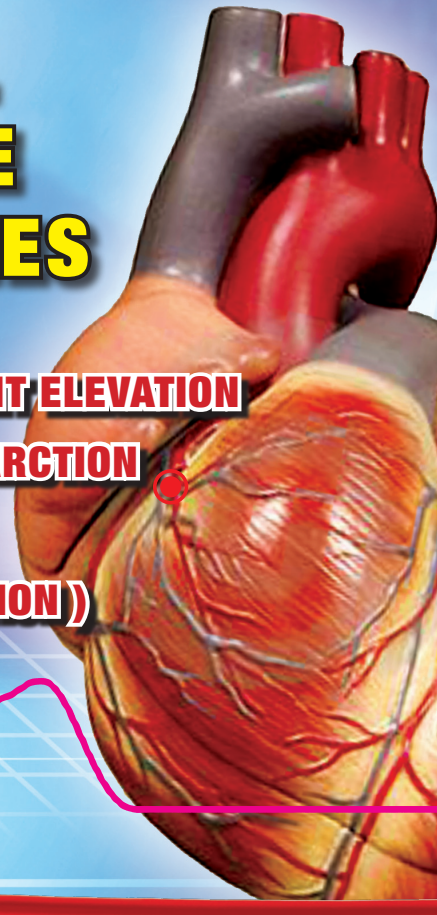
MOH/P/PAK/276.14 (GU)

CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI) 2014 - (3RD EDITION)



MINISTRY OF HEALTH MALAYSIA

NATIONAL HEART ASSOCIATION MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

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Statement of Intent

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Period of validity

This update was issued in 2014 and will be reviewed in 2019 or sooner if new evidence becomes available.

Clinical Practice Guidelines (CPG) Secretariat
c/o Health Technology Assessment (HTA) Unit
Medical Development Division
Ministry of Health Malaysia
4th floor, Block E1, Parcel E
62590 Putrajaya.

Electronic version available on the following website:
http:// www.moh.gov.my
http://www.acadmed.org.my

This document is an update and supersedes the previous CPG on STEMI (2007).

Message from the Director General of Health

ST segment myocardial infarction (STEMI) is the most deadly among the clinical presentations of acute coronary syndrome (ACS). Unlike many of medical conditions, STEMI is associated with high mortality and morbidity in its early stages, including sudden death. The National Cardiovascular Disease (NCVD) ACS Registry revealed that there was a 10% mortality rate for patients who were admitted to hospital with STEMI in 2006-2008.

Since the publication of the 2nd Edition of the Malaysian Clinical Practice Guidelines (CPG) for the management of STEMI in 2007, there have been advances in the way STEMI is managed by the medical community, and more specialised centres providing leading-edge care for this condition. Therefore, it is timely for the publication of this 3rd edition of the Malaysian CPG for STEMI.

It is testament to the commitment of the team of experts involved who are continuing to pursue the update of this and other CPGs. The pace of innovation in medicine has relentless in recent years, especially so in the area of cardiovascular medicine, in terms of both medical and interventional management.

There is a continual effort to not only update the CPGs but also improve the process of selecting and evaluating evidence. In addition, the incorporation of local data will make Malaysian CPGs more relevant document in the local context. I envisage many young physicians, generalists and allied health professionals will use these CPGs as a useful reference.

I acknowledge that this is not an insignificant effort given other clinical and leadership responsibilities of all those directly involved, and thank the team of authors and reviewers for their time and valuable contributions. I believe this CPG will be an invaluable document for healthcare providers involved in the management of STEMI and subsequently to improve health outcomes associated with this deadly condition.

(Datuk Dr. Noor Hisham bin Abdullah)
The Director General of Health,
Ministry of Health Malaysia

CPG Development Expert Panel

Chairperson:

Dr. Robaayah Zambahari
Senior Consultant Cardiologist
Institute Jantung Negara, Kuala Lumpur

Secretary:

Dr. Jeyamalar Rajadurai
Consultant Cardiologist
Subang Jaya Medical Centre, Selangor

Expert Panel Members

(in alphabetical order):

Dr. Alan Fong
Consultant Cardiologist
Hospital Umum Sarawak, Kuching

Dr. Aris Chandran
Consultant Physician
Hospital Raja Permaisuri Bainun, Ipoh

Dr. Choo Gim Hooi
Consultant Cardiologist
Subang Jaya Medical Centre, Selangor

Dr. Nurul Aida Salleh
Family Medicine Specialist
Klinik Kesihatan Tanglin, Kuala Lumpur

Dr. Omar Ismail
Consultant Cardiologist
Hospital Pulau Pinang, Penang

Dr. Oteh Maskon
Consultant Cardiologist
Pusat Perubatan Universiti Kebangsaan Malaysia,
Kuala Lumpur

Dr. Rahal Yusoff
Specialist in Internal Medicine
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Rosli Mohd Ali
Consultant Cardiologist
Institute Jantung Negara, Kuala Lumpur

Dr. Wan Azman Wan Ahmad
Consultant Cardiologist
Pusat Perubatan Universiti Malaya,
Kuala Lumpur

External Reviewers
(in alphabetical order):

Dr. Chan Hiang Chuan	*Consultant Emergency Physician* *Hospital Umum Sarawak,* *Kuching*
Dr. G.R. Letchumanan	*Consultant Physician* *Hospital Taiping, Perak*
Dr. K. Sree Raman	*Senior Consultant Physician* *Hospital Tunku Jaa'far,* *Negeri Sembilan*
Dr. Mahathar Abd Wahab	*Consultant Emergency Physician* *Hospital Kuala Lumpur,* *Kuala Lumpur*
Dr. Rashidi Ahmad	*Consultant Emergency Physician* *University Malaya Medical Centre,* *Kuala Lumpur*
Dr. Zaid Chelvaraj Abdullah	*Family Physician* *Klinik Caterall, Khoo and Raja Malek,* *Kuala Lumpur*
Dr. Zurkurnai Yusof	*Consultant Cardiologist* *Hospital Universiti Sains Malaysia,* *Kelantan*

Rationale and Process of Development of this CPG

Rationale :

Acute Myocardial Infarction (AMI) continues to be a major health problem for Malaysians due to a more sedentary lifestyle compared to past years, increasing trends of hypertension, diabetes, obesity and dyslipidaemia. There is also a high prevalence of smoking.

The 1st CPG on STEMI was published in 2001 with a 2nd edition in 2007. Rapid further developments have taken place since then.

This 3rd edition of the CPG on STEMI was developed to provide a clear and concise approach based on current evidence. We have summarised and adapted relevant clinical trial data and published literature to the local practice.

This CPG 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 comprised of cardiologists, general and family physicians from the government, private sector and universities.

Objectives:

These guidelines are intended to provide awareness and education in order to reduce the morbidity and mortality associated with STEMI by:

- Early recognition and appropriate timely reperfusion strategies.
- Evidence-based management.
- Effective secondary prevention measures to prevent recurrence.

Process:

The previous CPG published in 2007 was used as a base. In addition to the previous clinical questions that needed to be updated, the Expert Panel formulated new questions that needed to be addressed. These clinical questions were then divided into sections and each member was assigned one or more topics.

A review of current medical literature on STEMI from 2007 (the date of the last CPG) until 31st August 2013 was performed. Literature search was carried out using the following electronic databases – PubMed and Cochrane Database of Systemic Reviews. The following MeSH terms or free text terms were used either singly or in combination:

"Myocardial Infarction", "Acute Myocardial Infarction", "STEMI", "ST Elevation Myocardial Infarction" [MeSH]

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. Experts in the field were also contacted to obtain further information. International guidelines on STEMI- the American Heart Association (AHA)/American

College of Cardiology (ACC) and European Society of Cardiology (ESC) - were also studied. All literature retrieved were appraised by members of the Expert Panel and all statements and recommendations made were collectively agreed by the group. The grading of evidence and the level of recommendation used in this CPG was adapted from the American College of Cardiology/ American Heart Association and the European Society of Cardiology (Page vii).

After much discussion, the draft was then drawn up and submitted to the Technical Advisory Committee for CPGs, Ministry of Health Malaysia and key health personnel in the major hospitals of the Ministry of Health and the private sector for review and feedback.

Clinical Questions Addressed

- How do you diagnose STEMI?
- What is the best strategy to treat STEMI patients based on the current evidence available?
    - How to improve early diagnosis and pre-hospital care level?
    - How do you identify high-risk STEMI patients at diagnosis?
    - How to evaluate reperfusion strategies?
    - When to transfer from non-percutaneous coronary intervention (PCI) to PCI centres?
    - How to identify complications and manage appropriately?
    - How to risk stratify post-STEMI patients?
- How to reduce the risk of a subsequent cardiovascular event (secondary prevention)?
    - What is the role of cardiac rehabilitation?
- How to treat the following special groups?
    - Elderly
    - Diabetics
    - Women
    - Chronic Kidney Disease (CKD)
    - What are the follow-up strategies for these patients?

Target Group:

These guidelines are developed for all healthcare providers involved in the management of STEMI in adults.

Target Population:

These guidelines are developed to treat all adults with STEMI.

Dr. Robaayah Zambahari
Chairperson,
CPG for STEMI, 3rd edition

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.

LEVEL 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

(Available at: http://assets.cardiosource.com/Methodology_Manual_for_ACC_AHA_Writing-_Committees and at http://www.escardio.org/guidelines-surveys/escguidelines/about/Pages/rules-writing.aspx).

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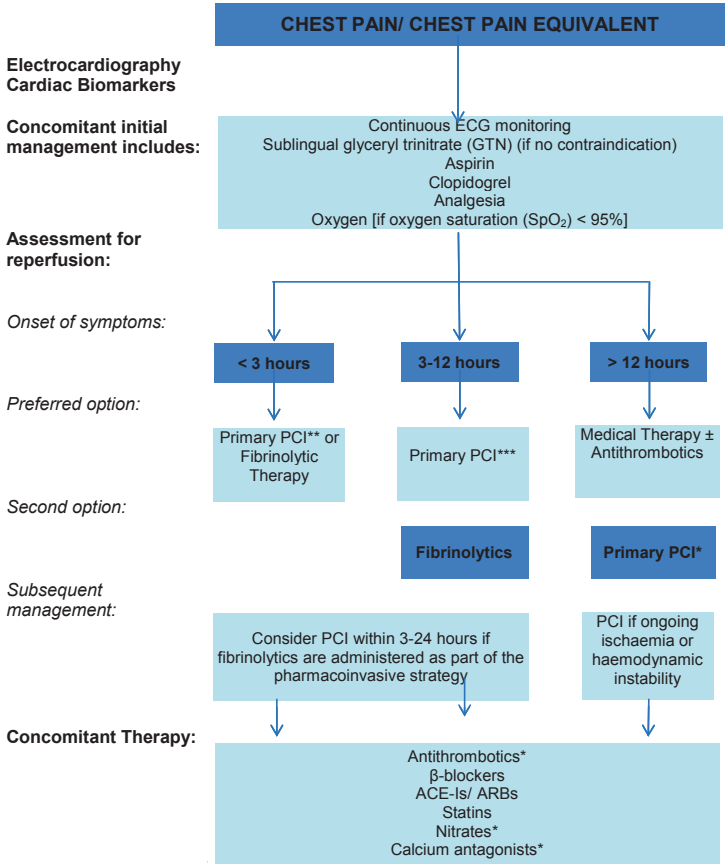
SUMMARY

- Cardiovascular disease (CVD) is an important cause of death in Malaysia.
- The diagnosis of STEMI is made in the presence of ischaemic type chest pain/ chest pain equivalent and characteristic evolutionary ST elevation in the resting electrocardiogram (ECG) or new onset left bundle branch block (LBBB).
- It should be confirmed by a rise and fall in cardiac biomarkers.
- **TIME LOST IS MYOCARDIUM LOST,** thus early diagnosis and treatment is important.
- Early management of STEMI involves pain relief, stabilisation of haemodynamics and assessment for reperfusion.
- The occluded infarct-related artery (IRA) should be opened as soon as possible. The appropriate and timely use of some form of reperfusion therapy is more important than the choice of therapy.
- Primary PCI is the reperfusion strategy of choice if it can be done in a timely manner by an experienced operator.
- If primary PCI cannot be performed, then fibrinolytic therapy should be administered with a DNT of less than 30 minutes.
- Concomitant pharmacotherapy includes aspirin, clopidogrel (or prasugrel or ticagrelor), ß-blockers, ACE-Is/ARBs and statins.
- Complications of STEMI include arrhythmias, left ventricular (LV) dysfunction and shock.
- High-risk patients should have early coronary angiography with a view to revascularisation. The others should be risk stratified according to the presence or absence of ischaemia, arrhythmias and LV function.
- Secondary prevention is important and includes the use of aspirin, βblockers, Angiotensin converting enzyme inhibitors (ACE-I)/ Angiotensin II receptors blocker (ARB) and statins.
- All patients should be encouraged to undergo cardiac rehabilitation.

Flow chart 1: Management of patients presenting with STEMI



*When clinically indicated
**Preferred option in: - high
- presence of contraindications to fibrinolytic therapy and/or
- PCI time delay [DBT – DNT] is less than 60 minutes
***If DBT is within 90 minutes

Table 2: Level of evidence and grade of recommendation for acute therapy of STEMI

RECOMMENDATION	GRADE OF RECOMMENDATION	LEVEL OF EVIDENCE
REPERFUSION THERAPY		
***Primary PCI**: Strategy of choice if: • DBT < 90 minutes. • There are contraindications to fibrinolysis. • High-risk patients.	 I I I	 A A A
***Fibrinolytic therapy**: Strategy of choice if: • DBT > 90 minutes. • No contraindications to fibrinolysis.	 I I	 A A
CONCOMITANT PHARMACOTHERAPY		
Aspirin: Loading dose of 300 mg followed by maintenance dose of 75 mg – 150 mg daily.	I	A
Clopidogrel: Loading dose of 300 mg followed by maintenance dose of 75 mg daily (for at least 1 month).	I	A
Prasugrel: Loading dose of 60 mg followed by maintenance dose of 10 mg (to be administered only prior to primary PCI).	II-a	B
Ticagrelor: Loading dose of 180 mg followed by maintenance dose of 90 mg twice daily (bd) to be administered to patients undergoing primary PCI.	II-a	B
Antithrombotic (heparin/ enoxaparin/ fondaparinux) to be given to patients: • Who received fibrin selective lytic agents. • With atrial fibrillation (AF). • With mural thrombus. • Routine administration to patients following fibrinolysis.	 I I I II-a	 A C C B
β-blockers: For all patients if no contraindications.	I	A
ACE-Is: For all patients with no contraindications.	I	A
Statins: For all patients if no contraindications.	I	A

**Please refer to flow chart 1 for details.*

Table 3: Level of evidence and grade of recommendation for secondary prevention post-STEMI

STRATEGY	GRADE OF RECOMMENDATION	LEVEL OF EVIDENCE	COMMENTS
Smoking Cessation	I	B	
Exercise	I	B	At least 30-60 minutes most days of the week.
CONCOMITANT PHARMACOTHERAPY			
Aspirin	I	A	Maintenance dose: 75-150 mg daily.
Clopidogrel	I	A	Maintenance dose 75 mg daily to be given for 1 month following fibrinolytic therapy and for longer periods post-primary PCI.
β-blockers	I	A	Consider long-term therapy for all patients if no contraindications.
ACE-Is	I	A	Started on first day and continued long-term for all patients if no contraindications.
ARBs	I	B	For ACE-I intolerant patients, consider valsartan.
Statins	I	A	Aim for low density lipoprotein-cholesterol (LDL-C) <2.0 mmol/L (preferably <1.8

Table 4: Indications for PCI in STEMI

INDICATIONS	GRADE OF RECOMMENDATION/ LEVEL OF EVIDENCE
Primary PCI in patients presenting < 12 hours of ischaemic symptoms:	
• < 3 hours and PCI time delay is < 60 minutes.	I, A
• 3-12 hours in a PCI centre or PCI transfer delay < 2 hours.	I, A
Primary PCI in patients presenting 12 to 24 hours of symptom onset with evidence of ongoing ischaemia.	II-a, B
Primary PCI in patients who have:	
• High-risk features – section 4.2 (C).	I, B
• Contraindications to fibrinolytics – section 4.2 (B).	I, B
Rescue PCI in patients who have evidence of failed reperfusion of the IRA diagnosed by persistent ST elevation and/or recurrent/ongoing chest pain.	I, A
Facilitated PCI is a strategy of immediate PCI < 1 hour after an initial pharmacological regimen (fibrinolytics ± Gp IIb/IIIa inhibitors).	III, A
Post-fibrinolysis and:	
• Routine angiography with a view to PCI and stenting between 3-24 hours in all STEMI patients (pharmacoinvasive therapy).	II-a, B
• Delayed selective angiography depending on presence of haemodynamic instability or residual ischaemia.	I, A
PCI of totally occluded vessel 3-28 days after MI and no reversible ischaemia.	III, B

1 INTRODUCTION

CVD remains an important cause of mortality in Malaysia, accounting for 20-25% of all deaths in public hospitals. This has remained unchanged for the last 10 years.[1] In Malaysia, patients with ACS present at a mean age of 59 ± 12 years, 6 years younger than those in the Global Registry of Acute Coronary Events (GRACE).[2,3] The in-hospital and 30-day mortality following STEMI is also high at 10% and 14% respectively.[3]

Since the publication of the last guidelines, the following efforts have been intensified in Malaysia:

- Educating healthcare providers and the public on the importance of early diagnosis and treatment of STEMI.
- Increasing the number of cardiovascular treatment centres within the public and private sectors.
- Early institution of reperfusion therapy in the emergency department, with a reduction in DNT (from 60 minutes in 2006 to 45 minutes in 2009 & 2010).[3]
- Increasing the number of primary PCI interventions in PCI-capable hospitals.
- The use of evidence based medicine post-STEMI – almost 90% usage of statins and aspirin.[3]

Despite these efforts, the in-hospital mortality still remains high. This is due to late presentation and occasional misdiagnosis leading to missed opportunity for appropriate reperfusion therapy. In addition, there is a lack of risk stratification resulting in non-recognition of high-risk patients who would otherwise benefit from revascularisation. There should be greater use of dual antiplatelet therapy (DAPT) post-STEMI.

Guidelines are intended to help in the management of patients. All the recommendations stated in this guideline may not be available to all eligible patients. Patient care should be individualised and sound clinical judgement still plays an important role in decision-making.

2 DEFINITION AND PATHOGENESIS

ACS is a clinical spectrum of ischaemic heart disease ranging from unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) to STEMI depending upon the degree and acuteness of coronary occlusion (See Figure 1). In unstable angina, myocardial injury is absent and cardiac biomarkers are normal. In myocardial infarction (MI) [both NSTEMI and STEMI] cardiac biomarkers are raised.

MI is a clinical diagnosis based on the presence of myocardial injury or necrosis as indicated by a rise and fall of serum cardiac biomarkers. In addition, there should be at least one of the following:[4]

i. Clinical history consistent with chest pain of ischaemic origin.
ii. ECG changes of ST segment elevation or presumed new LBBB.
iii. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
iv. Identification of an intracoronary (IC) thrombus by angiography or autopsy.

This new comprehensive definition of MI which utilises newer cardiac biomarkers and imaging techniques is more sensitive in diagnosing MI.[5]

'Reinfarction' is used for MI that occurs within 28 days of the incident event while recurrent MI occurs after 28 days.[4]

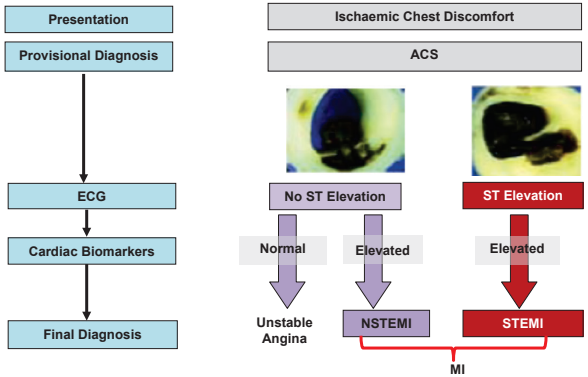


Figure 1: Clinical spectrum of ACS.
Adapted from Antman EM, Anbe DT, Armstrong PW et al. "ACC/AHA Guidelines for the management of patients with ST Elevation Myocardial Infarction" at www.acc.org

The Task Force for the Universal Definition of MI has classified MI into various types based on pathological and clinical features.[4] (Table 5, page 3)

The current CPG will primarily focus on spontaneous MI (MI type 1) with ST segment elevation on ECG.

Table 5: Clinical classification of MI[4]

Type 1: Spontaneous MI
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. The patient may have underlying severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD.
Type 2: MI secondary to an ischaemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anaemia, respiratory failure, 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 ischaemic and presumed new ischaemic 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 upper reference limits (URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic 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 embolisation, 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 ischaemia 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.Third universal definition of myocardial infarction.Journal of the American College of Cardiology.2012;60(16):1581-98.

2.1 Diagnosis

The diagnosis of STEMI is based on the presence of evolutionary changes of ST elevation in the resting ECG in patients presenting with chest pain or its equivalent and supported by the presence of raised cardiac biomarkers.

2.1.1 History

A thorough, targeted history is important in making the diagnosis of STEMI. Chest pain of STEMI begins abruptly and lasts for more than thirty minutes.[6] It is usually located in the centre of the chest, and may radiate to the jaw or down the left arm. It may occur at rest or with activity. The pain may just be a tightness or heaviness in the chest, but it is usually described as a pressure, squeezing or a severe crushing pain with a sense of impending doom associated with sweating, nausea, vomiting and shortness of breath. The pain may be of a burning quality and localised to the epigastria or interscapular region resulting in a misdiagnosis.

