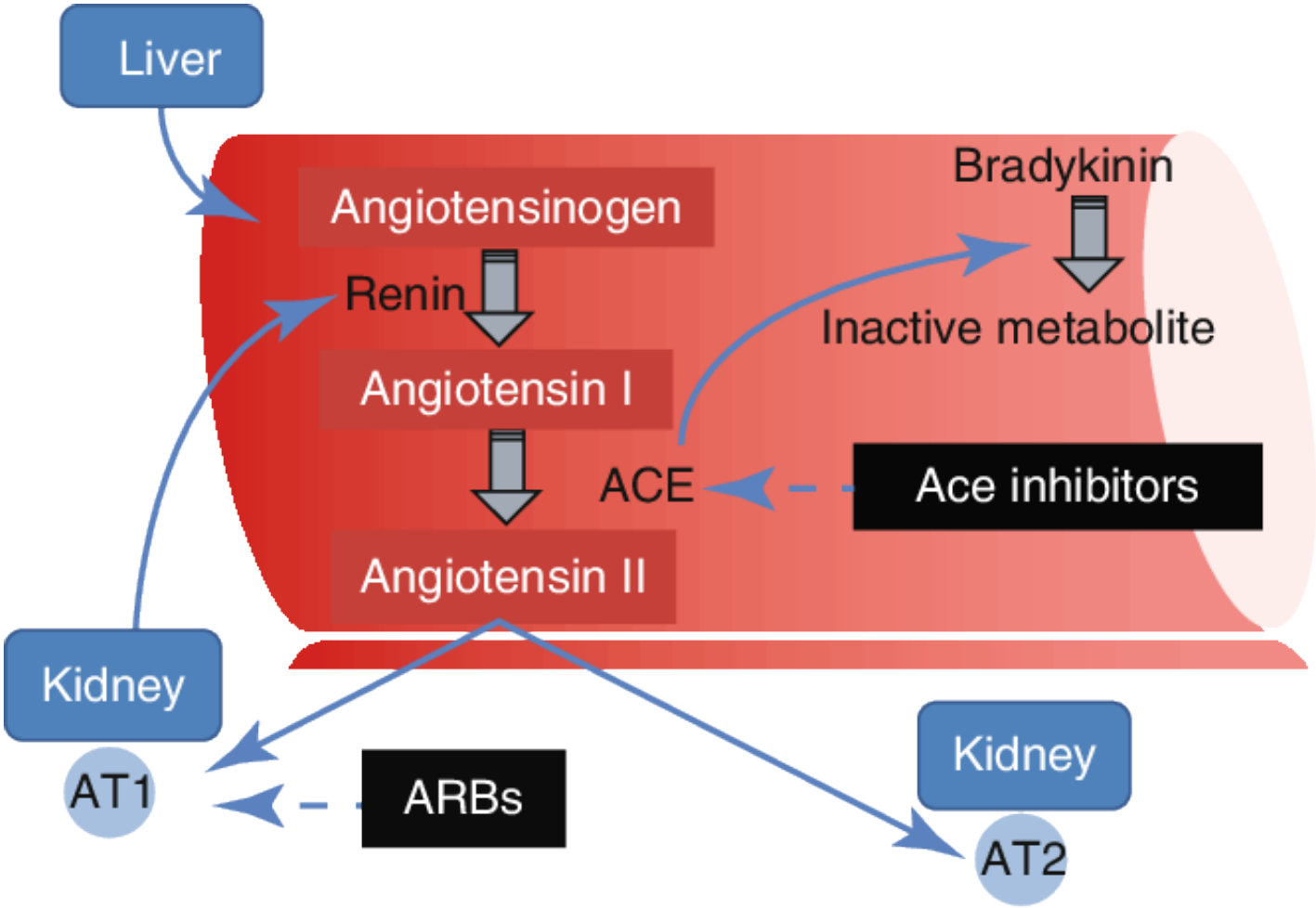
Cardiovascular Pharmacotherapy

Overview

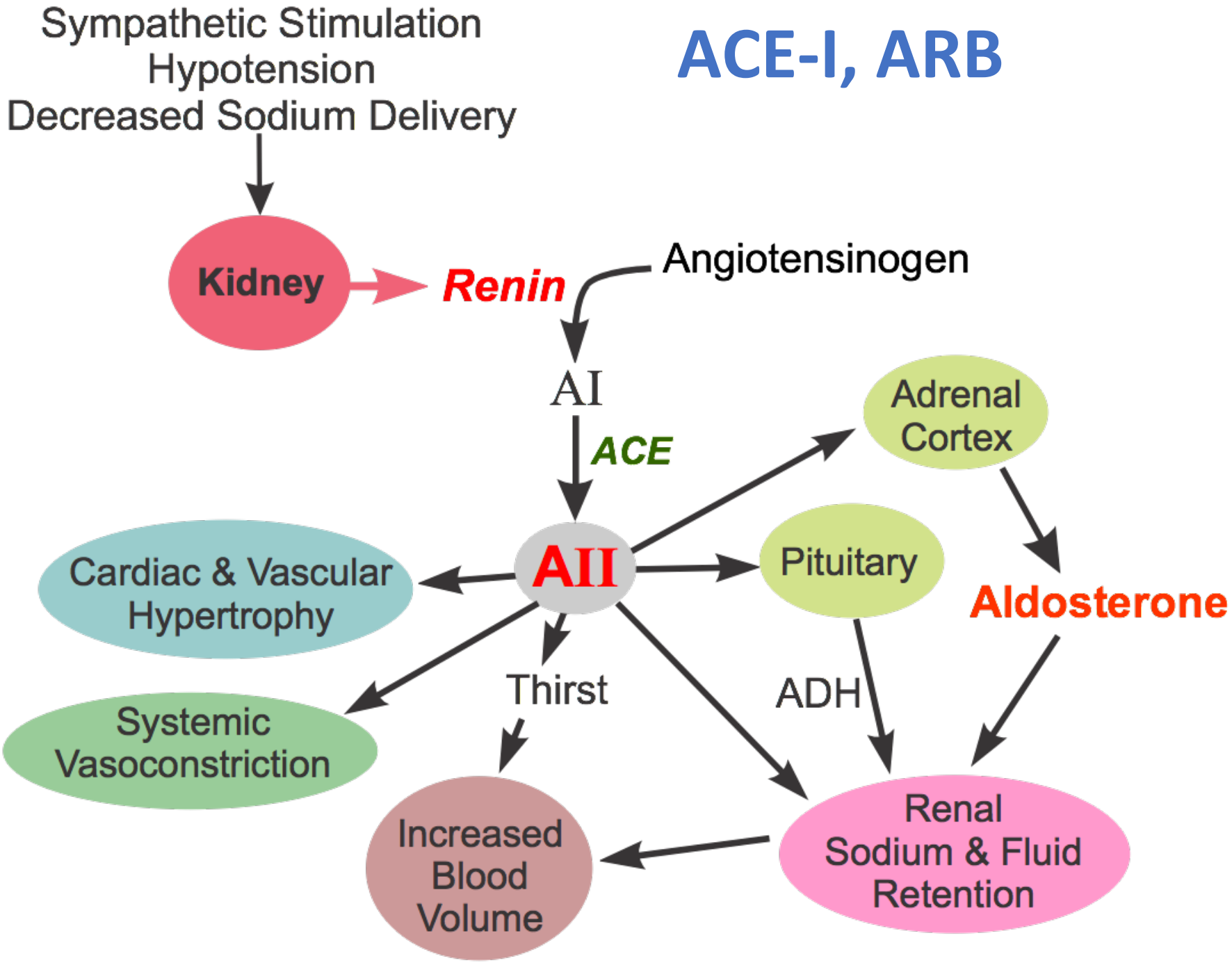
Mechanism of cardiovascular drugs

Indications and clinical use in cardiology

Renin-Angiotensin Inhibitors: Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers



ACE-I, ARB


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
Cardiac & Vascular Hypertrophy
AII
Pituitary
Aldosterone
Thirst
ADH
Systemic Vasoconstriction
Increased Blood Volume
Renal Sodium & Fluid Retention

Cardiorenal Effects of ACE Inhibitors

- Vasodilation (arterial & venous)
  - reduce arterial & venous pressure
  - reduce ventricular afterload & preload
- Decrease blood volume
  - natriuretic
  - diuretic
- Depress sympathetic activity
- Inhibit cardiac and vascular hypertrophy

ACE-I, ARB

Therapeutic Use:

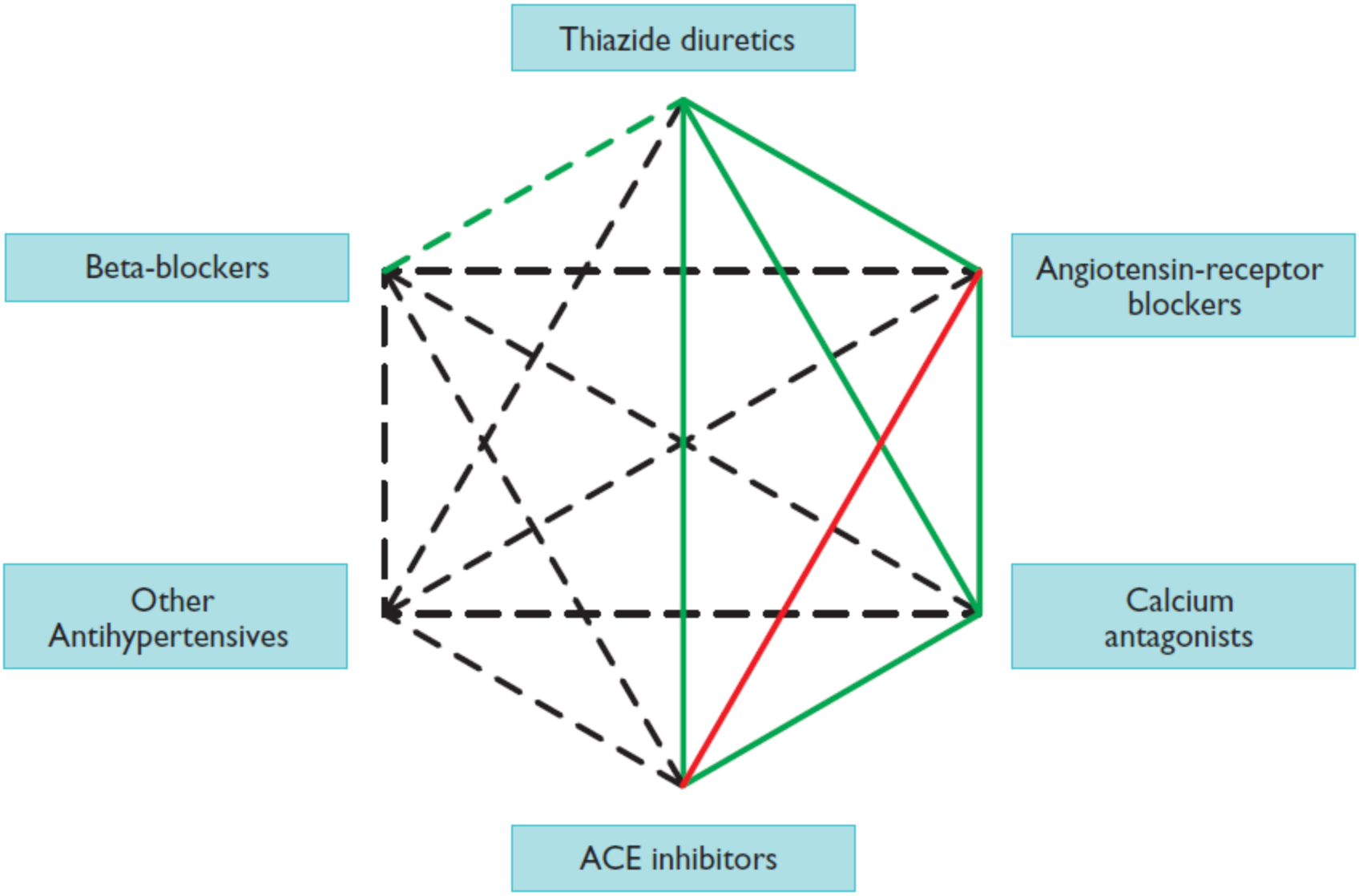
- Hypertension
- Heart failure
- Post-myocardial infarction

