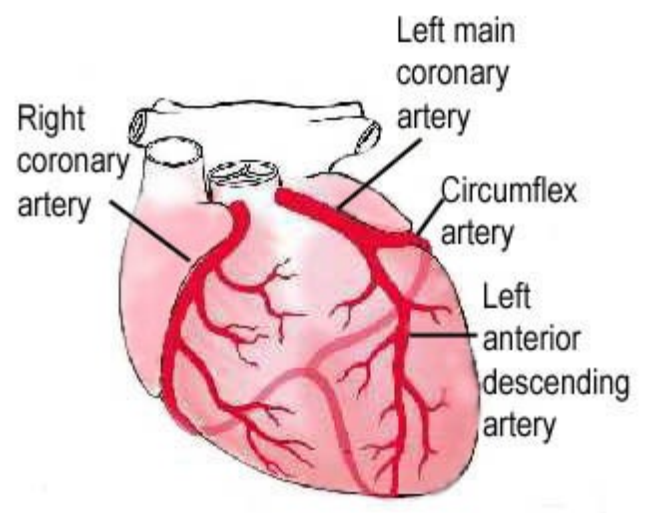
Treatment of Ischaemic Heart Disease /Coronary Artery Disease/

ISCHAEMIC HEART DISEASE

Group of diseases with the presence of myocardial ischemia, which occurs on the basis of the pathological process in the coronary vessels.

- Organic - atherosclerosis (95%), thrombus, arteritis..
- Functional - coronary spasm or combined

