NON-ST ELEVEATION MOCARDIAL INFARCTION

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Non-ST elevation myocardial infarction Clinical Guidance- Issued December 2019

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

ACS	Acute Coronary Syndrome
APTT	Activated Partial Thromboplastin Time
CAD	Coronary Artery Disease
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CK-MB	Creatine Kinase-Myocardial Band
CS	Coronary Sinus
DAPT	Dual Anti-Platelet Therapy
ECG	Electrocardiography
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GRACE	Global Registry of Acute Coronary Events
HBR	High Bleeding Risk
h-FABP	Heart-Type Fatty Acid-Binding Protein
hs-CTN	High-Sensitivity Cardiac Troponin
IDF	Insurance Drug Formulary
IV	Intravenous
LD	Loading Dose
LMWH	Low Molecular Weight Heparin
LVEF	Left Ventricular Ejection Fraction
MD	Maintenance Dose
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST Elevation Myocardial Infarction
OAC	Oral Anticoagulant
PCI	Percutaneous Coronary Intervention
SC	Subcutaneous
SFDA	Saudi Food and Drug Authority
STARS-1	Saudi Acute Myocardial infarction registry program
UFH	Unfractionated Heparin

Executive Summary

Non-ST-elevation myocardial infarction (NSTEMI) refers to a condition where there is a partial obstruction in one of the coronary arteries, leading to a decreased supply of oxygenated blood to the cardiac muscles. This condition gets its name because it doesn't have an easily identifiable electrical pattern (ST elevation) like the other main types of heart attacks[1].

Patients with acute chest discomfort but no persistent ST-segment elevation (non-ST-segment elevation acute coronary syndrome [NSTE-ACS]) exhibit electrocardiogram (ECG) changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo normalization of T waves; or the ECG may be normal[1].

According to the fourth universal definition of myocardial infarction (2018) and the 2022 ACC/AHA key data elements and definitions for chest pain and acute myocardial infarction, the different types of MI are: **type 1**: MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion); **type 2**: Ischemic MI in the context of a mismatch between oxygen supply and demand; **type 3**: Individuals experiencing cardiac fatality, displaying indications hinting at myocardial ischemia combined with assumed fresh ischemic electrocardiogram alterations or encountering ventricular fibrillation, yet passing away prior to the acquisition of blood specimens for biomarker analysis, or prior to the identification of elevated cardiac biomarker levels, or before myocardial infarction is confirmed through postmortem examination; **type 4a**: MI occurring within 48 hours of percutaneous coronary intervention (PCI). MI related to coronary intervention is defined as an increase in cardiac troponin (cTn) levels exceeding five times the upper reference limit (URL) of the 99th percentile in individuals with initially normal baseline concentrations; **type 4b**: Stent thrombosis associated with PCI; **type 4c**: MI associated with angiographically documented in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory, in the absence of any other culprit lesion or thrombus; **type 5**: MI within 48 hours of coronary artery bypass grafting (CABG)[2,3].

The symptoms of acute coronary syndromes (ACS) cover a wide spectrum. They can range from cardiac arrest or unstable heart function with cardiogenic shock (CS) caused by ongoing reduced blood supply to the heart or mechanical complications like severe mitral regurgitation, to cases where patients are already free of pain by the time, they seek medical attention. The primary symptom that triggers the diagnosis and treatment process in individuals suspected of having ACS is acute chest discomfort, which can be described as pain, pressure, tightness, or a burning sensation. Symptoms like chest pain, known as chest pain-equivalents, may include shortness of breath, pain in the upper abdomen, and pain in the left arm[1].

The incidence of ACS in males outnumbers that of females by a 3:2 ratio. The incidence in the United States is over 780,000, and of those, approximately 70% will have NSTEMI[4]. As for Saudi Arabia, the incidence of ACS was 8.2%, of whom 27.6% of patients were diagnosed with NSTEMI[5]. The first survey of the Saudi Acute Myocardial Infarction Registry Program (STARS-1 Program) published in 2019 provided some insights when it comes to the clinical characteristics, management, and outcomes of a representative sample of patients with acute MI in Saudi Arabia. It was found that 34.1% of enrolled patients had NSTEMI. In addition, compared to patients with STEMI, those with NSTEMI were more likely to be older, Saudi citizens, and have a history of angina, myocardial infarction, PCI, CABG (Coronary Artery Bypass Grafting), heart failure, chronic renal failure, diabetes, hypertension, and/or hypercholesterolemia[6].

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to non-ST elevation myocardial infarction (NSTEMI). The primary goal of the Council of Health Insurance in issuing NSTEMI guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with NSTEMI in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on Saudi, American, European and England guidelines issued within the last five years.

The management of NSTEMI involves a multidisciplinary approach. Initial medical treatment comprises a multitarget approach consisting of oxygen, antithrombotic agents, antianginal drugs, and statins[7].

The objectives of pharmacological therapy for NSTEMI involve reducing the demand for myocardial oxygen and/or enhancing the supply of oxygen to the myocardium, while also preventing additional thrombosis[7].

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of NSTEMI.

This report functions as an addendum to the prior CHI Non-ST elevation myocardial infarction report and seeks to offer guidance for the effective management of NSTEMI.

Regarding the management of NSTEMI, there were no additions of new drugs recommended in the guidelines, and there were no new drugs approved by the FDA. No changes or modifications were made to existing drugs. However, it is worth noting that the drug felodipine, which was previously used in Saudi Arabia, is no longer registered with the SFDA: therefore, felodipine is the only withdrawn drug.

Below is a table summarizing the major changes based on the different NSTEMI guidelines used to issue this report, and section 3 consists of the key recommendation synthesis for NSTEMI treatment.

Table 1. General Recommendations for the Management of Non-ST Elevation Myocardial Infarction (NSTEMI)

Management of NSTEMI		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn.	Class 3	2023 ESC Guidelines for the management of acute coronary syndromes[8]
Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months.	Class 1	2023 ESC Guidelines for the management of acute coronary syndromes[8]
An early invasive strategy within 24 hours is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischemia. • Transient ST-segment elevation • GRACE risk score >140	Class 1	2023 ESC Guidelines for the management of acute coronary syndromes[8]
Rhythm monitoring up to 24 hours or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias. Rhythm monitoring for > 24 hours is recommended in NSTEMI patients at increased risk for cardiac arrhythmia	Class 1	2023 ESC Guidelines for the management of acute coronary syndromes[8]

Consider continuing a beta-blocker for 12 months after an MI for people without reduced left ventricular ejection fraction	Not graded	2020 NICE Acute coronary syndromes guideline[9]
The preferred anticoagulants agents in patients with NSTE-ACS: • **Fondaparinux (2.5 mg SC daily) is recommended as having the most favorable efficacy–safety profile regardless of the management strategy.** • Enoxaparin (1 mg/kg SC twice daily) or unfractionated heparin (UFH) are recommended when fondaparinux is not available. • In patients on Fondaparinux (2.5 mg SC daily) undergoing PCI, a single IV 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.	Not graded	2020 Saudi clinical guidelines for acute coronary syndrome (ACS)[5]

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI NSTEMI report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the updated versions of the guidelines detailed in the 2020 CHI NSTEMI report and the corresponding recommendations.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation	2023 ESC Guidelines for the Management of Acute Coronary Syndromes[8]
2014 AHA/ACC guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes	N/A*
NICE guidelines for Unstable angina and NSTEMI early management 2010 last update 2013	2020 NICE Acute Coronary Syndromes[9]

**: no updated version available* (the existing version is the most recent one and no further updates or revisions have been made or released).

