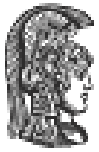


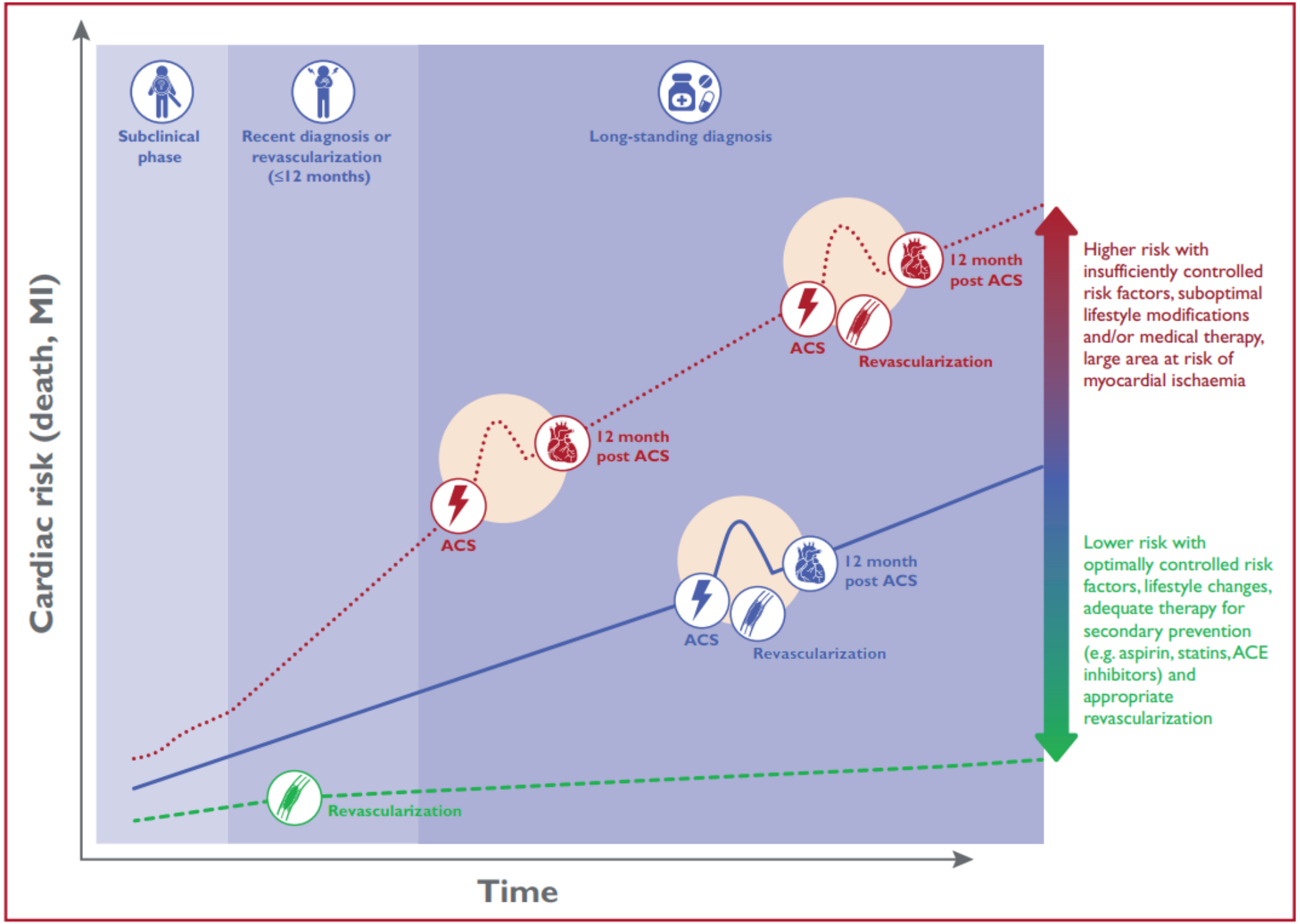
ΚΑΡΔΙΟΜΕΤΑΒΟΛΙΚΗ ΙΑΤΡΙΚΗ

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837
ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΑΘΗΝΩΝ

ΠΜΣ: Καρδιομεταβολική Ιατρική

Σταθερή στεφανιαία νόσος. Φαρμακευτική αγωγή.

Ιγνάτιος Οικονομίδης, Καθηγητής Καρδιολογίας ΕΚΠΑ
Κωνσταντίνος Κατωγιάννης, Ακαδημαϊκός Υπότροφος, Καρδιολόγος


Subclinical phase
Recent diagnosis or revascularization (≤12 months)
Long-standing diagnosis
Cardiac risk (death, MI)
Time
ACS
12 month post ACS
Revascularization
ACS
12 month post ACS
Revascularization
ACS
12 month post ACS
Revascularization
Higher risk with insufficiently controlled risk factors, suboptimal lifestyle modifications and/or medical therapy, large area at risk of myocardial ischaemia
Lower risk with optimally controlled risk factors, lifestyle changes, adequate therapy for secondary prevention (e.g. aspirin, statins, ACE inhibitors) and appropriate revascularization
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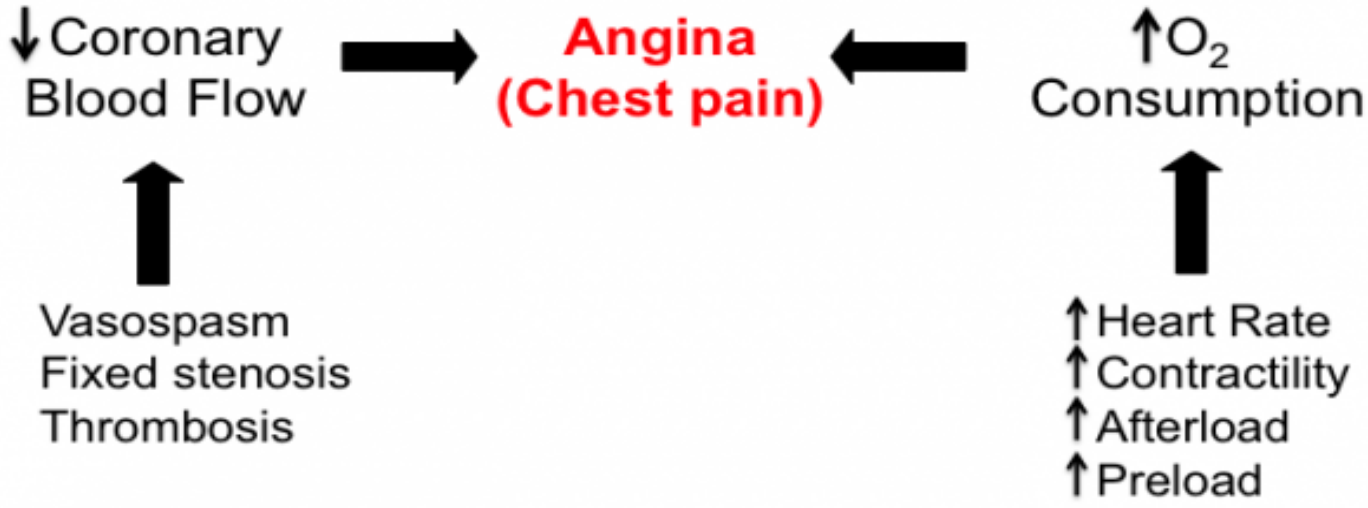
Traditional clinical classification of suspected anginal symptoms

Typical angina	Meets the following three characteristics: (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; (ii) Precipitated by physical exertion; (iii) Relieved by rest or nitrates within 5 min.
Atypical angina	Meets two of these characteristics.
Non-anginal chest pain	Meets only one or none of these characteristics.

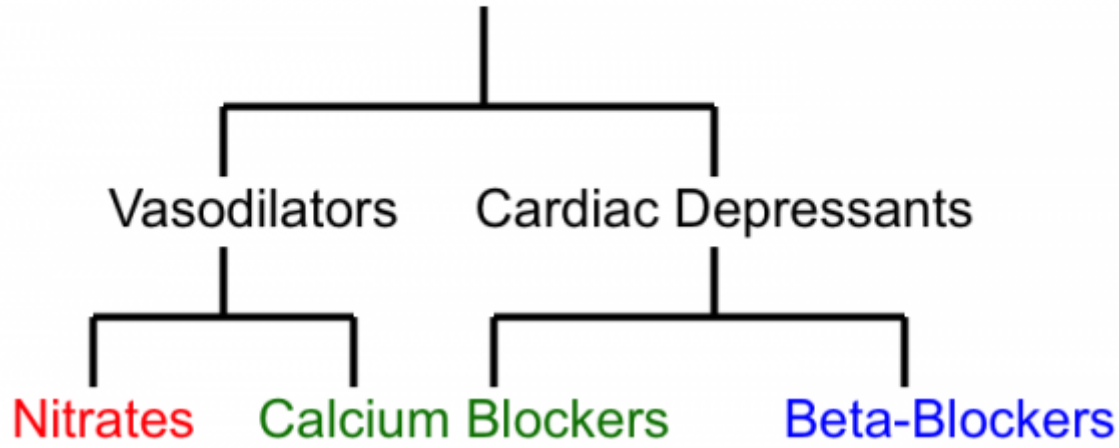
Canadian Cardiovascular Society Classification of Angina Pectoris

Class	Severity
Class I	Angina only during strenuous or prolonged physical activity.
Class II	Slight limitation, with angina only during vigorous physical activity.
Class III	Symptoms with everyday living activities, ie, moderate limitation.
Class IV	Inability to perform any activity without angina or angina at rest, ie, severe limitation.

Supply vs. Demand



Most Common Drugs Used in Treating Angina Pectoris

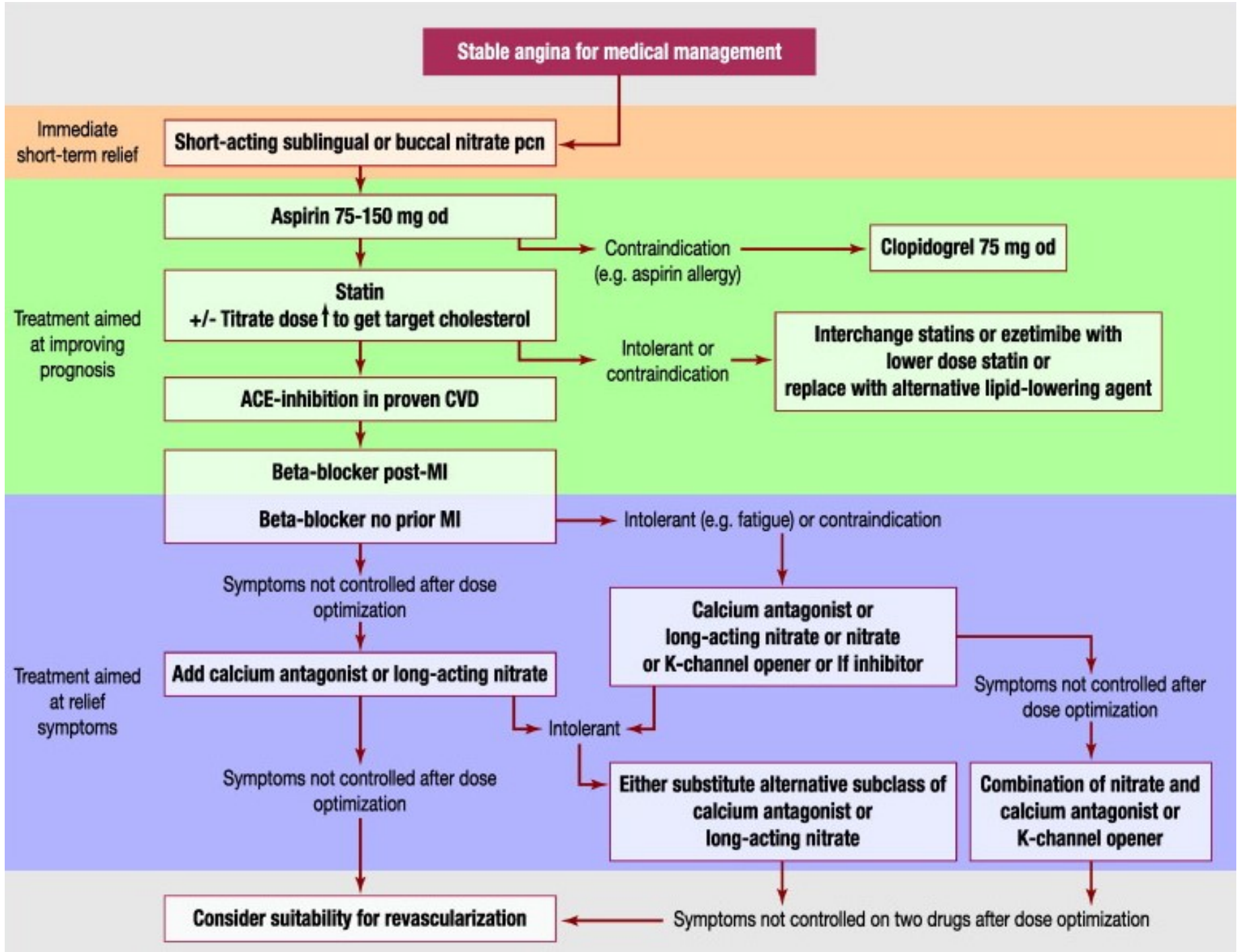


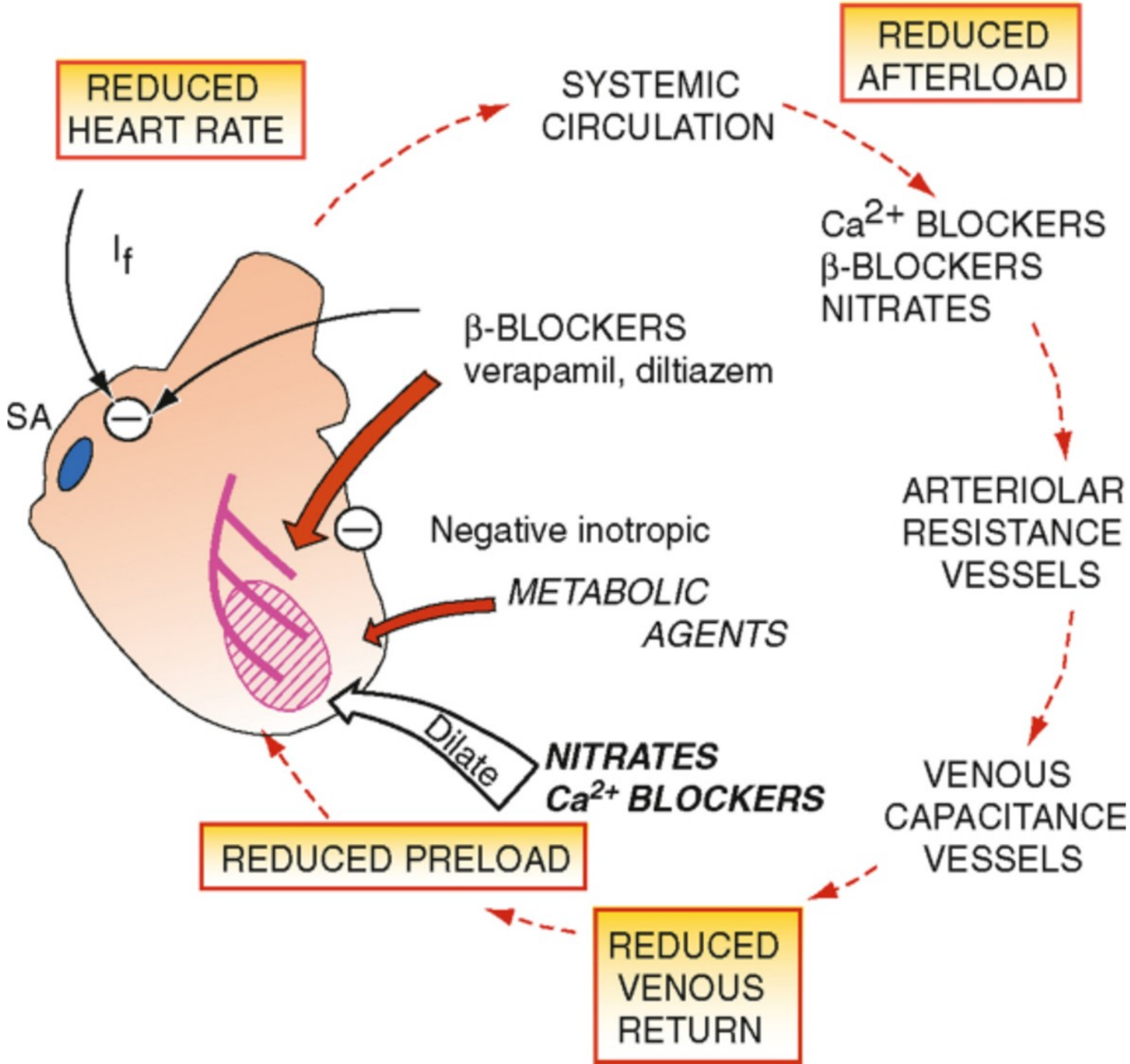
Treatment of coronary artery disease

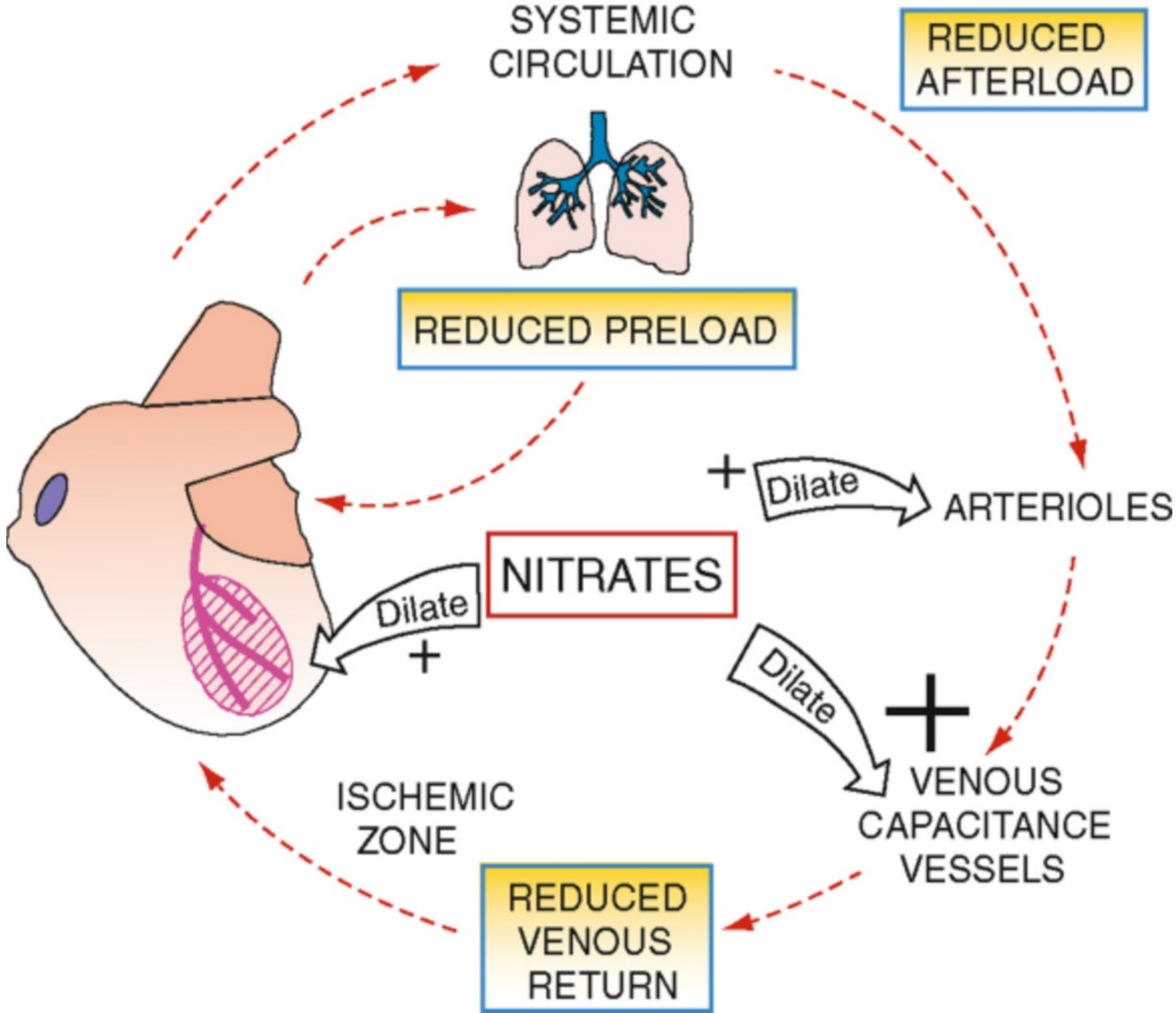
Treatment goals for patients with coronary artery disease include the following:

- Improve prognosis (*i.e* prolong survival).
- Reduce symptoms.
- Improve functional capacity.
- Improve quality of life.

