Antianginal agents & Ca^{2+} antagonists

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Myocardial ischemia

- imbalance: **supply < demand** (O_2)
  - tissue hypoxia → ↑ metabolites → **pain**
    - angina pectoris *(angere = to strangle, pectus = chest)*
    - but also: *"silent" ischemia*
- types of angina
  - effort (classic, exercise induced)
  - variant (vasospastic, Prinzmetal – localized vasospasm)
  - unstable (partially occlusive thrombus formation)

background: atherosclerosis / coronary artery disease

Myocardial ischemia

- possibilities for correction
  - **↓ demand**
    - ↓ cardiac work
    - change metabolism (less O_2 per ATP)
  - **↑ supply**
    - coronary dilation

Demand

(determinants of myocardial oxygen consumption)

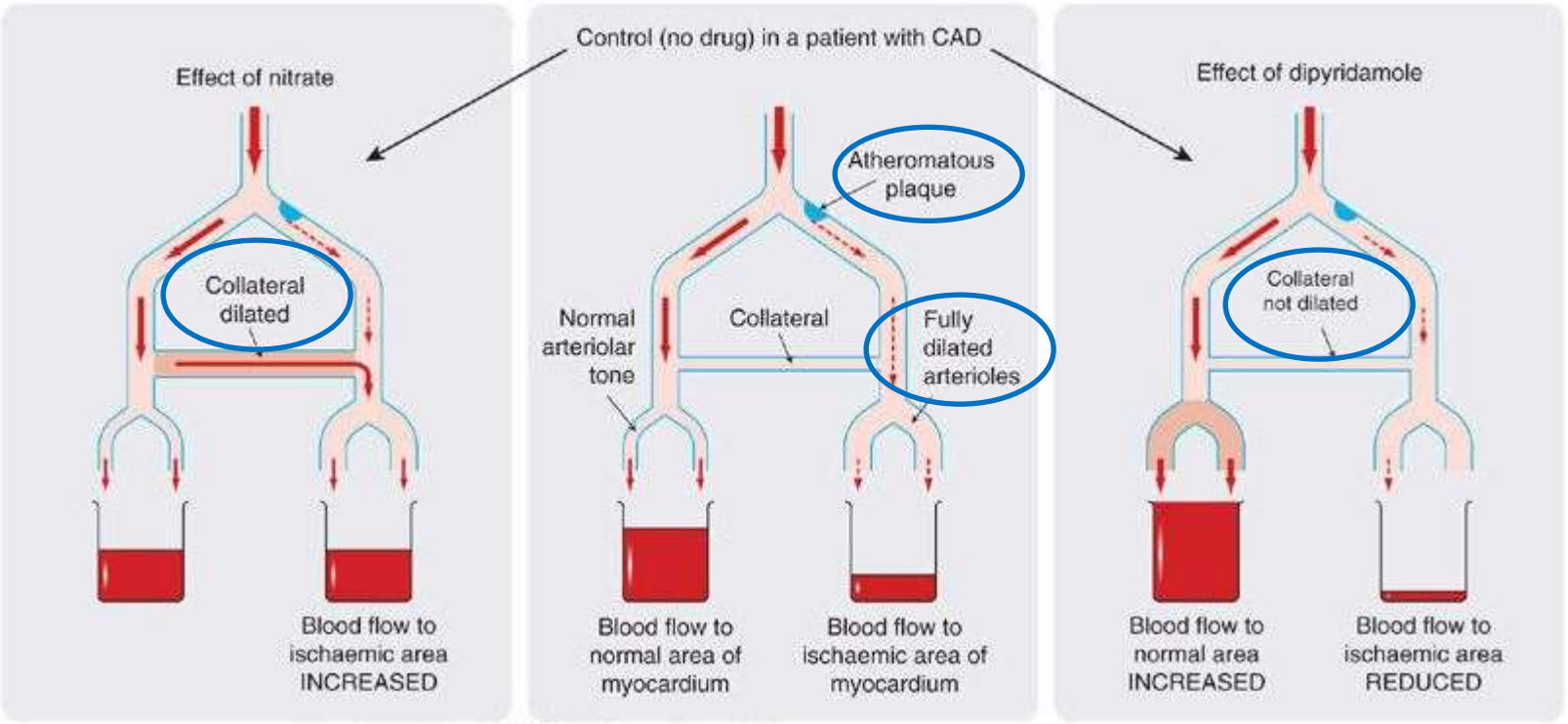
- heart rate
- contractility
- wall stress ← arterial pressure (systolic), peripheral venous tone (diastolic)
  - intraventricular pressure
  - ventricular radius (volume)
  - wall thickness

