Development of a Clinical Pathway for Acute Coronary Syndrome at Philippine General Hospital

Cecileen Anne M. Tuazon, MD* | Paul Anthony O. Alad, MD* | Albert Roy M. Rollorazo, MD* | Lauren Kay Evangelista, MD* | Ruth Divine Agustin, MD* | Valerie Ramiro, MD* | John Christopher Pilapil, MD* | Bianca Velando, MD* | Mark Joseph M. Abaca, MD† | Jerahmeel Aleson L. Mapili, MD† | Diana R. Tamondong-Lachica, MD,† | Eric Oliver D. Sison, MD*† | John C. Añonuevo, MD*† | Felix Eduardo R. Punzalan, MD*†

*Division of Cardiovascular Medicine, Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, Philippines

†Department of Medicine, Philippine General Hospital, University of the Philippines, Manila, Philippines

Corresponding author:
Cecileen Anne M. Tuazon, MD
Email: cecileentuazon@gmail.com

Declaration of conflicts of interest: None.

Abstract

BACKGROUND: Acute coronary syndrome (ACS) is a leading cause of admission and mortality in a tertiary care hospital in the Philippines. The significant burden of the disease necessitates that evidence-based care set by international and local guidelines be met to improve service delivery and quality of care (QOC). Institution-specific QOC studies showed gaps between guideline recommendations and compliance. Development and utilization of a clinical pathway are among the identified strategies to improve compliance. It is also crucial for implementation of standard-of-care set specific to a hospital setting based on its needs and resources.

METHODS: This is a descriptive research on the development of a clinical pathway for ACS appropriate for the emergency room setting of a tertiary care hospital from March 2021 to August 2022. Local QOC studies and evidence behind the latest international guideline recommendations on the management of ACS were reviewed to create the interim ACS Pathway. Two-level content validation of the interim pathway was done: internal validation with the consultants and fellows of the Division of Cardiovascular Medicine and external validation through focused group discussions with different hospital units and stakeholders to assess applicability and feasibility based on the resources of the setting, identify hindrances, and propose solutions in its implementation.

RESULTS: An evidence-based clinical pathway for ACS that encompasses identification and management of ST-segment elevation myocardial infarction and non–ST-segment elevation acute coronary syndrome with judicious use of locally available and feasible resources applicable for local emergency room hospital setting was created.

CONCLUSION: Review of local QOC studies and interdepartmental collaboration are necessary components in developing institution-specific clinical pathway for ACS.

KEYWORDS: acute coronary syndrome, clinical pathway, quality of care

INTRODUCTION

Background of the Study

Cardiovascular diseases remain to be the leading cause of mortality worldwide. The World Health Organization estimated that 17.9 million people died of cardiovascular diseases in 2019, representing 32% of global deaths. Of these, 85% were from acute coronary syndrome (ACS) and stroke.[1] In the Philippines, ischemic heart disease was consistently identified as the leading cause of mortality from 2013 to 2018.[2] The Philippine General Hospital (PGH) Department of Medicine annual report likewise identified ACS as among the leading cause of admission and mortality in 2019.[3] The significant burden of the disease demands that quality-of-care measures be met to improve clinical outcomes.

The interventions for ACS show the greatest incremental benefit when done within the recommended time frames. The relationship between time to treatment, myocardial salvage, and patient outcomes cannot be overemphasized. Several local and international guidelines were released in the recent years, setting the standards to improve delivery of care to these patients. The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) are the commonly cited reference in clinical practice in providing evidence-based medical care. Included in these recommendations are key performance and quality measures to improve the quality of care for patients with ST-segment elevation myocardial infarction (STEMI) and ST-segment elevation myocardial infarction (NSTEMI).[4–6]

Compliance to the guideline recommendations and improvement in the quality of care for patients with ACS should be upheld to the highest standard to optimize service delivery and improve clinical outcomes for these patients. Among the strategies that have been shown to improve compliance of physicians to guideline recommendations translating to improved short term clinical outcomes was the utilization of clinical order sets and clinical pathways.[7–9]

Quality-of-care studies on ACS in PGH dated back to the early 1990s. Punzalan et al[10] in 1999 found high adherence to the 1996 and 1999 AHA/ACC Guidelines on the Management of Acute Myocardial Infarction, respectively, although a gap in adherence was observed for exercise testing and heparin therapy.[10] In 2008, the study by Obrado et al[11] showed that the compliance to class I diagnostic examinations and medications was optimal except for the treadmill exercise test and thrombolytic therapy.

Studies since then have highlighted the adherence to guideline-recommended time frames including the door-to-electrocardiogram (ECG) time, door-to-balloon time, and door-to-needle time, as well as adherence to class I recommendations from guidelines. In 2010, of the patients presenting with chest pain and symptoms suggestive of an ACS, only 57% had an ECG done at the emergency room (ER). Of the patients who had and ECG, only 4.7% had their ECG done within 10 minutes of presentation. The average lag time to first ECG was 110.24 minutes.[12] In 2011, the door-to-ECG time remained beyond the guideline-recommended target, with an average time of 109 minutes. The door-to-needle time (average, 317 minutes) was also substandard. High compliance rate to guideline-recommended pharmacologic therapies was observed except for fibrinolytic therapy (67%).[13] In 2018, the study by Lim et al[14] among patients with STEMI showed that majority of the interventions for STEMI failed to reach acceptable performance standards. The reported door-to-ECG time (108.5 minutes), door-to-needle time (105 minutes), and door-to-balloon time (338 minutes) were beyond the guideline-recommended time frame. Timeliness of initiation of dual antiplatelet therapy upon diagnosis was also substandard.[14] In 2019, the study by Ramiro et al[15] in patients with STEMI showed that compliance to guideline-recommended time interval from ER arrival to initial ECG was only 13.79% and to reperfusion at 81.25%. A study conducted in the same year among patients with NSTEMI showed that the median time from arrival to first ECG is 60 minutes. Of the patients eligible for an early invasive strategy, only 12.5% were revascularized.[16]

In 2018, with the aim of providing the highest quality of service, the PGH Division of Cardiovascular Medicine (DCVM) created a clinical pathway for STEMI patients based on the recommendations of the ESC 2017 STEMI guidelines and the 2014 Philippine Heart Association Clinical Practice Guidelines for the diagnosis and management of patients with coronary artery disease.[17] The existing pathway applies only for patients presenting with STEMI. A significant proportion of patients presenting with non–ST-segment elevation ACS (NSTE-ACS), which also poses significant morbidity and mortality, is not represented in this pathway. A clinical pathway that will encompass the entire spectrum of ACS will provide a guide to the physicians to further improve quality of care, prevent delays in lifesaving interventions, and, ultimately, to improve patient outcomes. This paper aims to describe the development of a clinical pathway for ACS appropriate for the setting in PGH.

METHODOLOGY

Research Design

This is a descriptive research on the development of a clinical pathway for ACS appropriate for the setting in PGH.

Participant Selection and Data Collection

A core team of investigators consisting of fellows and consultants of the University of the Philippines (UP)–PGH DCVM reviewed the literature on the latest international guidelines and recommendations for ACS and the existing PGH STEMI pathway. After a thorough literature search, the investigators convened to draft the pathway in accordance to the guidelines and applicability in the local setting. Content validation of the interim pathway was done on two levels: internal validation with the DCVM and external validation with identified end-users and stakeholders of the pathway. Internal validation with content experts consisting of the fellows and consultants of the DCVM assessed the completeness, feasibility, and evidence

behind each of the contents of the pathway. The investigators revised the draft based on the recommendations of the content experts.

External validation was done through focused group discussions (FGDs) and assessed the feasibility and identified hindrances and solutions in its implementation. The participants were selected by the core team of investigators and included representatives from the Department of Emergency Medicine, Department of Internal Medicine, DCVM, Pharmacy, Health Operations, and Nursing. An invitation to participate in the FGD was personally sent to the offices of identified potential participants. The invitation included the details and purpose of the study and FGDs, the informed consent form together with the request to gather the participant's e-mail address, and the contact details of the primary investigator for any clarifications and questions regarding the study. Informed consent was obtained from all the participants.

To streamline the discussion for the FGD, the participants were provided with a copy of the proposed components and nodes of the pathway. Each participant was asked to tick if they agree, disagree, or provide a comment for revision to each node. The nodes with differing recommendation among the participants were prioritized during the FGDs. Care processes and medical orders for diagnostics and medications were included in the final pathway once consensus among panel members was reached (>50% agreement between panel members).

Data Management and Analysis

All data gathered during the literature review and FGDs were processed by the investigators. Inputs were carefully evaluated if they adhere to the latest clinical practice guidelines and were considered in the development of the pathway. The core team of investigators was primarily responsible in ensuring that the standards of care and appropriateness in the PGH setting were maintained.

The specific indication for appropriateness of use and time-specific interventions were outlined in the pathway including recommended diagnostic examinations, medications, noninvasive and invasive procedures, risk stratification, and referrals to general cardiology, interventional cardiology, cardiac rehabilitation, and intensive care unit. Variance to the standard of care was monitored and outlined. The pathway was revised accordingly by the investigators to develop the final clinical pathway for ACS based on the results of the content validation.

RESULTS

International Guidelines for Acute Coronary Syndrome

The core team of investigators from the fellows and consultants of the DCVM reviewed the latest guideline recommendations on the initial evaluation and management of ACS. Four guidelines were reviewed: 2020 ESC Guidelines for the management of ACSs in patients presenting without persistent ST-segment elevation,[6] 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes,[18] 2017 ESC Guidelines for the management of acute MI in patients presenting with ST-segment elevation,[5] and the 2013 American College of Cardiology Foundation/AHA Guideline for the management of STEMI.[19] Based on the review, 23 items were identified as essential in the ER management of patients with ACS. The key recommendations were extracted and are summarized in Table 1.

Internal Validation

The interim clinical pathway was presented to the consultants and fellows of the DCVM for content validation. The pathway was reviewed for completeness, and the evidence behind each node was reviewed. Recommendations were given to make the

Table 1. Summary of Key Recommendations Based on Review of International Guidelines

Recommendations	STEMI		NSTE-ACS	
	ESC	AHA/ACC	ESC	AHA/ACC
12-Lead ECG within 10 min	IB	IC	IB	IC
Measure cardiac troponins	IA	IC	IB	IA
Assess kidney function by eGFR	—	—	IC	
Measurement of glycemic status	—	—	IC	
Lipid profile	—	—	IC	IIaC
Aspirin	IB (PCI) IA (Fibrinolysis)	IA	IA (PCI)	IA
P2Y12 inhibitor	IA	IB	IA	
Prasugrel if for PCI			IB	IB
Ticagrelor			IB	IB
Clopidogrel			IC	IB

(continuation of Table 1)

Recommendations	STEMI		NSTE-ACS	
	ESC	AHA/ACC	ESC	AHA/ACC
Anticoagulant	IC (PCI) IA (Fibrinolysis)		IA	
Enoxaparin	IIa (PCI) IA (fibrinolysis)	IIa(PCI) IIb B*		IA
UFH	IC (PCI) IB (fibrinolysis)	IA (PCI/ CABG) IC (fibrinolysis)	IA (PCI)	IB
Fondaparinux	IIIB (PCI)		IB†	IB†
High-intensity statin	IA	IA	IA	IA
Risk assessment for diagnosis and short-term prognosis in NSTE-ACS	—	—	IA	IA
Reperfusion therapy in STEMI				
Reperfusion therapy in all patients with ischemic symptoms ≤12-h duration and persistent ST elevation	IA	IA	—	—
Fibrinolytic therapy within 12 h of symptom onset in primary PCI cannot be performed in a timely manner in STEMI	IA	IA	—	—
Fibrin specific agent is recommended in fibrinolysis	IB	—	—	—
Rescue PCI after failed thrombolysis	IA	IB	—	—
Routine PCI after fibrinolysis	IA	IIb B	—	—
Emergency CABG in patients with cardiogenic shock and coronary anatomy not suitable for PCI	IB	IB	—	—
CCU/ICCU for min of 24 h post-PCI	IC	IC	—	—
Reperfusion therapy in NSTE-ACS				
Immediate invasive strategy (<2 h) in patients with very high-risk features	—	—	IC	IA
Early invasive strategy (within 24 h) in patients with high-risk features	—	—	IA	IB
Selective invasive after noninvasive testing in those with low risk	—	—	IA	—
Emergency CABG in patients with cardiogenic shock and coronary anatomy not suitable for PCI	—	—	IB	
Admit to a monitored unit	—	—	IC	—
Noninvasive testing in NSTE-ACS				
Noninvasive stress-testing in low and intermediate risk patients	—	—	—	IB

ACC=American College of Cardiology; AHA=American Heart Association; CABG=coronary artery bypass graft; CCU=cardiac care unit; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; ICCU=intensive cardiac care unit; ESC=European Society of Cardiology; NSTE-ACS=non–ST-segment elevation acute coronary syndrome; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.

The core team of investigators adapted these recommendations and convened to draft an interim pathway for acute coronary syndrome. The interim pathway captured the key guideline recommendations using 20 nodes (3 diagnosis nodes, 6 decision nodes, and 11 action nodes), which are summarized in Table 2.

*Fibrinolysis in those younger than <75 years and no renal dysfunction.

†With single bolus of UFH at time of PCI.

