Behandlungsstrategie von akuten und chronischen Herzinsuffizienz, koronaren Herzkrankheit

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ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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.

NYHA I.

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B
ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	IIa	A
Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	I	B
ICD is recommended in patients: a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction, b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, in order to prevent sudden death and prolong life.	I	B

7. Pharmacological treatment of heart failure with reduced ejection fraction

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]
An ACE-I[d] is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition an ACE-I[d], for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I[d] and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]
Diuretics		
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.	I	B
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.	IIa	B
Angiotensin receptor neprilysin inhibitor		
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA[d]	I	B
***If*-channel inhibitor**		
Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).	IIa	B
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).	IIa	C
ARB		
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).	I	B
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.	IIb	C
Hydralazine and isosorbide dinitrate		
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.	IIa	B
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.	IIb	B
Other treatments with less-certain benefits		
Digoxin		
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).	IIb	B
N-3 PUFA		
An n-3 PUFA[e] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.	IIb	B

Treatments (or combinations of treatments) that may cause harm in patients with symptomatic (NYHA Class II–IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]
Thiazolidinediones (glitazones) are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	A
NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.	III	B
Diltiazem or verapamil are not recommended in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.	III	C
The addition of an ARB (or renin inhibitor) to the combination of an ACE-I and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia.	III	C

7.6.1 Calcium-channel blockers

Non-dihydropyridine calcium-channel blockers (CCBs) are not indicated for the treatment of patients with HFrEF. Diltiazem and verapamil have been shown to be unsafe in patients with HFrEF.[214]

There is a variety of dihydropyridine CCBs; some are known to increase sympathetic tone and they may have a negative safety profile in HFrEF. There is only evidence on safety for amlodipine[215] and felodipine[216] in patients with HFrEF, and they can be used only if there is a compelling indication in patients with HFrEF.

Recommendations for the treatment of hypertension in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class [a]	Level [b]
Step 1		
ACE-I (or ARB), a beta-blocker or an MRA (or a combination) is recommended to reduce blood pressure as first-, second- and third-line therapy, respectively, because of their associated benefits in HFrEF (reducing the risk of death and HF hospitalization). They are also safe in HFpEF.	I	A
Step 2		
A thiazide diuretic (or if the patient is being treated with a thiazide diuretic, switching to a loop diuretic) is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker and an MRA.	I	C
Step 3		
Amlodipine or hydralazine is recommended to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	I	A
Felodipine should be considered to reduce blood pressure when hypertension persists despite treatment with a combination of an ACE-I (or alternatively ARB but NOT together withan ACE-I), a beta-blocker, an MRA and a diuretic.	IIa	B
Moxonidine is not recommended to reduce blood pressure because of safety concerns in HFrEF patients (increased mortality).	III	B
Alpha-adrenoceptor antagonists are not recommended to reduce blood pressure because of safety concerns in HFrEF patients (neurohormonal activation, fluid retention, worsening HF).	III	A
Diltiazem and verapamil are not recommended to reduce blood pressure in patients with HFrEF because of their negative inotropic action and risk of worsening HF.	III	C

9. Treatment of heart failure with preserved ejection fraction

No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF or HFmrEF. However, since these patients are often elderly and highly symptomatic, and often have a poor quality of life,[307] an important aim of therapy may be to alleviate symptoms and improve well-being.[308]

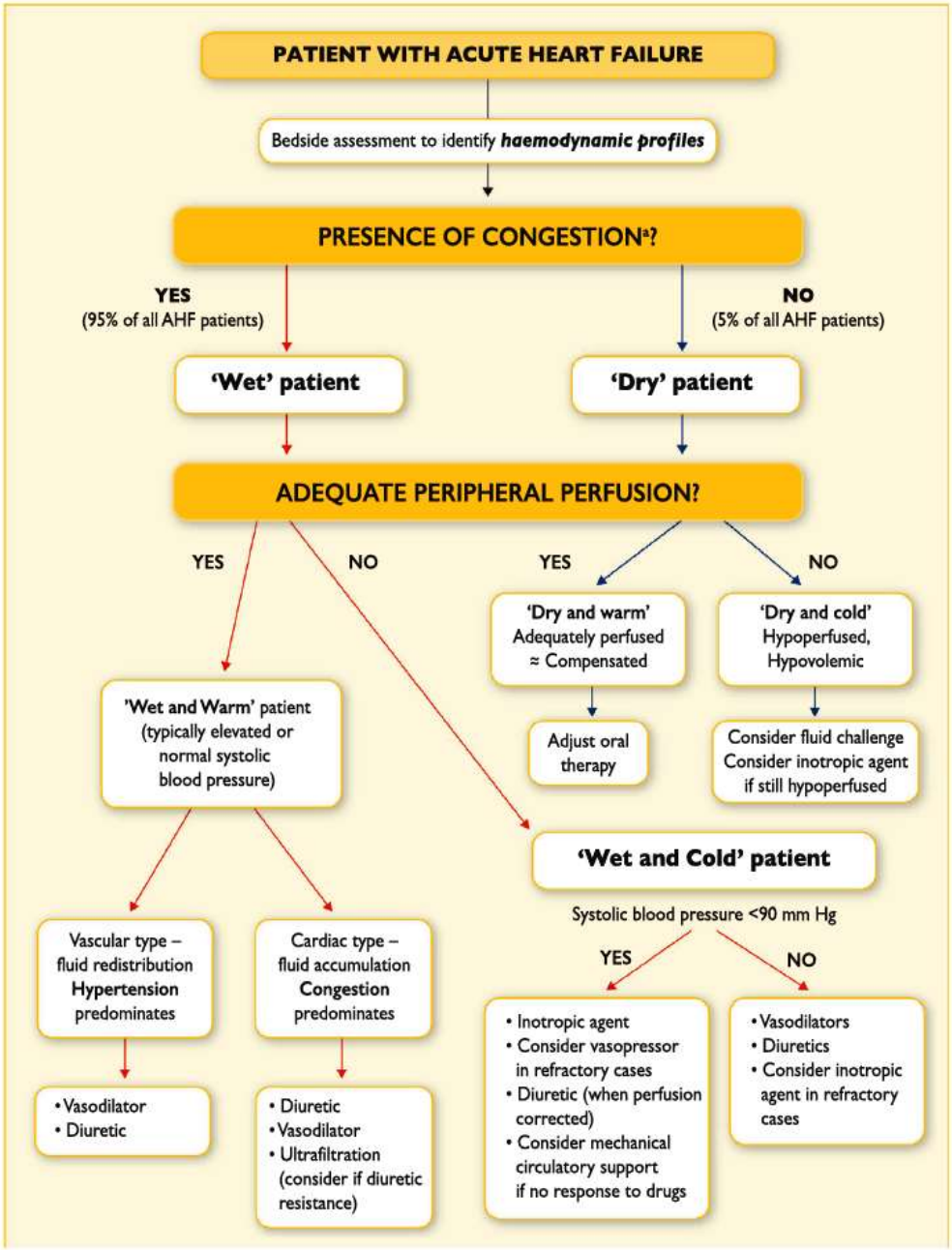
Recommendations	Class [a]	Level [b]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B

