Coronary Artery Disease
Unstable Angina and
Non-ST Elevation
Myocardial Infarction
(2009)
### 2010-2011 Board of Directors

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<tbody>
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</table>
**Coronary Artery Disease**

**ALGORITHM**

- **Chest discomfort/pain** (angina or anginal equivalent)
  - Is chest discomfort improved after 1 dose of NTG SL?
    - **N**
      - Is there continuing angina with or without ECG changes suggestive of UA/NSTEMI?
    - **Y**
      - Go to PHA CSAP guidelines
    - **Y**
      - Are cardiac biomarkers elevated?*
        - **N**
          - Unstable angina
        - **Y**
          - Are there high risk features using either GRACE, TIMI or PURSUIT risk models?
            - **N**
              - Treat as Unstable angina: Conservative strategy †
            - **Y**
              - Treat as NSTEMI: Invasive strategy
      - Go to PHA STEMI guidelines

  - **Y**
    - ECG suggestive of STEMI

* Cardiac Biomarkers are Troponin T or I, CPKMB
† Initial medical management should be instituted: aspirin 160-325mg tablet chew; nitrates sublingual or IV; anti-platelets and anticoagulants; beta-blockers if with continuing chest pain and with no contraindications; ACE-I/ ARB
PHI Clinical Practice Guidelines for the Management of Patient with Unstable Angina and Non-ST Elevation Myocardial infarction (UA/NSTEMI)

SUMMARY OF STATEMENTS

Statement 1: Diagnosis and Risk Assessment

Patients with the following symptoms and signs require immediate assessment for the initiation of ACS protocol:
• Chest pain or severe epigastric pain, non-traumatic in origin, with component typical of myocardial ischemia or MI: Central/substernal compression or crushing chest pain pressure, tightness, heaviness, cramping, burning, aching sensation.
• Unexplained indigestion, belching, epigastric pain.
• Radiating pain in neck, jaw, shoulders, back, 1 or both arms.
• Associated dyspnea.
• Associated nausea and/or vomiting.
• Associated diaphoresis.

Statement 2: Electrocardiogram

It is STRONGLY RECOMMENDED that a 12 lead ECG be obtained immediately within 10 minutes of ER presentation in patients with ongoing chest discomfort.

Statement 3: Treadmill Exercise Test

It is NOT RECOMMENDED to perform stress test within 48 hours of the last chest pain.

Statement 4: Biomarkers of Cardiac Injury

It is STRONGLY RECOMMENDED that troponin be measured in all patients with chest discomfort consistent with ACS. In patients with negative cardiac markers within 6 hours of the onset of pain, another sample should be drawn in the time frame 8-12 after symptom onset.

Statement 5: Other Biomarkers

It is NOT RECOMMENDED to request for Total CK (without MB), AST, SGOT, beta hydroxybutyric dehydrogenase, and/or lactate dehydrogenase (LDH) as markers for the detection of cardiac injury.

Statement 6: Risk Stratification

It IS RECOMMENDED for patients who present with chest discomfort or other ischemic symptom to undergo early risk stratification for risk of cardiovascular events (e.g., death or MI) based on an integration of the patient's history physical examination, ECG findings and result of cardiac biomarkers.

Statement 7: General Recommendations on Initial Management

It IS RECOMMENDED that the following management strategies should be instituted:

1. Bed rest with continuous ECG monitoring for ischemic and arrhythmia detection in patients with ongoing rest pain.
2. Supplemental oxygen should be administered to patients with UA/NSTEMI for patients with cyanosis of respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (SaO₂ greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia.

Statement 8: Nitrates

It IS RECOMMENDED that nitrates (sublingual tablet or spray), followed by intravenous administration, be administered for the immediate relief of ischemic and associated symptoms.

Statement 9: Beta blockers

It IS RECOMMENDED that beta-blocker by oral or IV route be administered if there is ongoing chest pain in the absence of contraindications.

Statement 10: Calcium channel blockers

It MAY BE RECOMMENDED to use oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindication and when beta-blockers and nitrates are maximally used.

Statement 11: Angiotensin Converting Enzyme Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB)

An ACE-I/ARB IS RECOMMENDED when hypertension persists despite treatment with nitroglycerin (NTG) and a beta-blocker in patients with LV systolic dysfunction or congestive heart failure (CHF), high risk chronic CAD, in post ACS (with or without) diabetes, and in chronic kidney disease (CKD) unless contraindicated.

Statement 12: Morphine sulfate

It IS RECOMMENDED that morphine sulfate be administered intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation are present.

Statement 13: Aspirin

It is STRONGLY RECOMMENDED that aspirin at initial dose of 160-325 mg non-enteric formulation, followed by 80-160 mg daily, be administered as soon as possible after presentation and continued indefinitely.

Statement 14: ADP receptor antagonists (Clopidogrel, Ticlodipine)

It IS STRONGLY RECOMMENDED to start clopidogrel for:
1. Patients in whom an early non-interventional approach is planned in addition to ASA as soon as possible in admission and administered for at least a month.
2. Patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance.
3. Patients in whom a PCI is planned and should be
Coronary Artery Disease

continued for at least 12 months in patients who are not at high risk for bleeding.