In the elderly, females and patients with diabetes, the index of suspicion has to be high because they may present with atypical symptoms such as unexplained fatigue, shortness of breath, dizziness, lightheadedness, unexplained sweating and syncope. They may not necessarily have chest pain.

Other important points to note in the history are the presence of:

- Previous history of ischaemic heart disease, PCI or CABG.
- Risk factors for atherosclerosis.
- Symptoms suggestive of previous transient ischaemic attack (TIA) or other forms of vascular disease.

Upon clinical suspicion of ACS, a 12-lead ECG should be performed and interpreted immediately within 10 minutes of first medical contact (FMC).

2.1.2 Electrocardiographic changes

The diagnosis of STEMI depends upon the presence of characteristic ECG changes. The presence of ST elevation in two contiguous leads in patients with symptoms of ischaemia is the cardinal feature of STEMI.

The cut-off points for new or presumed new ST segment elevation (in the absence of LVH and LBBB) is the presence of $\geq$ 0.1 mV ST segment elevation in all leads except leads V2-V3. In leads V2-V3, a cut-off point of $\geq$ 0.25 mV (in males < 40 years), $\geq$ 0.2 mV (in males $\geq$ 40 years) and $\geq$ 0.15 mV in females is used.[4]

The presence of a new onset or presumed new LBBB in a patient with typical chest pain of ischaemia may indicate an infarct and should be treated as STEMI.[7]

Occasionally the ECG may be non-diagnostic. Cardiac imaging techniques and cardiac biomarkers can help make the diagnosis in these difficult situations. (See Appendix I, page 51).

In the early stages of MI, the initial ECG may be normal, equivocal or show hyperacute T-wave changes only. In these patients if the index of suspicion of STEMI is high, the ECG should be repeated at close intervals of at least 15 minutes to look for progressive ST changes. Comparison with previous ECG's may also be helpful.

Patients with inferior STEMI should have an ECG recording of the right praecordial lead (V4R) to identify concomitant right ventricular (RV) involvement.8 In those with ST segment depression in leads V1-V3, it is advisable to have an ECG recording of the posterior chest wall (V7-V9) to identify a true infero-basal (formerly known as infero-posterior) STEMI. The cut-off point for ST segment elevation in the posterior leads is $\geq$ 0.05 mV ($\geq$ 0.1 mV in men < 40 years).[4]

The presence of ST elevation in lead AVR may be a predictor of left main/3 vessel CAD and carries an adverse prognosis.[9,10]

Table 6: ECG patterns of various STEMI locations[11]

Location	Leads	ECG findings
Anteroseptal	V1 – V3	ST elevation, Q wave
Extensive anterior	V1 – V6	ST elevation, Q wave
Posterior	V7 – V8	ST elevation, Q wave
Posterior	V1 – V2	ST depression, Tall R wave
Anterolateral	I, AVL, V5 – V6	ST elevation, Q wave
Inferior	II, III, AVF	ST elevation, Q wave
RV	V4R	ST elevation

2.1.3 Serum cardiac biomarkers

The history and ECG is of paramount importance in making the diagnosis of STEMI and determining the reperfusion strategy. A rise and fall in the levels of serum cardiac biomarkers support the diagnosis of STEMI. One should not however, wait for the results of these biomarkers before initiating reperfusion therapy.

These cardiac biomarkers include:[4]

- Cardiac Troponin T (cTnT) and Cardiac Troponin I (cTnI).
- Creatine Kinase-Myocardial Band (CK-MB).
- Creatine Kinase (CK).

For the relative timing, rate of rise, peak value, duration of elevation and properties of these cardiac biomarkers following STEMI, see Figure 2 (page 6) and Table 7 (page 7). In patients with clinical features and ECG diagnostic of STEMI, the preferred cardiac biomarker is CK-MB. In this situation, troponins are not necessary since there is already ECG evidence of myocardial injury.

If the clinical features and ECG are suspicious but non-diagnostic of MI, then the preferred biomarkers are troponins - cTn (I or T). The absence of ST elevation on the resting ECG and elevated troponin levels indicates NSTEMI (See Malaysian CPG on the Management of Unstable Angina/NSTEMI, 2011).

Troponins have near absolute specificity and high clinical sensitivity for myocardial necrosis. It rises within 3-4 hours of the onset of MI and is more likely to be positive 6 hours after symptom onset. Troponins are not useful for the detection of reinfarction because it remains elevated for 10-14 days and sometimes longer.

High sensitivity cTn has a negative predictive value of 95% as a single test on admission and almost 100% when repeated after 3 hours.12 For the usefulness of troponins in patients with CKD, refer to section 8.4. Troponins may also be raised in other conditions (See Appendix II, page 52).

CK-MB (measured by mass assay) is the next best alternative. Values differ between the genders.4,13 The measurement should be made at the time of first assessment and repeated 6-9 hours later:[14]

- To document the rise and/or fall exceeding the 99th percentile URL for the diagnosis of MI.
- If the first measurement is non-diagnostic and the clinical suspicion of MI is high.

CK-MB measurements are useful for the diagnosis of reinfarction. In a patient with recurrent chest pain following STEMI, a $\geq$ 20% increase in the value from the last sample suggests reinfarction.[4]

To ensure the reliability of these tests, each individual laboratory should maintain high quality laboratory practice and confirm the range of reference values in their specific setting.

Aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels are not sensitive or specific for acute MI with frequent false positive elevations.[14,15] The use of these biomarkers should be discontinued. Total CK measurement is also not recommended owing to its poor specificity and large distribution in skeletal muscles.[14]

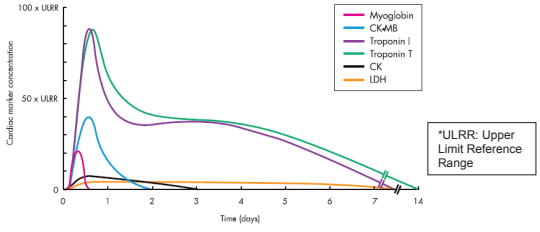


Figure 2: Time Course of Elevation of Serum Cardiac Biomarkers after STEMI

Adapted from "Clinical implications of the new definition of myocardial infarction". John K French, Harvey D White; Heart 2004; 90(1):99–106.

Table 7: Properties of serum cardiac biomarkers

Protein	First detection*	Duration of detection	Sensitivity	Specificity
CK-MB	2 – 3 hours	1 – 2 days	+++	+++
Troponin I	3 – 4 hours	7 – 10 days	++++	++++
Troponin T	3 –4 hours	7 – 14 days	++++	++++
CK	4 – 6 hours	2 – 3 days	++	++
* Hours after symptom onset.				

2.1.4 Other diagnostic modalities

Echocardiography is a particularly useful bedside imaging technique. It is useful in detecting:

- New regional wall motion abnormalities in difficult diagnostic situations.
- Mechanical complications of acute MI e.g. free wall rupture, acute ventricular septal defect (VSD), mitral regurgitation.

Other imaging techniques such as chest radiography, multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI) and radionuclide techniques may be useful investigations in the patient presenting with acute chest pain in difficult diagnostic situations.[16,17]

They help to:

- Rule out or confirm the presence of acute MI or ischaemia.
- Identify non-ischaemic conditions causing chest pain such as valvular heart disease, peri-myocarditis, pulmonary embolism, aortic dissection and pneumothorax

Key Messages:

- STEMI is diagnosed by the clinical history of chest pain, ECG changes of ST elevation/ presumed new LBBB and a rise and fall of serum cardiac biomarkers.
- Atypical presentations can occur in the elderly, women and in diabetics.
- If the initial ECG is non-diagnostic, it may need to be repeated at frequent intervals to detect evolving changes of STEMI.
- Too early a measurement can sometimes result in misleadingly low levels of serum cardiac biomarkers.

3 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 FMC. Most deaths following STEMI occur in the pre-hospital phase.

In STEMI, it is important to reduce total ischaemic time i.e. the time from symptom onset to the time of institution of reperfusion strategies. Total ischaemic time is a combination of:

- Time from arterial occlusion to symptom onset.
- Time from symptom onset to FMC.
- FMC to initiation of reperfusion strategies (DBT or DNT).

The public should be educated about:

- Symptoms of ACS.
- The importance of seeking early treatment at the nearest hospital.
- The benefits of early treatment – opening the blocked coronary artery as soon as possible so as to limit myocardial damage to the minimum and preserve heart function.
  "TIME IS MYOCARDIUM."

Immediate measures to be taken in suspected cases of ACS.

3.1 For the general public

- Seek immediate medical attention at the nearest hospital.
- Call for an ambulance (dial 999, hospital call centre or hospital direct line if known) or get someone to take you immediately to the nearest hospital.
- Do not drive yourself.
- If not on regular aspirin and with no history of allergy, chew and swallow one 300 mg tablet of aspirin immediately. Regular aspirin is preferred over enteric coated aspirin in this situation because of its faster onset of action.

3.2 For patients with known coronary heart disease (CHD)

- If the chest pain is suggestive of ACS (See section 2.1.1), take one dose of sublingual GTN and be rapidly transported to the nearest hospital.
- GTN should not be taken within 48 hours of taking phosphodiesterase inhibitors [sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra)]. It can result in severe vasodilatation, hypotension and even death.

3.3 For patients with known CHD and history of previous PCI and/ or CABG

- Go as soon as possible preferably to a PCI capable hospital provided there is no undue delay.

3.4 For the general practitioner / family physician

I,A
- Ask patient to chew and swallow one 300 mg tablet of (non-enteric coated) aspirin.[18]

I,C
- Give sublingual GTN if systolic blood pressure (SBP) is more than 90 mmHg.

I,A
- If the ECG shows ischaemic changes, give 300 mg of clopidogrel if available.[19, 20]

I,C
- Wherever possible, set up intravenous (IV) access.

I,C
- Give oxygen by mask/nasal prongs if the patient is dyspnoeic and/ or SpO2 is < 95%.

I,C
- Pain relief with titrated IV opiates [IV morphine 3-5 mg slowly]. IV antiemetic may be administered to prevent opioid induced vomiting.

I,C
- Avoid intramuscular injections since this could result in intramuscular haematomas if fibrinolytic agents are subsequently administered.

I,C
- Call an ambulance or ask the patient's relative or friend to send the patient immediately to the nearest hospital.

I,C
- Wherever possible, contact the doctor at the hospital so that the patient can be treated promptly on arrival.

3.5 For allied health care personnel

Immediate measures to be taken when there is an ambulance call:

- Note nature of complaint.
- Obtain name of caller, address, important land marks and telephone number.
- If possible, request that a relative or friend wait at a strategic place to help locate the patient.
- Dispatch an adequately equipped ambulance with trained paramedics immediately.
- Patient should be given oxygen if breathless, sublingual GTN and aspirin (if he/she has not taken) and transported to hospital. The cardiac rhythm should be continuously monitored.

Allied health 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, dyslipidaemia, and a family history of premature heart disease.
- To identify patients with STEMI based on history and characteristic ECG changes.
- On strategies to reduce DNT and DBT.
- In basic and advanced cardiopulmonary resuscitation (CPR).

Key Messages:

- The public and allied health care personnel should be educated on the importance of early diagnosis and the benefits of early treatment.
- Patients with suspected STEMI should be given aspirin and clopidogrel.
- These patients should be rapidly transported to the hospital for early institution of reperfusion strategies.

4 IN-HOSPITAL MANAGEMENT

Early management of STEMI is directed at:

- Pain relief.
- Establishing early reperfusion.
- Treatment of complications.

4.1 Initial recognition and management

I,A When the patient with suspected STEMI reaches the emergency department, evaluation and initial management should be prompt (FAST TRACK - RED ZONE) because the benefits of reperfusion therapy are greater the earlier it is instituted.[21-25]

I,C A quick targeted history should be taken and vital signs noted. The diagnosis should be confirmed with an ECG, which should be done as soon as possible, preferably within 10 minutes of the patient's arrival in the emergency department. It is important to monitor the patient continuously for arrhythmias.

Pain should be relieved with titrated IV morphine.

The patient's suitability for reperfusion by either fibrinolytic therapy or primary PCI should be quickly assessed.

The following should be done immediately and concomitantly in the emergency department (See flow chart 1, page x):

I,C • Assessment and stabilisation of the patient's haemodynamics.

I,C • Sublingual GTN if chest pain persists (avoid if SBP < 90 mmHg).

I,C • Continuous ECG monitoring.

I,A • 300 mg of non-enteric coated aspirin chewed and swallowed if not given earlier.[18]

I,A • Clopidogrel at a dose of 300 mg should be given, if not given earlier.[19, 20]

IIa,B • Alternatively, ticagrelor at a loading dose of 180 mg may be given if primary PCI is being considered.[26, 27] Ticagrelor has not been tested with fibrinolytic therapy.

I,C • Oxygen by nasal prongs/facemask if SpO2 is less than 95%.28

I,C • Venous access established and blood taken for cardiac biomarkers, full blood count, renal profile, glucose and lipid profile. Preferably two IV lines should be set up.

I,C • Pain relief - morphine should be administered IV at 2-5 mg by slow bolus injection every 5-15 minutes as necessary. Watch for adverse events – hypotension and respiratory depression. Anti-emetics (IV metoclopromide 10 mg or promethazine 25 mg) should be given with morphine and 8-hourly as necessary.

I,C • Intramuscular injections should be avoided.

I,C • Assessment for reperfusion strategy.

A patient's immediate and long term prognosis following STEMI can be predicted by using the Thrombolysis in Myocardial Infarction (TIMI) risk score (Appendix III, page 53) or the GRACE risk score (Appendix IV, pages 54 & 55).[29-31] The TIMI risk score was specifically developed for patients with STEMI while the GRACE risk score predicts in-hospital and 6-month mortality in patients with ACS. Risk assessment is a continuous process that should be repeated throughout hospitalisation and at the time of discharge.

4.2 Reperfusion strategies

The appropriate and timely use of some form of reperfusion therapy is more important than the choice of therapy.

I,A Early and prompt reperfusion is crucial as **TIME LOST** is equivalent to **MYOCARDIUM LOST**.[22, 32, 33]

I,A Overwhelming data has shown that prompt reperfusion therapy improves survival.[22, 32] The local NCVD-ACS registry data show that 73% of eligible patients in Malaysia receive fibrinolytic therapy and 7% receive primary PCI.3 The main reasons for not getting reperfusion is late presentation or having missed the diagnosis of MI.

I,A Primary PCI is superior to fibrinolytic therapy as a reperfusion strategy.[34, 35]

I,A However in patients who present within 3 hours of symptom onset and are at low-risk, both treatment strategies appear to have similar benefits.[36, 37]

In the majority of our hospitals, fibrinolytic therapy is more readily available and constitutes the main reperfusion strategy.

If both choices are available, the reperfusion strategy of choice is still primary PCI if it can be done in a timely manner by experienced operators in PCI capable centres.

The following factors are important considerations:

- Time from symptom onset to FMC.
- Time to PCI (time from hospital arrival to balloon dilatation i.e. DBT).
- Time to hospital fibrinolysis (time from hospital arrival to administration of fibrinolytic therapy i.e. DNT).
- Contraindications to fibrinolytic therapy.
- High-risk patients.

The best reperfusion strategy will depend upon:

A) Time from onset of symptoms to FMC

- **Early presentation (within 3 hours of symptom onset)**

I,A If both treatment options are readily available, they have been shown to be equally effective except for the following situations where primary PCI is the preferred strategy:[36, 37]

- o Fibrinolytic therapy is contraindicated.
- o In high-risk patients.
- o PCI time delay (DBT minus (–) DNT) is more than 60 minutes.38

- **Late presentation (3 to 12 hours of symptom onset)**

I,A Primary PCI is preferred. The DBT should be within 90 minutes if the patient presents at a PCI capable facility.

II-a,B If transferred from a centre with no PCI facilities, DBT should be less than 2 hours (including transfer delay).[39]

II-a,A If the time delay to primary PCI is longer than as mentioned, then the next best option is to give fibrinolytic therapy and make arrangements to transfer the patient to a PCI capable centre for pharmacoinvasive treatment.[40, 41]

- **Very late presentation (> 12 hours)**

I,A Both primary PCI and fibrinolytic therapy are not routinely recommended in patients who are asymptomatic and haemodynamically stable.[42,43]

I,C However, reperfusion therapy would still be beneficial in patients with persistent ischaemic symptoms, haemodynamic or electrical instability. In this subgroup, primary PCI is the preferred strategy.

B) Contraindications to fibrinolytic therapy

Absolute contraindications

- **Risk of intracranial haemorrhage**
  - History of intracranial bleed.
  - History of ischaemic stroke within 3 months.
  - Known structural cerebral vascular lesion (e.g. arteriovenous malformation).
  - Known intracranial neoplasm.

- **Risk of bleeding**
  - Active bleeding or bleeding diathesis (excluding menses).
  - Significant head trauma within 3 months.
  - Suspected aortic dissection.

Relative contraindications

- **Risk of intracranial haemorrhage**
  - Severe uncontrolled hypertension on presentation (blood pressure (BP) > 180/110 mmHg)*.
  - Ischaemic stroke more than 3 months.
  - History of chronic, severe uncontrolled hypertension.

- **Risk of bleeding**
  - Current use of anticoagulation in therapeutic doses [International Normalised Ratio (INR) > 2].
  - Recent major surgery < 3 weeks.
  - Traumatic or prolonged CPR > 10 minutes.
  - Recent internal bleeding (e.g. gastrointestinal or urinary tract haemorrhage) within 4 weeks.
  - Non-compressible vascular puncture.
  - Active peptic ulcer.

- **Others**
  - Pregnancy.
  - Prior exposure (> 5 days and within 12 months of first usage) to streptokinase (if planning to use same agent).[44]

* The BP should be reduced prior to institution of fibrinolytic therapy

C) *High-risk patients*

High-risk patients include:

- Large infarcts.
- Anterior infarcts.
- Hypotension and cardiogenic shock.
- Significant arrhythmias.
- Elderly patients.
- Post-revascularisation (post-CABG and post-PCI).
- Post-infarct angina.

I,A Primary PCI is the preferred strategy in patients in Category B and C.[45-47]

The goals of time to reperfusion therapy should be within:

I,A • 30 minutes DNT.[22, 32]

I,A • 90 minutes DBT.[38]

4.2.1 Fibrinolytic therapy

I,A Fibrinolytic therapy has been shown to reduce mortality when given within the appropriate time frame.[22, 25] When given within 2 hours from time of onset of symptoms (the "golden hour"), it is most beneficial and has been shown to be able to abort the infarction and reduce mortality by up to 50%.[22, 36, 48, 49]

I,A The DNT should be within 30 minutes.[22, 32] Strategies should be put in place to achieve this target. Fibrinolytic therapy should be made available in all hospitals and there should be protocols to initiate it in the emergency department. At present, achieving DNT < 30 minutes is one of the key performance indicators for emergency department personnel in public hospitals.

I,A Pre-hospital fibrinolytic therapy has been shown to achieve faster reperfusion.[36, 37]

4.2.1.1.1 Indications

Fibrinolytic therapy should only be given to patients with STEMI. It has no role and may even be detrimental in patients with NSTEMI.[50, 51]

4.2.1.1.2 Contraindications

See 4.2 (B).

4.2.1.1.3 Choice of fibrinolytic agent

Presently the agents available in Malaysia are:

Streptokinase

I,A This is the most widely used agent. It is not fibrin specific and it results in a lower patency rate of the occluded vessel at 60 minutes than fibrin specific agents.[52-55] Despite having a lower risk of intracranial haemorrhage, the reduction in mortality is less than with fibrin specific agents.[52, 55]

I,B Streptokinase is antigenic and promotes the production of antibodies. Thus the utilisation of this agent for reinfarction is less effective if given between 3 days and 1 or even 4 years after the first administration.44 PCI or fibrin specific agents should then be considered.

Regimen:

- 1.5 mega units in 100 ml normal saline or 5% dextrose over 1 hour.

Tenecteplase (TNK-tPA)

I,B The benefit of using TNK-tPA is that it causes more rapid reperfusion of the occluded artery than streptokinase and is given as a single bolus dose.[56, 57]

Regimen: TNK-tPA single IV bolus
30 mg if < 60 kg
35 mg if 60 to < 70 kg
40 mg if 70 to < 80 kg
45 mg if 80 to < 90 kg
50 mg if > 90 kg

This is a weight based regimen and thus there is a risk of bleeding if the weight has been overestimated. In patients over the age of 75, the dose should be reduced by 50%.[58]

Heparin or enoxaparin should be given immediately after the completion of fibrinolysis and needs to be given for 48 hours. Subcutaneous (SC) fondaparinux 2.5 mg daily may be given as an alternative for 8 days or till discharge.[59]

4.2.1.1.4 Indicators of successful reperfusion

There is no sensitive bedside clinical method to reliably detect successful reperfusion. Some useful guides are:

- Resolution of chest pain (may be confounded by the use of narcotic analgesics).

- Early return of ST segment elevation to isoelectric line or a decrease in the height of the ST elevation by 50% (in the lead that records the highest ST elevation) within 60-90 minutes of initiation of fibrinolytic therapy.[60]

- Early peaking of CK and CK-MB levels.

- Restoration and/or maintenance of haemodynamic and/or electrical stability.