Table 2. Interim ACS Pathway Recommendations by the Core Group of Investigators Based on the Review of Key Recommendations From International Guidelines

Interim ACS Pathway Nodes
Chest pain highly suggestive of acute coronary syndrome? -Sudden and severe in onset at rest that last at least 10 min? -Severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion? -Accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep
12-Lead ECG Troponin I Creatinine, capillary blood glucose, lipid profile, PT/PTT, CBC Aspirin 80 mg per tablet, four tablets to chew and swallow High-intensity statin
ST-segment elevation or acute LBBB (decision node)
STEMI
Primary PCI for STEMI
Candidate for PCI and PCI can be done in <120 min
Load P2Y12 inhibitor: Prasugrel 60 mg/ticagrelor 180 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available Load anticoagulant: UFH 70–100 IU/kg IV bolus Consider enoxaparin 0.5 mg/kg IV bolus Bivalirudin 0.75 mg/kg IV bolus in patients with HIT
Thrombolysis for STEMI
Candidate for thrombolysis and no contraindication to thrombolysis?
Load P2Y12 inhibitor: Clopidogrel 300 mg Load anticoagulant: Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 preferred over UFH (not to exceed 100 mg per injection)
Thrombolysis
Medical management for STEMI
Load P2Y12 inhibitor: Ticagrelor 180 mg preferred over clopidogrel 300 mg Load anticoagulant: UFH 60 IU/kg IV bolus (max 4000 IU) followed by an infusion of 12 IU/kg (max 1000 IU/h) for 24–48 h Consider enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection) Bivalirudin 0.75 mg/kg IV bolus in patients with HIT
Optimal medical therapy
Admit to ICU
STEMI proceeding to coronary angiogram
Coronary angiogram* *Timing of coronary angiogram: • STEMI after failed thrombolysis: <2 h • STEMI after successful thrombolysis: 2–24 h • Asymptomatic patients with STEMI >12 h : 48 h

(continuation of Table 2)

Candidate for revascularization? (decision node)
Favorable anatomy for PCI? (decision node)
(Permutations) - Candidate for revascularization and with favorable anatomy to PCI → PCI - Candidate for revascularization with unfavorable anatomy for PCI → CABG Not a candidate for revascularization → optimal medical therapy
Optimal medical therapy
Admit to ICU
NSTE-ACS
Very high-risk features? Hemodynamic instability, recurrent/refractory chest pain, acute heart failure, life-threatening arrhythmias, mechanical complications of MI, ST-segment depression >1 mm/six leads + ST-segment elevation aVr and/or V_1 or High-risk features? NSTEMI diagnosis, dynamic ECG changes, resuscitated cardiac arrest, GRACE >140
(If without very high of very high-risk features) Load P2Y12 inhibitor: Ticagrelor 180 mg preferred over clopidogrel 300 mg Load anticoagulant: UFH 70–100 IU/kg IV bolus Consider enoxaparin 0.5 mg/kg IV bolus Bivalirudin 0.75 mg/kg IV bolus in patients with HIT
Optimal medical therapy
Admit to ICU
NSTE-ACS patients proceeding to coronary angiogram
Coronary angiogram* **Timing of coronary angiogram:* • NSTE-ACS very high risk: <2 h • NSTE-ACS high risk: <24 h
Candidate for revascularization? (decision node)
Favorable anatomy for PCI? (decision node)
(Permutations) - Candidate for revascularization and with favorable anatomy to PCI → PCI • Load P2Y12 inhibitor: Prasugrel 60 mg preferred over ticagrelor 180 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available • Load anticoagulant: UFH 70–100 IU/kg IV bolus/fondaparinux 2.5 mg SC with UFH during time of PCI Consider enoxaparin 0.5 mg/kg IV bolus - Candidate for revascularization with unfavorable anatomy for PCI → CABG Not a candidate for revascularization → optimal medical therapy
Optimal medical therapy
Admit to ICU

ACS=acute coronary syndrome; CBC=complete blood count; CABG=coronary artery bypass graft; ECG=electrocardiogram; HIT=heparin-induced thrombocytopenia; ICU=intensive care unit; IV, intravenous; LBBB=left bundle-branch block; NSTEMI=non–ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; PT=prothrombin time; PTT=partial thromboplastin time; SC=subcutaneous; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.

pathway adaptable and feasible in the local setting. From the internal validation, 11 nodes were revised, and 5 new nodes were added. These are summarized in Table 3. The interim ACS Pathway after content validation with the core group and with the DCVM algorithm is shown in Figure 1.

All the consultants and fellows agreed on the presented care processes except on the timing of anticoagulation among NSTE-ACS patients. Because the risk stratification of NSTE-ACS will not affect the decision to give an anticoagulant, the consultants and fellows agreed to load the anticoagulant after the diagnosis of NSTE-ACS was made instead. Several nodes had modification based on the inputs of subspecialty consultants on heart failure, echocardiography, cardiac rehabilitation, interventional cardiology, and pharmacology (Appendix A). These suggested modifications were accepted by all the consultants and fellows of DCVM.

The first node was revised to clinical features suggestive of ACS to capture the other clinical presentation of ACS aside from chest pain. To further assist the end user of the pathway, the typical and atypical presentations, factors increasing the likelihood of ACS, and chest pain uncharacteristic of ACS were included in the footnote. The diagnostics requested upon presentation at the emergency department were revised to include the specific time frame for the performance of a 12-lead ECG, extraction of high-sensitivity troponin, inclusion of serum sodium and potassium in biochemistry, serum calcium and magnesium for patients presenting with arrhythmia, and referral to general medicine and adult cardiology. The manner by which routine medications were ordered were modified to specify the use of aspirin nonenteric tablets for loading and specify the name and dose of preferred high-intensity statin.

Table 3. Summary of ACS Pathway Nodes With Revisions From Internal Validation With the Division of Cardiovascular Medicine

Clinical features suggestive of ACS **Footnotes:** *Clinical features suggestive of ACS* • Typical angina: sudden and severe in onset at rest that lasts at least 10 min; severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion; and an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep • Factors in the patient's chest pain history that increase the likelihood of ACS: radiation to the right arm, both arms, or shoulders; association with exertion, diaphoresis, nausea, or vomiting; chest pain worse than previous angina or similar to previous MI; and chest pain described as pressure • Atypical angina (in women, older persons, and individuals with diabetes): jaw or shoulder pain in the absence of chest pain, nausea or vomiting, and diaphoresis • Presence of other risk factors: male sex, advanced age, history of diabetes, and history of previous MI • Uncharacteristic of myocardial ischemia: pleuritic pain; primary or sole location of the discomfort in the middle or lower abdominal region; pain that may be localized by the tip of one finger, particularly over the left ventricular apex; pain reproduced with movement or palpation of the chest wall or arms; constant pain that persists for many hours; very brief episodes of pain that last a few seconds or less; and pain that radiates into the lower extremities
-12-Lead ECG within 10 min -High-sensitivity troponin I -Creatinine, sodium, potassium, capillary blood glucose, lipid profile, PT/PTT, CBC -Calcium, magnesium (if with arrhythmia) -Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow -Atorvastatin 80 mg per tablet -Referral to general medicine and adult cardiology
STEMI
Coordinated STEMI transfers for PCI
Load antiplatelets and anticoagulant if not yet given from the other hospital: -Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow -Ticagrelor 180 mg/prasugrel 60 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available -Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis) Refer to general medicine, adult cardiology, and interventional cardiology
Primary PCI for STEMI

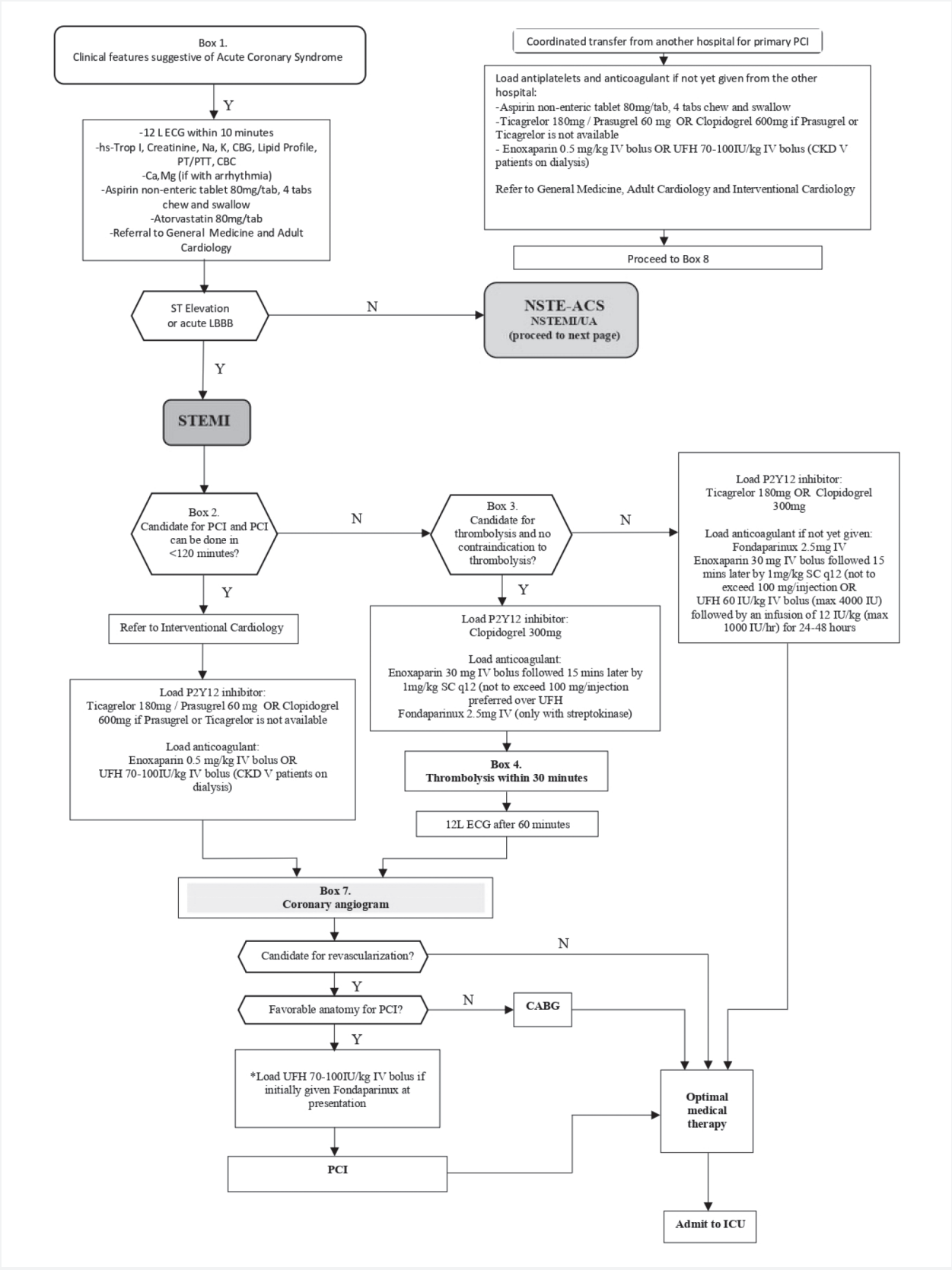
(continuation of Table 3)

