ST-ELEVATION MYOCARDIAL INFARCTION

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – – September 2023

To the CHI Original ST-Elevation Myocardial Infarction Clinical Guidance – Issued January 2020

Contents

Related Documents

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- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
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Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
apTT	Activated Partial Thromboplastin Time
CABG	Coronary Artery Bypass Graft
CHI	Council of Health Insurance
DAPT	Dual Antiplatelet Therapy
ECG	Electrocardiogram
FDA	Food and Drug Administration
IDF	CHI Drug Formulary
MI	Myocardial Infarction
OAC	Oral Anticoagulant
PCI	Percutaneous Coronary Intervention
PPCI	Primary Percutaneous Coronary Intervention
SCAI	SHOCK Stage Classification Expert
SFDA	Saudi Food and Drug Authority
STEMI	ST-Elevation Myocardial Infarction
UFH	Unfractionated heparin

Executive Summary

ST-segment elevation myocardial infarction (STEMI) is characterized by the presence of symptoms indicating myocardial ischemia, along with a persistent elevation of the ST segment on an electrocardiogram (ECG). It is identified by the release of biomarkers that indicate necrosis (cell death) of the heart muscle. An acute STEMI occurs when there is transmural myocardial ischemia, leading to injury or necrosis of the heart muscle[1].

STEMI occurs from the occlusion of one or more of the coronary arteries that supply the heart with blood. The cause of this abrupt disruption of blood flow is usually plaque rupture, erosion, fissuring or dissection of coronary arteries that results in an obstructing thrombus. The major risk factors for developing STEMI are dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of coronary artery disease[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 myocardial infarctions (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 h of coronary artery bypass grafting (CABG)[2,3].

In general, the global prevalence of MI in individuals < 60 years was found 3.8%. Also, following the assessment of 20 eligible investigations with a sample size of 5,071,185 individuals (> 60 years), this value was detected at 9.5%[4]. STEMI remains a major health care burden in the United States, with around 750,000 cases reported annually[5]. More than 3 million individuals develop STEMI each year, and more than 4 million people represent STEMI pathology[6]. In Saudi Arabia, the incidence of acute coronary syndrome (ACS) was 8.2%, and the diagnosis of STEMI represents 53.2% of the patients[7]. 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 65.9% of enrolled patients had STEMI. In addition, CAD risk factors were high; 52.7% had diabetes mellitus and 51.2% had hypertension. Revascularization for patients with STEMI included thrombolytic therapy (29%), primary percutaneous coronary intervention (PCI); (42.5%), neither (29%), or a pharmacoinvasive approach (3%)[8].

The goal of STEMI management is to reduce the risk of death and permanent cardiac injury associated with myocardial infarction (MI). Drug therapy is an integral component for the management of STEMI. Initial medical management consists of relief of ischemic pain with nitrates and morphine, antithrombotic measures including antiplatelet agents (aspirin, thienopyridines and glycoprotein IIb/IIIa inhibitors), systemic anticoagulation (heparin or bivalirudin), and beta-blockers.

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to the management of STEMI. The primary goal of the Council of Health Insurance (CHI) in issuing STEMI 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 STEMI in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on American and Saudi guidelines issued within the last five years. The European and Scottish guidelines did not change from the last CHI report.

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 STEMI.

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

Regarding the management of STEMI, there were no additions of new drugs recommended in the guidelines, and there were no new drugs approved by the Food and Drug Administration (FDA). No changes or modifications were made to existing drugs. No drugs were withdrawn from the Saudi Food and Drug Authority (SFDA) as well. Section 3 lists the key recommendations synthesis for STEMI treatment.

Below is a table summarizing the major changes based on the different STEMI guidelines used to issue this report:

Table 1. General Recommendations for the Management of ST-Elevation Myocardial Infarction

Management of STEMI		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
In patients with STEMI who have mechanical complications, coronary artery bypass grafting (CABG) is recommended at the time of surgery, with the goal of improving survival.	Class 1b	Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]
In patients with STEMI and evidence of failed reperfusion after fibrinolytic therapy, rescue percutaneous coronary intervention (PCI) of the infarct artery should be performed to improve clinical outcomes.	Class 1c	Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]
Revascularization of the Non-Infarct Artery in Patients With STEMI: In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis **is recommended** to reduce the risk of death or MI.	Class 1a	Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]
Revascularization of the Non-Infarct Artery in Patients With STEMI:	Class 2a	Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A

In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG **is reasonable** to reduce the risk of cardiac events.		Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]
Revascularization of the Non-Infarct Artery in Patients With STEMI: In selected hemodynamically stable patients with STEMI and low complexity multivessel disease, PCI of a non-infarct artery stenosis **may** be considered at the time of primary PCI to reduce cardiac event rates.	Class 2b	Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]

