Pharmacology of ischemic heart diseases: angina and infarction

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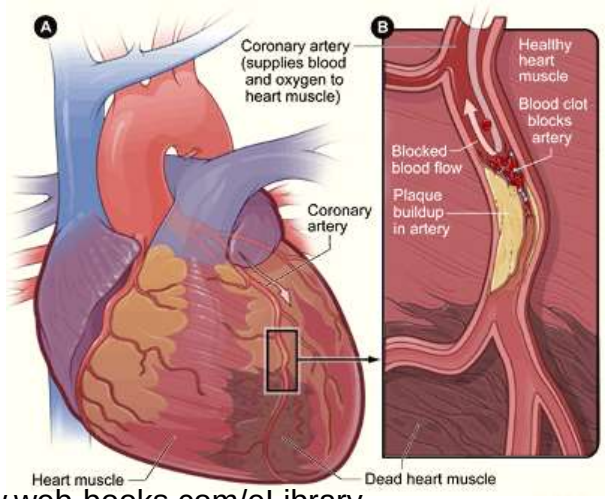
Ischemic area and infarction: importance of reperfusion



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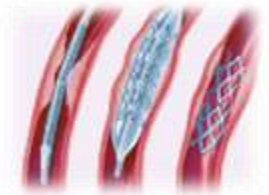
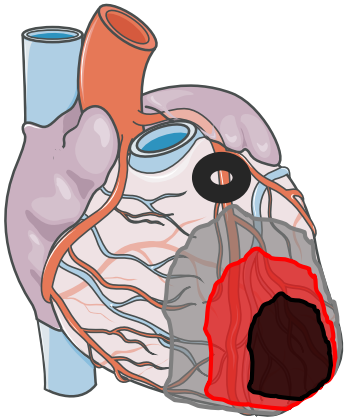
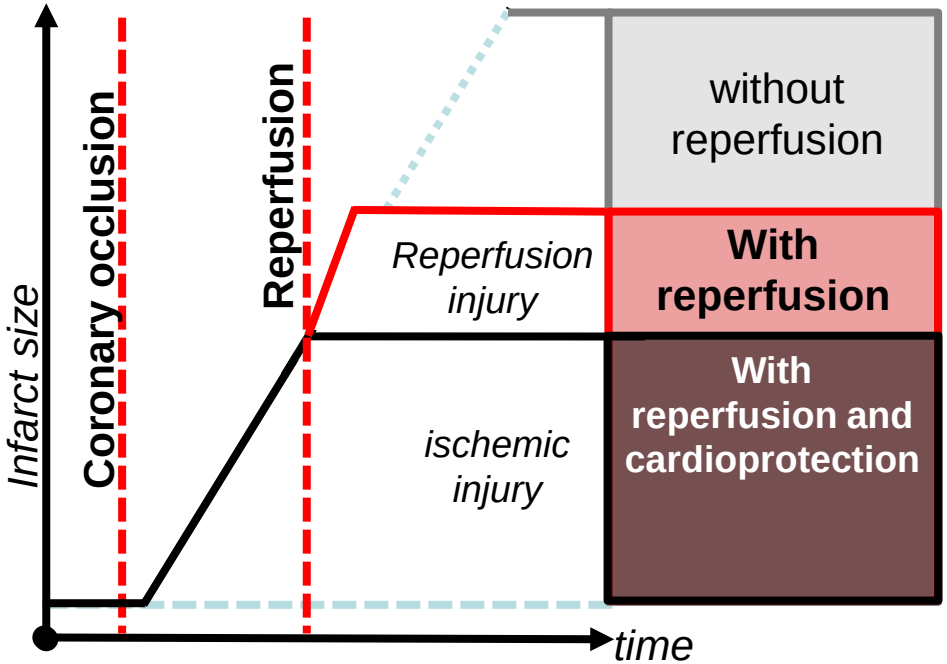


Reperfusion
(e.g., balloon angioplasty, szenting, and or fibrinolysis)





time = muscle,
muscle = life !

Guideline: European Heart Journal (2018)39, 119–177

Mortality after acute myocardial infarction is depending on the final infarct size

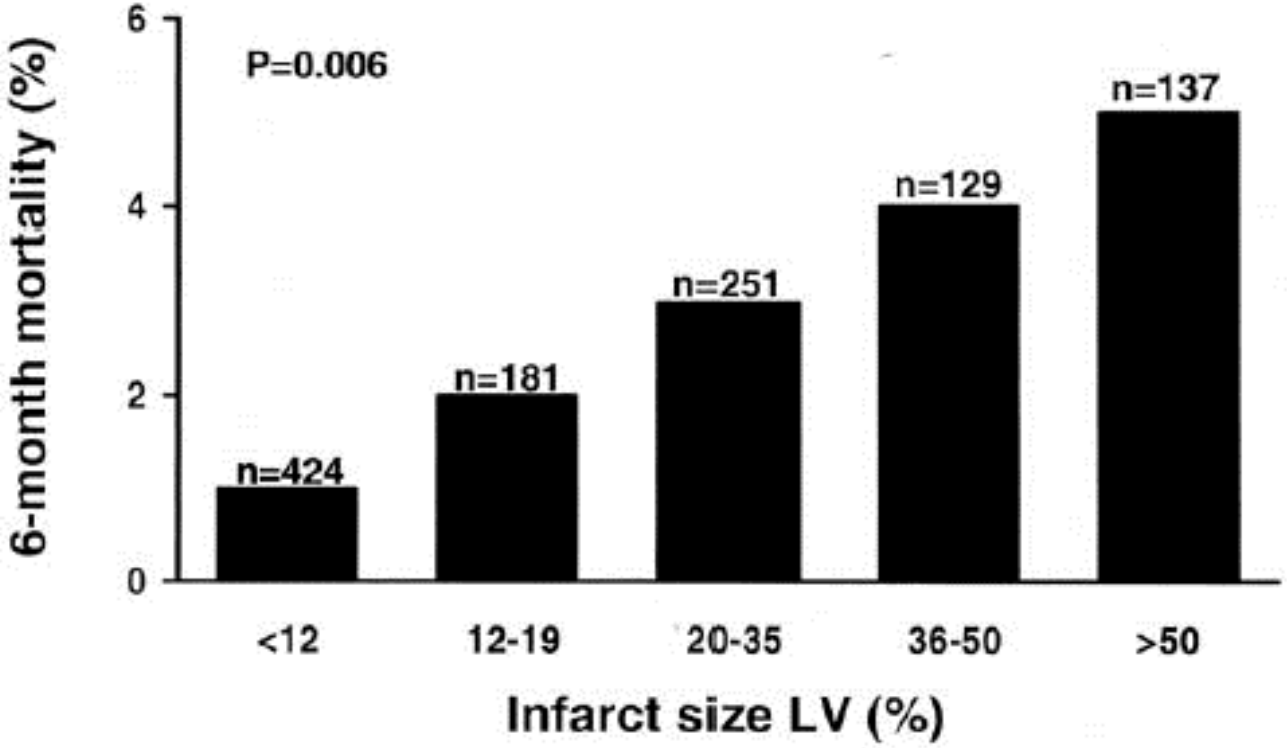
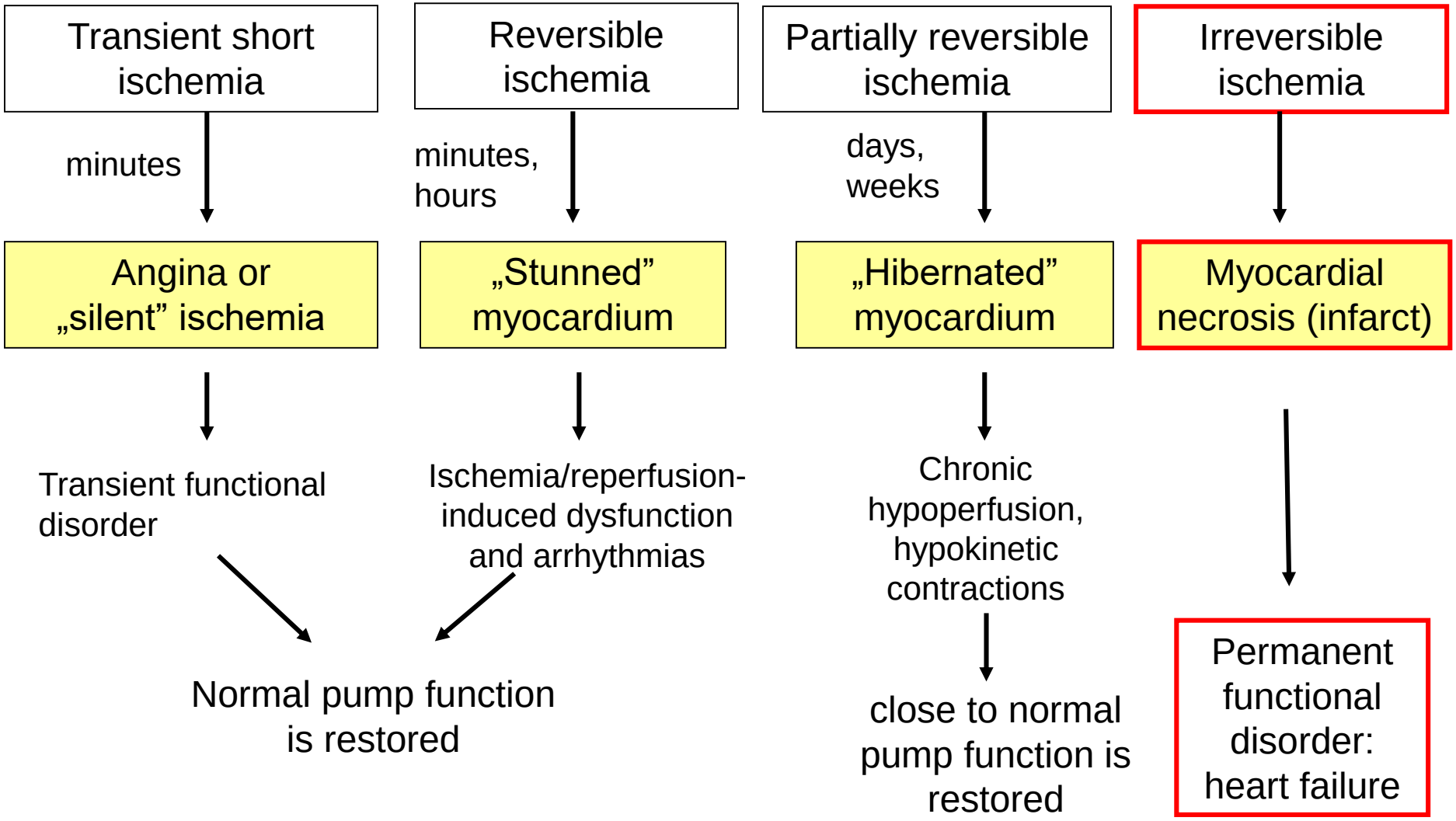
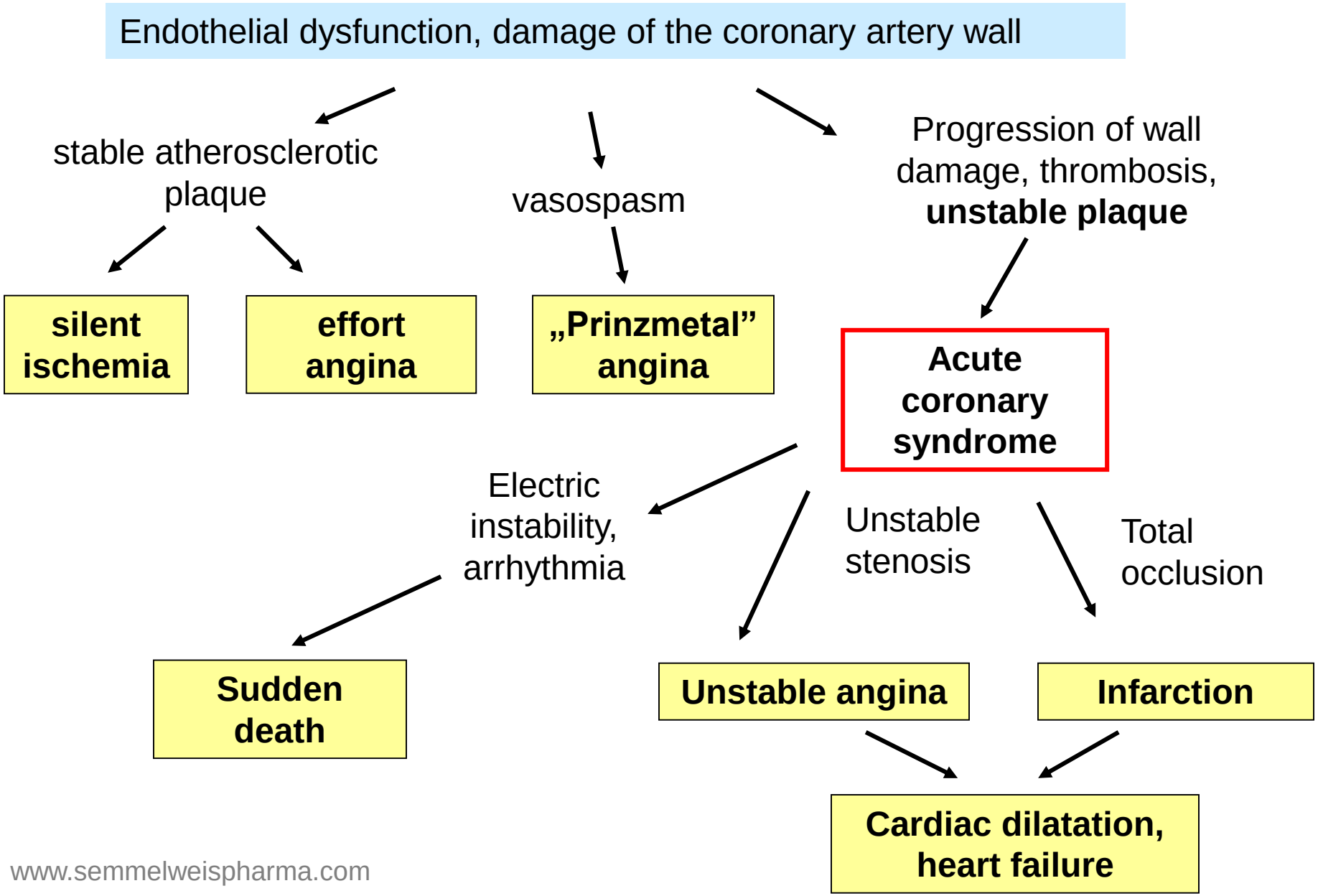


