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3RD EDITION 2021

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTE-ACS)*

** This is a combination of Unstable Angina and Non ST Elevation Myocardial Infarction (UA/NSTEMI)*

Ministry of Health Malaysia

National Heart Association of Malaysia

Academy of Medicine Malaysia

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MANAGEMENT OF NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTE-ACS)

3RD EDITION
2021

STATEMENT OF INTENT

This Guidelines was developed to be a guide for best clinical practice in the management of Non- ST Elevation Acute Coronary Syndrome (NSTE-ACS). This is a combination of both Unstable Angina (UA) and Non-ST Elevation Myocardial Infarction (NSTEMI). It is based on the best evidence currently available. Adherence to this Guidelines does not necessarily lead to the best clinical outcome in individual patient care. Thus, every health care provider is responsible for the management of his/her unique patient, based on the clinical presentation and management options available locally.

REVIEW OF THE GUIDELINES

This Guidelines was issued in 2021 and will be reviewed in 2026 or earlier if important new evidence becomes available.

CPG SECRETARIAT

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http://www.malaysianheart.org
http://www.moh.gov.my
http://www.acadmed.org.my

This is an update to the Clinical Practice Guidelines on UA/NSTEMI (published 2002 and 2011) It supersedes the previous CPGs on UA/NSTEMI (2002, 2011).

MESSAGE FROM THE DIRECTOR GENERAL OF HEALTH

Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS) accounted for 55.4% of all Acute Coronary Syndrome (ACS) reported from the National Cardiovascular Disease Database (NCVD) - ACS Registry between 2016 and 2017. NSTE-ACS including the non-ST elevation myocardial infarction and unstable angina is the dominant clinical manifestation of ACS in Malaysia hence ensuring the standardised and current clinical management for our clinicians is paramount for the safety of our patients.

A multi-pronged approach has seen improvement in the management of ACS over the last decade, in line with the development of both treatments and healthcare service delivery. However, since the publication of the previous Clinical Practice Guidelines (CPG) for the management of NSTE-ACS in 2011, new diagnostic and therapeutic measures have been introduced and practised. Therefore, the publication of the refreshed version of the 2021 Third Edition Clinical Practice Guideline on the Management of ST-Elevation Myocardial Infarction is timely.

Amongst the areas of focus in this brand-new CPG would be the in pre-hospital care, the use of cardiac troponins in the diagnostic work-up, a greater emphasis on risk stratification scores early in the inpatient management, and also the recommendation of an early invasive strategy for patients at the highest risk of adverse outcomes.

I am delighted with the research contribution by the various clinical and academic groups for the reference in this CPG, and I encourage such endeavours to continue for the improvement in both care and outcomes in patients. This CPG complements others that focus on the risk factors associated with the condition, including its sister condition, ST-elevation ACS in the CPG STEMI, 2019.

I thank the members of the Expert Panel and the External Reviewers, drawn from both the public and private sector of the Malaysian healthcare ecosystem, for their tireless work to produce this CPG. I would also like to acknowledge the National Heart Association of Malaysia and my colleagues at the Ministry of Health Malaysia for publishing this important update on the management of NSTE-ACS, 2021.

Tan Sri Dato' Seri Dr. Noor Hisham Bin Abdullah
Director-General of Health Malaysia

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RATIONALE AND PROCESS OF GUIDELINES DEVELOPMENT

Rationale:

Ischemic Heart disease is the main cause of mortality in Malaysia. Data from our National Cardiovascular Disease Database - Acute Coronary Syndrome (NCVD-ACS) Registry showed that the in-hospital, one month and 1-year mortality following NSTE-ACS is higher than that of other international registries. Thus, an update to our 2011 Clinical Practice Guidelines is timely.

This CPG consists of statements that include recommendations intended to optimize patient care guided by a systematic review of evidence and assessment of the benefits and harms of alternative care options, reflecting the latest literature, expert consensus, and wherever possible, public stakeholder comment.

This Guidelines has been prepared by a panel of committee members from the National Heart Association of Malaysia (NHAM) and Ministry of Health (MOH). The committee members were multidisciplinary and comprised cardiologists, internal, emergency and family medicine specialists and cardiac rehabilitation physicians from the government, private sector and universities. The external reviewers were also multidisciplinary and in addition to specialists, general practitioners were also included. Stakeholders - members of the general public - were also included as external reviewers.

The committee made use of the following resources in developing this CPG :-

- American College of Cardiology Foundation and American Heart Association (2010) Methodology manual and policies from the ACCF/AHA Task Force on Practice Guidelines
- European Society of Cardiology (ESC) Governing Policies and Procedures for the Writing of ESC Clinical Practice Guidelines and
- the Appraisal of Guidelines for Research and Evaluation [AGREE II] Tool

Objectives:

The objectives of this Guidelines are to provide guidance on:

- Systematic evaluation of patients presenting with chest pain to the Emergency Department to reduce the number of “missed Myocardial Infarctions”.
- Evidence-based therapeutic strategies in patients with NSTE-ACS to reduce the risk of recurrent Major Adverse Cardiac Events (MACE).
- Strategies to optimize patient care and reduce potential harm among the different subsets of patients with NSTE-ACS within the existing local frame-work of healthcare.

Process:

A review was carried out of the medical literature on Myocardial Infarction (MI)/Non ST Elevation Acute Coronary Syndrome / Non ST Elevation MI (NSTEMI) / Unstable Angina (UA)/Acute Coronary Syndromes (ACS) published since the issuing of the last CPG in 2011.

Literature search was carried out using the following electronic databases - PubMed and Cochrane Database of Systematic Reviews. The search was conducted for the period 2011 till 31st August 2019. The following MeSH terms or free text terms were used either singly or in combination:

"Acute Coronary Syndrome","ACS", "Myocardial infarction (MI)"; "NSTEMI"; Non ST Elevation Myocardial Infarction;" "UA"," Unstable Angina","Non ST Elevation Acute Coronary syndrome", "NSTE-ACS" "definition of MI"; "Myocardial injury", "ECG criteria of NSTE-ACS","Rule out Protocols for ACS"; "Risk Scores for ACS", "cardiac troponins", "Pre-hospital Management of ACS"; "Oxygen therapy in ACS"; "Risk stratification scores in NSTE-ACS"; "Cardiac rehabilitation", "secondary prevention post NSTE-ACS", "management of NSTE-ACS in women, the elderly, persons with chronic renal disease."

The search was filtered to clinical trials and reviews, involving humans and published in the English language. The relevant articles were carefully selected from this huge list. In addition, the reference lists of all relevant articles retrieved were searched to identify further studies. Regional CPGs were also studied. Experts in the field were also contacted to obtain further information. International Guidelines mainly that from the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology (ESC) were used as references.

The literature retrieved was appraised by members of the Expert Panel and all statements and recommendations made were collectively agreed by the group. The systemic reviews were conducted "in-house" and the committee appraised the quality of evidence collectively. The evidence was not systematically assessed for consistency, precision and directness. However, each of these attributes were implicitly judged when the committee appraised and graded the evidence and wrote the level of recommendation. The recommendations of the other international bodies – ACCF/ACC, ESC and The National Institute for Health and Care Excellence (NICE) Guidelines-were also studied to determine their applicability to the local population and heathcare.

The grading of the evidence and the level of recommendation used in this CPG as outlined in page 16, were adopted from that used by the American College of

Cardiology Foundation/ American Heart Association 2010 Methodology Manual and Policies by the ACCF/AHA Task Force on Practice Guidelines and the European Society of Cardiology Governing Policies and Procedures for Writing ESC Clinical Practice Guidelines 2017.

After much discussion, the draft was then drawn up and submitted to the Technical Advisory Committee for Clinical Practice Guidelines, MOH Malaysia and key health personnel in the major hospitals of the MOH and the private sector and general public for review and feedback.

Clinical Questions Addressed:

There were several topics and subtopics that were formulated addressing the diagnosis and management of NSTE-ACS (UA+ NSTEMI)

For **diagnosis:**

In a person presenting with chest pain/ chest pain equivalent:

- What features in the history would make one suspect this patient is having an ACS?
- In a patient with suspected ACS, how do you differentiate NSTE-ACS and STEMI based on:
  - ECG
  - Cardiac biomarkers - cardiac troponins/ Creatine Kinase Myocardial Band (CKMB). How useful are these?
    - Is there a role for cardiac troponins to be available in primary healthcare (cost-effectiveness)?
  - Echocardiogram: is it a useful diagnostic tool?
- Which patients presenting with chest pain in the ED can be safely sent home?
- How do we risk stratify patients with NSTE-ACS?
- Which patients require urgent referral for cardiac catheterization?

For ***therapy***, the topics and subtopics were formulated using the PICO method as follows:

P: Population - Persons with NSTE-ACS and risk stratified using either the TIMI or GRACE scores (Appendix IV and V, page 96 and 97) and at:

- Low risk of MACE
- Intermediate risk of MACE
- High risk of MACE
- Very high risk of MACE

I: Intervention:

- Oxygen vs no oxygen
- Pharmacotherapy
  - Nitrates
  - Morphine
  - Antithrombotics:
    - Antiplatelet therapy
    - Anticoagulants
      - Heparin/ fondaparinux
      - Direct oral anticoagulants (DOAC)
  - Renin Angiotensin Blockers:
    - Angiotensin converting enzyme inhibitors (ACE-I),
    - Angiotensin receptor blockers (ARB)
  - β-blockers
  - Mineralocorticoid antagonists (MRA)
  - Statins
- Interventional therapy - Percutaneous Coronary Intervention (PCI)

C: Comparison:

- Single antiplatelet therapy vs dual antiplatelet therapy (DAPT)
- Ticlopidine vs clopidogrel vs prasugrel vs ticagrelor as second antiplatelet agent
- DOAC + single antiplatelet vs DAPT
- Low molecular weight heparin vs unfractionated heparin vs fondaparinux
- ACE-I vs no ACE-I
- Nitrates vs no nitrates
- β-blockers vs no β-blockers
- High dose statins vs no statins
- Ivabradine vs no ivabradine
- Trimetazidine vs no trimetazidine
- PCI vs Medical therapy

O: Outcome:

1. Reduction in major cardiovascular adverse events (MACE -MI, heart failure, stroke, cardiovascular disease (CVD) death)
2. Reduction in all-cause mortality

Type of Question - Involves:

- Therapy - Pharmacotherapy, PCI
- Harm -
  - Increase in cardiovascular disease event rate (MACE -MI, heart failure, stroke, CVD death)
  - Increase in bleeding risk and stroke rate
  - Adverse effects due pharmacotherapy
- Prognosis - Reduction in MACE-MI, heart failure, stroke, CVD death and improvement in all-cause mortality

Type of Study

- Systematic review and meta-analysis
- Randomised controlled studies
- Cohort studies
- Registry data

Thus, there were numerous clinical questions formulated.
Examples of some of these Clinical Questions:

1. In a patient presenting with NSTE-ACS and with ongoing chest pains and at low risk of MACE (Major Cardiovascular Outcomes) is the administration of intravenous morphine for pain relief as compared to a non opiate, effective and safe?
2. In a patient presenting with NSTE-ACS and at low risk of MACE, taking into consideration the patient's bleeding risks (as assessed by the PRECISE-DAPT score, Appendix VI page 98), are double antiplatelet agents more effective than a single antiplatelet agent, in reducing:
   - MI, heart failure, stroke, cardiovascular disease (CVD) death
   - All-cause mortality
3. Would an initial interventional therapy when compared to intensive medical therapy alone in a patient presenting with NSTE-ACS and at low risk of MACE result in a reduction in:
   - MI, heart failure, stroke, cardiovascular disease (CVD) death
   - All-cause mortality.
4. Would an initial interventional therapy when compared to intensive medical therapy alone in a patient presenting with NSTE-ACS and at very high risk of MACE result in a reduction in:
   - MI, heart failure, stroke, cardiovascular disease (CVD) death
   - All-cause mortality.

Target Group:

This Guidelines is directed at all healthcare providers including general practitioners, medical officers, general, family and emergency physicians and cardiologists.

Target Population:

All patients (older than 18 years) presenting with chest pain and who have been diagnosed to have NSTE-ACS based on the history, ECG and cardiac biomarkers.

Period of Validity of the Guidelines:

This guideline needs to be revised at least every 5 years or sooner if significant changes have occurred, or new data is available that would influence the recommendations made.

Applicability of the Guidelines:

This Guidelines was developed taking into account our local healthcare resources. The following are available at all specialist government hospitals.

- ECG machines, measurement of cardiac biomarkers (including troponins), treadmill stress ECG's and echocardiograms.
- We have recommended that all specialist hospitals have facilities to measure cardiac troponins (preferably high sensitivity cardiac troponins). This should preferably be lab-based (depending on volume) or at least point of care (POC) kits. Cardiac troponins should replace the measurement of "cardiac enzymes"- lactate dehydrogenase, transaminases and creatine kinase.
- Most of the medications that are recommended in this Guidelines are already present in the Malaysian standard drug formulary.
- Very high risk/high risk patients should be identified early and transferred to hospitals with existing catheterization facilities. In accordance with the national health plan, the ministry has already proposed the setting up of catheterization laboratories in most of the state hospitals.

This Guidelines aims to streamline management of cardiac patients and educate healthcare professional on strategies to optimize existing resources. We do not anticipate barriers to its implementation.

Implementation of the Guidelines:

The implementation of the recommendations of a CPG is part of good clinical governance. To ensure successful implementation of this CPG we suggest:

- Increasing public awareness of CAD and its therapies.
- Continuing medical education and training of healthcare providers.
- Clinical audit - This is done by monitoring:
  - In - hospital mortality and morbidity in patients admitted with NSTE-ACS (NCVD-ACS registry)
  - Readmission rates for a cardiac related event in patients discharged with a diagnosis of NSTE-ACS. Elective admissions for cardiac procedures are excluded.
  - Documentation of the following;
    - In patients suspected of ACS, measurement and documentation of the Heart Score of the individual at ED.
    - Percentage of high-risk patients having their coronary angiogram performed < 48 hours when admitted to a PCI capable hospital.
    - In patients discharged with a diagnosis of NSTE-ACS,
      - Medications at discharge:
        - Aspirin
        - P2Y12 inhibitor
        - high intensity statins
      - Referral to a cardiac rehabilitation program

Dr Jeyamalar
Chairperson

Table 1: Levels of evidence and grades of recommendation

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
	II-a : Weight of evidence/opinion is in favour of its usefulness/efficacy.
	II-b : Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

LEVELS OF EVIDENCE	
A	Data derived from multiple randomised clinical trials or meta-analyses.
B	Data derived from a single randomised clinical trial or large non-randomised studies.
C	Only consensus of opinions of experts, case studies or standard of care.

Adapted from the

- *American College of Cardiology Foundation / American Heart Association and the European Society of Cardiology American College of Cardiology Foundation and American Heart Association (2010) Methodology manual and policies from the ACCF/AHA Task Force on Practice Guidelines. Available: http:// professional.heart.org/-/media/phd-files/guidelines-and-statements/methodology_manual_and_policies_ucm_319826.pdf.*
- *European Society of Cardiology: Governing Policies and Procedures for the Writing of ESC Clinical Practice Guidelines. Available at https://www.escardio.org/static-file/Escardio/Guilines/About/Recommendation-Guidelines-Production.pdf.*

LIST OF ABBREVIATIONS

Abbreviation	Description
ABC	Airway, Breathing, Circulation
ABCD	Airway, Breathing, Circulation and Defibrillation
ACC	American College of Cardiology
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ACT	Activated Clotting Time
ADP	Adenosine diphosphate
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
APTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AV	Atrio-Ventricular
BBB	Bundle Branch Block
Bd	Bis Die (Twice Daily)
BiPaP	Bi-Level Positive Airway Pressure
BMS	Bare Metal Stents
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCU	Cardiac Care Unit
CHD	Coronary Heart Disease
CIN	Contrast Induced Nephropathy
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine Kinase-Myocardial Band
CPG	Clinical Practice Guidelines

Abbreviation	Description
CPR	Cardiopulmonary Resuscitation
CrCL	Creatinine Clearance
CRP	Cardiac Rehabilitation Programme
cTn	Cardiac Troponins
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CoV	Coefficient of Variation
CVD	Cardiovascular Disease
CPAP	Continuous Positive Airway Pressure
D5W	5% Dextrose in Water
DAPT	Dual Antiplatelet Therapy
DBT	Door to Balloon Time
DES	Drug Eluting Stents
DM	Diabetes Mellitus
DNT	Door to Needle Time
DOAC	Direct Oral Anticoagulants
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
FMC	First Medical Contact
GFR	Glomerular Filtration Rate
Gp	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
GTN	Glyceryl Trinitrate
HF	Heart Failure
HRT	Hormone Replacement Therapy
Hs-cTn	High-Sensitivity Cardiac Troponins

Abbreviation	Description
HTA	Health Technology Assessment
IABP	Intra-Aortic Balloon Pump
IC	Intracoronary
ICD	Implantable Cardioverter-Defibrillator
INR	International Normalised Ratio
IO	Intraosseous
IRA	Infarct-Related Artery
IV	Intravenous
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
LMWH	Low Molecular Weight Heparin
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MACE	Major Adverse Cardiovascular Events
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
MOH	Ministry of Health Malaysia
MRI	Magnetic Resonance Imaging
MSCT	Multi-Slice Computed Tomography
NaCl	Sodium Chloride
NaHCO3	Sodium Bicarbonate
NCVD	National Cardiovascular Disease Database
NHAM	National Heart Association Malaysia
NSAID	Non-steroidal Anti-Inflammatory Drug
NSTEMI	Non ST Segment Elevation Myocardial Infarction
OAC	Oral Anticoagulants

Abbreviation	Description
Od	Once daily
PCI	Percutaneous Coronary Interventions
PCWP	Pulmonary Capillary Wedge Pressure
PEA	Pulseless Electrical Activity
PHC	Pre Hospital Care
RBBB	Right Bundle Branch Block
ROSC	Return of Spontaneous Circulation
r-TPA	Recombinant Tissue Plasminogen Activator
RV	Right Ventricular
RVI	Right Ventricular Infarction
SBP	Systolic Blood Pressure
SC	Subcutaneous
Scr	Serum Creatinine
SpO_2	Pulse Oximeter Oxygen Saturation
STEMI	ST Segment Elevation Myocardial Infarction
Tds	Ter Die Sumendus (Three Times Per Day)
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TMP	TIMI Myocardial Perfusion Grade
TNK-tPA	Tenecteplase
TVR	Target Vessel Revascularization
UFH	Unfractionated Heparin
ULRR	Upper Limit Reference Range
URL	Upper Reference Limits
VF	Ventricular Fibrillation
VPC	Ventricular Premature Contractions
VSD	Ventricular Septal Defect
VT	Ventricular Tachycardia

WHAT'S NEW IN THE CURRENT GUIDELINES

	Previous CPG UA/NSTEMI 2011	Current CPG NSTE-ACS 2021
Use of the term NSTE-ACS	Referred to as unstable angina (UA) and Non ST Elevation Myocardial Infarction (NSTEMI)	NSTE-ACS is a combination of • Unstable Angina (UA) ***and*** • Non ST Elevation MI (NSTEMI)
Definition of Infarction (MI) Myocardial		In accordance with the 4th Universal Definition (Section 2, pages 44 - 47)
Distinguishing the difference between myocardial injury and Myocardial Infarction (MI) - Recognition that all myocardial injury is not necessarily due to MI	No clear differentiation between myocardial injury and MI	Myocardial injury is reflected by a level above the 99th percentile upper reference limit (URL) of troponin. Myocardial injury may be due to: • Ischemia • Non-ischemic causes MI is myocardial injury due to ischemia. NSTE- ACS is MI without ST elevation seen on the resting ECG.
Pre-hospital Care/personnel	Brief statement about Pre-hospital Care/personnel	• Providing a structured format of response to an emergency call for "chest pain." • Ambulance responders should be trained and equipped to perform an ECG (with the use of Advanced Cardiac Care Device which is capable of ECG recording,transmission, and real-time ECG monitoring and telemetry). • If the ECG shows STEMI or the patient with NSTE-ACS has ongoing/ recurrent chest pain, they should be considered for immediate transfer to a PCI-capable hospital. High-risk unstable patients should be taken to the nearest hospital for stabilization first.

	Previous CPG UA/NSTEMI 2011	Current CPG NSTE-ACS 2020
Use of cardiac troponins (cTn), preferably High Sensitivity cardiac troponins hs-cTn	No mention of hs-cTn	• Recommendation for using cTn, preferably hs-cTn as the cardiac biomarker of choice in patients suspected to be having an ACS. • Guide on how to interpret elevated cardiac troponin levels. (Table 2, page 38 & Appendix II, page 94) • MI is defined as a rise and fall in cTn levels ***and*** with either clinical history of ischemic pain, ECG or \ echocardiographic features consistent with MI or in the presence of an intracoronary thrombus.
Risk Scores	No mention of "rule out ACS" processes in patients suspected of having ACS.	• In patients suspected of having an ACS, use of "rule-out ACS" Flowchart 1, page 35 in the ED in combination with the HEART score (or modified HEART score.) • In patients with definite NSTE-ACS, importance of risk stratification using either clinical features, (Table 3, page 39) TIMI or GRACE scores. (Appendix IV & V, pages 96 & 97) • In patients with definite NSTE-ACS, advocating the use of the PRECISE-DAPT score to assess bleeding risk. (Appendix VI, page 98)
Invasive strategy-Timing of intervention	• Patients with refractoryangina and/ or hemodynamic instability should be considered for urgent coronary angiography and revascularization • Intermediate/high risk patients should be considered for early Invasive strategy (<72 hours).	• Patients with definite NSTE-ACS who after risk stratification are at: ➢ Very high-risk should undergo an immediate invasive strategy (<2 h). ➢ High risk should be recommended for an early invasive strategy (<24 h). ➢ Intermediate risk - also recommended to undergo an invasive strategy but this may be delayed for a maximum of 72 h window period from admission to coronary angiography.

SUMMARY

Epidemiology:

- Ischaemic heart disease (IHD) remains the principal cause of death in Malaysia.
- The Malaysian NCVD-ACS registry 2016-2017 showed that our local in-hospital, 30-day and 1-year mortality remain high despite being on a downward trend. Our figures are higher than those in other international registries. (Table 4, page 39)

Definition:

- Acute Coronary Syndrome (ACS) is a clinical spectrum of IHD that develops because of an acute imbalance between myocardial oxygen demand and supply.
- Depending upon the acuteness of onset and the degree of coronary occlusion, it can range from (Flowchart 3, page 37) :
  - Non-ST Elevation Acute Coronary Syndrome **(NSTE-ACS)**. This is a combination of:
    - Unstable angina (UA) ***and***
    - Non-ST elevation myocardial infarction (NSTEMI)
  - ST elevation myocardial infarction **(STEMI)**
- In UA, myocardial injury is absent and cardiac biomarkers (troponins-cTn) are normal.
- Myocardial injury results in cell necrosis and cardiac biomarkers are raised. It may be due to severe ischemia and/or non ischemic causes (eg myocarditis).
- Myocardial Infarction **(MI)** is myocardial injury due to ischemia.
- According to the 4th Universal definition, MI is diagnosed when there is a significant rise and/or fall in cTn, with at least one value above the 99th percentile upper reference limit (URL), and accompanied with **at least one** of the following:
  - Clinical history consistent with chest pain of ischaemic origin of > 30 minutes.
  - ECG changes of ischemia/infarction and/or the development of pathological Q waves.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary (IC) thrombus by angiography or autopsy.
- There are no clear guidelines as to “significant rise and fall” of cTn levels. An expert consensus committee has suggested that changes in cTn concentrations of >20% should be used to define patients with an MI.
- **MI** may be **STEMI** or **NSTE-ACS** based on the ECG.