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 STEMI report, while 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 mentioned in the December 2019 CHI STEMI Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction)	N/A*
2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation	2023 ESC Guidelines for the Management of Acute Coronary Syndromes [10]
Saudi Clinical Practice Guidelines on Management of ST-Elevation Myocardial Infarction 2015	2020 National Clinical Practice Guidelines for the Diagnosis and Management of Acute Coronary Syndrome[11]
Scottish Intercollegiate Guidelines Network (SIGN) For Acute Coronary Syndrome 2016)	N/A*

**: 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[10].

Tables 3 and 4 detail the classes of recommendations and the levels of evidence used throughout the guideline.

Table 3. ESC Guidelines Classes of Recommendations

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. ESC Guidelines Levels of Evidence

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 STEMI, both new and revised, are detailed below:

- Pre-treatment with a P2Y12 receptor inhibitor may be considered in patients undergoing a primary PCI strategy. (Class 2b, LOE B)
- In patients who are event-free after 3–6 months of DAPT and who are not high ischemic risk, SAPT (preferably with a P2Y12 receptor inhibitor) should be considered. (Class 2a, LOE A)

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 3-6 months 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 high bleeding risk patients, aspirin or P2Y12 receptor inhibitor monotherapy after 1 month of DAPT may be considered. (Class 2b, LOE A)
- In patients requiring oral anticoagulants (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 represents the treatment strategies for patients with a working diagnosis of STEMI. A primary percutaneous coronary intervention (PPCI) strategy, which includes immediate angiography and PCI as needed, is the preferred reperfusion strategy, provided it can be performed in a timely manner (within 120 min of the ECG-based diagnosis). RCTs have shown that if the delay to treatment is similar, PPCI is superior to fibrinolysis in reducing mortality, non-fatal reinfarction, and stroke. However, in some circumstances, PPCI is not an immediate option and fibrinolysis should be initiated expeditiously as part of a pharmaco-invasive strategy, provided the patient presented within 12 hours of symptom onset.

