Therapy of Acute Coronary Syndromes

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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 (chewing).**

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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 (LMWH), or fondaparinux.**

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

- **A personalized approach that balances the risks of ischemia and bleeding is needed.**
- **They are primarily reserved as rescue therapy rather than routine use in the following situations:**

a) **High thrombotic burden.**

b) **Severe slow-flow/no-reflow during PCI.**

- **The are not recommended for patients with stable IHD undergoing PCI.**

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7. **A high-intensity statin should be administered prior to PCI (in patients > 75 years old, use 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. **A P2Y12 inhibitor should be administered to all patients.**

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6. High-risk patients should proceed to early angiography, and may receive a glycoprotein IIb/IIIa inhibitor GPI.
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.**
- **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) is 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: rarely used nowadays

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 a greater percentage of arteries is opened.**

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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
9. For streptokinase, prior treatment within the previous 6 months.

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Anticoagulants:

- **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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- **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).**