ACE-I, ARB → Hypertension

- RAS inhibitors are among the best tolerated of the antihypertensive drugs
- Reduce CV events and preventing deterioration of renal function in high-risk hypertensive patients
- “Dual RAS blockade”—either with an ACEI plus an ARB—is now contraindicated due to hypotension, acute kidney injury (AKI), and hyperkalemia
- As monotherapy, ACEIs are generally less effective in lowering BP in black patients and in older patients with low-renin hypertension, but they are quite effective in these groups when combined with a CCB or low-dose diuretic

ACE-I, ARB

- ARBs confer the same benefits as ACEIs in treating hypertension while avoiding the ACEI-related cough and angioedema
- ACEIs and ARBs have become standard first-line antihypertensive therapy for patients with diabetic and nondiabetic CKD, but evidence indicates that RAS inhibitors provide superior renal protection than do other antihypertensive agents, mainly for nondiabetic proteinuric CKD


Thiazide diuretics
Beta-blockers
Angiotensin-receptor blockers
Other Antihypertensives
Calcium antagonists
ACE inhibitors

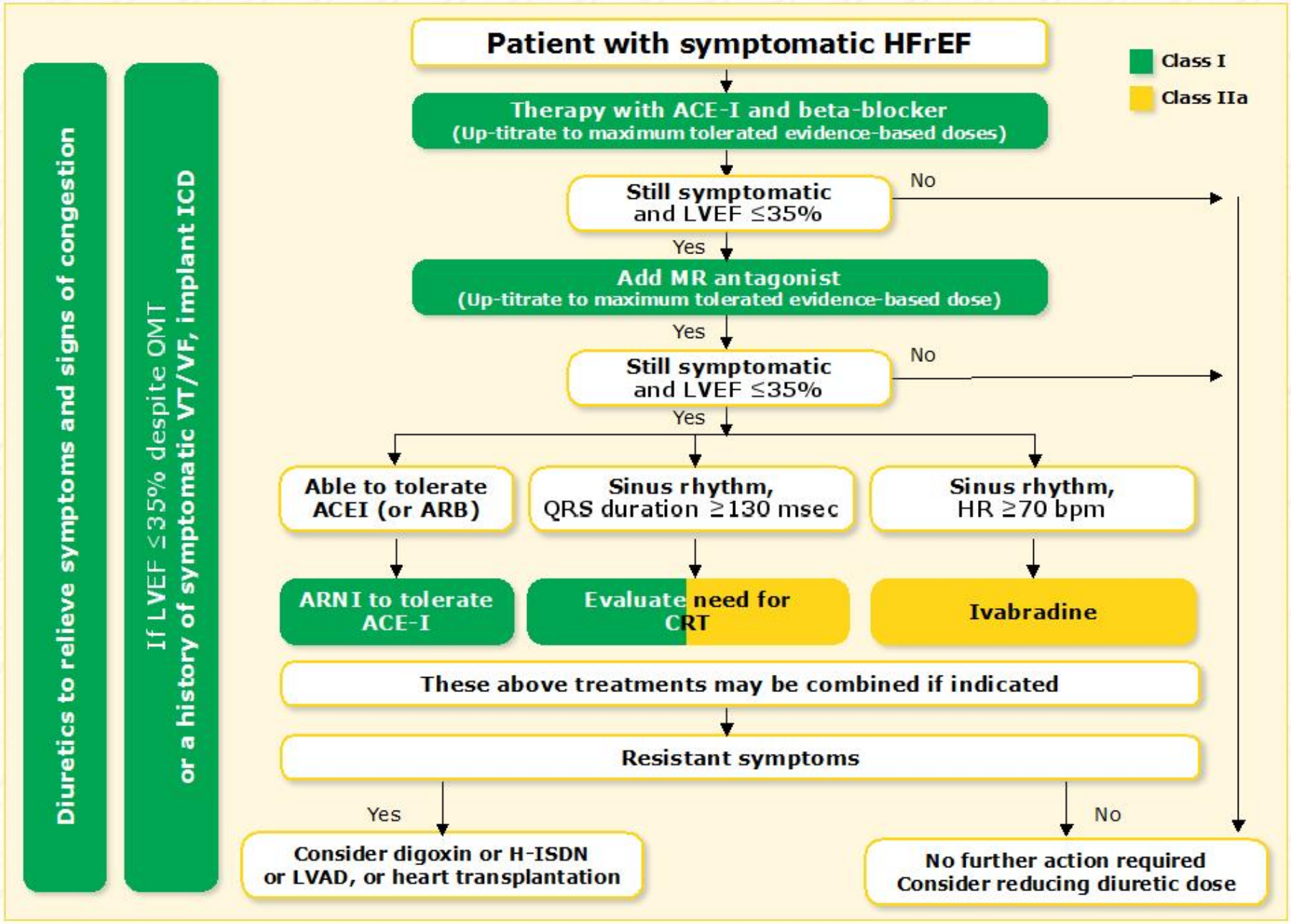
ACE-I, ARB → Heart failure

There is overwhelming evidence that ACEIs should be used in symptomatic and asymptomatic patients with a reduced EF (<40%). ACEIs stabilize LV remodeling, improve patient symptoms, prevent hospitalization, and prolong life.

Evidence-based doses of disease-modifying drugs in key randomized trials in HF with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 *o.d.*	10 *o.d.*
Trandolapril	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If -channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction



Side effects

dry cough (ACE-I)

angioedema (ACE-I)

hyperkalemia

ACEIs and ARBs can provoke hyperkalemia in the setting of CKD

fetal renal agenesis and other birth defects (contraindicated in pregnancy)

Contrindication ACE inhibitors

- Pregnancy
- History of angioedema
- Bilateral renal artery stenosis
- Known allergic reaction/other adverse reaction (drug-specific)

Cautions/seek specialist advice:

1. Significant hyperkalemia (K+>5.0 mmol/L)
2. Significant renal disfunction (creatinine >2.5 mg/dl or GFR <30 mL/min/1,73m2).
3. Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg).
4. Drug interactions to look out for:

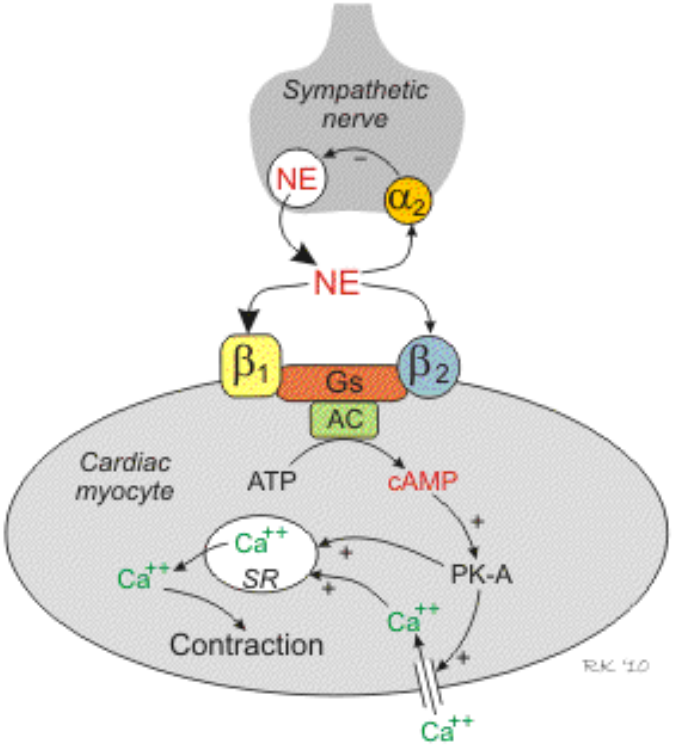
- K+ supplements/ K+-sparing diuretics, e.g. amiloride and triamterene (beware combination preparations with furosemide).
- MRAs.
- Renin inhibitors[c].
- NSAIDs[d].
- Trimethoprim/trimethoprim-sulfamethoxazole.
- 'Low-salt' substitutes with a high K+ content

Beta-Adrenoceptor Antagonists (Beta-Blockers)

bind to beta-adrenoceptors and block the binding of norepinephrine and epinephrine to these receptors

