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Non-ST Elevation Myocardial Infarction: Diagnosis and Management

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Abstract

Cardiovascular disease is expected to be the main cause of death globally due to the rapidly increasing prevalence of obesity, hypertension and diabetes mellitus. Atherosclerotic lesions and plaque rupture are the most common cause of myocardial infarction. Resting 12-lead ECG is the first diagnostic test for patients with chest pain and should be performed and interpreted within the first 10 min of the patient's admission to the emergency department. Cardiac biomarkers preferably, high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTEMI for the diagnosis, risk stratification and treatment. Rapid, efficient diagnosis and risk stratification of patients with chest pain will help to administer the appropriate medication and plan for the timing of invasive strategy and the choice of revascularization. This chapter helps to simply but elaborately discuss the diagnosis, risk stratification and the management of patients with non-ST elevation of myocardial infarction.

Keywords: myocardial infarction, percutaneous intervention, antiplatelet

1. Introduction

1.1. Definition of acute coronary syndrome

Acute coronary syndrome (ACS) is a term that describes an acute ischemic insult to the myocardium resulting from sudden reduction in coronary blood flow. The findings on the ECG will help to categorize patients into two major subdivision of major diagnostic and therapeutic consequences [1]:

1. Patients with acute chest pain and persistent >1 mm ST-segment elevation in ≥ 2 anatomically contiguous leads. This condition is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. The mainstay of treatment in these patients is immediate reperfusion with primary angioplasty or fibrinolytic therapy [2]. While biomarkers are useful for confirmatory and prognostic purposes, they are not required for the diagnosis of STEMI and should not delay treatment.
2. Patients with acute chest pain but no persistent ST-segment elevation. This condition is termed non-ST elevation ACS (NSTEMI-ACS). The ECG may be normal or there may be transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves. The NSTEMI-ACS can be subclassified to:
 1. Non-ST elevation myocardial infarction (NSTEMI) which denote cardiomyocyte necrosis and death by a rise in serum troponin levels.
 2. Unstable angina is defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis (cardiac biomarkers are not increased) [3, 4].

The application of high-sensitivity cardiac troponin measurements in daily clinical practice instead standard troponin assays showed increased detection of MI (4% absolute and 20% relative increase) and decreased diagnosis of unstable angina [5–7]. In comparison with NSTEMI patients, unstable angina patients do not have necrosis in their myocardial tissue and have a substantially lower risk of death. Unstable angina patients benefit less from intensified anti-platelet therapy and early invasive strategy [5–12]. NSTEMI encompasses a broad spectrum of ischemic injury to the myocardium, which is detected by elevation of serum cardiac biomarkers. It can be distinguished from unstable angina pectoris by normal serial cardiac biomarkers [1].

1.2. Non-ST elevation myocardial infarction

NSTEMI is an acute ischemic event causing cardiomyocyte death by necrosis in a clinical setting consistent with acute myocardial ischemia [8]. The leading symptom that initiates the diagnostic and therapeutic cascade in patients with suspected ACS is chest pain but to make a diagnosis of NSTEMI, one major criteria is typical rise and gradual fall in cardiac biomarkers (troponin or CKMB) in addition to one or more of the following:

1. Symptoms of ischemia.
2. ECG changes.
3. Imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality.
4. Intracoronary thrombus detected on angiography or autopsy [8].

1.3. Classification of myocardial infarction

The development of myocardial tissue-specific biomarkers and sensitive cardiac imaging techniques allows for early detection of very small amounts of myocardial injury or necrosis. Consequently MI has been redefined to encompass any necrosis in the setting of myocardial ischemia by any of the following possible etiologies [3, 8, 13]:

Type 1 MI: spontaneous MI caused by atherosclerotic plaque rupture, ulceration, fissure, erosion or dissection with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. The patient may have underlying severe CAD but in 5–20% of cases there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women [8, 10, 11, 14].

Type 2 MI: MI secondary to an increase in oxygen demand or decrease in supply. The myocardial necrosis results from causes other than coronary plaque instability [8]. Mechanisms include coronary artery spasm, coronary endothelial dysfunction, tachyarrhythmias, bradyarrhythmias, anemia, respiratory failure, hypotension and severe hypertension. In addition, in critically ill patients and in patients undergoing major non-cardiac surgery, myocardial necrosis may be related to injurious effects of pharmacological agents and toxins [9].

Type 3 MI: Sudden unexpected cardiac death before cardiac biomarkers obtained.

Type 4a MI: MI associated with percutaneous coronary intervention (PCI) where there is a greater than 5-fold rise in troponin during the first 48 h following the intervention [8].

Type 4b MI: MI associated with stent thrombosis.

Type 5 MI: MI associated with coronary bypass graft surgery (CABG), a greater than 10-fold rise from normal baseline levels in troponin during the first 48 h following the intervention [8].

2. Epidemiology and pathogenesis

2.1. Epidemiology

Cardiovascular disease (CVD) is the number one cause of death worldwide, accounting for 17.5 million deaths per year. Coronary heart disease mortality is decreasing in many developed countries, but it is increasing in developing and transitional countries, partly as a result of increasing longevity, urbanization, and lifestyle changes. Epidemiological data have shown that acute coronary syndrome cases with STEMI appear to be declining and that NSTEMI occurs more frequently than STEMI [15, 16]. In the United States, it is estimated that >780,000 people will experience an ACS each year, and approximately 70% of these will have NSTEMI [17]. Trends from the world's largest database of patients with ACS show that the percentage of patients with a diagnosis of NSTEMI is rising dramatically [18]. This is likely to be due

to the advent of more sensitive assays for myocardial injury, earlier pharmacotherapy, and reperfusion (and prevention) of STEMI [13, 18].

2.2. Pathophysiology

NSTEMI is a result of an acute imbalance between myocardial oxygen demand and supply, most commonly due to a reduction in myocardial perfusion. Type 1 MI is most commonly caused by a non-occlusive thrombus that develops in a disrupted atherosclerotic plaque, and leads to non-occlusive or near-complete thrombosis of a vessel supplying the myocardium.

Plaque rupture usually occurs at the weakest and thinnest part of the atherosclerotic cap (often at the shoulder region). Ruptured plaques contain large numbers of inflammatory cells including monocytes, macrophages, and T lymphocytes [19, 20]. Although one third of occlusions occur at a site with the greatest stenosis, most (66–78%) arise from lesions with <50% stenosis, and <5% arise from lesions exhibiting >70% stenosis [19]. It is thought that the lack of ST elevation is because the infarct does not involve the full thickness of the myocardium (not a transmural infarction). The severity of myocardial damage in NSTEMI depends on:

- Duration of ischemia and time to reperfusion
- Extent of underlying atherosclerosis
- Presence of collateral blood flow to the affected region
- Diameter of affected coronary vessel
- Degree of occlusion
- Presence of other comorbidities (i.e., diabetes, renal failure, or HTN).