Web Table 9.1 Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction

Trial	Intervention	Major inclusion criteria	Mean follow-up	Primary endpoints
PEP-CHF[320]	Perindopril vs placebo.	LV wall motion index ≥1.4 (corresponding to LVEF ≥40%), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age ≥70 y.	2.1 y	No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, P =0.35).
I-PRESERVE [318]	Irbesartan vs placebo.	LVEF ≥45%, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age ≥60 y.	4.1 y	No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, P =0.54).
CHARM-Preserved[319]	Candesartan vs placebo.	LVEF >40%, NYHA II–IV, history of cardiac hospitalization.	3.0 y	Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted P =0.12, adjusted P =0.051).
Aldo-DHF[330]	Spironolactone vs placebo.	LVEF ≥50%, NYHA II–III, peak VO_2 ≤25 mL/min/kg, diastolic dysfunction on echocardiography or atrial fibrillation, age ≥50 y.	1.0 y	Reduction in E/e' by – 1.5 (P < 0.001) No change in peak VO_2 (P =0.81).
TOPCAT[310]	Spironolactone vs placebo.	LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL, age ≥50 y.	3.3 y	No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20%, P =0.14).
SENIORS[173]	Nebivolol vs placebo.	HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months, age ≥70 y, 36% with LVEF >35%.	1.8 y	Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, P =0.04).
DIG-PEF[323]	Digoxin vs placebo.	HF with LVEF >45%, sinus rhythm.	3.1 y	No difference in combined HF mortality or HF hospitalization (21% vs 24%, P =0.14)
PARAMOUNT[309]	Sacubitril/ valsartan vs valsartan.	HF with LVEF ≥45%, NYHA II-III, NT-proBNP >400 pg/mL.	12 w	Reduction in NT-proBNP: ratio of change sacubitril/ valsartan 0.77, 95% CI 0.64–0.92 (P =0.005).
RELAX[311]	Sildenafil vs placebo.	HF with LVEF ≥45%, NYHA II-IV, peak VO_2 <60% of reference values, NT-proBNP >400 pg/mL or high LV filling pressures.	24 w	No change in peak VO_2 (P =0.90).

Pharmaka zur Behandlung von akuten Herzinsuffizienz

Figure 12.3 Management of patients with acute heart failure based on clinical profile during an early phase



Recommendations for the management of patients with acute heart failure: pharmacotherapy

Recommendations	Class[a]	Level[b]
Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.	I	C
In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.	I	B
It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients' symptoms and clinical status.	I	B
Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.	IIb	C
Vasodilators		
i.v. vasodilators should be considered for symptomatic relief in AHF with SBP >90 mmHg (and without symptomatic hypotension). Symptoms and blood pressure should be monitored frequently during administration of i.v. vasodilators.	IIa	B
In patients with hypertensive AHF, i.v. vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.	IIa	B
Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors		
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac output, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	IIb	C
An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion.	IIb	C
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	III	A
Vasopressors		
A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.	IIb	B
It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension.	I	C
In such cases intra-arterial blood pressure measurement may be considered.	IIb	C
Thrombo-embolism prophylaxis		
Thrombo-embolism prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contra-indication to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism.	I	B
Other drugs		
For acute control of the ventricular rate in patients with atrial fibrillation:		
a. digoxin and/or beta-blockers should be considered as the first-line therapy.[d]	IIa	C
b. amiodarone may be considered.	IIb	B
Opiates may be considered for cautious use to relieve dyspnoea and anxiety in patients with severe dyspnoea but nausea and hypopnea may occur.	IIb	B

Recommendations regarding management of patients with cardiogenic shock

Recommendations	Class [a]	Level [b]
In all patients with suspected cardiogenic shock, immediate ECG and echocardiography are recommended.	I	C
All patients with cardiogenic shock should be rapidly transferred to a tertiary care center which has a 24/7 service of cardiac catheterization, and a dedicated ICU/CCU with availability of short-term mechanical circulatory support.	I	C
In patients with cardiogenic shock complicating ACS an immediate coronary angiography is recommended (within 2 hours from hospital admission) with an intent to perform coronary revascularization.	I	C
Continous ECG and blood pressure monitoring are recommended.	I	C
Invasive monitoring with an arterial line is recommended.	I	C
Fluid challenge (saline or Ringer's lactate, >200 ml/15–30 min) is recommended as the first-line treatment if there is no sign of overt fluid overload.	I	C
Intravenous inotropic agents (dobutamine) may be considered to increase cardiac output.	IIb	C
Vasopressors (norepinephrine preferable over dopamine) may be considered if there is a need to maintain SBP in the presence of persistent hypoperfusion.	IIb	B
IABP is not routinely recommended in cardiogenic shock.	III	B
Short-term mechanical circulatory support may be considered in refractory cardiogenic shock depending on patient age, comorbidities and neurological function.	IIb	C

IABP – Intaaortic ballon pump

Pharmaka zur Behandlung von koronaren Herzkrankheit

Pharmakotherapie der koronaren Herzkrankheit

- **Das Herz benötigt eine besonders intensive Versorgung mit Sauerstoff und Substraten.**
- **Die Sauerstoffextraktion ist sehr hoch (70%) → eine Steigerung des Sauerstoffverbrauchs kann nur durch eine Zunahme der Herzdurchblutung abgedeckt werden.**
- **Der *Koronarwiderstand* ist abhängig von:**
  - **Gefäßtonus (vasale Komponente)**
  - **intramurale Druck in der Ventrikelwand (extravasale Komponente) – in der Diastole ↓**
- **Myokardiale Ischämie ist die Folge eines *Ungleichgewichts zwischen Zufuhr und Bedarf an Sauerstoff***
  - **Haupdeterminanten des Verbrauches**
    - **Herzfrequenz**
    - **Kontraktilität**
    - **Wandspannung (Vorlast, Nachlast)**
  - **Haupdeterminanten der Zufuhr**
    - **Koronarfluß (Koronarwiderstand)**
    - **O_2-Transportkapazität des Blutes**