Reducing the flow in coronary arteries>>> ischemia



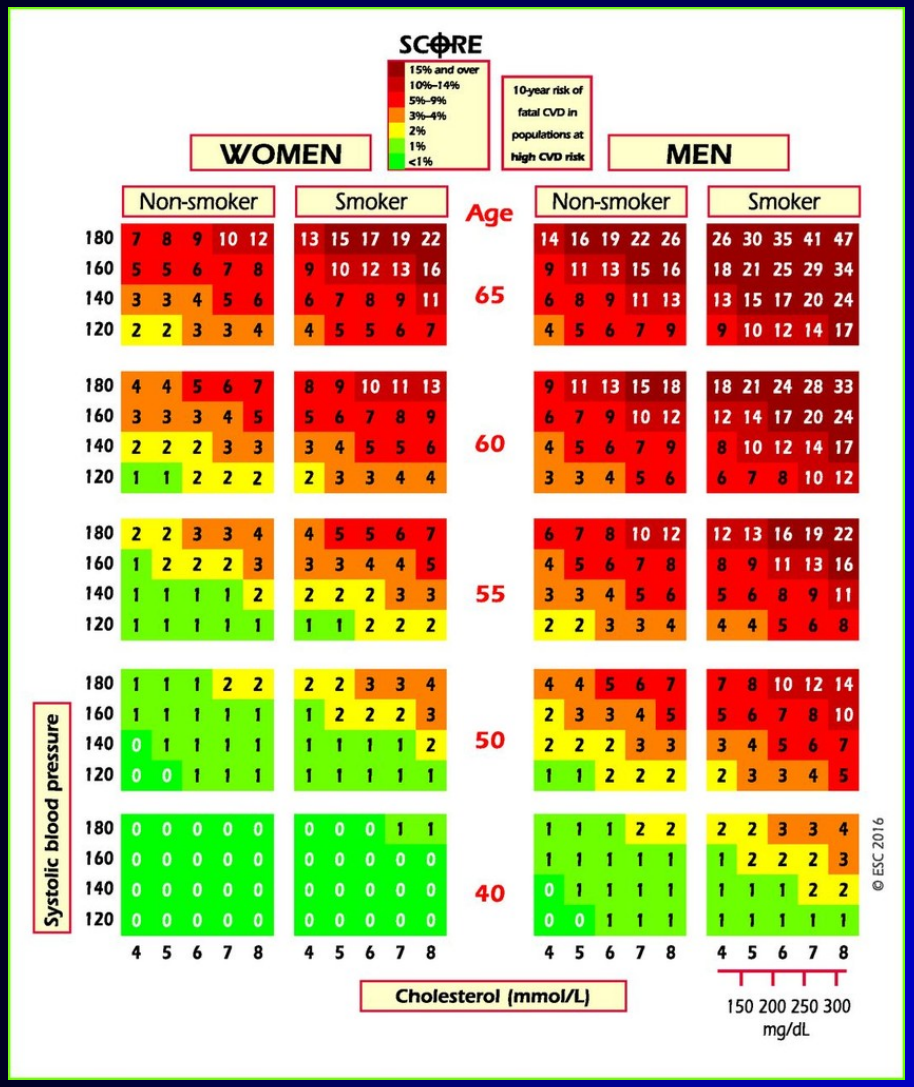
Ischaemic Heart Disese is part of

CARDIOVASCULAR DISEASES

Together with…

- Hypertenzion
- Chronic Hearth Failure
- Dysrhytmia

Risk factors and stratification



Risk factors

- gender
- Smoking status
- Cholesterol level
- Systolic blood pressure

RISK STRATIFICATION of CARCIOVASCULARS DISEASE

Strategy and type of pharmacotherapy

CARDIOVASCULAR DISEASES

Inhibition of RAAS

ACE inhibitors (ACEi)
AT_1 receptor antagonists (sartans)
Renin inhibitors
Natriuretic peptides

Inhibiton of sympathetic system*

Antagonization of β +/- α receptors

Increase of diuresis/natriuresis

Diuretics

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*Activation durig acute phase (NA, dobutamin)

Vasodilatation

Ca-channel blockers (CCB)
Activation of pottasium-channel (A-K_{ATP})
Nitrates and NO donors
Periferal vasoprotective drugs
Inhibitors of phosphodiesterase-5 (PDE-5)

↑myocardial contraction

Ca senzitizers
Inhibitors of phosphodiesterasis-3 (PDE-3)
Cardiac glycosides

Coordination of cardiac rhytm

Antidysrhytmics

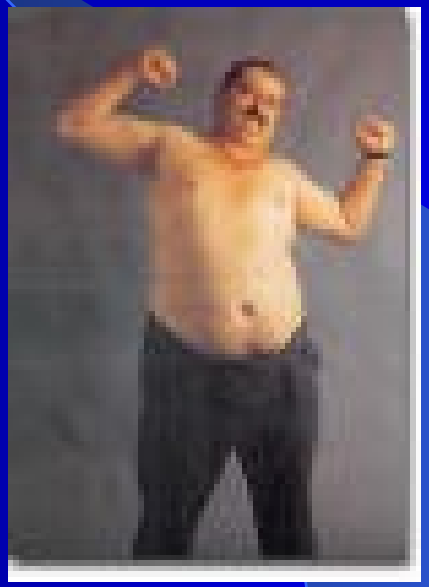
Drugs with positive effect on vascular endothelium

Vazoprotectives

ISCHAEMIC HEART DISEASE

Risk factors:

- Should not be influenced - age, gender, family history
- Should be influenced - hypertension, hyperlipoproteinaemia, smoking, stress, obesity, physical inactivity, dietary habits



ISCHAEMIC HEART DISEASE

CLASSIFICATION

- ✓ Acute (unstable) CAD

Unstable angina

Acute myocardial infarction

Sudden death

- ✓ Chronic (stable) CAD

Silent ischaemia

Angina pectoris

Syndrom X

Dysrhytmias

Mixed AP

Exertional AP

Variant AP

ANGINA PECTORIS

- Most frequent clinical manifestations of IHD caused by the myocardial ischemia, in which the patient has chest pain (stenocardia).
- Imbalance between myocardial oxygen supply and demand
- Anti-anginal drugs act indirectly by smooth muscle relaxation of coronary artery and reducing cardiac work

ANGINA PECTORIS

Classification of severity:

I. stenocardia provoked by extraordinary exertion
II. stenocardia provoked more than usual exertion
III. stenocardia provoked by regular exertion stenocardia
IV. stenocardia provoked by minimal exertion or at rest

Therapy of Ischaemic Heart Disese:

