جامعة بيرزيت
BIRZEIT UNIVERSITY

Acute Coronary Syndrome

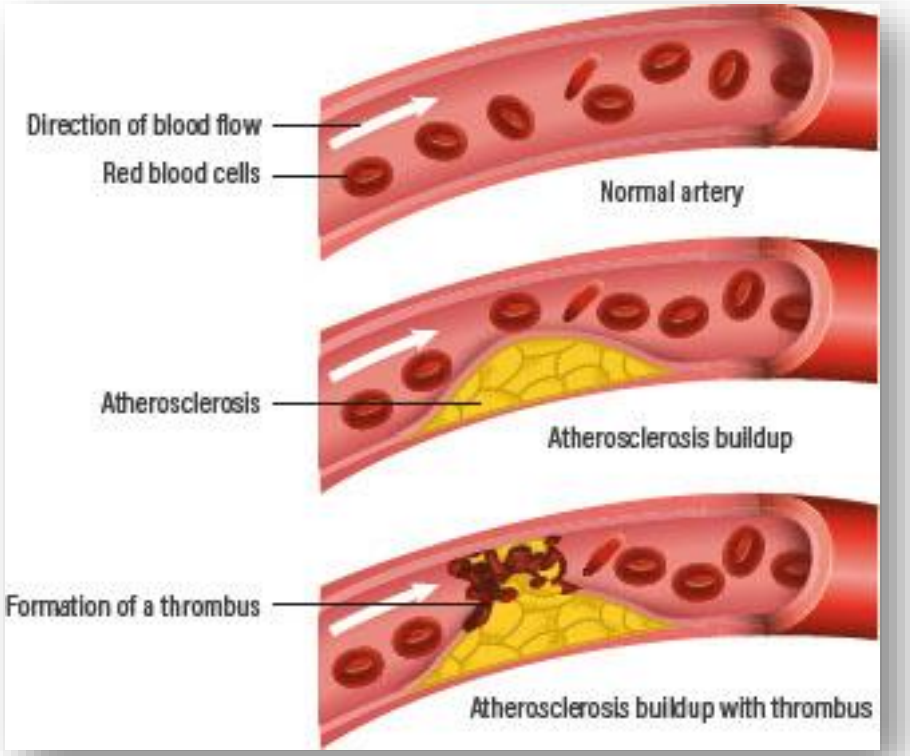
03/04/2025

BADER REMAWI

Pathophysiology

- **Acute coronary syndrome (ACS)**: an acute manifestation of coronary artery disease (CAD)

- <u>What typically happens in ACS</u>:
  - Ruptured atherosclerotic plaque →
  - Platelet accumulation and coagulation response →
  - Intracoronary thrombosis →
  - Acute reduction in coronary blood flow and oxygen supply →
  - Myocardial ischemia →
  - Myocardial infarction (MI) 'if left untreated' →
  - Myocyte necrosis and cell death



Clinical presentation

- Symptoms of ACS :
  - Typically, acute chest discomfort
  - More severe, prolonged, or refractory despite SL NTG
  - Persists for ≥ 10 minutes

- Complications of ACS:
  - MI, heart failure, cardiogenic shock, ventricular arrhythmias, death

- Types of ACS:
  - ST-segment elevation myocardial infarction (STEMI)
  - Non-ST-segment elevation myocardial infarction (NSTEMI)
  - Unstable angina (UA)

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS)

Clinical presentation

	STEMI	NSTEMI	UA (or alternative dx)
ACS symptoms	✓	✓	✓
ST-segment elevation on ECG	✓		
Elevated cardiac troponin	✓	✓	

Clinical presentation

- 12-lead Electrocardiogram (ECG):
  - The first step in evaluating a patient with ACS symptoms

- Cardiac Troponin (cTnI or cTnT):
  - Released from myocytes within 2 – 4 hours after myocardial injury
  - Measure at time of ED presentation AND 3 – 6 hours later (serial levels needed)
  - The most sensitive and specific biomarkers for detecting myocardial injury

- Risk stratification:
  - Using risk-assessment tools (e.g. TIMI risk score)
  - To assess the risk of Major Adverse Cardiac Events (MACE)

Clinical presentation

Tools to Assess Risk of Major Adverse Cardiac Events in Patients with Acute Coronary Syndrome

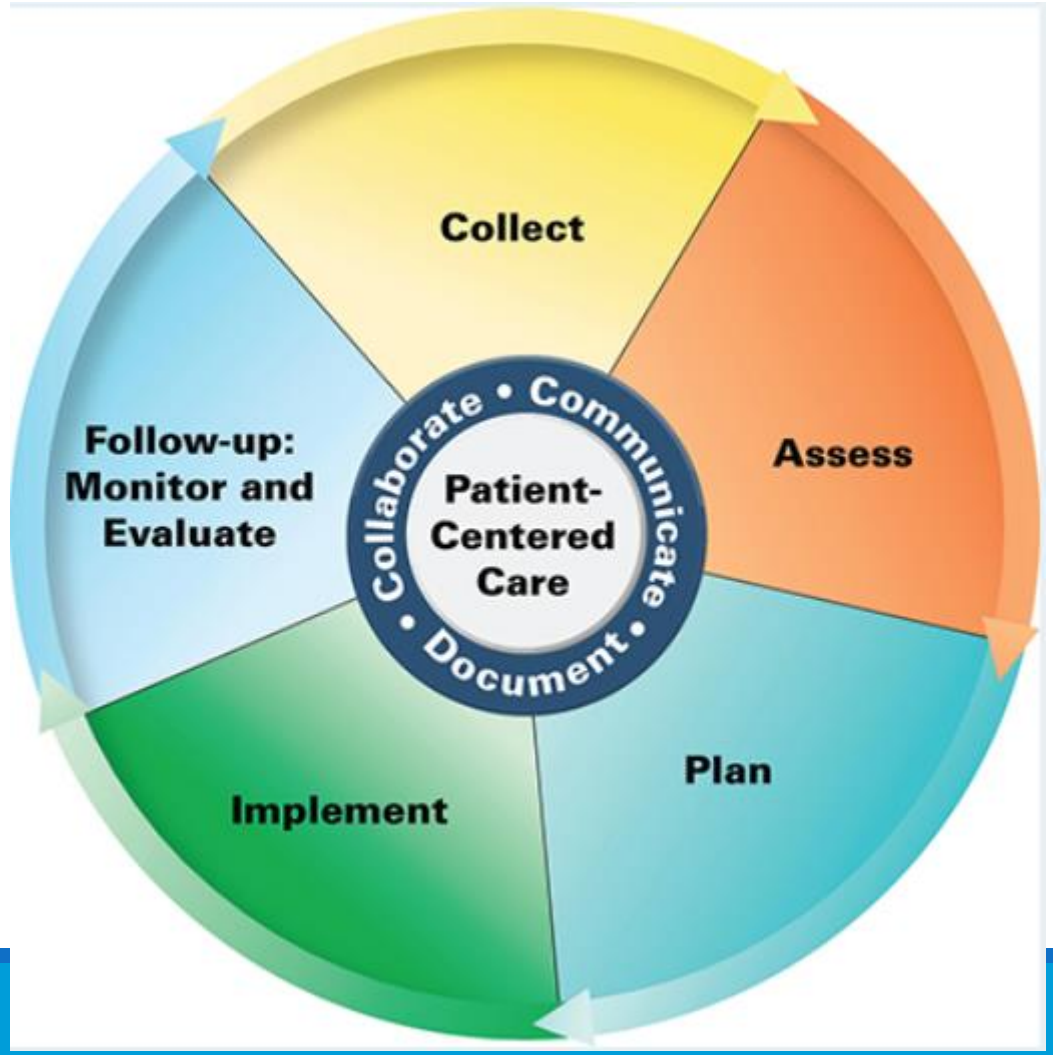
TIMI Risk Score (NSTE-ACS)
Each component worth 1 point
Age ≥65 years
≥3 CAD risk factors[a]
Known CAD[b]
Aspirin use within 7 days
≥2 angina episodes within 24 hours
Transient STE or ST depression
Elevated biomarkers (eg, cTn)

Calculate point total and determine risk for major adverse cardiac events
Low risk: 0-2 points
Intermediate risk: 3-4 points
High risk: ≥5 points

[a] Risk factors include a family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes, and current smoker.

[b] Prior coronary stenosis ≥50%.

Patient care process



Patient care process

Collect

- Patient characteristics (eg, age, sex, pregnant)
- Description of chest discomfort and/or related symptoms (eg, quality, location, severity, radiation, precipitating factors, palliative measures, time of onset, duration of symptoms)
- Patient medical (personal and family) and social histories (eg, tobacco/ethanol, drugs of abuse [eg, cocaine])
- Current medications with particular attention to phosphodiesterase-5 inhibitors, over-the-counter medications (eg, aspirin-containing medications, nonsteroidal anti-inflammatory drugs), and herbals/dietary supplement use
- History of allergy or intolerance to medications
- Objective data
  - Blood pressure, heart rate, respiratory rate, height, weight, O_2-saturation, physical exam
  - Labs: cTn, Scr, potassium, hemoglobin, platelets, lipid profile
  - Diagnostic tests: 12-lead ECG; coronary angiogram and stress testing as necessary

Patient care process

Assess

- Description of chest discomfort to determine differential diagnosis and classification of ACS
- Presence of provoking factors (eg, exertion, mental/emotional stress, tachyarrhythmia, high adrenergic state including the use of stimulant medications, exposure to cold)
- Presence/control of risk factors for CAD (eg, HTN, dyslipidemia, DM, smoking, obesity, family history of premature CAD)
- Presence of ACS-related complications (eg, HF, cardiogenic shock, arrhythmias, heart block, stroke)
- Previous/recent revascularization procedures (eg, PCI with/without stenting, CABG surgery)
- Presence of ST-segment elevation or equivalent on 12-lead ECG
- Risk for major adverse cardiac events (MACE) (eg, perform risk stratification [see Table 34-1])
- Contraindications or intolerance to medications used to treat/prevent angina symptoms and MACE
- Barriers that may impair adherence to the care plan

Patient care process

Plan*

- Initiate antithrombotic therapy to treat and prevent intracoronary thrombosis as well as drug therapy to alleviate angina symptoms and prevent MACE including specific drug(s), dose, route, frequency, and duration (see Figs. 34-2 and 34-3; Tables 34-2–34-5, 34-7, and 34-8).
- Monitoring parameters: efficacy (eg, resolution of signs and symptoms of angina and ACS-related complications) and adverse effects; frequency and timing of follow-up (see Table 34-10)
- Patient education: purpose of treatment, lifestyle modifications, planned procedures, drug-specific information (eg, indication, dose, route, frequency, adverse effects)
- Self-monitoring for recurrent angina symptoms, signs and symptoms of ACS-related complications, adverse effects, when to seek emergency medical attention
- Address barriers to adherence to medications and lifestyle modification
- Referrals to other providers (eg, primary care provider, endocrinologist, dietician, smoking cessation)

Patient care process

Implement*

- Provide patient education regarding all elements of the treatment plan as described above.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Schedule follow-up (eg, usually within 1-2 weeks but no later than 6 weeks after discharge).

Follow-up: Monitor and Evaluate

- Presence of angina symptoms, exercise tolerance, presence/control of CAD risk factors, presence/control of ACS-related complications
- Appropriate use and doses of evidence-based pharmacotherapy for ACS
- Presence of adverse effects and drug-drug interactions
- Patient adherence to treatment plan using multiple sources of information

**Collaborate with patients, caregivers, and other healthcare professionals.*

Treatment strategy

- Treatment decisions are based on:
  - ACS type (STEMI, NSTEMI, UA)
  - Risk-assessment (e.g. TIMI risk score)

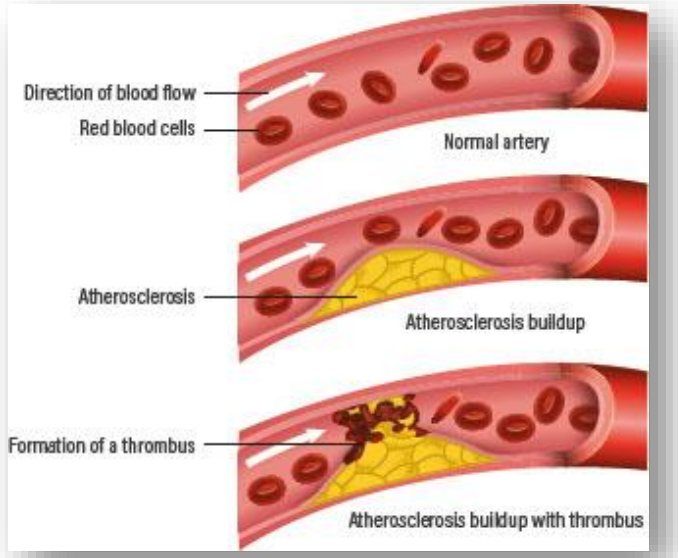
- When ACS is suspected, *expeditious* treatment is essential

- Patients should be educated to call ambulance when they develop severe ischemic symptoms
  - e.g. persistent chest pain, severe dyspnea, syncope or presyncope, palpitations
  - Goal is to achieve earlier reperfusion

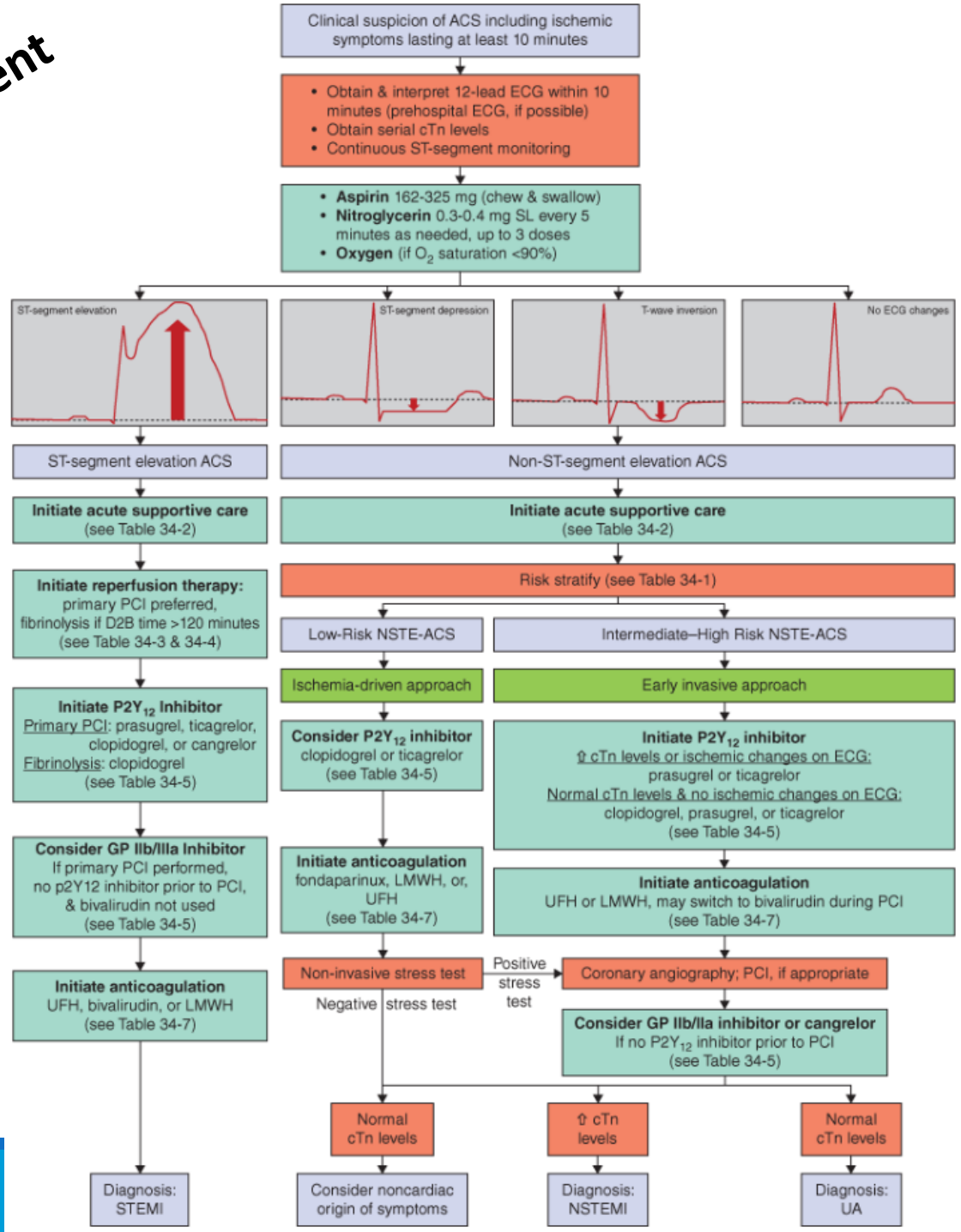
Desired outcomes of treatment

- Short-term goals:
  - Early restoration of blood flow to the infarct-related artery
    - To prevent infarct expansion (in MI)
    - To prevent complete occlusion and MI (in UA)
  - Prevention of death and other MI complications
  - Prevention of coronary artery re-occlusion
  - Relief of ischemic chest discomfort

- Long-term goals:
  - Control of atherosclerosis risk factors
  - Prevention of additional MACE (reinfarction, stroke, heart failure)
  - Improvement in quality of life



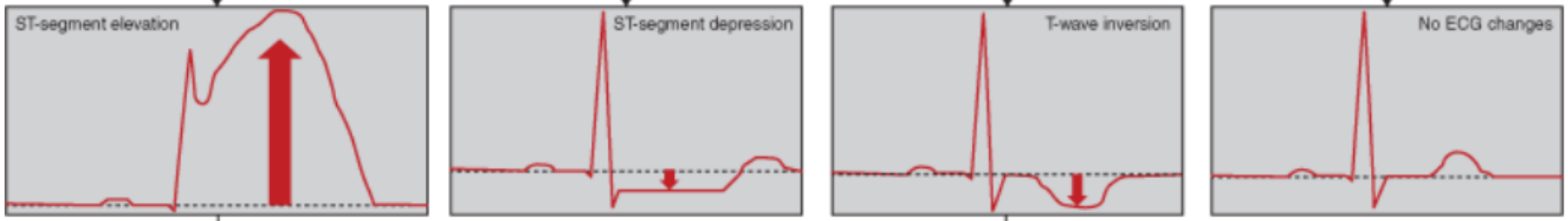
General approach to treatment



Clinical suspicion of ACS including ischemic symptoms lasting at least 10 minutes