1.1.1 ESC Guidelines for the Management of Acute Coronary Syndromes (2023)

The European Society of Cardiology (ESC) published their new clinical guidelines for the management of acute coronary syndromes (ACS) in August 2023. It is a combined guideline that outlines a common pathway for the treatment of all patients diagnosed with ACS and covers both STEMI and NSTEMI[8]. Tables 3 and 4 detail the classes of recommendations and the levels of evidence used throughout the guideline.

Table 3. Classes of Recommendations in ESC Guidelines

Class	Definition	Recommendation
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	**Is recommended or 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 if evidence/opinion is in favor 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**

Table 4. Levels of Evidence in ESC Guidelines

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

The main recommendations for the management of NSTEMI, both new and revised, are detailed below:

- In patients with suspected ACS, non-elevated (or uncertain) hs-cTn, no ECG changes and no recurrence of pain, incorporating CCTA or a non-invasive stress imaging test as part of the initial workup should be considered. (Class 2a, LOE A).
- An early invasive strategy within 24 h should be considered in patients with at least one of the following high-risk criteria: (class 2a, LOE A).

- Confirmed diagnosis of NSTEMI based on current recommended ESC hs-cTn algorithms.
- Dynamic ST-segment or T wave changes
- Transient ST-segment elevation
- GRACE risk score >140.

Recommendations for antiplatelets and anticoagulants therapy in acute coronary syndrome:

- If patients presenting with ACS stop DAPT to undergo coronary artery bypass grafting, it is recommended they resume DAPT after surgery for at least 12 months (Class 1, level C).

Recommendations for alternative antithrombotic therapy regimens:

- In patients who are event-free after 3-6months of DAPT and who are not high ischemic risk, single antiplatelet (preferably with a P2Y12 receptor inhibitor) should be considered (Class 2a, LOE A)
- P2Y12 inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment. (Class 2b, LOE A)
- In HBR patients, aspirin or P2Y12 receptor inhibitor monotherapy after 1 month of DAPT may be considered. (Class 2b, LOE A)
- In patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered. (Class 2b, LOE B)
- De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended. (Class 3, LOE B)

Recommendations for cardiac arrest and out-of-hospital cardiac arrest:

- Evaluation of neurological prognosis (no earlier than 72 h after admission) is recommended in all comatose survivors after cardiac arrest. (Class 1, LOE C)

Recommendations for technical aspects of invasive strategies:

- In patients with spontaneous coronary artery dissection, PCI is recommended only for patients with symptoms and signs of ongoing myocardial ischemia, a large area of myocardium in jeopardy, and reduced antegrade flow. (Class 1, LOE C)
- Intravascular imaging should be considered to guide PCI. (Class 2a, LOE A)

Recommendations for acute coronary syndrome comorbid conditions:

- It is recommended to base the choice of long-term glucose-lowering treatment on the presence of comorbidities, including heart failure, chronic kidney disease, and obesity. (Class 1, LOE A)
- An invasive strategy is recommended in cancer patients presenting with high-risk ACS with expected survival ≥6 months. (Class 1, LOE B)
- Aspirin is not recommended in cancer patients with a platelet count < 10 000/microL. (Class 3, LOE C)
- Clopidogrel is not recommended in cancer patients with a platelet count <30 000/microL. (Class 3, LOE C).
- In ACS patients with cancer and < 50 000/microL platelet count, prasugrel or ticagrelor are not recommended. (Class 3, LOE C).

Recommendations for long-term management:

- It is recommended to intensify lipid-lowering therapy during the index ACS hospitalization for patients who were on lipid-lowering therapy before admission. (Class 1, LOE C)
- Low-dose colchicine (0.5 mg once a day) may be considered, particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy. (Class 2b, LOE A)
- Combination therapy with a high-dose statin plus ezetimibe may be considered during index hospitalization. (Class 2b. LOE B)

Figure 1 is an algorithm for selecting an invasive strategy in patients with NSTEMI. In summary, very high-risk NSTEMI patients are recommended to undergo an immediate invasive strategy with emergency angiography and PCI if required. High-risk NSTEMI patients are recommended to undergo an inpatient invasive strategy and should be considered for an early invasive strategy (i.e. within 24 hours). For patients who do not meet any of the very high-risk or high-risk criteria (generally patients with clinical suspicion for NSTEMI and non-elevated troponins or patients with elevated troponins not meeting the criteria for MI), the strategy can be tailored based on the degree of clinical suspicion.

