Treatment strategy of ischemic heart disease

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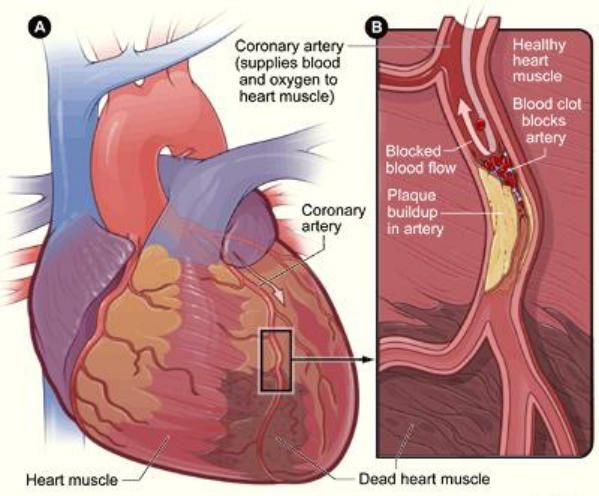
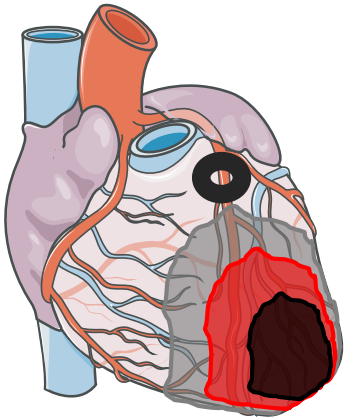
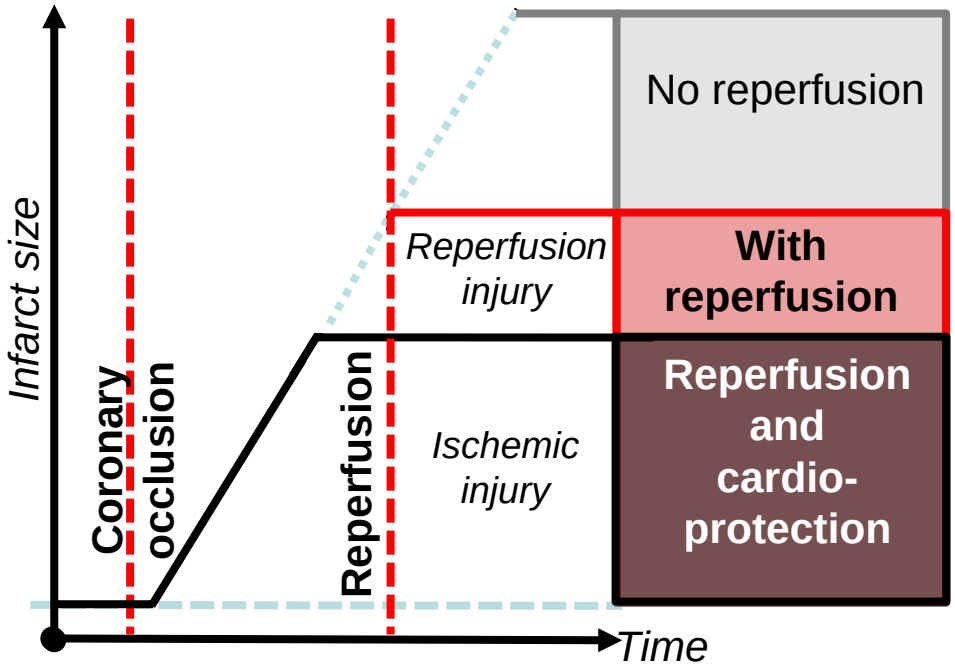
Ischemic zone and infarction: importance of reperfusion



Induce reperfusion
(eg. balloon angioplasty and stanting stents with antiproliferative drugs, and/or fibrinolytics)





Time is muscle, muscle is life!

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

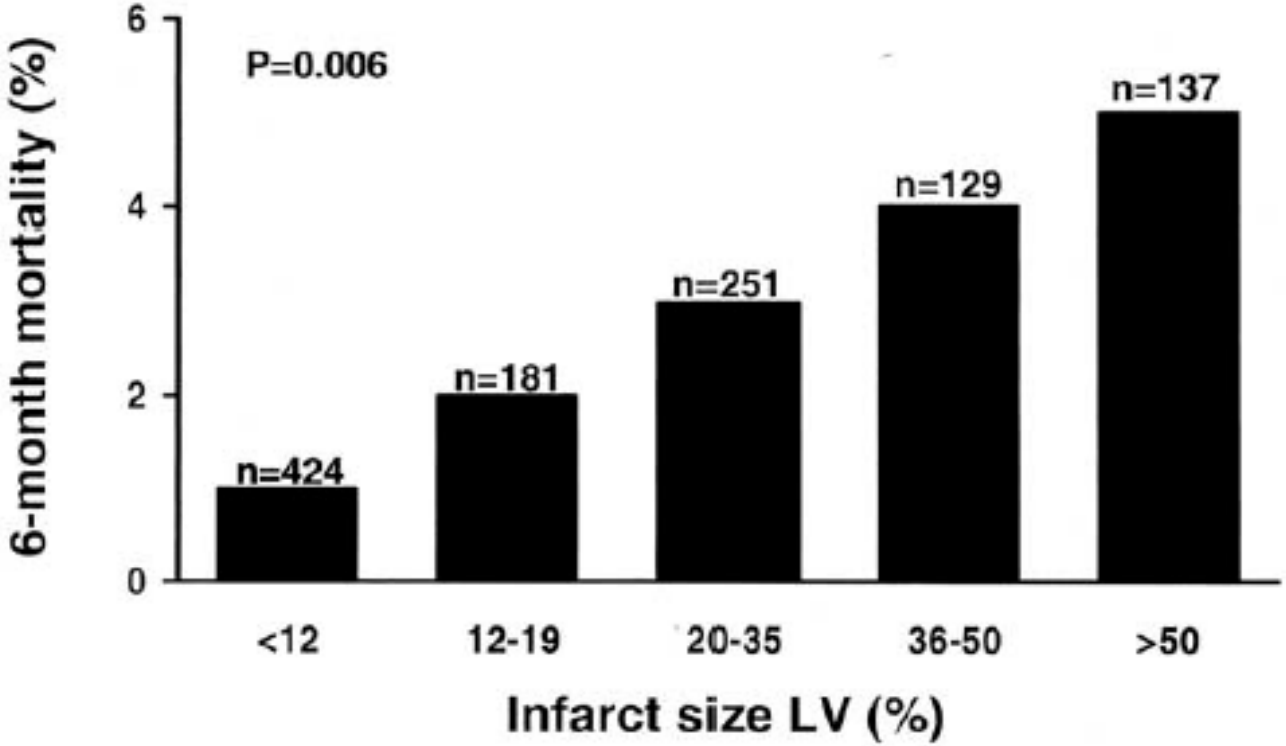
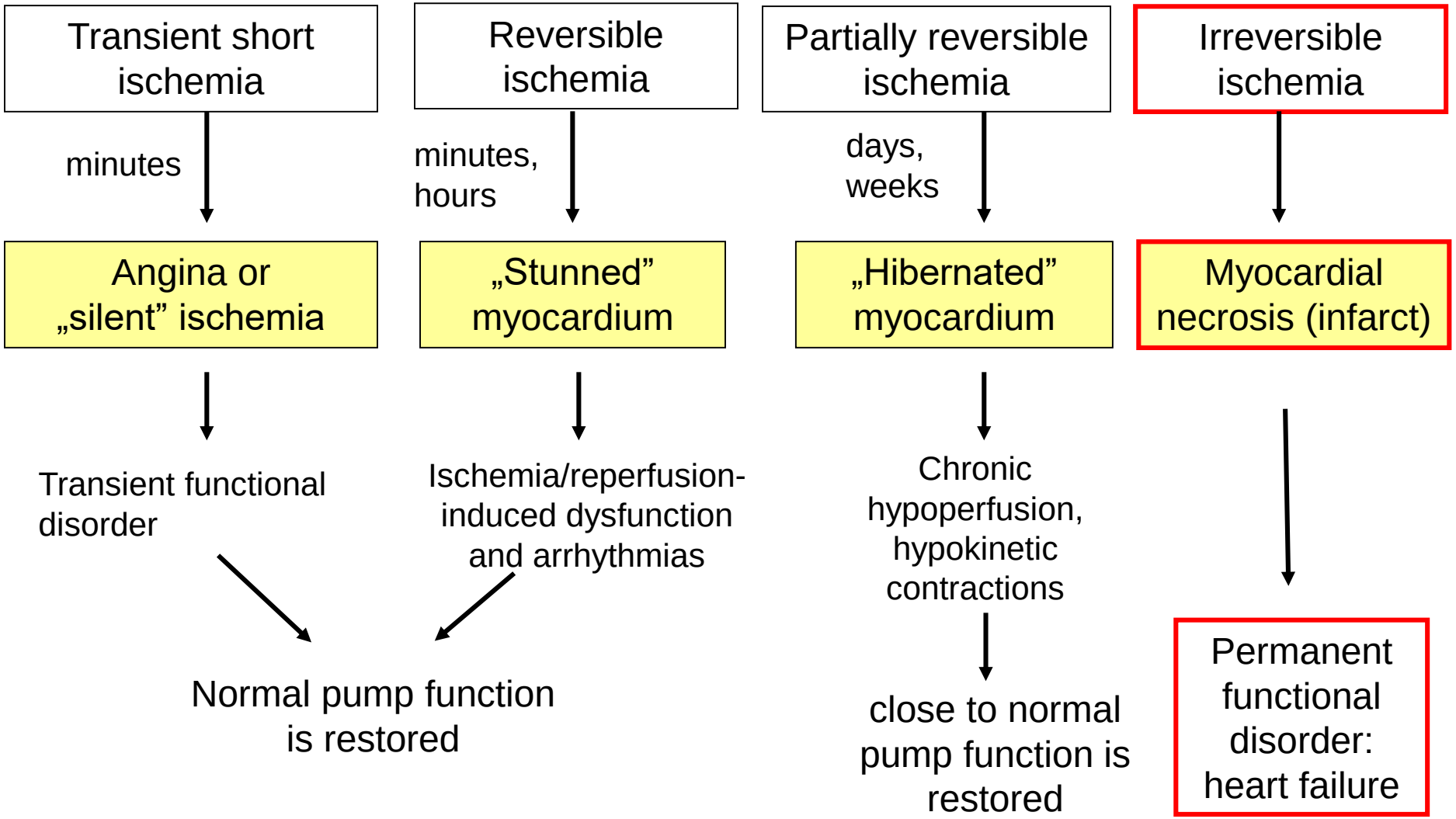
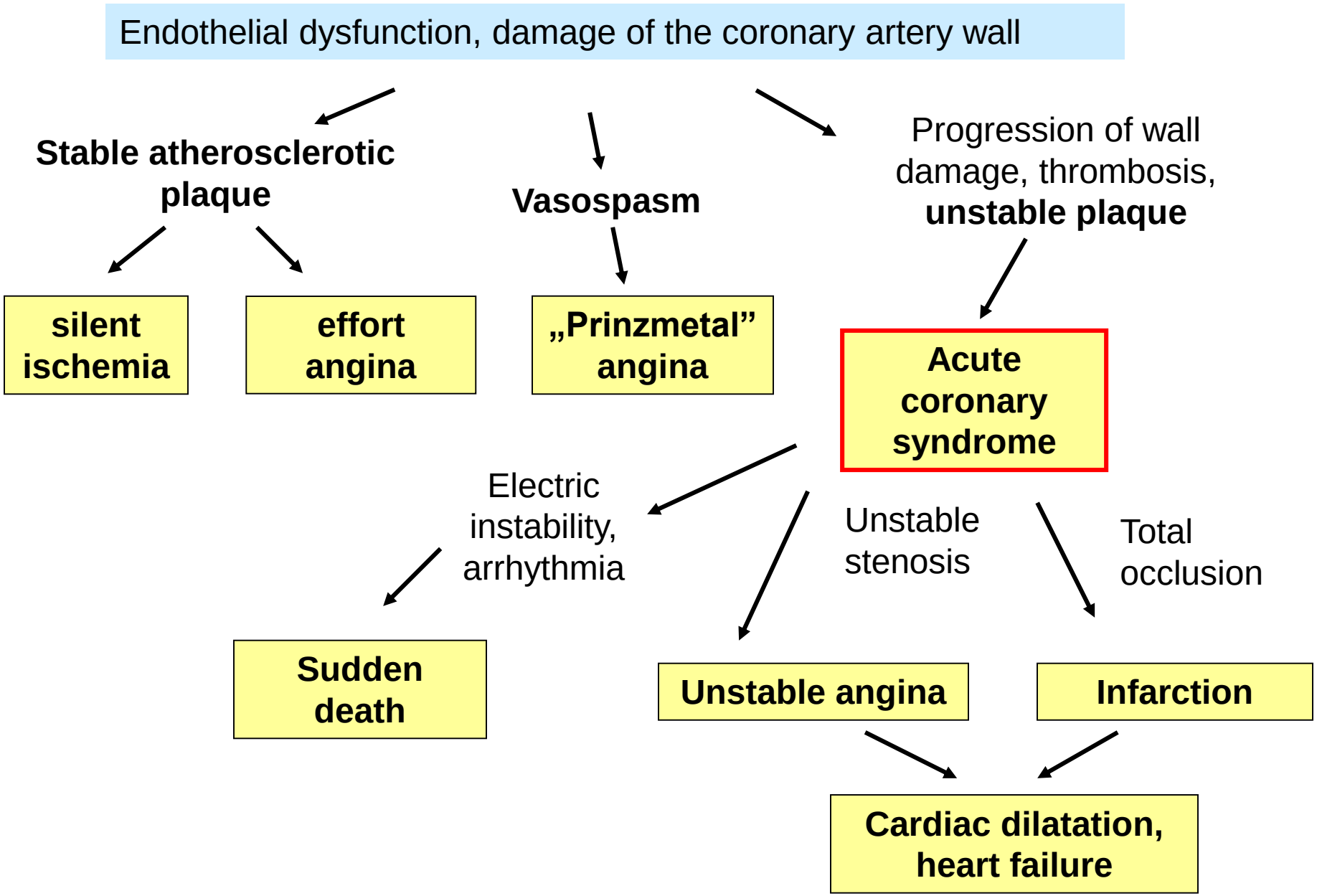