Large clinical trials typically measure the effect of an intervention on the risk of incident (*i.e* new) or recurring cardiovascular events, development of complications (*e.g* heart failure), and mortality. Such outcome measures are referred to as *hard endpoints*. Very few drugs have effects on hard endpoints, particularly mortality. The most effective drugs, as defined by the *number needed to treat*, in patients with stable coronary artery disease are arguably **aspirin (acetylsalicylic acid)** and **statins** (*Collins et al*). Other commonly used drugs, e.g angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), beta-blockers, calcium channel blockers, *etc* have little or no significant effect on hard endpoints. The effect of ACE inhibitors, ARBs and beta-blockers appear to be restricted to patients with hypertension, left ventricular dysfunction and/or heart failure.


Stable angina for medical management
Immediate short-term relief
Short-acting sublingual or buccal nitrate pcn
Aspirin 75-150 mg od
Contraindication (e.g. aspirin allergy)
Clopidogrel 75 mg od
Treatment aimed at improving prognosis
Statin
+/- Titrate dose ↑ to get target cholesterol
Intolerant or contraindication
Interchange statins or ezetimibe with lower dose statin or replace with alternative lipid-lowering agent
ACE-inhibition in proven CVD
Beta-blocker post-MI
Beta-blocker no prior MI
Intolerant (e.g. fatigue) or contraindication
Symptoms not controlled after dose optimization
Calcium antagonist or long-acting nitrate or nitrate or K-channel opener or If inhibitor
Treatment aimed at relief symptoms
Add calcium antagonist or long-acting nitrate
Symptoms not controlled after dose optimization
Intolerant
Symptoms not controlled after dose optimization
Either substitute alternative subclass of calcium antagonist or long-acting nitrate
Combination of nitrate and calcium antagonist or K-channel opener
Consider suitability for revascularization
Symptoms not controlled on two drugs after dose optimization


REDUCED HEART RATE
SYSTEMIC CIRCULATION
REDUCED AFTERLOAD
I_f
Ca^{2+} BLOCKERS
β-BLOCKERS
NITRATES
β-BLOCKERS
verapamil, diltiazem
SA
Negative inotropic
ARTERIOLAR RESISTANCE VESSELS
METABOLIC AGENTS
Dilate
NITRATES
Ca^{2+} BLOCKERS
VENOUS CAPACITANCE VESSELS
REDUCED PRELOAD
REDUCED VENOUS RETURN


SYSTEMIC CIRCULATION
REDUCED AFTERLOAD
REDUCED PRELOAD
+ Dilate
ARTERIOLES
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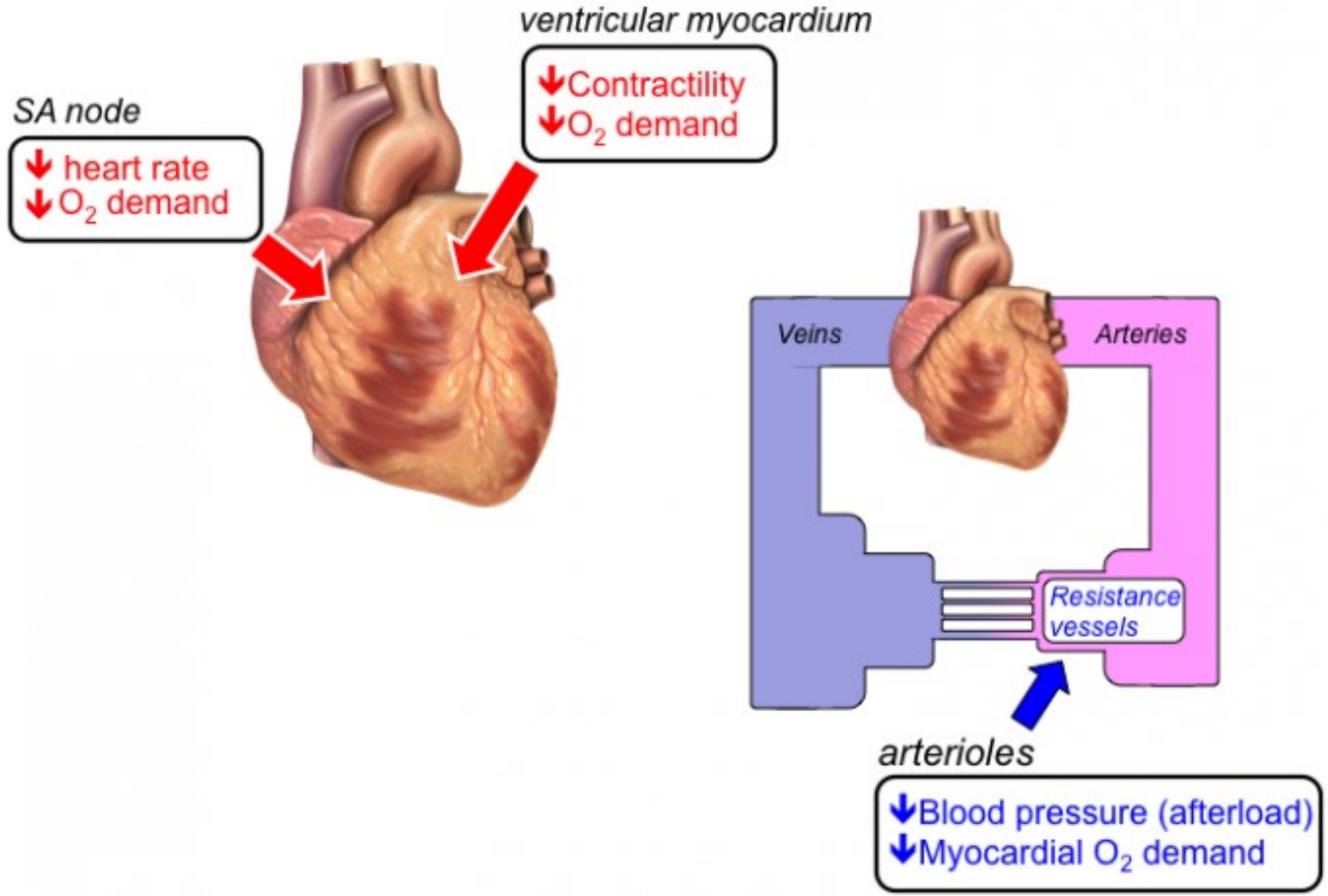
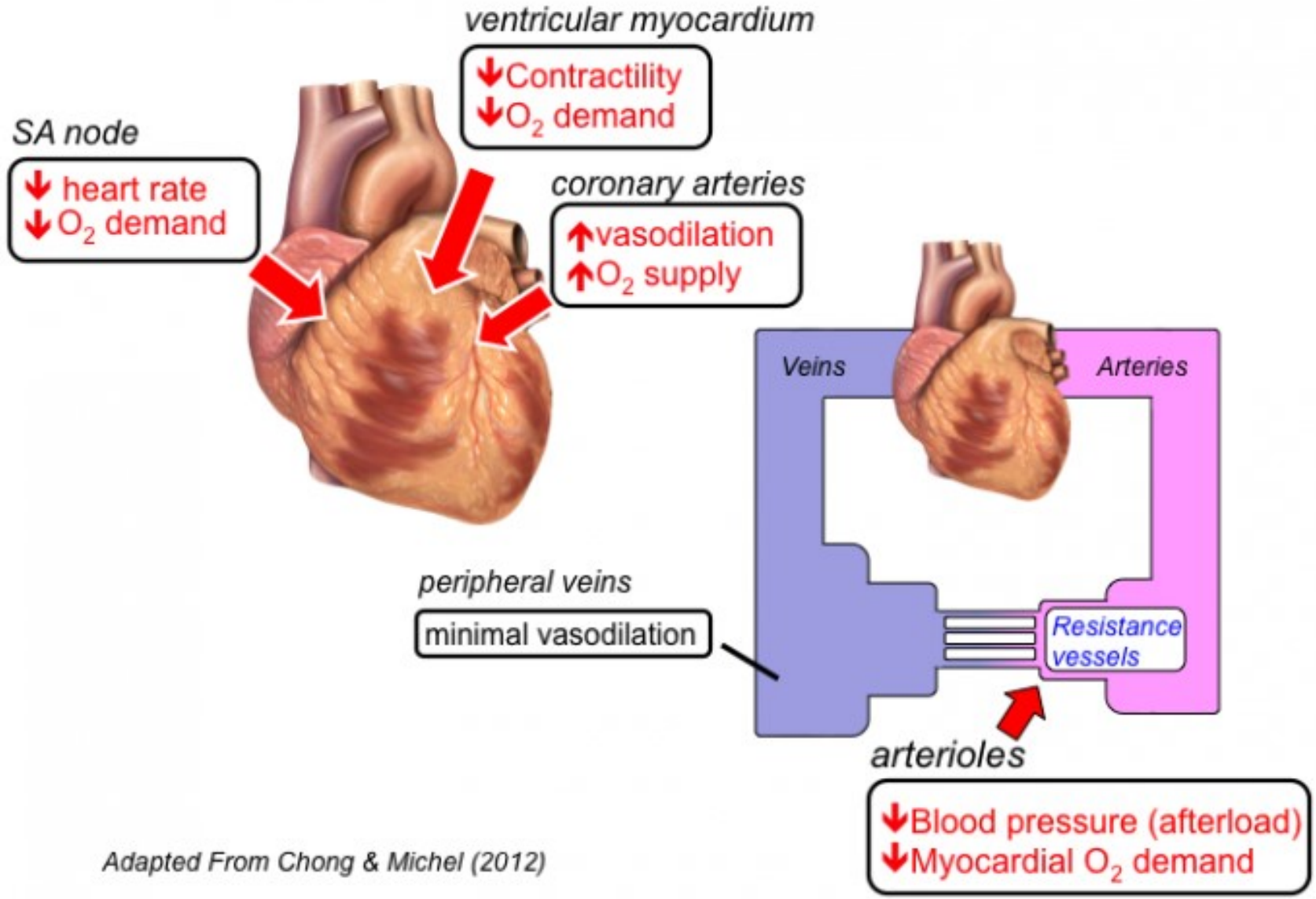
+
VENOUS CAPACITANCE VESSELS
ISCHEMIC ZONE
REDUCED VENOUS RETURN

Beta Blockers

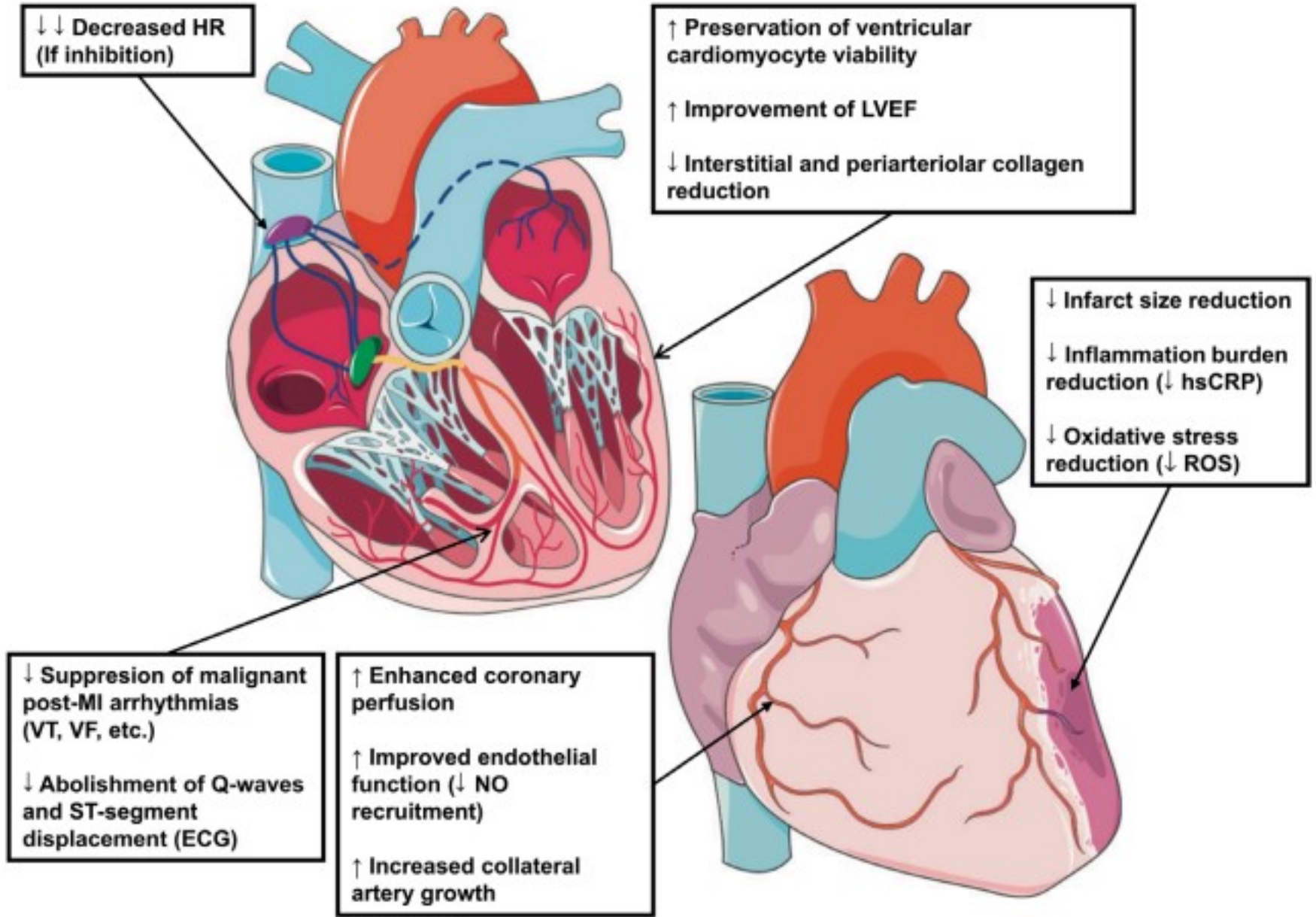


Calcium Channel Blockers



Adapted From Chong & Michel (2012)

Cardioprotective effects of **ivabradine** administration in the setting of acute coronary syndromes and myocardial infarction.



Ivabradine	Proven anti-anginal efficacy Combination with beta blocker in patients with elevated heart rate (>60 bpm) Reduction in total mortality and other hard clinical end points in heart failure patients No effect on blood pressure Possible role in microvascular remodelling
Ranolazine	Proven anti-anginal efficacy; does not affect heart rate or blood pressure Possible role in silent ischaemia Possible adjunctive role in reducing peri-procedural injury Possible anti-arrhythmic effects Possible antidiabetic effects Possible role in heart failure
Nicorandil	Potential cardioprotective role in acute myocardial infarction

ivabradine acts on the I_f current which regulates the intrinsic pacemaker activity of the sinoatrial node, resulting in reduction in heart rate and myocardial oxygen demand. Ivabradine also offers benefits beyond those associated with beta blocker therapy, with an effect on coronary dilation resulting in greater increase in coronary blood flow and hence maximisation of oxygen supply, and preservation of myocardial contractility and relaxation resulting in better ventricular filling and cardiac adaptation. Anti-anginal efficacy has been proven in clinical studies. As high resting heart rate (HR) is a cardiovascular risk factor (**figure 3**), and associated with increased myocardial ischaemia, it would be appropriate to target HR reduction using ivabradine. Such an approach has been associated with improved clinical outcomes.

ranolazine inhibits the late sodium influx across the sarcolemma, thereby attenuating abnormalities in ventricular repolarisation and contractility associated with myocardial ischaemia, as well as preventing calcium overload that causes cardiac ischaemia. Thus, ranolazine interrupts the positive feedback loop that perpetuates myocardial ischaemia and myocardial dysfunction. Ranolazine does not significantly alter heart rate or systolic blood pressure; for this reason, ranolazine could be of particular value in individuals with angina who are unable to increase other anti-anginal medications due to their haemodynamic effects. Effect of ranolazine 750 mg on exercise duration and time to onset of angina in patients with symptomatic angina treated with other anti-anginal therapy. Data from the CARISA study(34)The anti-anginal efficacy of ranolazine has been demonstrated in clinical trials (figure 4). In Europe, ranolazine is currently indicated as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta blockers and/or calcium antagonists), while in the US it has also been approved as first-line therapy.