It IS STRONGLY RECOMMENDED to discontinue clopidogrel for 5 to 7 days in patients whom elective CABG is planned.

Statement 15: Anticoagulants (Heparins)

It IS STRONGLY RECOMMENDED that anticoagulation with subcutaneous enoxaparine or intravenous unfractioned heparin (UFH) should be added to anti-platelet therapy with ASA and/or clopidogrel.

Statement 16: Glycoprotein IIb IIIa Inhibitors

It IS RECOMMENDED to use glycoprotein IIb IIIa inhibitors (tirofiban) in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin or with other high risk features in whom an invasive management strategy is not planned; or in patients undergoing PCI with or without clopidogrel administration.

Statement 17: Factor X Inhibitor

It IS RECOMMENDED to use fondaparinux, in lieu of enoxaparine, at a dose of 2.5 mg SC once daily in whom a conservative strategy is selected and who have an increased risk of bleeding.

Statement 18: Fibrinolytic Therapy

It IS NOT RECOMMENDED to use intravenous fibrinolytic therapy in patients with UA or in patients without acute ST-segment elevation, a true posterior MI, or a presumed MI, or a presumed new left bundle-branch block (LBBB).

Statement 19: Early Conservative versus Invasive Strategies

It IS RECOMMENDED that an early invasive strategy (as early as possible up to 72 hours) followed by revascularization (PCI or CABG) with any of the following high-risk indicators:

a. Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy.

b. Elevated cardiac biomarkers (TnT or TnI).

c. New or presumably new ST-segment depression.

d. Signs and symptoms of Heart Failure (HF) or new or worsening mitral regurgitation.

e. High-risk findings from noninvasive testing

f. Hemodynamic instability

g. Sustained ventricular tachycardia.

h. PCI within 6 months.

i. Prior CABG.

j. High-risk score (e.g., TIMI, GRACE).

k. Reduced LV systolic function (LVEF less than 40%).

Statement 20: Coronary angiography

It IS NOT RECOMMENDED in patients with extensive co-morbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization are not likely to outweigh the benefits or in patients with acute chest pain and a low likelihood of ACS or in patients who will not consent to revascularization regardless of the findings.

Statement 21: Percutaneous Coronary Intervention (PCI)

An early invasive PCI strategy IS RECOMMENDED for patients with UA/NSTEMI who have no serious co-morbidity and who have coronary lesions amenable to PCI and any of the high risk features.

PCI (or CABG) is also recommended for UA/NSTEMI patients with 1-2 vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high risk criteria on non invasive testing.

Statement 22: Coronary Artery Bypass Graft (CABG) Surgery

CABG IS RECOMMENDED for patients with significant left main disease and the preferred revascularization strategy for patients with multi-vessel coronary disease, with depressed systolic function (LVEF ≤50%), and diabetes.

Statement 23: It IS RECOMMENDED that the following specific instructions should be given

a. Lifestyle modification that includes smoking cessation, achievement or maintenance of optimal weight, daily exercise, and diet.

b. Daily exercise of 30 minutes or 5 days per week.

c. Consider referral of patients who are smokers to smoking cessation program or clinic and/or an out-patient cardiac rehabilitation program.

d. Intensive lipid-lowering therapy is strongly recommended by combining dietary interventions with pharmacotherapy using statins, or combining with other lipid-lowering agents to reduce LDLc <100 mg/dL. Further reduction to less than 70 mg/dL may be recommended.

e. A fibrate or niacin if high density lipoprotein (HDL) cholesterol is less than 40 mg/dL, occurring as an isolated finding or in combination with other lipid abnormalities.

f. Hypertension control to a blood pressure of less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease.

g. Tight control of hyperglycemia in diabetes. Goal is HbA1c of less than 7%.

h. Antiplatelet agents/Anticoagulants. (see page 158)

I. INTRODUCTION

Non-ST Elevation Myocardial Infarction (NSTEMI) is defined as a condition where there is no ST elevation on ECG but with elevation of cardiac enzymes. On the other hand, unstable angina (UA) is not associated with ST elevation or cardiac enzymes elevation but with ECG ST or T wave changes coupled with typical anginal pains. It is important to differentiate these above-mentioned conditions since prognosis and management can differ. For example, acute reperfusion therapy or thrombolyis is a contraindication for ACS patients without ST-segment elevation.

II. DIAGNOSIS AND RISK ASSESSMENT

Patients with a high likelihood of ischemia due to CAD are at greater risk of an untoward cardiac event than are patients with a lower likelihood of CAD. Therefore, an
assessments of the likelihood of CAD is the starting point for the determination of prognosis in patients who present with symptoms suggestive of an ACS.

Statement 1: Diagnosis and Risk Assessment

Patients with the following symptoms and signs require immediate assessment for the initiation of the ACS protocol:
- Chest pain or severe epigastric pain, non-traumatic in origin, with component typical of myocardial ischemia or MI: Central/substernal compression or crushing chest pain pressure, tightness, heaviness, cramping, burning, aching sensation.
- Unexplained indigestion, belching, epigastric pain.
- Radiating pain in neck, jaw, shoulders, back, 1 or both arms.
- Associated dyspnea.
- Associated nausea and/or vomiting.
- Associated diaphoresis.

