Therapy of Acute Coronary Syndromes

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.
- 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).

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

- **In addition, 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.**
4. **A $P2Y_{12}$ (ADP receptor) inhibitor (clopidogrel, prasugrel, or ticagrelor).**

Therapy of Acute Coronary Syndromes

5. **Anticoagulation with bivalirudin (direct thrombin inhibitor, leech), unfractionated heparin (UFH), enoxaparin, or fondaparinux.**
6. **A glycoprotein IIb/IIIa inhibitor (GPI) may be considered if UFH is selected as the anticoagulant for patients undergoing primary PCI.**
7. **A high-intensity statin should be administered prior to PCI.**

Therapy of Acute Coronary Syndromes

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.**
10. **An ACE inhibitor is recommended within the first 24 hours in patients with STEMI who have either an anterior wall MI or an LVEF ≤ 0.40 and no contraindications.**

Therapy of Acute Coronary Syndromes

11. **Morphine may be given to patients with refractory angina as an analgesic and a veno-dilator that lowers preload.**

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

Therapy of Acute Coronary Syndromes

- **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 GPI.**

Therapy of Acute Coronary Syndromes

6. **A $P2Y_{12}$ 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.**

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

- **A $P2Y_{12}$ 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.**
- **An angiotensin II receptor blocker and an aldosterone antagonist may be given to selected patients.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

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).**

Therapy of Acute Coronary Syndromes

Desired Outcomes:

Short-term desired outcomes in a patient with ACS:

1. **Early reperfusion to the infarct artery to prevent infarct expansion (in MI), or prevent complete occlusion and MI (in UA).**
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.**

Therapy of Acute Coronary Syndromes

Long-term desired outcomes:

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

Therapy of Acute Coronary Syndromes

- **General management measures for all STEMI, and high- and intermediate-risk NSTE-ACS patients also include:**

1. **Continuous multi-lead ECG monitoring for arrhythmias and ischemia.**
2. **Frequent measurement of vital signs.**
3. **Bed rest for 12 hours in hemodynamically stable patients.**
4. **Avoidance of the Valsalva maneuver (prescribe stool softeners routinely).**
5. **Pain relief.**

Therapy of Acute Coronary Syndromes

Antiplatelet Therapy in PCI and STEMI and NSTE-ACS:

- **All patients undergoing PCI with ACS should receive an initial dose of 162- or 325-mg of aspirin followed by a daily aspirin dose of 81 mg/day indefinitely.**
- **A $P2Y_{12}$ inhibitor antiplatelet (clopidogrel, prasugrel, ticagrelor, or IV cangrelor) should be administered as early as possible concomitantly with aspirin and then an oral $P2Y_{12}$ agent should ideally be continued for at least 12 months following PCI.**
- **Earlier discontinuation of the $P2Y_{12}$ inhibitor can be reasonable in patients at a high bleeding risk or with "overt bleeding".**

Therapy of Acute Coronary Syndromes

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 at least a 1 mm STE in two or more contiguous ECG leads.**
3. **Who have no absolute contraindications to fibrinolytic therapy.**
4. **Who are NOT able to be transferred to undergo primary PCI within 120 minutes of medical contact.**

Therapy of Acute Coronary Syndromes

- **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 over a non–fibrin-specific agent (streptokinase).**
- **Fibrin-specific fibrinolytics open a greater percentage of arteries.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

- **Patients with contraindications for fibrinolysis should NOT receive fibrinolytic therapy, and should be transferred to a hospital capable of performing PCI.**
- **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.**

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.

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

β-Blockers:

- **β_1-Blockade reduces heart rate (HR), myocardial contractility, and blood pressure (BP), thus, decreasing myocardial oxygen demand.**
- **The reduction in HR prolongs diastole, thus improving ventricular filling and coronary artery perfusion.**
- **β-blockers reduce the risk for recurrent ischemia, reduce infarct size, reduce risk of re-infarction, and reduce the occurrence of ventricular arrhythmias in the hours and days following MI.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

- 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.

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

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.**
- **Required:**
- https://www.uptodate.com/contents/mechanisms-of-benefit-of-lipid-lowering-drugs-in-patients-with-coronary-heart-disease

Therapy of Acute Coronary Syndromes

Nitrates:

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

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

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

Therapy of Acute Coronary Syndromes

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).**

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

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.

