**Introduction: Acute Coronary Syndrome**

Acute Coronary Syndrome (ACS) is a critical subtopic in Cardiology that every clinical pharmacist should understand. ACS refers to a spectrum of conditions characterized by decreased blood flow in the coronary arteries, such as unstable angina and myocardial infarction. It is a medical emergency, and early recognition and management can significantly improve patient outcomes. As pharmacists play a vital role in the multidisciplinary team managing these conditions, an in-depth understanding of ACS is essential.

**Clinical Presentation**

Acute Coronary Syndrome (ACS) typically presents with chest pain, often described as a crushing, burning, or pressure-like sensation, which may radiate to the jaw, neck, arms, or back. Other symptoms include shortness of breath, nausea, vomiting, diaphoresis, and light-headedness. It's worth noting that some patients, particularly women, the elderly, and those with diabetes, may present with atypical symptoms or be asymptomatic.

The risk factors for ACS can be divided into modifiable and non-modifiable:

Modifiable Risk Factors:

* Hypertension
* Hyperlipidemia
* Diabetes Mellitus
* Smoking
* Obesity
* Sedentary lifestyle
* Unhealthy diet

Non-modifiable Risk Factors:

* Age (men >45 years, women >55 years)
* Family history of premature coronary artery disease
* Gender (male)
* Ethnicity

The disease state is more common in older adults, with the incidence and prevalence increasing significantly with age. It also tends to affect more men than women, although post-menopausal women are at a similar risk as men.

**Pathophysiology**

Acute Coronary Syndrome (ACS) is primarily caused by an imbalance between myocardial oxygen supply and demand, leading to ischemia. This imbalance can occur due to various reasons, with the most common being the rupture of an atherosclerotic plaque in the coronary arteries.

The pathophysiology of ACS can be summarized as follows:

* Atherosclerotic Plaque Formation: Over time, accumulation of low-density lipoprotein (LDL) cholesterol in the arterial wall can lead to the formation of fatty streaks. This, coupled with inflammation, leads to the development of an atherosclerotic plaque.

* Plaque Rupture and Thrombosis: The rupture or fissuring of an atherosclerotic plaque exposes the thrombogenic components of the plaque core to circulating blood. This triggers platelet aggregation and activation of the coagulation cascade, resulting in the formation of a thrombus.

* Ischemia and Myocardial Damage: The thrombus can partially or completely occlude the coronary artery, reducing blood flow to the myocardium. If the occlusion persists, it can lead to ischemia and, eventually, myocardial necrosis. This is represented clinically as unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI), depending on the extent and duration of the ischemia.

Pharmacists should understand that the key goal in ACS management is to restore the balance between myocardial oxygen supply and demand, reduce the extent of myocardial damage, and prevent complications.

**Diagnostic Approach**

The diagnosis of Acute Coronary Syndrome (ACS) is a multifaceted process, combining elements of clinical history, physical examination, electrocardiographic findings, and cardiac biomarkers.

The initial step in diagnosing ACS is an exhaustive assessment of the patient's clinical history and physical examination. Symptoms suggestive of ACS, such as chest pain, shortness of breath, nausea, or fatigue, particularly when combined with known risk factors for coronary artery disease, warrant further investigation. Notably, ACS should be considered even in patients presenting with atypical symptoms, as the clinical presentation can vary considerably, especially among women, older adults, and people with diabetes.

**Electrocardiogram (ECG)**is the next crucial component in the diagnostic evaluation. ECG changes can provide vital clues to the type of ACS:

* ST-segment elevation myocardial infarction (STEMI) is characterized by persistent ST-segment elevation in two or more contiguous leads. The ST elevation is indicative of complete occlusion of a coronary artery, leading to transmural myocardial ischemia. This is a medical emergency requiring immediate reperfusion therapy.

* Non-ST-segment elevation ACS, comprising non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA), is associated with ST-segment depression, T-wave inversion, or may even have a normal ECG. In NSTEMI, there's partial or transient occlusion of a coronary artery, leading to subendocardial ischemia. In contrast, UA is characterized by reversible myocardial ischemia without evidence of myocardial necrosis.