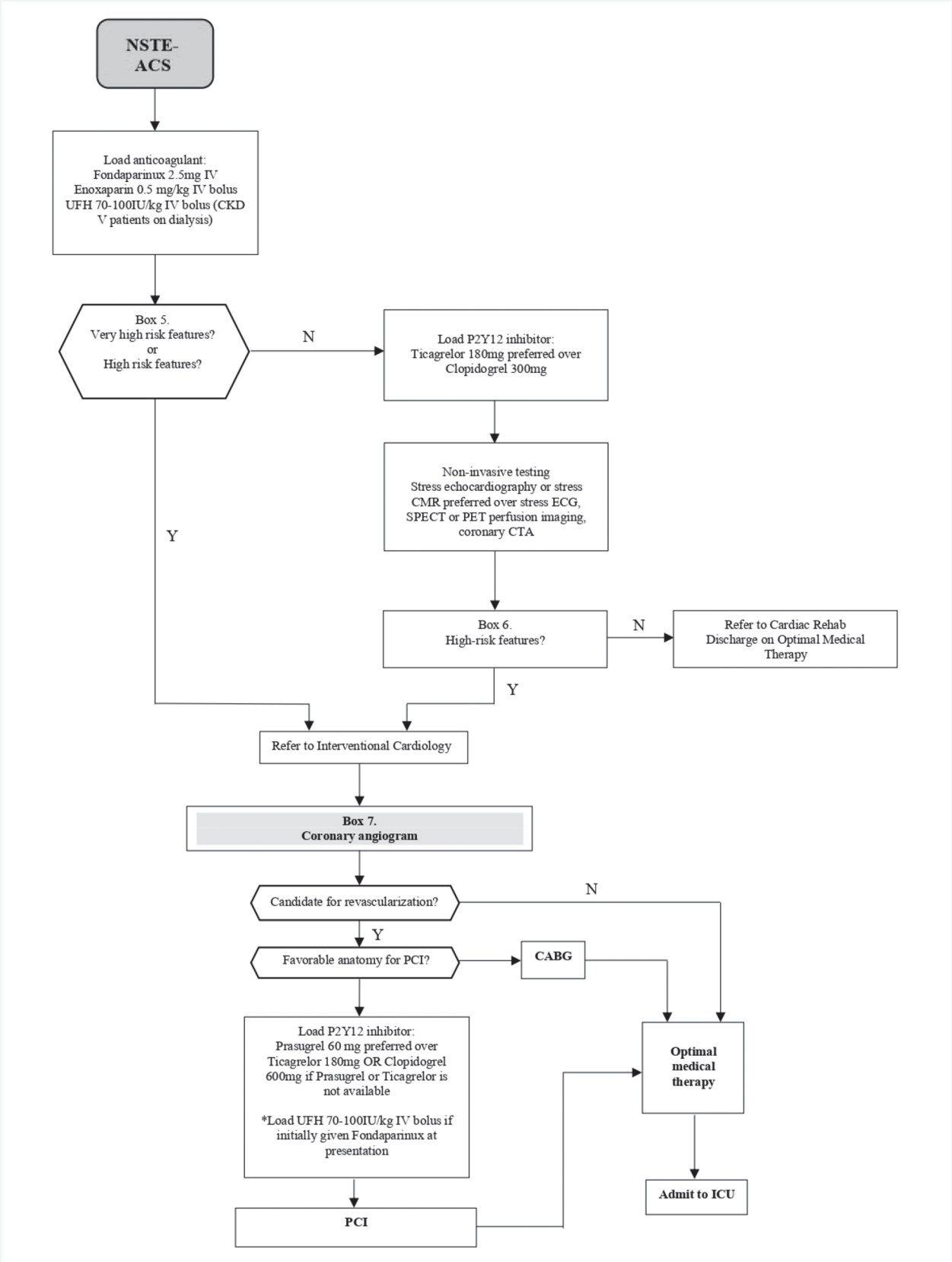
Candidate for PCI and PCI can be done in <120 min? **Footnotes:** *Indications for PCI* • Patients with STEMI and ischemic symptoms of less than 12-h duration • Those who have contraindications to fibrinolytic therapy irrespective of the time delay from first medical contact • Patients with STEMI and ongoing chest pain, electrical instability, cardiogenic shock, or acute severe HF, irrespective of time delay from MI onset • Atypical ECG presentations that should prompt PCI in patients with ongoing symptoms consistent with MI: ventricular paced rhythm, isolated posterior MI, ischemia due to left main coronary artery occlusion, or multivessel disease
Load P2Y12 inhibitor: Ticagrelor 180 mg/prasugrel 60 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available Load anticoagulant: Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis)
Thrombolysis for STEMI
Candidate for thrombolysis and no contraindication to thrombolysis? **Footnotes**: *Indication for thrombolysis:* patients with STEMI and onset of ischemic symptoms within the previous 12 h when it is anticipated that primary PCI cannot be performed within 120 min of first medical contact *Contraindications to thrombolysis: absolute contraindications* • Any prior intracranial hemorrhage • Known structural cerebral vascular lesion (eg, arteriovenous malformation) • Known malignant intracranial neoplasm (primary or metastatic) • Ischemic stroke within 3 mo except acute ischemic stroke within 4.5 h • Suspected aortic dissection • Active bleeding or bleeding diathesis (excluding menses) • Significant closed head or facial trauma within 3 mo • Intracranial or intraspinal surgery within 2 mo • Severe uncontrolled hypertension (unresponsive to emergency therapy) • For streptokinase, prior treatment within the previous 6 mo *Relative contraindications* • History of chronic, severe, poorly controlled hypertension • Significant hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg) • History of prior ischemic stroke > 3 mo • Dementia • Known intracranial pathology not covered in absolute contraindications • Traumatic or prolonged (>10 min) cardiopulmonary resuscitation • Major surgery (<3 wk) • Recent (within 2–4 wk) internal bleeding • Noncompressible vascular punctures • Pregnancy • Active peptic ulcer • Oral anticoagulant therapy
Load P2Y12 inhibitor: Clopidogrel 300 mg Load anticoagulant: Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection preferred over UFH Fondaparinux 2.5 mg IV (only with streptokinase)
Thrombolysis within 30 min
*12-Lead ECG after 60 min

(continuation of Table 3)

Medical management for STEMI
Load P2Y12 inhibitor: Ticagrelor 180 mg OR clopidogrel 300 mg Load anticoagulant if not yet given: Fondaparinux 2.5 mg IV Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection OR UFH 60 IU/kg IV bolus (max 4000 IU) followed by an infusion of 12 IU/kg (max 1000 IU/h) for 24–48 h
STEMI patients proceeding to coronary angiogram
(Permutations) Candidate for revascularization and with favorable anatomy to PCI → PCI *Load UFH 70–100 IU/kg IV bolus if initially given fondaparinux at presentation
NSTE-ACS
Load anticoagulant: Fondaparinux 2.5 mg IV Enoxaparin 0.5 mg/kg IV bolus UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis)
Very high-risk features? or High-risk features? **Footnotes:** *Very high-risk features* • Hemodynamic instability • Recurrent/refractory chest pain • Acute heart failure • Life-threatening arrhythmias • Mechanical complications of MI • ST-segment depression >1 mm/six leads + ST-segment elevation aVr and/or V_1 *High-risk features* • NSTEMI diagnosis • dynamic ECG changes • resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock • GRACE >140
*Noninvasive testing Stress echocardiography or stress CMR preferred over stress ECG, or SPECT or PET perfusion imaging, or coronary CTA
*High-risk features? (Permutations) *No high-risk features -Refer to cardiac rehabilitation -Discharge on optimal medical therapy With high-risk features -Refer to interventional cardiology

ACS=acute coronary syndrome; CBC=complete blood count; CMR=cardiac magnetic resonance imaging; CKD V=stage 5 chronic kidney disease; CTA=computed tomography angiography; DBP=diastolic blood pressure; ECG=electrocardiogram; HF=heart failure; IV=intravenous; MI=myocardial infarction; NSTEMI=non–ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; PET=positron emission tomography; PT=prothrombin time; PTT=partial thromboplastin time; SBP=systolic blood pressure; SC=subcutaneous; SPECT=single-photon emission computed tomography; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.
**Additional nodes from internal validation.*


Box 1.
Clinical features suggestive of Acute Coronary Syndrome
Y
-12 L ECG within 10 minutes
-hs-Trop I, Creatinine, Na, K, CBG, Lipid Profile, PT/PTT, CBC
-Ca,Mg (if with arrhythmia)
-Aspirin non-enteric tablet 80mg/tab, 4 tabs chew and swallow
-Atorvastatin 80mg/tab
-Referral to General Medicine and Adult Cardiology
ST Elevation or acute LBBB
N
NSTE-ACS
NSTEMI/UA
(proceed to next page)
Y
STEMI
Coordinated transfer from another hospital for primary PCI
Load antiplatelets and anticoagulant if not yet given from the other hospital:
-Aspirin non-enteric tablet 80mg/tab, 4 tabs chew and swallow
-Ticagrelor 180mg / Prasugrel 60 mg OR Clopidogrel 600mg if Prasugrel or Ticagrelor is not available
- Enoxaparin 0.5 mg/kg IV bolus OR UFH 70-100IU/kg IV bolus (CKD V patients on dialysis)
Refer to General Medicine, Adult Cardiology and Interventional Cardiology
Proceed to Box 8
Box 2.
Candidate for PCI and PCI can be done in <120 minutes?
N
Box 3.
Candidate for thrombolysis and no contraindication to thrombolysis?
N
Load P2Y12 inhibitor:
Ticagrelor 180mg OR Clopidogrel 300mg
Load anticoagulant if not yet given:
Fondaparinux 2.5mg IV
Enoxaparin 30 mg IV bolus followed 15 mins later by 1mg/kg SC q12 (not to exceed 100 mg/injection OR
UFH 60 IU/kg IV bolus (max 4000 IU) followed by an infusion of 12 IU/kg (max 1000 IU/hr) for 24-48 hours
Y
Refer to Interventional Cardiology
Load P2Y12 inhibitor:
Ticagrelor 180mg / Prasugrel 60 mg OR Clopidogrel 600mg if Prasugrel or Ticagrelor is not available
Load anticoagulant:
Enoxaparin 0.5 mg/kg IV bolus OR
UFH 70-100IU/kg IV bolus (CKD V patients on dialysis)
Y
Load P2Y12 inhibitor:
Clopidogrel 300mg
Load anticoagulant:
Enoxaparin 30 mg IV bolus followed 15 mins later by 1mg/kg SC q12 (not to exceed 100 mg/injection preferred over UFH
Fondaparinux 2.5mg IV (only with streptokinase)
Box 4.
Thrombolysis within 30 minutes
12L ECG after 60 minutes
Box 7.
Coronary angiogram
Candidate for revascularization?
N
Y
Favorable anatomy for PCI?
N
CABG
Y
*Load UFH 70-100IU/kg IV bolus if initially given Fondaparinux at presentation
PCI
Optimal medical therapy
Admit to ICU


NSTE-ACS
Load anticoagulant:
Fondaparinux 2.5mg IV
Enoxaparin 0.5 mg/kg IV bolus
UFH 70-100IU/kg IV bolus (CKD V patients on dialysis)
Box 5.
Very high risk features?
or
High risk features?
N
Load P2Y12 inhibitor:
Ticagrelor 180mg preferred over Clopidogrel 300mg
Non-invasive testing
Stress echocardiography or stress CMR preferred over stress ECG, SPECT or PET perfusion imaging, coronary CTA
Y
Box 6.
High-risk features?
N
Refer to Cardiac Rehab
Discharge on Optimal Medical Therapy
Y
Refer to Interventional Cardiology
Box 7.
Coronary angiogram
Candidate for revascularization?
N
Y
Favorable anatomy for PCI?
CABG
Load P2Y12 inhibitor:
Prasugrel 60 mg preferred over Ticagrelor 180mg OR Clopidogrel 600mg if Prasugrel or Ticagrelor is not available
*Load UFH 70-100IU/kg IV bolus if initially given Fondaparinux at presentation
Optimal medical therapy
Admit to ICU
PCI

Box 1

Clinical features suggestive of Acute Coronary Syndrome

- **Typical angina:** sudden and severe in onset at rest that last at least 10 minutes; severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion; and an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep
- **Factors in the patient's chest pain history that increase the likelihood of ACS**: radiation to the right arm, both arm, or shoulders; association with exertion, diaphoresis, nausea or vomiting; chest pain worse than previous angina or similar to previous myocardial infarction (MI); and chest pain described as pressure
- **Atypical angina (in women, older persons, and individuals with diabetes**): jaw or shoulder pain in the absence of chest pain; nausea or vomiting; and diaphoresis
- **Presence of other risk factors**: male sex, advanced age, history of diabetes, and history of previous myocardial infarction (MI)
- **Uncharacteristic of myocardial ischemia:** pleuritic pain; primary or sole location of the discomfort in the middle or lower abdominal region; pain that may be localized by the tip of one finger, particularly over the left ventricular apex; pain reproduced with movement or palpation of the chest wall or arms; constant pain that persists for many hours; very brief episodes of pain that last a few seconds or less; and pain that radiates into the lower extremities

Zipes *et.al.*, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.11 ed. 2019

Box 2

Indications for PCI:

- Patients with STEMI and ischemic symptoms of less than 12 hours' duration
- Those who have contraindications to fibrinolytic therapy irrespective of the time delay from first medical contact
- Patients with STEMI and ongoing chest pain, electrical instability, cardiogenic shock or acute severe HF, irrespective of time delay from MI onset
- Atypical ECG presentations that should prompt PCI in patients with ongoing symptoms consistent with MI: ventricular paced rhythm, isolated posterior myocardial infarction, ischaemia due to left main coronary artery occlusion or multivessel disease

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

Box 3

Indication for thrombolysis: patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact

Contraindications to thrombolysis: Absolute contraindications:

- any prior intracranial hemorrhage
- known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- known malignant intracranial neoplasm (primary or metastatic)
- ischemic stroke within 3 months except acute ischemic stroke within 4.5 hours
- suspected aortic dissection
- active bleeding or bleeding diathesis (excluding menses)
- significant closed head or facial trauma within 3 months
- intracranial or intraspinal surgery within 2 months
- severe uncontrolled hypertension (unresponsive to emergency therapy)
- for streptokinase, prior treatment within the previous 6 months

Relative contraindications:

- history of chronic, severe, poorly-controlled hypertension
- significant hypertension on presentation (SBP >180 mm Hg or DBP>110 mmHg)
- history of prior ischemic stroke > 3 months
- dementia
- known intracranial pathology not covered in absolute contraindications
- traumatic or prolonged (>10 min) cardiopulmonary resuscitation
- major surgery (< 3 weeks)
- recent (within 2 to 4 weeks) internal bleeding
- non-compressible vascular punctures
- pregnancy
- active peptic ulcer
- oral anticoagulant therapy