- Obtain & interpret 12-lead ECG within 10 minutes (prehospital ECG, if possible)
- Obtain serial cTn levels
- Continuous ST-segment monitoring

- **Aspirin** 162-325 mg (chew & swallow)
- **Nitroglycerin** 0.3-0.4 mg SL every 5 minutes as needed, up to 3 doses
- **Oxygen** (if O_2 saturation <90%)



ST-segment elevation ACS

Initiate acute supportive care (see Table 34-2)

Initiate reperfusion therapy: primary PCI preferred, fibrinolysis if D2B time >120 minutes (see Table 34-3 & 34-4)

Non-ST-segment elevation ACS

Initiate acute supportive care (see Table 34-2)

Risk stratify (see Table 34-1)

Low-Risk NSTE-ACS

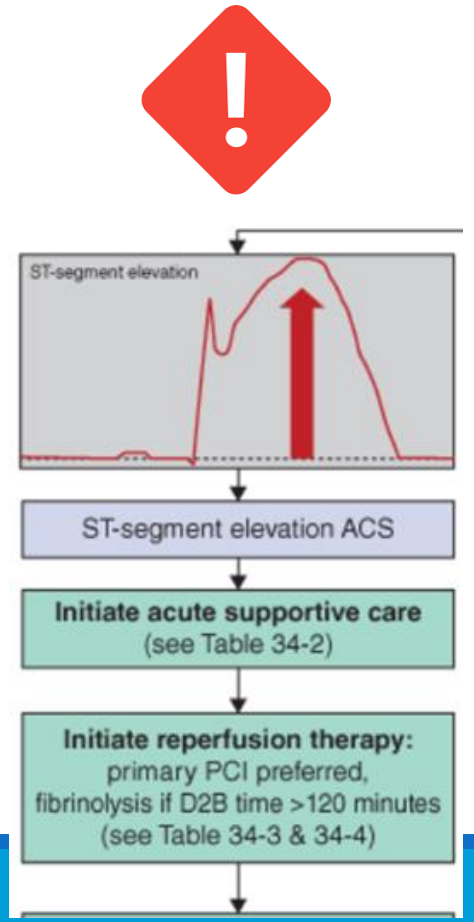
Ischemia-driven approach

Intermediate–High Risk NSTE-ACS

Early invasive approach

General approach to treatment
STEMI

- Patients are of the highest priority
- Complete coronary arterial occlusion
- Should be emergently referred to the cardiac catheterization lab for primary PCI
- Goal: mechanically/immediately restore blood flow to the infarct-related artery

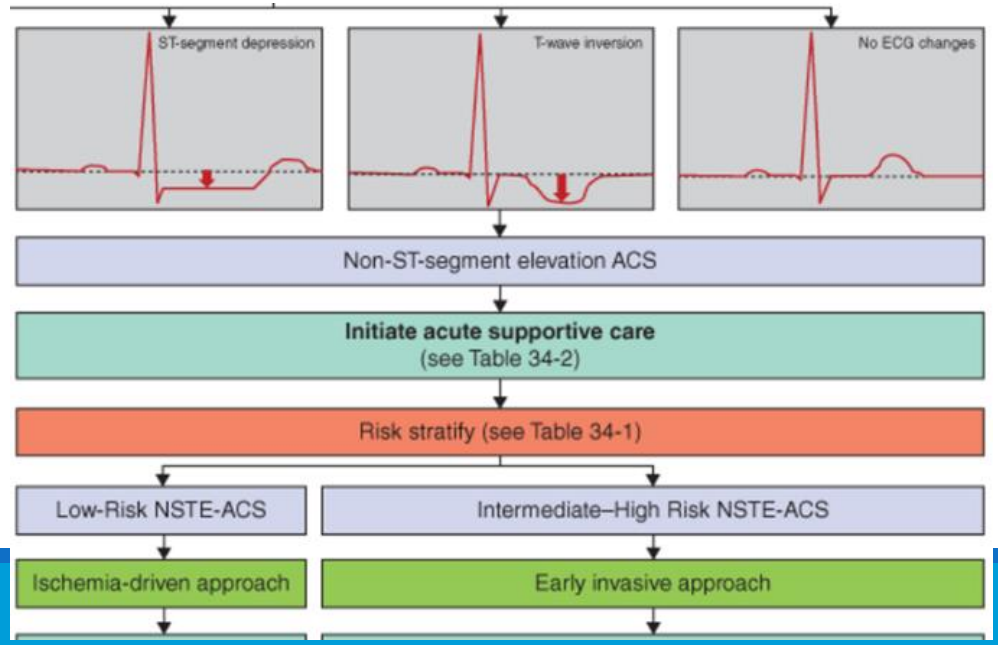


General approach to treatment
NSTE-ACS

- Partially occluded coronary artery with some residual perfusion
  - The need for and urgency to perform PCI is not as critical as STEMI

- Patients should undergo additional risk stratification to determine the best approach
  - **Intermediate-High-risk patients:** Early invasive approach (e.g. PCI)
  - **Low-risk patients (or PCI contraindication):** Ischemia-driven approach (conservative; medical with no planned PCI)

- <u>Regardless of the used approach</u>:
  - Admit patients to hospital
  - Rest in bed
  - Administer oxygen (if O_2 sat. < 90%)
  - Continuous ECG monitoring for arrhythmias and ischemia
  - Frequent measurement of vital signs
  - Ischemic pain relief
  - Prompt initiation of antithrombotic therapy



Acute supportive care

- MONA:
  - Historically-used mnemonic
  - Morphine, Oxygen, Nitroglycerin, Aspirin
  - Recommendations for the routine use of some therapies (e.g. morphine, oxygen) have been modified
  - The mnemonic ignores other potentially useful interventions to consider in early ACS

- $THROMBINS_2$:
  - Contemporary, more comprehensive mnemonic
  - Thienopyridine ($P2Y_{12}$ inhibitors), Heparin, RAAS (ACEI, ARB, MRA), Oxygen, Morphine, β-blocker, Intervention (e.g. PCI), Nitroglycerin, Statin/Salicylate (e.g. ASA)

Acute supportive care

- Initiate medications during the initial 24 hours of ACS treatment

Drug	Indication (Class of Recommendation)	Contraindication/ Caution	Dose/ Administration	Adverse Effects
Morphine	• Refractory pain (IIb)	• Known hypersensitivity • Hypotension • Bradycardia • Lethargic or moribund patient	• STEMI: 4-8 mg IV × 1 (lower dose in elderly), then 2-8 mg IV every 5-15 minutes PRN • NSTE-ACS: 1-5 mg IV every 5-30 minutes PRN	Constipation, nausea, vomiting, hypotension, respiratory depression
Oxygen	• Oxygen saturation < 90% (I)	• Chronic obstructive pulmonary disease • Carbon dioxide retention	• 2-4 L/min, increasing rate and/or changing to face mask PRN	Increased coronary vascular resistance, decreased coronary blood flow, increased mortality

Acute supportive care

Drug	Indication (Class of Recommendation)	Contraindication/ Caution	Dose/ Administration	Adverse Effects
Nitroglycerin	• Angina (I) • Uncontrolled hypertension (I) • Acute heart failure (I)	• SBP less than 90 mm Hg or greater than 30 mm Hg below baseline • Avoid if recent PDE5 inhibitor use: ○ Avanafil: within 12 hours ○ Sildenafil: within 24 hours ○ Vardenafil: within 24 hours ○ Tadalafil: within 48 hours • Use with caution if RV infarct suspected • Avoid abrupt cessation of IV nitroglycerin; wean gradually	• SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN • IV: 10 mcg/min titrated to symptom relief and desired blood pressure	Flushing, headache, hypotension, tachycardia

Acute supportive care

Drug	Indication (Class of Recommendation)	Contraindication/ Caution	Dose/ Administration	Adverse Effects
β-Blockers	• All patients without contraindications (I) • *Associated with mortality reduction, especially in patients with HFrEF*	• Decompensated heart failure • Low cardiac output state • Risk factors for cardiogenic shock: ○ Age 70 years or greater ○ SBP less than 120 mm Hg ○ Sinus tachycardia (HR greater than 110 bpm) ○ Sinus bradycardia (HR less than 60 bpm) ○ Killip class III ○ Prolonged time from symptom onset • High-grade AV block • Active asthma or reactive airway disease	• Carvedilol 6.25 mg BID; target dose is 25 mg BID as tolerated • Metoprolol ○ Oral: 25-50 mg Q 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose is 200 mg daily ○ IV: 5 mg Q 5 min as tolerated up to 3 doses, titrated to BP and HR; should only be considered if BP uncontrolled or refractory symptoms • Continue indefinitely in patients with concomitant HFrEF • Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease

Killip Classification of CHF after MI		30-day mortality
Class I	No clinical signs of heart failure	6%
Class II	Rales or crackles, gallop, elevated jugular venous pressure	17%
Class III	Frank acute pulmonary edema	38%
Class IV	Cardiogenic shock	81%

Acute supportive care

Drug	Indication (Class of Recommendation)	Contraindication/ Caution	Dose/ Administration	Adverse Effects
Calcium channel blockers	• Angina, normal LVEF, and contraindication or intolerance to β-blocker (I) • Angina refractory to β-blocker and normal LVEF (I) • Coronary vasospasm (I)	• Signs of heart failure • Low cardiac output state • Risk factors for cardiogenic shock: ○ Age 70 years or greater ○ SBP less than 120 mm Hg, sinus tachycardia (HR greater than 110 bpm) ○ Sinus bradycardia (HR less than 60 bpm) ○ Killip class III ○ Prolonged time from symptom onset • High-grade AV block	• Diltiazem 120-360 mg/day orally • Verapamil 240-480 mg/day orally • Amlodipine 5-10 mg orally once daily • Nicardipine 60-120 mg/day orally • Nifedipine ER 30-120 mg orally once daily	Hypotension, Diltiazem and Verapamil: heart failure, cardiogenic shock, bradycardia, AV block

Acute supportive care
Morphine

- Therapeutic effects:
  - Potent analgesic
  - Anxiolytic
  - Venodilator
  - Increases vagal tone → reduces heart rate

Improves patient comfort

Decreases oxygen demand

- Questionable safety:
  - Patients treated for ACS with IV morphine had higher rates of in-hospital death and MACE

- Proposed mechanism for IV morphine adverse effects in ACS patients:
  - Drug-drug interaction with $P2Y_{12}$ inhibitors
  - Morphine stimulates opioid receptors in GIT → Inhibition of gastric emptying → Slows antiplatelet absorption
  - Morphine commonly causes nausea and vomiting → Decreases antiplatelet absorption
  - Consequences: Less platelet inhibition

Acute supportive care
Nitroglycerin

- Poor evidence on nitrates effectiveness in:
  - Providing symptom relief
  - Reducing MACE

- Initially, administer SL NTG Q 5 minutes for up to 3 doses PRN for angina
- Subsequently, if patients still have persistent angina, consider IV NTG
  - Particularly in patients with uncontrolled HTN or HF

- NTG dilates coronary arteries → Useful for vasospasm-induced ACS
  - Particularly in patients with cocaine intoxication

- Hemodynamic tolerance to IV NTG:
  - Can occur within 8 to 12 hours
  - Requires higher doses and prolonged therapy

Acute supportive care
β-Blockers

- Good evidence on BBs effectiveness in:
  - Providing symptom relief (anti-ischemic effects)
  - Reducing MACE

- Conflicting evidence on BBs effectiveness in:
  - Reducing mortality (may depend on duration of therapy)

- Guideline recommendations:
  - ***ACC/AHA guidelines:***
    - Initiate oral β-blockers within the first 24 hours of presentation
    - Continue for at least 3 years
    - Continue indefinitely if concomitant left ventricular dysfunction (LVEF < 40%)
  - ***Other few guidelines:***
    - Discuss the benefits/risks of continuing β-Blockers beyond 12 months in post-MI patients with normal LVEF (> 40%)

Acute supportive care
β-Blockers

- β-Blockers in concomitant ACS and HF:
  - Avoid β-blocker in ACS with decompensated HF (left ventricular dysfunction)
  - Once HF symptoms are stabilized (compensated), initiate β-blocker before discharge

- Vasospasm-induced ACS (cocaine/methamphetamine acute intoxication):
  - Avoid β-blocker monotherapy
    - May cause coronary vasospasm via unopposed α1-adrenergic stimulation
  - Combine β-blocker with coronary vasodilator

- Early initiation of IV β-blockers may increase the risk of HF and cardiogenic shock
- IV β-blocker indication:
  - STEMI + (Acute uncontrolled HTN or refractory symptoms) + No contraindications

Acute supportive care
Calcium channel blockers

- Good evidence on CCBs effectiveness in:
  - Providing symptom relief (anti-ischemic effects)

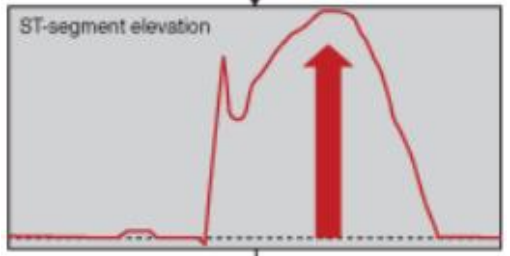
- Conflicting evidence on CCBs effectiveness in:
  - Reducing MACE
  - Reducing mortality

- Non-DHP CCBs are recommended alternatives to BBs
- Long-acting formulations should be used
  - Avoid immediate-release nifedipine (increases mortality risk in CAD, including ACS)

- CCBs dilates coronary arteries → Useful for vasospasm-induced ACS
  - If cocaine-induced vasospasm; CCBs are second line to IV NTG and BZD

Treatment strategies in STEMI
Reperfusion

- Goal: restoring blood flow to the infarct-related artery
- Outcomes: reperfusion caused a dramatic decrease in MI-related mortality
- Appropriate *choice* and *timing* of reperfusion are critical to improve outcomes
- Reperfusion strategies/choices:
  - Mechanical reperfusion: PCI (with or without stenting)
  - Pharmacological reperfusion: Fibrinolysis
- Strategies to reduce delay in reperfusion:
  - Prehospital assessment of the initial ECG
  - Transport to a hospital with PCI-capable facilities
  - Early administration of anti-ischemic medications



ST-segment elevation ACS

Initiate acute supportive care
(see Table 34-2)

Initiate reperfusion therapy:
primary PCI preferred,
fibrinolysis if D2B time >120 minutes
(see Table 34-3 & 34-4)

Initiate $P2Y_{12}$ Inhibitor
Primary PCI: prasugrel, ticagrelor, clopidogrel, or cangrelor
Fibrinolysis: clopidogrel
(see Table 34-5)

Consider GP IIb/IIIa Inhibitor
If primary PCI performed,
no p2Y12 inhibitor prior to PCI,
& bivalirudin not used
(see Table 34-5)

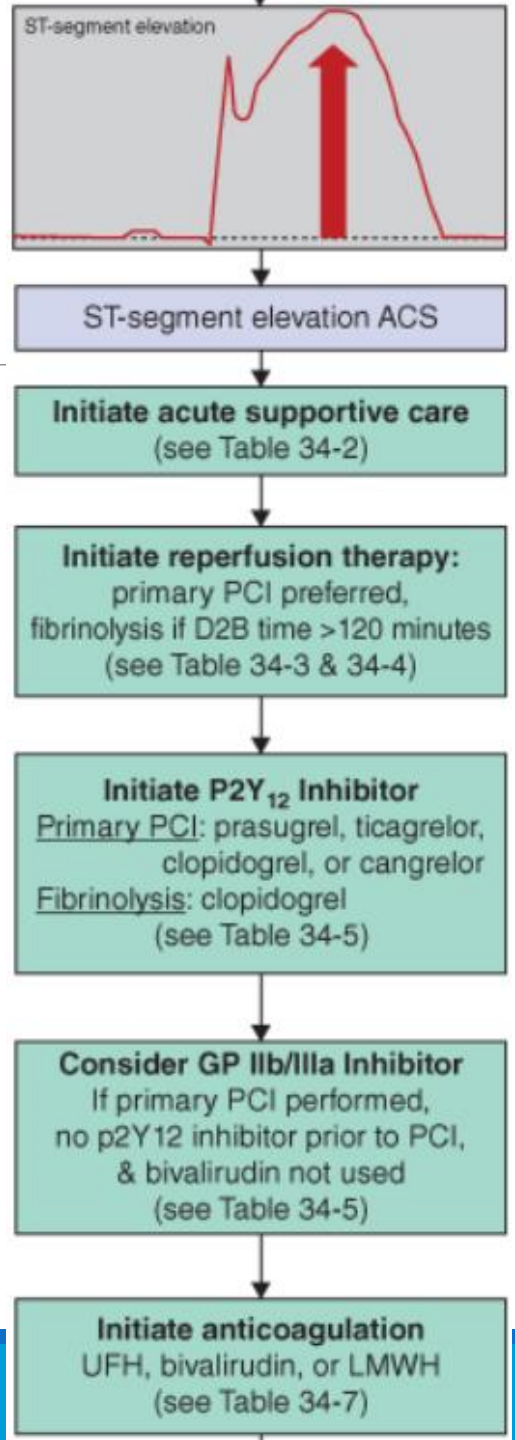
Initiate anticoagulation
UFH, bivalirudin, or LMWH
(see Table 34-7)

Treatment strategies in STEMI
Reperfusion: **Primary PCI**

- In STEMI, the maximum damage occurs in the first few hours of MI
  - Every minute delay → Additional myocardial cell damage (can be irreversible)
  - Blood flow should be *promptly* restored to the infarct-related artery

- Primary PCI (vs. fibrinolysis):
  - Improves survival, reduces risk of stroke & ICH, reduces reinfarction & recurrent ischemia
  - Mortality benefit of primary PCI over fibrinolysis is lost when D2B exceeds 120 min.
  - ***D2B time:*** Time from ED arrival '1st medical contact' to balloon deployment in the cath lab
  - D2B within 90 min. is associated with decreased mortality rates compared to 120 min.
  - Non-PCI capable hospital should try to transfer STEMI patients to a PCI-capable hospital
  - ***Door-in-door-out time (DIDO):*** the time from arrival to discharge at the first hospital
  - DIDO within 30 min. is recommended