The clinical presentation of patients with unstable angina and non-ST elevation MI present itself in variety of symptoms. However, the frequent and typical manifestations would be the following:
- Prolonged (>20 minutes) anginal pain at rest
- New onset severe angina
- Crescendo/accelerated angina
- Post MI angina

Statement 2: Electrocardiogram

It IS STRONGLY RECOMMENDED that a 12 lead ECG be obtained immediately within 10 minutes of ER presentation in patients with ongoing chest discomfort.

If the initial ECG is not diagnostic, but the patient remains symptomatic and there is high clinical suspicions for ACS, serial ECGs, initially at 15-30 minute intervals, should be performed to detect the potential for development of ST segment elevation or depression.

The ECG is critical not only to add support to the clinical suspicion of CAD but also to provide prognostic information that is based on the pattern and magnitude of the abnormalities. Importantly, transient ST-segment changes (greater than or equal to 0.05 mV) that develop during a symptomatic episode at rest and that resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD.

Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the 2 diagnosis is based ultimately on the detection in the blood of markers of myocardial necrosis.1,2

Statement 3: Treadmill Exercise Test

It IS NOT RECOMMENDED to perform stress test within 48 hours of the last chest pain.

In patients who continue to have typical chest pain, stress test should not be performed. However, stress test has been used as a predictive tool of prognosis in patients with non-diagnostic ECG provided there is no chest pain, no signs of heart failure and normal cardiac markers on repeat examination.3

Statement 4: Biomarkers of Cardiac Injury

It IS STRONGLY RECOMMENDED that troponin be measured in all patients with chest discomfort consistent with ACS. In patients with negative cardiac markers within 6 hours of the onset of pain, another sample should be drawn in the time frame 8-12 after symptom onset.

cTNT or cTNI are the preferred markers of myocardial injury because they are more sensitive than the traditional cardiac enzymes such as creatinine kinase (CK) or its isoenzyme MB (CKMB). Additionally, troponins are the best biomarker to predict short-term (<30 days) outcome with respect to MI and death.5,6 In patients with AMI, an initial rise in troponins in peripheral blood occurs after 3-4 hours. Troponin levels may persist for up to 2 weeks. In NSTEMI, minor elevation of troponins may be measurable only over 48-72 hours. The high sensitivity of troponin tests allows the detection of myocardial damage undetected by CKMB in up to one third of patients. With currently available assays, cTnI and cTnT are of equal sensitivity and specificity in the detection of cardiac damage.7 The choice should be made on the basis of cost and the availability of instrumentation at the institution.

A single negative test for troponins on arrival of the patient in the hospital is not sufficient for ruling out an ACS. Repeated blood sampling and measurements are required 6-12 hours after admission and after any further episodes of severe chest pains.

Statement 5: Other Biomarkers

It IS NOT RECOMMENDED to request for Total CK (without MB), AST, SGOT, beta hydroxybutyric dehydrogenase, and/or lactate dehydrogenase (LDH) as markers for the detection of cardiac injury.

Statement 6: Risk Stratification

It IS RECOMMENDED for patients who present with chest discomfort or other ischemic symptom to undergo early risk stratification for risk of cardiovascular events (e.g., death or MI) based on an integration of the patient’s history physical examination, ECG findings and result of cardiac biomarkers.

Early risk stratification is useful in (1) selection of the site of care (coronary artery unit, monitored step-down unit, or out-patient setting) and (2) selection of therapy, including platelet glycoprotein (GP) IIb-IIIa inhibitors and invasive management strategy. A number of risk assessment tools have been developed in assessing risk of death and ischemic events; these are the Thrombolysis in Myocardial Infarction (TIMI) risk score6, Platelet Glycoprotein IIb-IIIa in Unstable Angina (PURSUIT) risk model7, and the Global Registry of Acute Coronary Events (GRACE) risk model (See Figure 1).8,10,11 See Table 1 for the comparison of the 3 risk models.

The TIMI risk score is determined by the sum of the presence of 7 variables at admission (Age 65 years or older, at least 3 risk factors for CAD, prior coronary stenosis of 50% or more, ST-segment deviation on ECG presentation, at least 2 anginal events in prior 24 hours, use of aspirin in prior 7 days, elevated serum cardiac biomarkers); 1 point is given for each of these variables. (See Table 2 for the percentage of mortality rate, new or recurrent MI, or severe recurrent ischemia)
**Figure 1. GRACE Prediction Score Card and Nomogram for All-Cause Mortality from Discharge to 6 Months**