Classically it is thought that NSTEMI patients ultimately have a diagnosis of a non-Q-wave MI; however, 25% of patients with NSTEMI and elevated biomarkers go on to develop Q-wave MI in the weeks to follow [21]. In addition, approximately 25% of patients with a diagnosis of NSTEMI have a 100% occlusion of the affected artery on coronary angiography [22].

NSTEMI may also be caused by other mechanisms, such as dynamic obstruction (i.e., focal coronary artery spasm or Prinzmetal angina), severe progressive atherosclerosis, restenosis following percutaneous coronary intervention, recreational drug use (e.g., cocaine or other stimulants), arterial inflammation (i.e., vasculitis), or extrinsic causes leading to myocardial supply–demand mismatch (such as hypotension, hypovolemia, or hypoxia) [1].

3. Diagnostic approach

3.1. Clinical presentation

Patients presenting with chest pain or discomfort with suspected ACS require urgent evaluation. The clinical spectrum of NSTEMI may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or hemodynamic instability due to large myocardium

in jeopardy or cardiac arrest secondary to malignant ventricular ischemia. Therefore, it is essential to establish if the patient has ACS and if so, what is the likelihood the patient will have adverse clinical event [1]. Physicians will need to stratify the patients according to their risk status and according to the initial risk assessment to choose an appropriate management strategy. The initial risk assessment includes the history, examination, ECG, and cardiac biomarkers [1, 23].

3.2. History and examination

Angina pectoris is a kind of pain described as a sensation of tightness, heaviness, aching, burning, pressure, or squeezing typically localized at the retrosternal region. The pain can often radiate to the left arm but may also radiate to the lower jaw, neck, both arms, back, and epigastrium. It is associated with exertion or emotional stress and relieved by rest or administration of sublingual nitroglycerin [1].

In ACS patients other symptoms including sweating, nausea, abdominal pain, dyspnea and syncope may be present. Atypical presentations are also possible and characterized by epigastric pain, indigestion-like symptoms and isolated dyspnea. Atypical complaints are more often observed in the elderly, in women and in patients with diabetes mellitus, chronic renal disease or dementia [24, 25]. The relief of pain at rest increase the probability of myocardial ischemia while the relief of symptoms after nitrates administration is not specific for angina pectoris [25]. In patients presenting with suspected MI to the emergency department, overall, the diagnostic performance of chest pain characteristics for MI is limited [25].

Risk factors increase the likelihood of NSTEMI include: Older age, male gender, family history of CAD, diabetes, hyperlipidemia, hypertension, renal insufficiency, previous manifestation of CAD as well as peripheral or carotid artery disease.

Physical examination is frequently unremarkable in patients with suspected NSTEMI but may reveal HTN or hypotension, the presence of third and fourth heart sounds, and paradoxical splitting of the second heart sound. Cardiac auscultation may reveal a systolic murmur due to ischemic mitral regurgitation, which is associated with poor prognosis [26] or a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect) of a subacute and possibly undetected MI. Signs of heart failure (raised jugular venous pressure, bilateral crepitation on auscultation of the lungs) or cardiogenic shock may also be present, and these signify a worse prognosis.

3.3. Initial tests

3.3.1. Electrocardiogram

Resting 12-lead ECG is the first diagnostic test for patients with chest pain and should be performed and interpreted within the first 10 min of the initial admission to the hospital [27]. ECG is critical for the diagnosis of STEMI as the cause for the chest pain, this has a tremendous therapeutic implication for the patient.

While the ECG in the setting of NSTEMI may be normal in more than one-third of patients, a serial ECG at 15- to 30-min intervals should be performed to detect the developing abnormalities.

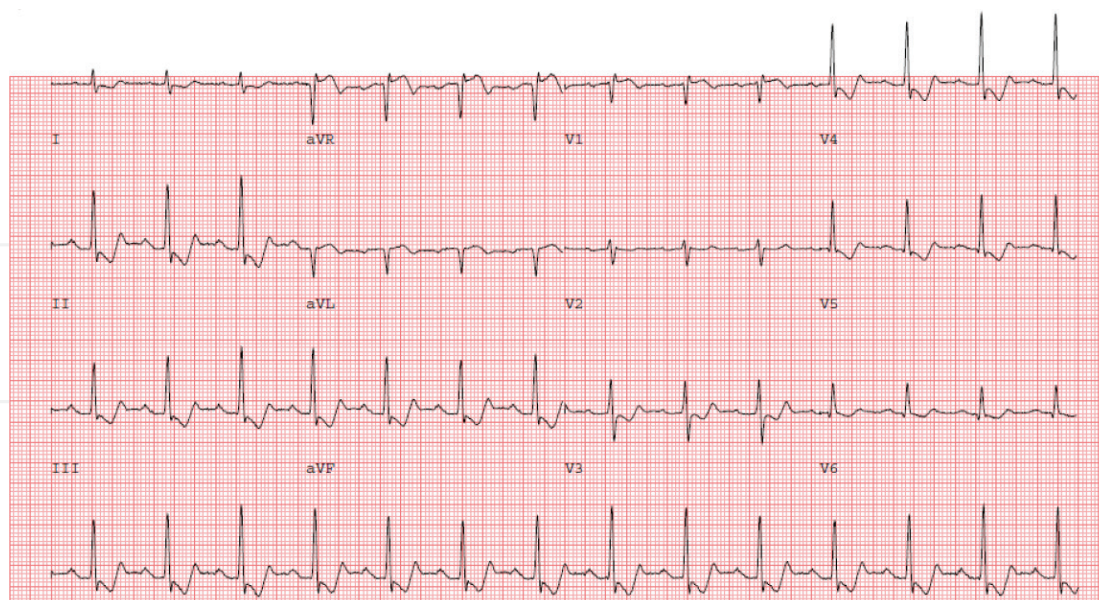


Figure 1. ECG showing ST depression in the inferolateral leads suggestive of inferior-lateral ischemia.

Classic ECG findings of ischemia in NSTEMI include horizontal or down sloping ST depression >0.5 mm and/or symmetrically inverted T waves >2.0 mm (**Figure 1**) [2, 28]. Standard leads may be inconclusive in some patients and additional leads may be necessary (e.g. in case of left circumflex artery occlusion or right ventricular MI may be detected only in V7–V9 and V3R and V4R, respectively) [8]. If it is possible a comparison with previous ECG's may be valuable. Diffuse precordial ST depression more pronounced in leads V4–V6 may indicate a culprit lesion located in the mid left anterior descending coronary artery, while changes more evident in leads V2–V3 may be more suggestive of a culprit lesion located in the left circumflex artery [29]. Diffuse ST depression including both precordial and extremity leads associated with ST-elevation ≥ 1 mm in lead aVR may indicate either left main coronary artery as the culprit lesion or proximal occlusion of the left anterior descending coronary artery in the presence of severe three-vessel CAD [30, 31].

3.3.2. Blood tests

- CBC: hemoglobin and hematocrit measurements may help to evaluate a secondary cause of NSTEMI (e.g., acute blood loss, anemia) and to evaluate thrombocytopenia to estimate risk of bleeding.
- BUN and serum creatinine: creatinine clearance should be estimated in NSTEMI patients and the doses of renally cleared drugs should be adjusted appropriately. In chronic kidney disease patients undergoing angiography, iso-osmolar contrast agents may be preferred [1, 15].
- Serum electrolytes: electrolyte derangements may predispose to cardiac arrhythmias.
- Liver function tests: useful if treatment with drugs that undergo hepatic metabolism is considered.

- Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP): measurement of BNP or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS, particularly cardiogenic shock associated with MI type 1 [1].
- Lipid profile: this test is indicated in the first 24 h of admission to the hospital to assess for lipid abnormalities and therefore the need for any lipid-lowering therapy.

3.3.3. Biomarkers

Clinical assessment, 12-lead ECG and biomarkers are crucial for the diagnosis, risk stratification and treatment of patients with suspected NSTEMI. Measurement, preferably, high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTEMI [7–9]. Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin. In patients with suspected myocardial ischemia, a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals indicates MI. Cardiac troponin levels rise rapidly (i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for several days [8, 9].

The use of high-sensitivity assays, has shortened the time interval to the second cardiac troponin, reduced substantially the delay to diagnosis, translating into shorter stays in the emergency department and lower costs [6–9, 32–35]. In patients presenting very early, the second cardiac troponin level should be obtained at 3 h, due to the time dependency of troponin release; serial cardiac troponin testing should be pursued if the clinical suspicion remains high or whenever the patient develops recurrent chest pain [36, 37]. The negative predictive value for MI in patients assigned ‘rule-out’ exceeded 98% [35–41] used in conjunction with clinical and ECG findings. The positive predictive value for MI in those patients meeting the ‘rule-in’ criteria was 75–80%.

3.3.4. Noninvasive imaging

Transthoracic echocardiography is useful to identify abnormalities suggestive of myocardial ischemia or necrosis (i.e. segmental hypokinesia or akinesia). Strain and strain rate imaging can detect subtle reduced regional function in the absence of overt wall motion abnormalities, which improve the diagnostic and prognostic value of conventional echocardiography [42, 43]. Evaluation of left ventricular systolic function by echocardiography, at the indexed hospital admission, is important to estimate prognosis. Echocardiography can help in discrimination of other pathologies including acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy or right ventricular dilatation associated with acute pulmonary embolism. Echocardiography is the diagnostic tool of choice for patients with hemodynamic instability of suspected cardiac origin [44].

3.3.5. Functional stress testing

In patients without ischemic changes on 12-lead ECGs and negative cardiac troponins (preferably high-sensitivity) who are free of chest pain for several hours, stress imaging can be performed during admission or shortly after discharge [1, 45, 46]. The sensitivity and specificity of these tests increase when combined with either nuclear imaging to look for myocardial

perfusion defects or echocardiography to assess wall motion abnormalities. Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy and superior prognostic value [47]. While studies have shown that normal exercise or pharmacological stress echocardiograms have high negative predictive value for ischemia and are associated with excellent patient outcomes ECG [48–50]. The addition of contrast to improve endocardial border detection and facilitate detection of ischemia [51].

To evaluate the extent of the CAD, a functional assessment using a submaximal exercise testing can be performed at 4 to 7 days after myocardial infarction, while symptom limited testing can be performed at 14 to 21 days post-myocardial infarction, when the patient has been free of active ischemic or heart failure symptoms [52].

3.3.6. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) can be used in the assessment of myocardial perfusion and wall motion abnormalities. Patients presenting with acute chest pain with a normal stress CMR have an excellent short and midterm prognosis [53]. CMR also permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial edema) [54, 55]. Moreover, CMR can facilitate the differential diagnosis between infarction and myocarditis or Takotsubo cardiomyopathy [56].

3.3.7. Nuclear myocardial perfusion imaging

Nuclear myocardial perfusion imaging has been shown to be useful for risk stratification in patients with acute chest pain suggestive for ACS. The presence of an area of myocardium that becomes deprived of perfusion during increased myocardial demand and reperfuses on stopping the activity on nuclear imaging stress tests is a reversible defect (**Figure 2**).

Resting myocardial scintigraphy, can be helpful for the diagnosis of patients presenting with chest pain without ECG changes or elevated cardiac troponins [57]. Combined stress–rest imaging may further enhance assessment of ischemia, while a normal study is associated with excellent outcome [58, 59].

4. Anatomical evaluation

Multidetector computed tomography (MDCT) provide noninvasive evaluation of coronary anatomy and atherosclerosis. Due to the high negative predictive value of coronary computed tomography angiography (CCTA), evidence suggests that CCTA is useful in patients with low to moderate risk of NSTEMI where a normal scan excludes CAD. When compared with the standard care (observation, serial enzymes followed by stress testing) for low-risk patients, CCTA reduced time to diagnosis, reduced length of emergency department stay, and had similar safety [60]. CCTA had high negative predictive values to exclude ACS and excellent outcome in patients presenting to the emergency department with low to intermediate pre-test probability for ACS and a normal coronary CT angiogram [61]. CCTA was proven

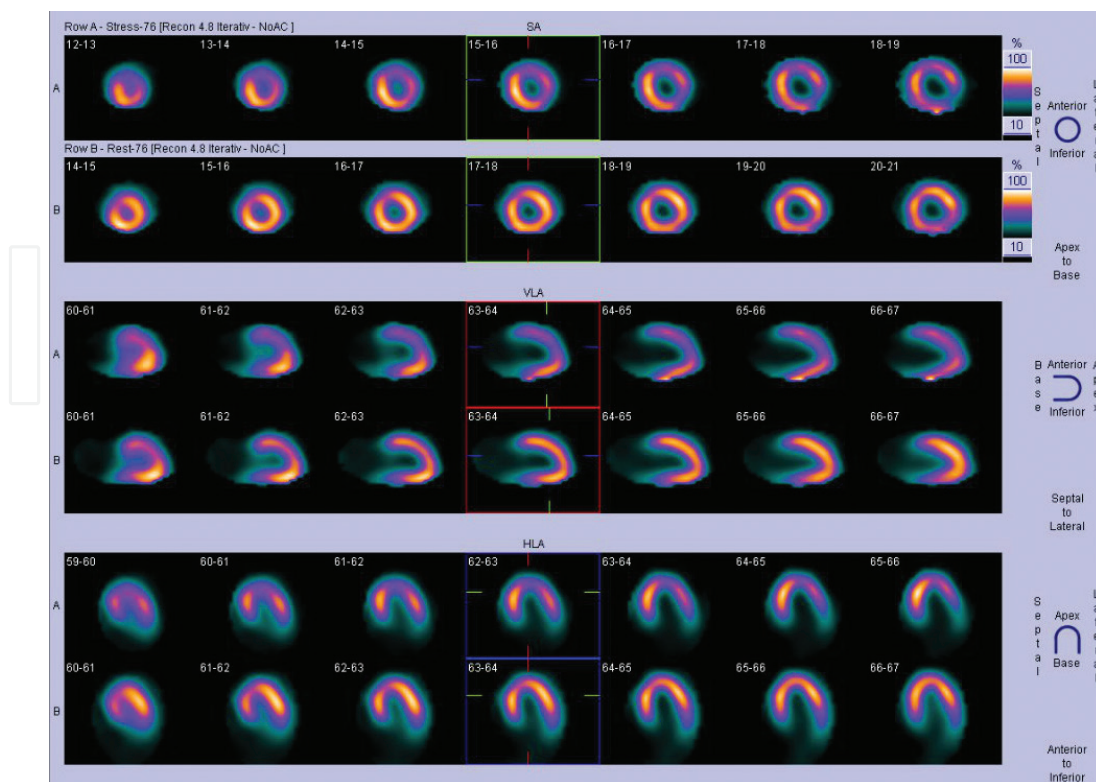


Figure 2. Myocardial nuclear perfusion scan showing anterior, lateral and inferior reversible scan. Coronary angiogram confirmed three vessel disease.