Supply

(determinants of coronary blood flow & myocardial oxygen supply)

- coronary vascular resistance (inverse correlation)
  - determinants of coronary resistance
    - metabolic products
    - autonomic activity
    - drugs
    - endothelial damage
      - damaged maybe cannot dilate (see also “coronary steal”)
- perfusion pressure (aortic diastolic pressure)
- duration of diastole

Coronary steal



no steal control steal

- nitrates are useful in angina
  - but they act not only on the coronaries
- dipyridamole is not useful in angina
  - maybe used as a diagnostic stress test

Role of drug therapy in angina

- many patients are **not** candidates for
  - revascularization by PCI (percutaneous coronary intervention)
  - coronary artery bypass graft surgery (CABG)
- substantial fraction do not achieve complete revascularization after PCI or CABG
- then: **drug therapy**
  - conventional antianginal drugs
  - newer antianginal drugs (mostly for refractory angina)

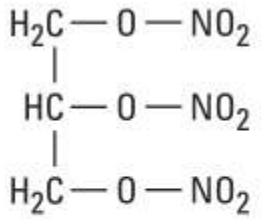
Antianginal drug groups

- organic **nitrates** (e.g. nitroglycerin)
  - primarily for acute treatment but also for prophylaxis
- **calcium channel blockers** (e.g. nifedipine)
  - for prophylaxis
  - dihydropyridines and non-dihydropyridines
- **β blockers**
  - for prophylaxis
- newer drugs
  - *ranolazine* – ic. Ca ↓ → ↓ contractility
  - *trimetazidine* – more effective use of O_2
  - *ivabradine* – ↓ heart rate

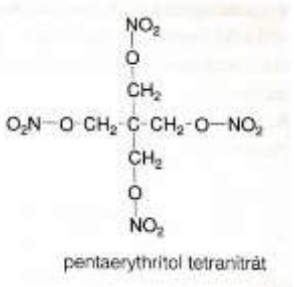
primarily: ↓ O_2 demand: ↓ heart rate / myocardial contractility / ventricular wall stress
additionally: ↑ O_2 supply: coronary dilation (major in variant angina)

Organic nitrates

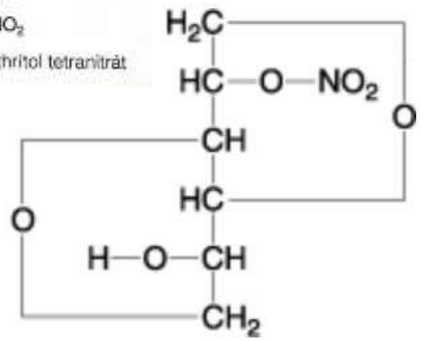
- **nitroglycerin** = glyceryl trinitrate (GTN)
  - prototype
  - volatile, adsorption to plastic - spray
- amyl nitrite
  - volatile, inhaled, obsolete
- isosorbide dinitrate (ISDN)
  - slower absorption than nitroglycerin, similar metabolism
- isosorbide-5-mononitrate (ISMN)
  - good oral bioavailability, slow onset, no acute use
- pentaerythritol tetranitrate
  - long duration of action
- nicorandil
  - combined: NO release and K^+ channel opening
- molsidomine
  - prodrug, not for acute therapy
  - spontaneous NO release / less tolerance ?
- nitroprusside
  - parenteral, hypertensive crisis (not angina), spontaneous NO release
  - venous AND arteriolar dilator, light sensitive, cianide poisoning, short duration



Nitroglycerin
(glyceryl trinitrate)



pentaerythritol tetranitrát



isosorbide mononitrate

Mechanism of action of nitrates

- **NO release** → guanylyl cyclase ↑ → cGMP ↑ → PKG ↑ → ↓ MLC phosphorylation → **smooth muscle relaxation**
  - enzymatic
    - GTN: mitochondrial aldehyde dehydrogenase (ALDH2) + others?
  - "direct" (non-enzymatic)
    - e.g. molsidomine
- preferentially **venodilation** (overdosing dangerous)
  - + epicardial coronaries + atherosclerotic stenosis + collateral vessels (*no "coronary steal"*)
- other smooth muscles
  - bronchi, GI, genitourinary – clinical value ?
- inhibition of *thrombocyte aggregation* (modest)