- **Non-pharmacological**

  life-style, smoking, diet…

- **Pharmacological**

- **Acute Intervention**

  PTCA /PCI

DRUG ELUTING STENTS

cytostatics (tacrolimus, sirolimus, paclitaxel…) slowly releases a drug to block cell proliferation

PTCA = Percutaneous transluminal coronary angioplasty

PCI = Percutaneous coronary intervention (angioplasty with stent)

Therapy

1. Stopping or slowing progress of atherogenesis

   ⇨ **LIPID-LOWERING DRUGS**

   Compenzation of DM ⇨ **ANTIDIABETICS**

2. Provention of vascular thrombus occlusion

   ⇨ **ANTIPLATELET DRUGS**

Obesity as disease ⇨ ANTI-OBESITY DRUGS

3. Improvement of coronary blood flow

Drugs that improve improve perfusion of the myocardium

⇨ **1. NITRATES and NO donors**
2. CALCIUM CHANNEL BLOCKERS - dihydropyridines
Pottasium-channel activation

4. Reducing the metabolic demand

(slow the heart)

⇨ **3. BETA-BLOCKERS**
2. CCB -non-dihydropyridines
4. IVABRADIN (I_f)

VASODILATOR DRUGS

Play a major role in the treatment of cardiovascular diseases (able to relax vascular smooth muscle)

VASODILATION should be achieved by:

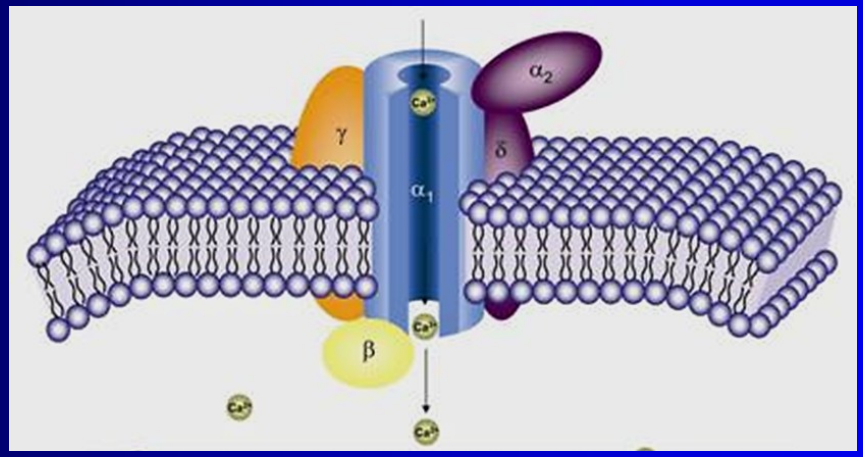
A. **Plasma membrane voltage-dependent calcium channel**
   - Calcium antagonists ⇨ **CCB**
   - Activation of ATP-sensitive pottasium channel ⇨ **A-K_{ATP}**

B. **Increasing cellular concentration of cAMP/cGMP**
   - Nitric oxide increase ⇨ **nitrates and NO donors**
   - Inhibition of phosphodiesterase-5 ⇨ **PDE-5 inhibitors**

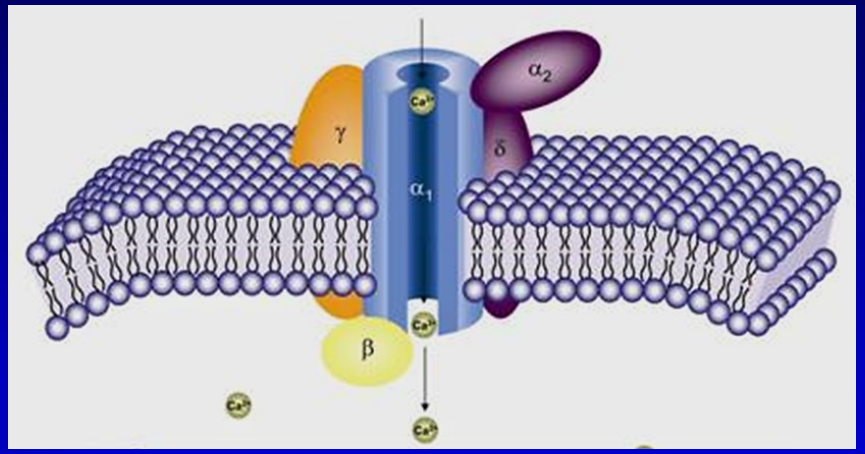
C. **Increase cytoplasmic cyclic nucleotides** ⇨ **prostacyclines**