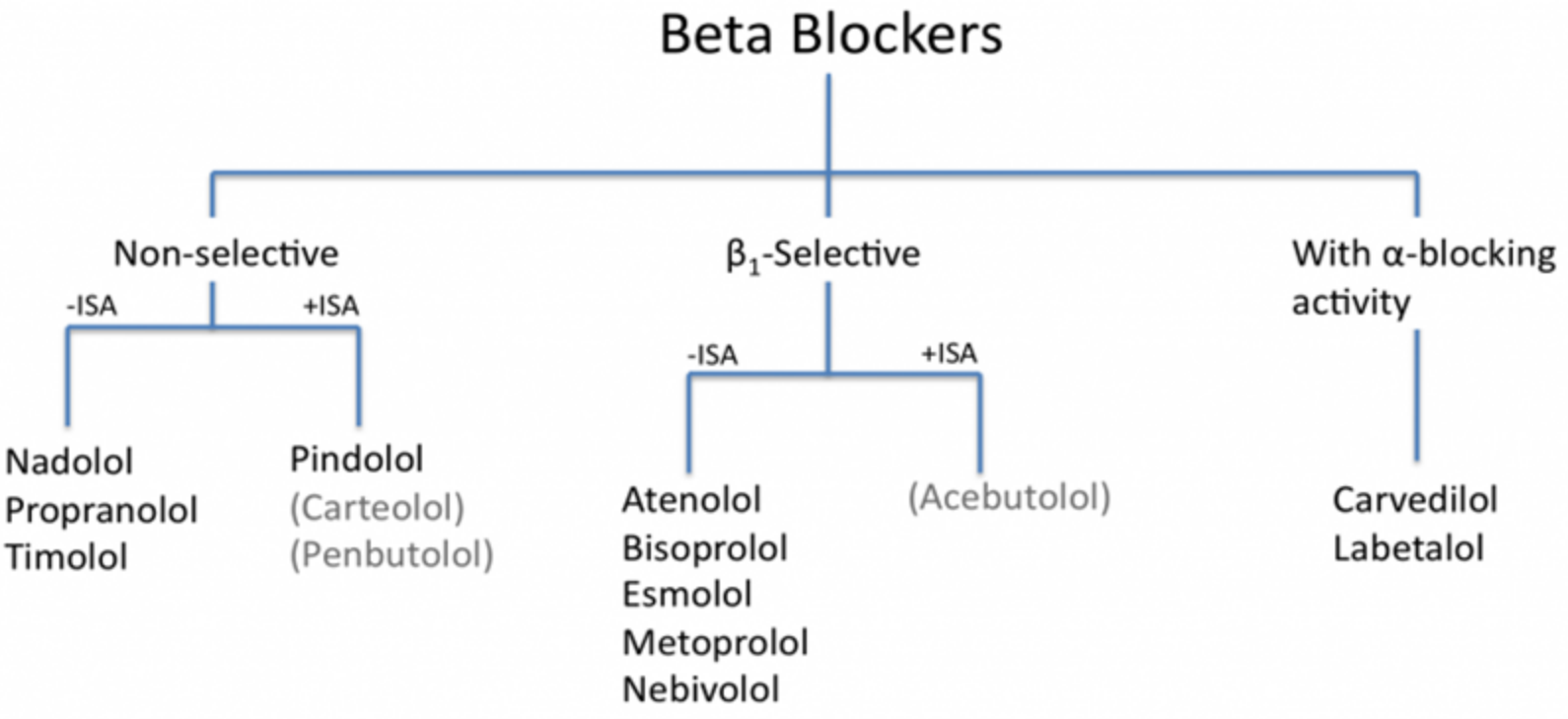
sympatholytic drugs

Some beta-blockers possess *intrinsic sympathomimetic activity (ISA) or membrane stabilizing activity (MSA).*

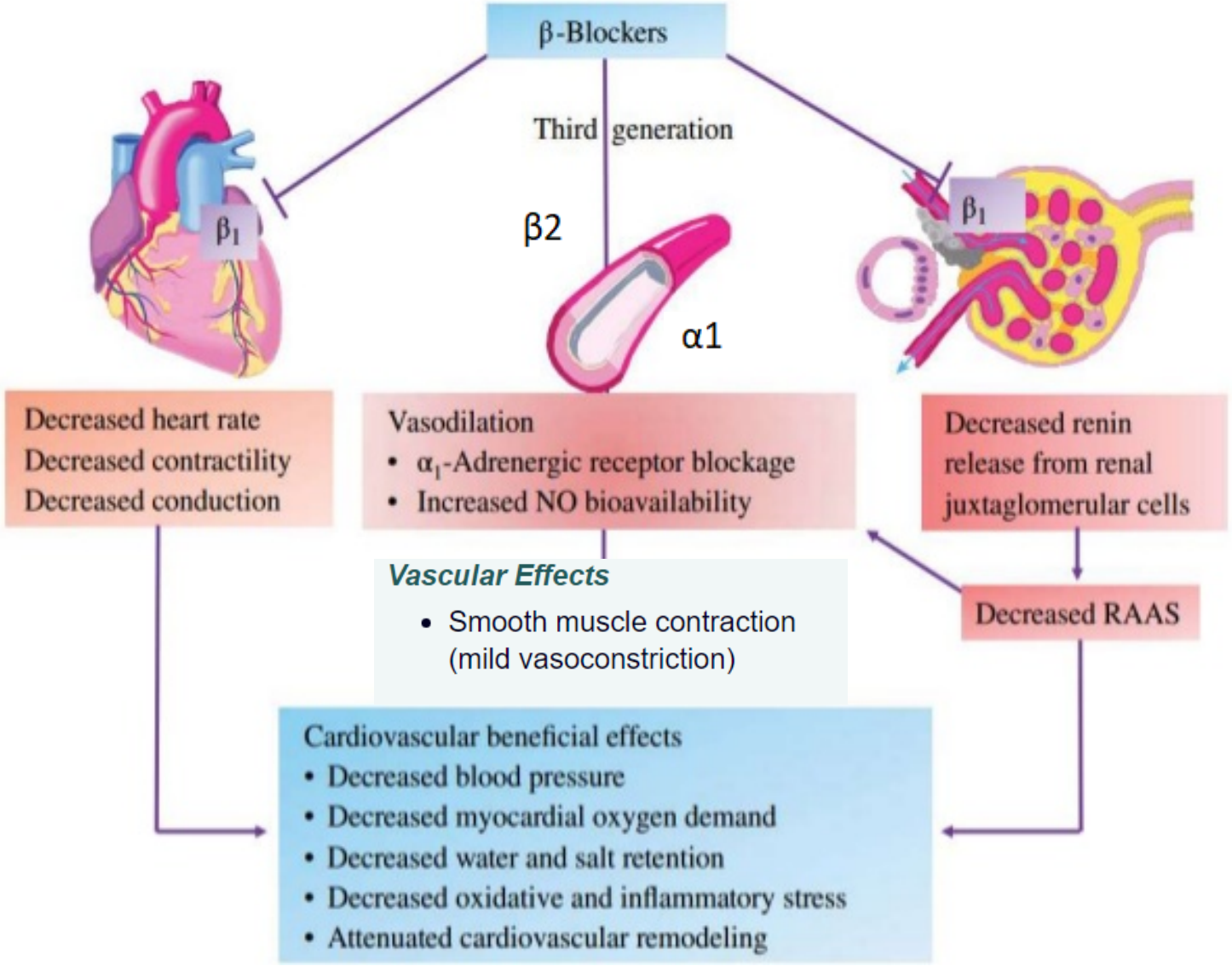


Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

Classification of Beta Blockers



ISA: Intrinsic Sympathomimetic Activity (partial agonists)
(Grey font: Drugs not emphasized at Tulane)


β-Blockers
Third generation
β2
α1
β1
β1
Decreased heart rate
Decreased contractility
Decreased conduction
Vasodilation
• α1-Adrenergic receptor blockage
• Increased NO bioavailability
Decreased renin release from renal juxtaglomerular cells
Vascular Effects
• Smooth muscle contraction (mild vasoconstriction)
Decreased RAAS
Cardiovascular beneficial effects
• Decreased blood pressure
• Decreased myocardial oxygen demand
• Decreased water and salt retention
• Decreased oxidative and inflammatory stress
• Attenuated cardiovascular remodeling

Therapeutic Indications Beta-Blockers

- hypertension
- angina
- myocardial infarction
- arrhythmias
- heart failure

Beta-Blockers → Hypertension

Reduce cardiac output

Acute treatment with a beta-blocker is not very effective in reducing arterial pressure because of a compensatory increase in systemic vascular resistance.

Chronic treatment with beta-blockers lowers arterial pressure possibly because of reduced renin release by the kidneys and effects of beta-blockade on central and peripheral nervous systems.

Angina and myocardial infarction

- B-blockers reduce oxygen demand by diminish heart rate, contractility, and arterial pressure
- relieve a patient of anginal pain
- decrease mortality in pts after myocardial infarction

(improving the oxygen supply/demand ratio, reducing arrhythmias, and their ability to inhibit subsequent cardiac remodeling)

Arrhythmias

B-blockers - class II antiarrhythmic drugs

inhibit sympathetic influences on cardiac electrical activity

sympathetic nerves increase:

- sinoatrial node automaticity by increasing the pacemaker currents, which increases sinus rate.
- conduction velocity (particularly at the atrioventricular node)
- stimulates aberrant pacemaker activity (ectopic foci).

Heart failure

- Although it seems counterintuitive that cardioinhibitory drugs such as beta-blockers would be used in cases of systolic dysfunction, clinical studies have shown quite conclusively that some specific beta-blockers actually reduce mortality and morbidity in symptomatic patients with HFrEF
- reduce deleterious cardiac remodeling

Evidence-based doses of disease-modifying drugs in key randomized trials in HF with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
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Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
If -channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Side effects of beta-blockers

bradycardia

reduced exercise capacity

heart failure

hypotension

atrioventicular nodal conduction block

bronchoconstriction (B2)

mask the tachycardia that serves as a warning sign for insulin-induced hypoglycemia in diabetic patients

Contra-indications:

1. Second- or third-degree AV block (in the absence of a permanent pacemaker).

2. Critical limb ischaemia.

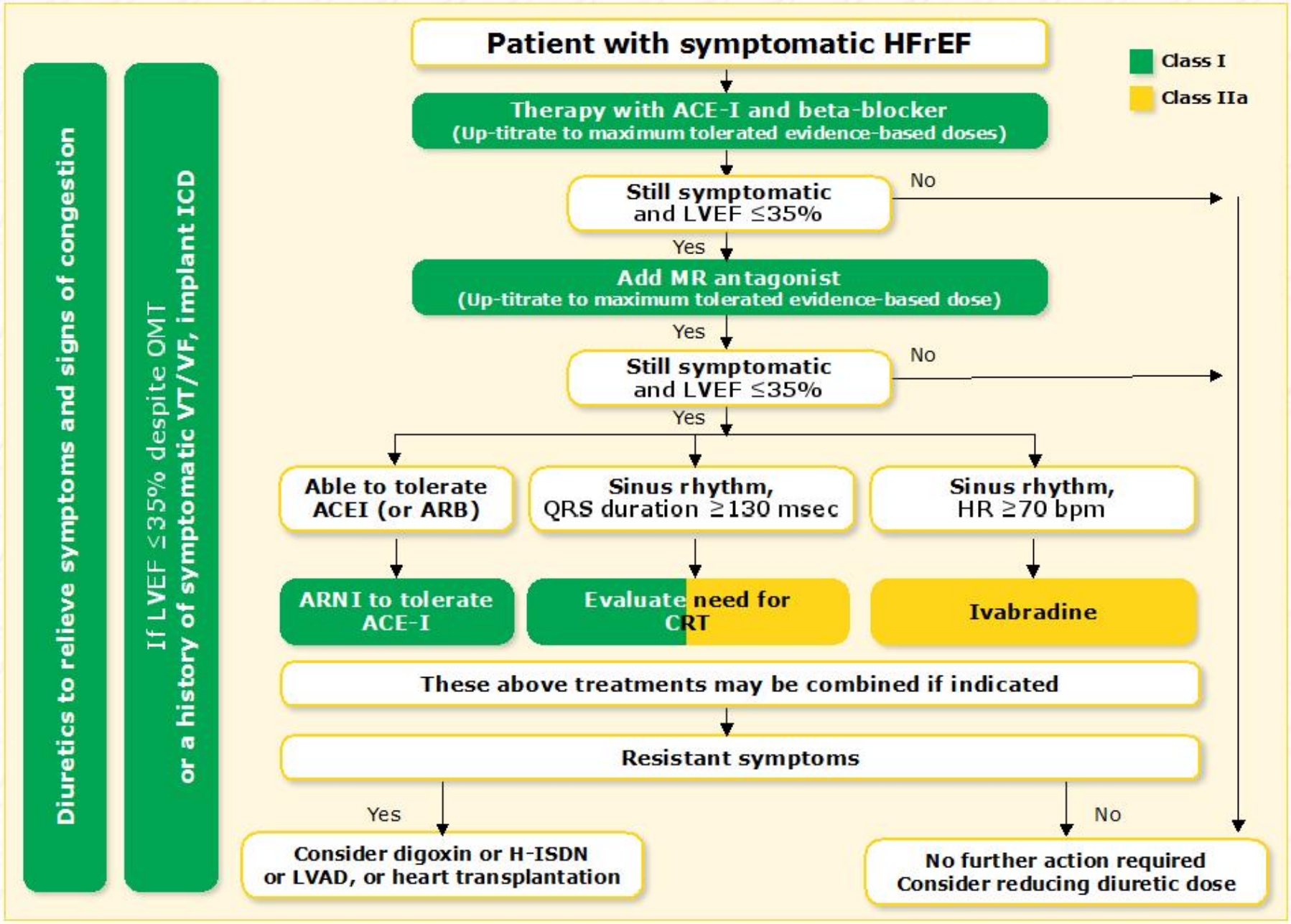
3. Asthma (relative contra-indication): if cardio-selective beta-blockers are indicated, asthma is not necessarily an *absolute* contra-indication