Pathogenesis:

- MI can be classified as 5 types depending on the pathology, clinical features, prognosis and treatment strategies. (Table 6, page 41) This CPG focuses on NSTE-ACS which is usually either:
  - Type 1 MI (spontaneous MI related to atherosclerotic plaque rupture, with ulceration, fissuring, erosion or dissection) or

- Type 2 MI (often due to an imbalance between myocardial oxygen supply and/or demand. It may occur in the presence of coronary atherosclerosis without plaque rupture or in the absence of atherosclerosis). This is an important cause of ACS in the elderly.

- The majority (66%-78%) of ACS arise from lesions with <50% stenosis and less than 5% arise from lesions exhibiting >70% stenosis.

Diagnosis:

- The combinations of history, physical examination and electrocardiogram (ECG) are important but may be insufficient to reliably rule in or rule out NSTE-ACS.
- Cardiac troponins (cTn) T and I are the most sensitive and specific biomarkers for myocardial injury and necrosis.
- Troponins are raised due to myocardial injury and this may be acute (associated with a rise and fall) or chronic. There are other causes of a raised cTn besides MI. (Table 2, page 38 & Appendix II, page 94).
- For a diagnosis of MI, the rise and fall of cTn should be accompanied by either a clinical history consistent with MI or with ECG or echocardiographic changes consistent with an MI or an intracoronary thrombus. (Section 2, pages 44 - 47)
- The cTn assays could be point of care (POC) kits or laboratory based. In general, POC kits have lower analytical sensitivity and too wide coefficient of variation (CoV) to detect troponins at the 99th URL. Almost all locally available laboratory-based assays can measure cTn at the 99th URL.

Triage/Risk Scores:

- Patients presenting with chest pain or chest pain equivalents may, based on the initial clinical history and ECG, have:
  - ***Very low likelihood of NSTE-ACS*** or have an alternative cause for their symptoms. These can be treated accordingly and be discharged from the Emergency Department (ED).
  - ***Definite NSTE-ACS or STEMI.*** These patients should be admitted and managed appropriately.
  - ***Possible or suspected NSTE-ACS.*** These patients have a normal or non- diagnostic ECG and need to be evaluated using a “rule out protocol” for ACS.
- Evaluation is a continuous process and it is possible for a patient to move from very low likelihood ACS to definite NSTE-ACS as the disease evolves.
- Patients with ***possible or suspected NSTE-ACS*** should be:
  - **Risk stratified using HEART (or modified HEART score) or TIMI risk scores** (Flowchart 1, page 35)

- Evaluated using the **"Rule out ACS"** (Flowchart 1, page 35). Following evaluation, these patients may be:
  - Discharged from ED and referred for an early outpatient cardiology (or in the absence of cardiology internal medicine) consult.
  - Admitted

- **Patients with definite NSTE-ACS should be risk stratified using either clinical features** (Table 3, page 39)**, TIMI or GRACE risk scores** (Appendix IV & V, pages 96 & 97).
  - This will help determine:
    - The prognosis of the patient
    - Management strategies
    - Selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting)
    - Selection of appropriate therapy and the need for coronary angiogram and revascularization
  - The risk of bleeding in a patient at high risk of bleeding should also be assessed using the PRECISE-DAPT score (Appendix VI, page 98).

Pre- Hospital Management:

- Public awareness about heart disease should be increased so that individuals will seek appropriate treatment early, thus reducing time from symptom onset to First Medical Contact.
- In patients suspected of having an ACS and not on regular aspirin and with no history of allergy, 300mg aspirin should be administered.
- Ambulance responders should be trained and equipped to perform an ECG.
- If the ECG shows STEMI or the patient with NSTE-ACS has ongoing/recurrent chest pain, they should be considered for immediate transfer to a PCI-capable hospital. High-risk unstable patients should be taken to the nearest hospital for stabilization first.

In-Hospital Management:

Emergency Department

- Patients with NSTE-ACS should be given:
  - Aspirin 300 mg stat (if not given earlier)
  - Oxygen if oxygen sat < 95%
  - Glyceryl Trinitrate (GTN - as a tablet, spray or intravenous infusion) for ongoing or recurrent chest pains
  - Intravenous (i.v. morphine with i.v. anti-emetics or i.v. fentanyl) for severe chest pains
  - Heparin (i.v. infusion unfractionated or subcutaneous (s.c.) low molecular weight (LMWH)) or s.c.fondaparinux

- In the presence of ongoing chest pains and/or hemodynamic instability, urgent coronary angiography with view to revascularization should be considered if facilities are available.
- In patients with recurrent/ongoing chest pain not due to ACS, appropriate investi gations need to be performed to exclude other diagnosis.

Pharmacotherapy

- Patients with NSTE-ACS should be on DAPT.
  - ➢ Aspirin should be given at the time of diagnosis.
  - ➢ The timing of the second antiplatelet agent will depend on the agent used. No firm recommendations can be made about pre-treatment.
    - Clopidogrel and ticagrelor, in general, can be administered early.
    - Prasugrel should be given after the coronary angiogram before proceeding to PCI.
  - ➢ Duration of DAPT will depend on the risk of bleeding versus the thrombotic risk. Ideally all patients should be given for 1 year but patients with high bleeding risk can be given DAPT for a shorter period of 3-6 months.
- Patients with NSTE-ACS treated medically (without an invasive strategy) should be on s.c. LMWH or s.c. fondaparinux for 2-8 days or until hospital discharge.
- High dose statins should be initiated soon after diagnosis.
- In patients who have angina/ischemia, β-blockers and/or CCBs should be prescribed as first-line treatment.
- Long-acting nitrates, trimetazidime and ranolazine are recommended as add-on therapy in patients who remain symptomatic. Ivabradine may also be considered for in patients with normal sinus rhythm, especially in those who have a contrain dication to or intolerance to β-blockers and if the resting HR is above 70/min.

Revascularization

- The selection of the optimal timing of invasive coronary angiography and revascu larization should be guided by the individual's risk for a MACE.
- Risk stratification can be done using clinical features (Table 3, page 39),TIMI or GRACE scores (Appendix IV & V, pages 96 & 97).
- Patients at:
  - ➢ very high-risk should undergo an immediate invasive strategy (<2 h).
  - ➢ high risk should be recommended for an early invasive strategy (<24 h).
  - ➢ intermediate risk - also recommended to undergo an invasive strategy but this may be delayed for a maximum of 72 h window period from admission to coronary angiography.
- Low risk patients should be assessed non-invasively for ischemia. (Flowchart 2, page 36). If symptoms and/or myocardial ischemia are present, they should be considered for an invasive coronary angiogram with view to revascularization.
- Wherever possible, complete revascularization should be performed either at the initial setting or as a staged procedure.

Discharge Medications:

- Patients should be on optimal medical therapy at discharge. This includes:
  - DAPT with aspirin + clopidogrel (or ticagrelor or prasugrel).
  - ***And*** High intensity statins to achieve LDL-C target of < 1.8 mmol/l (preferably < 1.4 mmol/l) or > 50% lower than baseline, whichever results in a lower level.
  - ***And*** in the presence of angina /myocardial ischemia, β-blockers and/or CCBs should be prescribed as first-line treatment and ivabradine, trimetazidine, long-acting nitrates and ranolazine are recommended as add-on therapy in patients who remain symptomatic.
  - ***And*** in the presence of LVEF< 40% and heart failure, β-blockers, Renin Angiotensin Blockers (ACEIs/ARBs) and Aldosterone Receptor Antagonists-spironolactone, eplerenone - should be given. SGLT2-inhibitors can be instituted in both stable diabetic and non-diabetic patients.

NSTE-ACS in Special Groups:

- Older persons:
  - When managing older patients, one should consider the biological age rather than the chronological age. (Section 8.1, pages 80 - 82)
  - The older patient has greater in-hospital and long-term benefits with an early invasive strategy. However, there is an increased risk of major bleeding.
- Women
  - In general, women develop Ischemic Heart Disease (IHD) about a decade later than men. Premenopausal women should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention.
  - Women who are low risk and cTn negative, should be treated medically.
  - Women who are cTn positive, should be considered for an invasive strategy.
- Chronic Kidney Disease (CKD)
  - In general, patients with CKD should be managed in a similar manner as those with normal renal function.
  - They, however, have a higher bleeding tendency and doses of medications need to be adjusted according to the renal function.
  - An invasive strategy is superior to a conservative strategy.The benefit, however, declines with lower renal function, and is less certain in those with renal failure or on dialysis.

Cardiac Rehabilitation:

- Cardiac rehabilitation has been shown to reduce mortality by approximately 20% - 25% and a trend towards reduction in non-fatal recurrent MI.

KEY MESSAGES

Key Messages 1#:

- IHD remains the principal cause of death in Malaysia.
- Our local in-hospital, 30-day and 1-year mortality is higher than those in other international registries. (Table 4, page 39)

Key Messages 2#:

- ACS is a clinical spectrum of IHD.
- Depending upon the acuteness of onset and degree of coronary occlusion, it can range from (Flowchart 3, page 37):
  - Non-ST Elevation Acute Coronary Syndrome **(NSTE-ACS)**. This is a combination of:
    - Unstable angina (UA) ***and***
    - Non-ST elevation myocardial infarction **(NSTEMI)**
  - ST elevation myocardial infarction **(STEMI)**

Key Messages 3#:

- According to the 4th Universal definition, **MI** is diagnosed when there is a significant rise and/or fall in cTn, with **at least one** value above the 99th percentile upper reference limit (URL), and accompanied with at least one of the following:
  - Clinical history consistent with chest pain of ischaemic origin of > 30 minutes.
  - ECG changes of ischemia/infarction and/or the development of pathological Q waves.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary (IC) thrombus by angiography or autopsy.
- **MI** may be **STEMI** or **NSTE-ACS** based on the ECG.

Key Messages 4#:

- MI can be classified as 5 types depending on the pathology, clinical features, prognosis and treatment strategies. (Table 6, page 41). This CPG focuses on **NSTE-ACS** which is usually either:
  - Type 1 MI (spontaneous MI related to atherosclerotic plaque rupture, with ulceration, fissuring, erosion or dissection) or
  - Type 2 MI (often due to an imbalance between myocardial oxygen supply and/or demand. It may occur in the presence of coronary atherosclerosis without plaque rupture or in the absence of atherosclerosis). This is an important cause of ACS in the older patient.
- The majority (66%-78%) of ACS arise from lesions with <50% stenosis and less than 5% arise from lesions exhibiting >70% stenosis.

Key Messages 5#:

- The combination of history, physical examination and electrocardiogram are important but may be insufficient to reliably rule in or rule out **NSTE-ACS**.
- Cardiac troponins T and I (cTn) are the most sensitive and specific biomarkers for myocardial injury and necrosis.
- Elevations of cTn should be correlated with the clinical condition of the patient and the ECG. (See definition of MI in Key Message 3#)

Key Messages 6#:

- Patients presenting with chest pain or chest pain equivalents, may, based on the clinical history and ECG, have:
  - **Very low likelihood of NSTE-ACS** or have an alternative cause for their symptoms. These can be treated accordingly and be discharged from ED.
  - **Definite NSTE-ACS or STEMI**. These patients should be admitted and managed as for STEMI or as for NSTE-ACS.
  - **Possible or suspected NSTE-ACS**. These patients have normal or non-diagnostic ECGs. They need to be evaluated using a “rule out protocol” for ACS. (Flowchart 1, page 35)
- Evaluation is a continuous process and it is possible for a patient to move from very low likelihood to definite NSTE-ACS

Key Messages 7#:

- Patients with NSTE-ACS should be on DAPT.
- Patients with NSTE-ACS treated medically (without an invasive strategy) should be on s.c. LMWH or s.c. fondaparinux for 2-8 days or until hospital discharge.
- High dose statins should be initiated soon after diagnosis.
- In patients who have angina/ischemia, β-blockers and/or CCBs should be prescribed as first-line treatment to reduce angina because it is widely available.
- Long-acting nitrates, trimetazidime and ranolazine are recommended as add-on therapy in patients who remain symptomatic. Ivabradine may also be considered for in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to β-blockers and if the resting HR is above 70/min.

Key Messages 8#:

- An early as opposed to a delayed invasive strategy is safe and associated with a lower risk of refractory ischemia and a shorter duration of hospital stay.
- All patients should receive optimal medical therapy-consisting of DAPT, statins and where necessary, anti-ischemic agents.

Key Messages 9#:

- When managing the older patient, one should consider the biological age rather than the chronological age.
- Older persons have greater in-hospital and long-term benefits with an early invasive strategy. However, there is an increased risk of major bleeding.
- Women should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention.
- Women who are low risk and cTn negative, should be treated medically. Women who are cTn positive, should be considered for an invasive strategy.
- In general, patients with CKD should be managed in a similar manner as those with normal renal function. They however have a higher bleeding tendency and doses of medications need to be adjusted according to the renal function.

Key Messages 10#:

- All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either as in-patient or during the first outpatient visit where available.

KEY RECOMMENDATIONS

Key Recommendations 1:

- Wherever possible, an ECG should be performed within 10 minutes of the First Medical Contact (FMC).
- All ambulances, government and private clinics should be equipped with ECG-capable devices. These should have computer-generated interpretation and wherever possible, reviewed by trained personnel.

Key Recommendations 2:

- All hospitals providing care for patients with acute chest pain or suspected MI should have access to cTn (subtypes T or I) testing, preferably hs-cTn.
- Clinicians must be familiar with their local cTn assays-point of care (POC) kits or laboratory based, the 99th percentile URL and the lower limit of detection (LoD) of the assay used in their respective hospitals.
- The value of cTn should be stated and not labelled as positive or negative.

Key Recommendations 3:

- **Patients presenting with chest pain** and who, after **initial assessment**, have:
  - **Definite NSTE-ACS or STEMI** should be admitted and managed accordingly.
  - **Very low likelihood of NSTE-ACS** or having an alternative cause for their symptoms should be treated accordingly and be discharged from ED.
  - **Suspected ACS** should:
    - Have the **cTn, preferably hs-cTn measured**.
    - Be **risk stratified using the HEART or TIMI risk scores and the "Rule out ACS" (Flowchart 1, page 35)**
- Using the **"Rule out ACS" (Flowchart 1, page 35)** patients who are suspected to be having ACS should be:
  - Discharged from ED and referred for an early outpatient cardiology (or in the absence of cardiology-internal medicine) consult.
  - Admitted for definitive management of NSTE-ACS.

Key Recommendations 4:

- Patients with definite NSTE-ACS should be risk stratified using clinical features (Table 3, page 39), TIMI or GRACE risk score (Appendix IV & V, pages 96 & 97). This will help determine:
  - Prognosis of the patient
  - Management strategies
  - Selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting)
  - Selection of appropriate therapy and the need for coronary angiogram and revascularization
- Their bleeding risk should also be assessed preferably with the PRECISE-DAPT score. (Appendix VI, page 98)

Key Recommendations 5:

- Public awareness about heart disease should be increased so that individuals will seek appropriate treatment early, thus reducing time from symptom onset to FMC.
- In persons with suspected NSTE-ACS, 300mg aspirin should be administered if not on regular aspirin and with no history of allergy. Soluble and chewable aspirin formulations are preferable to solid aspirin either chewed or swallowed.

Key Recommendations 6:

- Ambulance responders should be trained and equipped to perform an ECG.
- If the ECG shows STEMI or the patient with NSTE-ACS has ongoing/ recurrent chest pain, they should be considered for immediate transfer to a PCI-capable hospital.
- High-risk unstable patients should be taken to the nearest hospital for stabili zation first.

Key Recommendations 7:

- Patients with NSTE-ACS should be given:
  - Aspirin 300 mg stat (if not given earlier).
  - Oxygen if oxygen sat < 95%.
  - GTN for ongoing or recurrent chest pains.
  - i.v. morphine with i.v. anti-emetics or fentanyl for ongoing chest pains.
  - s.c. LMWH or s.c. fondaparinux.
- In the presence of ongoing chest pains and/or hemodynamic instability, urgent coronary angiography with view to revascularization should be considered.
- In patients with recurrent/ongoing chest pain not due to ACS, other important clinical conditions should also be considered.

Key Recommendations 8:

- Patients with NSTE-ACS should be on DAPT.
  - Aspirin should be given at the time of diagnosis.
  - The timing of the second antiplatelet agent will depend on the agent used. No firm recommendations can be made about pre-treatment.
    - Clopidogrel and ticagrelor, in general, can be administered early
    - Prasugrel should be given after the coronary angiogram before proceeding to PCI.
  - Duration of DAPT will depend on the risk of bleeding versus the thrombotic risk. Ideally all patients should be given for 1 year but patients with high bleeding risk can be given DAPT for a shorter period of 3-6 months.
- Patients with NSTE-ACS treated medically (without an invasive strategy) should be on s.c. LMWH or s.c. fondaparinux for 2-8 days or until hospital discharge

Key Recommendations 9:

- High dose statins should be initiated soon after diagnosis.
- In patients who have angina/ischemia, β-blockers and/or non-dihydropyridine CCBs should be prescribed as first-line treatment to reduce angina because it is widely available.
- Long-acting nitrates, trimetazidime and ranolazine are recommended as add-on therapy in patients who remain symptomatic. Ivabradine may also be considered for in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to β-blockers and if the resting HR is above 70/min.

Key Recommendations 10:

- The selection of the optimal timing of invasive coronary angiography and revascularization should be guided by the individual's risk for a MACE.
- Risk stratification can be done by using clinical criteria, (Table 3, page 39) TIMI score or GRACE score (Appendix IV & V, pages 96 & 97)
- Patients at:
  - Very high risk should undergo an immediate invasive strategy (<2 h).
  - High risk should be recommended for an early invasive strategy (<24 h).
  - Intermediate risk should also be recommended to undergo an invasive strategy but this may be delayed for a maximum of 72 h window period from admission to coronary angiography.
  - Low risk should be assessed non-invasively for ischemia.

Key Recommendations 11:

- All patients with NSTE-ACS should be on optimal medical therapy at discharge. This includes:
  - DAPT with aspirin + clopidogrel (or ticagrelor or prasugrel)
  - ***AND*** High intensity statins to achieve LDL-C target of < 1.8 mmol/l (preferably < 1.4 mmol/l) or a 50% reduction in LDL-C levels from baseline, the lower the level achieved, the better.
  - ***AND*** if angina /myocardial ischemia is present, β-blockers and/or CCBs should be prescribed as first-line treatment and ivabradine, trimetazidine, long-acting nitrates and ranolazine are recommended as add-on therapy in patients who remain symptomatic.
  - ***AND*** if the LVEF< 40% and heart failure, β-blockers, Renin Angiotensin Blockers (ACEIs/ARBs) and Aldosterone Receptor Antagonists- spironolactone, eplerenone should be given. SGLT2-inhibitors can be instituted in both stable diabetic and non-diabetic patients.

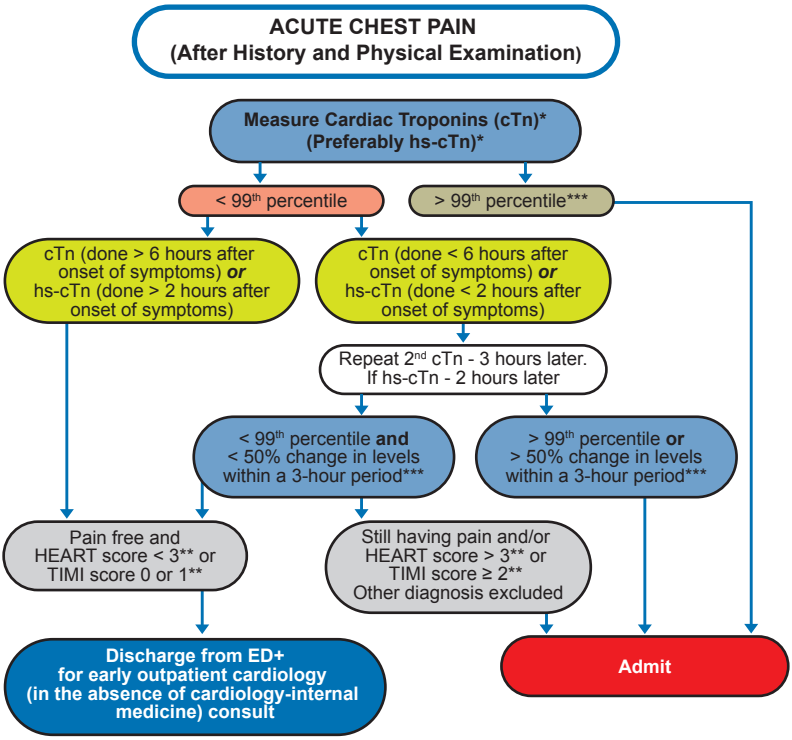
Key Recommendations 12:

- Low risk patients should be assessed non-invasively for ischemia. (Flowchart 2, page 36) If they have troubling symptoms and/or significant myocardial ischemia, they should be referred for coronary angiography with view to revascularization.

Key Recommendations 13:

- Audit of performance measures (Table 7, page 42) and outcome measures should be performed regularly to monitor and improve quality of care.

FLOWCHART 1: "Rule out" Protocol for patients suspected to have ACS using cardiac troponin (preferably hs-cTn) and 0/3 hour# protocol[10,14-16]

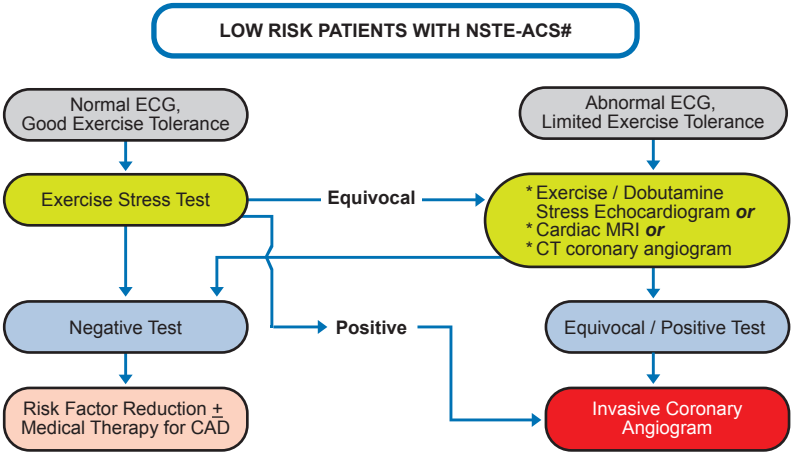


 # 0/3 refers to time from first blood test
**Correlate the result with the clinical condition of the patient (Table 2, page 38)*
***If cTn use HEART score for scoring and for hs-cTn use modified HEART score or TIMI score*
****If initial baseline cTn (or hs-cTn) is markedly > 99th percentile, a change of >20% is significant. If the baseline is < or around the 99th percentile URL, a change of at least 50% is required to be significant.*

+Discharge Care Plan after "Rule out ACS"

- Keep scheduled appointment for further cardiac assessment.
- Should chest pain/discomfort recur before your appointment, please go the nearest hospital.