D. **Blocade of endothelin system**
   - inhibition of endothelin rcp. ET_A a ET_B ⇨ **antagonists of endothelin rcp.**

- **CALCIUM Channel Blockers (CCB)/ CALCIUM Antagonists / CALCIUM Entry Blockers**



- Ca^{2+} channel blockers/ Ca^{2+} antagonists/ Ca^{2+} entry blockers/ works by blocking voltage-gated calcium channels type L in cardiac muscle and blood vessels.



sinoatrial node (SA) and atriventricular node (AV) – Ca^{2+} initiates action potentials ⇨ controlling cardiac rate and rhythm

↓ intracellular calcium leading to ↓ cardiac contractility

In blood vessels ↓ vascular smooth muscle and therefore ↑ vasodilation. Vasodilation decreases total peripheral resistance

Mechanism of Action

- block cellular entry of Ca^{2+} through **voltage-gated L-type channels**

Cardiac action
(SA, AV nodes)

negative inotropic, chronotropic and dromotropic effects

Vascular Smooth Muscle
(generalised arterial/arteriolar dilatation, coronary vasodilatation)
(biliary, urinary tract, uterus – less important therapeutically)

Vazodilatation
⇨ **periferal resistence decreased**

„selectivity“ of CCB

Classification

DIHYDROPYRIDINES

accoring to half life…

- Greater effect on vascular smooth muscle and coronary vessels than on the hearth

= relatively smooth muscle selective

NON-DIHYDROPYRIDINES

- Preferentially effects the heart **(AV block and cardiac slowing by their actions on conducting tissue, but causes reflex tachycardia)**

= relatively cardioselective

DIHYDROPYRIDINES

CCB

- **Short half-life**

  NIFEDIPIN

  immediatelly causes vazodilatation ⇨ **reflex tachycardia**

  SR drug form

- **Intermediatte half-life**

  FELODIPIN

  SR drug form

  NITRENDIPIN, LERKANIDIPIN

- **Long half-life**

  AMLODIPIN, LACIDIPIN

  Highly vasoselective

CCB

DIHYDROPYRIDINES

INDICATION

- Hypertenzion (monotherapy or combination)

CONTRAINDICATION

- Cardiogenic shock, acute hearth failure

ADVERSE EFFECTS

- Dose-dependent perimaleolar oedema flushes, gingival hyperplasia (dose-dependent).

Conventional drug forms

Headache, flushes, palpitation, hyponsension, rexlef tachycardia

CCB

NON-DIHYDROPYRIDINES

DILTIAZEM, VERAPAMIL

SA a AV nodes:

- negative chronotropic ⇩ action potential in SA node
- negative dromotropic effect ⇩ rate of conduction
- negative batmotropic effect ⇩ irritability
- negative inotropic effect ⇩ force of contraction

ANTIDYSRHYTMICS IV. class (Vaughan/Williams)

(SR – slow release forms)

CCB

NON-DIHYDROPYRIDINES

INDICATION

- Treatment and prophylaxy of supraventricular tachyarhytmias
- Treatment of preeclampsia (verapamil)

CONTRAINDICATION

- SA blocade, AV-blocade type 2.a 3.
- bradycardia (↓ 50 beats/min)
- Non-compensated heart failure with ↓ systolic function
- Gravidity (exemption for life-threatening condition – eclampsia)

NON-DIHYDROPYRIDINES

ADVERSE EFFECTS

- Negative inotropia - bradykardia
- obstipation (smooth muscle GI) (VERAPAMIL)

CCB

PHARMACOKINETICS

- High protein binding
- Variable bioavailability (0-30%)
- Variabile half-life
- cytochrom P450 involved - inhibitors CYP3A4 and substrate of P-gp