*COPD is not a contra-indication

Drug interactions to look out for (because of risk of bradycardia/atrioventricular block):

- Verapamil, diltiazem (should be discontinued).b
- Digoxin.
- Amiodarone.
- Ivabradine.

Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction



Mineralocorticoid receptor antagonists

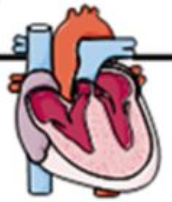
MRAs (spironolactone and eplerenone) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g. corticosteroids, androgens) receptors.

ALDOSTERONE

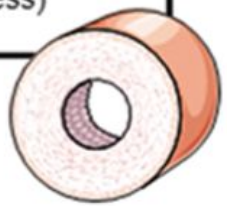
Inflammation
⇧Oxidative Stress

Vascular Endothelial Dysfunction
(Chronic effect causes shrinking and increased mechanical stiffness of endothelial cells and decrease in NO production)

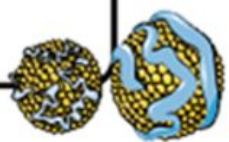
Cardiac & Vascular Fibrosis
(expression of procollagen genes and MR-induced fibroblast-dependent interstitial and perivascular collagen deposition)



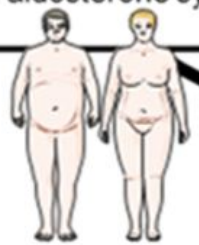
Hypertension
(arteriolar vasoconstriction & ⇧vascular stiffness)



Dyslipidemia
(⇧Triglycerides ⇩HDL-cholesterol)

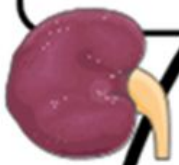


Obesity & Type 2 Diabetes
(intracrine production of aldosterone via cell expression of aldosterone synthase)



⇧Gluconeogenesis
(in part via stimulation of gene expression of hepatic gluconeogenic enzymes)

Renal Na^+/K^+ regulation
(⇧Na^+ reabsorption & K^+ excretion in the distal convoluted tubule)



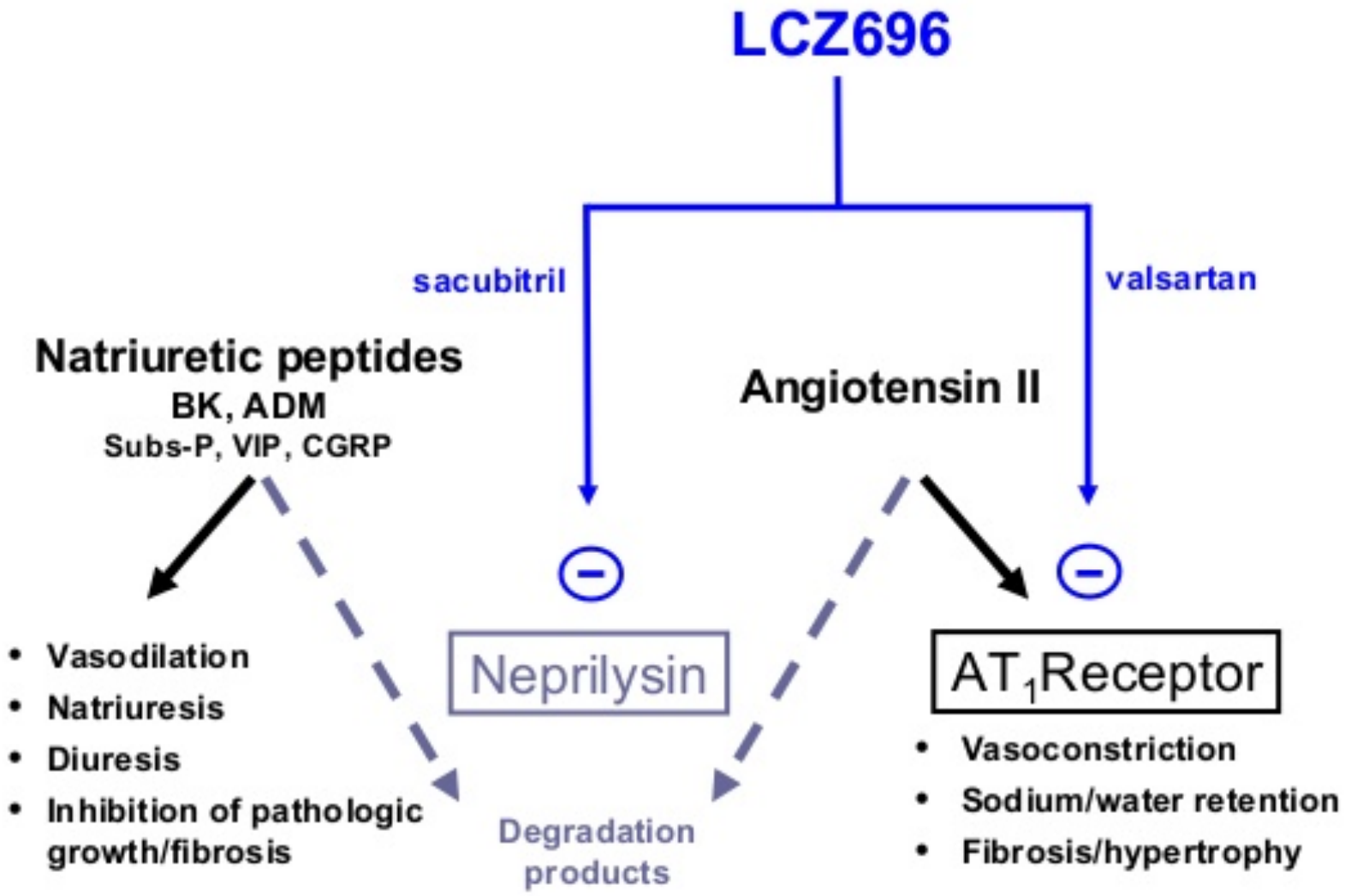
MRAs

Indication:

Symptomatic patients (despite treatment with an ACEI and a beta-blocker) with HFrEF and LVEF ≤35%

→reduce mortality and HF hospitalization

Angiotensin Receptor Neprilysin Inhibition (ARNI): LCZ696



Inclusion criteria - the PARADIGM-HF trial

- symptomatic HFrEF with LVEF ≤35%
- elevated plasma NP levels (BNP ≥150 pg/mL or
- NT-proBNP ≥600 pg/mL)
- an estimated GFR (eGFR) ≥30 mL/min/1.73 m2 of body surface area

Conclusion - the PARADIGM-HF trial

sacubitril/valsartan (97/103 mg b.i.d.) was superior to ACEI (enalapril 10mg b.i.d.) in reducing hospitalizations for worsening HF, cardiovascular mortality and overall mortality

Side effects of ARNI:

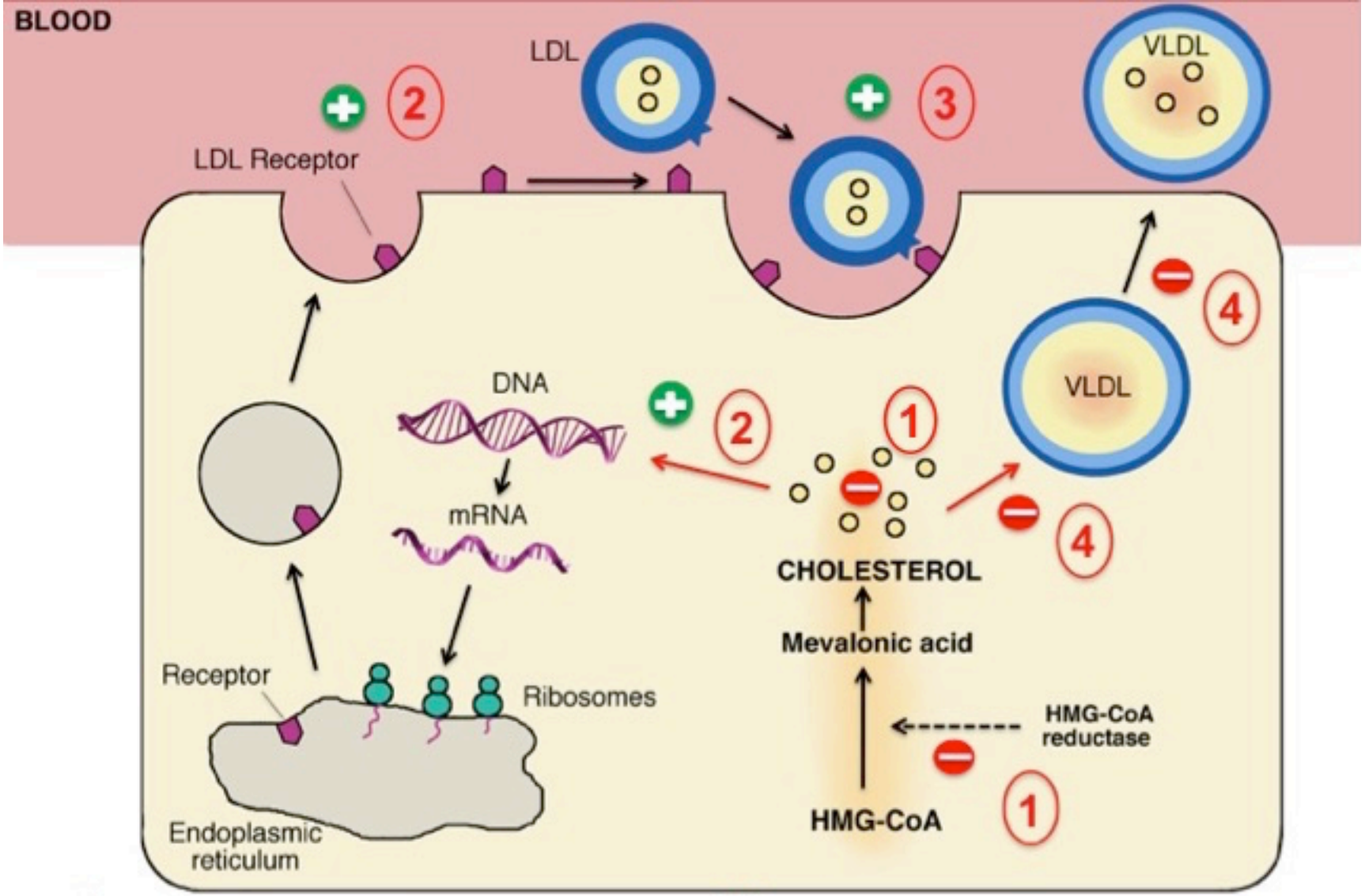
- Symptomatic hypotension
- angioedema

Drugs for treatment of hypercholesterolaemia

Statins

Ezetymib

PCSK9 inhibitors



1. Statins inhibit HMG-CoA reductase, leading to decreased concentration of cholesterol within the cell
2. Low intracellular cholesterol stimulates the synthesis of LDL receptors
3. Increased numbers of LDL receptors promotes uptake of LDL from blood
4. Low intracellular cholesterol decreases the secretion of VLDL

Understanding ANIMAL RESEARCH

Statins

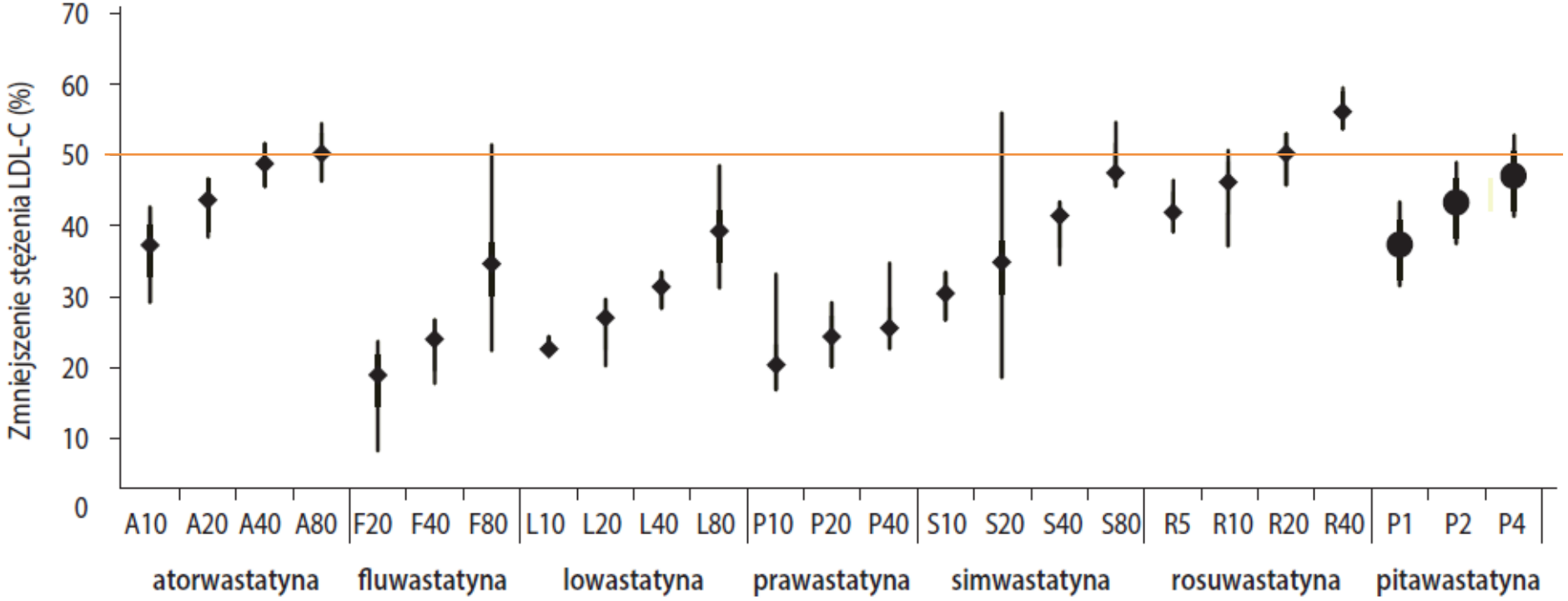
-substantially reduce CV morbidity and mortality in both primary and secondary prevention, in both genders and in all age groups

-have also been shown to slow the progression or even promote regression of coronary atherosclerosis

Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

A80 R20 R30 R40

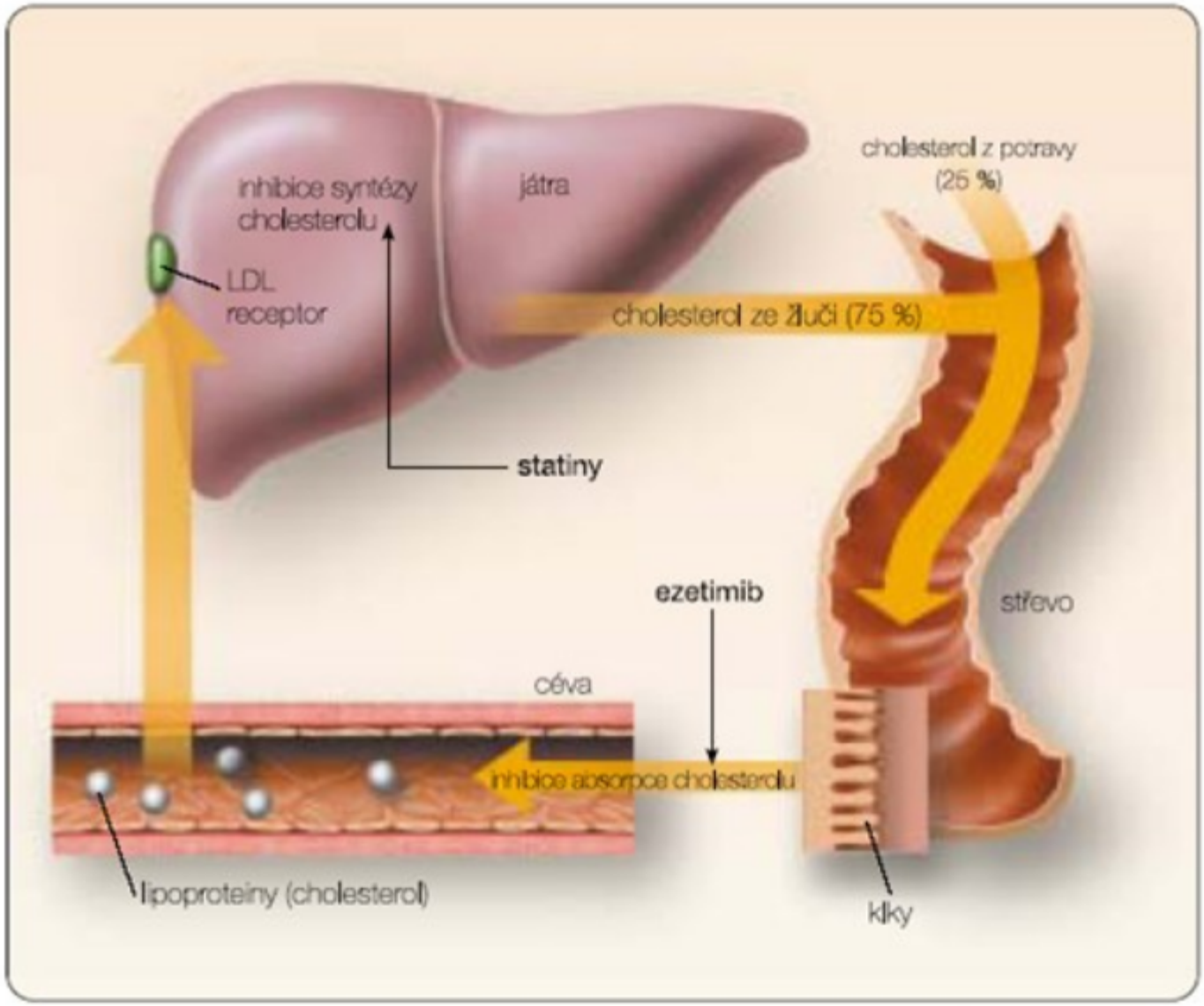


Weng TC et al. J Clin Pharm Ther, 2010; 35: 139–151
Mukhtar RY et al. Int J Clin Pract, 2015; 59: 239–252