**Cardiac biomarkers, especially troponins (T and I),** are an essential part of the diagnostic evaluation. These proteins are released into the bloodstream following myocardial injury. Elevated levels, particularly a rise and/or fall over time, are indicative of myocardial necrosis and hence diagnostic of NSTEMI. In contrast, UA is associated with normal troponin levels as there's no significant myocardial cell death.

Finally, risk stratification tools such as the GRACE or TIMI risk scores are often used in ACS to guide management decisions. These scores take into account various factors such as age, vital signs, ECG changes, and biomarker levels to stratify patients into low, intermediate, or high risk for adverse outcomes.

It's important to remember that while these tests are extremely helpful in diagnosing ACS, the absence of typical findings doesn't entirely exclude the disease, especially early after symptom onset. Therefore, high clinical suspicion warrants close monitoring and possible repeat testing.

Here is a table summarizing the key diagnostic features of the types of Acute Coronary Syndrome (ACS): STEMI, NSTEMI, and Unstable Angina.

|  |  |  |  |
| --- | --- | --- | --- |
| Type of ACS | ECG Changes | Cardiac Biomarkers (Troponin) | Description |
| STEMI | Unstable Angina | Elevated | Complete occlusion of a coronary artery leading to transmural myocardial ischemia. |
| NSTEMI | ST-segment depression, T-wave inversion, or normal | Elevated | Partial or transient occlusion of a coronary artery leading to subendocardial ischemia and myocardial necrosis. |
| Unstable Angina | ST-segment depression, T-wave inversion, or normal | Normal | Reversible myocardial ischemia without significant myocardial necrosis. |

## Management - Overview

The management of Acute Coronary Syndrome (ACS) is a multidisciplinary effort aimed at quickly restoring blood flow to the myocardium, preventing further myocardial damage, and reducing the risk of future cardiovascular events.

The first step in management is stabilizing the patient's condition with medications to relieve chest pain and improve heart function. These may include antiplatelet agents to inhibit clot formation, anticoagulants to prevent clot propagation, and medications such as beta-blockers and nitrates to decrease myocardial oxygen demand.

The next step is to determine the appropriate reperfusion strategy, which depends on the type of ACS. For ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy if it can be performed in a timely manner. Otherwise, fibrinolytic therapy may be considered. For non-ST-segment elevation ACS (NSTEMI and unstable angina), an early invasive strategy (i.e., diagnostic angiography with intent for revascularization) is recommended for high-risk patients, while a conservative strategy may be considered for low-risk patients.

Long-term management of ACS includes lifestyle modifications and chronic medications to reduce the risk of future cardiovascular events. These may include dual antiplatelet therapy, statins, beta-blockers, ACE inhibitors, and lifestyle modifications like smoking cessation, healthy diet, and regular exercise.

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### Pharmacotherapy

Pharmacotherapy for Acute Coronary Syndrome (ACS) is intricate, with the approach varying depending on the type of ACS—ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). The initial management focuses on stabilizing the patient, relieving ischemia, and preventing further thrombus formation, with a particular emphasis on reperfusion therapy for STEMI.

Initial Emergency Management

* **Aspirin:** An immediate loading dose of aspirin 162-325 mg should be administered orally unless contraindicated. This is followed by a maintenance dose of 81-162 mg daily.
  + The administration of aspirin should be immediate in all patients suspected of having ACS, unless contraindicated. The aspirin should be non-enteric coated and chewed for faster absorption.
  + Aspirin 300 mg rectally if NPO

**P2Y12 Inhibitors:** These agents work in tandem with aspirin to provide potent dual antiplatelet therapy (DAPT). This class includes:

* Clopidogrel: Historically was the first choice, with a loading dose of 600 mg followed by a maintenance dose of 75 mg daily for STEMI.
  + STEMI managed with Fibrinolytics: Age ≤75 y: 300-mg loading dose followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding
    - COR 1, LOE A (LD and 14 day) (C up to 1 year)
  + STEMI managed with Fibrinolytics: Age >75 y: no loading dose, give 75 mg followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding
    - COR 1, LOE A (LD and 14 day) (C up to 1 year)
* Prasugrel: A more potent P2Y12 inhibitor, typically reserved for patients undergoing PCI. The loading dose is 60 mg, followed by a maintenance dose of 10 mg daily.
  + Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.
  + Not listed as agent when STEMI managed with Fibrinolytics
* Ticagrelor: Another potent P2Y12 inhibitor, with a loading dose of 180 mg, then 90 mg twice daily.
  + Not listed as agent when STEMI managed with Fibrinolytics

* Cangrelor: An intravenous P2Y12 inhibitor used for patients requiring immediate, short-term P2Y12 inhibition, such as those undergoing PCI.
* Clinical Pearls
  + Remember that prasugrel should not be used in patients with a history of stroke or transient ischemic attack (TIA). Ticagrelor requires twice-daily dosing and can cause dyspnea due to its inhibition of adenosine uptake.

Choosing between P2Y12 Inhibitors: While clopidogrel, prasugrel, and ticagrelor are all options for P2Y12 inhibition, their use can be tailored based on individual patient factors. Prasugrel and ticagrelor are more potent and have been shown to reduce ischemic events compared to clopidogrel but at the expense of increased bleeding risk. Therefore, they might be preferred in younger patients without a history of stroke or bleeding. In contrast, clopidogrel might be a safer choice in older patients or those with a history of stroke or bleeding.

**IV GP IIb/IIIa Receptor Antagonist (in conjunction with URF or Bivalirudin**

* Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min)
* Tirofiban: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min
  + In patients with CrCl <30 mL/min, reduce infusion by 50%
* Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus
  + In patients with CrCl <50 mL/min, reduce infusion by 50%
  + Avoid in patients on hemodialysis
* Consider using when
  + Brief window between antiplatelets and arriving to PCI or didn’t get P2y12 Inhibtiors at all
  + Agents are us

**Anticoagulants:**

These are used alongside antiplatelet agents to prevent propagation of the clot. Options include:

* Unfractionated heparin (UFH): Often the first-line choice, with an initial bolus of 60 units/kg (maximum 4000 units), followed by an infusion of 12 units/kg/hour (maximum 1000 units/hour), adjusted based on aPTT.
  + STEMI managed by PCI
    - With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT
    - With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT
    - Given 1C recommendation from 2013 AHA STEMI Guidelines when managed with PCI
  + STEMI managed with Fibrinolytics
    - Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization.
    - COR 1, LOE C

* Enoxaparin: A low molecular weight heparin, given as 1 mg/kg subcutaneously every 12 hours (or every 24 hours if creatinine clearance <30 mL/min).
  + STEMI managed by PCI
    - Not listed with Heparin and Bivalirudin for patients being managed with PCI
  + STEMI managed with Fibrinolytics:
    - If age <75 y: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses)
    - If age ≥75 y: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first 2 doses)
    - Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h
    - Duration: For the index hospitalization, up to 8 d or until revascularization
    - COR 1, LOE A
      * Higher than Heparin
  + NSTEMI managed by PCI
    - 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses)
      * 30-mg IV bolus if beyond 8 hours since last dose
* Bivalirudin: Typically reserved for patients undergoing PCI, particularly those with a high risk of bleeding.
  + Bivalirudin: 0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH.
    - An additional bolus of 0.3 mg/kg can be given if needed.
  + Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min
  + Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding
* Fondaparinux:
  + STEMI managed with Fibrinolytics
    - Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization
    - COR 1, LOE B
    - Contraindicated if CrCl <30 mL/min
  + STEMI managed by PCI
    - Not recommended as sole anticoagulant for primary PCI