– **VERAPAMIL, DILTIAZEM**

DILTIAZEM, VERAPAMIL

⇨ ↑plazmatic concentration of statins

VERAPAMIL + digoxin

⇨ renal excretion decreased

Phenobarbital, fenytoin, karbamazepin ⇨ decrese plasmatic level of verapamil and diltiazem

❖ POTTASIUM-CHANNEL ACTIVATORS (A-K_{ATP})

Opening of K_{ATP} leads to ↑ sarcoplasmatic pottasium draslíku ⇨membrane hyperpolarisation ⇨ **ativation of Ca_L decreased**

I: patients who remain symptomatic despite optimal management

MINOXIDIL, NIKORANDIL **currently not available in CZ**

❖ Organic Nitrates

MECHANISM OF ACTION

Metabolised to nitric oxide – stimulation of guanylyl cyclase ⇨ incerasing formation of cGMP ⇨ ↓ intracellular calcium ⇨

Smooth muscle relaxation

Nitrates

Enzymatic step – reaction with tissue sulfhydryl (-SH) groups - S-nitrosothiol and **NO release**

Depletion of free SH-groups ⇨ **tolerance (with longer-acting drugs)**

NO donors

Should be administered with prolonged effect

Nitrates

Nitroglycerin was synthesized by the chemist Ascanio Sobrer in 1847

Nitroglycerin is converted to nitric oxide – NO - identical to the 'endothelium-derived relaxing factor' (EDRF)

- LOCAL: the direct effect on coronary artery tone - dilation of coronary arteries
- SYSTEMIC: venorelaxation – consequent reduction in central venous pressure – reduce preload
- Relaxation of larger muscular arteries – reduce afterload

Drugs Short-acting

- **GLYCERYL TRINITRATE**
  (Nitroglycerin®)
  $t_{1/2}$ 3 minutes
  risk of tachyfylaxis / repeated admin.
- **ISOSORBID DINITRATE** (ISDN)
  active metabolite ISMN with longer $t_{1/2}$

INDICATION

Treatment of stenokardias (sublingual)

Unstable angina i.v.

(i.v. infusion, higher doses lead to hypotension)
Acute heart failure, HT crisis, aortal aneurysm

ADMINISTRATION

SUBLINGUAL / i.v. / INHALATION

Short – acting (15-30 min)

DRUGS Long-acting

- **ISOSORBID 5-MONONITRÁT** (ISMN) ($t_{1/2}$ 5 hod.) metabolised more slowly
- Taken twice a day for prophylaxy – morning and lunch, nitrate-free period to avoid tolerance
- **MOLSIDOMIN**

INDICATION

Prophylaxy of Stable angina

ADMINISTRATION

Orally swallowed, SR formulation

ADVERSE EFFECTS

Usually well tolerated

- headache
- Ortostatic hypotension
- Tachycardia
- Flush
- Long-acting nitrates – tolerance, short-acting tachyphylaxis

CONTRAINDICATION

- Concomitant administration of PDE-V inhibitors (sildenafil,…)

VASODILATATORS…

- **Inhibitors of phosphodiesterase-5** (PDE-5-inhibitors)
- **Endothelin-1 receptor antagonists**
- **Syntetic analogs of prostacyclins**

❖ Inhibitors of phosphodiesterase-5 (PDE-5-inhibitors)

MECHANISM OF ACTION

Specifically inhibit isoform 5 of cGMP-dependent phosphodiesterase in in the corpus cavernosum ⇨ increased levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood

CONTRAINDICATION

- Arterial and orthostatic hypotension
- Aortal stenosis
- Hypertrofic cardiomyopathy
- Retinitis pigmentosa
- Retinopathy

DRUGS

INDICATION

Liší se rychlostí nástupu účinku a jeho délkou

Erectile dysfunction

Onset 1 hod; effect 4-6 hours

SILDENAFIL

VARDENAFIL

Pulmonary hypertension

Onset 2 hod; effect 24-48 hours

TADALAFIL

BHP

Pulmonary hypertension

Onset 30 min; effect 12-24 hours

AVANAFIL

ADVERSE EFFECTS

- headache, flush, dyspepsia, nasal congestion
- Mild or moderate transient difference in colour discrimination (blue/green)
- priapism

