Therapy of Acute Coronary Syndromes

Yacoub Irshaid, MD, PhD, ABCP
Department of Pharmacology, Faculty of Medicine

Therapy of Acute Coronary Syndromes

- **The cause of an acute coronary syndrome (ACS) is the rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, and aggregation, and the activation of the clotting cascade.**
- **Ultimately, a clot forms composed of fibrin and platelets.**

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- It includes ST-segment elevation (STE) myocardial infarction (MI) [STE MI] and non–ST-segment elevation (NSTE) ACS.
- Acute coronary syndromes (ACS) include unstable angina (UA) and myocardial infarction (MI).

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Desired Outcomes:

Short-term desired outcomes in a patient with ACS:

1. Early reperfusion therapy with primary percutaneous coronary intervention (PCI) of the infarct artery is recommended for patients presenting with ST-segment elevation myocardial infarction (STEMI) within 12 hours of symptom onset.

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2. **Prevention of death and other MI complications.**
3. **Prevention of coronary artery re-occlusion.**
4. **Relief of ischemic chest discomfort.**
5. **Resolution of ST-segment and T-wave changes on the ECG.**

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Long-term desired outcomes:

1. **Control of CV risk factors.**
2. **Prevention of re-infarction, stroke, and HF.**
3. **Improving the quality-of-life.**

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- **All patients with STEMI and without contraindications should receive within the first day of hospitalization and preferably in the emergency department (ED):**

1. **Intranasal oxygen (if oxygen saturation is low).**
2. **Sublingual (SL) nitroglycerin (NTG).**
3. **Aspirin.**

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4. **A P2Y12 (ADP receptor) inhibitor (clopidogrel, prasugrel, or ticagrelor).**
5. **Anticoagulation with bivalirudin (direct thrombin inhibitor), unfractionated heparin (UFH), enoxaparin, or fondaparinux.**

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6. **A glycoprotein IIb/IIIa inhibitor (GPI): (abciximab, eptifibatide, and tirofiban).**

- **Management demands a personalized approach that balances the competing risks of ischemia and bleeding.**
- **In patients with large thrombus burden, no-reflow or slow flow intravenous, these agents are reasonable to improve procedural success.**
- **The are not recommended for patients with stable ISD undergoing PCI.**

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7. A high-intensity statin should be administered prior to PCI (in patients > 75 years old, moderate intensity).
8. Intravenous (IV) β-blockers and IV NTG should be administered cautiously in selected patients.
9. Oral β-blockers should be initiated within the first day in patients without contraindications.

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10. An ACE inhibitor is recommended within the first 24 hours in patients with STEMI who have either an anterior wall MI or LVEF ≤ 0.40 with no contraindications.
11. Morphine may be given to patients with refractory angina as an analgesic and a veno-dilator that lowers preload.

- Morphine slows the absorption of oral antiplatelet agents due to decreased gastric motility.

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- **In the absence of contraindications, all patients with NSTE-ACS should be treated in the ED with:**

1. **Intranasal oxygen (if oxygen saturation is low).**
2. **SL NTG.**
3. **Aspirin.**
4. **An anticoagulant (UFH, enoxaparin, fondaparinux, or bivalirudin).**
5. **High-risk patients should proceed to early angiography, and may receive a glycoprotein IIb/IIIa inhibitor GPI.**

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6. **A P2Y12 inhibitor should be administered to all patients.**
7. **A high-intensity statin should be administered prior to PCI.**
8. **IV β-blockers and IV NTG should be administered cautiously in selected patients.**
9. **Oral β-blockers should be initiated within the first day in patients without contraindications.**

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10. **ACEI are also indicated in non ST-segment elevation myocardial infarction (NSTEMI) patients with hypertension, systolic left ventricular dysfunction, heart failure (HF), or diabetes.**

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Secondary prevention guidelines suggest that following MI from either STEMI or NSTE-ACS:

- **All patients, in the absence of contraindications, should receive indefinite treatment with aspirin, a β-blocker, a moderate-to-high intensity statin, and an angiotensin-converting enzyme (ACE) inhibitor for secondary prevention of death, stroke, or recurrent infarction.**

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- **A P2Y12 inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients treated medically (without PCI or thrombolytics).**
- **Clopidogrel should be continued for at least 14 days, and ideally 1 year, in patients with STEMI treated with fibrinolytics.**

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- **An angiotensin II receptor blocker and an aldosterone antagonist may be given to selected patients.**
- **For all patients with ACS, treatment and control of modifiable risk factors such as hypertension (HTN), dyslipidemia, obesity, smoking, and diabetes mellitus (DM) are essential.**

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Ventricular Remodeling Following an Acute MI:

- **Ventricular remodeling is a process that occurs in several cardiovascular conditions including HF and MI.**
- **It is characterized by: left ventricular (LV) dilation and reduced pumping function of the LV, leading to HF.**
- **Because HF represents one of the principal causes of morbidity and mortality following an MI, preventing ventricular remodeling is an important therapeutic goal.**
- **ACE-inhibitors, ARBs, β-blockers, and aldosterone antagonists can slow down or reverse ventricular remodeling through inhibition of the renin–angiotensin–aldosterone system and/or through improvement in hemodynamics (decreasing preload, afterload or neurohormonal activation).**

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Patients may also need:

1. **Bed rest for 12 hours in hemodynamically stable patients.**
2. **Avoidance of the Valsalva maneuver (prescribe stool softeners routinely).**
3. **Pain relief.**

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Antiplatelet Therapy in PCI and STEMI and NSTE-ACS:

- **All patients should receive an initial dose of 162- or 325-mg of aspirin (should be chewed) followed by a daily aspirin dose of 81 mg/day indefinitely.**
- **A P2Y12 inhibitor antiplatelet (clopidogrel, prasugrel, ticagrelor, cangrelor) should be administered concomitantly with aspirin and should ideally be continued for at least 12 months following PCI.**

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- **Earlier discontinuation of the P2Y12 inhibitor can be reasonable in patients at high bleeding risk or with "overt bleeding".**

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Fibrinolytic Therapy:

Administration of a fibrinolytic agent is indicated in patients:

1. **With STEMI who present within 12 hours of the onset of chest discomfort to a hospital NOT capable of primary PCI.**
2. **Who have no absolute contraindications to fibrinolytic therapy.**
3. **Who are NOT able to be transferred to undergo primary PCI within 2 hours of medical contact.**

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- **A door-to-needle time of less than 30 minutes from the time of hospital presentation until start of fibrinolytic therapy is recommended.**
- **A fibrin-specific agent (alteplase, reteplase, or tenecteplase) is preferred, since it opens a greater percentage of arteries.**

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- **The mortality benefit of fibrinolysis is highest with early administration and diminishes after 12 hours.**
- **The use of fibrinolytics between 12-24 hours after symptom onset should be limited to patients with ongoing ischemia.**

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Adverse effects:

- **Intracranial hemorrhage (ICH) and major bleeding are the most serious.**
- **The risk of ICH is higher with fibrin-specific agents than with streptokinase.**
- **The risk of systemic bleeding other than ICH is higher with streptokinase than with other more fibrin-specific agents.**

Absolute Contraindications to Fibrinolytic Therapy

1. Active internal bleeding.
2. Previous intracranial hemorrhage at any time; ischemic stroke within 3 months (except acute ischemic stroke within ~4 hours)
3. Known intracranial neoplasm.
4. Known structural cerebral vascular lesion (A-V malformation).
5. Suspected aortic dissection.
6. Significant closed head or facial trauma within 3 months.
7. Intracranial or intraspinal surgery within 2 months.
8. Severe uncontrolled hypertension (unresponsive to emergency therapy).
9. For streptokinase, prior treatment within the previous 6 months.

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- In patients who have a contraindication to fibrinolytics and PCI, or who do NOT have access to a facility that can perform PCI, treatment with an anticoagulant for up to 8 days is recommended.