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

Zipes *et.al.*, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.11 ed. 2019

Box 4

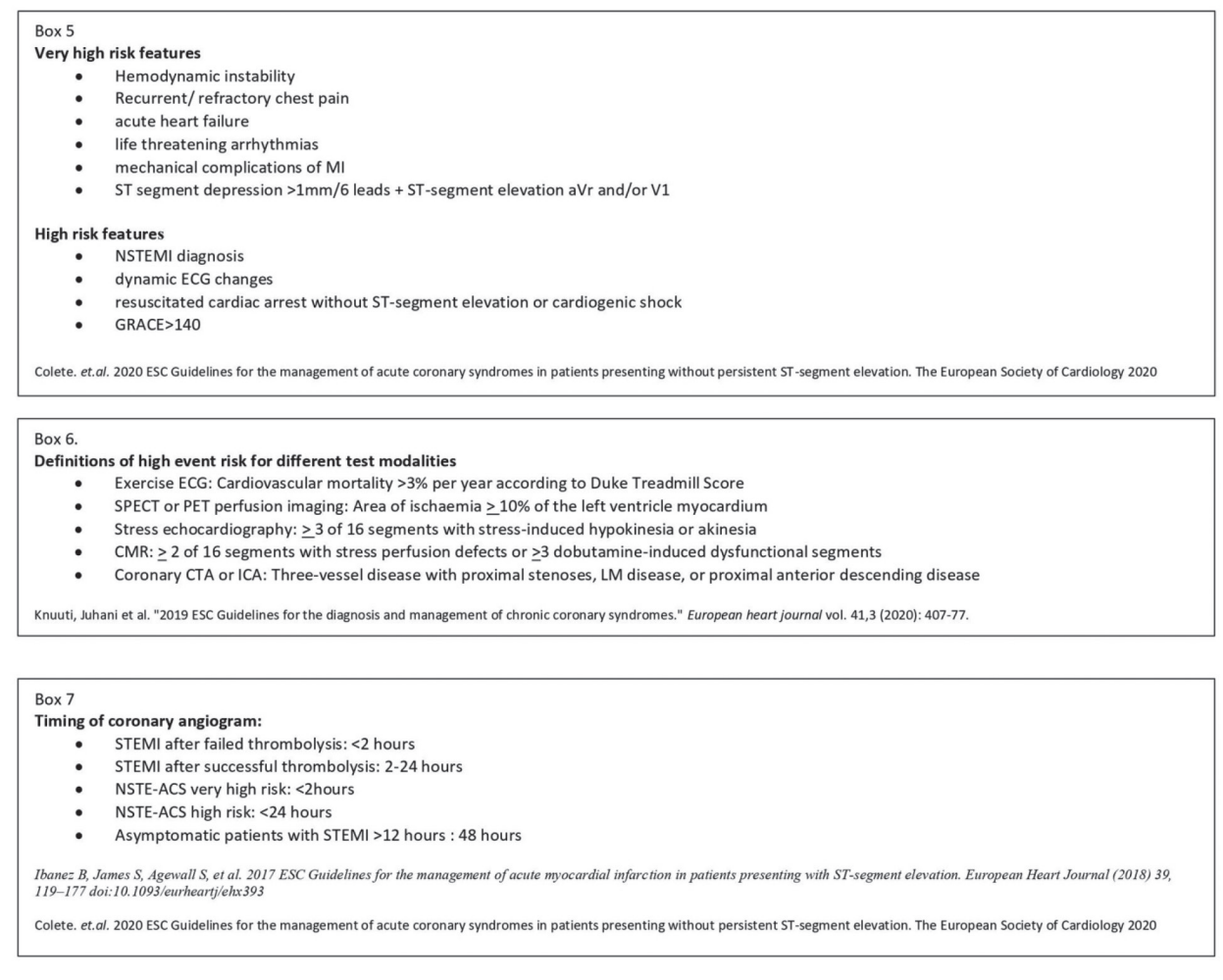
Thrombolytic agents

- Alteplase 15 mg IV bolus then 0.75 mg/kg IV (up to 50 mg) over 30 minutes then 0.5 mg/kg IV (up to 35 mg) over 60 minutes
- Streptokinase 1.5 million units over 30-60 mins i.v.

Criteria for successful thrombolysis

- ST-segment resolution >50% at 60-90 minutes
- Typical reperfusion arrhythmia
- Disappearance of chest pain

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393



Box 5

Very high risk features

- Hemodynamic instability
- Recurrent/ refractory chest pain
- acute heart failure
- life threatening arrhythmias
- mechanical complications of MI
- ST segment depression >1mm/6 leads + ST-segment elevation aVr and/or V1

High risk features

- NSTEMI diagnosis
- dynamic ECG changes
- resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock
- GRACE>140

Colete. *et.al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The European Society of Cardiology 2020

Box 6.

Definitions of high event risk for different test modalities

- Exercise ECG: Cardiovascular mortality >3% per year according to Duke Treadmill Score
- SPECT or PET perfusion imaging: Area of ischaemia ≥ 10% of the left ventricle myocardium
- Stress echocardiography: ≥ 3 of 16 segments with stress-induced hypokinesia or akinesia
- CMR: ≥ 2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments
- Coronary CTA or ICA: Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease

Knuuti, Juhani et al. "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes." *European heart journal* vol. 41,3 (2020): 407-77.

Box 7

Timing of coronary angiogram:

- STEMI after failed thrombolysis: <2 hours
- STEMI after successful thrombolysis: 2-24 hours
- NSTE-ACS very high risk: <2hours
- NSTE-ACS high risk: <24 hours
- Asymptomatic patients with STEMI >12 hours : 48 hours

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

Colete. *et.al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The European Society of Cardiology 2020

Figure 1. Interim acute coronary syndrome pathway from content validation with the Core Group of Investigators and the Division of Cardiovascular Medicine.

In the STEMI arm of the pathway, 2 nodes were added to capture the interventions for coordinated transfers from other hospitals for percutaneous coronary intervention (PCI) for STEMI. A referral to interventional cardiology was added for patients eligible for PCI. Ticagrelor was prioritized over prasugrel because only ticagrelor is readily available in the country. Enoxaparin was prioritized over unfractionated heparin (UFH) for anticoagulation of STEMI patients for PCI or thrombolysis due to difficulty in monitoring activated partial thromboplastin time in the emergency department and the delay in the turnaround time of laboratory result. Fondaparinux was added and prioritized as an anticoagulant option in medically managed STEMI patients. For patients who were initially given fondaparinux and proceeded to PCI, additional UFH bolus will be given at the time of intervention. In the footnotes, indications for PCI, contraindications to thrombolysis, and the options for thrombolytic agent were included. The time frame for thrombolysis and postthrombolysis ECG was specified.

In the NSTE-ACS arm of the pathway, fondaparinux was prioritized over enoxaparin and UFH. Three nodes were added to capture the role of noninvasive testing in the management of NSTE-ACS patients without very high- or high-risk features. Those without high-risk features on noninvasive testing will be referred to cardiac rehabilitation and may be discharged from the hospital.

External Validation

Content validation through FGDs with identified stakeholders was done. The interim ACS Pathway was assessed for feasibility, and recommendations were given to make it applicable to the local setting. All stakeholders agreed to the presented care processes but recommended an additional node to admit low-risk NSTE-ACS patients to the ward while waiting for the schedule and results of noninvasive testing. From the external validation, nine nodes were revised, and one node was added. The results of the external validation are summarized in Table 4 (Appendix B).

Table 4. Summary of ACS Pathway Nodes With Revisions From External Validation With Stakeholders

-12-Lead ECG within 10 min -High-sensitivity troponin I -Creatinine, sodium, potassium, calcium, magnesium, CBG, lipid profile, PT/PTT, CBC -Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow -Atorvastatin 80 mg per tablet/rosuvastatin 40 mg per tablet -Referral to adult cardiology
STEMI
Coordinated STEMI transfers for PCI
Load antiplatelets and anticoagulant if not yet given from the other hospital, in the absence of contraindications: -Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow -Clopidogrel 600 mg OR ticagrelor 180 mg/prasugrel 60 mg -Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 units/kg IV bolus (CKD V patients) Refer to adult cardiology and interventional cardiology
Primary PCI for STEMI
Load P2Y12 inhibitor: Clopidogrel 600 mg OR ticagrelor 180 mg/prasugrel 60 mg Load anticoagulant: Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 units/kg IV bolus (CKD V patients)
Thrombolysis for STEMI
Load P2Y12 inhibitor: Clopidogrel 300 mg Load anticoagulant: Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg (not to exceed 100 mg per injection) SC q12 preferred over UFH Fondaparinux 2.5 mg IV (only with streptokinase)
12-Lead ECG after 60 min from start of thrombolysis
Medical management for STEMI
Load P2Y12 inhibitor: Clopidogrel 300 mg OR ticagrelor 180 mg Load anticoagulant if not yet given: Fondaparinux 2.5 mg IV Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg (not to exceed 100 mg per injection) SC every 12 h OR UFH 60 units/kg (max 4000 units) IV bolus followed by an infusion of 12 units/kg (max 1000 units/h) for 24–48 h (CKD V patients)
STEMI patients proceeding to coronary angiogram
Permutations: Candidate for revascularization and with favorable anatomy to PCI → PCI *Load UFH 70–100 units/kg IV bolus if initially given fondaparinux at presentation
NSTE-ACS
Load anticoagulant: Fondaparinux 2.5 mg IV Enoxaparin 0.5 mg/kg IV bolus UFH 70–100 units/kg IV bolus (CKD V patients)

(continuation of Table 4)

(No very high-risk or high-risk features) Admit to ward
NSTE-ACS patients proceeding to coronary angiogram
- Candidate for revascularization and with favorable anatomy to PCI → PCI • Load P2Y12 inhibitor: Clopidogrel 600 mg, OR prasugrel 60 mg preferred over ticagrelor 180 mg • Load UFH 70–100 IU/kg IV bolus if initially given fondaparinux at presentation

ACS=acute coronary syndrome; CBC=complete blood count; CKD V=stage 5 chronic kidney disease; ECG=electrocardiogram; IV=intravenous; PCI=percutaneous coronary intervention; PT=prothrombin time; PTT=partial thromboplastin time; SC=subcutaneous; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.

Serum calcium and magnesium were included as part of the routine laboratories regardless if arrhythmia was part of the presentation. The options for high-intensity statin, which are available in the hospital pharmacy (atorvastatin 80 mg and rosuvastatin 40 mg), were specified. Direct referral to adult cardiology service for all ACS patients was recommended. Clopidogrel was prioritized as the P2Y12 inhibitor to be given in the emergency department as this is the only P2Y12 inhibitor that is readily available in the hospital pharmacy. For clarity of physician order on anticoagulation, "IU" was replaced with "units," and the maximum dose was moved next to the unit per kilogram (unit/kg) dose of the drug enclosed in parenthesis. Patients with NSTE-ACS without very high- or high-risk features will be admitted to the ward while being scheduled for noninvasive testing.

Acute Coronary Syndrome Pathway

The 2-level content validation led to the creation of an evidence-based clinical pathway for ACS applicable to the local ER hospital setting (Figure 2). The pathway will be initiated when a patient presents with clinical features of ACS. The symptom of ACS is typically described as sudden and severe in onset at rest that lasts at least 10 minutes: severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion; and an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep. Some factors in the patient's chest pain history also increase the likelihood of ACS such as radiation to the right arm, both arms, or shoulders; association with exertion, diaphoresis, nausea, or vomiting; chest pain worse than previous angina or similar to previous myocardial infarction (MI); and chest pain described as pressure. The presence of other risk factors increases the likelihood of ACS such as male sex, advanced age, history of diabetes, and history of previous MI. In women, the elderly, and individuals with diabetes, angina may present atypically as jaw or shoulder pain in the absence of chest pain, nausea or vomiting, and diaphoresis.

If the clinical feature is suggestive of an ACS, a set of orders will be ordered at the ER setting. A 12-lead ECG should be done within 10 minutes. Blood samples for high-sensitivity troponin I, creatinine, sodium, potassium, calcium, magnesium, random capillary blood glucose, nonfasting lipid profile, prothrombin time, partial thromboplastin time, and complete blood count will be extracted and sent to the laboratory. Aspirin (nonenteric) 320 mg and high-intensity statin using atorvastatin 80 mg or rosuvastatin 40 mg will be loaded. A referral to the adult cardiology will be made.

ST-Segment Elevation Myocardial Infarction

If the initial ECG shows ST-segment elevation on contiguous leads or an acute left bundle-branch block, then the course of management will follow the STEMI arm of the pathway. For any patient presenting with STEMI, the treatment strategies are as follows, depending on their clinical presentation, onset of symptoms, and presence or absence of contraindication to the different treatment strategies: primary PCI, thrombolysis, or medical management.

Primary Percutaneous Intervention for ST-Segment Elevation Myocardial Infarction

Patients presenting with STEMI and ischemic symptoms of less than 12-hour duration will be offered primary PCI. Patients with ongoing chest pain, electrical instability, cardiogenic shock, or acute severe HF will likewise be offered primary PCI irrespective of time delay from MI onset, as well as those with contraindications to thrombolytic therapy irrespective of time of delay from first medical contact. Patients with atypical ECG presentations (ongoing chest pain, electrical instability, cardiogenic shock or acute severe HF, irrespective of time delay from MI onset) and with ongoing symptoms consistent with MI are also candidates for primary PCI. For these patients, immediate referral to interventional cardiology will be made, and primary PCI done within 120 minutes. These patients will be given a P2Y12 inhibitor (clopidogrel 600 mg or ticagrelor 180 mg or prasugrel 60 mg) and an anticoagulant (enoxaparin 0.5 mg/kg intravenous [IV] bolus OR UFH 70–100 units/kg IV bolus).