Pharmacokinetics of nitrates

- nitroglycerine (GTN)
  - for acute use:
    - **sublingual** tablet, **spray**
    - avoids first pass effect
    - quick onset (peak ~ 4 perc)
    - short duration ($t_{1/2}$ ~ 1-3 min)
      - high dose is not possible
  - for chronic use (longer duration)
    - larger oral doses
    - transdermal patches
    - buccal slow release
- isosorbide mononitrate
  - oral F=100%
  - slow onset → no acute use

Therapeutic indications of nitrates

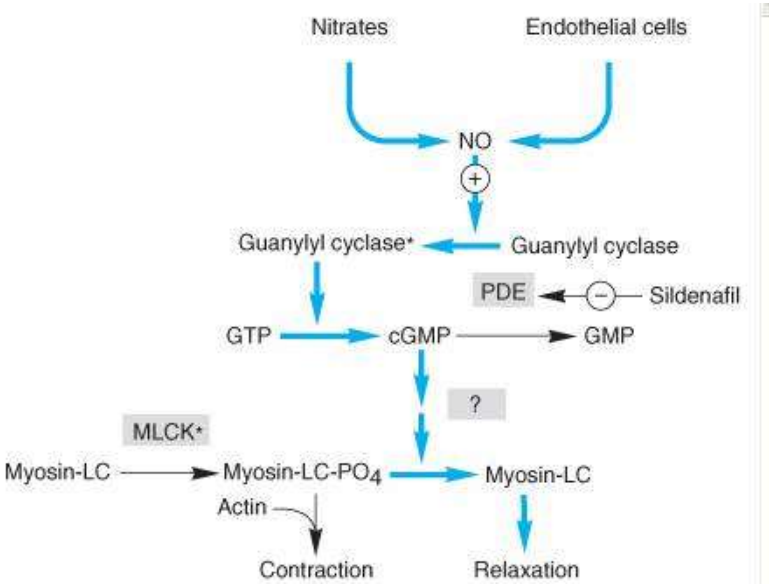
- any type of angina
  - effort – main: ↓venous return → ↓intracardial vol. / ↓end-diastolic pressure → ↓ wall stress → ↓O_2 demand
  - unstable - ? – coronary dil / ↓ O_2 demand / ↓ platelet aggregation
  - Prinzmetal's variant – coronary relaxation
- in combination
  - β-blockers or Ca channel blockers
- for acute treatment and also for prophylaxis
- prolonged administration ?
  - tolerance ? / mortality ?

Nitrate tolerance, adverse effects, interactions

- **tolerance**
  - mechanism ?
    - neurohumoral activation, SH depletion, free radicals, inactivation of mitochondrial aldehyde reductase / guanylyl cyclase ...
  - to avoid/decrease: **intermittent dosing**
- adverse effects – dose dependent!
  - throbbing headache / flushing of face
  - orthostatic hypotension
  - reflex tachycardia
  - methemoglobinemia
    - see nitrate → nitrite – in nursing newborns
    - were used in cyanide poisoning
  - ↑ intracranial pressure (in case of overdose) – contraindication
- interactions
  - sildenafil (Viagra®)
  - antihypertensive drugs

Interaction of nitrates with PDE5 inhibitors

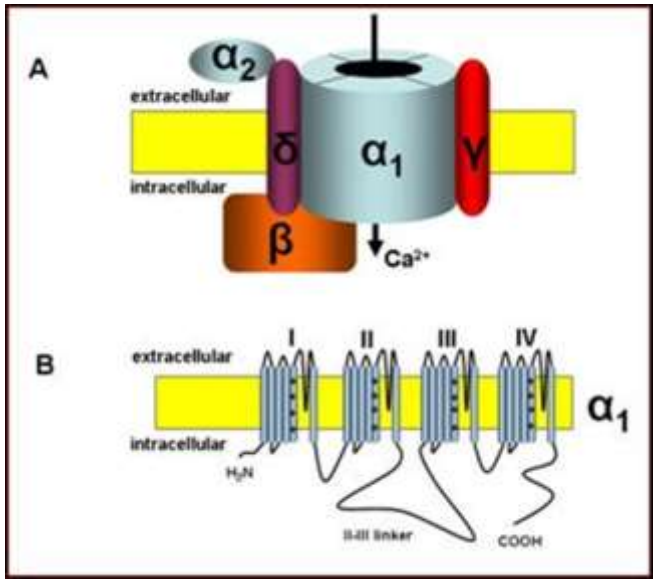
- risk factors for erectile dysfunction ≈ coronary artery disease
- PDE5 inhibitors: sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra)
- profound cGMP ↑ → severely reduced BP