The occurrence of 'reperfusion arrhythmias' is not a reliable indicator of successful reperfusion. An exception is accelerated idioventricular rhythm and sudden sinus bradycardia which have been correlated with a patent infarct-related coronary artery after fibrinolytic therapy or primary PCI.[60]

4.2.1.1.5 Failed fibrinolysis

Failure of fibrinolytic agents to open the occluded IRA is manifested as continuing chest pain, persistent ST segment elevation and haemodynamic instability. These patients are more likely to develop complications such as heart failure (HF) and arrhythmias.

I,B The treatment of choice for these patients is rescue PCI.[61, 62]

III,B They should not be given a second dose of a fibrinolytic agent. This is because there has been no difference in event free survival demonstrated whether these patients are given a repeat dose of a fibrinolytic agent or are treated conservatively.[63]

4.2.2 PCI

4.2.2.1 Primary PCI

I,A Primary PCI is the preferred reperfusion strategy in patients with ischaemic symptoms < 12 hours when it can be performed in a timely manner and promptly by experienced operators in centres performing a sufficient number of primary PCI procedures.[34, 39, 64, 65]

4.2.2.2 Transfer of patient

Transfer of patients with STEMI to PCI capable centres should be considered in the following situations:

I,B • Onset of ischaemic symptoms < 12 hours and fibrinolytic therapy is contraindicated irrespective of time delay from FMC.66, 67

I,B • Cardiogenic shock irrespective of time delay.45, 68

I,C • STEMI presenting with acute HF. These patients should be stabilised rapidly and ventilated if necessary prior to transfer. Another option is to give fibrinolytic therapy and transfer the patient within 24 hours for a pharmacoinvasive strategy.

I,B • When symptoms have been present between 3 and 12 hours and PCI can be performed within 2 hours (preferably as soon as possible).[39, 64, 65, 69, 70]

IIa,B • Failed fibrinolytic therapy or reocclusion post-fibrinolysis (See Rescue PCI under chapter 4.2.2.3).[60-63, 71]

IIa,B • As part of a pharmacoinvasive strategy in stable patients who have been given fibrinolytics and an elective PCI can be performed within 3 and 24 hours.[41, 72-76]

4.2.2.3 PCI post-fibrinolysis or patients who did not receive fibrinolysis

Following fibrinolysis, or in patients who did not receive fibrinolysis, PCI may be performed in the following situations:

IIa,B • Failed reperfusion or reocclusion after fibrinolytic therapy.[60-63, 71]

I-,B • Cardiogenic shock or acute pulmonary oedema that develops after initial presentation.[47, 68, 77, 78]

IIa,B • Stable patients within 3-24 hours post-fibrinolysis as part of a pharmacoinvasive strategy.[42, 72-76, 79]

I,B • Intermediate or high-risk findings on pre-discharge non-invasive ischaemia testing.[80, 81]

I,C • Spontaneous or easily provoked myocardial ischaemia such as recurrence of chest pains and/or dynamic ECG changes.

Failed fibrinolytic therapy is manifested as one or more of the following:

- Ongoing chest pains.
- Persistent hyper-acute ECG changes (< 50% resolution of ST elevation in the lead showing the greatest degree of ST elevation at presentation).[60]
- Haemodynamic and electrical instability.

Rescue PCI is initiated very early (1 to 2 hours) after failed fibrinolytic therapy.

I,A It is associated with a reduction in HF, reinfarction and a trend towards reduction in mortality but with increased risk of bleeding and stroke. Hence these patients should be individually evaluated.[62, 63]

4.2.2.4 Facilitated PCI

This refers to a strategy of planned immediate PCI (< 1 hour) after an initial pharmacologic regimen consisting of a reduced dose of a fibrinolytic agent, glycoprotein (Gp) IIb/IIIa inhibitor or a combination of these agents. The purpose of facilitated PCI was to achieve earlier reperfusion but retain the benefits of primary PCI.

III,A This strategy was associated with increased mortality and major bleeding. It is thus not recommended.[82-86]

4.2.2.5 Routine angiography and PCI after thrombolysis (pharmacoinvasive therapy)

This refers to stable patients routinely undergoing angiography and PCI 3-24 hours post- fibrinolysis, irrespective of the absence or presence of ongoing myocardial ischaemia and reperfusion status.

II-a,B Given the advances in PCI and antithrombotic therapy, recent studies show that routine angiography with the intent to perform PCI with stenting between 3 and 24 hours after fibrinolysis improved patient outcomes as compared to symptom or ischaemia guided delayed intervention. This strategy has resulted in a significant reduction in mortality and reinfarction rates without an increase in adverse events.[64, 70, 71, 75, 87-89]

4.2.2.6 Delayed selective angiography and PCI

I,A Patients with STEMI who have not had coronary angiography within 24 hours should be considered for delayed selective angiography. This refers to a strategy of doing angiography and PCI only if there is spontaneous or inducible ischaemia.

III,B Stable patients who are not at high-risk (Refer to section 4.2 (C) for high risk) and who did not undergo early (<24 hours) angiography should undergo non-invasive ischaemia testing.[80, 81] If spontaneous or inducible ischaemia is present, then angiography and appropriate revascularisation should be performed.

III,B Routine PCI of totally occluded coronary arteries 3-28 days after STEMI is not recommended unless there is ischaemia demonstrated.[90]

4.2.3 Technical considerations and pharmacotherapy during primary PCI

For a favourable outcome, it is important to obtain good TIMI 3 epicardial flow as well as optimum reperfusion of the myocardial microvasculature91, 92 (TIMI myocardial perfusion grade – TMP) (Refer to the Malaysian CPG on the Management of PCI, 2009).

4.2.3.1 Antiplatelet therapy to support primary PCI for STEMI

I,A • Oral aspirin 300 mg should be given before primary PCI.[93-95]

• In addition, a P2Y12 receptor inhibitor should also be given:

I,A *o* Clopidogrel 300-600 mg loading dose to be given as early as possible[95-97], *or*

II-a,B *o* Prasugrel 60 mg loading dose to be given after the coronary angiogram has been performed [98, 99], *or*

II-a,B *o* Ticagrelor 180 mg loading dose to be given as early as possible.[26, 27]

II-a,A • Gp IIb/IIIa inhibitors may be considered in selected patients:

o Abciximab.[100-102]

II-a,B o Tirofiban.[103, 104]

4.2.3.2 Antithrombotic therapy to support primary PCI for STEMI

- IV unfractionated heparin (UFH) with additional bolus to maintain activated clotting time (ACT) above 275.[105]
- IV low molecular weight heparin (LMWH) – enoxaparin.[106]
- IV fondaparinux is not recommended because of the risk of catheter thrombosis.[59]
- Bivalirudin infusion.

4.2.3.3 PCI access site

- Both femoral and radial access is feasible depending on operator experience.[107,108]
- Radial access has the advantage of reducing bleeding complications. However when larger devices are necessary and the use of intra-aortic balloon pump (IABP) is anticipated, femoral access may be preferable.

4.2.3.4 Technical tips during procedure

I,A • Primary PCI should be performed on the IRA.

I,B • Complete revascularisation may be attempted on critical lesions in non-culprit vessels in the same procedure when patient is in cardiogenic shock.

II-a,B • PCI is indicated in a non-infarct artery at a later time when there is evidence of myocardial ischaemia.[80, 81,109]

4.2.3.5 Drug eluting stents (DES) versus bare metal stents (BMS) for STEMI

Both DES and BMS are effective in the setting of STEMI. Randomised trials have not shown any mortality advantage of DES over BMS. However, DES is associated with lower target vessel revascularisation (TVR) without any effect on all-cause mortality.[110, 111]

4.2.3.6 Distal embolisation and the use of adjunctive devices and pharmacotherapy

Thrombus burden is usually large if the patient presents late or the IRA is ectatic. Predictors of slow flow and no-reflow (TIMI 0) of the IRA are:[112-114]

- Vessel diameter ≥ 3.5 mm.
- Treatment of the right coronary artery.
- Higher TIMI thrombus score.
- Angiographic findings such as:
  - *o* "Cut-off" sign (i.e. abrupt occlusion of the epicardial vessel) seen on the coronary angiogram.
  - *o* Persistent contrast stasis just proximal and/or distal to the obstruction.
  - *o* Longer lesions.
  - *o* Thrombus of > 5 mm proximal to occlusion.
  - *o* Floating thrombus.

The following steps can be taken to prevent distal embolisation:

- Aspiration catheter - aspiration of thrombus prior to PCI was associated with improved tissue reperfusion and medium term survival when compared with conventional PCI.[115-117] A recent study however did not show any reduction in 30-day mortality with routine IC thrombus aspiration prior to primary PCI.[118]
- Distal embolic protection - meta-analysis showed that these devices had a neutral effect on mortality.[115]
- Gp IIb/IIIa inhibitors - abciximab therapy during primary PCI showed short term benefit especially in high-risk patients.[119-122] The data on its effect on long-term survival is however conflicting.

4.2.3.7 Management of no reflow

No reflow (TIMI 0) or slow reflow (TIMI 1 and 2) may occur transiently or may persist after primary PCI.

No-reflow may occur as a consequence of:

- Microvascular dysfunction from vasospasm.
- Distal embolisation.
- Intimal dissection/intramural haematoma.

It is associated with poor recovery of LV function and a higher incidence of post-MI complications.

Management includes:

- IC nitroglycerin. 100 - 200 µg boluses.
- IC verapamil 100 – 200 µg boluses.
- IC adenosine 100 – 200 µg boluses.
- IC nitroprusside 50 – 100 µg boluses.
- Others: IC papaverine, IC nicorandil.

Key Messages

- Primary PCI is superior to fibrinolysis for STEMI when performed in a timely manner (DBT < 90 minutes and PCI time delay < 60 minutes) at experienced centres.
- When fibrinolytic therapy is administered, the DNT should be less than 30 minutes.
- Whenever possible, patients given fibrinolytic therapy should be considered for a pharmacoinvasive approach (elective angiogram within 3-24 hours post fibrinolysis).

4.3 Cardiac Care Unit (CCU) management

4.3.1 General measures

All STEMI patients should be admitted to a CCU or equivalent unit equipped with adequate monitoring facilities.

Following successful reperfusion, uncomplicated cases may be kept for a minimum of 24 hours before transfer to a step-down unit. They can sit out of bed and undertake self-care the next day. Patients with STEMI complicated by significant myocardial damage and arrhythmias need longer bed rest and may need to be kept in the CCU longer.

Sedatives may be useful. Titrated IV opioids may be administered to relieve pain.

Use of bedside commode and assisted bedside washing should be safe in most patients.

The Valsalva manoeuvre has been shown to precipitate dangerous haemodynamic and electrocardiographic changes.[123] Prevention of constipation with stool softeners is encouraged.

4.3.2 Monitoring

The general condition of the patient, vital signs, pulse oximetry and the cardiac rhythm should be continuously monitored following STEMI.

4.3.3 Concomitant therapy

4.3.3.1 Oxygen

I,C
- Oxygen is indicated in the presence of hypoxaemia (SpO2 < 95%).[28] It is reasonable to administer it to all patients within the first 6 hours.[28] Oxygen, via nasal prongs, at 2-4 litres/minute is usually adequate. One should aim to maintain the SpO_2 above

4.3.3.2 Antiplatelet agents

A) Aspirin

I,A
- Aspirin is indicated in all patients at diagnosis and should be continued indefinitely unless contra indicated.
- The initial dose of 100-300 mg should be followed by a maintenance dose of 75 – 150 mg daily.[18, 97]

B) Clopidogrel

I,A
- Clopidogrel, when given together with aspirin and fibrinolytic therapy in STEMI, has been shown to reduce the odds of an occluded IRA, death or reinfarction without increasing the risk of bleeding or cerebrovascular accidents.[19, 20, 97]

- In patients less than 75 years of age given fibrinolysis, a loading dose of 300 mg may be administered followed by a maintenance dose of 75 mg daily. In older patients, a loading dose of 75 mg may be adequate.[20]

- In patients considered for primary PCI, a higher loading dose of 300-600 mg may be necessary.

- DAPT is recommended for at least:
  - o 1 month after fibrinolytic therapy.[20]
  - o 1 month and preferably up to a year following PCI with BMS.[124]
  - o 12 months following PCI with DES.[124, 125]

C) Prasugrel

IIa,B
- It may be preferred as an alternative to clopidogrel in patients with STEMI undergoing primary PCI, particularly diabetics.[98]
- The loading dose is 60 mg, and should be given after the coronary angiogram. The maintenance dose is 10 mg/day.[98, 99]
- It is not recommended for patients > 75 years old, < 60 kg weight, have a past history of TIA or stroke due to a higher risk of major bleeding.

D) Ticagrelor

IIa,B Ticagrelor was shown to significantly reduce cardiovascular endpoints when compared to clopidogrel in patients with STEMI undergoing primary PCI.26, 27 Patients given fibrinolytic therapy were excluded from the trial.

- The loading dose is 180 mg and given early after the diagnosis. The maintenance dose is 90 mg bd.

- This agent is short acting and thus can be used in patients who may need surgery without increasing the risk of bleeding.

- 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.

- There was also a small increase in non-CABG related major bleeding.[27]

In the trials, both ticagrelor and prasugrel were given for 1 year.[27, 98]

4.3.3.3 Antithrombotic therapy

These agents are administered to patients who received fibrinolytic therapy and did not undergo PCI.[59, 126-128] They include: (Table 8, page 24)

I,C
- UFH[126]

I,A
- LMWH - enoxaparin[127, 128]
  o 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.[128]

- Anti Xa inhibitor - fondaparinux
  o May be given to those patients treated medically including those not receiving fibrinolytic therapy.[129] In STEMI patients not undergoing primary PCI and not receiving fibrinolytic therapy, fondaparinux was shown to reduce mortality and reinfarction without increasing bleeding and stroke rates when compared to UFH or placebo.[129]
  o It is associated with an increase in catheter-related thrombus and coronary angiographic complications. Thus, fondaparinux is not recommended as the sole anticoagulant during PCI.[59]

Currently, newer oral anti Xa inhibitors (rivaroxaban, apixaban) are being evaluated in ACS patients receiving standard therapy. At present, no specific recommendation can be made on these new agents.[130, 131]

- Gp IIb/IIIa inhibitors - used mainly in the setting of primary or emergency PCI.[100-104] It is administered IC and may be followed by an infusion in the presence of thrombus or slow/ no reflow.[132, 133]

The dose of antithrombotics should be reduced in the presence of CKD(See section 8.4, page 43).

Table 8: Recommended dosages of antithrombotics in STEMI

Heparin	Dosage	Duration of therapy
Enoxaparin	< 75 years: 30 mg IV bolus, SC 1.0 mg/kg bd	Until hospital discharge
	≥ 75 years: no bolus, SC 0.75 mg/kg bd	
UFH	60 U/kg bolus (max 4000 U)	≥ 48 hours
	Infusion 12 U/kg/h (max 1000 U/h) – to maintain an activated partial thromboplastin time (APTT) of 1.5 – 2.5 x control	
Fondaparinux	IV 2.5 mg bolus, followed by SC 2.5 mg once daily (od)	8 days or until hospital discharge

4.3.3.4 ß-blockers

I,A Current recommendations are to use oral ß-blockers in all stable patients without specific contraindications.[134-136] Patients who cannot tolerate ß-blockers initially should be evaluated for suitability prior to discharge.

Contraindications to ß-blockers:
1) Bradycardia < 60/minute.
2) SBP < 100 mmHg.
3) Pulmonary congestion with crepitations beyond the lung bases.
4) Signs of peripheral hypoperfusion.
5) Second or third degree atrio-ventricular (AV) block.
6) Asthma or chronic obstructive airway disease
7) Severe peripheral vascular disease.

Table 9: Recommended dosages of ß-blockers in STEMI

Type	Initiation dose	Target dose
Metoprolol	25 mg bd	100 mg bd
Atenolol	25 mg od	100 mg od
Propranolol	5 mg tds	80 mg tds
Carvedilol	3.125 mg bd	25 mg bd
Bisoprolol	1.25 mg od	10 mg od

4.3.3.5 ACE-Is and ARBs

I,A Early use of ACE-Is (within 24 hours) following STEMI has been shown to improve survival.137 ACE-Is should be started when the BP is stable and SBP remains above 100 mmHg.

The benefits of ACE-Is are greatest in patients with:

I,A • HF.[137, 138]

I,A • Anterior infarcts.[137, 139]
• Asymptomatic LV dysfunction [LV ejection fraction (LVEF)] < 40% on echocardiography).[140, 141]

I,A In patients who cannot tolerate ACE-Is, the ARB, valsartan, has been shown to have a similar survival benefit in patients post-STEMI with LV dysfunction.[142]

I,B Contraindications to ACE-I and ARB therapy:
- SBP < 100 mmHg.
- Established contraindications e.g. bilateral renal artery stenosis.

The dose of ACE-I/ARB should be reduced or stopped if there is:
- o An increase in S^{cr} of ≥ 30% from baseline within 2 weeks after initiation.
- o Persistent hyperkalaemia (> 5.6 mmol/L).

(Refer to 4th edition Malaysian CPG for Management of Hypertension, 2013)

Table 10: Recommended dosages of ACE-Is and ARBs in STEMI

Type	Initiation dose	Target dose
Captopril	6.25 mg bd – tds	25 – 50 mg tds
Ramipril	2.5 mg bd	10 mg od
Enalapril	2.5 – 5 mg od	10 mg od
Lisinopril	5 mg od	10 mg od
Perindopril	2 mg od	8-10 mg od
Valsartan	40 mg – 80 mg od	160 mg bd

4.3.3.6 Mineralocorticoid receptor antagonists

I,B Mineralocorticoid receptor antagonists when added to ß-blockers and ACE-Is, have been shown to reduce mortality and hospitalisations when given to patients post-MI with impaired LV function and mild HF.[143]

4.3.3.7 Statins

I,A All patients with STEMI should be prescribed statins regardless oftheir baseline cholesterol level. Early and intensive high dose statins in ACS have been proven to produce superior benefits in reduction of major adverse cardiac events.[144-147]

I,A In a number of studies, high loading or re-loading dose of statins have been shown to be beneficial in preventing peri-procedural MI in ACS patients undergoing PCI.[147-151]

4.3.3.8 Nitrates

III,A The routine use of nitrates has not been shown to have a survival benefit.[152, 153]

I,C Nitrates can be considered in patients with:
- Continuing chest pain and / or ischaemia.
- HF.
- Hypertension.

In the acute stage, IV nitrates are recommended because of their rapid onset of action, ease of titration and potential for prompt termination in the event of side effects. After the first 48 hours, oral or topical nitrates may be continued in patients with persisting ischaemia and/or HF.

Contraindications to nitrate therapy:
- Hypotension (SBP < 90 mmHg).
- RV infarction (RVI).
- History of phosphodiesterase-5 inhibitor ingestion depending upon the half-life of

Table 11: Recommended doses of nitrates

Compound	Route	Dosage	Time of onset
Nitroglycerine, GTN	IV	5 – 200 µg/minute*	1 minute
	Sublingual	0.3 - 0.6 mg, can repeat up to 3 times at 5 minute intervals	2 minutes
	GTN spray	0.4 - 0.8 mg per metered dose, no more than 3 sprays at 5 minute intervals	2 minutes
	Transdermal patch	0.2 - 0.8 mg over 12 hours on, then 12 hours off	1 - 2 hours
Isosorbide dinitrate	IV	1.25 – 5 mg/hour	1 minute
	Transdermal patch	2.5 – 10 mg	3 - 4 minutes
	Oral	10 – 20 mg, bd/tds	30-60 minutes
Isosorbide mononitrate extended release	Oral	30-60 mg, od	60 minutes
*The dose of IV nitrates should be titrated every 5 - 10 minutes until symptoms and/or ischaemia is relieved and the desired haemodynamic response is obtained.			

4.3.3.9 Calcium channel blockers

III,A There is no data to support the routine use of calcium channel blockers post-STEMI.[154, 155]

However they may be used as adjunctive therapy in patients with hypertension and/or on-going ischaemia despite ß-blockers and nitrates.

II-a,B In patients who cannot tolerate ß-blockers, verapamil or diltiazem may be used for secondary prevention.[156]

Calcium channel blockers should be avoided in patients with LV dysfunction and pulmonary congestion. Verapamil and diltiazem should not be given in the presence of bradycardia and AV block.

4.3.3.10 Others – magnesium, lignocaine, glucose – insulin potassium infusions

III,A Magnesium and lignocaine are not recommended for routine use in patients with STEMI.[153, 157]

II-b,A Although earlier studies and meta-analysis seem to indicate that glucose-insulin-potassium infusions are beneficial, more recent studies have not shown reduction in mortality or infarct size.[158, 159]

Key Messages:

- All patients should receive 300 mg aspirin and 75-300 mg clopidogrel followed by a maintenance dose of 75-150 mg of aspirin long-term and 75 mg of clopidogrel daily.
- Patients who underwent PCI require DAPT for up to a year.
- All patients should be on β-blockers if there are no specific contraindications.
- Other medications that have been shown to improve survival if given early are ACE-Is (or ARBs if ACE-I intolerant) and statins.

4.4 Complications of STEMI

These are:

- Arrhythmias.
- LV dysfunction and shock.
- Mechanical complications.
- RV infarction.
- Others e.g. pericarditis.

4.4.1 Arrhythmias

These include:

A) Tachyarrhythmias

- **Pulseless ventricular tachyarrythmias**
  This is either pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF). Defibrillate immediately. Early VF occurs within the first 48 hours and is due to electrical instability. Late VF is associated with large infarcts and poor pump function and carries a poor prognosis (refer to algorithm 1, page 49).