Figure 4. Six-month mortality in 1,122 patients in the Collaborative Organization for RheothRX Evaluation (CORE) trial, according to the

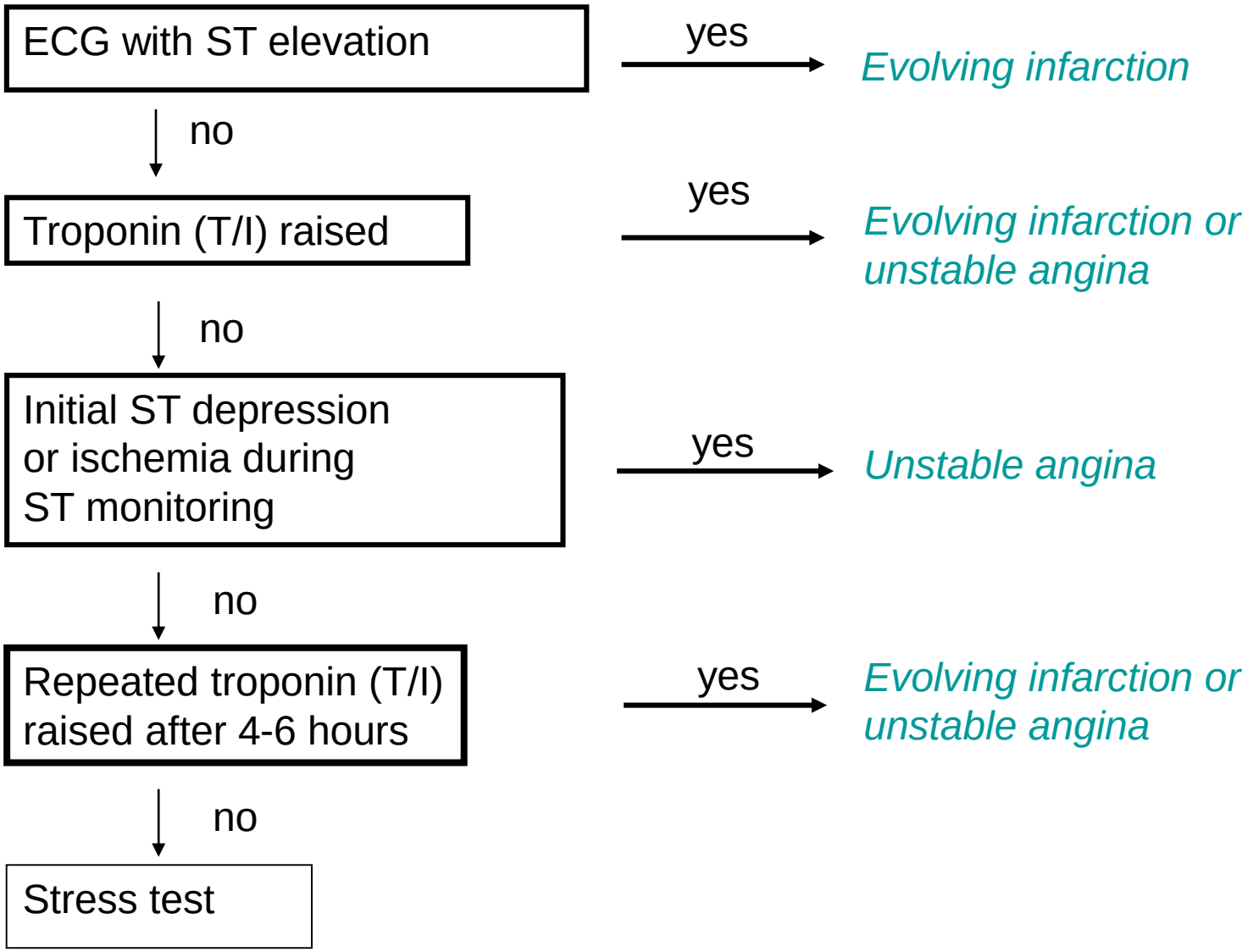
Clinical symptoms of myocardial ischemia with different severity: **1. mechanical dysfunction, 2. arrhythmias, 3. infarction**



Clinical manifestations of myocardial ischemia



Evaluation scheme for chest pain (ECG, biomarkers)



Treatment of ischemic heart disease

Aims:

- prevention of mortality induced by infarction, arrhythmias and heart failure
- attenuation of angina pain

Treatment sequence:

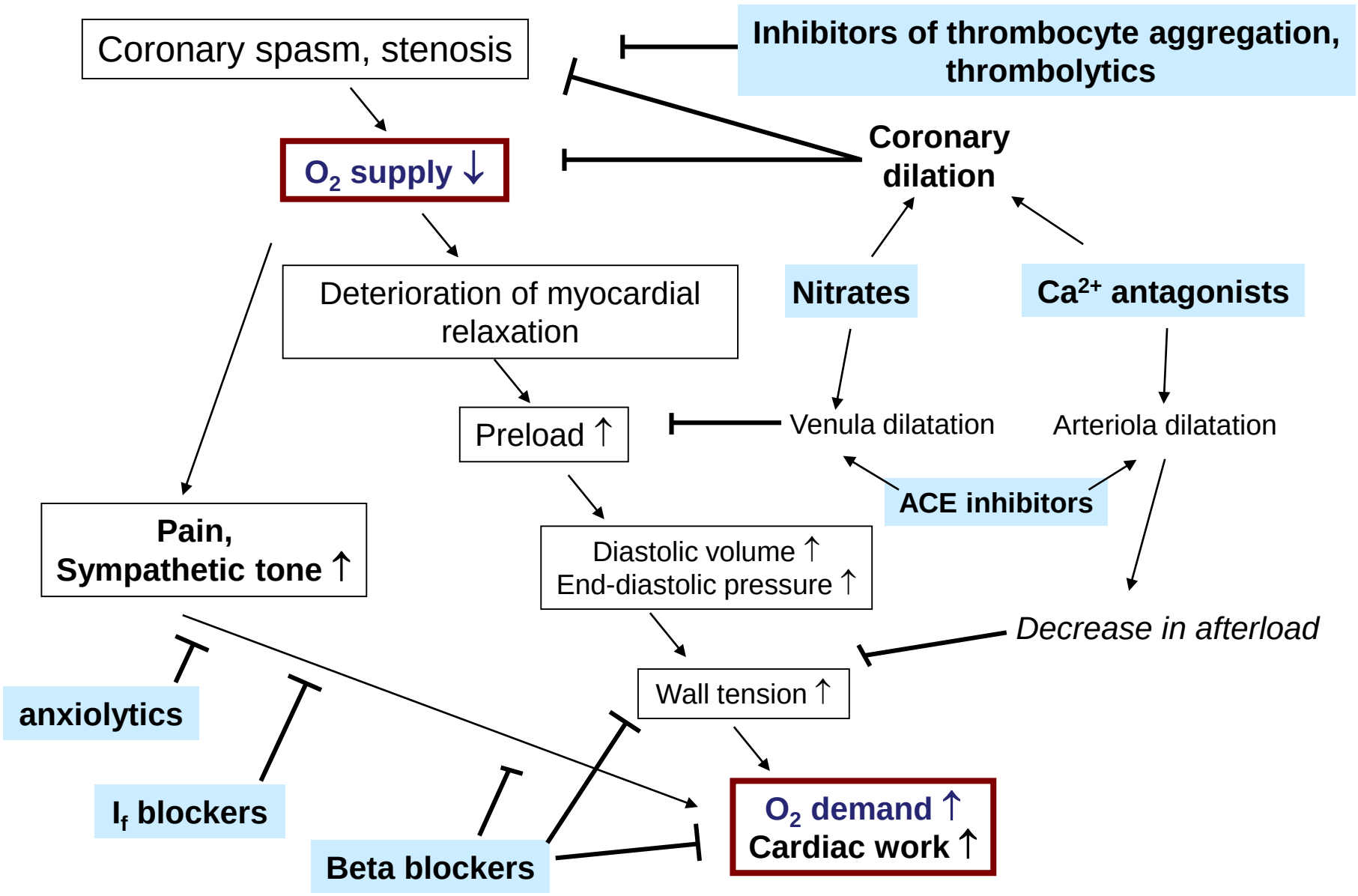
1. non-pharmacological: lifestyle change, elimination of risk factors, diet, dietary supplements

