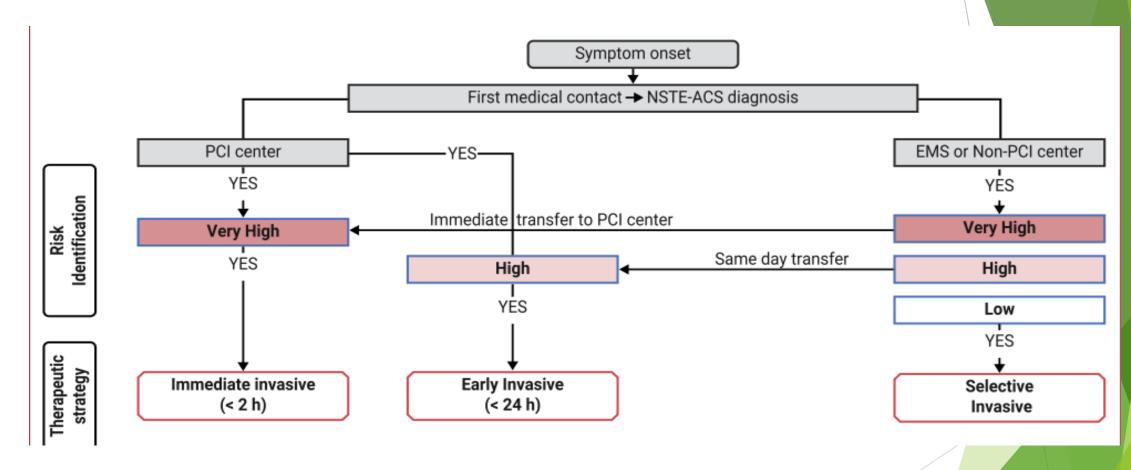
Invasive Treatment in patients with NSTEMI

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Timing of invasive strategy



Immediate invasive

Very high risk

- Haemodynamic instability
- Cardiogenic shock
- Recurrent/refractory chest pain despite medical treatment
- Life-threatening arrhythmias
- Mechanical complications of MI
- Acute heart failure clearly related to NSTE-ACS
- ST-segment depression >1 mm/6 leads plus ST-segment elevation aVr and/or V1

Early invasive

High risk

- Established NSTEMI diagnosis
- Dynamic new or presumably new contiguous ST/T-segment changes (symptomatic or silent)
- Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock
- GRACE risk score >140

Grace score

GRACE score

)(Global Registry of Acute Coronary Events

)Age (years		
40>	0	
49-40	18	
59-50	36	
69-60	55	
79-70	73	
80≤	91	

Killip class		
Class I	0	
Class II	21	
Class III	43	
Class IV	64	

)Heart rate (bpm		
70>	0	
89-70	7	
109-90	13	
149-110	23	
199-150	36	
200<	46	

Creatinine

(mg/dL)	
0.0- 0.39	2
0.4-0.79	5
0.8-1.19	8
1.2-1.59	11
1.6-1.99	14
0.2-3.99	23
>4	31

)Systolic BP (mmHg		
80>	63	
99-80	58	
119-100	47	
139-120	37	
159-140	26	
199-160	11	
200<	0	

Cardiac arrest at admission	43
Elevated cardiac markers	15
ST-segment deviation	30

Eur Heart J 2005; 26 (9):865-872.

- Among unselected NSTE-ACS patients, an early invasive strategy is not superior over a delayed invasive strategy with regard to composite clinical endpoints
- Benefit with an early invasive strategy is strongly associated with the patient's risk profile

- ▶ Benefit with an early invasive strategy is not modified by ST segment/T-wave changes, despite the fact that ST-segment depression has been consistently identified as a predictor for an adverse outcome.
- Based on the individual patient-based meta-analysis patients with elevated biomarkers, GRACE score >140, age >75 years, and diabetes showed a mortality benefit from an early invasive approach.

- Several meta-analyses have pooled data of multiple RCTs assessing different timing intervals of ICA. None of them observed a benefit with an early invasive strategy with respect to the endpoints death, non-fatal MI, or stroke among unselected NSTE-ACS patients.
- a collaborative meta-analysis comparing an early/immediate invasive to a delayed invasive strategy using a modified individual patient data approach observed a survival benefit in high-risk patients, although tests for interaction were inconclusive.