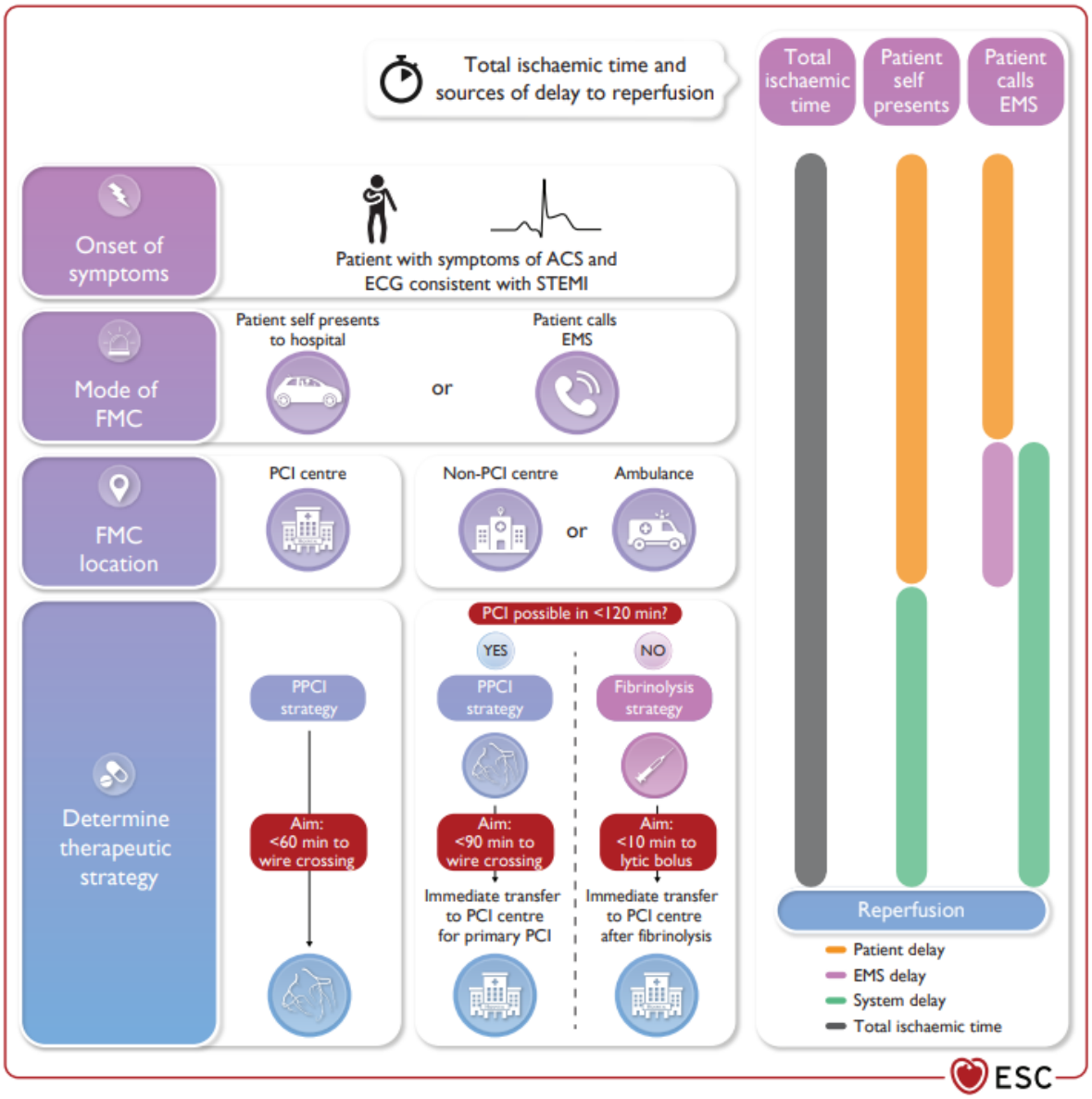

Figure 1. *Modes of Presentation and Pathways to Invasive Management and Myocardial Revascularization in Patients Presenting with STEMI. Retrieved from Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. Published online August 25, 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 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.

