Clinical outcome of patients with Acute Coronary Syndrome (ACS) admitted at coronary care unit (CCU) at Benha University Hospital: Gender specific differences

thesis
Submitted for fulfillment of M. D. degree in cardiovascular medicine

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إن آمل إلا الإصلاح حسباً لما توفيقه إلا بالله عليه تولت وعليه أنيب

صدق الله العظيم

سورة م١٨ الآية (88)
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<td>Two dimensional</td>
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<td>3D</td>
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<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
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<td>ACE</td>
<td>Angiotensin converting Enzyme</td>
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<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
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<td>ADP</td>
<td>Adenosine Di Phosphate</td>
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<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<tr>
<td>ANGPTL2</td>
<td>Angiopoietin-related protein 2</td>
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<tr>
<td>APTT</td>
<td>Activated Partial Thromboplastine Time</td>
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<tr>
<td>ATP</td>
<td>Adenosine Tri-Phosphate</td>
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<td>ARBSs</td>
<td>Angiotensin Receptor Blockers</td>
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<td>BMS</td>
<td>Bare Metal Stent</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CCBs</td>
<td>Calcium Channel Blockers</td>
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<tr>
<td>CCU</td>
<td>Coronary Care Unit</td>
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<td>CFR</td>
<td>Coronary Flow Reserve</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CVD</td>
<td>Cardio Vascular Disease</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<tr>
<td>CAG</td>
<td>Coronary Angiography</td>
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<td>CK</td>
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<td>CMVD</td>
<td>Coronary Micro Vascular Disease</td>
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<td>CVS</td>
<td>Coronary Vaso Spasm</td>
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<td>CRP</td>
<td>C-Reactive Protein</td>
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<td>CYP2C19</td>
<td>CYtochrome P 2C19</td>
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<td>DAPT</td>
<td>Dual Anti-Platelets Therapy</td>
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<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<tr>
<td>DES</td>
<td>Drug Eluting Stent</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<td>DNAm</td>
<td>Deoxyribonucleic acid methylated</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EDV</td>
<td>End diastolic volume</td>
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<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
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<td>EMS</td>
<td>Emergency Service</td>
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<tr>
<td>ESV</td>
<td>End systolic volume</td>
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<tr>
<td>ER</td>
<td>Emergency Room</td>
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<td>FFR</td>
<td>Fractional Flow Reserve</td>
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<td>FH</td>
<td>Familial Hypercholesterolemia</td>
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<td>GCS</td>
<td>Global circumferential strain</td>
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<td>GLPSS</td>
<td>Global longitudinal Peak Systolic strain</td>
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<td>GP IIb/IIIa</td>
<td>Glyco Protein IIb/IIIA</td>
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<td>HDL-C</td>
<td>High Denisty Lipoprotein - Cholesterol</td>
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<tr>
<td>HFpEF</td>
<td>Heart Failure with preserved Ejection Fraction</td>
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<td>HIT</td>
<td>Heparine Induced Thrombocytopenia</td>
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<tr>
<td>HRT</td>
<td>Hormone Replacement Therapy</td>
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<td>HTN</td>
<td>HyperTensioN</td>
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<tr>
<td>LAD</td>
<td>Left Anterior Descending artery</td>
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<td>LDL-C</td>
<td>Low Denisty Lipoprotein – Cholesterol</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>MACEs</td>
<td>Major adverse cardiac events</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>MR</td>
<td>Mitral Regurgitation</td>
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<td>NSTE-ACS</td>
<td>Non ST segment Elevation -Acute Coronary Syndrome</td>
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<td>NSTEMI</td>
<td>Non ST segment Elevation Myocardial Infarction</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>PCSK9</td>
<td>Proprotein convertase subtilisin/kexin type 9</td>
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<tr>
<td>PF4</td>
<td>Platelet Factor 4</td>
</tr>
<tr>
<td>PPCI</td>
<td>Primary percutaneous coronary intervention</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
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<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
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<td>REM</td>
<td>Remodeling</td>
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<td>RIC</td>
<td>Remote Ischemic Conditioning</td>
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<td>RV</td>
<td>Right ventricle</td>
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<td><strong>RWMA</strong></td>
<td>Regional Wall Motion Abnormality</td>
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<td><strong>SBP</strong></td>
<td>Systolic Blood Pressure</td>
</tr>
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<td><strong>SCAD</strong></td>
<td>Spontaneous Coronary Artery Dissection</td>
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<tr>
<td><strong>STE</strong></td>
<td>Speckle tracking echocardiography</td>
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<tr>
<td><strong>STEMI</strong></td>
<td>ST segment elevation myocardial infarction</td>
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<td><strong>TAPT</strong></td>
<td>Tripple Anti Platelets Therapy</td>
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<td><strong>TIMI</strong></td>
<td>Thrombolysis In Myocardial Infarction</td>
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<tr>
<td><strong>UA</strong></td>
<td>Unstable Angina</td>
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<td><strong>UFH</strong></td>
<td>Un Fractionated Heparine</td>
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<td><strong>WMSI</strong></td>
<td>Wall motion score index</td>
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Cardiovascular disease is the leading cause of death in both men and women, accounting for one-third of all deaths. (Rosamond, et al., 2007).

Acute coronary syndrome (ACS), characterized by acute change in plaque with sudden impairment of coronary blood flow, is associated with the higher rates of adverse clinical events across the entire spectrum of coronary artery disease (CAD). (Fuster, et al., 2005).

Previous study had demonstrated that women with CAD have a higher mortality rate and undergo fewer therapies recommended by international guidelines than men, and that women with CAD undergoing percutaneous coronary intervention (PCI) are generally older and more often affected by multiple comorbidities than men. (Ahmed and, Dauerman, 2013).

Even after adequate statistical adjustment for confounding and modifying factors, results have been inconsistent with regard to whether female sex is a risk factor for unfavorable outcomes following PCI. (Singh, et al. 2008), (Wada, et al. 2017).

Although several studies have shown an improvement of prognosis in women over time, overall outcomes remain worse for women compared with men, (Vaccarino, et al., 1995), providing a strong rationale for focusing on the study of sex-based differences in the outcome of acute coronary syndromes (ACS).
Aim of the work

To evaluate the clinical outcome of patients with acute coronary syndrome (ACS), regarding gender specific differences.
Concept and Definition

Acute Coronary Syndrome (ACS) is the clinical spectrum of unstable ischemic heart disease, in which myocardial ischemia/necrosis is caused by rapid narrowing/obstruction of coronary artery as a consequence of atheromatous plaque disruption and thrombogenesis. (*Fuster, et al. 1992*).

In early stage atherosclerosis, intima thickening occurs, due to infiltration and accumulation of macrophages and lipids. During atherosclerotic plaque formation, the vessel wall may expand and preserve the vessel lumen (positive remodeling). As the plaque progresses, the lumen becomes narrowed and effort angina may develop. Inflammation plays an important role in the development and progression of atherosclerosis. In some lesions, accumulated lipid components may develop a necrotic core that is rich in inflammatory cells and cholesterol crystal.

Fibroatheroma has necrotic core and, if its fibrous cap becomes thin, is prone to rupture (vulnerable plaque). It is generally believed that rupture of vulnerable plaque followed by thrombogenesis is the leading cause of ACS. (*Virmani, et al. 2000*).

On the other hand, pathological studies have revealed that some patients have intracoronary thrombus without plaque rupture. It is recognized that erosion is one of the mechanisms that leads to thrombus without rupture, and, although not so frequent, calcified nodules are another. ACS may develop from less severe stenotic lesions that don’t cause effort angina. (*Little, et al. 1988*). It should be emphasized that unstable angina (UA), Acute Myocardial Infarction (AMI), and sudden cardiac death (SCD), caused by myocardial ischemia are cardiac events
caused by thrombogenesis that are distinct from plaque progression in effort angina, and are addressed together as ACS.

AMI is subdivided into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), because of the difference in initial stratification of diagnosis and treatment (Figure 1). UA and AMI are clinically differentiated by elevation of cardiac biomarkers. However, it is often difficult to distinguish between UA and NSTEMI at presentation.

**Figure (1).** Diagnostic flow of ACS. ECG, electrocardiogram; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
During initial evaluation, are managed together as NSTE-ACS. STEMI is ACS with persistent ST-segment elevation or new left bundle-branch block. Electrocardiographic ST-segment elevation on electrocardiogram (ECG). generally reflects transmural ischemia caused by acute thrombotic occlusion of a coronary artery (figure 2). Necrosis occurs first in the subendocardial myocardium and then, with longer durations of coronary occlusion, involves progressively more of the transmural ischemic zone myocardium. (Reimer, et al. 1977).

Reperfusion therapy salvages ischemic myocardium by restoring coronary blood flow. (Chazov, et al. 1976) reported 5 cases of STEMI who underwent reperfusion therapy with intracoronary nitroglycerin and streptokinase infusion in 1979. Since then, several studies have demonstrated significant reduction in mortality with intravenous streptokinase in the late 1980. (ISIS-2.1988).
Figures (2). Diagrammatic representation of ACS types

In recent years, percutaneous coronary intervention (PCI) with coronary stent implantation has become widely applied and the prognosis of STEMI has dramatically improved.

Because prompt restoration of coronary blood flow is essential to maximize benefits of reperfusion therapy, a strategy to minimize time from onset to reperfusion is of primary importance for patients with STEMI.

Patients with NSTE-ACS have persistent or transient ST-segment depression, T-wave abnormalities or no electrocardiographic changes at presentation. Because patients with NSTE-ACS generally have residual blood flow through a non-obstructive coronary lesion or sufficient
collaterals, the management strategy for NSTE-ACS should be clearly distinguished from STEMI. The spectrum of NSTE-ACS is wide and variable, from patients without elevation of cardiac biomarkers to those with hemodynamic collapse due to left main trunk disease. (figure 3).

Figure (3): diagrammatic representation of ECG for patient with NSTEMI

During initial evaluation, prompt diagnosis and risk stratification should be appropriately provided to select the treatment strategy. Because it is often difficult to distinguish between UA and NSTEMI at presentation, they are managed together as NSTE-ACS. By the time of hospital discharge, the final diagnosis is given according to elevation of cardiac biomarkers.(Braunwald, et al. 2000).

In the past, elevation of CK/CK-MB was used for clinical diagnosis of MI. In 2000, the ESC and ACC proposed a new definition of MI, a universal definition, in which cardiac troponin was adopted as the preferred cardiac biomarker. (Alpert, et al. 2000). Because cardiac troponin has higher sensitivity and specificity over CK/CK-MB,
numerous patients who were formerly diagnosed as unstable angina by CK/CK-MB criteria are now diagnosed as NSTEMI.

**Definitions of myocardial infarction (figure 4,5,6,7,8):**

*Criteria for acute, evolving or recent MI*
Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a. ischemic symptoms;
   b. development of pathologic Q waves on the ECG;
   c. ECG changes indicative of ischemia (ST segment elevation or depression); or
   d. coronary artery intervention (e.g., coronary angioplasty).
2. Pathologic findings of an acute MI.

*Criteria for established MI*
Any one of the following criteria satisfies the diagnosis of established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathologic findings of a healed or healing MI.

*Figure (4):* definition of myocardial infarction (*Alpert, J., et al.2000*)
Criteria for acute myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
  - Symptoms of ischaemia;
  - ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (LBBB)];
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than $3 \times 99$th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized.
- For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than $5 \times 99$th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.
- Pathological findings of an acute myocardial infarction.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a healed or healing myocardial infarction.

Figure (5): definition of myocardial infarction (*Thygesen, et al., 2007*)
Review of literature

Criteria for acute myocardial infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia.

Under these conditions any one of the following criteria met the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin (cTn)) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischaemia.
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.

- Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia or (ii) new ischaemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI 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.

Criteria for prior myocardial infarction

Any one of the following criteria met the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
- Pathological findings of a prior MI.

Figure (6): definition of myocardial infarction (Tehrani, et al, 2013)
**Fourth universal definition of myocardial infarction**

<table>
<thead>
<tr>
<th>Criteria for myocardial injury</th>
<th>Criteria for acute myocardial infarction (types 1, 2 and 3 MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.</td>
<td>The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:</td>
</tr>
<tr>
<td>· Symptoms of myocardial ischaemia;</td>
<td>· New ischaemic ECG changes;</td>
</tr>
<tr>
<td>· New ischaemic ECG changes;</td>
<td>· Development of pathological Q waves;</td>
</tr>
<tr>
<td>· Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;</td>
<td>· Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MI).</td>
</tr>
</tbody>
</table>

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

<table>
<thead>
<tr>
<th>Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous coronary intervention (PCI) related MI is termed type 4a MI.</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (CABG) related MI is termed type 5 MI.</td>
</tr>
<tr>
<td>Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values &gt; 5 times for type 4a MI or &gt; 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or failing, must meet the criteria for a &gt; 5 or &gt; 10 fold increase and manifest a change from the baseline value of &gt; 20%. In addition with at least one of the following:</td>
</tr>
<tr>
<td>· New ischaemic ECG changes (this criterion is related to type 4a MI only);</td>
</tr>
<tr>
<td>· Development of new pathological Q waves;</td>
</tr>
<tr>
<td>· Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;</td>
</tr>
<tr>
<td>· Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side branch occlusion/thrombus, disruption of collateral flow or distal embolization.</td>
</tr>
<tr>
<td>Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.</td>
</tr>
<tr>
<td>Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria.</td>
</tr>
<tr>
<td>Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria for prior or silent/ unrecognized myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one of the following criteria meets the diagnosis for prior or silent/ unrecognized MI:</td>
</tr>
<tr>
<td>· Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes;</td>
</tr>
<tr>
<td>· Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology;</td>
</tr>
<tr>
<td>· Patho-anatomical findings of a prior MI.</td>
</tr>
</tbody>
</table>

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**Figure (7):** definition of myocardial infarction *(Thygesen, et al. 2018)*

Needless to say, symptoms, ECG and imaging findings of myocardial ischemia are also required. Because cardiac troponin may be elevated in some other conditions, including aging, renal dysfunction and congestive heart failure, cardiac troponin should be measured serially to detect its rise and/or fall.
The term reinfarction is applied to AMI occurring within 28 days after the index episode of AMI (figure 8).

Figure (8): diagrammatic representation of ECG for patient with STEMI underwent reinfarction

If the AMI occurs after 28 days following the index episode, it is referred to as recurrent myocardial infarction. Although the universal definition classified myocardial infarction into 5 types, (Thygesen, et al. 1980), this guideline mainly deals with spontaneous myocardial infarction (type 1), which is caused by thrombogenesis related to atherosclerotic plaque rupture, erosion and so on, and refers to myocardial infarction secondary to an ischemic imbalance (type 2)..
**Epidemiology**

ACS refers to a spectrum of clinical presentations, including AMI, UA, and sudden cardiac death, and is often associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery. Here I will mainly describe AMI, for which abundant epidemiologic evidence is available.

The data demonstrated that the overall age-adjusted incidence of AMI (/100,000 persons/year). markedly increased by about 4-fold, from 7.4 in 1979 to 27.0 in 2008; the incidence of AMI for males (/100,000 persons/year). is 824 in Finland, 823 in United Kingdom, 605 in Canada, 508 in the United States, 314 in France, and 270 in Italy. *(Tunstall-Pedoe, et al. 1994).*

The incidence of AMI showed a male predominance, as demonstrated in the Takashima AMI registry (100.7 in males vs. 35.7 in females in 1999–2001). and the Niigata and Nagaoka study (41.9 in males vs. 5.3 in females in 1994–1996). Moreover, the 3-fold higher incidence of AMI in males remains largely unchanged throughout the last three decades. *(Takii, et al. 2010).*

Furthermore, it was reported that the mean age of onset of AMI was older in female patients than in male patients, with an age difference of 10 years, which is similar to results of overseas studies such as the Framingham Heart Study. *(Lerner, et al. 1986).*

This may be due to the cardiovascular protective effects of female hormones, namely oestrogens, which are evident before menopause but rapidly decrease thereafter. In Western countries, it was previously
The decline in the incidence of AMI may be attributed to the reduction in the prevalence of coronary risk factors and the increase in the prevalence of the pre-critical use of cardioprotective drugs, including angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), b-blockers, and statins. (Yeh, et al. 2010).

However, a report from the Miyagi AMI Registry Study demonstrated that, during the last 30 years in Japan, the age-adjusted incidence of AMI significantly increased in the first decade (1985–1994), but has remained unchanged in the last 2 decades (1995–2004 and 2005–2014). The same trend was noted for male patients, whereas age adjusted AMI incidence significantly decreased in female patients in the last decade (2005–2014). (Cui, et al. 2017).

Indeed, it was previously reported that the increased prevalence of dyslipidaemia in younger AMI patients related to dietary habits and westernized lifestyle was responsible, at least in part, for the increased incidence of AMI in this population. (Cui, et al. 2017) Additionally, smoking rates in young people are high, with a rate of ~50% in males and 30% in females. These results suggest that more strict control of coronary risk factors is needed in young populations to reduce the future occurrence of AMI.

The 30-day mortality from AMI in Japan was reported to be 7.1% in the OACIS Study33 and 9.4% in the HIJAMI Study. (Kasanuki, et al., 2005). In the J-MINUET Study, which is a registry of Japanese patients hospitalized for AMI diagnosed by the new universal definition, there
was no significant difference in hospital mortality between STEMI and NSTEMI with CK elevation (7.1% vs. 7.8%), whereas the mortality rate was significantly lower in NSTEMI without CK elevation (1.7%) than in STEMI or NSTEMI with CK elevation. (Ishihara, et al. 2015).

In Western countries, hospital mortality of AMI decreased between the 1980s and late 2000s, along with improvement in critical care for AMI (e.g., reperfusion therapy). (Schmidt, et al. 2012). The same trend in reduced hospital mortality of AMI was also noted in Asian countries, Taiwan and Korea, between the late 1990s and early 2000s. (Lee, et al. 2008).

Meanwhile, during the last 30 years in Japan, although in-hospital cardiac mortality of AMI progressively decreased during the 1st and 2nd decades (1985–1994 and 1995–2004), no further improvement was noted in the last decade (2005–2014), irrespective of sex. (Lee, et al. 2017). It is important to note that hospital mortality of AMI continues to be higher in female patients than in male patients today. (Cui, et al. 2017).

It is generally considered that the poorer outcome of female AMI patients could be caused by multiple factors, including higher age, longer time from onset to admission, poorer condition on admission such as coexisting heart failure, and lower rate of performing primary PCI. (Lee, et al. 2017).

A number of western studies have shown that patients with NSTEMI have a worse long-term prognosis compared with those with STEMI. In the GRACE registry, the 6-month post-discharge mortality rate was 3.6% and 6.2% in patients with STEMI and those with NSTEMI, respectively. (Goldberg, et al. 2004).
Similarly, the J-MINUET study recently reported that long-term outcome of NSTEMI patients was worse than STEMI patients, a consistent finding with Western countries. This could be explained by the fact that NSTEMI patients have more comorbid factors and more extensive CAD than STEMI patients. (*Ishihara, et al. 2017*).

Furthermore, a recent report from the French National Registry survey demonstrated that chronic-phase mortality has consistently declined in STEMI patients between 1995 and 2015, whereas chronic-phase mortality reached a plateau in NSTEMI patients after 2010. (*Puymirat, et al. 2017*).

**Risk Assessment at Initial Diagnosis**

When patients with chest pain arrive at a hospital, available information (e.g., age, current medical history, past medical history, physical findings, 12-lead ECG, laboratory findings) should be used to determine whether ACS is highly suspected or not. Patients are classified into 4 categories according to the probability of ACS: non-cardiac disease, chronic stable angina, possible ACS, and definite ACS.

When definite or probable ACS is diagnosed, it is important for prognostic improvement to stratify the short-term prognosis (cardiac death and non-fatal cardiac event) and promptly treat appropriately. While it is sometimes necessary to determine treatment protocol without waiting for cardiac enzyme results, which are essential for clinical diagnosis of myocardial infarction, it is important to assess the risk quickly based on available information and provide information on predictable prognosis to patients and their families.
1. Risk Assessment Based on Medical History and Physical Findings

Classification of UA accounting for severity, clinical presentation, and treatment status was proposed by Braunwald in 1989 (Table 1) (Tong, et al. 2005). There have been many reports that this classification is useful in predicting the short-term prognosis (Angioi, et al. 2005) and contributes to decision of treatment strategy (Chia, et al. 2008).