2. pharmacotherapy

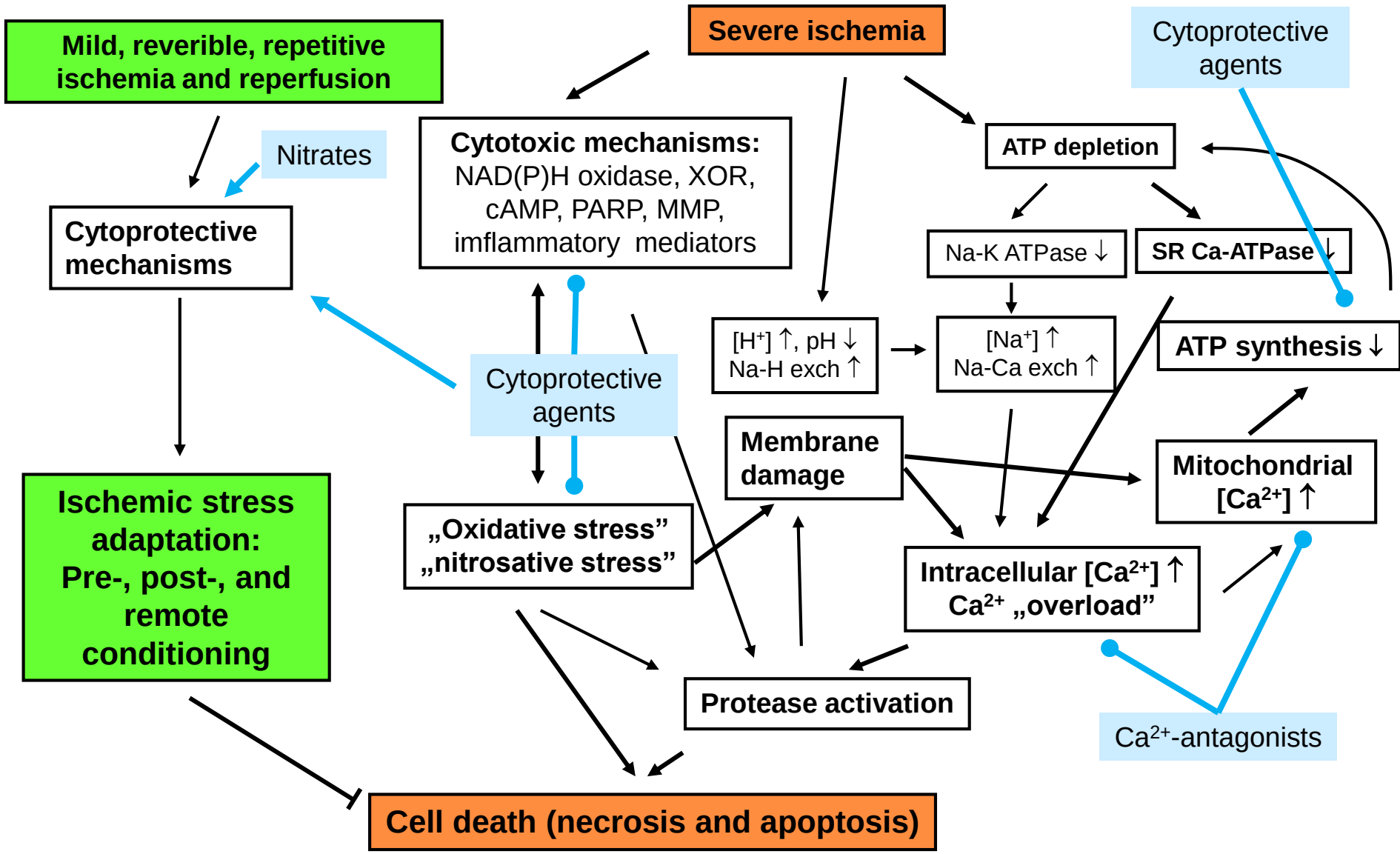
3. invasive therapy, revascularization (in AMI or severe cases):

- **p**ercutaneous **c**oronary **i**ntervention (PCI)
- revascularization surgery (bypass)
- immadiate intravenous thrombolysis

Pathophysiology of ischemic heart diseases: drug targets



Cellular mechanism of myocardial ischemia: potential targets for cardioprotective drugs



Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers, e.g., bisoprolol, carvedilol

Thrombocyte aggregation inhibitor

Antihyperlipidemic treatment

ACE inhibitor or
Angiotensin receptor blocker

Nitrates

Calcium channel blocker

Trimetazidine
Molsidomine
Ranolazine
Nicorandil
Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.

Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers

Thrombocyte aggregation inhibitor

COX1 inhibitor: aspirin
P2Y12 inhib: clopidogrel, ticagrelor
thrombin inhibitor: dabigatran
GPIIb/IIIa inhibitors: tirofiban

Antihyperlipidemic treatment

ACE inhibitor or
Angiotensin receptor blocker

Nitrates

Calcium channel blocker

Trimetazidine
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Ivabradine

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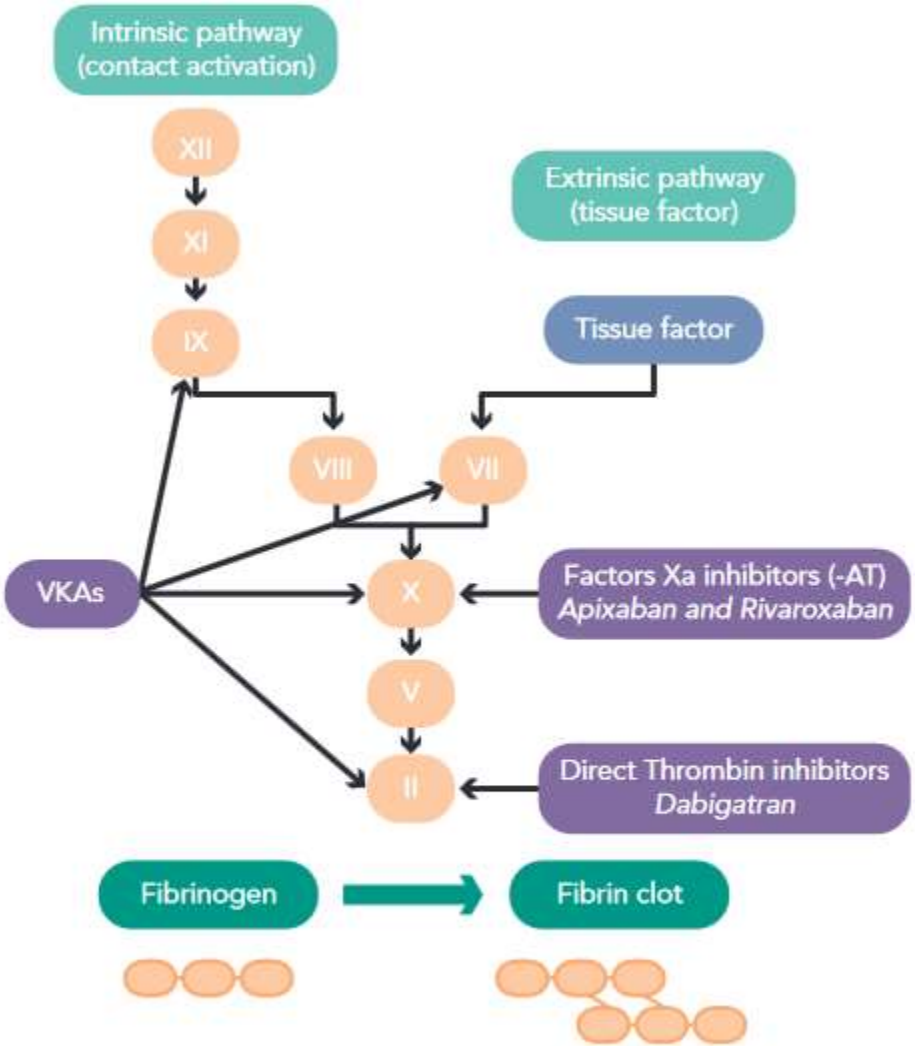
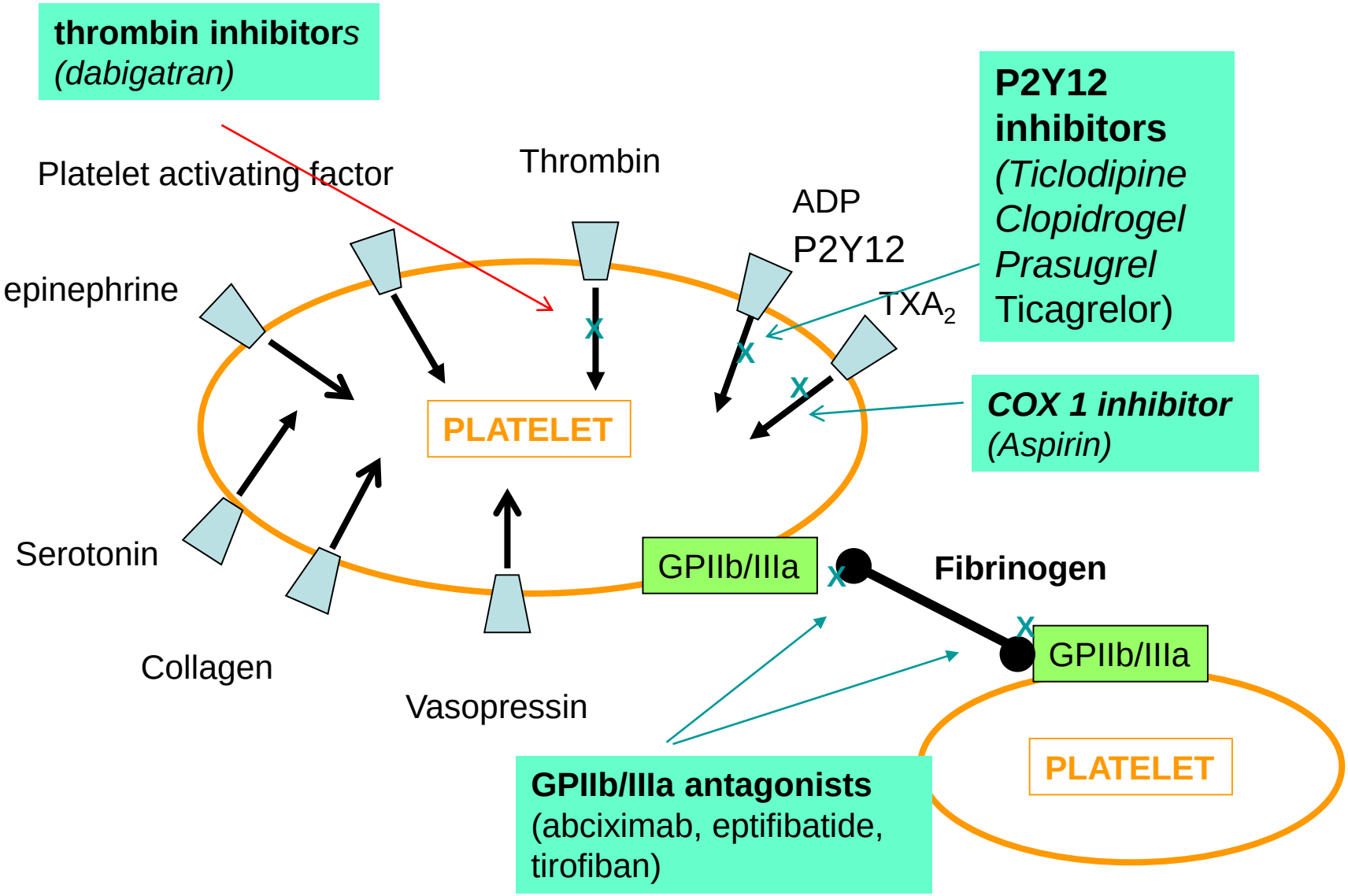