Klinische Syndrome myokardialer Ischämien

- **stabile Syndrome**
  - ***chronische stabile Angina***

    (Anginaanfälle nur unter körperliche Belastung)
- **instabile Syndrome**
  - ***plötzlicher Herztod***

    (Todeseintritt innerhalb einer Stunde nach Beginn der Ischämiesymptome)
  - ***akuter Myokardinfarkt***

    (myokardiale Nekrose)
  - ***instabile Angina***

    (Angina-pectoris-Schmerzen in ihrer Frequenz und Dauer progressiv Ansteigen)
- **Sonderformen**
  - ***vasospastische (Prinzmetal) Angina***

    (Spasmen eines oder mehrerer großer Koronargefäße)
  - ***stumme Ischämien***

    (75 % aller myokardialen Ischämien – ohne Schmerz)

Prinzipien der Angina-pectoris-Therapie

Sauerstoffangebot ↑

- **Dilatation größerer Koronargefäße**
  - Nitrovasodilatatoren
  - Calciumkanalblocker
- **Senkung der extravasalen Komponente des Koronar-widerstandes (intramurale Druck)**
  - Nitrovasodilatatoren
  - (Herzinsuffizienz: ACE-Hemmer)
- **Verlängerung der Diastoledauer**
  - β-Adrenozeptor-Antagonisten
  - bestimmte Calciumkanalblocker (Verapamil, Diltiazem)
- **Prophylaxe bzw. Auflösung intravasaler Strömunghindernisse**
  - Acetylsalicylsäuere
  - Thrombolyse, Heparin

Sauerstoffbedarf ↓

- **Senkung der intramyokardialen Wandspannung**
  - **Nachlastsenkung**
    - Calciumkanalblocker
    - ACE-Hemmer
  - **Vorlastsenkung**
    - Nitrovasodilatatoren
- **Senkung von Kontraktilität und Herzfrequenz**
  - β-Adrenozeptor-Antagonisten
  - bestimmte Calciumkanalblocker (Verapamil, Diltiazem)

Nitrovasodilatatoren, NO-Donator-Substanzen I.

- organische Nitrit- und Nitratester, die enzymatisch im glatten Gefäßmuskel NO freisetzen (unter Verbrauch von Thiolgruppen) → Guanylylcylase ↑ → cGMP↑ → Gefäßrelaxation
  - Glyceroltrinitrat (Nitroglycerin)
  - Isosorbiddinitrat
  - Isosorbidmononitrat
  - Pentaerythritoltetranitrat

- antianginöses Wirkprinzip
  - Dilatation der venösen Kapazitätgefäße → Vorlast ↓
  - Dilatation der Koronararterien (Lösung des Koronarspasmus)

- Pharmakokinetik
  - rasche und vollständige Resorption, aber: presystemische Elimination (first pass effect) → Anfallskupierung: sublingual
  - Metabolisierung in der Leber
  - Ausscheidung mit Harn

Nitrovasodilatatoren, NO-Donator-Substanzen II.

- therapeutische Anwendung
  - Anfallskupierung
    - sublinguale Verabreichung (bei schwerer Angina i.v.)
    - Nitroglycerin: ~0,5 mg, Wirkungseintritt innerhalb 1 Min, Wirkungsdauer 15-30 Min
    - Isosorbiddinitrat: ~5 mg, Wirkungseintritt innerhalb 5 Min, Dauer1-2 Stunden
  - Intervallbehandlung (Anfallsprophylaxe)
    - konstante tägliche Dosierung oral (Retardkapseln – für einige Stunden anhaltende Wirkung) oder transdermal (Nitroglycerin)

Nitrovasodilatatoren, NO-Donator-Substanzen III.

- **Problemen und unerwünschte Wirkungen**
  - **Nitrattoleranz (nitratfreies Intervall → rasch reversibel)**
  - **Kopfschmerzen, orthostatischer Hypotension, Schwindel, Hautrötung**
  - **Bildung von Mäthemoglobin (in geringen Ausmaß, ohne klinische Konsequenz)**

Molsidomin

- **Prodrug (in der Leber → Linsidomin), setzt NO nicht-enzymatisch frei**
- **wenig Selektivität für Venen → sowohl Vorlast, als auch Nachlast ↓**
- **weniger ausgeprägte (fehlende?) Toleranzentwicklung**
- **nur zur Intervalltherapie verwendbar**

Nicorandil

- **Nicotinamid Nitratester**
- **Vasodilatation: Vorlast ↓, Nachlast ↓**
- **K_{ATP} Aktivation – protektive Wirkung („preconditioning”)**

Calciumkanalblocker

Blockieren L-Typ spannungsabhängige Calciumkanälen

- **1,4-Dihydropyridine (DHP)**

  Nifedipin, Nitrendipin, Nicardipin, Felodipin, Nisoldipin, Isradipin, Amlodipin, Lacidipin usw.

- **Blockieren Calciumkanäle vor allem in der Blutgefäße**
- **Arterien und die Widerstandfefäße sind mehr Empfindlich → Nachlastsenkung**
- **besonders gut sind zur Kupierung Vasospastischer Angina**
- **bei instabilen Angina – potentiell gefährlich → als Monotherapie Kontraindiziert**
- **weitere Indikation: Hypertonie**

- **Benzothiazepine**

  Diltiazem

- **Phenylalkylamine**

  Verapamil

- **Blockieren Calciumkanäle sowohl in der Blutgefäße als auch im Herz**
- **arterielle Vasodilatation (Nachlastsenkung) + negativ inotrope und chronotrope Wirkungen**
- **weitere Indikationen: Hypertonie, tachycarde Herzrhythmusstörungen**
- **Kombination mit β-Blocker ist kontraindiziert (additive Herzwirkungen – gefährlich)**