**Table 1. Classification of UA**

<table>
<thead>
<tr>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I: New-onset severe angina or angina with changing pattern</td>
</tr>
<tr>
<td>- Angina that occurred in the past 2 months</td>
</tr>
<tr>
<td>- At least 3 attacks of angina daily or angina on exertion with changing pattern defined as attacks caused by light exercise. No angina at rest is observed.</td>
</tr>
<tr>
<td>Class II: Subacute angina at rest</td>
</tr>
<tr>
<td>- At least 1 attack of angina at rest in the past month, but no attack in 48 hours</td>
</tr>
<tr>
<td>Class III: Acute angina at rest</td>
</tr>
<tr>
<td>- At least 1 attack of angina at rest in 48 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A: Secondary unstable angina (triggered by non-cardiac factors, including anemia, pyrexia, hypotension, and tachycardia)</td>
</tr>
<tr>
<td>Class B: Primary unstable angina (without non-cardiac factors as listed for Class A)</td>
</tr>
<tr>
<td>Class C: Post-infarction unstable angina (unstable angina within 2 weeks after the onset of myocardial infarction)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Untreated or undergoing minimal treatment for angina</td>
</tr>
<tr>
<td>2) Undergoing usual treatment for stable angina (usual doses of β-blockers, long-acting nitrates, or Ca antagonists)</td>
</tr>
<tr>
<td>3) Undergoing maximal treatment with antianginal medication, including intravenous nitroglycerin</td>
</tr>
</tbody>
</table>

Abbreviations: UA, unstable angina. (Source: Prepared based on Braunwald E. 1999[4])

In addition, the classification has been shown to correlate with the severity of coronary angiographic lesions (Mathew, et al. 2001) and complications of PCI. Class II (subacute), Class III (acute), Class B (primary UA), and Class C (post-infarction angina) are considered moderate to high risk. Braunwald et al. pointed out that angina at rest persisting for 20 minutes or more, pulmonary edema complicated by
ischemia, angina with third heart sounds or rales, and angina with hypotension had poor short-term prognosis.

The TIMI risk score, which is often used for risk assessment in patients with NSTE-ACS, is calculated from 7 factors: age (≥65 years); at least 3 coronary risk factors (family history, hypertension, hypercholesterolemia, diabetes mellitus, and smoking); known significant (≥50%). coronary stenosis; ST changes ≥0.5 mm on ECG; at least 2 episodes of angina in 24 hours; aspirin use in the past 7 days; and increased cardiac markers; therefore, most of these factors can be assessed immediately after transport of patients (Table 2). As the score increases, the incidence of major cardiovascular complications in the following 2 weeks increases synergistically. *(Sabatine, et al. 2004)*.

**Table 2.** TIMI Risk Score for Predicting the Prognosis of NSTE-ACS

<table>
<thead>
<tr>
<th>Factor (Age ≥65 years)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 CAD risk factors</td>
<td>No 0</td>
</tr>
<tr>
<td>Hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, or current smoker</td>
<td>Yes +1</td>
</tr>
<tr>
<td>Known CAD (stenosis ≥50%)</td>
<td>No 0</td>
</tr>
<tr>
<td>Aspirin use in past 7 days</td>
<td>Yes +1</td>
</tr>
<tr>
<td>≥2 episodes of angina in 24 hours</td>
<td>No 0</td>
</tr>
<tr>
<td>ST changes ≥0.5 mm on ECG</td>
<td>Yes +1</td>
</tr>
<tr>
<td>Positive cardiac marker</td>
<td>No 0</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; ECG, electrocardiogram. *(Source: Prepared based on Antman EM, et al. 2000)*

Since treatment strategy for NSTE-ACS differs depending on the risk, early risk assessment is more important. Factors influencing the prognosis of STEMI include age, Killip class, time to reperfusion, cardiac arrest, heart rate (tachycardia), systolic blood pressure (hypotension), infarction site (anterior), previous myocardial infarction, diabetes...
mellitus, smoking status, renal function, sex, and low body weight. (Mehilli, et al. 2002). Killip classification (Table 3) is convenient in assessment of the severity made primarily based on auscultatory findings and is useful for prediction of the prognosis. (Killip, et al. 1967).

Cardiogenic shock, classified as Killip Class IV, is the most common cause of in-hospital mortality, with a mortality rate as high as 40% to 70%. However, it has been shown that advances in treatment, primarily early reperfusion therapy, contribute to improvement in survival for patients with shock. (Jeger, et al. 2006).

Cardiogenic shock associated with myocardial infarction is generally defined as hypotension (<90 mmHg). persisting for at least 30 minutes with signs of peripheral circulatory failure despite adequate LV filling pressure. However, decreased tissue perfusion with blood pressure of 90 mmHg or higher is considered as pre-shock and treatment should be the same as for shock.

The GRACE ACS risk, which is used for overall risk assessment in patients with ACS, including STEMI and NSTE-ACS, is designed to calculate the probability of death and probability of death or myocardial infarction at admission and at 6 months by weighting 8 risk factors: age, heart rate, systolic blood pressure, initial serum creatinine, Killip class, hospitalization due to cardiac arrest, positive cardiac biomarker, and ST-segment deviation (Table 3).
Table 3. GRACE ACS Risk Model Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Heart rate (bpm)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>&lt;70</td>
</tr>
<tr>
<td>40-49</td>
<td>70-89</td>
</tr>
<tr>
<td>50-59</td>
<td>90-109</td>
</tr>
<tr>
<td>60-69</td>
<td>110-149</td>
</tr>
<tr>
<td>70-79</td>
<td>140-159</td>
</tr>
<tr>
<td>≥80</td>
<td>≥200</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>55</td>
<td>23</td>
</tr>
<tr>
<td>73</td>
<td>36</td>
</tr>
<tr>
<td>91</td>
<td>46</td>
</tr>
</tbody>
</table>


This model can be used to stratify the risk (low risk, moderate risk, or high risk) for STEMI and NSTEMI-ACS separately, and predict the hospital mortality and prognosis at 6 months after being discharged alive for each risk group. (*Eagle, et al. 2004*).

The TIMI risk score was the first risk score and has been validated most extensively. The score is easy to use in an ER, since all factors in
this risk score can be readily assessed based on medical history and examinations in ER.

However, it was reported that the prediction accuracy of this score was lower than that of the GRACE risk score. (Yan, et al. 2007). The GRACE risk score is relatively complex to calculate, (Abu-Assi, et al. 2010), but its clinical utility has been verified extensively.

The TIMI and GRACE risk scores, which can be calculated through websites on the Internet, are easy to use in emergency care.

2. Risk Assessment Based on ECG

The 12-lead ECG plays a central role in diagnostic and triage pathways for ACS and provides important prognostic information. The presence of Q waves on the presentation ECG was reported to reflect a more advanced stage of infarct evolution. This ECG marker has been reported to be associated with poor clinical outcomes in patients with STEMI treated with PCI as well as fibrinolysis. (Armstrong, et al. 2009).

QRS score is a quantitative index of myocardial damage calculated not only by the number of Q waves but also by increased Q wave width and decreased R wave amplitude and width. QRS score may be a more accurate indicator of the stages of infarct evolution than the mere presence or absence of Q waves. It has been shown that higher QRS score on the presentation ECG is associated with a larger infarct size, and higher long-term mortality in 2,607 patients with STEMI undergoing primary PCI. (Shiomi, et al. 2017).

In patients with anterior STEMI, the more proximal the occlusion, the more extensive the area at risk. ST-segment depression in inferior leads, ST-segment elevation in lead aVR, and complete right bundle
branch block have been shown to be suggestive of LAD occlusion proximal to the first septal branch. In particular, ST-segment depression in inferior leads is very useful, whereas ST-segment elevation in lead aVR and complete right bundle branch block are shown to have high specificities, but low sensitivities. *(Kosuge, et al. 2012).*

In patients with inferior STEMI, those with RV infarction have a poor prognosis. RV infarction during inferior STEMI can be accurately diagnosed by ST-segment elevation $\geq 1.0$ mm (0.1 mV) in the right precordial lead, especially lead V4R. *(Matetzky, et al. 1999).*

However, ST-segment elevation in right precordial leads has been reported to be short lived, disappearing within 10 hours after onset of symptoms in half of patients with inferior AMI and RV involvement. *(Matetzky, et al. 1999).*

ECG diagnosis is often difficult in patients with bundle branch block. Patients with right or left bundle branch block, especially the latter, have a worse clinical profile and poorer prognosis. and therefore, a clinical suspicion of AMI in the presence of bundle branch block is an indication for emergent CAG to perform timely reperfusion therapy. *(Ibanez, et al. 2018).*

In patients with NSTE-ACS, ST-segment depression $\geq 0.5$ mm (0.05 mV) is a strong predictor of poor outcomes. *(Kosuge, et al. 2009).* The degree, extent, and serial changes of ST-segment depression, not only its presence or absence, can facilitate early risk stratification in patients with NSTE-ACS. *(Kosuge, et al. 2009).* ST segment elevation in lead aVR with extensive ST-segment depression is highly suggestive of severe ischemia due to left main or multi-vessel disease. *(Kosuge, et al. 2009).*
In patients with NSTE-ACS, negative T waves are associated with a relatively benign prognosis as compared with ST-segment depression. *(Savonitto, et al. 1999)*. However, it is reported that patients with negative T waves in ≥6 leads have a poor prognosis. *(Damman, et al. 2012)*. In addition, negative T waves in precordial leads suggest severe ischemia of the LV anterior wall due to LAD disease. *(Kannan, et al. 2015)*.

QRS prolongation has been shown to be more sensitive than ST-segment changes for the detection of myocardial ischemia. A prolonged QRS duration is associated with severe ischemia in patients with ACS. *(Kosuge, et al. 2009)*.

### 3. Risk Assessment Based on Cardiac Biomarker

It has been reported that the short-term mortality rate of patients seen in an emergency department due to chest pain increased linearly from 1.0% to 7.5% according to the increment in cardiac troponin I despite lack of ST elevation on ECG and normal CK-MB, *(Newby, et al. 1998)*, and the increase in cardiac troponin T is the most useful factor for 30-day prognostic prediction in patients with ST-T change on ECG and increased serum CK-MB in addition to chest pain. *(Ohman, et al. 1996)*.

It has been reported that the measurement of highly sensitive cardiac troponins is useful in early diagnosis of not only STEMI, but also NSTEMI, with a higher level associated with a higher mortality rate. *(Giannitsis, et al. 2010)*. Blood C-reactive protein (CRP) is a marker that reflects acute inflammation, and it has been reported that the incidence of early cardiac events was 3 times higher in UA patients with a CRP level ≥0.3 mg/dL than in those with a CRP level <0.3 mg/dL. CRP attracted attention as a marker of unstable atheroma in coronary artery sclerosis, *(Liuzzo, et al. 1994)*. and increases in measures of acute
inflammatory reaction in UA were considered to indicate persistent instability or possible recurrence even in asymptomatic patients. *(Biasucci, et al. 1999).*

In the CANTOS study, which evaluated the efficacy of an anti-inflammatory IL-1β inhibitor in previous myocardial infarction patients with a highly sensitive CRP level of ≥2 mg/L, the mortality rates from myocardial infarction, stroke, and cardiovascular disease in the 4-year observation period decreased with decreases in CRP, again highlighting CRP as a useful biomarker. The 2014 ACC/AHA Guidelines for Management of NSTE-ACS stated that B-type natriuretic peptide (BNP) is a new biomarker that may provide prognostic information (Class IIb, level B). *(Amsterdam, et al. 2014).*

In addition, hyperglycemia is a strong predictor of mortality and heart failure in non-diabetic patients, *(Foo, et al. 2003).* and renal impairment affects the short- and long-term prognosis. *(Wison, et al. 2003).* Since serum creatinine, which is affected by age and sex, is a limited measure of renal function, creatinine clearance and estimated glomerular filtration rate (eGFR) are used.

For ACS, diagnosis, severity assessment, and prognostic prediction can be made based on medical history, brief medical examination, and other examinations, and it is important to collect medical history and obtain physical examination findings quickly and accurately. However, not a few patients with ACS have atypical or no symptoms. In a US study involving more than 430,000 patients with AMI, 33% had no chest pain at presentation, and the chest pain-free group had a higher proportion of elderly patients (74 years vs. 67 years), female patients (49% vs. 38%).
diabetic patients (33% vs. 25%), and patients with history of heart failure (26% vs. 12%) than the chest pain group.(Kosuge, et al. 2005).

AMI patients with no chest pain tend to have a longer time to hospital presentation and a delayed diagnosis. As a consequence, fewer patients receive appropriate treatment or reperfusion therapy, with a 2.21 times higher hospital mortality, requiring caution. Coronary care unit (CCU) care is essential for patients considered to be high risk at initial diagnosis, and moderate risk patients should be managed accordingly. Low-risk patients may be managed on an outpatient basis. Since assessment only at arrival may fail to detect all high-risk patients, treatment protocol should be determined through symptom monitoring, ECG, and assessment of cardiac markers over time, with change in treatment strategy considered if reassessment reveals increased risk.

**Initial Therapy**

1 *Oxygen*

While oxygen should be given when there are signs of hypoxemia, heart failure, or shock, routine oxygen administration is not recommended. Oxygen saturation should be monitored immediately upon hospital arrival to assess the need for oxygen.

2 *Nitrates*

Nitrates have the pharmacological action of dilating the venous system, arterial system, and coronary arteries. Dilation of peripheral veins reduces LV preload and volume, and dilation of peripheral arteries reduces blood pressure and afterload, which lowers myocardial oxygen consumption. These drugs are also widely used for dilation of coronary
and bypassed arteries, to improve blood flow to ischemic myocardium, and to prevent and reverse coronary vasospasm.

Many studies have found nitrates to be effective for pump failure and postinfarction angina in the acute stage of myocardial infarction. They have also become widely used due to their ability to shrink infarcted areas, prevent remodeling of the LV myocardium, and reduce mortality rates.

Several large clinical trials in Europe and the United States (ESPRIM, 215 GISSI-3, 216 ISIS-4) failed to confirm the ability of nitrates to reduce mortality and refuted their effectiveness. Therefore, while nitrates have been shown to improve prognosis by reducing blood pressure, caution must be exercised so that the use of other drugs with antihypertensive action (β-blockers, ACE inhibitors, etc.) is not hindered.

Patients with ischemic chest discomfort can be given nitroglycerin sublingually or via oral spray. If the symptoms do not markedly improve after administration of 1 nitroglycerin tablet, call an ambulance. Intravenous nitroglycerin is indicated for chest discomfort, to control hypertension and treat pulmonary congestion. Nitrates are indicated during the first 24 to 48 hours in patients experiencing repeated ischemic attacks.

However, administration should be avoided in patients with systolic blood pressure <90 mmHg, a decrease of ≥30 mmHg from normal blood pressure, severe bradycardia (<50/bpm), tachycardia (>100/bpm), or suspected acute inferior and RV infarction. Caution is warranted in elderly or dehydrated patients, as nitrates can excessively lower blood pressure. Nitrates are contraindicated within 24 hours after taking erectile dysfunction medication (Viagra, others), as excessively lowering
blood pressure can induce myocardial ischemia or shock. \textit{(Webb, et al. 2000)}.

\textbf{3 Analgesics}

Persistent chest pain can increase myocardial oxygen consumption, expand the infarct area, and induce arrhythmia. Therefore, prompt analgesia or sedation should be provided.

Regardless of whether nitrates were used, morphine hydrochloride can be effective for persistent pain. Further, because morphine hydrochloride is a vasodilator, it is effective for pulmonary congestion, but therefore should not be administered to patients who may have reduced circulating blood volume. If morphine causes blood pressure to decline, elevate the legs to provide fluid loading, but proceed with caution as this can exacerbate pulmonary congestion. Morphine hydrochloride 2–4 mg is given intravenously; if the effect is insufficient, an additional 2–8 mg can be given every 5–15 minutes.

However, monitor the respiratory status, fluctuations in blood pressure, and side effects such as vomiting. Use with caution, particularly in inferior AMI, as vagotonia tends to reduce blood pressure in association with vomiting. Intravenous administration of buprenorphine (0.1–0.2 mg) is effective for chest symptoms and diazepam (2.5–5.0 mg) for sedation, but be cautious of respiratory depression.
4 Antithrombotic Therapy

Antiplatelet Agents

Many trials have shown aspirin to be useful for improving the prognosis of AMI. The large ISIS-2 trial found that aspirin alone reduced vascular-related mortality by 23±4%, compared to that when combined with thrombolytic therapy.

Administration after the acute stage has also been shown to reduce vascular-related mortality. Studies have shown that the sooner aspirin is administered, the greater the improvement in mortality rate. (Yasue, et al. 1999). Therefore, except in patients with severe blood disorders, aspirin-induced asthma, or hypersensitivity to aspirin, aspirin should be given as soon as possible. Even outside hospital, patients can chew 162–200 mg of aspirin to obtain a rapid effect. Aspirin should not be used in patients known to be hyper-sensitive, and caution is needed in patients with blood diseases or severe liver disorders.

Further, while bleeding tendency associated with increased hemorrhagic complications of cardiovascular surgery has been reported, an increase in the reoperation rate was not observed. (Chesebro, et al. 1982).

Patients with a history of upper gastrointestinal bleeding who take low-dose aspirin have been found to have higher rates of gastrointestinal complications, including peptic ulcer and bleeding. (Chan, et al. 2001).

Helicobacter pylori eradication or proton pump inhibitor (PPI). administration is effective for preventing recurrence, though guidelines state that bacterial eradication combined with PPI is more effective than eradication alone.
Administering clopidogrel to STEMI patients who have undergone PCI has been shown to reduce cardiovascular mortality, nonfatal myocardial infarctions, and total mortality, with only a small increase in major bleeding. (Lev, et al. 2008).

In combination with aspirin, loading STEMI patients with 300 mg of clopidogrel prior to PCI, then starting 75 mg/day the next day, has been shown to reduce the risk of cardiovascular events. Clopidogrel has also been shown to be effective in patients who have undergone fibrinolytic therapy and patients who have not undergone reperfusion therapy.

Administration of clopidogrel to NSTEMI patients was found to reduce the risk of vascular-related events (cardiovascular death, myocardial infarction, and stroke), compared to that in a control group that received a placebo (Yusuf, et al. 2001).

Aspirin (81–162 mg/day). has been shown to reduce the rates of short- and long-term cardiovascular events. In primary PCI for STEMI, DAPT with 300 mg loading and 75 mg maintenance dose of clopidogrel on top of aspirin reduced cardiovascular event risk. (Sabatine, et al. 2005). In the COMMIT trial, DAPT with aspirin plus clopidogrel reduced the cardiovascular composite endpoint of short term mortality, MI, and stroke without increasing bleeding risk. (Chen, et al. 2005).

Prasugrel achieves a faster and more consistent degree of P2Y12 inhibition compared to clopidogrel. In PRASFITACS, a Japanese clinical trial comparing prasugrel vs. clopidogrel, 20 mg loading/3.75 mg maintenance dose of prasugrel plus aspirin was associated with a numerically lower rate of cardiovascular events as compared with 300 mg loading/3.75 mg maintenance dose of clopidogrel plus aspirin in ACS patients receiving PCI. (Saito, et al. 2014). In the TRITON trial,
(Wiviott, et al. 2007). which adopted 60 mg loading and 10 mg maintenance doses of prasugrel, prasugrel was associated with an increased risk of bleeding.

In NSTEMI patients in whom coronary anatomy is not known, use of prasugrel is not recommended. In Japan, ticagrelor is approved for patients for whom DAPT is indicated but other P2Y12 inhibitors are not suitable. The PLATO trial compared ticagrelor plus aspirin vs. clopidogrel plus aspirin in patients with STEMI/NSTEMI. DAPT with ticagrelor plus aspirin was associated with reduced risk of cardiovascular events, all-cause mortality, and stent thrombosis, with similar risk of major bleeding as compared with DAPT with clopidogrel plus aspirin.(Wallentin, et al. 2009).

**SELATOGREL**
Formerly known as ACT-246475, is a novel, potent, reversible and selective non-thienopyridine antagonist of the P2Y12 receptor developed for subcutaneous administration. Results from preclinical, phase 1,2 studies have shown selatogrel to have rapid absorption and sustained and reversible P2Y12 inhibitory effects with a larger therapeutic window compared to the oral P2Y12 inhibitors. (Milluzzo, et al. 2020).

In ACS patients with atrial fibrillation, anticoagulation plus DAPT (triple therapy: TAPT) is often administered. However, TAPT is associated with a significantly higher risk of bleeding. In recent clinical trials including WOEST, PIONEER AF-PCI, and REDUAL (PCI, dual antithrombotic therapy with anticoagulation plus clopidogrel was associated with significantly reduced bleeding events while not increasing thrombotic events. (Cannon, et al. 2017).
These clinical trials suggest TAPT could be worse than the dual antithrombotic regimen using an anticoagulant agent plus clopidogrel.

In patients on anticoagulation, dual antithrombotic regimen with an oral anticoagulant and clopidogrel (without aspirin) after PCI should be considered at discharge. Since there are no data to support optimal duration/dosing of antithrombotic agents regarding TAPT, clinicians should evaluate thrombotic and bleeding risk in each patient to individualize the medication.