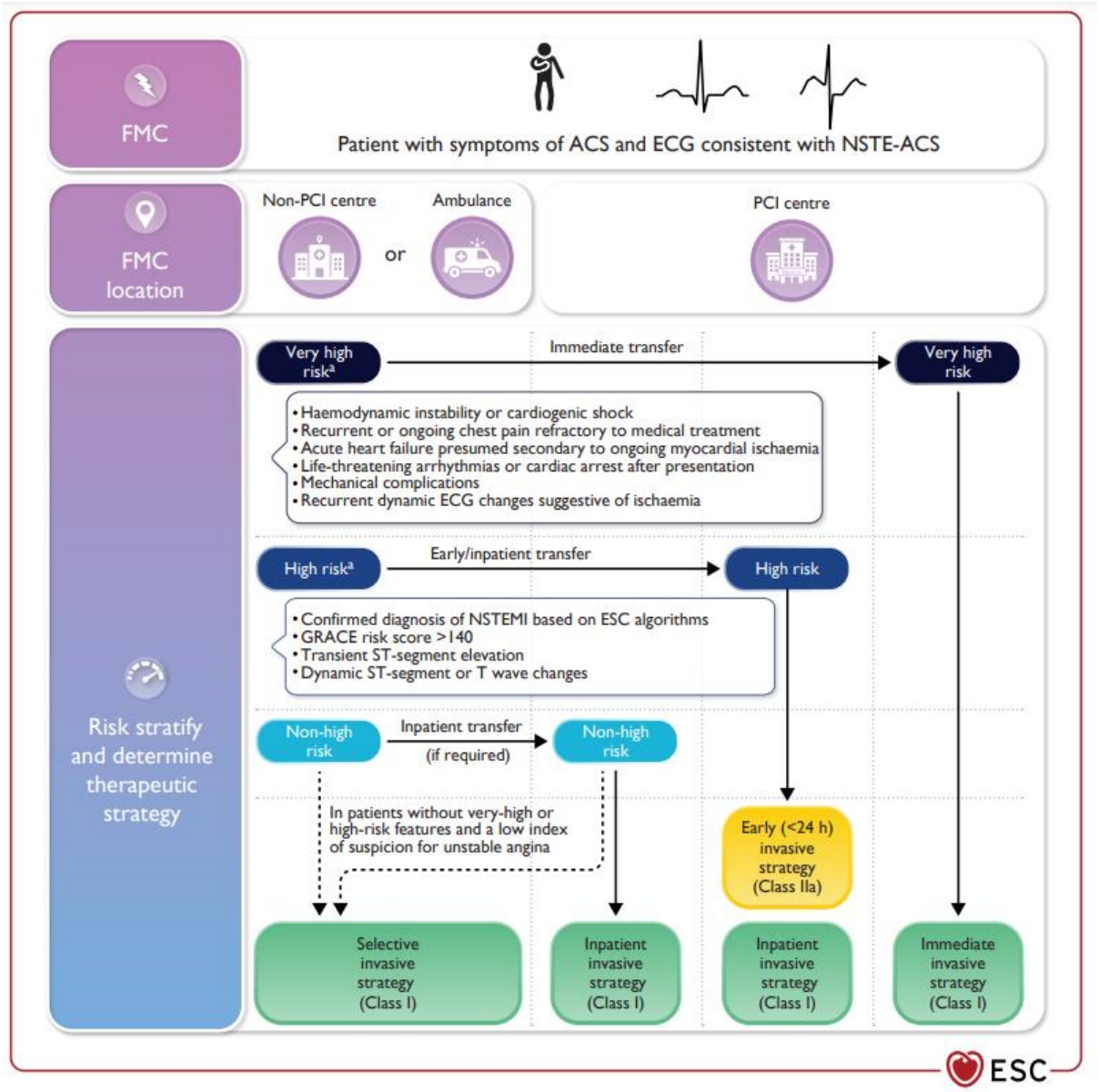

Figure 1. *Selection of Invasive Strategy and Reperfusion Therapy in Patients Presenting with NSTEMI. Retrieved from Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. Published online August 25, 2023. doi:10.1093/eurheartj/ehad191.*

Antiplatelet drugs play a key role in the acute phase of treatment for ACS. Table 5 summarizes the dosing regimens of the available oral and intravenous antiplatelet drugs. The choice of antiplatelet regimen should take the bleeding risk of the patient into account.

Table 5. Regimens and Doses of Antiplatelet and Anticoagulant Drugs in Non-ST-Segment Elevation Acute Coronary Syndrome

Antiplatelet drugs	
Aspirin	Loading dose (LD) of 150-300 mg orally or 75-250 mg intravenous (IV) if oral ingestion is not possible, followed by oral maintenance dose (MD) of 75-100 mg daily
Clopidogrel	LD of 300-600 mg orally, followed by a MD of 75 mg daily, no specific dose adjustment in chronic kidney disease (CKD) patients
Prasugrel	LD of 60 mg orally, followed by a MD of 10 mg daily. In patients aged ≥ 75 years, prasugrel should be used with caution, but a dose of 5 mg daily should be used if treatment is deemed necessary. No specific dose adjustment in CKD patients. **Prior stroke is a contraindication for prasugrel**
Ticagrelor	LD of 180 mg orally, followed by a MD of 90 mg twice daily. No specific dose adjustment in CKD patients
Cangrelor	Bolus of 30 mg/kg IV followed by 4 mg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer)
GP IIb/IIIa receptor inhibitors (IV)	
Eptifibatide	Double bolus of 180 µg/kg IV (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to 18 hours
Tirofiban	Bolus of 25 µg/kg IV over 3 minutes, followed by an infusion of 0.15 µg/kg/min for up to 18 hours
Anticoagulant drugs (for use before and during PCI)	
UFH	• 70-100 U/kg IV bolus when no GP IIb/IIIa inhibitor is planned followed up by an IV infusion until the invasive procedure. • 50-70 U/kg IV bolus with GP IIb/IIIa inhibitors
Enoxaparin	0.5 mg/kg IV bolus
Bivalirudin	0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 hours after the procedure as clinically warranted
Fondaparinux	2.5 mg/d subcutaneously (only before PCI)
Oral anticoagulant drugs	
Rivaroxaban	Very low MD of 2.5 mg twice daily (in combination with aspirin) for long-term extended antithrombotic treatment in a secondary prevention setting of coronary artery disease (CAD) patients

While continuation of anticoagulation after PCI is not necessary in the vast majority of patients (i.e. those without an indication for long-term OAC), **post-interventional antiplatelet treatment is mandatory in ACS patients**. Following PCI, a default DAPT regimen consisting of a potent P2Y12 receptor inhibitor (prasugrel or ticagrelor) and aspirin is generally recommended for 12 months, irrespective of the stent type, unless there are contraindications. In specific clinical scenarios, the default DAPT duration can be shortened, extended, or modified. The recommended default antithrombotic treatment options for ACS patients without an indication for OAC are shown in figure 2.