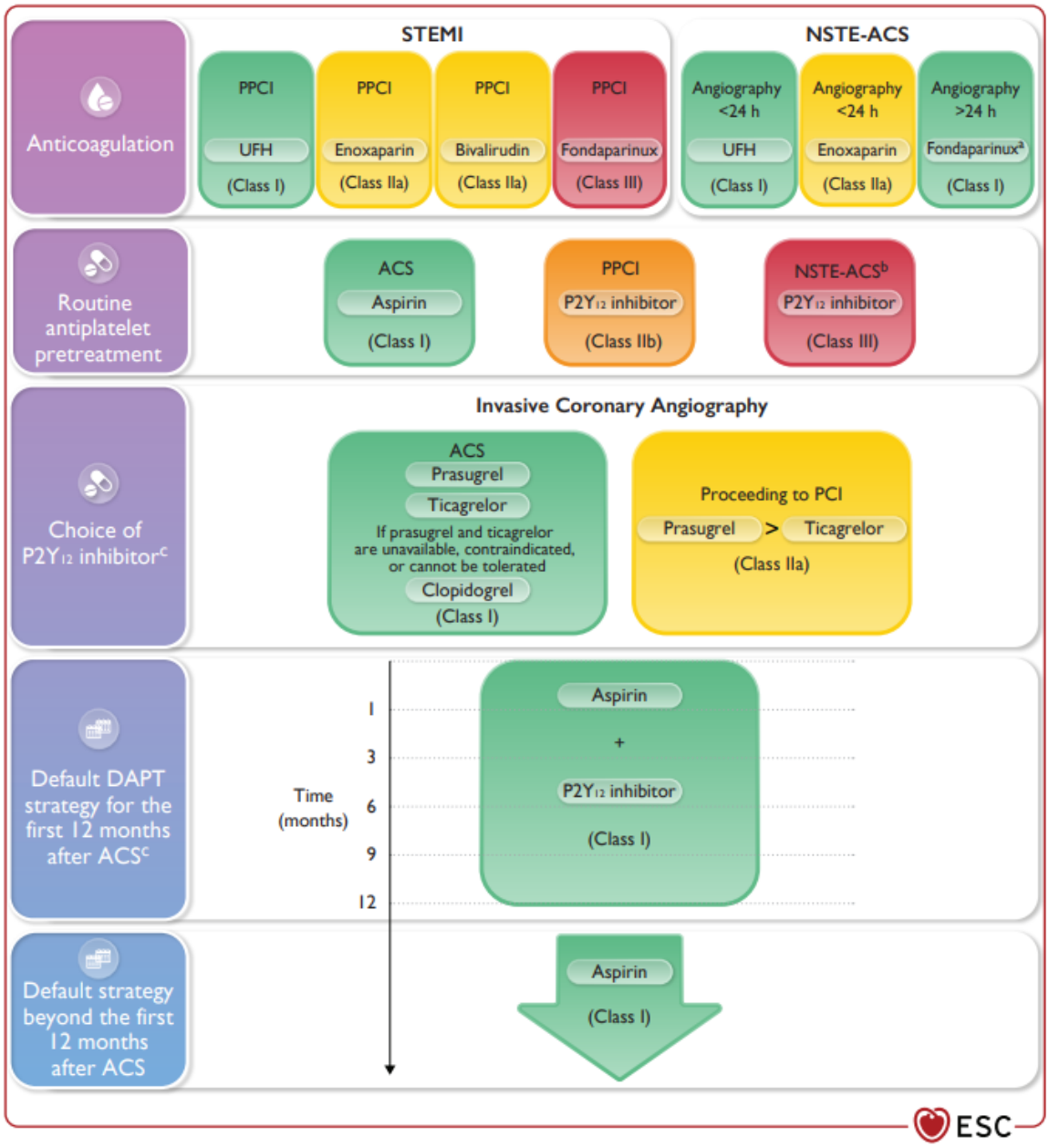

Figure 2. *Recommended Default Antithrombotic Therapy Regimens in Acute Coronary Syndrome Patients Without an Indication for Oral Anticoagulation. Retrieved from Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. Published online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

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

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

Preferred dual antiplatelet therapy (DAPT) in patients undergoing primary PCI:

- Aspirin is recommended as soon as possible for all patients without contraindications. The recommended loading dose of aspirin is 150-300 mg orally.
- Ticagrelor (loading dose 180 mg orally, followed by 90 mg twice per day for 12 months) or clopidogrel if ticagrelor is not available (clopidogrel loading dose 600 mg orally once, followed by 75 mg once/day for 12 months), is recommended before or at latest at the time of PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

Preferred DAPT in patients receiving fibrinolysis:

- Aspirin is recommended as soon as possible for all patients without contraindications. The recommended loading dose of Aspirin is 150-300 mg orally.
- Clopidogrel is indicated in addition to aspirin. Clopidogrel loading dose is 300 mg orally, followed by 75 mg once/day for 12 months (in patients ≥75 years of age, the loading dose is 75 mg followed by 75 mg once/day for 12 months).

Preferred anticoagulant therapy in patients undergoing primary PCI:

- We recommend routine use of unfractionated heparin (UFH) for procedural anticoagulation in patients with STEMI undergoing primary PCI.

Preferred anticoagulant therapy in patients receiving fibrinolysis:

- Enoxaparin IV followed by SC is preferred over UFH.
- UFH is given as a weight adjusted IV bolus followed by an infusion if enoxaparin is not available.

Recommended therapy at discharge from hospital:

- Aspirin (81–162 mg/day) should be continued indefinitely unless it is not tolerated or an indication for anticoagulation becomes apparent.
- Clopidogrel should be prescribed if aspirin is contraindicated.

- DAPT in the form of aspirin plus ticagrelor, or clopidogrel, if ticagrelor is not available, is recommended for 12 months after PCI, unless there are contraindications such as excessive bleeding.
- Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.
- Angiotensin-converting enzyme (ACE) inhibitors should be considered in all patients in the absence of contraindications.
- It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation. It is recommended to start high-dose statin therapy as early as possible regardless of initial LDC-C level, unless contraindicated. 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 Additional Guidelines

This section includes the added guidelines to the previous CHI STEMI report.

Table 6. List of Additional Guidelines

Additional Guidelines
2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]
2020 NICE Guideline for Acute Coronary Syndrome[12]
2021 Evidence-Based Practices in the Cardiac Catheterization Laboratory: A Scientific Statement from the **American Heart Association**[13]

1.2.1 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines (2021)

The main recommendations from the guidelines jointly published by the American College of Cardiology (ACC), the American Heart Association (AHA) and the SHOCK Stage Classification Expert (SCAI) in 2021 are listed below[9]. Classes of recommendations and levels of evidence are defined in appendix A.

- In patients with STEMI who have mechanical complications (e.g., ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction or rupture, or free wall rupture), CABG is recommended at the time of surgery, with the goal of improving survival. (Class 1b)

- In patients with STEMI and evidence of failed reperfusion after fibrinolytic therapy, rescue PCI of the infarct artery should be performed to improve clinical outcomes. (Class 1c)
- In patients with STEMI, emergency CABG should not be performed after failed primary PCI:
    - In the absence of ischemia or a large area of myocardium at risk
    - If surgical revascularization is not feasible because of a no-reflow state or poor distal targets. (Class 3)
- Revascularization of the Non-Infarct Artery in Patients With STEMI:
    - In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis is recommended to reduce the risk of death or MI. (Class 1a)
    - In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG is reasonable to reduce the risk of cardiac events. (Class 2a)
    - In selected hemodynamically stable patients with STEMI and low complexity multivessel disease, PCI of a non-infarct artery stenosis may be considered at the time of primary PCI to reduce cardiac event rates. (Class 2b)
- In patients with STEMI and CKD, coronary angiography and revascularization are recommended, with adequate measures to reduce the risk of AKI. (Class 1c)
- In patients with STEMI, routine aspiration thrombectomy before primary PCI is not useful. (Class 3a)