- **Ventricular tachycardia (VT)**
  VT in the setting of STEMI may arise from either ischaemia (usually within 48 hours) or from myocardial scar due to the infarct (late onset). Treatment of ischaemia may result in the termination of the tachycardia (refer to algorithm 2, page 50).

- **Ventricular premature contractions (VPC)**
  These are often benign and do not require treatment. Correct underlying ischaemia, hypoxia and electrolyte disturbances.

- **Accelerated idioventricular rhythm**
  These do not require any treatment. This is a sign suggestive of successful reperfusion.

- **Atrial fibrillation (AF)**
  This is more commonly seen in the elderly and is associated with large infarcts. It denotes a poorer prognosis and carries an increased risk of thromboembolism (refer to algorithm 3, page 51).

B) Bradyarrhythmias

- **Sinus bradycardia**
  This does not require treatment unless associated with symptoms and/or hypotension.

- **Atrio-ventricular (AV) block**
  First degree and second degree type 1 (Mobitz 1) do not need treatment. Patients with second degree type 2 (Mobitz 2) and complete AV block may not require treatment if haemodynamically stable. If unstable, urgent temporary pacing is necessary. Atropine may be given in the interim (maximum 3 mg) (refer to algorithm 4, page 52).

  Patients with anterior infarcts who develop second degree (Mobitz 2) and complete AV block carry a worse prognosis. Even if haemodynamically stable, these patients require temporary pacing.

  In inferior MI, the inferior wall of the RV may be friable. Insertion of a temporary wire may lead to RV perforation. Thus extra care is equired to prevent this complication.

- **Asystole and pulseless electrical activity (PEA)**
  Rhythms which require defibrillation (pulseless VT/VF) are called shockable rhythms while asystole and PEA are non-shockable rhythms.

  For the management of asystole and PEA, refer to algorithm 1, page 49.

4.4.2 LV dysfunction and cardiogenic shock

LV dysfunction is the single strongest predictor of mortality following STEMI. The mechanisms responsible for acute LV dysfunction include \ myocardial necrosis, myocardial stunning, atrial and ventricular arrhythmias and valvular dysfunction (pre-existing and/or new).

Co-morbidities such as infection, pulmonary disease, renal dysfunction, diabetes, anaemia and drugs may aggravate HF.

4.4.2.1 Presentation

The clinical manifestation of LV dysfunction varies from asymptomatic to cardiogenic shock. An important prognostic indicator is LVEF which can be assessed objectively using echocardiography.

A useful clinical classification of LV dysfunction is the Killip's Classification. [42,160] (Table 12, page 29)

Table 12: Clinical classification of LV dysfunction in STEMI (Killip' Classification)

KILLIP CLASS[160]	CLINICAL FEATURES	APPROXIMATE PROPORTION OF PATIENTS WITH AMI (%)[42]	30 DAY-MORTALITY (%)[42]
I	No signs of LV failure	71	7
II	S3 gallop, bibasal crackles	23	20
III	Acute pulmonary oedema	3.7	39
IV	Cardiogenic shock	2.4	70

4.4.2.2 Investigations

Echocardiography is an essential tool and needs to be performed early to assess LV function and volumes, valvular function, extent of myocardial damage and to detect mechanical complications.

Other investigations that may be helpful in the management include:

- Chest radiograph (to assess extent of pulmonary congestion).
- ECG (for the detection of arrhythmias, ischaemia or reinfarction).
- Arterial blood gases.

4.4.2.3 Management

A) Acute Heart Failure

Acute management includes the following:

- Oxygen – by nasal prongs/face mask to maintain SpO2 above 95%. Consider non-invasive ventilation [bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP)] early if SpO2 cannot be maintained with high flow face mask.

- Diuretics – IV frusemide.
- IV nitrates.
- Inotropes if hypotensive.
  - o Noradrenaline should be the first choice agent. It is started at the lowest dose and titrated till the SBP is more than 80 mmHg.[161]
  - o Dopamine should be refrained as it has been associated with a higher mortality when used in patients with cardiogenic shock.[161]
- In patients who are hypoxic or exhausted and are unable to achieve satisfactory SpO2 despite non-invasive ventilation, endotracheal intubation and ventilatory support may be required.

B) Cardiogenic shock

This condition occurs in 6–10% of all cases of STEMI and remains a leading cause of death, with hospital mortality rates approaching 70%.[162]

The typical presentation is of a low cardiac output state (hypotension with SBP < 90 mmHg, resting tachycardia, altered mental status, oliguria, cool peripheries) and pulmonary congestion. The haemodynamic criteria are an

elevated central filling pressure [pulmonary central wedge pressure (PCWP)] of > 18 mmHg and cardiac index is < 2.2 L/min/m2. Insertion of a pulmonary artery catheter may be helpful in the diagnosis and management of these patients.

Emergency PCI may be life-saving and should be considered early irrespective of the time delay from onset of MI. The use of IABP has not shown a definite benefit and its use should be individualised.[163]

LV assist device may be considered for patients who do not respond to conventional therapies.

When cardiogenic shock is due to a mechanical defect, urgent surgical repair is indicated. Concomitant CABG surgery in these patients remains an issue of debate. The decision must be individualised.

4.4.3 Mechanical complications

These include the following:

- Free wall rupture - it is usually fatal and presents with sudden cardiovascular collapse and haemopericardium.
- Ventricular septal rupture.
- Mitral regurgitation.

The diagnosis should be suspected in patients with sudden clinical deterioration and suggested by the presence of new murmurs or diminished heart sounds. The diagnosis can be confirmed by echocardiography In these patients early surgery should be considered.

Ventricular septal rupture requires urgent surgical repair, but there is no agreement on the optimal timing for surgery.

4.4.4 Right Ventricular Infarct (RVI)

Patients with RVI may have varying clinical presentation, from asymptomatic to cardiogenic shock.[164] Haemodynamically significant RVI complicates approximately 5-10% of all STEMI. It occurs in 30 – 50% of patients with infero basal (formerly known as infero-posterior) MI and is associated with a significantly higher mortality. RVI can also occur in patients with extensive anterior STEMI.

4.4.4.1 Clinical diagnosis

The presence of RVI should be sought in all patients with inferior STEMI. The clinical triad of hypotension, clear lung fields and elevated jugular venous pressure in the setting of inferior STEMI is suggestive of RVI.

ST elevation in the right praecordial leads (V4R) is the most specific finding in diagnosing RVI.[8] However, this ECG finding may be transient, often resolving within 8-10 hours.

4.4.4.2 Management

Treatment strategies depend on the severity of peripheral hypoperfusion and the degree of co-existing LV dysfunction. Drugs that reduce the preload,such as nitrates and diuretics should be avoided.

Management includes:

- Optimisation of IV fluids (saline or colloids) is the key therapy to correct the hypotension.
- Inotropes.

Failure to respond to these measures usually indicates concomitant LV dysfunction These patients require more aggressive management with afterload reducing agents such as nitroprusside and IABP.

4.4.5 Others

4.4.5.1 Chest pain post-STEMI

Chest pain post-STEMI may be due to reinfarction, ischaemia or pericarditis. Non cardiac causes must also be considered.

A) Reinfarction

Reinfarction occurs in about 3-4% of patients who had undergone fibrinolytic therapy and received aspirin.[165] Reinfarction may be diagnosed by:

- Recurrence of ischaemic type chest pain.

- Recurrence of ST segment elevation of at least 0.1 mv in at least two contiguous leads and/or
- Re-elevation of serum cardiac biomarkers - CK-MB (≥ 20% increase in the value from the last sample).[4]

Death, severe HF and arrhythmias are more common in these patients. They should be considered for rescue PCI.

B) Post-infarct angina
Early recurrent angina, especially after successful reperfusion with fibrinolytic therapy may occur in up to 18% of patients.166, 167 The ECG in these patients may show ST segment changes or pseudo-normalisation of inverted T-waves. These patients should be sent for early coronary angiography with a view to revascularisation.

C) Pericarditis
Pericarditis secondary to STEMI may produce pain as early as the first day and as late as 6 weeks.[168] The pain classically becomes worse on deep inspiration and may be relieved when the patient sits up and leans forward. A pericardial rub may be detected.

Dressler's syndrome (post-MI syndrome) usually occurs 2-10 weeks after STEMI. This is immunologically mediated.[169] It is treated with aspirin 600 mg 3-4 times a day.

Acetaminophen or narcotic analgesics may be reasonable if aspirin, even in higher doses, is not effective.

Glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) are potentially harmful for treatment of pericarditis after STEMI and are best avoided in the first 4 weeks of STEMI.[170, 171]

4.4.5.2 LV thrombus and arterial embolism

The prevalence of LV mural thrombus has been reduced from 20% to 4% in the era of primary PCI.[172,173] The majority of these occur following anterior or large infarcts. Anticoagulation therapy is recommended for 3-6 months or till the LV thrombus disappears or organises on echocardiography.[174]

4.4.5.3 Deep venous thrombosis (DVT)

In high-risk patients (prolonged bed rest, HF, unable to mobilise), prophylactic anti-coagulation therapy (SC heparin 5000 units bd, LMWH – e.g. enoxaparin 40 mg od) may be considered until the patient is ambulant.

4.5 Urgent/Emergent CABG surgery:

Urgent/emergent CABG surgery should be considered in the following situations:

- At the time of surgical repair of post-infarction VSD or mitral valve regurgitation (See section 4.4.3).
- Patients with failed reperfusion whose coronary anatomy and clinical profile are suitable.

In general, CABG surgery in this group of patients carries a very high in hospital mortality rate.

Key Messages:

- Important complications following STEMI are arrhythmias and HF.
- HF may be due to extensive myocardial damage or mechanical complications.

5 RISK STRATIFICATION POST-STEMI

Risk stratification of patients post-STEMI serves to prognosticate and identify appropriate treatment strategies. Risk stratification starts from admission and is a continuing process. It is especially important in patients treated medically and those with multivessel disease who underwent PCI of the IRA only. The GRACE score predicts in-hospital and 6-month mortality (Appendix IV, page 56 & 57).

Ideally, all patients with poor prognostic indicators who did not undergo primary PCI should have a coronary angiogram during the index hospitalisation.

These include:

- Older persons (> 75 years).
- Female gender.
- Previous MI.
- Anterior MI.
- Inferior MI with RV involvement.
- Diabetes mellitus (DM).
- Persistent or recurrent ischaemia as manifested by post-infarction angina or ST segment depression at rest.
- Hypotension.
- HF.
- AF and late (after 48 hours) ventricular arrhythmias.
- Presumably new LBBB.
- Previous CABG or PCI.

All other patients who did not undergo coronary angiography should be risk stratified early. This may be done by assessing:

- LV function
  - o Clinical, chest X-ray, echocardiogram, radionuclide studies or cardiac MRI.

- Presence of myocardial ischaemia
  - o Clinical (recurrent angina).
  - o Exercise stress testing in asymptomatic patients.
    - This may be done from day 5 post-STEMI (sub-maximal stress test with a target heart rate of 70% of maximum predicted heart rate) up to 6 weeks post-STEMI (maximal with a target heart rate of 90% of maximumpredicted heart rate for age or symptom limited).
    - If the pre-discharge sub-maximal stress test is negative, the patient should be subjected to a maximal or symptom limited stress test within 6 weeks after discharge.
    - For those who cannot exercise, consider dobutamine stress echocardiogram, radionuclide perfusion studies or cardiac MRI.

- Presence of malignant ventricular arrhythmias.

I,A In the presence of angina, inducible ischaemia or late ventricular arrhythmia early coronary angiography with a view to revascularisation is indicated.[80]

I,C In patients with poor LV function, myocardial viability studies (dobutamine stress echocardiogram, radionuclide perfusion studies or cardiac MRI) would help to differentiate scarred from viable ischaemic myocardium.

II-a,B Patients with severe CAD, angina, viable myocardium and reversible ischaemia with mild LV dysfunction (LVEF > 35%) are more likely to benefit from revascularisation.[175]

Patients with palpitations, near faints and syncope require comprehensive evaluation to determine the cause of their symptoms and risk of sudden cardiac death. This includes:

- Serum electrolytes.
- Resting ECG.
- 24-hour ambulatory ECG recording.
- Evaluation of LV function.
- Assessment for reversible myocardial ischaemia.
- Coronary angiography.

In these patients, reversible causes such as electrolyte disturbances and ischaemia should be corrected.

The following medications have been shown to reduce the incidence of sudden death:

I,A • ß-blockers.[176, 177]

I,A • ACE-Is.[178]

I,B • Mineralocorticoid antagonists.[143]

IIb,B • Statins.[179, 180]

In addition, the following patients should be considered for an implantable cardioverter-defibrillator (ICD):

I,A • Secondary prevention in patients with resuscitated sudden cardiac death.[181-183]

IIb,B • Primary prevention in patients with LV dysfunction [ejection fraction (EF) < 30%]. ICD may be considered 40 days post-STEMI and 3 months post-revascularisation.[184-186]

Key Messages:

- All patients post-STEMI should be risk stratified either clinically or by using GRACE risk score.
- High-risk patients should be referred to cardiology centres.

6 DURATION OF HOSPITALISATION

The duration of hospital stay following STEMI will depend on the extent of myocardial damage, presence of complications and comorbidities.

Early (same day) transfer to the referring centres may be considered in selected low-risk uncomplicated patients after successful primary PCI.

Asymptomatic patients with uncomplicated STEMI may be discharged after 3-5 days particularly if the IRA has been successfully reperfused.[187, 188] Patients with significant LV dysfunction or other complications may require a longer hospital stay.

7 SECONDARY PREVENTION

Patients who survive the initial course of STEMI are at increased risk of morbidity and mortality because of reinfarction and the development of other complications such as HF and late onset arrhythmias. Thus, it isimportant that efforts be made to reduce this risk.

Secondary prevention should be initiated in-hospital. Patients should be advised on the benefits and importance of lifestyle changes. A close collaboration between the cardiologist, the general/family physician, the rehabilitation specialist, pharmacists and dietician is important.

These lifestyles measures include:

7.1 Cessation of smoking

In patients with known CHD, smoking cessation reduced CHD mortality by 36% as compared to those who continued smoking.[189] Following MI, smoking cessation reduced subsequent mortality by nearly 50%.[189]

I,B This lifestyle change confers a risk reduction which is at least as great as other pharmacological interventions. Stopping smoking is potentially the most effective of all secondary prevention measures.[190]

I,B Trials of nicotine replacement therapy using either transdermal nicotine patch or nicotine chewing gum have proven to greatly increase abstention rates after cessation. Nicotine patches have been demonstrated to be safe in ACS patients.[191] Such pharmacological therapy, as well as physician-guided counselling and nurse-directed programmes are cost-effective and should be encouraged.[192, 193]

The safety of electronic cigarettes is uncertain at this time.

7.2 Diet and weight control

I,B Dietary intervention has been shown to reduce cardiac event rates post-STEMI.[194-196]

Recommendations include:

- Total calorie intake should be tailored to the desirable body weight.
- Substituting saturated and trans fat with monounsaturated and polyunsaturated fat from vegetables and marine sources.
- Reducing total fat to 30% of total calorie intake.
- More high fibre food and whole grains which have low glycaemic index instead of more rapidly digested carbohydrates.
- More fruits, nuts and vegetables.
- Increasing intake of omega 3-fatty acids by eating fish at least twice a week.[197, 198]
- Reducing salt intake – no added table salt.
- Increasing intake of oat ß-glucan to at least 3 g a day will lower total and LDL-C by 5-10%.[199]

7.3 Regular exercise

I,B Exercise training as part of coronary rehabilitation programmes was associated with a reduction in cardiac mortality in patients with CHD.[200-203] Exercise-based rehabilitation has been shown to be effective at reducing all-cause mortality and the risk of reinfarction, as well as improving risk factors, exercise capacity and health-related quality of life after STEMI.[204, 205] Thirty minutes of moderate intensity aerobic exercise at least five times per week is recommended.[202] It should be supplemented with an increase in daily lifestyle activities such as walking up stairs whenever possible.[201]

7.4 Control of hypertension

I,A After STEMI, prognosis is affected by both the pre-existing and the subsequent BP. The higher the pre-existing BP, the higher the fatality rate.[206] After ACS, the BP goal should be systolic < 140 mmHg but not < 110 mmHg.[207] Drugs of choice include ß-blockers, ACE-Is and ARB (if ACE-I intolerant). In addition, lifestyle modification (reduced salt intake, increased physical activity and weight loss) usually helps achieve these goals.

7.5 Good glycaemic control

IIb,B Good control of the blood glucose is important and should be individualised.[208-210]

7.6 Antiplatelet agents

I,A
- Aspirin – low dose aspirin 75-100 mg daily is indicated indefinitely after STEMI unless contraindicated.[18, 211]

I,B
- In patients who cannot tolerate aspirin, alternatives include:
  - Clopidogrel, 75 mg daily.[19, 20]

I,C
  - Ticlopidine, 250 mg b.d.

I,A DAPTs should be given for at least one month post-fibrinolytic therapy for secondary prevention.[20, 212]

I,A Following primary PCI, DAPT with combination of aspirin and clopidogrel or ticagrelor or prasugrel is recommended.[26, 27, 98,120]

DAPT with aspirin and oral adenosine diphosphate (ADP) receptor antagonist is recommended to be continued for up to 12 months after STEMI[124], with a strict minimum:

I,C
- 1 month for patients receiving BMS.

IIb,B
- 6 months for patients receiving DES.[213-215]

7.7 ß-blockers

I,A The benefit of long-term treatment with ß-blockers after STEMI is well established from clinical trials conducted in the pre-thrombolytic era.[216]

I,A Oral treatment with ß-blockers is indicated in patients with HF or LV dysfunction.[217-220] When patients are haemodynamically stable, ß-blockers may be initiated.

7.8 ACE-Is and ARBs

I,A ACE-Is are indicated starting within the first 24 hours of STEMI in high-risk patients (LVEF < 40% or who have experienced HF in the early phase, DM or an anterior infarct) and should be continued indefinitely if there are no contraindications.[137, 221]

IIa,A In all other patients, ACE-Is should be considered.[222-224]

I,B In ACE-I intolerant patients, an ARB may be used preferably valsartan.[142, 225]

7.9 Mineralocorticoid antagonists

I,B Mineralocorticoid antagonists, e.g. eplerenone should be considered in patients with LVEF < 40% and HF in the absence of renal failure or renal impairment.[143]

7.10 Lipid-lowering therapy

I,C • A lipid profile should be taken as soon as possible after presentation.

I,A • Statins at high dose should be initiated early after admission in patients with STEMI who do not have contraindication or history of intolerance, regardless of initial cholesterol values and continued indefinitely.[144, 145, 226, 227]

I,B • Target LDL-C should be < 2.0 mmol/L.[228-231]

I,B • Recent studies indicate that lowering LDL-C even further (< 1.8 mmol/L) confers greater benefits.[145, 232-234]

7.11 Oral anticoagulants (warfarin)

I,C • In patients with a clear indication for oral anticoagulation e.g. LV thrombus, AF with CHA_2DS_2-VASC score ≥ 2 or mechanical prosthetic valve, oral anticoagulation must be implemented in addition to antiplatelet therapy (Appendix V, page 58).

• The optimal duration of triple therapy is unknown and clinical judgement should consider the risk of bleeding versus the risk of stent thrombosis.

• There is insufficient data on the use of new oral anticoagulant agents at this time.

IIa,B • In patients with LV thrombus, warfarin should be given for 3-6 months or till the thrombus disappears or organises.[172, 235]

7.12 Others

III,A • Hormone replacement therapy (HRT) is not beneficial for secondary prevention.[236, 237]

III,A • Vitamin E and antioxidants have no clinical benefit.[238-240]

III,C • Garlic, lecithin, Vitamin A and C are not beneficial.

Key Messages:

- Secondary prevention interventions such as smoking cessation, statin therapy, control of diabetes, hypertension and lifestyle changes can reduce mortality and cardiac event rate post-STEMI.
- Healthcare providers must provide patient education and encourage compliance.

8 SPECIAL GROUPS

8.1 STEMI in the elderly

Patients above the age of 75 years have a much higher in-hospital as well as 1-year mortality.[241-243] This may be explained by their atypical and delayed presentations, co-morbidities and under-utilisation of reperfusion strategies.[244, 245] Diagnosis may be delayed because of:

- Atypical symptoms such as dyspnoea, syncope and acute confusion.
- Non-diagnostic and difficult to interpret ECGs.
- Non-diagnostic cardiac biomarkers. The baseline troponin levels may be elevated in as many as 22% of the elderly without an MI because of pre-existing cardiac and renal disease.[246, 247] Thus, a high index of suspicion must be present to make a diagnosis of ACS in the elderly. The trend of a rise and fall cardiac biomarker levels is critical to the diagnosis.

Management

Elderly patients were excluded from most of the large trials and data is mainly derived from post-hoc analysis.[242] One should consider the biological age rather than the chronological age of the patient when making management decisions. The elderly are a heterogenous group and the risk-benefit ratio of each intervention should be individualised.[248]

CKD is common in these patients and may increase the risk of bleeding. Most drugs are excreted by the kidneys and doses need to be adjusted. Creatinine clearance (CrCL) should be estimated using the Cockcroft-Gault (Appendix VI, page 59), Modification of Diet in Renal Disease (MDRD) equations (Appendix VII, page 59) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations (Appendix VIII, page 59).