**Other Medications and Therapies**

* Morphine: Used if chest pain is not relieved by nitroglycerin. However, it should be used judiciously as it can delay the absorption of oral antiplatelet agents.
  + While morphine is an option for pain control in ACS, it can delay the absorption of P2Y12 inhibitors and should be used judiciously. In fact, some recent observational data suggest potential harm with morphine use in ACS, although these findings need to be confirmed in randomized trials.
* Oxygen
  + Only use if O2 Saturations less than 90%
  + No data supporting prophylactic use of oxygen supplementation
* Nitroglycerin: Used for immediate relief of ischemic chest pain. It's typically given sublingually as a 0.4 mg tablet or spray. If pain persists, intravenous nitroglycerin can be considered.
  + Caution in patients with:
    - Inferior STEMI due to preload dependance
    - History of PDE-3 Inhibitors

* Data may not be strong in current management of STEMI as much of data was prior to PCI
* Beta Blockers
  + Consider IV beta blockers  if no signs of heart failure or in shock within 24 hours
  + Start PO within 24 hours if no signs of heart failure or in shock

**Reperfusion Therapy**

Reperfusion therapy is the mainstay of treatment for STEMI patients. The preferred method is primary percutaneous coronary intervention (PCI), if it can be performed within 90-120 minutes of first medical contact. If primary PCI is not available or feasible, fibrinolytic therapy should be considered. This includes:

* Alteplase (t-PA): A tissue plasminogen activator that catalyzes the conversion of plasminogen to plasmin, leading to fibrinolysis. The total dose should not exceed 100 mg and is given over 1.5 hours: 15 mg IV bolus, then 0.75 mg/kg (up to 50 mg) over the next 30 minutes, then 0.5 mg/kg (up to 35 mg) over the next 60 minutes.

* Reteplase (r-PA): A non-glycosylated deletion mutant of tissue plasminogen activator. It is given as two IV bolus injections, each 10 units, 30 minutes apart.

* Tenecteplase (TNK-tPA): A genetically engineered variant of tissue plasminogen activator. The dose is weight-based and given as a single IV bolus over 5 seconds: <60 kg: 30 mg; 60 to <70 kg: 35 mg; 70 to <80 kg: 40 mg; 80 to <90 kg: 45 mg; ≥90 kg: 50 mg.
* Clinical Pearls
  + Time is of the essence. Fibrinolytic therapy should be administered as soon as possible (within 30 minutes of hospital arrival) in STEMI patients when primary PCI is not available or cannot be performed within 120 minutes. Remember that each fibrinolytic agent has a different dosing regimen, and dosing errors can lead to increased risk of bleeding, including intracranial hemorrhage

**Long-term Management**

Long-term management focuses on preventing further cardiovascular events and includes classes of drugs such as beta-blockers, ACE inhibitors/ARBs, and statins. Dual antiplatelet therapy is typically continued for at least 12 months in all patients with ACS, regardless of whether they underwent revascularization. Beta-blockers and ACE inhibitors/ARBs are indicated in patients with left ventricular dysfunction, while statins are recommended for all patients with ACS. Early initiation of beta-blockers (within the first 24 hours) in ACS patients without contraindications has been shown to reduce short-term mortality. However, they should be used with caution in patients with signs of heart failure, significant left ventricular dysfunction, or risk for cardiogenic shock.

**Major Differences in Treatment of STEMI, NSTEMI, and UA**

The major difference in the treatment of STEMI compared to NSTEMI and UA is the use of immediate reperfusion therapy in STEMI, either by primary PCI or fibrinolytic therapy if PCI is not feasible. In contrast, NSTEMI and UA are initially managed with medications alone, with coronary angiography generally performed within 24-72 hours. In high-risk NSTEMI or UA patients, an early invasive strategy is preferred, while in low-risk patients, a conservative (initially non-invasive) strategy may be adopted.  
Risk Stratification in NSTEMI and UA: The decision to pursue an early invasive strategy (i.e., coronary angiography and revascularization within 24 hours) versus a conservative strategy in patients with NSTEMI and UA depends on their risk profile. High-risk features include elevated cardiac biomarkers, dynamic ST-T wave changes, hemodynamic instability, and a GRACE score of >140. Patients without these high-risk features may be managed conservatively, with coronary angiography reserved for those who fail medical therapy.