Figure 4. Six-month mortality in 1,122 patients in the Collaborative Organization for RheothRX Evaluation (CORE) trial, according to the

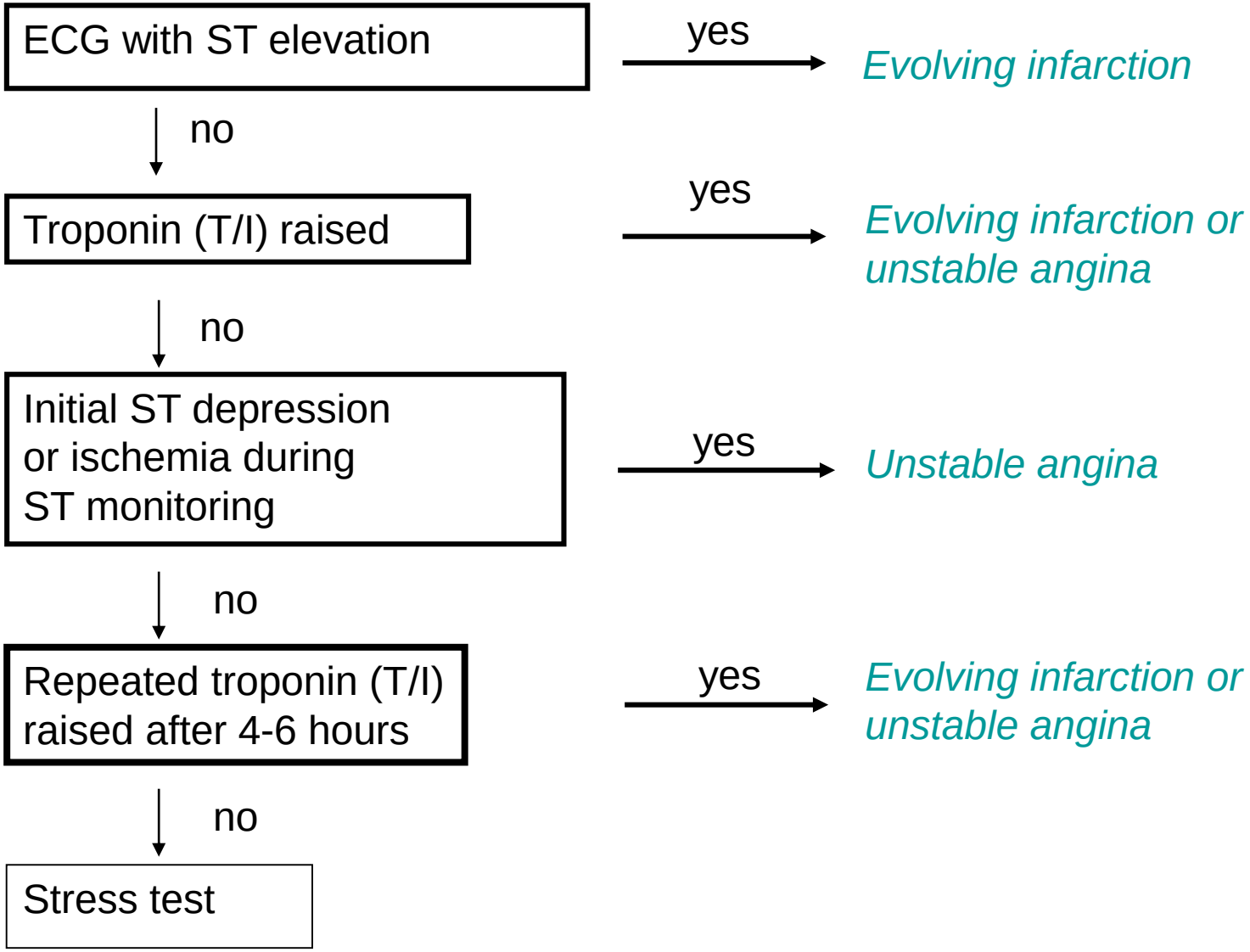
Clinical symptoms of myocardial ischemia with different severity: **1. mechanical dysfunction, 2. arrhythmias, 3. infarction**