Therapy of Acute Coronary Syndromes

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.**

Therapy of Acute Coronary Syndromes

Secondary Prevention Following MI:

The long-term goals following MI are to:

1. **Control modifiable CHD risk factors.**
2. **Prevent the development of systolic HF.**
3. **Prevent recurrent MI and stroke.**
4. **Prevent death, including sudden cardiac death.**
5. **Prevent stent thrombosis following PCI.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

- **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.**

Therapy of Acute Coronary Syndromes

- **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.**
- **Clopidogrel should be continued for at least 14 days in patients with STEMI NOT undergoing PCI.**
- **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.**

Therapy of Acute Coronary Syndromes

- **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.**
- **They should be continued indefinitely.**
- **Hypotension should be avoided because coronary artery filling may be compromised.**
- **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).**

Therapy of Acute Coronary Syndromes

- **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.**
- **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.**

Therapy of Acute Coronary Syndromes

- **All patients, regardless of low-density lipoprotein cholesterol level, should ideally be prescribed a high-intensity statin.**
- **Patients aged greater than 75 years may be prescribed a moderate-intensity statin as initial therapy because they are at higher risk of adverse drug effects.**
- **Other agents such as ezetimibe and PCSK9 inhibitors (alirocumab and evolocumab) can be used in patients already receiving statins for secondary prevention (preference given to ezetimibe).**