- PCI adjunctive therapy: Antiplatelets; Anticoagulants

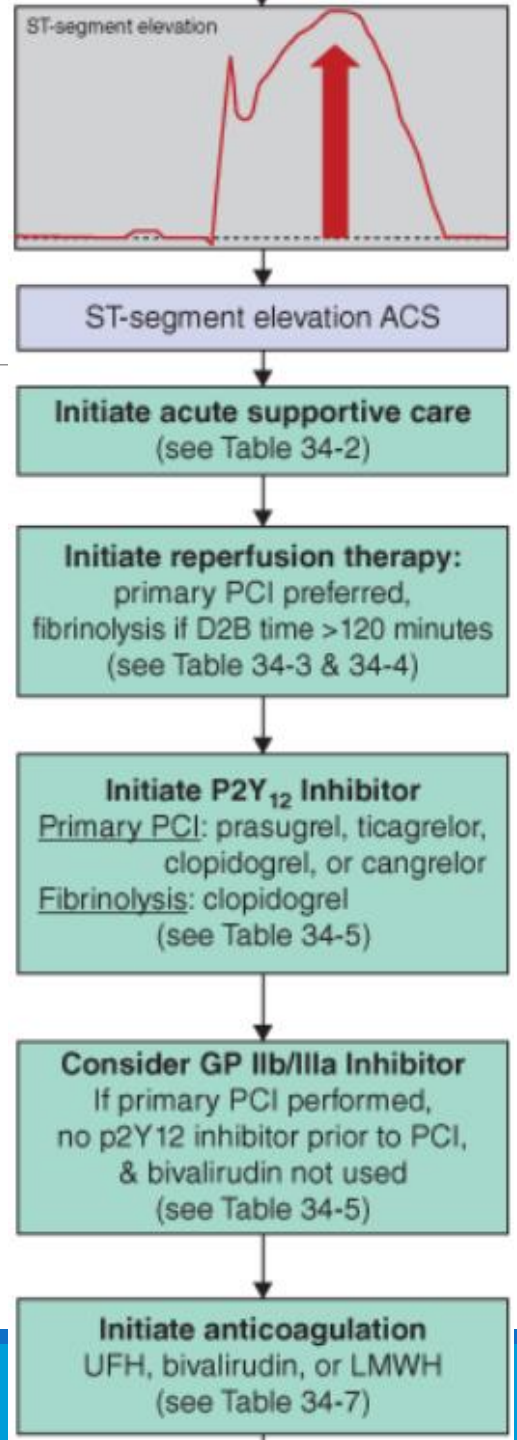


Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

- MOA:
  - Fibrinolytics are plasminogen activators (Plasminogen ----> Plasmin)
  - Plasmin breaks down the fibrin strands within the thrombus → Restoring blood flow

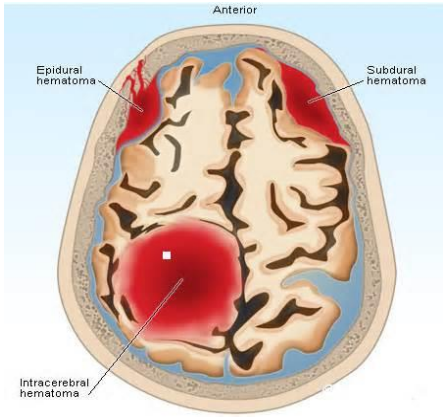
- Indication:
  - Alternative to primary PCI when not possible within D2B time of 120 min.
    - Immediate contraindications to contrast dye
    - No PCI-capable facilities (transfer time would exceed 120 minutes)
    - Patient presented at off-peak hours (staff shortage)…

- Administration time:
  - If PCI would not be possible within 120 minutes of hospital arrival, administer fibrinolytic therapy within 30 minutes of hospital arrival (if no contraindication)
  - ***Door-to-needle time (DNT):*** time from hospital arrival to the initiation of IV fibrinolytic
  - Pre-hospital fibrinolysis (e.g. by EMS) can be helpful

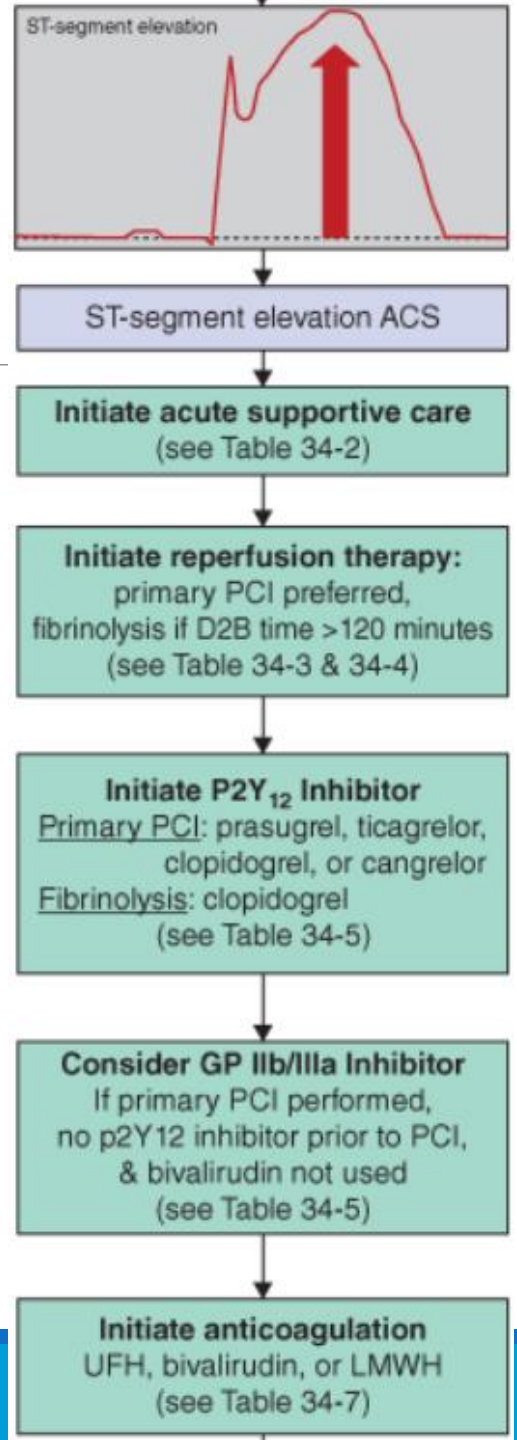


Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

- Risks of fibrinolysis:
  - Slight but significant risk for stroke (mainly ICH)
    - Occurs in ~ 1 % of patients
  - Non-cerebral bleeding
    - Occurs in ~ 13 % of patients



- Significant predictors for ICH:
  - Advanced age
  - Lower total body weight
  - Female sex
  - Preexisting cerebrovascular disease
  - Systolic and diastolic HTN at time of presentation



Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

Indications to Fibrinolytic Therapy for STEMI
• **Symptoms of ACS with an onset within 12 hours of first medical contact**
• **ST-segment elevation of 1 mm or greater in two contiguous leads or new left bundle branch block on a 12-lead ECG**
• **Anticipated that primary PCI cannot be performed within 120 minutes of first medical contact (D2B > 120 min.)**

- Use of fibrinolytics in patients with symptom durations exceeding 12 hours (up to 24 hours):
  - Only for patients with clinical and/or ECG evidence of ongoing ischemia
  - Lower survival benefit compared to fibrinolytic use within 12 hours of symptom onset

Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

Absolute Contraindications	Relative Contraindications
• Any prior hemorrhagic stroke	• BP >180/110 mm Hg on presentation or history of chronic poorly controlled hypertension
• Ischemic stroke within 3 months (except in past 4.5 hours)	• History of ischemic stroke greater than 3 months before
• Intracranial neoplasm or arteriovenous malformation	• Recent major surgery (less than 3 weeks before)
• Active internal bleeding	• Traumatic or prolonged CPR (greater than 10 minutes)
• Aortic dissection	• Recent internal bleeding (within 2-4 weeks)
• Considerable facial trauma or closed-head trauma in the past 3 months	• Active peptic ulcer
• Intracranial or intraspinal surgery within 2 months	• Noncompressible vascular punctures
• Severe, uncontrolled hypertension (unresponsive to emergency therapy)	• Pregnancy
• For streptokinase, treatment within the previous 6 months (if considering streptokinase again)	• Known intracranial pathology (dementia)
	• Oral anticoagulant therapy

Patients with absolute contraindication to fibrinolytics should be transferred to a PCI-capable hospital (consider *delayed* PCI)

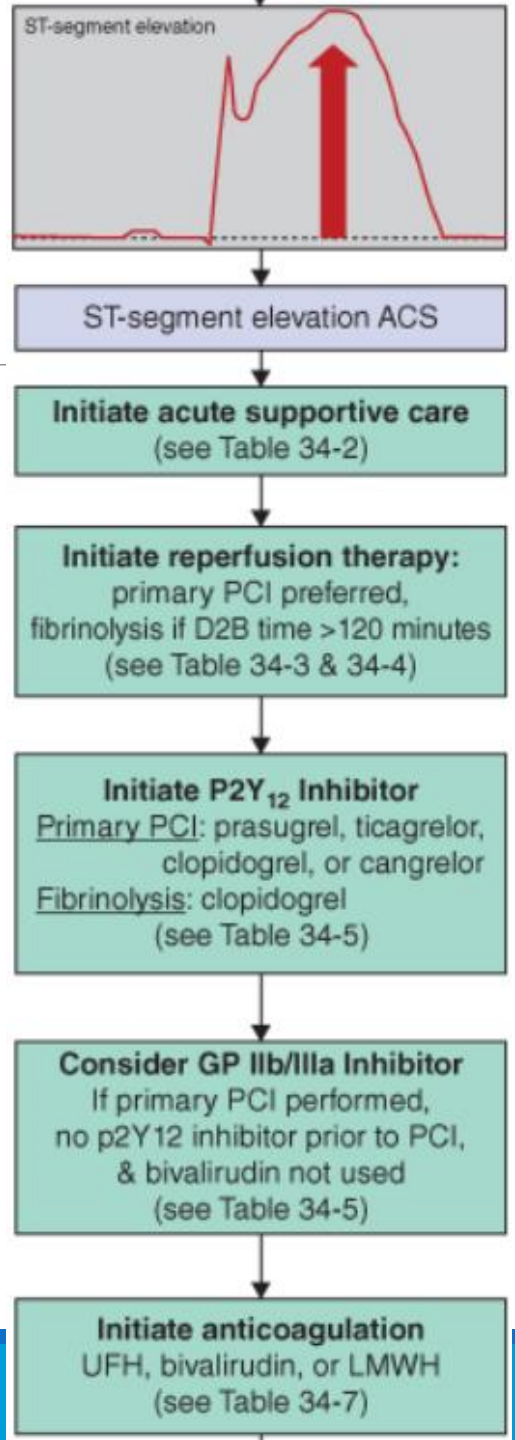
Relative contraindications to fibrinolytics (e.g. BP >180/110 mm Hg) should be mitigated where possible (e.g. give antihypertensives) before administration to reduce the risk of ICH

Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

- Fibrinolytics:
  - Fibrin-specific agents (alteplase, reteplase, tenecteplase)
  - Non-fibrin-specific agents (streptokinase)

- Fibrin-specific agents are recommended over non-fibrin-specific agents:
  - Greater reperfusion success
  - Less systemic bleeding

- Fibrin-specific agents:
  - All are equally effective in reducing mortality
  - Lower risk of major bleeding with tenecteplase



Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

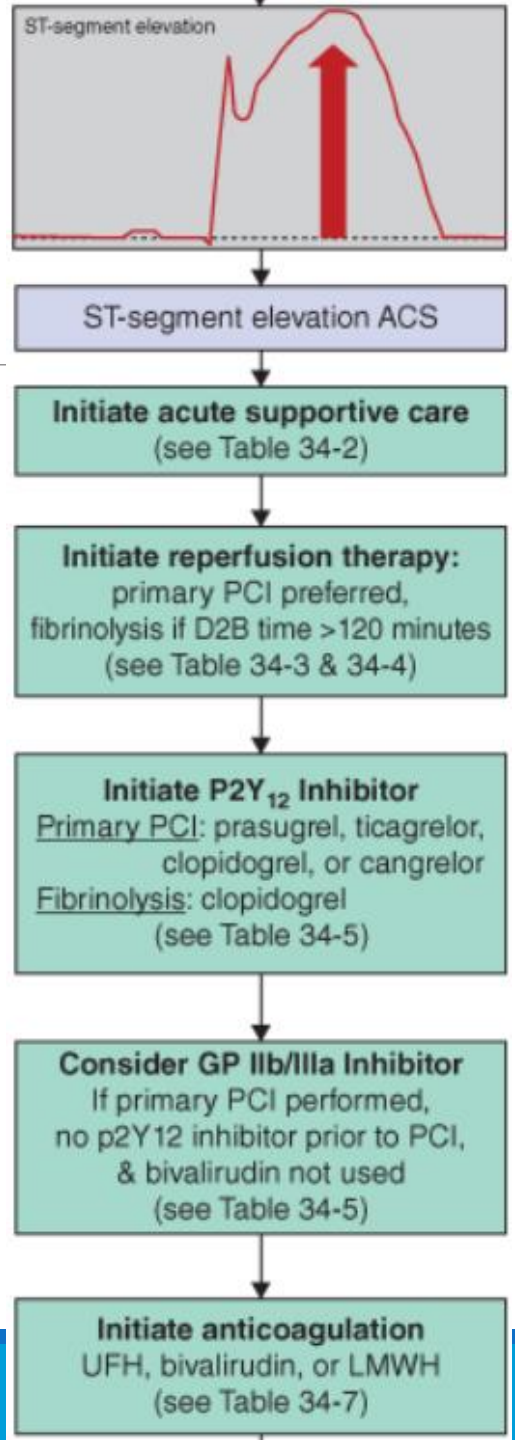
Drug	Dosing Considerations	Notes
Alteplase (tPA)	15 mg IVP over 1-2 minutes, then 0.75 mg/kg (max 50 mg) IV over 30 min, then 0.5 mg/kg (max 35 mg) IV over 60 min;	Total dose not to exceed 100 mg
Reteplase (rPA)	10 units IVP over 2 min × 2 doses given 30 min apart	
Tenecteplase (TNK-tPA)	< 60 kg: 30 mg IVP	In patients ≥ 75 years, the dose may be reduced by 50% to decrease the risk of ICH
	60-69 kg: 35 mg IVP	
	70-79 kg: 40 mg IVP	
	80-89 kg: 45 mg IVP	
	> 90 kg: 50 mg IVP	

Treatment strategies in STEMI
Reperfusion: **Fibrinolysis**

- Fibrinolysis adjunctive therapy:
  - Antiplatelets; Anticoagulants (like PCI)
  - Goals: improve vessel patency, prevent re-occlusion

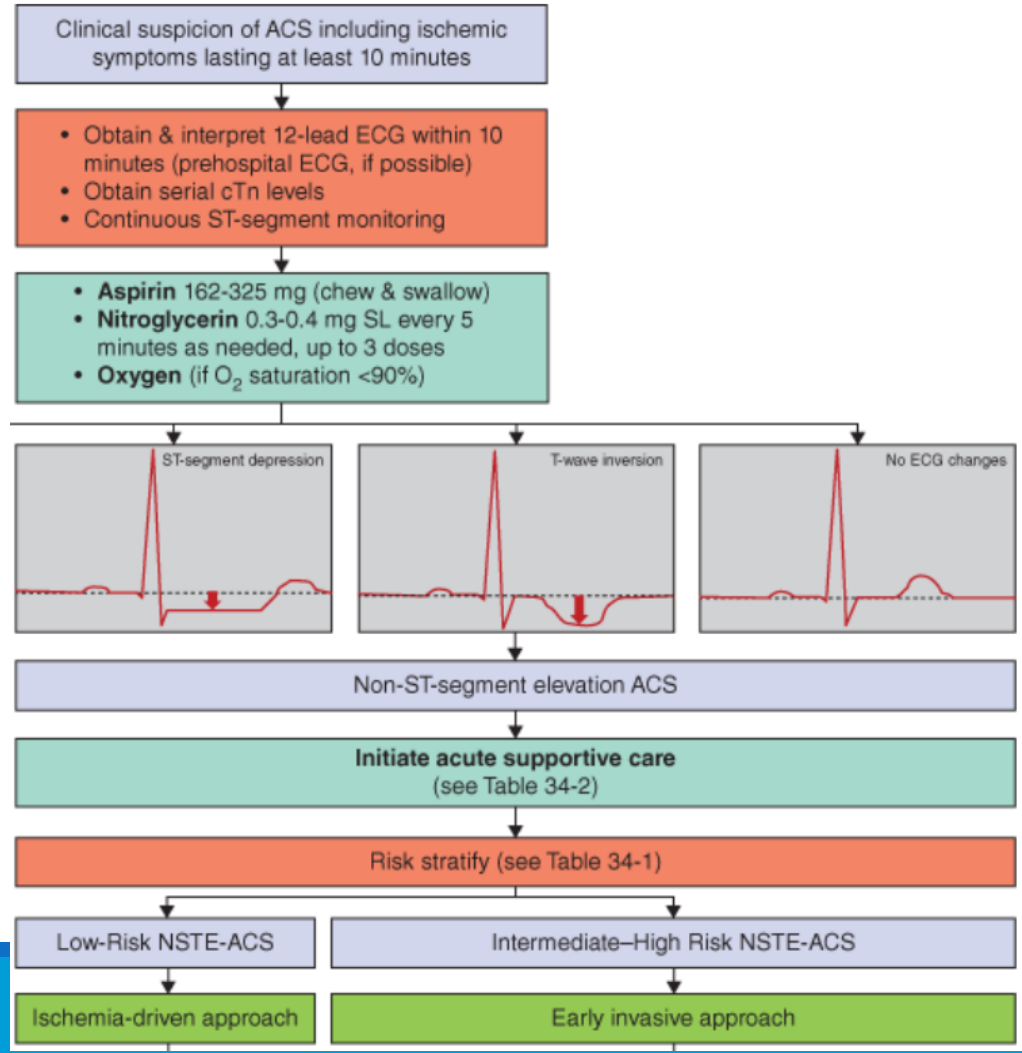
- Early angiography after fibrinolytic therapy:
  - Pharmaco-invasive approach
  - May reduce CV events compared to immediate PCI
  - Increased rate of ICH