- VERDICT trial studied the impact of timing on the endpoint hospital admission for heart failure and observed a trend towards less heart failure hospitalization in favour of an early invasive strategy.
- Meta-analyses have consistently reported that an early invasive strategy is associated with a lower risk of recurrent/refractory ischaemia and a shorter length of hospital stay.

Selective invasive strategy

- Patients with no recurrence of symptoms and none of the very high or high-risk criteria listed in the recommendation table regarding timing of invasive strategy are to be considered at low risk of short-term acute ischemic events.
- stress echocardiography or stress CMR

Patients who are not candidates for invasive coronary angiography

- advanced age, female sex, chronic kidney disease (CKD), diabetes mellitus, prior heart failure/revascularization, history of cancer, and frailty
- poor prognosis of this population, with in-hospital mortality of 6-9% that rises up to 20 and 50% at 6 months and 3 years
- Advanced age or female sex alone, in the absence of severe comorbidities or frailty, should not be considered as a sufficient reason not to perform ICA.

Patients with coronary artery disease not amenable to revascularization

- Patients diagnosed with severe CAD who are not amenable to any type of revascularization are at very high risk of recurrent ischemic events.
- these patients are women, old and/or suffering from severe CKD, with multivessel CAD, and a history of MI or prior revascularization.

- increased cardiovascular mortality, both in-hospital and long-term
- ► These patients should undergo an aggressive secondary prevention treatment with potent antiplatelet therapy and anti anginal agents.

Vascular access

- Among patients undergoing PCI, access-related bleeding accounts for 30-70% of total bleeding events.
- Rival & matrix study have demonstrated significantly lower rates of access site-related bleeding, surgical access site repair, and blood transfusion with radial compared to femoral access.

radial access is recommended as the preferred approach in NSTE-ACS patients undergoing invasive assessment with or without PCI. However, dependent on their hemodynamic situation during index PCI and procedural technical aspects, femoral access might be selectively chosen instead of radial access.

Revascularization strategies

data from the British Cardiac Intervention Society PCI database showed significantly lower cumulative mortality rates with single-stage complete revascularization compared to culprit-lesion-only PCI (22.5 vs. 25.9%, P=0.0005) at a median follow-up of 4.1 years (interquartile range 2.2-5.8) among 21 857 NSTE-ACS patients with multi vessel CAD undergoing PCI. This long-term benefit was observed despite an initial increase in in hospital mortality with single-stage complete revascularization In contrast to the STEMI setting, there is only one dedicated randomized trial examining the role of single vs. staged multi vessel PCI in NSTE-ACS patients.(SMILE trial)

The complete single-stage coronary revascularization resulted in less major adverse cardiovascular and cerebrovascular events (defined as cardiac death, death, reinfarction, rehospitalization for unstable angina, repeat coronary revascularization, and stroke at 1 year) compared to complete coronary revascularization in multistage PCI during the index hospitalization (HR 0.55, 95% CI 0.36-0.83, P=0.004). This benefit was largely determined by a significant reduction in repeat revascularization with single-stage multi vessel PCI (HR 0.52, 95% CI 0.31-0.88, P=0.01)

► However, since pursuing completeness of revascularization for some patients with complex coronary anatomy may increase the risk of PCI or require CABG, it is reasonable, in the absence of robust clinical data, to tailor the need for, and timing of, complete revascularization to functional relevance of all stenosis, age, general patient condition and comorbidities, and LV function.

Coronary artery bypass grafting

Approximately 5-10% of NSTE-ACS patients require CABG and these represent a challenging subgroup given their high-risk characteristics compared with patients undergoing elective CABG. In the absence of randomized data, optimal timing for non-emergency CABG in NSTE-ACS patients should be determined individually. The risk of ischemic events, possibly related to suboptimal antiplatelet therapy while awaiting surgery, is less than 0.1%, while perioperative bleeding complications associated with platelet inhibitors is higher than 10%.

In patients with ongoing ischemia or hemodynamic instability and with an indication for CABG, emergency surgery should be performed and not postponed as a consequence of antiplatelet treatment exposure.