RARE: Vasodilatation and hypotension, dysrhytmia and heart failure

SILDENAFIL A VARDENAFIL inhibit partly also **PDE 6** involved in phototransduction cascade in retina

Drug interactions !

nitrates or another drugs ↑cGMP

❖ Endothelin-1 receptor antagonists

INDICATION Pulmonary hypertension

MECHANISM OF ACTION

Block binding of endothelin-1 to ET_A a ET_B – pulmonary arthery pressure decreased

DRUGS

BOSENTAN - *competitive non-selective antagonist of rcp* ET_A *i* ET_B

AMBRISENTAN *-selective antagonist of receptoru* ET_A

Teratogenic.

ADVERSE EFFECTS

Hepatotoxicity (FDA requires monthly monitoring of liver function tests), anaemia (hematocrit)

❖ Syntetic analogs of prostacyclins

INDICATION

Pulmonary hypertension

Prostacyclins = prostaglandines PGI_2

MECHANISM OF ACTION

Increase cyclic nucleotides by increasing adenylyl cyclase aktivity – directly acting vasodilatators

DRUGS

EPOPROSTENOL: only i.v. infusion, $t_{1/2}$ 3-5 min.

ILOPROST: $t_{1/2}$ 20-25 min.
i.v., peroral or inhalation

TREPROSTINIL: s.c. nebo i.v. infusion

3. Improvement of coronary blood flow

Drugs that improve improve perfusion of the myocardium

⇨ **NITRATES and NO donors**

CALCIUM CHANNEL BLOCKERS - dihydropyridines

Pottasium-channel activation

⇨ **BETABLOKÁTORY**

BKK-non-dihydropyridiny

BRADINY

4. Reducing the metabolic demand

(slow the heart)

B-adrenoceptor antagonists
(beta-blockers, β sympatolytics)

MECHANISM OF ACTION

Reverzible antagonization of adrenergic **β receptors**
(antagonists of endogenous katecholamins)

Competitive antagonists (intrinsic activity = 0) or

Partial agonists (ISA - intrinsic sympathomimetic activity)

Non- selective
cardioselective

Cardiovascular effects of BB

- **Antihypertensive action**

reducing sympathetic activity, decreased heart rate, reduction in cardiac output, reduction of renin release

- **Myocardial action**

negative chronotropic (HR), inotropic (contractility) dromotropic (vedení vzruchu) a bathmotropic (excitability)

- **Cardioprotective effects**

- **antiischaemic** (decreased heart rate, reduction in cardiac output ⇨ decreased **myocardial oxygen consumption**)

- **antidysrhythmic** (II. class) ⇨ better **coronary flow**

Antagonisation of endogenous katecholamins
(through β rcp.)

- bronchoconstriction
- reduction of renin release
- metabolic effects (↓glycogenolysis, lipolysis)
- Antiglaucomatic effect

Long term use of β blockers ⇨ hypersensitization , receptor up-regulation ⇨ **REBOUND FENOMEN**

CLASSIFICATION

- **lipophylic**
- **hydrophylic**

- **Selectivity** (non-selective x cardioselective)
- **Partial agonistic aytivity** (with ISA x withou ISA)
- **Combined effect** (antagonisation of α -receptor, direct vasodilatation)

ISA - β_1 rcp. ⇨ increase the heart rate at rest, but reduce during exercise

PHARMACOKINETIC

Depends on lipophylity/hydrophylity

Lipophylic

- High resorption from GI
- High first pass efect and protein-binding
- Longer $t_{1/2}$
- Central effects (cross HEB)
- **CYP2D6** metabolization

METOPROLOL
Preferably SR form

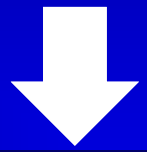
- ✓ Genetic polymorphism ⇨ **AUC difference 10-30x**
- ✓ Drug interaction with CYP2D6 inhibitors

PHARMACOKINETIC

Depends on lipophylity/hydrophylity

Hydrophylic

- Decreased resorption
- Don´t cross HEB
- ↓ $t_{1/2}$
- Renal excretion – **glomerulal filtration**