beneficial in the triage of low- to intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischemia on ECG and/or inconclusive cardiac troponins. At 6 months follow-up, there were no difference in the incidence of MI, post discharge emergency department visits or rehospitalizations, and no deaths in comparison to traditional management. Also, there were reduction in the cost and length of stay associated with MDCT [60, 62–65]. But there was an increase in the use of invasive angiography [65]. CCTA is not indicated for patients with high-risk features and it is not useful in patients with known CAD [66]. Other factors limiting CCTA include severe calcifications and tachycardia. CT imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism, aortic dissection and tension pneumothorax [67].

5. Risk assessment and outcomes

ACS management requires continuous risk stratification for death or recurrent MI. Quantitative assessment of ischemic risk by means of scores is superior to the clinical assessment alone to further triage and assist in the selection of treatment options [1]. A number of risk scores exist which incorporate a number of variables, the GRACE risk score and the TIMI risk score are examples.

The GRACE risk score provides the most accurate stratification of risk both on admission and at discharge [68, 69]. The GRACE 2.0 risk calculator provides a direct estimation, of mortality

while in hospital, at 6 months, at 1 year and at 3 years. The combined risk of death or MI at 1 year is also provided [70]. Variables used in the GRACE 2.0 risk calculation include age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers and ST deviation. The TIMI risk score uses seven variables in an additive scoring system: age ≥ 65 years, three or more CAD risk factors, known CAD, aspirin use in the past 7 days, severe angina (two or more episodes within 24 h), ST change ≥ 0.5 mm and positive cardiac marker [71]. Patients with a TIMI score of 0–2 are low risk, 3–4 are intermediate risk, and 5–7 are high risk. All-cause mortality, rate of MI, and rate of urgent revascularization at 14 days increase in proportion to the number of risk factors present on the TIMI score. It is simple to use, but its discriminative accuracy is inferior to that of the GRACE risk score [1, 71].

6. Hospital care and standard medical therapies

The aim of initial evaluation is to relieve pain and ischemia, prevent further thrombosis or embolism, and correct hemodynamic abnormalities and treat life-threatening complication.

All patients should undergo early risk estimation based on the medical history, physical exam, ECG findings, and cardiac markers.

7. Initial management

Initial medical therapy is indicated in all patients, with variation in some choices of agent according to risk stratification.

7.1. Cardiac rhythm monitoring

Early revascularization, effective antithrombotic therapy and administration of beta-blockers have reduced the incidence of life threatening arrhythmias in the acute phase of MI to $<3\%$, with most of the arrhythmic events occurring within 12 h of symptom onset [72, 73]. Patients with life-threatening arrhythmias frequently had prior heart failure, low LV ejection fraction ($EF < 30\%$) and triple vessel CAD.

NSTEMI patients at low risk for cardiac arrhythmias require rhythm monitoring for ≤ 24 h or until coronary revascularization (whichever comes first) in an intermediate or coronary care unit, while individuals at intermediate to high risk for cardiac arrhythmia may require rhythm monitoring for >24 h in an intensive or coronary care unit or in an intermediate care unit, depending on the clinical presentation, degree of revascularization and early post-revascularization course.

All patients require oxygen saturation measurement using pulse oximetry [1]. Although in the past oxygen was routinely given to all patients, there is no evidence to support this practice [74]. Moreover, results of the Air Versus Oxygen in ST-elevation Myocardial Infarction (AVOID) trial have shown that routine supplemental oxygen may increase myocardial infarct size, and raise rates of recurrent MI and cardiac arrhythmia in patients with ST-elevation

MI but without hypoxia. Guidelines now recommend supplemental oxygen therapy only in patients who are hypoxemic (arterial oxygen saturation < 90%), or in those who have respiratory distress or other high-risk features for hypoxemia [1, 15, 75].

7.2. Pharmacological treatment of ischemia

The goal of pharmacological anti-ischemic therapy is to decrease myocardial oxygen demand (secondary to a decrease in heart rate, blood pressure, preload or myocardial contractility) or to increase myocardial oxygen supply (by administration of oxygen or through coronary vasodilation).

Pain relief is indicated in the initial management of all patients. Those with ongoing ischemic discomfort should receive a trial of sublingual nitroglycerin (0.4 mg) every 5 min for a total of three doses. Sublingual nitroglycerin reduces myocardial oxygen demand and enhances myocardial oxygen delivery. Intravenous nitroglycerin is recommended in patients with no symptom relief after sublingual nitroglycerin. Under careful blood pressure monitoring, the dose should be titrated upwards until symptoms are relieved, and in hypertensive patients until blood pressure is normalized, unless side effects (notably headache or hypotension) occur. Beyond symptom control, there is no indication for nitrate treatment [76]. In patients with recent intake of a phosphodiesterase type 5 inhibitor (i.e. within 24 h for sildenafil or vardenafil and 48 h for tadalafil), nitrates should not be administered due to the risk of severe hypotension. Nitroglycerin should not be given if systolic BP is <90 mmHg or there is a concern about right ventricular infarction [77]. If the patient does not respond to nitroglycerin, intravenous morphine can be administered in the absence of any contraindications [1]. Morphine causes vasodilation and may produce reductions in heart rate (through increased vagal tone) and systolic BP to further reduce myocardial oxygen demand. It should be given instead of nitroglycerin when nitroglycerin is contraindicated. Morphine should be used with caution, one randomized, double-blind trial found that morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction [78, 79].

7.2.1. Beta-blockers

Oral beta-blockers are recommended for routine use in all patients unless contraindicated. Beta-blockers competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure and myocardial contractility. Randomized trials with threatened or evolving MI have shown lower rates of progression to MI with beta-blocker treatment [80].

The beneficial effects of beta-blockers derived from several meta-analyses were a significant 8 and 13% relative risk reduction for in-hospital and first week mortality following MI respectively with no increase in cardiogenic shock [81, 82].

A registry study of NSTEMI patients found that the use of B-Blocker blockers within 24 h of hospital admission in patients at risk of developing cardiogenic shock (i.e. age > 70 years, heart rate > 110 beats/min, systolic blood pressure < 120 mmHg), the observed shock or death rate was significantly increased [83]. Therefore, early administration of beta-blockers should be avoided in these patients if the ventricular function is unknown.