### Key Guidelines and Evidence

Key Guideline Recommendations for STEMI Management

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines provide evidence-based recommendations for the management of patients with ST-elevation myocardial infarction (STEMI). Some of the key recommendations include:

* For patients presenting within 12 hours of symptom onset, primary percutaneous coronary intervention (PCI) has a Class I recommendation if it can be performed in a timely manner by an experienced provider (Class I, LOE A).
* Fibrinolytic therapy is recommended when primary PCI cannot be performed within 120 minutes of first medical contact, in the absence of contraindications (Class I, LOE A). Time to treatment is critical.
* Aspirin 162-325 mg should be given before primary PCI (Class I, LOE B). A P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) should also be given as early as possible (Class I, LOE A).
* For anticoagulation during primary PCI, unfractionated heparin (Class I, LOE C) or bivalirudin (Class I, LOE B) are recommended.
* Routine upstream use of a glycoprotein IIb/IIIa inhibitor is not recommended (Class III: No Benefit, LOE A). May be considered in specific high-risk situations.
* Cardiogenic shock and severe heart failure are indicative of emergency revascularization, irrespective of time delay from MI onset (Class I, LOE B).
* After successful fibrinolysis, early catheterization with intent for PCI is reasonable when logistically feasible, even in stable patients (Class IIa, LOE B). Rescue PCI is recommended for failed reperfusion (Class I, LOE B).
* Beta blockers should be started within 24 hours in the absence of contraindications (Class I, LOE B).
* High intensity statins are indicated for all STEMI patients (Class I, LOE A). Dual antiplatelet therapy should be given for at least 1 year after stent placement.
* Goal door‐to‐balloon time less than 90 minutes
* In the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC. (Level of Evidence: A)

**Landmark Trials:**

The CURE Trial showed that adding clopidogrel to aspirin reduced the risk of cardiovascular death, MI, or stroke in patients with ACS. However, this was at the expense of an increased risk of major bleeding.

The PLATO Trial demonstrated that ticagrelor was superior to clopidogrel in reducing cardiovascular death, MI, or stroke in patients with ACS. However, ticagrelor was associated with a higher rate of non-CABG major bleeding.

The TRITON-TIMI 38 Trial showed that in patients with ACS undergoing PCI, prasugrel was superior to clopidogrel in reducing the rate of cardiovascular death, MI, or stroke. However, prasugrel was associated with an increased risk of major bleeding.

The ATLAS ACS 2-TIMI 51 Trial showed that in patients with recent ACS, adding low-dose rivaroxaban to standard antiplatelet therapy reduced the risk of the composite endpoint of cardiovascular death, MI, or stroke. However, rivaroxaban was associated with an increased risk of major bleeding and intracranial hemorrhage.

### Tips for Board Exam Questions:

1. Know the critical timeframes. Time is muscle in ACS. Key thresholds include presenting within 12 hours of symptom onset for potential reperfusion therapy, goal door-to-balloon time <90 min for STEMI patients, and 120 min door-to-needle time for fibrinolytic administration if PCI is not available.
2. Differentiate STEMI, NSTEMI, and unstable angina based on ECG and cardiac marker findings. STEMI is diagnosed by ST elevation on ECG. NSTEMI is distinguished by positive cardiac markers without ST elevation. Unstable angina demonstrates ischemic symptoms without biomarker elevation.
3. Recall guideline-recommended therapies. High yield topics include dual antiplatelet therapy, anticoagulation, reperfusion strategy selection, and appropriate use of invasive procedures. Know the medications, doses and contraindications. Strict adherence to guidelines is key to improving ACS outcomes.

### Summary: Acute Coronary Syndrome

ACS requires prompt recognition, risk stratification, and initiation of evidence-based therapies to restore coronary blood flow, reduce myocardial oxygen demand, inhibit thrombus extension, prevent adverse outcomes, and relieve ischemic symptoms. Immediate reperfusion for STEMI is critical. Combination antiplatelet and anticoagulant therapy form the foundation of ACS pharmacotherapy. Secondary prevention with statins, beta blockers, ACE inhibitors/ARBs, and dual antiplatelet therapy significantly improves long-term outcomes.

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