In the management of STEMI in the elderly:

II-a,B • Primary PCI - this is the preferred reperfusion strategy if facilities are available and the patient is eligible for PCI.[249-252] Procedural success is highly variable. Elderly patients are more likely to have PCI related complications especially bleeding.[253]

II-a,B • Fibrinolytic therapy - there is an increased risk of intracranial haemorrhage in the elderly and the risks of bleeding have to be carefully considered in those older than 75 years.[254-256]

• Adjunctive therapy - when compared with younger patients, the elderly have a greater absolute reduction with most evidence based medications.[257]

II-a,B o Aspirin - at a dose of 75 to 150 mg in the absence of contraindications.[242, 258]

II-a,B o Clopidogrel - the absolute benefits of clopidogrel are similar, but relative benefits are less in the elderly. Patients undergoing PCI with higher TIMI risk scores or prior revascularisation are more likely to benefit.[124, 259, 260] A loading dose when compared to a conventional dose of clopidogrel did not result in an increased bleeding risk in the elderly.[261] The need for a loading dose needs to be individualised.

II-a,B o Ticagrelor – ticagrelor has a similar efficacy as clopidogrel in patients aged ≥ 75 years of age and those < 75 years of age. There was no increased risk of bleeding[262]

III,B o Prasugrel - should be avoided in patients > 75 years of age.[98]

II-a,B o Enoxaparin was found to be more effective than UFH in the majority of subgroups except in patients > 75 years of age in whom there is no available data.[242, 263] The dose however needs to be adjusted.[128, 264] (Table 8, page 24)

I,A • Secondary prevention - the benefit associated with the use of ß-blockers, ACE-Is and statins is similar to, and often greater than, that observed in younger patients.[135, 265-271]

II-a,B • The elderly benefit from cardiac rehabilitation and exercise training.[272, 273]

II-a,C • Risk stratification - this has to be individualised and patient preferences are important in determining further management. The presence of on-going ischaemia, symptomatic malignant arrhythmias and a depressed LV function are poor prognostic indicators and would generally necessitate a more aggressive approach. Both PCI and CABG, when indicated, can be carried out in the elderly with acceptable morbidity and mortality by experienced operators. The risks are however higher than in younger patients.

8.2 STEMI in diabetics

Blood glucose level was associated with adverse outcomes independent of prior diabetic status in patients following STEMI.[274, 275] This poor prognosis in diabetics occurred despite successful reperfusion of the infarct-related vessel.[275] Local NCVD registry data indicate that diabetics with STEMI did worse than would be expected from their TIMI risk score.[29]

Management

I,A Diabetic patients should be treated in a similar manner as non-diabetics. Primary PCI is the reperfusion strategy of choice in these high-risk patients.[276]

Adjunctive therapy includes:

I,A
- Antiplatelet agents – aspirin and clopidogrel or prasugrel or ticagrelor.[18-20, 26, 27, 98]

I,B
- Prasugrel has been found to be more effective in diabetics.[98]

IIb,B
- Gp IIb/IIIa inhibitors – Meta-analysis and registry data indicate that early administration of abciximab in diabetic patients resulted in infarct-related artery patency before and after primary PCI, and a trend towards an improvement in 1- year survival.[277, 278]

Diabetes is a well-recognised risk factor for contrast induced nephropathy (CIN).[279] In the setting of STEMI, an elevated pre-procedural glucose level is associated with a greater risk for CIN even in patients without known diabetes.[280] For prevention of CIN, see Appendix IX and X , pages 60 & 61)

IIb,B There is still a lack of consensus on the optimal management of blood sugars during the acute event.[281, 282] Intensive insulin therapy to achieve normoglycaemia in the acute setting has not been shown to reduce mortality and is associated with an increase in the episodes of hypoglycaemia. A low blood sugar level (< 4.5 mmol/L) has also been associated with adverse outcomes. A general consensus is to keep blood sugars between 6-10 mmol/L in the acute setting and then aim for optimal control following discharge.[282, 283]

8.3 STEMI in women

Women have a higher mortality following STEMI.[284-289] They are generally about 10 years older when they develop CHD and have more comorbidities.[285]

Women tend to have atypical symptoms and generally do not present with classical ischaemic-type chest pain. They are more likely to have fatigue, neck pain, syncope, nausea, right arm pain, dizziness and jaw pain.[286] Subjective reports of sleep disturbance preceding MI seem to be common in women.[287] Women are more likely to present with cardiogenic shock.[288-290]

Management

In general, women should be treated the same as men taking into consideration the following:[258, 291, 292]

I,A
- Primary PCI is the preferred reperfusion strategy. Women however, have higher early all-cause and cardiac mortality after primary PCI and they also have higher bleeding risk.[288] Women are less likely to undergo coronary angiography and reperfusion and those who underwent primary PCI tend to have longer DBT.[288, 293]

- Women given fibrinolytics [recombinant tissue plasminogen activators (r-TPA)] had a higher incidence but lower mortality from bleeding than men.[294]

I,A
- Adjunctive therapy is similar in both genders.[264, 295, 296] Women however have higher bleeding risk.

IIa,B
- Cardiac rehabilitation – women, especially older women, are under-referred for cardiac rehabilitation. Efforts should be initiated to overcome these barriers.[297]

I,B
- Continuing HRT after STEMI does not confer a benefit nor pose a worrisome increase in risk. When considering the need for HRT for menopausal symptoms, clinical judgement is necessary.[298, 299]

Key messages:

- Diagnosis of STEMI in the elderly, diabetics and women is difficult and a high index of suspicion is important.
- Treatment is the same although the elderly and women tend to have higher bleeding risk.

8.4 STEMI in renal disease

Patients with all grades of CKD (Appendix VI, VII & VIII, page 59) have a worse prognosis after an MI compared to those with normal renal function; those on dialysis may have as high as 74% mortality at 2 years.[29, 300, 301] The S_{cr} at admission predicts long-term mortality even after successful primary PCI. 1 in 6 survivors develop worsening renal function during the admission and this is also associated with increased mortality even in patients with normal renal function at baseline.[302]

Patients with CKD tend to be older, have more comorbidities such as diabetes and be on more cardio-protective medications. They are more likely to present without chest pain, be in Killip Class III or IV and present as NSTEMI.[303] Troponins may be elevated in patients with CKD even in the absence of ACS. A rise and fall in cardiac biomarkers is essential to make a diagnosis of MI. Small studies seem to indicate that Troponin I may be more specific for myocardial necrosis than Troponin T in CKD.[304]

The optimal mode of reperfusion in patients with CKD presenting with STEMI has not been addressed in large prospective trials. Registry data

indicate that 30-day and 1-year mortality were higher in those treated with primary PCI as compared to those given fibrinolytics and those who were not reperfused. This suggests that fibrinolytics may be the preferred strategy in these patients especially in those with glomerular filtration rate (GFR) < 30 ml/minute.[305, 306]

The success rate of emergency PCI in patients with CKD is generally lower and an unsuccessful primary PCI can result in worsening renal function due to haemodynamic instability and CIN.[307] Patients with CKD tend to have more extensive atherosclerosis and more complex calcified lesions.[307] In some patients with multivessel coronary involvement and haemodynamic instability, complete revascularisation by CABG may be superior to PCI.

CIN is higher among patients undergoing primary PCI as compared to elective procedures. It occurs in as high as 20-30% of cases and is associated with adverse 1- year mortality.[308] Half of these patients may go on to develop persistent renal failure.309 For the prevention of CIN, see Appendix IX & X, pages [60-61]. Recent studies have shown high-dose statin therapy to reduce the incidence of CIN.[310-312]

Management

Patients with CKD were excluded from most clinical trials and most of the available data is derived from post-hoc analyses. These patients have higher rates of bleeding and the doses of antithrombotic agents need to be adjusted accordingly. (Table 13, page 44)

- Fibrinolytic therapy may be the preferred strategy particularly in patients with GFR < 30 ml/minute.[305, 306]

IIa,C

Table 13: Dosages of Antithrombotics in CKD

	LOADING DOSE	MAINTENANCE DOSE
UFH	No change	No change
Enoxaparin	30 mg IV	1 mg/kg SC every 24 hours if CrCL < 30 ml/minute
Fondaparinux	Avoid if CrCL < 30 ml/minute	Avoid if CrCL < 30 ml/minute
Eptifibatide	180 mcg/kg	IV infusion 1.0 mcg/kg/minute if CrCL < 50 ml/minute
Tirofiban	IV infusion 0.4 mcg/kg/minute for 30 minutes	IV infusion 0.05 mcg/kg/minute if CrCL <30 ml/minute

Modified from ACC/AHA 2007 Guidelines for the Management of Patients with UA/NSTEMI. J Am Coll Cardiol 2007; 50:1-157.

Adjunctive therapy:

IIa,B

- Standard care: aspirin 75-100 mg and clopidogrel 75 mg.
  - This regime was found to be non-inferior to Gp IIb/IIIa inhibitors or loading dose of clopidogrel. Standard care was associated with less bleeding.[313]
  - In patients with mild to moderate CKD who underwent primary PCI, a 600 mg loading dose of clopidogrel was not found to be beneficial. This dose however did not increase the in-hospital major bleeding rate.[314-316]
  - Ticagrelor reduced mortality and major cardiovascular events more than clopidogrel.[26, 317, 318]

IIa,B

- Antithrombotics:
  - Fondaparinux - in patients with mild to moderate CKD, fondaparinux was more effective than enoxaparin largely explained by the lower rates of bleeding.[319] However, it should be avoided in patients with CrCL <30 ml/minute.
  - Bivalirudin was not superior to heparin and Gp IIb/IIIa inhibitors but was associated with less bleeding.[320-322]

IIa,B

- Adjunctive therapy: meta-analyses and post-hoc analyses of studies in patients with mild to moderate CKD have noted benefits with aspirin, ß-blocker and statin therapy.[323, 324]

In patients on dialysis, there is a lack of evidence concerning the cardiovascular benefits of ACE-Is and ARBs, ß-blockers and statins.[325, 326] Aspirin may result in greater bleeding risks in these patients.

Key messages:

- Treatment of STEMI in patients with CKD should be individualised.
- Fibrinolytic therapy may be the preferred reperfusion strategy.
- In view of bleeding risk, lower doses of aspirin (75 – 100 mg) and clopidogrel (75 mg) should be given.

9 CARDIAC REHABILITATION IN STEMI

All post-STEMI patients (including those post-PCI or CABG) should undergo comprehensive cardiac rehabilitation. The mortality benefits of cardiac rehabilitation persist even in the era of more aggressive treatment strategies of STEMI.[200, 327]

This programme aims at improving the long-term prognosis and optimising the physical, psychological and social well-being of the patient. It comprises prescribed exercise training and education, counselling, risk factor modification and behavioural interventions. Cardiac rehabilitation should start in the CCU, continue in the outpatient setting and extend to community care. It is a proven

effective intervention and every effort must be made to ensure minimal dropouts so as to maximise beneficial effects of the programme.

The components are as follows:

- Patient assessment for appropriateness of programme.
- Ongoing medical surveillance (BP/ lipids/ diabetes control).
- Nutritional counselling.
- Smoking cessation.
- Psychosocial counselling.
- Physical activity counselling - resumption of sexual activity (after 1 week*), driving, work, exercise and air travel (after 2 weeks*).[328] A simple rule of thumb is to resume sexual activity if the patient can climb 2 flights of stairs comfortably.
- Exercise training.
- Pharmacological treatment (optimum up-titration or maximum tolerable dose).

**stable uncomplicated cases*

Patient education regarding lifestyle modification is vital and enhances compliance and commitment to therapy. Family members should be encouraged to learn basic CPR.

Structure of a cardiac rehabilitation programme (CRP) consists of 4 phases:
- Phase 1: Inpatient CRP: focus on patient education.
- Phase 2: Outpatient CRP.
- Phase 3: Extended CRP (for patients with impaired functional status initially, requiring an extended course before returning to usual activity in the community).
- Phase 4: Lifetime CRP.

10 FUTURE DEVELOPMENTS

Since the publication of the 2nd CPG, newer technologies have emerged in the diagnosis and management of STEMI. While some of these technologies are currently being subjected to clinical trials, others that have proven effective, are being gradually integrated in the care of patients with STEMI.

New technological advances include:

- Diagnostics – new biomarkers e.g. high sensitivity troponins and point-of-care measurements.[329]
- Risk stratification – genetic testing to identify individuals at high-risk of developing ACS and reinfarction following STEMI.[330, 331]
- Bioinformatics - advanced ECG diagnostics allowing diagnosis of STEMI at FMC and relaying this information to healthcare personnel thus resulting in earlier reperfusion strategies.[332]
- Imaging techniques – high resolution hand-held echocardiography to assist in the diagnosis of STEMI in the presence of non-diagnostic ECGs.[333]
- Therapeutics – newer antithrombotics, novel lipid lowering agents

and myocardial preservation in the acute phase of STEMI utilising stem cells, myocytes, growth factors and other agents.[334,335]
- Interventional - bioresorbable scaffolds in STEMI, mechanical thrombectomy, distal embolic protection devices, and other adjunctive technologies.[336-338]
- Regenerative medicine - stem cell therapies.

11 CHECKLISTS FOR FOLLOW-UP VISIT

The following should be assessed at each follow-up visit:

- Assess the presence or absence of cardiac symptoms and determine the functional class of the patient.
- Evaluate patients' psychosocial (anxiety & depression) status and the social integration and support network.
- Review pre-discharge risk assessment and evaluate:
  - o Presence of residual ischaemia.
  - o LV function.
  - o Current medications and optimise their doses.
- Treat to target.
  - o BP: < 140/90 mmHg.
  - o Lipids: LDL-C < 2.0 mmol/L, preferably < 1.8 mmol/L.
  - o Diabetic control: targets should be individualised.
  - o Achieve and maintain ideal body weight and waist circumference.

12 CLINICAL AUDIT INDICATORS

Performance measures should be used with the goal of improving quality of care for STEMI.

Process performance measures focus on aspects of care that are delivered to a patient, while outcome measures focus on end-points such as mortality or hospitalisation.

Suggested process performance indicators include:
- % of patients with suspected ACS who had an ECG done within 10 minutes of arrival in the emergency department
- % of patients with STEMI who received fibrinolytic therapy within 30 minutes (DNT) or
- % of patients with STEMI who received primary PCI within 90 minutes (DBT)
- % of patients discharged on DAPT
- % of patients discharged on ß-blockers
- % of patients discharged on statins
- % of patients discharged on ACE-I/ARB
- % of patients who received an echocardiogram prior to discharge
- % of patients referred for cardiac rehabilitation
- % of smokers receiving quit smoking advice

In non-PCI capable hospitals,
- % of patients who received ischaemic testing (e.g. sub-maximal stress test, stress echocardiogram) prior to discharge

In PCI capable hospitals,
- % of patients receiving primary PCI
- % of patients undergoing coronary angiography during index admission

Suggested outcome measures indicators include:
- In-hospital mortality

Refer to Appendix XI for calculation of the above.

13 IMPLEMENTING THE GUIDELINES AND RESOURCE IMPLICATIONS

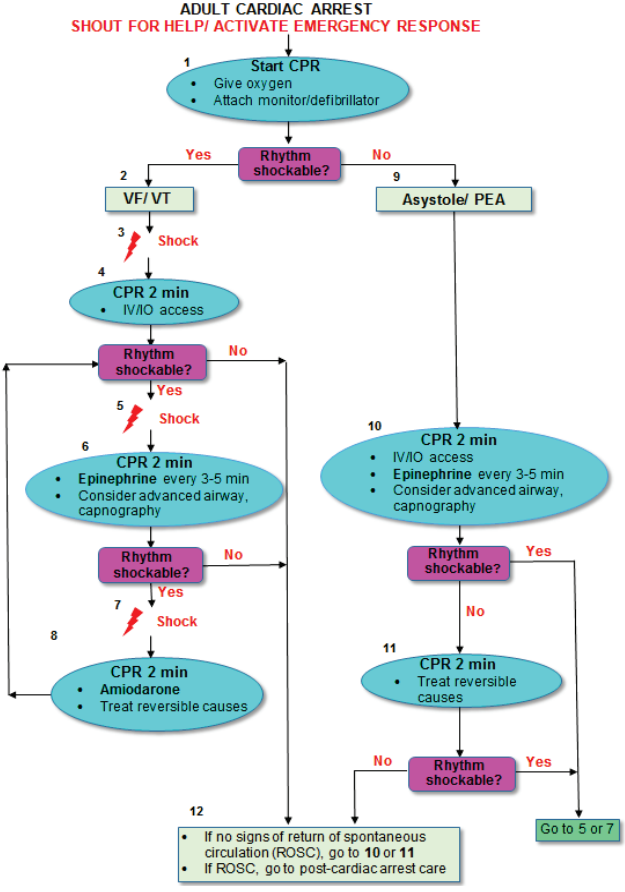
STEMI is one of the common causes of death in Malaysia and patients can present at all levels of healthcare. To ensure that patients receive good evidence based care, the information in this CPG must be successfully disseminated.

In improving outcomes, time is essence and early diagnosis assumes paramount importance. Patients should be educated to seek early treatment if they have symptoms of suspected ACS. Healthcare personnel need to have a high index of suspicion of ACS, make the diagnosis promptly and institute timely treatment.

This can be done by ensuring:
- regular public education via forums, mass media etc.
- continuous medical education of healthcare providers via regular seminars, lectures and roadshows.
- widespread availability of this CPG to healthcare providers via printed copies, electronic websites etc.
- regular audit of the performance and outcome indicators mentioned in section 12.
- availability of the drugs mentioned in this CPG. Most of these are already available in the Ministry of Health drug formulary. Healthcare personnel need however, to be educated on their appropriate and timely usage.
- a work-in-progress towards providing 24 hour coverage for primary PCI or pharmacoinvasive therapy.
- seamless care i.e. coordinated linkage between primary healthcare personnel and the tertiary cardiac centres.

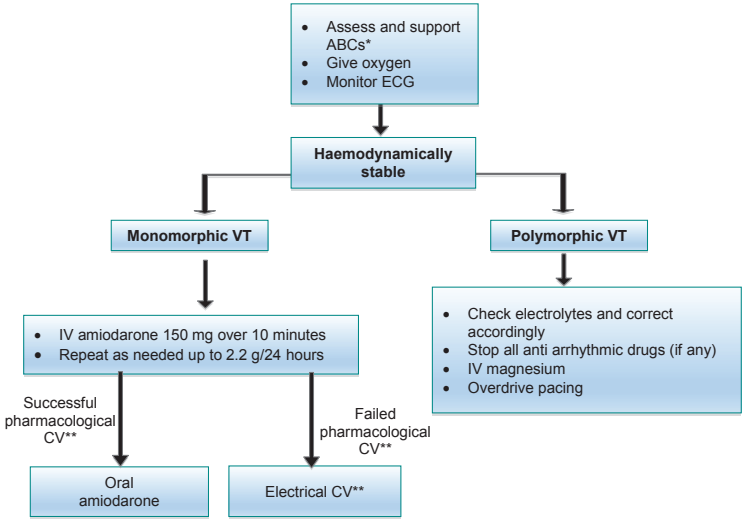
ALGORITHMS

ALGORITHM 1: PULSELESS ARRHYTHMIAS



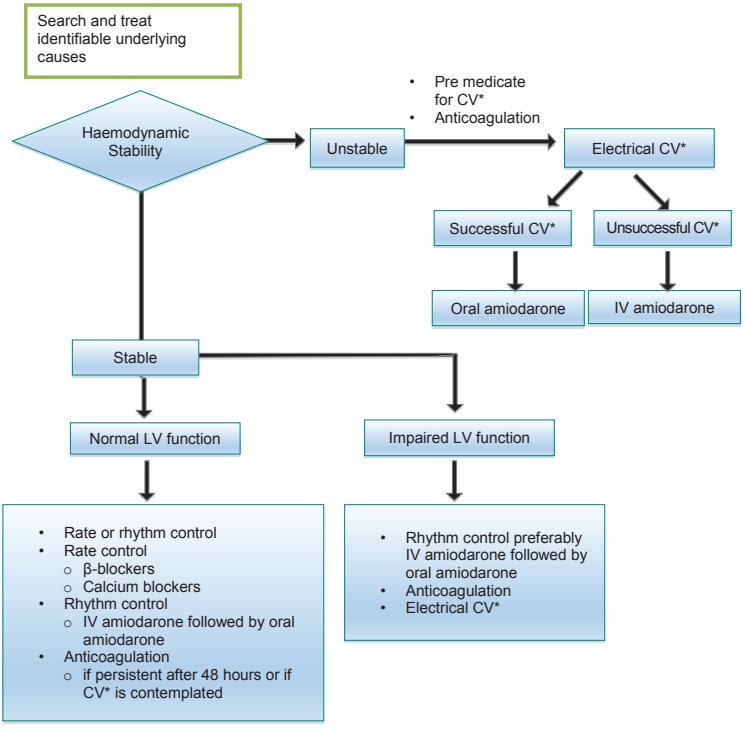
Adapted from 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation.2010; 122:S729-S767

ALGORITHM 2: STABLE VENTRICULAR TACHYCARDIA
(if unstable for immediate synchronised cardioversion)



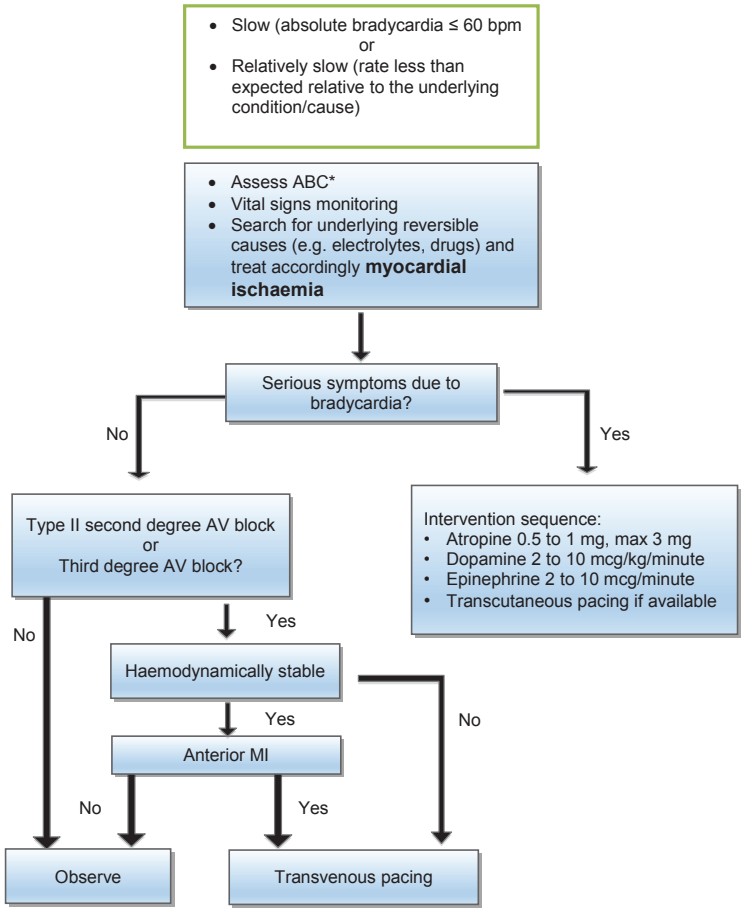
*ABC: airway, breathing, circulation
** CV: cardioversion

ALGORITHM 3: ATRIAL FIBRILLATION



*CV: cardioversion

ALGORITHM 4: BRADYCARDIA



*ABC: airway, breathing and circulation

APPENDICES

APPENDIX I: DIFFICULTIES IN ECG DIAGNOSIS OF MI

The following conditions may cause ECG changes that may be confused with that of STEMI:

- Prior MI with Q-waves and/or persistent ST elevation.
- Early repolarisation.
- LBBB.
- Right ventricular pacing.
- Pre-excitation.
- Peri-/myocarditis.
- Pulmonary embolism.
- Subarachnoid haemorrhage.
- Metabolic disturbances such as hyperkalaemia.
- Cardiomyopathy.
- Cholecystitis.
- Tricyclic antidepressants or phenothiazines.
- J point elevation syndromes, e.g. Brugada syndrome.