Mechanisms of action of antianginal drugs

Drugs	Mechanisms of action
Beta-blockers	Beta-blockers reduce heart rate, contractility, and atrioventricular conduction, thus reducing myocardial oxygen demand and time-to-angina onset during exercise. By prolonging the diastolic period, beta-blockers may increase the perfusion of ischaemic areas. Beta-blockers differ with respect to several clinical features, including cardioselectivity ($beta_1$ selectivity) and sympathomimetic activity, but their clinical efficacy seems to be equivalent.[137] The most used beta-blockers in Europe are those with predominant $beta_1$ blockade (e.g. metoprolol, bisoprolol, atenolol, and nebivolol). Carvedilol, a non-$beta_1$-selective beta-blocker, is also frequently used.
CCBs	CCBs act chiefly by vasodilation and reduction of the peripheral vascular resistance. CCBs are a heterogeneous group of drugs that can be classified chemically into the DHPs and the non-DHPs, their common pharmacological property being selective inhibition of the L-channel opening in vascular smooth muscle and in the myocardium. DHP drugs (amlodipine, nifedipine, and felodipine) have a greater vascular selectivity. The non-DHPs (diltiazem and verapamil) decrease heart rate and myocardial inotropism, both effects contributing to their antianginal properties and to their adverse effects.
Nitrates	By means of their active component nitric oxide, nitrates offer angina relief by dilatation of peripheral and coronary arteries, and, mostly, peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload.[138,139]
Ivabradine	Ivabradine is a heart rate-lowering drug that selectively inhibits the sinus node I_f pacemaker current, thereby decreasing myocardial oxygen demand without an effect on inotropism or BP.[140]
Nicorandil	Nicorandil promotes systemic venous and coronary vasodilation, and stimulates the ATP-sensitive potassium channels of the vascular smooth muscle, with no effect on contractility or conduction.
Ranolazine	Ranolazine is a selective inhibitor of the late inward sodium current, which, at doses of 500 - 2000 mg daily, exerts beneficial effects on angina frequency and exercise tolerance test through inhibition of calcium overload in the cardiomyocytes, without substantial changes in heart rate or BP.[141,142]
Trimetazidine	Although no single pharmacological mechanism has been universally accepted, trimetazidine is known to target deranged cellular energetics, particularly in ischaemic myocardial tissue. In persons with diabetes, trimetazidine improves HbA1c and glycaemia.[143,144]

ATP = adenosine triphosphate; AV = atrioventricular; BP = blood pressure; CCB = calcium channel blocker; DHP = dihydropyridine; HbA1c = glycated haemoglobin.

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[138,145,146]	• 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

Major side effects, contraindications, drug interactions and precautions of anti-ischaemic drugs

Drug class	Side effects[a]	Contraindications	DDIs	Precautions
CCBs[146,147] [heart rate-lowering (diltiazem and verapamil)]	• Bradycardia • Heart conduction defect • Decreased inotropism • Constipation • Gingival hyperplasia	• Low heart rate or heart rhythm disorder • Sick sinus syndrome • Congestive heart failure	• Negative inotropes (beta-blockers, sodium channel blockers) • Bradycardic drugs • CYP3A4 substrates	• Low BP
CCBs[138,147] (dihydropyridines)	• Headache • Ankle swelling • Fatigue • Flushing • Reflex tachycardia • Gingival hyperplasia	• Cardiogenic shock • Severe aortic stenosis • Obstructive cardiomyopathy • Low BP	• CYP3A4 substrates	• Hepatic impairment
Ivabradine[149,150]	• Visual disturbances (phosphenes) • Headache, dizziness • Bradycardia • Atrial fibrillation • Heart block	• Heart rate <70 b.p.m. • Acute myocardial infarction • Severe hepatic disease	• QTc-prolonging drugs • Combination with strong CYP450 or CYP3A4 inhibitors	• Age >75 years • Severe renal failure • Combination with verapamil or diltiazem • Not to be used in patients with tachyarrhythmias
Nicorandil[146,151]	• Headache • Flushing • Dizziness, weakness • Nausea • Hypotension • Oral, anal, or gastrointestinal ulceration	• PDE5 inhibitors • Cardiogenic shock • Acute heart failure • Low BP	• PDE5 inhibitors (sildenafil or similar drugs)	• Non-steroidal anti-inflammatory drugs are not advised in association with nicorandil

Major side effects, contraindications, drug interactions and precautions of anti-ischaemic drugs

Drug class	Side effects[a]	Contraindications	DDIs	Precautions
Nicorandil[146,151]	• Headache • Flushing • Dizziness, weakness • Nausea • Hypotension • Oral, anal, or gastrointestinal ulceration	• PDE5 inhibitors • Cardiogenic shock • Acute heart failure • Low BP	• PDE5 inhibitors (sildenafil or similar drugs)	• Non-steroidal anti-inflammatory drugs are not advised in association with nicorandil
Trimetazidine[152,153]	• Movement disorders • Gastric discomfort • Nausea • Rash, pruritus, or urticaria • Headache	• Allergy • Parkinson's disease • Tremors and movement disorders • Severe renal impairment	• None reported	• Moderate renal impairment • Elderly
Ranolazine[154,155]	• Dizziness • Constipation • Nausea • Asthenia • QT prolongation	• Liver cirrhosis • Severe renal impairment • Moderate or severe hepatic impairment • Potent CYP3A4 inhibitors • Class Ia or III antiarrhythmics (other than amiodarone)	• CYP450 substrates (digoxin, simvastatin, and cyclosporine) and inhibitors (including CCBs) • QTc-prolonging drugs	Careful dose titration in patients with: • Mild-to-moderate renal impairment • Mild hepatic impairment • Concomitant treatment with CYP3A4 and P-gp inhibitors

Patients with angina and/or dyspnoea and coronary artery disease - Lifestyle management

Recommendations	Class	Level
Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.	I	A
Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle.	I	A
Exercise-based cardiac rehabilitation is recommended as an effective means for patients with CCS to achieve a healthy lifestyle and manage risk factors.	I	A
Involvement of multidisciplinary healthcare professionals (e.g. cardiologists, GPs, nurses, dieticians, physiotherapists, psychologists, and pharmacists) is recommended.	I	A
Psychological interventions are recommended to improve symptoms of depression in patients with CCS.	I	B
Annual influenza vaccination is recommended for patients with CCS, especially in the elderly.	I	B

Recommendations for antianginal drugs in patients with chronic coronary syndrome (1)

Recommendations	Class	Level
General strategy		
It is recommended to tailor the selection of antianginal drugs to the patient's characteristics, comorbidities, concomitant medications, treatment tolerability, and underlying pathophysiology of angina, also considering local drug availability and cost.	I	C
Selection of antianginal medication		
Short-acting nitrates are recommended for immediate relief of angina.	I	B
Initial treatment with beta-blockers and/or CCBs to control heart rate and symptoms is recommended for most patients with CCS.	I	B
If anginal symptoms are not successfully controlled by initial treatment with a beta-blocker or a CCB alone, the combination of a beta-blocker and a DHP-CCB should be considered, unless contraindicated.	IIa	B
Long-acting nitrates or ranolazine should be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIa	B

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for antianginal drugs in patients with chronic coronary syndrome (2)

Recommendations	Class	Level
Selection of antianginal medication cont.		
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.	IIa	B
Ivabradine should be considered as add-on antianginal therapy in patients with left ventricular systolic dysfunction (LVEF <40%) and inadequate control of symptoms, or as part of initial treatment in properly selected patients.	IIa	B
Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate control of symptoms while on treatment with beta-blockers and/or CCBs, or as part of initial treatment in properly selected patients.	IIb	B
Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF >40%, and no clinical heart failure.	III	B
Combination of ivabradine with non-DHP-CCB or other strong CYP3A4 inhibitors is not recommended.	III	B
Nitrates are not recommended in patients with hypertrophic cardiomyopathy or in co-administration with phosphodiesterase inhibitors.	III	B

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (1)

Recommendations	Class	Level
Long-term antithrombotic therapy in patients with CCS and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.	I	A
After CABG, aspirin 75–100 mg daily is recommended lifelong.	I	A
In patients *without* prior MI or revascularization but with evidence of significant obstructive CAD, aspirin 75–100 mg daily is recommended lifelong.	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at enhanced ischaemic risk and without high bleeding risk (options and definitions in Table 6 and in the Supplementary data online, *Tables S2* and *S3*).	IIa	A

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Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (2)

Recommendations	Class	Level
Long-term antithrombotic therapy in patients with CCS and no clear indication for oral anticoagulation cont.		
In CCS or stabilized post-ACS patients who underwent PCI and were initially treated with ticagrelor-based DAPT, who remain at high ischaemic risk and are not at high bleeding risk, ticagrelor monotherapy 90 mg b.i.d. may be considered as an alternative to dual or other single antiplatelet therapy.	IIb	C
Antithrombotic therapy post-percutaneous coronary intervention in patients with CCS and no indication for oral anticoagulation		
In CCS patients with no indication for oral anticoagulation, DAPT consisting of aspirin 75–100 mg and clopidogrel 75 mg daily for up to 6 months is recommended as the default antithrombotic strategy after PCI-stenting.	I	A
In patients at high bleeding risk but not at high ischaemic risk, it is recommended to discontinue DAPT 1–3 months after PCI and to continue with single antiplatelet therapy.	I	A

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (3)

Recommendations	Class	Level
Antithrombotic therapy post-percutaneous coronary intervention in patients with CCS and no indication for oral anticoagulation cont.		
Stopping DAPT after 1–3 months from PCI-stenting may be considered in patients who are not at high bleeding risk nor at high risk of ischaemic events.	IIb	B
In CCS patients undergoing high-thrombotic risk stenting (e.g. complex left main stem, 2-stent bifurcation, suboptimal stenting result, prior stent thrombosis, previously known CYP2C19 *2/*3 polymorphisms), prasugrel or ticagrelor (in addition to aspirin) may be considered instead of clopidogrel, for the first month, and up to 3–6 months.	IIb	C
Long-term antithrombotic therapy in patients with CCS and an indication for oral anticoagulation		
In CCS patients with a long-term indication for OAC, an AF therapeutic dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (4)

Recommendations	Class	Level
Antithrombotic therapy post-PCI in CCS patients with an indication for oral anticoagulation		
In patients with an indication for OAC who undergo PCI, initial low-dose aspirin once daily is recommended (loading dose when not on maintenance dose) in addition to OAC and clopidogrel.	I	C
In patients who are eligible for OAC, DOAC (unless contraindicated) is recommended in preference to VKA.	I	A

After uncomplicated PCI in CCS patients with concomitant indication for OAC:
• early cessation of aspirin (≤1 week);
• followed by continuation of OAC and clopidogrel:
  • up to 6 months in patients not at high ischaemic risk; or
  • up to 12 months in patients at high ischaemic risk;
• followed by OAC alone;
is recommended.
	I	A

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (5)

Recommendations	Class	Level
Antithrombotic therapy post-PCI in CCS patients and an indication for oral anticoagulation cont.		
When concerns about high bleeding risk prevail over concerns about stent thrombosis or ischaemic stroke: rivaroxaban 15 mg daily should be considered in preference to rivaroxaban 20 mg daily for the duration of concomitant antiplatelet therapy;	IIa	B
dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg twice daily for the duration of concomitant antiplatelet therapy.	IIa	B
In patients with an indication for VKA in combination with single or dual antiplatelet therapy, targeting VKA intensity to an INR in the lower part of the recommended range and to a time in therapeutic range >70% should be considered.	IIa	B
The use of ticagrelor or prasugrel is generally not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for antithrombotic therapy in patients with chronic coronary syndrome (6)

Recommendations	Class	Level
Antithrombotic therapy post-coronary artery bypass grafting		
It is recommended to initiate aspirin post-operatively as soon as there is no concern over bleeding.	I	B
DAPT may be considered after CABG in selected patients at greater risk of graft occlusion and at low risk of bleeding.	IIb	B
Use of proton pump inhibitors		
A proton pump inhibitor is recommended in patients at increased risk of gastrointestinal bleeding for the duration of combined antithrombotic therapy (antiplatelet therapy and/or OAC).	I	A
A proton pump inhibitor should be considered when a single antithrombotic (antiplatelet or anticoagulant) drug is used, considering the gastrointestinal bleeding risk of the individual patient.	IIa	A

Options for extended intensified antithrombotic therapy

Drug	Dose	Clinical setting	NNT (ischaemic outcomes)	NNH (bleeding outcomes)
Co-administered with aspirin 100 mg o.d.				
Rivaroxaban (COMPASS trial; vs. placebo)	2.5 mg b.i.d.	Patients with CAD or symptomatic PAD at high risk of ischaemic events	77	84 (modified-ISTH major bleeding)
Co-administered with low-dose aspirin 75–162 mg o.d.				
Clopidogrel, (6505/9961 of DAPT trial; vs. placebo)	75 mg/day	Post MI in patients who have tolerated DAPT for 1 year (25% ACS, 22% previous MI)	63	105 (moderate and severe GUSTO bleeds, or BARC 2, 3, and 5 bleeds)
Prasugrel, (3456/9961 of DAPT trial; vs. placebo)	10 mg/day (5 mg/day if body weight <60 kg or age ≥75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year	63	105 (as above)
Ticagrelor (PEGASUS-TIMI 54; vs. placebo)	60/90 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	84	81 (TIMI major bleeds)

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Recommendations for lipid-lowering drugs in patients with chronic coronary syndrome

Recommendations	Class	Level
Lipid-lowering treatment with an LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C vs. baseline is recommended.	I	A
A high-intensity statin up to the highest tolerated dose to reach the LDL-C goals is recommended for all patients with CCS.	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For patients who are statin intolerant and do not achieve their goal on ezetimibe, combination with bempedoic acid is recommended.	I	B
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.	I	A
For patients who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, combination with bempedoic acid should be considered.	IIa	C
For patients with a recurrent atherothrombotic event (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B

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Recommendations for SGL2 inhibitors and/or glucagon-like peptide-1 receptor agonists in patients with CCS

Recommendations	Class	Level
CCS patients with type 2 diabetes		
SGLT2 inhibitors with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
GLP-1 receptor agonists with proven CV benefit are recommended in patients with T2DM and CCS to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication.	I	A
CCS patients without type 2 diabetes		
The GLP-1 receptor agonist semaglutide should be considered in overweight (BMI >27 kg/m2) or obese CCS patients without diabetes to reduce CV mortality, MI, or stroke.	IIa	B

Recommendations for anti-inflammatory drugs in patients with chronic coronary syndrome

Recommendations	Class	Level
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.	IIa	A

Recommendations for angiotensin-converting enzyme inhibitors in patients with chronic coronary syndrome

Recommendations	Class	Level
In CCS patients, ACE-Is (or ARBs) are recommended in the presence of specific comorbidities, such as hypertension, diabetes, or heart failure.	I	A
ACE-Is should be considered in CCS patients at very high risk of cardiovascular events.	IIa	A

Figure 1

Central illustration: Clinical presentations of CCS and mechanisms of myocardial ischaemia