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

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

<table>
<thead>
<tr>
<th>Medical History</th>
<th>Points</th>
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<tbody>
<tr>
<td><strong>1. Age in Years</strong></td>
<td></td>
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<tr>
<td>≤29</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>0</td>
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<tr>
<td>40-49</td>
<td>18</td>
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<tr>
<td>50-59</td>
<td>36</td>
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<td>60-69</td>
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</tr>
<tr>
<td>70-79</td>
<td>73</td>
</tr>
<tr>
<td>80-89</td>
<td>91</td>
</tr>
<tr>
<td>≥90</td>
<td>100</td>
</tr>
<tr>
<td><strong>2. History of Congestive Heart Failure</strong></td>
<td>24</td>
</tr>
<tr>
<td><strong>3. History of Myocardial Infarction</strong></td>
<td>12</td>
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<tr>
<th>Findings at Initial Hospital Presentation</th>
<th>Points</th>
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<tbody>
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<td><strong>4. Resting Heart Rate</strong></td>
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<tr>
<td>≤49.9</td>
<td>0</td>
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<tr>
<td>50-69.9</td>
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<td>70-89.9</td>
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<tr>
<td>90-109.9</td>
<td>14</td>
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<tr>
<td>110-149.9</td>
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<td>150-199.9</td>
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<tr>
<td>≥200</td>
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<th>Findings During Hospitalization</th>
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<td><strong>7. Initial Serum Creatinine, mg/dL</strong></td>
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<td>0-0.39</td>
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<tr>
<td>0.4-0.79</td>
<td>3</td>
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<tr>
<td>0.8-1.19</td>
<td>5</td>
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<tr>
<td>1.2-1.59</td>
<td>7</td>
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<tr>
<td>1.6-1.99</td>
<td>9</td>
</tr>
<tr>
<td>2-3.99</td>
<td>15</td>
</tr>
<tr>
<td>≥4</td>
<td>20</td>
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<tr>
<td><strong>8. Elevated Cardiac Enzymes</strong></td>
<td>15</td>
</tr>
<tr>
<td><strong>9. No In-Hospital Percutaneous Coronary Intervention</strong></td>
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<table>
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<td>7</td>
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<td>8</td>
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<td>9</td>
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</table>

Total Risk Score (Sum of Points)
Mortality Risk (From Ploy)

1. Bed rest with continuous ECG monitoring for ischemic and prolonged manifestation of ischemia for 12 to 24 hours, an attempt should be made to reduce the dose of intravenous NTG if hypertension was present.

**Statement 7: General Recommendations on Initial Management**

**It IS RECOMMENDED** that the following management strategies should be instituted:

1. Bed rest with continuous ECG monitoring for ischemic and arrhythmia detection in patients with ongoing rest pain.

2. Supplemental oxygen should be administered to patients with UA/NSTEMI for patients with cyanosis of respiratory distress; finger pulse oximetry or arterial blood gas determination to confirm adequate arterial oxygen saturation (SaO2; greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia.

**Statement 8: Nitrates**

It IS RECOMMENDED nitrates (sublingual tablet or spray), followed by intravenous administration, be administered for the immediate relief of ischemic and associated symptoms.

For initial management of anginal pains, three 0.4 mg sublingual NTG tablets or spray taken 5 min apart can be administered. If symptoms are not relieved, intravenous NTG may be initiated at a rate of 10 mcg/min through continuous infusion with nonabsorbing tubing and increased by 10 mcg per min every 3 to 5 min until some symptom or blood pressure response is noted. Caution should be used when systolic blood pressure falls to less than 110 mm Hg in previously normotensive patients or greater than 25% below the starting mean arterial blood pressure if hypertension was present.

Although recommendations for a maximum dose are not available, a ceiling of 200 mcg per min is commonly used. When patients have been free of pain and other manifestations of ischemia for 12 to 24 hours, an attempt should be made to reduce the dose of intravenous NTG and switch to oral or topical nitrates (See Table 3 for list of Anti-anginal Drugs).

It is not recommended to administer NTG or other nitrates within 24 hours of sildenafil use. Sildenafil inhibits the phosphodiesterase (PDE5) that degrades cyclic guanosine monophosphate (cGMP), and cGMP mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-mediated vasodilatation is markedly exaggerated and prolonged in the presence of sildenafil. Nitrate use within 24 hours after sildenafil or the administration of sildenafil in a patient who has received a nitrate within 24 hours has been associated with profound hypotension, MI, and even death.12

<table>
<thead>
<tr>
<th>TIMI Risk Score (7 variables)*</th>
<th>PURSUIT Risk Model (6 variables)†</th>
<th>GRACE Risk Model (8 variables)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age 65 years or older</td>
<td>- Age</td>
<td>- Older age</td>
</tr>
<tr>
<td>- At least 3 risk factors for CAD</td>
<td>- Heart rate</td>
<td>- Heart rate</td>
</tr>
<tr>
<td>- Prior coronary stenosis of 50% or more</td>
<td>- Systolic blood pressure</td>
<td>- Systolic blood pressure</td>
</tr>
<tr>
<td>- ST-segment deviation on ECG presentation</td>
<td>- ST-segment deviation</td>
<td>- ST-segment depression</td>
</tr>
<tr>
<td>- At least 2 anginal events in prior 24 hours</td>
<td>- Signs of heart failure</td>
<td>- Killip classification</td>
</tr>
<tr>
<td>- Elevated serum cardiac biomarkers</td>
<td>- Cardiac enzymes</td>
<td>- Positive initial cardiac markers</td>
</tr>
<tr>
<td>- Use of aspirin in prior 7 days</td>
<td></td>
<td>- Serum Creatinine Level</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cardiac arrest at hospital arrival</td>
</tr>
</tbody>
</table>