β-Adrenozeptor-Antagonisten

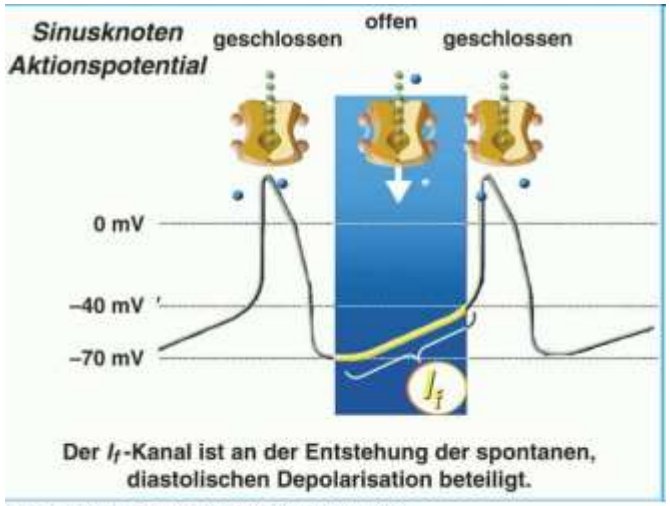
- z.B. Propranolol, Metoprolol, Pindolol, Atenolol, Acebutolol, Bisoprolol, Carvedilol
- Antianginöse Wirkprinzip: Senkung des Sauerstoffbedarfs des Herzens
- Die sind kontraindiziert bei Vasospastischen Angina
- Weitere Indikationen, Nebenwirkungen u.s.w – letzter Semester

ACE-Hemmer

- z.B. Captopril, Enalapril, Lisinopril, Fosinpril, Spirapril, Trandolapril, Perindopril, u.s.w.
- Nachlastsenkung
- weitere günstige Wirkungen

Ivabradin

- I_f-Kanal-Hemmer, ausschließlich herzfrequenzsenkende Wirkung
- Behandlung der chronischen stabilen Angina Pectoris
- NW: dosisabhängig und rückbildungsfähig Lichtwahrnehmungen im Sinne isolierter Aufhellungen im Gesichtsfeld (Hemmung einer Variation des If-Kanals, der sich in der Retina befindet)
- Bradycardie, Kopfschmerzen



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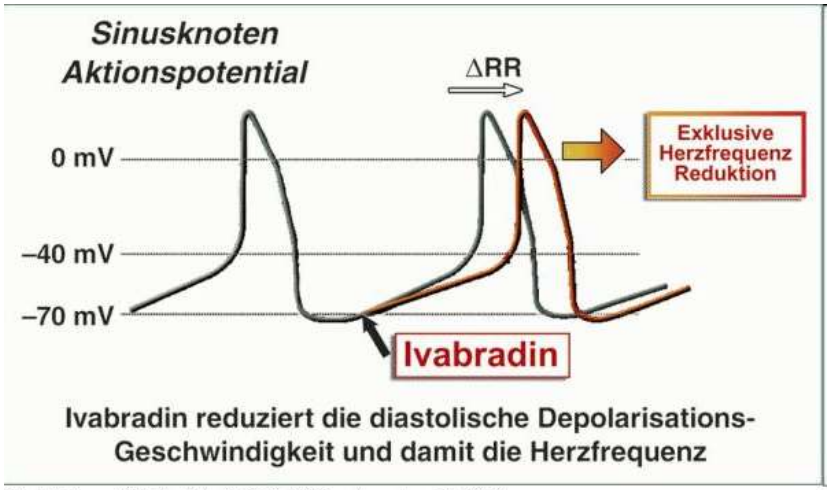

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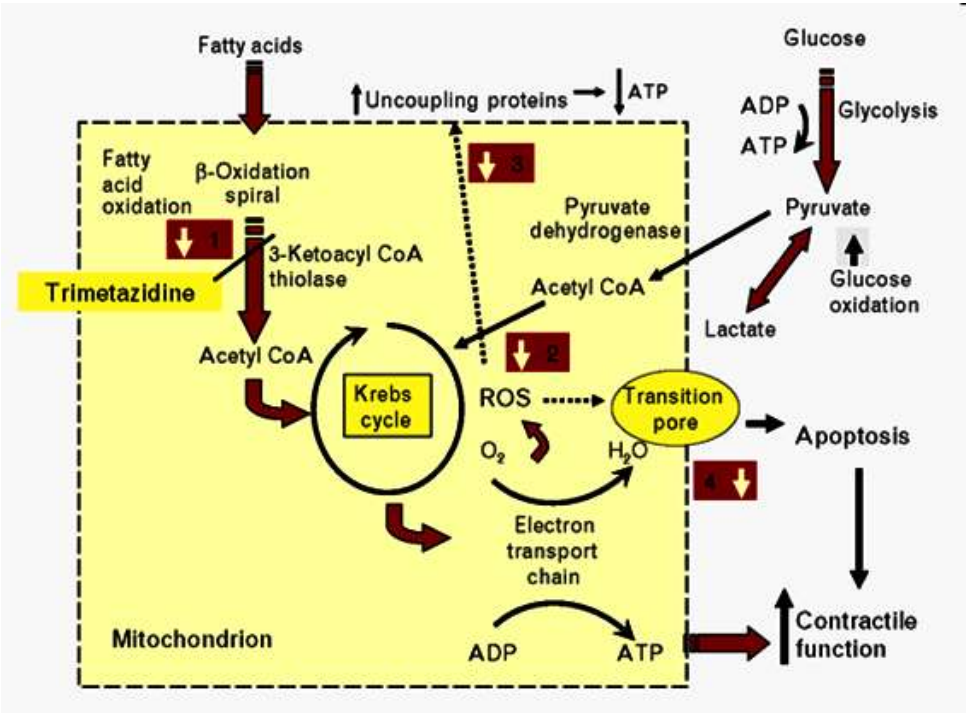
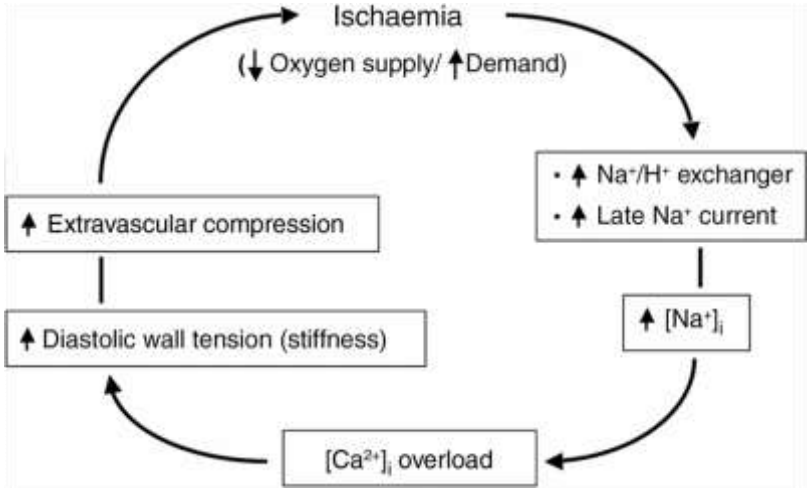
Trimetazidin