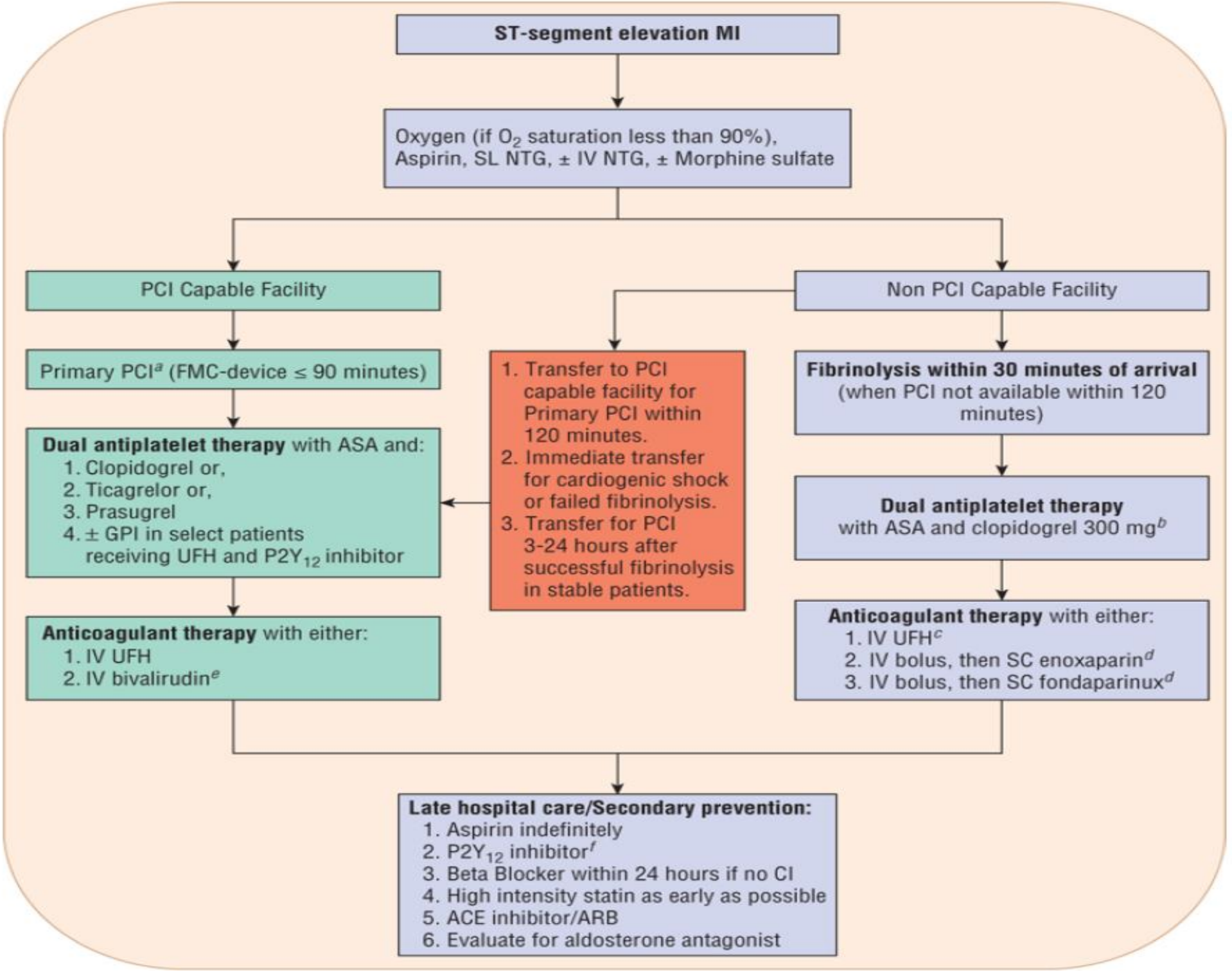
Therapy of Acute Coronary Syndromes

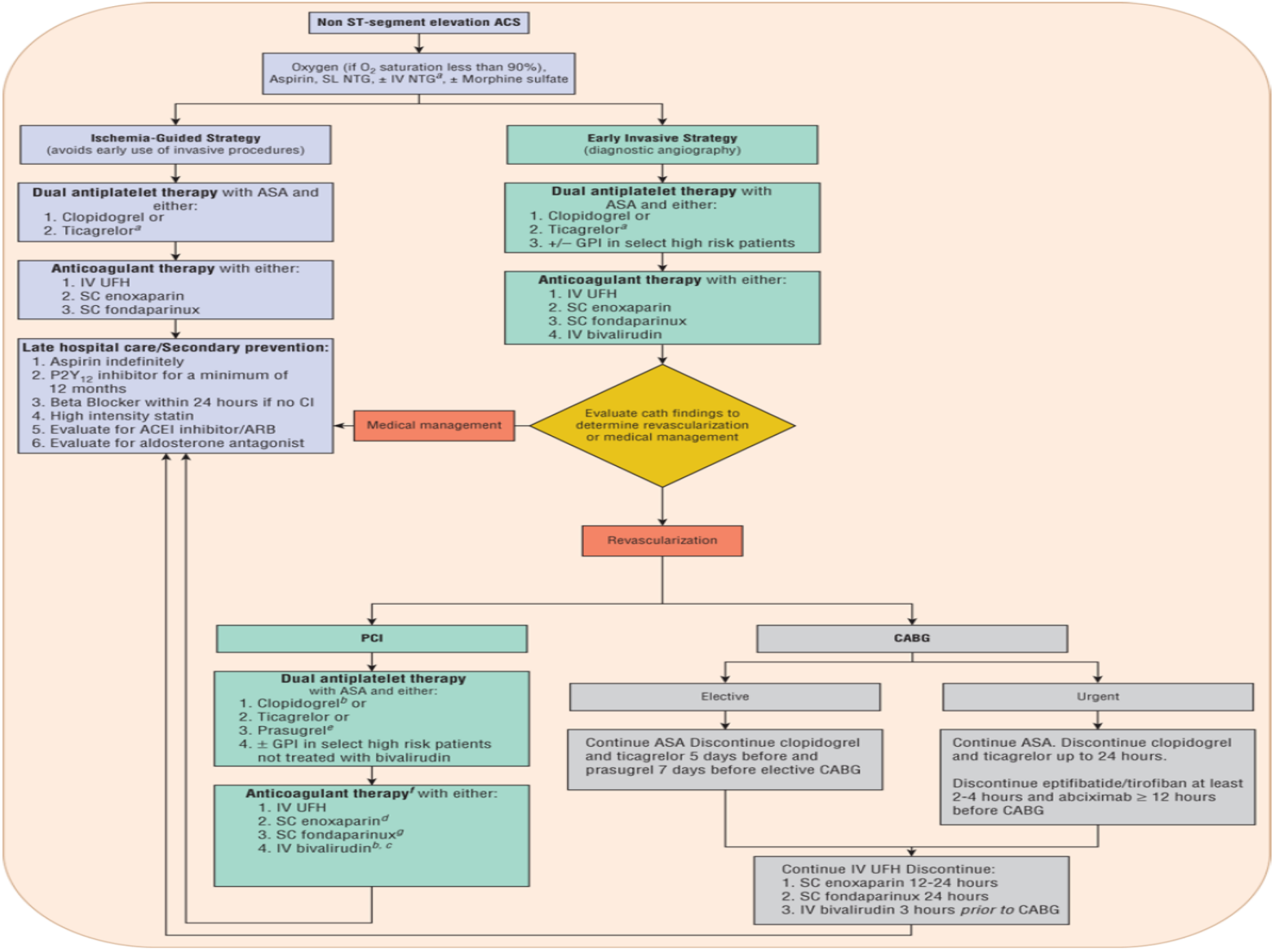
Other Modifiable Risk Factors:

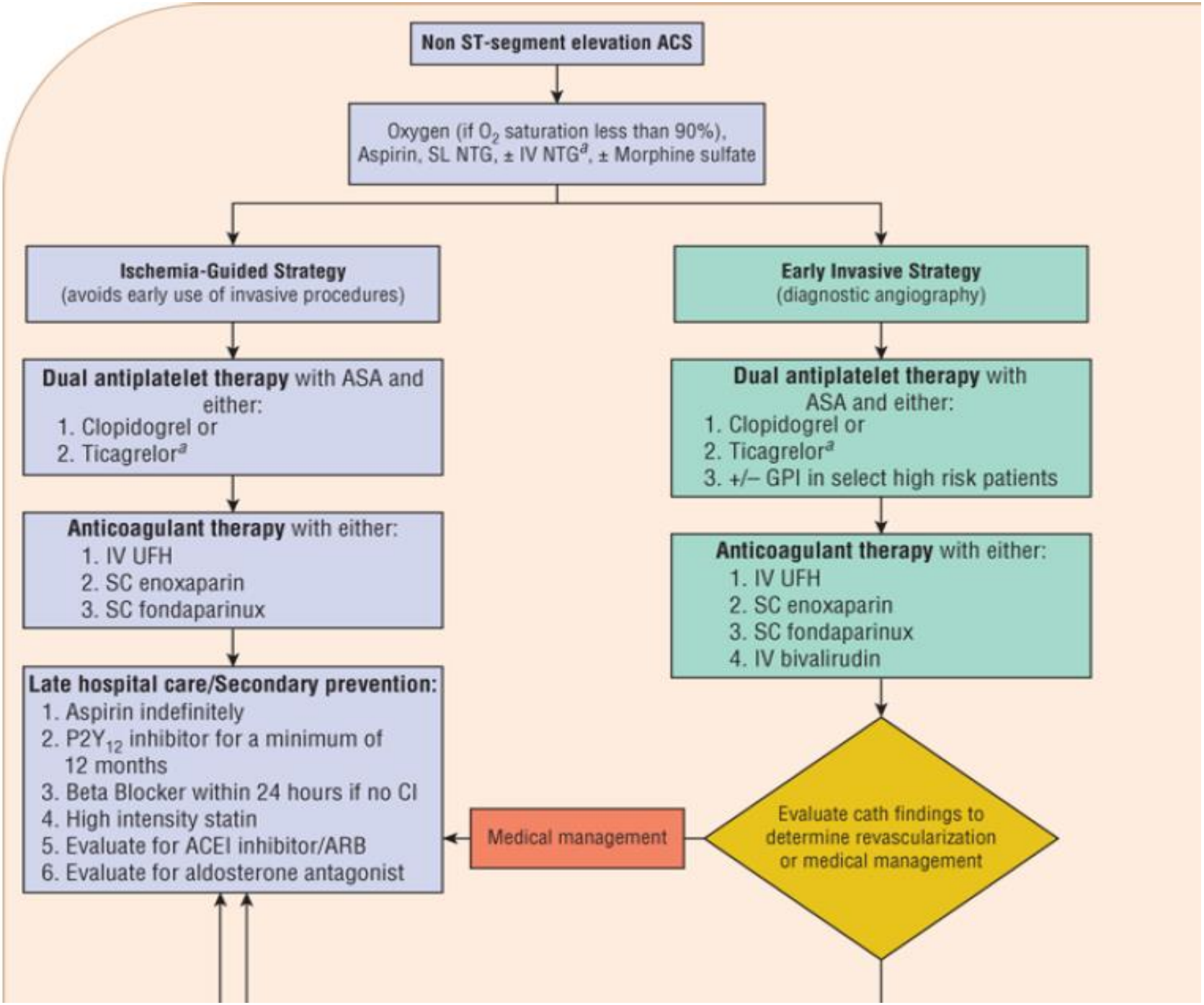
- **Smoking cessation, managing HTN, weight loss, exercise, and tight glucose control for patients with DM, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.**
- **Behavioral therapy aided with nicotine replacement alone or combined with bupropion (Antidepressant that decreases cravings for and withdrawal symptoms of nicotine) or varenicline (a partial agonist of the nicotinic acetylcholine receptor, used to treat smoking addiction), for smoking cessation should be considered in appropriate patients.**