Table 5. List of Calcium Antagonists in clinical use locally available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydropyridines</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate release: 30-90 mg daily orally</td>
</tr>
<tr>
<td></td>
<td>Slow release: 30-180 mg daily</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td>Isradipine</td>
<td>2.5-10 mg twice daily</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-40 mg 3 times daily</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Immediate release: 30-80 mg 4 times daily</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-320 mg once daily</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release: 80-160 mg 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Slow release: 120-480 mg once daily</td>
</tr>
</tbody>
</table>

The administration of the following treatment strategies can be done but with caution:
2. Immediate-release dihydropyridine calcium antagonists in the presence of a beta-blocker.

However, it is not recommended to administer immediate-release dihydropyridine calcium antagonists in the absence of a beta-blocker.

Statement 11: Angiotensin Converting Enzyme Inhibitor (ACE-I) or Angiotensin Receptor Blockers (ARB)

An ACE-I/ARB IS RECOMMENDED when hypertension persists despite treatment with nitroglycerin (NTG) and a beta-blocker in patients with LV systolic dysfunction or congestive heart failure (CHF), high risk chronic CAD, in post ACS (with or without) diabetes, and in chronic kidney disease (CKD) unless contraindicated.

ACE-Is have been shown to reduce mortality rate in patients with AMI or who recently had an MI and have LV systolic dysfunction, in diabetic patients with LV dysfunction, and in a broad spectrum of patients with high-risk chronic CAD, including patients with normal LV function.

An ACE-I is recommended for all post-ACS patients. ARBs should also be considered in patients who are
intolerant to ACE-I and/or who have heart failure or MI with LVEF<40%.

Statement 12: Morphine sulfate

**It is recommended** that morphine sulfate be administered intravenously when symptoms are not immediately relieved with NTG or when acute pulmonary congestion and/or severe agitation are present.

Morphine sulfate 1 to 5 mg intravenously (IV) is recommended for patients whose symptoms are not relieved after three serial sublingual NTG tablets or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered along intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 min as needed to relieve symptoms and maintain patient comfort. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory and/or circulatory depression. Meperidine hydrochloride can be substituted in patients who are allergic to morphine.

**IV. ANTI-PLATELET AND ANTI-THROMBOTIC THERAPY**

Statement 13: Aspirin

**It is strongly recommended** that aspirin at initial dose of 160-325 mg non-enteric formulation, followed by 80-160 mg daily, be administered as soon as possible after presentation and continued indefinitely.

The administration of aspirin has the strongest evidence of clinical benefit in all spectrum of ACS.23-24

Statement 14: ADP receptor antagonists (Clopidogrel, Ticlodipine)

**It is strongly recommended** to start clopidogrel for:
1. Patients in whom an early non-interventional approach is planned in addition to ASA as soon as possible in admission and administered for at least a month.
2. Patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance.
3. Patients in whom a PCI is planned and should be continued for at least 12 months in patients who are not at high risk for bleeding.

The trial, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) also provides strong evidence for the addition of clopidogrel to ASA on admission in the management of patients with UA and NSTEMI. The optimal duration of therapy with clopidogrel has not been determined, but the favorable results in CURE were observed over a period averaging 9 months.25-26 (See Table 6 or listing and dosages of different anti-thrombotic and anticoagulant drugs)

**It is strongly recommended** to discontinue clopidogrel for 5 to 7 days in patients whom elective CABG is planned.

### Table 6. Anti-thrombotic Therapy

<table>
<thead>
<tr>
<th>Oral anti-platelet therapy</th>
<th>Intravenous anti-platelet therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td><strong>Abciximab</strong> (ReoPro- pulled out from the local market)</td>
</tr>
<tr>
<td>Initial dose of 160-325 mg non-enteric formulation followed by 80-160 mg/d of an enteric or a non-enteric formulation</td>
<td>0.25 mg/kg bolus followed by infusion of 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 to 24 hours</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></td>
<td><strong>Eptifibatide</strong></td>
</tr>
<tr>
<td>75 mg/d, a loading dose of 4-8 tablets (300-600 mg) can be used when rapid onset of action is required</td>
<td>180 mcg/kg IV bolus (second bolus after 10 min for PCI) followed by infusion of 2.0 mcg/kg⁻¹·min for 72 to 96 hours</td>
</tr>
<tr>
<td><strong>Ticlodipine</strong></td>
<td><strong>Tirofiban</strong></td>
</tr>
<tr>
<td>250 mg twice daily, a loading dose of 500 mg can be used when rapid onset of inhibition is required, monitoring of platelet and while cell counts during treatment is required</td>
<td>0.4 mcg/kg⁻¹·min for 30 minutes followed by infusion of 0.1 mcg/kg⁻¹·min for 48 to 96 hours A high dose regimen (bolus 25 ug/kg + 0.15 ug/kg/min infusion for 18 hours) is tested in clinical trials</td>
</tr>
<tr>
<td><strong>Heparins</strong></td>
<td><strong>Fondaparinux</strong></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>2.5 mg subcutaneously daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
</tr>
<tr>
<td>Nadroparin</td>
<td></td>
</tr>
<tr>
<td>Unfractioned Heparin (UFH)</td>
<td></td>
</tr>
<tr>
<td>120 IU/kg subcutaneously every 12 hours (maximum 10,000 IU twice daily)</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg subcutaneously every 12 hours, the first dose may be preceded by a 30 mg IV bolus</td>
<td></td>
</tr>
<tr>
<td>86 IU/kg every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Bolus 60-70 U/kg (maximum 5000 U) IV followed by infusion of 12-15 U/kg/k (maximum 1000 U/hour) titrated to aPTT 1.5-2.5 times control</td>
<td></td>
</tr>
<tr>
<td><strong>Fondaparinux</strong></td>
<td></td>
</tr>
<tr>
<td>2.5 mg subcutaneously daily</td>
<td></td>
</tr>
</tbody>
</table>
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Statement 15: Anticoagulants (Heparins)