Antithrombotic Therapy in Primary PCI

1 Antiplatelet Therapy

a. Aspirin, Thienopyridine Antiplatelet Drugs

Stents are usually implanted in primary PCI. Appropriate administration of antiplatelet drugs is important for preventing stent thrombosis. The release of adenosine diphosphate (ADP) from platelets in response to stimuli from the surrounding environment plays an important role in thrombogenesis. ADP released from platelets causes platelet aggregation through binding to the P2Y12 ADP receptor on the cell membrane of platelets. Prasugrel and clopidogrel are called thienopyridine antiplatelet drugs and inhibit the binding of ADP to the P2Y12 ADP receptor, thereby suppressing platelet aggregation and thrombogenesis. The start of the administration of a thienopyridine antiplatelet agent in combination with aspirin (DAPT), before stent implantation for the prevention of stent thrombosis has been proven to suppress the occurrence of stent thrombosis and has become standard care after stent implantation. Aspirin suppresses platelet aggregation through
blockage of the production of thromboxane A2 by inhibiting cyclooxygenase.

Antiplatelet drugs should be adequately acting at the time of stent implantation. This is because stent thrombosis following stent implantation is likely to develop within 24 hours after the procedure. The research on the current status of PCI in patients with AMI in Japan revealed that stent thrombosis mostly developed within 10 days, especially within 1 day, after stent implantation. (Nakamura, et al. 2013). Emergent PCI in patients with ACS must often be performed before antiplatelet drugs adequately exert their effects. The pathological condition of ACS in which thrombi are present at the lesion also increases the risk of stent thrombosis. In order to reduce the risk of stent thrombosis, the loading doses of aspirin and ADP P2Y12 receptor antagonists should be administered in preparation for coronary revascularization with PCI when the conduct of emergency catheterization is decided upon.

For facilitating aspirin absorption, it is recommended that patients chew aspirin at a dose of 162 to 325 mg. In the past, ticlopidine at a dose of approximately 200 mg/day was administered. The use of ticlopidine was, however, reportedly associated with, though infrequently, side effects, such as leukopenia, severe liver dysfunction, or thrombotic thrombocytopenic purpura.

Clopidogrel is widely used at present. The administration of clopidogrel at a loading dose of 300 mg before PCI promptly exerts its effects and is highly effective in preventing stent thrombosis. Following stent implantation, it is recommended to administer clopidogrel 75 mg/day and concomitant aspirin orally. Administration of these drugs is
recommended for 1 month in cases of bare metal stents and for at least 6 months to 1 year in cases of drug-eluting stents.\textit{(Sabatine, et al. 2005)}.

Prasugrel is a third generation thienopyridine antiplatelet drug. Compared with clopidogrel, prasugrel has a simple metabolic pathway, exerts its effects promptly, and is less affected by CYP2C19 polymorphism and there is hence little difference in efficacy between individuals.

In the TRITON-TIMI 38 trial, a large clinical trial conducted in the United States and Europe to obtain approvals, there were fewer thrombotic events in the prasugrel group than in the clopidogrel group. In the United States and Europe, a loading dose of 60 mg and a maintenance dose of 10 mg are approved for prasugrel.

In patients who underwent primary PCI, cilostazol, an antiplatelet drug that inhibits phosphodiesterase III, was as effective as ticlopidine.\textit{(Ochiai, et al. 1999)} However, conversely, it was associated with frequent stent thrombosis when compared with ticlopidine after stent implantation.\textit{(Takeyasu, et al. 2005)}.

\textbf{b. Other Antiplatelet Drugs}

One of the antiplatelet drugs that could be used is platelet membrane glycoprotein IIb/IIIa inhibitor, because it failed to demonstrate efficacy. It is a potent platelet aggregation inhibitor, which inhibits the binding of fibrinogen and thereby inhibits platelet aggregation. In countries other than Japan, a large clinical study demonstrated that platelet membrane glycoprotein IIb/IIIa inhibitor was effective in stabilizing angina pectoris in the short term and improving the early outcomes of revascularization in patients with unstable angina on aspirin and heparin.
CANGRELOR

Cangrelor is an intravenous, fast-acting, potent and direct acting platelet adenosine diphosphate (ADP) P2Y12 inhibitor that has rapidly reversible effects. When a bolus of cangrelor is administered, the antiplatelet effect is immediate, and the effect can be maintained with a continuous infusion. The plasma half-life of cangrelor is approximately 3 to 5 minutes, and platelet function is restored within 1 hour after cessation of infusion. (Breet., et al. 2011).

c. Duration of DAPT

First generation DESs had a problem that the DESs were associated with a higher rate of stent thrombosis beyond 1 year after implantation compared with BMSs and therefore required prolonged DAPT. The development of second generation and third generation DESs since 2009 has decreased the incidence of stent thrombosis and has shortened the duration of DAPT. There is no definite conclusion on the duration of DAPT to prevent stent thrombosis. It is a matter of a trade-off between thrombosis prophylaxis and hemorrhagic complications, because prolonged DAPT would increase the incidence of hemorrhagic complications. (figure 9)
Patients with atrial fibrillation who are on oral anticoagulants need to continue to take anticoagulants even after they suffered from ACS. There is a concern about bleeding risk when patients who require long-term oral anticoagulation therapy, such as warfarin therapy, start to receive antiplatelet therapy additionally in preparation for PCI. With regard to this concern, the WOEST study was conducted. It showed that the risks of bleeding as well as all-cause mortality and cardiovascular events were lower in the group receiving anticoagulants plus clopidogrel only than in the group receiving anticoagulants plus the dual antiplatelets of aspirin and clopidogrel.

On the other hand, there was no difference in the risk of stent thrombosis between the groups. No optimal antithrombotic therapy has been established in patients on oral anticoagulants after PCI. It is, however, desirable to reduce the duration of concomitant administration

**Figure (9):** clinical scores for dual antiplatelets therapy (DAPT) duration.
of 3 antithrombotic agents consisting of warfarin, aspirin, and clopidogrel as much as possible.

2. Anticoagulant Therapy

a. Unfractionated Heparin

There is established evidence from the pre-reperfusion era that unfractionated heparin (UFH) is effective in treatment of patients with ACS. Now, PCI is usually performed in the acute phase and UFH is generally used during PCI. Recommend a bolus injection of intravenous UFH at a dose of 70 to 100 units/kg and maintenance of activated coagulation time (ACT) at 250 seconds or longer. (O’Gara, et al. 2013). A small study involving patients with ACS confirmed no efficacy of treatment with heparin alone, and concomitant administration of aspirin and heparin is therefore recommended. The anticoagulation effect of heparin differs largely between individuals. ACT or activated partial thromboplastin time (APTT) should therefore be monitored.

Sudden discontinuation of heparin may activate thrombin and thereby cause thrombogenicity. (Granger, et al. 1995). Tapering is recommended before discontinuation of heparin therapy. Heparin-induced thrombocytopenia (HIT) develops at a rate of approximately 3%. Patients with a platelet count of less than 100,000 should be treated with caution. HIT is classified into type I and type II. Type I HIT is caused by a non-immune mechanism. In Type II HIT, heparin-dependent antibodies are produced. Type I HIT causes a transient thrombocytopenia (a decrease by 10 to 20%), attributed to the physical and biological characteristics of heparin itself, which occurs within the first few days of heparin administration and resolves even if heparin therapy is continued. In Type II HIT, a fall in platelet count to less than
50% of baseline level occurs after 5 to 14 days of commencement of heparin due mainly to the production of anti-PF4/heparin complex antibodies (HIT antibodies).(figure 10)

Type II HIT may be complicated by serious arteriovenous thrombosis. Treatment with heparin needs to be promptly switched to anticoagulation therapy with argatroban. It is reported that low molecular weight heparin, compared with unfractionated heparin, is similarly or more effective in increasing reperfusion rate and decreasing the rates of reinfarction and mortality (Eikelboom, et al. 2005). and does not increase the risk of hemorrhagic complications in patients with STEMI. (Silvain, et al. 2012), the use of low molecular weight heparin is not approved for PCI in patients with STEMI.

![Diagram](image.png)

**Figure (10).**: diagrammatic representation of heparin induced thrombocytopenia (HIT).

Newer anticoagulants such as direct thrombin inhibitors, are being used as an alternative to unfractionated heparin. They directly bind to active sites of thrombin, providing more predictable pharmacokinetic profile.
and a greater reduction in thrombin compared with unfractionated heparine. Direct thrombin inhibitors are short acting which allow for rapid titration to achieve desired anticoagulation. Heparine induced thrombocytopenia and other immune mediated thrombocytopenias are not seen with direct thrombin inhibitors. (Lee, et al. 2011).

**B. low molecular weight heparine (LMWH):**

The Efficacy and Safety of subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial (Blazing, et al. 2004) randomly assigned 3171 patients with angina at rest or NSTEMI either LMWH (Enoxaparin, 1 mg/kg SQ twice daily) or IV UFH (target aPTT 55–85 seconds). Therapy was continued for a minimum of 48 hours (maximum 8 days). All patients received aspirin (100–325 mg daily). The median duration of therapy for both groups was 2.6 days. At 14 days, the risk of death, recurrent angina, or MI was 16.6% among patients receiving LMWH and 19.8% for patients given UFH (16% risk reduction). A similar risk reduction (15%) for the composite outcome was observed at 30 days. The benefit of LMWH treatment was maintained at 1 year. (Murphy, et al. 2007).

**3. β-Blockers**

β-blockers can decrease heart rate, myocardial contraction and blood pressure, and as a result of these, myocardial oxygen consumption is reduced. Consequently it is expected that the progression of myocardial necrosis decreases and patients’ prognosis improves if β-blockers are administered in the early phase of NSTE-ACS and STEMI, the time when myocardial ischemia develops. In fact, the efficacy of β-blockers was proven in a clinical study more than a half century ago. (Sommers, et al. 1972).
However, the use of β-blockers is still controversial and its recommendation in guidelines changes frequently because the efficacy of the drug was refuted in several clinical studies done later. The discordance in the guidelines is partly because of difference in drug indication between NSTE-ACS and STEMI, and between conservative or fibrinolysis days and the PCI era.

Regarding NSTE-ACS, even overseas there is limited evidence available for the effectiveness of β-blockers. In the CRUSADE registry, the effects of early (within 24 hours from onset) administration of β-blockers in 72,054 NSTE-ACS patients from 509 institutes in the United States were studied. (Miller, et al. 2007). As a result, hospital mortality was significantly reduced by 34%.

From a retrospective study done in England, early (within 4 hours from admission) oral administration of low-dose bisoprolol (1.25–2.5 mg) significantly improved the rates of arrhythmias and cardiac death as compared to delayed (within 5 to 24 hours) administration. (Maclean, et al. 2015).

The effects of intravenous metoprolol followed by oral administration in patients with STEMI were examined in the COMMIT study with a cohort comprised of almost 90% STEMI patients. As a result, although early intravenous administration of β-blockers in STEMI patients without heart failure reduced reinfarction and ventricular fibrillation, cardiogenic shock immediately after drug administration was increased. (Chen, et al. 2005). In the METO-CARD study, with only a limited number of participants, the effects of pre reperfusion intravenous administration of β-blockers in patients with STEMI in the era of primary PCI were studied. (Ibanez, et al. 2013).
Intravenous administration of metoprolol in anterior STEMI patients without heart failure symptoms reduced infarction size, and consequently increased LVEF without any adverse events within 24 hours after administration. On the other hand, the EARLY-BAMI study with similar concept to the METO-CARD study failed to show reduced infarction size. (Roolvink, et al. 2016).

Furthermore, the effects of early administration of β-blockers are not same between studies limited by primary PCI as the reperfusion method. In some studies, the authors speculate that the reason why metoprolol increased adverse events is its relatively long half-life of 3-4 hours.

### 4. Renin-Angiotensin-Aldosterone Inhibitors

Administration of ACE inhibitors is recommended in patients with reduced LV function (LVEF ≤40%). or symptomatic heart failure particularly in its early phase after ACS onset. (ISIS-4, et al. 1995). Meta-analysis by the ACE Inhibitor Myocardial Infarction Collaborative Group revealed that administration of ACE inhibitors within 0 to 36 hours from ACS onset significantly reduced 30-day mortality.

The effect is sizable, particularly within a week after ACS onset. Furthermore, the effect is more pronounced in high risk patients with Killip class 2 or 3 and heart rate on admission ≥100 bpm or in those with anterior myocardial infarction.

The VALIANT study examined the effects of ARB administered in the early phase of ACS. Although any additional effects of ARB over ACE inhibitors are not clear, valsartan adding on standard therapy as an
alternative to ACE inhibitors prevented cardiovascular events similar to ACE inhibitors.

The effects of the mineralocorticoid receptor inhibitor eplerenone were examined in the REMINDER study in STEMI patients without heart failure symptoms. As a result, NT-pro BNP was decreased by additional administration of eplerenone. With a similar method, the ALBATROSS study revealed that single injection of potassium canrenoate 200 mg followed by oral administration of spironolactone 25 mg reduced mortality by up to 80% in patients with STEMI. *(Beygui, et al. 2016).*

**5. Nitrates, Nicorandil**

Nitrates can improve myocardial ischemia not only by endothelium-independent coronary dilatation but also by the inhibitory effects of myocardial oxygen consumption due to pre- and afterload reduction of the left ventricle. On the other hand, nicorandil, which is a combination drug of both nitrate and adenosine triphosphate (ATP)-sensitive potassium-channel opener improves microvascular circulation by dilatation of vascular smooth muscle cells and nitrate-like effects.

In ISIS-4, a prospective randomized control trial of nitrate in 58,050 ACS patients within 24 hours after onset, orally administered long-acting isosorbide mononitrate did not improve mortality at 5 weeks. *(ISIS-4, et al. 2005).*

**6. Calcium Channel Blockers (CCBs).**

A meta-analysis of western populations with UA revealed that calcium channel blockers (CCBs) did not inhibit the onset of myocardial
infarction. *(Held, et al. 1989)*. It was reported that Japanese patients with myocardial infarction have 3 times the rate of coronary spasm based on challenge tests as compared to western patients in the early phase after onset. *(Pristipino, et al. 2000)*. In this way, since coronary spasm could play an important role in the basic pathogenesis of myocardial infarction, it is possible that CCBs have more potential for secondary.

In fact, in 2 prospective randomized controlled studies in Japanese patients, CCBs were proven to have a similar protective effect for cardiovascular events as compared with β blockers. *(Nakagomi, et al. 2011)*. However, short-acting dihydropyridine CCBs may induce myocardial ischemia due to sympathetic nervous system activation, tachycardia and hypotension.

### 7. Lipid-Lowering Therapy

#### 1 Cholesterol Management in the Acute Phase of ACS

Many large-scale clinical trials have demonstrated that low-density lipoprotein cholesterol (LDL-C)-lowering therapies with statins reduce cardiovascular events in patients with AMI, and a body of evidence for lowering LDL-C has been established. In PROVE IT-TIMI 22 the benefits of atorvastatin therapy were evident within 30 days of randomization. The MIRACL trial demonstrated an early benefit from treating ACS patients intensively with statins vs. placebo. Given these trials, the early benefit from treating ACS patients intensively with statins has been demonstrated in Western populations. Intravascular ultrasound studies have also reported that intensive LDL-C lowering therapy with maximum tolerable doses of statins leads to regression of coronary atherosclerotic plaques, and that the reduction in plaque volume is positively correlated with the decrease in LDL-C. *(Tsujita, et al. 2015)*. In
Japan, prospective clinical trials for ACS have been performed, which investigated not only cardiovascular events as a primary endpoint but also changes in coronary plaque. 


Furthermore, the relationship between plaque regression and mid- to long-term cardiovascular events was investigated in observational studies, in which short term plaque regression was demonstrated to be a predictor of future better cardiovascular outcomes. (Dohi, et al. 2010). Extended-ESTABLISH trial demonstrated that early atorvastatin treatment improved long-term outcomes for patients with ACS. Given this result, early administration of the maximum tolerated dose of strong statin medication (atorvastatin, pitavastatin, rosuvastatin). is also recommended in ACS patients.

The target of LDL-C in post-ACS management is set at <50 mg/dL,

Intensive LDL-C lowering with statins reduced cardiovascular events even in patients with low baseline cholesterol <80 mg/dL to similar extent to those with higher levels. Additionally, statin treatment was associated with improved outcomes in patients with AMI and LDL-C levels below 50 mg/dL. (Lee, et al. 2011). Based on these findings, statin therapy is recommended regardless of the LDL-C level prior to statin treatment. However, there is no contemporary evidence regarding the lower limit. (Lee, et al. 2011).

2 Latent Familial Hypercholesterolemia (FH).

Familial hypercholesterolemia (FH). is a highly prevalent autosomal dominant genetic disorder presenting with three major signs: high LDL cholesterolemia, tendon xanthoma/ skin xanthoma, and premature coronary artery disease.
Patients with FH have an increased risk of developing premature atherosclerotic diseases due to sustained high levels of LDL-C from birth. Heterozygous FH is estimated to affect one in 200–500 people in Japan and is the most frequent genetic disorder, and therefore is often encountered in daily practice. It has also been reported that the prevalence of FH in patients with ACS is approximately 10 times greater than in the general population. An observational study in Japanese patients with AMI reported that 2 in 7 patients with Achilles tendon thickening (≥9 mm) met all three diagnostic criteria for adult heterozygous FH. (Ohmura, et al. 2017).

During screening for FH in ACS patients, it is important to note the level of LDL-C is lower during the acute phase of ACS (Nakamura, et al. 2006) than the daily baseline level, and that Achilles tendon thickening is not obvious in young individuals. Therefore, early and careful screening for FH is necessary, especially in patients with ACS.

3-Management of LDL-C and Considerations for Non-Statin LDL-C-Lowering Medications During the Acute Phase of ACS

The maximum tolerable dose of a strong statin is recommended from the acute phase of ACS, but it is difficult to establish a target level of LDL-C in the acute phase of ACS. In patients who do not achieve the target level of LDL-C in the chronic phase (<50 mg/dL/ 50% reduction), even when FH is suspected and the maximum statin dose is given, consider using ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. Ezetimibe or PCSK9 inhibitors are also considered in statin-intolerant patients who have statin-induced disorders such as hepatic dysfunction, renal dysfunction, and myolysis.
STEMI

1. Fibrinolysis

- **Indications for Fibrinolysis**

  there are not many PCI-capable medical centers compared to foreign countries, fibrinolysis is the first option for patients with STEMI who receive reperfusion therapy. Fibrinolysis has an established effect in patients with STEMI or myocardial infarction with bundle branch block. The earlier the reperfusion with fibrinolysis in patients within 12 hours of symptom onset, the lower the mortality and rate of complications. *(Bonnefoy, et al. 2009).* The use of fibrinolysis should be considered in STEMI patients who cannot be promptly transferred to a PCI capable medical center. Fibrinolysis is recommended in STEMI patients within 12 hours of symptom onset when they cannot be treated with primary PCI within 2 hours of the diagnosis. The effect of fibrinolysis decreases as time from onset increases. The use of primary PCI should be considered especially more than 3 hours after onset. *(Armstrong, et al. 2013).*

- **Contraindications to Fibrinolysis**

  Fibrinolysis is not contraindicated in patients after brief and successful cardiopulmonary resuscitation. Fibrinolysis will not be effective or may even increase bleeding risk in patients with repeat cardiac arrest. Fibrinolysis increase bleeding risk in patients after prolonged successful cardiopulmonary resuscitation and is therefore relatively contraindicated in such patients. Absolute and relative contraindications to fibrinolysis are listed below.
• **Absolute Contraindications:**

1. Previous intracranial hemorrhage.
2. Cerebral infarction within the past 6 months.
3. Intracranial neoplasm or arteriovenous malformation.
4. Recent major trauma, surgery, or head trauma.
5. Gastrointestinal bleeding within the past month.
6. Active bleeding.
7. Known or suspected aortic dissection.

• **Relative Contraindications:**

1. Previous cerebrovascular disorder not included in absolute contraindications.
2. Ongoing anticoagulant therapy.
3. Pregnancy or within 1 month postpartum.
4. Uncontrolled severe hypertension (blood pressure ≥180/110 mmHg).
5. Advanced liver disease.
6. Active peptic ulcer.
7. Prolonged cardiopulmonary resuscitation.

**Assessment of Reperfusion:**

In treatment with fibrinolysis, patency of the infarct related artery has been assessed by non-invasive markers, including symptom relief,
hemodynamic/electrical stabilization, and resolution of ST-segment elevation with ECG.

If successful reperfusion is achieved, significant increases in serum concentrations of CK and CK-MB fraction are observed to 5–10 times higher than baseline at 6–90 minutes after initiation of fibrinolysis. *(Stewart,* et al.*1998).* If those findings are not observed, failure to achieve successful reperfusion of the infarct-related artery can be predicted. Some reports also demonstrated the usefulness of transthoracic Doppler echocardiography for evaluation of distal LAD reperfusion. *(Lee,* et al.*2005).*

Assessment of ST-segment elevation resolution on ECG is a useful non-invasive tool to estimate coronary microvascular dysfunction and obstruction. Poor ST-segment elevation resolution has been shown to be associated with microvascular dysfunction, larger infarct size, and worse clinical outcomes, compared to complete ST-segment elevation resolution. *(Buller,* et al.*2008).* Cardiac magnetic resonance with delayed enhancement is also a useful tool to detect microvascular dysfunction and obstruction. *(Niccoli,* et al.*2016).*

**PCI Following Fibrinolysis**

Approaches to PCI after fibrinolysis have traditionally been classified into facilitated PCI and rescue PCI. Facilitated PCI is defined as planned PCI that is performed shortly after initiating fibrinolysis in preparation for PCI. Rescue PCI is defined as PCI that is performed after failed fibrinolysis or following fibrinolysis for some reasons. The distinction between these 2 approaches is currently considered of no importance in selecting treatment options for STEMI.
This guideline describes PCI following fibrinolysis without distinguishing between them. The success of recanalization should be verified in patients after fibrinolysis when primary PCI is not available. Systematic PCI, in which patients are transferred to PCI-capable medical centers after fibrinolysis and undergo angiography and PCI, is reportedly associated with favorable treatment outcomes compared to fibrinolysis alone, although fibrinolysis is recently performed less frequently in medical centers where PCI is unavailable. *(Cantor, et al. 2009)*.