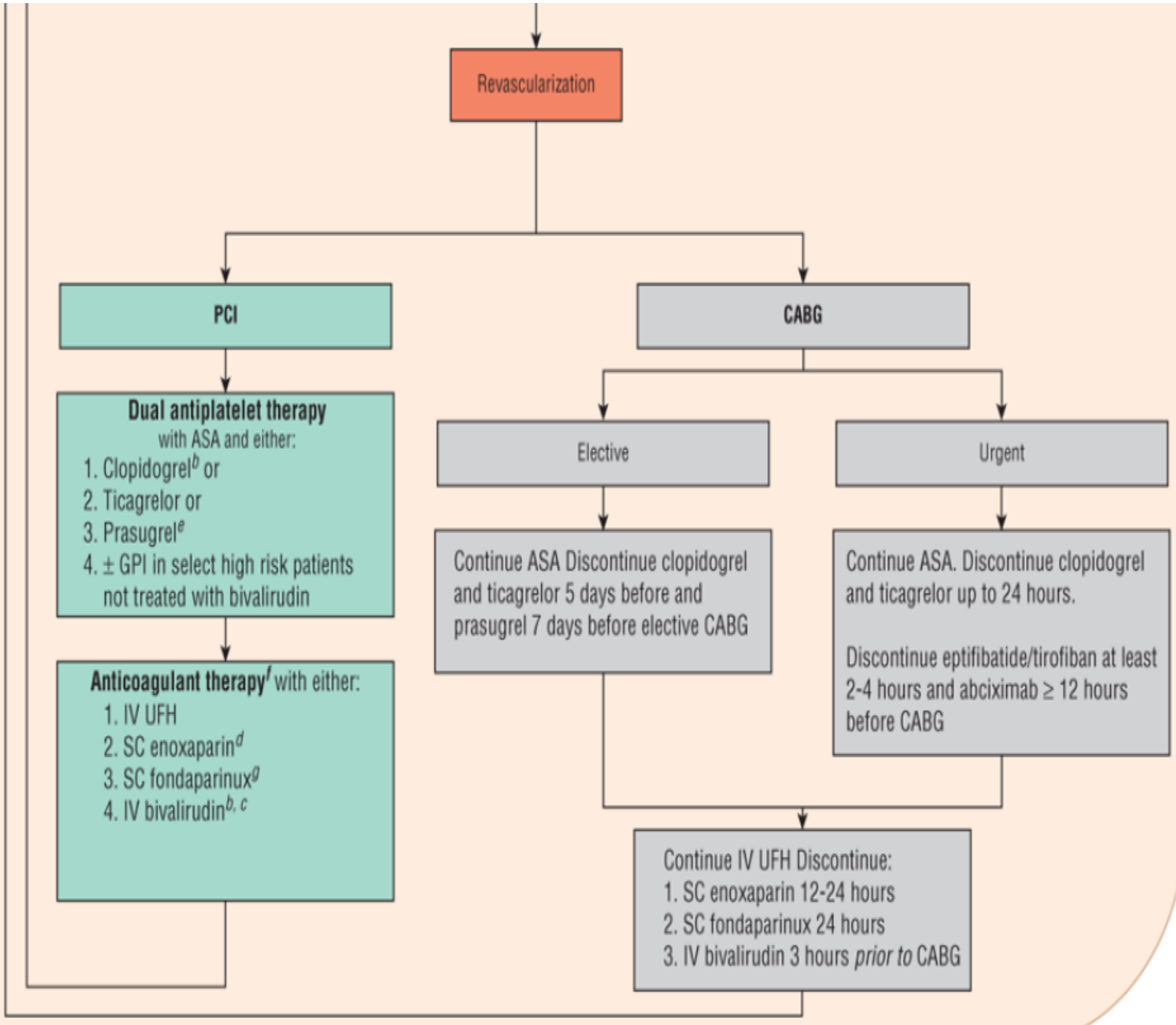
Therapy of Acute Coronary Syndromes

- **HTN should be strictly controlled according to published guidelines.**
- **Patients who are overweight should be educated on the importance of regular exercise, healthy eating habits, and reaching and maintaining an ideal weight.**
- **Moderate intensity aerobic exercise for at least 30 minutes, 7 days/wk (minimum 5 days/wk) is recommended.**
- **The goal body mass index is less than 25 kg/m^2.**
- **Blood glucose control is important, because DM is associated with 4-fold increase in mortality in these patients.**