Contraindications include heart rate <60 bpm, systolic BP <100 mmHg, moderate or severe associated left ventricular failure, PR interval on the ECG >0.24 s, second- or third-degree heart block, active asthma/reactive airways disease, severe COPD, hypotension, right ventricular infarction, and cardiogenic shock. Beta-blockers should not be administered in patients with symptoms possibly related to coronary vasospasm or cocaine use, as they might favor spasm by leaving alpha-mediated vasoconstriction unopposed by beta-mediated vasodilation.

7.3. Initial antiplatelet/anticoagulant

7.3.1. Bleeding risk assessment

The CRUSADE bleeding risk score considered baseline patient characteristics (i.e. female gender, history of diabetes, history of peripheral vascular disease or stroke), admission clinical variables (i.e. heart rate, systolic blood pressure, signs of heart failure) and admission laboratory values (i.e. hematocrit, calculated creatinine clearance) to estimate the patient's likelihood of an in-hospital major bleeding event [84].

The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) bleeding risk score was derived from a pooled cohort recruited in the ACUITY and HORIZONS-AMI trials [85]. Six independent baseline predictors were identified including: female gender, advanced age, elevated serum creatinine, white blood cell count, anemia and presentation as NSTEMI or STEMI and one treatment-related variable [use of unfractionated heparin and a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor rather than bivalirudin alone]. This risk score identified patients at increased risk for non-CABG-related major bleeds at 30 days and subsequent 1-year mortality. However, it has not been validated in an independent cohort.

Changes in interventional practice, such as increasing use of radial access, reduction in the dose of UFH, use of bivalirudin, diminished use of GPIIb/IIIa inhibitors and administration of more effective inhibitors of the platelet adenosine diphosphate (ADP) receptor P2Y₁₂ (P2Y₁₂ inhibitors), may all modify the predictive value of risk scores. Ischemic and bleeding risks need to be weighed in the individual patient, although many of the predictors of ischemic events are also associated with bleeding complications [84, 85]. Overall, CRUSADE and ACUITY scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE found to be the most discriminatory [86].

7.4. Platelet inhibition

7.4.1. Aspirin

Aspirin (chewed) is indicated immediately for all patients suspected of having an acute coronary syndrome unless contraindicated or already taken [1]. Aspirin should be continued at a daily maintenance dose thereafter [1]. Aspirin, an irreversible COX-1 inhibitor, suppresses thromboxane A₂ production preventing platelet aggregation, and reduces the incidence of death and nonfatal MI in patients with unstable angina or acute MI [87, 88]. Aspirin has been shown to achieve a 30–51% reduction in future coronary events [89]. A meta-analysis

suggests that aspirin administration (up to 2 years) is associated with a highly significant 46% odds reduction in major vascular events [90]. There was no difference between higher-dose (300–325 mg/day) and lower dose (75–100 mg/day) aspirin [91].

7.4.2. *P2Y₁₂ inhibitors*

7.4.2.1. *Clopidogrel*

Clopidogrel (300–600 mg loading and 75 mg/day maintenance dose) is an inactive prodrug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite. Clopidogrel is a selective and irreversible inhibitor of platelet P2Y₁₂ receptors and thus inhibits ADP-induced platelet aggregation [92, 93]. Dual antiplatelet therapy (DAPT) comprising aspirin and clopidogrel has been shown to reduce recurrent ischemic events in the NSTEMI-ACS setting compared with aspirin alone [94, 95]. However, up to 10% of patients treated with the combination of aspirin and clopidogrel will have a recurrent ischemic event in the first year after an ACS, with a rate of stent thrombosis of up to 2% [96]. There is substantial inter individual variability in the antiplatelet response to this drug and an increased risk of ischemic and bleeding events in Clopidogrel hypo- and hyper-responders, respectively [97–100]. There is evidence that key gene polymorphisms are involved in both the variability of active metabolite generation and clinical efficacy of Clopidogrel [101–104].

7.4.2.2. *Prasugrel*

Prasugrel (60 mg loading and 10 mg/day maintenance dose) is a prodrug that irreversibly blocks platelet P2Y₁₂ receptors with a faster onset and a more profound inhibitory effect than clopidogrel. In the TRITON-TIMI 38, Prasugrel reduced recurrent CV event in ACS patients scheduled for PCI in comparison to clopidogrel, significantly driven by reduction in MI [105]. There were more severe bleeding complications with prasugrel, due to an increase in spontaneous and fatal bleeds [106]. Based on the marked reduction in definite or probable stent thrombosis observed in the TRITON-TIMI 38 prasugrel should be considered in patients with stent thrombosis despite compliance with clopidogrel therapy [100, 107]. Prasugrel is contraindicated in patients with prior stroke/transient ischemic attack due to evidence of net harm in this group in TRITON-TIMI 38. In addition, the study showed no apparent benefit in patients >75 years of age or with low bodyweight (<60 kg) [105].

7.4.2.3. *Ticagrelor*

Ticagrelor is an oral, reversibly binding P2Y₁₂ inhibitor with a plasma half-life of 6–12 h.

Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with Clopidogrel, as well as a faster offset of action with more rapid recovery of platelet function [108].

In the PLATO trial, the primary composite efficacy endpoint (death from CV causes, MI or stroke) was significantly reduced with ticagrelor compared with similar reductions for CV and all-cause mortality [109, 110]. There was increased risk of non-CABG-related major bleeds with ticagrelor compared with Clopidogrel but no difference in life-threatening or fatal bleeds [110].

There was a reduction in definite stent thrombosis with ticagrelor in the NSTEMI-ACS subgroup. In addition to increased rates of minor or non-CABG-related major bleeding events with ticagrelor, adverse effects included dyspnea (without bronchospasm), increased frequency of asymptomatic ventricular pauses and increases in uric acid [109, 111, 112].

All patients should be given dual antiplatelet therapy with a P2Y₁₂ receptor inhibitor in addition to aspirin. If the patient is intolerant of aspirin or it is otherwise contraindicated, a P2Y₁₂ receptor inhibitor can be given instead of aspirin, but two different P2Y₁₂ receptor inhibitors should not be given together. P2Y₁₂ receptor inhibitors can reduce mortality and morbidity, but they are associated with an increased risk of bleeding [113, 114]. Ticagrelor and prasugrel are newer P2Y₁₂ agents, which trials have shown to have a faster onset of action and greater efficacy compared with Clopidogrel [1, 115]. However, the risk of bleeding is also greater with these two P2Y₁₂ agents compared with Clopidogrel [116, 117].

Clinicians need to tailor therapy to strike a balance between a newer agent that may have a faster onset of action and greater antiplatelet effect, but could potentiate bleeding (especially in those with prior TIA or stroke). Regardless of which P2Y₁₂ receptor inhibitor is chosen, a loading dose should be given as soon as possible in most patients and then a maintenance dose continued for a minimum of 12 months [118].