- If patients fail fibrinolytic therapy:
  - Transfer to a PCI-capable facility for a possible 'rescue PCI'



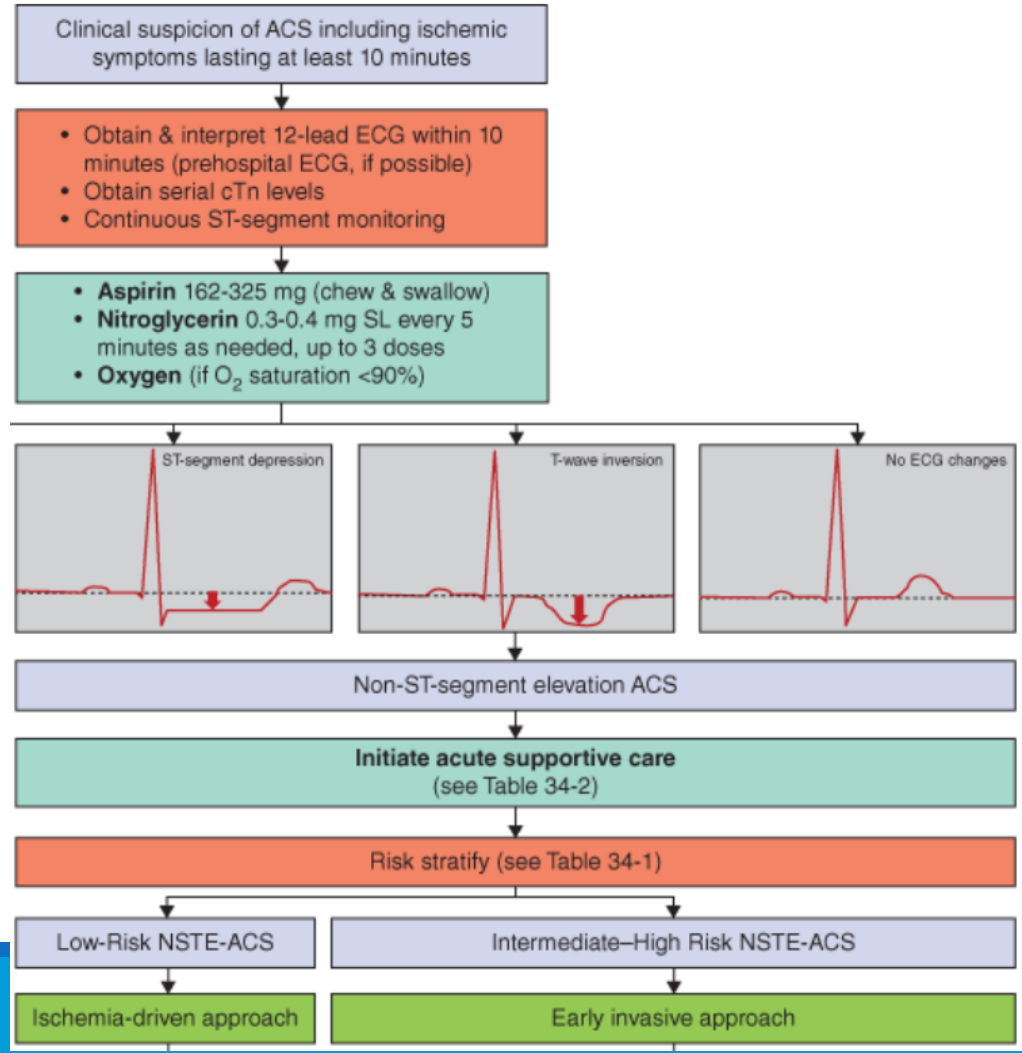
Treatment strategies in NSTE-ACS
Early invasive approach

- Indication: Intermediate-High-risk NSTE-ACS
- Procedure: Diagnostic angiography performed early in the hospital (typically within the first 24 hours) with the plan to perform revascularization/PCI (if appropriate; depending on the coronary anatomy)
- Outcomes: Improves CV outcomes in NSTE-ACS patients; especially in those with the highest risk for MACE
- Risk stratification: Important to determine the intermediate-high-risk patients who will benefit most from this approach



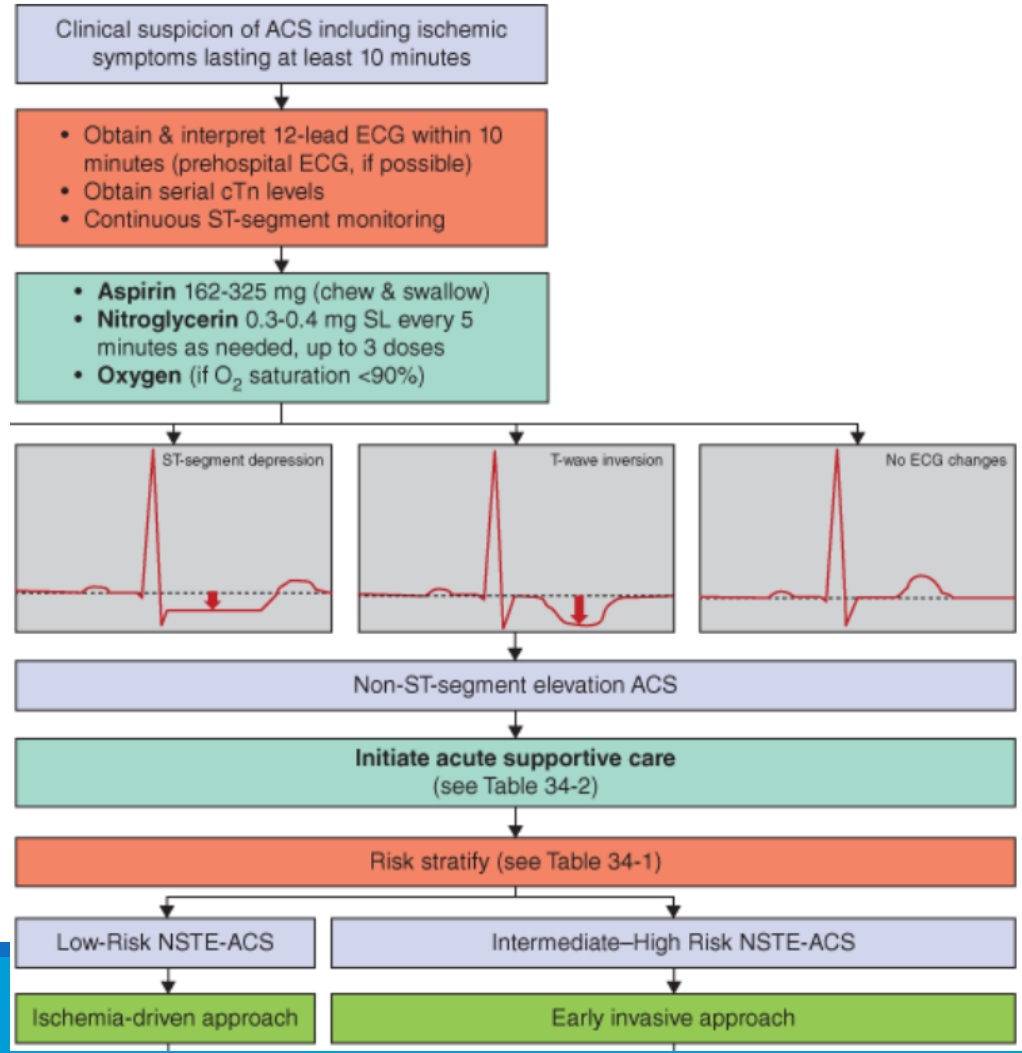
Treatment strategies in NSTE-ACS
Early invasive approach

- Superiority of early invasive approach over ischemia-guided approach in patients with:
  - Advanced age (> 70 years)
  - Previous MI or revascularization
  - ST-segment changes
  - HF (especially LVD)
  - Elevated cTn
  - DM
  - Positive results from non-invasive stress tests



Treatment strategies in NSTE-ACS
Early invasive approach

- Guidelines recommend an early invasive strategy in patients with:
  - Elevated risk for death or MI (intermediate-high-risk)
  - Refractory angina
  - Acute HF
  - Cardiogenic shock
  - Arrhythmias

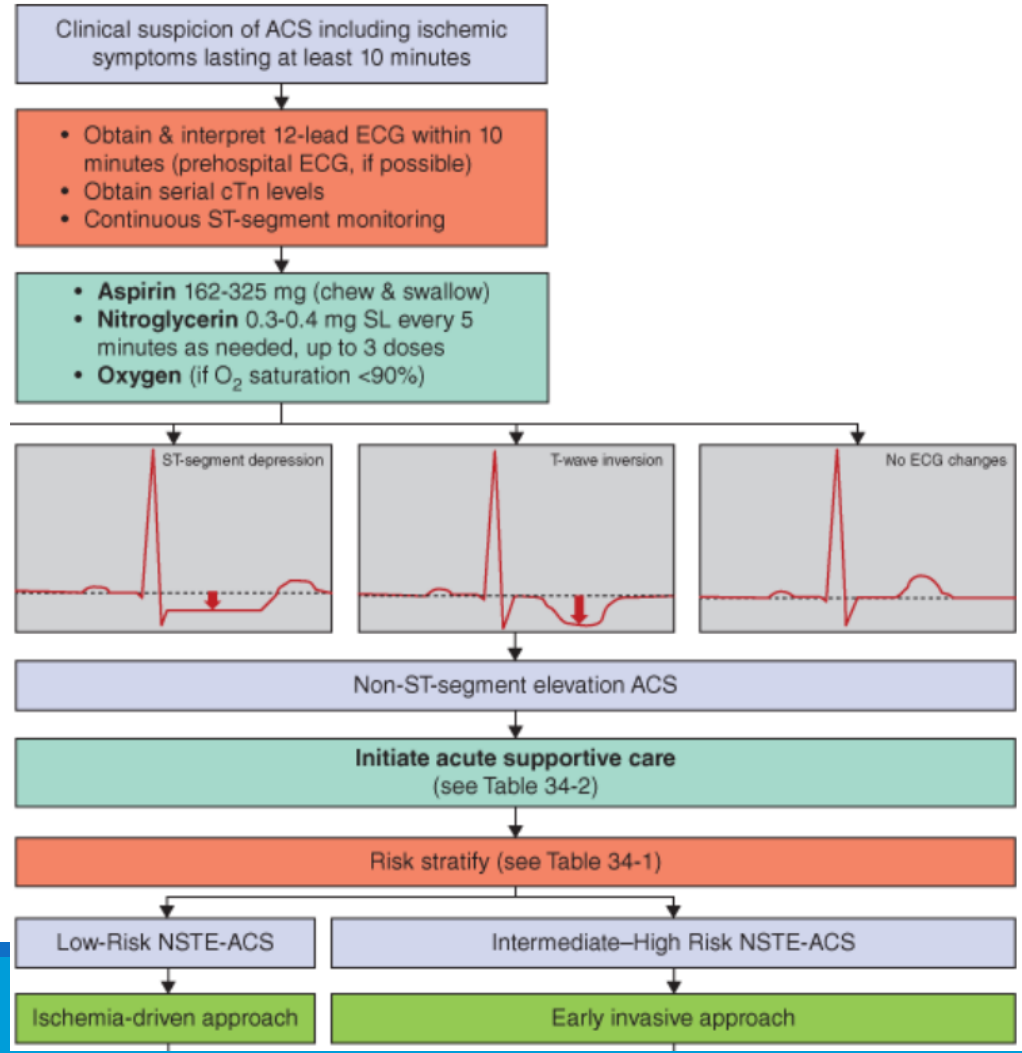


Treatment strategies in NSTE-ACS
Ischemia-guided approach

- More conservative approach:
  - Watch and wait, medical management
  - Giving anti-ischemic, antiplatelet, & anticoagulant agents
  - PCI is not *initially* planned

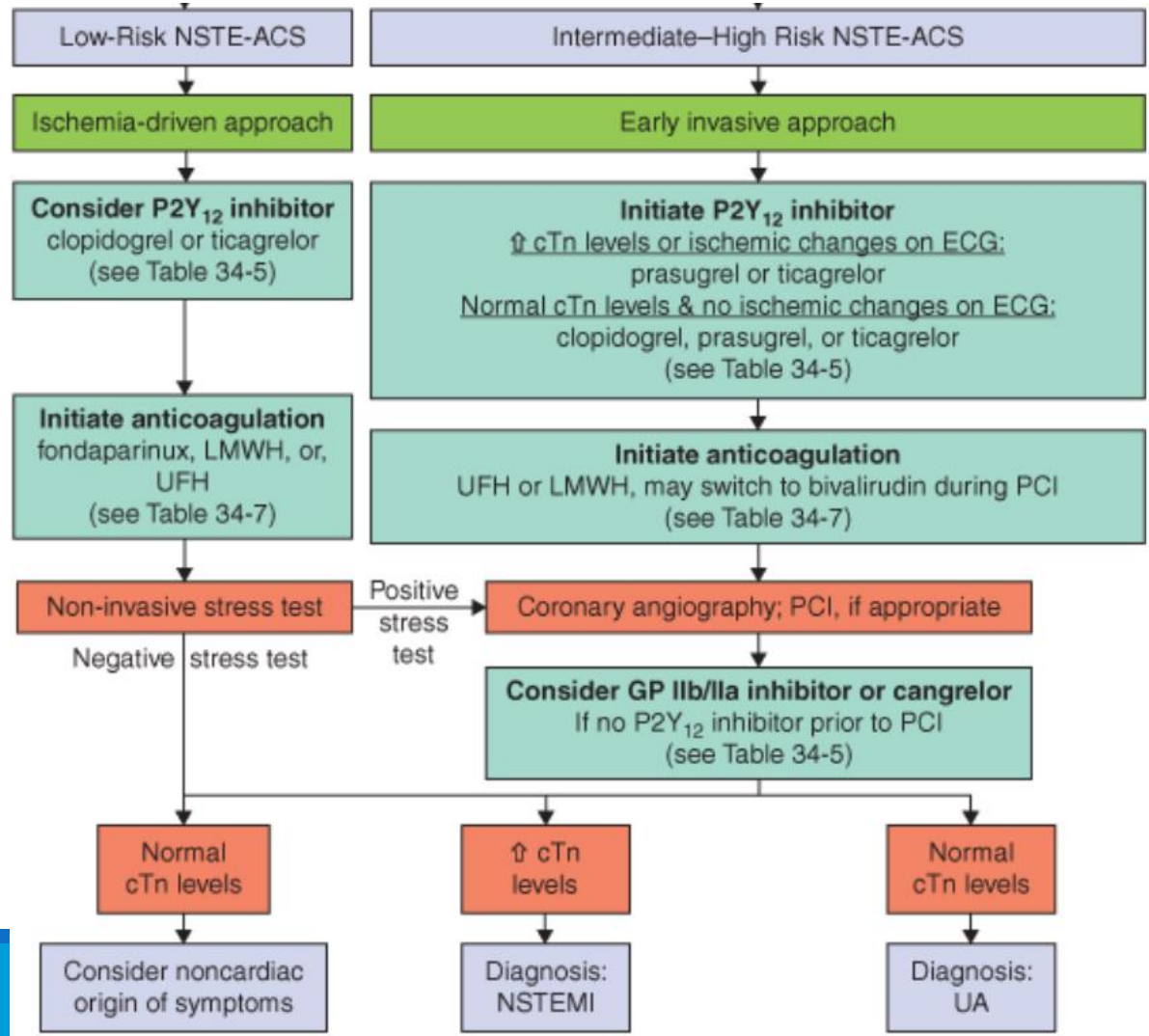
- Indications:
  - Low-risk NSTE-ACS
  - Serious comorbidities or CIs to angiography/PCI (e.g. CKD)
  - Revascularization risks outweigh the benefits

- Guidelines recommend an ischemia-guided strategy in:
  - Low likelihood of ACS
  - Women without troponin elevation
  - Patients who do not consent for revascularization



Treatment strategies in NSTE-ACS
Ischemia-guided approach

- Indications to perform invasive coronary angiography & possible PCI in low-risk patients:
  - Development of recurrent symptoms
  - Non-invasive diagnostic testing (e.g. +ve stress test, coronary CT angiography) suggests obstructive CAD



Treatment strategies in ACS
Reperfusion: **CABG**

- CABG surgery in ACS (STEMI/NSTEMI/UA) is a high-risk procedure!
  - Higher mortality risk than CABG in SIHD
  - PCI and fibrinolysis are preferred

- Still, CABG can be used in select patients with ACS
  - Refractory symptoms / Ongoing ischemia (failed PCI/fibrinolysis)
  - Hemodynamic instability
  - Left main CAD or triple vessel disease
  - Complex coronary anatomy not suitable for PCI