Some reports demonstrate no differences in mortality rate between systematic PCI and primary PCI. It is thus important to transfer patients to PCI-capable medical centers after performing fibrinolysis in order to assess whether such patients are at high risk and have indications for systematic PCI. *(Cantor, et al. 2009)*.

2. Primary PCI

- **Indications for Primary PCI**

  Reperfusion therapy for STEMI is now widely accepted as an acute treatment of myocardial infarction and its efficacy has been established in patients within 12 hours of symptom onset. It is of importance to restore coronary blood flow promptly and securely without any complications. In treating STEMI, it is important for improved prognosis to establish TIMI 3 reperfusion as soon as possible with fibrinolysis or PCI.

  PCI is preferred for treating STEMI in current clinical practice. The use of PCI as the first line for reperfusion without preceding fibrinolysis is called primary PCI. In principal, PCI should be performed by accredited, skilled operators, certified by the board of a PCI-related Society in experienced centers.
Prognosis of patients with STEMI depends on the time required to establish reperfusion of the infarct-related culprit artery after symptom onset. Primary PCI is considered appropriate reperfusion therapy when it is performed in patients with STEMI within 12 hours of symptom onset by a skilled team and reperfusion is achieved within 90 minutes from the arrival of the patient at the medical institution.

A meta-analysis of 23 randomized controlled trials published in the Lancet in 2003 reported that primary PCI was superior to fibrinolysis in improving the prognosis of patients with STEMI. *Keeley, et al. 2003*.

Primary PCI therefore has become a standard of care. There are however some circumstances, such as in remote areas and outer islands, when primary PCI is not available as first choice and the use of fibrinolysis is adequate due to long distances to PCI-capable medical centers. In these circumstances, it is recommended to transfer the patient to a PCI-capable medical center after fibrinolysis. *Cantor, et al. 2009*.

It is crucial in treating STEMI to shorten the total ischemic time, the time from symptom onset to reperfusion. Door to balloon time is widely used as an index of early reperfusion in primary PCI for STEMI and PCI-capable medical centers aim for door to balloon time shorter than 90 minutes.

Of note, a door to balloon time shorter than 90 minutes was associated with favorable long-term clinical outcomes only in patients who presented early to medical institutions, that is, within 2 hours of symptom onset. These results indicate the importance of reduction in total ischemic time, which includes door to balloon time. A door to device time shorter than 90 minutes is a minimum acceptable time, but not a target time. The goal should be to make the time from the diagnosis of
STEMI to wire crossing of the lesion shorter than 60 minutes, considering the fact that a shorter total ischemic time to recanalization is associated with more favorable prognosis.

In contrast, primary PCI provides limited benefits in patients with STEMI after 12 hours of symptom onset, who are hemodynamically and electro-physiologically stable and asymptomatic. (Shiomi, et al. 2012). Primary PCI with bare metal stents (BMS) is associated with lower incidence of revascularization although it is not associated with a lower mortality rate compared with plain old balloon angioplasty in treating STEMI. (Nordmann, et al. 2004).

In recent years, drug-eluting stents (DES) have been frequently used in the treatment of STEMI. Many clinical studies have reported that DES and BMS are equivalent with respect to the incidence of death and myocardial infarction, and DES are superior to BMS with respect to the rate of repeat revascularization. (Stone, et al. 2009).

The use of DES is, therefore, more strongly considered when patient characteristics and/or lesion characteristics are potentially associated with a high risk of restenosis. However, bleeding risk due to oral dual antiplatelet therapy (DAPT) and a need for an invasive procedure, e.g. an operation, within several days, should be taken into account before using DES. With regard to the timing of stent implantation for the infarct-related culprit lesion, a treatment strategy called “deferred” or “delayed” stent implantation was proposed, in which stent implantation was withheld after the initial angioplasty has stabilized the blood flow through the infarct-related culprit lesion.

This strategy might reduce the risk of thromboembolism and thereby improve clinical outcomes. The DANAMI 3-DEFER trial,
(Kelbak, et al. 2016). A study that assessed whether delayed stent implantation reduces the risk of impaired myocardial blood flow and improves the clinical course of patients with STEMI compared to conventional PCI, showed no between-group differences in all-cause mortality, heart failure hospitalization, or recurrence of nonfatal myocardial infarction, but confirmed a significantly higher rate of unscheduled target vessel revascularization in the deferred stent group. Routinely delaying stent implantation in patients with STEMI as a treatment strategy is thus considered to have no benefit.

**PPCI in patients with MVD:**

1. **Indication for and Timing of Coronary Revascularization**

   It is not rare that patients with STEMI have multivessel disease. Approximately 50% of patients with STEMI reportedly have multivessel disease. (Wald, et al. 2013). Prognosis is worse in patients with STEMI when they have multivessel disease. It is therefore important to consider coronary revascularization for residual CAD. There is, however, no clear evidence for an appropriate timing of revascularization for residual coronary artery lesion and an appropriate timing of cardiac stress test to determine the indication for revascularization in patients with STEMI.

2. **PCI of Residual Lesions**

   Previous research on PCI for residual CAD varied in terms of randomization/non-randomization and the timing of PCI. This may have contributed to the inconsistency of previous research, although performing primary PCI of the infarct-related artery only and staged PCI for residual non-infarct-related artery later was considered to reduce the incidence of adverse events. (Vlaar, et al. 2011).
There are few randomized trials that may resolve the discrepancy between these arguments. In one randomized trial, 214 subjects with STEMI and multivessel disease were assigned to either of the following 3 arms: arm 1 consisted of subjects who underwent revascularization of the infarct-related culprit coronary lesion only; arm 2 consisted of subjects who underwent simultaneous revascularization for the infarct-related culprit coronary lesion and residual CAD, and arm 3 consisted of subjects who underwent revascularization with staged PCI for residual CAD.

The rate of major cardiovascular events during the mean observation period of 2.5 years was significantly higher in the “revascularization of the infarct-related culprit coronary lesion only” arm. (Politi, et al. 2010) Following this trial, 5 randomized trials were conducted to compare PCI of the infarct-related culprit lesion only to complete revascularization: the PRAMI trial (n=465, observation period: 23 months), (Wald, et al. 2013) Compare-Acute trial (n=885, observation period: 12 months), (Smits, et al. 2017) and TRANSLATE-ACS Observational trial (n=6,601, observation period: 12 months), (Ibrahim, et al. 2017) in which PCI for residual CAD was simultaneously performed with index PCI; the DANAMI-3-PRIMULTI trial (n=627, observation period: 27 months), in which staged PCI was performed during hospitalization; and the CvLPRIT trial (n=296, observation period: 12 months), (Gershlick, et al. 2015) in which immediate PCI or staged PCI was performed during hospitalization. Residual coronary artery lesion with angiographic stenosis of 50% or greater and that with stenosis of 70% or greater were considered indications for PCI in the PRAMI trial and in the CvLPRIT trial, respectively.

Fractional flow reserve (FFR). was used to determine indications for PCI in the other 2 trials. The rate of major events was significantly lower
in the complete revascularization group in each trial, although composite endpoints differed between trials. There was no significant difference between groups in all-cause mortality in all trials. The rate of repeat revascularization was lower in the complete revascularization group in the PRAMI, DANAMI- 3-PRIMULTI, and Compare-Acute trials.

In the TRANSLATE-ACS Observational trial, readmission rate within 6 weeks was lower in the complete revascularization group, but there were no between-group differences in the incidence of readmission or angina pectoris within 1 year. In addition, 3 meta-analyses demonstrated no effects of PCI for residual lesion on the rate of death or myocardial infarction. *(Elgendy, et al. 2017)*.

It is often difficult to determine the timing of PCI for lesions in non-infarct-related arteries in AMI patients with multivessel disease complicated by cardiogenic shock. The CULPRIT-SHOCK trial randomized 706 AMI patients with multivessel disease complicated by cardiogenic shock to either of the following groups and assessed the composite endpoint of death or severe renal failure requiring renal replacement therapy within 30 days of randomization: a group of patients that simultaneously underwent PCI of the culprit lesion and all coronary arterial lesions with stenoses of 70% or greater (n=355); and the other group of patients that first underwent PCI of the culprit lesion only and then staged PCI if non-invasive stress test or FFR indicated PCI (n=351)*(Thiele, et al. 2017)*.

According to recent guidelines ..full revascularization became claa III recommendation but patient would benefit from culprite vessel revascularization and to do completeness before discharge as class IIa recommendatiuon.
The results showed that the risk of the composite endpoint of death or severe renal failure leading to renal replacement therapy within 30 days after randomization was lower in the “culprit lesion only PCI plus optional staged PCI” group than in the “simultaneous residual multi-lesion PCI” group. Simultaneous PCI of severe stenoses in non-infarct related arteries perfusing viable myocardium in acute phase may reduce the hibernation of those areas and the occurrence of ischemic attack, thereby promoting early recovery of cardiac function. On the other hand, a prolonged time, increased complexity of the procedure and consequently increased amount of contrast media may cause contrast nephropathy. There is also another idea that PCI of residual lesions should be performed after the stabilization of plaques unless ischemic attack occurs, since simultaneous PCI in the acute phase when plaques are fragile may cause side branch occlusion or distal occlusion.

Clear evidence is lacking to support the use of simultaneous PCI in emergency patients with cardiogenic shock. It is fundamental to determine a treatment strategy based on the advantages and disadvantages to individual patients and estimation of the success rate of each procedure.

3. Emergent CABG

Prompt reperfusion is the priority in treating STEMI patients. Since PCI can be performed faster than CABG in many cases, there are few instances where CABG is selected as the reperfusion therapy. Emergent CABG is indicated, if distal site of the infarct-related artery is considered to be suitable for CABG, the lesion is anatomically inappropriate for PCI, PCI is unsuccessful, or there is a complication such as coronary artery perforation during PCI. However, with recent advances in PCI
techniques, there are few cases in which emergent CABG is required. (Pi, et al. 2019).

**NSTE-ACS**

*Conservative Strategy versus Invasive Strategy*

Treatment strategy for patients with suspected ACS is divided into 2 strategies according to timing of Coronary angiography (CAG) and coronary revascularization. Conservative strategy prioritizes medical treatment and invasive treatment is not performed routinely unless patients have ongoing or recurrent chest pain or hemodynamic instability. This strategy has advantages to be able to stabilize the culprit lesion with statins and antithrombotic agents and to avoid unnecessary invasive procedures with inherent procedural risk. In invasive strategy, CAG, followed by PCI, is routinely performed for all patients.

The results of clinical trials comparing conservative strategy and early invasive strategy have changed over time. In the era of balloon angioplasty, the TIMI IIIB trial reported that early invasive strategy was superior to conservative strategy in terms of hospital stay and readmission rate in high-risk patients, although the risk for major adverse cardiac events was neutral between the two groups.

The DANAMI trial, which enrolled patients with prior myocardial infarction and myocardial ischemia, showed significantly lower incidence of adverse cardiac events (death, myocardial infarction, re-admission for UA) in early invasive treatment than in conservative treatment. (Madsen, et al. 1997).
However, invasive treatment strategy was associated with significantly higher in-hospital and one-year higher cardiac adverse events in the VANQWISH trial. (Boden, et al.1998). The advantage of early invasive over conservative strategy was demonstrated in the FRISC-II, TACTICS-TIMI18, and RITA3 trials conducted in the era of PCI using stents. In the FRISC-II trial, the cumulative incidence of major adverse cardiac events at 6 months was significantly lower in the early invasive strategy group than in the conservative group (9.4% vs. 12.1%). (FRagmin, et al.1999).

Early invasive strategy was associated with lower major adverse cardiac events than conservative strategy in the TACTICS-TIMI 18, in which all patients were administered the GP IIb/IIIa antagonist tirofiban with a mean interval of 22 hours before coronary angiography (15.9% vs. 19.4%). (Cannon, et al.2001).

In the ICTUS trial, however, there was no significant difference between early invasive and selective invasive strategies in NSTEMI patients with high troponin level, although early invasive strategy significantly reduced readmission. (de Winter, et al.2005). In several trials such as TACTICS-TIMI 18 and FRISC II trials, the advantages of early invasive therapy were observed only in high-risk patients with moderate to high TIMI risk score, high troponin level, or ST change. (Cannon, et al.2001).

Majority of trials reporting no advantage with invasive strategy over conservative strategy were conducted before the introduction of stents, (van Domburg, et al.1998). and important factors were varied among trials such as revascularization rate, the rate of stent use, mortality of surgery, and the rate of GP IIb/ IIIa inhibitors. In the era of stents, the
advantages of early invasive strategy over conservative strategy were demonstrated despite of a non-statistically significant higher risk of early complications such as CK elevation. *(van Miltenburg-van Zijl, et al. 2019)*. Optimal antiplatelet therapy facilitates the benefits of early revascularization.

1. **Invasive Strategy**

- **Timing of Invasive Strategy**

  Invasive strategy is divided into 3 categories according to the timing of CAG and coronary revascularization (table 4). Early invasive strategy has the potential to reduce the risk of ischemic events in the time course of ACS, while preceding antiplatelet therapy may reduce the risk of complications related to thrombosis at the time of revascularization.

1. **Immediate Invasive Strategy (Within 2 Hours).**

  Very high-risk patients are recommended to receive immediate invasive strategy, because this category of patients have poor prognosis without optimal treatment. This category of patients was generally excluded from randomized controlled trials. If patients present to non-PCI capable hospitals, immediate transfer is highly recommended.

  The ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes) trials compared immediate intervention (median 70 minutes) with delayed intervention (next day: median 21 hours).

  The primary endpoint of the peak troponin value during hospitalization, as well as the key secondary endpoint comprising death, myocardial infarction, or urgent revascularization at 1-month follow-up,
were not significantly different between the 2 groups. Therefore, the need to perform immediate CAG is not necessarily clear.

However, it is reasonable to perform emergent coronary angiography followed by PCI if needed in patients who have congestive heart failure as a complication, ongoing chest pain, a large area of ischemia as indicated by ECG findings, hemodynamic instability, and/or life threatening arrhythmias. Survivors of out-of-hospital cardiac arrest without ST segment elevation need to be managed with an individualized approach.

Conscious survivors are recommended to receive immediate CAG, while comatose survivors are recommended to receive CAG after surveillance for other causes of cardiac arrest. (Noc, et al. 2014).

2. Early Invasive Strategy (Within 24 Hours).

Early invasive strategy is defined as the treatment strategy in which CAG is performed within 24 hours after admission. Early invasive strategy is recommended if patients fulfill at least one high-risk criteria. These patients should be transferred to PCI capable centers immediately if initially presenting to non-PCI capable centers.

The CRUSADE study reported that the incidence of in-hospital adverse events was not significantly different between patients presenting on weekdays and those on weekends, although time to catheterization was significantly delayed in patients presenting on weekends than those on weekdays (median 46.3 vs. 23.4 hours, P<0.0001). (Ryan, et al. 2005).

The ISAR-COOL trial evaluated the efficacy of antithrombotic pretreatment using unfractionated heparin, aspirin, clopidogrel, and tirofiban for 3 to 5 days with early intervention with a composite primary
endpoint of 30-day incidence of large nonfatal myocardial infarction and all-cause death. (Neumann, et al. 2003) In this trial, the primary endpoint was reached in 11.6% in the antithrombotic treatment group and 5.9% in the early intervention group (P=0.04).

The merit of early intervention over antithrombotic pre-treatment was attributed to the higher incidence of events before intervention in the antithrombotic pre-treatment group.

**Table 4.** Selection of Treatment Strategy and Timing in NSTE-ACS Risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Immediate invasive strategy (within 2h)</td>
</tr>
<tr>
<td></td>
<td>Recurrent or ongoing chest pain refractory to medical treatment</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Life-threatening arrhythmias or cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Mechanical complication (acute mitral regurgitation etc.)</td>
</tr>
<tr>
<td></td>
<td>Transient ST-segment elevation, or recurrent dynamic ST-T changes</td>
</tr>
<tr>
<td></td>
<td>Rise and fall in cardiac troponin compatible with myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>New ECG changes (dynamic ST-T changes)</td>
</tr>
<tr>
<td></td>
<td>GRACE risk score &gt;140</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Delayed invasive strategy (within 72h)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Renal insufficiency (GFR &lt;60 mL/min/1.73 m²)</td>
</tr>
<tr>
<td></td>
<td>LV dysfunction (LVEF &lt;40%)</td>
</tr>
<tr>
<td></td>
<td>Early post-infarction angina</td>
</tr>
<tr>
<td></td>
<td>Prior coronary revascularization (PCI, CABG)</td>
</tr>
<tr>
<td></td>
<td>GRACE risk score: 108-140</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Early conservative strategy</td>
</tr>
<tr>
<td></td>
<td>None of the above-mentioned factors, clinically suitable for conservative strategy</td>
</tr>
<tr>
<td></td>
<td>GRACE risk score &lt;109</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; GFR, glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting. (Source: Prepared based on Antman EM, et al. 2009®)

In the TIMACS trial, 3,031 ACS patients without ST segment elevation were randomly assigned to undergo either routine early intervention (coronary angiography within 24 hours after randomization).
or delayed intervention (coronary angiography beyond 36 hours after randomization). (Mehta, et al. 2009). Although the primary endpoint of a composite of death, myocardial infarction or stroke at 6 months was not significantly different between the 2 groups (9.6% vs. 11.3%, P=0.15), a composite of death, myocardial infarction or refractory ischemia at 6 months was significantly lower in the early intervention group than in the delayed intervention group (9.5% vs. 12.9%, P=0.003).

The VERDICT study assigned 2,147 patients with NSTE-ACS within 12 hours of onset to coronary revascularization within 12 hours (median 4.7 hours) or between 48–72 hours (median 61.6 hours) and compared the long-term outcomes (over 4.3 years). (Kofoed, et al. 2018).

There was no difference between the groups in the main composite endpoint (all-cause death, nonfatal myocardial infarction, hospitalization due to refractory myocardial ischemia, and/or heart failure), but in patients with a GRACE score >140, the prognosis was better in the group who received treatment within 12 hours. Based on the results above, the benefit of earlier revascularization in patients with GRACE score >140 is evident and delays in CAG and coronary revascularization are undesirable.

3. Delayed Invasive Strategy (Within 72 Hours).

Delayed invasive strategy with CAG within 72 hours after admission is recommended if patients do not suffer from recurrence of symptoms and fulfill at least one of the moderate risk criteria. Those patients should undergo CAG within 72 hours even in needing transfer. Cardiovascular disease (CVD) remains the most common cause of morbidity and mortality in Europe, accounting for 49% of deaths in women and 40% of deaths in men. (Townsend, et al. 2016). Over the last four decades, age
adjusted mortality for CVD has continuously declined, however, to a lesser extent in women than in men.\textit{(Gupta, et al. 2014)}.

Recent studies report a significant increase in case fatality rates of acute coronary syndromes (ACS) in young women <55 years of age, while a decrease in mortality from coronary artery disease (CAD) has occurred in younger men.\textit{(Arora, et al. 2019)}.

Despite growing evidence demonstrating sex and gender differences in baseline risk factors, coronary anatomy and function, symptoms presentation, comorbidities, treatment efficacy, and outcomes of ACS, mechanisms behind these differences are largely unexplored.\textit{(Vaccarino, et al. 2019)}.

These knowledge gaps are nourished by the persistent underrepresentation of women in cardiovascular clinical trials and a lack of basic science evidence obtained from female animals and cells owing to a manifold refuted concern that inclusion of females will increase variability, as well as double sample size and costs.\textit{(Ghare, et al. 2019)}.

On talking about contemporary evidences shedding light on sex and gender differences in the clinical presentation of ACS as well as in diagnostic accuracy of tests, invasive treatment, pharmacotherapy, and outcomes.
Sex differences in coronary biology

Women have significantly smaller epicardial coronary arteries than men, even after adjustment for age, body habitus, and left ventricular mass. (Hiteshi, et al. 2014). Baseline and hyperaemic myocardial blood flow, as assessed by positron emission tomography (PET), is typically higher in women as compared to men resulting in a similar global coronary flow reserve (CFR) in men and women. (Haider, et al. 2019).

Although exact mechanisms are lacking, the smaller diameter of female epicardial coronary arteries together with their higher baseline myocardial blood flow have been suggested to result in a significant increase in endothelial shear stress conditions in women. (Patel, et al. 2016).