FLOWCHART 2: Non-invasive investigation of Low Risk Patients with NSTE-ACS*



** The choice of investigation will depend on the available resources and expertise.*

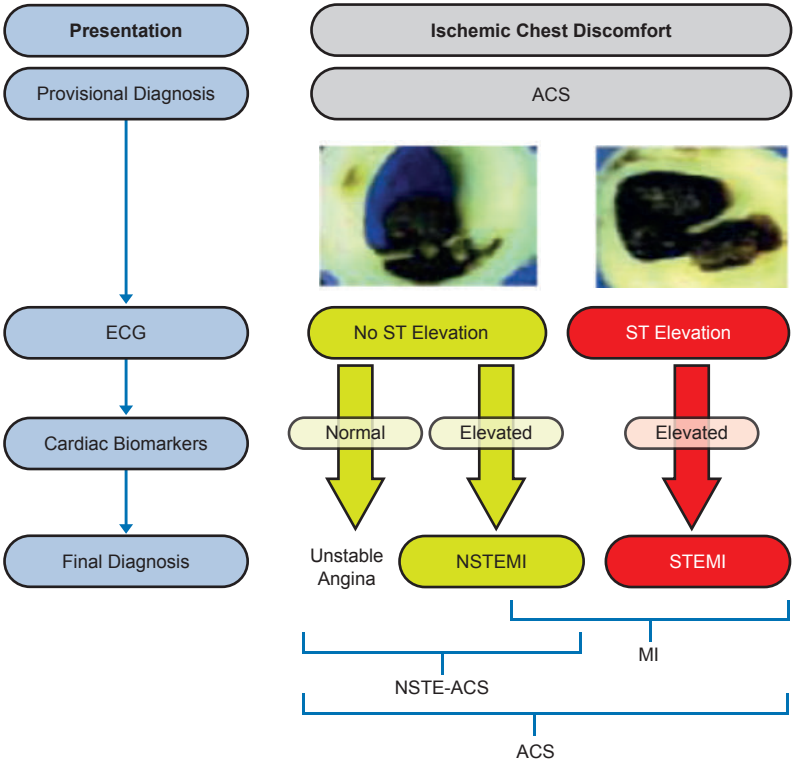
 # Low risk patients have:

- *no angina in the past*
- *no ongoing angina*
- *no prior use of antianginal therapy*
- *normal ECG*
- *normal cardiac biomarkers*
- *younger age group*
- *normal LV function*

Patients who have undergone revascularization and with residual/recurrent ischemia or a change in symptoms should be investigated as above.

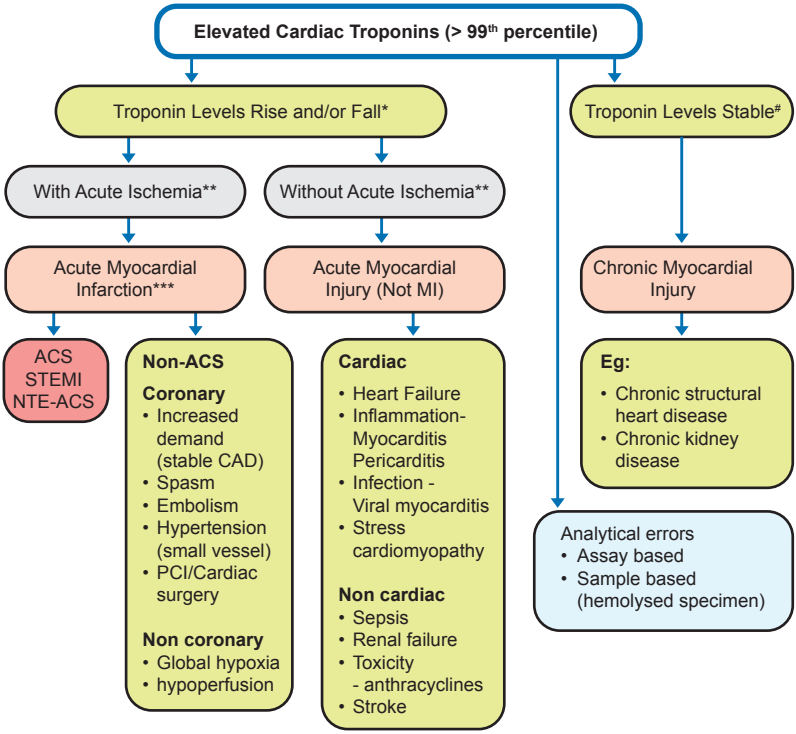
All Intermediate/High Risk NSTE-ACS patients should be considered for coronary angiography and revascularization.

FLOW CHART 3: Pathogenesis of ACS



Adapted from Amsterdam EA, Wenger N, Brindis RG et al. "2014 ACC/AHA Guidelines for the management of patients with Non ST Elevation Acute Coronary Syndromes" Circulation. 2014;130:e344-e426.

Table 2: Interpreting Cardiac Troponins



* A repeat cTn may be necessary depending on the clinical condition of the patient and the physician's judgement.

** Ischemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease.

*** Requires a rise and/or fall of troponins above the 99th percentile URL together with evidence of ischemia with at least one of the following:

1) Ischemic type chest pain of >30 mins ***or,***
2) electrocardiography (ECG) changes of new ischemia ***or,***
3) development of pathologic Q-waves in the ECG ***or***
4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Stable denotes ≤20% variation of troponin values in the appropriate clinical context.

Adapted from:

- *Thygesen K et al. Fourth universal definition of myocardial infarction. Eur Heart J 2019; 40 (3): 237-269*
- *Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2012; 60(23):2427-2463*

Table 3: Risk stratification for NSTE-ACS

Very-High-Risk Criteria
- Haemodynamic instability or cardiogenic shock
- Recurrent or ongoing chest pain refractory to medical treatment
- Recurrent dynamic ST-T wave changes +/- intermittent ST-elevation
- Life-threatening arrhythmias or cardiac arrest
- Acute heart failure
- Mechanical complications of MI

High-Risk Criteria
- Rise or fall in cardiac troponin compatible with MI
- Dynamic ST- or T-wave changes (symptomatic or silent)
- GRACE score >140
- TIMI risk score >4

Intermediate-Risk Criteria
- Diabetes mellitus
- LVEF <40% or congestive heart failure
- Early post-infarction angina
- Prior revascularization (PCI/CABG)
- GRACE risk score >109 and <140
- TIMI risk score 3 & 4

Low-Risk Criteria
- Any characteristics not mentioned above

Table 4: In hospital, 30-day and 1-year mortalities in the NCVD 2014-2015, NCVD 2016-2017, GRACE, CZECH-2 AND FAST MI Registries

	NCVD 2014-2015[3]		NCVD 2016-2017[2]		GRACE[4]	CZECH-2[5]	FAST MI[6]
	UA	NSTEMI	UA	NSTEMI	NSTEMI	NSTEMI	NSTEMI
In hospital mortality	1.6%	8.0%	1.0%	7.5%	2.9%	4.1%	1.9%
30day mortality	2.8%	10.9%	2.2%	11.5%		4.7%	
1 year mortality	10.6%	23.9%	9.6%	23.6%			

Table 5: Level of evidence and grade of recommendation for Pharmacotherapy in NSTE-ACS

INTERVENTION	GRADE OF RECOMMENDATION	LEVEL OF EVIDENCE	COMMENTS
CONCOMITANT PHARMACOTHERAPY			
Aspirin	I	A	Maintenance dose : 75-150 mg daily.
+ Clopidogrel ***OR***	I	A	Maintenance dose 75 mg daily to be given as part of DAPT for at least 1 year.
+Ticagrelor ***OR***	I	B	Maintenance dose 90 mg twice daily to be given as part of DAPT for at least 1 year.
+ Prasugrel	I	B	Maintenance dose 10 mg daily to be given as part of DAPT for at least 1 year.
+High intensity statins	I	A	Aim for low density lipoprotein-cholesterol (LDL-C) <1.8 mmol/L), the lower the better.
+ UFH ***OR***	I	A	In medically treated patients, given for 2-8 days or till hospital discharge.
s.c. LMWH ***OR***	I	A	In medically treated patients, given for 2-8 days or till hospital discharge.
s.c. Fondaparinux ***OR***	I	A	In medically treated patients, given for 2-8 days or till hospital discharge.
+ β-blockers	I	A	Consider long-term therapy (> 1 year) for patients with LVEF ≤40%.
	IIb	B	Routine administration (> 1 year) in all patients post NSTE-ACS with no angina / ischemia and normal LV function.
+ ACE-Is	I	A	Started on first day and continued long-term (>1 year) for patients with LVEF ≤40%, anterior infarcts and diabetes.
	IIb	B	Routine administration in all patients post NSTE-ACS > 1 year.
ARBs	I	B	Started on first day and continued long-term (>1 year) for patients with LVEF ≤40%, anterior infarcts and diabetes.
	IIb	B	Routine administration in all patients post NSTE-ACS > 1 year.
Nitrates, CCB, Ivabradine, ranolazine, trimetazidime	IIa	B	Indicated for residual/recurrent ischemia.

Table 6: Clinical Classification of MI

Type 1: Spontaneous MI due to coronary athero-thrombosis
Spontaneous MI related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.

Type 2: MI secondary to an imbalance between myocardial oxygen demand and supply unrelated to acute coronary athero-thrombosis
MI that occurs due to an imbalance between myocardial oxygen supply and/or demand. It may occur in the presence of coronary atherosclerosis without plaque rupture or in the absence of atherosclerosis e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, coronary artery dissection, tachy/bradyarrhythmias, anemia, respiratory failure, sepsis, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).

Type 3: MI resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemic and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: MI related to PCI
MI associated with PCI is arbitrarily defined by elevation of cardiac troponin (cTn) values 5 x > 99th percentile URL in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated but are stable or falling. In addition, either

(i) symptoms suggestive of myocardial ischemia, or
(ii) new ischemic ECG changes or new LBBB, or
(iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow-or no-flow or embolization, or
(iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: MI related to stent thrombosis
MI associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: MI related to coronary artery bypass surgery (CABG)
MI associated with CABG is arbitrarily defined by elevation of cardiac biomarker values 10 x 99th percentile URL in patients with normal baseline cTn values (99th percentile URL). In addition, either

(i) new pathological Q waves or new LBBB, or
(ii) angiographic documented new graft or new native coronary artery occlusion, or
(iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Adapted from Thygesen K et al. Fourth universal definition of myocardial infarction. Eur Heart J 2019; 40 (3): 237-269

Table 7: Performance and Outcome Measures

PERFORMANCE MEASURES	
DOCUMENTATION OF THE FOLLOWING	**TARGETS**
Access to hs Troponin Testing in all EDs = $\frac{\text{Total number of EDs using hs-cTn}}{\text{Total number of EDs}}$ x 100%	50%
Measurement and Documentation of HEART Score at Emergency Department = $\frac{\text{Total number of patients with suspected ACS for which HEART score is documented}}{\text{Total Number of patients with suspected ACS seen in ED}}$ x 100%	70%
Percentage of High-Risk Patients Admitted to PCI Capable Hospitals and Undergoing Angiogram Within 48 hours = $\frac{\text{Total number of high-risk patients undergoing coronary angiogram within 48 hours}}{\text{Total Number of high-risk patients admitted}}$ x 100%	50%
Medications at Discharge: • Aspirin • P2 Y^{12} inhibitors • High intensity statins $\frac{\text{Total number of patients with NSTE-ACS who were discharged with aspirin (or P2 Y}^{12}\text{ inhibitors) or (high intensity statins)}}{\text{Total Number of patients with NSTE-ACS who were discharged}}$ x 100%	90% 90% 90%
Cardiac Rehabilitation = $\frac{\text{Total number of patients with NSTE-ACS who were referred for cardiac rehabilitation}}{\text{Total Number of patients with NSTE-ACS who were discharged}}$ x 100%	50%
OUTCOME MEASURES	
In-hospital mortality and morbidity in patients admitted with ACS (NCVD registry). Readmission rates for a cardiac related event in patients discharged with a diagnosis of ACS. Elective admissions for cardiac procedure are excluded.	

1. INTRODUCTION

Ischemic heart disease (IHD) remains the principal cause of death in Malaysia. In 2017, IHD was responsible for 13.9% of deaths, followed by pneumonia (12.7%) and cerebrovascular diseases (7.1%). It is the principal cause of death for all major ethnic groups being highest among Indians (19.5%),13.3% Bumiputera (12.3% Malays, others 1.01%), and 13.2% Chinese.[1]

Patients with IHD may present with stable coronary artery disease (CAD) - (now called - Chronic Coronary Syndromes) or acute coronary syndrome (ACS). ACS is a clinical spectrum from NSTE-ACS (combination of unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI)) to ST elevation myocardial infarction (STEMI).

From the Malaysian National Cardiovascular Disease Database Acute Coronary Syndrome (NCVD-ACS) Registry 2016-2017: [2]

- 44.6% of ACS patients were STEMI.
- 55.4% of ACS patients were NSTE-ACS (28.0% were NSTEMI and 27.4% were UA).

Patients with NSTE-ACS were older (60.5 vs 56.3 years), more likely females (27.2% vs 14.2%) and had more CVD risk factors (comorbidities) compared to those who presented with STEMI. [2]

Of those presenting with NSTE-ACS:[2]

- 42.2% were in the intermediate-high TIMI risk score
  - 35.1% were in the intermediate risk group - (TIMI 3 & 4)
  - 7.1% were in the high-risk group - (TIMI 5,6 & 7)
- The in-hospital mortality was 7.5%.

Compared to the previous registry data, our patients are now receiving more Guideline Directed Therapy (GDT). The use of DAPT and statins were more than 90%.[2] More patients underwent coronary angiography during the index admission and 35.9% of NSTEMI and 20.2% of patients with UA had percutaneous coronary intervention (PCI).[2]

The in-hospital, 30-day and 1-year mortality were:[2]

- 7.5%, 11.5% and 23.6% for NSTEMI respectively
- 1.0%, 2.2% and 9.6% for UA respectively.

These figures are slightly lower than that seen in the NCVD 2014-2015 but still higher than that of other registries.[3-6] (Table 4, page 39)

The Malaysian Clinical Practice Guidelines (CPGs) on Stable Coronary Artery Disease 2018, 2nd Ed and ST Elevation Myocardial Infarction 4th Ed, 2019 were recently updated.[7,8] The last CPG on UA/NSTEMI was published in 2011. Since then, there have been significant advances in the understanding of the pathophysiology and management. Thus, an update is timely to keep abreast with contemporary evidence.

Key Messages 1#:
- IHD remains the principal cause of death in Malaysia.
- Our NCVD-ACS registry shows that our in-hospital, 30-day and 1-year mortality is still high despite being lower than in previous years. Our figures are higher than those in other international registries. (Table 4, page 39)

2. DEFINITION OF TERMS

ACS is a clinical spectrum of IHD that develops because of an imbalance between myocardial oxygen demand and supply. It is usually due to a reduction in supply. Depending upon the acuteness of onset and the degree of coronary occlusion, it can range from: (Flowchart 3, page 37)

- Non-ST Elevation Acute Coronary Syndrome **(NSTE-ACS)**. This is a combination of:
  - Unstable angina (UA) ***and***
  - Non-ST elevation myocardial infarction (NSTEMI)
- ST elevation myocardial infarction **(STEMI)**

The pathology is dynamic. A patient presenting with UA may progress to NSTEMI or even STEMI.

2.1 Unstable Angina

Patients with UA are a heterogenous group. According to Braunwald's classification, updated in 2000, UA may be classified as (Appendix I, page 93)[9] :

I. New onset of severe angina or accelerated angina; no rest pain
II. Angina at rest, subacute - Angina at rest within past month but not within preceding 48 hours.
III. Angina at rest, acute - Angina at rest within 48 hours

It may be further classified according to clinical circumstances into either :

A) Secondary - develops in the presence of extracardiac disease
B) Primary - develops in the absence of extracardiac disease
C) Post-infarct - develops within 2 weeks of an acute MI

In UA, myocardial injury is absent and cardiac biomarkers (troponins-cTn) are normal. In myocardial injury, cardiac biomarkers are raised.

2.2 Myocardial Infarction

2.2.1 Definition of Myocardial Injury and Myocardial Infarction

It is important to distinguish between myocardial injury and Myocardial Infarction (MI). Myocardial injury may be due to:[10]

- Ischemia - MI and/or
- Non-ischaemic causes (eg. myocarditis, renal failure)

MI is myocardial injury due to ischemia and is defined pathologically as myocardial cell death due to prolonged ischemia.[10]

2.2.1.1 Cardiac Biomarkers in the Diagnosis of Myocardial Injury and Myocardial Infarction

The cardiac biomarkers of choice for the diagnosis are the cardiac troponins - cTn (both I and T), preferably high-sensitivity (hs-cTn). Elevation of cTn indicates myocardial necrosis. A level above the 99th percentile Upper Reference Limit (URL) is abnormal and indicative of myocardial injury.[10]

All locally available commercial laboratory-based assays indicate this level, the exact value varying depending on the reagents and assays used. The point of care (POC) kits, however, although giving a more rapid result, are not sensitive enough to detect this low level.

With the current definition, UA patients in Braunwald's Classification Stage III b, will be re-classified as NSTEMI. In one study, this re-classification increased the diagnosis of MI by 47%.[11] This re-classification is of prognostic importance because these patients will now be treated more aggressively with GDT.[12]

cTn should always be interpreted in the clinical setting. Many cTn elevations, especially below certain cut-off points and cTn elevations without a rise and fall, are myocardial injuries and not MI (Table 2, page 38 & Appendix II, page 94).

A rise and/or fall in the cTn level is indicative of acute injury, while a persistently elevated level is indicative of chronic injury[10] (Table 2, page 38). Persistently elevated cTn levels such as that present in those with pre-existing CAD, impaired renal function, and persons older than 75 years appear predictive of a higher long-term mortality.[13]

According to the 4th Universal definition, **MI** is diagnosed when there is a significant rise and/or fall in cTn, with at least one value above the 99th percentile URL, and accompanied with **at least one** of the following:[10]

- Clinical history consistent with chest pain of ischemic origin of > 30 minutes.
- ECG changes of ischemia/infarction and/or the development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Identification of an intracoronary (IC) thrombus by angiography or autopsy.

The exact value for the rise and fall is not addressed in most guidelines. The criteria for determining a pathological rise between two serial cTn values are assay-dependent.[10] The National Academy of Clinical Biochemistry Guidelines and an expert consensus committee have suggested that in patients with possible ACS and baseline (initial result) cTn (or hs-cTn) results:[10,14-16]

- Markedly above > 99th percentile URL, changes in concentrations of >20% from baseline should be used to define an MI.
- < 99th percentile URL and especially with hs-cTn assays, a change of 50-60% from baseline has been suggested to overcome biological and analytical variations.

The assays used should have a coefficient of variation (CoV) of < 10% at the 99th percentile URL.[10,14-16] (Section 4.4, pages 51-54).

2.2.1.2 ECG in the Diagnosis of Myocardial Injury and Myocardial Infarction

In myocardial injury, the ECG is either normal or showing non-specific changes and without the typical features of ischemia/infarction.

MI may be **STEMI** or **NSTE-ACS** based on the ECG. (Flowchart 3, page 37)

STEMI is diagnosed when there is:

- ST elevation of ≥ 1 mm in 2 contiguous leads including right precordial leads# ***or***
- A new onset LBBB in the resting ECG
- In a patient with ischemic type chest pains of > 30 minutes ***and***
- Accompanied by a rise and fall in cardiac biomarkers.

 # In leads V2-V3 the cut-off point is ≥ 0.25 mV in males < 40 years, ≥ 0.2 mV in males ≥ 40 years and ≥ 0.15 mV in females and in posterior chest leads V7-9 ≥ 0.05 mV and ≥ 0.1 mV in men < 40 years.[10]

In **NSTE-ACS**, ST elevation is absent on the resting ECG.

UA and NSTEMI differ from each other:

- In NSTEMI, the ischemia is severe enough to cause sufficient myocardial injury to release detectable cardiac biomarkers. The diagnosis of NSTEMI is established if a cardiac biomarker is detected. Often, there is a lapse of time from myocardial injury before these biomarkers can be detected. As such, in the early stages, UA and NSTEMI often cannot be differentiated.
- In NSTEMI, ST/T changes may be present in the ECG, whereas in UA they are usually absent and even if they are present, are usually transient.

Key Messages 2#:

- Acute Coronary Syndrome is a clinical spectrum of IHD that develops because of an imbalance between myocardial oxygen demand and supply.
- Depending upon the acuteness of onset and the degree of coronary occlusion, it can range from (Flowchart 3, page 37):
  - Non-ST Elevation Acute Coronary Syndrome **(NSTE-ACS)**. This is a combination of:
    - Unstable angina (UA) ***and***
    - Non-ST elevation myocardial infarction (NSTEMI)
  - ST elevation myocardial infarction **(STEMI)**
- In UA, myocardial injury is absent and cardiac biomarkers (cTn) are normal.
- Myocardial injury can lead to cell death and cardiac biomarkers are raised. It may result from severe ischemia and/or non ischemic causes (e.g., myocarditis).
- Myocardial Infarction (MI) is myocardial injury due to ischemia.

Key Messages 3#:

- According to the 4th Universal definition, **MI** is diagnosed when there is a significant rise and/or fall in cTn, with **at least one** value above the 99th percentile URL, and accompanied with at least one of the following:[2]
  - Clinical history consistent with chest pain of ischemic origin of > 30 minutes.
  - ECG changes of ischemia/infarction and/or the development of pathological Q waves.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary (IC) thrombus by angiography or autopsy.
- **MI** may be **STEMI** or **NSTE-ACS** based on the ECG.

3. PATHOGENESIS

ACS is commonly due to atherosclerotic plaque rupture, fissure or ulceration with superimposed thrombosis and coronary vasospasm. Depending on the acuteness of onset and the degree of occlusion and the presence of collaterals, patients can present as NSTE-ACS or STEMI. In NSTE-ACS the thrombus is either non-occlusive or there is complete thrombosis of a vessel that is well collateralized.