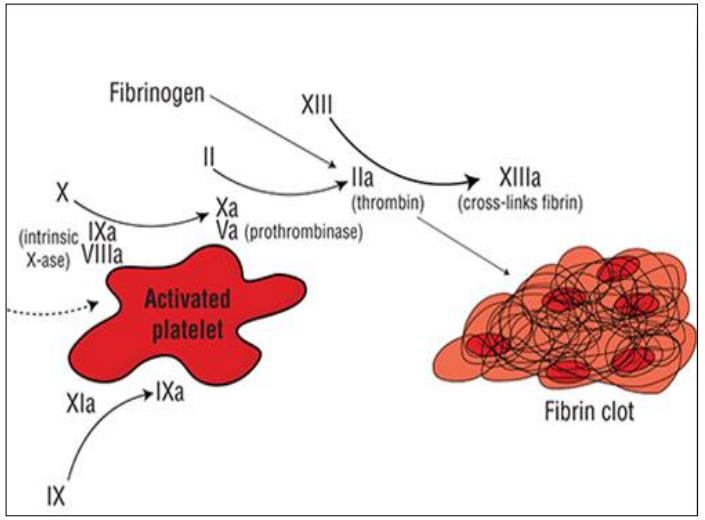
Antithrombotic therapy

- Thrombus formation → ACS

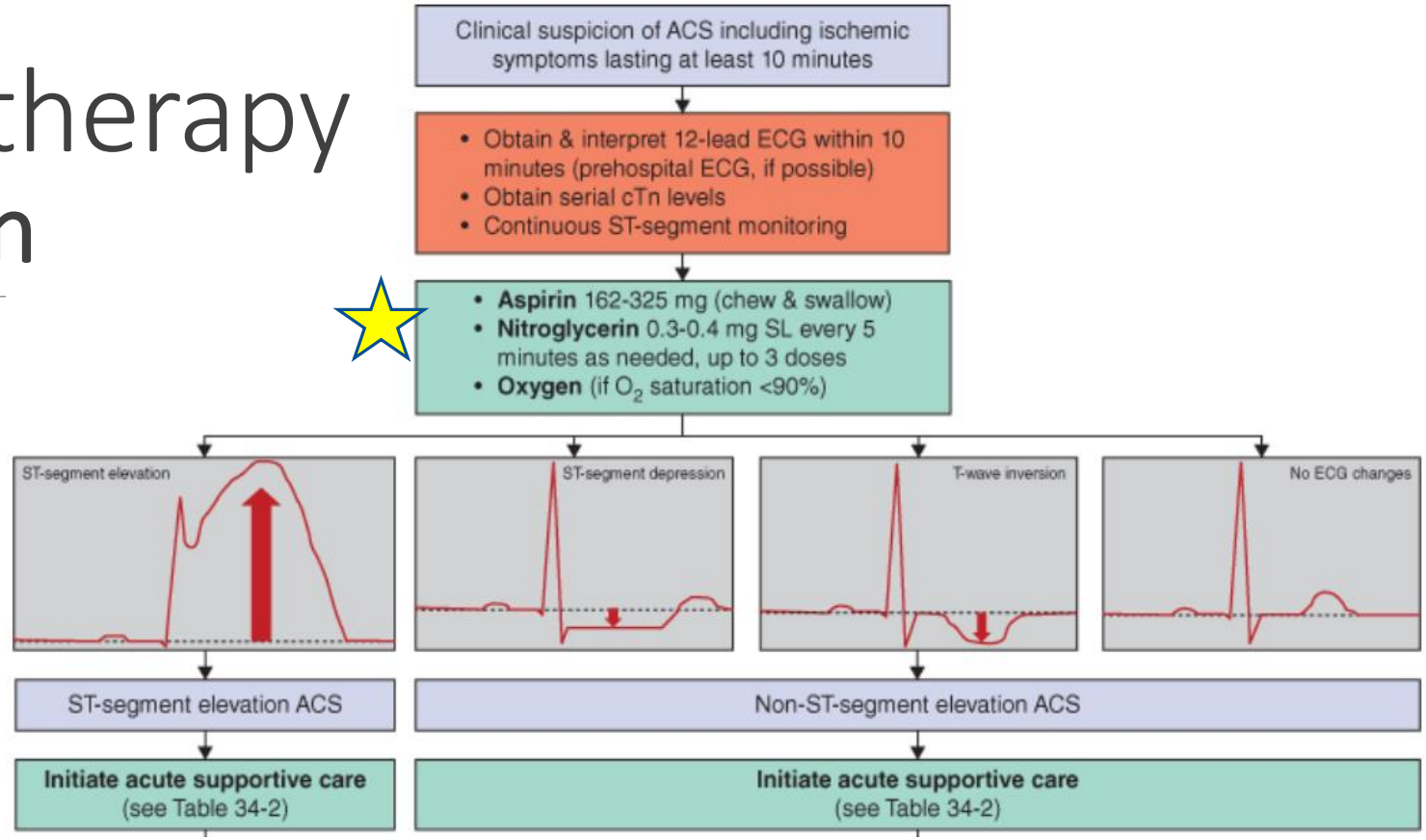
- Antithrombotic agents:
  - Antiplatelets (platelets dominate the pathophysiologic process in arterial thrombosis)
  - Anticoagulants (central role of thrombin in both platelet activation and coagulation)

- Choice of antithrombotic agent is challenging:
  - Not all agents have been studied across the spectrum of ACS
    - STEMI vs. NSTE-ACS
  - Not all agents have been studied across the management strategies of ACS
    - STEMI: Primary PCI vs. Fibrinolysis
    - NSTE-ACS: Early invasive vs. Ischemia-driven

- Duration of antithrombotic therapy post-discharge:
  - Most patients are continued on long-term antiplatelet therapy only
  - Long-term anticoagulant therapy may be necessary for some high-risk groups



Antithrombotic therapy
Antiplatelets: **Aspirin**



Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
Aspirin				
Loading dose	162-325 mg	162-325 mg	162-325 mg	162-325 mg
Maintenance dose	81 mg daily	81 mg daily	81 mg daily	81 mg daily

Antithrombotic therapy
Antiplatelets: **Aspirin**

- Aspirin is recommended for *all* ACS patients without contraindications
  - Regardless of ACS type or management strategy

- Loading dose:
  - 162 - 325 mg (non-enteric coated tablet) given asap
  - Tablet/s should be chewed and swallowed to allow for faster dissolution time and platelet inhibition (onset < 30 minutes compared to ~ 60 minutes when tablets are consumed whole)

- Maintenance dose:
  - 81 mg daily; continue indefinitely
  - Higher doses (300 - 325 mg) do not reduce CV death, MI, or stroke compared to lower doses (75 - 100 mg) and significantly increase GI bleeding risk

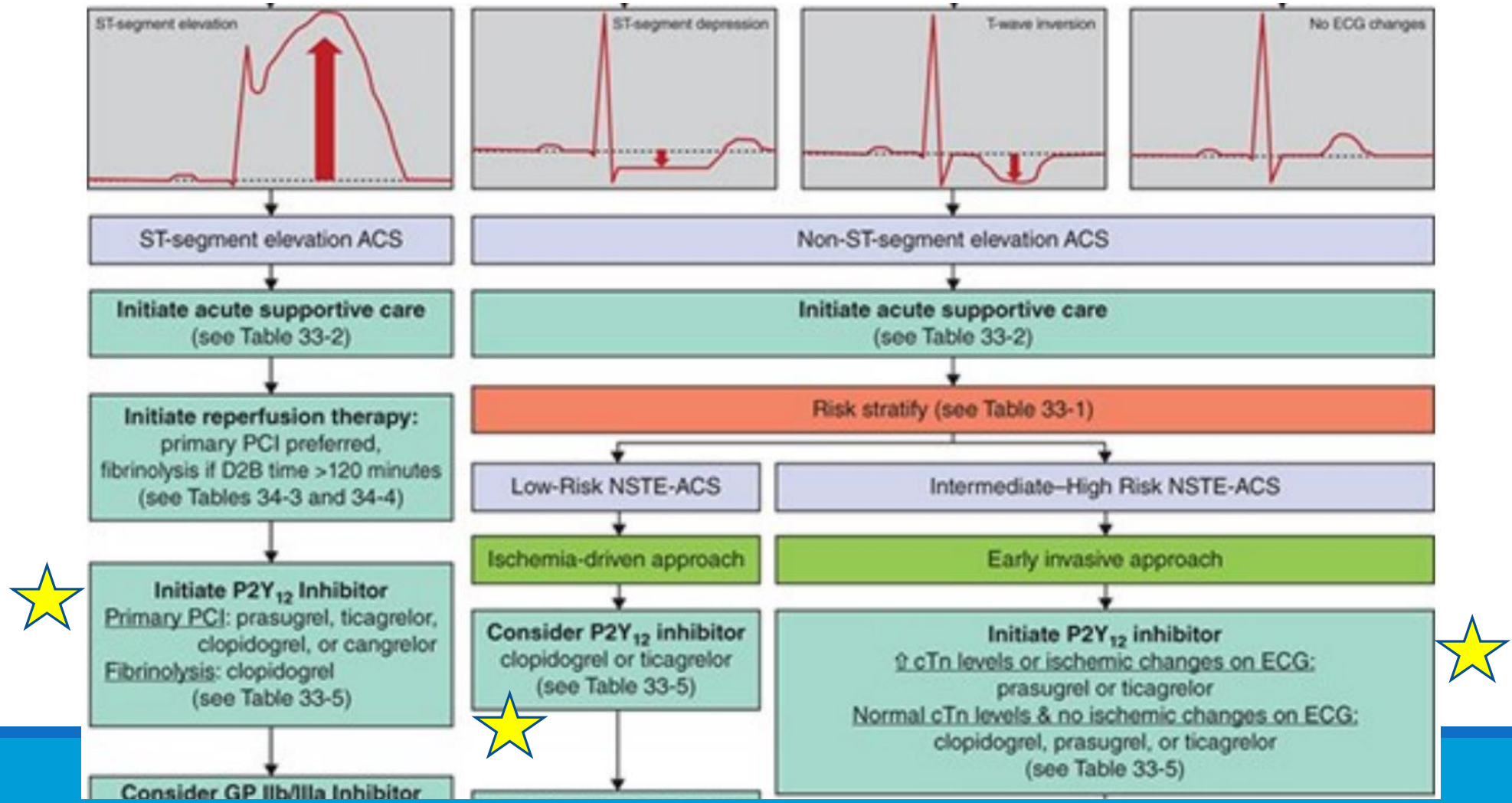
Antithrombotic therapy
Antiplatelets: **Aspirin**

- Contraindications are rare:
  - Hypersensitivity
  - Major GI intolerance

- Adverse effects:
  - Dyspepsia and GI bleeding (due to inhibition of GI-protective prostaglandins)
  - Can be minimized by using low-dose and/or enteric-coated formulation

- Alternatives:
  - Clopidogrel
  - Ticagrelor (less evidence)

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors**



Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors**

- ASA is typically combined with an oral $P2Y_{12}$ inhibitor in ACS (DAPT)

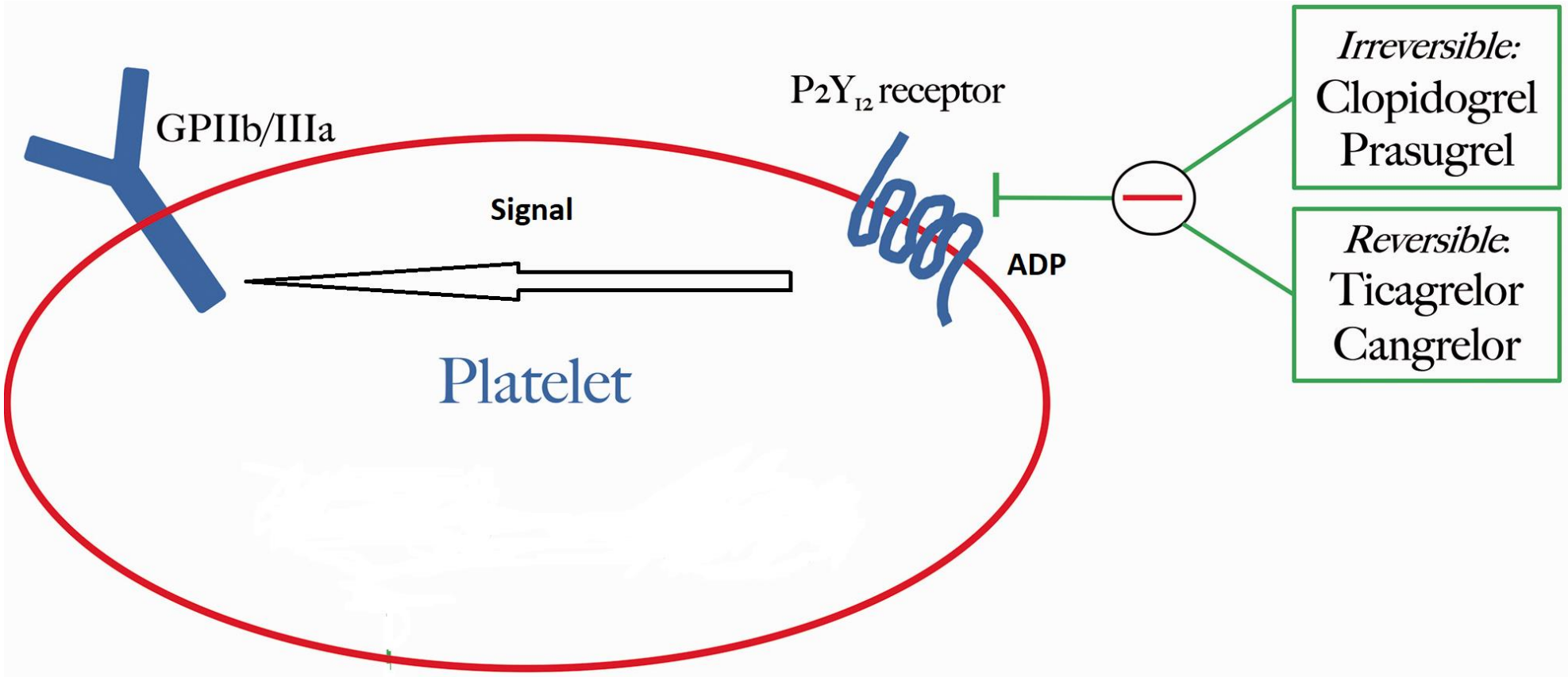
- $P2Y_{12}$ inhibitors:
  - Oral agents: clopidogrel, prasugrel, ticagrelor
  - IV agent: cangrelor

- MOA:
  - Block $P2Y_{12}$ receptor → Decrease ADP binding with $P2Y_{12}$ receptor →
  - Decrease GP IIb/IIIa receptor activation → Inhibit platelet activation and aggregation

- PK:
  - More frequent dosing with Ticagrelor (BID) and Cangrelor (continuous infusion)

- ADR:
  - Bleeding (Prasugrel > Clopidogrel)

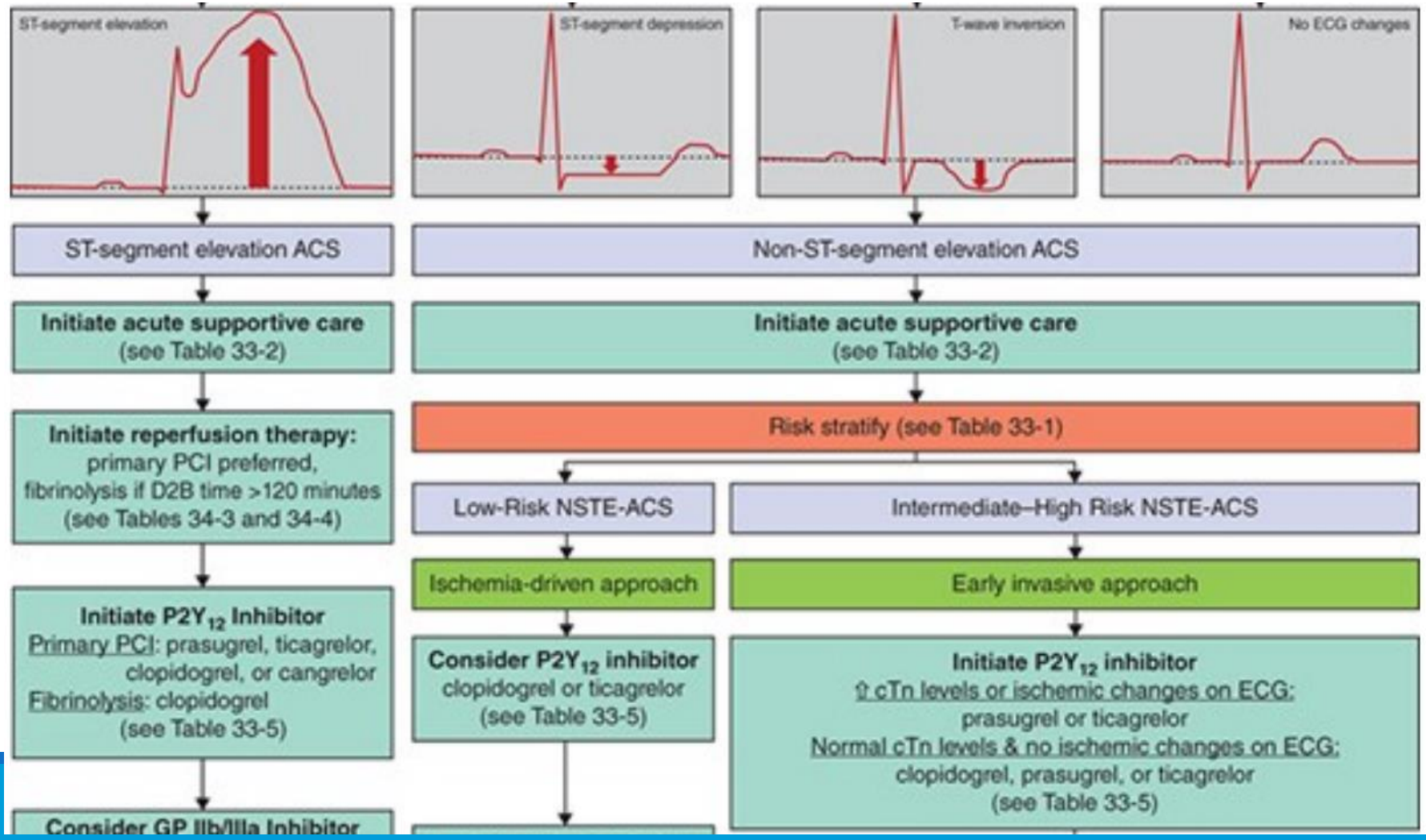
Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors**



Property	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Drug class	Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine	ATP analogue
Absorption	≥50%	80%	36%	100%
Tmax	2 hours	30 minutes	60 minutes	2 minutes
Onset of action	75 mg: 3-5 days			2 minutes
	300 mg: 6-8 hours	10 mg: 3 days	90 mg: 2-3 days	
	600 mg: 2-4 hours	60 mg: 30-60 minutes	180 mg: 60 minutes	
Metabolism	Hepatic	Hepatic	Hepatic	ATPases in vascular endothelium
(CYP isoenzymes)	(2C19, 3A4, 1A2, 2B6)	(2B6, 3A4, 2C9, 2C19)	(3A4, 2C9)	
Prodrug	Yes	Yes	No	No
$P2Y_{12}$ Binding	Irreversible	Irreversible	Reversible	Reversible
Half-life	6 hours	7 hours	12 hours	3-5 minutes
Platelet recovery after cessation of therapy	~5 days	~7 days	~3 days	1-2 hours