Given that low endothelial shear stress has been associated with focal lipid accumulation, pathologic remodelling, and plaque instability, (Koskinas, et al. 2013), it has been hypothesized that higher shear stress conditions in female coronary arteries may contribute to sex differences in susceptibility to CAD. (Kerkhof, et al. 2018).

These sex differences might be particularly relevant during premenopausal ages owing to oestrogen dependent effects on endothelial mediators such as nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factor (Miller, et al. 2008). (table 5).

The vascular actions of oestrogen are primarily mediated via oestrogen receptor a signalling promoting an anti-inflammatory, low-vascular resistance phenotype that is protected from CVD. (Deroo, et al. 2006). Oestrogen receptor a-mediated effects are blunted in the absence of oestrogen which is consistent with variations seen in
vascular stiffness throughout the lifespan of women. (Staessen, et al. 2001).

Importantly, increased vascular stiffness strongly correlates with blood pressure, diastolic dysfunction, impaired ventricular coupling, and left ventricular remodelling and is thought to play a role in disease conditions preferentially affecting postmenopausal women such as heart failure with preserved ejection fraction (HFpEF). or isolated systolic hypertension. (DuPont, et al. 2019).

Finally, women display distinct coronary plaque characteristics with a more diffuse and non-obstructive disease pattern, reduced overall plaque burden, and calcium content as well as less signs of necrosis in the plaque core (Lansky, et al. 2012). (table 5). Accordingly, while plaque rupture is the primary mechanisms responsible for myocardial infarction (MI). in men, plaque erosion is the major cause of coronary thrombosis in women, particularly in premenopausal women (Johnson, et al. 2019). (Figure 11).

Despite an overall lower plaque burden in women, coronary artery calcium scoring has recently been demonstrated to be a stronger risk predictor for future cardiovascular events in women as compared to men. (Shaw, et al. 2018). Thus, coronary artery calcium scoring has been recommended for evaluation of asymptomatic women with a 10-year CVD risk >7.5% by a recent expert consensus statement. (Thygesen, et al. 2019).
Table 5  Effects of oestrogen and testosterone on plaque development, atherothrombosis, coagulation, vascular injury and healing. Evidence from experimental and clinical studies.

<table>
<thead>
<tr>
<th>Atherosclerosis Risk Factors</th>
<th>Estrogens</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL oxidation ↓</td>
<td>LDL binding ↓</td>
<td>Conflicting effects on lipids</td>
</tr>
<tr>
<td>VSMC proliferation ↓</td>
<td>VSMC migration ↓</td>
<td>Expression of pro-atherogenic genes ↑</td>
</tr>
<tr>
<td>EC proliferation ↑</td>
<td>EC migration ↑</td>
<td>WBC adherence to EC ↑</td>
</tr>
<tr>
<td>CRP ↑</td>
<td>Pro-inflammatory (TNF-α, IFNγ, IL-6, CCL2) cytokine production ↑</td>
<td>Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ) ↓</td>
</tr>
<tr>
<td>Hematopoietic stem cell differentiation ↑</td>
<td>Baseline platelet activity ↑</td>
<td>CRP ↓</td>
</tr>
<tr>
<td>Coronary calcification ↓</td>
<td>Platelet inhibition by PG12 ↑</td>
<td>Plaque volume ↑, VCAM-1 expression ↑ (controversial data)</td>
</tr>
</tbody>
</table>

| Thrombus Formation | ADP, adenosine diphosphate; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2 (inhibitor of apoptosis); CCL2, C-CMotif chemokine ligand 2; CRP, C-reactive protein; EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; F, factor; IFNc, interferon c; IL, interleukin; LDL, low density lipoprotein; NADPH, nicotinamide adenine dinucleotide phosphate; PAI-1, plasminogen activator inhibitor-1; PG12, prostaglandin I2; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF-a, tumour necrosis factor-a; TXA2, thromboxane A2; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell; WBC, white blood cell. aControversial data exist with regard to the effect of oestrogen and testosterone on platelet aggregation responses and myocardial injury. | Platelet response to ADP ↑ |
| | Baseline platelet activity ↓ | TXA2 platelet aggregation ↑ |
| | Baseline platelet activity ↑ | Plasma fibrinogen level ↑ |
| | Platelet inhibition by PG12 ↑ | Infarct size ↓, protection from ischemic injury * |

<table>
<thead>
<tr>
<th>Vasoreactivity</th>
<th>Vasodilatation</th>
<th>Vasodilatation (coronaries) via inhibition of L-type Ca2+ channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNOS activity ↑</td>
<td>Nitric oxide bioavailability ↑</td>
<td>Vasoconstriction (aorta)</td>
</tr>
<tr>
<td>Nitric oxide bioavailability ↑</td>
<td>Endothelium ↓</td>
<td>Attenuation of the vasodilatory effect of adenosine</td>
</tr>
<tr>
<td>EDHF-mediated relaxation ↑</td>
<td>PGI2 ↑</td>
<td>Endothelium-independent VSMC relaxation ↑</td>
</tr>
<tr>
<td>PGI2 ↑</td>
<td>Sympathoadrenal responsiveness ↓</td>
<td>Thromboxane A2 synthase ↑</td>
</tr>
<tr>
<td>Blood pressure ↓</td>
<td>Blood pressure ↑</td>
<td>Blood pressure ↑</td>
</tr>
</tbody>
</table>

| Vascular Apoptosis | Mitochondrial ROS production ↓ | Pro-apoptotic effect (Caspase-3 ↑ Bcl-2 ↓) |
|--------------------| Antioxidant defense mechanism ↑ | Apoptosis following ischemia/ reperfusion injury ↓ via STAT3 activation ↑ |
| Antioxidant gene expression ↑ | NADPH oxidase activity ↓ | Mitochondrial stabilization via KATP channels following ischemia/reperfusion injury ↑ |
| NADPH oxidase activity ↓ | Endothelial progenitor cells ↑ | |
| EC apoptosis ↓ | VEGF expression ↑ | |
| VEGF expression ↑ | EC proliferation ↑ | |
| EC proliferation ↑ | EC migration ↑ | |

ADP, adenosine diphosphate; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2 (inhibitor of apoptosis); CCL2, C-CMotif chemokine ligand 2; CRP, C-reactive protein; EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; F, factor; IFNc, interferon c; IL, interleukin; LDL, low density lipoprotein; NADPH, nicotinamide adenine dinucleotide phosphate; PAI-1, plasminogen activator inhibitor-1; PG12, prostaglandin I2; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF-a, tumour necrosis factor-a; TXA2, thromboxane A2; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell; WBC, white blood cell. aControversial data exist with regard to the effect of oestrogen and testosterone on platelet aggregation responses and myocardial injury.
**Figure (11).** Mechanisms and characteristics of myocardial ischaemia in women and men. FFR, fractional flow reserve; INOCA, ischaemia and no obstructive coronary artery disease; MINOCA, myocardial infarction with no obstructive coronary artery disease.
Influence of sex and gender on cardiovascular risk

- Traditional risk factors

Although traditional risk factors for CVD are the same in women and men, differences in prevalence and impact of these risk factors vary between both sexes (Garcia, et al.2016). (Figure 9).

This is especially seen in ACS, as women who present with ACS are generally older and have more comorbidities, including a higher prevalence of hypertension, dyslipidaemia, diabetes, heart failure, and atrial fibrillation. Women with early-onset type 1 and type 2 MI have received growing attention as a group affected by inequalities in health outcomes, (Gabet, et al.2017).

Mechanisms for these differential outcomes are unclear, but data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study indicate that younger women have a worse pre-event health status vs. men, including lower overall and mental health qualities of life, (Dreyer, et al.2016).

Smoking, like diabetes mellitus, has been shown to have a stronger impact on women, as there is a 25% increased risk for fatal and non-fatal cardiovascular events in female smokers as compared to male ones, independent of other risk factors (Huxley, et al.2011). (Figure 12).
Figure (12).: Sex differences in pathophysiology, presentation and outcomes of acute coronary syndromes. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction
Smoking-related cardiovascular risk was highest among young and middle-aged women. (Njolstad, et al. 1996). Diabetes also carries a differential risk between sexes, with diabetic women being at significantly higher risk of developing CAD or HFpEF than their male counterparts (Beckowski, et al. 2018). (Figure 12).

Finally, a significant role in the case of younger women is also played by family history as women <65 years with a maternal history of MI encounter a four times higher risk of ACS than same-aged men or older women. (Banerjee, et al. 2009).

- Non-traditional risk conditions

Data emerging from the VIRGO study indicate that young and middle-aged women hospitalized for type 1 and type 2 MI were more likely to have lower socioeconomic status, higher levels of psychosocial burden, such as depression and poorer physical/mental health, and overall lower quality of life compared to men (Banerjee, et al. 2017). (Figure 8).

Accordingly, depression, trauma, and perceived stress have been identified as powerful predictors of cardiovascular risk in young and middle-aged women. (Rich-Edwards, et al. 2012). This trend is not surprising, given that psychosocial stress has substantially increased for women during the last two decades due to a continuous increase in women’s economic participation and educational attainment. (Schwab, et al. 2016).

Further, low socioeconomic status is an established variable inversely associated with global coronary risk and imposes a higher excess risk on women as compared to men (Backholer, et al. 2016). (Figure 12).
Of note, recent work states that feminine roles and personality traits, but not female sex itself, are associated with higher rates of ACS as compared to masculine characteristics, however, objective evidence of this vulnerability is still insufficient. *(Pelletier, et al. 2016).*

It is increasingly appreciated that the gut microbiome, harbouring trillions of microbial cells, plays an important role in the development of CAD. *(Pedersen, et al. 2016).* Indeed, systemic trimethylamine N-oxide levels—a pro-atherogenic and pro-thrombotic metabolite produced by the gut microbiome—was shown to predict 30-day and 6-month event free survival in women and men with suspected ACS. *(Li, et al. 2017).*

In addition, there is emerging evidence for sex differences in microbiome-mediated contribution to cardiovascular risk factors and comorbidities including inflammatory processes, autoimmune disease, cardiometabolic disorders, and major depression. *(Chella, et al. 2018).*

Men and women have different genetic backgrounds, energy and nutritional requirements across the lifespan, as well as differences in gastrointestinal transit time, which can contribute to sex differences in microbiome. *(Gomez, et al. 2015).*

Future studies will show the potential of gut microbes to provide novel diagnostic and therapeutic targets tailored to the female and male cardiovascular system.

- **Female-specific risk factors**

  Premenopausal women are thought to be relatively protected against CVD when compared to age-matched men, with early menopausal transition and postmenopausal status shown to be associated with adverse risk for CVD and mortality. *(de Kat, et al. 2017).*
Oestrogen withdrawal at menopause has many negative effects on cardiovascular function and metabolism including alterations in body fat distribution, endothelial dysfunction, vascular inflammation, sympathetic tone, and a higher insulin resistance contributing to hypertension. (Vitale, et al. 2009). In fact, menopause is accompanied by an accelerated age-related rise in cardiac and peripheral sympathetic nerve activity, most likely related to an impaired central modulation of baroreflex function or a direct inhibitory influence of oestrogen on sympathetic nerve activity. (Burger, et al. 2018).

However, although initially supported by large observational studies, (Grodstein, et al. 2000), randomized controlled trials largely failed to show any cardiovascular benefit of menopausal hormone replacement therapy (HRT). and even demonstrated an increased event rate in post-menopausal women with a recent ACS. (Hodis, et al. 2003).

Thus, the use of HRT for primary and secondary prevention of CVD remains controversial and is currently not recommended. (Mancia, et al. 2013).

Nevertheless, a re-analysis of the Women’s Health Initiative data led to the so-called ‘timing hypothesis’, indicating that HRT might be beneficial when initiated during early menopause. (Hodis, et al. 2016). Notably, while these data suggest that specific subgroups of postmenopausal women might profit from HRT, the use of oestrogen-containing contraceptives in premenopausal women with known CVD is generally not recommended. (Hodis, et al. 2016).

In fact, although the risk is small in absolute numbers, combined oral contraceptives have been associated with hypertension as well as a
significant increase in venous and arterial thrombosis. *(Lidegaard, et al. 2012).*

Interestingly, changes in iron status have been suggested as an alternative mechanism accounting for the risk increase seen in postmenopausal women. Indeed, concurrent but inverse alterations occur between iron and oestrogen levels in healthy women during menopausal transition; whereas oestrogen decreases because of the cessation of ovarian functions, iron increases as a result of decreasing menstrual period. *(Zimmermann, et al. 2007).*

Higher iron plasma levels and associated alterations in iron metabolism after early-onset menopause are believed to exert detrimental effects on the cardiovascular system via induction of inflammatory cascades. *(Muka, et al. 2017).*

Conversely, several observational reports claim that iron deficiency independently predicts adverse cardiovascular outcomes in women and men. *(Zeller, et al. 2018).* Thus, the iron hypothesis remains controversial owing to the lack of adequately designed clinical trials and the fact that current biomarkers of iron status are not validated.

As iron deposits in the heart tissue might impact cardiovascular endpoints, T2 star (T2*). cardiac magnetic resonance imaging may offer an opportunity to improve our mechanistic understanding for the role of iron in CAD. *(Kobayashi, et al. 2018).*

Pregnancy is often quoted as providing a glimpse into a woman’s future health status with numerous pregnancy-related complications associated with increased cardiovascular risk. *(Rich-Edwards, et al. 2014).* A recent meta analysis concluded that the risk of CAD was highest in
women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes (*Grandi, et al. 2019*). (Figure 11).

Moreover, the development of gestational diabetes has been shown to increase the risk for CAD by two to three-fold even 25 years after delivery,(*McKenzie-Sampson, et al. 2018*), while preterm delivery (<37 weeks gestation). in the first pregnancy was independently associated with a 1.5-fold increased risk of CAD. (*Tanz, et al. 2017*).

Notably, a combination of these risk factors seems to potentiate cardiovascular risk as the occurrence of major coronary events and mortality was nearly six-fold increased after preeclampsia in combination with preterm delivery and/or infants born small for gestational age. (*Riise, et al. 2017*).

Accordingly, adding pregnancy complications to traditional risk models led to significant improvements of CVD risk prediction among a representative sample of Norwegian women. (*Markovitz, et al. 2019*).

**Potential future risk marker: epigenetic modifications**

Epigenetic modifications of the genome might constitute a novel pathway leading to sexual dimorphism in ACS. DNA-methylation (DNAm)., the best-understood epigenetic modification, defines cell’s identity, is vital for normal cellular processes and adaptation to environmental changes. (*Feinberg, et al. 2018*).

However, dysregulated DNAm contributes to adverse changes in gene expression and may affect cardiovascular risk factors including obesity, atherosclerosis, inflammation, hypertension, blood lipids, and glucose metabolism, subsequently leading to increased risk of developing CAD. (*Braun, et al. 2016*).
Although epigenetic mechanisms have emerged as potential future risk factors in CVD, this field of research is still in a pioneer stage; to date, few studies with small sample sizes have investigated associations of DNAm with ACS. Of note, Li et al. reported that more than 11 000 differentially methylated CpGs exist between ACS cases and controls, thereby covering 5071 genes involved in ACS-related biological processes. (Brown, et al. 2018).

Similarly, alterations in DNAm of ANGPTL2, a pro-inflammatory gene, were found in post-ACS patients as compared to their healthy age-matched controls. Sex differences at the level of DNAm and associations of global and gene-specific DNAm with traditional risk factors have been described, supporting the hypothesis that epigenetic mechanisms may play a role in shaping sex differences in ACS (Garcia-Calzon, et al. 2018), (Landen, et al. 2019). (Figure 13).
Figure (13).: Sexually dimorphic epigenetic regulation of acute coronary syndrome. Potential sex-specific interplay between environmental changes, cardiovascular risk factors, and epigenetic modifications (e.g. DNA methylation or histone modification) impacting atherosclerotic plaque development and cardiovascular risk during a lifetime. ACS, acute coronary syndrome; cRNA, coding RNA; DNA, deoxyribonucleic acid; IncRNA, long noncoding RNA; miRNA, micro RNA; RNA, ribonucleic acid.
However, despite epigenetics being increasingly linked to sexual dimorphism in the cardiovascular system, there is lack of adequately designed epigenetic studies assessing sex-specific effects of epigenetics in the development of ACS.

- **Mental stress and myocardial injury**

  Recent data indicate that women, especially young women, are particularly vulnerable to the detrimental associations of mental stress and cardiovascular health (Rutledge, et al. 2016). (Figure 11). Accordingly, women seem to perceive greater psychological stress following an acute type 1 or type 2 MI as compared to men, which, in turn, is associated with worse recovery and prognosis. (Xu, et al. 2015).

  As young women with ischaemic heart disease are a group with unexplained high mortality, these gender differences in mental stress responses are of particular importance and emphasize the need for a better evaluation of the psychosocial domain in order to risk stratify these women. The underlying psychological and biological mechanisms accounting for the adverse vascular response to psychological stress in women are not well understood.

Further, a link between the limbic system and long-term cardiovascular outcomes has recently been demonstrated (Tawakol, et al. 2017). and gender-stratified data indicate that this link might be pathogenic in women, but not in men. (Fiechter, et al. 2019).

- **Ischaemia and non-obstructive coronary artery disease (INOCA).**

Increasing evidence supports the notion that obstructive CAD alone is insufficient to explain symptoms of myocardial ischaemia. (Pizzi, et al. 2016). Indeed, microvascular angina, defined as symptoms and objective evidence of myocardial ischaemia along with non-obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve >0.80) and a reduction of CFR and/or inducible microvascular spasm, (Ong, et al. 2018), affects approximately 50% of patients with non-obstructive CAD or normal imaging findings. (Jespersen, et al. 2012).

Despite the absence of obstructive epicardial stenosis in these patients, they may present with severe myocardial ischaemia (ischaemia and non-obstructive CAD). or even MI (MI and non-obstructive CAD). These conditions are more frequently observed in women, given the lower burden of obstructive CAD in the female population (Figure 11). In fact, the presence of microvascular angina is twice as prevalent in women than men. (Jespersen, et al. 2012).

The former portends a particularly high risk in women, as event-free survival is reduced in women with impaired CFR or coronary reactivity. As PET-derived CFR reflects the haemodynamic effects of focal, diffuse and microvascular CAD on myocardial tissue perfusion, impaired CFR
seems to be an important target for coronary microvascular disease (CMVD). risk reduction in women. Indeed, CMVD might also contribute to the pathogenesis of HFpEF, another condition more commonly observed in women. (Srivathara, et al. 2016).

Thus, is it crucial that symptomatic patients who do not show regional ischaemia associated with flow-limiting epicardial CAD undergo further testing. Although some studies demonstrate an improvement of prognosis by revascularization therapies (coronary artery bypass grafting, CABG). in patients with severely impaired CFR, (Taqueti, et al. 2015), treatment of CMVD usually includes standard anti-ischaemic drugs (b-blockers, angiotensin-converting enzyme inhibitors, and nitrates).

The diagnosis of CMVD requires a complex diagnostic work-up such as myocardial perfusion PET or invasive vasoreactivity testing; thus, optimal clinical assessment and pre-test risk stratification is crucial in order to avoid unnecessary costs and risk.

In this regard, a blunted heart rate response during pharmacological stress testing has recently been shown to be a strong predictor of impaired CFR in women and may be a helpful marker to risk-stratify the heterogeneous population of patients with non-obstructive CAD. (Haider, et al. 2019).
• Gender and symptoms of myocardial ischaemia

Chest pain or pressure is the presenting symptom in >80% of women and men with ACS. However, women present with a greater number of additional non-chest pain symptoms than men such as neck pain, fatigue, dyspnoea, or nausea. (Lichtman, et al. 2018).

Further, women are more likely than men to present without chest pain and more often attribute their symptoms to a non-heart-related condition such as acid reflux, stress, or anxiety. (Lichtman, et al. 2018). Also, women in general wait longer to seek medical attention and are less likely to have diagnostic electrocardiography changes and elevated troponin levels on admission (Figure 12).

Accordingly, women are at an increased risk for an incorrect diagnosis and delayed treatment as evidenced by numerous studies reporting substantial system delays in women. (Gebhard, et al. 2019). In addition, women who present with ACS tend to be older and have more comorbidities than their male counterparts. (Blomkalns, et al. 2005).

Of note, however, young age and the absence of chest discomfort are among the strongest predictors of a missed diagnosis of ACS and inappropriate discharge from the emergency department. (Pope, et al. 2000). 

Further, recent observational studies in younger demographic groups report a higher prevalence of comorbidities including depression, hypertension, diabetes, and obesity in younger women with ACS as compared to age-matched men, suggesting that gender -disparities in effective management and outcomes of ACS cannot be attributed to age alone. (Chandrasekhar, et al. 2018).
• Differential diagnosis of acute coronary syndrome

Contemporary strategies for managing patients presenting with typical or atypical symptoms, an abnormal electrocardiography and raised serum troponin presume a diagnosis of an acute type 1 MI. However, in up to 10% of all patients, and in up to one-third of female patients, no culprit coronary lesion is identified angiographically. *(Mehta, et al. 2016).*

In these cases, the differential diagnosis includes apparently non-significant CAD such as plaque erosion, arrhythmias, coronary vasospasm (CVS), spontaneous coronary artery dissection (SCAD), Takotsubo cardiomyopathy, and myocarditis (Figure 12).