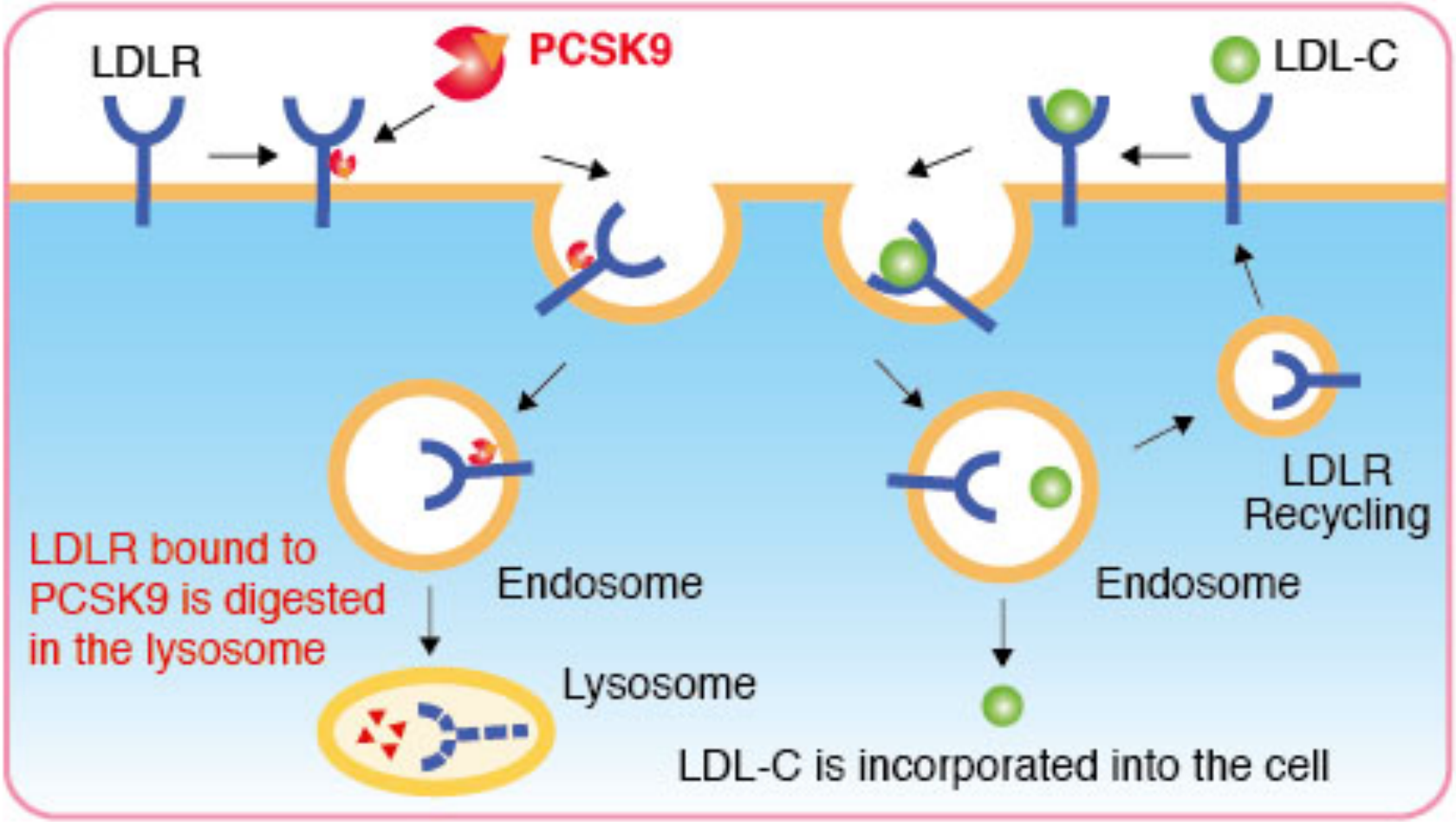
Side effects of statins

- muscular pain
- statin-induced myopathy
- rhabdomyolysis → severe muscular pain, muscle necrosis and myoglobinuria potentially leading to renal failure and death
- elevation of alanine aminotransferase (ALT)
- small increase in the incidence of diabetes

Statins + ezetymib (cholesterol absorption inhibitor)



PCSK9 inhibitors



monoclonal antibodies that reduce LDL-C levels by 60%

ESC
European Society of Cardiology
European Heart Journal (2017) **0**, 1–48
doi:10.1093/eurheartj/ehx419

ESC GUIDELINES

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS

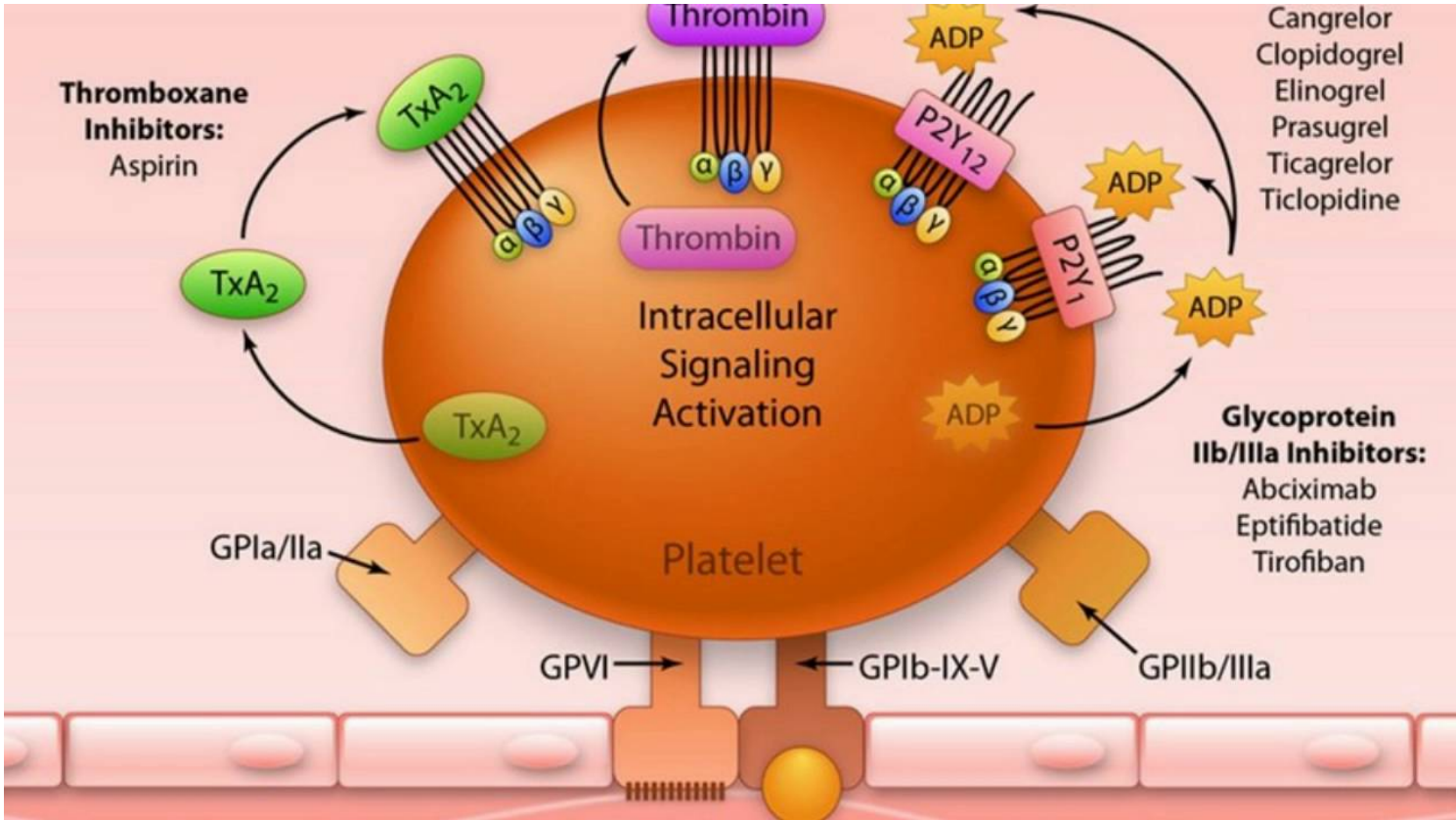
The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS)

DAPT – dual antiplatelet therapy

Aspirin

P2Y12 Inhibitor:
clopidogrel
prasugrel
ticagrelor

Indication for DAPT:
coronary intervention
myocardial infarction



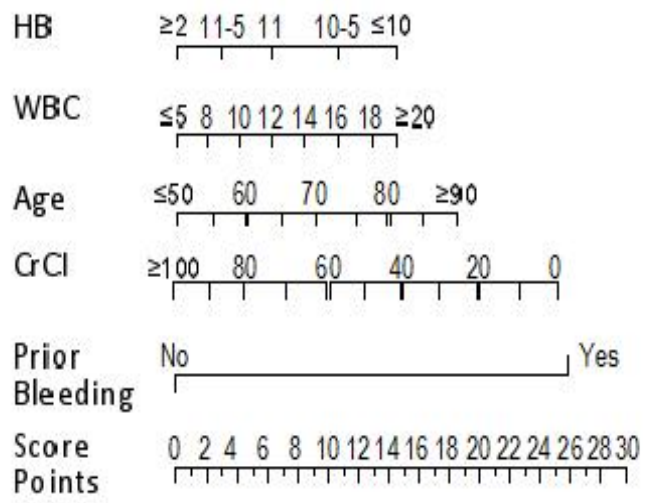
DAPT – dual antiplatelet therapy

Current evidence suggests that DAPT mitigates the risk of stent thrombosis across the whole spectrum, from acute to very late event

ischaemic vs. bleeding risks for any given DAPT duration; the use of scores might prove useful to tailor DAPT duration in order to maximize ischaemic protection and minimiz bleeding risks in the individual patient

Risk scores validated for dual antiplatelet therapy duration decision-making

ESC European Society of Cardiology

	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 −2 pt −1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	−2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Use of risk scores as guidance for the duration of dual antiplatelet therapy

ESC European Society of Cardiology

Recommendations	Class	Level
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A

$P2Y_{12}$ inhibitor selection and timing

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications.	I	B

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

$P2Y_{12}$ inhibitor selection and timing *(continued)*

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Recommendations	Class	Level
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.	I	A
Clopidogrel (300 mg loading dose in patients ≤75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.	I	A

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Measures to minimize bleeding while on dual antiplatelet therapy

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Recommendations	Class	Level
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75–100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

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Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute setting

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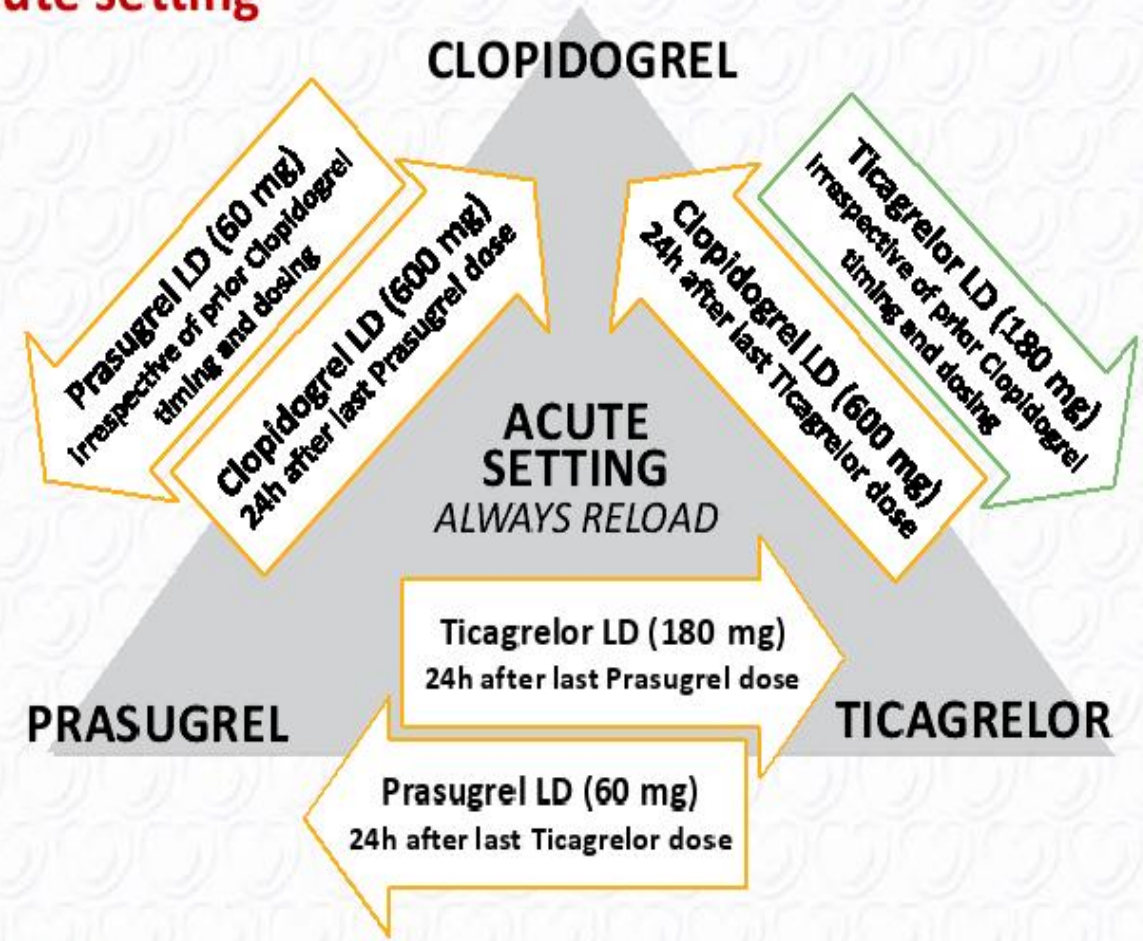