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Clopidogrel)**

The only $P2Y_{12}$ inhibitor to be evaluated in STEMI patients receiving reperfusion with fibrinolytics



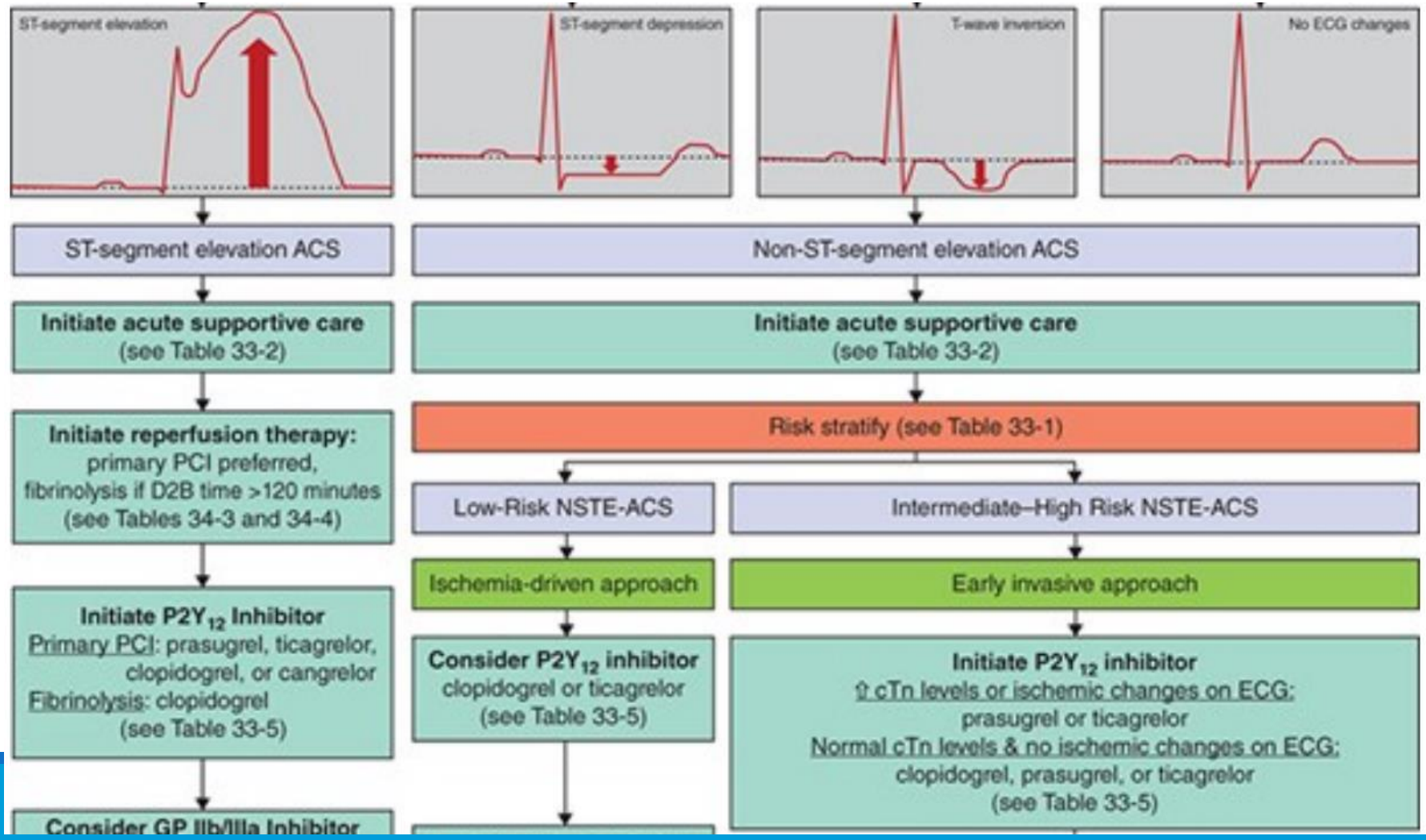
Antithrombotic therapy
Antiplatelets: $P2Y_{12}$ inhibitors (Clopidogrel)

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
$P2Y_{12}$ inhibitors				
Clopidogrel				
Loading dose	600 mg	300 mg Age greater than 75 years: No loading dose given	600 mg	300 mg
Maintenance dose	75 mg daily	75 mg daily	75 mg daily	75 mg daily

- **PCI (for STEMI & early invasive strategy):** Higher LD (600 mg) to decrease post-PCI thrombotic complications
- **Fibrinolysis (for STEMI):** Lower LD (300 mg) to decrease bleeding risk
- **Ischemia-driven strategy:** Lower LD (300 mg) as for low-risk patients

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Prasugrel)**

No evidence with fibrinolysis (STEMI) and Ischemia-driven approach (NSTE-ACS)



Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Prasugrel)**

	STEMI		NSTE-ACS	
Drug	**Primary PCI**	**Fibrinolytic Reperfusion**	**Early Invasive Strategy**	**Ischemia-Driven Strategy**
Prasugrel		No recommendation		No recommendation*
Loading dose	60 mg		60 mg	
Maintenance dose	10 mg daily		10 mg daily	
	Weight less than 60 kg: 5 mg daily		Weight less than 60 kg: 5 mg daily	

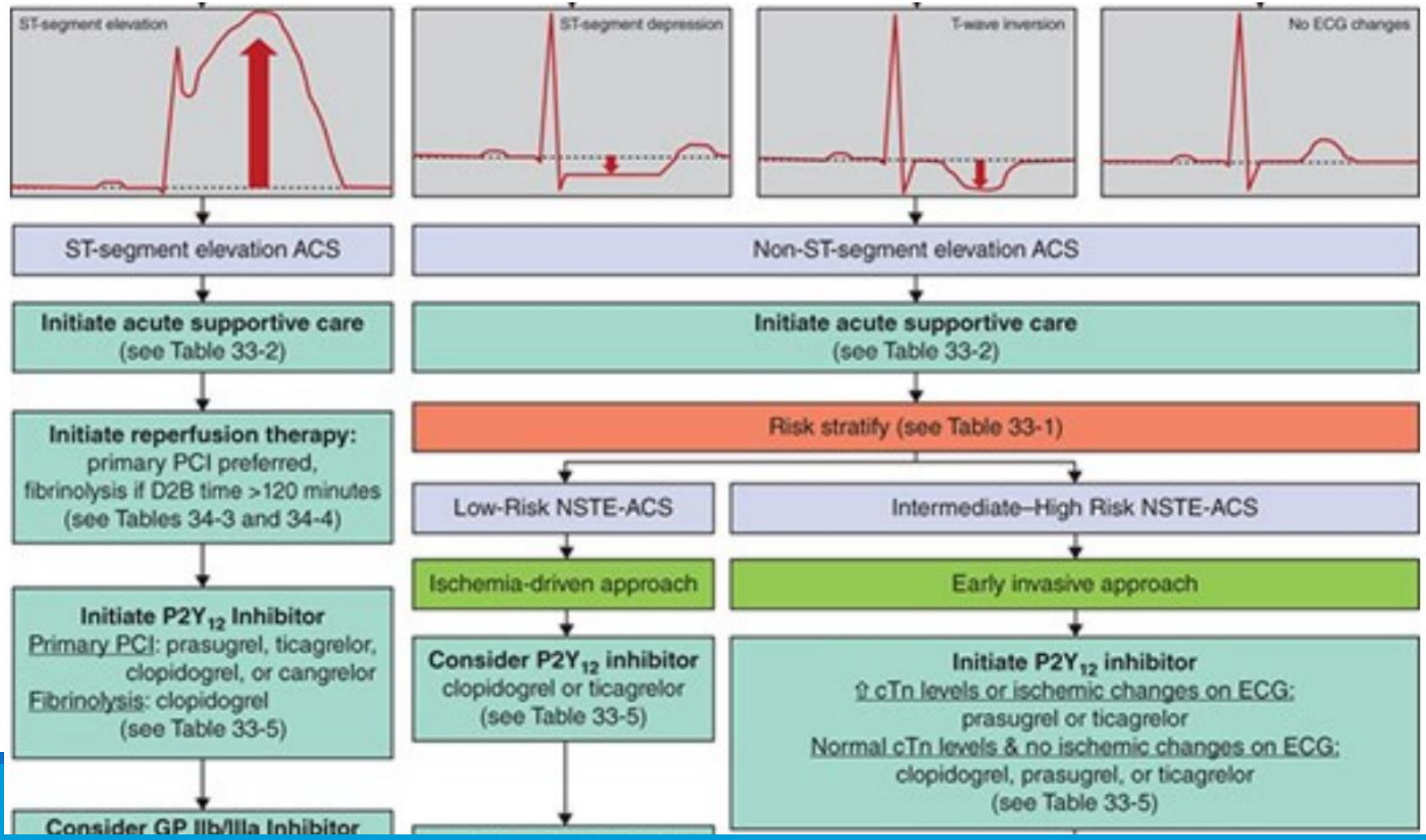
- More efficient conversion to active metabolites than clopidogrel →

  Faster and more potent platelet inhibition → More potent MACE reduction + More major and fatal bleeding

- Absolute contraindication:
  - History of stroke or TIA
- Warnings/Precautions:
  - Age > 75 years: Avoid (except if prior MI or DM)
  - Weight < 60 kg: Lower MD

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Ticagrelor)**

No evidence with fibrinolysis (STEMI)



Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Ticagrelor)**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
Ticagrelor		No recommendation		
Loading dose	180 mg		180 mg	180 mg
Maintenance dose	90 mg twice daily		90 mg twice daily	90 mg twice daily

- Faster and more potent platelet inhibition compared to clopidogrel →

  More potent MACE reduction + More major (but not fatal) bleeding
- (Prasugrel + ASA) vs (Ticagrelor + ASA) in ACS patients undergoing PCI (STEMI or Early invasive strategy):
  - Lower rates of death, MI, or stroke with Prasugrel group
  - Similar rates of major bleeding
- **Contraindication:** Chronic ASA daily doses of > 100 mg (high ASA dose attenuates the benefit of ticagrelor; unknown mechanism!)
- **Warning:** Elderly (increased risk of bleeding; clopidogrel may be safer in patients ≥ 70 or 80 years)

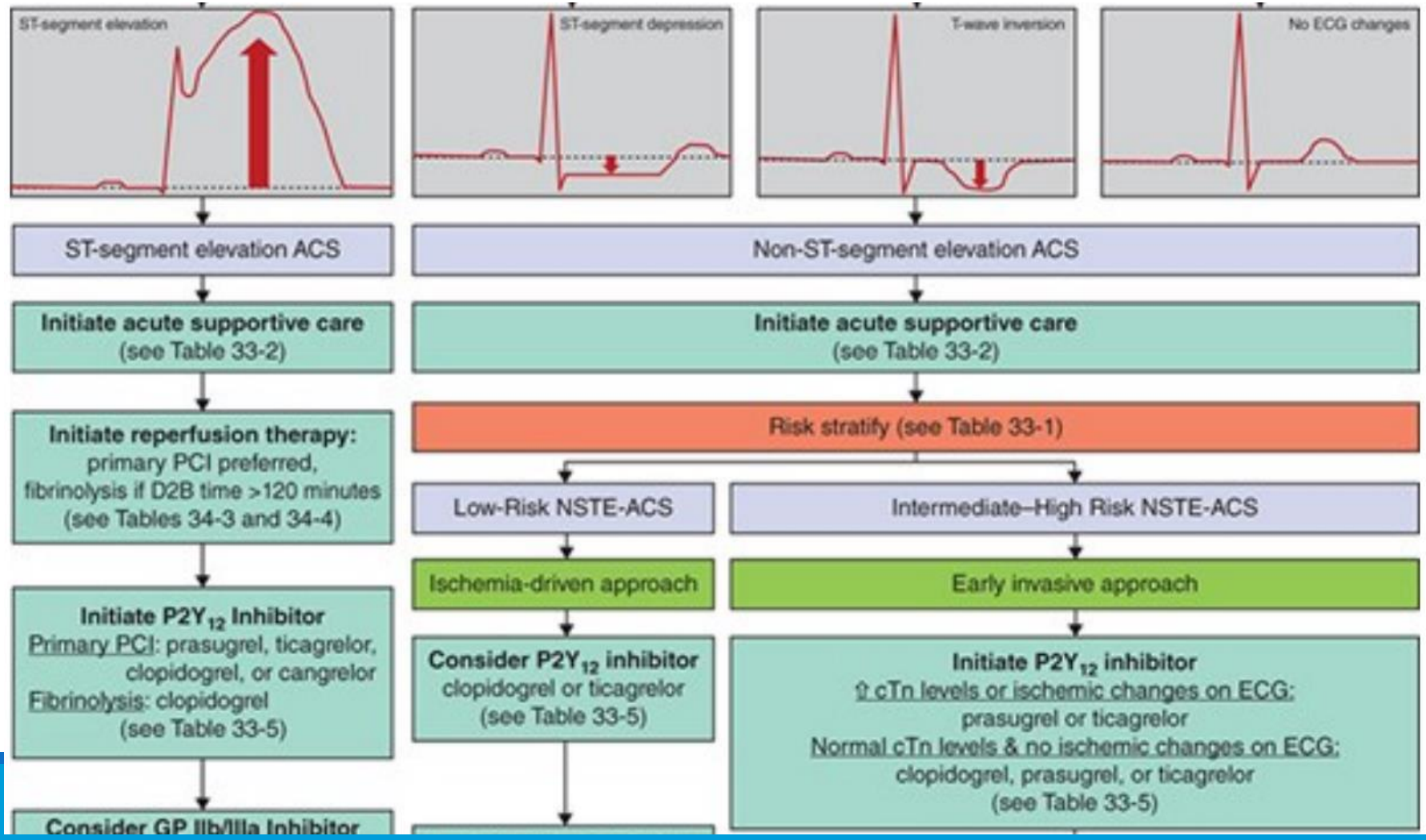
Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Ticagrelor)**

- Metabolized by CYP3A4 (not a prodrug):
  - CI with strong CYP3A4 inhibitors (azole antifungals, protease inhibitors…)
  - CI with strong CYP3A4 inducers (carbamazepine, phenytoin, rifamycins, St. John's Wort…)
  - Inhibits the metabolism of simvastatin and lovastatin (doses should not exceed 40 mg QD for both statins)

- P-gp competition with digoxin; can increase digoxin concentrations by 30% - 50%

- Ticagrelor inhibits adenosine uptake and metabolism by erythrocytes →
- Increased adenosine concentrations →
- Unique adverse effects (compared to other $P2Y_{12}$ inhibitors):
  - Dyspnea (a reason for drug DC, typically mild - moderate, requires no specific therapy, usually dissipates within 2 – 4 weeks)
  - Asymptomatic ventricular pauses
  - Increased uric acid
  - Increased serum creatinine (mild)

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Cangrelor)**



Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Cangrelor)**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
Cangrelor	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation	30 mcg/kg IV bolus, followed by 4 mcg/kg/min IV infusion for at least 2 hours or duration of PCI	No recommendation

- Cangrelor for PCI:
  - Significant reduction in MACE
  - Increase in minor (but not major) bleeding

- Dosage for PCI:
  - **Before PCI:** Cangrelor (bolus dose followed by an infusion)
  - **After PCI:** Discontinue cangrelor infusion; Switch to oral $P2Y_{12}$ inhibitor (LD followed by MD)

Antithrombotic therapy
Antiplatelets: **$P2Y_{12}$ inhibitors (Cangrelor)**

- Metabolized by blood ATPases
  - Hepatic/renal dysfunction is not likely to impact the cangrelor PK

- Fast return to normal platelet function after cangrelor discontinuation
  - Once Cangrelor infusion is discontinued → No more platelet inhibition
  - Safety advantage over other $P2Y_{12}$ inhibitors in terms of bleeding or transition to CABG

- Similar chemical structure to Ticagrelor
  - Adenosine effects; Dyspnea may occur, but with lower incidence and DC rate (due to shorter half life)

Antithrombotic therapy
Switching antiplatelet agents

- **Escalation of therapy**: Switching clopidogrel to a more potent $P2Y_{12}$ inhibitor (ticagrelor, prasugrel)

- Possible indications:
  - Heightened risk for coronary event or stent thrombosis
  - Development of drug interaction, intolerance, or nonadherence
  - Identification of a genetic polymorphism to clopidogrel
  - Confirmation of inadequate platelet inhibition

- Loading doses are generally needed when escalating therapy

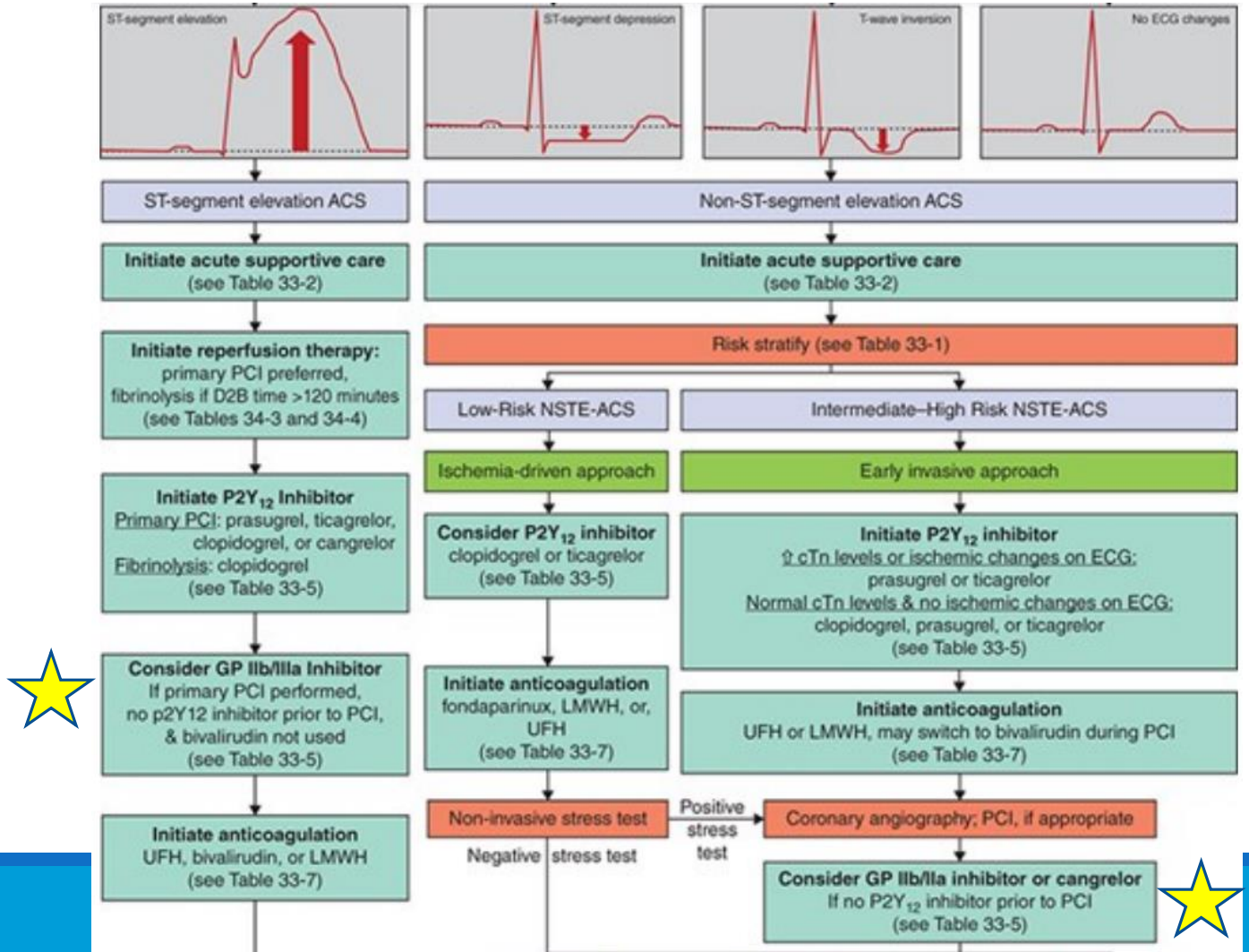
Antithrombotic therapy
Switching antiplatelet agents