While magnetic resonance imaging studies indicate that the latter seems to be present in the majority of cases where a culprit lesion is not identified, *(Baccouche, et al. 2009)*. a high index of suspicion for Takotsubo cardiomyopathy, CVS, and SCAD should be maintained when evaluating women. *(Ghadri, et al. 2015).*

Takotsubo cardiomyopathy is characterized by transient left ventricular dysfunction resulting from severe emotional stress and usually resolves with a favourable prognosis. Although Takotsubo cardiomyopathy only accounts for up to 3% of all ACS cases, it is twice as prevalent in postmenopausal women *(Ghadri, et al. 2015).* (Figure12).

Spontaneous coronary artery dissection is an infrequent and often missed differential diagnosis of ACS and is characterized by a spontaneous separation of coronary arterial layers ultimately leading to

Recent epidemiological series suggest that SCAD occurs in 1–4% of ACS cases and may be the cause of ACS in up to 35% of women <50 years of age and in 43% of pregnancy-related ACS (Hayes, et al. 2018) (Figure 13) The latter is associated with a poorer prognosis than pregnancy-unrelated SCAD .(Tweet, et al. 2017).

In-hospital mortality rates of SCAD are low, however, up to 14% of patients require urgent in hospital revascularization. Non-atherosclerotic SCAD is typically associated with female sex, multiparity, physical, and emotional stress triggers, systemic arteriopathies including fibromuscular dysplasia, inflammatory, connective tissue disorders, coronary artery spasm, and hormonal therapy. (Hayes, et al. 2018).

Although hormonal changes seem to play a major role in female SCAD, much remains to be explored on detailed molecular mechanisms by which sex hormones modulate arterial wall architecture and endothelial function.

Coronary vasospasm is caused by intense vasoconstriction of coronary arteries occurring most often at rest, particularly between midnight and early morning. Although the prognosis is generally considered benign, CVS can lead to total or subtotal vessel occlusion and subsequent ACS.

Coronary vasospasm is diagnosed by coronary angiography and provocative testing and has been detected in 49% of patients with ACS in a German population. (Ong, et al. 2008).
Coronary vasospasm appear to be more prevalent among men than women, affecting mainly age groups between 40 and 70 years and is more common in Asian populations as compared to Western countries (Hung, et al. 2014). (Figure 1). Vascular mechanisms triggering CVS episodes include transient sympatho-vagal imbalance as well as decreased bioavailability of vasodilators such as nitric oxide. (Egashira, et al. 1996). Age, high-sensitivity C-reactive protein, and smoking have all been identified as significant risk predictors of CVS. (Hung, et al. 2014). The latter has been suggested to account for the higher prevalence of CVS seen in men.

- **Diagnosis and disease management of acute coronary syndrome**

Another issue remaining actively debated is whether there are still inequities in diagnosis and disease management, leading to gender disparities in outcomes among patients with ACS. An excess risk for mortality in women with ACS, in particular for younger women. (Nielsen, et al. 2014).

Female coronary pathophysiology such as a higher prevalence of CMVD and non-obstructive CAD, atypical symptoms, delay in seeking care, underutilization of evidence-based diagnostics and therapies, and a higher rate of complications during revascularization have all been suggested to account for these findings.

Indeed, management strategies for ACS have largely been the same for women and men while focused predominantly on obstructive CAD: risk stratification schemes for ACS including the HEART, the Global Registry of Acute Coronary Events (GRACE)., and the TIMI risk scores.
as well as the Killip classification are derived from predominantly male populations and their ability to adequately risk-stratify women with suspected ACS remains debatable. *(Agrawal, et al. 2015).*

Similarly, current clinical practice does not consider sex-specific cut-off values for cardiac troponin given the small differences in high sensitive troponin I between men and women. However, evidence demonstrates improved risk stratification in patients with ACS when a sex-specific 99th centile threshold of high sensitive troponin I is being used. *(Cullen, et al. 2016).*

Whether the lack of sex-specific guidelines or the high percentage of women presenting with atypical symptoms and comorbidities account for the fact that women are less likely than men to undergo invasive revascularization remains to be determined. *(Worrall-Carter, et al. 2016).*

In addition, low adherence to prescribed therapies as well as underutilization of cardiac rehabilitation and pharmacotherapies in women with ACS has been reported. *(Resurreccion, et al. 2019).*

Indeed, women are less likely than men to receive optimal secondary prevention with anti-platelet and lipid-lowering therapies even after angiographic documentation of disease. *(Peters, et al. 2018).*

These disparities persist in contemporary practice, despite studies documenting the reduction of this excess mortality when optimal care is provided. *(Li, et al. 2016).*
• Outcomes of acute coronary syndrome in women and men

**Short- and long-term mortality**

Although there is evidence that gender-disparities in short-term ACS mortality can be overcome in high-quality percutaneous coronary intervention (PCI). centres,(Ghadri,*et al*.2015).

Studies have consistently demonstrated less favourable short-term outcomes in women with ACS as compared to men, particularly after ST-elevation myocardial infarction (STEMI).(Cenko,*et al*.2018). The female susceptibility to adverse short-term outcomes following STEMI was attributed to their older age at presentation, the higher prevalence of comorbid conditions in women as well as longer system delays and underutilization of guideline directed therapies in women with ACS. (Cenko,*et al*.2019).

Accordingly, sex and gender differences were attenuated when adjustment for comorbidities was performed.(Vaccarino,*et al*.2005). In contrast to short-term outcomes, gender-specific data regarding long-term morbidity and mortality following ACS are conflicting.

While long-term outcomes were similar for women and men in earlier studies, more recent work indicates that long-term morbidity and mortality following ACS is higher in women as compared to men, though these gender-disparities are no longer evident following adjustment for baseline variables.(Zachura,*et al*.2019).
Of note, however, studies report consistently worse short- and long-term outcomes in young and middle-aged women as compared to age-matched men. (Dreyer, et al. 2015).

As previously discussed, this demographic group presents with an overall worse health status and encounters significant system delays and inequities in diagnosis and treatment, all of which might explain the excess risk in this population. (D’Onofrio, et al. 2015).

- **Outcomes of coronary revascularization**

  Current guidelines recommend immediate coronary angiography in patients with type 1 MI—STEMI as well as in patients with type 1 MI—NSTEMI (non-ST-elevation myocardial infarction), presenting with refractory angina or electrical/haemodynamic instability independent of gender.

  An early invasive strategy (within 24 h of diagnosis), is recommended for individuals with NSTEMI and stable clinical presentation but high-risk features according to current (gender unspecific) risk scores. Benefits of an early invasive strategy have been proven for both, men and women, while a very early invasive strategy within 12 h of diagnosis improved outcomes in high-risk NSTEMI patients, but did not benefit women. (Kofoed, et al. 2018).

  Of note, despite an overall benefit of invasive revascularization, female sex has consistently been associated with an increased risk of bleeding and vascular complication during PCI (Lichtman, et al. 2014), which underscores the need to consider key biological differences such as vessel size and prevalence of non-obstructive CAD and to strictly apply guideline-directed care in women.
Indeed, an increased risk of restenosis, repeat revascularization, and access-site complications in women attributable to their smaller coronary arteries and the frequent occurrence of radial artery vasospasm and subsequent radial-to-femoral access crossover all need to be taken into account when treatment decisions in women are made (Mason, et al. 2018). (Figures 11 and 12).

While there are currently no gender-specific data available on outcomes in patients with acute type 1 MI unsuitable for PCI who undergo early CABG, observational studies report higher risks for short- and long-term mortality following CABG in women as compared to age-matched men, even when adjusted for age and comorbidities. (Dalen, et al. 2019).

Instead, perioperative complications seem to be similar in women and men, except for a higher incidence of sternal wound infections in female patients. (Schoell, et al. 2019).

Women’s smaller arteries and the challenges of surgical grafting to smaller targets, a longer cross clamp time per graft, a lesser use of internal mammary artery grafts in women, and a worse preoperative health status in women might all account for the gender differences in outcomes following CABG surgery.

Importantly, recent studies report a significant increase in the incidence of ACS in pregnant women. (Smilowitz, et al. 2018). The latter is consistent with the recent rise seen in prevalence of CAD in younger, premenopausal women. (Arora, et al. 2019).

According to latest European Society of Cardiology guidelines, primary PCI is recommended in pregnant patients with acute type I MI—
STEMI consistent with standard indications for revascularization (class I recommendation), while a non-invasive approach is favoured in stable, low-risk patients with type 1 MI—NSTEMI (class IIa recommendation). (Regitz-Zagrosek, et al. 2018).

- **Risk of thrombosis and bleeding**

  The risks of thrombosis and bleeding differ between men and women. These sex differences have been attributed to the higher age of women with ACS, comorbidities, and body weight. (Renda, et al. 2019).

  In addition, women experience fluctuations of pro-thrombotic activity and haemostasis that are related to the menstrual cycle, the use of hormonal contraceptives or HRT, pregnancy, and menopause, (Renda, et al. 2019).

  All of which might contribute to sex differences in the thrombotic or haemorrhagic burden in women with ACS. Indeed, the higher risk of bleeding complications during PCI observed in women might in part be related to an oestrogen-dependent increase of prostacyclin secretion and nitric oxide bioavailability as well as a direct inhibitory effect of oestrogen on platelet aggregation. (Sowers, et al. 2005).

  Of note, however, there is conflicting evidence regarding sex differences in baseline and on treatment platelet reactivity. (Singla, et al. 2013). In fact, while some studies report a more pronounced platelet adhesion to the site of injury in men as compared to women, (Lawrence, et al. 1995), others have demonstrated a greater baseline and agonist-induced platelet reactivity and aggregation in women (Alexander, et al. 2006), (Becker, et al. 2006).
The latter contrasts with an up to 25% longer in vivo bleeding time in women as compared to men. Thus, further research is necessary to disentangle the complex interaction between haemostasis, sex, and hormone status at baseline and in the context of an ACS.

In mainly postmenopausal cohorts, smaller arteries and related access-site complications as well as inappropriate dosing of antithrombotic agents irrespective of body weight have been suggested to account for their excess bleeding risk. (Ahmed, et al. 2009).

Indeed, female sex was associated with an enhanced risk of non-bypass related bleeding events in the prasugrel and ticagrelor arms of the TRITON-TIMI 38 and the PLATO trials. (Wallentin, et al. 2009).

In contrast, no interaction between female sex and excess bleeding was seen in a meta analysis comparing clopidogrel plus aspirin vs aspirin, (Berger, et al. 2009). and a recent meta-analysis reported a comparable efficacy and safety profile of potent P2Y12 inhibitors including prasugrel, ticagrelor, and intravenous cangrelor in women and men. (Lau, et al. 2017).

In contrast, however, recent data from the CRUSADE initiative indicate that women with type 1 MI—NSTEMI were more likely to receive excess glycoprotein (GP) IIb/IIIa doses than men, with the latter being associated with an increased risk of bleeding. (Alexander, et al. 2006). Taken together, these data indicate that sex should not influence patient selection for the administration of P2Y12 inhibitors; however, special attention has to be paid in women to properly apply weight- and age-adjustments of anti-thrombotic agents including GPIIb/IIIa inhibitors, heparins, and prasugrel. Indeed, up to one-fourth of
sex-related differences in bleeding risk seem to be avoidable. (*Alexander, et al. 2006*).

As previously outlined, a significant rise in the incidence of ACS is currently being observed in pregnant women. (*Smilowitz, et al. 2018*). Pregnancy is a procoagulant state, aimed at preventing bleeding at the time of delivery and is characterized by an increase in the levels of coagulation factors, fibrinogen, and von-Willebrand factor, a reduction of activity of protein S and C, and an increase in plasminogen activator inhibitor type 1 and 2. (*Trigg, et al. 2011*).

Unfortunately, current guidelines provide little information regarding the use of antiplatelet therapy in pregnant women with ACS. A recommendation is only given for aspirin, short-term heparinization during PCI and for clopidogrel, which should solely be used when strictly necessary and for the shortest duration. The use of GPIIb/IIIa inhibitors, bivalirudin, prasugrel, and ticagrelor is not recommended due to the lack of data in pregnant women. (*Regitz-Zagrosek, et al. 2018*).
Study Design:

This was an observational, cohort, single center study that included all patients with ACS who were admitted at coronary care unit at “Benha University hospital” in the period from April 2019 to April 2020, we aimed to study the clinical outcome in this category of patients and to evaluate the impact of gender on this outcome.

Key inclusion criteria:

* patients with all categories of ACS with (UA-NSTEMI-STEMI).

Key exclusion criteria:

* patients with stable CAD
* patients with comorbidities which may have impact on the life span of the study population

Methods

Baseline evaluation:

All patients had review of medical history including

Demographic data (age, sex), risk factors of coronary artery disease (Diabetes mellitus, HTN-dyslipidemia, smoking – Family History of ischemic heart disease), prior history of coronary artery disease, prior history of intervention, other comorbidities, cardiac medications.

Full clinical examination

With particular emphasis on the pulse and blood pressure of the patients, as well as auscultation of the back to elicit the presence of any clinically detectable pulmonary venous congestion, auscultation of the heart for the presence of third heart sounds or audible murmurs.
Baseline Electrocardiography:

- Twelve leads ECG will be done for each patient.
- Cardiac biomarkers: including troponins and CK-MB

Transthoracic Echocardiography:

All patients evaluated at baseline and 6 months follow up by transthoracic echocardiography and speckle tracking, for the assessment of regional wall abnormalities and overall left ventricular systolic function and Global Longitudinal Peak Systolic Strain (GLPSS).

Speckle tracking echocardiography:

Longitudinal strain measurements with the implementation of 2D speckle tracking performed as previously described (Aggeli et al 2013). End-systole identified as corresponding to the aortic valve closure measured by pulsed-Doppler.

The operator traced the endocordial border on an end-diastolic frame and the software automatically tracked the border on the subsequent frames.

Adequate tracking can then be verified in real-time and corrected if deemed necessary by adjusting the region of interest or manually correcting the border to ensure optimal tracking. After the tracking process is completed myocardial deformation is plotted in time versus strain graphs, where it is possible to identify the different phases of cardiac cycle. Circumferential, radial strain parameters and their changes from rest (BASE), to low stress (MIN), peak stress (MAX), and recovery (REC), estimated.
Peak radial and circumferential strain (systolic and early diastolic), measured from mid short-axis view at rest, low and high dobutamine doses. Peak longitudinal strain measured from apical 4-, 3-chamber and 2-chamber views. Global strain analysis performed. According to the existing guidelines, GLPSS calculated from loops acquired from 2-, 3- and 4-chamber views (Aggeli et al., 2013).

**Study end points:**

**Primary end point:**

- A composite end point of inhospital and 6 months major adverse cardiovascular events including (all cause mortality, myocardial infarction, heart failure, need for revascularization) with gender specific differences.

**Secondary end point:**

- 6 months GLPSS in patients with ACS.

**Study Follow up:**

1) In hospital follow up: For clinical and echocardiographic evaluation with gender specific differences.

2) 6 months follow up including left ventricular remodeling using speckle tracking (GLPSS) and clinical outcome with gender specific differences.

**Statistical methods**

- Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United States)
- Numerical data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages.

- Comparisons between both genders were done using an independent t-test. Percent change of GLPSS at six months was compared using Mann Whitney U test. Categorical data were compared using the Chi-square test or Fisher’s exact test if appropriate.

- All P values were two-sided. P values less than 0.05 were considered significant.
Results

Study Population

The mean age was 58 ±12 years (56 ±11,62 ±11, in male and female respectively ,P-value<0.001), 40 % of patients were diabetic with (30%,59% in males and females respectively , p value <0.001).

As regard hypertensive 47 % of patients were hypertensives with (36%,68% in males and females respectively , p value<0.001) regarding smoking 41% were smokers with (36%,0.9% in males and females respectively with p value <0.001) ,As regards prior CAD there were 25 % of study population (23%.29% in males and females respectively ,p value <0.001) Of those 26% patients with prior PCI. (31%,19% in males and females respectively, P-value<0.023). There were no significant differences between both genders as regard CAGB, comorbidities, and dyslipidaemia. (table 6)

Table (6). General characteristics of study population & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years).</td>
<td>Mean±SD n (%)</td>
<td>58 ±12</td>
<td>56 ±11</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>409 (40).</td>
<td>204 (30).</td>
<td>205 (59).</td>
<td>&lt;0.001</td>
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<td>Hypertension</td>
<td>480 (47).</td>
<td>241 (36).</td>
<td>239 (68).</td>
<td>&lt;0.001</td>
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<td>Smoking</td>
<td>424 (41).</td>
<td>241(36).</td>
<td>3 (0.9).</td>
<td>&lt;0.001</td>
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<tr>
<td>Dyslipidemia</td>
<td>32 (3.1)</td>
<td>20 (2.9)</td>
<td>12 (3.4)</td>
<td>0.675</td>
</tr>
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<td>Prior CAD</td>
<td>255 (25)</td>
<td>153 (23)</td>
<td>102 (29)</td>
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<tr>
<td>Prior PCI</td>
<td>67 (26).</td>
<td>48 (31).</td>
<td>19 (19).</td>
<td>0.023</td>
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<tr>
<td>Prior CAGB</td>
<td>27 (10).</td>
<td>17 (11).</td>
<td>10 (10).</td>
<td>0.74</td>
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<tr>
<td>Comorbidities</td>
<td>149 (15).</td>
<td>95 (14).</td>
<td>54 (15).</td>
<td>0.541</td>
</tr>
</tbody>
</table>

CAD= coronary artery disease , PCI= percutaneous coronary intervention , CAGB= coronary artery bypass grafting
Results

Symptoms on admission

- chest pain was the main presenting symptom that was reported in 95% of the study population (97%, 92% in males and females respectively, p value 0.001). Dyspnea was reported in 5% (3%, 8% in males and females respectively, p value 0.001). Study population presented with arrhythmia was 2% (2%, 2% in males and females respectively, p value 0.7). Regarding cardiogenic shock, it was reported in 2% of study population (2%, 3% in males and females respectively, p value 0.07). (table 7)

Table (7). Symptoms on admission & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>n (%)</td>
<td>980 (95)</td>
<td>657 (97)</td>
<td>323 (92)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>n (%)</td>
<td>48 (5)</td>
<td>20 (3)</td>
<td>28 (8)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>n (%)</td>
<td>20 (2)</td>
<td>14 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Shock</td>
<td>n (%)</td>
<td>21 (2)</td>
<td>10 (2)</td>
<td>11 (3)</td>
</tr>
</tbody>
</table>

Clinical examination:

- The mean heart rate (80±19, 79±18, 81±20 in males and females respectively, P-value=0.17).
- Mean blood pressure were (127/80±32, 127/80±32, 128/80±34 in males and females, P-value=0.6).
- As regards the Killip class, the majority (89%) were class I. There were no significant differences between both genders regarding heart rate, SBP, DBP, Killip class. (table 8)
Table (8). Clinical examination of the study population & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>80 ±19</td>
<td>79 ±18</td>
<td>81 ±20</td>
<td>0.17</td>
</tr>
<tr>
<td>Systolic blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td>127 ±25</td>
<td>127 ±25</td>
<td>128 ±26</td>
<td>0.637</td>
</tr>
<tr>
<td>Diastolic blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td>80 ±14</td>
<td>80 ±14</td>
<td>80 ±15</td>
<td>0.633</td>
</tr>
<tr>
<td>KILLIP CLASS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I n%</td>
<td>918(89)</td>
<td>607(90)</td>
<td>311(89)</td>
<td>0.948</td>
</tr>
<tr>
<td>II</td>
<td>76 (7)</td>
<td>50 (7)</td>
<td>26 (7)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>27 (3)</td>
<td>17 (3)</td>
<td>10 (3)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>7 (1)</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Type of ACS :

- The majority (48%) of the study population presented with STEMI (54%, 38% in males and females respectively, p value <0.001).
- where NSTEMI patients were 16% with (16%, 16% in males and females respectively, p value <0.001). (table 9), (figure 14)
- who presented with UA were 36% of study population with (31%, 45% in males and females respectively P value <0.001).