! Renal insuficiency

Variable half-life …2-10 min (esmolol - hydrophylic); 30-50 hod (nebivolol- lipophylic)

Drugs

1) „1. generation“

NON_SELECTIVE $\beta_1 + \beta_2$ receptors	
	sotalol hydrophilic **timolol** hydrophilic *Antiglaucomatic drug*
ISA +	**karteolol**

CARDIOSELEKTIVE β_1 selective	
	atenolol hydrophilic **betaxolol** hydrophilic (less) **bisoprolol** hydrophilic (less) **metoprolol** lipophylic **esmolol** hydrophilic **$t_{1/2}$ = 2-10 min**
ISA +	**acebutolol** hydrophilic **celiprolol** hydrophilic ISA na β_2-rp ⇨**VAZODILATATION**
Combined	**nebivolol** lipophylic **$t_{1/2}$= 30-50 hours**

Metabolised to an active metabolite that potentiates the L/NO pathway - **vasodilatation**

2) Betablockers with combined activity

(alpha and beta antagonists)

„2. generation“

CARVEDILOL - lipophylic

- Selective antagonist of **α_1-rp** ⇨ **vazodilatation**
- Non-selective antagonist of **β-receptors**
- Reduction of renin release - ↓ RAAS
- Antioxidative effect
- **INDICATION**: hypertension, chronic cardiac failure

LABETALOL - hydrophylic

- Selective antagonist of **α_1-rp** ⇨ **vazodilatation**
- Non-selective antagonist of **β-receptors**
- Partial agonist (ISA) of **β_2-rp**
- **INDICATION**: hypertension in pregnancy, *i.v. severe hypertension crisis*

MAIN INDICATION

1. **ANGINA PECTORIS**
   - Monotherapy or combination, not first
2. **MYOCARDIAL INFARCTION**
   - mainly negative chronotropic effect, antidysrhythmic effect
3. **Secondary prevention following myocardial infarction**
4. **HYPERTENSION**
   - Monotherapy or combination, not longer first choice

MAIN INDICATION

4. Hearth Failure

sympato-adrenergic hyperactivation decreased, antidysrhytmic effect

BISOPROLOL, METOPROLOL (SR), **KARVEDILOL, NEBIVOLOL**

only in well-compensated patients <u>because of negative inotropic effect !</u>

5. Therapy and prophylaxy of dysrhytmias (II. class)

supraventricular dysrhytmias, atrial fibrilation or flutter

OTHER USES:

- **Thyrotoxicosis**
- **Severe infantile haemangioma**
- **Benign essential tremor**
- **Anxiety to control symptoms**
  (palpitation, treamor…)
- **Glaucoma**
  e.g. Timolol eye drops

!! Up to 80 % eye drops should be absorbed - systemic effect - bradycardia and bronchospasm !

ADVERSE EFFECTS

Non-selective BB (through β_2-rcp).

- **BRONCONSTRICTION** ⇨ relative KI: pacients with AB/CHOPN (…cardioselective nebivolol)
- **COLD EXTREMITIES**
- **ERECTILE DYSFUNCTION**
- **HYPOGLYCAEMIA**
- **FATIGUE, INSOMNIA**
- **CARDIOVASCULAR**
  - ✓ hypotension
  - ✓ bradykardia
  - ✓ AV-blocades

CONTRAINDICATION

- **Hearth failure** (exception well-compenated HF, low doses)
- **SA a AV blocades** (II. and III. grades)
- **Hypotension**
- **Bradycardia** (<50 beats/min)

RELATIVE CONTRAINDICATION

- **Astma bronchiale**
- **COPD**
- **Diabetes mellitus**
- **Depression**
- **Erectile dysfunction**