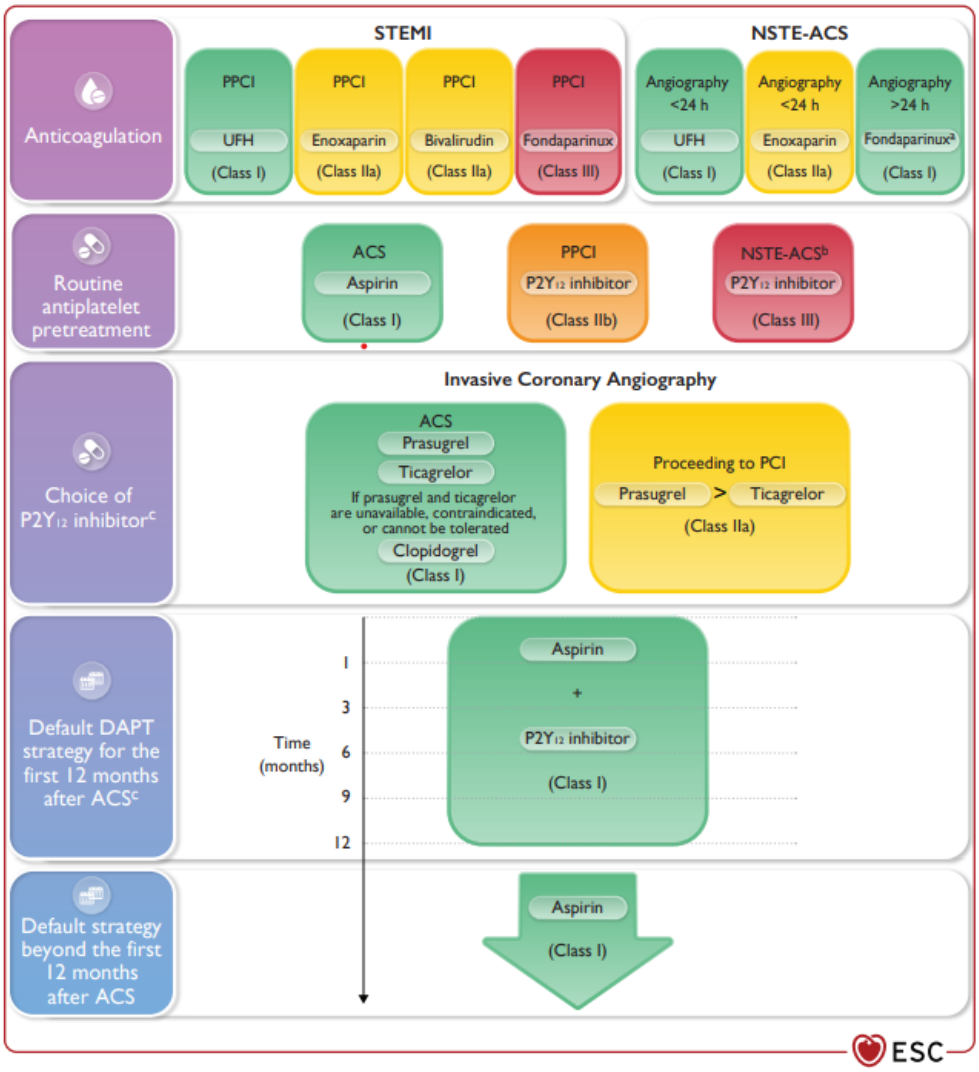

Figure 2. *Recommended Default Antithrombotic Therapy Regimens in Acute Coronary Syndrome Patients Without an Indication for Oral Anticoagulation. Retrieved from Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. Published online August 25, 2023. doi:10.1093/eurheartj/ehad191.*

1.1.2 2020 NICE Acute Coronary Syndromes

The National Institute of Health and Care Excellence (NICE) guidelines for the management of acute coronary syndromes were updated from 2015 to 2020. The main recommendations are detailed below[9]:

- Dual antiplatelet therapy (DAPT) should not be offered to people with chest pain before a diagnosis of unstable angina or NSTEMI is made.
- Immediate coronary angiography should be performed in people with unstable angina or NSTEMI if their clinical condition is unstable.
- Coronary angiography (with follow-on PCI if indicated) should be considered within 72 hours of first admission for people with unstable angina or NSTEMI who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) and no contraindications to angiography (such as active bleeding or comorbidity).
- Ticagrelor, as part of dual antiplatelet therapy with aspirin, is recommended in people with unstable angina or NSTEMI when PCI is not indicated, unless they have a high bleeding risk.
- Clopidogrel, as part of dual antiplatelet therapy with aspirin, or aspirin alone, can be considered for people with unstable angina or NSTEMI when PCI is not indicated if they have a high bleeding risk.
- Continue DAPT for up to 12 months after an MI unless contraindicated.
- Prasugrel or ticagrelor in combination with an anticoagulant that is needed for an ongoing separate indication for anticoagulation should not be routinely offered.
- A beta-blocker continued for 12 months after an MI can be considered for people without reduced left ventricular ejection fraction.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI NSTEMI report, along with their recommendations.

Table 6. List of Additional Guidelines

Additional Guidelines
2020 Saudi Clinical Guidelines for Acute Coronary Syndrome (ACS)[10]
2020 National Clinical Practice Guidelines for the Diagnosis and Management of Acute Coronary Syndrome[11]

2021 Evidence-Based Practices in the Cardiac Catheterization Laboratory: a Scientific Statement From the American Heart Association[12]

1.2.1 Saudi Clinical Guidelines for Acute Coronary Syndrome (2020)

The ACS Clinical Advisory Group published in June 2020 its clinical guidelines for the management of ACS, and the main recommendations are summarized below[5]:

The Global Registry of Acute Coronary Events (GRACE) risk score (tables 7 and 8) provides the most accurate stratification of risk both on admission and at discharge.

Table 7. GRACE Risk Score Assessment Tool

GRACE Risk Score Variables	
In-hospital risk score	**6-month risk score**
Age	Age
Heart rate	History of congestive heart failure
Systolic blood pressure	History of myocardial infarction
Serum creatinine level	Heart rate
Killip class	Systolic blood pressure
Cardiac arrest at admission	ST- segment depression
Elevated cardiac markers	Serum creatinine
ST-segment deviation	Elevated cardiac markers
	No in-hospital PCI

Table 8. GRACE Risk Score Interpretation

Score	**Percentage of risk by 6 months for all-cause mortality**
60 – 100	~ 3% risk
100 – 140	~ 8% risk
140 – 180	~ 20% risk
> 180	> 40% risk

- Among patients with NSTE-ACS with very high-risk criteria (on-going ischemia, hemodynamic compromise, arrhythmias, mechanical complications of MI, acute heart failure, recurrent dynamic or widespread ST-segment and/or T-wave changes on ECG), an **immediate** invasive strategy is recommended **(within 2 hours of admission).**

- In the absence of very high-risk criteria, for patients with NSTE-ACS with high-risk criteria (GRACE score > 140, dynamic ST-segment and/or T-wave changes on ECG or rise and/or fall in troponin compatible with MI) an **early** invasive strategy is recommended **(within 24 hours of admission).**
- In the absence of high-risk criteria, for patients with NSTE-ACS with intermediate-risk criteria (such as recurrent symptoms or substantial inducible ischemia on provocative testing), an invasive strategy is recommended **(within 72 hours of admission).**
- Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 81–162mg/day long-term regardless of treatment strategy.
- Ticagrelor, or Clopidogrel if Ticagrelor is not available, is recommended before or at latest at the time of PCI and should be maintained over 12 months irrespective of revascularization strategy and stent type, unless there are contraindications such as excessive risk of bleeding.
- The preferred anticoagulants agents in patients with NSTE-ACS:
    - Fondaparinux (2.5 mg SC daily) is recommended as having the most favorable efficacy–safety profile regardless of the management strategy.
    - Enoxaparin (1 mg/kg SC twice daily) or UFH are recommended when fondaparinux is not available.
    - In patients on Fondaparinux (2.5 mg SC daily) undergoing PCI, a single IV 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.
    - Enoxaparin should be considered as the anticoagulant for PCI in patients pre-treated with SC enoxaparin.
    - Crossover between UFH and low-molecular weight heparin (LMWH) is not recommended.
- Oral treatment with beta-blockers is indicated in patients with heart failure and or who have a left-ventricular ejection fraction (LVEF) < 40% unless contraindicated.
- Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia.
- An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.
- Prophylactic treatment with antiarrhythmic drugs is not indicated any may be harmful.