Figure 3 represents the population eligible for PCI/CABG:

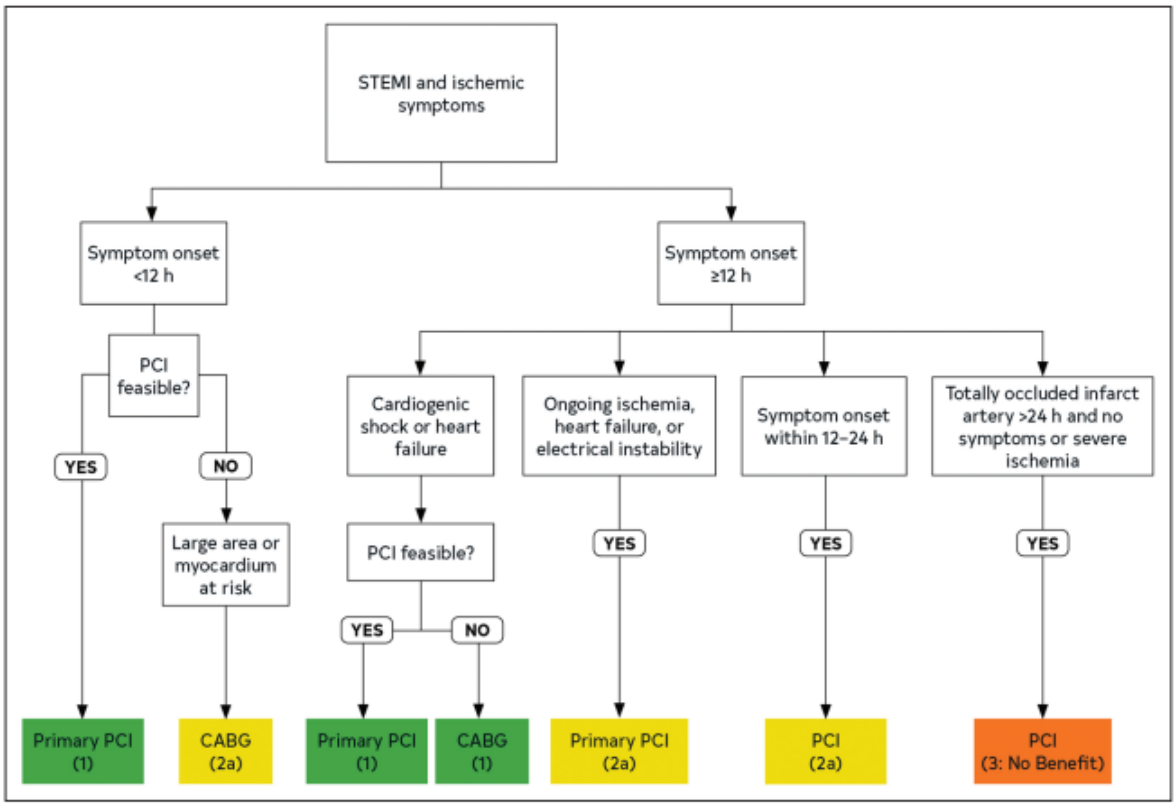

Figure 3. *Indications for Revascularization in STEMI (Patients Without Fibrinolytics). Retrieved from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(3):E18-E114. doi:10.1161/CIR.0000000000001038.*

Figure 4 represents revascularization of non-Infarct-related coronary artery lesions in patients with STEMI.