It is STRONGLY RECOMMENDED that anticoagulation with subcutaneous enoxaparine or intravenous unfractioned heparin (UFH) should be added to anti-platelet therapy with ASA and/or clopidogrel.

Heparin exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and Factor Xa. Four large trials have compared LMWH vs UFH. ESSENCE and TIMI IIb have shown moderate benefit of LMWH over UFH while FRIC and FRAXIS showed unfavorable results for LMWH. The advantage of LMWH is the ease of administration and the absence of a need for monitoring. LMWH stimulates platelets less than UFH hence less frequent association with heparin induced thrombocytopenia. LMWH is more frequently associated with mucosal bleeding but not major bleeding.

During UFH, APTT should be measured at baseline, then 6 hours thereafter. When 2 consecutive APTT values are therapeutic, the measurements may be made every 24 hours and if necessary, dose adjustments carried out. Serial Hb/Hct & PC measurements are recommended at least daily during UFH therapy. Most of the trials that evaluate the use of UFH in UA/STEMI have continued therapy for 2-5 days. The optimal duration of therapy remains undefined.

Enoxaparin may be preferable to UFH as an anticoagulant in patients with UA/NSTEMI, unless CABG is planned within 24 h. This statement was supported by data from that of ESSENCE, TIMI IIb, INTERACT and EVET trials.

Statement 16: Glycoprotein IIb IIIa Inhibitors

It is RECOMMENDED to use glycoprotein IIb IIIa inhibitors (tirofiban) in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin or with other high risk features in whom an invasive management strategy is not planned; or in patients undergoing PCI with or without clopidogrel administration.

Five trials were conducted using GPIIb/IIIa inhibitors in UA/NSTEMI. In PRISM and PRISM PLUS, tirofiban appears to be beneficial in high risk patients whether they underwent PCI or not. However, no benefit is observed in low risk patients. In PURSUIT trial, eptifibatide also showed benefit whether they are treated medically or with PCI. However, in GUSTO IV, Abciximab showed no advantage over placebo in medically treated patients where PCI is not planned.

Statement 17: Factor X Inhibitor

It is RECOMMENDED to use fondaparinux, in lieu of enoxaparine, at a dose of 2.5 mg SC once daily in whom a conservative strategy is selected and who have an increased risk of bleeding.

The only selective factor-Xa inhibitor locally available for clinical use is fondaparinux. This is a synthetic pentasaccharide modeled after the anti-thrombin-binding sequence of UFH. It exerts a selective anti-thrombin-mediated inhibition of factor-Xa. Several advantages have been cited for its clinical uses over heparins. It does not induce the formation of heparin-PF4 complexes, hence heparin induced thrombocytopenia (HIT) is unlikely to occur with fondaparinux, therefore, monitoring of platelet count is not necessary. Additionally, the use of Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting time (ACT), pro-thrombin (PT), and thrombin times (TT). This drug is eliminated mainly by the renal route and should not be given if CrCl is lower than 30 mL/min.

However, this anticoagulant has propensity for increased rate of catheter-associated thrombosis.

Statement 18: Fibrinolytic Therapy

It is NOT RECOMMENDED to use intravenous fibrinolytic therapy in patients with UA or in patients without acute ST-segment elevation, a true posterior MI, or a presumed MI, or a presumed new left bundle-branch block (LBBB).

The failure of IV thrombolytic therapy to improve clinical outcomes in the absence of AMI was clearly demonstrated in the TIMI IIb, ISIS 2, GISSI 1 trials.

V. CORONARY REVASCULARIZATION

Statement 19: Early Conservative versus Invasive Strategies

It is RECOMMENDED that an early invasive strategy (as early as possible up to 72 hours) followed by revascularization (PCI or CABG) with any of the following high-risk indicators:

a. Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy.

b. Elevated cardiac biomarkers (TnT or TnI).

c. New or presumably new ST-segment depression.

d. Signs or symptoms of heart failure (HF) or new or worsening mitral regurgitation.

e. High-risk findings from non-invasive testing.

f. Hemodynamic instability.

g. Sustained ventricular tachycardia.

h. PCI within 6 months.

i. Prior CABG.

j. High-risk score (e.g., TIMI, GRACE).

k. Reduced LV systolic function (LVEF less than 40%).