❖ Bradines

MECHANISM OF ACTION

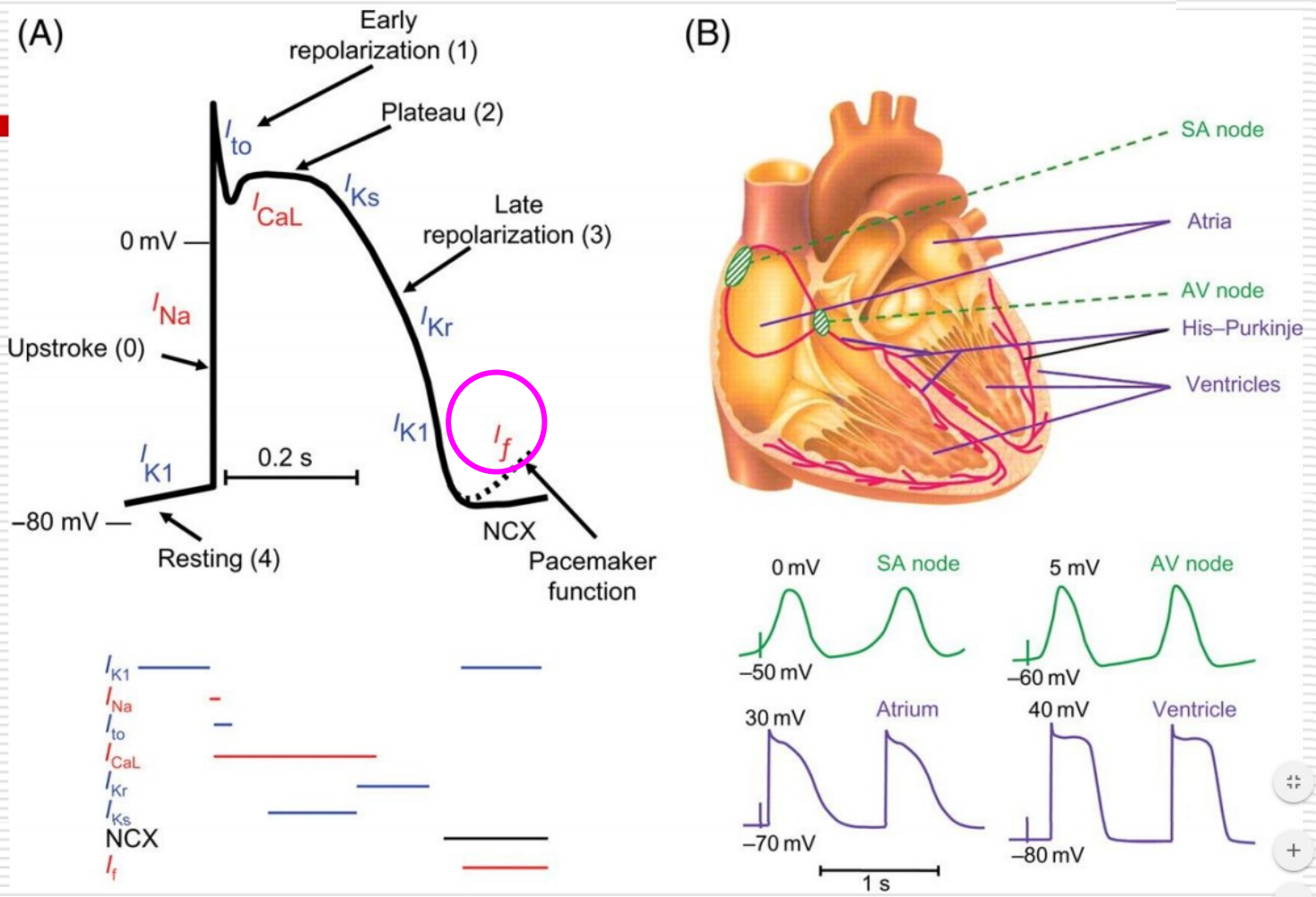
Selective inhibition the pacemaker **I_f in SA node** ⇨ slowing the heart rate ⇨ allowing more time for blood to flow to the myocardium (only negative chronotropic effect)

DRUG

IVABRADIN

INDICATION

- Symptomatic treatment of myocardial ischaemia in patients with AP / chronic heart failure NYHA II-IV
  - in adults unable to tolerate or with a contra-indication to the use of beta-blockers or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker



Michael G et al. Cardiovasc Res 2009;81:491-499