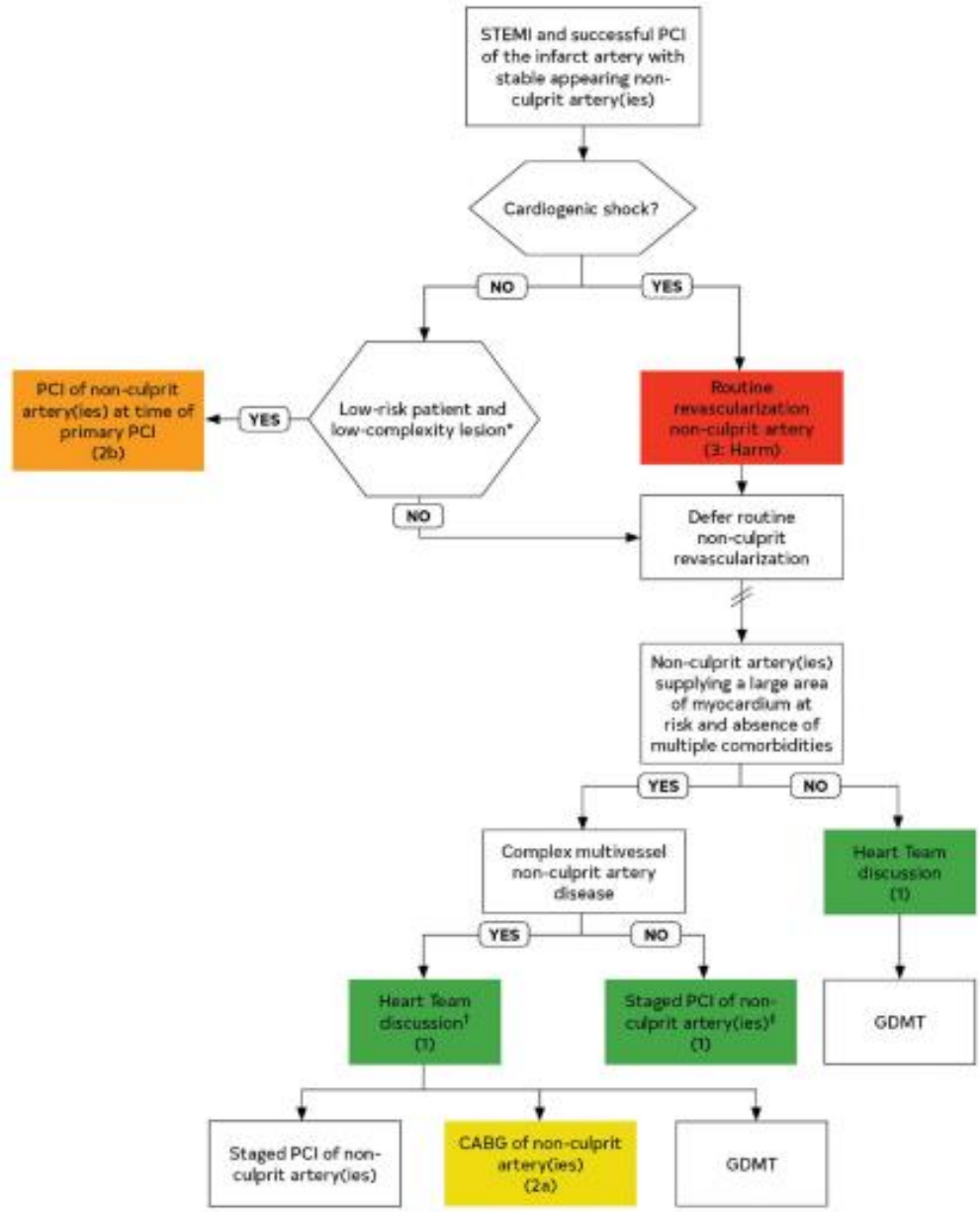

Figure 4. *Revascularization of Non-Infarct-Related Coronary Artery Lesions in Patients With STEMI. Retrieved from Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(3):E18-E114. doi:10.1161/CIR.0000000000001038.*

1.2.2 NICE Acute Coronary Syndrome (2020)

The recommendations of the NICE 2020 Acute coronary syndrome are listed below[12]:

- A single loading dose of 300-mg aspirin as soon as possible is recommended in patients presenting with acute STEMI unless there is clear evidence that they are allergic to it.

- Routine glycoprotein IIb/IIIa inhibitors or fibrinolytic drugs before arrival at the catheter laboratory is not recommended in people with acute STEMI for whom primary PCI is planned.
- Coronary angiography, with follow-on primary PCI if indicated, is recommended as the preferred coronary reperfusion strategy for people with acute STEMI, if:
    - presentation is within 12 hours of onset of symptoms;
    - primary PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given.
- For people with acute STEMI who are having primary PCI:
    - Prasugrel, as part of dual antiplatelet therapy with aspirin, if they are not already taking an oral anticoagulant (use the maintenance dose in the prasugrel summary of product characteristics; for people aged 75 and over, think about whether the person's risk of bleeding with prasugrel outweighs its effectiveness, in which case offer ticagrelor or clopidogrel as alternatives).
    - Clopidogrel, as part of dual antiplatelet therapy with aspirin, if they are already taking an oral anticoagulant.
- If stenting is indicated, a drug-eluting stent should be offered to people with acute STEMI undergoing revascularization by primary PCI.
- Fibrinolysis is recommended in people with acute STEMI presenting within 12 hours of onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given.
- When treating people with fibrinolysis, an antithrombin is recommended to be given at the same time.