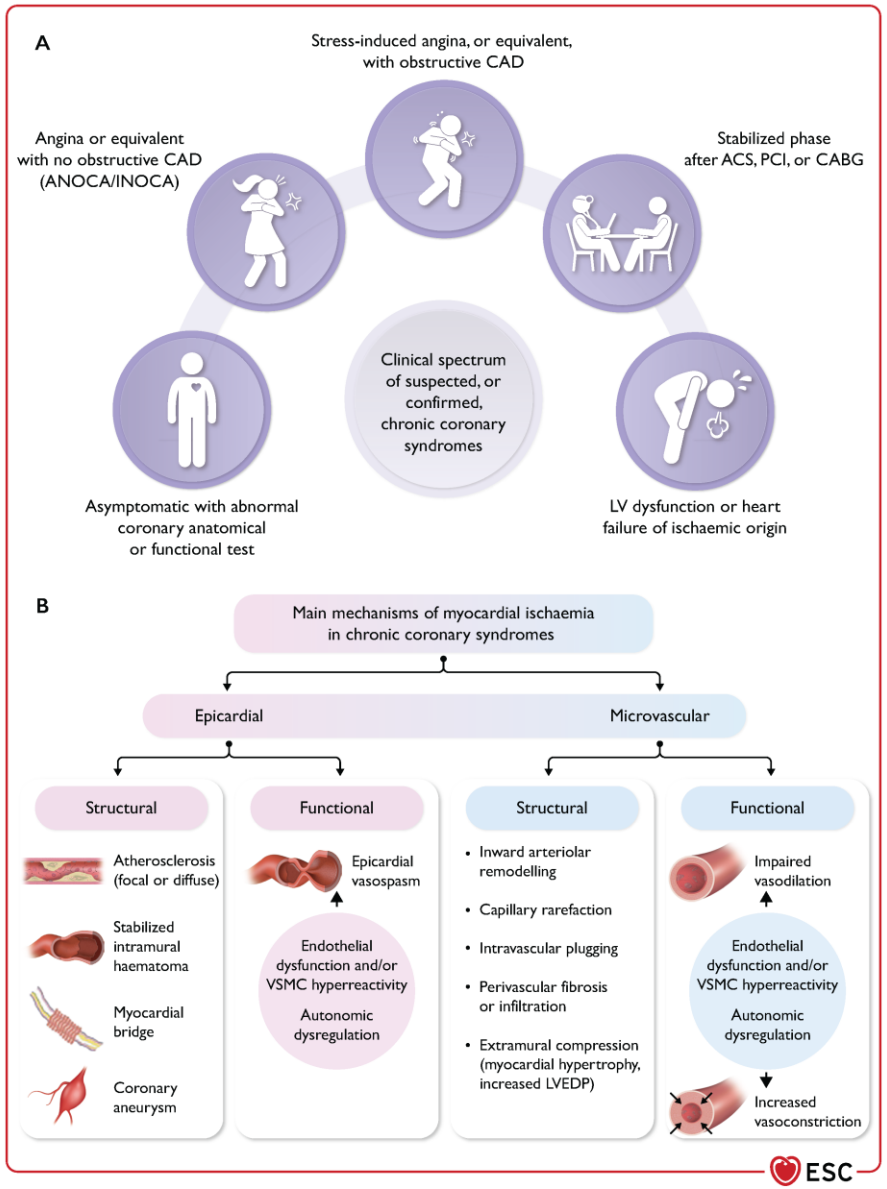

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Figure 2

Stepwise approach to the initial management of individuals with suspected CCS

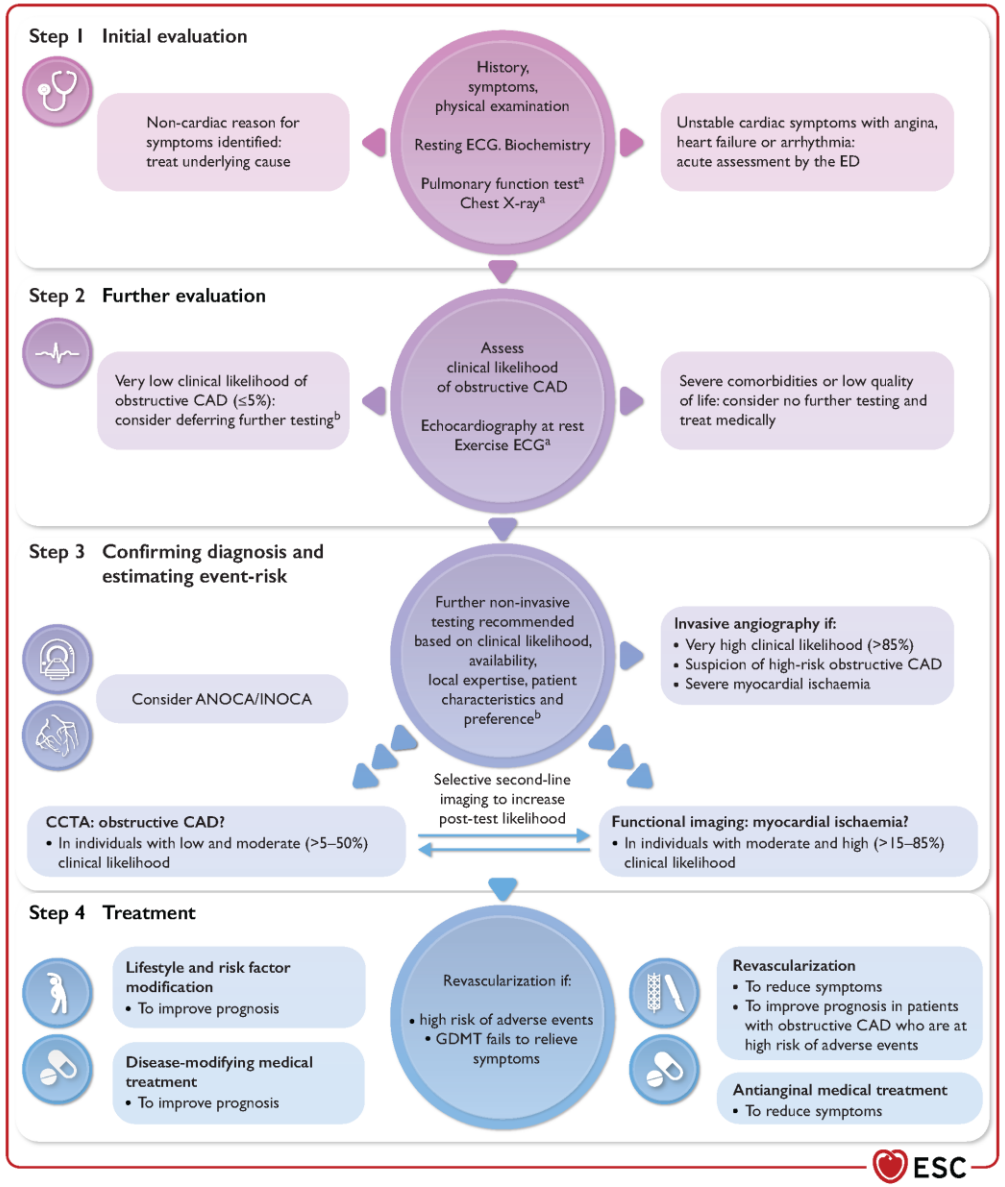

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Figure 3

Main CCS symptoms: angina and exertional dyspnoea

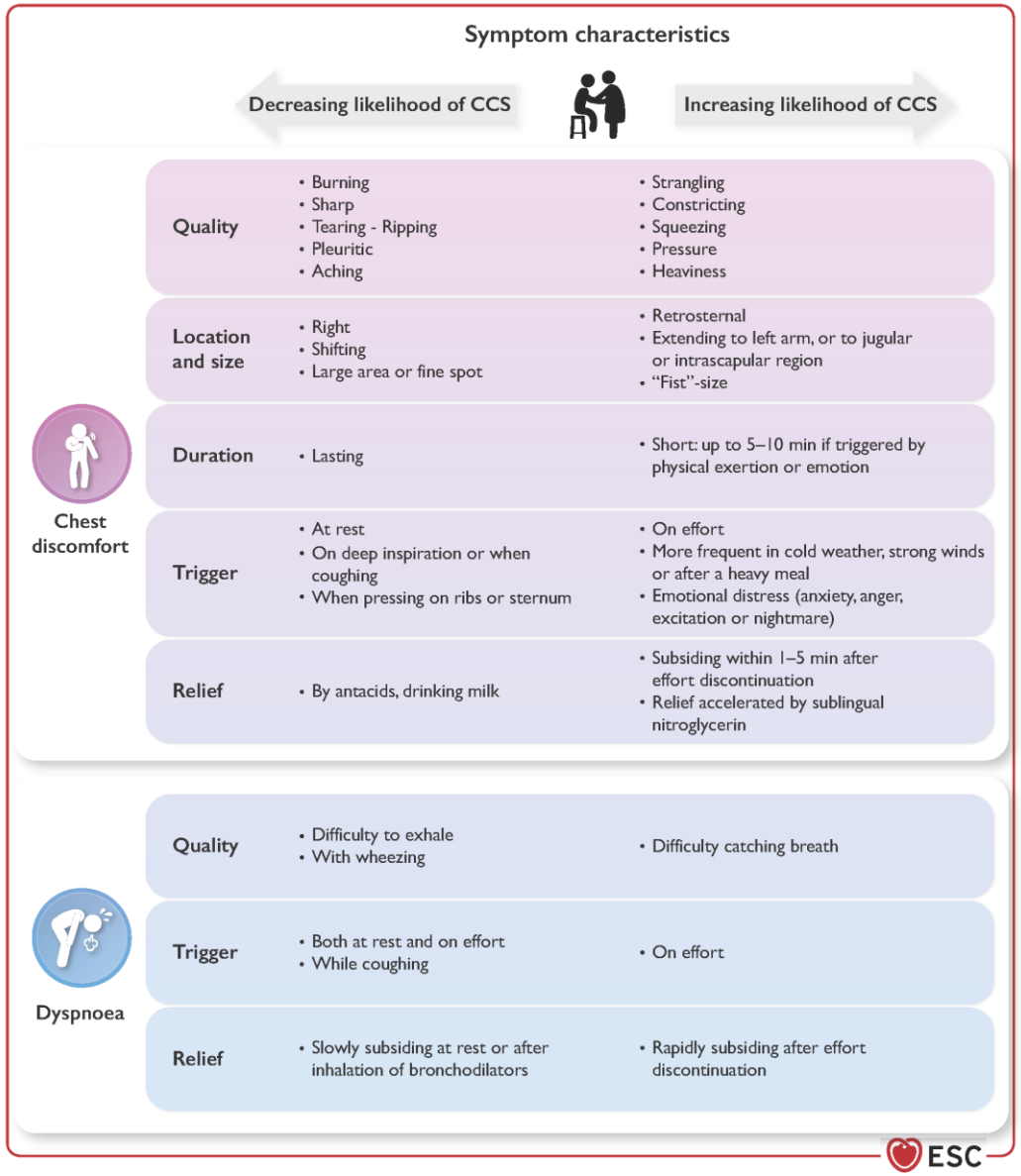

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Figure 4

Estimation of the clinical likelihood of obstructive CAD

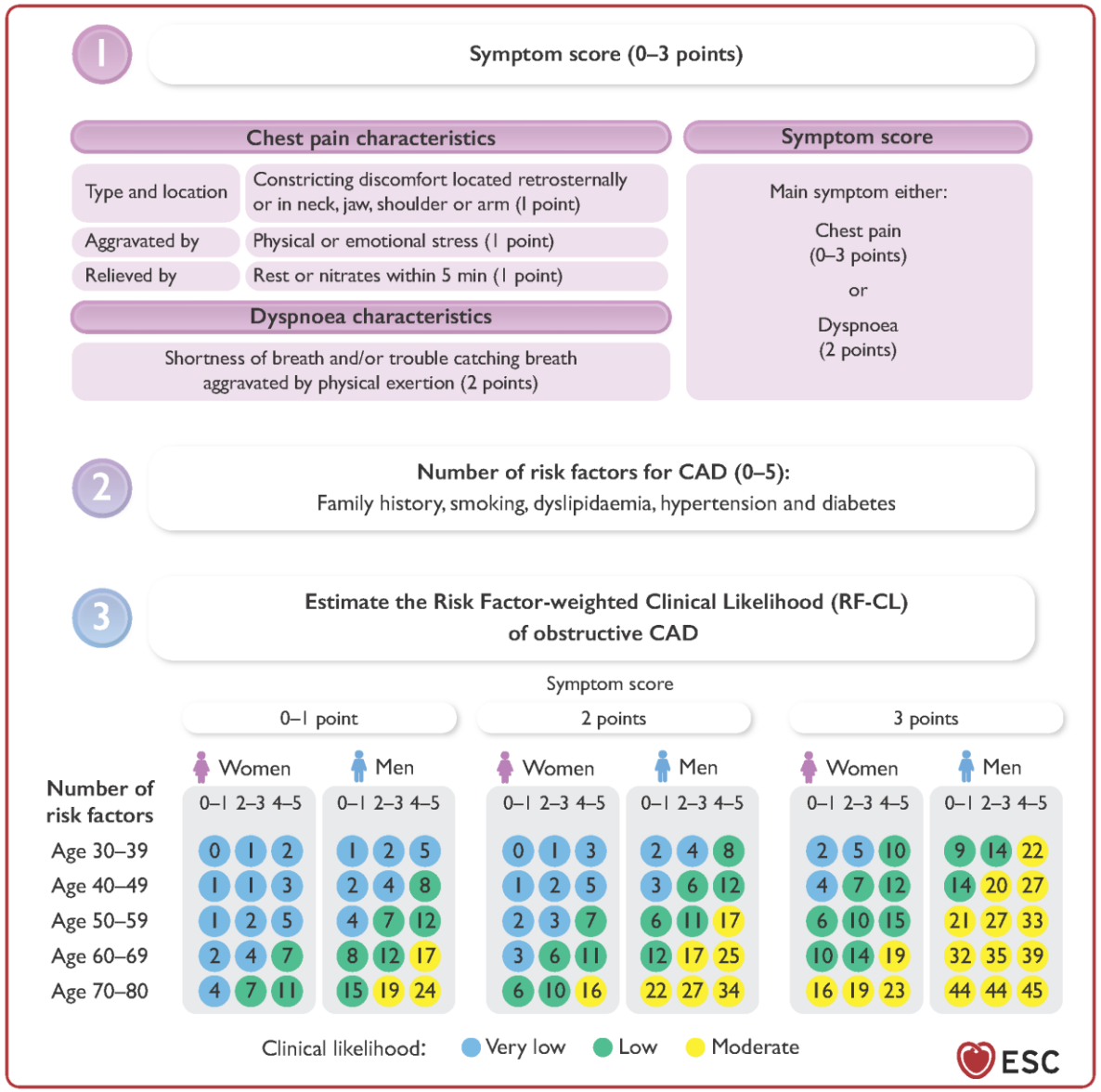

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Figure 5

Adjustment and reclassification of the estimated clinical likelihood of obstructive CAD

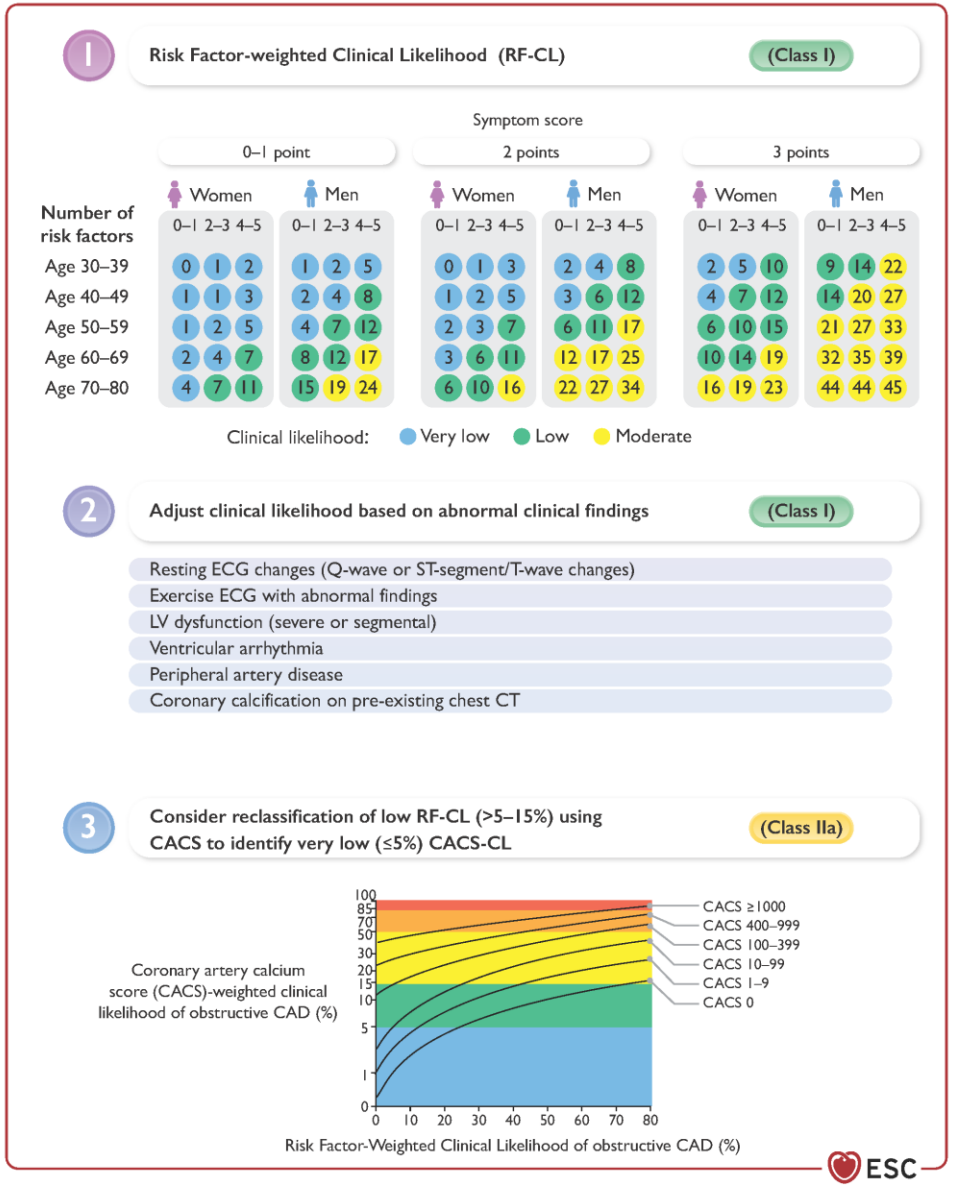

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Figure 6

Appropriate first-line testing in symptomatic patients with suspected CCS

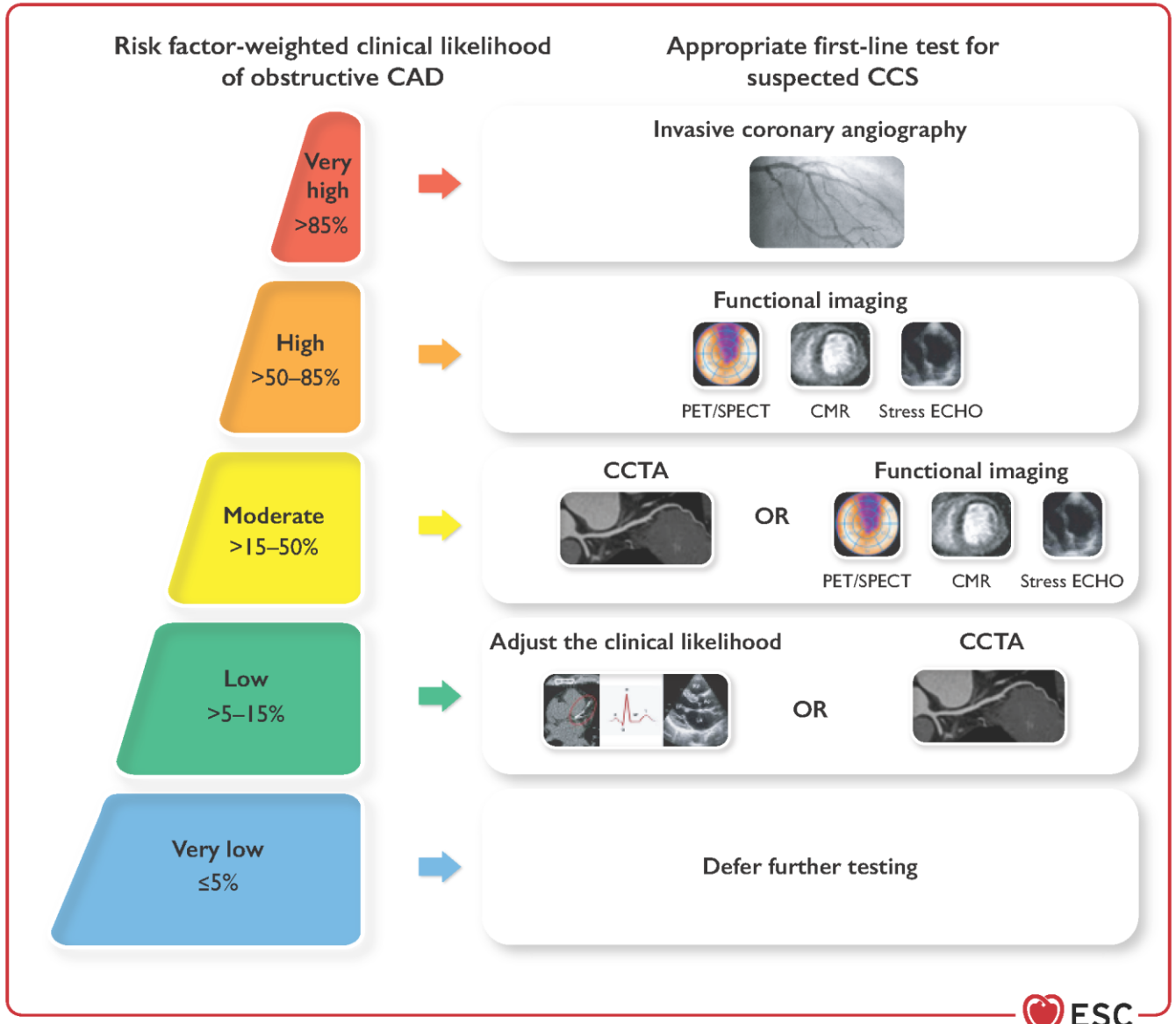

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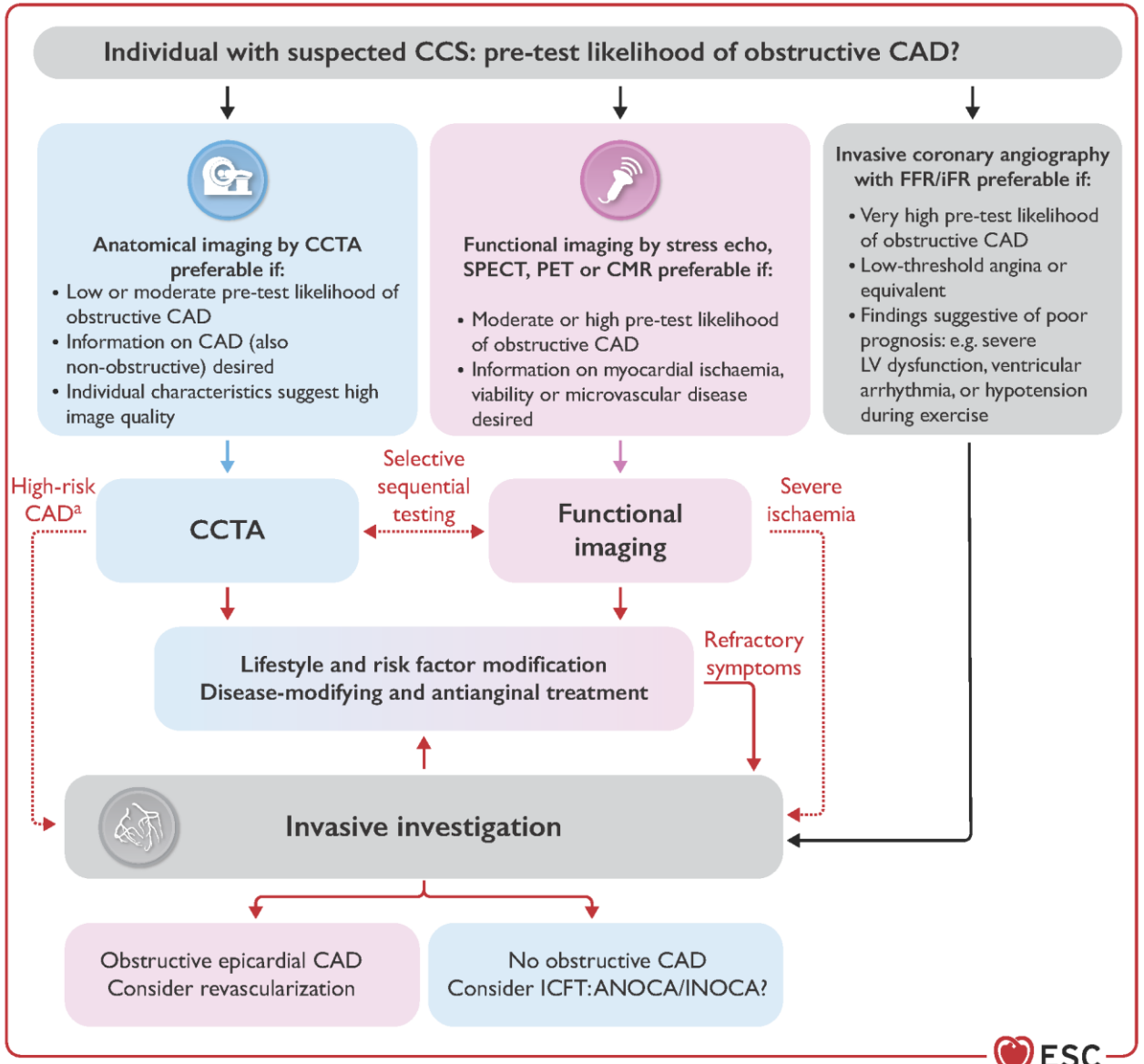
Figure 7