- blockiert die 3-Ketoacyl-CoA-Thiolase → hemmt die Beta-Oxidation von Fettsäuren. (pFOX inhibitor = partial inhibition of fatty acid oxidation pathway in the myocardium)
- Dadurch wird die Glucoseoxidation verstärkt. Die Energiegewinnung durch die Glucoseoxidation verbraucht in den ischämischen Zellen weniger Sauerstoff als die Beta-Oxidation.
- Dadurch wird der Energiestoffwechsel bei einer Ischämie aufrechterhalten.
- Zytoprotektion, Limitierung der intrazell. Azidose, weniger Änderungen in der Ion-Homeostasis, Prevention der Bildung der freien Radikalen



- Behandlung der chronischen stabilen Angina Pectoris



Ranolazin

- **„selektiver Inhibitor des späten Natrium-Einstroms (I_{Na}-late) durch den kardialen Natriumkanal“**
- **später Natrium-Einstrom – Beitrag zu Na und Ca-Erhöhung (ungünstig)**
- **Dadurch werden die intrazelluläre Akkumulation des Ions und infolgedessen die Calcium-Überladung der Zelle verringert.**
- **darüber hinaus ein Fettsäureoxidationshemmer,**
- **wirkt antagonistisch an adrenergen und agonistisch an serotonergen Rezeptoren, Metaboliten von Ranolazin stimulieren Opioidrezeptoren. Klinische Bedeutung diesen Mechanismen ?**
- **Ergänzungstherapie zur symptomatischen Behandlung von Patienten mit stabiler Angina pectoris. 2x/Tag**
- **Ranolazin kann das QT-Intervall verlängern. Weitere NW-en: Schwindel, Kopfschmerzen, Verstopfung, Erbrechen, Übelkeit**

Angina-Behandlung: Zusammenfassung

- **Stabile Angina**
  - **Anfallskupierung: sublinguale Nitrate**
  - **Intervalltherapie: alle drei antianginös wirkende Arzneimittelgruppen (aber: keine Kombination von β-Blockern mit Verapamil oder Diltiazem!)**

- **Vasospastische Angina**
  - **Anfälle: sublinguale Nitrate**
  - **Intervalltherapie: Calciumkanalblocker (DHP + Verapamil oder Diltiazem), hoch dosiert**

- **Instabile Angina**
  - **akute Phase: Aufnahme in einen Klinik, Antikoagulantien (niedermolekulares Heparin), Nitrate i.v., β-Blockern oder Verapamil/Diltiazem (DHP kontraindiziert!)**
  - **subakute Phase: Antikoagulantien, Nitrate (oral oder Pflaster)**
  - **chronische Phase: Antithrombotika (Aspirin oder Clopidogrel)**

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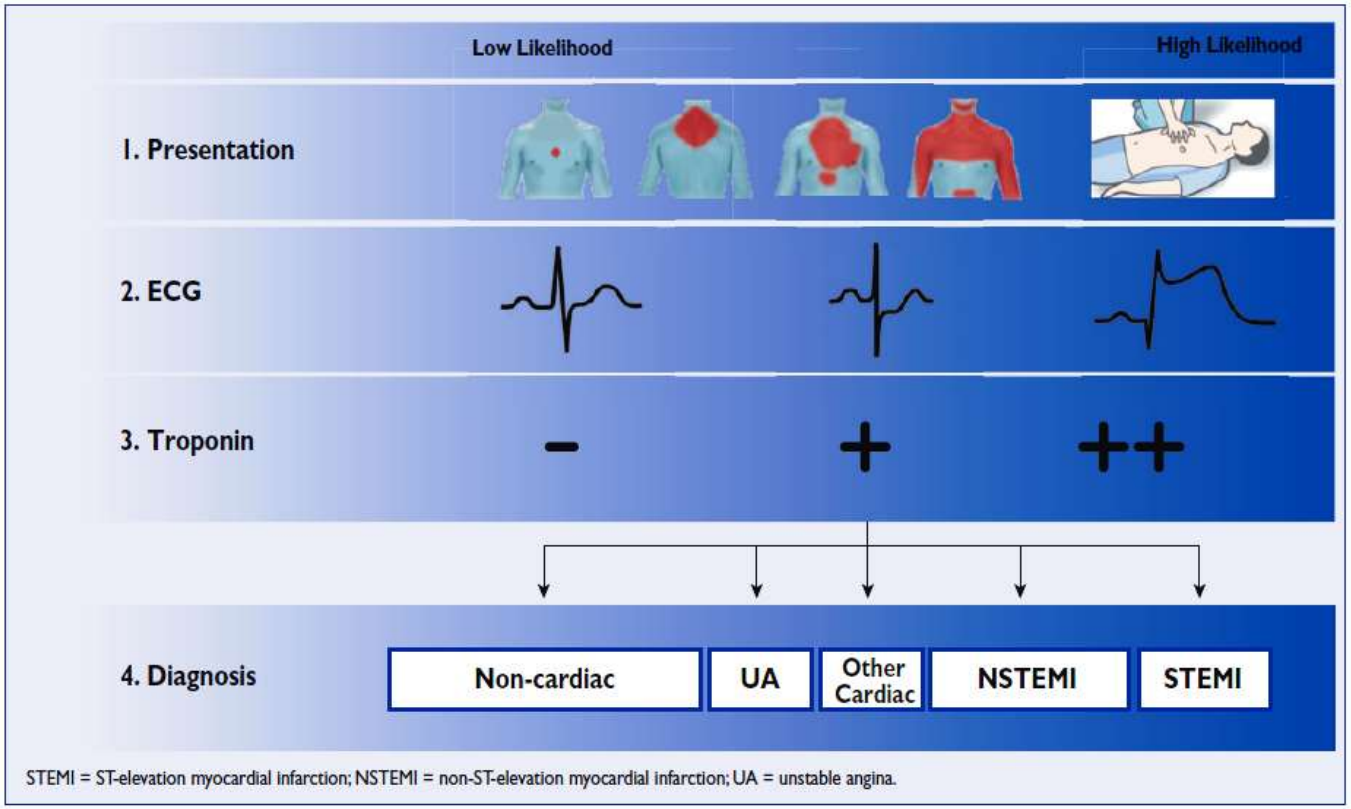
2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation



The development of ischemic heart disease

Normal vessel lumen

Stable angina
Atherosclerotic plaque

Non-stable angina
Atherosclerotic plaque with bleeding and a thrombus partially closing the vessel lumen

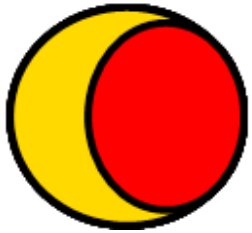
No myocardial necrosis

Non-Q-wave myocardial infarction (MI)

ASC
Acute coronary syndrome

Myocardial infarction (MI)
Atherosclerotic plaque with a thrombus occluding the coronary artery

Ischemic heart disease: treatment strategy

Invasive treatment		*Drug treatment*
Stable angina PTCA, stent		**Nitrates, β-blockers, Ca antagonists**
ACS: non-stable angina + non-Q-wave MI Coronary angiography and if appropriate percutaneous trans-luminal coronary angioplasty (PTCA), stent or coronary bypass surgery		**Nitrates, β-blockers, Ca antagonists** **Anticoagulation therapy**: heparin, LMW-heparin, rivaroxaban, dabigatran, no lab monitoring! (Coumarins: strict lab monitoring!) direct thrombin inhibitors: hirudin **Antiplatelet therapy:** aspirin, ADP receptor inhibitors: ticlodipine, Clopidrogel, prasugrel; GP IIb / IIIa antagonists: eptifibatide, tirofiban, etc.
Myocardial infarction Immediate PTCA, stent, or bypass surgery		Immediate **i.v. thrombolysis, anticoagulation, antiplatelet therapy**

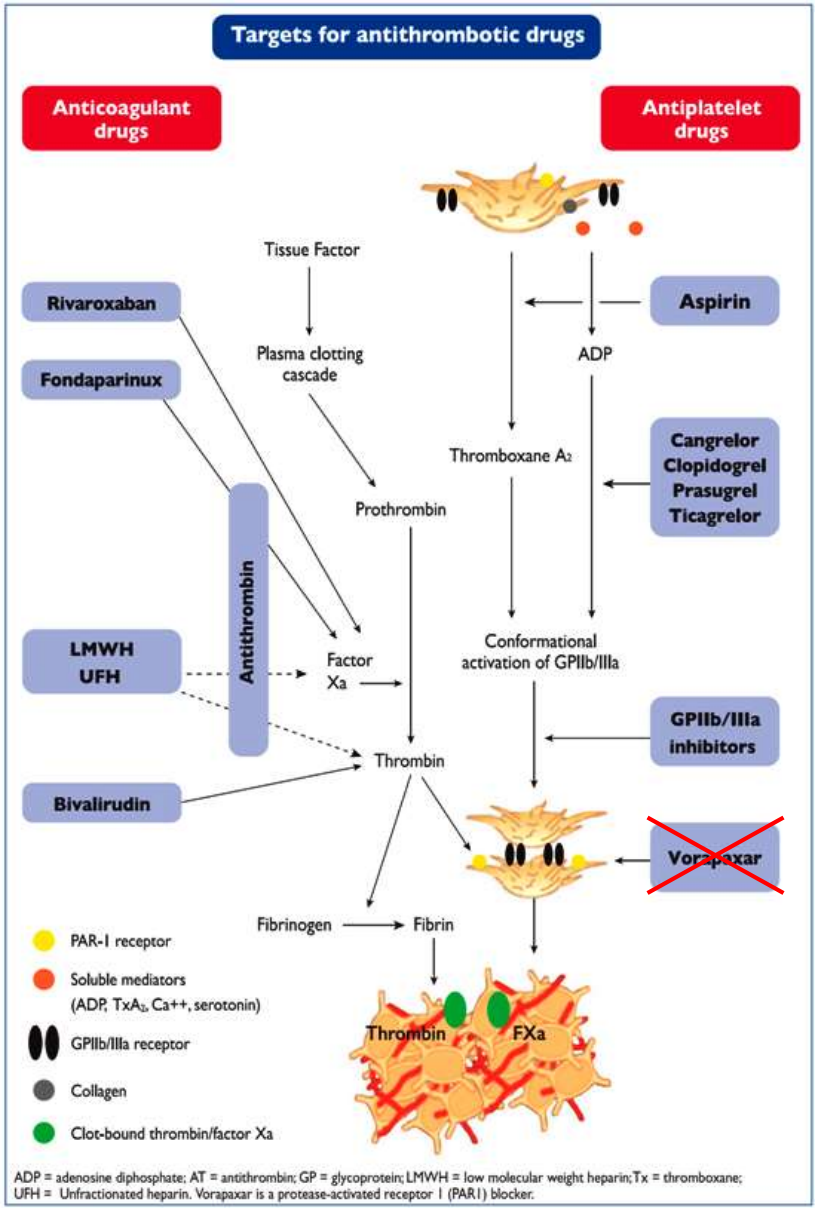
Pharm. treatment of ACS – treatment of ischaemia

Recommendations for anti-ischaemic drugs in the acute phase of non-ST-elevation acute coronary syndromes

Recommendations	Class[a]	Level[b]
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B
Sublingual or i.v. nitrates are recommended to relieve angina;[d] i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I	C
In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B

Zeichen der Herzinsuffizienz nach Infarkt: die Killip-Klassifikation		
Syst. Blutdruck	**Killip-Klassen**	
≥ 90 mmHg (stabil)	Klasse I	keine Zeichen der Herzinsuffizienz
	Klasse II	Lungenstauung: Rasselgeräusche in der unteren Hälfte der Lunge; S3-Galopp
	Klasse III	manifestes Lungenödem: Rasselgeräusche in unterer und oberer Hälfte der Lunge
< 90 mmHg (instabil)	Klasse IV	kardiogener Schock

Pharm. treatment of ACS – antithrombotic drugs



Pharm. treatment of ACS – antithrombotic drugs

Recommendations for platelet inhibition in non-ST-elevation acute coronary syndromes

Aspirin is recommended for all patients without contraindications at an initial oral loading dose[d] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B

$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B
Intravenous antiplatelet therapy		
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C
Cangrelor may be considered in $P2Y_{12}$ inhibitor–naive patients undergoing PCI.	IIb	A
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A