- **De-escalation of therapy**: Switching a more potent $P2Y_{12}$ inhibitor (ticagrelor, prasugrel) to clopidogrel

- Possible indications:
  - Bleeding
  - A new indication to concurrently use an oral anticoagulant
  - Cost is limiting medication access or leading to suboptimal adherence

- Loading doses are generally not needed when de-escalating therapy
  - Except when switching from Ticagrelor

Antithrombotic therapy
Antiplatelets: **GP IIb/IIIa inhibitors**

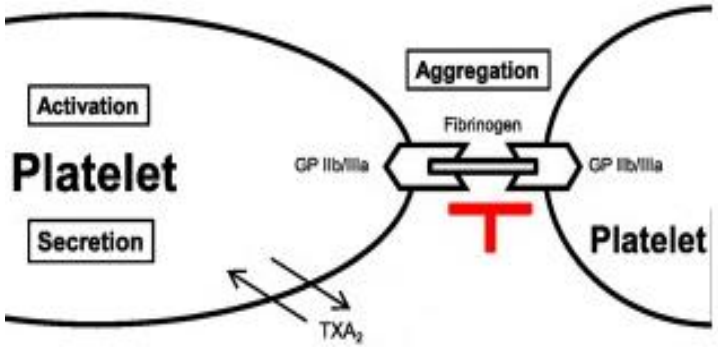


Antithrombotic therapy
Antiplatelets: **GP IIb/IIIa inhibitors**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic Reperfusion	Early Invasive Strategy	Ischemia-Driven Strategy
GP IIb/IIIa inhibitor				
Eptifibatide	180 mcg/kg IV bolus (just before PCI) × 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI	No recommendation	180 mcg/kg IV bolus (just before PCI) × 2 given 10 minutes apart, followed by 2 mcg/kg/min IV infusion started after first bolus and continued for 18-24 hours after PCI	No recommendation
	CrCl less than 50 mL/min (0.83 mL/s): Reduce infusion by 50%		CrCl less than 50 mL/min (0.83 mL/s): Reduce infusion by 50%	
	Hemodialysis: Avoid use		Hemodialysis: Avoid use	
Tirofiban	25 mcg/kg IV bolus (just before PCI), followed by 0.15 mcg/kg/min for up to 18 hours	No recommendation	25 mcg/kg IV bolus (just before PCI), followed by 0.15 mcg/kg/min for up to 18 hours	No recommendation
	CrCl less than 60 mL/min (1.0 mL/s): Reduce infusion by 50%		CrCl less than 60 mL/min (1.0 mL/s): Reduce infusion by 50%	

Antithrombotic therapy
Antiplatelets: **GP IIb/IIIa inhibitors**

- Agents:
  - Eptifibatide (peptide)
  - Tirofiban (non-peptide)
- Available only as IV infusions



- MOA:
  - Reversibly inhibit fibrinogen binding to activated GP IIb/IIIa receptors (final step in platelet aggregation)
  - Platelet function recovery occurs in 2 - 4 hours after discontinuation of the infusion

- GP IIb/IIIa inhibitors should always be administered with UFH or LMWH
  - Improved protection against persistent platelet activation

Antithrombotic therapy
Antiplatelets: **GP IIb/IIIa inhibitors**

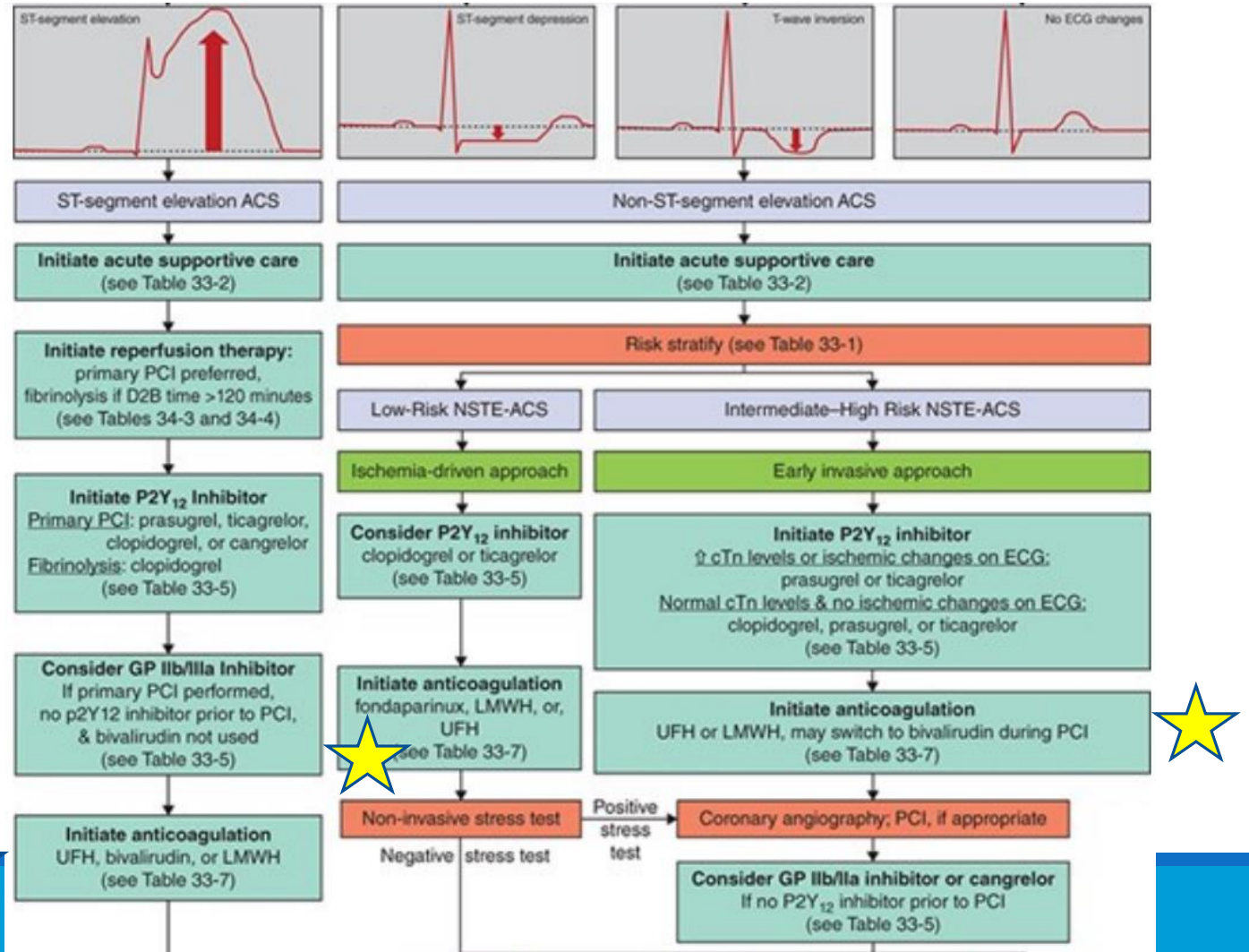
- Adverse effects:
  - Bleeding: platelet transfusion is not helpful
  - Thrombocytopenia: significant; occurs in ~ 0.5% of patients
    - GP IIb/IIIa inhibitor induced-thrombocytopenia vs. Heparin-induced thrombocytopenia (HIT)
    - GP IIb/IIIa inhibitor induced-thrombocytopenia: occurs more rapidly (within hours) + platelet count nadir is typically lower (~ 20,000/µL)

- Evidence: Significantly reduce MACE (still, diminished use over time)

- Indications:
  - Reserved for high-risk patients with elevated cTn (MI)
  - PCI (STEMI or NSTEMI 'early invasive approach') + Not preloaded with $P2Y_{12}$ inhibitor + Not treated with Bivalirudin

- Avoid in:
  - NSTE-ACS patients undergoing ischemia-driven approach (no benefit)
  - STEMI patients undergoing fibrinolysis (significant increase in major bleeding and ICH)

Antithrombotic therapy
Anticoagulants



Antithrombotic therapy
Anticoagulants

- MOA:
  - Inhibiting factor Xa (indirectly) +/-
  - Inhibiting factor IIa (indirectly or directly)

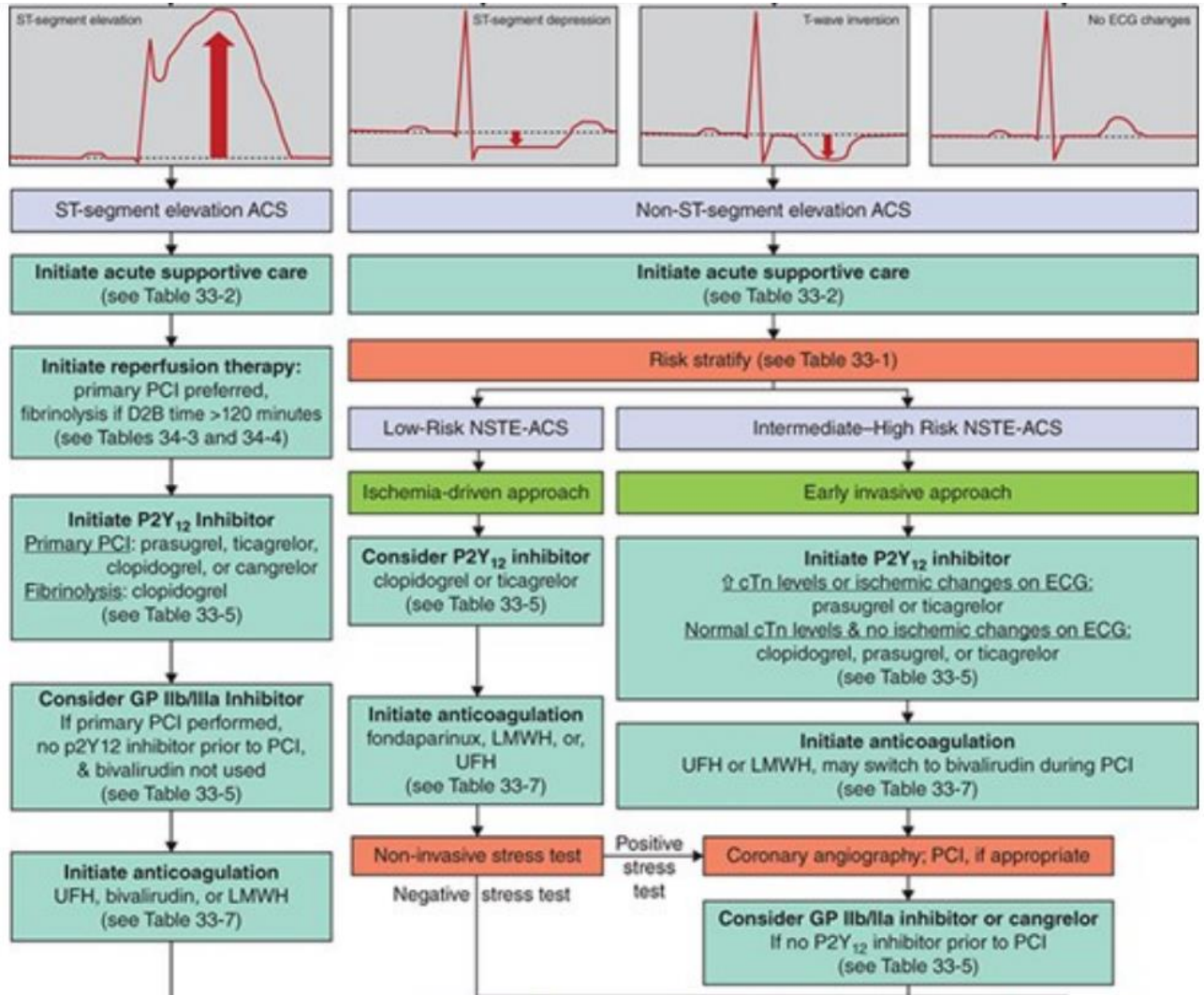
- Used concurrently with antiplatelets in ACS patients for better antithrombotic effects

- Duration of therapy (compared to antiplatelets):
  - Usually a single anticoagulant is used in ACS patients for the initial few days of hospitalization
  - Usually two antiplatelets (DAPT) is used in ACS patients for at least a year

- Formulations used in acute management of ACS:
  - Injectable agents (more evidence than oral agents)
  - IV, SC

Antithrombotic therapy
Anticoagulants: **UFH**

Based on wide use/experience, UFH is indicated across ACS spectrum and management strategies

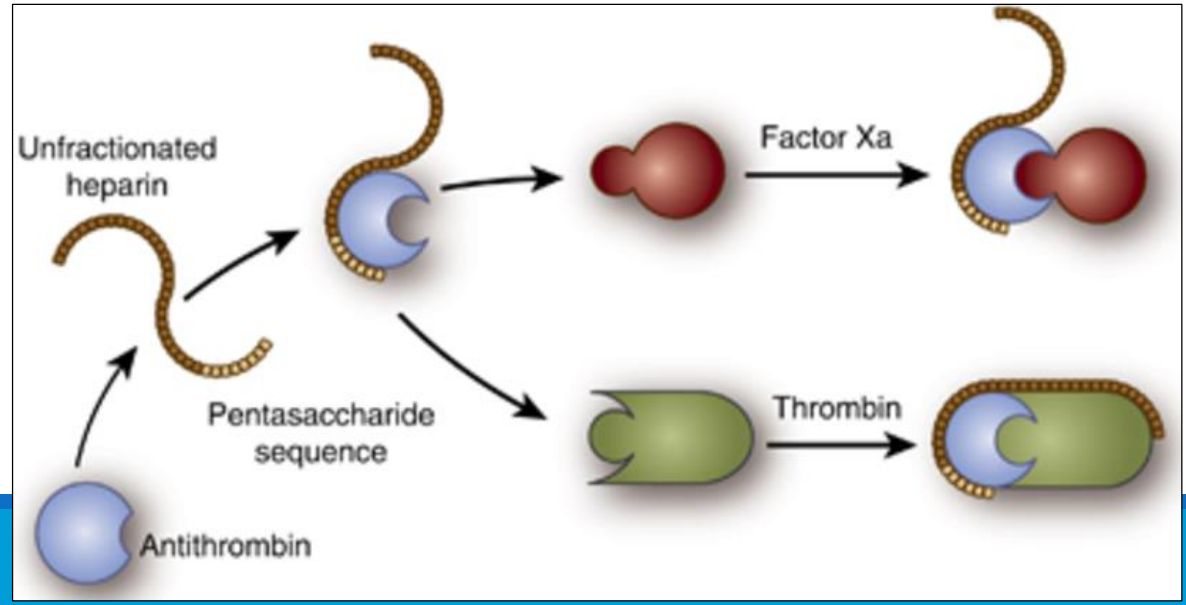


Antithrombotic therapy
Anticoagulants: **UFH**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic reperfusion	Early invasive strategy	Ischemia-driven strategy
Unfractionated heparin	• No GP IIb/IIIa: 70-100 units/kg IV bolus to achieve a therapeutic ACT • GP IIb/IIIa: 50-70 units/kg IV bolus to achieve a therapeutic ACT	• 60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1,000 units/hr)	• 60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1,000 units/hr)	• 60 units/kg (maximum initial bolus: 4,000 units) IV bolus, followed by 12 units/kg/hr (maximum initial infusion rate: 1,000 units/hr)

Antithrombotic therapy
Anticoagulants: **UFH**

- MOA:
  - Sulfated polysaccharide
  - Unique pentasaccharide sequence binds to anti-thrombin (AT) →
  - Increases AT affinity for clotting factor inhibition →
  - Inhibits clotting factors IIa ‘thrombin’, IXa, Xa, XIa, XIIa
  - Most impact on factors IIa and Xa
  - Inhibits factor Xa and IIa ‘thrombin’ in 1:1 ratio