AT = antithrombin; VKA = vitamin K antagonist.
From: January et al, 2014.[1] By permission of Elsevier on behalf of American College of Cardiology. © AHA/ACC/HRS 2014.

Antiplatelet drugs (inhibitors of thrombocyte aggregation)



Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers

Thrombocyte aggregation inhibitor

Antihyperlipidemic treatment

HMGCoA reductase inhibitors: statins
Cholesterol absorp inhib: ezetimibe
triglyceride lowering: fenofibrate
PCSK9 inhibitor: evolocumab
metabolism enhancer: niacin

ACE inhibitor or
Angiotensin receptor blocker

Nitrates

Calcium channel blocker

Trimetazidine
Molsidomine
Ranolazine
Nicorandil
Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.

Prevention of atherosclerosis, antihiperlipidemic drugs

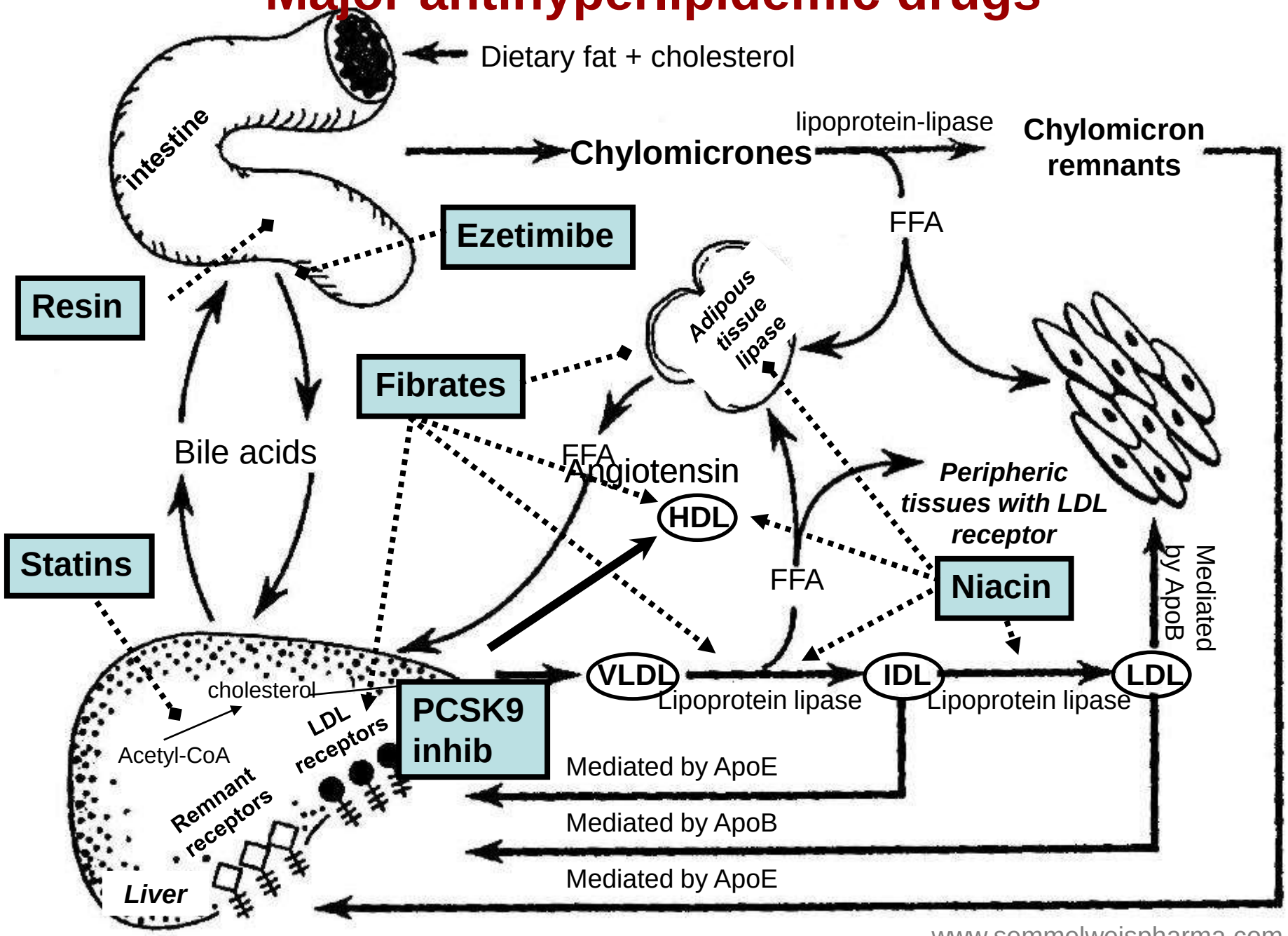
1. **Lifestyle changes: regular training**
- increased HDL
- amelioration of endothelial dysfunction

2. **Diet:**
- low saturated fatty acids, low trans fatty acids
- Fish oil (omega-3 fatty acids): decrease triglyceride level
  (omega-3 fatty acids are not effective in preventing further heart and stroke in patients who have had a heart attack)
- Moderate consumption of alcohol: increased HDL level (but also increased triglyceride level!)
- Folic acid, B_6- and B_{12}- vitamins: decreased homocysteine level
- Antioxidants (not proven)

3. Estrogen (women – menopausa)

4. Drugs:
- ACE inhibitors: amelioration of endothelial dysfunction
- **Drugs decreasing the lipid levels of the blood**

Major antihyperlipidemic drugs



Statin intolerance and its mangement

Severe side effects of statins:
• rhabdomyolysis, myopathy
• mostly when taken together with drugs metabolised by CYP3A4 and CYP2C enzymes, e.g. fibrates, macrolides)

Statin „intolerance”
• myalgia,
• increased biomarkers (CK)

Management of statin intolerance:
• change to other statin
• dose reduction
• lose dose statin in combination with ezetimibe
• discontinuation of statins (ezetimibe, PCSK9 inhibitors)

Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers

Thrombocyte aggregation inhibitor

Antihyperlipidemic treatment

ACE inhibitor or
Angiotensin receptor blocker

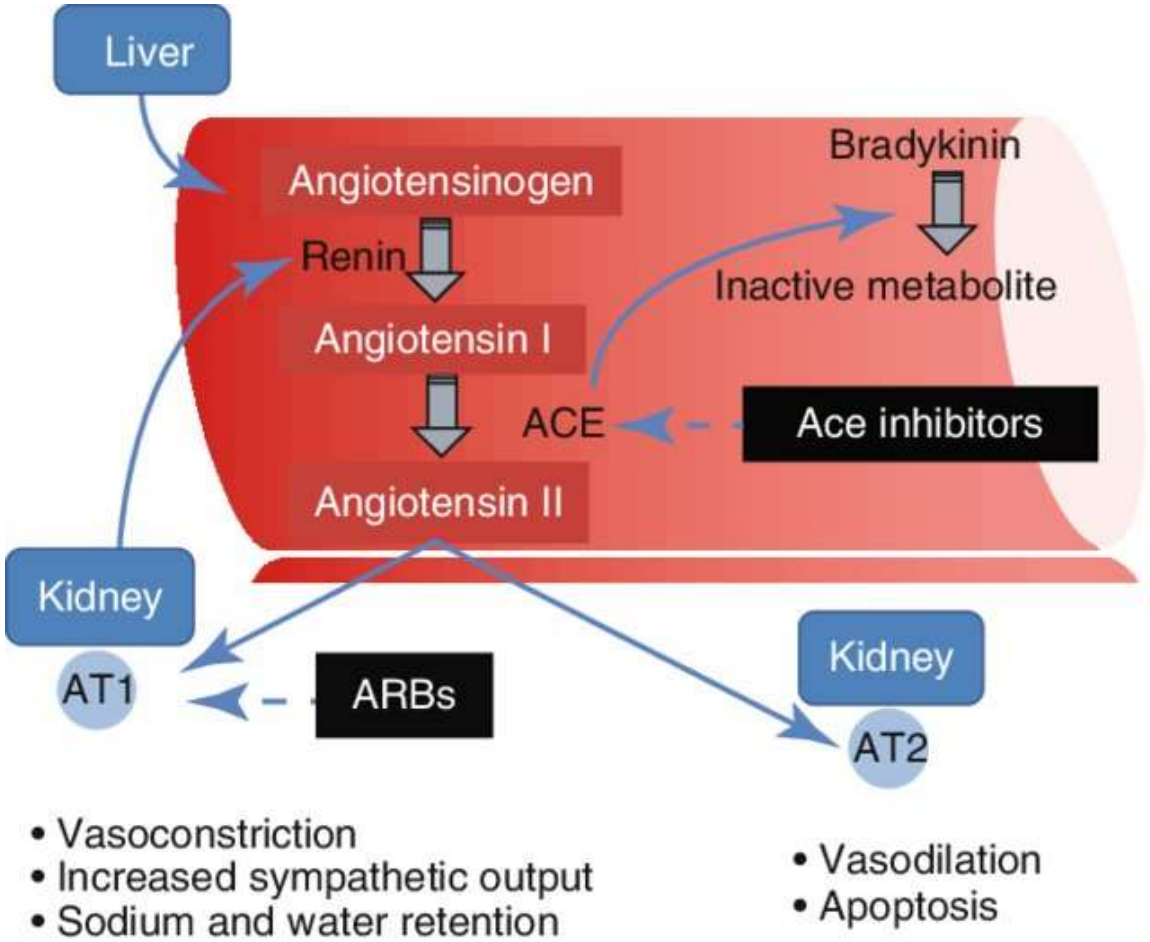
ACE inhibitors:
ramipril, perindopril
ARBs:
telmisartan, valsartan

Nitrates

Calcium channel blocker

Trimetazidine
Molsidomine
Ranolazine
Nicorandil
Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.



DOI: 10.1007/978-1-4614-8948-1_16

Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers

Thrombocyte aggregation inhibitor

Antihyperlipidemic treatment

ACE inhibitor or
Angiotensin receptor blocker

Nitrates

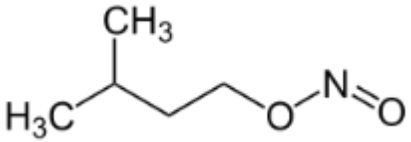
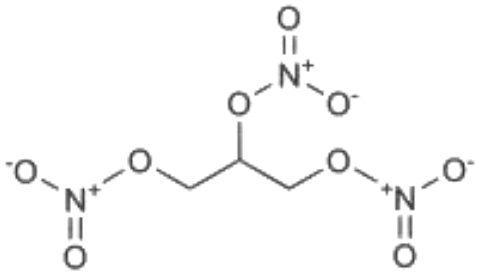
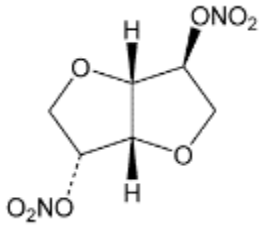
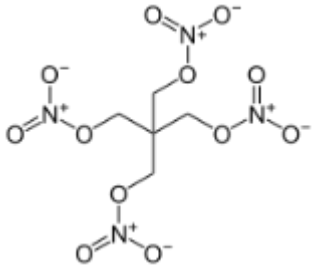
glyceryl trinitrate (nitroglycerine)
isosorbid mononitrate

Calcium channel blocker

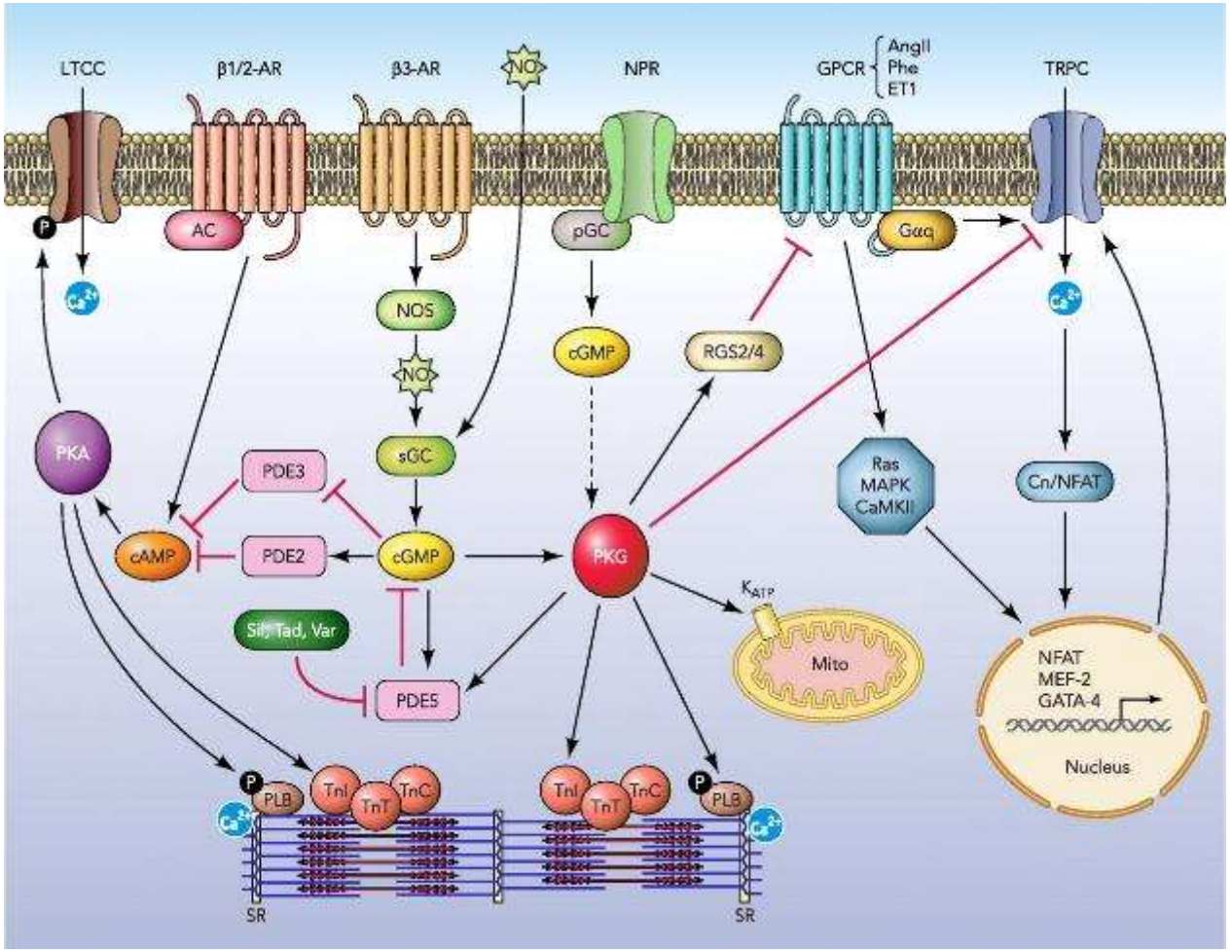
Trimetazidine
Molsidomine
Ranolazine
Nicorandil
Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.

Organic nitrates available for clinical use

Drug	**Dosing**
Amyl nitrite 	inhalation (0.18 or 0.3 mL)
Glyceryl trinitrate 	sublingual tablet: 0.5-1 mg spray, aerosol: 0.4 mg intravenous: 5-200 μg/min oral, retard tabl, transdermal: 2.5-13 mg
Isosorbide mononitrate, dinitrate 	Tabl. or caps.: 40-100 mg/day
Pentaerythritol tetranitrate 	20-120 mg/day (for prevention of ischemic attack)

Effect of NO-donor drugs on the myocardium

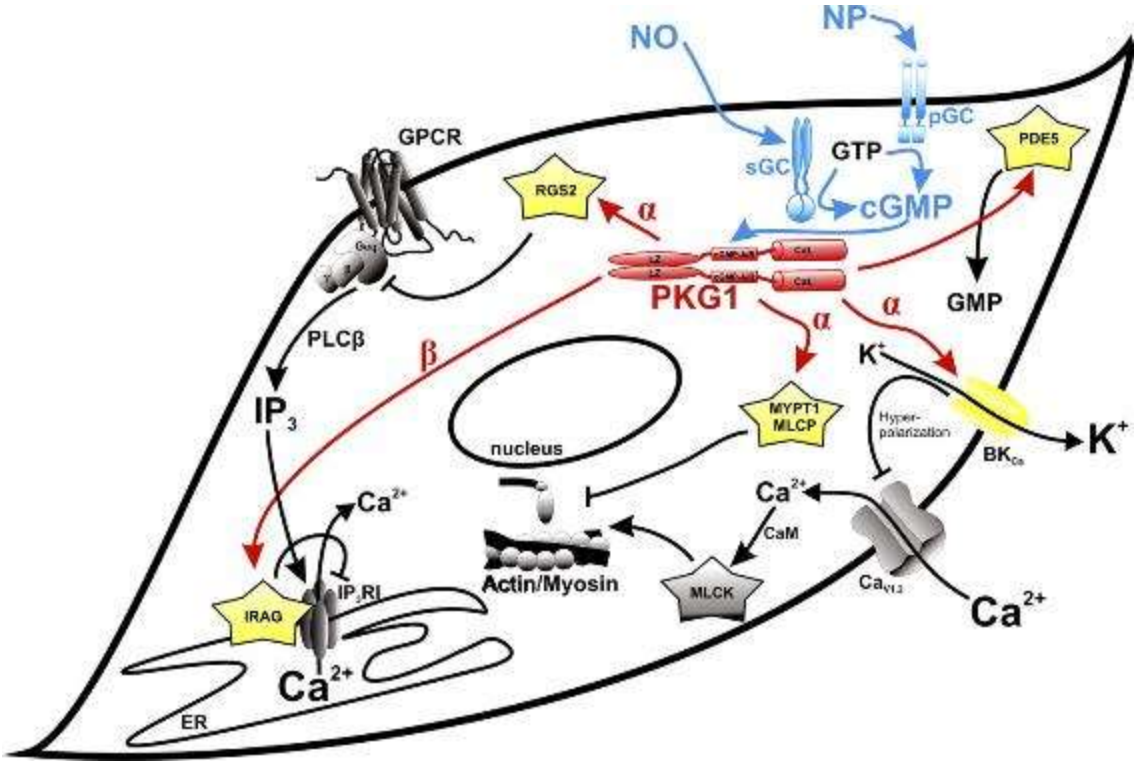


- decreasing cytosolic and mitochondiral Ca^{2+}-load
- increasing SR Ca^{2+}-uptake
- increasing relaxation
- decreasing heart rate