Clinical manifestations of myocardial ischemia



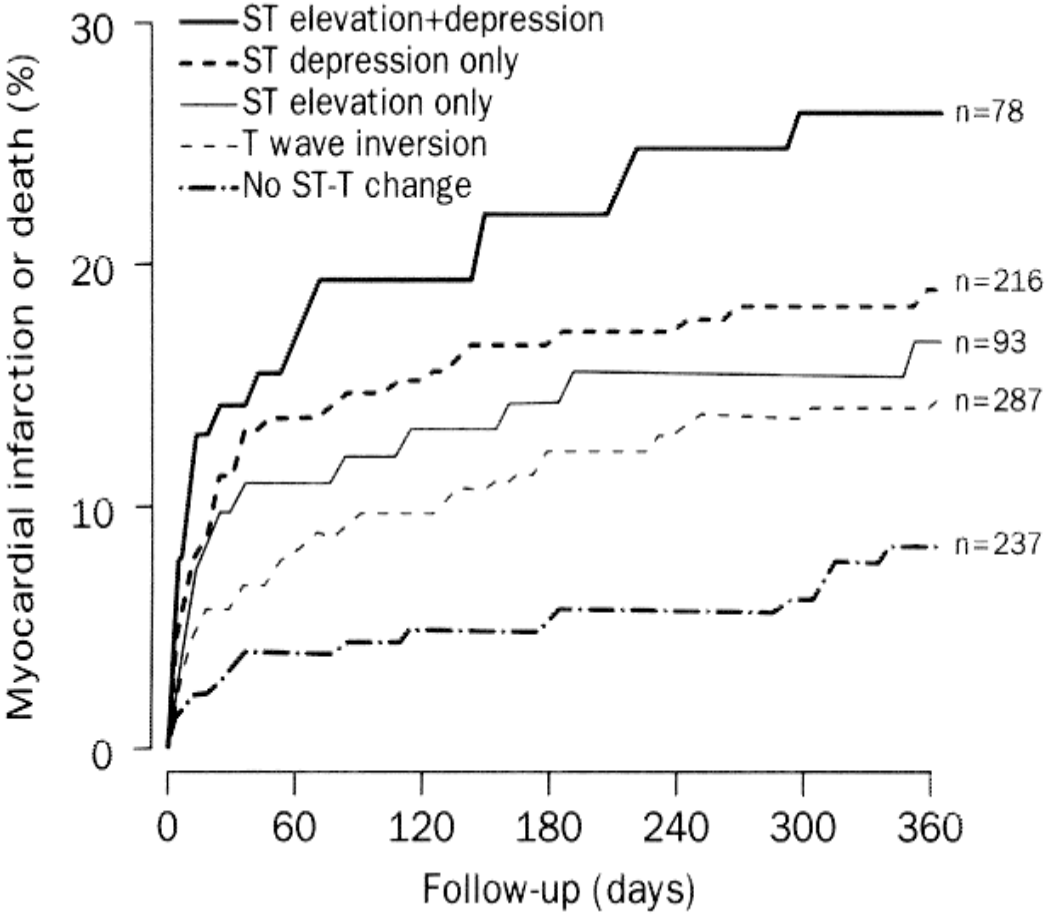
Evaluation scheme for chest pain (ECG, biomarkers)



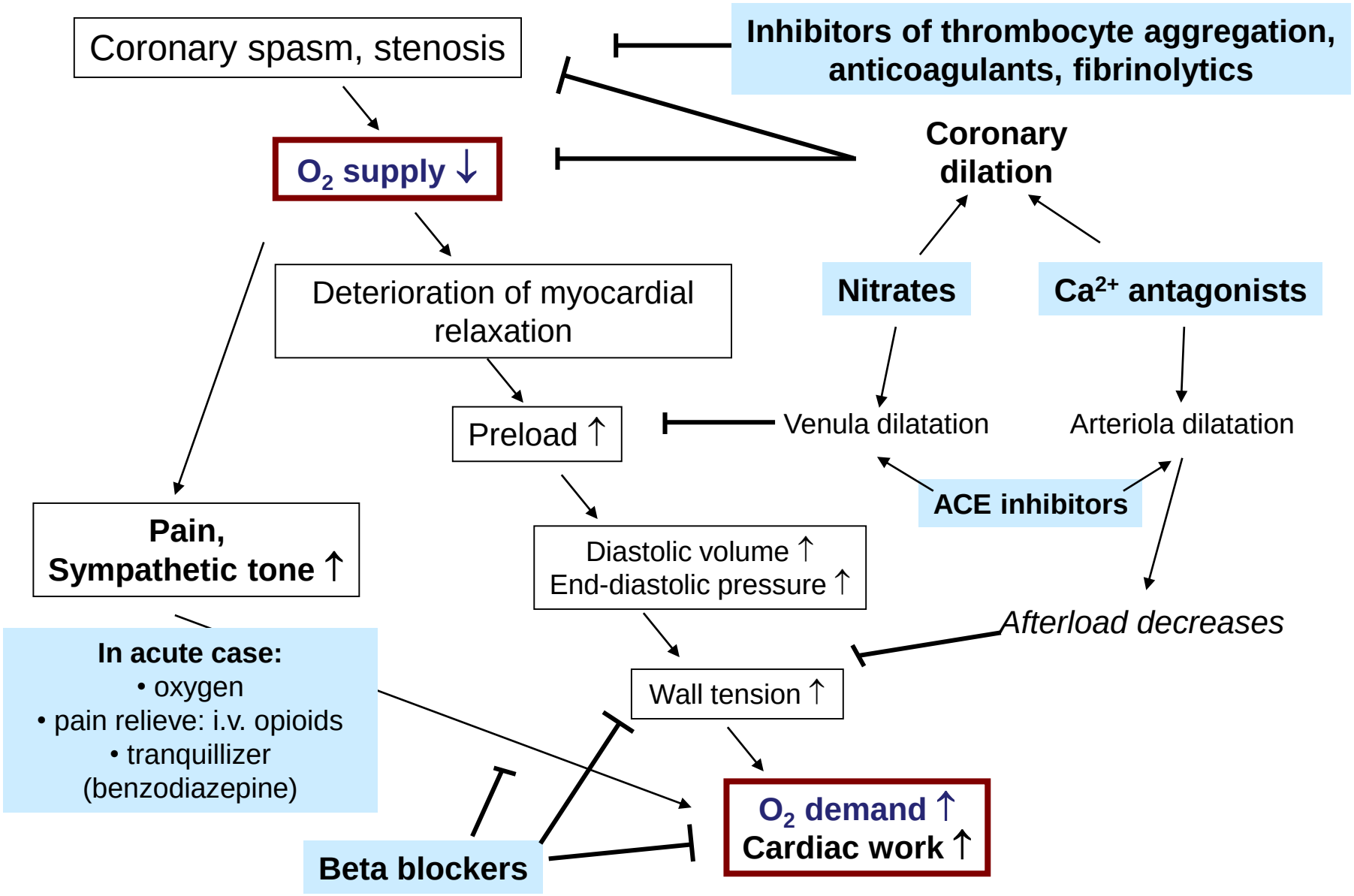
ST-T alteration are strong prognostic markers for myocardial infarction or death within 1 year in patient with suspected acute coronary syndrome

The Risk study Group, Nyman et al.:J Intern Med 234: 293, 1993

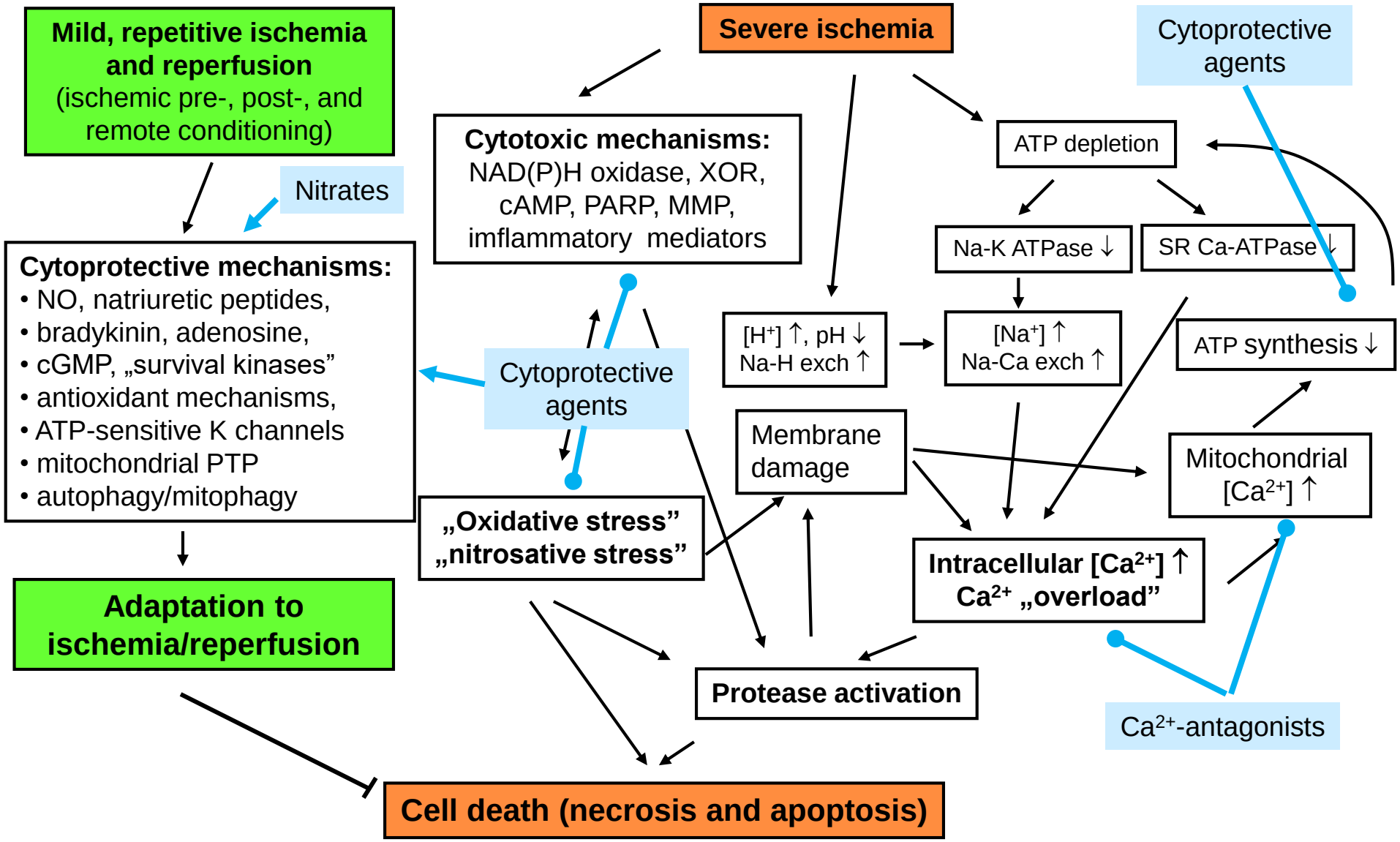
- In patients with unstable angina but without evidence of acute MI, the ST-segment depression is the most predictive for future adverse cardiac outcome
- Isolated T-wave inversion or normal ECG at presentation carries good prognosis.