indications of PDE5 inhibitors: **erectile dysfunction, pulmonary hypertension**

Ca^{2+} channel blockers

- **voltage activated** Ca^{2+} channels
  - several types: **L,** *T*, N, P/Q, R
    - **currently** used drugs are **L-type** Ca^{2+} channel blockers (mostly)
  - **depolarization** → opening → EC Ca^{2+} entry → contraction
    - although different in smooth muscle and heart



Ca^{2+} channel blockers

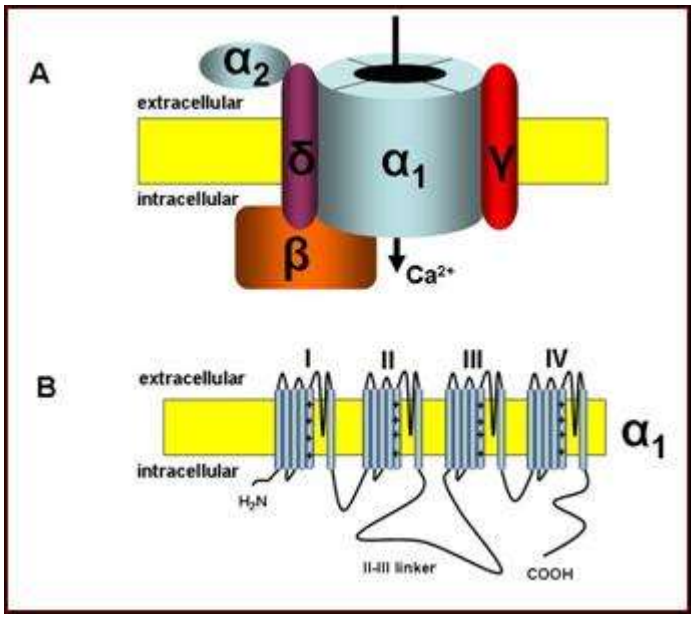
tissue selectivity

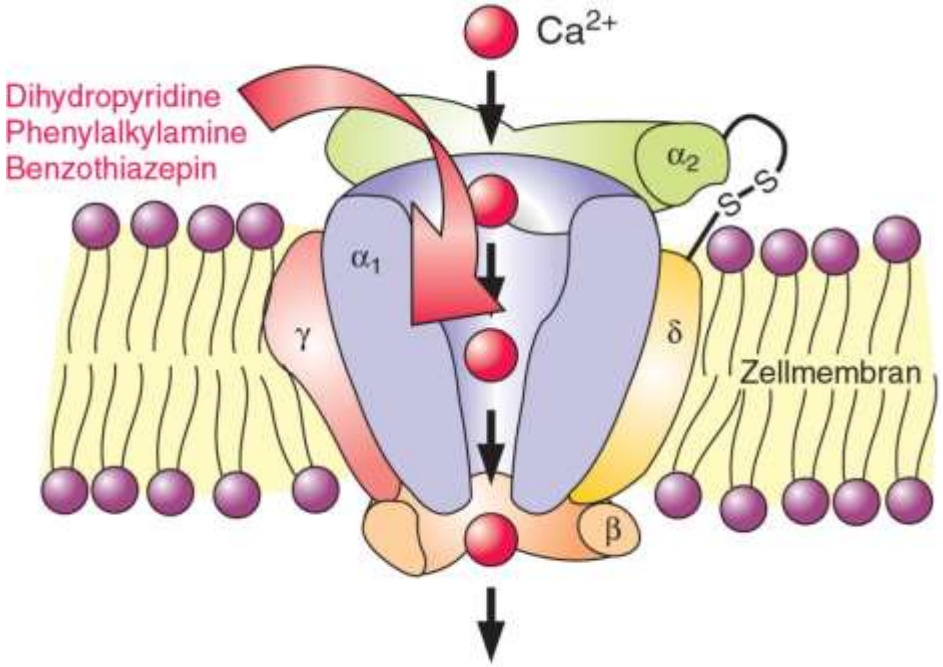
- **vascular smooth muscle relaxation**
  - primarily dihydropyridines: **nifedipine, amlodipine ...**
  - **predominantly arterial → blood pressure and TPR ↓**
  - coronaries → variant angina
  - vascular bed selectivity: e.g. nimodipine – cerebral arteries (evidence?)
- **heart: negative inotrop**, chronotrop, dromotrop
  - cardiac myocytes, SA, AV nodal cells
  - primarily: **verapamil** / **diltiazem**
- **other tissues**: no / less effect (relative)
  - skeletal muscle, bronchi, neural tissue / gastroint., genitourin.