Thrombolysis for ST-Segment Elevation Myocardial Infarction

Patients presenting with STEMI and ischemic symptoms of

less than 12-hour duration and in whom it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact will be offered thrombolysis in the absence of contraindications. P2Y12 inhibitor in the form of clopidogrel 300 mg and an anticoagulant (enoxaparin 30 mg IV bolus followed 15 minutes later by 1 mg/kg (not to exceed 100 mg per injection) subcutaneously every 12 hours preferred over UFH OR fondaparinux 2.5 mg IV only for those who received streptokinase will be given. Thrombolysis will be performed within 30 minutes from presentation. Options for thrombolytic agents are alteplase and streptokinase. The patients will be reassessed postthrombolysis for success of intervention, which includes performance of a 12-lead ECG within 60 minutes. Patients whose symptoms persist after thrombolysis or those whose ECG showed <50% resolution of ST-segment elevation are considered to have a failed thrombolysis and should be referred promptly to interventional cardiology for PCI. The timing of coronary angiogram for failed thrombolysis is less than 2 hours, whereas for those with successful thrombolysis is within 2 to 24 hours.

Medical Management for ST-Segment Elevation Myocardial Infarction
Patients with STEMI who are not candidates to either PCI or thrombolysis will be medically managed. These patients will be given P2Y12 inhibitor (clopidogrel 300 mg or ticagrelor 180 mg) and an anticoagulant (fondaparinux 2.5 mg IV OR enoxaparin 30 mg IV bolus followed 15 minutes later by 1 mg/kg [not to exceed 100 mg per injection] subcutaneously every 12 hours OR UFH 60 units/kg [max 4000 units] IV bolus followed by an infusion of 12 units/kg [max 1000 units/h] for 24–48 hours). They will be admitted to the intensive care unit where they will receive optimal medical therapy for ACS.

Coordinated STEMI Transfer for Primary Percutaneous Intervention
Patients coming in as coordinated transfer from another hospital for primary PCI for STEMI will be given aspirin 320 mg, P2Y12 inhibitor clopidogrel 600 mg or ticagrelor 180 mg or prasugrel 60 mg), an anticoagulant (enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 units/kg IV bolus for CKD V patients), and a high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) if not previously given at the other hospital. These patients will be referred immediately to adult cardiology and interventional cardiology service for primary PCI.

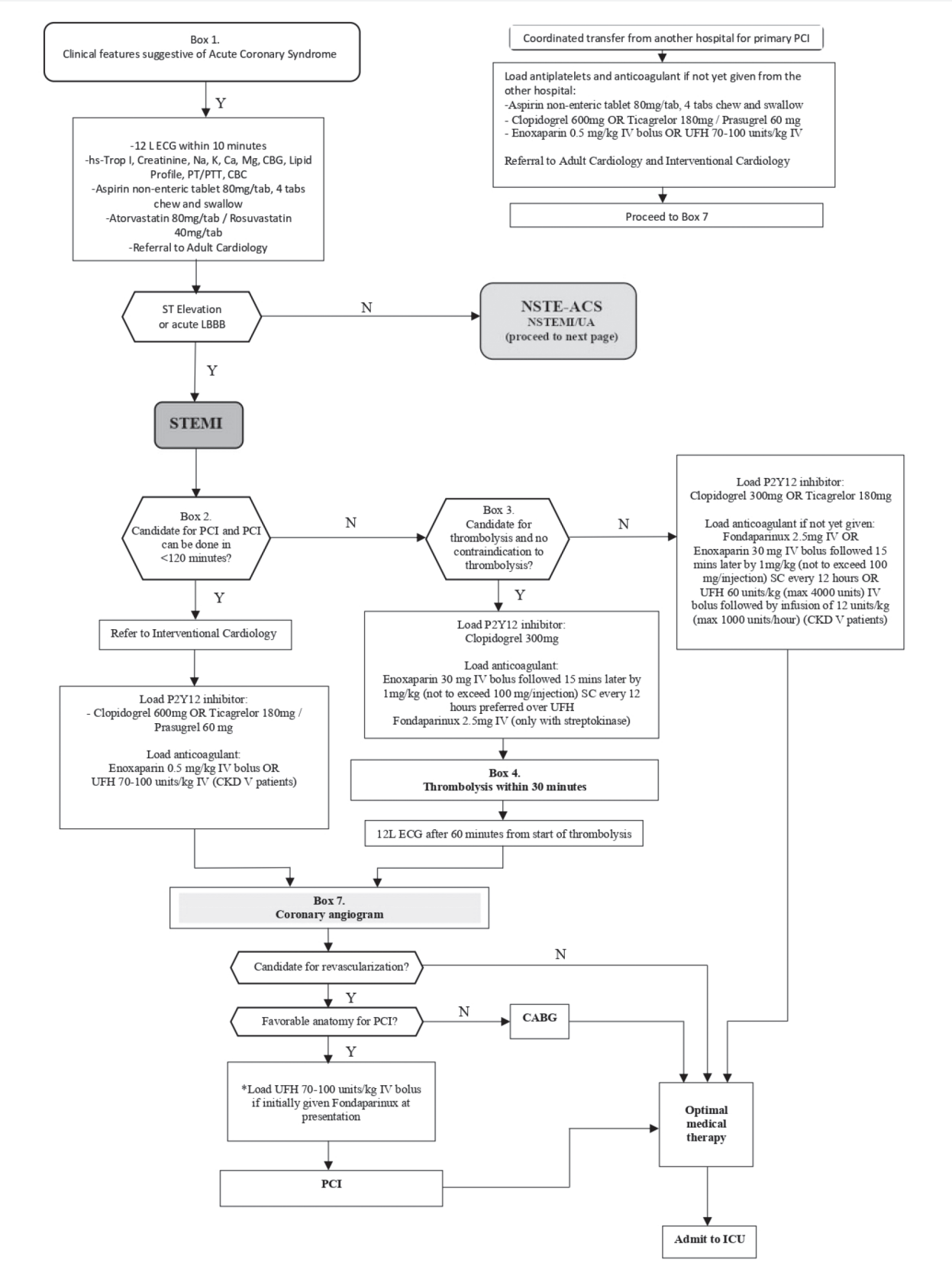
STEMI Patients Proceeding to Coronary Angiogram
The coronary angiogram will identify patients who are candidates for revascularization via either PCI or coronary artery bypass graft (CABG) and those who will be medically managed. Those who are candidates for revascularization and with favorable anatomy will undergo primary PCI. Patients who were initially given fondaparinux will receive UFH 70 to 100 units/kg IV bolus at the time of intervention. Those who are candidates for revascularization but with unfavorable anatomy for PCI will be referred to the thoracocardiovascular surgery service for CABG. After the procedure, these patients will be admitted to the ICU and will receive optimal medical therapy. Patients who are not candidates for revascularization will be admitted to the ICU and will receive optimal medical therapy.

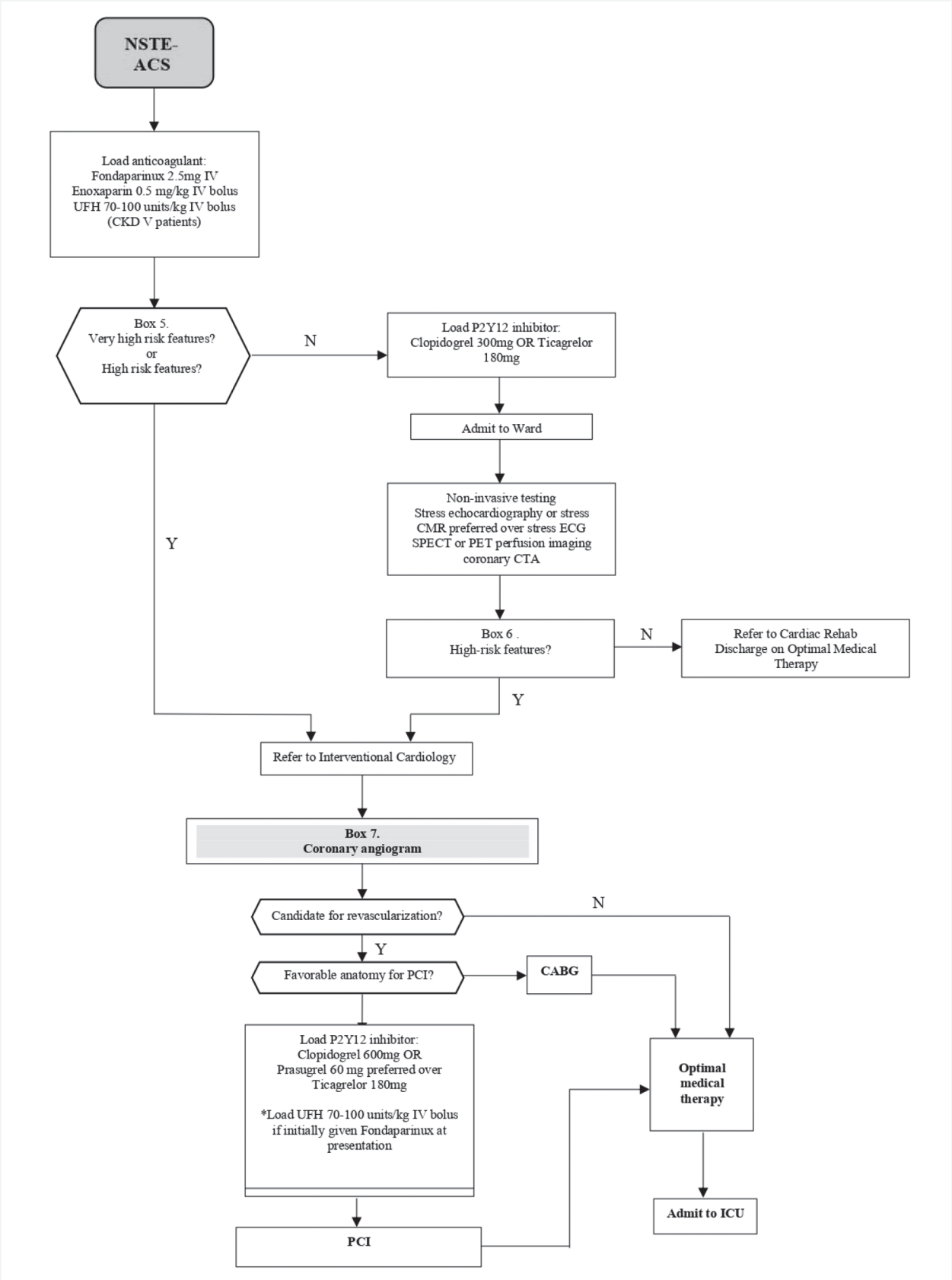
Non–ST-Segment Elevation Acute Coronary Syndrome
If the initial ECG shows no ST-segment elevation on contiguous leads or an acute left bundle-branch block, then the course of management will follow the NSTE-ACS arm of the pathway. For any patient presenting with NSTE-ACS, the treatment strategies are as follows depending on the presence or absence of very high- or high-risk features: invasive or noninvasive strategy. These patients will receive an anticoagulant (fondaparinux 2.5 mg IV or enoxaparin 0.5 mg/kg IV bolus, or UFH 70–100 units/kg IV bolus) in the absence of contraindications, regardless of planned treatment strategy.

Invasive Strategy for NSTE-ACS
Patients with NSTE-ACS who have any of the very high-risk (hemodynamic instability, recurrent/refractory chest pain, acute heart failure, life-threatening arrhythmias, mechanical complications of MI, or ST-segment depression >1 mm/six leads + ST-segment elevation aVr and/or V_1) or high-risk features (NSTEMI diagnosis, dynamic ECG changes, resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock, or GRACE >140) will be referred to interventional cardiology for coronary angiogram. The timing for coronary angiogram for NSTE-ACS patients with very high-risk features is less than 2 hours and less than 24 hours for those with high-risk features.

Patients with NSTE-ACS who do not have any of the very high-risk or high-risk features mentioned above will receive a P2Y12 inhibitor (clopidogrel 300 mg or ticagrelor 180 mg), will be admitted to the ward, and will be scheduled for noninvasive testing. The choices for noninvasive testing are stress echocardiography, stress cardiac magnetic resonance imaging, stress ECG, single-photon emission computed tomography, positron emission tomography perfusion imaging, or coronary computed tomography angiography. Patients without high-risk features on noninvasive will referred to the cardiac rehabilitation team and will be discharged on optimal medical therapy. Patients with high-risk features on noninvasive testing will be referred to interventional cardiology service for coronary angiogram.