1.2.2 National Clinical Practice Guidelines for the Diagnosis and Management of Acute Coronary Syndrome (2020)

The Saudi Heart Association published its national clinical practice guidelines for the diagnosis and management of acute coronary syndrome in December 2020, and the main recommendations are listed below[11]:

Recommended antiplatelet therapy in patients with NSTE-ACS guidance:

- Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 81–162mg/day long-term regardless of treatment strategy.
- Ticagrelor, or clopidogrel if ticagrelor is not available, is recommended before or at latest at the time of PCI and should be maintained over 12 months irrespective of revascularization strategy and stent type, unless there are contraindications such as excessive risk of bleeding.

Antiplatelet therapy in the setting of coronary artery bypass surgery:

- It is recommended to continue low-dose aspirin until CABG.
- In stabilized patients requiring CABG who are on DAPT, discontinuation of Ticagrelor and Clopidogrel 5 days before surgery should be considered.

The preferred anticoagulants agents in patients with NSTE-ACS:

- Fondaparinux (2.5 mg SC daily) is recommended as having the most favorable efficacy–safety profile regardless of the management strategy.
- Enoxaparin (1 mg/kg SC twice daily) or UFH are recommended when fondaparinux is not available.
- In patients on Fondaparinux (2.5 mg SC daily) undergoing PCI, a single IV 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.
- Enoxaparin should be considered as the anticoagulant for PCI in patients pre-treated with SC enoxaparin.
- Crossover between UFH and LMWH is not recommended.

The role of Beta-blockers in NSTE-ACS patients

- Oral treatment with beta-blockers is indicated in patients with heart failure and or who have a LVEF < 40% unless contraindicated.
- Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.

- Early initiation of beta-blockers treatment is recommended in patients with on-going ischemic symptoms and without contraindications.
- Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia.

Lipid lowering therapy during hospitalization and after discharge for NSTE-ACS patients:

- Obtaining a lipid profile in all NSTE-ACS patients as soon as possible after presentation is recommended.
- Initiating high-dose statin therapy as early as possible regardless of initial LDC-C level, unless contraindicated, is recommended.
- An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.
- In patients with LDL-C ≥ 1.8 mmol/L (70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered.

1.2.3 Evidence-Based Practices in the Cardiac Catheterization Laboratory a Scientific Statement from the American Heart Association (2021)

The recommendations of the evidence-based practices in the cardiac catheterization laboratory are listed below[12]:

- Treatment with metformin pre- and post-procedure should be continued in those without severe renal dysfunction.
- Glucose-lowering agents should not be withheld before catheterization procedures. Data on half-dose insulin regimens are insufficient.
- ACE or ARB inhibitors should be held if eGFR rate < 60 mL/min before catheterization procedures.
- Oral anticoagulants before diagnostic procedures should be continued in patients with high risk of thrombotic complications and when trans radial access can be used.

Section 2.0 Drug Therapy

This section comprises four subsections: the first one contains the newly recommended drugs SFDA registered, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market and the fourth one contains drugs that are not mentioned in the guideline, but SFDA registered, and FDA/EMA approved.

2.1 Additions

2.1.1 Argatroban

Argatroban characteristics are listed in the table below[13]:

Table 9. Drug Therapy with Argatroban

SCIENTIFIC NAME ARGATROBAN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	I21.4
Drug Class	ANTICOAGULANT
Drug Sub-class	Direct Thrombin Inhibitor
ATC Code	B01AE03
Pharmacological Class (ASHP)	Anticoagulant- Direct thrombin inhibitor
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	Initial: Begin infusion of 25 mcg/kg/minute and administer bolus dose of 350 mcg/kg (over 3 to 5 minutes). ACT should be checked 5 to 10 minutes after bolus infusion; proceed with procedure if ACT >300 seconds.

	Following initial bolus: ACT <300 seconds: Give an additional 150 mcg/kg bolus, and increase infusion rate to 30 mcg/kg/minute (recheck ACT in 5 to 10 minutes). ACT >450 seconds: Decrease infusion rate to 15 mcg/kg/minute (recheck ACT in 5 to 10 minutes). Once a therapeutic ACT (300 to 450 seconds) is achieved, infusion should be continued for the duration of the procedure. If dissection, impending abrupt closure, thrombus formation during PCI, or inability to achieve ACT >300 seconds: An additional bolus of 150 mcg/kg, followed by an increase in infusion rate to 40 mcg/kg/minute may be administered (recheck ACT after each additional bolus or change in infusion rate).
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Percutaneous coronary intervention: Avoid use in patients with clinically significant hepatic impairment or elevations of ALT/AST ≥3 × ULN (has not been studied).
Prescribing edits*	AGE
AGE (Age Edit): Only approved for PCI in adults: for the pediatric population (<18 years) it has not been studied	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	

PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** chest pain, hypotension, gastrointestinal hemorrhage, headache, back pain **Most serious**: angina pectoris, ischemic heart disease.
Drug Interactions*	**Category X**: • Apixaban • Dabigatran Etexilate • Defibrotide • Edoxaban • Hemin • Mifepristone • Omacetaxine • Rivaroxaban • Urokinase • Vorapaxar
Special Population	Critically ill patients: Use with caution in critically ill patients.
Pregnancy	Information related to argatroban in pregnancy is limited. Use of parenteral direct thrombin inhibitors in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid.
Lactation	It is not known if argatroban is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to argatroban or any component of the formulation; major bleeding. Canadian labeling: Additional contraindications (not in US labeling): Hereditary fructose intolerance.