Initial management of symptomatic patients with suspected CCS



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(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Figure 8

Ruling in and ruling out functionally significant obstructive CAD by sequential anatomical (CCTA) and functional (DSE) testing

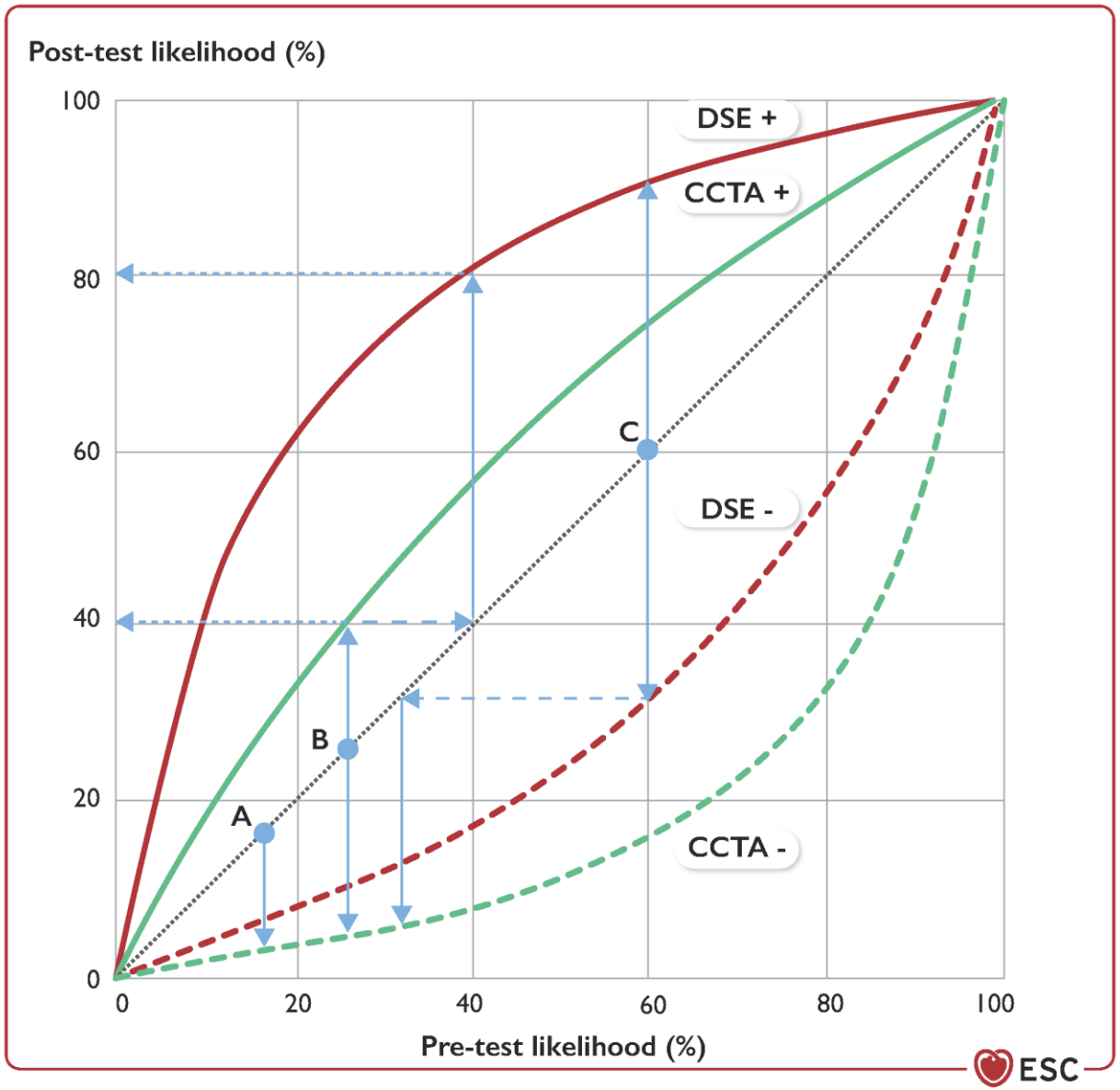

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Figure 9

Possible combinations of antianginal drugs

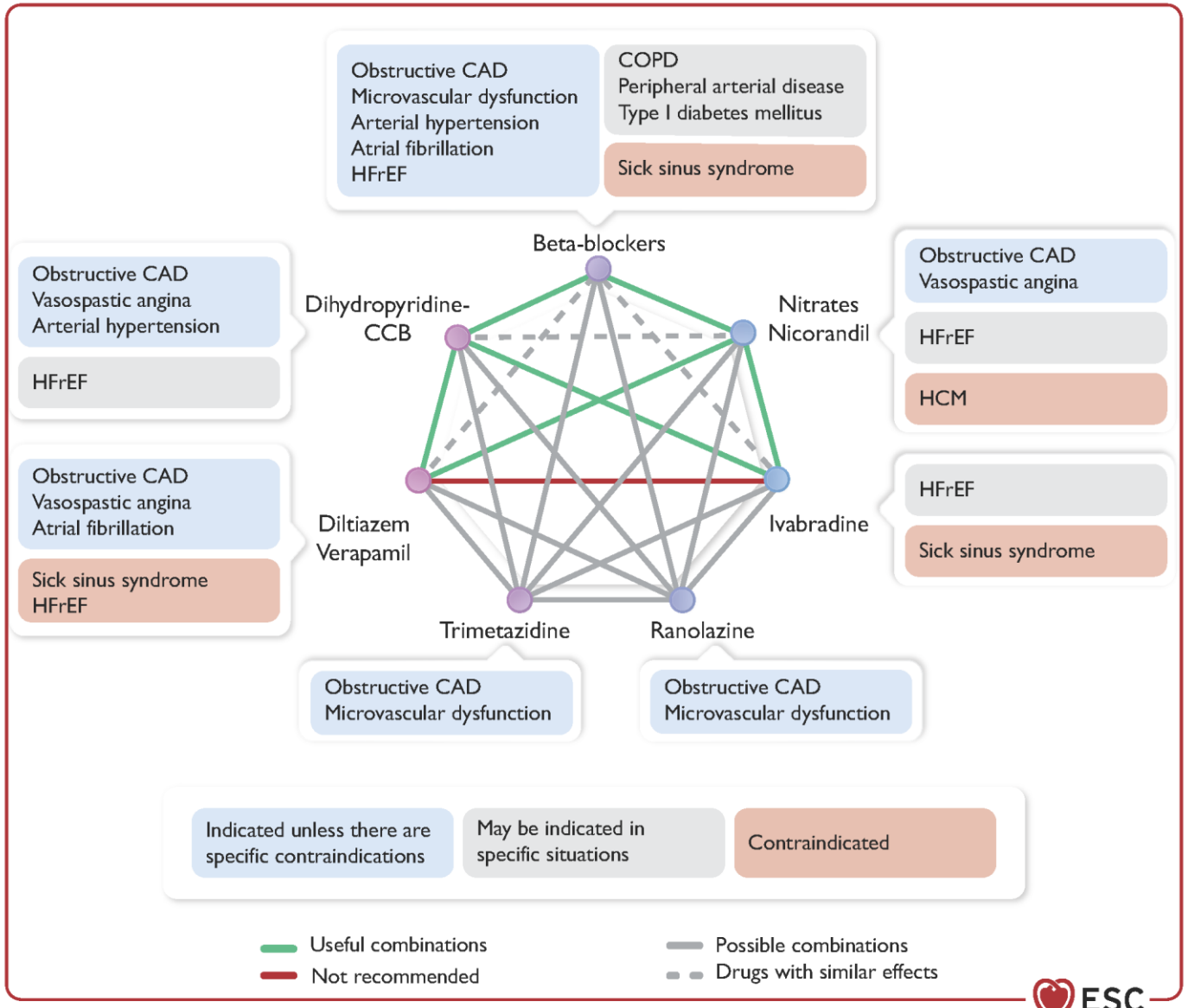

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Figure 10

Antithrombotic drugs for chronic coronary syndromes: pharmacological targets

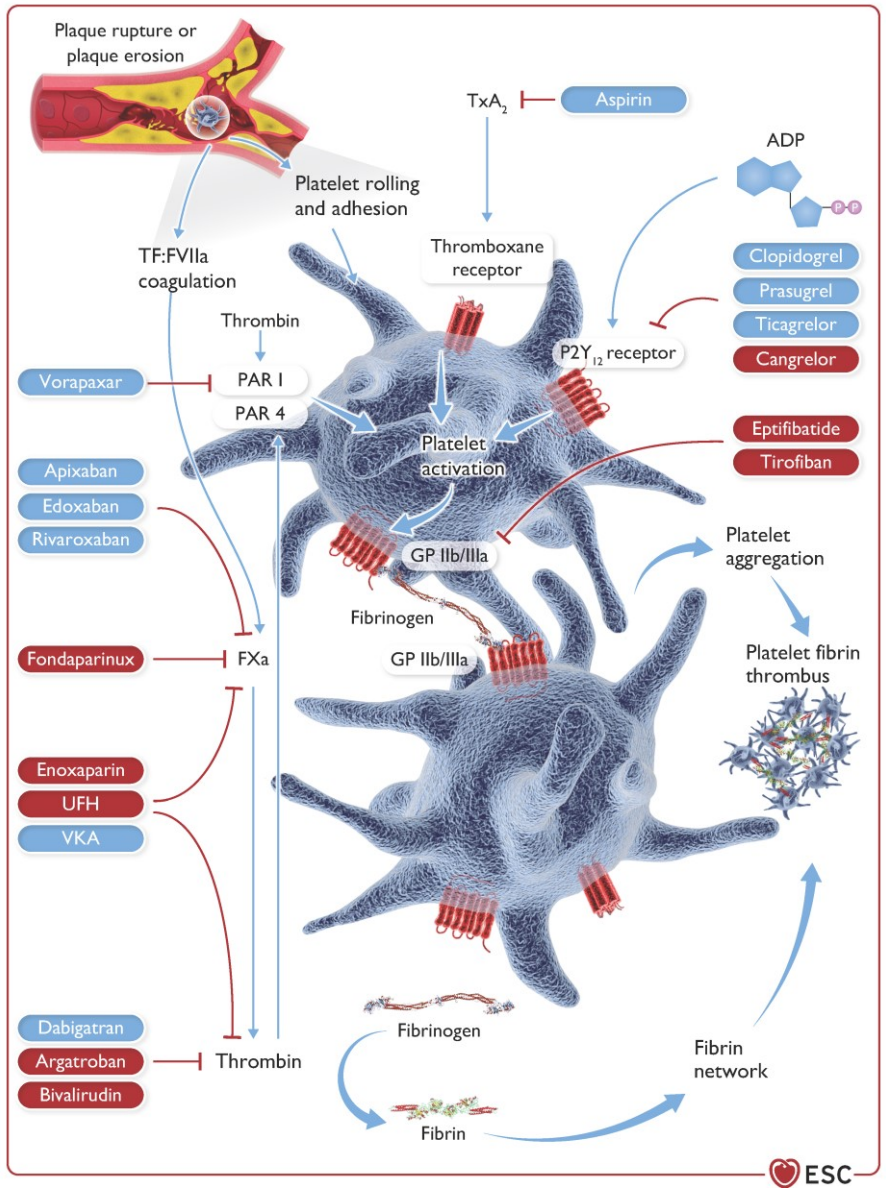

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Figure 11

Antithrombotic treatment in CCS patients undergoing PCI

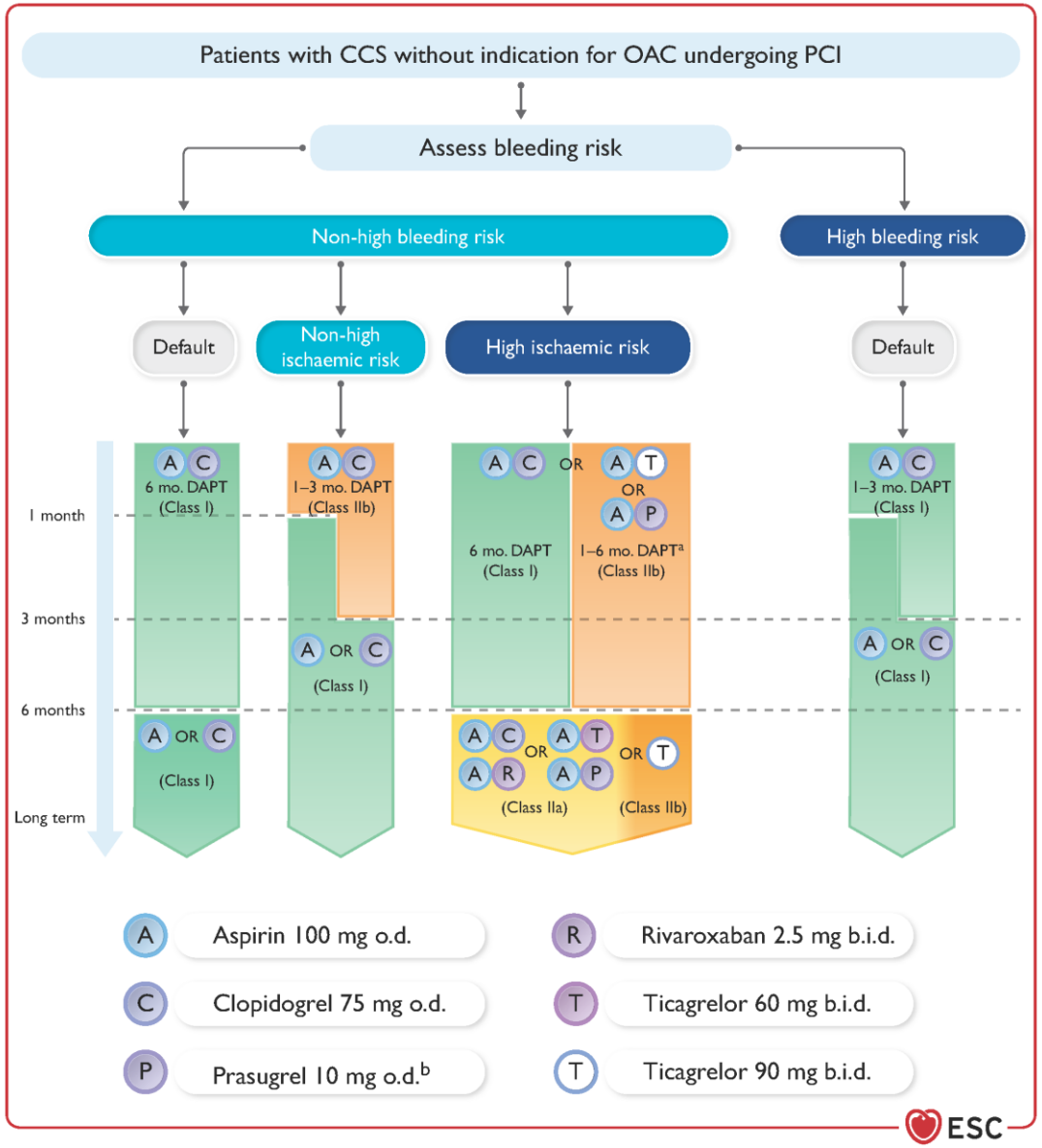

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Figure 12

Prevalence of disease characteristics in patients with ANOCA/INOCA referred for invasive coronary functional testing