Management for people with STEMI not treated with PCI:

- Ticagrelor, as part of dual antiplatelet therapy with aspirin, is recommended in people with acute STEMI not treated with PCI, unless they have a high bleeding risk.
- Clopidogrel, as part of dual antiplatelet therapy with aspirin, or aspirin alone, should be considered in people with acute STEMI not treated with PCI, if they have a high bleeding risk.

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[13]:

- Treatment with metformin pre- and post-procedure in those without severe renal dysfunction should be continued.

- Glucose-lowering agents before catheterization procedures should not be withheld. 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 guidelines but are SFDA registered, and FDA/EMA approved.

2.1 Additions

2.1.1 Argatroban

Argatroban characteristics are listed in the table below[14]:

Table 7. 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). <u>Percutaneous coronary intervention:</u> 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 STEMI 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 8. 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

There are no withdrawn drugs in the treatment of STEMI. The drugs used for the management of STEMI are still the same.

2.4 Other Drugs

2.4.1 Cangrelor

FDA approved Cangrelor on June 24th, 2015[15].

EMA approved Cangrelor on March 23rd, 2015[16].

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

The recommended dose of Cangrelor for percutaneous coronary intervention is[17]:

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 approved eptifibatide on May 18th, 1998[18].

EMA approved eptifibatide on January 11th, 2016[19].

Eptifibatide is used for ST elevation myocardial infarction as off-label use 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[20].

2.4.3 Reteplase

FDA approves Reteplase on September 3rd, 2003[21].

EMA approves Reteplase on November 9th, 1996[22].

Reteplase is used for ST-elevation myocardial infarction (STEMI), acute at a dose of 10 units IV over 2 minutes, followed by a second dose 30 minutes later of 10 units IV over 2 minutes[23].

To note that Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy. Thrombolytic therapy is an option in centers without PCI capability, followed by transfer to a PCI-capable center. Administer thrombolytic therapy within 30 minutes of first medical contact (in ambulance or emergency department) if primary PCI cannot be performed within 120 minutes; if primary PCI is not available, may still consider thrombolysis in patients who present late (within 12 to 24 hours of symptom onset) and have ongoing ischemia or extensive ST elevation. Administer aspirin, clopidogrel, and anticoagulant therapy (ie, unfractionated heparin, enoxaparin, or fondaparinux) in combination with thrombolytic therapy.

Section 3.0 Key Recommendations Synthesis

Revascularization of the Non-Infarct Artery in Patients With STEMI:

- In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis **is recommended** to reduce the risk of death or MI. (class 1a)
- In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG **is reasonable** to reduce the risk of cardiac events. (Class 2a)
- In selected hemodynamically stable patients with STEMI and low complexity multivessel disease, PCI of a non-infarct artery stenosis **may be considered** at the time of primary PCI to reduce cardiac event rates. (Class 2b)

In patients with STEMI and CKD, coronary angiography and revascularization are recommended, with adequate measures to reduce the risk of AKI. (Class 1c)

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI STEMI report** and aims to provide recommendations to aid in the management of 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 STEMI. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Classes of Recommendations and Levels of Evidence

Table 9. ACC/AHA/SCAI Class of Recommendations

The ACC/AHA/SCAI 2021 guideline used this table below for classes of recommendations:[9]

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

Table 10. ACC/AHA/SCAI Levels of Evidence

The ACC/AHA/SCAI 2021 guideline used this table below for levels of evidence[9]:

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

Appendix B. Scope Review

Section	Rationale/Updates
Addition of a new section: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines[9]	<u>Missed recommendations:</u> • In patients with STEMI who have mechanical complications (e.g., ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction or rupture, or free wall rupture), CABG is recommended at the time of surgery, with the goal of improving survival. (Class 1b) • In patients with STEMI and evidence of failed reperfusion after fibrinolytic therapy, rescue PCI of the infarct artery should be performed to improve clinical outcomes. (Class 1c) • In patients with STEMI, emergency CABG should not be performed after failed primary PCI: In the absence of ischemia or a large area of myocardium at risk If surgical revascularization is not feasible because of a no-reflow state or poor distal targets. (Class 3) • Revascularization of the Non-Infarct Artery in Patients With STEMI: In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis is recommended to reduce the risk of death or MI. (class 1a) In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG is reasonable to reduce the risk of cardiac events. (Class 2a) In selected hemodynamically stable patients with STEMI and low complexity multivessel disease, PCI of a non-infarct artery stenosis may be considered at the time of primary PCI to reduce cardiac event rates. (Class 2b) • In patients with STEMI and CKD, coronary angiography and revascularization are recommended, with adequate measures to reduce the risk of AKI. (Class 1c) • In patients with STEMI, routine aspiration thrombectomy before primary PCI is not useful. (Class 3)

