1) Vessel wall relaxation at excentric stenosis
2) Block vasoconstriction induced by exercise
3) Coronary spasm block (variant AP)
4) Decreased heart rate
   - increased perfusion
   - decreased metabolic demand
   (non-dihydropyridines)
CAPE II - MONOTERAPY
Stress ECG – increase time to ischemia

![Bar chart showing the effect of amlodipin and diltiazem on time to ischemia in stress ECG, with a statistically significant result (P < 0.05).](image)
CAPE II: monoterapy x combination amlodipine + BB against diltiazem + nitrates stress ECG

amlopdipine + BB
diltiazem + ISMN
PREVENT: unstable AP and invasive interventions


[Graph showing cumulative event/procedure rate (%)]

Unstable AP/heart failure
- Placebo: 35%
P = .01
- Amlodipin: 30%

Revascularisation
- Placebo: 43%
P = .001
- Amlodipin: 30%
PREVENT: important CV events

Contraindications and AR

- **Non-dihydropyridine CCB**
  - AR – bradycardia, negative innotropic effect, hypotension, obstipation
- **CI** – srdeční selhání, převodní poruchy, hypotenze

- **Dihydropyridine CCB**
  - AR – frequent perimaleolar oedema, hypotension, reflex tachykardia
  - CI – only hypotension
ACE INHIBITORS
IHD ACE INHIBITORS

- Significant improvement of prognosis for secondary prevention - even for patients with normal LV function (study HOPE, EUROPA)

- Not clear - that improvement during secondary prevention is due to ACE inhibition or decreased BP only
Primary end point: CV-death + MI + stroke

P < 0.0003

STUDY EUROPA

Primary endpoint - mortality + MI + resuscit.

Placebo cases per year - 2.4 %

Remme P et al., NEJM 2003
POTASSIUM CHANNELS
ACTIVATORS
NICORANDIL

CLINICAL EFFECTS

• antiangina effectiveness comparable to BB, CCB and nitrates

• Alternative choice - BB a CCB when contraindicated or side effects

• Combination with BB possible

  additive effect for „preconditioning“
• 5126 patients with CHD and stable AP – optimal treatment

• follow up 1-3 y, ø 1,6 ± 0,5

• Randomization nicorandil 10 mg b.i.d. → 20mg b.i.d vs. placebo

• Primary end-point: CV mortality + nonfatal MI + hospitalization for angina attack

_Lancet 2002;359:1269-75_
BETA-BLOCKERS
BETA-BLOCKER
CLINICAL EFFECTS

- negative innotropic effect:
  - LV filling time – prolongation
  - coronary bed perfusion - improvement

- negative innotropic effect

- metabolic demand decreased

- BP decrease

- antiarrhythmic properties (increased fibrillation threshold)
BETA-BLOCKER
CLINICAL EFFECTS

• β blockade₁ juxtaglomerular receptor → renin production decreased

• Catecholamine release in CNS - decreased

• Antioxidand properties ??

• cytoprotektive efect – even at high catecholamine level

• Apoptoses inhibition
1) antiischemic effect (better myocardial perfusion, decreased metabolic demand)

2) antiarrhythmic effect

3) inhibition of hyperactive regulations:
   - catecholamine release
   - renin-angiotensin-aldosterone activation
   - apoptosis
ACUTE DEATH REDUCTION FOR MI BETA-BLOCKERS (meta-analysis)

Placebo (n = 2721)

Metoprolol (n = 2753)

Cumulative number of deaths

Follow-up (years)

P = 0.002

40%

FAVORITS

BETAXOLOL, BISOPROLOL

• high cardioselectivity without ISA, hydrophilic
- long halflife (15-20 hours)
- small biodegradation variability

METOPROLOL

• high cardioselectivity without ISA, lipophilic
- short and variable halflife
- excelent clinical trials – widely used BB
SINUSE NODE INHIBITORS
(BRADINES)

$I_f$ current inhibitors
(hyperpolarisation) bradycardia only
IVABRADIN

↓ heart rate
(min⁻¹)

↑ work-load tolerance
(s)