Pathophysiology of ischemic heart disease: drug targets



Cellular mechanism of myocardial ischemia: potential targets for cardioprotective drugs



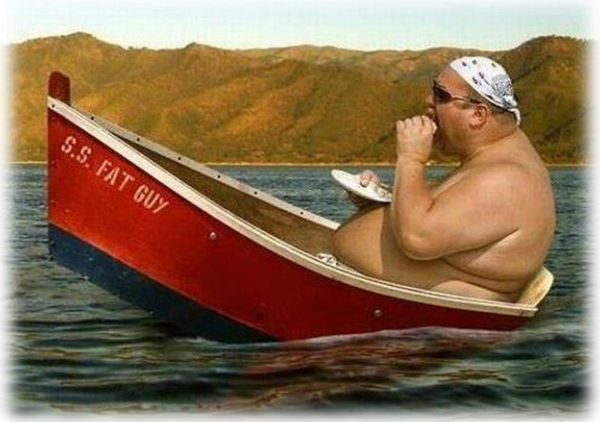
Treatment of ischemic heart disease

Aim:

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

Treatment sequence:

1. lifestyle change, diet (e.g. trans fat), elimination and treatment of risk factors (**smoking, hypertension, diabetes, hyperlipidemia, obesity, depression**)



2. drug therapy (baseline + symptomatic)

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

- **p**ercutaneous **c**oronary **i**ntervention (PCI): coronary dilation, stent implantation *(supplemented with mechanical post- and/or remote conditioning)*
- revascularisation surgery (bypass)
- immediate intravenous thrombolysis

Drug treatment of stabile coronary heart disease

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(life-long to prevent cardiovascular events and death)

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(anti-anginal treatment)

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(aspirin and/or P2Y12 blocker)

Antihyperlipidemic treatment
(statins, ezetimibe, PCSK-9 inhibitors)

ACE inhibitor or
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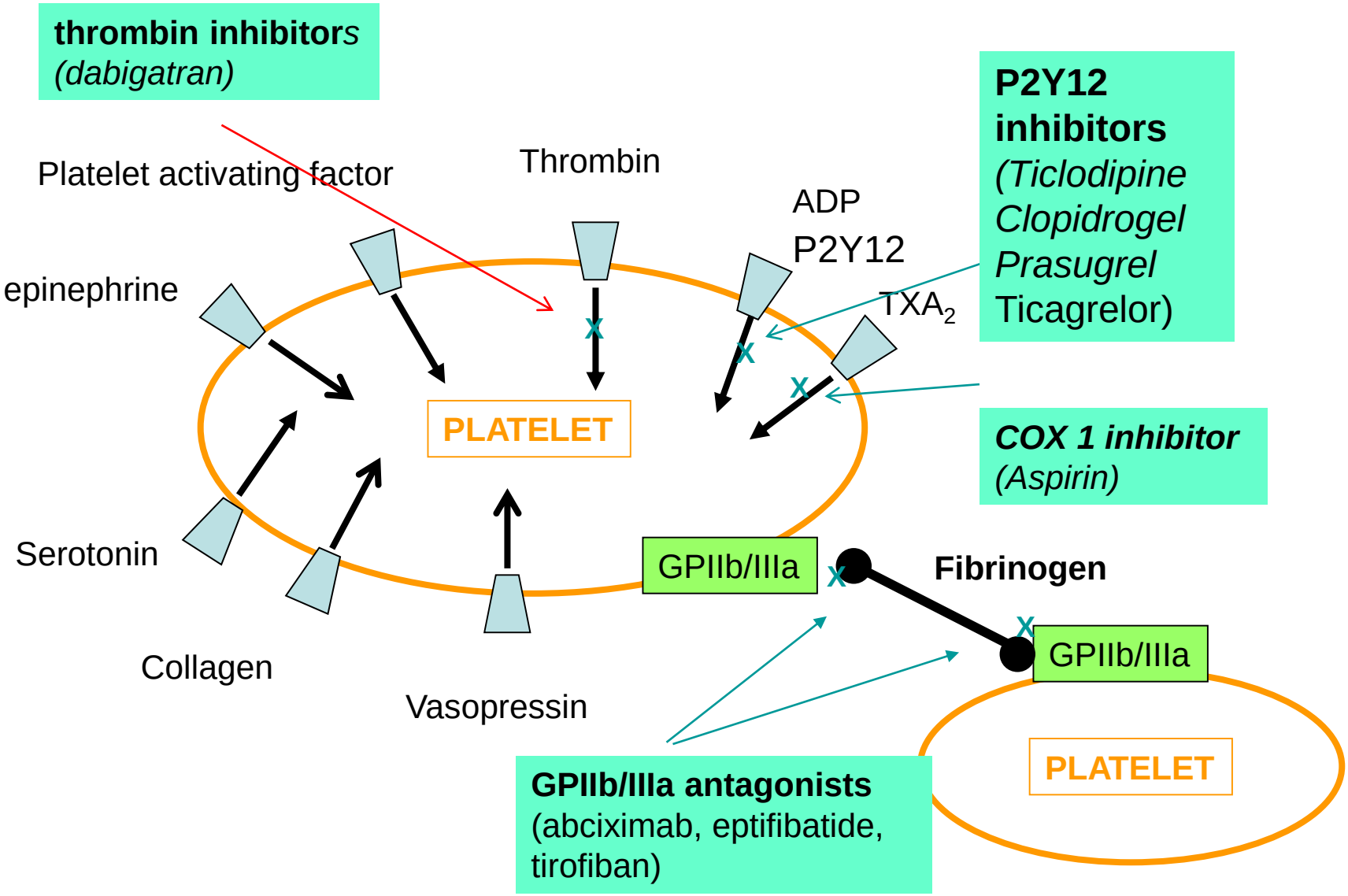
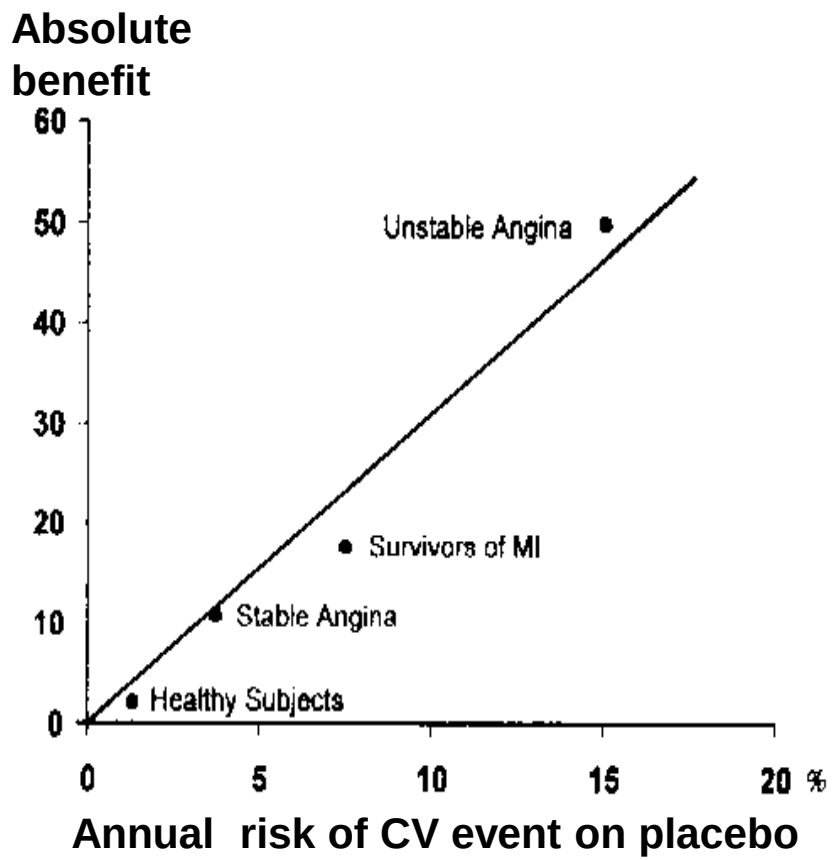
Antiplatelet drugs (inhibitors of thrombocyte aggregation)



Antiplatelet treatment with aspirin

- Aspirin is one of the most effective agents for the prevention of cardiovascular (CV) diseases (angina, MI, transient ischemic attacks, stroke)
- **Inhibits irreversibly the activity of COX1** enzyme
- **Optimal dosing for CV prevention: 75-350 mg/d**, higher doses do not augment effectivity
- **Many patients use incorrectly other NSAIDs**, for the prevention of cardiovascular events
- *Cox2 inhibitors do not have antiplatelet effect (e.g. diclophenac)*
- *Acetaminophen (paracetamol) does not possess antiplatelet activity*



Subjects in whom a vascular event is prevented by aspirin per 1000 treated patients