NSTE-ACS Patients Proceeding to Coronary Angiogram
Similar to STEMI, the coronary angiogram will identify NSTE-ACS patients who are candidates for revascularization via either PCI or CABG and those who will be medically managed. Those who are candidates for revascularization with a favorable anatomy will undergo primary PCI. The timing of the loading of P2Y12 inhibitor for patients initially presenting with very high- or high-risk features will be during this time when the coronary anatomy is known, and the patient is to proceed to PCI. Patients who were initially given fondaparinux will receive UFH 70 to 100 units/kg IV bolus. Those who are candidates for revascularization but with unfavorable anatomy for PCI will be referred to the thoracocardiovascular surgery service for CABG. After the procedure, these patients will be admitted to the ICU


Box 1.
Clinical features suggestive of Acute Coronary Syndrome
Y
-12 L ECG within 10 minutes
-hs-Trop I, Creatinine, Na, K, Ca, Mg, CBG, Lipid Profile, PT/PTT, CBC
-Aspirin non-enteric tablet 80mg/tab, 4 tabs chew and swallow
-Atorvastatin 80mg/tab / Rosuvastatin 40mg/tab
-Referral to Adult Cardiology
ST Elevation or acute LBBB
N
NSTE-ACS
NSTEMI/UA
(proceed to next page)
Y
STEMI
Box 2.
Candidate for PCI and PCI can be done in <120 minutes?
N
Box 3.
Candidate for thrombolysis and no contraindication to thrombolysis?
N
Load P2Y12 inhibitor:
Clopidogrel 300mg OR Ticagrelor 180mg
Load anticoagulant if not yet given:
Fondaparinux 2.5mg IV OR
Enoxaparin 30 mg IV bolus followed 15 mins later by 1mg/kg (not to exceed 100 mg/injection) SC every 12 hours OR
UFH 60 units/kg (max 4000 units) IV bolus followed by infusion of 12 units/kg (max 1000 units/hour) (CKD V patients)
Y
Refer to Interventional Cardiology
Load P2Y12 inhibitor:
- Clopidogrel 600mg OR Ticagrelor 180mg / Prasugrel 60 mg
Load anticoagulant:
Enoxaparin 0.5 mg/kg IV bolus OR
UFH 70-100 units/kg IV (CKD V patients)
Y
Load P2Y12 inhibitor:
Clopidogrel 300mg
Load anticoagulant:
Enoxaparin 30 mg IV bolus followed 15 mins later by 1mg/kg (not to exceed 100 mg/injection) SC every 12 hours preferred over UFH
Fondaparinux 2.5mg IV (only with streptokinase)
Box 4.
Thrombolysis within 30 minutes
12L ECG after 60 minutes from start of thrombolysis
Coordinated transfer from another hospital for primary PCI
Load antiplatelets and anticoagulant if not yet given from the other hospital:
-Aspirin non-enteric tablet 80mg/tab, 4 tabs chew and swallow
- Clopidogrel 600mg OR Ticagrelor 180mg / Prasugrel 60 mg
- Enoxaparin 0.5 mg/kg IV bolus OR UFH 70-100 units/kg IV
Referral to Adult Cardiology and Interventional Cardiology
Proceed to Box 7
Box 7.
Coronary angiogram
Candidate for revascularization?
N
Y
Favorable anatomy for PCI?
N
CABG
Y
*Load UFH 70-100 units/kg IV bolus if initially given Fondaparinux at presentation
PCI
Optimal medical therapy
Admit to ICU


NSTE-ACS
Load anticoagulant:
Fondaparinux 2.5mg IV
Enoxaparin 0.5 mg/kg IV bolus
UFH 70-100 units/kg IV bolus
(CKD V patients)
Box 5.
Very high risk features?
or
High risk features?
N
Load P2Y12 inhibitor:
Clopidogrel 300mg OR Ticagrelor 180mg
Admit to Ward
Non-invasive testing
Stress echocardiography or stress CMR preferred over stress ECG
SPECT or PET perfusion imaging
coronary CTA
Box 6 .
High-risk features?
N
Refer to Cardiac Rehab
Discharge on Optimal Medical Therapy
Y
Y
Refer to Interventional Cardiology
Box 7.
Coronary angiogram
Candidate for revascularization?
N
Y
Favorable anatomy for PCI?
CABG
Load P2Y12 inhibitor:
Clopidogrel 600mg OR
Prasugrel 60 mg preferred over Ticagrelor 180mg
*Load UFH 70-100 units/kg IV bolus if initially given Fondaparinux at presentation
Optimal medical therapy
Admit to ICU
PCI

Box 1

Clinical features suggestive of Acute Coronary Syndrome

- **Typical angina:** sudden and severe in onset at rest that last at least 10 minutes; severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion; and an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep
- **Factors in the patient's chest pain history that increase the likelihood of ACS**: radiation to the right arm, both arm, or shoulders; association with exertion, diaphoresis, nausea or vomiting; chest pain worse than previous angina or similar to previous myocardial infarction (MI); and chest pain described as pressure
- **Atypical angina (in women, older persons, and individuals with diabetes**): jaw or shoulder pain in the absence of chest pain; nausea or vomiting; and diaphoresis
- **Presence of other risk factors**: male sex, advanced age, history of diabetes, and history of previous myocardial infarction (MI)
- **Uncharacteristic of myocardial ischemia:** pleuritic pain; primary or sole location of the discomfort in the middle or lower abdominal region; pain that may be localized by the tip of one finger, particularly over the left ventricular apex; pain reproduced with movement or palpation of the chest wall or arms; constant pain that persists for many hours; very brief episodes of pain that last a few seconds or less; and pain that radiates into the lower extremities

Zipes *et.al.*, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.11 ed. 2019

Box 2

Indications for PCI:

- Patients with STEMI and ischemic symptoms of less than 12 hours' duration
- Those who have contraindications to fibrinolytic therapy irrespective of the time delay from first medical contact
- Patients with STEMI and ongoing chest pain, electrical instability, cardiogenic shock or acute severe HF, irrespective of time delay from MI onset
- Atypical ECG presentations that should prompt PCI in patients with ongoing symptoms consistent with MI: ventricular paced rhythm, isolated posterior myocardial infarction, ischaemia due to left main coronary artery occlusion or multivessel disease

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

Box 3

Indication for thrombolysis: patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact

Contraindications to thrombolysis: Absolute contraindications:

- any prior intracranial hemorrhage
- known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- known malignant intracranial neoplasm (primary or metastatic)
- ischemic stroke within 3 months except acute ischemic stroke within 4.5 hours
- suspected aortic dissection
- active bleeding or bleeding diathesis (excluding menses)
- significant closed head or facial trauma within 3 months
- intracranial or intraspinal surgery within 2 months
- severe uncontrolled hypertension (unresponsive to emergency therapy)
- for streptokinase, prior treatment within the previous 6 months

Relative contraindications:

- history of chronic, severe, poorly-controlled hypertension
- significant hypertension on presentation (SBP >180 mm Hg or DBP>110 mmHg)
- history of prior ischemic stroke > 3 months
- dementia
- known intracranial pathology not covered in absolute contraindications
- traumatic or prolonged (>10 min) cardiopulmonary resuscitation
- major surgery (< 3 weeks)
- recent (within 2 to 4 weeks) internal bleeding
- non-compressible vascular punctures
- pregnancy
- active peptic ulcer
- oral anticoagulant therapy

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

Zipes *et.al.*, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.11 ed. 2019

Box 4

Thrombolytic agents

- Alteplase 15 mg IV bolus then 0.75 mg/kg IV (up to 50 mg) over 30 minutes then 0.5 mg/kg IV (up to 35 mg) over 60 minutes
- Streptokinase 1.5 million units over 30-60 mins i.v.

Criteria for successful thrombolysis

- ST-segment resolution >50% at 60-90 minutes
- Typical reperfusion arrhythmia
- Disappearance of chest pain

Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal (2018) 39, 119–177 doi:10.1093/eurheartj/ehx393

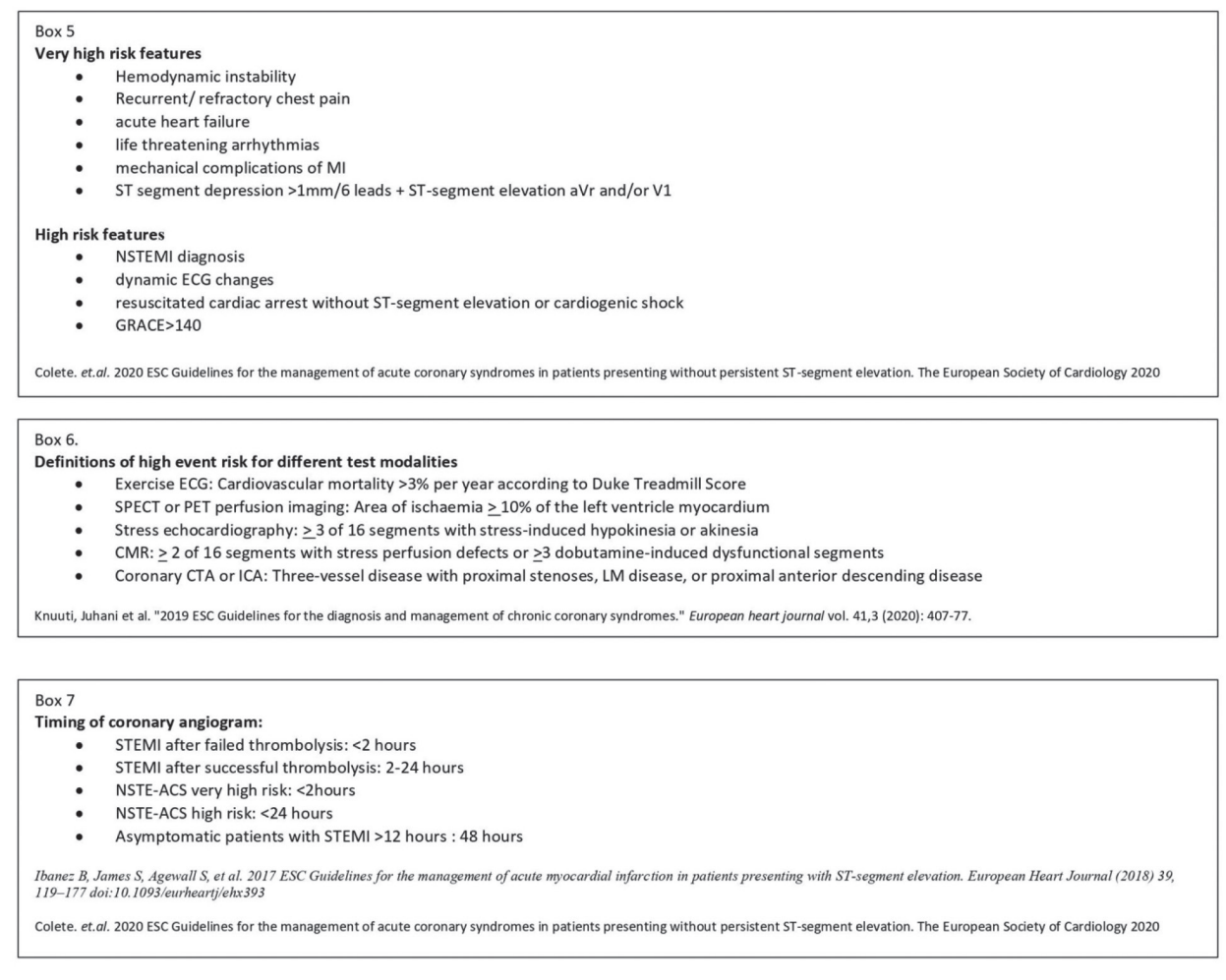


Figure 2. Acute coronary syndrome pathway from content validation with the stakeholders.

and will receive optimal medical therapy. Patients who are not candidates for revascularization will be admitted to the ICU and will receive optimal medical therapy.

DISCUSSION

The creation of an institution-specific pathway for ACS took into consideration not only the recommendations from the latest guidelines but also the applicability and feasibility of the recommendations in the local setting. During the process of internal and external validation, several revisions were made to ensure that pathway can be carried out in the local setting while adhering to the guideline recommendations. Because of some limitations in the local settings, some interventions were prioritized over another despite lower level of evidence.

A P2Y12 inhibitor is recommended in addition to aspirin among ACS patients. The ACC/AHA NSTE-ACS guidelines gave class IB recommendation for ticagrelor, prasugrel, and clopidogrel as P2Y12 inhibitors in patients with ACS. In the latest ESC NSTE-ACS guidelines, ticagrelor and prasugrel were given class IB recommendation, whereas clopidogrel was given class IC recommendation. These recommendations were based mainly on the results of the PLATO and TRITON-TIMI 38 trials, which showed reduction in composite outcomes of death from vascular cause, MI, and stroke among ACS patients given ticagrelor and prasugrel, respectively, as compared with clopidogrel.[20,21] Although all of these P2Y12 inhibitors are locally available in the Philippines, only clopidogrel is part of the Philippine National Drug Formulary and hence the only P2Y12 inhibitor readily available in PGH Pharmacy. Prioritizing the use ticagrelor or prasugrel to these patients may cause potential delay in management as these drugs have to be bought outside of the hospital. Hence, clopidogrel was prioritized as the P2Y12 inhibitor in the ACS Pathway.

Parenteral anticoagulation is likewise recommended in all patients presenting with ACS in the absence of contraindications. Options for anticoagulation are UFH, enoxaparin, and fondaparinux. Although all are locally available in PGH Pharmacy and despite the higher class of recommendation for and lower cost of UFH, the difficulty in monitoring activated partial thromboplastin time at the ER and the delay in the turnaround time of laboratory result made it the less ideal drug in the local ER setting. Further, the results of the

OASIS-5 and OASIS-6 trials supported the use of fondaparinux in ACS patients. In the OASIS-5 trial, fondaparinux was noninferior in the primary outcome of death, MI, or refractory ischemia at 9 days and reduced major bleeding compared with enoxaparin in NSTE-ACS.[22] In the OASIS-6 trial, fondaparinux resulted to lower primary endpoint of death and MI at 30 days with no difference in severe bleeding at 9 days compared with UFH among STEMI patients.[23] Hence, enoxaparin and fondaparinux were bumped up as the first anticoagulants in the list in the ACS Pathway.