Monitoring Requirements	Monitor hemoglobin, hematocrit, signs and symptoms of bleeding. Monitor ACT before dosing, 5 to 10 minutes after bolus dosing, and after any change in infusion rate and at the end of the procedure. Additional ACT assessments should be made every 20 to 30 minutes during extended percutaneous coronary intervention procedures.
Precautions	**Bleeding:** Use extreme caution in patients with hematologic conditions associated with increased bleeding (eg, congenital or acquired bleeding disorders, GI lesions); recent puncture of large vessels or organ biopsy; spinal anesthesia; immediately following lumbar puncture; recent cerebrovascular accident (CVA), stroke, intracerebral surgery, or other neuraxial procedure; severe hypertension; renal impairment; recent major surgery; recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding. **Hypersensitivity**: Airway, skin, and generalized hypersensitivity reactions have been reported. **Hepatic impairment**: Use with caution in patients with hepatic impairment; dosage reduction is necessary; may require >4 hours to achieve full reversal of anticoagulant effects. Avoid use during PCI in patients with clinically significant hepatic impairment or elevations of ALT/AST ≥3 times ULN (has not been studied).
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of NSTEMI treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 10. Argatroban HTA Analysis

Medication	Agency	Date – HTA Recommendation
Argatroban	CADTH	N/A
	NICE	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

Conclusion Statement – Argatroban

Argatroban is a direct thrombin inhibitor that can be used for PCI in adults at a dose beginning with infusion of 25 mcg/kg/minute and administer bolus dose of 350 mcg/kg (over 3 to 5 minutes) while checking ACT every 5 to 10 minutes after bolus infusion. Monitor for bleeding as it is a major side effect of this anticoagulant.

2.2 Modifications

There are no new modifications regarding the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

Felodipine was withdrawn from SFDA for NSTEMI treatment.

2.4 Other Drugs

2.4.1 Cangrelor

FDA approves Cangrelor on June 24th, 2015[14].

EMA approves Cangrelor on March 23rd, 2015[15].

Cangrelor is used for the treatment of coronary disease or in PCI procedures.

The recommended dose of Cangrelor for percutaneous coronary intervention is[16]:

IV: 30 mcg/kg bolus prior to percutaneous coronary intervention (PCI) followed immediately by an infusion of 4 mcg/kg/minute continued for at least 2 hours or for the duration of the PCI, whichever is longer.

Transitioning patients to oral $P2Y_{12}$ antagonist therapy after percutaneous coronary intervention:

- *Conversion to clopidogrel:* Administer 600 mg of clopidogrel immediately after discontinuing cangrelor infusion. Do not administer clopidogrel prior to cangrelor discontinuation.
- *Conversion to prasugrel:* Administer 60 mg of prasugrel immediately after discontinuing cangrelor infusion. Do not administer prasugrel prior to cangrelor discontinuation.
- *Conversion to ticagrelor:* Administer 180 mg of ticagrelor at any time during cangrelor infusion or immediately after discontinuing cangrelor infusion.

2.4.2 Eptifibatide

FDA approves eptifibatide on May 18th, 1998[17].

EMA approves eptifibatide on January 11th, 2016[18].

Eptifibatide is used for Non-ST elevation acute coronary syndromes at a dose of Bolus of 180 mcg/kg (maximum: 22.6 mg) IV beginning after diagnostic coronary angiography, just before PCI, followed by a continuous infusion of 2 mcg/kg/minute (maximum: 15 mg/hour); a second bolus of 180 mcg/kg (maximum: 22.6 mg) should be administered 10 minutes after the first bolus; continue infusion for up to 18 to 24 hours after PCI[19].

Section 3.0 Key Recommendations Synthesis

- Among patients with NSTE-ACS with very high-risk criteria (on-going ischemia, hemodynamic compromise, arrhythmias, mechanical complications of MI, acute heart failure, recurrent dynamic or widespread ST-segment and/or T-wave changes on ECG), an **immediate** invasive strategy is recommended **(within 2 hours of admission).**
- In the absence of very high-risk criteria, for patients with NSTE-ACS with high-risk criteria (GRACE score >140, dynamic ST-segment and/or T-wave changes on ECG or rise and/or fall in troponin compatible with MI) an **early** invasive strategy is recommended **(within 24 hours of admission).**
- In the absence of high-risk criteria, for patients with NSTE-ACS with intermediate-risk criteria (such as recurrent symptoms or substantial inducible ischemia on provocative testing), an invasive strategy is recommended **(within 72 hours of admission).**
- The preferred anticoagulants agents in patients with NSTE-ACS:
    - Fondaparinux (2.5 mg SC daily) is recommended as having the most favorable efficacy–safety profile regardless of the management strategy.
    - Enoxaparin (1 mg/kg SC twice daily) or UFH are recommended when fondaparinux is not available.
    - In patients on Fondaparinux (2.5 mg SC daily) undergoing PCI, a single IV 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.
    - Enoxaparin should be considered as the anticoagulant for PCI in patients pre-treated with SC enoxaparin.
    - Crossover between UFH and LMWH is not recommended.

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI NSTEMI report** and aims to provide recommendations to aid in the management of non-ST elevation myocardial infarction. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with NSTEMI. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
2. Anderson H V., Masri SC, Abdallah MS, et al. 2022 ACC/AHA Key Data Elements and Definitions for Chest Pain and Acute Myocardial Infarction: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Data Standards. *Circ Cardiovasc Qual Outcomes*. 2022;15(10):E000112. doi:10.1161/HCQ.0000000000000112
3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation*. 2018;138(20):e618-e651. doi:10.1161/CIR.0000000000000617
4. Hajira Basit. Epidemiology of NSTEMI worldwide. Published online 2023. Accessed June 16, 2023. https://www.ncbi.nlm.nih.gov/books/NBK513228/#:~:text=Males%20outnumber%20females%20by%20a,approximately%2070%25%20will%20have%20NSTEMI.
5. Clinical Features and Management Model of Acute Coronary Syndrome in Saudi Arabia. *J Cardiol Curr Res*. 2016;7(5). doi:10.15406/jccr.2016.07.00263
6. Alhabib KF, Kinsara AJ, Alghamdi S, et al. The first survey of the Saudi Acute Myocardial Infarction Registry Program: Main results and long-term outcomes (STARS-1 Program). *PLoS One*. 2019;14(5). doi:10.1371/journal.pone.0216551
7. Pollack C V., Amin A, Wang T, et al. Contemporary NSTEMI management: the role of the hospitalist. *Hosp Pract (1995)*. 2020;48(1):1-11. doi:10.1080/21548331.2020.1701329
8. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. Published online August 25, 2023. doi:10.1093/eurheartj/ehad191
9. *Acute Coronary Syndromes NICE Guideline*.; 2020. www.nice.org.uk/guidance/ng185
10. *CLINICAL GUIDELINES FOR ACUTE CORONARY SYNDROME (ACS)*.
11. *PREFACE*.
12. Bangalore S, Barsness GW, Dangas GD, et al. Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement from the American Heart Association. *Circulation*. 2021;144(5):E107-E119. doi:10.1161/CIR.0000000000000996
13. lexicomp. lexicomp argatroban. Published online 2022. Accessed August 14, 2023. https://online-lexi-

com.ezproxy.lau.edu.lb:2443/lco/action/doc/retrieve/docid/multinat_f/4669026?cesid=36szSrYZUgY&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dargatropan%26t%3Dname%26acs%3Dfalse%26acq%3Dargatropan#