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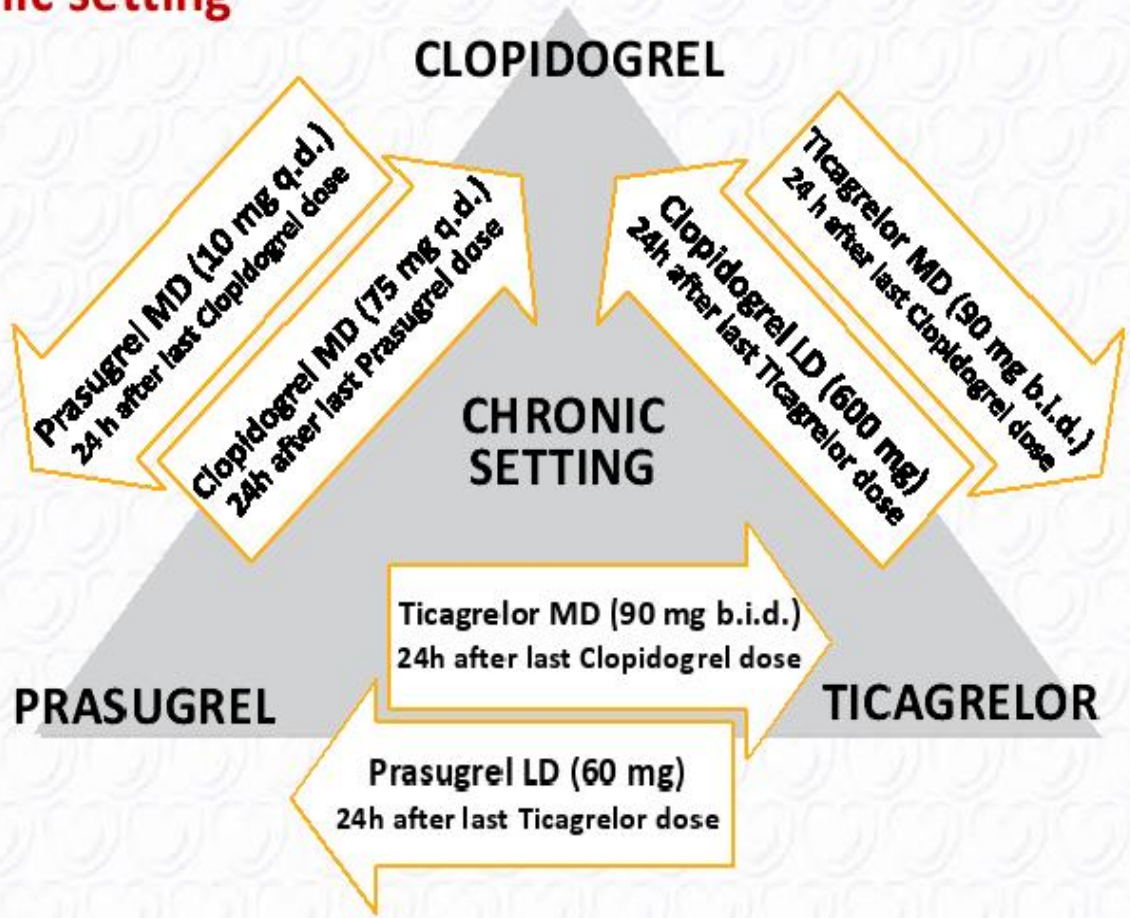
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for switching between oral $P2Y_{12}$ inhibitors in the chronic setting



2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
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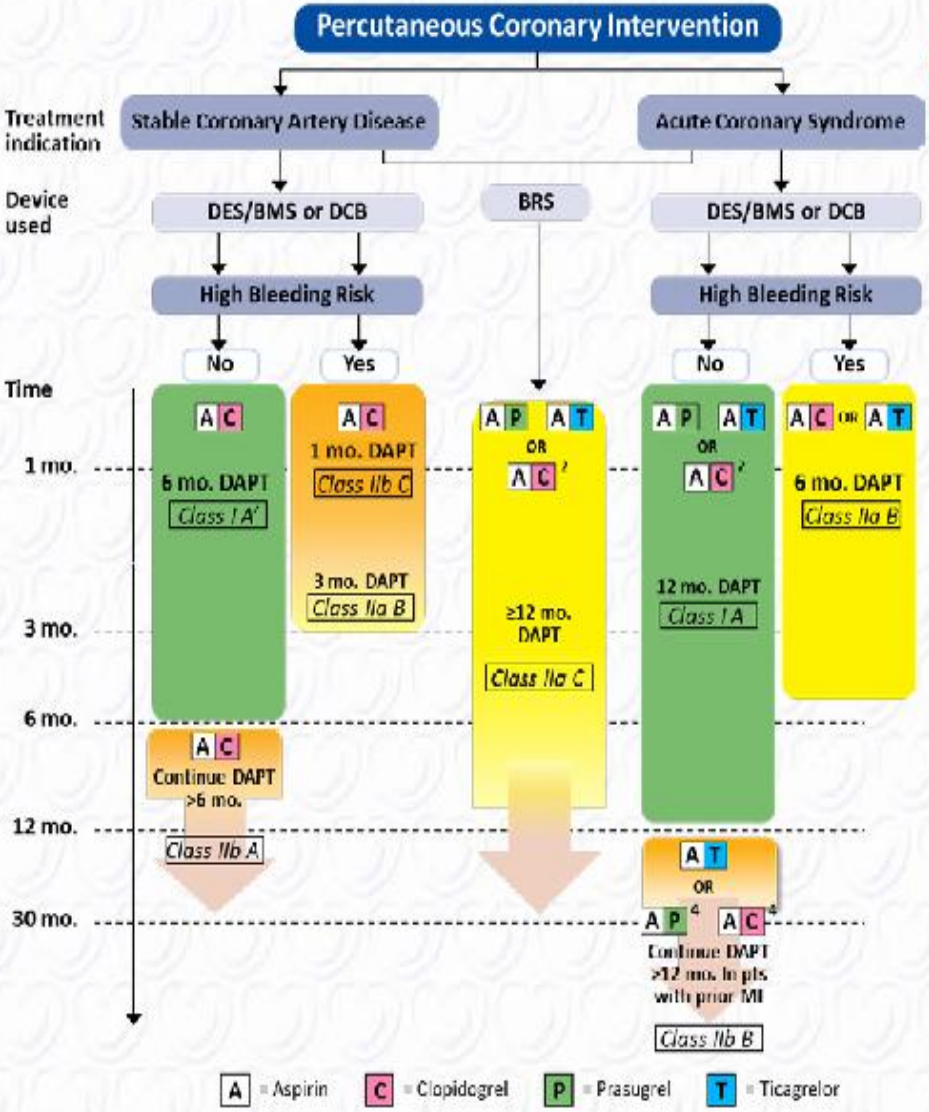
Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention



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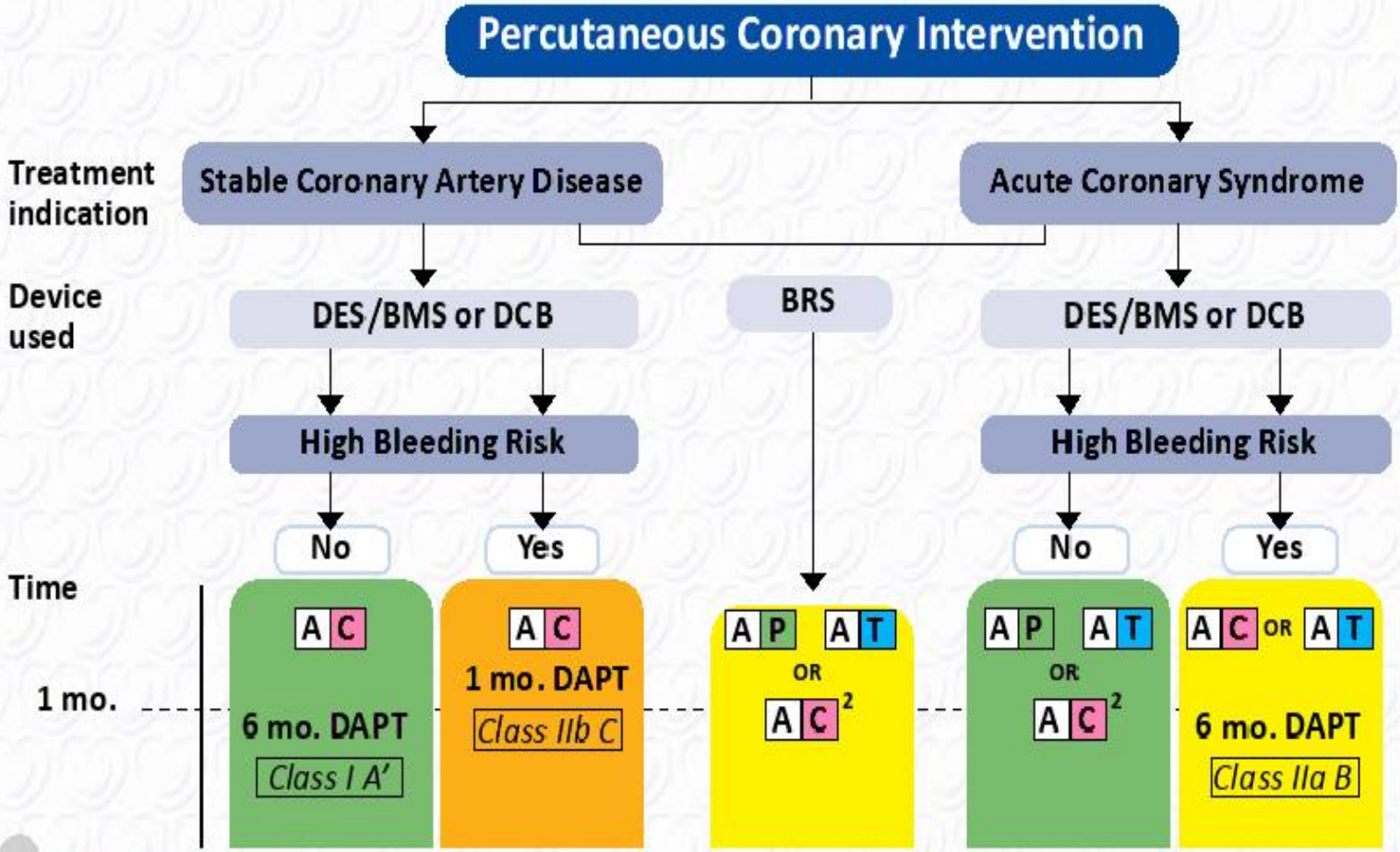