Percutaneous coronary intervention vs. coronary artery bypass surgery

► For complex cases, Heart Team discussion and use of the SYNTAX score are recommended, particularly given its ability to predict death, MI, and revascularization in multi vessel CAD NSTEACS patients undergoing PCI. Furthermore, calculation of a Society of Thoracic Surgeons (STS) score is recommended to assess in-hospital or 30-day mortality, and in-hospital morbidity after CABG among high-risk patients.

► Clinical and anatomical characteristics in favour of CABG are considered to be diabetes, reduced LV ejection fraction (LVEF) (<40%), contraindications to DAPT, recurrent diffuse in-stent restenosis, anatomical and technical aspects likely resulting in incomplete revascularization with PCI, and the need for concomitant cardiovascular surgery.

▶ Those in favour of PCI are clinical and anatomical characteristics, such as presence of severe comorbidity (not reflected by scores), advanced age/frailty or reduced life expectancy, restricted mobility, conditions that affect the rehabilitation process, anatomical and technical aspects likely resulting in incomplete revascularization with CABG surgery due to poor quality or missing conduits, severe chest deformation or scoliosis, sequelae of chest radiation, and porcelain aorta.

Management of patients with ongoing myocardial ischemia

These patients are characterized by an overwhelming risk of developing STEMI, onset of life-threatening arrhythmias, acute heart failure, and CS. They should undergo coronary angiography within 2 h of hospital admission with intent to perform revascularization. Based on published data, this approach reduces in-hospital mortality and mortality at early and mid-term follow-up, as well as reducing the risk of new MI in the pre-catheterization period and the length of hospital stay.

Management of patients with cardiac arrest

- The management of patients presenting with resuscitated cardiac arrest and concomitant NSTE-ACS needs to be individualized according to their hemodynamic and neurological status.
- In out-of-hospital cardiac arrest and no ST-elevation without CS, an unselected immediate invasive strategy is not superior over a delayed invasive strategy, as recently shown in the randomized Coronary Angiography after Cardiac Arrest (COACT) trial.

In comatose survivors, echocardiography should be performed immediately for further evaluation of differential diagnoses. If aortic dissection or pulmonary embolism is suspected, CT is recommended.

Recommendations for coronary revascularization

Recommendations	Classa	Level ^b
Timing of invasive strategy		
 An immediate invasive strategy (<2 h) is recommended in patients with at least one of the following very high-risk criteria: Haemodynamic instability or CS. Recurrent or refractory chest pain despite medical treatment. Life-threatening arrhythmias. Mechanical complications of MI. Heart failure clearly related to NSTE-ACS. Presence of ST-segment depression >1 mm in ≥6 leads additional to ST-segment elevation in aVR and/or V1. 	•	c
 An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria: Diagnosis of NSTEMI suggested by the diagnostic algorithm recommended in section 3. Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischaemia. Transient ST-segment elevation. 273,362 GRACE risk score >140. 271,272,277 	•	A
A selective invasive strategy after appropriate ischaemia testing or detection of obstructive CAD by CCTA is recommended in patients considered at low risk. ^{267,268,363}	•	A
Delayed as opposed to immediate angiography should be considered among haemodynamically stable patients without ST-segment elevation successfully resuscitated after out-of-hospital cardiac arrest. 358,364	lla	В

Technical aspects		
Radial access is recommended as the standard approach, unless there are overriding procedural considerations. 336,337		A
 DES are recommended over bare-metal stents for any PCI irrespective of: Clinical presentation. Lesion type. Planned non-cardiac surgery. Anticipated duration of DAPT. Concomitant anticoagulant therapy. 354,365,366 	•	A
It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the patient's clinical status and comorbidities, as well as their disease severity [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for stable CAD. However, the decision on immediate PCI of the culprit stenosis does not require Heart Team consultation.	•	В
Complete revascularization should be considered in NSTE-ACS patients without CS and with multivessel CAD.	lla	с
Intracoronary imaging should be considered to diagnose SCAD if suspected.	lla	С
Complete revascularization during index PCI may be considered in NSTE-ACS patients with multi- vessel disease. ³⁴⁵	ПР	В
FFR-guided revascularization of a non-culprit NSTE-ACS lesion may be used during index	ПР	В