} decreased oxygen demand
cytoprotection

Dong I. Lee, and David A. Kass Physiology 2012;27:248-258

Effect of NO-donor drugs on smooth muscle cells

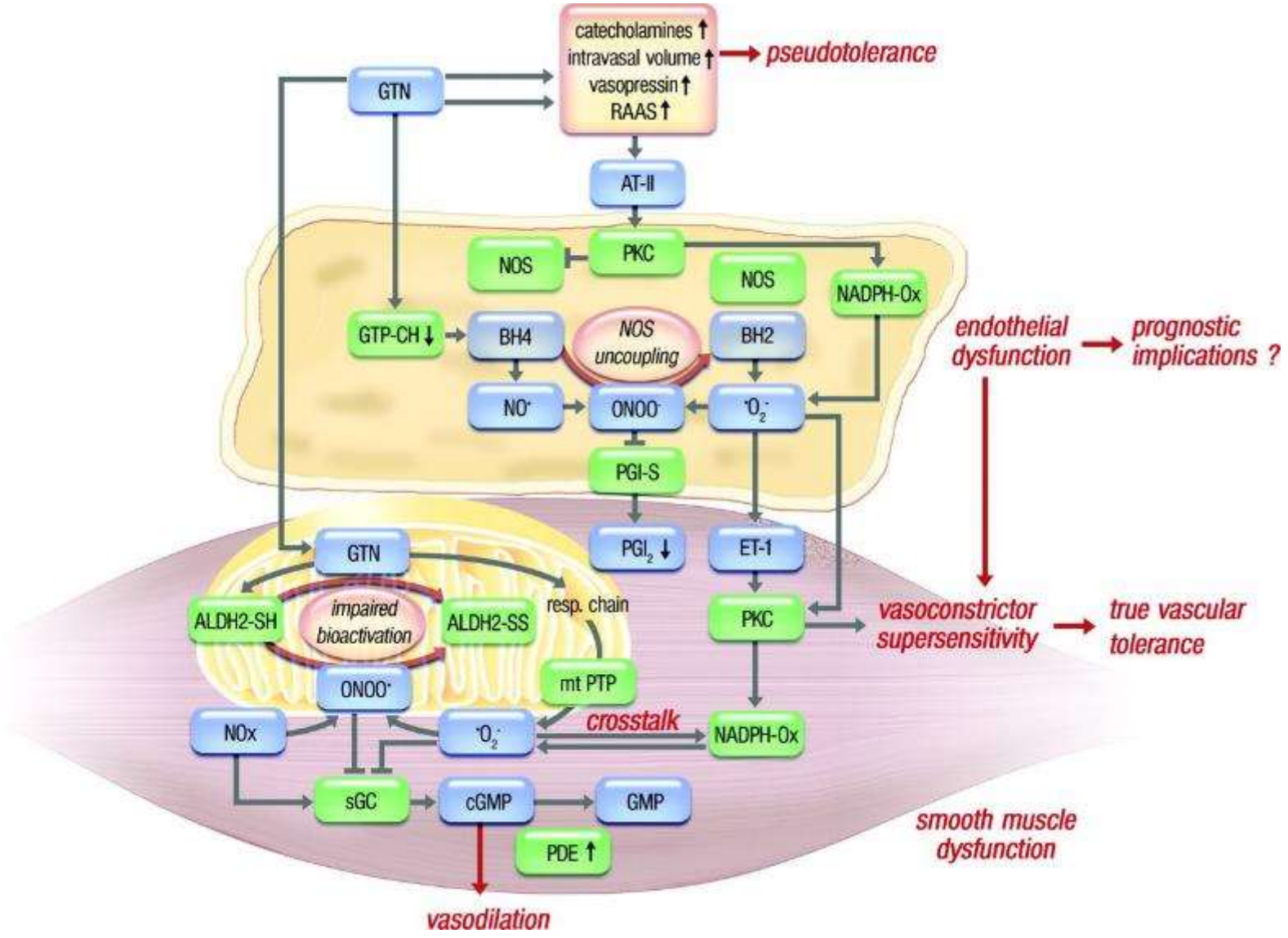


- decreasing cytosolic Ca^{2+}-load
- decreasing contractility

} vasorelaxation

AJP- Heart and Circulatory Physiology 2011 Vol. 301 no. 3, H672-H682

Molecular mechanisms of nitrate tolerance



Münzel et al. Circulation. 2011;123:2132-2144

Therapy of angina by nitrates: special dosage schedules to avoid nitrate tolerance

PREPARATION	DOSING SCHEDULE
- Isosorbide dinitrate	30 mg at 7 am and 1 pm
- Isosorbide mononitrate	20 mg at 8 am and 3 pm
- Isosorbide mononitrate extended release	120-240 mg daily
-Transdermal nitrate patches	7.5-10 mg/12 hours patches removed after 12 hours
- Phasic release nitroglycerine patch	15 mg, most of it is released in the first 12 h

Side-effects of nitrates

Serious side-effects, dose-dependent:

- syncope and hypotension (hypotension may cause cerebral ischemia)
- tachycardia (frequent)
- bradycardia in AMI
- methemoglobinemia (prolonged high dosage)

Other side-effects:

- headache (limit dose frequently)
- facial flushing
- **halitosis (sublingual)**
- **dyscoloration of the oral mucosa**

May increase cardiovascular mortality?

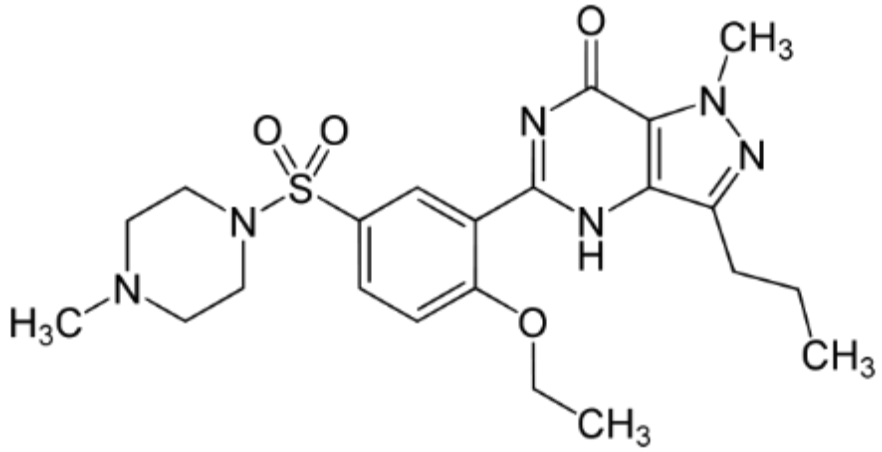
- due to tolerance (oxidative/nitrosative stress)

Contraindications of nitrates

- angina caused by *hypertrophic obstructive cardiomyopathy*: nitrates may increase outflow obstruction (ranolazine)
- *Cardiac tamponade or constrictive pericarditis*: the already compromised diastolic filling may be aggravated by reduced venous return.

PDE5 inhibitors – interaction with NO donors

Sildenafil
Tadalafil
Vardenafil



- selective inhibition of PDE_5 in the corpus cavernosum: relaxation of smooth muscle cells
- **elevation of cGMP level** → interaction with nitrates → blood pressure ↓
- PDE_3 inhibition in the heart → contractility ↑
- PDE_6 in the eye → vision problems
- lengthening cardiac repolarisation, long QT – arrhythmias
- pharmacokinetics: CYP3A4, 2C9: interaction with macrolid antibiotics, grapefruit; pentobarbital, rifampicin

Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

Symptomatic treatment
(anti-anginal treatment)

Beta-receptor blockers

Thrombocyte aggregation inhibitor

Antihyperlipidemic treatment

ACE inhibitor or
Angiotensin receptor blocker

Nitrates

Calcium channel blocker
verapamil, diltiazem

Trimetazidine
Molsidomine
Ranolazine
Nicorandil
Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.

Side effects of Ca^{2+}-channel blockers

Serious side effects:

- cardiac depression, bradycardia
- AV-block, cardiac arrest, cardiac failure (verapamil)
- arrhythmia (torsade de pointes, long QT)

Minor side effects:

- dizziness, hypotension, headache, flushing,
- palpitation, nausea, constipation, peripheric edema
- coughing, muscular cramps, gingival hypertrophy

May increase mortality?

- aggravation of myocardial ischemia only by some short acting dihydropyridines

Drug treatment of stabile coronary heart disease

Baseline treatment
(life-long to prevent cardiovascular events and death)

- Beta-receptor blockers
- Thrombocyte aggregation inhibitor
- Antihyperlipidemic treatment
- ACE inhibitor or Angiotensin receptor blocker

Symptomatic treatment
(anti-anginal treatment)

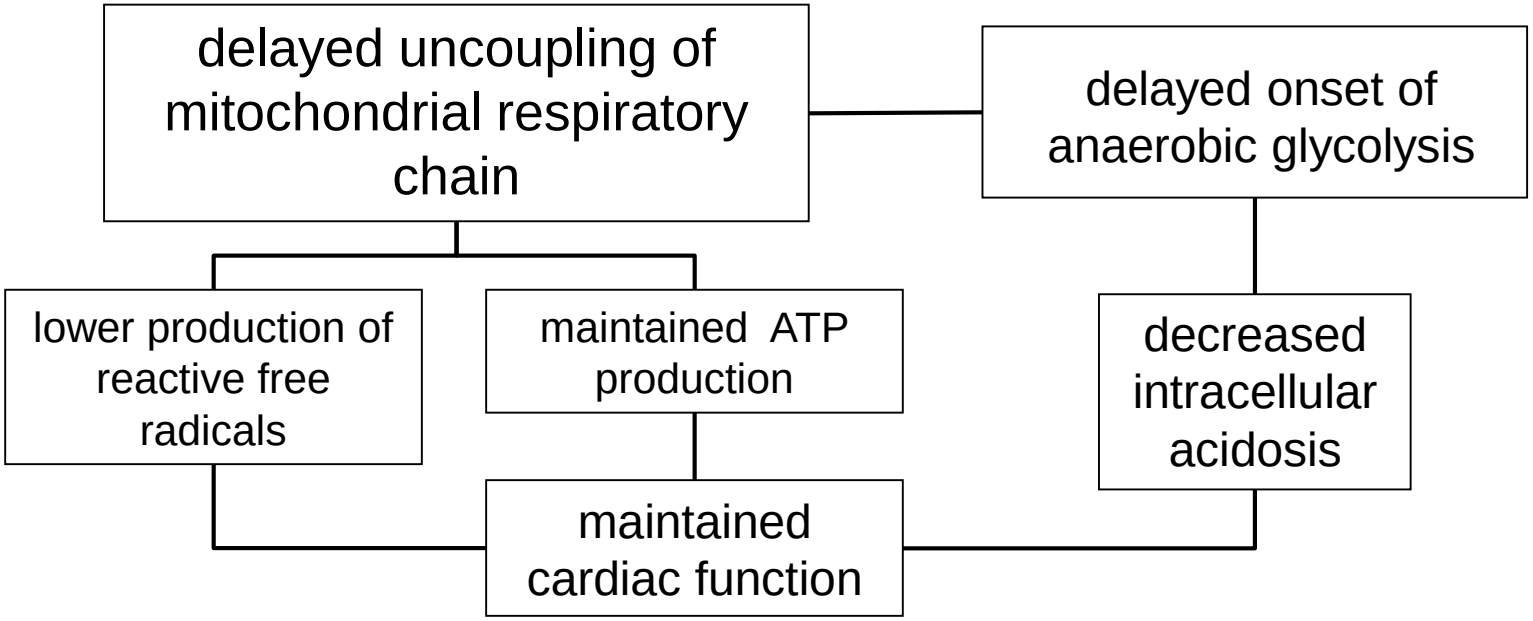
- Nitrates
- Calcium channel blocker
- Trimetazidine
  Ranolazine
  Molsidomine
  Nicorandil
  Ivabradine