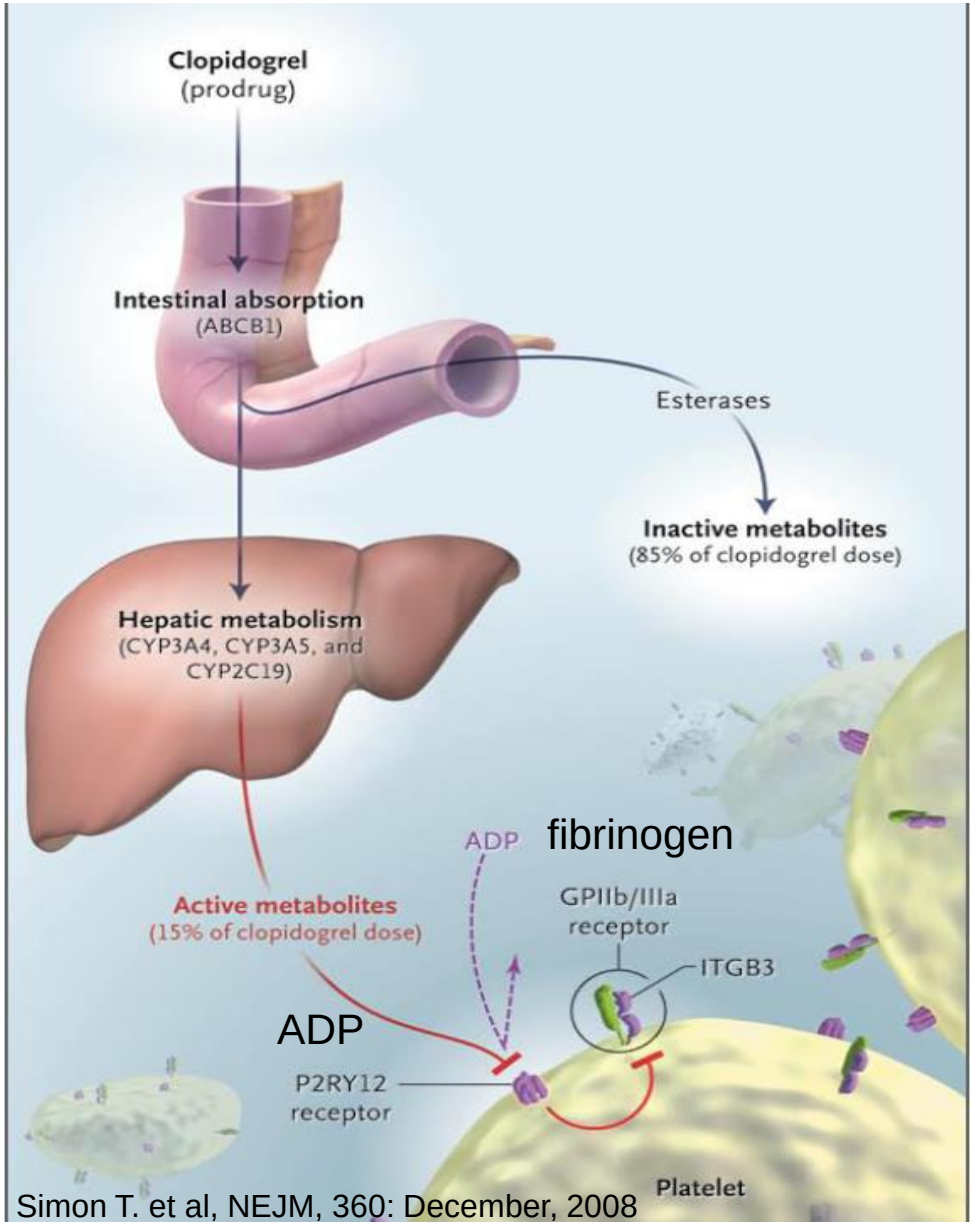
Patrono et al: Chest, 114S, 1998 (5th ACCP Consc Conf Antithrobic Th)

The effect of preventive aspirin treatment on cardiovascular (CV) events

	Aspirin CV events % (No of cases)	Placebo CV events % (No of cases)	Odds reduction %	
High risk	**11.4 (36536)**	**14,7 (36711)**	**27**	
Low risk	**4,46 (14608)**	**4,85 (14604)**	**10**	
All studies	**9,5 (51144)**	**11.9 (51315)**	**25**	**P< 0,00001**

- **Meta analysis:** aspirin (75-325 mg/d) vs placebo
- **Serious CV events:** MI, stroke, CV death
- **High risk:** previous MI, acute MI, previous stroke or transient ischemic event, other high risk (angina, etc.)
- **Low risk:** primary prevention

Clopidrogel: absorption and metabolism



Simon T. et al, NEJM, 360: December, 2008

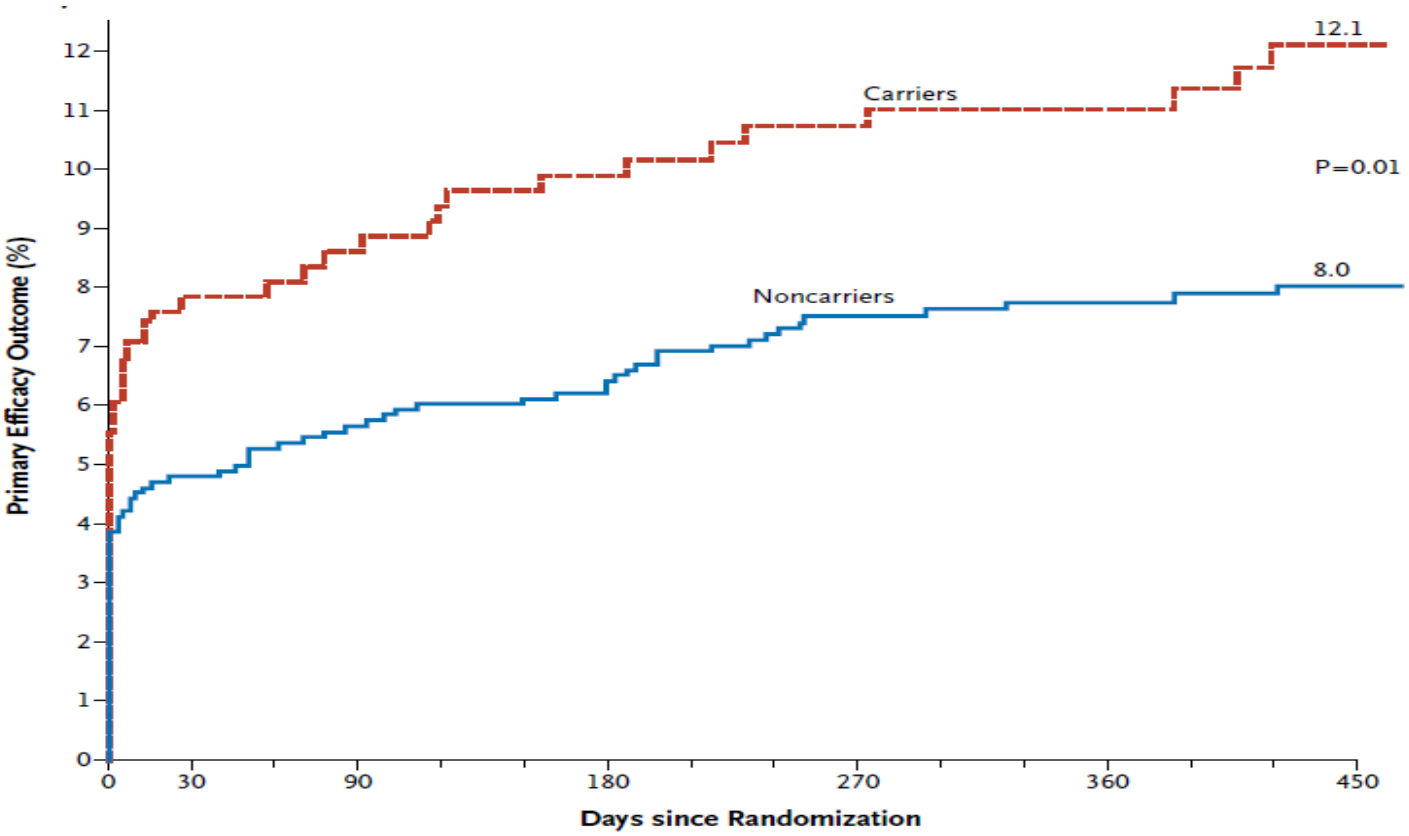
- Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying ***CYP2C19 loss-of-function alleles had a higher rate of subsequent*** **cardiovascular events** than those who were not.

- Proton pump inhibitors might decrease the activitiy of clopidrogel

Clopidrogel: individual metabolic and functional differences (CYP2C19 reduced function allele carriers – non-carriers)

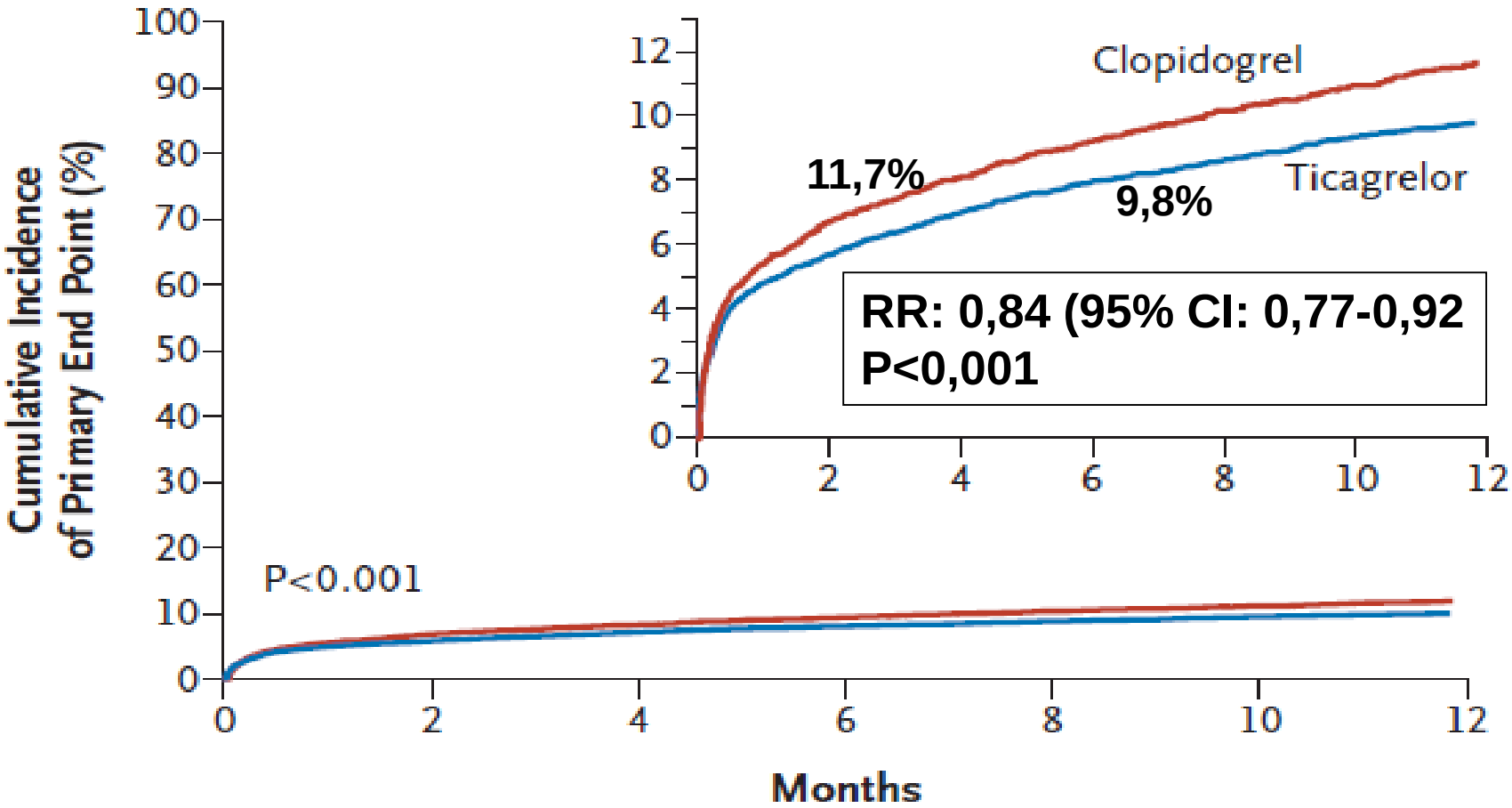
Mega LJ, NEJM 10.1056/nejmoa0809171

A composite of death from cardiovascular causes, myocardial infarction, or stroke (%)