Recommendations for non-ST-segment elevation acute coronary syndrome patients with heart failure or cardiogenic shock

Recommendations	Classa	Level ^b
Emergency coronary angiography is recommended in patients with CS complicating ACS. 205,416,417	1	В
Emergency PCI of the culprit lesion is recommended for patients with CS due to NSTE-ACS, independent of the time delay from symptom onset, if the coronary anatomy is amenable to PCI. ^{205,417}		В
Emergency CABG is recommended for patients with CS if the coronary anatomy is not amenable to PCI. ^{205,417}	- 1	В
It is recommended to perform emergency echocar- diography without delay to assess LV and valvular function and exclude mechanical complications.	- 1	c
In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is recommended, as decided by the Heart Team.	•	c
For NSTE-ACS-related mechanical complications, the use of IABP should be considered.	lla	c
In selected patients with ACS and CS, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.	ПР	c
Routine use of IABP in patients with CS and no mechanical complications due to ACS is not recommended. 413,414,415	·	В
Routine immediate revascularization of non-cul- prit lesions in NSTE-ACS patients with multivessel disease presenting with CS is not recommended. ^{346,408}		В

Recommendations for patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome

Recommendations	Class ^a	Level ^b
Risk stratification in CKD		
It is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal renal function.	1	С
It is recommended to assess kidney function by eGFR in all patients.	1	С
Myocardial revascularization in patients with	CKD	
Use of low- or iso-osmolar contrast media (at lowest possible volume) are recommended in invasive strategies. 205,441,442,445,446	1	A
Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL in invasive strategies.	lla	с
As an alternative to the pre- and post-hydration regimen, tailored hydration regimens may be considered. 441,448	ШЬ	В
CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year. 449,450	lla	В

Recommendations for older persons with non-ST-segment elevation acute coronary syndrome

Recommendations	Classa	Level ^b
It is recommended to apply the same diagnos- tic strategies in older patients as for younger patients. ⁴⁵⁸	ı	В
It is recommended to apply the same interven- tional strategies in older patients as for younger patients. 463,467	ı	В
The choice of antithrombotic agent and dosage, as well as secondary preventions, should be adapted to renal function, as well as specific contraindications. 461	ı	В

MINOCA

- ► This incorporates a heterogeneous group of underlying causes that may involve both coronary and non-coronary pathological conditions, with the latter including cardiac and extra cardiac disorders. Compared with patients with obstructive CAD, NSTE-ACS patients diagnosed with MINOCA are more likely to be younger and female, and less likely diabetic, hypertensive, or dyslipidemic, suggesting a predominant role of non-atherosclerotic related etiologies and of unusual or usual risk factors like psychosocial aspects, insulinresistance, and inflammation.
- Although associated with better prognosis compared to patients with ACS patients with obstructive CAD, MINOCA patients have a lower survival rate than healthy individuals matched for age and sex.

Table 14 Diagnostic criteria of myocardial infarction with non-obstructive coronary arteries

The diagnosis of MINOCA is made in patients with AMI fulfilling the following criteria:

- 1. AMI (modified from the 'Fourth Universal Definition of Myocardial Infarction' criteria):
- Detection of a rise or fall in cardiac troponin with at least one value above the 99th percentile upper reference limit and
- Corroborative clinical evidence of infarction as shown by at least one of the following:
 - a. Symptoms of myocardial ischaemia
 - b. New ischaemic electrocardiographic changes
 - c. Development of pathological Q waves
 - d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic cause
 - e. Identification of a coronary thrombus by angiography or autopsy
- 2. Non-obstructive coronary arteries on angiography:
- Defined as the absence of obstructive disease on angiography (i.e. no coronary artery stenosis ≥50%) in any major epicardial vessel^a
 This includes patients with:
- Normal coronary arteries (no angiographic stenosis)
- Mild luminal irregularities (angiographic stenosis <30% stenoses)
- Moderate coronary atherosclerotic lesions (stenoses >30% but <50%)
- **3.** No specific alternate diagnosis for the clinical presentation:
- Alternate diagnoses include, but are not limited to, non-ischaemic causes such as sepsis, pulmonary embolism, and myocarditis

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^aNote that additional review of the angiogram may be required to ensure the absence of obstructive disease.