The majority (66%-78%) of ACS arise from lesions with <50% stenosis and less than 5% arise from lesions exhibiting >70% stenosis.[17-20] From postmortem studies and in vivo studies using intravascular ultrasound, four pathologic pathways to ACS have been postulated:[21]

MI can be classified as 5 types depending on the pathology, clinical features, prognosis and treatment strategies.[10] (Table 6, page 41). This CPG focuses on NSTE-ACS which is usually either:

- Type 1 MI (spontaneous MI related to atherosclerotic plaque rupture, with ulceration, fissuring, erosion or dissection) or
- Type 2 MI (often due to an imbalance between myocardial oxygen supply and/or demand. It may occur in the presence of coronary atherosclerosis without plaque rupture or in the absence of atherosclerosis).

Type 2 MI is an important cause of ACS in the elderly. Distinguishing Type 2 MI from troponin release due to non-coronary diseases is often difficult and challenging (Table 2, page 38 & Appendix II, page 94)

Key Messages 4#:

- MI can be classified as 5 types depending on the pathology, clinical features, prognosis and treatment strategies. (Table 6, page 41). This CPG focuses on NSTE-ACS which is usually either:
  - Type 1 MI (spontaneous MI related to atherosclerotic plaque rupture, with ulceration, fissuring, erosion or dissection) or
  - Type 2 MI (often due to an imbalance between myocardial oxygen supply and/or demand. It may occur in the presence of coronary athero sclerosis without plaque rupture or in the absence of atherosclerosis). This is an important cause of ACS in the older person.
- The majority (66%-78%) of ACS arise from lesions with <50% stenosis and less than 5% arise from lesions exhibiting >70% stenosis.

4. DIAGNOSIS

4.1 History

The symptoms of NSTE-ACS may be indistinguishable from that of STEMI. These include:

- **Chest pain**
  - This is the presenting symptom in most patients. Typical anginal chest pain has traditionally been described as a central pain or pressure, aggravated by emotional or physical stress and relieved by rest or GTN.
  - Features that increase the probability of ischemic chest pain are pain radiating to both arms, pain similar to prior ischemic episodes, a change in the pattern of pain over the past 24 hours and associations with sweating[22,23] and exertion.
  - Features that reduced the probability that the chest pain is ischemic in origin is variation with respiration or position, localisation to a point, pain reproduced on palpation and described as sharp or stabbing.[22-26]
  - The relief of symptoms after nitrate administration is not specific for angina pain neither is relief with the “GI cocktail” indicative that it is non-cardiac.[27,28]

- Chest pain at rest carries a worse prognosis than symptoms elicited during physical exertion. In patients with intermittent symptoms, an increasing number of episodes preceding the index event also adversely affects prognosis.[29]

- **Other symptoms**
  - 8% of ACS patients did not present with chest pain.[30] They were more likely to be women, diabetics and the elderly.
  - Atypical symptoms or angina equivalents included dyspnea (50%), unexplained sweating (25%), nausea and vomiting (24%), syncope and presyncope (19%), fatigue and epigastric discomfort.[30]
  - Shoulder pain, sweating and a higher symptom distress score were more likely to indicate an ischemic origin of the symptoms.[22-24]

In patients with these presentation(s) and with a prior history of coronary artery disease (CAD) including prior abnormal stress test and peripheral arterial disease, diabetes and other CVD risk factors and renal disease and a family history of premature CVD, the index of suspicion of ACS should be high.[22,31-33] Traditional cardiac risk factors although not helpful for the confirmation or exclusion of ACS, help raise the suspicion that symptoms may be ischemic in origin.[34]

There are cross-cultural and gender differences in symptoms reported by patients with suspected ACS.[35,36] Such differences are however not clinically relevant because most of the symptoms display limited diagnostic value for ACS.[35]

"Atypical" symptoms cannot rule out ACS, while "typical" symptoms cannot rule it in. Therefore, if a patient has symptoms that are compatible with ACS and an alternative cause cannot be identified, clinicians must strongly consider the need for further investigations.[37]
The diagnosis of ACS is more frequently missed in:[38,39]

- women
- those presenting with dyspnea
- in the presence of a normal ECG and
- in the presence of comorbidities

These patients had higher mortality than those who have received appropriate GDT following a diagnosis of ACS.[30,37-39]

4.2 Physical Examination

The physical examination in ACS is generally unremarkable. The objective of the physical examination is to identify:

- Possible etiologies such as aortic stenosis, hypertrophic cardiomyopathy, signs of hypercholesterolemia (xanthomas, xanthalesmas).

- Precipitating causes such as uncontrolled hypertension, anemia, thyrotoxicosis, infection.
- Consequences of NSTE-ACS such as hypotension, heart failure and arrhythmias.
- Other comorbid conditions such as lung disease, peripheral vascular disease.

Presence of left ventricular failure (hypotension, respiratory crackles or S3 gallop) and arrhythmias carry a poor prognosis. Carotid bruits or peripheral vascular disease indicates extensive atherosclerosis and a higher likelihood of concomitant CAD.

In addition, the physical examination may help identify other causes for the chest pain e.g., pericardial rub indicating pericarditis, tracheal shift and unequal air entry indicating pneumothorax, low oxygen saturation and unilateral swollen tender calf muscles suggesting pulmonary embolism, and vesicles and scabs for herpes zoster.

4.3 Electrocardiography (ECG)

The ECG adds support to the diagnosis and provides prognostic information.[40-45] A recording made during an episode of chest pain is particularly valuable.

I,C Wherever possible, an ECG should be performed at the First Medical Contact (FMC) as this increases the likelihood of recognising transient changes.[46] It should be performed within 10 minutes of FMC.[47]

In a small prospective study, 12.5% of pre-hospital ECGs in patients who were alert and experiencing chest pain or other symptoms consistent with those caused by myocardial ischemia had clinically significant abnormalities that were transient and not seen on the initial ECG done in the Emergency Department. [46]

I,C All ambulances, government and private clinics should be equipped with 12-lead ECG-capable devices.

I,C These should have computer-generated interpretations and wherever possible, this should be reviewed by trained personnel. These computer-generated ECG reports have a wide variation in the proportion false-positive (0% to 42%) and false-negative (22% to 42%) results. Thus, it should not be used as the sole means to diagnose ACS.[48,49]

ECG features that were associated with the highest 30-day incidence of death or reinfarction in ACS patients were[44]:

- A combination of ST elevation (of at least 0.5 mm in at least 2 contiguous leads) and ST depression (of at least 0.5 mm in 2 contiguous leads) - **(12.4%)**
- ST-segment depression of greater than 0.5 mm (alone or with concomitant T-wave inversion - **(10.5%)**
- ST-segment elevation of at least 0.5 mm in at least 2 contiguous leads - **(9.4%)**
- Isolated T wave inversion (>1 mm in leads including the normalisation of a known negative T-wave) - **(5.5%).**

Other possible ECG changes include flat T waves, T inversions in a non-dominant R wave lead, presence of Q waves and poor R wave progression in the anterior chest leads.

A new (or presumed new onset) LBBB and should be treated as STEMI.

I,C A normal ECG does not exclude NSTE-ACS.[49] Serial ECGs should be performed as the changes may evolve.

I,C We recommend all patients be provided a copy of their ECG for personal keeping for comparison at future health encounters.

A missed diagnosis of ACS carries a worse prognosis.[38,39]

4.4. Cardiac Biomarkers

I,A Cardiac troponins (cTn) T and I are the most sensitive and specific biomarkers for myocardial injury and necrosis.[10,50]

Where there is access to cTn testing, other biomarkers (AST, LDH, CK, CKMB and myoglobin) are not useful for the initial diagnosis of acute MI.[51] This is due to their lower sensitivity and specificity.[52,53] CKMB may be used to monitor for reinfarction.

IIb, B In settings where cTns are not available, CKMB will be the alternate but less preferred option.[10,54]

After acute MI, cTn becomes detectable at 6 hours using the conventional older cTn assays and may remain elevated for up to 14 days. Hs-cTn assays detect cTn release at an earlier time point than the older cTn tests leading to an improved early sensitivity for a diagnosis of MI.[15]

cTn are markers of myocardial necrosis and not specific markers for MI. The

rise and/or fall of cTn with at least one value greater than the 99th percentile is a key criterion in addition to other clinical features for the diagnosis of MI.[10] (Section 2.2.1.1, pages 45-46)

The hs-cTn assay is currently replacing the conventional cTn assay in the market. The term "high sensitivity (hs)" reflects the assay's characteristics and not a different type of cTn. A "high sensitivity," assay must meet 2 criteria:[55]

1. Have a coefficient of variation (CoV) or imprecision of less than or equal to 10% at the 99th URL ***and***
2. Have measurable concentrations below the 99th percentile that are attainable with an assay at a concentration value above the assay's limit of detection for at least 50% (ideally >95%) of healthy individuals.

At present, most commercially available hs-cTn assays attain a CoV of < 10% at the 99th URL indicating that the result is less affected by analytical noise and exhibits lower inter-test variability.[16] The true test of how well the % CoV of assays will hold up is when assays are used daily in clinical practice and each laboratory evaluates their assay performance regularly.[16]

I,C

Good preanalytical sampling is important as the hs-cTn assays are so sensitive that poor sample quality, most commonly hemolysed specimen, can be a problem.[16]

Hs-cTn measurement (using the 99th percentile threshold) was found to be the most effective cardiac biomarker for diagnosing MI with an incremental cost-effectiveness ratio (ICER) of less than the £20,000-30,000/QALY threshold (ICER £7487-17,191/QALY).[56]

Using the lowest absolute concentrations which can be reliably detected, Limit of Detection (LoD), absolute value of < 5ng/L has a 5-fold reduced chance of missing an MI compared to using the 99th percentile cut-off.[57] It, however, increases by 3-fold the admission rate and unnecessary treatment of patients who may not have an MI.[58]

Absolute changes in nanograms per litre using hs-cTn assays have better diagnostic accuracy for MI than relative change values.[59] This finding was consistent in both the older patient and in those with impaired renal function. [59] The higher the cTn level, the higher is the likelihood of MI.[59]

Almost 13% of patients presenting with raised hs-cTn and chest pain eventually prove not to have MI.[60] This may reflect myocardial injuries and not MI. Many

primarily cardiac disorders as well as non-cardiac disorders with cardiac involvement may lead to myocardial injury and thereby hs-cTn elevations.[10,15,61,62] (Section 2, pages 44-47, Table 2, page 38 & Appendix II, page 94)

A cTn elevation is not exclusive for ACS thus causing some problems in the interpretation of the results. It may be present in 1% of a healthy reference population.[63] In a meta-analysis, about 47% of individuals had elevated cTn after endurance training and using hs-cTn most marathon runners had increased levels.[64]

In critically ill patients, the mechanisms of an elevated cTn is unclear and there is no consensus on the appropriate approach and management. A history of CAD with typical ischaemic ECG changes may indicate a Type I MI.

False positive cTn (no myocardial injury) results due to analytical issues are very rare. These include cross reaction from other immuno-reactive proteins and some neuromuscular diseases.[15,61,62]

I,A All hospitals providing care for patients with acute chest pain or suspected MI should have access to cTn, preferably hs-cTn (subtypes T or I) testing.[10,50-53]

Concentrations for hs-cTn assays should be expressed in nanograms per litre instead of the commonly published units of micrograms per liter.[15,16,55] The cut off points differ among the different assays and the different generation assays by the same vendor. Some assays have sex-specific values - females tend to have lower hs-cTn levels.[66,66] An ongoing prospective study however, found that sex based cut- off values had little clinical impact on the diagnosis of MI and that the uniform 99th percentile should remain the standard of care when using hs-cTn T levels.[67]

I,C Clinicians must be familiar with their local cTn assays-point of care (POC) kits or lab based. In general,

- POC kits have lower analytical sensitivity and too wide CoV to detect cTn at the 99th percentile URL.
- Use of POC kits in areas without access to central labs could potentially reduce unnecessary referrals or transfers of cases and result in overall cost savings. [57,68,69]
- Almost all locally available laboratory-based assays can measure hs-cTn at the 99th percentile URL.

I,C It is important for each clinician to be familiar the 99th percentile URL and the lower limit of detection (LoD) of the cTn assay used in their respective hospitals.

I,C It is inappropriate to label cTn results as positive and negative.[15] Hs cTn can be used to:

- Rule in MI - significant rise and/or fall of cTn with at least one value greater than the 99th percentile URL in combination with other clinical criteria. (Universal definition of MI).[10]
- Rule out MI (Section 5.1, pages 55 - 59)

Rule out does not equate to discharge. It requires consideration of other causes of chest pain, early out-patient assessment for possible stable CAD or optimisation of care in patients with known CAD.

Rule in strategies help commence appropriate GDT earlier for NSTE-ACS.

4.5 Other Diagnostic Modalities

These include:

- Echocardiography / Point of care ultrasound (POCUS):[70-73]
  - ➢ Echocardiography is a safe modality that assists in the rapid diagnosis and management of MI.
  - ➢ It helps detect:
    - LV systolic function - This is an important prognostic indicator.
    - Transient reversible regional wall motion abnormalities which may be present during ischemia.
    - Complications of MI such as inter-ventricular shunts, papillary muscle dysfunction and peri-myocardial effusion.
- Radiograph-Routine Chest Radiograph is not advised in all patients presenting with chest pain suspicious of ACS. The decision should be individualised.

Key Messages 5#:

- The combination of history, physical examination and ECG is important but may be insufficient to reliably rule in or rule out NSTE-ACS.
- Cardiac troponins (cTn), preferably hs-cTn, both T and I are the most sensitive and specific biomarkers for myocardial injury and necrosis.
- Elevations of cTn should be correlated with the clinical condition of the patient and the ECG. (See definition of MI, Section 2, page 44-47 & Table 2, page 38)

Key Recommendations 1:

- An ECG should be performed within 10 minutes of the First Medical Contact (FMC).
- All ambulances, government and private clinics should be equipped with ECG-capable devices. These should have computer-generated interpretation and wherever possible, reviewed by trained personnel.

Key Recommendations 2:

- All hospitals providing care for patients with acute chest pain or suspected MI should have access to cTn (subtypes T or I) testing, preferably hs-cTn.
- Clinicians must be familiar with their local cTn assays-point of care (POC) kits or laboratory based, the 99th percentile URL and the lower limit of detection (LoD) of the assay used in their respective hospitals.
- The exact value of the cTn result should be stated and not as positive or negative.

5. RISK SCORES

In patients presenting to the ED with chest pain, it is important:

- To timely recognize ACS. This will enable patients with ACS (including those who are cardiac biomarker negative) to be treated rapidly and appropriately and non-ACS patients to be rapidly discharged from a busy ED.
- To prognosticate ACS patients and help guide further management.
  - A low-risk patient for ACS that is safe for discharge from ED is defined as one who has a < 1% risk of MACE or death at ≥ 30-days follow up.[74]
  - A high-risk patient with typical history of ischaemic pains and diagnostic ECG changes, can be quickly triaged to the monitored area.

5.1 Risk Scores to "Rule out ACS"

The initial history, physical examination, and ECG alone are not always reliable in predicting the presence of CAD and myocardial ischemia.[76] Even in patients presenting with acute chest pain, clinical evaluation alone did not confirm or exclude the diagnosis of ACS.[75-78]

Cardiac biomarkers especially assays measuring hs-cTn are very sensitive and can detect myocardial injury earlier than conventional older assays. However, they are not specific and need to be interpreted in the clinical context since there are other conditions besides MI that can give rise to raised cTn.[10,61,62,76] (Table 2, page 38 & Appendix II, page 94)

Based on the limitations of the diagnostic work-up, there will invariably be a "missed diagnosis" of MI in the ED. The test threshold, the point of probability at which the harms associated with elevated cTn testing and work-up exceed the risks of untreated disease, has been estimated to be approximately 2% for ED patients presenting with suspected cardiac chest pain.[79] However, in a survey, most ED physicians caring for patients with symptoms suggestive of ACS, will only accept an arbitrary maximum of 1% for missed diagnosis for MACE within 30 days of ED discharge.[80]

Patients presenting with chest pain or chest pain equivalents may, based on the clinical history and ECG, have:

- ***Very low likelihood of NSTE-ACS*** or have an alternative cause for their symptoms. These can be treated accordingly and be discharged from ED.
- ***Definite NSTE-ACS or STEMI.*** These patients should be admitted and managed accordingly.
- ***Possible or suspected NSTE-ACS.*** These patients have normal or non-diagnostic ECGs. They need to be evaluated using a "rule out protocol" for ACS.

I,C

Evaluation is a continuous process and it is possible for a patient to move from "very low likelihood" of ACS to definite NSTE-ACS as new information becomes available or as the patient's clinical condition changes.

5.1.1 "Rule out" ACS pathways (Flowchart 1, page 35)

Following a targeted clinical evaluation and an ECG, blood is taken for measurement of cTn, preferably hs-cTn.

There are several algorithms based on cTn or hs-cTn to **rule out "ACS"**:

- **HEART (History, ECG, Age, Risk Factor, Troponin) Pathway** - the HEART score and cTn < 99th percentile at 0 and 3 hours [81,82]
- **European Society of Cardiology (ESC) 3-hour# Pathway**[83] -
  - If onset of pain > 6 hours and baseline hs-cTn at presentation <99th percentile.
  - If symptom onset is < 6 hours, a repeat test at 3 hours is:
    - Unchanged/no significant change (dependent on assay) ***and***
    - < 99th percentile ***and***
    - Patient is pain free ***and***
    - GRACE score < 140
- **ESC 1-hour# Pathway**[83] - measures baseline and absolute changes in hs-cTn levels within the first hour. The cutoff levels within the 0 h/1 h algorithm are assay specific.

 # The time of the blood test is time 0 and the time of the second blood test is either 1 hour or 3 hours later.

The cut off levels for the different hs-cTn vary with the assays used. Some have sex-specific cut-off points. It is important to check with the local vendor the respective values.

I,A These accelerated hs-cTn diagnostic "rule-out" protocols for patients with suspected ACS using early serial troponin testing with either the 1h algorithm or the 0 and 2 h algorithm are cost effective strategies with reduced ED-length of stay, overall hospital savings and are safe. [84-92]

The committee advocates Flowchart 1, page 35 using cTn, preferably hs-cTn, as a rule-out pathway.

POC kits have a rapid turn-around time but are not sensitive.

IIb,C When using POC kits[93]:

- When the reading is elevated, admit the patient for further evaluation.
- If the reading is normal or non-detectable and the clinical suspicion is high, repeat after 6 hours.

cTn have to be interpreted in the clinical context of the patient. [10,61,62,76] Other key clinical data, such as the patient's chest pain features, past medical history, and ECG have to be considered particularly when contemporary hs-cTn assays are used[10,14-16] (Table 2, page 38 & Appendix II, page 94).

Various clinical prediction risk scores have been developed to complement the "rule out" cTn-based algorithms in patients who are suspected to have ACS.

The common **"rule out" risk scores** are:

- HEART (History, ECG, Age, Risk Factor, Troponin) Score [81] (Appendix III, page 95)
- TIMI risk score[94] (Appendix IV, page 96)
- ADAPT-ADP[95]
- ASPECT[96]
- Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (HFA/CSANZ) rule[97,98]

The HEART score is the commonest risk score being used in our EDs although there have been no validation studies in our local population. Despite its use in different patient populations, the cTn type used and timeline of follow-up, a low-risk HEART score had high sensitivity, negative predictive value, and negative likelihood ratio for predicting short-term MACE. [99-103]

Based on the HEART score, patients with suspected ACS can be stratified into:[81]

- ≥ 7: High risk - 72.7% risk of a major adverse event#
- 4-6: Intermediate risk - 20.3% risk of a major adverse event#
- ≤ 3: Low risk - 2.5% risk of a major adverse event#

#Endpoints- MI, revascularization by PCI or CABG, death plus a combined endpoint of AMI, PCI, CABG and death.

The modified HEART score uses hs-cTn rather than cTn.[100]

The TIMI score although commonly used, was not designed for application to undifferentiated patients presenting with chest pain and suspected ACS. To improve its performance as a "rule out" risk score, modifications have been studied including using a cut off of 0 or 1 for low risk.[75] In a prospective cohort study, in conjunction with a single contemporary cTn assay taken at admission, the HEART score outperformed the TIMI and GRACE scores in predicting 30-day MACE.[103]

We advocate measurement of clinical risk scores for ACS - the HEART score (or modified HEART score if hs-cTn is used) or TIMI risk score 0-1 and the "rule out" protocol in Flowchart 1, page 35.

About 2.1-3.3% of ACS patients are however, "missed" by the Heart Score.[77,78,91] Thus clinical judgement is still important before discharging the patient from the ED. Persistent or recurrent symptoms during the ED stay should prompt one to re-evaluate the patient.

It is important to remember that these are risk stratification strategies rather than definitive diagnostic strategies. Further investigations may be necessary to determine the cause of the chest pains. (e.g. stable coronary artery disease or non-coronary cause of chest pain)

5.1.2 Patients in the "Indeterminate Group"- those who do not "rule in" or "rule out" for ACS

The high sensitivity and Negative Predictive Value (NPV) of hs-cTn algorithms obviate the need for further testing to rule out MI.

The "rule out" and "rule in" ACS protocols will identify a middle group that warrants further observation and/or investigation. This includes patients with:

- Ongoing/recurrent chest symptoms without significant ECG or cTn elevations. In these patients, alternative causes for the chest symptoms should be excluded.

- Elevated cTn /hs-cTn levels but without a significant rise and fall. These patients are typically elderly patients with pre-existing CAD and high long-term mortality.[13]
- Mildly raised cTn levels, equivocal results and patients who cannot be confidently ruled out or ruled in for MI.
- UA with a negative cTn /hs-cTn.

These patients need to be properly evaluated and given appropriate treatment and at the same time avoiding unnecessary admissions, pharmacological therapy or invasive procedures.

Depending on the available facilities and the clinical status of the patient, they may be (in accordance with Flowchart 1, page 35):

- Admitted
- Observed in the observational area of the ED
- Referred for an early cardiology (or in the absence of cardiology, internal medicine) out-patient consult.

Other diagnostic modalities in these patients include:[104]

- Repeating ECG to look for serial changes in patients with ongoing chest pain.
- Echocardiography/POCUS to look for new wall motion abnormalities.
- Functional stress testing with or without imaging -
  - ➢ Exercise/ pharmacological stress testing
    - Stratifies these intermediate risk patients to a near zero short-term risk of ACS.
- Coronary angiography - non-invasive computer tomography coronary angiography (CTCA) or conventional (invasive) coronary angiography. A systematic review in 2017 found CTCA if available, appropriate in all settings of acute chest pain suspicious of ACS.[105]

For the non-invasive investigation of these low risk patients, please refer to Flowchart 2, page 36 and the Malaysian Clinical Practice Guidelines on Management of Stable Coronary Artery Disease, 2018, 2nd Ed.[7]

These patients should be advised on lifestyle modification (dietary changes, regular exercise, smoking cessation). If the likelihood of underlying CAD is high, they should be started on antiplatelet agents, high intensity statins and appropriate anti-ischemic therapy (Section 7.3, pages 69-76).

5.2 Risk scores for Prognostication in NSTE-ACS

Patients with NSTE-ACS have an increased risk of death, recurrent MI, recurrent symptomatic ischemia, serious arrhythmias, heart failure and stroke.