drug	vasodilation	contractility ↓	automaticity ↓	conduction ↓
verapamil	4	4	5	5
diltiazem	3	2	5	4
nifedipine	5	1	1	0

relative effects: 0 = no effect, 5 = prominent effect

Mechanism of action / basis of selectivity





- all bind to α1 – but at **different sites**
- reduced Ca^{2+} influx → relax. / neg. inotropy / ↓ SA / ↓ AV
- verapamil – **use dependent** blockade / **↓ rate of recovery** of the slow Ca^{2+} channel in SA and AV nodes → cardiac eff.

Mechanism of action

- smooth muscle relaxation
  - **vascular**
    - **predominantly arterial → blood pressure and TPR ↓**
    - coronaries → variant angina
    - different vascular selectivity: verapamil ↔ nifedipine
    - vascular bed selectivity: e.g. nimodipine
  - bronchiolar, GI, uterine
- cardiac muscle contractility ↓
- SA node pacemaker rate ↓
- AV nodal conduction rate ↓

verapamil (diltiazem)

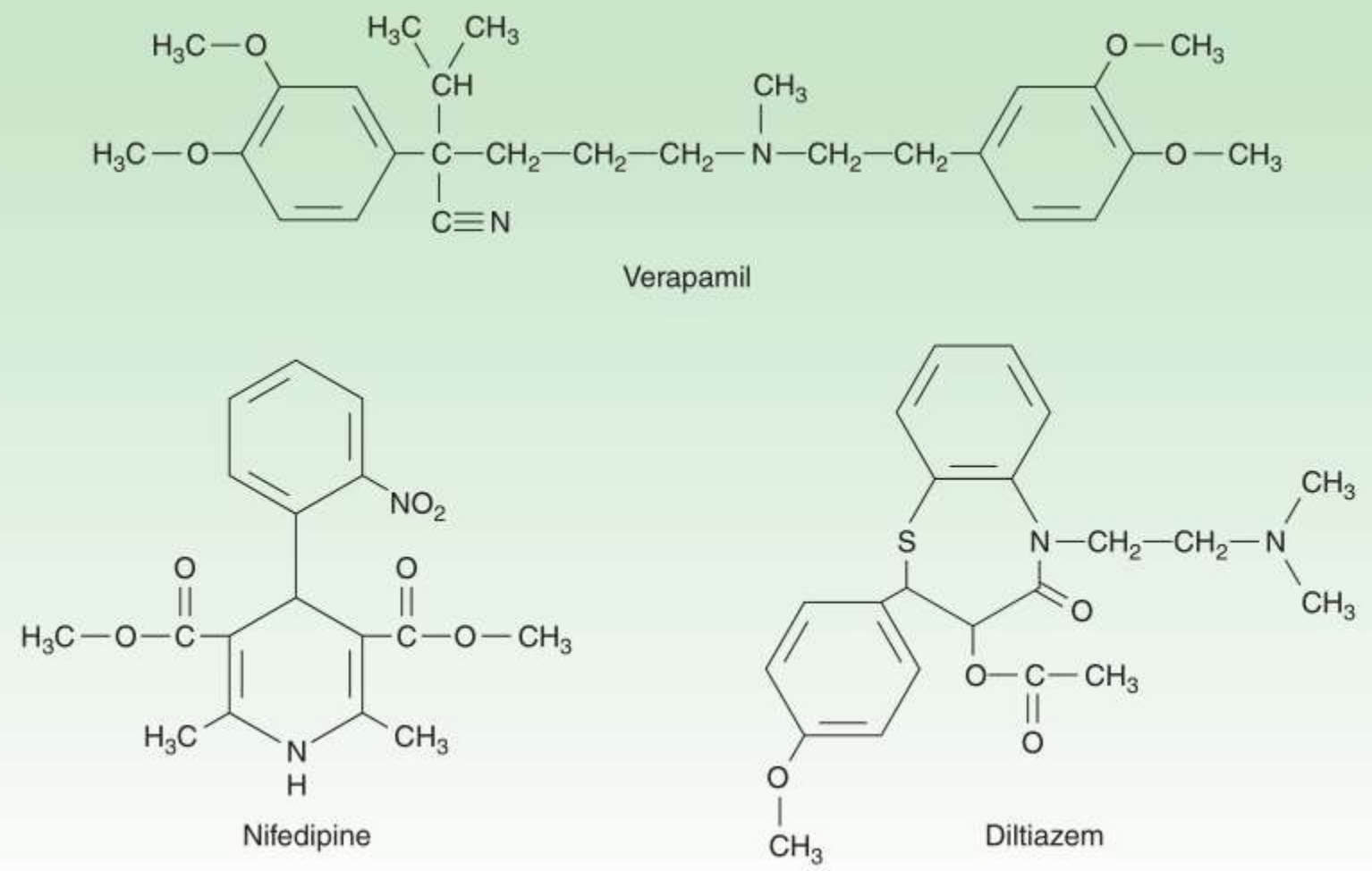
Classification

- chemical
  - phenylalkilamine: verapamil
  - benzothiazepine: diltiazem
  - dihydropyridines (DHP): nifedipine, amlodipine ...
- functional
  - heart active (verapamil / diltiazem) – **no tachycardia**
  - vessel active (DHP) – tachycardia (baroreflex)

drug	vasodilation	contractility ↓	automaticity ↓	conduction ↓
verapamil	4	4	5	5
diltiazem	3	2	5	4
nifedipine	5	1	1	0

relative effects: 0 = no effect, 5 = prominent effect

Chemical structures



Pharmacokinetics

- Absorption
  - good oral abs. + high first pass hepatic metabolism →↓ oral bioavail.
  - iv.: *verapamil, nifedipine, nimodipine*, nicardipine
  - bioavail.↑: grapefruit juice, cirrhosis, saturation of metabol.
  - fast absorption → quick onset → high C_{max}