Appendix C. PubMed Search

Below is the result of the PubMed search conducted for STEMI guideline search:

Query	Filters	Search Details	Results
(((ST Elevation Myocardial Infarction[MeSH Terms]) OR (ST Segment Elevation Myocardial Infarction[MeSH Terms])) OR (ST Elevated Myocardial Infarction[Title/Abstract])) OR (STEMI[Title/Abstract])	Guideline, in the last 5 years	("st elevation myocardial infarction"[MeSH Terms] OR "st elevation myocardial infarction"[MeSH Terms] OR "st elevated myocardial infarction"[Title/Abstract] OR "STEMI"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	8

Appendix D. Treatment Algorithm

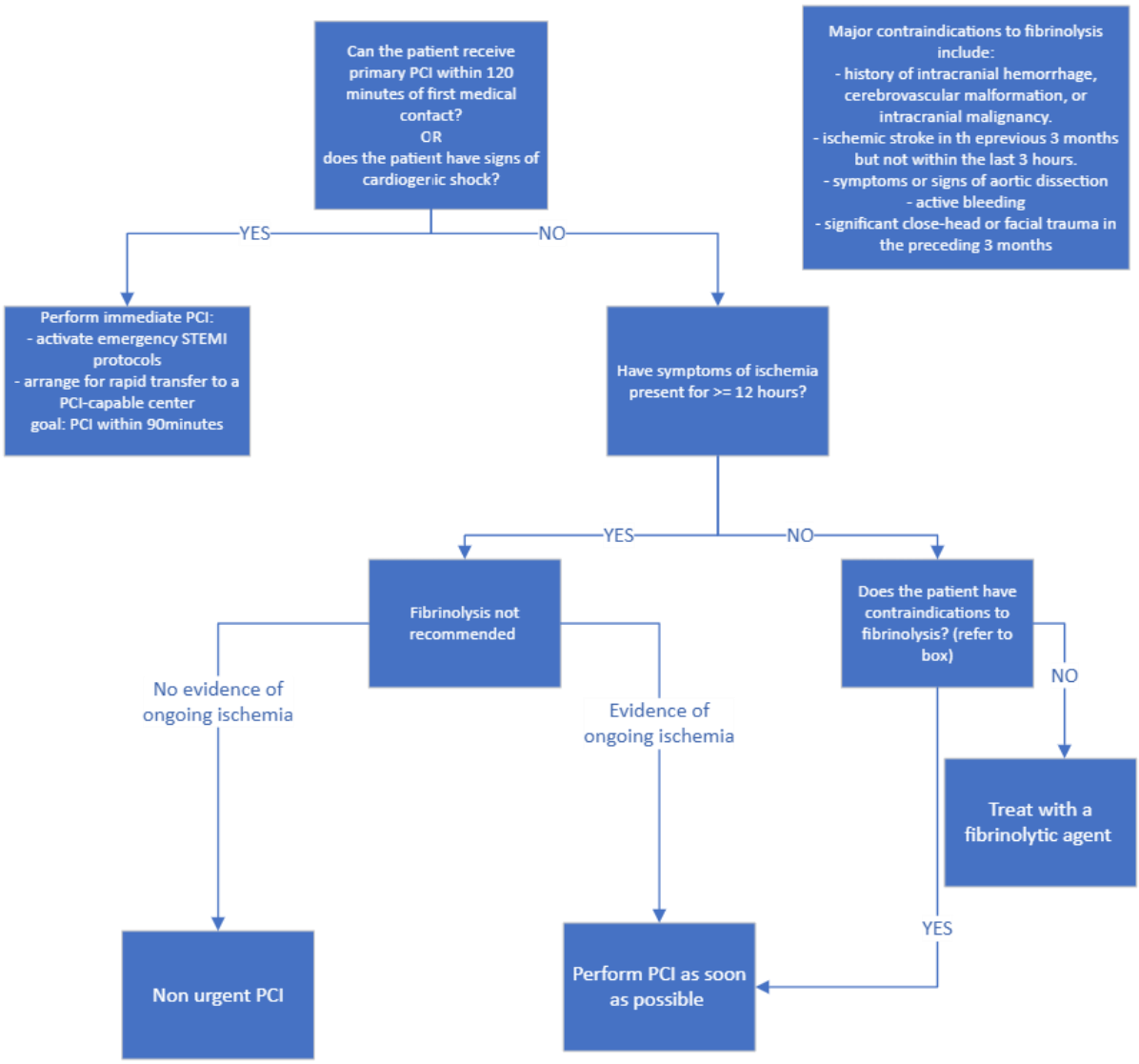

Figure 5. *Treatment Algorithm for the Management of ST-Elevation Myocardial Infarction (STEMI)*