Table (9). Type of ACS on admission & according to gender

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA n(%)</td>
<td>367 (36)</td>
<td>208 (31)</td>
<td>159 (45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSTEMI n(%)</td>
<td>164 (16)</td>
<td>107 (16)</td>
<td>57 (16)</td>
<td></td>
</tr>
<tr>
<td>STEMI n(%)</td>
<td>497 (48)</td>
<td>363 (54)</td>
<td>134 (38)</td>
<td></td>
</tr>
</tbody>
</table>
Figure (14) Type of ACS on admission & according to gender

فضل segments in STEMI patients:

- anterior wall was reported in majority of cases 25% with (25%, 23% in males and females respectively, p value <0.612). followed by inferior wall reported in 14% with (12%, 20% in males and females respectively, p value 0.014), while the least frequent segment involved was posterior and inferolateral walls 1% with (1%, 1% in males and females respectively, p value 1.0) and 1% with (2%, 1% in males and females respectively, p value 0.447) respectively. (table 10), (figure 15)

- There were no significant differences between both genders as regards all target segments of STEMI except for inferior wall.
Table (10). Target segment of STEMI & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (497)</th>
<th>Males (n = 363)</th>
<th>Females (n = 134)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>n (%)</td>
<td>123 (25)</td>
<td>92 (25)</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>n (%)</td>
<td>20 (4)</td>
<td>17 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Extensive anterior</td>
<td>n (%)</td>
<td>31 (6)</td>
<td>23 (6)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>High lateral</td>
<td>n (%)</td>
<td>26 (5)</td>
<td>18 (5)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Missed anterior</td>
<td>n (%)</td>
<td>49 (10)</td>
<td>35 (10)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Inferior</td>
<td>n (%)</td>
<td>69 (14)</td>
<td>42 (12)</td>
<td>27 (20)</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>n (%)</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>INF RT</td>
<td>n (%)</td>
<td>40 (8)</td>
<td>32 (9)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>INF post</td>
<td>n (%)</td>
<td>40 (8)</td>
<td>30 (8)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>INF RT post</td>
<td>n (%)</td>
<td>27 (5)</td>
<td>17 (5)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>INF RT LAT post</td>
<td>n (%)</td>
<td>21 (4)</td>
<td>17 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Post</td>
<td>n (%)</td>
<td>5 (1)</td>
<td>4 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Missed inf</td>
<td>n (%)</td>
<td>25 (5)</td>
<td>17 (5)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>n (%)</td>
<td>17 (3)</td>
<td>14 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>n (%)</td>
<td>7 (1)</td>
<td>6 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
**Results**

![Bar chart showing the target segment of STEMI according to gender](chart.png)

**Figure (15).** Target segment of STEMI & according to gender
**Echo-cardiographic Data**

- Baseline left ventricular EF of the study population was 54±12 (53±12,57±12 in males and females respectively, P-value <0.001). (figure 16), regarding RWMA was reported in (66%) of the study population (71%,55% in males and females respectively, p value <0.001), as regard moderate mitral regurge was found in 12% with (10%,15% in males and females respectively) and severe mitral regurge was reported in 7% with (4%, 13% in males and females respectively, p value <0.001), regarding Mean EDD was 4.88±1.04 in the whole study population. It was significantly higher in males (4.95) than females (4.75); the P-value was 0.045. and Mean ESD was 3.73±0.91, and it showed no significant differences between both genders. and regarding Mean 3D EF was 50, and it was significantly higher in females (53%). compared to males (49%); the P-value was <0.001.(table 11).

![Figure 16](image)

Figure (16). Ejection fraction in the whole study population & according to gender
Table (11). Echocardiographic Data & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EF</strong></td>
<td>Mean ±SD</td>
<td>54 ±12</td>
<td>53 ±12</td>
<td>57 ±12</td>
</tr>
<tr>
<td><strong>RWMA</strong></td>
<td>n (%)</td>
<td>677 (66)</td>
<td>483 (71)</td>
<td>194 (55)</td>
</tr>
<tr>
<td><strong>MR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NoMR</td>
<td>n (%)</td>
<td>401 (39)</td>
<td>275 (41)</td>
<td>126 (36)</td>
</tr>
<tr>
<td>Moderate</td>
<td>n (%)</td>
<td>120 (12)</td>
<td>69 (10)</td>
<td>51 (15)</td>
</tr>
<tr>
<td>Severe</td>
<td>n (%)</td>
<td>70 (7)</td>
<td>25 (4)</td>
<td>45 (13)</td>
</tr>
<tr>
<td><strong>VSR</strong></td>
<td>n (%)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>EDD</strong></td>
<td>Mean ±SD</td>
<td>4.88 ±1.04</td>
<td>4.95 ±1.04</td>
<td>4.75 ±1.02</td>
</tr>
<tr>
<td><strong>ESD</strong></td>
<td>Mean ±SD</td>
<td>3.73 ±0.91</td>
<td>3.8 ±0.91</td>
<td>3.61 ±0.92</td>
</tr>
<tr>
<td><strong>3D EF</strong></td>
<td>Mean ±SD</td>
<td>50 ±12</td>
<td>49 ±11</td>
<td>53 ±12</td>
</tr>
</tbody>
</table>

EF = Ejection fraction
RWMA = regional wall motion abnormality
MR = Mitral regurge
VSR = Ventricular septal rupture
EDD = End diastolic dimension
ESV = End systolic dimension

**WMSI in different ACS types**

WMSI showed an overall significant difference between different types of ACS. Overall P-value was <0.001. Post-hoc analysis revealed that it was significantly lower in UA (1.15) than NSTEMI (1.25) and STEMI (1.29) with No significant difference was reported between NSTEMI and STEMI (table 12),(figure 17).
Table (12). WMSI in different ACS types

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1028)</th>
<th>UA (n = 367)</th>
<th>NSTEMI (n = 164)</th>
<th>STEMI (n = 497)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMSI Mean ±SD</td>
<td>1.23 ±0.26</td>
<td>1.15 ±0.22</td>
<td>1.25 ±0.28</td>
<td>1.29 ±0.25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**figure (17). WMSI in different ACS types**

- Regarding **GLPSS**, Mean GLPSS of the study population at baseline was -16.9±3.6 with (-16.7±3.7, -17.3±3.5 in males and females respectively, p value 0.012), and at 6 months, the Mean GLPSS was -13.1±3.1 with (-13.2±3.1, -12.8±2.9 in males and females respectively, p value 0.052). (table 13), (figure 18).
### Table (13). GLPSS at baseline & 6 months outcome & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean ±SD</td>
<td>-16.9 ±3.6</td>
<td>-16.7 ±3.7</td>
<td>-17.3 ±3.5</td>
<td>0.012</td>
</tr>
<tr>
<td>At six months</td>
<td>Mean ±SD</td>
<td>-13.1 ±3.1</td>
<td>-13.2 ±3.1</td>
<td>0.052</td>
</tr>
<tr>
<td>% change Median</td>
<td>-25.3</td>
<td>-22.28</td>
<td>-30.44</td>
<td>0.002</td>
</tr>
</tbody>
</table>

GLPSS = Global Longitudinal Peak Systolic Strain

**Figure (18).** GLPSS at baseline & 6 months in the whole study population & according to gender
In hospital Management strategy:

Conservative management was applied to 59% of studied patients (56%, 65% in males and females respectively, p value 0.007), thrombolytic therapy was applied to 33% of studied patients with (36%, 25% in males and females respectively, p value 0.001). Regarding interventional therapy, was applied to 6% (7%, 5% in males and females respectively, p value = 0.336), PPCI was the most frequent intervention being applied to 33% of study population with (40%, 18% in males and females respectively, p value = 0.105), rescue PCI was applied to 26% with (23%, 29% in males and females respectively, p value = 0.62). (table 14), (figure 19).

All patients with NSTE-ACS were on conservative management except for patients with (refractory chest pain to all line of medical treatment, malignant arrhythmia unresponsive to anti ischemic and anti arrhythmic medications, hemodynamic compromisation). underwent emergency PCI which was applied to 22% with (16%, 35% in males and females respectively, p value = 0.107). and The least frequent interventions were pharmaco-invasive PCI which applied to 2% of patients with (2%, 0% in males and females respectively, p value = 1.0). and There were no significant differences between both genders as regards all interventional therapies. (table 14), (figure 19).
Results

Table (14). In hospital management strategy & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>n(%)</td>
<td>605 (59)</td>
<td>379 (56)</td>
<td>226 (65)</td>
</tr>
<tr>
<td>Thrombolytic</td>
<td>n(%)</td>
<td>334 (33)</td>
<td>245 (36)</td>
<td>89 (25)</td>
</tr>
<tr>
<td>Intervention</td>
<td>n(%)</td>
<td>60 (6)</td>
<td>43 (7)</td>
<td>17 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 60)</th>
<th>Males (n = 43)</th>
<th>Females (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPCI</td>
<td>n(%)</td>
<td>20 (33)</td>
<td>17 (40)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>P PTCA</td>
<td>n(%)</td>
<td>8 (13)</td>
<td>6 (14)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Emergency PCI</td>
<td>n(%)</td>
<td>13 (22)</td>
<td>7 (16)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>n(%)</td>
<td>15 (26)</td>
<td>10 (23)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Pharmaco-invasive PCI</td>
<td>n(%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

figure (19). In hospital management strategy & according to gender
**Results**

- **In Hospital Outcome:**

  - the most frequent complication was mortality accounting for 5% with (4%, 6% in males and females respectively, p value=0.146), followed by re-hospitalization due to acute coronary syndrome was reported in 4% with (5.3%,4.9% in males and females respectively, p value=0.756), regarding Re-infarction reported in 1% with (1%,1.4% in males and females respectively, p value=0.575), stroke (total =1%, male =1%, female =1%, p value=0.87), and major non cerebral bleeding was in 0.8% (0.6%,0.9% in males and females respectively, p value=0.695). There were no significant differences between both groups regarding all reported in hospital outcome (table 15), (figure 20).

<table>
<thead>
<tr>
<th></th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-infarction</td>
<td>n (%)</td>
<td>12 (1)</td>
<td>7 (1)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>n (%)</td>
<td>11 (1)</td>
<td>7 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>n (%)</td>
<td>7 (1)</td>
<td>4 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Re-hospitalization</td>
<td>n (%)</td>
<td>53 (4)</td>
<td>36 (5.3)</td>
<td>17 (4.9)</td>
</tr>
<tr>
<td>Mortality</td>
<td>n (%)</td>
<td>48 (5)</td>
<td>27 (4)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>ECG changes</td>
<td>n (%)</td>
<td>229(22)</td>
<td>146 (22)</td>
<td>83 (24)</td>
</tr>
</tbody>
</table>
Results

Figure (20). in hospital outcome& according to gender

Six months outcome:

- Thirteen % of patients were readmitted due to acute coronary syndrome with (12%,12% in males and females respectively ,p value=0.188), and Re-vascularization occurred in 6% of patients with (6%,7% in males and females respectively ,p value=0.282).as regard Heart failure was reported in 5% with (4%,6% in males and females respectively ,p value=0.197). regarding Mortality occurred in 1% with 1 %,1% in males and females respectively,p value=0.285), stroke occurred in 0.3% with (0.3%,0.3% in males and females respectively ,p value=1.0).(table 16),(figure 21).

- There were no significant differences between both genders regarding re-ischemia, stroke, heart failure, revascularization, and mortality. (table 16),(figure 21).
Results

Table (16). six months outcome & according to gender

<table>
<thead>
<tr>
<th></th>
<th>Total (1028)</th>
<th>Males (n = 678)</th>
<th>Females (n = 350)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-ischemia</td>
<td>n (%)</td>
<td>133 (13)</td>
<td>81 (12)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>Stroke</td>
<td>n (%)</td>
<td>3 (0.3)</td>
<td>2 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>n (%)</td>
<td>52 (5)</td>
<td>30 (4)</td>
<td>22 (6)</td>
</tr>
<tr>
<td>Re-vascularization</td>
<td>n (%)</td>
<td>62 (6)</td>
<td>37 (6)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>n (%)</td>
<td>10 (1)</td>
<td>5 (1)</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

Figure (21). six months outcome & according to gender
The incidence and presentation of cardiovascular disease differ between men and women, possibly because of the protective effect of oestrogen. The direct actions of oestrogen on blood vessels may contribute substantially to this cardiovascular protective effect, but a lipid-lowering effect may also be involved. (Medina, et al. 2020).

Rupture of an atherosclerotic plaque is the most common type of plaque complication, but in some cases the thrombus appears to be superimposed on a de-endothelialised, but otherwise intact, plaque (“plaque erosion”). This is more often seen in younger individuals and women. (Rosengren, et al. 2004). In an autopsy study of women who had died suddenly from coronary heart disease or who had died from non-coronary causes, women >50 years were much more likely to have a ruptured plaque than were younger, premenopausal women, suggesting that oestrogen affects plaque stabilisation. Plaque erosion, which is possibly the major substrate for thrombosis in premenopausal women, may not be inhibited by oestrogen. (Burke, et al. 2001).

It is likely that the variations in clinical presentation that we observed reflect, to some extent, a different and possibly less severe disease in younger women. In the current study we evaluate the clinical outcome of patients with acute coronary syndrome (ACS), regarding gender specific differences.

There are many possible causes of the gender differences in CVD, Although women and men share most classic risk factors, the significance and the relative weighting of these factors are different. As regatrd to LGaG Locorotondo Some researchers have documented that age, hypertension, total cholesterol and low-density lipoprotein (LDL)-cholesterol have a great influence in men. But smoking, diabetes,
triglyceride and high-density lipoprotein (HDL)-cholesterol levels mainly have effect on women. *(LGaG Locorotondo, 2015).*

In our study, the mean age of the study population was 58 years. It was significantly higher in females (62 years) compared to males (56 years); and this was concordant with *LGaG Locorotondo* who showed that Cardiovascular disease has a significant correlation with age, but varies in gender. In men, the risk profile of cardiovascular disease increases linearly over time and the atherosclerotic process is constantly evolving. Conversely, because estrogen has a beneficial effect on the cardiovascular system, women during the fertile age can be protected from atherosclerosis. *(LGaG Locorotondo, 2015).*

However, according to *Stoberock, et al* the incidence of stroke among menopausal women increases significantly and the prevalence of hypertension in women over 75 years is also higher than that of men *(Stoberock, et al., 2016).* and those results was in concordance with results of our study. 46.7% were hypertensive. Hypertension was significantly higher in females (68.3%) compared to males (35.5%); the P-value was <0.001.

And this was discordant with *Ciarambino* who told that Hypertension is strongly associated with cardiovascular disease and is an important cause of left ventricular hypertrophy, (diastolic). heart failure and stroke *(Ciarambino, 2018).*

A different trend has been observed about systolic and diastolic blood pressure (BP) between genders. Systolic BP is higher in young men compared to young females. In fact, in young men the most frequent form of hypertension is isolated systolic hypertension according to *Burt, et al.* *(Burt, et al, 1995).* We found that mean systolic and diastolic
blood pressure were 127 & 80, respectively. There were no significant differences between both genders regarding heart rate, SBP, DBP, shock, and Killip class. Regarding dyslipidemia, there were no significant differences between both genders in our study; this was LGaG Locorotondo who found that total cholesterol is an important cardiovascular risk factor for both men and women, but elevated low-density lipoprotein cholesterol (LDLC) is more likely to increase the risk of cardiovascular in men than in women while high-density lipoprotein cholesterol (HDL-C) levels mainly act in women.

The prevalence of elevated total cholesterol is similar between gender (Appelman, et al. 2015). According to a meta-analysis (Sarah, et al. 2007), in both men and women, each 1 mmol/L total cholesterol reduction can reduce the risk of mortality from CHD with about a half lower in early middle age (40–49 years), about a third lower half in later middle age (50–69 years old), and about a sixth lower in old age (70–89 years old). (Appelman, et al. 2015).

The LDL-C has a greater influence in men than women (LGaG Locorotondo, 2015). At a young age (<50 years), women are at a lower risk of suffering from hypercholesterolemia than men. However, the LDL-C level rises by 14% during the menopause (Abbey, et al. 1999). So women over the age of 65 have higher average LDL-C than men.

Therefore, it can be important to reevaluate the lipid profile after menopause and find a premenopausal threshold. Besides, there is substantial evidence supporting that the use of statins to reduce LDL-C can reduce the risk of subsequent coronary heart disease (Laslett, et al. 2012).
Discussion

It has been shown that reduced HDL-C is responsible for CHD in both young and old women and predicts CHD mortality more in women than in men (LGaG Locorotondo, 2015). And the Framingham study has shown that a low HDL-C implicates a higher CHD risk in women than in men (Kanne, et al, 1971).

Regarding Smoking, in our study, 41.2% were smokers. Smoking was significantly higher in males (62.1%). compared to females (0.9%); the P-value was <0.001. As incidence but regarding effect, it was concordant with Grundtvig, et al and Prescott, et al.

Grundtvig, et al found that at younger ages (<50 years). smoking is more deleterious in women than in men, with a larger negative impact of the same number of cigarettes smoked per day. (Grundtvig, et al, 2009).

And Tsang, et al who found that the association between smoking and CVD risk was higher in women than in men. Their study(DANISH study). showed that women who smoke had a 50% greater CHD risk than their male counterparts. (Tsang, et al, 2000).

Smoking is associated with a greater risk of a first acute myocardial infarction (AMI). in women than in men according to Maas AHEM, Appelman YEA (Maas AHEM, Appelman YEA.2010).

It may be due to smoking causing a downregulation of the oestrogen-dependent vasodilatation of the endothelial wall (Gao, et al. 2019). The expected burden of smoking-related diseases may become greater in women than in men, not only because of changes of the role of smoking in sociology, but also because of a potentially stronger association between prolonged smoking and the risk of CVD in women than in men as postulated by Giovino, et al. (Giovino, et al. 2012).
As regard Diabetes, our study showed that, 39.8% were diabetics. It was significantly higher in females (58.6%). compared to males (30.1%).; the P-value was <0.001. this was in agreement with Bassuk, et al that showed that increases coronary heart disease risk of threefold to sevenfold in women and of twofold to threefold in men. (Bassuk, et al. 2010).

also Maas AHEM, Appelman YEA found that women with diabetes had a 50% higher risk of fatal CHD compared with men with diabetes. The causes of the higher mortality in women are multifactorial and may be related to heavier risk factor burden, more involvements in inflammatory factors, smaller coronary vessel size, and treatment of diabetes in women are usually less positive. Maas AHEM, Appelman YEA (Maas AHEM, Appelman YEA. 2010).

The mean heart rate was 80 b.p.m. Mean systolic and diastolic blood pressure were 127& 80, respectively. 2.0% were shocked. As regards the Killip class, the majority (89.3%). were class I. There were no significant differences between both genders regarding heart rate, SBP, DBP, shock, and Killip class.

95.3% of the whole study population presented with chest pain. It was significantly higher in males (96.9%). compared to females (92.3%). P-value was 0.001. 4.7% of the whole study population presented with dyspnea. It was significantly higher in females (8.0%). compared to males (2.9%); the P-value was <0.001. 1.9% of the whole study population presented with arrhythmia. It showed no significant difference between both genders. P-value was 0.7

And this was concordant with (FU, et al). who showed that ACS patients in this study most frequently reported that they had high chest
pain or discomfort. This finding is consistent with the Chinese Acute Myocardial Infarction (CAMI) study. ([**FU, et al. 2014**](https://doi.org/10.1002/ajh.23158)). ([**Milner, et al.**](https://doi.org/10.1002/ajh.23158)) have reported that 20%–33% of AMI patients report ‘atypical’ (e.g. other than mid-sternal or mid-sternal with radiation to the left neck, shoulder or arm) pain or discomfort. ([**Milner, et al. 2002**](https://www.ncbi.nlm.nih.gov/pubmed/12070313)). Approximately 60% of patients in this study reported ‘atypical’ pain or discomfort.

Other studies have identified that ACS patients report a variety of symptoms including back pain, as Ghezeljeh et al as well as neck or throat pain. ([Ghezeljeh, et al. 2010](https://www.ncbi.nlm.nih.gov/pubmed/20125238)). The patients in this study also reported having symptoms other than pain or discomfort, which included sweating, having unusual fatigue, weakness, shortness of breath/difficulty breathing and dizziness. Women in this study were more likely to have unusual fatigue, weakness, shortness of breath/difficulty breathing or dizziness relative to men. Indeed, other researchers have found women reported having more fatigue, weakness, shortness of breath or dizziness than men. ([Arora, et al. 2015](https://www.sciencedirect.com/science/article/pii/S0195668X15000363)).

Other studies have indicated that diaphoresis was reported more by men, ([Arslanian-Engoren, et al. 2006](https://www.ncbi.nlm.nih.gov/pubmed/16855882)), whereas our study revealed that it was a common symptom in both men and women, with no gender differences.

According to [**Davis, et al**](https://doi.org/10.2147/CPRJ.S216461) Overall, less than half of the patients in this study attributed their symptoms to ACS (although women were more likely than men to attribute their symptoms to ACS). The reasons for patients’ erroneous attribution of symptoms may be associated with poor knowledge of cardiac symptoms ([**Davis, et al. 2013**](https://www.ncbi.nlm.nih.gov/pubmed/24058150)). or a gender difference in the pain threshold. ([**Monroe, et al. 2015**](https://www.ncbi.nlm.nih.gov/pubmed/26364039)).
The lower perception of pain or discomfort in women than men might have influenced the gender differences noted. Moreover, psychosocial factors (mood, attention, expected pain, etc.) might affect the interpretation of pain or discomfort and attribution of symptoms to ACS and subsequent action. (Canto, et al., 2014).