    - deleterious: more pronounced baroreceptor reflex activation
    - except for e.g. amlodipine, lacidipine, sustained release nifedipine
- Distribution
  - high plasma protein binding
- Elimination
  - variable half-lives (1.3-64 h)
    - longer half life is more desirable
    - sustained-release forms (e.g. nifedipine)
  - extensive liver metabolism
    - inactive or weakly active metabolites
    - *verapamil, diltiazem*: CYP3A4 / P-gp blockade → drug interactions

Duration of action of DHPs

- short
  - *nifedipine**, *nimodipine*, nicardipine
- intermediate
  - *felodipine*, *nisoldipine*, nitrendipine, isradipine
- long
  - *amlodipine, lacidipine*

*but see sustained release formulations

Clinical use of Ca^{2+} channel blockers

- **antihypertensive**
- **antianginal**
- antiarrhythmic (*verapamil, diltiazem*)
- other
  - hypertrophic cardiomyopathy
  - migraine
  - Raynaud's phenomenon
  - preterm labor
  - post subarachnoid hemorrhage *(nimodipine)*

Ca^{2+} channel blockers in angina

- peripheral vasodilation
  - predominantly arterial
  - blood pressure and TPR ↓ → **↓ afterload** → ↓ wall stress (systolic) → **↓ O_2 demand**
- coronary dilation
  - important primarily in **variant angina**
  - most effective prophylaxis in variant angina
- other heart effects (non-dihydropyridines)
  - ↓ contractility / ↓ frequency

Other indications of Ca^{2+} channel blockers

- supraventricular tachyarrhythmias - verapamil
  - paroxysmal supraventricular tachycardia (PSVT)
  - atrial fibrillation / flutter (except +WPW)
- hypertension
  - chronic: no short acting oral dihydropyridines
  - acute: i.v. clevidipine, nicardipine, verapamil / oral nifedipine