- CMR is one of the key diagnostic tools in this algorithm for the differential diagnosis of Takotsubo syndrome, myocarditis, or true MI. CMR has the ability to identify the underlying cause in as many as 87% of patients with MINOCA.
- In the sub-endocardium, late gadolinium enhancement may indicate an ischemic cause, while sub epicardial localization may indicate cardiomyopathies or myocarditis, and the absence of relevant late gadolinium enhancement with edema and associated specific wall motion abnormalities is a hallmark of Takotsubo syndrome.

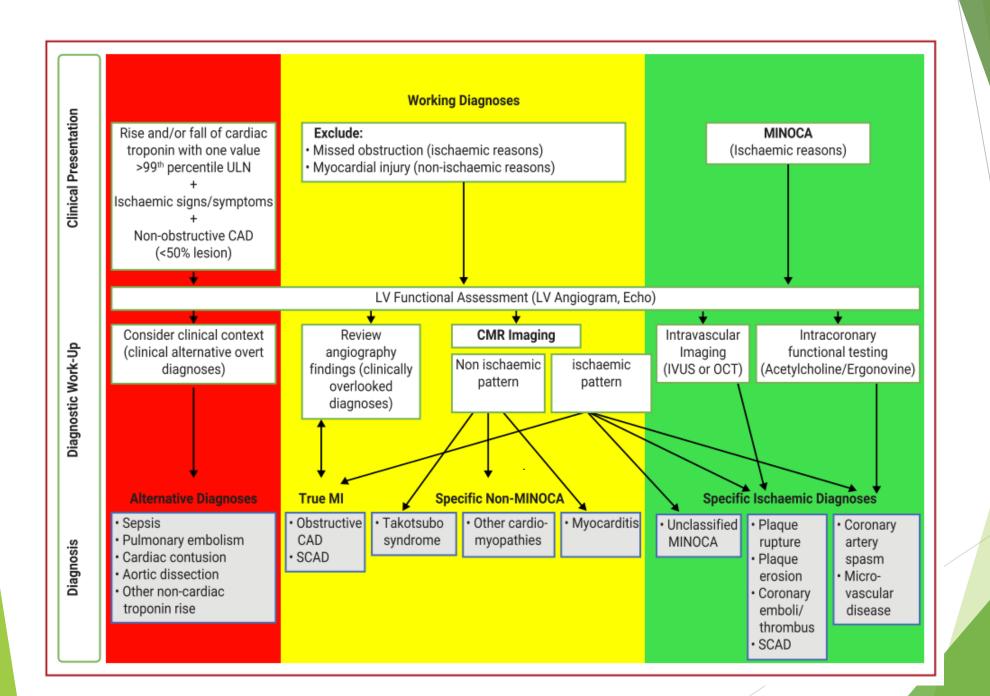
In a meta analysis of five studies involving 556 patients with an initial diagnosis of MINOCA, CMR identified myocarditis as the primary cause in 33% of patients.

- Intracoronary acetylcholine or ergonovine testing may be performed when coronary or microvascular spasm is suspected.
- Intracoronary imaging with IVUS or OCT may also be valuable for the detection of unrecognized causes at coronary angiography, especially when thrombus, plaque rupture or erosion, or SCAD are suspected.
- Pulmonary embolism should also be considered as an alternative diagnosis as a possible cause of myocardial injury, and this diagnosis may be excluded with additional D-dimer testing, BNP, and/or CT pulmonary angiography.
- other conditions with an imbalance between myocardial oxygen supply and demand or elevation of cardiac troponin such as hypertensive crisis, tachy arrhythmias, sepsis, severe anemia, and cardiac contusion.

Patients with an initial diagnosis of MINOCA, and an underlying cause identified during the diagnostic work-up, should be treated and followed up according to the guidelines of the specific diagnosis.

However, despite optimal work-up, the cause of MINOCA remains undetermined in 8-25% of patients.