Two different treatment strategies, termed “early conservative” and “early invasive” have evolved for patients with UA/NSTEMI. In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-T segment changes or a strongly + stress tests despite vigorous medical therapy). In the early invasive strategy, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and revascularization if possible within 24-48 hours after presentation to the ED.

TIMI-IIIB was the first trial to compare strategies of routine catheterization and revascularization in addition to medical therapy and selective use of aggressive treatment.

The FRISC II and TACTICS trials support the use of catheterization and revascularization for selected patients with an acute coronary syndrome. The greater benefits derived from percutaneous coronary intervention (PCI) in the TACTICS and FRISC trials can be explained in part by the use of stents and GP-receptor blockers and lower peri-procedural complications.

A conservative strategy may be instituted for patients with low-risk score (e.g., TIMI, GRACE) or according to
Statement 20: Coronary angiography

It IS NOT RECOMMENDED in patients with extensive co-morbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization are not likely to outweigh the benefits or in patients with acute chest pain and a low likelihood of ACS or in patients who will not consent to revascularization regardless of the findings.

Statement 21: Percutaneous Coronary Intervention (PCI)

An early invasive PCI strategy IS RECOMMENDED for patients with UA/NSTEMI who have no serious co-morbidities and who have coronary lesions amenable to PCI and any of the high risk features (See Statement 19).

PCI (or CABG) is ALSO RECOMMENDED for UA/NSTEMI patients with 1-2 vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high risk criteria on non invasive testing.

Statement 22: Coronary Artery Bypass Graft (CABG) Surgery

CABG IS RECOMMENDED for patients with significant left main disease and the preferred revascularization strategy for patients with multi-vessel coronary disease, with depressed systolic function (LVEF ≤ 50%), and diabetes.

VI. HOSPITAL DISCHARGE

Statement 23: It is RECOMMENDED that the following specific instructions should be given

a. Lifestyle modification that includes smoking cessation, achievement or maintenance of optimal weight, daily exercise, and diet.

b. Daily exercise of 30 minutes or 5 days per week.

c. Consider referral of patients who are smokers to smoking cessation program or clinic and/or an out-patient cardiac rehabilitation program.

d. Intensive lipid-lowering therapy is strongly recommended by combining dietary interventions with pharmacotherapy using statins, or combining with other lipid-lowering agents to reduce LDLc <100 mg/dL. Further reduction to less than 70 mg/dL may be recommended.

e. A fibrate or niacin if high density lipoprotein (HDL) cholesterol is less than 40 mg/dL, occurring as an isolated finding or in combination with other lipid abnormalities.

f. Hypertension control to a blood pressure of less than 140/90 mm Hg or less than 130/80 mm Hg if patient has diabetes or chronic kidney disease.

g. Tight control of hyperglycemia in diabetes. Goal is HbA1c of less than 7%.

h. Antiplatelet agents/Anticoagulants.

h.1. Aspirin

1. For all post-PCI stented patients without allergy or increased risk of bleeding, aspirin 160 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 80 mg to 160 mg daily.

2. In patients for whom the physician is concerned about risk of bleeding, lower-dose 80 mg to 160 mg of aspirin is reasonable during the initial period after stent implantation.

h.2 Clopidogrel

1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for at least indefinitely if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).

2. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI and non-STEMI patients who undergo PCI without reperfusion therapy.

References:


17. Beeveres DG, Sleigh P. Short acting dicyclomycin (vasodilating)
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30. FRAXIS study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6 day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction. FRAXIS* (FRAXIS in ischaemic Syndrome). Eur Heart J 1999;20:1553-62.
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The following index lists therapeutic classifications as recommended by the treatment guideline. For the prescriber’s reference, available drugs are listed under each therapeutic class. For drug information, please refer to the Philippine Drug Directory System (PPD, PPD Pocket Version, PPD Text, PPD Tabs).