Early assessment would help in determining the:

- Prognosis of the patient
- Management strategies
- Selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting)
- Selection of appropriate therapy and the need for coronary angiogram and revascularization

Risk is highest at the time of presentation but remains elevated past the acute phase. By 6 months NSTE-ACS mortality rates may equal or exceed those of STEMI.[44]

There are many ways of risk stratifying these patients with NSTE-ACS:

- Clinical features as in Table 3
- Risk scores such as;
  - HEART (History, ECG, Age, Risk Factor, Troponin) Score (Appendix III):
    - Predicts 30-day MACE.[81,106]
  - TIMI (Thrombolysis in Myocardial Infarction) Risk Score (Appendix IV):
    - Predicts 14-day outcomes.[94]
  - GRACE (Global Registry of Acute Coronary Events) Risk Score (Appendix V):
    - Predicts in-hospital and 6-month death or recurrent MI.[107]

I,C We advocate TIMI or GRACE risk scoring in these patients with definite NSTE-ACS.[94,107]

I,C This highlights the importance of clinical parameters in assessing prognosis. These validated risk scores refine risk stratification, thereby improving patient care in routine clinical practice.

These risk scores help dictate the appropriate strategy (invasive versus ischaemic- guided) and the timing of the strategy (early versus late invasive) in patients with NSTE-ACS.[108]

The very-high-risk and high-risk patients should be considered for transfer to a PCI-capable centre as soon as possible (Table 3, page 39).

5.3 Risk Scores for Bleeding

Hemorrhagic complications are an independent risk factor for subsequent mortality in ACS patients and in those undergoing PCI. In patients at low risk, it is important to weigh the benefits of PCI versus the bleeding risk of the procedure and subsequent need for dual anti-platelet therapy (DAPT). Patients at high bleeding risk may be considered for newer generation stents and shorter duration of DAPT.

These patients can be identified by the following risk scores:

- ACUITY HORIZONS-AMI Bleeding Risk Score - identifies patients at increased risk for non-CABG-related bleeding and subsequent 1-year mortality[109]
- CRUSADE Bleeding Risk Score -predicts in-hospital major bleeding[110]
- BleeMACS score- predicts 1-year post discharge bleeding[111]
- TRILOGY-ACS- a tool to predict risk of bleeding on DAPT.[112]
- PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy) - tool for the prediction of out-of-hospital bleeding during DAPT. [113,114]

We advocate using the PRECISE-DAPT risk score in patients at high risk of bleeding.[113,114](Appendix VI, page 98)

These scores are calculated based on age, clinical status and hemodynamics at presentation, serum creatinine and haematocrit level and the use and combinations of antiplatelets and anticoagulants.

Key Messages 6#:

- Patients presenting with chest pain or chest pain equivalents, may, based on the clinical history and ECG, have:
  - **Very low likelihood of NSTE-ACS** or have an alternative cause for their symptoms. These can be treated accordingly and be discharged from ED.
  - **Definite NSTE-ACES or STEMI.** These patients should be admitted and managed as for STEMI or as for NSTE-ACS.
  - **Possible or suspected NSTE-ACS.** These patients have normal or non-di agnostic ECGs. They need to be evaluated using a “rule out protocol” for ACS. (Flowchart 1, page 35)
- Evaluation is a continuous process and it is possible for a patient to move from very low likelihood to definite NSTE-ACS

Key Recommendations 3:

- Patients with chest pain suspected to be due to ACS should have their cTn, preferably hs-cTn, measured.
- **Patients with suspected ACS should be risk stratified using the HEART or TIMI risk scores and the "Rule out ACS" Flowchart 1, page 35**
- Using the "Rule out ACS" Flowchart 1, patients may be:
  - Discharged from ED
  - Referred for an early outpatient cardiology (or in the absence of cardiology, internal medicine) consult
  - Admitted for definitive management of NSTE-ACS.

Key Recommendations 4:

- **Patients with definite NSTE-ACS should be risk stratified using clinical features** (Table 3, page 39)**, TIMI or GRACE risk scores** (Appendix IV & V, pages 96-97). This will help determine:
  - Prognosis of the patient
  - Management strategies
  - Selection of the site of care (coronary care unit, monitored step-down ward or outpatient setting)
  - Selection of appropriate therapy and the need for coronary angiogram and revascularization
- Patients with high bleeding risk should be assessed using the PRECISE DAPT bleeding score (Appendix VI, page 98).

6 PREHOSPITAL MANAGEMENT

6.1 For the General Public

Public awareness about heart disease should be increased so that individuals will seek appropriate treatment early, thus reducing time from symptom onset to FMC.

The public should be educated about:

- Symptoms of ACS.
- The importance of seeking early treatment at the nearest clinic or hospital.

Reducing the time delay from onset of symptoms to First Medical Contact (FMC) remains challenging. From the time of onset of chest pain to presentation at the Emergency Unit, time delays can vary from a median of 2.1 hours in Singapore, 2.4 hours in New Zealand to 8.3 hours in Japan.[115-118]

Contributary causes include older age, female sex, presence of diabetes mellitus, patients attributing symptoms to noncardiac causes and awaiting symptom resolution, lack of health insurance coverage and poor access to transportation.[115-118]

A meta-analysis indicated that only around half of the studied interventions report any success in reducing prehospital delay.[119] It is unclear what differentiates effective from non-effective interventions to reduce prehospital delays.[119] The Behaviour Changing Techniques (BCT) most commonly identified within interventions were: [119]

- Action planning
- Information about health consequences
- Problem-solving
- Information on signs and symptoms and instruction on what to do

It was, however, not possible to establish which particular BCT was more effective.[119]

Immediate measures to be taken by the individual in suspected cases of ACS:

- Seek immediate medical attention at the nearest clinic or hospital.
- Call for an ambulance (dial 999) or get someone to take you immediately.
- Do not drive yourself.
- I,C If not on regular aspirin and with no history of allergy, chew 300mg aspirin immediately. Soluble and chewable aspirin formulations are preferable to solid aspirin either chewed or swallowed.[120,121] Regular aspirin is preferred over enteric coated aspirin in this situation because of its faster onset of action.[122]
- Although all Guidelines advise the use of aspirin as soon as possible after the onset of symptoms, there is a lack of randomised trial data and a risk of misdiagnosis. In a small retrospective study, patients receiving aspirin before admission were less likely to present with NSTE-ACS.[123]
- I,C For patients with known CHD, history of previous PCI and/or CABG, take one dose of GTN either as a sublingual tablet or spray and 300mg of chewable aspirin (if not taken earlier).
- I,C If the patient is already on aspirin 75-150mg, it is advisable to take an additional 300mg of aspirin.
- The 999 dispatchers will provide additional care instructions before the arrival of the pre-hospital care (PHC) providers.

6.2 Primary Care Clinics

Chest pain is one of the more common presentations in primary care facilities. In less urban areas, it may be the most accessible healthcare facility to the patient.

Management will begin with assessment of the patient by:

I,C
- Taking history and physical examination. It is important to look for haemodynamic instability. (Sections 4.1 & 4.2, pages 48-50)

I,C
- Performing an ECG - This is an essential investigation and should be made routinely available in all primary care settings. A patient with a non-interpretable ECG may have NSTE-ACS. Also, a normal ECG does not exclude NSTE-ACS. (Section 4.3, pages 50-51)
- Measuring cardiac biomarkers (cTn) - Presently, this is usually done at the hospital level where definitive treatment can also be given.

In suspected NSTE-ACS:

- If the primary care facility does not have ambulance facilities, call 999 to assist in patient transfer to hospital.
- Ask patient to chew and swallow aspirin 300mg (non-enteric coated) if not already done so.[124,125]
- Serve sublingual GTN, if SBP is more than 90mmHg and patient has recurrent or ongoing chest pains.
- Administer oxygen therapy via face mask or nasal prongs if patient is dyspnoeic and/or SpO2 is < 95%.
- Set up IV access, if possible.
- Administer IV morphine as indicated.
- Inform the hospital prior to transfer.

6.3 Medical Emergency Coordination Centre (MECC) and Ambulance Responders

When a patient presents with chest pain, it is of paramount importance to determine if:

- The pain is cardiac in origin.
- If cardiac in origin, is it due to:
  - **STEMI** - requires immediate treatment to reopen the occluded infarct related artery preferably by Primary Percutaneous Coronary Intervention (PCI) if this can be done in a timely manner.[8]
  - **NSTE-ACS** - UA or NSTEMI. The initial management is medical.

When there is a 999 call, the caller is first directed to Telekoms who will verify the authenticity of the caller. It is then directed to a Medical Emergency Coordination Centre (MECC), who will then:

A. Identify the chief complaint

- If the complaint is chest pain or a chest pain equivalent (eg chest heaviness, discomfort which may be associated with sweating and/or shortness of breath), a validated protocol will be used addressing:
  - Nature of complaint and severity including level of alertness.
  - Difficulty breathing.
  - Changing of skin colour (pallor / blue).
  - Previous history of heart attack or angina.
  - Use of medications in the past 12 hours.
- Pre-arrival instructions will be given and this includes immediate self-care or bystander care while waiting for ambulance arrival.
- Ambulance teams dispatched to the scene should be trained and equipped to perform an ECG (with the use of Advanced Cardiac Care Device which is capable of ECG recording, transmission, and real-time ECG monitoring and telemetry).
- If the ECG (after interpretation by trained personnel) shows features of **STEMI**, the patient should be transported to the nearest hospital preferably with PCI-capable services.[8] Please refer to the 2019 Malaysian Clinical Practice Guidelines on Management of ST Elevation Myocardial Infarction.[8]

I,B

- If the patient with NSTE-ACS has ongoing/ recurrent chest pain, they too should be considered for immediate transfer to a PCI-capable hospital.
- High-risk unstable patients should be taken to the nearest hospital for stabilization first.
- Supportive care should be provided:
  - Monitor the patient's hemodynamics continuously prior to and during transfer including continuous ECG monitoring.

I,A

  - Give 300mg of chewable aspirin (if not taken earlier.)[124,125]

I,C

  - GTN either as a sublingual tablet or spray if there are no contraindications.

Pre-hospital care personnel should be trained to:

- Identify patients at high risk of developing ACS such as those with prior heart disease, the elderly, presence of multiple cardiovascular risk factors - diabetes, smoking, hypertension, dyslipidemia, and a family history of premature heart disease.
- Interpret the ECG, identify and treat common arrhythmias. There should be periodic feedback reports and other quality improvement measures in the interpretation of ECGs.[126]

- Identify patients with NSTE-ACS and STEMI based on history and characteristic ECG changes after consultation with the ED physician/ medical officer
- Assess, stabilise and monitor the patient's hemodynamics continuously prior to and during transfer

Key Recommendations 5:

- Public awareness about heart disease should be increased so that individuals will seek appropriate treatment early, thus reducing time from symptom onset to FMC.
- If the person is suspected to have an ACS and is not on regular aspirin with no history of allergy, 300mg aspirin should be administered. Soluble and chewable aspirin formulations are preferable to solid aspirin either chewed or swallowed.

Key Recommendations 6:

- Ambulance responders should be trained and equipped to perform an ECG.
- If the ECG shows STEMI or the patient with NSTE-ACS has ongoing/ recurrent chest pain, they should be considered for immediate transfer to a PCI-capable hospital. High-risk unstable patients should be taken to the nearest hospital for stabilization first.

7. IN - HOSPITAL MANAGEMENT

7.1 Emergency Department

When the patient with suspected ACS reaches the emergency department, evaluation and initial management should be prompt. Patients can be either triaged to the red or yellow zone according to the Malaysian Triage Scale.

A quick targeted history should be taken, and vital signs noted.

- A 12 lead ECG should be taken within 10 minutes of the patient's arrival in the emergency department.[127,128] This should be compared with prehospital ECGs or that taken earlier if available.

Based on the initial clinical evaluation, the patient may have:

- Definite STEMI
- NSTE-ACS with ongoing chest pain. If the initial ECG does not show ST elevation but the patient is suspected of having a STEMI in view of the prolonged ischaemic-type chest pain of > 30 minutes and recurrent/on going chest pains, the following steps may be taken:

- Repeating the ECG at 15-minute intervals to detect evolving changes of ischemia/infarction.
- The use of additional chest leads may be helpful in detecting STEMI at uncommon and difficult to detect sites:
  - Additional posterior chest wall leads (V7-V9) can detect a posterior MI (circumflex occlusion).[10,129-132]
  - Right precordial leads (V3R and V4R) may be necessary to identify concomitant Right Ventricular (RV) infarction in the presence of an inferior wall MI.[10,133]

- If STEMI has been excluded, the patient may fall into 3 categories as outlined in Section 5.1:
  - **Very low likelihood to be ACS** or have an alternative cause for their symptoms. These can be treated accordingly and be considered for discharge.
  - **Definite NSTE-ACS**
  - **Possible or suspected NSTE-ACS** - In these individuals the HEART Score (or modified HEART score) or TIMI score should be calculated, the cTn, preferably hs-cTn measured and the "rule out protocol" Flowchart 1, page 35 be used.

In patients with **NSTE-ACS**, the following should be done:

- Venous access established and blood taken for measurement of cardiac biomarkers (cTn-preferably hs cTn).
- The following are instituted:

I,A
  - Aspirin (300mg) if not taken prior to arrival.[124,125]

I,A
  - Oxygen is administered in patients with hypoxemia.[134-137]
    - SpO2 ≤ 90%
    - SpO2 > 90 - ≤ 95%

IIa,B
  - In the presence of ongoing chest pain, GTN sublingual tablet (0.3- 0.6 mg) or spray (0.4-0.8 mg) should be administered every 5 minutes for up to three doses if no contraindications exists (such as hypotension). Nitrates only help with symptom relief.

I,C
  - If symptoms are unrelieved:
    - Serial ECGs should be taken every 10-15minutes until the patient is pain free and compared with pre-existing ECGs to look for changes of STEMI.
    - Assess the need for i.v. GTN and/or
    - i.v. morphine at 2-5 mg by slow bolus injection every 5-15 minutes as necessary. Watch for adverse events - hypotension and respiratory depression. Antiemetic (i.v. metoclopramide 10 mg or promethazine 25mg) should be given with morphine and 8-hourly as necessary. Morphine should be used cautiously.[138] i.v. fentanyl 50mcg in titrated doses may also be considered.

I,A
I,B

- s.c. LMWH or s.c. fondaparinux should be given.[139-143]
- In the presence of ongoing chest pains and/or hemodynamic instability, urgent coronary angiography with view to revascularization should be considered if facilities are available.[107,144-150]

In patients with chest pain not due to ACS, other important clinical conditions should also be considered. Some of these can be life threatening.

Non-ischemic cardiovascular causes of chest pain

- Aortic dissection
- Pulmonary embolism
- Pericarditis and myocarditis

Non-cardiovascular causes of chest pain

- Gastrointestinal causes (e.g. gastro-esophageal reflux, oesophageal spasm, peptic ulcer, pancreatitis, biliary disease)
- Musculoskeletal causes (e.g. costochondritis, cervical radiculopathy, fibrositis)
- Pulmonary (e.g. pneumonia, pleuritis, pneumothorax)
- Other etiologies (e.g. herpes zoster, panic attack)

Key Recommendations 7:

- Patients with NSTE-ACS should be given:
  - Aspirin 300 mg stat (if not given earlier)
  - ***And*** Oxygen if oxygen saturation < 95%
  - ***And*** GTN for ongoing or recurrent chest pains
  - ***And*** i.v. morphine with i.v. anti-emetics or fentanyl for ongoing chest pains
  - ***And*** s.c. low molecular weight heparin or fondaparinux
- In the presence of ongoing chest pains and/or hemodynamic instability, urgent coronary angiography with view to revascularization should be considered.
- In patients with recurrent/ ongoing chest pain not due to ACS, other important clinical conditions should also be considered.

7.2 Level of Care

Following risk stratification as outlined in section 5.2, page 60 the patient may be admitted to:

- Coronary care unit (CCU) - Very high risk and High-risk individuals
- High dependency Unit - Moderate risk individuals
- General ward - Low risk individuals

Stable, low-risk NSTE-ACS may be managed appropriately on telemetry wards and result in a reduction in hospital costs and critical care capacity.[151]

7.3. Pharmacotherapy

In NSTE-ACS the commonest pathophysiology (Type 1 MI) is a ruptured or fissured plaque with superadded thrombosis leading to varying degrees of occlusion of the vessel. Thus, anti-thrombotic therapy (both antiplatelet and anticoagulant) plays a more important role in management than anti-ischemic agents.

In Type 2 MI, the underlying etiology needs to be addressed. Anti-ischemic agents play a more important role than antiplatelets and antithrombotic agents.

7.3.1 Antiplatelet therapy

7.3.1.1 Acetylsalicylic acid (ASA/Aspirin)

I,A
- Recommended loading dose: 300mg. This should be chewed or crushed.[124,125] Enteric-coated aspirin is not recommended as an initial loading dose because of its slow onset of action.
- Maintenance dose: 75-100mg daily lifelong regardless of treatment strategy.[152-154]

III,B
- An aspirin dose of 300-325mg daily is associated with an increased risk of gastrointestinal bleeding without greater efficacy.[153,154] This was seen when aspirin was used alone and in combination with a P2Y12 inhibitor such a clopidogrel.[155]
- For patients taking ticagrelor, the aspirin maintenance dose should be ≤100mg daily.[156,157]

IIa,A
- Proton pump inhibitors (PPI) in combination with DAPT should be considered for patients who are at high risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/corticosteroid use or two or more of the following: age ≥65 years, dyspepsia, gastro-esophageal reflux disease, Helicobacter pylori infection, chronic alcohol use)[158,159]
- In those patients allergic to aspirin, the available options include:
  - More potent P2Y12 inhibitors (ticagrelor or prasugrel) alone
  - Cilostazol with clopidogrel [160]
  - Triflusal with clopidogrel [161,162]
  - Aspirin desensitisation [163,164]

7.3.1.2 P2Y12 inhibitors (Appendix VII, page 99)

These may be given as:

I,A
- A substitute to patients who are intolerant or allergic to aspirin.

I,A
- As part of DAPT

The different P2Y12 inhibitors each have their own special characteristics that may prompt one being favoured over another in various circumstances. Recognising the characteristic differences in the agents can help with the choice of the best agent for individual patients. (Appendix VII, page 99)

Both ticagrelor and prasugrel have similar efficacy and bleeding rates when used as part of DAPT at 7 days, 1 month and 1 year.[165-168] A recent study found prasugrel to be superior to ticagrelor in reduction of death, MI or stroke without an increase in major bleeding.[169]

7.3.1.2.1 Clopidogrel

I,A
- Loading dose: 300 to 600mg, maintenance dose: 75mg daily.[152,170]

I,A
- The benefits of long term clopidogrel when added to aspirin was seen in NSTE-ACS patients treated medically, those undergoing PCI or coronary artery bypass grafting.[152,171,172]
- Clopidogrel versus prasugrel. In ACS patients:
  - undergoing PCI, prasugrel significantly reduced MACE but there was an increase in severe bleeding complications when compared to clopidogrel.[173]
  - who are medically managed, MACE and severe bleeding rates were similar between prasugrel and clopidogrel groups.[174]
- Clopidogrel versus ticagrelor. In ACS patients:
  - with or without PCI, ticagrelor significantly reduced MACE compared to clopidogrel and severe bleeding rates were similar.[156]

IIa,B
- The use of clopidogrel for up to a year as part of a strategy of DAPT was found to be cost effective.[175]

7.3.1.2.2 Prasugrel

I,B
- Prasugrel may be considered as a second antiplatelet agent after the coronary angiogram has been performed. (No pre-treatment)
- Loading dose: 60mg, maintenance dose: 10mg/day.[173,176]

III,A
- It is not recommended due to a higher risk of major bleeding in patients who are:[173,176]
  - > 75 years old or,
  - < 60kg weight or,
  - have prior history of transient ischemic attack or stroke.

IIa,B
- It should be considered in patients who present with stent thrombosis despite compliance with clopidogrel therapy.[177]

7.3.1.2.3 Ticagrelor

I,B

- Loading dose: 180mg, maintenance dose: 90mg twice daily.[156,178]
- When compared to clopidogrel, ticagrelor resulted in a significant reduction in cardiac end points in patients undergoing an early invasive or medically treated strategy.[156,178]
- Potential drawback is dyspnoea and transient ventricular pauses during the first week. This was rarely associated with symptoms or need for a pacemaker. Caution should be exercised in patients with heart block.

7.3.1.3 Timing of Initiation of DAPT

- When given as part of DAPT, the timing of initiation of the second antiplatelet agent is not clear. There are a few randomised trials directly comparing pre-treatment with initiation at the time of angiography.[179]
- Unlike in STEMI, NSTE-ACS patients are a heterogenous group and include patients with multivessel disease who may be more suitable for coronary artery bypass surgery or maybe even have normal coronaries.
- Although most Guidelines advocate pre-treatment, no recommendation for or against pre-treatment with these agents can be formulated because of the lack of trial data.

I,C

- The exact timing is left to the clinical judgement of the attending physician.

7.3.1.4 Duration of DAPT

I,A

- In NSTE-ACS patients, with or without PCI, DAPT is recommended for up to 12 months unless there are contraindications such as excessive risk of bleeds.[152,171,180-182]

I,B

- In ACS patients who underwent PCI and at high risk of bleeding, DAPT maybe continued for 3 to 6 months.[181,182]

IIb,B

- Continuing DAPT for more than 12 months significantly reduces MACE at the expense of an increase in major bleeding. [183,184]

7.3.1.5 Switching a potent P2Y12 to clopidogrel

- In patients with NSTE-ACS undergoing PCI, ticagrelor or prasugrel is usually preferred to clopidogrel.
- However, many patients may need to be switched to clopidogrel due to an increased risk of bleeding, other side effects (eg dyspnoea with ticagrelor) and costs. [165,185-188]
- The following approaches maybe considered:[165,185-188]
  - Those on ticagrelor:
    - De-escalate to clopidogrel with a loading dose of 300-600mg followed by 75mg daily, to be initiated at the time of the next scheduled ticagrelor dose.

- Those on prasugrel:[185]
  - De-escalate directly to clopidogrel 75mg (without a loading dose) at the time of the next scheduled prasugrel dose.

7.3.1.6 Glycoprotein (GP) IIb/IIIa Inhibitors (Appendix VIII, page 100)

IIb,B

- These agents are no longer used pre-procedure/ "upstream" because studies have not found this practice to be superior to the provisional selective use after angiography. It is also associated with an increased risk of bleeding.[189,190]
- Their main use is in patients who have been found to have a large thrombus burden at the time of coronary angiography.
- These agents include:
  - Abciximab
  - Tirofiban
  - Eptifibatide

7.3.2 Anticoagulant Therapy (Appendix IX, page 101)

I,A

- In NSTE-ACS patients managed medically, parenteral anticoagulation is recommended as soon as possible after the diagnosis.[139,140,191]
- The type of agent used may vary depending on whether the patient is managed by an early invasive or a conservative approach, issues of cost and local practice.
- The duration of anticoagulant therapy in patients treated medically would vary between 2-8 days.