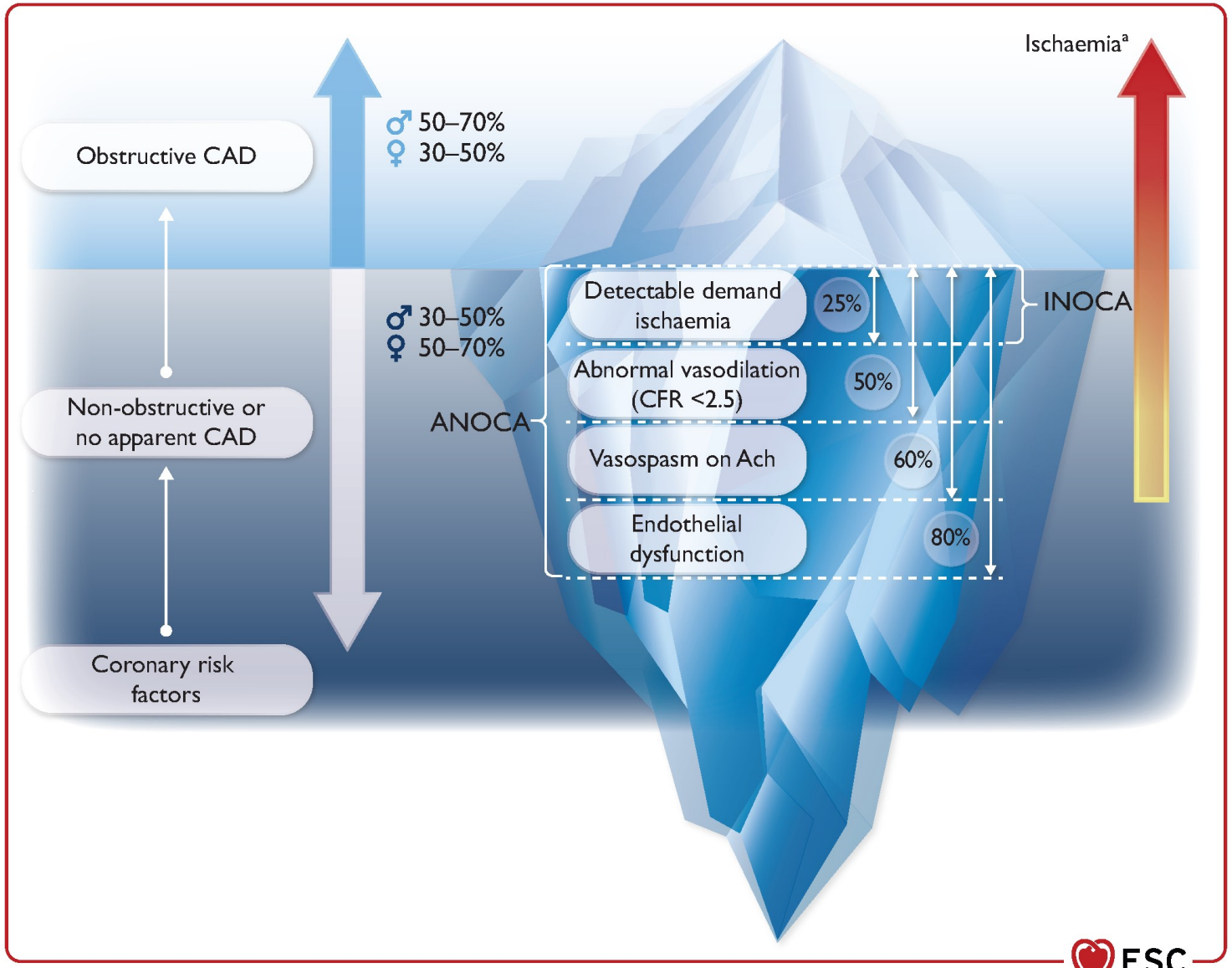

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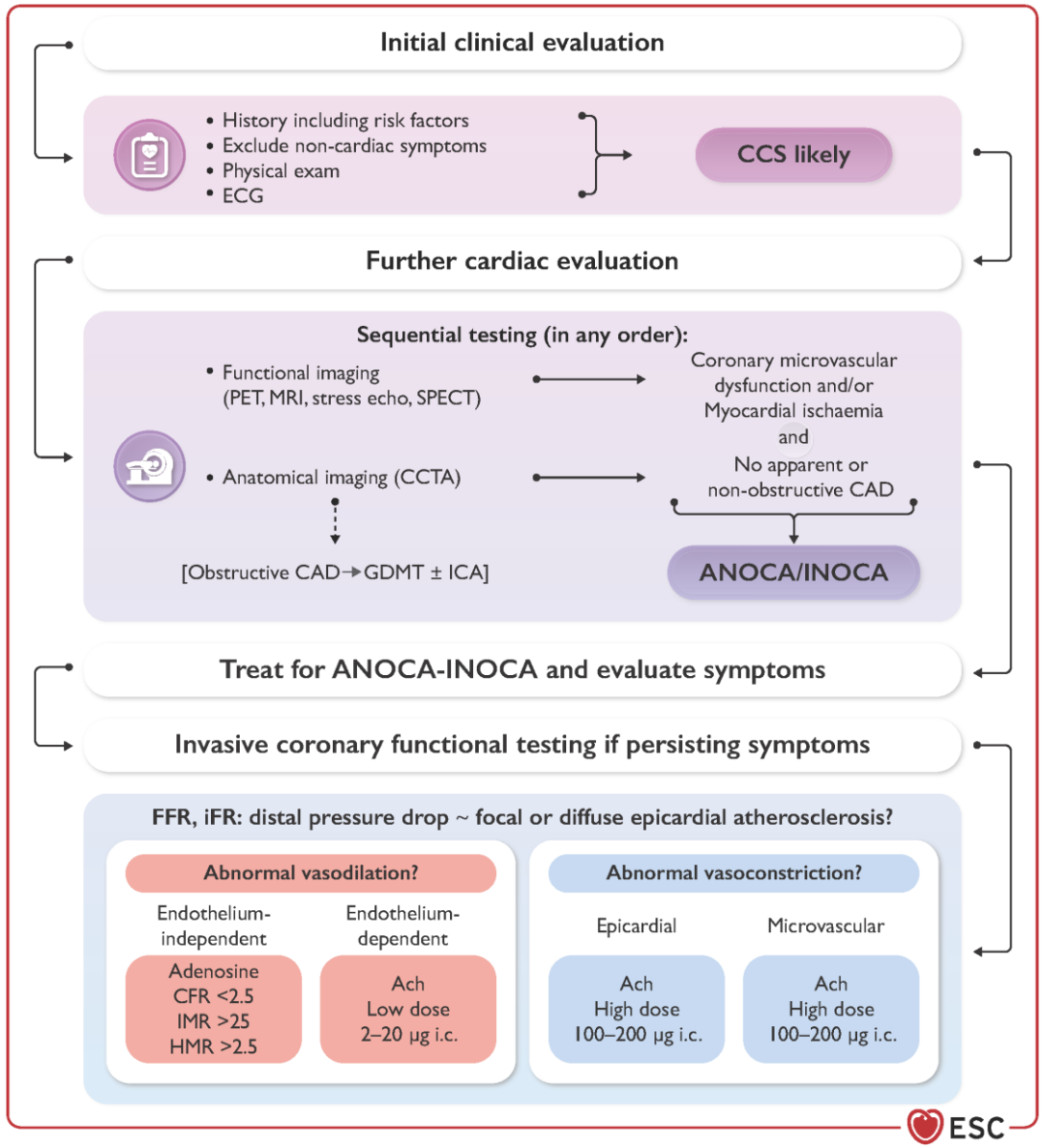
Figure 13

Diagnostic algorithm for patients with angina /ischaemia with non-obstructive coronary arteries



2024 ESC Guidelines for the management of chronic coronary syndromes (European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Figure 14

Spasm provocation and functional testing protocol

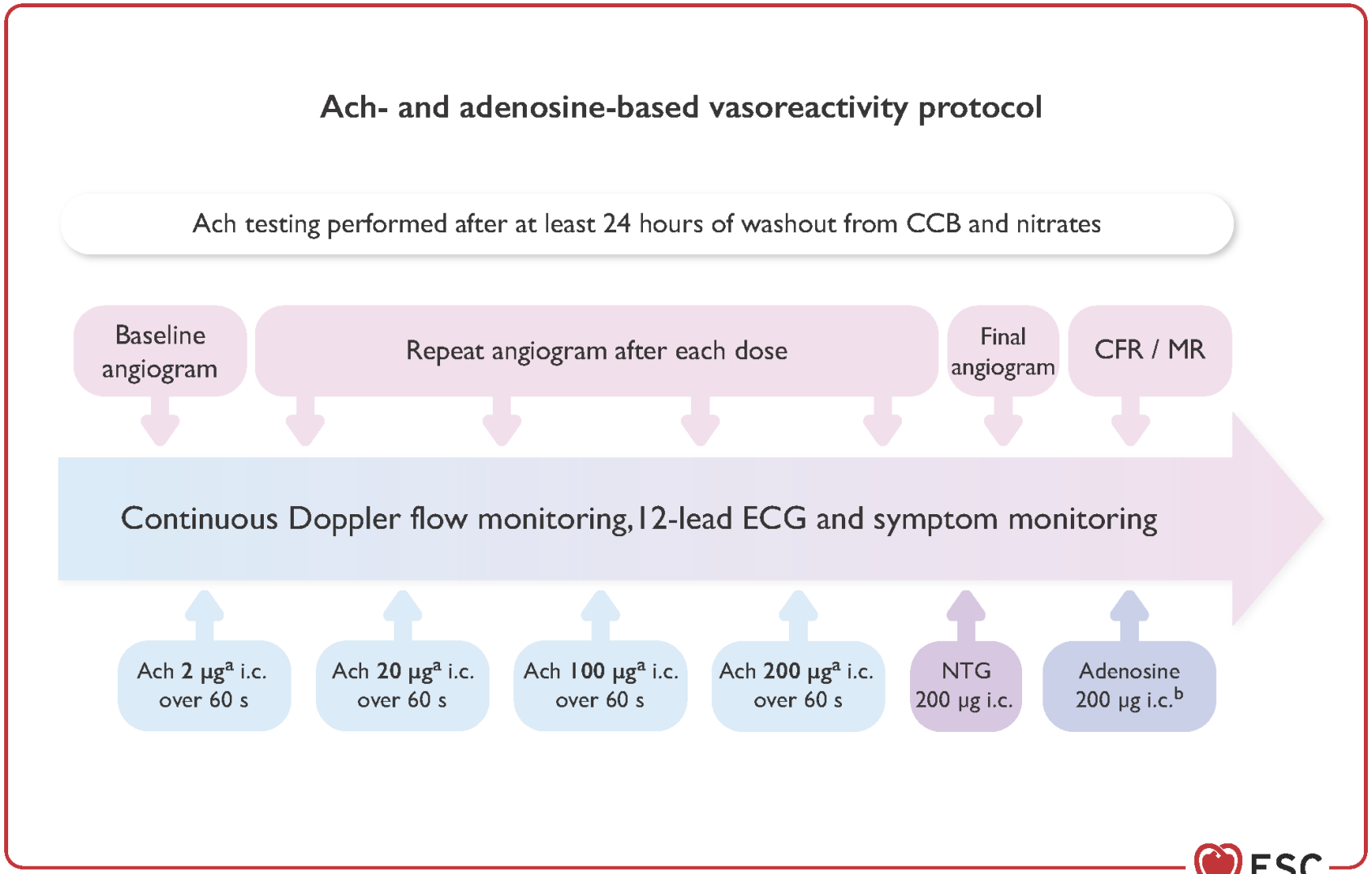


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Figure 15

Treatment of angina/ischaemia with non-obstructive coronary arteries

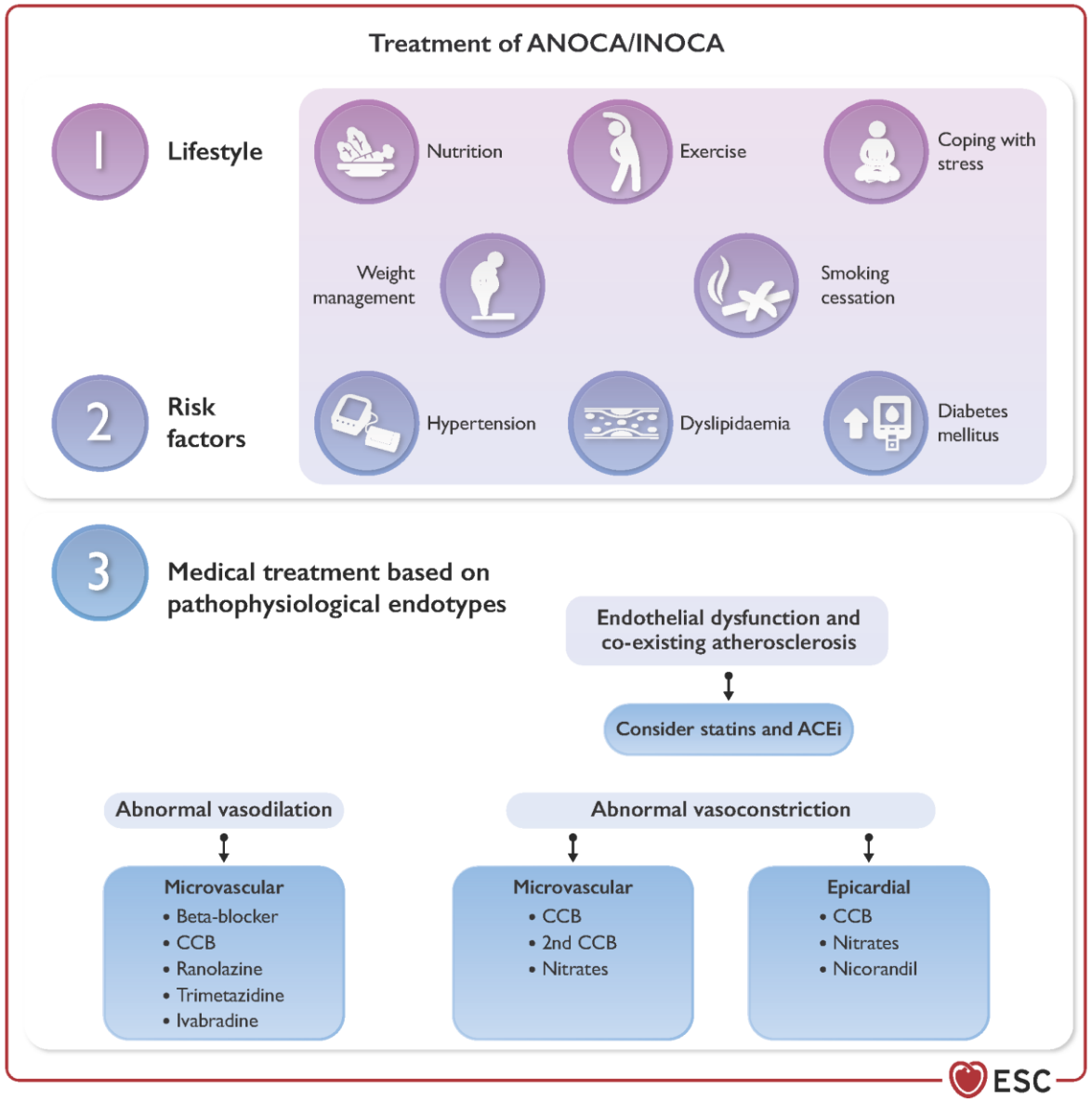

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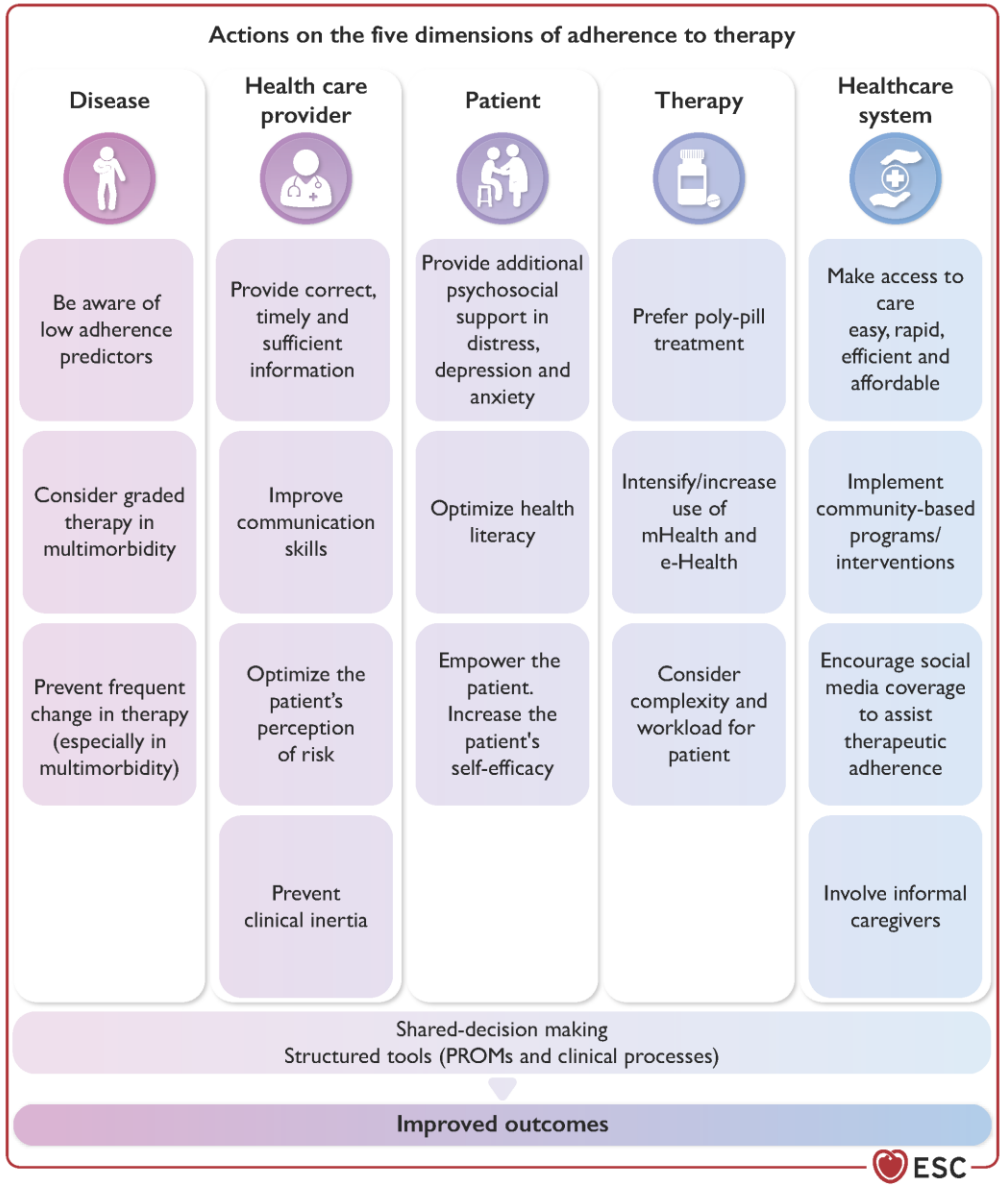
Figure 16