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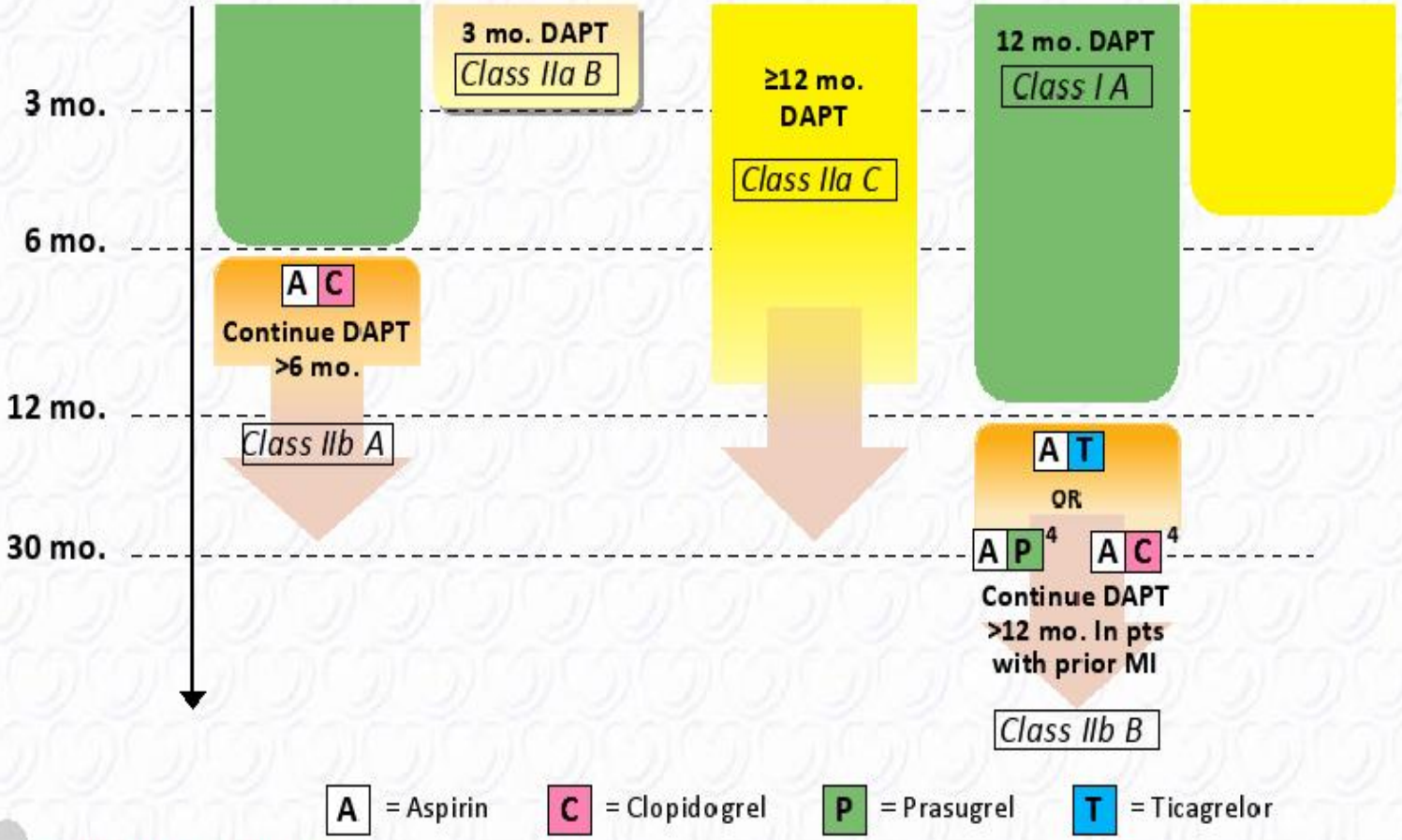

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Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI)

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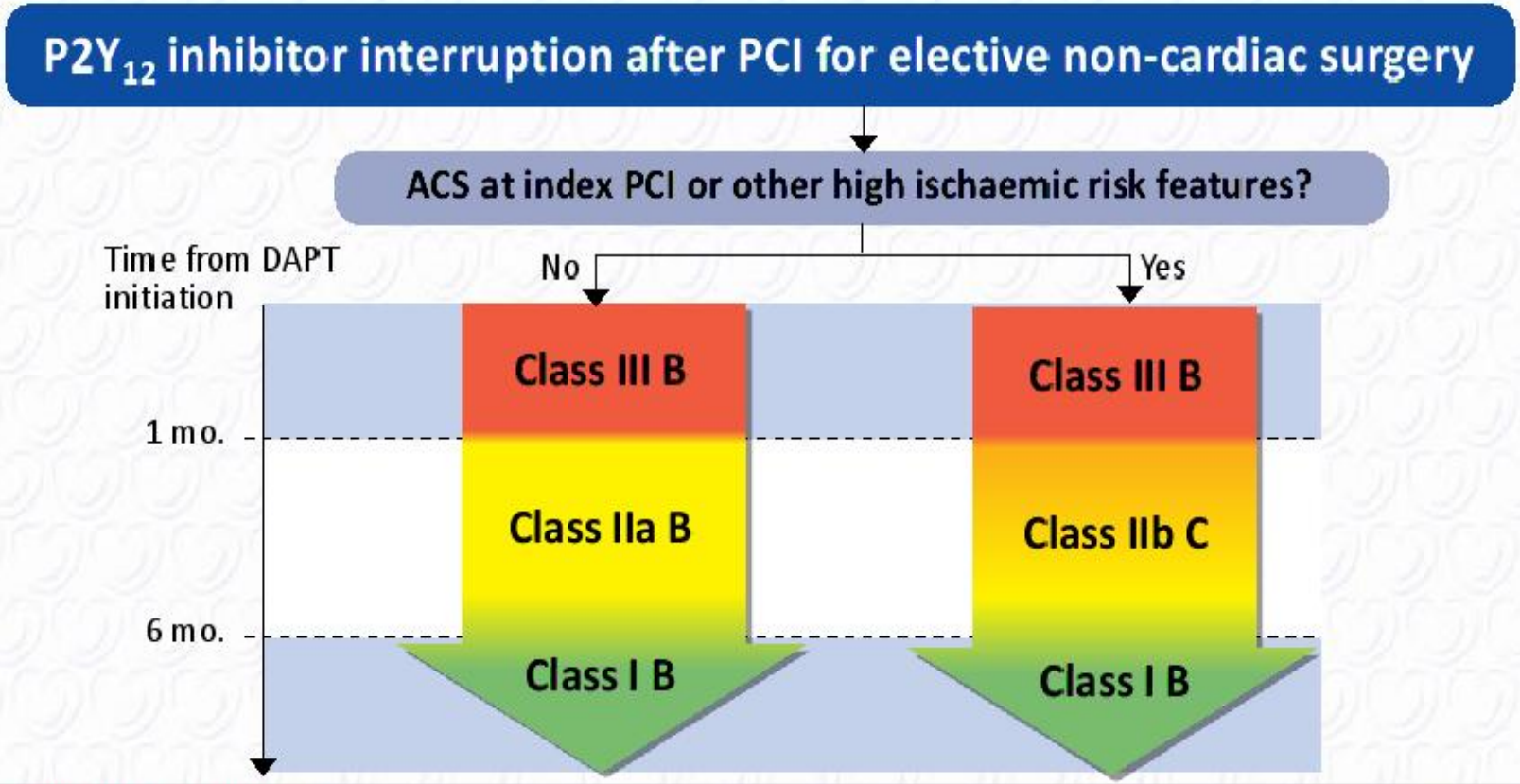

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
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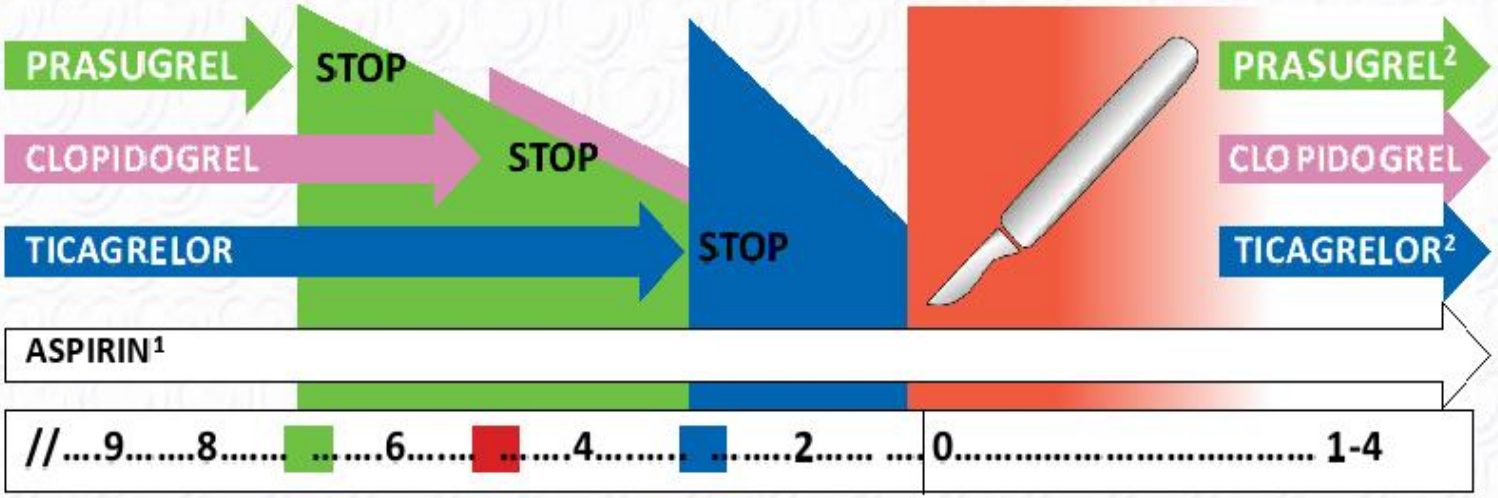
Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery



= Expected average platelet function recovery

[1] Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

[2] In patients not requiring OAC.

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