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Anticoagulants:

- **For patients undergoing primary PCI: either UFH or bivalirudin should be used.**
- **Anticoagulation is discontinued immediately following the PCI procedures.**
- **Bivalirudin would be a preferred anticoagulant for patients with a history of heparin-induced thrombocytopenia undergoing PCI.**

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- **For fibrinolysis: UFH, enoxaparin, or fondaparinux may be used.**
- **UFH is continued for 48 hours, and enoxaparin or fondaparinux are continued for the duration of hospitalization, up to 8 days.**
- **For patients who do not undergo reperfusion therapy: UFH for 48 hours, and enoxaparin or fondaparinux for the duration of hospitalization.**

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β-Blockers:

1. **β_1-Blockade reduces heart rate (HR), myocardial contractility, and blood pressure (BP), thus, decreasing myocardial oxygen demand.**
2. **The reduction in HR prolongs diastole, thus improving ventricular filling and coronary artery perfusion.**

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β-blockers reduce:

1) **the risk for recurrent ischemia**
2) **infarct size**
3) **risk of re-infarction**
4) **the occurrence of ventricular arrhythmias**

in the hours and days following MI.

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- **Initiating IV followed by oral β-blockers early in the course of STEMI was associated with a lower risk of re-infarction or ventricular fibrillation, but an early risk of cardiogenic shock, especially in patients presenting with pulmonary congestion or systolic BP less than 120 mm Hg.**
- **Oral beta blockers are preferred over IV in the management of ACS.**

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- **Initiation of β-blockers, particularly when administered IV, should be limited to patients who present with HTN and/or have ongoing signs of myocardial ischemia and do NOT demonstrate any signs or symptoms of acute HF.**
- **Careful monitoring for signs of hypotension and HF should be performed following β-blocker initiation and prior to any dose titration.**

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- **The most serious adverse effects early in ACS are hypotension, acute HF, bradycardia, and heart block.**
- **β-blockers should be initiated before hospital discharge in most patients following treatment of acute HF.**
- **They should be continued for at least 3 years in patients with normal LV function, and indefinitely in patients with LV systolic dysfunction and LVEF ≤ 0.4.**

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Statins:

- **A high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) should be administered to all patients without contraindications prior to PCI (regardless of prior lipid-lowering therapy) to reduce the frequency of peri-procedural MI following PCI.**

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Nitrates:

- **One SL NTG tablet should be administered every 5 minutes for up to 3 doses in order to relieve myocardial ischemia.**
- **In patients with persisting ischemic chest discomfort for more than 5 minutes after the first dose, IV NTG can be initiated in all patients who have persistent ischemia, HF, or uncontrolled high BP in the absence of contraindications.**

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- **IV NTG should be continued for approximately 24 hours after ischemia is relieved.**
- **Nitrates promote the release of nitric oxide from the endothelium which results in venodilation, and vasodilation in large coronary arteries.**
- **Venodilation lowers preload and myocardial oxygen demand.**
- **Arterial vasodilation may lower BP, thus reducing myocardial oxygen demand.**

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- **Arterial vasodilation also relieves coronary artery vasospasm and improves myocardial blood flow and oxygenation.**
- **Nitrates have NO mortality benefit (IV or oral).**
- **The most significant adverse effects of nitrates are: tachycardia, flushing, throbbing headache, and hypotension.**

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- **Nitrate administration is contraindicated in patients who have received oral phosphodiesterase-5 inhibitors (sildenafil and vardenafil) within the last 24 hours, and tadalafil within the last 48 hours.**

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Calcium Channel Blockers:

- **In the setting of STEMI, they are used for relief of ischemic symptoms only in patients who have certain contraindications to β-blockers.**
- **Agent that lowers HR (diltiazem or verapamil) are preferred unless the patient has LV systolic dysfunction, bradycardia, or heart block, when either amlodipine or felodipine may be used.**
- **Nifedipine should be avoided (→ reflex sympathetic stimulation, tachycardia, and worsened myocardial ischemia).**