- ► The benefit of DAPT (aspirin + P2Y₁₂ receptor inhibitor) should be considered based on pathophysiological considerations.
- Pharmacological therapy with aspirin, statins, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), and calcium channel blockers (in case vasospasm is still suspected) as routine treatment may be suggested. These medications have shown significant long-term beneficial effects in terms of all-cause mortality (statins, beta-blockers), cardiovascular death (statins), AMI (beta-blockers), stroke (statins), and MACE (statins, ACE inhibitor/ARB) at 12 months in a national registry.



Recommendations for myocardial infarction with non-obstructive coronary arteries

Recommendations	Class ^a	Level ^b	
In all patients with an initial working diagnosis of MINOCA, it is recommended to follow a diagnostic algorithm to differentiate true MINOCA from alternative diagnoses.	1	С	
It is recommended to perform CMR in all MINOCA patients without an obvious underlying cause. ³⁷⁰	1	В	
It is recommended to manage patients with an initial diagnosis of MINOCA and a final established underlying cause according to the disease-specific guidelines.	1	С	ESC 2020
Patients with a final diagnosis of MINOCA of unknown cause may be treated according to secondary prevention guidelines for atherosclerotic disease.	IIb	С	0

Long-term management of non-ST-segment elevation acute coronary syndrome

Recommendations for lifestyle managements after non-ST-segment elevation acute coronary syndrome

Recommendations	Class ^a	Level ^b
Improvement of lifestyle factors in addition to appropriate pharmacological management is recommended in order to reduce all- cause and cardiovascular mortality and morbidity and improve health-related quality of life. 487–497	1	A
Cognitive behavioural interventions are recommended to help individuals achieve a healthy lifestyle. 498 – 500	1	A
Multidisciplinary exercise-based cardiac rehabilitation is recommended as an effective means for patients with CAD to achieve a healthy lifestyle and manage risk factors in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life. 487,497,501	1	A
Involvement of multidisciplinary healthcare professionals (cardiologists, general practitioners, nurses, dieticians, physiotherapists, psychologists, pharmacists) is recommended in order to reduce all-cause and cardiovascular mortality and morbidity, and improve health-related quality of life. 492,499,502,503	1	Α
Psychological interventions are recommended to improve symptoms of depression in patients with CAD in order to improve health-related quality of life. 504,505	1	В
Annual influenza vaccination is recommended for patients with CAD, especially in the older person, in order to improve morbidity. 505-511	1	В

Recommendations for pharmacological long-term management after non-ST-segment elevation acute coronary syndrome (excluding antithrombotic treatments)

Recommendations	Classa	Levelb
Lipid-lowering drugs		
Statins are recommended in all NSTE-ACS patients. The aim is to reduce LDL-C by ≥50% from baseline and to achieve LDL-C <1.4 mmol/L (<55 mg/dL). ^{533,534}		A
If the LDL-C goal ^c is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended. ^{514,535}	1	В
If the LDL-C goal ^c is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended. ^{520,535}	•	В
If the current NSTE-ACS episode is a recurrence within less than 2 years of a first ACS, while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered. 520,535	ШЬ	В
ACE inhibitors or ARBs		
ACE inhibitors (or ARBs in cases of intolerance to ACE inhibitors) are recommended in patients with heart failure with reduced LVEF (<40%), diabetes, or CKD unless contraindicated (e.g. severe renal impairment, hyperkalaemia, etc.) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity. 536-538		A
Beta-blockers		
Beta-blockers are recommended in patients with systolic LV dysfunction or heart failure with reduced LVEF (<40%). ^{539–541}		A
In patients with prior MI, long-term oral treatment with a beta-blocker should be considered in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity. ^{542–547}	lla	В
MRAs		
MRAs are recommended in patients with heart failure with reduced LVEF (<40%) in order to reduce all-cause and cardiovascular mortality and cardiovascular morbidity. 548,549	•	^
Proton pump inhibitors		
Concomitant use of a proton pump inhibitor is recommended in patients receiving aspirin monotherapy, DAPT, DAT, TAT, or OAC monotherapy who are at high risk of gastrointestinal bleeding in order to reduce the risk of gastric bleeds. 169		A

Thanks for your attention