7.5. Anticoagulation

Anticoagulation therapy (subcutaneous low molecular weight heparin, intravenous unfractionated heparin, or the alternative agents fondaparinux or bivalirudin) should be started on earliest recognition of NSTEMI. The anticoagulant is used in conjunction with antiplatelet therapy already started (i.e., aspirin and a P2Y₁₂ receptor inhibitor). If fondaparinux is used during angiography/PCI, guidelines recommend that UFH be used in addition [1].

Anticoagulation should not be given if there are contraindications like major bleeding, history of adverse drug reaction or heparin-induced thrombocytopenia.

The antiplatelet and anticoagulation regimens should be started before the diagnostic angiogram. Triple antiplatelet therapy, in which an intravenous GP IIb/IIIa inhibitor is added to a P2Y₁₂ receptor inhibitor, aspirin, and anticoagulation, can be considered for high-risk patients; however, it should be avoided in patients at high risk of bleeding [1]. Although guidelines recommend the use of GP IIb/IIIa inhibitors in NSTEMI, the level of evidence for their routine use is weak at best, particularly as results from randomized trials are conflicting [119, 120].

8. Conservative approach

Anticoagulation treatment should be added to aspirin and a P2Y₁₂ receptor inhibitor at the earliest recognition of NSTEMI and continued for at least 48 h to hospital discharge and/or until symptoms abate and objective markers demonstrate a trend toward normal [121]. Agents include subcutaneous LMWH, intravenous UFH, or fondaparinux, according to clinician choice.

9. Ischemia-guided strategy versus early invasive strategies

9.1. Rationale and timing for early invasive strategy

Once initial management is instigated, the decision should be made as to whether the patient requires treatment using an invasive or noninvasive approach. The decision to pursue an invasive approach or medical management is made on an individual basis [122]. Invasive strategy carries risks but the benefit includes diagnostic accuracy, risk stratification and revascularization. The timing for coronary angiography and the selection of the revascularization modality depend on numerous factors, including clinical presentation, comorbidities, risk stratification, presence of high-risk features specific for a revascularization modality, frailty, cognitive status, estimated life expectancy and functional and anatomic severity as well as pattern of CAD. Guidelines recommend that high-risk patients routinely undergo early (12–24 h) coronary angiography and angiographically directed revascularization if possible unless patients have serious comorbidities, including cancer or end-stage liver disease, or clinically obvious contraindications, including acute or chronic (CKD 4 or higher) renal failure or multi-organ failure [1, 123, 124].

9.2. Routine invasive coronary angiography

Invasive coronary angiography allows to confirm the diagnosis of ACS related to obstructive epicardial CAD, to guide antithrombotic treatment, identify the culprit lesions and assess the suitability of coronary anatomy for PCI or CABG. Routine invasive strategy in NSTEMI has been shown to improve clinical outcomes and lower risk of death, reduce recurrent ischemic episodes, subsequent rehospitalization and revascularization [125–127].

Urgent and immediate angiography is indicated if patients do not stabilize with intensive medical treatment [1]. Guidelines recommend that an invasive approach is appropriate if any of the following high-risk features are present [1, 15]:

- Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
- Rise and fall in cardiac biomarkers (troponin T or I) consistent with MI
- New or dynamic ST-T wave changes
- Signs or symptoms of heart failure, or new or worsening mitral regurgitation
- Hemodynamic instability
- Life-threatening arrhythmia
- PCI within 6 months
- Prior CABG
- High-risk score (i.e., TIMI, GRACE)
- Mild to moderate renal dysfunction

- Diabetes mellitus
- Reduced left ventricular function (ejection fraction <40%).

9.3. Pattern of coronary artery disease

Angiographic patterns of CAD in NSTEMI patients are diverse, ranging from normal epicardial coronary arteries to a severely and diffusely diseased coronary arteries. Up to 20% of patients with NSTEMI-ACS have no lesions or non-obstructive lesions of epicardial coronary arteries, while among patients with obstructive CAD, 40–80% have multivessel disease [128–130].

Culprit lesions in the infarct-related artery are more often located within the proximal and mid segments, the left anterior descending coronary artery is the most frequent culprit vessel in both STEMI and NSTEMI-ACS (in up to 40% of patients). Left main coronary artery disease may be the underlying condition in 10% and a failure of bypass graft in 5% [128–132].

9.4. Identification of the culprit lesion

Culprit lesion on coronary angiography usually have features suggestive of acute plaque rupture. Vulnerable plaques are usually consisted from thin-cap fibroatheroma, and when rupture of the plaque happens they are characterized morphologically by the presence of at least two of the following features: intraluminal filling defects consistent with thrombus, plaque ulceration (i.e. presence of contrast and hazy contour beyond the vessel lumen), plaque irregularity (i.e. irregular margins or overhanging edges), dissection or impaired flow [132–134]. Multiple complex plaques observed in up to 40% of NSTEMI patients with obstructive CAD [132, 134–138]. One-quarter of NSTEMI patients present with an acute occluded coronary artery and two-thirds of the occlusions are already collateralized at the time of angiographic examination [138, 139].

Identification of the culprit lesion or the differentiation between an acute/subacute and chronic occlusion may sometimes be challenging based solely on angiography data. The additive value of the information from the ECG using lead localization and the regional wall motion abnormalities by Echocardiography can help identify the culprit lesion. Intracoronary imaging like optical coherence tomography can help to identify non-obstructive thin-cap fibroatheroma while vasospasm can be provoked by test such as acetylcholine [140–142]. The value of Fractional flow reserve (FFR) guided PCI in NSTEMI patient has not been properly addressed. The achievement of maximal hyperemia may be unpredictable in NSTEMI because of the dynamic nature of coronary lesions and the associated acute microvascular dysfunction. As a result, FFR may be overestimated and the hemodynamic relevance of a coronary stenosis underestimated [142].

9.5. Timing of invasive strategy

Routine intervention has been associated with an improved outcome [143–146] however, the optimal timing of the intervention has not been well established. Early intervention might

prevent ischemic events that could occur while the patient is awaiting a delayed procedure [147]. Alternatively, by treating a patient with intensive antithrombotic therapy and delaying intervention for several days, procedure-related complications might be avoided with intervention on a more stable plaque [148]. Thus, the question of when to intervene in patients with acute coronary syndromes without ST-segment elevation has not been definitively answered.

Immediate invasive strategy (<2 h from hospital admission) is recommended in very-high-risk NSTEMI-ACS patients with intent to perform vascularization because of the poor short- and long-term prognosis if left untreated.

Early invasive strategy (<24 h): Early invasive strategy is defined as coronary angiography performed within 24 h of hospital admission. Multiple studies showed no significant difference between early or delayed intervention groups in the rate of death, MI, stroke or major bleeds [130, 149–151].

In the early versus delayed invasive intervention in acute coronary syndromes clinical trial, prespecified analyses showed that early intervention improved the primary outcome in the third of patients who were at highest risk (GRACE risk score > 140) but not in the two thirds at low-to-intermediate risk (GRACE risk score ≤ 140) [129]. Early invasive strategy is recommended in patients with at least one high-risk criterion.

Delayed invasive strategy (<72 h): This is the recommended maximal delay for angiography in patients with low to intermediate risk [127, 149].