7.3.2.1 Heparin

This includes:

I,B

- Unfractionated heparin (UFH)
  - For high risk NSTE-ACS patients undergoing an early invasive approach, UFH had similar efficacy to enoxaparin.[192,193]

I,A

I,B

- Low Molecular Weight Heparin (LMWH) - Enoxaparin
  - It is best used in NSTE-ACS patients treated conservatively.[141,194,195]
  - In patients > 75 years of age and with renal impairment (serum creatinine (Scr) > 200 µmol/L in women and > 250 µmol/L in men), UFH is preferable to LMWH.[196]

7.3.2.2 Anti-Xa inhibitors

This includes:

I,B
III,A
- Fondaparinux [142,143]
  - It is best used in NSTE-ACS patients treated conservatively.
  - It is associated with an increase in catheter-related thrombus and coronary angiographic complications. Thus, it is not recommended as the sole anticoagulant during PCI.
- If used in patients with NSTE-ACS and the patient requires an invasive strategy, UFH should be given during the procedure.
- In patients with NSTE-ACS, fondaparinux was found to be more cost effective and associated with less short and midterm bleeding events compared with enoxaparin.[197-199]

IIb,B Presently newer oral anti-Xa inhibitors are undergoing evaluation for ACS. A meta-analysis showed that the addition of Direct Oral Ant-Coagulants (DOAC) to DAPT in patients with NSTE-ACS did not show any significant treatment effect at the risk of increased bleeding.[200]

7.3.3 Anti-ischemic Drug Therapy

These agents may be given either for relief of ischemia (symptoms) or for improvement of prognosis.

7.3.3.1 β-blockers (Appendix X, page 102)

- There is limited randomised trials addressing the efficacy of β-blockers in NSTE-ACS.[201,202]

I,A
- β-blockers should be given to patients with heart failure and/or LV dysfunction (LVEF < 40%), continuing angina and/ or ischemia.[203-207]

IIb,A
- There is limited evidence to administer it routinely in all patients.[208-211]
- In the absence of contraindications, β-blockers may be administered after the patient has been stabilized and prior to hospital discharge.[202]
- Relative contraindications for β-blockers include:
  - Patients with marked first-degree AV block (PR interval > 0.24s).
  - Second - or third-degree AV block.
  - History of bronchial asthma
  - Severe peripheral arterial disease
  - Acute decompensated LV dysfunction
  - Cardiogenic shock.

I,A
- For patients who have LVEF <40% and those who subsequently develop left ventricular systolic dysfunction consider bisoprolol, carvedilol, long acting metoprolol or nebivolol.[203-207]
- A lower starting dose of 1.25mg daily for bisoprolol/nebivolol or carvedilol 3.125mg twice daily should be initiated. This should be slowly up-titrated till the target dose or the maximally tolerated dose is achieved.

7.3.3.2 Inhibitors of the Renin Angiotensin System-Angiotensin Converting Enzyme Inhibitors (ACEI) / Renin Angiotension Receptor Blockers (ARB) (Appendix XI, page 103)

I,A
- Once clinically and haemodynamically stable, ACEI may be initiated and continued for life in all patients with LVEF <40% and in those with hypertension, diabetes mellitus, or CKD, unless contraindicated.[212,213]

I,A
- For those who are ACEI intolerant, ARBs are recommended in patients with HF and/or LVEF <40%. [214-216]

7.3.3.3 Lipid Modifying Drugs

I,A
- High dose statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40mg daily) should be initiated as soon as possible after the diagnosis of ACS.[217-225]
- It is safe and has been shown to improve outcomes regardless of baseline LDL-C levels. [217,218,224-226]

I,A
- For patients who are already taking low or moderate-intensity statins, statin therapy should be intensified.[217]
- Target LDL-C should be < 1.8mmol/L (preferably < 1.4mmol/L) or a reduction of at least 50% from the baseline, the lower the better. [217,227-235]

I,A
- In patients whose LDL-C ≥ 1.8mmol/L despite maximally tolerated therapy, the addition of non-statin therapy (ezetimibe and PCSK-9 Inhibitors) should be considered.[232-235]

I,A
- Patients with LDL-C > 2.6 months on maximally tolerated statins following an ACS and had a greater benefit with further lowering of the LDL-C with the addition of PCSK-9 inhibitors.[234]
- Refer to 2017 Malaysian Clinical Practice Guidelines on Dyslipidemia, 4th Ed.[217]

7.3.3.4 Nitrates (Appendix XII, page 104)

I,C
- Nitrates help with symptom relief only. They should be used cautiously in the presence of a low BP.
- Intravenous nitrates may be administered in the following situations:
  - ➢ No symptom relief after 3 doses of sublingual GTN
  - ➢ Presence of dynamic ECG changes
  - ➢ Presence of left ventricular failure
  - ➢ Concomitant high blood pressure.
- Patients who require intravenous GTN for more than 24 hours may need periodic increases in the infusion rate and use of nontolerance-producing regimens (e.g., intermittent dosing) to maintain efficacy.[236]
- Oral or topical nitrates can be used as alternatives to intravenous GTN for patients who do not have refractory or recurrent ischemia.

- Oral nitrates may be given after 12 to 24 hours of pain free period. Rebound angina may occur with abrupt cessation of nitrates.[237]
- Contraindications to nitrate therapy:
  - Hypotension (SBP < 90 mmHg)
  - RV infarction
  - History of ingestion of phosphodiesterase-5 inhibitors in the preceding 24 to 48 hours (depending upon the half-life of the agent).[238-240]

7.3.3.5 Calcium Channel Blockers (CCBs) (Appendix XIII, page 105)

CCBs may be used in the following situations:

IIa,B
- A non-dihydropyridine CCB (e.g. verapamil or diltiazem) may be used as an alternative to β-blockers in patients who are not able to tolerate or who have contraindications.[241-243]

IIa,B
- Verapamil, diltiazem, slow release nifedipine or amlodipine can be administered in patients with continuing or recurring angina despite adequate doses of nitrates and β-blockers.[241-243]
- Prinzmetal's angina (variant angina)
- Long-acting CCBs and nitrates maybe used for patients with coronary artery spasm.

III,A
- Immediate-release nifedipine is contraindicated. [244,245]

7.3.3.6 Other Anti-ischemic agents

These include:

- Ivabradine

I,B
  - Ivabradine has been shown to improve symptoms and reduce cardiovascular hospitalisation, fatal and non-fatal MI and the need for coronary revascularization in patients with stable CAD, moderate LV dysfunction and HR >70 bpm.[246-251]

IIa,B
  - Ivabradine may be considered for symptomatic treatment of stable CAD in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to β-blockers and if the resting HR is above 70/min.[246-248]

- Ranolazine

IIa,B
  - Compared to placebo, or as additional to current anti-anginal therapy, ranolazine improved angina symptoms, exercise tolerance, and decreased angina attacks and GTN consumption.[252-258]

- Trimetazidine

IIa,B
  - In small clinical studies, trimetazidine has been shown to be effective in providing angina symptom relief, reduction in the need for nitrates, time to onset of ST depression and improving functional capacity.[259-261] It is useful as monotherapy and in combination with other anti-ischaemic agents.[259-261]

Key Recommendations 8:

- Patients with NSTE-ACS should be on DAPT.
  - ➢ Aspirin should be given at the time of diagnosis.
  - ➢ The timing of the second antiplatelet agent will depend on the agent used. No firm recommendations can be made about pre-treatment.
    - Clopidogrel and ticagrelor, in general, can be administered early
    - Prasugrel should be given after the coronary angiogram before proceeding to PCI.
  - ➢ Duration of DAPT will depend on the risk of bleeding versus the thrombotic risk. Ideally all patients should be given for 1 year but patients with high bleeding risk can be given DAPT for a shorter period of 3-6 months.
- Patients with NSTE-ACS treated medically (without an invasive strategy) should be on s.c. LMWH or s.c. fondaparinux for 2-8 days or until hospital discharge.

Key Recommendations 9:

- High dose statins should be initiated soon after diagnosis.
- In patients who have angina/ischemia, β-blockers and/or non-dihydropyridine CCBs should be prescribed as first-line treatment to reduce angina because it is widely available.
- Long-acting nitrates, trimetazidime and ranolazine are recommended as add-on therapy in patients who remain symptomatic. Ivabradine may also be considered for in patients with normal sinus rhythm, especially in those who have a contraindication to or intolerance to β-blockers and if the resting HR is above 70/min.

7.4 Revascularization Strategies

There is a strong rationale for early revascularization in patients with NSTE-ACS who are at intermediate/high risk and very high risk for MACE post NSTE-ACS. (section 5.2. page 60)

Contemporary pharmacotherapy (availability of more potent antiplatelet agents, the use of high intensity statin), percutaneous coronary intervention (PCI) techniques and newer devices have reduced the hazards of the procedure especially among experienced operators performing these in high-risk patients during the index hospital admission.

The decision for coronary angiography with view to revascularization should be weighed against the benefits and harm of the procedure, patient preferences, ischaemic and bleeding risks, and the impact of other major co-morbidities.

The indication for coronary angiography and the timing for myocardial revascularization depends on:

- Clinical presentation
- Risk scores (as outlined in section 5.2, page 60)
- Comorbidities
- Presence of high-risk features
- Frailty
- Cognitive status
- Estimated life expectancy
- Functional and anatomic severity of the underlying CAD

Potential benefits of early coronary angiography and revascularization are:

- Diagnostic accuracy
- Better risk stratification
- Faster symptom relief
- Improved short and long-term prognosis and quality of life
- Shortened duration of hospitalisation

Patients with features indicating that they are very high risk/high risk and presenting to non-PCI capable centres should be considered for immediate transfer to a PCI capable centre after initial stabilization.[108]

7.4.1 Routine early invasive management [144-148]

The rationale for this strategy is to:

- Confirm the diagnosis and identify the culprit lesion
- Rapidly risk stratify patients by assessing their coronary anatomy
- Allow for earlier revascularization and preventing MACE
- Facilitate early discharge

I,B It has been shown to improve clinical outcomes, reduce recurrent ACS events, subsequent rehospitalisation and revascularization.[149,262-265] However, no reduction in mortality has been observed.

Thus, an early invasive strategy in high-risk NSTE-ACS patients predominantly reduces recurrent ischemia (rather than the hard outcomes of recurrent MI or death). This strategy reduces length of stay and cost but it creates a logistical burden on cardiac catheterisation labs, especially during weekends.[108] Also, the cost-effectiveness of this approach in those with substantial co-morbidities or in the setting of rural or remote patients has not been studied.

7.4.2 Urgent vs early invasive management

I,B
- Urgent invasive strategy - (Immediate, as soon as possible)
  - Ideally the management should be similar to STEMI in terms of the rapidness to revascularization.
  - Patients with very high risk NSTE-ACS have a poor short and long-term prognosis if left untreated.[149,150]

I,A
- Early invasive strategy (within 24 h of hospital admission)
  - It is recommended in patients with at least one high-risk criteria.[266-268]
  - This implies timely transfer of patients from non-PCI centres to PCI capable hospitals.

I,A
- Invasive strategy (within 72 h of hospital admission)
  - This is the recommended maximal delay for angiography in patients with at least one intermediate risk criteria, recurrent symptoms or known ischemia on non-invasive testing.[150,262]

III,B
- Routine invasive coronary angiogram is not recommended in low risk patients. Patients with no recurrence of symptoms and none of the criteria as listed in Table 2, page 38 are to be considered at low risk of ischaemic events.[148,269]

I,A These patients are recommended to have non-invasive assessment for inducible or silent ischemia.[270]

III,C In patients with extensive comorbidities, an invasive strategy should only considered after evaluating the risk-benefit ratio (e.g., hepatic, renal, pulmonary failure, cancer).

7.4.3. Routine early conservative management (selective invasive therapy)

I,C This strategy can be advocated at non-PCI capable centres, where there are barriers to PCI, in the elderly or in frail patients and patients with comorbidities such as dementia, severe chronic renal insufficiency or cancer.

The use of aggressive anticoagulant and antiplatelet agents has also reduced the incidence of adverse outcomes in patients managed conservatively. [148,269-271] Selective coronary angiography/ revascularization is indicated for those who cannot be stabilised medically or in whom objective evidence of significant ischemia is provoked in the sub-acute phase.

IIa, A A conservative strategy is recommended for women who are stabilised and remain biomarker negative.[149,272]

IIa, A An early invasive or conservative strategy are both reasonable options for men who are stabilised and remain biomarker negative.[149,272]

In initially stabilised patients, an ischemia-guided strategy may be considered for patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events.[269,273,274]

I,C

Patients with NSTE-ACS treated conservatively are at risk of developing recurrent adverse cardiac events. Thus, these patients need to be evaluated periodically for reversible ischemia using non-invasive tests. If there is a change in symptoms or clinical condition or if ischemia is present, they should be considered for coronary angiography and revascularization.

The main advantage offered by this selective ischemia-guided strategy is that some patients' conditions stabilise during medical therapy and will not require coronary angiography and revascularization. Consequently, it may potentially avoid costly and possibly unnecessary invasive procedures.

Wherever possible, patients who have undergone intervention should undergo complete revascularization either at the same sitting or as a staged procedure.[275] The PCI of non-culprit lesions especially if they are between 50-70%, should be guided by Fractional Flow Reserve measurement:[7,276]

- FFR < 0.8 - intervene
- FFR > 0.8 - medical therapy

Key Messages 8#:

- An early as opposed to a delayed invasive strategy is safe and associated with a lower risk of refractory ischemia and a shorter duration of hospital stay.

Key Recommendations 10:

- The selection of the optimal timing of invasive coronary angiography and revascularization should be guided by the individual's risk for a MACE. (Table 2, page 38) Patients at:
  - Very high risk should undergo an immediate invasive strategy (<2 h).
  - High risk should be recommended for an early invasive strategy (<24 h).
  - Intermediate risk are recommended to undergo an invasive strategy but this may be delayed for a maximum of 72 h window period from admission to coronary angiography.
  - Low risk should be assessed non-invasively for ischemia.
- All patients should receive optimal medical therapy consisting of DAPT, statins and where necessary, anti-ischemic agents.

8. NSTE-ACS IN SPECIAL GROUPS

8.1 NSTE-ACS in Older Persons

Age is a powerful risk factor for CVD and also an independent risk factor for adverse outcomes after CVD events, for complications after cardiovascular procedures and interventions, and for side effects of pharmacotherapy.[277] International registries show that 32% to 43% of NSTE-ACS, and about 24% - 28% of STEMI admissions were for patients aged ≥ 75 years.[278,279]

These older persons with NSTE-ACS are more likely to be women, have lower body mass indices, higher prevalence of such comorbidities as hypertension, heart failure, atrial fibrillation, Transient Ischemic Attack/stroke, anemia and renal insufficency.[280,281]

The mortality rate after a first non-STEMI in the oldest old patients is highest: with respect to 1-year outcomes, among patients who were 65 - 79, 80 - 84, 85 - 89, and at least 90 years old, mortality increased progressively from 13.3% to 23.6%, 33.6%, and 45.5%, respectively.[282]

8.1.1 Clinical Presentation

A high index of suspicion is necessary to make a diagnosis of NSTE-ACS in older patients. Only 40% of those aged >85 years had chest pain on presentation compared with 77% of those aged <65 years.[283] Older patients were more likely to present with[278]:

- Dyspnea (49%)
- Diaphoresis (26%)
- Nausea and vomiting (24%)
- Neurological symptoms such as acute confusional states and syncope (19%)

Acute pulmonary edema is a common presentation of NSTE-ACS in the older person.

Type 2 MI is also common in this age group, NSTE-ACS occurring in the setting of another acute illness e.g. tachycardia, pneumonia, sepsis, bleeding episodes.

ECGs are often non diagnostic and serial ECGs are recommended to detect evolving changes. [278]

Cardiac troponins are commonly elevated > 99th percentile URL in older patients presenting without ACS or other acute illnesses known to cause to troponin elevation.[284,285] In one study almost 40% of patients aged > 70years had elevated troponins.[285] The conventional cut-off value (99th percentile: 0.014 ng/mL) provided low specificity, particularly in older adults.[286]

The observed increased hs-cTn levels is associated with the presence of pre-existing comorbidities which are independent of the effects of age.[287] Mild elevations of hs-cTnT levels are common in older patients, and increased hs-cTn levels are an independent prognostic marker in this population.[288,289] Elevations in cTn were independently associated with future cardiac events in older women without apparent clinical manifestations.[290] A different hs-cTnT cut-off may be required for patients older than 70 years but this is currently undefined.[286-289]

8.1.2. Management

Comparatively fewer studies have been conducted in older adults - specifically older persons are under-represented in many studies on CAD. Therefore, the strength of recommendations for this age group is somewhat lower than that supporting recommendations in younger adults, highlighting the dire need to conduct more research studies in this patient population.

There is limited trial data to guide management in the older person especially in the setting of advanced age (more than 75 years) or significant comorbidity (e.g. prior stroke, renal impairment). One should consider the biological age rather than the chronological age of the patient when making management decisions. This is almost always based on physician judgement rather than on biological age predictors. There are several existing predictors which are still in the research stage - the most plausible candidates being the epigenetic clock and telomere length.[291]

Older patients are a heterogenous group and the risk benefit ratio of each intervention should be individualised. As renal impairment is very common in older adults, creatinine clearance should be calculated to enable appropriate drug dosing (Appendix XIV, page 105).

Pharmacotherapy should also take into account the older person's pill burden, potential drug-drug interactions and the older person's life expectancy. Cooperation with experienced pharmacists is therefore desirable to optimise pharmacotherapy.

8.1.2.1 Pharmacotherapy

- Antiplatelet Agents
  - I,A — Both aspirin and clopidogrel (especially in those undergoing PCI) confer greater benefits in older adults.[279,292]
  - I,B — Clopidogrel is the P2Y12 inhibitor of choice in older persons > 75 years.[293]
  - IIa,B — Prasugrel may be used in patients older than 75 years at the reduced dose of 5mg.[294,295]

- Anticoagulants

I,A
  - Both UFH and LMWH are equally effective in older persons.[293,296] However bleeding risk is high with both agents. A reduced dose of 0.75-1.0mg/kg twice daily should be used in patients aged ≥75 years.[293]

I,B
  - Fondaparinux is recommended in older NSTE-ACS patients and those with STEMI who are not undergoing primary PCI. Fondaparinux is associated with less bleeding than heparin and is as efficacious.

- Others:

I,A
  - A high-dose statin regimen provides greater protection against death or MACE than a low-or moderate-dose statin regimen in older persons.[297,298]

8.1.2.2 Revascularization

IIa,B
- Older patients have greater in-hospital and long-term benefits with an early invasive strategy.[299-301] However, there is an increased risk of major bleeding.

I,C
- When selecting patients for an early invasive strategy, the risk benefit ratio must be considered. Most older patients with NSTE-ACS have multivessel disease for which CABG is more suitable than PCI. Patient preferences and frailty are important considerations in decision making. In addition, duration of hospitalization and post-surgery convalescence may be prolonged in older patients after CABG and, therefore, should be considered in counselling the patient.
- For patients with multi vessel disease and not suitable for CABG, partial revascularization of the culprit lesion may be a consideration.

8.1.2.3 Cardiac Rehabilitation

IIa,B
- Observational studies show that older patients have as much benefit as younger patients with cardiac rehabilitation after an ACS.[302,303]

8.2 NSTE-ACS in Women

Women develop CAD about a decade later than men (after menopause) and at that age have more comorbidities such as obesity, diabetes, hypertension and osteoarthritis.[304,305] However, with the use of evidence-based treatment, women have the same survival as men.[306]

Premenopausal women who develop NSTE-ACS however, have a higher in-hospital mortality and worse long term outcomes than men of the same age.[304]

8.2.1 Clinical Presentation

Women presenting with ACS often have atypical symptoms such as neck and shoulder ache and dyspnea. Often, women have non-specific ECG changes such as T wave changes even in the absence of heart disease, thus making the diagnosis of CAD difficult.

8.2.2 Management

Women with NSTE-ACS:

I,B
- should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention, with attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents to reduce bleeding risk[304, 307-311]

I,A
- and high-risk features (ie, troponin positive) should undergo an early invasive strategy[149,312,313]

III,B
- and low-risk features and troponin negative should not undergo early invasive treatment because of the lack of benefit[149,312] and the possibility of harm.[149]

8.3 NSTE-ACS in Chronic Kidney Disease (CKD)

In patients with ACS, the presence of CKD is an additional high-risk feature associated with increased mortality. The more severe the CKD, the higher the mortality.[314-316]

8.3.1 Diagnosis

The diagnosis of ACS in patients with CKD is often difficult though essential.

- Traditional diagnostic tools such as symptoms and ECG's are not always helpful.
- The interpretation of cardiac biomarkers may also be difficult.
  - cTn are increased in patients with CKD in the absence of clinical myocardial ischemia, making their interpretation problematic.[317]
  - While older cTn tests had a false-positive rate of 30% to 85% in patients with stage 5 CKD, the hs-cTn tests display elevated levels in almost 100% of these patients.[62,317]
  - In suspected ACS, it is important to do serial testing of cTn over 6-8 hours rather than to rely on a single test result.[318]
  - A distinct rise and fall in the levels over baseline correlated with clinical suspicion of an ACS (new ischemic ECG changes or new regional wall motion abnormalities on echocardiography), strongly support the diagnosis of MI.[318,319] A rise and/or fall is cTn may also occur in acute volume overload and congestive heart failure.[10]
  - Studies have shown that chronically elevated cTn levels is predictive of increased risk of mortality and cardiovascular events.[320-322]

8.3.2 Management

Patients with renal impairment were excluded from most clinical trials. In general, the management of patients with CKD is similar to those with normal renal function except for the following differences:

- Patients with CKD have more co-morbidity and are usually older.[314]
- They are at increased bleeding risks. The doses of antithrombotic agents need to be adjusted accordingly to avoid excessive bleeding (Appendix VII, page 99).[323]
- Medications:
  - Antiplatelet agents -
    - Although DAPT has become the standard of care in patients with ACS and normal renal function, the benefits in persons with CKD are uncertain and are potentially outweighed by bleeding hazards.[323,324] In these patients, treatment should be individualised.
  - Anticoagulants -
    - Heparin (both UFH and LMWH) are widely used in ACS. The bleeding risk of these agents however increases with the increasing severity of baseline renal insufficiency.[323] Dose adjustments are important. (Appendix IX, page 101)
  - Fondaparinux is contraindicated in severe renal failure (CrCl <20 mL/min)[293] There are limited clinical data available on the use of Fondaparinux for the treatment of UA/NSTEMI and STEMI in patients with creatinine clearance between 20 to 30 ml/min.[325] Therefore, the physician should determine if the benefit of treatment outweighs the risk.
  - Others - Similar absolute reduction in short-term mortality were observed with the use of:
  - Aspirin - 21% absolute reduction in mortality in dialysis patients, and a 23% reduction in non-dialysis patients.[326]
  - β-blocker therapy was associated with a 14% absolute reduction in mortality in both the dialysis and non-dialysis patients.[326]
  - ACE-inhibitor use was associated with a 16% absolute reduction in 30-day mortality in dialysis patients and a 5% reduction in non-dialysis patients.[326]
  - Statins in combination with ezetimibe, however, was found only to be beneficial in mild to moderate CKD. In patients on dialysis, there is a lack of evidence concerning the cardio vascular benefits of statins.[327]

I,B

- Revascularization:
  - An invasive strategy is superior and associated with a decrease in mortality when compared to an initial conservative strategy (invasive management only after failed medical therapy or for objective evidence of ischemia).[314]

- An early invasive strategy is superior to a delayed invasive strategy, the benefit, however, declines with lower renal function, and is less certain in those with renal failure or on dialysis. [314,328,329]
  - PCI in patients with CKD is associated with increased risks of:
  - bleeding
  - worsening renal function and acute on chronic renal failure due to contrast nephropathy and/or cholesterol embolization. Strategies should be taken to reduce this risk.
  - the procedure -These patients often have calcified, tortuous vessels which increases the risk and complexity of PCI.