Other indications of Ca^{2+} channel blockers

- hypertrophic cardiomyopathy
  - verapamil – improved LV outflow obstruction
- migraine
  - for prophylaxis only
- Raynaud's phenomenon
  - nifedipine, felodipine, diltiazem
- preterm labor
  - not primary
- post subarachnoid hemorrhage
  - nimodipine
  - prevent cerebral vasospasm

Adverse effects

- arteries
  - headache, flushing, dizziness
    - immediate release oral nifedipine
  - peripheral edema (ankle edema)
    - increased hydrostatic pressure
- other
  - gastroesophageal reflux
  - constipation – verapamil
- heart
  - worsening of ischemia / angina
    - excessive hypotension / “coronary steal” / ↑ O_2 demand
  - bradycardia, transient asystole, exacerbation of heart failure
    - iv. verapamil + SA / AV disease or β-blocker use

Specific dihydropyridines

- ***nifedipine***
  - prototype, short acting, acute use or sustained rel.
- *amlodipine*
  - delayed onset, long acting
- *felodipine*
  - intermediate duration, even greater vascular specificity
- *lacidipine*
  - lipophilic, slow onset, long duration, vascular selectivity, antioxidant activity
- *nimodipine*
  - cerebral vessel specific
- isradipine
  - typical peripheral vasodilation, negative chronotrop but little effect on AV conduction, no rise in heart rate
- clevidipine
  - newer, iv only, quick onset, short duration, artery specific
- nicardipine
  - oral and iv., coronary selective ?, good for cerebral vasospasms ?

β blockers in angina

- not vasodilators (with a few exceptions)
- useful effects in angina
  - ↓ *heart rate* / ↓ contractility / ↓ blood pressure
    - ↓ O_2 requirement
    - ↑ *diastolic perfusion time* → ↑ *coronary perfusion*
- clinical use
  - effort angina (silent!)
    - in stable angina clinical trials: β blockers > Ca blockers
  - after myocardial infarction
  - but **do not use in vasospastic angina**

β blockers

- undesirable effects in angina
  - ↑ end-diastolic volume / ↑ ejection time
    - might ↑ O_2 requirement
    - to prevent: combination with nitrates

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	*Reflex[1] increase*	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	*Increase*	None or decrease
Contractility	*Reflex[1] increase*	Decrease	None
Ejection time	Decrease[1]	*Increase*	None

[1]Baroreceptor reflex.

Note: Undesirable effects are shown in italics.

Adverse effects of β-receptor blockers

- bradycardia
- bronchoconstriction (in asthma)
- cardiac decompensation
  - see interaction with verapamil
- cold hands and feet
- sedation, vivid dreams, depression
- VLDL ↑, HDL/LDL ratio ↓
- hypoglycemia ? – IDDM
- worsening of peripheral vascular disease
- β-receptor up-regulation
  - gradual dose tapering

Ranolazine

- relatively **new** drug in angina (Ranexa®)
- reduces a late sodium current (I_{Na})
  - Na-Ca exchanger Na entry ↓ → ic. Ca ↓ → contractility → ↓ O_2 demand
- for chronic treatment in **stable angina**
  - primarily in those **who are unresponsive to other**
- antiarrhythmic properties
- potential PK drug interactions
  - liver metabolism (CYP3A4, CYP2D6) / P-gp
- may prolong QT interval

Trimetazidine

- a metabolic modulator
  - partially ↓ fatty acid oxidation pathway (pFOX inhibitor)
    - fatty acid oxidation requires more O_2 per ATP
    - inhibition seems to improve metabolic status
- approved in Europe (but not in US)
- no significant effects on heart rate
- Parkinson's disease risk ↑ (EMA, 2012)
  - second line

Ivabradine

- a bradycardic
  - relatively selectively blocks I_f Na channel (funny current)
  - ↓ heart rate
    - blocks hyperpolarization-activated Na ch in SA node
  - no other hemodynamic effects
- reduces the number of anginal attacks
  - not for acute treatment
- free of GI and bronchial effects

Drugs in unstable angina & acute coronary syndromes

- antiplatelet therapy
  - combination of aspirin and clopidogrel
- iv. heparin or sc. LMWH
- if PCI with stenting
  - glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide)
- nitroglycerin
- β-blockers
- lipid-lowering
- ACE-inhibitor