According to King-Shier, et al. The assessment of symptoms was only one element in the study patients’ decision-making to seek medical care. Indeed, fear and having a friend or relative direct the decision to seek medical care is common, and has previously been identified as being different for men and women (King-Shier, et al., 2015).

In our study, the majority of the study population presented with STEMI (48.3%), 16.0% were NSTEMI, and 35.0% presented with unstable angina. There was a significant association between clinical presentation and gender. 30.7% of males presented with unstable angina compared to 45.4% in females. 15.8% of males shown with NSTEMI compared to 16.3% in females. 53.5% of males presented with STEMI compared to 38.3%. P-value was <0.001.

This was in agreement with Young, et al. found that women were found to present with ST elevation less often than men, but more often with unstable angina. This finding may reflect different pathophysiologic processes, with ST elevation being secondary to occlusive thrombus and unstable angina reflecting subtotal occlusion. This study in a large, comparatively unselected, sample of patients from Europe and the Mediterranean basin expands on these prior findings, demonstrating that this difference seems to be confined to younger patients, with a significant interaction between age and sex. (Young, et al., 2018).
In our study, the most frequent target segment affected was anterior (24.7%), followed by inferior (13.9%), while the least frequent vessels involved were posterior and inferolateral (1% and 0.6%, respectively). There were no significant differences between both genders as regards all vessels affected. This was discordant with (Kostis, et al.) and (Salomaa, et al.) they found that Infarct size has been demonstrated to be smaller in women than in men. (Salomaa, et al. 1995). A systematic investigation of the consequences of including milder cases revealed that the increase in event rates and the decrease in case fatality due to the inclusion of non-fatal, probable AMIs were larger for women than for men. (Salomaa, et al. 1997). In a validation study, a diagnosis of AMI was found not to be supported in a higher proportion of women (9%) than in men (5%). (Kostis, et al. 1994). It is probable that the pattern of more unstable angina and less ST elevation in younger patients that we observed reflects the same phenomenon.

- THE mean EF of our study population was 54%. It was significantly higher in females (57%) compared to males (53%); the P-value was <0.001.

- Interestingly, the use of echocardiography for the early assessment of LV function in ACS patients with non-ST elevation ACS has a class I indication at the 2015 ESC guidelines while in the extensive AHA/ACC guidelines for ST and for NSTEMI, the evaluation of LV function is indicated only before discharge (class I indication). (Roffi, et al. 2016).

- LVEF has long been recognized as one of the most important predictors of mortality in patients with an MI and in patients with coronary artery disease in general.
So our results was concordant with The added predictive effect of early evaluation of LVEF in patients admitted with NSTEMI/ACS was described by Bosch et al who evaluated 1104 patients from the PRISM-plus trial registry whose LVEF was obtained during admission. Adding LVEF to the TIMI score model improved mortality prediction. The odds for in hospital death significantly increased for each 1% decrease in LVEF. The mortality rate was 3.3 times higher within each TIMI score stratum in patients with an LVEF<48% (Bosch, et al. 2005).

RWMA was present in (65.9%) of the study population. It was significantly higher in males (71.2%) compared to females (5.4%); the P-value was <0.001. Examinations were performed independently by five experienced investigators who were blind to study protocol and the patient population. Wall motion of each LV segment were assessed visually according to movement and systolic thickening in a 17-segment model (3 segments per wall). All segments were determined as a 4 point scale (1: normokinesia, 2: hypokinesia, 3: akinesia, 4: dyskinesia). Wall motion score index (WMSI) were calculated by a mean value of all segments for each point with average range in unsatable angina… and NSTEMI… and STEMI ….

This was concordant with results of Shenouda, et al who found that In ACS, the echocardiographic regional myocardial deformation is very accurate in detecting early recovery of LV myocardial function after culprit lesion revascularization. Also, the findings of this study support the current practice regarding the crucial importance of proximal epicardial vessel PCI treatment on LV function compared to more distal lesions. Finally, they also support
the fundamental importance of preserving basal LV regional function by optimum revascularization. *(Shenouda, et al. 2020).*

- Moderate and severe mitral regurgition represented 11.7% and 6.8%, respectively. MR showed a significant association with gender; 45.6% of males had mild MR compared to 36.6% in females, and 3.7% of males had severe MR compared to 12.9% in females; the P-value was <0.001.

- Our data was in agreement with data published by *(Abd-Aljabar, et al. 2018).* stated that Mitral regurgitation as a complication of MI is a poor prognosis. It is about severity is 13% to 45%. Fibrinolysis decreases the incidence of rupture; rupture was reported to occur after some days without fibrinolysis.

- Mean GLPSS in the whole study population at baseline was -16.9. It was significantly higher in females (-17.3) than males (-16.7); the P-value was 0.012. At 6 months, the Mean GLPSS was -13.1. It showed borderline significance between both genders; the P-value was 0.052. At six months, the GLPSS % change in the whole study population was -25.3. It was significantly higher in females (-30%) than males (-22.2%). P-value was 0.002.

Those results were corresponding to *Caspar*, et al. Longitudinal 2D strain has a good diagnostic value and can efficiently localize the culprit lesion in patients presenting with NSTE-ACS but apparent normal global and regional systolic function. *(Caspar, et al. 2017).*

In our study, 85.9% of the whole patients received conservative management. It was significantly higher in females (64.6%). compared to males (55.9%). P-value was 0.007. 32.5% of the whole patients received
thrombolytic therapy. It was significantly higher in males (36.1%) compared to females (25.4%). P-value was 0.001. 5.8% of the whole patients underwent intervention, and there was no significant difference between both genders regarding interventional therapy. Which was, **PPCI** was the most frequent intervention, followed by **rescue PCI** (25.7%) and **emergency PCI** (21.7%). The least frequent intervention pharmacoinvasive PCI (1.7%). There were no significant differences between both genders as regards all interventional therapies.

Our results were concordant with Guo, *et al* who showed that The systematic review and meta-analysis suggests that the prognosis of male patients with coronary artery disease after percutaneous coronary intervention is better than that of females, except for long-term revascularization. *(Guo, *et al.*2018)*, and there were no difference in acute reperfusion therapy between younger men and women, whereas older women were less likely to be treated than men of the same age. It is not clear to what extent the high mortality in older patients is amenable to improvement, but studies suggest that older, as well as younger, patients benefit from thrombolysis, as mentioned by *Stenestrand and Wallentin* and from treatment with b-blockers and aspirin *(Stenestrand, Wallentin.2003)*.

In our study population, the most frequent complication was mortality (4.7%), followed by re-hospitalization (4.2%), re-infarction (1.2%), stroke (1.1%), and hemorrhage (0.8%). There were no significant differences between both groups regarding all reported complications.

Re-ischemia occurred in 12.9% of the study population. Revascularization occurred in 6.0%.
Heart failure occurred in 5.1% and nearly 2/3rd were males and this was discordant with Members, et al who showed that, Currently, approximately three million American adult women aged 20 and older are suffering from heart failure. Although both men and women have this cardiac syndrome, women are more prone to have the heart failure and have higher rates of hospitalization and mortality compared with men (Members, et al. 2016).

In addition to Nichols, et al who found that Heart failure is also strongly related to diabetes that the presence of diabetes increases the risk of heart failure by 40% (Heart failure is also strongly related to diabetes that the presence of diabetes increases the risk of heart failure by 40% (Nichols, et al. 2004). and (Kannel, et al., 1971) found that The gender difference in HF risk, first shown in the Framingham Heart Study, was that men were 2 times more likely to have heart failure (P < 0.05), compared with 5 times in women with the respective non-diabetic population (P < 0.01)., Ciarambino also found that. The potential cause of the increased risk of heart failure in women with diabetes is not fully understood, but is likely to be related to gender differences in the diagnosis and treatment of coronary heart disease (Ciarambino, 2018). regarding Outcome after hospitalisation for AMI has been demonstrated to be worse in women, (Gottlieb, et al. 2000). particularly at younger ages. (Vaccarino, et al. 1999). In an analysis based on the same registry as in the present study, there was no difference in inhospital mortality after adjustment for age and comorbidity. An interaction between age and sex has been demonstrated with respect to outcome after AMI, with younger, but not older, women having higher in-hospital mortality. (Vaccarino, et al. 1999). To a great extent, however, this is explained by differences in baseline clinical characteristics. (White, et al. 1993). However, the high in-
hospital mortality in younger women is counterbalanced by a higher mortality outside the hospital among men. (MacIntyre, et al. 2001). This could possibly reflect more ST-elevation AMI among men, with a high early mortality.

In our study, Mortality occurred in 1.0%, and stroke occurred in 0.3%. There were no significant differences between both genders regarding re-ischemia, stroke, heart failure, revascularization, and mortality. However, As a result, most cardiologists have mistakenly ignored the appropriate CVD management strategies for women has led to an alarming increasing in female mortality (LGaG Locorotondo, 2015).
Conclusion:

Although substantial progress has been made towards improving gender- and sex-specific ACS disease management and outcomes, contemporary reports indicate a persistent knowledge gap with regard to optimal risk-stratification and management in female ACS patients.

Prominent patient and system delays in women with AMI result from limited awareness for the latent CVD risk in women, a lack of sex-specific thresholds within clinical guidelines, and subsequent limited performance of contemporary diagnostic approaches in women, all of which are the result of a persistent underrepresentation of women in cardiovascular studies.

In addition, little is known about the influence of socioenvironmental and contextual factors on gender-specific disease manifestation and outcomes.

The main finding was the interaction between age and sex with respect to clinical presentation, with younger women presenting with less ST elevation and more unstable angina. Among those who underwent angiography, less extensive atherosclerosis was found in women compared to men, irrespective of age.

These differences suggest variations in pathophysiology, with later onset of atherosclerosis in women but different pathophysiology with respect to ACS in younger, but not in older, women.

These differences may be due to the influence of sex hormones and should be further explored in order to provide better insights into the atherosclerotic process.
**Recommendations:**

Thus, future research will have to overcome barriers accounting for the low numbers of women enrolled in ACS trials and to explore sex and gender differences in biology, environment, and psychosocial complexity.

Finally, improved interdisciplinary and cooperative care in women’s health has recently been suggested as an attractive model to target cardiovascular health inequalities between women and men linked to modifiable risk factors and social determinants of health.
1. Our study was observational.

2. Limited percent of patients who had PPCI due to limited supplies in our cath lab limiting us strongly in applying primary PCI for every STEMI patient and restricting us from being adherent strongly to recent guidelines.


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المتلازمة الحادة: تتميز متلازمة الشريان التاجي الحادة بتغير حاد في لويحات الشرايين التاجية المتصلبة مع ضعف نفاذ في تدفق الدم في الشريان التاجي كما ترتبط بالارتفاع معدلات الأحداث الاكلينيكيه العكسية عبر النطاق الكامل لممرض الشريان التاجي.

وقد أظهرت دراسات سابقة أن النساء المصابات بقصور الشريان التاجي لديهن معدل وفيات أعلى ويضخمن لعلاجات أقل مقارنة بالرجال، وأن النساء المصابات بقصور الشريان التاجي يخصصون للتدخل في الشريان التاجي عن طريق الجلد بشكل عام أكبر سنًا ويتاثرون في كثير من الأحيان بأمراض مصاحبة متعددة أكثر من الرجال. حتى بعد التعديل الإحصائي الكافي لعوامل التعديل، كانت النتائج غير متستقة فيما يتعلق بما إذا كان الجنس الأنثوي هو عامل خطر للنتائج غير المواتية بعد التدخل على الشريان التاجي عن طريق الجلد.

على الرغم من أن العديد من الدراسات قد أظهرت تحسنًا في التشخيص لدى النساء بمرور الوقت، تظل النتائج الإجمالية أسوأ بالنسبة للنساء مقارنة بالرجال، وتتوفر أساسًا منطقيًا قويًا للتركيز على دراسة الجنس.

الهدف من الدراسة:

هدف هذه الدراسة تقييم النتائج الاكلينيكية للمرضى الذين يعانون من متلازمة الشريان التاجي الحادة فيما يتعلق بالاختلافات بين الجنسين.

المرضى وطرق الدراسة:

هيكلية الدراسة:

دراسة رصدية، يوصف تسلسل لكل حالة، وفي مركز واحد، والتي تشمل جميع المرضى الذين يعانون من متلازمة الشريان التاجي الحادة الذين تم حجزهم في وحدة العناية التاجية في "مستشفى جامعة بنها" في الفترة من أبريل 2019 إلى أبريل 2020.
الملخص العربي

بروتوكول الدراسة:
- قمنا في هذه الدراسة بتقييم النتائج الالكترونية لهذه الفئة من المرضى سواء أثناء الإقامة في المستشفى أو في المتابعة لمدة 6 أشهر.
- بالإضافة إلى إعادة تشكيك البطين الأيسر (تُعرف بأنها زيادة حجم البطين الأيسر في آخر الانقباض بمعن 20% أو أكثر بعد ستة أشهر من الفحص الأول). في المرضى الذين يعانون من متلازمة الشريان التاجي الحادة باستخدام تتبع البقع التي تم إجراؤها عند دخول الحال أو أثناء فترة الحجز ومتابعة لمدة 6 أشهر.
- وقد قارنا في الدراسة - بشكل أساسي - النتائج بين الذكور والإناث المصابين

 punta de la entrevista:

 نقطة النهاية الأولية:
وفيات 6 أشهر ، احتشاء عضلة القلب ، سكتة دماغية ، إعادة الترويه للشريان التاجي .

 نقطة النهاية الثانوية:
استخدام تتبع البقع لمدة 6 أشهر في مرضى متلازمة الشريان التاجي الحادة .

 جميع المرضى خضوا لما يلي:
• التقييم الأساسي:
 لقد حصل جميع المرضى على مراجعة للتاريخ الطبي بما في ذلك). العمر ، الجنس ، عوامل الخطورة لمرض الشريان التاجي (البول السكري-ارتفاع ضغط الدم - اختلال مستوى الدهون بالدم - التدخين). ، التاريخ السابق لمرض الشريان التاجي ، التاريخ السابق للتدخل للشريان التاجي عن طريق الجلد ، الأمراض المصاحبة الأخرى ، الأدوية).

 الفحص الالكتروني الكامل:
 مع التركيز بشكل خاص على البضحة وضغط الدم للمريض ، وكذلك فحص الصدر لاستنباط وجود أي احتقان وردي رئوي يمكن اكتشافه اكلينيكيا و فحص القلب لوجود أصوات قلب ثالث أو لغط مسموعة

 تخطيط القلب الكهربائي الأساسي:
 يتم عمل اثني عشر خطًا لتطبيع القلب لكل مريض.

 المؤشرات الحيوية للقلب:
 بما في ذلك التروبوتين .
الملخص العربي

اشعة موجات صوتية على القلب عند الحجز:

سيتم تقييم جميع المرضى عن طريق اشعه الموجات الصوتية على القلب لتقييم اضطرابات الحركة في اجزاء معينه أو كليه والوظيفة الانقباضية الشاملة للبطين الأيسر.

المتابعة:

اشتملت المتابعة 6 أشهر تقييم المتغيرات الاكلينيكية بين المرضى من الذكور والإثاث بما في ذلك جميع أسباب الوفيات واحتشاء عضلة القلب والسكتة الدماغية وفشل القلب وإعادة تكوين الأوعية الدموية.

تم عمل اشعه تصوير بالدوبلر للمرضى الذين يعانون من متلازمة الشريان التاجي الحادة بعد 6 أشهر من الحجز بالعناية لمعرفه مدى إعادة تشكيك البطين الأيسر باستخدام تتبع البقع (جي أل بي اس تتبع البقعة).

اشعة تصوير بالدوبلر باستخدام تتبع البقع:

- تم إجراء قياسات الإجهاد الطولي مع تنفيذ تتبع البقع ثنائية الأبعاد كما هو موضح سابقا وتم تحديد نهاية الانقباض على أنه مطابق لإغلاق الصمام الأورطي المقاس بالدوبلر النبضي.
- تم تتبع حدود البطانة الداخلية في البطين الأيسر على إطار نهاية الانبساط وتم تتبع البرامج تلقائيا للحدود على الإطارات اللاحقة. مما مكن بعد ذلك التحقق من التتبع الملائم في الوقت الفعلي وتصحيحه إذا لزم الأمر عن طريق تعديل منطقة الاهتمام أو تصحيح الحدود يدويًا لضمان التتبع الأمثل.
- بعد اكتمال عملية التتبع ، تم رسم اضطرابات حركة اجزاء من عضلة القلب في الوقت المقابل للرسوم البيانية للضغط ، حيث يمكن تحديد المراحل المختلفة لدورة القلب.
- كذلك تم قياس معدلات الإجهاد المحيطي والشعاعي وتغيراتها من الراحة إلى الضغط المنخفض ، ذروة الإجهاد والتعافي.
- تم قياس ذروة الإجهاد الشعاعي والمحيطي (الانقباضي والانبساطي المبكر). من عرض منتصف المحور القصير عند الراحة ، وجرعات الدوبوتامين المنخفضة والمرتفعة.
- تم قياس الانفعال الطولي الذروة من وجهات النظر القمية رباعي وثلاثي غرف وثنائي الغرف.
النتائج التي أثبتها البحث:

- على الرغم من إحراز تقدم كبير نحو تحسين إدارة ونتائج أمراض متلازمة الشريان التاجي الحادة الخاصة بالجنس، تشير التقارير المعاصرة إلى وجود فجوة معرفية مستمرة فيما يتعلق بالتقسيم الطبي للمخاطر وإدارتها في مرضى متلازمة الشريان التاجي الحادة الإناث.

- ينتج التأخير البارز للمريض والنظام لدى النساء المصابات باحتشاء حاد بعضة القلب عن الوعي المحدود بمخاطر الأمراض القلبية الوعائية الكامنة لدى النساء، ونقص العتبات الخاصة بالجنس ضمن الإرشادات الأكليينية، والأداء المحدود الناجح للتشخيص المعاصر لدى النساء، وكلها نتيجة استمرار نقص تمثيل النساء في دراسات القلب والأوعية الدموية.

- بالإضافة إلى ذلك، لا يُعرف الكثير عن تأثير العوامل الاجتماعية والبيئية والسياقية على مظاهر المرض النوعي والنتائج.

- كانت النتيجة الرئيسية هي التفاعل بين العمر والجنس فيما يتعلق بالظهور الأكلييني، مع ظهور النساء الأصغر سنًا مع ارتفاع مقطع الأس تي أقل وذبحة صدرية غير مستقرة. من بين أولئك الذين خضعوا لتصوير الأوعية، وجد أن تصلب الشرايين أقل انتشارًا لدى النساء مقارنة بالرجال، بغض النظر عن العمر.

- تشير هذه الاختلافات إلى اختلافات في الفيزيولوجيا المرضية، مع ظهور تصلب الشرايين لاحقًا عند النساء ولكن تختلف الفيزيولوجيا المرضية فيما يتعلق بالمتلازمة الشريان التاجي الحادة في النساء الأصغر سنًا، ولكن ليس لدى النساء الأكبر سنًا.

- قد تكون هذه الاختلافات ناتجة عن تأثير الهرمونات الجنسية ويجب استكشافها بشكل أكبر من أجل تقديم رؤى أفضل حول عملية تصلب الشرايين.

لذا فجاءت توصياتنا بالتالي:

- سيتعين على البحث المستقبلي التغلب على الحواجز التي تمتلئ الأعداد المنخفضة من النساء المسجلات في تجارب متلازمة الشريان التاجي الحادة واستكشاف الفروق بين الجنسين والنساء في علم الأحياء، والبيئة، والتعقيد النفسي والاجتماعي.

- أخيرًا، تحسين الرعاية متعددة التخصصات والتعاونية للمرأة إذ تم اقتراح صحة المرأة مؤخرًا كنموذج جذاب لاستهداف عدم المساواة في صحة القلب والأوعية الدموية بين النساء والرجال المرتبطة ببعض الخطر القابل للتعديل والتحديات الاجتماعية للصحة.
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**Notes:**
- PCI: Percutaneous coronary intervention
- Meds: Medications
- Recovery: Recovered from the condition
- Death: Died from the condition
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الناتج الاكلينيكي لمرضى متلازمة قصور الشريان التاجي الحادة المحفزون في وحدة رعاية الشرايين التاجية في مستشفى بنها الجامعي: الاختلافات بين الجنسين

بروتوكول رسالة للحصول علي درجة الدكتوراه في امراض القلب والأوعية الدموية

القدم من الطبيب

مروه كمال محمود السيد

ماجستير قلب وأوعية دموية – كلية الطب جامعة بنها

مُتمِّنَّوَتُ إِنْ حَرَّمَنَّكُمُ الْكَانَةَ، فَإِنَّ هَذَا الْكَانَةُ الْمُؤُوذَّةُ لِلْيَدِينَ كَانَتِ الْاَلْمَعْشَقَةُ إِلَّا أَنْ أَقْضَىَ الْحَمْدُ لِلَّهِ وَأَنْتَ عَلَى مَرْجَعِكُمُ الْقَدِيرَ

أ.د. محمد عبده سالم

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جامعة بنها

2021