In these difficult situations where the ECG is non-diagnostic, cardiac imaging techniques such as echocardiogram looking for presumed new wall motion abnormalities or elevation of cardiac biomarkers will help in making the diagnosis.

Adapted from Thygesen K et al. Third universal definition of myocardial infarction. Journal of the American College of Cardiology.2012;60(16):1581-98.

APPENDIX II: ELEVATIONS OF CARDIAC TROPONIN IN THE ABSENCE OF OVERT ISCHAEMIC HEART DISEASE.

Damage related to secondary myocardial ischaemia (MI type 2)
Tachy- or bradyarrhythmias
Aortic dissection and severe aortic valve disease
Hypo- or hypertension, e.g. haemorrhagic 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 ischaemia
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, Mair J, Katus H, Plebani M, Venge P, Collinson P, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J. 2010;31(18):2197-204.

APPENDIX III: TIMI RISK SCORE FOR STEMI[30]

Categories	Options	Points
Age (years)	☐ < 65 ☐ 65 - 74 ☐ ≥ 75	0 2 3
Weight < 67 kg	☐ Yes ☐ No	1 0
SBP < 100 mmHg	☐ Yes ☐ No	3 0
Heart rate > 100 bpm	☐ Yes ☐ No	2 0
Killip Class II-IV	☐ Yes ☐ No	2 0
Anterior ST segment elevation or LBBB	☐ Yes ☐ No	1 0
Diabetes, history of hypertension, history of angina	☐ Yes ☐ No	1 0
Time to treatment > 4 hours	☐ Yes ☐ No	1 0

Note:
TIMI Risk Score: 0 – 14 plausible points

- Low and moderate risk: 5 points and below
- High-risk: 6 points and above

APPENDIX IV: GRACE ACS RISK MODEL[339]

A) At Admission (in-hospital/to 6 months)

Categories	Options
Age (years)	☐ <30 ☐ 30 – 39 ☐ 40 – 49 ☐ 50 – 59 ☐ 60 – 69 ☐ 70 – 79 ☐ 80 – 89 ☐ 90 – 100
Heart rate (bpm)	☐ < 50 ☐ 50 – 69 ☐ 70 – 89 ☐ 90 – 109 ☐ 110 – 149 ☐ 150 – 199 ☐ ≥ 200
SBP (mmHg)	☐ <80 ☐ 80 – 99 ☐ 100 – 119 ☐ 120 – 139 ☐ 140 – 159 ☐ 160 – 199 ☐ ≥ 200
Creatinine (mg/dL)	☐ 0 – 0.39 ☐ 0.4 – 0.79 ☐ 0.8 – 1.19 ☐ 1.2 – 1.59 ☐ 1.6 – 1.99 ☐ 2.0 – 3.99 ☐ ≥ 4
CHF (Killip Class)	☐ I (No CHF) ☐ II (Rales and/or jugular venous distention) ☐ III (Pulmonary oedema) ☐ IV (Cardiogenic shock)
Cardiac arrest at admission	☐ Yes ☐ No
ST segment deviation	☐ Yes ☐ No
Elevated cardiac enzymes/markers	☐ Yes ☐ No

B) At Discharge (to 6 months)[339]

Categories	Options
Age (years)	☐ <30 ☐ 30 – 39 ☐ 40 – 49 ☐ 50 – 59 ☐ 60 – 69 ☐ 70 – 79 ☐ 80 – 89 ☐ 90 – 100
Heart rate (bpm)	☐ < 50 ☐ 50 – 69 ☐ 70 – 89 ☐ 90 – 109 ☐ 110 – 149 ☐ 150 – 199 ☐ ≥ 200
SBP (mmHg)	☐ <80 ☐ 80 – 99 ☐ 100 – 119 ☐ 120 – 139 ☐ 140 – 159 ☐ 160 – 199 ☐ ≥ 200
Creatinine (mg/dL)	☐ 0 – 0.39 ☐ 0.4 – 0.79 ☐ 0.8 – 1.19 ☐ 1.2 – 1.59 ☐ 1.6 – 1.99 ☐ 2.0 – 3.99 ☐ ≥ 4
Congestive HF	☐ Yes ☐ No
In-hospital PCI	☐ Yes ☐ No
In-hospital CABG	☐ Yes ☐ No
Past history of MI	☐ Yes ☐ No
ST segment depression	☐ Yes ☐ No
Elevated cardiac enzymes/markers	☐ Yes ☐ No

APPENDIX V: CHA_2DS_2- VASc SCORE[340]

Categories	Options	Points
Age (years)	☐ < 65 ☐ 65 - 74 ☐ ≥ 75	0 1 2
Sex	☐ Male ☐ Female	0 1
Congestive HF history	☐ Yes ☐ No	1 0
Hypertension history	☐ Yes ☐ No	1 0
Stroke/TIA history	☐ Yes ☐ No	2 0
Vascular disease history	☐ Yes ☐ No	1 0
DM history	☐ Yes ☐ No	1 0

Score:

- CHA_2DS_2- VASc score = 1: low to moderate-risk and should consider antiplatelet/ anticoagulation.
- CHA_2DS_2- VASc score ≥ 2: moderate to high-risk and should be anticoagulated.

APPENDIX VI: CALCULATION OF CrCL BY COCKCROFT-GAULT EQUATION

Estimated GFR (eGFR) (ml/minute) = $\frac{(140\text{-age}) \times \text{weight}}{(0.814 \times S_{Cr}\ [\mu mol/L])}$ or $\frac{1.2\ (140\text{-age})}{S_{Cr}\ [\mu mol/L]}$

Note: For women, multiply by 0.85

Severity Of CKD[341]

Severity of CKD	CrCL
Normal to mild	> 60 ml/minute
Moderate	30-59 ml/minute
Severe	< 30 ml/minute

APPENDIX VII: CALCULATION OF CrCL BY MDRD EQUATION[342]

- GFR (mL/minute/1.73m^2) = 175 × Scr$^{-1.154}$ × Age$^{-0.203}$ × 0.742 (if female) × 1.212 (if African American).

APPENDIX VIII: CALCULATION OF CrCL BY CKD-EPI EQUATION[343, 344]

- GFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black].
- Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

APPENDIX IX: PREVENTION OF CIN

Agent	Concentration	Dose /Flow Rate
Sodium Chloride (NaCl)	0.9% solution	The regime used would vary depending upon the patient's condition and time of admission in relation to the procedure. These regimes include: • Rate of 1.0-1.5 ml/kg/hour for 3-12 hours before and 6-24 hours after the procedure ensuring a urine flow rate of 150 ml/hour. • 0.9% NaCl @ 1 ml/kg/hour for 12 hours pre- and for 12 hours post-contrast administration. Reduce rate to 0.5 ml/kg/hour if LVEF < 40%. • Isotonic NaCl @ 3 ml/kg/hour for 1-3 hours pre- and for 6 hours post-contrast administration.
Sodium bicarbonate (NaHCO3)	154 mEq/L in 5% dextrose in water (154 ml of 1000 mEq/l of NaHCO3 + 850 ml of 5% dextrose)	3 ml/kg/hour for 1 hour before the contrast followed by an infusion of 1 ml/kg/hour for 6 hours after the procedure.[345]
N-acetylcysteine		Oral 1200 mg bd, one day before and one day after the contrast.[346, 347] IV 1200 pre-procedure and 1200 mg bd x 48 hours.[348]

APPENDIX X: PREVENTION OF CIN (GRADE OF RECOMMENDATION AND LEVEL OF EVIDENCE)

	ACC/ESC Classification
Contrast agent • Isosmolar agent or low osmolar agents. • Use minimal volume.	I, B I, C
Avoid nephrotoxic agents e.g. NSAIDs	I, C
Saline infusion	II-a, B[348, 349]
NaHCO3	II-a, B[348, 350-352]
Acetylcysteine	II-b, B[347, 350,353-356]
Pre-treatment with high dose statins	II-a, B[310-312]
Metformin • If eGFR < 45 ml/minute, stop at the time of contrast injection and should not be restarted for at least 48 hours and only if renal function remains stable. • It is generally unnecessary to stop metformin 48 hours prior to contrast injection but special care should be taken in patients with severe or acute renal dysfunction.	II-a, C II-a, C

APPENDIX XI: CLINICAL AUDIT INDICATORS FOR STEMI

• % of patients with suspected ACS who had an ECG done within 10 minutes of arrival in the emergency department	=	Number of patients with suspected ACS who had an ECG done within 10 minutes of arrival in the emergency department / Total number of patients with suspected ACS seen in the emergency department	X 100
• % of patients with STEMI who received fibrinolytic therapy within 30 minutes (DNT)	=	Number of patients with STEMI who received fibrinolytic therapy within 30 minutes (DNT) / Total number of patients with STEMI who received fibrinolytic therapy	X 100
• % of patients with STEMI who received primary PCI within 90 minutes (DBT)	=	Number of patients with STEMI who received primary PCI within 90 minutes (DBT) / Total number of patients with STEMI who underwent primary PCI	X 100
• % of patients discharged on DAPT	=	Number of patients with STEMI who are discharged on DAPT / Total number of patients with STEMI who are eligible for DAPT	X 100

APPENDIX XI: CLINICAL AUDIT INDICATORS FOR STEMI (continued)

• % of patients discharged on β-blockers	=	Number of patients with STEMI who are discharged on β-blockers / Total number of patients with STEMI who are eligible for β-blockers	X 100
• % of patients discharged on statins	=	Number of patients with STEMI who are discharged on statins / Total number of patients with STEMI who are eligible for statins	X 100
• % of patients discharged on ACE-I/ARB	=	Number of patients with STEMI who are discharged on ACE-I/ARB / Total number of patients with STEMI who are eligible for ACE-I/ARB	X 100
• % of patients who received an echocardiogram prior to discharge	=	Number of STEMI patients who received an echocardiogram prior to discharge / Total number of patients admitted with STEMI	X 100
• % of patients referred for cardiac rehabilitation before discharge	=	Number of STEMI patients referred for cardiac rehabilitation before discharge / Total number of patients admitted with STEMI	X 100
• % of patients receiving quit smoking advice	=	Number of STEMI patients receiving quit smoking advice / Total number of patients admitted with STEMI who are smokers	X 100
• % of patients who received ischaemic testing (e.g. sub-maximal stress test, stress echocardiogram) prior to discharge	=	Number of patients who received ischaemic testing (e.g. sub-maximal stress test, stress echocardiogram) prior to discharge / Total number of patients admitted with STEMI	X 100

APPENDIX XI: CLINICAL AUDIT INDICATORS FOR STEMI (continued)

• % of patients receiving primary PCI	=	Number of patients receiving primary PCI / Total number of patients admitted with STEMI who are eligible for primary PCI	X 100
• % of patients undergoing coronary angiography during index admission	=	Number of patients who underwent coronary angiography during index admission / Total number of patients admitted with STEMI	X 100
• % of in-hospital mortality	=	Number of STEMI deaths / Total number of patients admitted with STEMI	X 100

GLOSSARY

Abbreviation	Description
ABC	Airway, Breathing, Circulation
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
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

Abbreviation	Description
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine Kinase-Myocardial Band
CPG	Clinical Practice Guidelines
CPR	Cardiopulmonary Resuscitation
CrCL	Creatinine Clearance
CRP	Cardiac Rehabilitation Programme
cTn	Cardiac Troponins
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CV	Cardioversion
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
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
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

Abbreviation	Description
LVH	Left Ventricular Hypertrophy
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
od	Once daily
PCI	Percutaneous Coronary Interventions
PCWP	Pulmonary Capillary Wedge Pressure
PEA	Pulseless Electrical Activity
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	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 Revascularisation
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

REFERENCES

1. Health Facts 2012. Malaysia: Health Information Centre, Planning and Development Division, Ministry Of Health Malaysia, 2012.
2. Goodman SG, Huang W, Yan AT, Budaj A, Kennelly BM, Gore JM, et al. The expanded Global Registry of Acute Coronary Events: baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J. 2009;158(2):193-201 e1-5.
3. Wan Ahmad WA, Sim KH. Annual Report of the NCVD-ACS Registry, Year 2007 & 2008. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database 2010.
4. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581-98.
5. Salomaa V, Koukkunen H, Ketonen M, Immonen-Raiha P, Karja-Koskenkari P, Mustonen J, et al. A new definition for myocardial infarction: what difference does it make? Eur Heart J. 2005;26(17):1719-25.
6. Morris DC. "Chest Pain" in Patients with Myocardial Infarction. In: Hurst JW, Morris DC, editors. Chest Pain. New York: Futura Publishing Company Inc.; 2001.
7. Jain S, Ting HT, Bell M, Bjerke CM, Lennon RJ, Gersh BJ, et al. Utility of left bundle branch block as a diagnostic criterion for acute myocardial infarction. Am J Cardiol. 2011;107(8):1111-6.
8. Zehender M, Kasper W, Kauder E, Schonthaler M, Geibel A, Olschewski M, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. N Engl J Med. 1993;328(14):981-8.
9. Kosuge M, Ebina T, Hibi K, Morita S, Endo M, Maejima N, et al. An early and simple predictor of severe left main and/or three-vessel disease in patients with non-ST-segment elevation acute coronary syndrome. Am J Cardiol. 2011;107(4):495-500.
10. Vorobiof G, Ellestad MH. Lead aVR: dead or simply forgotten? JACC Cardiovasc Imaging. 2011;4(2):187-90.
11. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Single Volume, 9th Edition. Expert Consult Premium ed: Saunders; 2012. p. 154.
12. Keller T, Zeller T, Ojeda F, Tzikas S, Lillpopp L, Sinning C, et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA. 2011;306(24):2684-93.
13. Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-6.
14. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000;36(3):959-69.
15. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH, Cannon CP, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Clin Chem. 2007;53(4):547-51.
16. Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation. 2005;112(15):2318-23.
17. Ritchie JL, Bateman TM, Bonow RO, Crawford MH, Gibbons RJ, Hall RJ, et al. Guidelines for clinical use of cardiac radionuclide imaging. Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Radionuclide Imaging), developed in collaboration with the American Society of Nuclear Cardiology. J Am Coll Cardiol. 1995;25(2):521-47.
18. The Second International Study of Infarct Survival Collaborative Group I-. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction. Lancet. 1986;10:397-402.

19. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352(12):1179-89.

20. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet. 2005;366(9497):1607-21.

21. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010;304(7):763-71.

22. Fibrinolytic Therapy Trialist (FTT) CG. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet. 1994;343(8893):311-22.

23. Rathore SS, Curtis JP, Chen J, Wang Y, Nallamothu BK, Epstein AJ, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ. 2009;338:b1807.

24. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation. 2004;109(10):1223-5.

25. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011;124(23):2512-21.

26. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.

27. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010;122(21):2131-41.

28. Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. Cochrane Database Syst Rev. 2013;8:CD007160.

29. Selvarajah S, Fong AY, Selvaraj G, Haniff J, Uiterwaal CS, Bots ML. An Asian validation of the TIMI risk score for ST-segment elevation myocardial infarction. PLoS One. 2012;7(7):e40249.

30. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation. 2000;102(17):2031-7.

31. MDCalc. GRACE ACS Risk and Mortality Calculator. http://www.mdcalc.com/grace-acs-risk-and-mortality-calculator/ (accessed 10 Jan 2010); Available from: http://www.mdcalc.com/grace-acs-risk-and-mortality-calculator/.

32. De Luca G, Suryapranata H, Zijlstra F, van 't Hof AW, Hoorntje JC, Gosselink AT, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. J Am Coll Cardiol. 2003;42(6):991-7.

33. Boersma E, Mercado N, Poldermans D, Gardien M, Vos J, Simoons ML. Acute myocardial infarction. Lancet. 2003;361(9360):847-58.

34. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361(9351):13-20.

35. Aversano T, Aversano LT, Passamani E, Knatterud GL, Terrin ML, Williams DO, et al. Thrombolytic therapy vs primary percutaneous coronary intervention for myocardial infarction in patients presenting to hospitals without on-site cardiac surgery: A randomized controlled trial. JAMA. 2002;287(15):1943-51.

36. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: A randomised study. Lancet. 2002;360(9336):825-9.

37. Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial-PRAGUE-2. Eur Heart J. 2003;24(1):94-104.

38. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: Is timing (almost) everything? Am J Cardiol. 2003;92(7):824-6.

39. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med. 2003;349(8):733-42.

40. Bakal JA, Westerhout CM, Cantor WJ, Fernandez-Aviles F, Welsh RC, Fitchett D, et al. Evaluation of early percutaneous coronary intervention vs standard therapy after fibrinolysis for ST-segment elevation myocardial infarction: Contribution of weighting the composite endpoint. Eur Heart J. 2013;34(12):903-8.

41. Borgia F, Goodman SG, Halvorsen S, Cantor WJ, Piscione F, Le May MR, et al. Early routine percutaneous coronary intervention after fibrinolysis vs standard therapy in ST-segment elevation myocardial infarction: A meta-analysis. Eur Heart J. 2010;31(17):2156-69.

42. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico. (GISSI) Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction Lancet. 1986;1(8478):397-402.

43. Hamptom J, Wilcox R. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. Lancet. 1993;342(8874):759-66.

44. Elliott JM, Cross DB, Cederholm-Williams SA, White HD. Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. Am J Cardiol. 1993;71(8):640-5.

45. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999;341(9):625-34.

46. Wu AH, Parsons L, Every NR, Bates ER. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol. 2002;40(8):1389-94.

47. Zahn R, Schiele R, Schneider S, Gitt AK, Wienbergen H, Seidl K, et al. Primary angioplasty versus intravenous thrombolysis in acute myocardial infarction: Can we define subgroups of patients benefiting most from primary angioplasty? Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction Registry and the Myocardial Infarction Registry. J Am Coll Cardiol. 2001;37(7):1827-35.

48. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: Reappraisal of the golden hour. Lancet. 1996;348(9030):771-5.

49. Taher T, Fu Y, Wagner GS, Goodman SG, Fresco C, Granger CB, et al. Aborted myocardial infarction in patients with ST-segment elevation: insights from the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Trial Electrocardiographic Substudy. J Am Coll Cardiol. 2004;44(1):38-43.

50. Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, Knatterud GL, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol. 1995;26(7):1643-50.

51. TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation. 1994;89(4):1545-56.

52. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329(10):673-82.

53. ISIS-3 Collaborative Group. A randomized comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992;39:753-70.

54. Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. Am J Cardiol. 1994;74(12):1220-8.

55. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med. 1993;329(22):1615-22.

56. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction: Current status and new horizons for pharmacological reperfusion, part 1. Circulation. 2001;103(23):2862-6.

57. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. Lancet. 1999;354(9180):716-22.

58. Armstrong PW, Gershlick A, Goldstein P, Wilcox R, Danays T, Bluhmki E, et al. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. Am Heart J. 2010;160(1):30-5 e1.

59. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomized trial. JAMA. 2006;295(13):1519-30.