The group took into consideration that the Department of Emergency Medicine and the Department of Laboratories are handling emergency cases other than ACS. As such, only the most essential laboratories must be requested initially to avoid potential delay in the turnaround time of the results of the laboratories among these patients, which could affect their management. A discussion was made whether extracting a nonfasting lipid profile at the ER setting would be more beneficial rather than obtaining it anytime during admission or at the outpatient department. Patients with established coronary artery disease are at very high risk for cardiovascular events. Data from 170,000 participants in 26 randomized trials comparing more versus less intensive low-density lipoprotein cholesterol (LDL-C) lowering with statins showed greater reductions in the risks of cardiovascular death, nonfatal MI, ischemic stroke, and coronary revascularization in more intensive statin therapy. Further, it showed that for each 1-mmol/L LDL-C reduction, the risk of occlusive vascular events is reduced by a fifth irrespective of baseline cholesterol concentration, suggesting that reduction of LDL-C by 2 to 3 mmol/L would reduce risk by approximately 40% to 50%. The recent ESC guidelines hence recommend as a class IA recommendation the use of high-intensity statin to lower LDL-C by 50% or greater from baseline and to achieve LDL-C of less than 1.4 mmol/L (<55 mg/dL). If the LDL-C is not achieved within 4 to 6 weeks of maximally tolerated statin dose, addition of ezetimibe is recommended. This is based on the IMPROVE-IT trial, which showed that the addition of ezetimibe to statin therapy among patients with ACS is associated with a reduction in cardiovascular mortality, major cardiovascular event, or nonfatal stroke when compared with statin therapy alone (34.7% vs 32.7%; P = 0.016).[24] When the recommended LDL-C level cannot be achieved within 4 to 6 weeks with maximally tolerated statin and ezetimibe dose, the recent ESC guidelines recommend the addition of PCSK9 inhibitor. This is based on the results of the FOURIER trial, which showed an absolute reduction of 1.5% in major cardiovascular events when evolocumab was added to statin therapy.[25] Latest guidelines recommend obtaining a lipid profile in all STEMI patients as soon as possible after presentation as baseline. After ACS, phasic changes in serum lipid and lipoprotein levels occur after 24 hours—specifically, reduced total cholesterol, LDL, and high-density lipoprotein, and elevated triglyceride levels.[26] Hence, it is important to obtain baseline values at the ER setting as this would guide succeeding management.

Important in the proper management of ACS patients are the timely results of different laboratories. A complete blood count and coagulation parameters may show anemia as a potential cause of ischemia and are also useful in predicting risk of bleeding. The creatinine clearance may guide the dosages of some medications used for ACS, as well as the choice of contrast agent. Electrolyte imbalances must be corrected to reduce risk of complications such as arrhythmia. The turnaround time for the releasing of the results of these tests is thus an important point of discussion during the FGDs.

CONCLUSION

Despite the limitations set by the resources in the local hospital setting, an ACS Pathway was created balancing the recommendations and evidence from international guidelines, as well as practicality with what is available in the local setting. Review of existing quality-of-care studies, latest international clinical practice guidelines, and interdepartmental collaboration with identified stakeholders were necessary components in the creation of an institution-specific pathway for ACS.

RECOMMENDATIONS

An ACS Pathway form was created to improve compliance to the pathway and to monitor variance in its implementation. Additional studies on pathway implementation (i.e., adherence to time-bound interventions, underuse and/or overuse of interventions) and how the new pathway has influenced patient outcomes (e.g., mortality, morbidity, quality of life, cost of care) are necessary to improve pathway utility and impact.

ACKNOWLEDGMENTS

This study was supported by a research grant from the PGH Expanded Hospital Research Office.

With sincere gratitude, the study team acknowledges the invaluable contribution of the stakeholders during content validation of the development of PGH ACS Pathway.

PGH ACS Pathway Core Team

Project Consultants
John C. Añonuevo, MD
Felix Eduardo R. Punzalan, MD
Eric Oliver D. Sison, MD
Diana Tamondong-Lachica, MD

DCVM Fellows
Valerie Ramiro, MD
Ruth Divine Agustin, MD
Lauren Kay Evangelista, MD
Cecileen Anne Tuazon, MD
Paul Anthony Alad, MD
Albert Rollorazo, MD
John Christopher Pilapil, MD
Bianca Velando, MD

Internal Medicine Residents
Mark Joseph Abaca, MD
Jerahmeel Aleson Mapili, MD

PGH DCVM Panel (Internal Validation)
Consultants
Eugenio B. Reyes, MD
Jose Donato A. Magno, MD
Richard Henry P. Tiongco II, MD
Giselle G. Gervasio, MD
Jaime Alfonso M. Aherrera, MD
Francisco Tranquilino, MD
Frederick Philip Gloria, MD

Fellows
Brian Fidel Belvis, MD
Roxanne Yen Bongcawil, MD
Julian Alexander Huibonhoa, MD
Namphril Malaluan, MD
Marie Kirk Patrich Maramara, MD
Aiza Katrina Reyes, MD
Paula Victoria Cheng, MD
Zane Oliver Nelson, MD
Bryan Ramirez, MD
Sonny Sendon, MD
Bai Sitti Ameerah Asleah Tago, MD
Tam Adrian Aya-ay, MD
Kaye Lustestica, MD
Sherry Mae Mondido, MD
Mark Sabando, MD
Aaron Christian Earl Vidad, MD

List of Stakeholders (External Validation)
Pharmacy
Pamela D. Nala, RPh
Rubina R. Abaya, RPh

Nursing
Paul Froilan U. Garma, RN

Medicine
Frederick Philip B. Gloria, MD

Adult Cardiology
Eugenio B. Reyes, MD

Emergency Medicine
Maria Isabelle Pineda-Leonardia, MD

Health Operations
Homer Co, MD

REFERENCES

1. World Health Organization. *Cardiovascular Diseases*. Geneva, Switzerland: WHO; 2021.
2. Department of Health. *The 2018 Philippine Health Statistics*. 2018
3. Roque VL, Besa JJ, Medina H, Nicolas A, Magnaye FM. *2019 Ward Services Year-End Report*. 2020. Internal document.
4. Jneid H, Addison D, Bhatt, DL, et al. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction: a report of the American College of Cardiology/ American Heart Association Task Force on Performance Measures. *Circulation* 2017;10(10).
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;39(2):119–177.
6. 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.
7. Biviano AB, Rabbani LRE, Paultre F, et al. Usefulness of an acute coronary syndrome pathway to improve adherence to secondary prevention guidelines. *Am J Cardiol* 2003;91(10):1248–1250. doi:10.1016/S0002-9149(03)00276-5.
8. Mehta RH, Montoye CK, Gallogly M, et al. Improving quality of care for acute myocardial infarction: the Guidelines Applied in Practice (GAP) initiative. *J Am Med Assoc* 2002;287(10):1269–1276. https://doi.org/10.1001/ jama.287.10.1269.
9. Ozdas A, Speroff T, Waitman L, et al. Integrating "best of care" protocols into clinicians' workflow via care provider order entry: impact on quality-of-care indicators for acute myocardial infarction. *J Am Med Inform Assoc* 2006;13(2):188–196. doi:10.1197/jamia.M1656.
10. Punzalan FE, Lim-Quianzon D, Pestano N, et al. The quality of care of patients with acute myocardial infarction in the University of the Philippines—Philippine General Hospital. 1999. Internal report.
11. Obrado M, Punzalan F, Tranquilino F, Reyes E. Pattern of physicians in the in-hospital Management of acute coronary syndrome and their compliance to existing guidelines; a quality of care study. 2008. Internal report.
12. Magno JD, Santella C, Punzalan FE. Timely rhythm assessment for chest pain at the emergency room (TRACER). UP-PGH Cardiovascular Section. 2010. Internal report.
13. Alcover JD, Punzalan FE, Reyes EB. Quality of care for acute coronary events at the Philippine General Hospital emergency room: a two-month study. *UP PGH Cardiovascular Research Compendium* 2012;1(1).

14. Lim K, Chan M. Quality of care assessment of the management of St-elevation myocardial infarction in patients admitted in the Philippine General Hospital. 2018. Internal report.
15. Ramiro V, Tiongson M, Taquiso J et al. Quality of care assessment of adult patients with ST-elevation myocardial infarction at the emergency room of a tertiary hospital in the Philippines. 2019. Internal report.
16. Reymatias J, Tiongson MD, Evangelista LK, Reganit PF, Punzalan FER. Quality of care in adult patients with non–ST-segment elevation acute coronary syndrome at the University of the Philippines—Philippine General Hospital Emergency Room. 2019. Internal report.
17. Evangelista LKE, et al. Compliance of physicians at a tertiary hospital in the Philippines to the ST-elevation myocardial infarction pathway. 2019. Internal report.
18. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64(24):e139–e228.
19. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127(4):e362–e425.
20. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045–1057.
21. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357(20):2001–2015.
22. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007;50(18):1742–1751.
23. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006;295(13):1519–1530.
24. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372(25):2387–2397.
25. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376(18):1713–1722
26. Shrivastava AK, Singh HV, Raizada A, Singh SK. Serial measurement of lipid profile and inflammatory markers in patients with acute myocardial infarction. *EXCLI J* 2015;14:517–526.

APPENDIX A

Internal Validation of the Interim ACS Pathway Nodes

Interim ACS Pathway Nodes	Decision
Chest pain highly suggestive of acute coronary syndrome? -Sudden and severe in onset at rest that last at least 10 min? -Severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion? -Accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep	Accepted with modification Modify to clinical features suggestive of ACS to encompass other atypical presentations of ACS other than chest pain. (Echo consultant) Indicate clinical features as stated in Braunwald, include features that are uncharacteristic of ischemic origin of angina. (Adult cardiology consultant) Include features as a footnote. (Adult cardiology consultant)
12-Lead ECG Troponin I Creatinine, capillary blood glucose, lipid profile, PT/PTT, CBC Aspirin 80 mg per tablet, four tablets to chew and swallow High-intensity statin	Accepted with modification Include time frame to perform the initial 12-lead ECG within 10 min. (Interventional cardiology [IC] consultant) Specify high-sensitivity troponin I. Also available in the hospital. (IC consultant and cardiology fellow) Include Na, K in routine biochemistry (IC consultant) Conditional order of serum Ca and Mg for patients presenting with arrhythmia (IC consultant) Specify nonenteric tablet for loading of aspirin. (Professor of pharmacology and IC consultant) Specify the name and dose of preferred high-intensity statin—atorvastatin 80 mg per tablet since most of the trials for ACS used atorvastatin. (IC and adult cardiology consultants)
ST elevation or acute LBBB (decision node)	Accepted
ST-segment elevation myocardial Infarction	
Primary PCI for STEMI	
	Accepted Add node for coordinated STEMI transfers for PCI. (IC fellow and consultant)
Candidate for PCI and PCI can be done in <120 min	Accepted with modification Indicate indications for PCI in the footnote. (Adult cardiology consultant)
Load P2Y12 inhibitor: Prasugrel 60 mg/ticagrelor 180 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available Load anticoagulant: UFH 70–100 IU/kg IV bolus Consider enoxaparin 0.5 mg/kg IV bolus Bivalirudin 0.75 mg/kg IV bolus in patients with HIT	Accepted with modification List medications by priority. Prasugrel and ticagrelor with same strength of recommendation in the 2017 ESC guidelines for STEMI but only ticagrelor is readily available hence should be prioritized. (IC consultants and professor of pharmacology) Because of the difficulty of monitoring aPTT levels at the ER and delayed turnaround time of results, prioritize enoxaparin. Remove bivalirudin. Specify subgroup of dialytic patients to receive UFH. (IC consultant)

(continuation of Appendix A)

Thrombolysis for STEMI	
Candidate for thrombolysis and no contraindication to thrombolysis?	Accepted with modification Indicate contraindications to thrombolysis and options with dose of thrombolytic agent in the footnote. (Adult cardiology consultant)
Load P2Y12 inhibitor: Clopidogrel 300 mg Load anticoagulant: Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 preferred over UFH (not to exceed 100 mg per injection)	Accepted with modification Specify fondaparinux and dose for patients who will be given streptokinase as thrombolytic agent. (Professor of pharmacology, IC consultants and cardiology fellow)
Thrombolysis	Accepted with modification Include time frame. (Adult cardiology consultant)
	Accepted Insert additional node to assessment of result of thrombolysis—repeat ECG after thrombolysis. (Adult cardiology consultant)
Medical management for STEMI	
Load P2Y12 inhibitor: Ticagrelor 180 mg preferred over clopidogrel 300 mg Load anticoagulant: UFH 60 IU/kg IV bolus (max 4000 IU) followed by an infusion of 12 IU/kg (max 1000 IU/h) for 24–48 h Consider enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection) Bivalirudin 0.75 mg/kg IV bolus in patients with HIT	Accepted with modification Prioritize fondaparinux and enoxaparin for medically managed STEMI due to difficulty monitoring aPTT and results of OASIS trial. (Professor of pharmacology and IC consultant)
Optimal medical therapy	Accepted
Admit to ICU	Accepted
STEMI proceeding to coronary angiogram	
Coronary angiogram* * Timing of coronary angiogram: • STEMI after failed thrombolysis: <2 h • STEMI after successful thrombolysis: 2–24 h • Asymptomatic patients with STEMI >12 h : 48 h	Accepted
Candidate for revascularization? (decision node)	Accepted
Favorable anatomy for PCI? (decision node)	Accepted

(continuation of Appendix A)