14. FDA approval of cangrelor. Published online 2015. Accessed August 21, 2023. https://www.mdedge.com/chestphysician/article/100743/interventional-cardiology-surgery/fda-approves-cangrelor-intravenous

15. EMA approval of cangrelor. Published online 2015. Accessed August 21, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/kengrexal

16. lexicomp. lexicomp of cangrelor. Published online 2023. Accessed August 21, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/doc/retrieve/docid/multinat_f/5720271?cesid=5qwqeZ6mg0g&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dcangrelor%26t%3Dname%26acs%3Dfalse%26acq%3Dcangrelor#

17. fda approval of eptifibatide. Published online 1998. Accessed August 21, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20718_Integrilin.cfm#:~:text=Approval%20Date%3A%205%2F18%2F1998

18. EMA. ema eptifibatide. Published online 2016. Accessed August 21, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/eptifibatide-accord

19. lexicomp. lexicomp of eptifibatide. Published online 2023. Accessed August 21, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/doc/retrieve/docid/multinat_f/4668714?cesid=1IJuMGBw1dJ&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Deptifibatide%26t%3Dname%26acs%3Dfalse%26acq%3Deptifibatide#

Section 6.0 Appendices

Appendix A. Class of Recommendations and Level of evidence

Table 7. Class of Recommendations

The ESC 2020 guidelines used the table below for classes of recommendations[1]:

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or 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

Table 8. Level of Evidence

The ESC 2020 guideline used the table below for levels of evidence[1]:

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 the experts and/or small studies, retrospective studies, registries.**

Appendix B. Scope Review

Section	Rationale/Updates
Section 1.1 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation 2015	**2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation** [1] <u>Updated recommendations:</u> • For diagnostic purposes, it is not recommended to routinely measure additional biomarkers such as CK, CK-MB, h-FABP, or copeptin, in addition to hs-cTn (Class 3) • Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI. (Class 2a) • It is not recommended to administer routine pre-treatment with a P2Y12 receptor inhibitor to patients in whom the coronary anatomy is not known and early invasive management is planned (Class3). • In patients with NSTE-ACS who cannot undergo an early invasive strategy, pre-treatment with a P2Y12 receptor inhibitor may be considered depending on bleeding risk. (Class 2b) • De-escalation of P2Y12 inhibitor treatment (e.g., with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment, or guided by platelet function testing, or CYP2C19 genotyping depending on the patient's risk profile and availability of respective assays. (Class 2b) • Discontinuation of antiplatelet treatment in patients treated with OACs is recommended after 12 months (Class1). • DAT with an OAC and either ticagrelor or prasugrel may be considered as an alternative to TAT with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used.

	(Class 2b) • An early invasive strategy within 24 h is recommended in patients with any of the following high-risk criteria: • Diagnosis of NSTEMI. • Dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischemia. • Transient ST-segment elevation. • GRACE risk score >140. (Class 1) • Delayed, as opposed to immediate, angiography should be considered in hemodynamically stable patients without ST-segment elevation successfully resuscitated after an out-of-hospital cardiac arrest (class 2a) • Complete revascularization should be considered in NSTE-ACS patients without cardiogenic shock and with multivessel CAD. (Class 2a) • Rhythm monitoring up to 24 h or to PCI (whichever comes first) is recommended in NSTEMI patients at low risk for cardiac arrhythmias (class 1) (was class 2a) • Rhythm monitoring for >24 h is recommended in NSTEMI patients at increased risk for cardiac arrhythmia (class 1) (was class 2a) • GRACE risk score models should be considered for estimating prognosis (class 2a) (was class 1 for other risk scores) • Bivalirudin may be considered as an alternative to UFH (was mandatory now may be) • Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients at high risk of ischemic events and without increased risk of major or life-threatening bleeding (class 2a) (was class 2b)
Section 1.3 NICE guidelines for	**2020 NICE Acute coronary syndromes guideline** [9] <u>Updated recommendations:</u>

Unstable angina and NSTEMI early management 2010 last update 2013	• Do not offer dual antiplatelet therapy to people with chest pain before a diagnosis of unstable angina or NSTEMI is made. • Offer immediate coronary angiography to people with unstable angina or NSTEMI if their clinical condition is unstable. • Consider coronary angiography (with follow-on PCI if indicated) within 72 hours of first admission for people with unstable angina or NSTEMI who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) and no contraindications to angiography (such as active bleeding or comorbidity). • Offer ticagrelor, as part of dual antiplatelet therapy with aspirin, to people with unstable angina or NSTEMI when PCI is not indicated, unless they have a high bleeding risk. • Consider clopidogrel, as part of dual antiplatelet therapy with aspirin, or aspirin alone, for people with unstable angina or NSTEMI when PCI is not indicated, if they have a high bleeding risk. • Continue dual antiplatelet therapy for up to 12 months after an MI unless contraindicated. • Do not routinely offer prasugrel or ticagrelor in combination with an anticoagulant that is needed for an ongoing separate indication for anticoagulation. • Consider continuing a beta-blocker for 12 months after an MI for people without reduced left ventricular ejection fraction.
2020 Saudi clinical guidelines for acute coronary syndrome (ACS) (clinical guidelines for acute coronary syndrome (acs), n.d.)	<u>Missing recommendations:</u> • The GRACE risk score provides the most accurate. stratification of risk both on admission and at discharge. • Among patients with NSTE-ACS with very high-risk criteria (on-going ischemia, hemodynamic compromise, arrhythmias, mechanical complications of MI, acute heart failure, recurrent dynamic or widespread ST-segment and/or T-wave changes on ECG), an immediate invasive strategy is recommended (within 2 hours of admission).

	• In the absence of very high-risk criteria, for patients with NSTE-ACS with high-risk criteria (GRACE score >140, dynamic ST-segment and/or T-wave changes on ECG or rise and/or fall in troponin compatible with MI) an early invasive strategy is recommended (within 24 hours of admission) • In the absence of high-risk criteria, for patients with NSTE-ACS with intermediate-risk criteria (such as recurrent symptoms or substantial inducible ischemia on provocative testing), an invasive strategy is recommended (within 72 hours of admission). • Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 81–162mg/ day long-term regardless of treatment strategy. • Ticagrelor, or Clopidogrel if Ticagrelor is not available, is recommended before or at latest at the time of PCI and should be maintained over 12 months irrespective of revascularization strategy and stent type, unless there are contraindications such as excessive risk of bleeding. • The preferred anticoagulants agents in patients with NSTE-ACS - Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favorable efficacy–safety profile regardless of the management strategy. - Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available. - In patients on Fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single IV 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. - Enoxaparin should be considered as the anticoagulant for PCI in patients pre-treated with s.c. enoxaparin. - Crossover between UFH and LMWH is not recommended. • Oral treatment with beta-blockers is indicated in patients with heart failure and or who have a LVEF <40% unless contraindicated.

	• Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia. • An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended. • Prophylactic treatment with antiarrhythmic drugs is not indicated any may be harmful.

Appendix C. PubMed Search

The following is the result of the PubMed search conducted for NSTEMI guideline search.

Query	Filters	Search Details	Results
(((((((((Non-ST Elevated Myocardial Infarction[MeSH Terms]) OR (Non ST Elevated Myocardial Infarction[Title/Abstract])) OR (NSTEMI[Title/Abstract])) OR (Non-ST-Elevation Myocardial Infarction[Title/Abstract])) OR (Infarction, Non-ST-Elevation Myocardial[Title/Abstract])) OR (Infarctions, Non-ST-Elevation Myocardial[Title/Abstract])) OR (Myocardial Infarction, Non-ST-Elevation[Title/Abstract])) OR (Myocardial Infarctions, Non-ST-Elevation[Title/Abstract])) OR (Non ST Elevation Myocardial Infarction[Title/Abstract])) OR (Non-ST-Elevation Myocardial Infarctions[Title/Abstract])	Guideline, in the last 5 years	("non st elevated myocardial infarction"[MeSH Terms] OR "non st elevated myocardial infarction"[Title/Abstract] OR "NSTEMI"[Title/Abstract] OR "non st elevation myocardial infarction"[Title/Abstract] OR "infarction non st elevation myocardial"[Title/Abstract] OR (("infarctation"[All Fields] OR "infarcted"[All Fields] OR "infarctic"[All Fields] OR "infarcting"[All Fields] OR "Infarction"[MeSH Terms] OR "Infarction"[All Fields] OR "infarct"[All Fields] OR "Infarctions"[All Fields] OR "infarcts"[All Fields] OR "infarctive"[All Fields]) AND "non st elevation myocardial"[Title/Abstract]) OR "myocardial infarction non st elevation"[Title/Abstract] OR (("myocardial infarction"[MeSH Terms] OR ("Myocardial"[All Fields] AND "Infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("Myocardial"[All Fields] AND "Infarctions"[All Fields]) OR "myocardial infarctions"[All Fields]) AND "Non-ST-Elevation"[Title/Abstract]) OR "non st elevation myocardial infarction"[Title/Abstract] OR "non st elevation myocardial infarctions"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	3

Appendix D. Treatment Algorithm

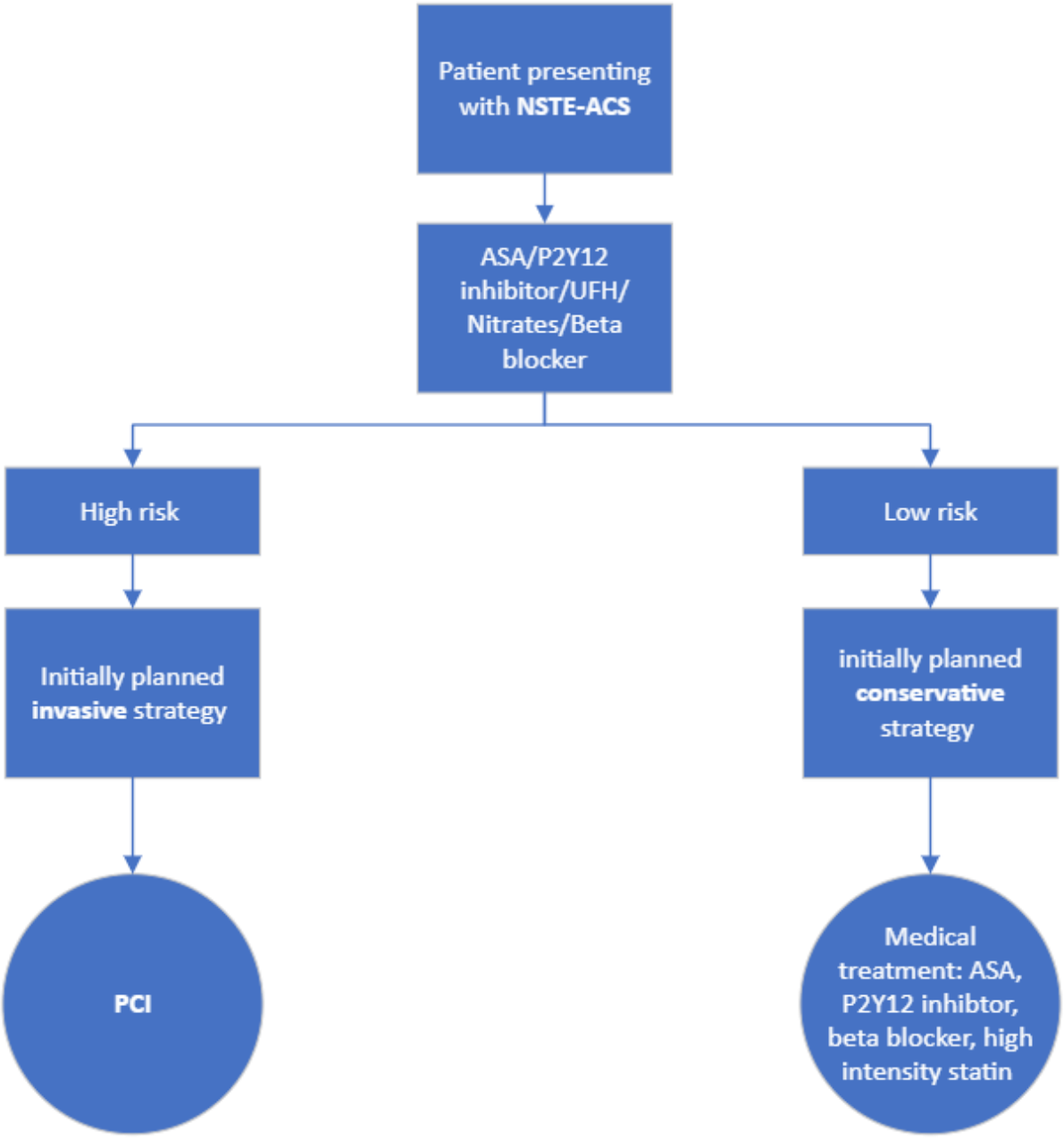

Figure 3. *Treatment Algorithm for the Management of Non-ST Elevation Myocardial Infarction (NSTEMI)*