Guideline: European Heart Journal 2020 14;41(3):407-477.

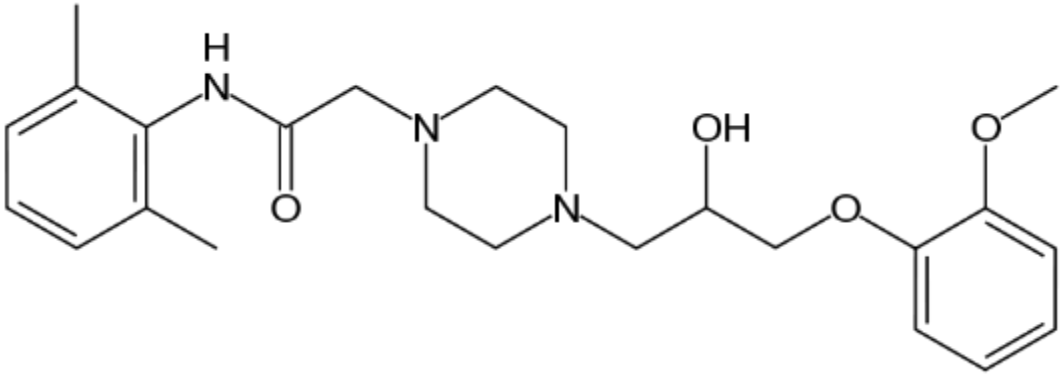
metabolic modulators: trimetazidine

Shifts cardiac metabolism from fatty acid oxidation to glucose oxidation

- increases the oxygen-efficacy of energy metabolism: more ATP/oxygen produced
- adjuvant therapy in stable angina
- no hemodynamic effect
- fast-acting, t.i.d.



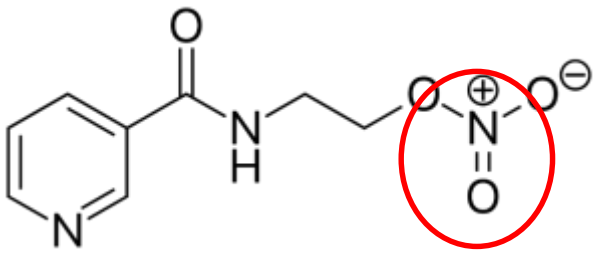
Novel drugs in the treatment of ischemic heart disease: ranolazine



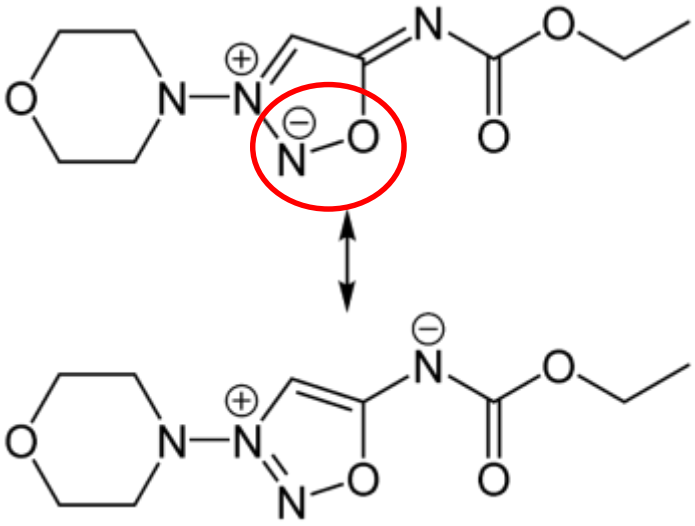
- inhibitor of late sodium channels in myocardial cells
- decreases intracellular Na^+, activates Na/Ca transporter: decreased intracellular Ca^{2+}-overload
- decreases fatty acid oxidation of the myocardium
- decreases cardiac work, cytoprotective
- indicated in stable angina, obstructive hypertrophic cardiomyopathy
- CYP3A4 inhibitors: interaction
- Contraindication: decreased hepatic or renal function

Antianginal agents with structure similar to nitrates

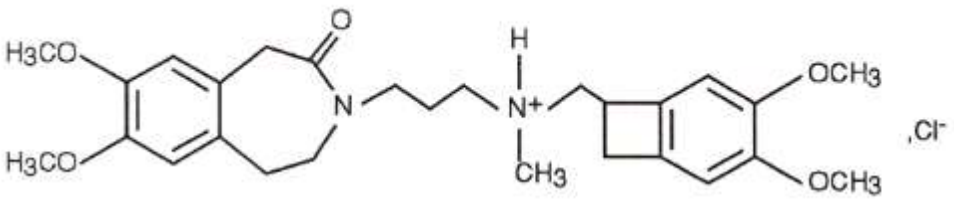
nicorandil



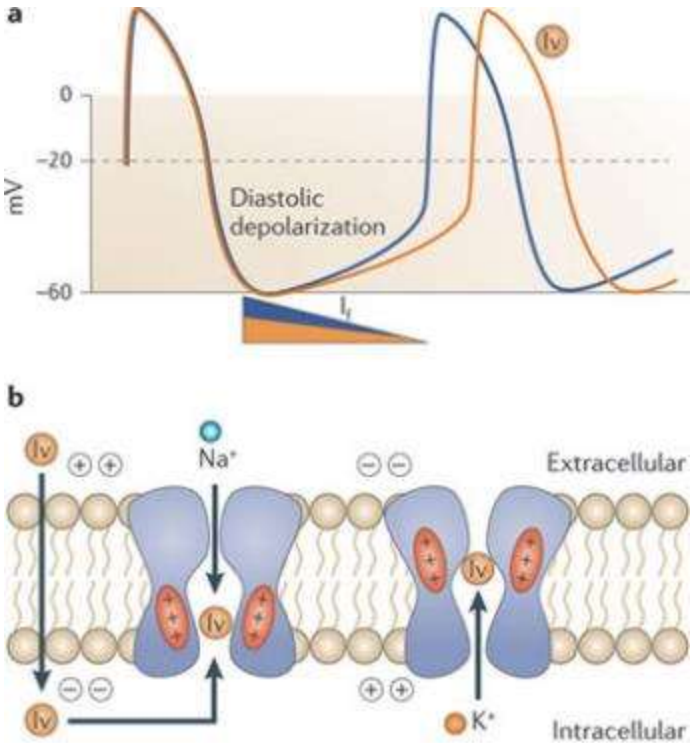
molsidomine



Novel drugs in the treatment of ischemic heart disease: ivabradine



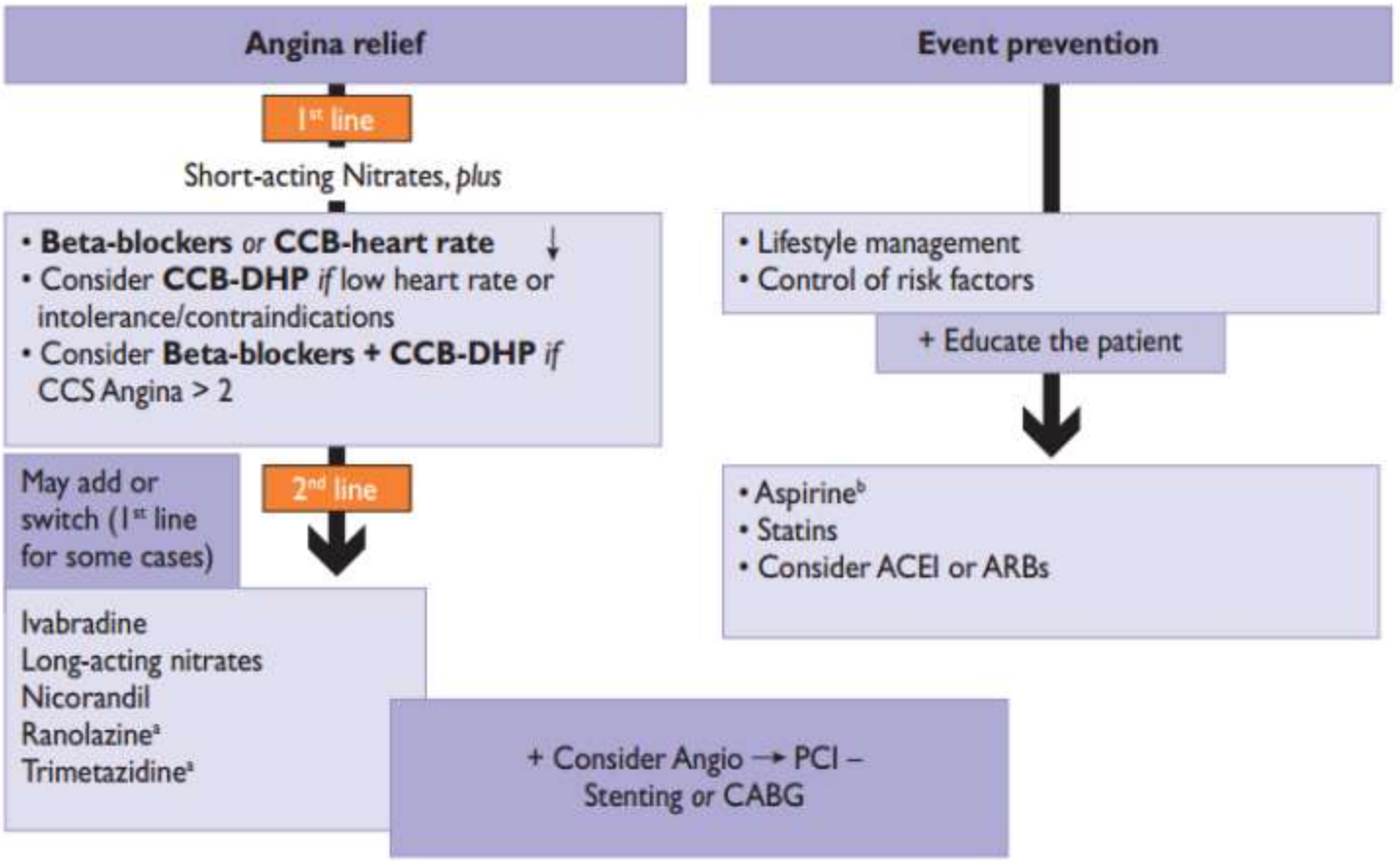
- Decreases the activity of the sinoatrial node by reducing the „pacemaker” I_f current (HCN1-4 channels)
- Decreases heart rate
- No effect on conduction parameters, ventricular repolarization, or contractile force
- Efficacy is similar to that of beta-blockers or calcium antagonists
- in chronic effort angina if HR ≥ 70/min
- contraindication: sick sinus syndrome