(Permutations) - Candidate for revascularization and with favorable anatomy to PCI → PCI - Candidate for revascularization with unfavorable anatomy for PCI → CABG Not a candidate for revascularization → optimal medical therapy	Accepted with modification For patients proceeding to PCI, load UFH if initially given fondaparinux at presentation. (IC consultant)
Optimal medical therapy	Accepted
Admit to ICU	Accepted
NSTE-ACS	
	Accepted Insert node on loading of anticoagulant since risk stratification will not change the decision to give an anticoagulant. (Adult cardiology and IC consultants)
Very high-risk features? Hemodynamic instability, recurrent/refractory chest pain, acute heart failure, life-threatening arrhythmias, mechanical complications of MI, ST-segment depression >1 mm/six leads + ST-segment elevation aVr and/or V_1 or High-risk features? NSTEMI diagnosis, dynamic ECG changes, resuscitated cardiac arrest, GRACE >140	Accepted with modification Clarify resuscitated cardiac arrest under high-risk features as resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock. (IC consultants)
(If without very high of very high-risk features) Load P2Y12 inhibitor: Ticagrelor 180 mg preferred over clopidogrel 300 mg Load anticoagulant: UFH 70–100 IU/kg IV bolus Consider enoxaparin 0.5 mg/kg IV bolus Bivalirudin 0.75 mg/kg IV bolus in patients with HIT	Accepted with modification Move loading of anticoagulant before risk stratification node. (Heart failure consultant) Prioritize fondaparinux with class IB recommendation and also already part of PNDF as well. Specify UFH for dialytic patient. (Professor of pharmacology and IC consultant)
Optimal medical therapy	Accepted
Admit to ICU	Accepted
	Accepted Add node to capture noninvasive testing for low risk NSTE-ACS patients for further risk stratification. If with high-risk features, refer for coronary angiogram. If no high-risk features, refer to cardiac rehab and discharge on optimal medical therapy. (Heart failure and adult cardiology consultants)

(continuation of Appendix A)

NSTE-ACS patients proceeding to coronary angiogram	
Coronary angiogram* * Timing of coronary angiogram: • NSTE-ACS very high risk: <2hours • NSTE-ACS high risk: <24 h	Accepted
Candidate for revascularization? (decision node)	Accepted
Favorable anatomy for PCI? (decision node)	Accepted
(Permutations) - Candidate for revascularization and with favorable anatomy to PCI → PCI • Load P2Y12 inhibitor: Prasugrel 60 mg preferred over ticagrelor 180 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available • Load anticoagulant: UFH 70–100 IU/kg IV bolus/fondaparinux 2.5 mg SC with UFH during time of PCI Consider enoxaparin 0.5 mg/kg IV bolus - Candidate for revascularization with unfavorable anatomy for PCI → CABG - Not a candidate for revascularization → optimal medical therapy	Accepted with modification Move loading of anticoagulant to prior to risk stratification. (Heart failure consultant) For patients for PCI, load UFH if initially given fondaparinux at presentation. (Professor of pharmacology and IC consultant)
Optimal medical therapy	Accepted
Admit to ICU	Accepted

ACS=acute coronary syndrome; aPTT=activated partial thromboplastin time; CBC=complete blood count; CABG=coronary artery bypass graft; ECG=electrocardiogram; HIT=heparin-induced thrombocytopenia; ICU=intensive care unit; IV=intravenous; LBBB=left bundle-branch block; NSTEMI=non–ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; PT=prothrombin time; PTT=partial thromboplastin time; SC=subcutaneous; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.

APPENDIX B

External Validation of the Interim ACS Pathway Nodes

Interim ACS Pathway Node	Decision (% agreement between stakeholders)
Clinical features suggestive of ACS **Footnotes:** *Clinical features suggestive of ACS* • Typical angina: sudden and severe in onset at rest that last at least 10 min; severe pain, pressure, or discomfort in the chest that radiates to the jaw or arms and worsens with exertion; and an accelerating pattern of angina that develops more frequently, with greater severity, or that awakens the patient from sleep • Factors in the patient's chest pain history that increase the likelihood of ACS: radiation to the right arm, both arms, or shoulders; association with exertion, diaphoresis, nausea, or vomiting; chest pain worse than previous angina or similar to previous MI; and chest pain described as pressure • Atypical angina (in women, older persons, and individuals with diabetes): jaw or shoulder pain in the absence of chest pain; nausea or vomiting; and diaphoresis • Presence of other risk factors: male sex, advanced age, history of diabetes, and history of previous MI • Uncharacteristic of myocardial ischemia: pleuritic pain; primary or sole location of the discomfort in the middle or lower abdominal region; pain that may be localized by the tip of one finger, particularly over the left ventricular apex; pain reproduced with movement or palpation of the chest wall or arms; constant pain that persists for many hours; very brief episodes of pain that last a few seconds or less; and pain that radiates into the lower extremities	Accepted (100%)
-12-Lead ECG within 10 min -High-sensitivity troponin I -Creatinine, sodium, potassium, PT/PTT, CBC -Calcium, magnesium (if with arrhythmia) -Atorvastatin 80 mg per tablet -Referral to general medicine and adult cardiology	Accepted with modification (83%) Include cardiac-related electrolytes Ca and Mg as part of routine orders Add high-intensity statin Rosuvastatin 40 mg per tablet as an alternative to atorvastatin 80 mg per tablet, whichever is available at the pharmacy Direct referral to adult cardiology to prevent delays in urgent intervention
-Nonfasting lipid profile	Accepted (67%)
-CBG	Accepted (100%)
-Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow	Accepted (100%)
- Atorvastatin 80 mg per tablet	Accepted (100%)

(continuation of Appendix B)

STEMI	
Candidate for PCI and PCI can be done in <120 min? **Footnotes:** *Indications for PCI* • Patients with STEMI and ischemic symptoms of less than 12-h duration • Those who have contraindications to fibrinolytic therapy irrespective of the time delay from first medical contact • Patients with STEMI and ongoing chest pain, electrical instability, cardiogenic shock or acute severe HF, irrespective of time delay from MI onset • Atypical ECG presentations that should prompt PCI in patients with ongoing symptoms consistent with MI: ventricular paced rhythm, isolated posterior myocardial infarction, ischemia due to left main coronary artery occlusion or multivessel disease	Accepted (100%)
Refer to interventional cardiology	Accepted (83%)
Load P2Y12 inhibitor: Ticagrelor 180 mg/prasugrel 60 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available	Accepted with modification (83%) Prioritize clopidogrel since this is the only P2Y12 inhibitor, which is part of the PNDF and available in the hospital pharmacy. This will likewise allow the nursing team to carry-out the orders in a timely manner.
Load anticoagulant: Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis)	Accepted with modification (100%) For clarity of order, spell out IU to units.
Thrombolysis for STEMI	
Candidate for thrombolysis and no contraindication to thrombolysis? **Footnotes:** *Indication for thrombolysis:* patients with STEMI and onset of ischemic symptoms within the previous 12 h when it is anticipated that primary PCI cannot be performed within 120 min of first medical contact *Contraindications to thrombolysis: absolute contraindications:* • Any prior intracranial hemorrhage • Known structural cerebral vascular lesion (eg, arteriovenous malformation) • Known malignant intracranial neoplasm (primary or metastatic) • Ischemic stroke within 3 mo except acute ischemic stroke within 4.5 h • Suspected aortic dissection • Active bleeding or bleeding diathesis (excluding menses) • Significant closed head or facial trauma within 3 mo • Intracranial or intraspinal surgery within 2 mo • Severe uncontrolled hypertension (unresponsive to emergency therapy) • For streptokinase, prior treatment within the previous 6 mo	Accepted (100%)

(continuation of Appendix B)

Relative contraindications • History of chronic, severe, poorly controlled hypertension • Significant hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg) • History of prior ischemic stroke >3 mo • Dementia • Known intracranial pathology not covered in absolute contraindications • Traumatic or prolonged (>10 min) cardiopulmonary resuscitation • Major surgery (< 3 wk) • Recent (within 2–4 wk) internal bleeding • Noncompressible vascular punctures • Pregnancy • Active peptic ulcer • Oral anticoagulant therapy	
Load P2Y12 inhibitor: Clopidogrel 300 mg Load anticoagulant: Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection preferred over UFH Fondaparinux 2.5 mg IV (only with streptokinase)	Accepted with modification (100%) For clarity of order, change q12 to every 12 h
Thrombolysis within 30 min	Accepted (100%)
12-Lead ECG after 60 min	Accepted (83%)
Medical management for STEMI	
Load P2Y12 inhibitor: Ticagrelor 180 mg OR clopidogrel 300 mg Load anticoagulant if not yet given: Fondaparinux 2.5 mg IV Enoxaparin 30 mg IV bolus followed 15 min later by 1 mg/kg SC q12 (not to exceed 100 mg per injection) OR UFH 60 IU/kg IV bolus (max 4000 IU) followed by an infusion of 12 IU/kg (max 1000 IU/h) for 24–48 h	Accepted with modification (100%) Prioritize clopidogrel as the P2Y12 of choice for reasons stated above For clarity of order, change q12 to every 12 h and IU to units. Maximum dose should be written after the dose/kg instead of after the frequency (ie, enoxaparin 1 mg/kg [not to exceed 100 mg per injection] SC every 12 h)
Load antiplatelets and anticoagulant if not yet given from the other hospital: -Aspirin nonenteric tablet 80 mg per tablet, four tablets to chew and swallow -Ticagrelor 180 mg/prasugrel 60 mg OR clopidogrel 600 mg if prasugrel or ticagrelor is not available -Enoxaparin 0.5 mg/kg IV bolus OR UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis)	Accepted with modification (100%) Prioritize clopidogrel as the P2Y12 inhibitor for reasons already stated above Spell out IU to units
Refer to general medicine, adult cardiology, and interventional cardiology	Accepted with modification (83%) Direct referral to adult cardiology, adult cardiology to refer to interventional cardiology

(continuation of Appendix B)

STEMI patients proceeding to coronary angiogram	
Coronary angiogram **Footnotes:** *Timing of coronary angiogram:* • STEMI after failed thrombolysis: <2 h • STEMI after successful thrombolysis: 2–24 h • Asymptomatic patients with STEMI >12 h : 48 h	Accepted (100%)
Candidate for revascularization?	Accepted (100%)
Candidate for revascularization, favorable anatomy for PCI? Yes → Load UFH 70–100 IU/kg IV bolus if initially given fondaparinux at presentation → PCI No → CABG	Accepted with modification (100%) Spell out IU to units Accepted (83%)
Not a candidate for revascularization → optimal medical therapy	Accepted (83%)
Optimal medical therapy	Accepted (83%)
Admit to ICU	Accepted (83%)
NSTE-ACS	
Load anticoagulant: Fondaparinux 2.5 mg IV Enoxaparin 0.5 mg/kg IV bolus UFH 70–100 IU/kg IV bolus (CKD V patients on dialysis)	Accepted with modification (100%) Spell out IU to units
Very high-risk features? or High-risk features? **Footnotes:** *Very high-risk features* • Hemodynamic instability • Recurrent/refractory chest pain • Acute heart failure • Life-threatening arrhythmias • Mechanical complications of MI • ST-segment depression >1 mm/six leads + ST-segment elevation aVr and/or V_1 *High-risk features* • NSTEMI diagnosis • Dynamic ECG changes • Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock • GRACE >140	Accepted (100%)

(continuation of Appendix B)

NSTE-ACS with very high- or high-risk features	
Refer to interventional cardiology	Accepted (100%)
NSTE-ACS with low-risk features	
Load P2Y12 inhibitor: ticagrelor 180 mg preferred over clopidogrel 300 mg	Accepted with modification (100%) Prioritize clopidogrel for reasons stated above
Noninvasive testing Stress echocardiography or stress CMR preferred over stress ECG, or SPECT or PET perfusion imaging, or coronary CTA	Accepted with modification (83%)
High-risk features on noninvasive testing? Yes → refer to Interventional Cardiology No → Refer to cardiac rehab and discharge on optimal medical therapy	Accepted (83%)
NSTE-ACS patients proceeding to coronary angiogram	
Coronary angiogram **Footnotes:** *Timing of coronary angiogram:* • NSTE-ACS very high risk: <2hours • NSTE-ACS high risk: <24 h	Accepted (100%)
Candidate for revascularization?	Accepted (100%)
Candidate for revascularization, favorable anatomy for PCI? Yes → Load P2Y12 inhibitor: prasugrel 60 mg preferred over ticagrelor 180 mg OR clopidogrel 600 mg if prasugrel or Tigacrelor is not available Load UFH 70–100 IU/kg IV bolus if initially given Fondaparinux at presentation → PCI No → CABG	Accepted with modification (100%) Prioritize clopidogrel for reasons stated above Spell out IU to units Accepted (83%)
Not a candidate for revascularization → optimal medical therapy	Accepted (83%)
Optimal medical therapy	Accepted (83%)
Admit to ICU	Accepted (83%)

ACS=acute coronary syndrome; CBC=complete blood count; CMR=cardiac magnetic resonance imaging; CKD V=stage 5 chronic kidney disease; CTA=computed tomography angiography; DBP=diastolic blood pressure; ECG=electrocardiogram; HF=heart failure; IV=intravenous; MI=myocardial infarction; NSTEMI=non–ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; PET=positron emission tomography; PT=prothrombin time; PTT=partial thromboplastin time; SBP=systolic blood pressure; SC=subcutaneous; SPECT=single-photon emission computed tomography; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.