ST-segment elevation MI
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG, ± Morphine sulfate
PCI Capable Facility
Non PCI Capable Facility
Primary PCI[a] (FMC-device ≤ 90 minutes)
1. Transfer to PCI capable facility for Primary PCI within 120 minutes.
2. Immediate transfer for cardiogenic shock or failed fibrinolysis.
3. Transfer for PCI 3-24 hours after successful fibrinolysis in stable patients.
Fibrinolysis within 30 minutes of arrival (when PCI not available within 120 minutes)
Dual antiplatelet therapy with ASA and:
1. Clopidogrel or,
2. Ticagrelor or,
3. Prasugrel
4. ± GPI in select patients receiving UFH and $P2Y_{12}$ inhibitor
Dual antiplatelet therapy with ASA and clopidogrel 300 mg[b]
Anticoagulant therapy with either:
1. IV UFH
2. IV bivalirudin[e]
Anticoagulant therapy with either:
1. IV UFH[c]
2. IV bolus, then SC enoxaparin[d]
3. IV bolus, then SC fondaparinux[d]
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor[f]
3. Beta Blocker within 24 hours if no CI
4. High intensity statin as early as possible
5. ACE inhibitor/ARB
6. Evaluate for aldosterone antagonist


Non ST-segment elevation ACS
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG[a], ± Morphine sulfate
Ischemia-Guided Strategy (avoids early use of invasive procedures)
Early Invasive Strategy (diagnostic angiography)
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
3. +/– GPI in select high risk patients
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
4. IV bivalirudin
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor for a minimum of 12 months
3. Beta Blocker within 24 hours if no CI
4. High intensity statin
5. Evaluate for ACEI inhibitor/ARB
6. Evaluate for aldosterone antagonist
Medical management
Evaluate cath findings to determine revascularization or medical management
Revascularization
PCI
CABG
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel[b] or
2. Ticagrelor or
3. Prasugrel[e]
4. ± GPI in select high risk patients not treated with bivalirudin
Anticoagulant therapy[f] with either:
1. IV UFH
2. SC enoxaparin[d]
3. SC fondaparinux[g]
4. IV bivalirudin[b, c]
Elective
Urgent
Continue ASA Discontinue clopidogrel and ticagrelor 5 days before and prasugrel 7 days before elective CABG
Continue ASA. Discontinue clopidogrel and ticagrelor up to 24 hours.
Discontinue eptifibatide/tirofiban at least 2-4 hours and abciximab ≥ 12 hours before CABG
Continue IV UFH Discontinue:
1. SC enoxaparin 12-24 hours
2. SC fondaparinux 24 hours
3. IV bivalirudin 3 hours *prior to* CABG


Non ST-segment elevation ACS
Oxygen (if O_2 saturation less than 90%), Aspirin, SL NTG, ± IV NTG[a], ± Morphine sulfate
Ischemia-Guided Strategy
(avoids early use of invasive procedures)
Early Invasive Strategy
(diagnostic angiography)
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
Dual antiplatelet therapy with ASA and either:
1. Clopidogrel or
2. Ticagrelor[a]
3. +/– GPI in select high risk patients
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
Anticoagulant therapy with either:
1. IV UFH
2. SC enoxaparin
3. SC fondaparinux
4. IV bivalirudin
Late hospital care/Secondary prevention:
1. Aspirin indefinitely
2. $P2Y_{12}$ inhibitor for a minimum of 12 months
3. Beta Blocker within 24 hours if no CI
4. High intensity statin
5. Evaluate for ACEI inhibitor/ARB
6. Evaluate for aldosterone antagonist
Medical management
Evaluate cath findings to determine revascularization or medical management


Revascularization
PCI
CABG
Dual antiplatelet therapy
with ASA and either:
1. Clopidogrel[b] or
2. Ticagrelor or
3. Prasugrel[e]
4. ± GPI in select high risk patients not treated with bivalirudin
Anticoagulant therapy[f] with either:
1. IV UFH
2. SC enoxaparin[d]
3. SC fondaparinux[g]
4. IV bivalirudin[b, c]
Elective
Urgent
Continue ASA Discontinue clopidogrel and ticagrelor 5 days before and prasugrel 7 days before elective CABG
Continue ASA. Discontinue clopidogrel and ticagrelor up to 24 hours.
Discontinue eptifibatide/tirofiban at least 2-4 hours and abciximab ≥ 12 hours before CABG
Continue IV UFH Discontinue:
1. SC enoxaparin 12-24 hours
2. SC fondaparinux 24 hours
3. IV bivalirudin 3 hours *prior to* CABG