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Early Pharmacotherapy for NSTE-ACS:

- **In general, early pharmacotherapy of NSTE-ACS is similar to that of STEMI.**

Fibrinolytic Therapy:

- **Fibrinolytic therapy is NOT indicated in any patient with NSTE-ACS because it is associated with increased mortality.**

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Anticoagulants:

- **All patients should receive UFH, enoxaparin, fondaparinux, or bivalirudin.**

Antiplatelet drugs:

- **Clopidogrel (300 or 600-mg loading dose followed by 75 mg daily) can be used in addition to low-dose aspirin.**
- **Low-dose aspirin is continued indefinitely.**

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Glycoprotein IIb/IIIa Receptor Inhibitors:

- **For patients managed with conservative strategy but who experience recurrent ischemia (chest discomfort and ECG changes), HF, or arrhythmias after initial medical therapy necessitating a change in strategy to angiography and revascularization, a GPI may be added to aspirin and clopidogrel prior to the angiogram.**

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Duration of Anticoagulant Therapy:

a) at least 48 hours for UFH,
b) until the patient is discharged from the hospital (or 8 days, whichever is shorter) for either enoxaparin or fondaparinux,
c) until the end of PCI or angiography procedure (or up to 72 hours following PCI) for bivalirudin.

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Nitrates and β-Blockers:

- **Use is similar to that for STEMI.**

Calcium channel blockers:

- **Should NOT be administered to most patients with ACS.**
- **Indications for calcium channel blockers are similar to that of STEMI.**

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- **Pharmacotherapy, which has been proven to decrease mortality, HF, re-infarction or stroke, and stent thrombosis, should be initiated prior to hospital discharge for secondary prevention.**
- **All patients, in the absence of contraindications, should receive indefinite treatment with aspirin, an ACE inhibitor, and a "high-intensity" statin for secondary prevention of death, stroke, or recurrent infarction.**

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- **A β-blocker should be continued for at least 3 years in patients with normal LV function and indefinitely in patients with LVEF ≤ 0.4 or HF symptoms.**
- **It may be reasonable to continue a β-blocker indefinitely in patients without contraindications and with normal LVEF.**
- **β-blockers should be used in patients with a previous MI.**

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- **A $P2Y_{12}$ inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided strategy of treatment.**
- **All patients should be prescribed short-acting, SL NTG or NTG spray to relieve any anginal symptoms when necessary, and should be instructed on its use.**

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- **ACE Inhibitors should be initiated in all patients following MI to reduce mortality, decrease re-infarction, and prevent the development of HF, because of their ability to prevent cardiac remodeling, and should be continued indefinitely.**
- **Hypotension should be avoided because coronary artery filling may be compromised.**

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- **Adverse effects: hypotension, cough (30% of patients), acute renal failure, hyperkalemia, and angioedema.**
- **If patients cannot tolerate chronic ACE inhibitor therapy secondary to adverse effects, ARBs can be used (candesartan, valsartan, or losartan).**

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- **Aldosterone plays an important role in HF and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, LV hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias.**

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- **To reduce mortality, aldosterone antagonists (spironolactone or eplerenone), should be considered within the first 7 days following MI in all patients who are already receiving an ACE inhibitor (or ARB) and a β-blocker and have an LVEF ≤ 0.40 and either HF symptoms or DM.**
- **Spironolactone decreases all-cause mortality in patients with stable severe HF.**

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Other Modifiable Risk Factors:

- **Smoking cessation, managing HTN, weight loss, exercise, and tight glucose control for patients with DM, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.**

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Smoking cessation:

- **Behavioral therapy aided with nicotine replacement alone or combined with:**

a) **Bupropion (Antidepressant that decreases cravings for and withdrawal symptoms of nicotine)**

b) **Varenicline (a partial agonist of the nicotinic acetylcholine receptor, used to treat smoking addiction).**