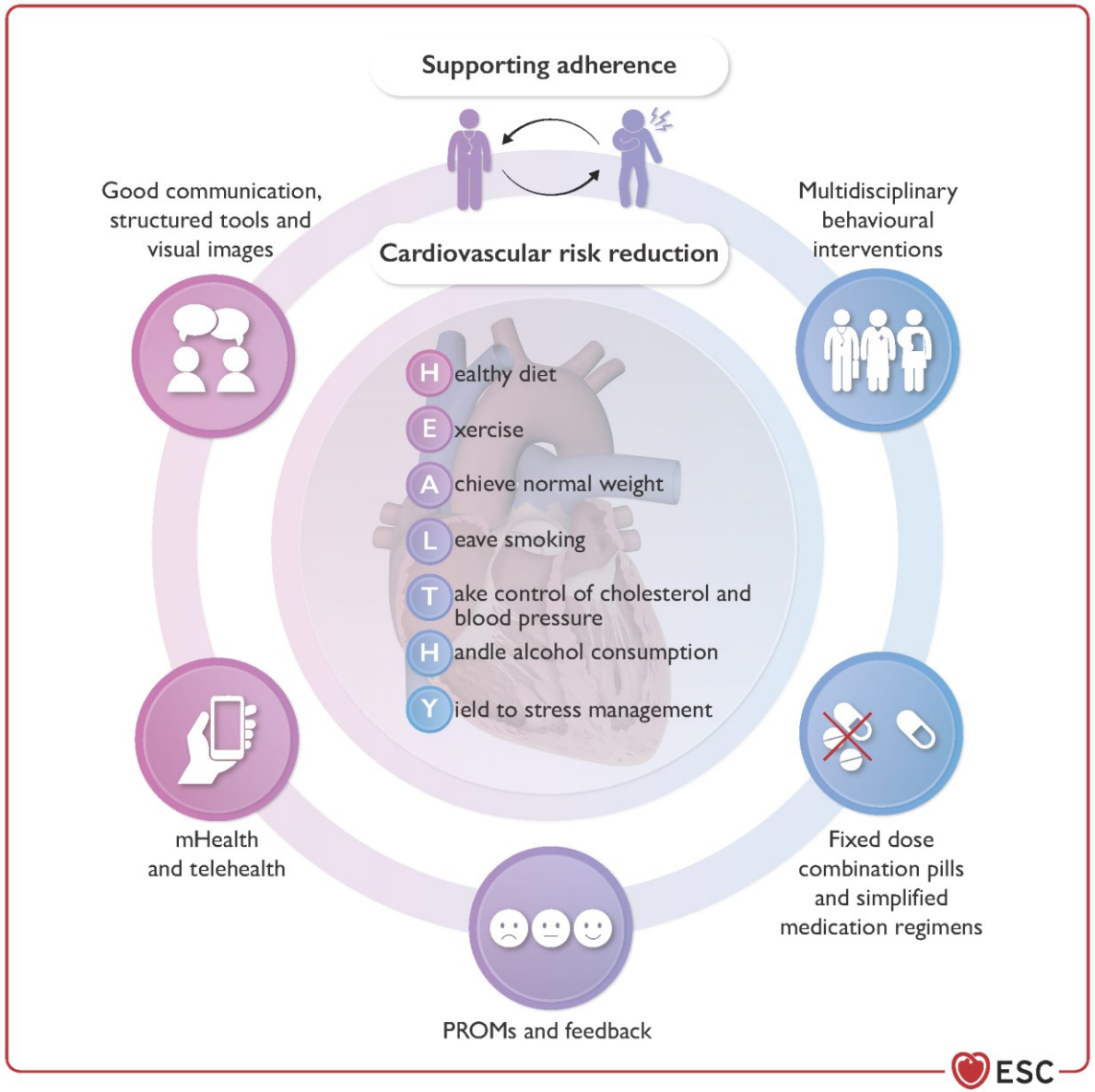
Actions on the five dimensions of adherence to therapy



2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Figure 17

Strategies for long-term adherence to a healthy lifestyle



2024 ESC Guidelines for the management of chronic coronary syndromes
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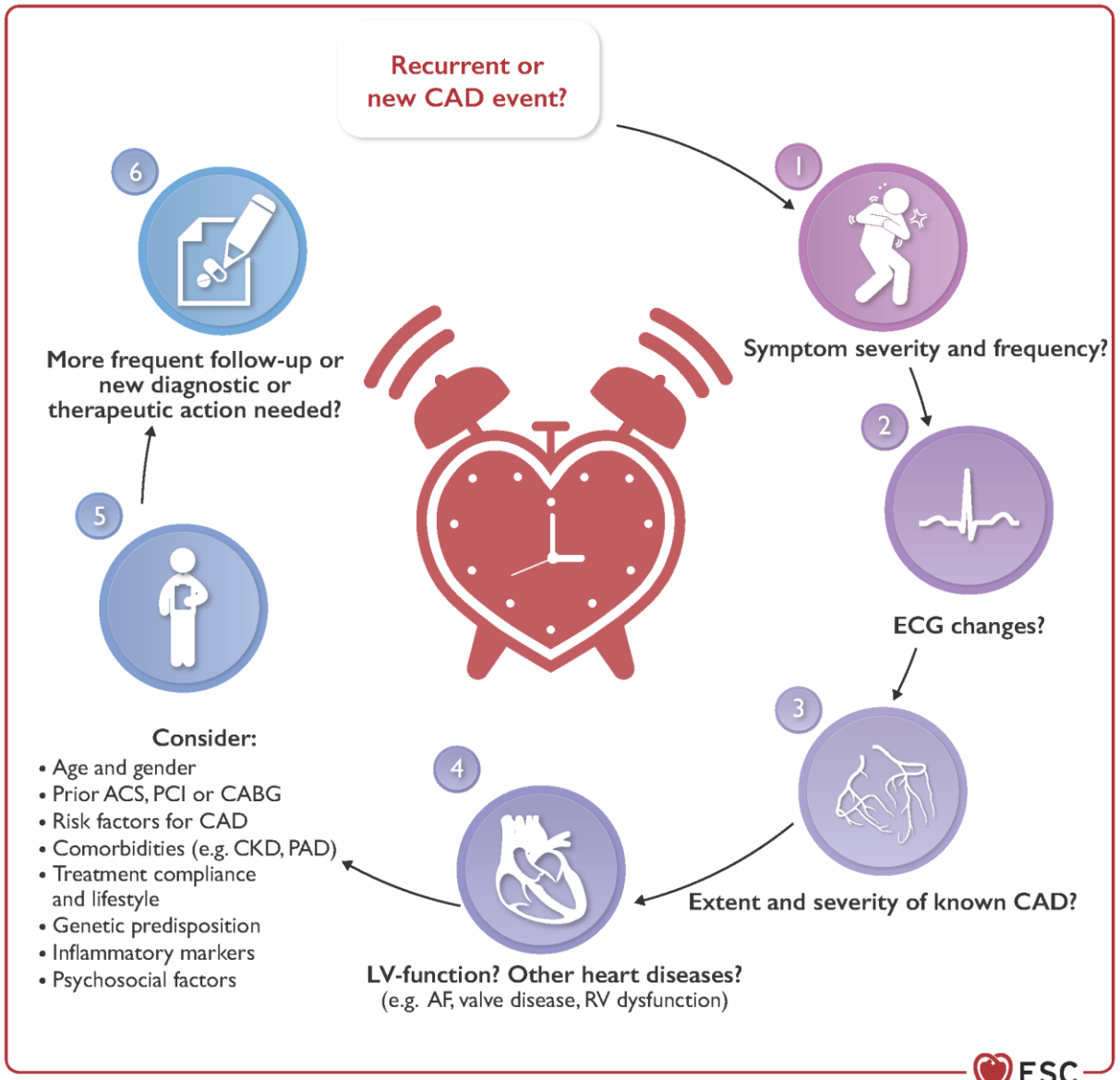
Figure 18

Approach for the follow-up of patients with established CCS



2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

Patients with angina and/or dyspnoea and coronary artery disease –

Long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences.

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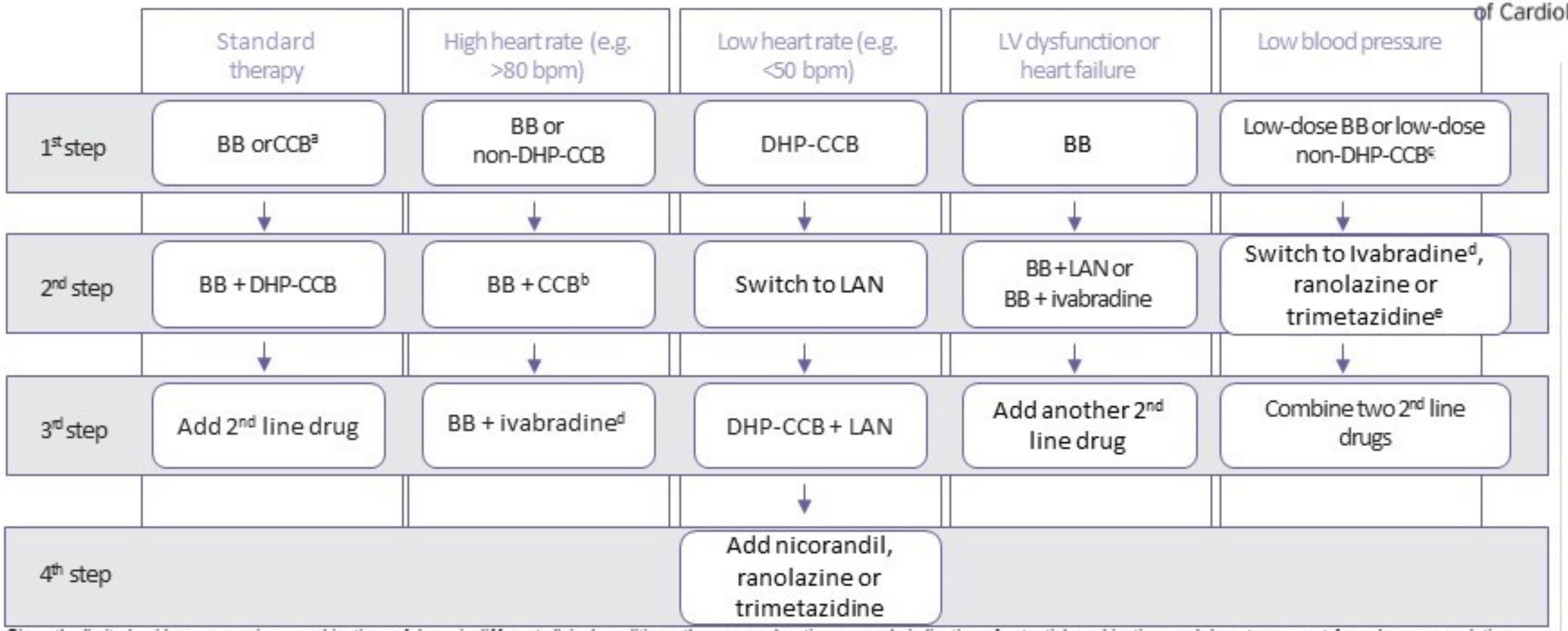

Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB = non-dihydropyridine calcium channel blocker. [a]Combination of a BB with a DHP-CCB should be considered as first step; combination of a BB or a CCB with a second-line drug may be considered as a first step; [b]The combination of a BB and non-DHP-CCB should initially use low doses of each drug under close monitoring of tolerance, particularly heart rate and blood pressure; [c]Low-dose BB or low-dose non-DHP-CCB should be used under close monitoring of tolerance, particularly heart rate and blood pressure. [d]Ivabradine should not be combined with non-DHP-CCB. [e]Consider adding the drug chosen at step 2 to the drug tested at step 1 if blood pressure remains unchanged.

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ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

Patients with angina and/or dyspnoea and coronary artery disease - Anti-ischaemic drugs (1)

Recommendations	Class	Level
General considerations		
Medical treatment of symptomatic patients requires one or more drug(s) for angina/ischaemia relief in association with drug(s) for event prevention.	I	C
It is recommended that patients are educated about the disease, risk factors, and treatment strategy.	I	C
Timely review of the patient's response to medical therapies (e.g. 2-4 weeks after drug initiation) is recommended.	I	C

Patients with angina and/or dyspnoea and coronary artery disease - Anti-ischaemic drugs (2)

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Recommendations	Class	Level
Angina relief		
Short-acting nitrates are recommended for immediate relief of effort angina.	I	B
First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms.	I	A
If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered.	IIa	C
Initial first-line treatment with the combination of a beta-blocker and a DHP-CCB should be considered.	IIa	B
Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms.	IIa	B
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.	IIa	B

Patients with angina and/or dyspnoea and coronary artery disease - Anti-ischaemic drugs (3)

ESC European Society of Cardiology

Recommendations	Class	Level
Angina relief		
Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.	IIa	B
In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance.	IIb	C
In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance.	IIb	B
Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy and co-administration of phosphodiesterase inhibitors.	III	B

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (1)

Recommendations	Class	Level
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75-100 mg daily is recommended in patients with a previous MI or revascularization.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack.	IIb	B
Aspirin 75-100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (2)

Recommendations	Class	Level
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with high risk of ischaemic events[a] and without high bleeding risk.[b]	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischaemic events[c] and without high bleeding risk.[b]	IIb	A

[a] Diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, PAD, or CKD with eGFR 15-59 mL/min/1.73 m^2.
[b] Prior history of intracerebral haemorrhage or ischaemic stroke, history of other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure requiring dialysis or with eGFR <15 mL/min/1.73 m^2.
[c] At least one of the following: multivessel/diffuse CAD, diabetes mellitus requiring medication, recurrent MI, PAD, HF, or CKD with eGFR 15-59 mL/min/1.73 m2

Patients with angina and/or dyspnoea and coronary artery disease

Treatment options for dual antithrombotic therapy

Drug option	Dose	Indication	Additional cautions
Clopidogrel	75 mg o.d.	Post-MI in patients who have tolerated DAPT for 1 year	
Prasugrel	10 mg o.d. or 5 mg o.d. if body weight <60 kg or age >75 years	Post-PCI for MI in patients who have tolerated DAPT for 1 year	Age >75 years
Rivaroxaban	2.5 mg b.i.d.	Post-MI >1 year or multivessel CAD	eGFR 15-29 mL/min/1.73 m^2
Ticagrelor	60 mg b.i.d.	Post-MI in patients who have tolerated DAPT for 1 year	

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (3)

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Recommendations	Class	Level
Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm		
Aspirin 75-100 mg daily is recommended following stenting.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1-3 months) is indicated due to risk or the occurrence of life-threatening bleeding.	I	A
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) should be considered for 3 months in patients with a higher risk of life-threatening bleeding.	IIa	A

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (4)

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Recommendations	Class	Level
Antithrombotic therapy post-PCI in patients with CCS and in sinus rhythm		
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.	IIb	C
Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of aspirin intolerance.	IIb	C

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (7)

Recommendations	Class	Level
Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.)[a] is used in preference to a VKA in combination with antiplatelet therapy.	I	A

[a] See summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75-80 years, and/or drug interactions.

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (11)

Recommendations	Class	Level
Use of proton-pump inhibitors		
Concomitant use of a proton-pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, or OAC monotherapy who are at high risk of gastrointestinal bleeding.	I	A

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (12)

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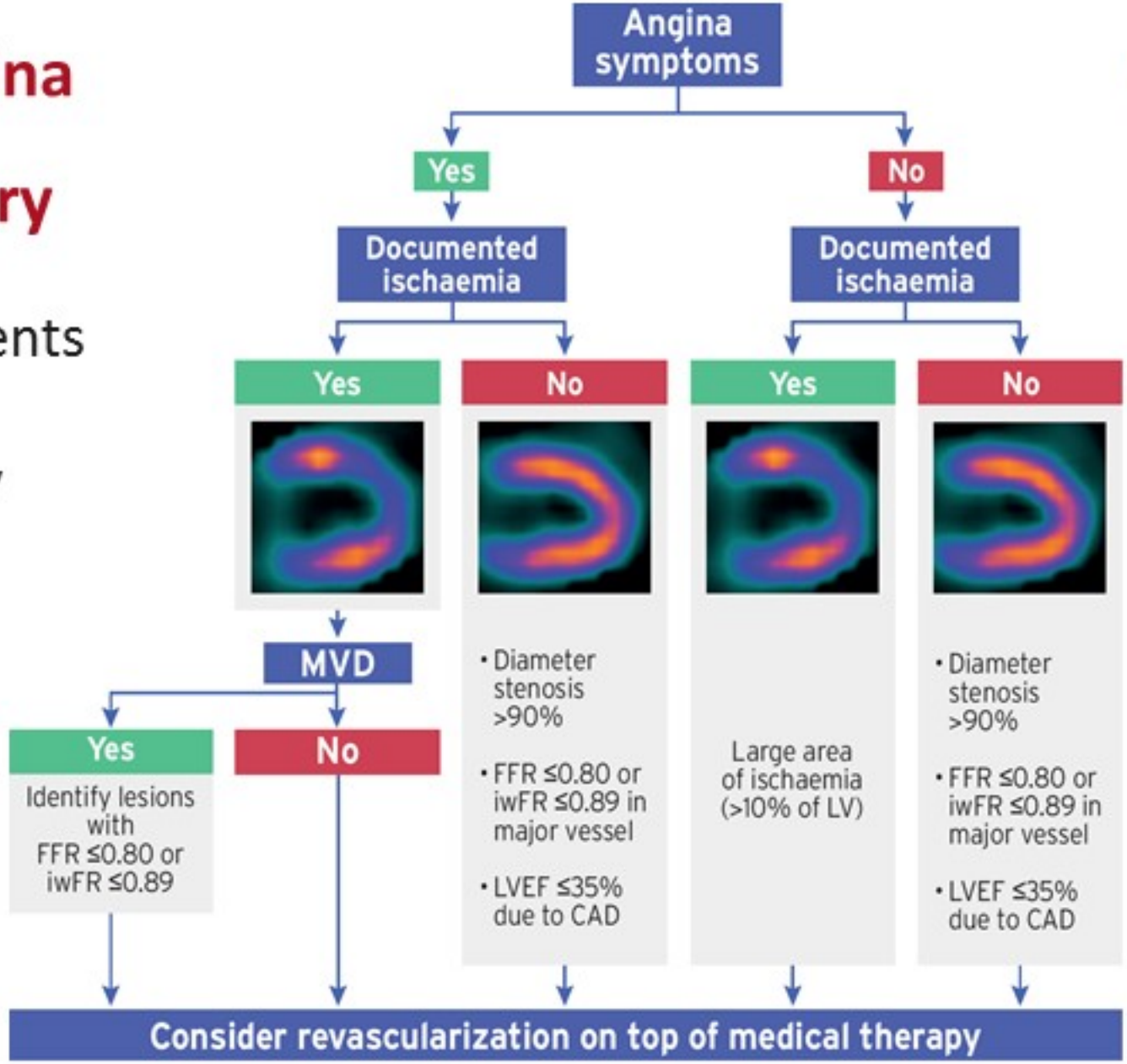
Recommendations	Class	Level
Lipid-lowering drugs		
Statins are recommended in all patients with CCS.	I	A
If a patient's goal is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B
For patients at very high risk who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
ACE inhibitors		
ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).	I	A
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.	IIa	A

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (13)

Recommendations	Class	Level
Other drugs		
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.	I	A
In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.	IIa	B