### CARDIOVASCULAR DRUGS

#### Anticoagulants
- Dalteparin
- Flomax
- Enoxaparin
- Fondaparinux
- Heparin
- Heparin Leo
- Nadroparin

#### Antiplatelet Agents
- Abciximab
- Aspirin
- Ticlopidine

#### ACE Inhibitors
- Cialisapril/Hydrochlorothiazide
- Enalapril
- Lisinopril
- Losartan

#### Beta blockers
- Beta blockers

#### Candesartan
- Blopres
- Candesartan/Hydrochlorothiazide
- Eprosartan
- Teveten
- Eprosartan/Hydrochlorothiazide

#### Captopril
- Capoten
- Captril
- Drugmaker’s Biotech Captopril
- Hartylox
- Primace
- Septuagen

#### Cilazapril
- Vasodad
- Cilazapril/Hydrochlorothiazide
- Vasodad Plus

#### Cilazapril
- Vascace
- Cilazapril/Hydrochlorothiazide
- Vascace Plus

#### Co-Aprovel
- BP Norm

#### Co-Diovan
- Diovan

#### Co-Ram
- Ramipril/Felodipine

#### CoRexapril
- Sartan

#### Co-Runote
- Normoten/Normoten 100

#### Candesartan
- Blopress
- Candesartan / Hydrochlorothiazide
- Blopress Plus

#### Candesartan
- Teveten
- Eprosartan
- Eprosartan/Hydrochlorothiazide

#### Candesartan
- Aprovel
- Izart
- Winthrop Irbesartan

#### Irbesartan
- Angiocard
- Angijsartan
- Anzar
- Arboic
- Bepsar
- Cozaar
- Doxar
- Ecozart
- Getzar
- Hartzar
- Hypertan
- Hypertreel
- Lifezar
- Losacar
- Losargard
- Lozart
- Myotan
- Neosartan
- Normoten/
- Normoten 100
- Pharex Losartan Potassium
- Sartan
- Vivasartan
- Wilopres
- Xartan

#### Eprosartan
- Tevedient

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten

#### Eprosartan
- Teveten
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Drugmaker’s Biotech Atenolol
Tenormin
Tensimini
Therabloc

Atenolol/Chlorthalidone
Tenoretic

Bisoprolol
Concore

Bisoprolol/Chlorothiazide
Bisopuls
Ziac

Esmolol

Metoprolol succinate
Betazok

Metoprolol tartrate
Betacloc
Cardioesel
Cardiostat
Cardiotab
Carditec
Drugmaker’s Biotech Metoprolol
Gerblock
Metobloc
Metocare
Metostad
Neobloc
Neox 50/Neox 100
Pharex Metoprolol
RiteMED Metoprolol
Valxevin
Zionel

Metoprolol/Hydrochlorothiazide
Betazide

Pindolol
Pyndale
Visken

Pindolol/Clozapamide
Viskalidix

Propranolol
Drugmaker’s Biotech
Propranolol
Inderal

Timolol

Calcium Antagonists
Amlodipine besylate
Aforbes
Amaday
Ambes
Ambesyl
Ambloc
Amcal
Amlocor
Amodac
Amodine
Amlomin
Amlomed-5
Amvasc
Amvasc BE
Angivas
Calblock
Coram
Convex
Dailyvasc
Hyperta
Lopicard
Norblock
Norvasc
Pharex Amodipine Besylate
Ritemed Amodipine
Sedipin
Vasalat
Vascar
Vaselec
Vasprim
Winthrop Amodipine besilate

Amlodipine besylate/
Atevassin calcium
Envacar

Amodipine besylate/valsartan
Exforge

S-Amodipine
Amlodes
Asomex

Diltiazem
Dilatam
Dilzem/Dilzem SA/Dilzem OD/
Dilzem SR
Drugmaker’s Biotech Diltiazem
Dyacal
RiteMed Diltiazem

Felodipine
Dilahex
Dilofen ER
Felop ER Tab
Felpin
Pnendi ER
Versant XR

Felodipine/Metoprolol
Logimax

Felodipine/Ramipril
Triapr

Irbesidipine
Nifedipine
Adalat/Adalat Gitz/
Adalat Retard
Calcibloc
Calcibloc OD
Drugmaker’s Biotech Nifedpine
Hebilopin
Nicardia

Nicardipine
Cardepine

Verapamil
Isotropin/Isotrop SR

Verapamil/Trandolapril
Tarka/Tarka Forte

Organic Nitrates
Isosorbide dinitrate
Isoket
Isoket IV
Isoket Spray
Isordil

Isosorbide mononitrate
Angistad/Angistad SR
Elantan
Elantan Long
GlaxoSmithKline ISMN 60
Imdur Durules
Isomonit
Monosorb
Vasotrate-20
Vasotrate-60 OD

Nitroglycerin
Deponit NT 5/Deponit NT 10
Minitran
Nitrostat
Transderm-Nitro

Statins
Atevassin calcium
Atoptar
Ator-10/ Ator-20/
Ator-40/ Ator-80
Atroact-10
Avamox
Cholesta
Lipitor

Atevassin/Amodipine besylate
Envacar

Fluvastatin
Lescol/Lescol XL

Pravastatin
Lipostat
Pravaz

Rosuvastatin
Crestor
Rustor

Simvastatin
Afordol
Altovasst
Cardiosim
Drugmaker’s Biotech Simvastatin
Endovaz
Eurocor
Ivast
Lipivas
Lipix
Lochol
Normastin
Orovas
Pharex Simvastatin
Qualistat
RiteMed Simvastatin
Saveor
Simbthree
Simvax
Simvasyn
Simvaz
Simvogel
Sistat-20
Vamstat
Vastacor
Vastat
Vastex
Vastilain
Vidastat
Wilsim
Winthrop Simvastatin
Ximvast
Zivas
Zocor/Zocor HP
Zostatin

Simvastatin/ezetimibe
Vytorin

Meperidine HCl

Morphine Sulfate
Hizon Morphine Sulfate
MST Continus

Naloxone