9.6. Selective invasive strategy

Patients with no recurrence of symptoms and none of the risk criteria (low risk patient), a non-invasive stress test preferably with imaging for inducible ischemia is recommended before deciding on an invasive strategy [152].

9.7. Conservative treatment

A conservative, early medical management strategy may be appropriate in patients with a low risk score, such subpopulations may not benefit from early invasive management especially low-risk women with NSTEMI [123, 124, 126]. Older patients may be considered at high risk for invasive approach regarding complications, but the benefit may be satisfactory from such approach in this subgroup [153–155]. Patients in whom an invasive strategy may be withheld by the treating physicians may include very elderly or frail patients, patients with comorbidities such as dementia, severe chronic renal insufficiency, or cancer and patients at high risk of bleeding complication. Ultimately patients care should be individualized and left at the discretion of the treating physician.

In the medically managed NSTEMI-ACS patients, the CURE study demonstrated that treatment with clopidogrel in addition to aspirin for 3–12 months, significantly lower the primary outcome (a composite of death from CV causes, non-fatal MI or stroke at 1 year) but there were significantly more major bleeds [94].

The association between clopidogrel use and the composite of death or MI was significant among patients presenting with NSTEMI compared with those presenting with unstable angina [156].

In the TRILOGY ACS trial, prasugrel was not associated with a statistically significant reduction in the primary endpoint (death, MI or stroke) but there were more frequent TIMI major and minor bleeding [157]. In the PLATO study, the incidence of the primary endpoint was lower with ticagrelor than with clopidogrel, but at the expense of higher incidence of TIMI major bleeds in the ticagrelor-treated patients [158].

10. Percutaneous coronary intervention: technical aspects and challenges

Stent implantation in the setting of NSTEMI-ACS helps to reduce abrupt vessel closure and restenosis associated with balloon angioplasty and it should be considered the standard treatment strategy (**Figure 3** and movies online). New-generation drug eluting stents are recommended over bare metal stents in NSTEMI-ACS [159–161]. Dual antiplatelet therapy (DAPT) is recommended for 12 months irrespective of stent type, but DAPT may be extended depending on the number of stents and the total stents' length used, patients with high risk of ischemic events recurrence and if patient's bleeding risk is low. The benefit of thrombectomy has not been assessed prospectively in NSTEMI-ACS but cannot be recommended, considering the lack of benefit observed in STEMI [162].

Complications of PCI include PCI-induced MI; coronary perforation, dissection, or rupture; cardiac tamponade; malignant arrhythmias; cholesterol emboli; and bleeding from the access site. Contrast-induced nephropathy is a common and potentially serious complication, especially in patients with baseline impaired renal function [163]. Early and late stent thromboses are catastrophic complications. Radial access, performed by experienced operators, is associated with lower bleeding risk and recommended over the transfemoral access in ACS [164, 165].

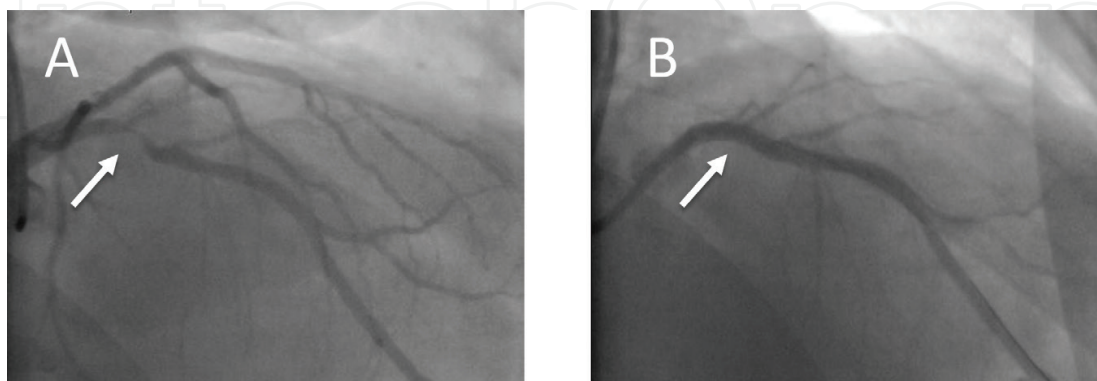


Figure 3. Angiogram of 54 years old gentleman presented with NSTEMI, ECG showed ST depression in the anterior leads. The angiogram confirmed a severe stenotic lesion in the proximal LAD (A) which stented successfully (B). Video clips of the angiogram available online.

11. Revascularization strategies and outcomes

In patients with complex, multivessel disease presenting with NSTEMI, the decision whether to do complete vs. incomplete revascularization and whether to do the complete revascularization at the index admission or to stage it is challenging and need to be tailored to age, general patient condition and comorbidities. A complete revascularization strategy of significant lesions should be pursued in multivessel disease patients with NSTEMI-ACS based on several studies showing the benefit of early intervention when compared with the conservative approach [143, 166, 167]. Also, recent trials have shown a detrimental prognostic effect of incomplete revascularization [168, 169].

Pursuing completeness of revascularization for some patients with complex coronary anatomy may mean increasing the risk of PCI especially in the presence of complex chronic total occlusions or referring to CABG.

The decision to treat all the significant lesions in the same setting or to stage the procedures should be based on clinical presentation, comorbidities, complexity of coronary anatomy, ventricular function, revascularization modality and patient preference.

With respect to outcomes, periprocedural complications of PCI as well as the long-term ischemic risk remain higher in NSTEMI-ACS than in stable patients, despite contemporary management. Accordingly, the risk of CV death, MI or stroke in NSTEMI-ACS patients in recent trials was approximately 10 and 15% at 1 and 2 years follow-up, respectively [110, 170]. For ACS patients who underwent PCI, revascularization procedures represent the most frequent, most costly and earliest cause for rehospitalization [171, 172].

12. Coronary artery bypass surgery

Approximately 10% of NSTEMI patients may require CABG during their index hospitalization [173]. The proportion of patient with NSTEMI undergoing CABG for NSTEMI decreased from 2001 to 2009, while the proportion of patients undergoing coronary angiography and PCI markedly increased [174]. CABG in the setting of NSTEMI is challenging mainly because of the difficulties in balancing ischemic and bleeding risks in relation to the timing of surgery and perioperative antithrombotic therapy. In addition, NSTEMI patients present with a higher proportion of surgical high-risk characteristics, including older age, female gender, left main coronary disease and LV dysfunction compared with patients undergoing elective CABG [175].

13. Percutaneous coronary intervention vs. coronary artery bypass surgery

The main advantages of PCI in the setting of NSTEMI are faster revascularization of the culprit lesion, a lower risk of stroke and the absence of deleterious effects of cardiopulmonary

bypass on the ischemic myocardium, on the other hand, CABG may more frequently offer complete revascularization in advanced multivessel CAD. The decision to perform PCI or CABG was left to the discretion of the investigator. A post hoc analysis of NSTEMI-ACS patients with multivessel CAD included in the ACUTY trial showed that 78% underwent PCI while the remaining patients were treated surgically [176]. There were no differences in mortality at 1 month and 1 year between the two modalities. PCI treated patients experienced lower rates of stroke, MI, major bleeds and renal injury, but had significantly higher rates of unplanned revascularization than CABG during the periprocedural period and at 1 year [177–179].