Patients with angina and/or dyspnoea and coronary artery disease

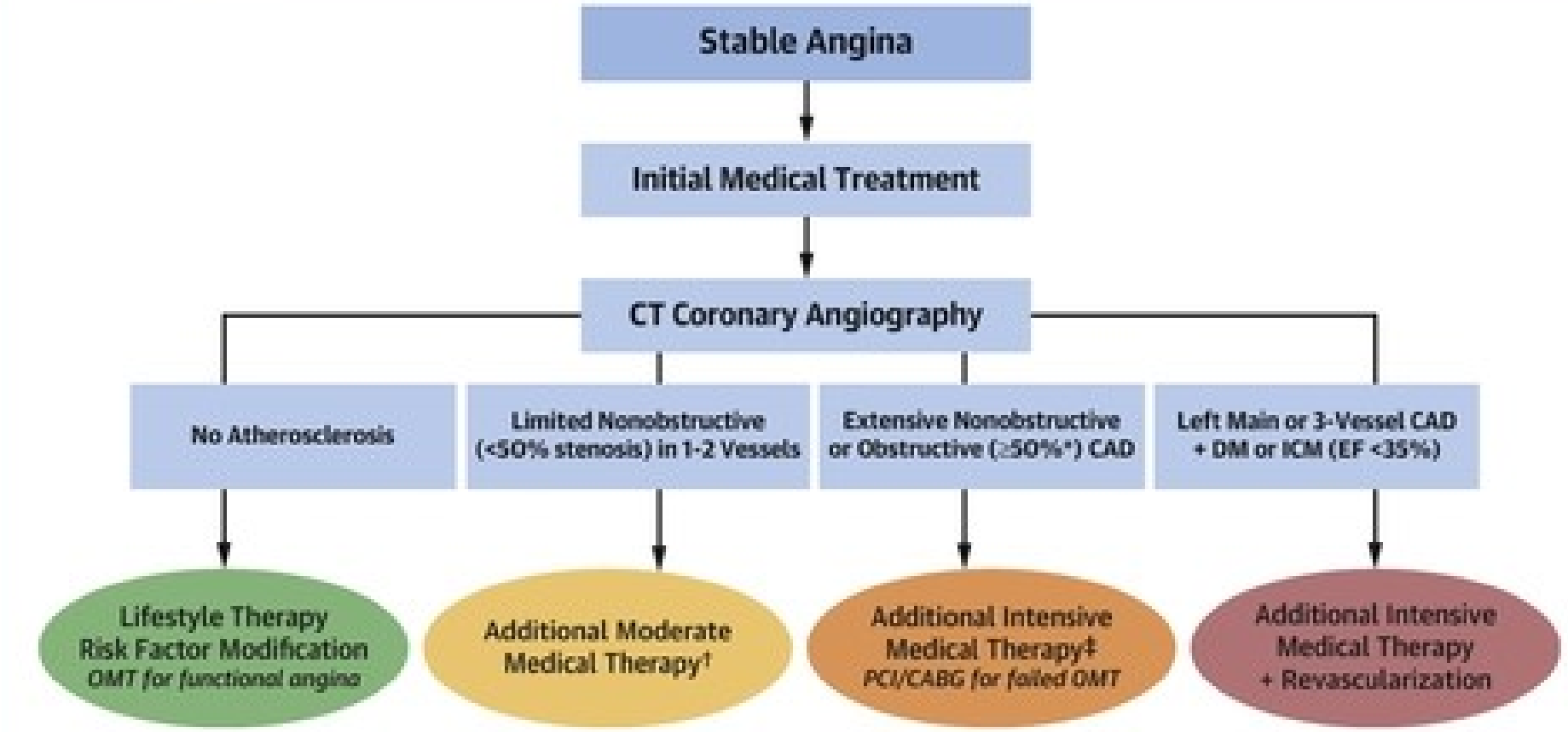
Decision tree for patients undergoing invasive coronary angiography



CAD = coronary artery disease;
FFR = fractional flow reserve;
iwFR = instantaneous wave-free ratio;
LV = left ventricle;
LVEF = left ventricular ejection fraction;
MVD = multivessel disease.

ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

CENTRAL ILLUSTRATION: Contemporary Evaluation and Management of Stable Angina



Ferraro, R. et al. J Am Coll Cardiol. 2020;76(19):2252-66.

Figure 6. Prevalence of co-morbidities in patients with chronic stable angina(48)

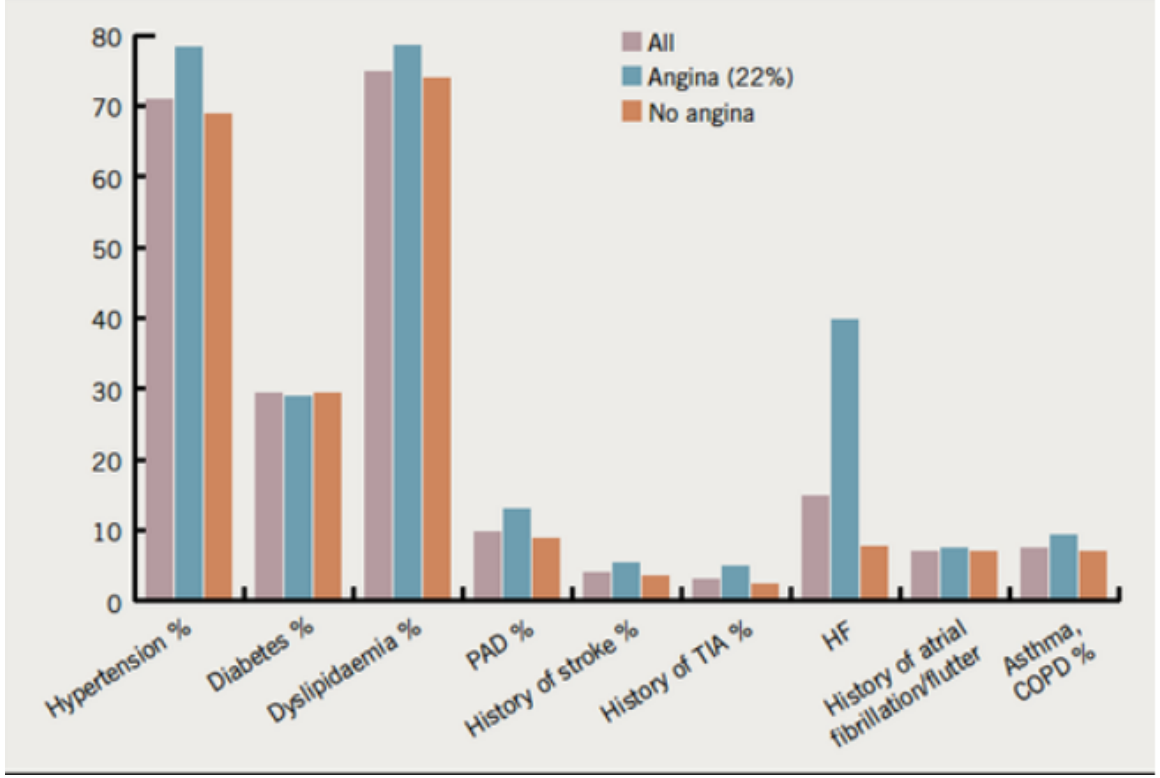
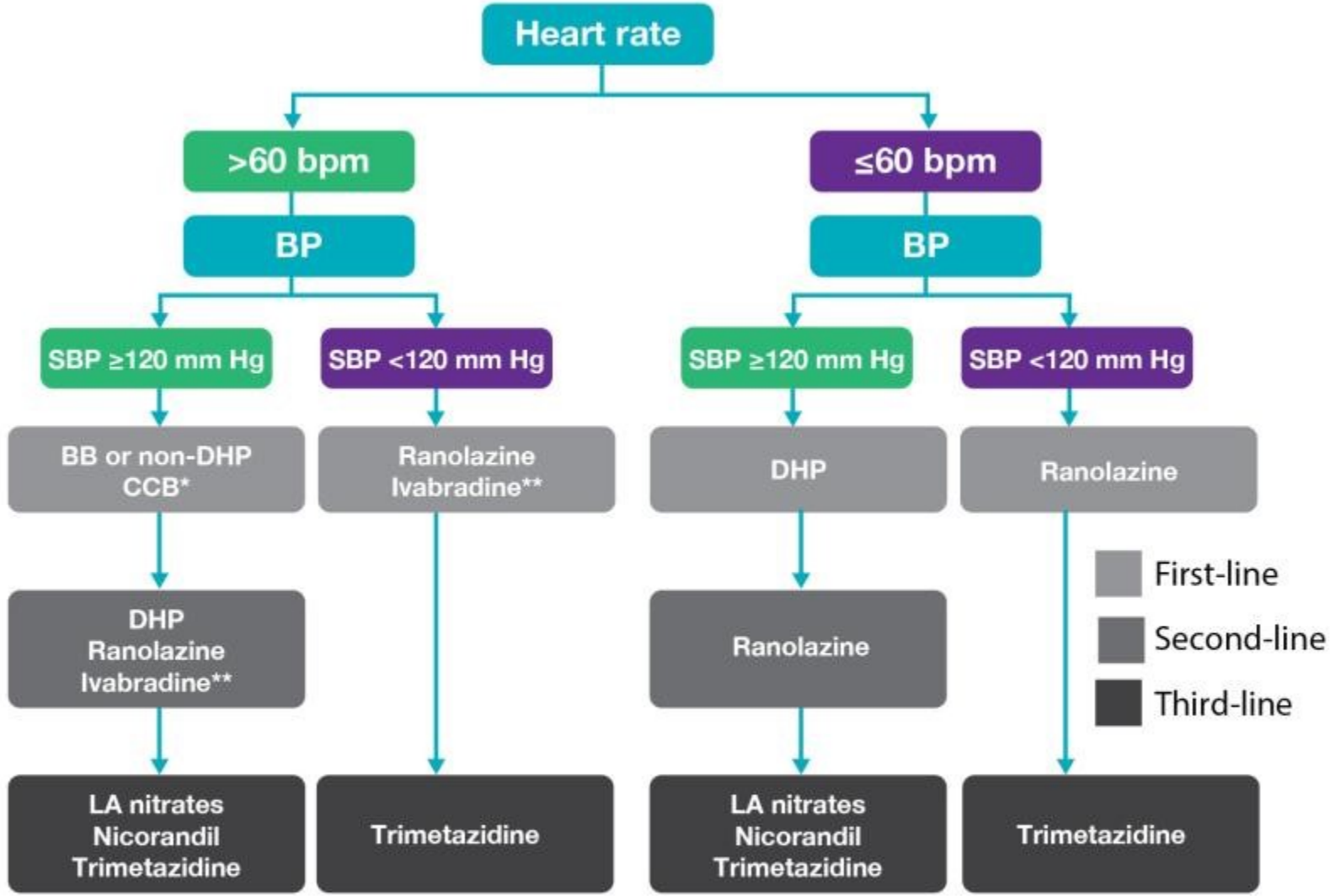


Table 8. Co-morbidities relevant to treatment of myocardial ischaemia

	Beta blockers	Calcium channel blockers	Nitrates	Ivabradine	Ranolazine
General recommendation in guidelines	1st line	2nd line	2nd line current efficacy unknown	2nd line HR >60 bpm	2nd line
Heart failure	Improves outcomes	Contraindicated	Safe	Improves outcomes	May be used
Atrial fibrillation	Indicated	Indicated	Safe	No effect	May be used
Hypotension	Limited	Limited	Limited	May be used	May be used
AV block	Contraindicated	Diltiazem and verapamil contraindicated	May be used	May be used	May be used
Bradycardia	Limited	Limited	Limited	Limited	May be used
COPD/asthma	Limited	May be used	May be used	May be used	May be used
Diabetes	Difficult control	May be used	May be used	May be used	May be used

Key: AV = atrioventricular; bpm = beats per minute; COPD = chronic obstructive pulmonary disease; HR = heart rate

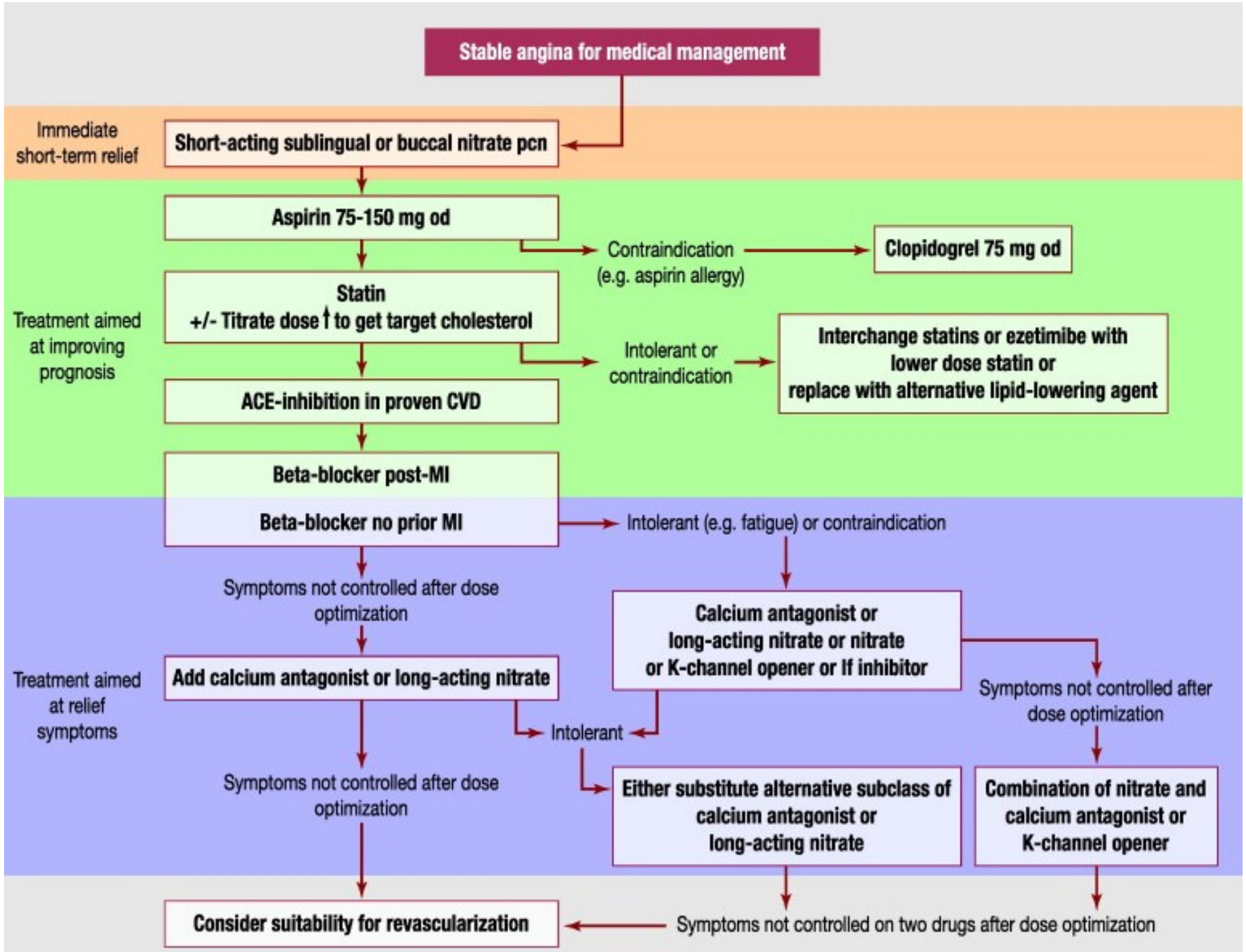
Figure 2. Treatment algorithm for chronic stable angina



*Normal ejection fraction; **heart rate >70 bpm

BB = beta-blocker; BP = blood pressure; CCB = calcium-channel blocker; DHP = dihydropyridine; LA = long-acting; SBP = systolic blood pressure

Adapted from E-Journal of Cardiology Practice, 2017: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Stable-angina-pectoris-which-drugs-or-combinations-to-use-in-which-patients.



Ευχαριστώ για την προσοχή σας!

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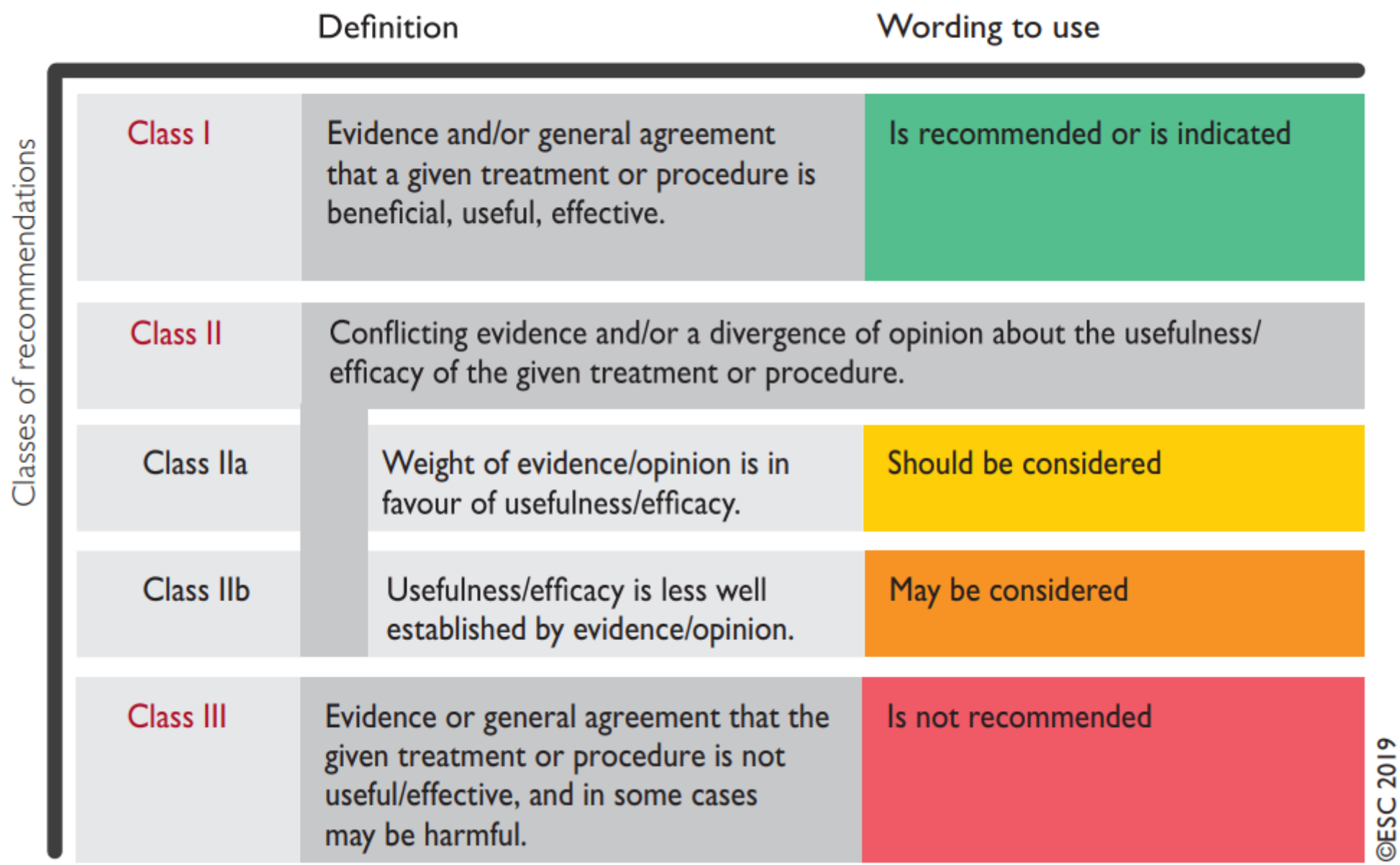
Classes of recommendations



Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.