60. Sutton AG, Campbell PG, Price DJ, Grech ED, Hall JA, Davies A, et al. Failure of thrombolysis by streptokinase: detection with a simple electrocardiographic method. Heart. 2000;84(2):149-56.

61. Gershlick AH, Stephens-Lloyd A, Hughes S, Abrams KR, Stevens SE, Uren NG, et al. Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. N Engl J Med. 2005;353(26):2758-68.

62. Sutton AG, Campbell PG, Graham R, Price DJ, Gray JC, Grech ED, et al. A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. J Am Coll Cardiol. 2004;44(2):287-96.

63. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, Foody JM, Krumholz HM, Phillips CO, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: A meta-analysis of randomized trials. J Am Coll Cardiol. 2007;49(4):422-30.

64. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. Eur Heart J. 2000;21(10):823-31.

65. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: A meta-analysis. Circulation. 2003;108(15):1809-14.

66. Grzybowski M, Clements EA, Parsons L, Welch R, Tintinalli AT, Ross MA, et al. Mortality benefit of immediate revascularization of acute ST-segment elevation myocardial infarction in patients with contraindications to thrombolytic therapy: A propensity analysis. JAMA. 2003;290(14):1891-8.

67. Zahn R, Schuster S, Schiele R, Seidl K, Voigtlander T, Meyer J, et al. Comparison of primary angioplasty with conservative therapy in patients with acute myocardial infarction and contraindications for thrombolytic therapy. Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. Catheter Cardiovasc Interv. 1999;46(2):127-33.

68. Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, et al. One-year survival following early revascularization for cardiogenic shock. JAMA. 2001;285(2):190-2.

69. Pinto DS, Kirtane AJ, Nallamothu BK, Murphy SA, Cohen DJ, Laham RJ, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation. 2006;114(19):2019-25.

70. Nielsen PH, Terkelsen CJ, Nielsen TT, Thuesen L, Krusell LR, Thayssen P, et al. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). Am J Cardiol. 2011;108(6):776-81.

71. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: A multiple meta-analyses approach according to the type of strategy. J Am Coll Cardiol. 2006;48(7):1326-35.

72. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-elevation myocardial infarction). J Am Coll Cardiol. 2010;55(2):102-10.

73. Cantor WJ, Fitchett D, Borgundvaag B, Ducas J, Heffernan M, Cohen EA, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med. 2009;360(26):2705-18.

74. Di Mario C, Dudek D, Piscione F, Mielecki W, Savonitto S, Murena E, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): An open, prospective, randomised, multicentre trial. Lancet. 2008;371(9612):559-68.

75. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): A randomised controlled trial. Lancet. 2004;364(9439):1045-53.

76. White HD. Systems of care: Need for hub-and-spoke systems for both primary and systematic percutaneous coronary intervention after fibrinolysis. Circulation. 2008;118(3):219-22.

77. Steg PG, Kerner A, Van de Werf F, Lopez-Sendon J, Gore JM, Fitzgerald G, et al. Impact of in-hospital revascularization on survival in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. Circulation. 2008;118(11):1163-71.

78. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont MC, Lopez-Sendon J, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: Observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004;109(4):494-9.

79. D'Souza SP, Mamas MA, Fraser DG, Fath-Ordoubadi F. Routine early coronary angioplasty versus ischaemia-guided angioplasty after thrombolysis in acute ST-elevation myocardial infarction: A meta-analysis. Eur Heart J. 2011;32(8):972-82.

80. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: The SWISSI II randomized controlled trial. JAMA. 2007;297(18):1985-91.

81. Madsen JK, Grande P, Saunamaki K, Thayssen P, Kassis E, Eriksen U, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. Circulation. 1997;96(3):748-55.

82. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med. 2008;358(21):2205-17.

83. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: Quantitative review of randomised trials. Lancet. 2006;367(9510):579-88.

84. Stone GW. Angioplasty strategies in ST-segment-elevation myocardial infarction: part II:

Intervention after fibrinolytic therapy, integrated treatment recommendations, and future directions. Circulation. 2008;118(5):552-66.

85. Borden WB, Faxon DP. Facilitated percutaneous coronary intervention. J Am Coll Cardiol. 2006;48(6):1120-8.

86. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): Randomised trial. Lancet. 2006;367(9510):569-78.

87. Scheller B, Hennen B, Hammer B, Walle J, Hofer C, Hilpert V, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol. 2003;42(4):634-41.

88. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs primary percutaneous intervention early after ST-elevation myocardial infarction: The WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J. 2006;27(13):1530-8.

89. Thiele H, Engelmann L, Elsner K, Kappl MJ, Storch WH, Rahimi K, et al. Comparison of pre-hospital combination-fibrinolysis plus conventional care with pre-hospital combination-fibrinolysis plus facilitated percutaneous coronary intervention in acute myocardial infarction. Eur Heart J. 2005;26(19):1956-63.

90. Hochman JS, Lamas GA, Buller CE, Dzavik V, Reynolds HR, Abramsky SJ, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med. 2006;355(23):2395-407.

91. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. Circulation. 2002;105(16):1909-13.

92. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, McCabe CH, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. Circulation. 1999;99(15):1945-50.

93. Jolly SS, Pogue J, Haladyn K, Peters RJ, Fox KA, Avezum A, et al. Effects of aspirin dose on ischaemic events and bleeding after percutaneous coronary intervention: Insights from the PCI-CURE study. Eur Heart J. 2009;30(8):900-7.

94. Barnathan ES, Schwartz JS, Taylor L, Laskey WK, Kleaveland JP, Kussmaul WG, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation. 1987;76(1):125-34.

95. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363(10):930-42.

96. Patti G, Barczi G, Orlic D, Mangiacapra F, Colonna G, Pasceri V, et al. Outcome comparison of 600- and 300-mg loading doses of clopidogrel in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: Results from the ARMYDA-6 MI (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Myocardial Infarction) randomized study. J Am Coll Cardiol. 2011;58(15):1592-9.

97. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): A randomised factorial trial. Lancet. 2010;376(9748):1233-43.

98. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. Lancet. 2009;373(9665):723-31.

99. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay J-F, et al. Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes. N Engl J Med. 2013;369(11):999-1010.

100. Brener SJ, Barr LA, Burchenal JE, Katz S, George BS, Jones AA, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. Circulation. 1998;98(8):734-41.

101. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002;346(13):957-66.

102. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344(25):1895-903.

103. ten Berg JM, van 't Hof AW, Dill T, Heestermans T, van Werkum JW, Mosterd A, et al. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. J Am Coll Cardiol. 2010;55(22):2446-55.

104. Valgimigli M, Campo G, Percoco G, Bolognese L, Vassanelli C, Colangelo S, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: The MULTISTRATEGY randomized trial. JAMA. 2008;299(15):1788-99.

105. Chew DP, Bhatt DL, Lincoff AM, Moliterno DJ, Brener SJ, Wolski KE, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. Circulation. 2001;103(7):961-6.

106. Silvain J, Beygui F, Barthelemy O, Pollack C, Jr., Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: Systematic review and meta-analysis. BMJ. 2012;344:e553.

107. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. Lancet. 2011;377(9775):1409-20.

108. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol. 2012;60(24):2481-9.

109. Hannan EL, Samadashvili Z, Walford G, Holmes DR, Jr., Jacobs AK, Stamato NJ, et al. Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. JACC Cardiovasc Interv. 2010;3(1):22-31.

110. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, et al. Meta-analysis of randomized trials on drug-eluting stents vs bare-metal stents in patients with acute myocardial infarction. Eur Heart J. 2007;28(22):2706-13.

111. Pasceri V, Patti G, Speciale G, Pristipino C, Richichi G, Di Sciascio G. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. Am Heart J. 2007;153(5):749-54.

112. Napodano M, Ramondo A, Tarantini G, Peluso D, Compagno S, Fraccaro C, et al. Predictors and time-related impact of distal embolization during primary angioplasty. Eur Heart J. 2009;30(3):305-13.

113. Yip HK, Chen MC, Chang HW, Hang CL, Hsieh YK, Fang CY, et al. Angiographic morphologic features of infarct-related arteries and timely reperfusion in acute myocardial infarction: predictors of slow-flow and no-reflow phenomenon. Chest. 2002;122(4):1322-32.

114. Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: A TIMI 14 substudy. Circulation. 2001;103(21):2550-4.

115. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: A comprehensive meta-analysis of randomized trials. Eur Heart J. 2008;29(24):2989-3001.

116. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): A 1-year follow-up study. Lancet. 2008;371(9628):1915-20.

117. Sardella G, Mancone M, Bucciarelli-Ducci C, Agati L, Scardala R, Carbone I, et al. Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: The EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. J Am Coll Cardiol. 2009;53(4):309-15.

118. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013;369(17):1587-97.

119. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: A meta-analysis of randomized trials. JAMA. 2005;293(14):1759-65.

120. Ortolani P, Marzocchi A, Marrozzini C, Palmerini T, Saia F, Taglieri N, et al. Long-term effectiveness of early administration of glycoprotein IIb/IIIa agents to real-world patients undergoing primary percutaneous interventions: Results of a registry study in an ST-elevation myocardial infarction network. Eur Heart J. 2009;30(1):33-43.

121. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. Circulation. 2008;117(2):296-329.

122. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008;29(23):2909-45.

123. Taggart P, Sutton P, John R, Lab M, Swanton H. Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre. Br Heart J. 1992;67(3):221-9.

124. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. Lancet. 2001;358(9281):527-33.

125. Steinhubl SR, Berger PB, Mann JT, 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. JAMA. 2002;288(19):2411-20.

126. de Bono DP, Simoons ML, Tijssen J, Arnold AE, Betriu A, Burgersdijk C, et al. Effect of early intravenous heparin on coronary patency, infarct size, and bleeding complications after alteplase thrombolysis: results of a randomised double blind European Cooperative Study Group trial. Br Heart J. 1992;67(2):122-8.

127. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. Circulation. 2003;108(2):135-42.

128. Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med. 2006;354(14):1477-88.

129. Oldgren J, Wallentin L, Afzal R, Bassand JP, Budaj A, Chrolavicius S, et al. Effects of fondaparinux

in patients with ST-segment elevation acute myocardial infarction not receiving reperfusion treatment. Eur Heart J. 2008;29(3):315-23.

130. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365(8):699-708.

131. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

132. Stone GW, Maehara A, Witzenbichler B, Godlewski J, Parise H, Dambrink JH, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA. 2012;307(17):1817-26.

133. Friedland S, Eisenberg MJ, Shimony A. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol. 2011;108(9):1244-51.

134. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318(7200):1730-7.

135. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med. 1998;339(8):489-97.

136. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366(9497):1622-32.

137. ACE Inhibitor MI Collaborative Group. Evidence for early beneficial effect of ACE inhibitors started within the first day in patients with AMI: Results of systematic overview among 100000 patients. Circulation. 1996;94:1-90.

138. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993;342(8875):821-8.

139. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995;332(2):80-5.

140. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992;327(10):669-77.

141. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333(25):1670-6.

142. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893-906.

143. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21.

144. Angeli F, Reboldi G, Garofoli M, Ramundo E, Verdecchia P. Very early initiation of statin therapy and mortality in patients with acute coronary syndrome. Acute Card Care. 2012;14(1):34-9.

145. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350(15):1495-504.

146. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: A randomized controlled trial. JAMA. 2001;285(13):1711-8.

147. Fonarow GC, Wright RS, Spencer FA, Fredrick PD, Dong W, Every N, et al. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. Am J Cardiol. 2005;96(5):611-6.

148. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. J Am Coll Cardiol. 2009;54(6):558-65.

149. Gibson CM, Pride YB, Hochberg CP, Sloan S, Sabatine MS, Cannon CP, et al. Effect of intensive statin therapy on clinical outcomes among patients undergoing percutaneous coronary intervention for acute coronary syndrome. PCI-PROVE IT: A PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) Substudy. J Am Coll Cardiol. 2009;54(24):2290-5.

150. Kim JS, Kim J, Choi D, Lee CJ, Lee SH, Ko YG, et al. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. JACC Cardiovasc Interv. 2010;3(3):332-9.

151. Yun KH, Jeong MH, Oh SK, Rhee SJ, Park EM, Lee EM, et al. The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome. Int J Cardiol. 2009;137(3):246-51.

152. Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343(8906):1115-22.

153. ISIS- 4 Collaborative Group. A randomised factorial trial assessing oral captopril, oral mononitrate and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet. 1994;345:669-85.

154. Held PH, Yusuf S. Calcium antagonists in the treatment of ischemic heart disease: Myocardial infarction. Coron Artery Dis. 1994;5(1):21-6.

155. Goldbourt U, Behar S, Reicher-Reiss H, Zion M, Mandelzweig L, Kaplinsky E. Early administration of nifedipine in suspected acute myocardial infarction. The Secondary Prevention Reinfarction Israel Nifedipine Trial 2 Study. Arch Intern Med. 1993;153(3):345-53.

156. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. Am J Cardiol. 1991;67(15):1295-7.

157. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. JAMA. 1988;260(13):1910-6.

158. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: The CREATE-ECLA randomized controlled trial. JAMA. 2005;293(4):437-46.

159. Timmer JR, Svilaas T, Ottervanger JP, Henriques JP, Dambrink JH, van den Broek SA, et al. Glucose-insulin-potassium infusion in patients with acute myocardial infarction without signs of heart failure: The Glucose-Insulin-Potassium Study (GIPS)-II. J Am Coll Cardiol. 2006;47(8):1730-1.

160. Killip T, 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20(4):457-64.

161. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779-89.

162. Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. Circulation. 2009;119(9):1211-9.

163. Thiele H, Zeymer U, Neumann F-J, Ferenc M, Olbrich H-G, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287-96.

164. Kinch JW, Ryan TJ. Right ventricular infarction. N Engl J Med. 1994;330(17):1211-7.

165. Ohman EM, Amstrong PW, Guerci AD, et al, For the GUSTO Trial Investigators. Reinfarction after thrombolytic therapy: Experience from GUSTO trial. Circulation. 1993;88:1-490.

166. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987;76(1):142-54.

167. Topol EJ, Califf RM, George BS, Kereiakes DJ, Rothbaum D, Candela RJ, et al. Coronary arterial thrombolysis with combined infusion of recombinant tissue-type plasminogen activator and urokinase in patients with acute myocardial infarction. Circulation. 1988;77(5):1100-7.

168. Tofler GH, Muller JE, Stone PH, Willich SN, Davis VG, Poole WK, et al. Pericarditis in acute myocardial infarction: Characterization and clinical significance. Am Heart J. 1989;117(1):86-92.

169. Khan AH. The postcardiac injury syndromes. Clin Cardiol. 1992;15(2):67-72.

170. Berman J, Haffajee CI, Alpert JS. Therapy of symptomatic pericarditis after myocardial infarction: retrospective and prospective studies of aspirin, indomethacin, prednisone, and spontaneous resolution. Am Heart J. 1981;101(6):750-3.

171. Bulkley BH, Roberts WC. Steroid therapy during acute myocardial infarction. A cause of delayed healing and of ventricular aneurysm. Am J Med. 1974;56(2):244-50.

172. Keeley EC, Hillis LD. Left ventricular mural thrombus after acute myocardial infarction. Clin Cardiol. 1996;19(2):83-6.

173. Rehan A, Kanwar M, Rosman H, Ahmed S, Ali A, Gardin J, et al. Incidence of post myocardial infarction left ventricular thrombus formation in the era of primary percutaneous intervention and glycoprotein IIb/IIIa inhibitors. A prospective observational study. Cardiovasc Ultrasound. 2006;4:20.

174. Cregler LL. Antithrombotic therapy in left ventricular thrombosis and systemic embolism. Am Heart J. 1992;123(4 Pt 2):1110-4.

175. Carson P, Wertheimer J, Miller A, O'Connor CM, Pina IL, Selzman C, et al. Surgical Treatment for Ischemic Heart Failure (STICH) Trial: Mode of Death Results. JACC Heart Fail. 2013;1(5):400-8.

176. Nuttall SL, Toescu V, Kendall MJ. Beta Blockade after myocardial infarction. Beta blockers have key role in reducing morbidity and mortality after infarction. BMJ. 2000;320(7234):581.

177. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J. 2004;25(15):1341-62.

178. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. J Am Coll Cardiol. 1999;33(3):598-604.

179. Mitchell LB, Powell JL, Gillis AM, Kehl V, Hallstrom AP. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics versus Implantable Defibrillators (AVID) trial. J Am Coll Cardiol. 2003;42(1):81-7.

180. Chiu JH, Abdelhadi RH, Chung MK, Gurm HS, Marrouche NF, Saliba WI, et al. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. Am J Cardiol. 2005;95(4):490-1.

181. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996;335(26):1933-40.

182. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337(22):1576-83.

183. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol. 2004;43(8):1459-65.

184. Lee KL, Hafley G, Fisher JD, Gold MR, Prystowsky EN, Talajic M, et al. Effect of implantable defibrillators on arrhythmic events and mortality in the multicenter unsustained tachycardia trial. Circulation. 2002;106(2):233-8.

185. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-83.

186. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med. 2004;351(24):2481-8.

187. Kociol RD, Lopes RD, Clare R, Thomas L, Mehta RH, Kaul P, et al. International variation in and factors associated with hospital readmission after myocardial infarction. JAMA. 2012;307(1):66-74.

188. Mark DB, Newby LK. Early hospital discharge after uncomplicated myocardial infarction: are further improvements possible? Eur Heart J. 2003;24(18):1613-5.

189. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. JAMA. 2003;290(1):86-97.

190. Thomson CC, Rigotti NA. Hospital- and clinic-based smoking cessation interventions for smokers with cardiovascular disease. Prog Cardiovasc Dis. 2003;45(6):459-79.

191. Meine TJ, Patel MR, Washam JB, Pappas PA, Jollis JG. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am J Cardiol. 2005;95(8):976-8.

192. The Tobacco Use and Dependence Clinical Practice Guideline Panel S, and Consortium Representatives. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report JAMA. 2000;283(24):3244-54.

193. Taylor CB, Houston-Miller N, Killen JD, DeBusk RF. Smoking cessation after acute myocardial infarction: effects of a nurse-managed intervention. Ann Intern Med. 1990;113(2):118-23.

194. Barzi F, Woodward M, Marfisi RM, Tavazzi L, Valagussa F, Marchioli R, et al. Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial. Eur J Clin Nutr. 2003;57(4):604-11.

195. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. JAMA Intern Med. 2013;173(19):1808-19.

196. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779-85.

197. Kwak SM, Myung SK, Lee YJ, Seo HG, Korean Meta-analysis Study, Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Arch Intern Med. 2012;172(9):686-94.

198. Risk, Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, Barlera S, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013;368(19):1800-8.

199. Othman RA, Moghadasian MH, Jones PJ. Cholesterol-lowering effects of oat beta-glucan. Nutr Rev. 2011;69(6):299-309.

200. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. Am J Med. 2004;116(10):682-92.

201. Shephard RJ, Balady GJ. Exercise as cardiovascular therapy. Circulation. 1999;99(7):963-72.

202. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33(13):1635-701.

203. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801.

204. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials. Am Heart J. 2011;162(4):571-84 e2.

205. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2011(7):CD001800.

206. Haider AW, Chen L, Larson MG, Evans JC, Chen MH, Levy D. Antecedent hypertension confers increased risk for adverse outcomes after initial myocardial infarction. Hypertension. 1997;30(5):1020-4.

207. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes? Relationship of blood pressure and cardiovascular events in the PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122(21):2142-51.

208. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.

209. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-59.

210. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.

211. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849-60.

212. Sabatine MS, Morrow DA, Montalescot G, Dellborg M, Leiva-Pons JL, Keltai M, et al. Angiographic and clinical outcomes in patients receiving low-molecular-weight heparin versus unfractionated heparin in ST-elevation myocardial infarction treated with fibrinolytics in the CLARITY-TIMI 28 Trial. Circulation. 2005;112(25):3846-54.

213. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: The Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125(3):505-13.

214. Park SJ, Park DW, Kim YH, Kang SJ, Lee SW, Lee CW, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010;362(15):1374-82.

215. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125(16):2015-26.

216. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis. 1985;27(5):335-71.

217. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. Lancet. 2001;357(9266):1385-90.

218. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8.

219. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. Lancet. 1999;353(9146):9-13.

220. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised controlled trial. Lancet. 2003;362(9377):7-13.

221. Fourth International Study of Infarct Survival Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995;345(8951):669-85.

222. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: Randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782-8.

223. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342(3):145-53.

224. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351(20):2058-68.

225. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: The OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002;360(9335):752-60.

226. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.

227. Briel M, Vale N, Schwartz GG, de Lemos JA, Colivicchi F, den Hartog FR, et al. Updated evidence on early statin therapy for acute coronary syndromes: meta-analysis of 18 randomized trials involving over 14,000 patients. Int J Cardiol. 2012;158(1):93-100.

228. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet. 2002;360(9326):7-22.

229. Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: The Prospective Pravastatin Pooling Project. Circulation. 2000;102(16):1893-900.

230. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. JAMA. 2004;291(9):1071-80.

231. Ministry of Health Malaysia. 4th Edition of Clinical Practice Guidelines for Management of Dyslipidemia 2011. Putrajaya, Malaysia: 2011 June 2011.

232. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL study: A randomized controlled trial. JAMA. 2005;294(19):2437-45.

233. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352(14):1425-35.

234. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295(13):1556-65.