Key Messages 9#:

- When managing older patients, one should consider the biological age rather than the chronological age.
- Older persons have greater in-hospital and long term benefits with an early invasive strategy. However, there is an increased risk of major bleeding.
- Women should be managed with the same pharmacological therapy as that for men for acute care and for secondary prevention.
- Women who are low risk and cTn negative, should be treated medically while those who are cTn positive, should be considered for an invasive strategy.
- In general, patients with CKD should managed in a similar manner as those with normal renal function. They however have a higher bleeding tendency and doses of medications need to be adjusted according to the renal function.
- In patients with CKD, an early invasive strategy is superior to a delayed invasive strategy. The benefit, however, declines with lower renal function, and is less certain in those with renal failure or on dialysis.

9. POST-HOSPITAL DISCHARGE

The acute phase of NSTE-ACS is usually 1 to 3 months. The risk of recurrence of ischemic events, STEMI or death is highest during this period. Following this, most patients assume a clinical course similar to that of patients with chronic stable angina.

Several lifestyle modification measures and drug therapies have been shown to be effective in improving long-term outcome. However, they are underutilized. Therefore, health care providers should ensure that patients with NSTE-ACS receive appropriate treatment post-hospital discharge and ensure that patients remain compliant to treatment.

Important discharge instructions (both verbal and written instructions) should include:

- symptoms indicating worsening myocardial ischemia (chest pain/equivalent and/or dyspnea) and how to seek emergency care.
- education on the benefits and potential side effects of the prescribed medications.
- instructions on the proper and safe use of sublingual nitrates.
- lifestyle modification such as:
  - smoking cessation,
  - weight reduction and maintaining an ideal body weight
  - regular exercise and
  - a balanced diet
- importance of treating CVD risk factors (lipids, blood pressure, glucose) to target.
- scheduling of timely follow-up appointments and dates for further investigations.
- referral to a cardiac rehabilitation program where appropriate.

Refer to Malaysian CPG on Primary and Secondary Prevention of Cardiovascular Disease 2017, 1st Ed for further details.[330]

9.1 Medications Post-Discharge (Table 5)

These should include:

A. Antiplatelet agents

- DAPT consisting of a combination of:
  - 75-100mg daily aspirin.[125,153] Currently, studies are still being conducted to look at the optimal dose of aspirin in secondary prevention.[331]
    + (Plus) a P2Y12 Inhibitor either
  - 75mg daily clopidogrel[152,153] (both medically treated and following PCI) ***or***
  - 90mg bid ticagrelor[156,332] (both medically treated and following PCI) ***or***
  - 10mg daily prasugrel.[173,176] (following PCI)
- The duration of DAPT in patients with NSTE-ACS will depend on the thrombotic / ischemic versus bleeding risks. Ideally all patients should receive DAPT for 9-12 months (both medically treated patients, those post PCI and those who have undergone CABG).[181,182]
- However, in patients with high bleeding risks, a shorter period of DAPT of 3 to 6 months may be considered.[181,182,333]

B. Lipid Modifying Therapy

I,A

- There is a large body of evidence that early initiation of high dose statin therapy improves outcome regardless of baseline LDL-C levels in patient with ACS.[218-220,334-338]

I,A
- More aggressive lipid lowering further lowers cardiovascular event rates.[217,227,228, 339-343]
- If target LDL-C levels are not attained on maximally tolerated statin therapy and especially if it still remains > 2.6 mmol/l, consider the addition of ezetimibe and/or PCSK-9 inhibitors.[232-235]

C. In the presence of LVEF < 40% and /or Heart Failure

These should include:

I,A
- β -blockers[203-207]

I,A
- Renin Angiotensin Blockers (ACEIs/ARBs)[212-216,344-348]

I,A
- Aldosterone Receptor Antagonists- spironolactone, epleronone[349-351]

IIa,B
- Ivabradine - may be considered in patients on optimal medical therapy with diuretics, ACE-I, MRA and β-blockers, and[247,352]
  - ➢ still symptomatic (NYHA class II-III), and
  - ➢ having a LVEF ≤ 35%, and
  - ➢ having a resting heart rate of ≥ 70 beats/min.

I,A
- Sodium-glucose co-transporter-2 (SGLT2) inhibitors - these agents have been shown to reduce cardiovascular events in both diabetic and non-diabetic patients. In the large trials, they have been been instituted when the patient is stable.[353-356]

IIa,A
- Angiotensin Receptor-Neprilysin Inhibitor (ARNi) has been shown to cause a greater reduction in NT- Pro BNP levels than ACEI in patients with acute decompensated heart failure.[357] However when instituted early in patients post ACS (STEMI and NSTE-ACS), it did not outperform ACEI in cardiovascular event reduction.[358]

D. In the presence of Angina and/or myocardial ischemia

Anti-ischaemic therapy includes:[7]
- Sublingual nitroglycerin should be administered and patients instructed on its use.
- β-blockers and/or CCBs should be prescribed as first-line treatment to reduce angina because it is widely available.
- Ivabradine, trimetazidine, long-acting nitrates and ranolazine are recom mended as add-on therapy in patients who remain symptomatic.

E. Other co-existing Clinical conditions:

IIa,B
- Atrial Fibrillation

  In NSTE-ACS patients with AF who had undergone PCI, the use of DOAC with antiplatelet therapy is associated with a lower risk of bleeding than the standard triple therapy (DAPT + warfarin).[353-355]

The following **regimens** may be considered:

1. Warfarin + DAPT

IIa,B
- Target INR in the lower part of the recommended target range (INR: 2)[356,357]
- The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.[358]

2. DOAC + DAPT

IIa,B
- Dabigatran 110 or 150mg twice daily + aspirin <100mg daily + clopidogrel 75mg once daily for one to six months depending on bleeding risks followed by antiplatelet monotherapy and dabigatran 110 or 150mg twice daily.[353] ***or***

IIa,B
- Rivaroxaban 15mg once daily (10mg if CrCl 30-50ml/min) + aspirin + clopidogrel 75mg once daily for one to six months depending on bleeding risks followed by antiplatelet monotherapy and rivaroxaban 15mg once daily.[354] ***or***

IIa,B
- Rivaroxaban 2.5mg twice daily and aspirin 75-100mg once daily and clopidogrel 75mg once daily for one to 12 months.[354] The duration of DAPT with this combination will depend on the risk of stent thrombosis versus bleeding risk.

IIa,B
- Apixaban 5mg bid and clopidogrel 75mg once daily for 6 months resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events when compared to regimens that included warfarin, aspirin, or both.[355]

- Diabetes and/or proteinuria and/or CKD
  - Renin Angiotensin Blockers (ACEIs/ARBs)
- Hypertension
  - β-blockers,
  - Renin Angiotensin Blockers,
  - calcium channel blockers

IIb,B Evidence supporting the routine use of β-blockers and ACEI/ARB > 1-year post NSTE-ACS for the treatment of stable CAD only is less well established. [208-211, 359-362]

9.2 Investigations During Follow Up (Flowchart 2, page 36)

In the outpatient evaluation of low risk NSTE-ACS patients, the following investigations maybe considered:

- Echocardiogram to assess LV function
- Treadmill stress test
- Stress echocardiogram - treadmill or pharmacological stress
- Nuclear perfusion study
- Cardiac Magnetic resonance imaging (CMR) - stress MRI for ischemia and perfusion MRI for viability

Patients with significant demonstrable ischemia should be considered for revascularization.

Key Recommendations 11:

- Patients should be on optimal medical therapy at discharge. This includes:
  - DAPT with aspirin + clopidogrel (or ticagrelor or prasugrel)
  - ***And*** High intensity statins to achieve LDL-C target of < 1.8 mmol/l (preferably < 1.4 mmol/l), the lower the better.
  - ***And*** in the presence of angina /myocardial ischemia, β-blockers and/or CCBs should be prescribed as first-line treatment and ivabradine, trimetazidine, long-acting nitrates and ranolazine are recommended as add-on therapy in patients who remain symptomatic.
  - ***And*** in the presence of LVEF< 40% and heart failure, β-blockers, Renin Angiotensin Blockers (ACEIs/ARBs) and Aldosterone Receptor Antagonists-spironolactone, eplerenone should be given. SGLT2-inhibitors can be instituted in both stable diabetic and non-diabetic patients..

Key Recommendations 12:

- Low risk patients should be assessed non-invasively for ischemia. (Flowchart 2, page 36)
- If they have troubling symptoms and/or significant myocardial ischemia, they should be referred for coronary angiography with view to revascularization.

10. CARDIAC REHABILITATION

Cardiac rehabilitation is aimed at improving the physical and psychological well-being of the patient. It has been shown to reduce mortality by approximately 20%-25%.[363-365] There was also a trend towards reduction in non-fatal recurrent MI over a median follow-up of 12 months.[366]

Angina management programs have been shown to decrease the episodes of chest pain by 70%, reduce nitrate use by 65% and improve exercise tolerance by 57%.[366]

I,B All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either as in-patient or during the first outpatient visit where available.[367-371]

These comprehensive programs provide patient education, enhance regular exercise, monitor risk factors, and address lifestyle modification.[372] Aerobic exercise training can generally begin 1 to 2 weeks after discharge in patients treated with PCI or CABG.[373] Mild-to-moderate resistance training can be

considered and started 2 to 4 weeks after aerobic training.[374] Additional restrictions apply when residual ischemia is present and patient has not been revascularized.

III,B Exercise training should not be prescribed in patients during the first week after an acute MI and in those with progressive and unstable angina.[375]

I,B Regular physical activity reduces symptoms in patients with cardiovascular disease, enhances functional capacity, improves other risk factors such as insulin resistance and glucose control, and is important in weight control.[372]

Smoking is an independent risk factor for CVD that accelerates atherosclerosis and has been linked with other mechanisms that precipitate thrombosis, hemorrhage, or vasoconstriction, which can all lead to ACS. It also interacts with other CV risk factors, such as hypertension, glucose intolerance and low serum levels of HDL-C.[376,377] The risk of developing diabetes is 30 - 40% higher for active smokers than nonsmokers.[376]

I,B Stopping smoking is an important and effective preventive measure.[376] There is significant reduction on morbidity within the first 6 months of quitting and the risks of CVD almost equals the risk of never smokers after 10 - 15 years of cessation.[376] For smoking interventions please refer to the Malaysian CPG on Prevention of Cardiovascular Disease. 1st Ed, 2017[378] and the Recommendations of the Steering Committee on Tobacco control in Malaysia (Appendix XV,pages 106-110).[384]

10.1 Cardiac Rehabilitation Programs (CRP)

These include:

- Counselling and educating the patient and family members on CAD and medications used to treat the conditions.
- Beginning an exercise program.
- Helping the patient modify risk factors such as high blood pressure, smoking, high blood cholesterol, physical inactivity, obesity and diabetes.
- Providing vocational guidance to enable the patient to return to work.
- Supplying information on physical limitations.
- Educating and ensuring compliance to medications.
- Providing emotional support.

There are 4 Phases using the Wenger Model:[376]

- Acute phase (Phase I):
  - This is the in-hospital period immediately following the MI and leading up to discharge.
  - It involves early mobilisation of the patient.
  - It can be started after 48 hours of hospitalisation in stable patients.
- Convalescent phase (Phase II):
  - This is at home/convalescent hospital.
  - This continues the program started in phase I until the myocardial scar has matured.
- Training phase (Phase III):
  - This is initiated after about 4 to 6 weeks and the patient is safe for aerobic exercise.
- Maintenance (Phase IV):
  - This is home-based regular exercise to maintain aerobic conditioning gains made in phase III.

Exercise training programs should include warm-up, resistance training, endurance training, and cool-down. Examples:

- Warm-up: stretching, warm-up exercise, low-intensity (slow) walking.
- Main exercises: aerobic exercise and resistance training at prescribed intensity.
- Cool-down: low-intensity (slow) walking, stretching, cooling-down exercise.

10.2 Return to Physical Activity

Physical activity can be resumed at 50% of maximal exercise capacity in a patient with preserved LV function without inducible ischemia within 1 week post-discharge. This should be gradually increased over time preferably guided by treadmill stress test.

Exercise begins with low-level aerobic exercises of the upper and lower limbs at an intensity that is below his/her angina threshold.

Daily walking can be encouraged soon after discharge for most patients.

I,B It is strongly recommended that post-ACS patients achieve ≥30 minutes of low-moderate aerobic activity such as brisk walking on at least 5 days per week within 2 weeks of discharge.[330]

10.3 Risk Factor Modification:

- Smoking cessation - Patients who quit smoking can reduce the rate of reinfarction and death as early as 1 year.
- Weight - Achieve or maintain optimal body weight.
- Exercise - Encourage a minimum of 30 - 60 minutes of moderate activity 5 times weekly (walking, cycling, swimming or other equivalent aerobic activities).
- Diet - To consume low cholesterol or low saturated fat diet.
- Lipids - Aim for an LDL-C < 1.8mmol/l, preferably <1.4mmol/l.
- Hypertension - Aim for a blood pressure of <140/85mmHg. In diabetics the target is < 130/80mmHg. In elderly patients, a higher BP target may be acceptable.
- Diabetes mellitus - Optimal glycemic control in diabetes. (Refer CPG on Diabetes)

10.4 Return to Sexual Activity and Fitness for Commercial Air Travel

Refer to Malaysian CPG on the Management of ST Elevation Myocardial Infarction, 2019, 4th Ed.[8]

Key Messages 10#:

- All eligible patients with NSTE-ACS should be referred to a comprehensive cardiovascular rehabilitation program either as in-patient or during the first outpatient visit where available

11. MONITORING OF ACTIVITY AND QUALITY ASSURANCE

Implementation of the recommendations listed in this CPG can be accomplished by:

- Continuous medical education via regular seminars, lectures and roadshows particularly at the district hospital and family medicine clinics. Education and training is the most important aspect of the implementation of this CPG.
- Widespread availability of this CPG to healthcare providers via printed copies, electronic websites, etc.

Key Recommendations 13:

- Regular audit of performance and outcome measures (Table 7, page 42) should be performed periodically to monitor and improve quality of care.

Appendix I: BRAUNWALD'S CLASSIFICATION OF UNSTABLE ANGINA*

Severity	CLINICAL CIRCUMSTANCES		
	A Develops in Presence of Extracardiac Condition That Intensifies Myocardial Ischemia **(Secondary UA)**	B Develops in Absence of Extracardiac Condition **(Primary UA)**	C Develops Within 2 weeks of MI **(Postinfarction UA)**
I-New onset of severe angina or accelerated angina; no rest pain	I A	IB	IC
II-Angina at rest within past month but not within preceding 48 hours (angina at rest, subacute)	IIA	IIB	IIC
III-Angina at rest within 48 hours (angina at rest, acute)	IIIA	IIIB-T_{neg} IIIB-T_{pos}	IIIC

UA : Unstable angina; T : Troponins

**Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation. 2000 ;102 :118-22.*

Appendix II: ELEVATIONS OF CARDIAC TROPONIN IN THE ABSENCE OF OVERT ISCHEMIC HEART DISEASE.

Damage related to secondary myocardial ischemia (MI type 2)
Tachy - or bradyarrhythmias
Aortic dissection and severe aortic valve disease
Hypo - or hypertension, e.g. hemorrhagic shock, hypertensive emergency
Acute and chronic HF without significant concomitant CAD
Hypertrophic cardiomyopathy
Coronary vasculitis, e.g. systemic lupus erythaematosus, Kawasaki syndrome
Coronary endothelial dysfunction without significant CAD e.g., cocaine abuse
Damage not related to myocardial ischemia
Cardiac contusion
Cardiac incisions with surgery
Radiofrequency or cryoablation therapy
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents, e.g. anthracyclines, Herceptin, carbon monoxide poisoning
Severe burns affecting > 30% of body surface
Indeterminant or multifactorial group
Apical ballooning syndrome
Severe pulmonary embolism or pulmonary hypertension
Peripartum cardiomyopathy
Renal failure
Severe acute neurological disease e.g., stroke, trauma
Infiltrative disease e.g., amyloidosis, sarcoidosis
Extreme exertion
Sepsis
Acute respiratory failure
Frequent defibrillator shocks

Adapted from Thygesen K et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010; 31:2197-2204.

Appendix III : HEART SCORE# ++

HEART SCORE		
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST segment depression	2
	Non-specific repolarization disturbances	1
	Normal	0
Age	≥ 65 years	2
	> 45 - < 65 years	1
	≤ 45 years	0
Risk Factors	⩾ 3 risk factors* *or* history of atherosclerotic disease**	2
	1 or 2 risk factors	1
	No known risk factors	0
Troponins	≥ 3 x normal	2
	> 1 - < 3 x normal	1
	≤ normal limit	0

** Risk factors include: currently treated diabetes mellitus, current or recent smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of coronary artery disease, obesity (body mass index >30).*

*** History of atherosclerotic disease include: coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease, irrespective of the risk factors for coronary artery disease.*

#Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J. 2008;16(6):191-196.

+ In Modified Heart Score, the hs-cTn is used instead of cardiac troponins.

++ Willems MN, van de Wijngaart DJ, Bergman H, et al. Addition of heart score to high-sensitivity troponin T versus conventional troponin T in risk stratification of patients with chest pain at the coronary emergency rooms. Neth Heart J. 2014;22:552–556.

APPENDIX IV: TIMI RISK SCORE FOR UA/NSTEMI*

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0-1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6-7	40.9

** Derived from clinical trial data*

The TIMI risk score is determined by the sum of the presence of 7 variables at admission:
1 point is given for each of the following variables:

- Age 65 y or older
- At least 3 risk factors for CAD (family history of premature CAD, hypertension > 140/90 or on antihypertensives, Low HDL cholesterol (< 40 mg/dL), current cigarette smoker, diabetes mellitus)
- Known CAD (coronary stenosis of ≥ 50%)
- Use of aspirin in prior 7 days
- ST-segment deviation (≥ 0.5mm) on ECG
- At least 2 anginal episodes in prior 24 h
- Elevated serum cardiac biomarkers

Total Score = 7 points

Low Risk : ≤ 2 point
Moderate Risk : 3 - 4 points
High Risk : ≥ 5 points

Adapted from :
Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000; 284 : 835-42 .

Appendix V: GRACE PREDICTION SCORE CARD AND NOMOGRAM FOR ALL CAUSE MORTALITY FROM DISCHARGE TO 6 MONTHS*

Risk Calculator for 6-Month Postdischarge Mortality After Hospitalization for Acute Coronary Syndrome

Record the points for each variable at the bottom left and sum the points to calculate the total risk score. Find the total score on the x-axis of the nomogram plot. The corresponding probability on the y-axis is the estimated probability of all-cause mortality from hospital discharge to 6 monts

Medical History

	Points
① Age in Years	
≤ 29	0
30 - 39	0
40 - 49	18
50 - 59	36
60 - 69	55
70 - 79	73
80 - 90	91
≥ 90	100
② History of Congestive Heart Failure	24
③ History of Myocardial Infarction	12

Findings at Initial Hospital Presentation

	Points
④ Resting Heart Rate, Beats/min	
≤ 49.9	0
50 - 69.9	3
70 - 89.9	9
90 - 109.9	14
110 - 149.9	23
150 - 199.9	35
≥ 200	43
⑤ Systolic Blood Pressure, mm Hg	
≤ 79.9	24
80 - 99.9	22
100 - 139.9	18
120 - 139.9	14
140 - 159.9	10
160 - 199.9	4
≥ 200	0
	1
⑥ ST-Segment Depression	11

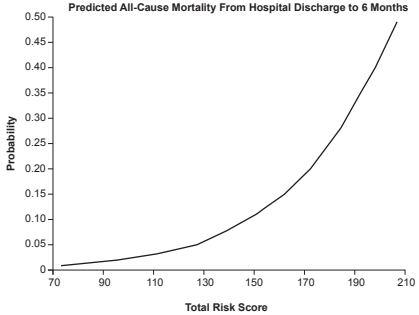
Findings During Hospitalization

	Points
⑦ Initial Serum Creatinine, mg/dL	
0 - 0.39	1
0.4 - 0.79	3
0.8 - 1.19	5
1.2 - 1.59	7
1.6 - 1.99	9
2 - 3.99	15
≥ 4	20
⑧ Elevated Cardiac Enzymes	15
⑨ No In Hospital Percutaneous Coronary Invervention	14

Points

① .....
② .....
③ .....
④ .....
⑤ .....
⑥ .....
⑦ .....
⑧ .....
⑨ .....