General recommendations		
A proton pump inhibitor in combination with DAPT is recommended in patients at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/corticosteroid use or two or more of the following: age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori* infection, chronic alcohol use).	I	B
In patients on $P2Y_{12}$ inhibitors who need to undergo non-emergency major non-cardiac surgery,[f] postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and for 7 days for prasugrel, should be considered if clinically feasible and unless the patient is at high risk of ischaemic events.	IIa	C
In case of a non-cardiac surgical procedure that cannot be postponed or of a bleeding complication, discontinuation of the $P2Y_{12}$ inhibitor may be considered after a minimum of 1 and 3 months from PCI with BMS and new-generation DES, respectively.	IIb	C

BMS = bare-metal stent; CABG = coronary artery bypass graft; DAPT = dual (oral) antiplatelet therapy; DES = drug-eluting stent; GPIIb/IIIa = glycoprotein IIb/IIIa; NSAID = non-steroidal anti-inflammatory drug; NSTE-ACS = non-ST-elevation acute coronary syndromes; PCI = percutaneous coronary intervention.

Pharm. treatment of ACS – antithrombotic drugs

Recommendations for anticoagulation in non-ST-elevation acute coronary syndromes

Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as an alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B
In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B
Enoxaparin should be considered as an anticoagulant for PCI in patients pretreated with s.c. enoxaparin.	IIa	B
Additional ACT-guided i.v. boluses of UFH during PCI may be considered following initial UFH treatment.	IIb	B
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

ACT = activated clotting time; GPIIb/IIIa = glycoprotein IIb/IIIa; i.v. = intravenous; LMWH = low molecular weight heparin; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; s.c. = subcutaneous; TIA = transient ischaemic attack; UFH = unfractionated heparin.

Pharm. treatment of ACS

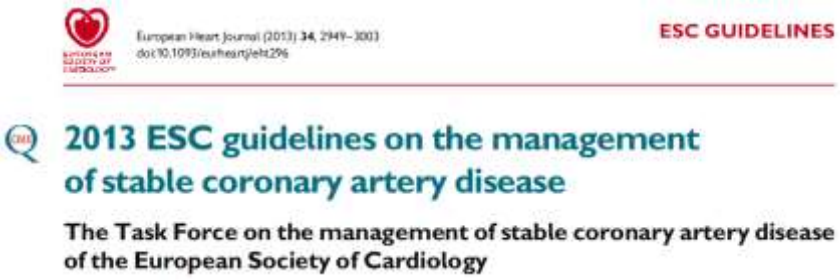
Recommendations for long-term management after non-ST-elevation acute coronary syndromes

It is recommended to advise all patients on lifestyle changes (including smoking cessation, regular physical activity and a healthy diet).	I	A
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long term.	I	A
An ACE inhibitor is recommended in patients with LVEF ≤40% or heart failure, hypertension or diabetes, unless contraindicated. An ARB provides an alternative, particularly if ACE inhibitors are not tolerated.	I	A
Beta-blocker therapy is recommended in patients with LVEF ≤40%, unless contraindicated.	I	A
Mineralocorticoid receptor antagonists, preferably eplerenone, are recommended in patients with LVEF ≤35% and either heart failure or diabetes after NSTE-ACS but no significant renal dysfunction or hyperkalaemia.[d]	I	A
A diastolic blood pressure goal of <90 mmHg is recommended (<85 mmHg in diabetic patients).	I	A

Participation in a well-structured cardiac rehabilitation programme to modify lifestyle habits and increase adherence to treatment should be considered.	IIa	A
In patients with LDL cholesterol ≥70 mg/dL (≥1.8 mmol/L) despite a maximally tolerated statin dose, further reduction in LDL cholesterol with a non-statin agent[e] should be considered.	IIa	B
A systolic blood pressure goal of <140 mmHg should be considered.	IIa	B

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NSTE-ACS = non-ST-elevation acute coronary syndromes.

Pharmacological management of stable coronary artery disease (SCAD) patients


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

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

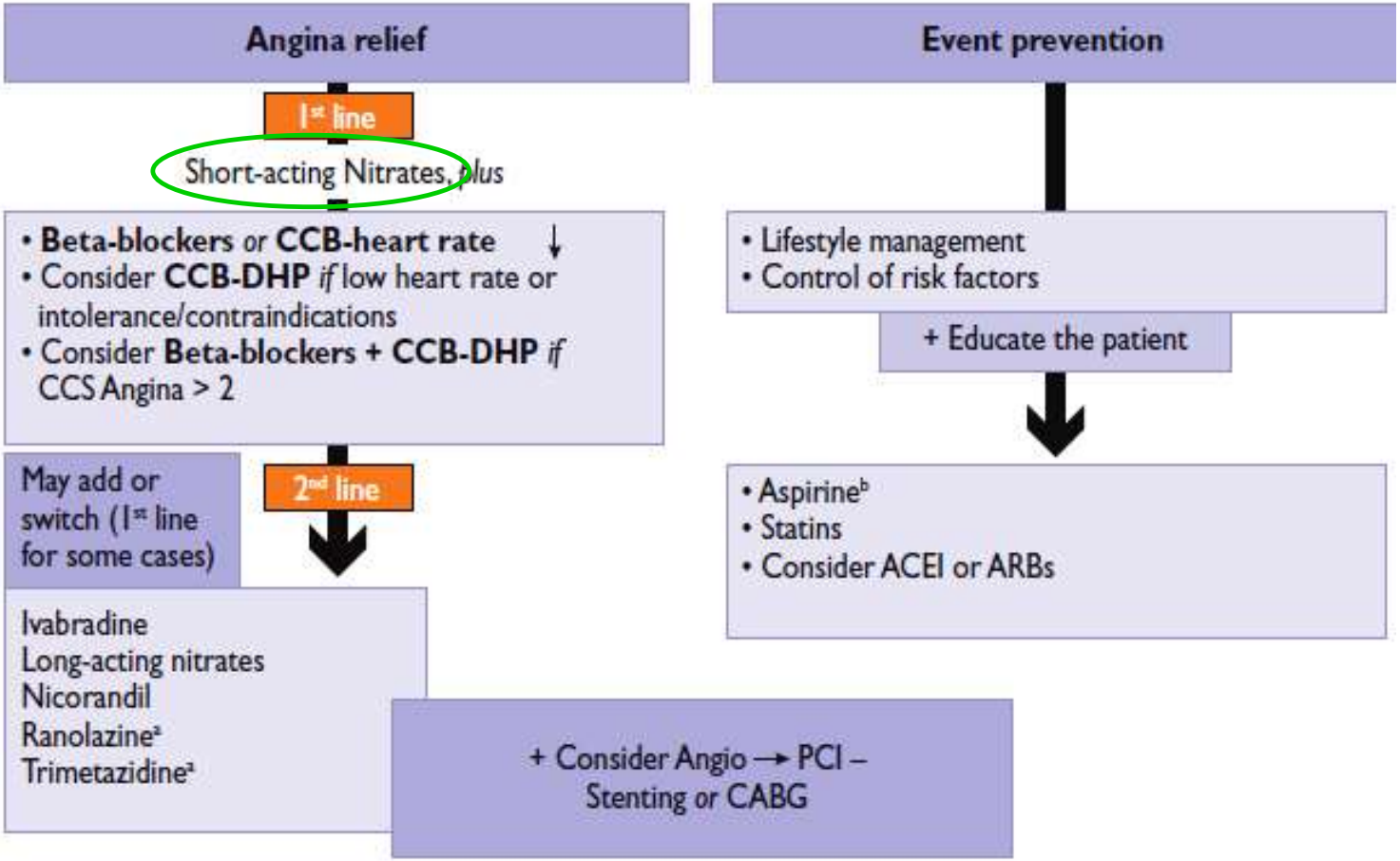
Aims:

1. **Relief of anginal symptoms**
2. **Prevent the occurrence of CV events**

Optimal medical therapy (OMT) for angina relief in SCAD – substance classes:

- **Nitrates**
  - **Short-acting nitrates for acute effort angina**
  - **Long-acting nitrates for angina prophylaxis**
- **Beta-blockers**
- **Calcium channel blockers**
  - **Non-dihydropyridine** (heart rate-lowering calcium channel blockers)
  - **Dihydropyridines**
- **Ivabradine**
- **Nicorandil** (nitrate derivative of nicotinamide)
- **Trimetazidine** (anti-ischaemic metabolic modulator)
- **Ranolazine** (selective inhibitor of late sodium current with anti-ischaemic and metabolic properties)
- **Allopurinol** (an inhibitor of xanthine oxidase that reduces uric acid in persons with gout, is also anti-anginal)
- **Molsidomine** (direct NO donor has anti-ischaemic effects similar to those of isosorbide dinitrate)

Pharmacological management of stable coronary artery disease (SCAD) patients



CABG: coronary artery bypass graft;
CCS: Canadian Cardiovascular Society;
PCI: percutaneous coronary intervention.

Pharmacological management of stable coronary artery disease (SCAD) patients

Angina/ischaemia relief

No demonstration of benefit on prognosis

Short-acting nitrates are recommended.	I	B
First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa	B
For second-line treatment, trimetazidine may be considered.	IIb	B
According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.	I	C
In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.	IIa	C
In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B

Pharmacological management of stable coronary artery disease (SCAD) patients

Side-effects, contraindications, interactions and precautions of anti-ischaemic drugs.

Drug class	Side effects [a]	Contraindications	DDI	Precautions
Short-acting and long-acting nitrates[329]	• Headache • Flushing • Hypotension • Syncope and postural hypotension • Reflex tachycardia • Methaemoglobinaemia	• Hypertrophic obstructive cardiomyopathy	• PDE5 inhibitors (sildenafil or similar agents) • α-adrenergic blockers • CCBs	-
ß-blockers[291, 293, 302,b]	• Fatigue, depression[304] • Bradycardia • Heart block • Bronchospasm • Peripheral vasoconstriction • Postural hypotension • Impotence • Hypoglycaemia/mask hypoglycaemia signs	• Low heart rate or heart conduction disorder • Cardiogenic shock • Asthma • COPD caution; may use cardioselective ß-blockers if fully treated by inhaled steroids and long-acting ß-agonists[330] • Severe peripheral vascular disease • Decompensated heart failure • Vasospastic angina	• Heart-rate lowering CCB • Sinus-node or AV conduction depressors	• Diabetics • COPD[330]
CCBs: heart-rate lowering[303, 304]	• Bradycardia • Heart conduction defect • Low ejection fraction • Constipation • Gingival hyperplasia	• Low heart rate or heart rhythm disorder • Sick sinus syndrome • Congestive heart failure • Low BP	• Cardiodepressant (ß-blockers, flecainide) • CYP3A4 substrates	-
CCBs: Dihydropyridines[27, 305, 331]	• Headache • Ankle swelling • Fatigue • Flushing • Reflex tachycardia	• Cardiogenic shock • Severe aortic stenosis • Obstructive cardiomyopathy	• CYP3A4 substrates	-

Pharmacological management of stable coronary artery disease (SCAD) patients

Side-effects, contraindications, interactions and precautions of anti-ischaemic drugs.

Drug class	Side effects [a]	Contraindications	DDI	Precautions
Ivabradine[307]	• Visual disturbances • Headache, dizziness • Bradycardia • Atrial fibrillation • Heart block	• Low heart rate or heart rhythm disorder • Allergy • Severe hepatic disease	• QTc prolonging drugs • Macrolide antibiotics • Anti-HIV • Anti-fungal	• Age >75 years • Severe renal failure
Nicorandil[177]	• Headache • Flushing • Dizziness, weakness • Nausea • Hypotension • Oral, anal, gastrointestinal ulceration	• Cardiogenic shock • Heart failure • Low blood pressure	• PDE5 inhibitors (Sildenafil or similar agents)	-
Trimetazidine[315, 316]	• Gastric discomfort • Nausea • Headache • Movement disorders	• Allergy • Parkinson disease • Tremors and movement disorders • Severe renal impairment	• None reported	• Moderate renal impairment • Elderly
Ranolazine[317,218, 318]	• Dizziness • Constipation • Nausea • QT prolongation	• Liver cirrhosis	• CYP450 substrates (digoxin, simvastatin, cyclosporine) • QTc prolonging drugs	-
Allopurinol[323]	• Rash • Gastric discomfort	• Hypersensitivity	* Mercaptopurine / Azathioprine	• Severe renal failure

Pharmacological management of stable coronary artery disease (SCAD) patients

Event prevention

Low-dose aspirin daily is recommended in all SCAD patients.	I	A
Clopidogrel is indicated as an alternative in case of aspirin intolerance.	I	B
Statins are recommended in all SCAD patients.	I	A
It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).	I	A