While the majority of patients with single-vessel CAD should undergo ad hoc PCI of the culprit lesion, the revascularization strategy in an individual NSTEMI-ACS patient with multivessel CAD should be discussed in the context of a Heart Team and be based on the clinical status as well as the severity and distribution of the CAD and the lesion characteristics. The SYNTAX score was found to be useful in the prediction of death, MI and revascularization among NSTEMI-ACS patients undergoing PCI and may help guide the choice between revascularization strategies [180].

14. Long-term management post-stabilization

Cardiac rehabilitation is a structured program that provides heart attack survivors with the tools, motivation, and support needed to change behavior and increase chance of survival. Typically, cardiac rehabilitation programs use group therapy to supervise and promote beneficial exercise, as well as to provide emotional support. The aims of cardiac rehabilitation are to:

- Increase functional capacity
- Stop cigarette smoking
- Modify lipids and lipoproteins
- Decrease body weight and fat stores
- Reduce BP
- Improve psychosocial well-being
- Prevent progression and promote plaque stability
- Restore and maintain optimal physical, psychological, emotional, social, and vocational functioning.

Cardiac rehabilitation should be started on discharge and after clearance by an outpatient physician. The basic prescription should include aerobic and weight-bearing exercise 4–5 times per week for >30 min.

15. Pharmacologic strategies include the following

- Aspirin should be continued indefinitely at a low dose if the patient is tolerant and not contraindicated.

- A P2Y₁₂ receptor inhibitor should be continued for up to 12 months. For patients with aspirin allergy, long-term P2Y₁₂ receptor inhibitor use is suggested [1, 181].
- Oral beta-blockers should be continued indefinitely, especially in patients with reduced left ventricular function.
- All patients with NSTEMI should start high-intensity statin therapy (moderate-intensity if not a candidate for high-intensity statin) in hospital regardless of cholesterol levels, and if there are no contraindications [182]. Two trials demonstrated superior outcomes in patients treated with atorvastatin within 12 h of receiving PCI, and it may provide benefit when given early in NSTEMI [183, 184]. A high-intensity statin is defined as a daily dose that lowers LDL-C by approximately >50%, while a moderate-intensity statin daily dose lowers LDL-C by approximately 30–50%. Statin therapy is particularly important in patients who have hyperlipidemia, diabetes, prior MI, or CAD. Statins inhibit the rate-limiting step in cholesterol synthesis. They may also reduce vascular inflammation, improve endothelial function, and decrease thrombus formation in addition to lowering LDL [185]. The addition of ezetimibe to the statin regimen may also be considered to achieve lower LDL targets [186].
- ACE inhibitors should be started in all patients with left ventricular systolic dysfunction (ejection fraction <40%), heart failure, HTN, diabetes, stable chronic kidney disease [1, 15]. They are started after 24 h. The goal BP is at least <140/90 mmHg (including patients with CKD or diabetes) [187].
- Aldosterone antagonists should be used in all patients with left ventricular dysfunction (ejection fraction ≤40%), a history of diabetes mellitus, or evidence of congestive heart failure. Aldosterone blockade should not be used in patients with serum creatinine >2.5 mg/dL in men or > 2.0 mg/dL in women, as well as in patients with hyperkalemia (potassium >5.0 mEq/L) [188].

16. Prognosis

Patients who have experienced NSTEMI have a high risk of morbidity and death from a future event. The rate of sudden death in patients who have had an MI is 4–6 times the rate in the general population [189]. Life-threatening ventricular arrhythmias (sustained VT or VF) occurring after 48 h from the index acute coronary syndrome portend a poor prognosis, and are most frequently associated with left ventricular dysfunction. The benefit of implantable cardioverter-defibrillators, for both primary and secondary prevention, in patients with significant left ventricular dysfunction has been well demonstrated [190, 191]. Implantation for primary prevention should be considered at a minimum of 40 days following hospital discharge based on current recommendations [192].

Data from the era prior to medical therapy and revascularization suggest that the risk of cardiovascular death following an MI in the absence of treatment is approximately 5% per year, with a death rate after hospital discharge in the first year of about 10%. Pharmacotherapy, lifestyle changes, and cardiac rehabilitation are well demonstrated to be beneficial and together are additive in reducing mortality [193].

17. Monitoring

Patient monitoring after discharge is essential part of patient care. A follow-up should be arranged within the first 1 to 2 weeks of discharge and monthly visits should be scheduled thereafter. Lipids should be monitored at least every 6 months until a target LDL <70 mg/dL is reached in patients who have had an MI or have CAD. The need for follow-up cardiac ultrasounds is at the discretion of the physician. However, cardiac ultrasounds are necessary to evaluate and monitor ventricular function [1].

Smoking cessation, promotion of physical activity and joining the cardiac rehabilitation is extremely helpful. Psychosocial risk factors such as anxiety and depression should be addressed. Depression in particular has been associated with a poor prognosis [194]. All medications should be reviewed at every follow-up visit to encourage patient compliance and optimal dosing [1].

In patients who have undergone direct reperfusion, further noninvasive stress testing or further imaging is indicated only if stenosis of intermediate severity (luminal narrowing of 50–70%) is present in a non-culprit artery. Patients with recurrent ischemic-type pain after reperfusion may need angiography after medical therapy to evaluate for further stenosis or occlusion [195].

All patients, regardless of whether a stent was placed, should be treated with a P2Y₁₂ receptor inhibitor for up to 12 months and low-dose aspirin daily as long as tolerated. This should be given for 1 month after bare-metal stent implantation, 3 months after sirolimus drug-eluting stent implantation, 6 months after paclitaxel drug-eluting stent implantation, and ideally up to 12 months if they are not at high risk for bleeding [195]. A scientific advisory from several major health organizations describes the risks of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents [196].

18. Management of patients with cardiogenic shock

Cardiogenic shock may develop in up to 3% of NSTEMI-ACS patients during hospitalization and has become the most frequent cause of in-hospital mortality in this setting [197–199]. One or more partial or complete vessel occlusions may result in severe heart failure, especially in cases of pre-existing LV dysfunction, reduced cardiac output and ineffective peripheral organ perfusion. More than two-thirds of patients have three-vessel CAD. Cardiogenic shock may also be related to mechanical complications of NSTEMI, including mitral regurgitation related to papillary muscle dysfunction or rupture and ventricular septal or free wall rupture. In patients with cardiogenic shock, immediate coronary angiography is indicated and PCI is the most frequently used revascularization modality. If the coronary anatomy is not suitable for PCI, patients should undergo emergent CABG. The value of intra-aortic balloon counter pulsation in MI complicated by cardiogenic shock has been challenged [200]. Extracorporeal membrane oxygenation and/or implantable LV assist devices may be considered in selected patients.

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