N = 360

Borer J.S. et al., Circulation 2003;107:817-23
## IVABRADIN vs ATENOLOL

**PRIMARY END-POINT – LOADING TIME**

<table>
<thead>
<tr>
<th>n</th>
<th>atenolol</th>
<th>ivabradine</th>
<th>$P$ for non inf.</th>
<th>better [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non inf.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iva 5 mg bid</td>
<td>595</td>
<td></td>
<td></td>
<td>6.7 [-7.4; 20.8]</td>
</tr>
<tr>
<td>vs ate 50 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td>$P &lt;0.0001$</td>
</tr>
<tr>
<td>at M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iva 7.5 mg bid</td>
<td>300</td>
<td></td>
<td></td>
<td>10.3 [-8.3; 28.8]</td>
</tr>
<tr>
<td>vs ate 100 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td>$P &lt;0.0001$</td>
</tr>
<tr>
<td>at M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iva 10 mg bid</td>
<td>298</td>
<td></td>
<td></td>
<td>15.7 [-2.9; 34.3]</td>
</tr>
<tr>
<td>vs ate 100 mg od</td>
<td>286</td>
<td></td>
<td></td>
<td>$P &lt;0.0001$</td>
</tr>
<tr>
<td>at M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Diagram:
- For Iva 5 mg bid vs ate 50 mg od at M1:
  - IVABRADIN (Iva) at 5 mg twice daily:
    - 595 patients
  - ATENOLOL (Ate) at 50 mg once daily:
    - 286 patients
  - Difference in loading time:
    - Mean difference: 6.7 seconds
    - 95% CI: [-7.4; 20.8]
    - $P <0.0001$

- For Iva 7.5 mg bid vs ate 100 mg od at M4:
  - IVABRADIN (Iva) at 7.5 mg twice daily:
    - 300 patients
  - ATENOLOL (Ate) at 100 mg once daily:
    - 286 patients
  - Difference in loading time:
    - Mean difference: 10.3 seconds
    - 95% CI: [-8.3; 28.8]
    - $P <0.0001$

- For Iva 10 mg bid vs ate 100 mg od at M4:
  - IVABRADIN (Iva) at 10 mg twice daily:
    - 298 patients
  - ATENOLOL (Ate) at 100 mg once daily:
    - 286 patients
  - Difference in loading time:
    - Mean difference: 15.7 seconds
    - 95% CI: [-2.9; 34.3]
    - $P <0.0001$
METABOLIC MODULATORS
ENERGY OUTCOMES OPTIMALIZATION

- During ischemia – (pH decrease) inhibition of glycolysis
- FA β-oxidation main source of energy
- switch from FA β-oxidation to glycolysis by trimetazidine or ranolazine
- 15% increase macroergic phosphates
- membrane stabilization
TRIMETAZIDINE

- Modulation (inhibition 3-KAT) during ischemic shift to glycolysis
- Optimization of energetic metabolism of kardiomyocytes
- No change in hemodynamic
- Well tolerated

3-KAT = 3-ketoacyl-CoA thioláza
Fatty acids

pyruvate dehydrogenase

glucose

Anaerobic glycolysis

Lactic acid

CO₂

pyruvate

acetyl CoA

Krebs cycle

fosforylation

TRIMETAZIDIN

ATP

mechanism of action

METABOLIC MODULATORS
TRIMETAZIDINE
clinical effectiveness

- Combination with BB, CCB, nitrates
- Second choice therapy when BB or CCB contraindicated
- Additional therapy for all patients with non compensated stable AP
RECOMMENDED COMBINATIONS

• beta-blockers + dihydropyridine CCB
• beta-blockers + ISMN
• beta-blockers + trimetazidine
• CCB + trimetazidine
• Triple-combination: BB + CCB (DHP) + trimetazidine

• Acute attack: CCB + nitrates
COMPLEX TREATMENT IHD:

- a) stop atherogenic progression – plaque stabilization – elimination of endothelial dysfunction
- b) avoid arterial thrombotic occlusion (ev. rapid restoration of perfusion)
- c) decrease of myocardial ischemia
  - improvement of flow through ischemic myocard
  - decrease myocardial metabolic requirements
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