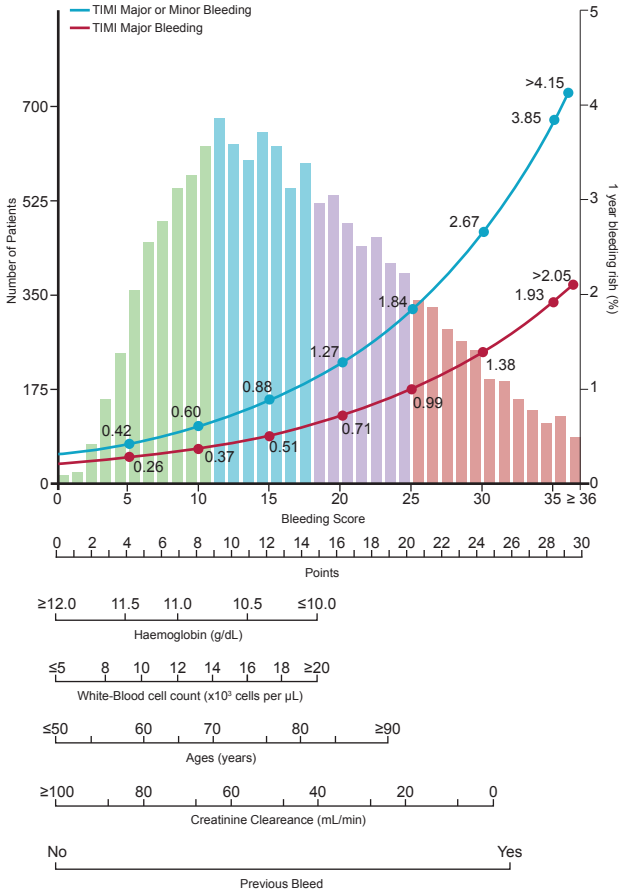
Total Risk Score _____(Sum of Points)
Mortality Risk _____(From Plot)



Derived from international registry of ACS patients

**Fox KAA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial, infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study(GRACE), BMJ, 2006:333:1091*

Appendix VI: PRECISE -DAPT SCORE *



Costa F, van Klaveren D, James S, Heg D, Räber L et al. PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073):1025-1034

Available at : http://www.precisedaptscore.com/predapt/webcalculator.html

Appendix VII: P2Y12 INHIBITORS*

	Clopidogrel	Prasugrel	Ticagrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine
Administration	Oral	Oral	Oral
Dose	300 - 600mg orally then 75mg a day	60mg orally then 10mg a day	180mg orally then 90mg twice a day
Dosing in CKD			
• **Stage 3** (eGFR 30–59 mL/min/1.73m2)	No dose adjustment	No dose adjustment	No dose adjustment
• **Stage 4** (eGFR 15–29 mL/min/1.73m2)	No dose adjustment	No dose adjustment	No dose adjustment
• **Stage 5** (eGFR <15 mL/min/1.73m2) (e.g., stent thrombosis prevention)	Use only for selected indications (e.g., stent thrombosis prevention)	Not recommended	Not recommended
Withdrawal before surgery	5 days[c]	7 days[c]	5 days[c]
Nonbleeding significant side effects	None	None	Dyspnea, elevated serum creatinine, elevated uric acid
Plasma half-life of active P2Y12 inhibitor[d]	30 - 60 min	30 - 6 0 min[e]	6 - 12 hours
Inhibition of adenosine reuptake	No	No	Yes

**Adapted from Roffi M, Patrono C, Collet J-P, et.al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3): 267-315*

[a] 50% inhibition of ADP-induced platelet aggregation.
[b] Onset of effect may be delayed if intestinal absorption is delayed (e.g. by opiate).
[c] Shortening may be considered if indicated by platelet function tests and low bleeding risk.

Appendix VIII: GLYCOPROTEIN (GP) IIb/IIIa INHIBITORS*

	Abciximab	Tirofiban	Eptifibatide
Type	Antibody	Nonpeptide	Cyclic peptide
Inhibition	Non-competitive	Competitive	Competitive
Plasma half-life	10 - 30 min	2 hours	2.5 hours
Recovery of platelet function	Slow (24-48h)	Fast (4-8h)	Fast (<4h)
Antigenicity	Present	Absent	Absent
Clearance	Platelet binding, **unbound substance via proteolytic cleavage**	Renal (98%)	Renal (60-70%) Biliar (20-30%)
Recommended dose	IV bolus 0.25 mg/kg, infusion 0.125 µg/kg/min (max.10 µg/min)	IV bolus 25 µg/kg or 10 µg/kg, infusion 0.15 µg/kg/min	IV bolus 180 µg/kg, infusion 2 µg/kg/min
Dosing in CKD			
• **Stage 3** (eGFR 30 - 59 mL/min/1.73m2)	No dose adjustment	No dose adjustment	No adjustment of bolus, reduce infusion rate to 1 µg/kg/min i eGFR <50 mL/min/1.73m2
• **Stage 4** (eGFR 15 - 29 mL/min/1.73m2)	No dose adjustment	No adjustment of bolus, reduce infusion to 0.05 µg/kg/min	Not Recommended
• **Stage 5** (eGFR <15 mL/min/1.73m2)	No dose adjustment	Not recommended	Not recommended

References:

- *Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3): 267-315.*
- *Washam JB, Herzog CA, Beitelshees AL, Cohen MG, Henry TD, Kapur NK, Mega JL, Menon V, Page RL, 2nd, Newby LK. Pharmacotherapy in chronic kidney disease patients presenting with acute coronary syndrome: a scientific statement from the American Heart Association. Circulation. 2015;131(12): 1123-49.*
- *De Luca G. Glycoprotein IIb-IIIa inhibitors. Cardiovasc Ther. 2012;30(5): e242-54.*

Appendix IX: ANTICOAGULANT AGENTS*

	FONDAPARINUX	ENOXAPARIN	UFH
Dose	SC 2.5mg daily	SC 1 mg/kg BD	IV bolus 60 IU/kg (max 4000 IU), infusion 12IU/kg/hour (max 1000 IU/hour) adjusted to maintain aPTT 1.5 - 2.0x normal
Duration of therapy	8 days or duration of hospitalisation	2 - 8 days	2 - 8 days
Dosing in CKD			
• **Stage 3** CrCl 30 - 59 ml/min	No dose adjustment	No dose adjustment	No dose adjustment
• **Stage 4** CrCl 15 - 29 mL/min	Not recommended if CrCl < 20 ml/min**	SC 1 mg/kg OD	No dose adjustment
• **Stage 5** CrCl < 15 mL/min	Not recommended	SC 1 mg/kg OD	No dose adjustment

**As stated in MIMS Malaysia (https://www.mims.com/malaysia) and IBM Micromedex drug Reference. Retrieved 27th July 2019*

***There are limited clinical data available on the use of Fondaparinux for the treatment of UA/NSTEMI and STEMI in patients with creatinine clearance between 20 to 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk.It is not recommended when CrCl< 20 ml/min. https://india-pharma.gsk.com/media/701015/arixtra.pdf (Accessed 14th October 2019).*

Appendix X: β-blockers in NSTE-ACS*

β-blockers	Bisoprolol	Carvedilol	Metoprolol
Initiation dose	1.25mg od	3.125mg bd	25mg bd
Target dose	10mg od	25mg bd	100mg bd
Dose equivalence [80]	5mg	25mg	100mg
Hepatic impairment	Used with caution	Severe liver disease: avoid	Used with caution
Renal impairment	CrCl < 40mL/min: used with caution	No adjustment needed	No adjustment needed
• **Stage 4:** CrCl 15-30mL/min			
• **Stage 5:** CrCl < 15mL/min			
Metabolism	Liver: 50%	Liver	Liver
Elimination	Renal: 50 - 60% unchanged	Fecal / biliary	Renal: 95%

**As stated in MIMS Malaysia (https://www.mims.com/malaysia) and IBM Micromedex drug Reference. Retrieved 27th July 2019.*

Appendix XI: ACEI/ARB in NSTE-ACS*

ACE/ARB	Captopril	Ramipril	Enalapril	Perindopril
Initiation dose	6.25mg bd-tds	2.5mg bd	2.5-5mg od	2mg od (perindopril erbumine) / -2.5mg od (perindopril arginine)
Target dose	25 - 50mg tds	10mg od	20mg bd	8 - 10mg od
Dose equivalence [107]	50mg	2.5mg	5mg	4mg
Dose adjustment				
Hepatic impairment	No dose adjustment			
Renal impairment				
• **Stage 3:** CrCl 30-59mL/min	> 40ml/min 25-50mg daily. Max: 150mg daily.	Not necessary to adjust the initial dose. Max: 5mg/day.	No dose adjustment	2mg or 2.5mg od
• **Stage 4:** CrCl 15-29mL/min	21-40mL/min 25mg daily. Max: 100mg daily. 10-20mL/min 12.5mg daily. Max: 75mg daily.	10-30mL/min Initially, 1.25mg/day. Max: 5mg/day.	≤ 30 mL/min Initially, 2.5mg/day.	2mg or 2.5mg every other day
• **Stage 5:** CrCl < 15mL/min	< 10mL/min 6.25mg daily. Max: 37.5mg daily.	-		2mg or 2.5mg on dialysis days
Metabolism	Liver	Liver	Liver	Liver
Elimination	Renal: >95%	Renal: 60% Fecal: 40%	Renal: 61% Fecal: 33%	Renal: 75%

**As stated in MIMS Malaysia (https://www.mims.com/malaysia). Retrieved 28th July 2019.*

Appendix XII: Recommended dosages of Nitrates*

		Glyceryl trinitrate (GTN)					Isosorbide dinitrate		Isosorbide mononitrate
Route	Sublingual	Intra-venous	Spray	Patch	Buccal	Topical (2% ointment)	Intra-venous	Oral	Oral (long-acting)
Dose	0.3 - 0.6 mg, can repeat up to 3 times at 5 minute intervals	5 - 200 µg/min†	0.4 - 0.8 mg per metered dose, no >3 sprays at 5 minute intervals	2.5 - 20 mg over 12 hours on, then 12 hours off	2 mg, placed between the gum and upper lip, increase to 3 mg if necessary. Severe angina: 5 mg may be given	Apply 0.5 - 2 inches on a convenient area of the skin bd or every 3-4 hours if necessary; cover the area after application	2 - 12mg/hr	10-20mg, 2-3 times daily	30 - 60mg daily
Time of Onset	1 - 3 min	1 - 2 min	2 min	40 - 60 min	1 - 3 min	20 - 60 min	1 min	30 - 60 min	1 - 2 hours
Maximum dose	3 doses within 15 min	400 µg/min	3 sprays min within 15	20mg/day	15mg/day	6 applications/day	20mg/hr	240mg/day	240mg/day
Dose adjustment	No dose adjustment in renal/hepatic impairment								
Metabolism	Liver	Liver	Liver	Liver	Liver	Liver	Liver	Liver	Liver
Elimination	Renal: 22%	Renal: 22%	Renal: 22%	Renal: 22%	Renal: 22%	Renal: 22%	Renal: 80 - 90%	Renal: 80 - 90%	Renal: 78%

**As stated in MIMS Malaysia (https://www.mims.com/malaysia). Retrieved 27th July 2019.*
†Initially, 10 mcg/min, increase in increment of 10 mcg/min at approximately 30-minute intervals, according to patient requirement

Appendix XIII: CCBs*

CCB	Diltiazem	Verapamil	Amlodipine	Nifedipine ER
Dose	Immediate release, 30 - 90mg tds; Slow release, 100 - 200mg od	Immediate release, 40 - 80mg tds; Slow release, 120 - 240mg od	2.5 -10mg od	Slow release, 30 - 90mg od
Dose Equivalence [86]	-	-	2.5mg	20mg
Maximum Dose	360mg/day	480mg/day	10mg/day	120mg/day
Hepatic Impairment	Used with caution/consider dose reduction	Used with caution/low dose	Initial dose: 2.5mg od	Caution: may need to reduce dose
Renal Impairment	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Metabolism	Liver	Liver	Liver	Liver
Elimination	Renal: 35% Fecal: 60 - 65%	Renal: 70%	Renal: 60% Fecal: 20 - 25%	Renal: 70 - 80% Fecal: 20%

**As stated in MIMS Malaysia (https://www.mims.com/malaysia). Retrieved 27th July 2019.*

APPENDIX XIV: CALCULATION OF eGFR FOR DRUG DOSING ADJUSTMENTS

Estimated GFR (eGFR) can be derived from various equations including:

- CKD-EPI Creatinine (CKD -EPI) Equation- (most commonly used)
- Modification of Diet in Renal Disease Study (MDRD) Equation.

In a local population, the CKD-EPI Equation performs just as well as CKD-MDRD for GFR 60-89ml/min and better at the other GFR levels.[380]

In practice, there are number of simple calculators that may be accessed to calculate eGFR, for example:
https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi
https://www.mdcalc.com/mdrd-gfr-equation

Creatinine clearance (Cr Cl) is determined by the Cockcroft-Gault (CG) Equation.In the past, this equation was used for drug dosing adjustments based on creatinine clearance. However, in more recent practice, the CKD-EPI equation tends to be used for drug dosing based on eGFR, especially for newer generation drugs. However, drug dosing adjustment should be done according to the United States Food and Drug Administrative - or European Medicines Agency-approved product labelling.

APPENDIX XV :SMOKING AND CHRONIC NON COMMUNICABLE DISEASES

Recommendations of the Steering Committee on Tobacco control in Malaysia

Smoking of tobacco and tobacco products (cigarette, electronic cigarette/ vape, shisha, pipe, cigar etc.) can lead to various complications of chronic non communicable diseases (NCD) such as coronary heart disease, cancers and chronic lung disease. It is the main cause of death worldwide whereby 6 million people die every year as a consequence of this habit (WHO Tobacco Fact Sheet, 2016).

Smoking has been classified as a chronic disease under Tobacco/Nicotine Dependence in International Classification of Diseases (ICD)-10 diagnostic code since 2015 and Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (DSM-IV Criteria).

In Malaysia, smoking kills around 20,000 people a year (Tobacco Atlas, 2015) while the cost of treating three out of six chronic diseases related to tobacco was estimated around MYR 2.92 billion (Global Adults Tobacco Survey, 2011).

The National Health Morbidity Survey (NHMS) 2019 estimated that the prevalence of current tobacco smoker in Malaysia age 15 years and above was 21.3%, with approximately 4.8 million people with males being higher than females (male: 40.5%, female: 1.2%). There was a small decline from the 2015 NHMS where the prevalence of active tobacco smoker was 22.8%, male was 43% and female was 1.4%.

The Tobacco and E-cigarette Survey Among Adolescents (TECMA) 2016 has stated the prevalence of smoker among adolescent age between 13 to 15 years was 14.8% as compared to 13.2% which was reported in the National Health and Morbidity Survey (NHMS): Adolescent Health 2017. The prevalence of smoker among boys dropped from 26.1% in 2016 (TECMA) to 20.6% in 2017 (NHMS). However, the prevalence of smoker among girls increased from 2.4% in 2016 (TECMA) to 5.7% in 2017 (NHMS).

Hence, the decision for treatment of smoking to be integrated with other chronic non communicable diseases was made during the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) Steering Committee Meeting in December 2019 chaired by the honorable Health Minister of Malaysia.

The treatment for smoking is based on Clinical Practice Guideline: Treatment for Tobacco Use Disorder 2016-(Tables A-D)

Table A: Assessment And Treatment Tobacco Use Disorder

ASSESSMENT & TREATMENT
Ask and document smoking status for all patients.
Provide brief advice on quit smoking at every visit to all smokers.
Assess level of nicotine addiction using Modified Fagerström Test for Cigarette Dependence Questionnaire **(COMPULSORY)** and verify smoking status using carbon monoxide (CO) breath analyser **(IF AVAILABLE)**.
Offer pharmacotherapy to **all smokers** who are attempting to quit, unless contraindicated.
If selected, use NRT for at least eight to twelve weeks, whereas varenicline should be used for at least twelve weeks.
Combination therapy (e.g., two NRTs, a non-NRT, e.g. bupropion with a NRT) is better than monotherapy in smoking cessation treatment and may be most useful for those smokers at highest risk of relapse.
Use smoking cessation medications with caution in special populations (e.g., children and adolescents, pregnant, breastfeeding women, psychiatric and substance abuse disorder patients).
Arrange a minimum of six to eight face to face follow-up sessions for smoking cessation interventions in six months through counselling support team (Health education officer, pharmacists or any officer trained for quit smoking services).

Table B: Modified Fagerstrom Test For Cigarette Dependence Questionnaire

Question	Option	Point
How soon after you wake up do you smoke your first cigarette?	☐ Within 5 minutes ☐ 5 to 30 minutes ☐ 31 to 60 minutes ☐ After 60 minutes	☐ 3 ☐ 2 ☐ 1 ☐ 0
Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?	☐ Yes ☐ No	☐ 1 ☐ 0
Which cigarette would you most hate to give up; which cigarette do you treasure the most?	☐ The first one in the morning ☐ Any other one	☐ 1 ☐ 0
How many cigarettes do you smoke each day?	☐ 10 or fewer ☐ 11 to 20 ☐ 21 to 30 ☐ 31 or more	☐ 0 ☐ 1 ☐ 2 ☐ 3
Do you smoke more during the first few hours after waking up than during the rest of the day?	☐ Yes ☐ No	☐ 1 ☐ 0
Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?	☐ Yes ☐ No	☐ 1 ☐ 0

Scoring:

7 to 10 points = Highly Dependent
4 to 6 points = Moderately Dependent
Less than 4 points = Minimally Dependent

Table C: Pharmacological Intervention - Nicotine Based Smoking Cessation Drugs

Drug	Dosage	Prescribing Instructions	Precautions	Side Effects
Nicotine Gum (2 mg, 4 mg)	2 mg gum for patients smoking < 20 cigs/day, 4 mg gum for ≥ 20 cigs/day. Use up to 12 weeks with no more than 24 pieces/day.	Chewing technique: chew slowly until a peppery or minty taste emerges, then parked between cheek and gum. Repeat the chewing routine for about 30 minutes then discard. Chew the gum on a fixed schedule (at least one piece every 1-2 hours during waking hours) for at least 1-3 months. Do not eat or drink 15 minutes before using or while gum is in the mouth.	Pregnancy and lactating women: Should be used only if the increased likelihood of smoking abstinence, with its potential benefits, outweighs the risk of nicotine replacement and potential concomitant smoking. Cardiovascular diseases: should be used with caution among those in the immediate (within 1 to 2 weeks) post myocardial infarction period, serious arrhythmias and worsening angina pectoris.	Mouth soreness, hiccups,dyspepsia, and jaw ache.
Nicotine Patch	**NiQuitin®** : 21, 14 and 7 mg Smokers of ≤10 cigarettes daily: Start 14 mg daily for 6 wk, then reduce to 7 mg daily for 2 wk. Smokers of >10 cigarettes daily: Start 21 mg daily for 6 wk, then reduce to 14 mg daily for 2 wk; finish w/7 mg daily for 2 wk. **Nicorette®** : 25,15 and 10 mg Heavy smoker - One 25-mg patch/16 hr daily for 1st 8 wk, then one 15-mg patch/16 hr daily for the next 2 wk & one 10-mg patch/16 hr daily for the final 2 wk. Light smoker - One 15-mg patch/16 hr daily for 1st 8 wk then one 10-mg patch/16 hr daily for the final 4 wk.	Apply a new patch on a relatively hairless location (e.g., upper arm or shoulder) as soon as the patient wakes up. Smokers with time-to-first cigarette (TTFC) of 30 minutes or less may benefit from putting the patch immediately before sleeping. Remove the patch after 16 or 24 hours. Rotate and avoid using the same site of application for ~ 1 week.		Skin reactions, insomnia.
Nicotine Lozenge (2 mg, 4 mg)	**NiQuitin®:** 4mg: suitable for smokers who have their time to first cigarette is < 30 minutes after waking up. 2mg: suitable for smokers who have their time to first cigarette is > 30 minutes after waking up. **Dosage regimen:** Week 1-6: 1 lozenge 1-2 hourly. Min: 9 lozenge/day. Week 7-9: 1 lozenge 2-4 hourly. Week 10-12: 1 lozenge 4-8 hourly. Max: 15 lozenge/day. Max duration: 24 wk	Should not be chewed or swallowed. Do not eat or drink while lozenge is in the mouth. One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated until the lozenge is completely dissolved (approximately 20-30 minutes for standard lozenges).		Nausea, vomiting, dyspepsia, hiccups, flatulence, oral discomfort.

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Nicotine gum:
https://www.mims.com/malaysia/drug/info/nicotine (Accessed 27/11/2020)
https://www.mims.com/malaysia/drug/info/nicorette%20icy%20mint%20gum (Accessed 27/11/2020)
https://www.uptodate.com/contents/nicotine-drug-information?-search=nicorette+gum&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1 (Accessed 27/11/2020)
Nicotine Patch:
Niquitin® : 21, 14 and 7 mg - https://quest3plus.bpfk.gov.my/front-end/attachment/66/pharma/223639/V_888_20170714_074615_D4.pdf (Accessed 27/11/2020)
Nicorette®: https://www.mims.com/malaysia/drug/info/nicorette%20invisi%20transdermal%20patch (Accessed 27/11/2020)
https://www.mims.com/malaysia/drug/info/nicotine (Accessed 27/11/2020)
Nicotine Lozenge:
NiQuitin Mint Lozenges PIL Booklet - https://quest3plus.bpfk.gov.my/front-end/attachment/66/pharma/211166/V_3818_20170714_084514_D3.pdf (Accessed 27/11/2020)

Table D: Pharmacological Intervention - Non-Nicotine Based Smoking Cessation Drugs

Drug	Dosage	Prescribing Instructions	Precautions	Side Effects
Varenicline (0.5mg, 1mg)	Days 1-3: 0.5 mg once daily; Days 4-7: 0.5 mg twice daily; Day 8-end of treatment: 1 mg twice daily. Minimum treatment duration is 12 weeks.	Start 1-2 weeks before quit date. Best taken with a bit of food. Administer after eating and with a full glass of water.	Renal insufficiency, and lactating women. Dosing renal impairment: CrCl <30 mL/minute: Initial: 0.5 mg once daily; maximum maintenance dose: 0.5 mg twice daily or 1mg daily Not recommended in end stage renal disease, pregnancy, children and adolescents.	Nausea, headache, insomnia and abnormal dreams.
Bupropion (150mg)*	Begin 1-2 weeks prior to quit date with 150 mg o.m. for 3 days, then increase to 150 mg b.i.d. for 12 weeks following the quit date. (unsure references) Initially, 150 mg once daily for 6 days then increased to 150 mg bid, give 8 hr between doses for 7-9 wk. Discontinue treatment if abstinence is not achieved by 7th wk. Max: 300 mg daily. (Zyban's product leaflet)	If insomnia is marked, take the PM dose earlier (in the afternoon, at least 8 hours after the first dose) may provide some relief. Begin dosing one week before quit day. May be used with a nicotine transdermal system. (Zyban's product leaflet)	Pregnancy and lactating women Close monitoring of patients for clinical worsening, emergence of suicidality, agitation, irritability & unusual changes in behaviour. Excessive use or abrupt discontinuation of alcohol or sedatives. Need to adjust dose in patients with renal or hepatic impairment including mild to moderate & severe livercirrhosis. Patients w/ a recent history of MI or unstable heart disease. Contraindicated in individuals with a history of seizure disorder, a history of an eating disorder, who are using another form of bupropion (Wellbutrin SR) or who have used an MAO inhibitor in the past 14 days.	Insomnia, headache and dry mouth.

**(not registered in Malaysia)*
Varenicline:
https://quest3plus.bpfk.gov.my/front-end/attachment/286/pharma/211119/V_27277_20190409_142806_D3.pdf (Accessed 27/11/2020)
https://www.uptodate.com/contents/varenicline-drug-information?search=varenicline%20drug%20information&source=panel_search_result&selectedTitle=1~32&usage_type=panel&kp_tab=drug_general&display_rank=1#F2975297 (Accessed 27/11/2020)
Bupropion* *(Not available and not registered in Malaysia):*
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Zyban/pdf/ZYBAN-PI-MG.PDF (Accessed 27/11/2020)

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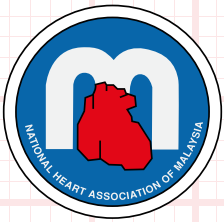

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