Ticagrelor vs clopidrogel

Wallentin et al, 10.1056/NEJM. Moa09044327 361, 2009

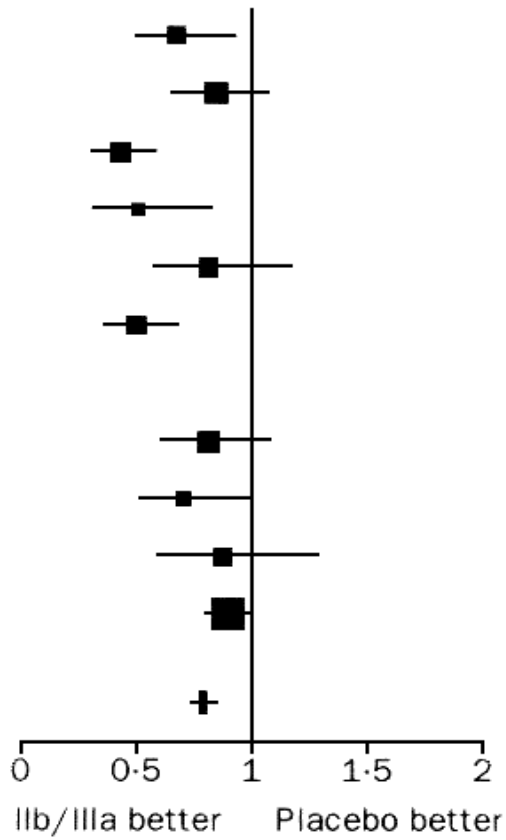


- Composite endpoint: Cardiovascular mortality, MI, stroke
- T: 180 mg/d starting dose, 2x90 mg/d; Clopidrogel: 300-600 mg starting dose, 75 mg/d

The effect of platelet GPIIb/IIIa receptor antagonist

Topol et al.: Lancet, 353:227, 1999

Trial	Agent	No	Placebo (%)	IIb/IIIa (%)	OR (95% CI)
Percutaneous coronary intervention trials					
EPIC	Abciximab	2099	10·1	7·0	
IMPACT-II	Eptifibatide	4010	8·4	7·1	
EPILOG	Abciximab	2792	9·1	4·0	
CAPTURE	Abciximab	1265	9·0	4·8	
RESTORE	Tirofiban	2139	6·3	5·1	
EPISTENT	Abciximab	2399	10·2	5·2	
Unstable angina/non-Q-wave MI trials					
PRISM	Tirofiban	3231	7·0	5·7	
PRISM Plus	Tirofiban	1570	11·9	8·7	
PARAGON	Lamifiban	2282	11·7	11·3	
PURSUIT	Eptifibatide	10 948	15·7	14·2	
Overall		**32 735**	**11·1**	**9·0**	



Aspirin or aspirin + heparin background therapy
Overall RR: 0,79 (0,73-0,85)
Bleeding is not significant if heparin therapy is correctly administered

Death or non-lethal MI < 30 days

Drug treatment of stabile coronary heart disease

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

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Ranolazine
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Ivabradine

Prevention of atherosclerosis, antihiperlipidemic drugs

1. Lifestyle changes: regular training

- increased HDL
- amelioration of endothelial dysfunction

2. Diet:

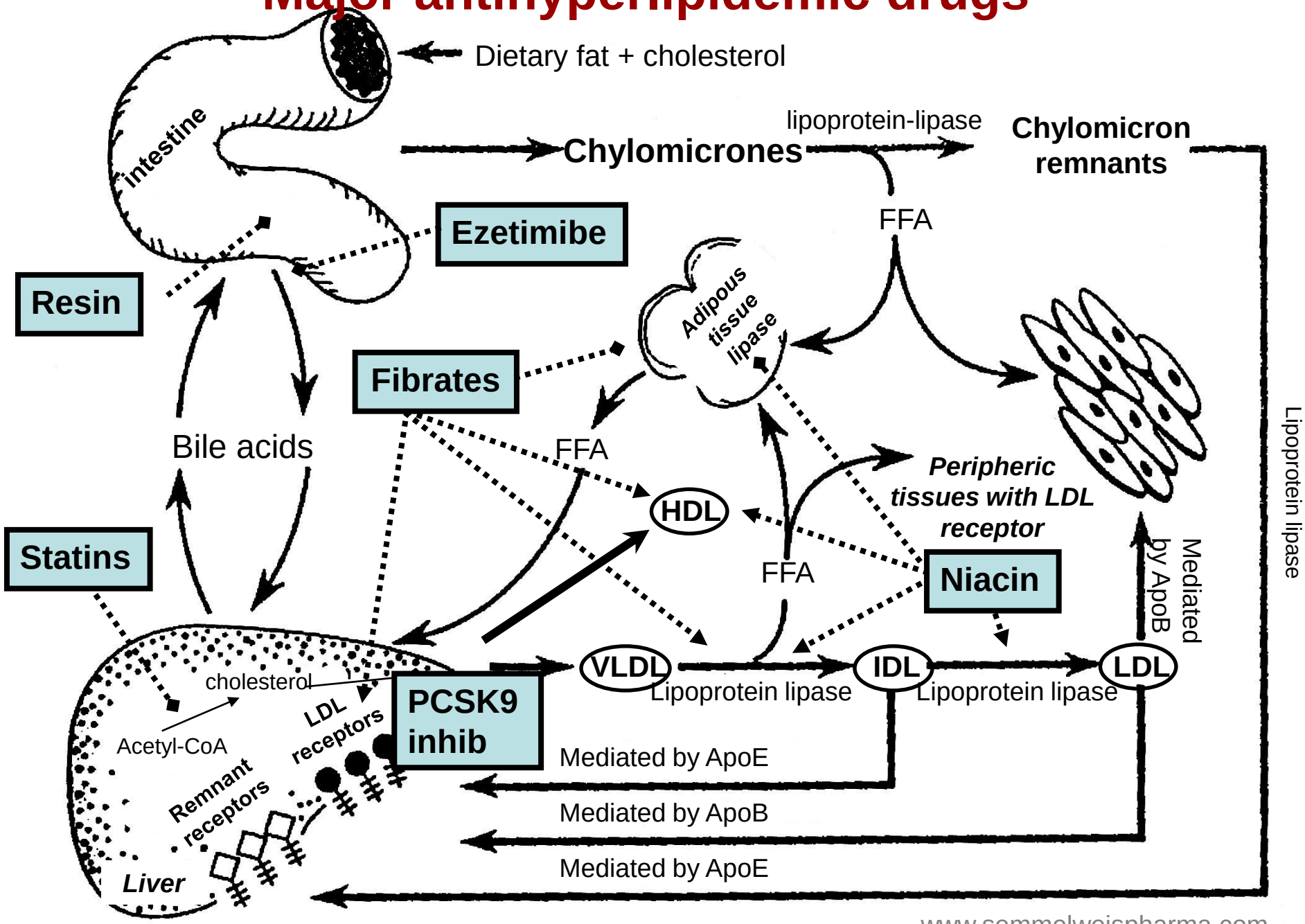
- low saturated fatty acids, low trans fatty acids
- Fish oil (omega-3 fatty acids): decrease triglyceride level
  (omega-3 fatty acids are not effective in preventing further heart and stroke in patients who have had a heart attack)
- Moderate consumption of alcohol: increased HDL level (but also increased triglycerid 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



SCORE - Cardiovascular risk stratification

SCORE

15% and over	
10% - 14%	
5% - 9%	
3% - 4%	
2%	
1%	
< 1%	

10-year risk of fatal CVD in populations at **high CVD risk**

Age	Women										Men									
	Non-smoker					Smoker					Non-smoker					Smoker				
Systolic blood pressure (mmHg)	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8	4	5	6	7	8
65																				
180	7	8	9	10	12	13	15	17	19	22	14	16	19	22	26	26	30	35	41	47
160	5	5	6	7	8	9	10	12	13	16	9	11	13	15	16	18	21	25	29	34
140	3	3	4	5	6	6	7	8	9	11	6	8	9	11	13	13	15	17	20	24
120	2	2	3	3	4	4	5	5	6	7	4	5	6	7	9	9	10	12	14	17
60																				
180	4	4	5	6	7	8	9	10	11	13	9	11	13	15	18	18	21	24	28	33
160	3	3	3	4	5	5	6	7	8	9	6	7	9	10	12	12	14	17	20	24
140	2	2	2	3	3	3	4	5	5	6	4	5	6	7	9	8	10	12	14	17
120	1	1	2	2	2	2	3	3	4	4	3	3	4	5	6	6	7	8	10	12
55																				
180	2	2	3	3	4	4	5	5	6	7	6	7	8	10	12	12	13	16	19	22
160	1	2	2	2	3	3	3	4	4	5	4	5	6	7	8	8	9	11	13	16
140	1	1	1	1	2	2	2	2	3	3	3	3	4	5	6	5	6	8	9	11
120	1	1	1	1	1	1	1	2	2	2	2	2	3	3	4	4	4	5	6	8
50																				
180	1	1	1	2	2	2	2	3	3	4	4	4	5	6	7	7	8	10	12	14
160	1	1	1	1	1	1	2	2	2	3	2	3	3	4	5	5	6	7	8	10
140	0	1	1	1	1	1	1	1	1	2	2	2	2	3	3	3	4	5	6	7
120	0	0	1	1	1	1	1	1	1	1	1	1	2	2	2	2	3	3	4	5
40																				
180	0	0	0	0	0	0	0	0	1	1	1	1	1	2	2	2	2	3	3	4
160	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	2	2	2	3
140	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2
120	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1