235. Reeder GS, Lengyel M, Tajik AJ, Seward JB, Smith HC, Danielson GK. Mural thrombus in left ventricular aneurysm: Incidence, role of angiography, and relation between anticoagulation and embolization. Mayo Clin Proc. 1981;56(2):77-81.

236. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605-13.

237. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.

238. Lonn E, Bosch J, Yusuf S, Sheridan P, Pogue J, Arnold JM, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. JAMA. 2005;293(11):1338-47.

239. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet. 2002;360(9326):23-33.

240. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and Mineral Supplements in the Primary Prevention of Cardiovascular Disease and Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013.

241. Singh M, Peterson ED, Roe MT, Ou FS, Spertus JA, Rumsfeld JS, et al. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ Cardiovasc Interv. 2009;2(1):20-6.

242. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: A scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115(19):2549-69.

243. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet. 2002;359(9304):373-7.

244. Rittger H, Hochadel M, Behrens S, Hauptmann KE, Zahn R, Mudra H, et al. Age-related differences in diagnosis, treatment and outcome of acute coronary syndromes: Results from the German ALKK registry. EuroIntervention. 2012;7(10):1197-205.

245. Dziewierz A, Siudak Z, Rakowski T, Dubiel JS, Dudek D. Age-related differences in treatment strategies and clinical outcomes in unselected cohort of patients with ST-segment elevation myocardial infarction transferred for primary angioplasty. J Thromb Thrombolysis. 2012;34(2):214-21.

246. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J. 2011;32(11):1379-89.

247. Eggers KM, Lind L, Ahlstrom H, Bjerner T, Ebeling Barbier C, Larsson A, et al. Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. Eur Heart J. 2008;29(18):2252-8.

248. Mandawat A, Mandawat A, Mandawat MK. Percutaneous coronary intervention after ST-segment elevation myocardial infarction in nonagenarians: use rates and in-hospital mortality. J Am Coll Cardiol. 2013;61(11):1207-8.

249. Grines C. A prospective randomized trial of primary angioplasty and thrombolytic therapy in elderly patients with acute myocardial infarction. Available from: http://www.trialresultscenter.org/study9541-senior-PAMI.htm2005; Available from: http://www.trialresultscenter.org/study9541-senior-PAMI.htm.

250. Bueno H, Betriu A, Heras M, Alonso JJ, Cequier A, Garcia EJ, et al. Primary angioplasty vs fibrinolysis in very old patients with acute myocardial infarction: TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) randomized trial and pooled analysis with previous studies. Eur Heart J. 2011;32(1):51-60.

251. Shelton RJ, Crean AM, Somers K, Priestley C, Hague C, Blaxill JM, et al. Real-world outcome from ST elevation myocardial infarction in the very elderly before and after the introduction of a 24/7 primary percutaneous coronary intervention service. Am Heart J. 2010;159(6):956-63.

252. Danzi GB, Centola M, Pomidossi GA, Consonni D, De Matteis S, Stabile A, et al. Usefulness of primary angioplasty in nonagenarians with acute myocardial infarction. Am J Cardiol.

2010;106(6):770-3.

253. Dodson JA, Wang Y, Chaudhry SI, Curtis JP. Bleeding-avoidance strategies and outcomes in patients ≥ 80 years of age with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the NCDR CathPCI Registry). Am J Cardiol. 2012;110(1):1-6.

254. White HD. Thrombolytic therapy in the elderly. Lancet. 2000;356(9247):2028-30.

255. Thiemann DR, Coresh J, Schulman SP, Gerstenblith G, Oetgen WJ, Powe NR. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation. 2000;101(19):2239-46.

256. Soumerai SB, McLaughlin TJ, Ross-Degnan D, Christiansen CL, Gurwitz JH. Effectiveness of thrombolytic therapy for acute myocardial infarction in the elderly: Cause for concern in the old-old. Arch Intern Med. 2002;162(5):561-8.

257. Alexander KP, Newby LK, Armstrong PW, Cannon CP, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: A scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115(19):2570-89.

258. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ. 1994;308(6921):81-106.

259. Budaj A, Yusuf S, Mehta SR, Fox KA, Tognoni G, Zhao F, et al. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation. 2002;106(13):1622-6.

260. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation. 2003;108(14):1682-7.

261. Puymirat E, Aissaoui N, Coste P, Dentan G, Bataille V, Drouet E, et al. Comparison of efficacy and safety of a standard versus a loading dose of clopidogrel for acute myocardial infarction in patients ≥ 75 years of age (from the FAST-MI registry). Am J Cardiol. 2011;108(6):755-9.

262. Husted S, James S, Becker RC, Horrow J, Katus H, Storey RF, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes. 2012;5(5):680-8.

263. Gianni M, Bosch J, Pogue J, Probstfield J, Dagenais G, Yusuf S, et al. Effect of long-term ACE-inhibitor therapy in elderly vascular disease patients. Eur Heart J. 2007;28(11):1382-8.

264. Cohen M, Antman EM, Gurfinkel EP, Radley D. Enoxaparin in unstable angina/non-ST-segment elevation myocardial infarction: Treatment benefits in prespecified subgroups. J Thromb Thrombolysis. 2001;12(3):199-206.

265. Dornbrook-Lavender KA, Roth MT, Pieper JA. Secondary prevention of coronary heart disease in the elderly. Ann Pharmacother. 2003;37(12):1867-76.

266. Krumholz HM, Radford MJ, Wang Y, Chen J, Marciniak TA. Early beta-blocker therapy for acute myocardial infarction in elderly patients. Ann Intern Med. 1999;131(9):648-54.

267. Foody JM, Rathore SS, Galusha D, Masoudi FA, Havranek EP, Radford MJ, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: Evidence for an age-statin interaction. J Am Geriatr Soc. 2006;54(3):421-30.

268. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363(9411):757-67.

269. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. Lancet. 2002;360(9346):1623-30.

270. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: Results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007;115(6):700-7.

271. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: A hierarchical bayesian meta-analysis. J Am Coll Cardiol. 2008;51(1):37-45.

272. Lavie CJ, Milani RV, Littman AB. Benefits of cardiac rehabilitation and exercise training in secondary coronary prevention in the elderly. J Am Coll Cardiol. 1993;22(3):678-83.

273. Ades PA, Waldmann ML, Polk DM, Coflesky JT. Referral patterns and exercise response in the rehabilitation of female coronary patients aged greater than or equal to 62 years. Am J Cardiol. 1992;69(17):1422-5.

274. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet. 2000;355(9206):773-8.

275. De Luca G, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, Thuesen L, et al. Impact of diabetes on long-term outcome after primary angioplasty: Insights from the DESERT cooperation. Diabetes Care. 2013;36(4):1020-5.

276. Timmer JR, Ottervanger JP, de Boer MJ, Boersma E, Grines CL, Westerhout CM, et al. Primary percutaneous coronary intervention compared with fibrinolysis for myocardial infarction in diabetes mellitus: Results from the Primary Coronary Angioplasty vs Thrombolysis-2 trial. Arch Intern Med. 2007;167(13):1353-9.

277. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation. 2001;104(23):2767-71.

278. Dziewierz A, Mielecki W, Siudak Z, Rakowski T, Janzon M, Birkemeyer R, et al. Early abciximab administration before primary percutaneous coronary intervention improves clinical outcome in diabetic patients with ST-segment elevation myocardial infarction (EUROTRANSFER Registry). Atherosclerosis. 2012;223(1):212-8.

279. Lindsay J, Apple S, Pinnow EE, Gevorkian N, Gruberg L, Satler LF, et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. Catheter Cardiovasc Interv. 2003;59(3):338-43.

280. Stolker JM, McCullough PA, Rao S, Inzucchi SE, Spertus JA, Maddox TM, et al. Pre-procedural glucose levels and the risk for contrast-induced acute kidney injury in patients undergoing coronary angiography. J Am Coll Cardiol. 2010;55(14):1433-40.

281. Zhao YT, Weng CL, Chen ML, Li KB, Ge YG, Lin XM, et al. Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: A contemporary meta-analysis of randomised controlled trials. Heart. 2010;96(20):1622-6.

282. Kosiborod M, McGuire DK. Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. Circulation. 2010;122(25):2736-44.

283. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.

284. Vaccarino V, Krumholz HM, Berkman LF, Horwitz RI. Sex differences in mortality after myocardial infarction. Is there evidence for an increased risk for women? Circulation. 1995;91(6):1861-71.

285. Schiele F, Meneveau N, Seronde MF, Descotes-Genon V, Chopard R, Janin S, et al. Propensity score-matched analysis of effects of clinical characteristics and treatment on gender difference in outcomes after acute myocardial infarction. Am J Cardiol. 2011;108(6):789-98.

286. Coventry LL, Finn J, Bremner AP. Sex differences in symptom presentation in acute myocardial infarction: A systematic review and meta-analysis. Heart Lung. 2011;40(6):477-91.

287. Cole CS, McSweeney JC, Cleves MA, Armbya N, Bliwise DL, Pettey CM. Sleep disturbance in women before myocardial infarction. Heart Lung. 2012;41(5):438-45.

288. Sadowski M, Gasior M, Gierlotka M, Janion M, Polonski L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: A large multicentre national registry. EuroIntervention. 2011;6(9):1068-72.

289. Benamer H, Tafflet M, Bataille S, Escolano S, Livarek B, Fourchard V, et al. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. EuroIntervention. 2011;6(9):1073-9.

290. Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, et al. Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction. Am J Cardiol. 2013;111(3):312-8.

291. Lundberg G, King S. Coronary revascularization in women. Clin Cardiol. 2012;35(3):156-9.

292. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy-II: Maintenance of vascular graft or arterial patency by antiplatelet therapy. BMJ. 1994;308(6922):159-68.

293. Lee CY, Hairi NN, Wan Ahmad WA, Ismail O, Liew HB, Zambahari R, et al. Are there gender differences in coronary artery disease? The Malaysian National Cardiovascular Disease Database - Percutaneous Coronary Intervention (NCVD-PCI) Registry. PLoS One. 2013;8(8):e72382.

294. Mehta RH, Stebbins AS, Lopes RD, Califf RM, Pieper KS, Armstrong PW, et al. Comparison of incidence of bleeding and mortality of men versus women with ST-elevation myocardial infarction treated with fibrinolysis. Am J Cardiol. 2012;109(3):320-6.

295. Mehilli J, Neumann FJ, Ndrepepa G, King L, Schulz S, Maimer Rodrigues da Cunha F, et al. Sex-related effectiveness of bivalirudin versus abciximab and heparin in non-ST-segment elevation myocardial infarction. Am Heart J. 2013;165(4):537-43.

296. Truong QA, Murphy SA, McCabe CH, Armani A, Cannon CP. Benefit of intensive statin therapy in women: Results from PROVE IT-TIMI 22. Circ Cardiovasc Qual Outcomes. 2011;4(3):328-36.

297. Daniels KM, Arena R, Lavie CJ, Forman DE. Cardiac rehabilitation for women across the lifespan. Am J Med. 2012;125(9):937 e1-7.

298. Bretler DM, Hansen PR, Sorensen R, Lindhardsen J, Ahlehoff O, Andersson C, et al. Discontinuation of hormone replacement therapy after myocardial infarction and short term risk of adverse cardiovascular events: Nationwide cohort study. BMJ. 2012;344:e1802.

299. Pines A. Post-myocardial infarction hormone therapy revisited. Climacteric. 2012;15(6):538-41.

300. Yamaguchi J, Kasanuki H, Ishii Y, Yagi M, Nagashima M, Fujii S, et al. Serum creatinine on admission predicts long-term mortality in acute myocardial infarction patients undergoing successful primary angioplasty: Data from the Heart Institute of Japan Acute Myocardial Infarction (HIJAMI) Registry. Circ J. 2007;71(9):1354-9.

301. Kumler T, Gislason GH, Kober L, Gustafsson F, Schou M, Torp-Pedersen C. Renal function at the time of a myocardial infarction maintains prognostic value for more than 10 years. BMC Cardiovasc Disord. 2011;11:37.

302. Amin AP, Spertus JA, Reid KJ, Lan X, Buchanan DM, Decker C, et al. The prognostic importance of worsening renal function during an acute myocardial infarction on long-term mortality. Am Heart J. 2010;160(6):1065-71.

303. Komukai K, Ogawa T, Yagi H, Date T, Suzuki K, Sakamoto H, et al. Renal insufficiency is related to painless myocardial infarction. Circ J. 2007;71(9):1366-9.

304. Adams JE, 3rd, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, et al. Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation. 1993;88(1):101-6.

305. Dragu R, Behar S, Sandach A, Boyko V, Kapeliovich M, Rispler S, et al. Should primary percutaneous coronary intervention be the preferred method of reperfusion therapy for patients with renal failure and ST-elevation acute myocardial infarction? Am J Cardiol. 2006;97(8):1142-5.

306. Chan MY, Becker RC, Sim LL, Tan V, Lee CH, Low AF, et al. Reperfusion strategy and mortality in ST- elevation myocardial infarction among patients with and without impaired renal function. Ann Acad Med Singapore. 2010;39(3):179-84.

307. Koganei H, Kasanuki H, Ogawa H, Tsurumi Y. Association of glomerular filtration rate with unsuccessful primary percutaneous coronary intervention and subsequent mortality in patients with acute myocardial infarction: From the HIJAMI registry. Circ J. 2008;72(2):179-85.

308. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 2004;44(9):1780-5.

309. Wi J, Ko YG, Shin DH, Kim JS, Kim BK, Choi D, et al. Prediction of Contrast-Induced Nephropathy With Persistent Renal Dysfunction and Adverse Long-term Outcomes in Patients With Acute Myocardial Infarction Using the Mehran Risk Score. Clin Cardiol. 2013;36(1):46-53.

310. Patti G, Ricottini E, Nusca A, Colonna G, Pasceri V, D'Ambrosio A, et al. Short-term, high-dose Atorvastatin pretreatment to prevent contrast-induced nephropathy in patients with acute coronary syndromes undergoing percutaneous coronary intervention (from the ARMYDA-CIN [atorvastatin for reduction of myocardial damage during angioplasty-contrast-induced nephropathy] trial. Am J Cardiol. 2011;108(1):1-7.

311. Leoncini M, Toso A, Maioli M, Tropeano F, Villani S, Bellandi F. Early high-dose rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome. Results from Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome (PRATO-ACS Study). J Am Coll Cardiol. 2013.

312. Li W, Fu X, Wang Y, Li X, Yang Z, Wang X, et al. Beneficial effects of high-dose atorvastatin pretreatment on renal function in patients with acute ST-segment elevation myocardial infarction undergoing emergency percutaneous coronary intervention. Cardiology. 2012;122(3):195-202.

313. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med. 2012;156(6):445-59.

314. Best PJ, Steinhubl SR, Berger PB, Dasgupta A, Brennan DM, Szczech LA, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J. 2008;155(4):687-93.

315. Keltai M, Tonelli M, Mann JF, Sitkei E, Lewis BS, Hawken S, et al. Renal function and outcomes in acute coronary syndrome: Impact of clopidogrel. Eur J Cardiovasc Prev Rehabil. 2007;14(2):312-8.

316. Kim JY, Jeong MH, Moon JH, Ahn YK, Chae SC, Hur SH, et al. Impact of Clopidogrel loading dose in patients with chronic kidney disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Am J Cardiol. 2012;110(11):1598-606.

317. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: Results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2010;122(11):1056-67.

318. Montalescot G, Silvain J. Ticagrelor in the renal dysfunction subgroup: subjugated or substantiated? Circulation. 2010;122(11):1049-52.

319. Fox KA, Bassand JP, Mehta SR, Wallentin L, Theroux P, Piegas LS, et al. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non ST-segment elevation acute coronary syndromes. Ann Intern Med. 2007;147(5):304-10.

320. Mehran R, Nikolsky E, Lansky AJ, Kirtane AJ, Kim YH, Feit F, et al. Impact of chronic kidney disease on early (30-day) and late (1-year) outcomes of patients with acute coronary syndromes treated with alternative antithrombotic treatment strategies: An ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) substudy. JACC Cardiovasc Interv. 2009;2(8):748-57.

321. Saltzman AJ, Stone GW, Claessen BE, Narula A, Leon-Reyes S, Weisz G, et al. Long-term impact of chronic kidney disease in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. JACC Cardiovasc Interv. 2011;4(9):1011-9.

322. Chew DP, Lincoff AM, Gurm H, Wolski K, Cohen DJ, Henry T, et al. Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). Am J Cardiol. 2005;95(5):581-5.

323. Chonchol M, Benderly M, Goldbourt U. Beta-blockers for coronary heart disease in chronic kidney disease. Nephrol Dial Transplant. 2008;23(7):2274-9.

324. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92.

325. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med. 2012;157(4):251-62.

326. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: A systematic review and meta-analysis. Ann Intern Med. 2012;157(4):263-75.

327. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation. 2011;123(21):2344-52.

328. Griffin BP, Callahan TD, Menon V, Wu WM, Cauthen CA, Dunn JM. Manual of cardiovascular medicine. 4th ed. Philadelphia, London: Lippincott Williams & Wilkins; 2013. p. 95-6.

329. Newby LK, Jesse RL, Babb JD, Christenson RH, De Fer TM, Diamond GA, 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):2427-63.

330. Kiliszek M, Burzynska B, Michalak M, Gora M, Winkler A, Maciejak A, et al. Altered gene expression pattern in peripheral blood mononuclear cells in patients with acute myocardial infarction. PLoS One. 2012;7(11):e50054.

331. Vogel B, Keller A, Frese KS, Kloos W, Kayvanpour E, Sedaghat-Hamedani F, et al. Refining diagnostic microRNA signatures by whole-miRNome kinetic analysis in acute myocardial infarction. Clin Chem. 2013;59(2):410-8.

332. Clark EN, Sejersten M, Clemmensen P, Macfarlane PW. Automated electrocardiogram interpretation programs versus cardiologists' triage decision making based on teletransmitted data in patients with suspected acute coronary syndrome. Am J Cardiol. 2010;106(12):1696-702.

333. Weston P, Alexander JH, Patel MR, Maynard C, Crawford L, Wagner GS. Hand-held echocardiographic examination of patients with symptoms of acute coronary syndromes in the emergency department: The 30-day outcome associated with normal left ventricular wall motion. Am Heart J. 2004;148(6):1096-101.

334. Mukherjee D, Eagle KA. The use of antithrombotics for acute coronary syndromes in the emergency department: Considerations and impact. Prog Cardiovasc Dis. 2007;50(3):167-80.

335. Kohli P, Desai NR, Giugliano RP, Kim JB, Somaratne R, Huang F, et al. Design and rationale of the LAPLACE-TIMI 57 trial: A phase II, double-blind, placebo-controlled study of the efficacy and tolerability of a monoclonal antibody inhibitor of PCSK9 in subjects with hypercholesterolemia on background statin therapy. Clin Cardiol. 2012;35(7):385-91.

336. Kajiya T, Liang M, Sharma RK, Lee CH, Chan MY, Tay E, et al. Everolimus-eluting bioresorbable vascular scaffold (BVS) implantation in patients with ST-segment elevation myocardial infarction (STEMI). EuroIntervention. 2013;9(4):501-4.

337. Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. J Am Coll Cardiol. 2013;62(16):1409-18.

338. Mathur A, Acharji S, Anand S, Singh M, Lakshama-Nadoss U, Prasad H, et al. Embolic protection during primary PCI: A 2013 update. Minerva Cardioangiol. 2013;61(2):181-8.

339. Global Registry of Acute Coronary Events (GRACE). Acute Coronary Syndrome (ACS) - GRACE ACS Risk Model. http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html (accesssed 10 Jan 2010); Available from: http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html.

340. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.

341. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.

342. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461-70.

343. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

344. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis. 2010;56(3):486-95.

345. Bolognese L, Falsini G, Schwenke C, Grotti S, Limbruno U, Liistro F, et al. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced nephropathy and tissue reperfusion in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Contrast Media and Nephrotoxicity Following Primary Angioplasty for Acute Myocardial Infarction [CONTRAST-AMI] Trial). Am J Cardiol. 2012;109(1):67-74.

346. McCullough PA, Bertrand ME, Brinker JA, Stacul F. A meta-analysis of the renal safety of isosmolar iodixanol compared with low-osmolar contrast media. J Am Coll Cardiol. 2006;48(4):692-9.

347. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Paolo Elia P, et al. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J. 2004;25(3):206-11.

348. Maioli M, Toso A, Leoncini M, Micheletti C, Bellandi F. Effects of hydration in contrast-induced acute kidney injury after primary angioplasty: A randomized, controlled trial. Circ Cardiovasc Interv. 2011;4(5):456-62.

349. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements. 2012;2:1-138.

350. Brar SS, Hiremath S, Dangas G, Mehran R, Brar SK, Leon MB. Sodium bicarbonate for the prevention of contrast induced-acute kidney injury: A systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4(10):1584-92.

351. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: A randomized trial. JAMA. 2008;300(9):1038-46.

352. Merten GJ, Burgess WP, Gray LV, Holleman JH, Roush TS, Kowalchuk GJ, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: A randomized controlled trial. JAMA. 2004;291(19):2328-34.

353. Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate PercutaneouS Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. J Am Coll Cardiol. 2010;55(20):2201-9.

354. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med. 2000;343(3):180-4.

355. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med. 2006;354(26):2773-82.

356. Droppa M, Desch S, Blase P, Eitel I, Fuernau G, Schuler G, et al. Impact of N-acetylcysteine on contrast-induced nephropathy defined by cystatin C in patients with ST-elevation myocardial infarction undergoing primary angioplasty. Clin Res Cardiol. 2011;100(11):1037-43.

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