Nature Reviews Drug Discovery 10, 903-914

European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

2013 ESC guidelines on the management of stable coronary artery disease



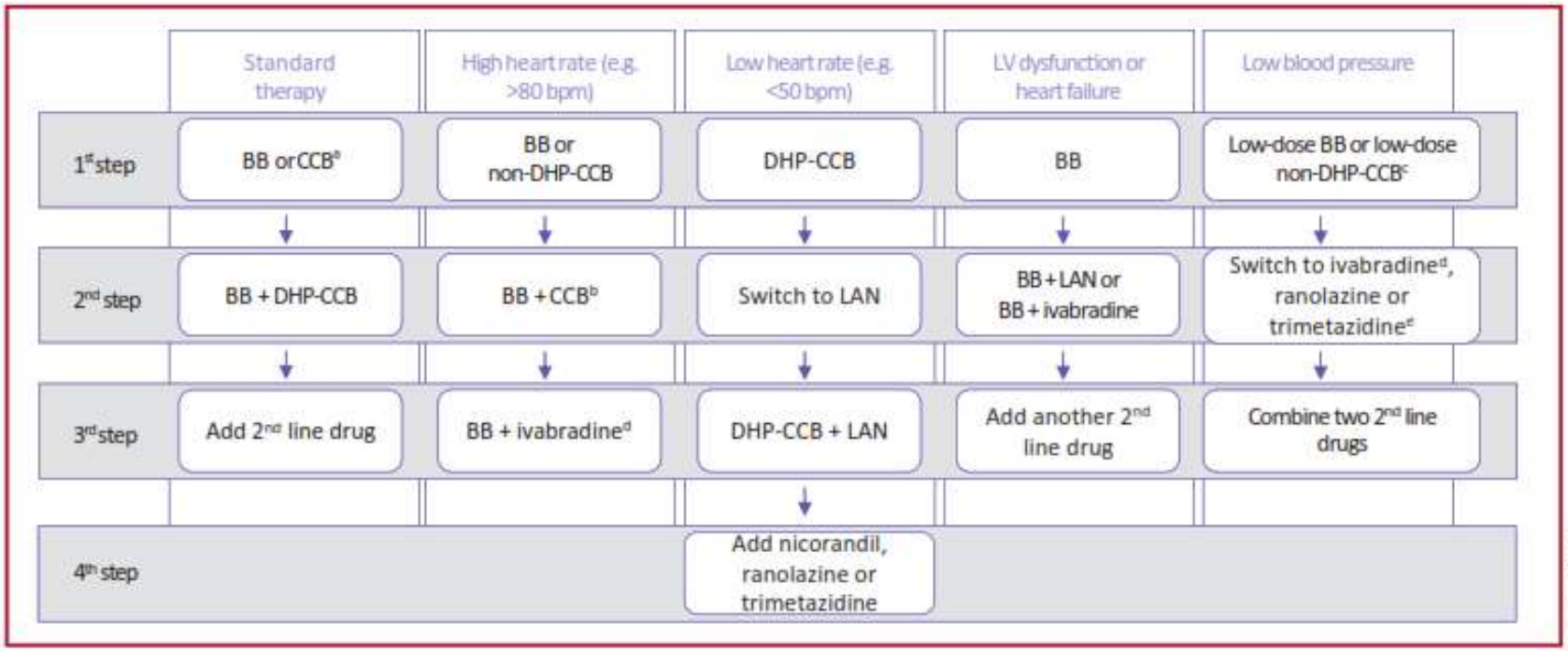
CCB: Ca-channel blockers
DHP: Dihydropyridine

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 407–477
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)



ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–19
doi:10.1093/eurheartj/ehz425

2019 ESC Guidelines on the diagnosis and management of chronic coronary syndromes: supplementary data

Supplementary Table 3 **Major side effects, contraindications, drug–drug interactions, and precautions of anti-ischaemic drugs**

Drug class	Side effects[a]	Contraindications	DDIs	Precautions
Short- and long-acting nitrates[138,143,146]	• Headache • Flushing • Hypotension • Syncope and postural hypotension • Reflex tachycardia • Methaemoglobinaemia	• Hypertrophic obstructive cardiomyopathy • Severe aortic stenosis • PDE5 inhibitors	• PDE5 inhibitors (sildenafil or similar drugs) • Alpha-adrenergic blockers • CCBs	• Allow a nitrate-free or nitrate-low interval of about 10–14 h with long-acting nitrates
Beta-blockers[b] [147,148]	• Fatigue, depression • Bradycardia • Heart block • Decreased inotropism • Bronchospasm • Peripheral vasoconstriction • Postural hypotension • Impotence • Hypoglycaemia/mask hypoglycaemia signs	• Low heart rate or heart conduction disorder • Cardiogenic shock • Asthma • COPD caution; may use beta$_1$-selective blockers if fully treated by inhaled steroids and long-acting beta-agonists • Severe peripheral vascular disease • Decompensated heart failure • Vasospastic angina	• Heart rate-lowering CCBs • Sinus node or atrioventricular conduction depressors	• Diabetes • COPD

Continued

Other options in the treatment of ischemic heart disease

1. Vitamins, and vitamin-like substances

• Omega-3 fatty acids, eicosapentaenic acid (EPA), docosahexaenic acid (DHA) ⟶ **do not** decrease serum triglyceride and formation of atherosclerotic plaques

• Coenzyme Q_{10} (ubiquinone, **ubidecarenone**): antioxidant, ATP production (in chronic heart failue)

• B_6-, B_{12}-vitamins, folic acid: decrease serum homocysteine level

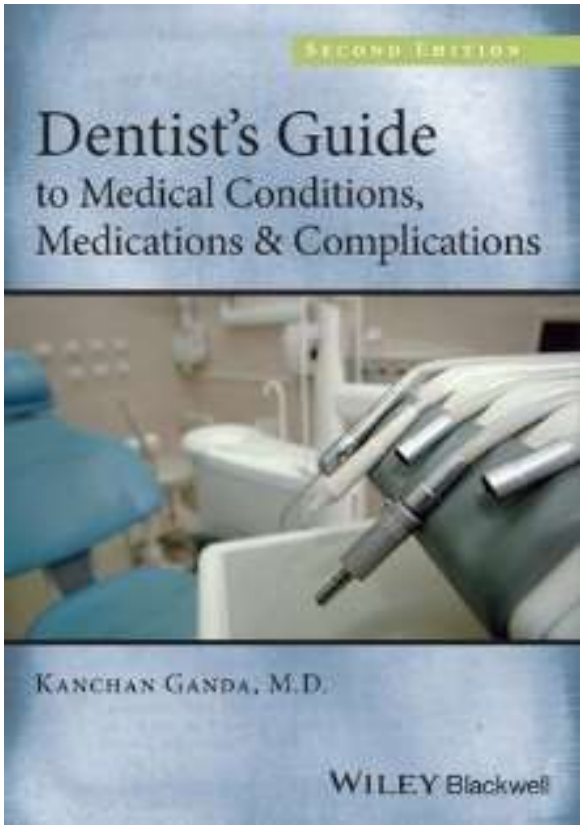
2. „Advanced therapies" (gene- and cell-therapy) - regenerative medicine (under development)

• gene therapy: e.g., NO synthase
• tissue regenerative therapy: e.g., stem cell implantation, exosomes

3. Coronary stents coated with antiproliferative drugs:

• rapamycin, sirolimus, paclitaxel, etc.

Optional literature



patients at high risk for myocardial infarction.

- All glycoprotein IIb/IIIa inhibitors increase the safety of acute PCI.
- Low molecular weight heparin (LMWH) and intravenous unfractionated heparin (UH) are comparable anticoagulants in the treatment of unstable angina.
- LMWH is preferred initially, because anticoagulation activity cannot be measured during PCI.
- Direct thrombin inhibitors are potential alternatives to heparin, particularly in the presence of heparin-induced thrombocytopenia.
- Direct thrombin inhibitors are associated with higher rates of bleeding, but they are slightly better at reducing myocardial infarction when compared to heparin.

Nitrates

Intravenous nitrates may be used in the treatment of ischemic chest pain, symptoms of heart failure, or hypertension, but they are not associated with appreciable long-term clinical benefit.

Acute Angina Attack

Refer to Chapter 9 for a discussion of etiology, clinical features, and management of stable and unstable angina attacks.

Angina Pectoris–Associated Suggested Dental Guidelines

Anesthetics for Stable Angina

Local anesthetics with or without epinephrine can be used. Use maximum 2 carpules of 2% lidocaine (Xylocaine), 0.5% bupivacaine (Marcaine), 4% prilocaine HCL (Citanest Forte), 3% mepivacaine (Carbocaine), 4% prilocaine HCL (Citanest Plain), 4% septocaine (Articaine), or 2% mepivacaine (Carbocaine) with 1:20,000 levonordefrin (NeoCobefrin).

Anesthetics for Unstable Angina

Avoid LAs with epinephrine.

Analgesics and Antibiotics for Angina Pectoris

There are no analgesics or antibiotics contraindicated per se with stable or unstable angina; however, be discreet in prescribing narcotic analgesics in the

Kanchan Ganda