Cholesterol (mmol/L)

150 200 250 300
mg/dL

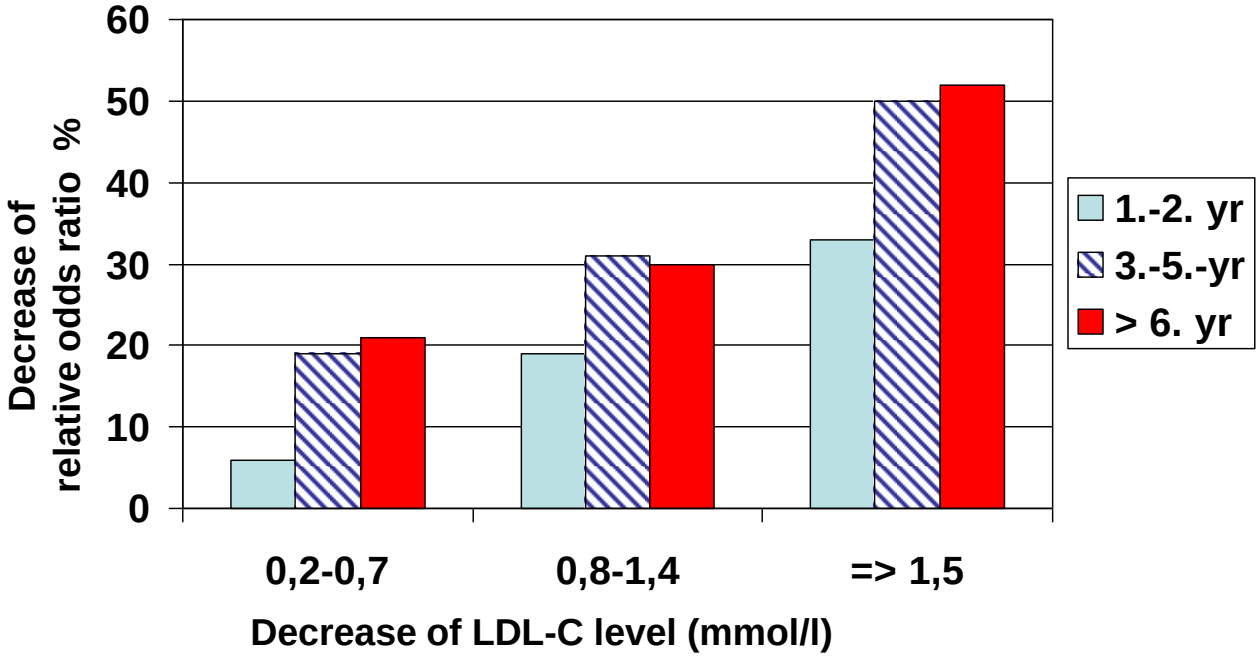
Treatment strategy of hyperlipidemia is based on estimated cardiovascular risk

- High risk - intensive statin treatment (if necessary combined with ezetimibe)
- Hypertiglyceridemia – fibrates (mostly fenofibrate)
- Mixed hyperlipidemia – statin + fibrate

Risk factor lowering in the therapy of ischemic heart disease

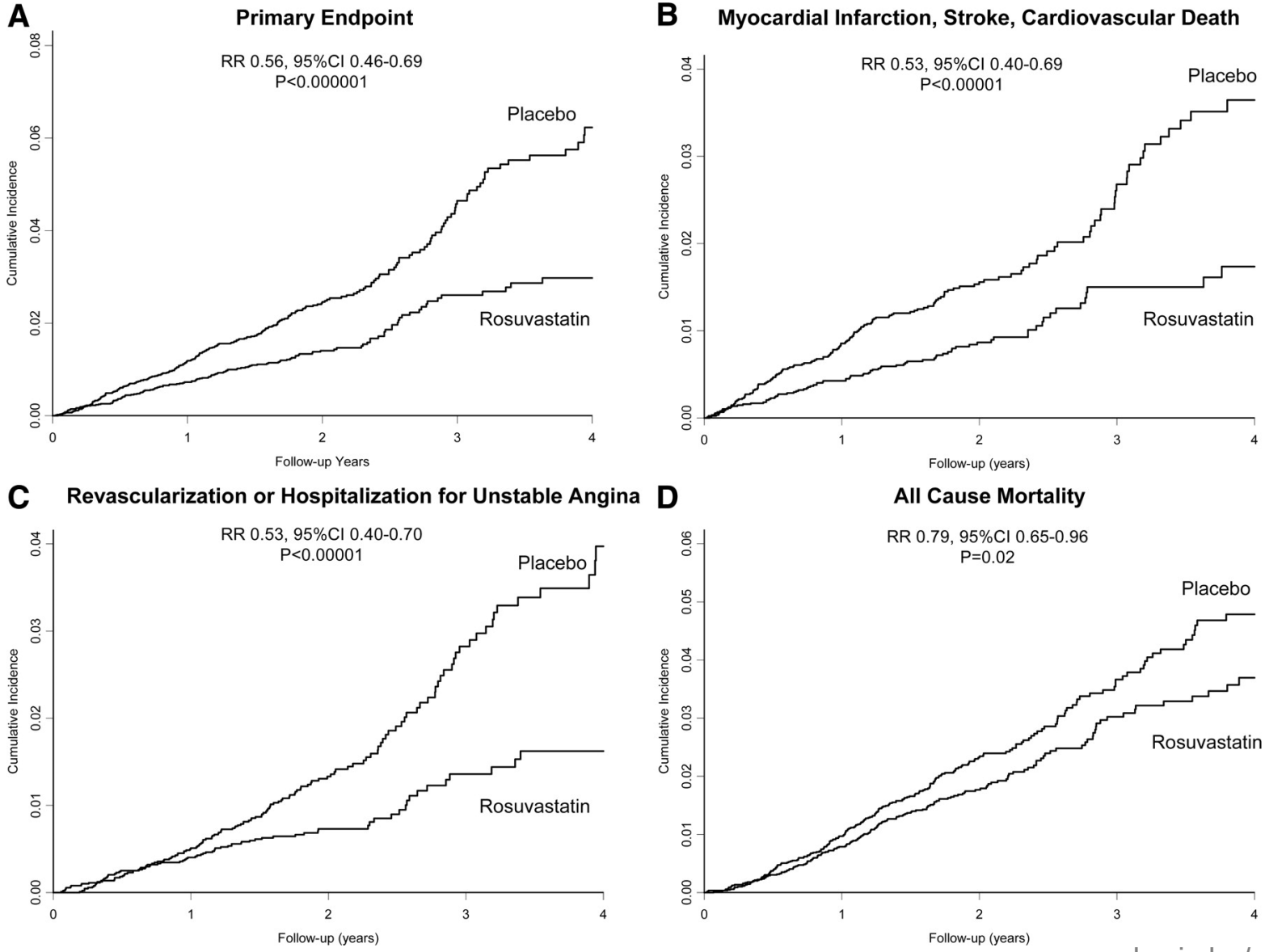
- The decrease of the odds ratio of ischemic cardiac events in relation to LDL-cholesterol lowering therapy

Law MR et al. BMJ. 3261423. 2003



- Quit smoking
- Dibetes mellitus,
- blood pressure lowering
- weight reducion
- depression

Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER): Rationale and Prespecified Analyses



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)

IMPROVE-IT: 'Modest' Benefit When Adding Ezetimibe to Statins in Post-ACS Patients

Primary End Point and Individual Components (7-Year Event Rates)

Clinical Outcomes	Simvastatin, n=9077 (%)	Ezetimibe/Simvastatin, n=9067 (%)	*P*
Primary end point (Cardiovascular death, MI, unstable angina, coronary revascularization, or stroke)	34.7	32.7	0.016
All-cause death	15.3	15.4	0.782
MI	14.8	13.1	0.002
Stroke	4.8	4.2	0.052
Ischemic stroke	4.1	3.4	0.008
Unstable angina	1.9	2.1	0.618
Coronary revascularization	23.4	21.8	0.107

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Ramipril vs. Placebo - HOPE trial

HOPE trial: NEJM 342: 145, 2000

- **Composite endpoint – death, myocardial infarction, stroke**
- **High risk patiens were involved**
- **Ramipril: 10 mg/d (2,5; 5; 10)**

Relative risk:

Composite.ep.:0,78 (0,70-0,86) p< 0,001

Card-vasc. death: 0,75 (0,64-0,87) p< 0,001

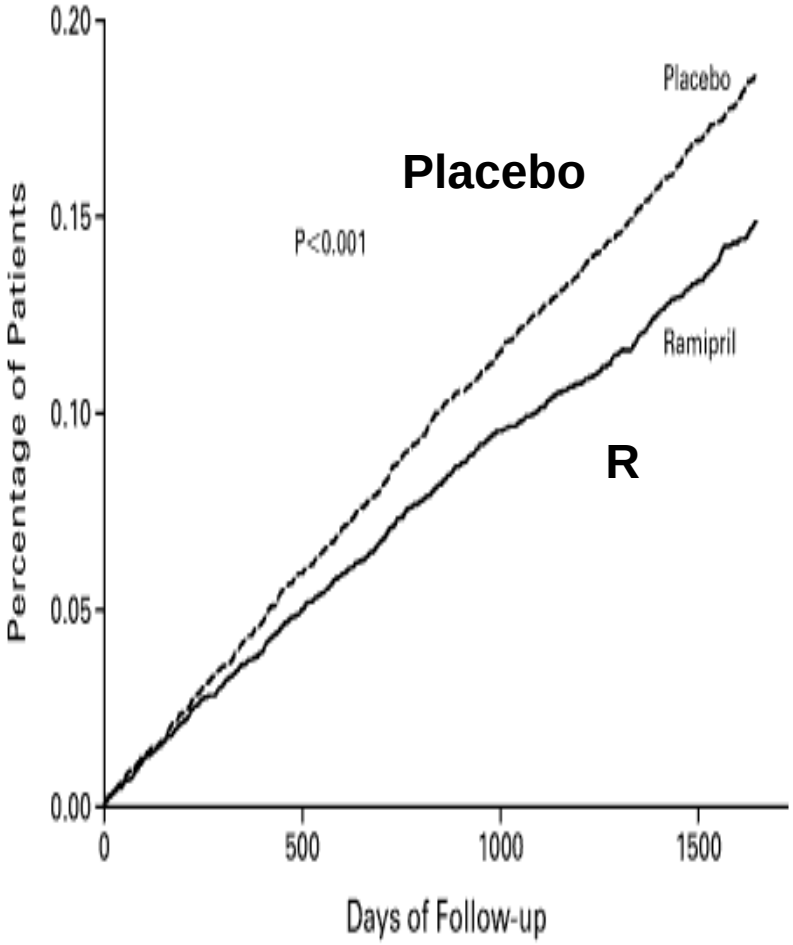
MI: 0,80 (0,71-0,91) p< 0,001

Stroke: 0,69 (0,56-0,84) p< 0,001

Overall.: 0,84 (0,75-0,95) p< 0,001

New diab. m.: 0,68 (0,53-0,87) p< 0,03

Composite end-points



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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

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Ca-channel blocker (CCB) treatments vs. placebo

Blood Pressure Lowering Treatment Trialsit' Collaboration, Lancet, 356:1955, 2000

Patiens: 2815 / 2705 Endpoint	Event % CCB / placebo	Relative Risk RR (95% CI)	P
Stroke	1,9 / 3,1	0,61 (0,44-0,85)	S
Coronary disease	2,8 / 3,5	0,79 (0,59-1,06)	S
Heart failure	1,5 / 2,1	0,72 (0,48-1,07)	S
Major CV event	5,9 / 8,2	0,72 (0,59-0,87)	S
CV death	2,3 / 3,3	0,72 (0,52-0,98)	S
Overall mortality	5,0 / 5,7	0,87 (0,70-1,09)	NS

Short acting dihydropiridins – avoid – mortality increases

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Trimetazidine (metabolic modulator)

Shift cardiac metabolism from fatty acid oxidation to glucose oxidation (increases the efficacy of energy metabolism, more ATP/oxygen consumed)

- effects on the energy metabolism of the myocardial cells „direct cytoprotective" no hemodynamic effect
- Kinetics: fast oral absorption (max. blood level in 2 h), excretion in the kidneys (half lifetime 4-5 h)
- Dosage: 60 mg/day (in 3 dosing)

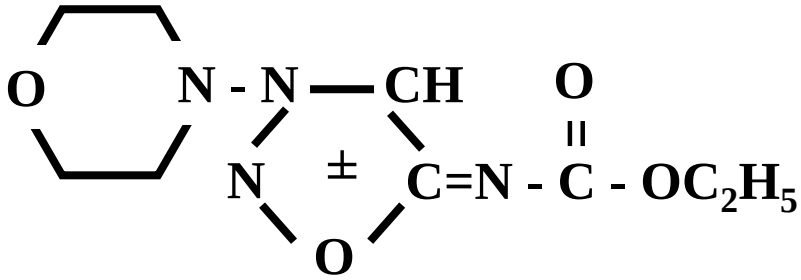
Delays uncoupling of mitochondrial respiratory chain

- Inhibits the production of reactive free radicals
- maintaines ATP production

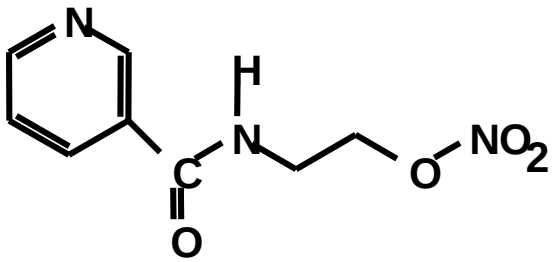
Delays the onset of anaerob glycolysis

- Decrease intracellular acidosis

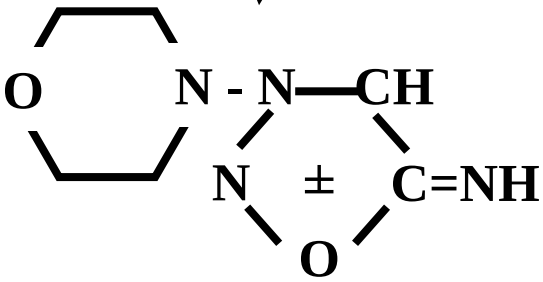
New antianginal agents with structure similar to nitrates



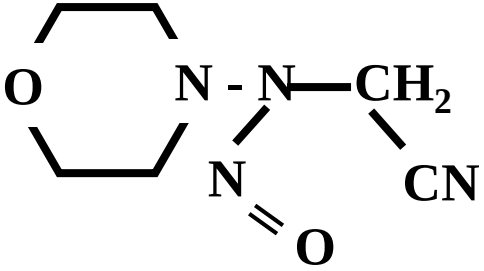
molsidomine



Nicorandil



SIN-1

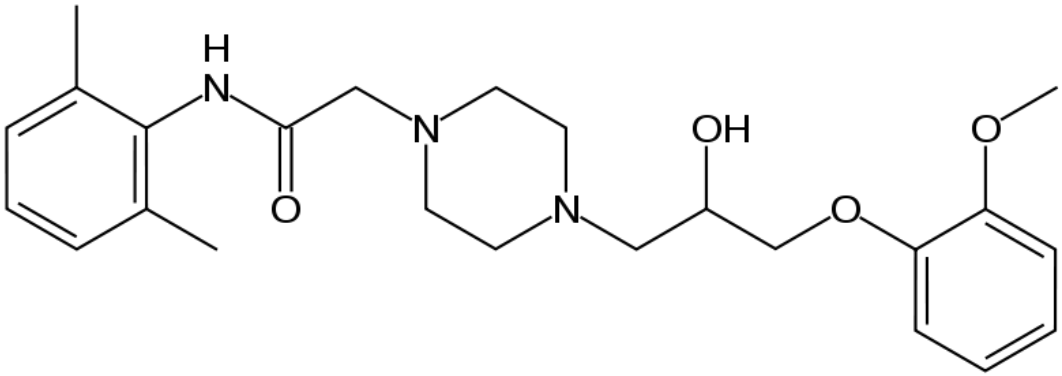


SIN-2

NO

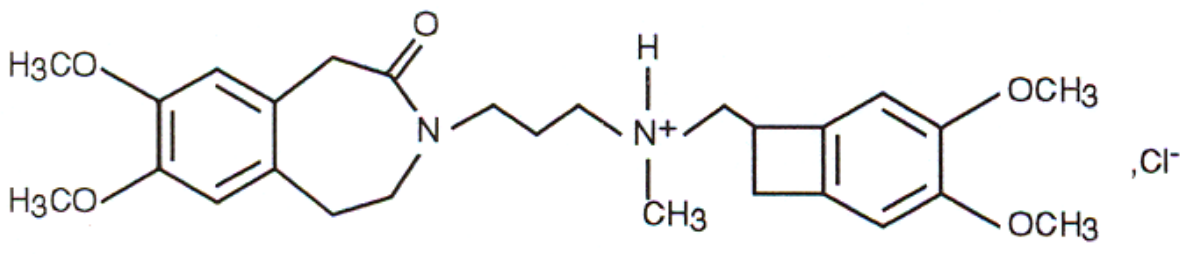
Inhalation of NO gas: only to treat pulmonary hypertension

Ranolazine



- Inhibitor of the late sodium channel in the myocardial cells - decreases intracellular Na, thereby activating Na/Ca transporter – thereby decreasing intracellular Ca overload
- Decreases fatty acid oxidation of the myocardium
- Decreases cardiac work, cytoprotectivee

Ivabradin



- New mechanism of the action: causes bradycardia by decreasing the activity of sinus node reducing the „pacemaker” I_f current
- Decreases heart rate without modifying the electric conduction parameters and contractile force
- Two large randomized double-blind study proves that its efficacy is similar to that of beta-blockers or calcium antagonists
- indication: stabile effort angina (new: heart failure)
- contraindication: sick sinus syndrome

Indication of major drugs in stable ischemic heart disease

Table 15. Indications for Individual Drug Classes in the Treatment of Hypertension in Patients With SIHD*

	Recommended Drugs					
Indication	Diuretic	Beta Blocker	ACE Inhibitor	ARB	Calcium-Channel Blocker	Aldosterone Antagonist
Heart failure	●	●	●	●		●
LV dysfunction			●	●		
After myocardial infarction		●	●	●		●
Angina		●			●	
Diabetes mellitus		●	●	●		
Chronic kidney disease			●	●		

*Table indicates drugs that should be considered and does not indicate that all drugs should necessarily be prescribed in an individual patient (eg, ACE inhibitors and ARB typically are not prescribed together).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; and LV, left ventricular.

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

New trends in the treatment of ischemic heart disease I.:

Vitamins, and vitamin-like substances

• Omega-3 fatty acids, eicosapentaenic acid (EPA), docosahexaenic acid (DHA) ⟶ decrease serum triglyceride and the formation of atherosclerotic plaques

• Coenzyme Q_{10} (ubiquinon) ⇨ antioxidant, ATP production (in heart failue)

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

„Advanced therapy medicial products (gene, cell and tissue therapy)

• Transfer of genes encoding the synthesis of cytoprotective substances (e.g. adrenomedullin, NO synthase)

• Regenerative therapy:

- stem cell implantation (mesenchymal, embryonal)
- engineered heart tissue transplantation
- skeletal myoblast implantation

Stimulators of ischemic stress adaptation to decrease infarct size

- under development, there are still no drugs on the market that can reduce infarct size (so far disappointing clinical trials)