Antithrombotic therapy
Anticoagulants: **UFH**

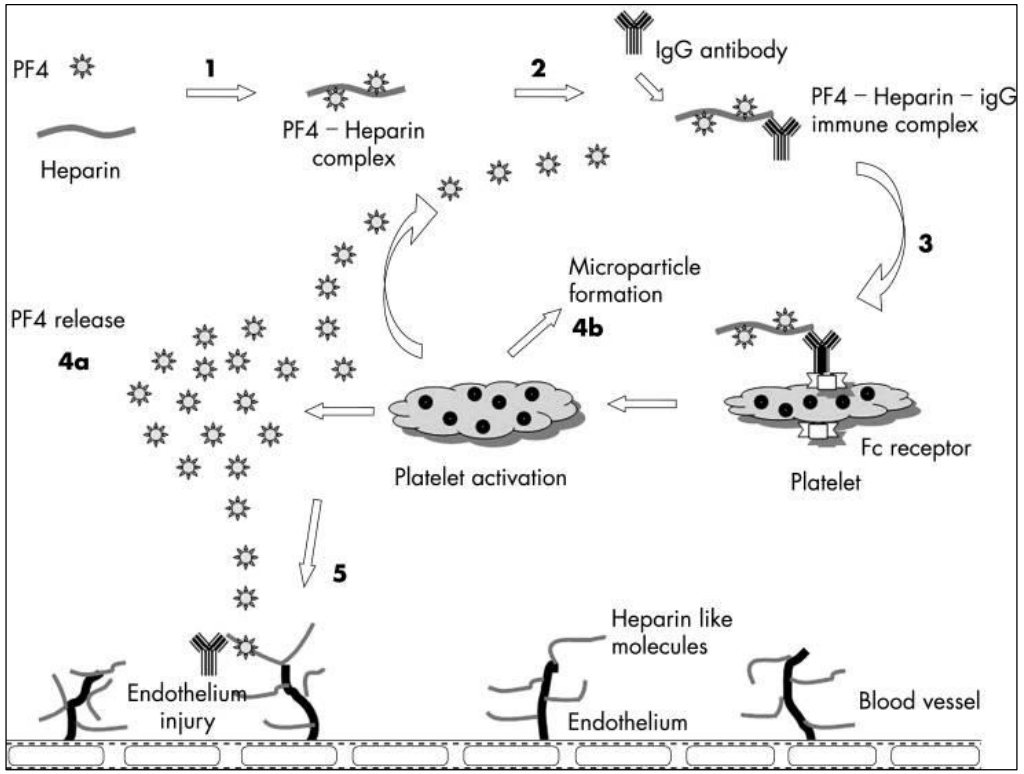
- PK:
  - Rapidly metabolized in the reticuloendothelial system in the liver by a heparinase via desulfation →
  - Short duration of action

- UFH (large, negatively charged) can bind with endothelial cells, plasma proteins, & macrophages →
- Significant interpatient variability of the anticoagulant effect of UFH (unpredictable response) →
- Need to monitor activated partial thromboplastin time (aPTT)
  - Q 6 hours until two consecutive readings are within the therapeutic range, then
  - Q 24 hours for the duration of UFH therapy
  - Same monitoring schedule with UFH dose adjustments
  - Recommended aPTT goal: 1.5 – 2 times the institution's control value (normal aPTT ~ 25 - 35 seconds)

Antithrombotic therapy
Anticoagulants: **UFH**

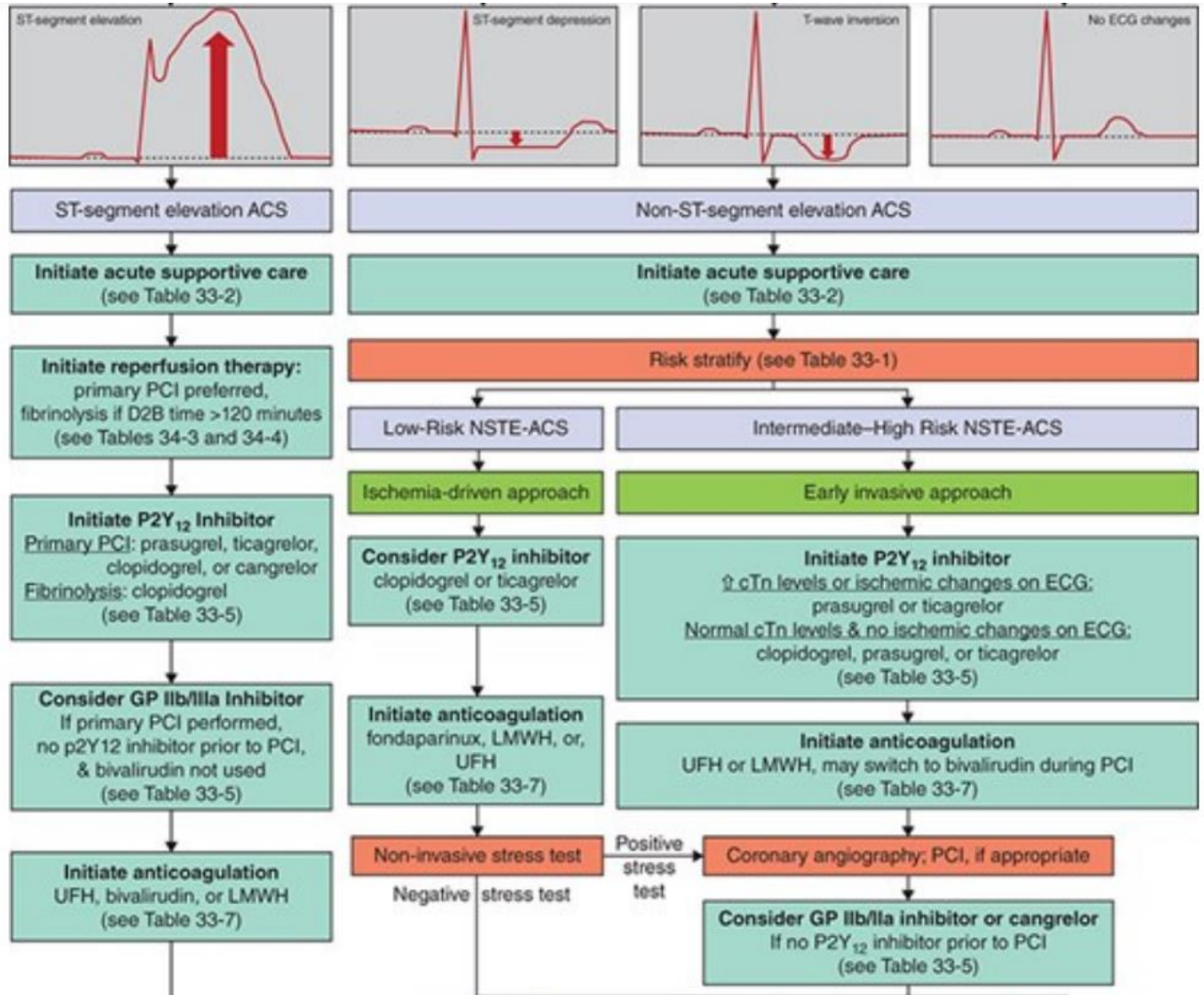
- Need to monitor platelet counts QD or QOD for HIT
  - Fall in platelet counts + Hypercoagulable state
  - Can lead to TE complications (e.g. PE, DVT)
  - HIT typically presents ≥ 5 days after UFH exposure
  - HIT can occur within hours of UFH exposure if the patient has been exposed to UFH in the last 3 months

- If HIT is suspected:
  - D/C UFH
  - Start anticoagulation with IV direct thrombin inhibitor
    - Argatroban, Bivalirudin



Ultimately, the IgG-coated platelets are consumed by MΦs

Antithrombotic therapy
Anticoagulants: **LMWH**



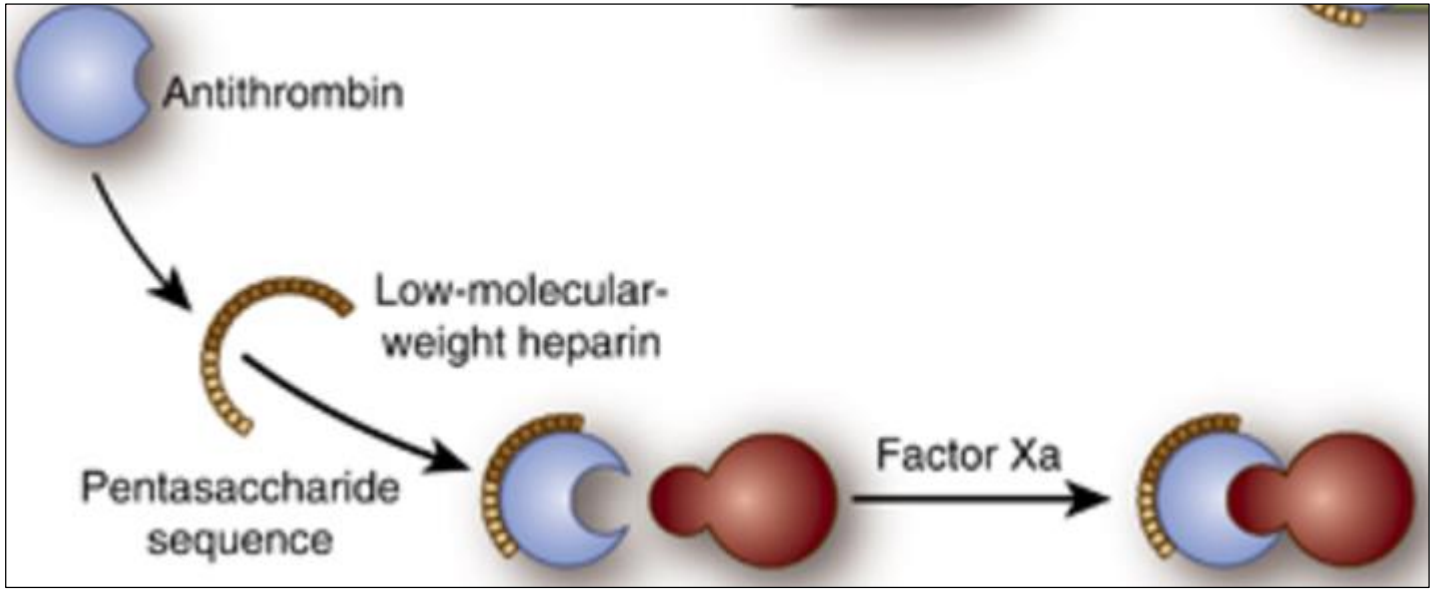
Enoxaparin is indicated across ACS spectrum and management strategies

Antithrombotic therapy
Anticoagulants: **LMWH**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic reperfusion	Early invasive strategy	Ischemia-driven strategy
Enoxaparin	• 0.5 mg/kg one time IV bolus	• 30 mg IV bolus, followed by 1 mg/kg SC every 12 hours for up to 8 days or hospital discharge • SC doses should be initiated within 15 minutes of the IV bolus. The first two SC doses should be capped at 100 mg • CrCl less than 30 mL/min (0.5 mL/s): 30 mg IV bolus, followed by 1 mg/kg SC every 24 hours; the first SC dose should be capped at 100 mg • Age 75 years or more: • No IV bolus. Initiate at 0.75 mg/kg SC every 12 hours; the first two SC doses should be capped at 75 mg • CrCl less than 30 mL/min (0.5 mL/s) AND age 75 years or more: • No IV bolus. Initiate at 1 mg/kg every 24 hours; the first dose should be capped at 100 mg	• 1 mg/kg SC every 12 hours until PCI • A 0.3 mg/kg IV bolus should be given if PCI occurs before two SC doses have been given, or if the last dose was given 8 hours or more prior to PCI • CrCl less than 30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours • An initial 30 mg IV bolus can be given	• 1 mg/kg SC every 12 hours for the duration of hospitalization • An initial 30 mg IV bolus can be given • CrCl less than 30 mL/min (0.5 mL/s): 1 mg/kg SC every 24 hours

Antithrombotic therapy
Anticoagulants: **LMWH**

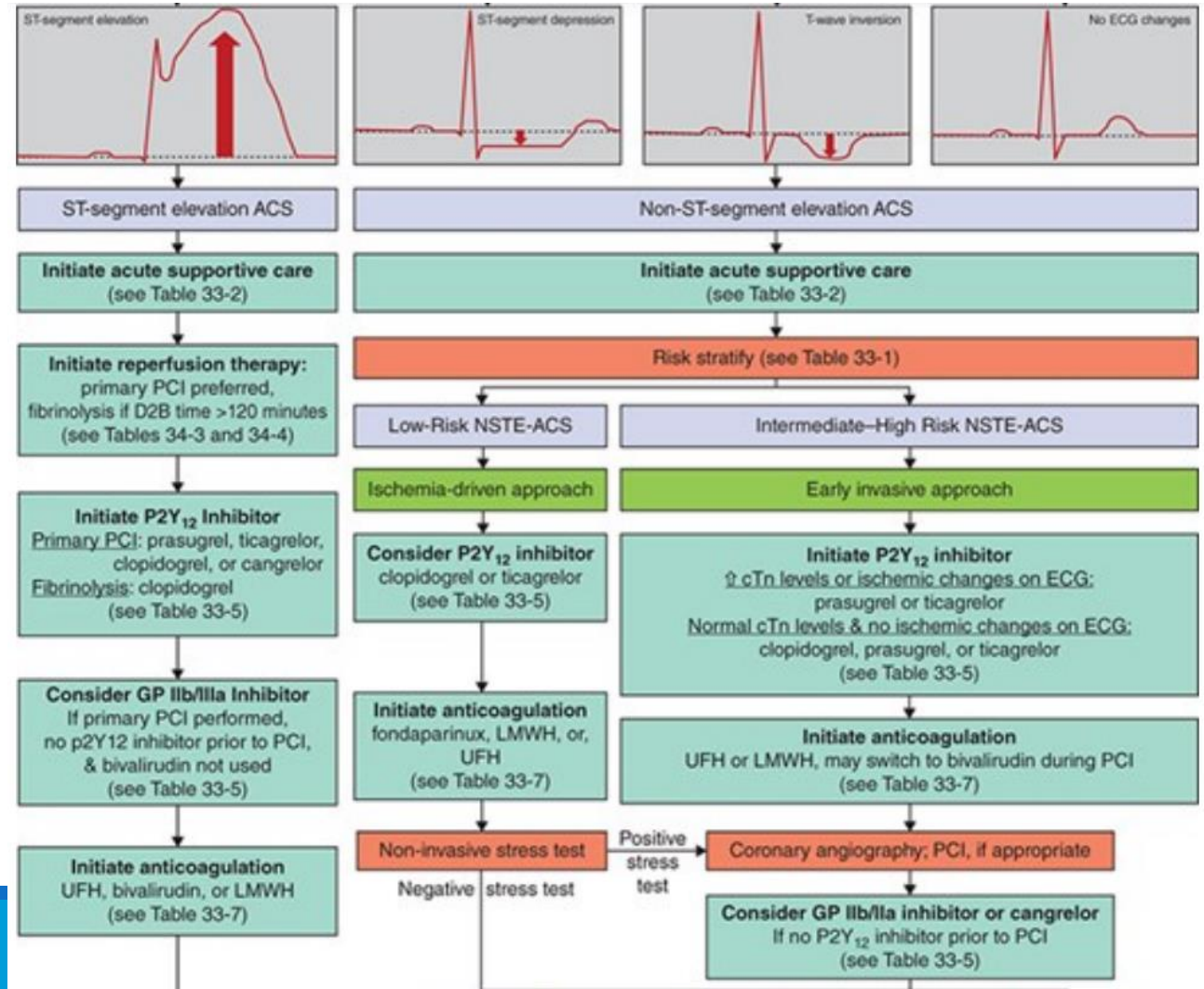
- MOA:
  - Binds to anti-thrombin (AT) →
  - Increases AT affinity for clotting factor inhibition →
  - Inhibits factor Xa and IIa ‘thrombin’ in 3:1 or 4:1 ratio



Antithrombotic therapy
Anticoagulants: **LMWH**

- Predicable anticoagulant response →
- No need for *routine* therapeutic monitoring
- Anti-Xa monitoring may be needed in:
  - Pediatrics, pregnancy, obesity (weight > 190 kg), severe renal insufficiency (e.g. ClCr < 30 mL/min)
- Lower incidence of HIT
  - LMWH (< 2%) vs. UFH (2 – 5%)
  - Monitoring of platelet counts is still warranted
  - LMWH is not a safe alternative in patients with UFH-induced HIT
- Enoxaparin:
  - The most widely studied LMWH in ACS
  - The only LMWH recommended in the ACC/AHA guidelines

Antithrombotic therapy
Anticoagulants: **Fondaparinux**



Fondaparinux can be considered in NSTE-ACS patients undergoing ischemia-driven approach who are at high bleeding risk

Fondaparinux is rarely used in STEMI (due to higher risk of catheter-related thrombosis following PCI)

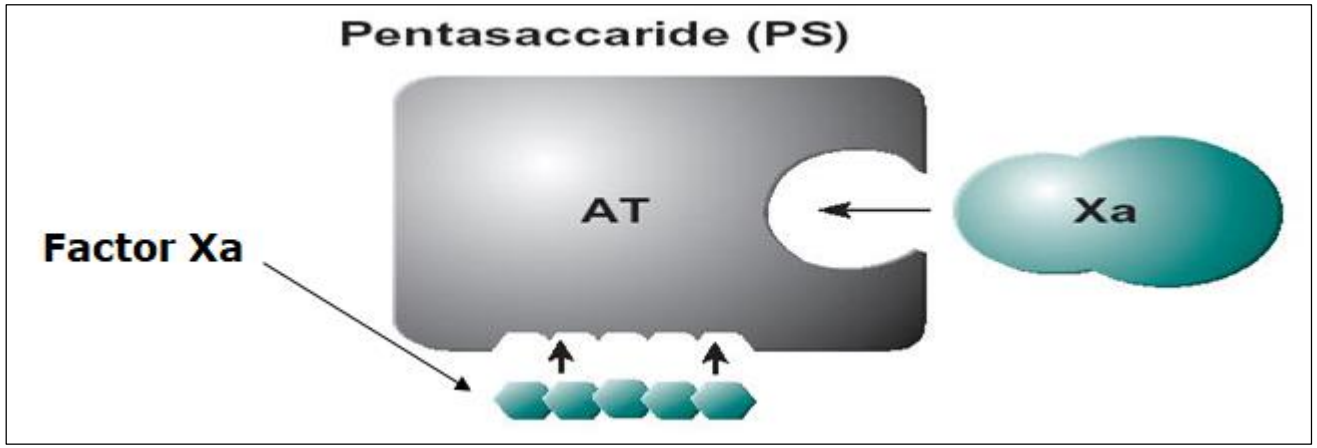
Fondaparinux is rarely used in NSTE-ACS patients undergoing invasive management approach (due to higher risk of catheter-related thrombosis following PCI)

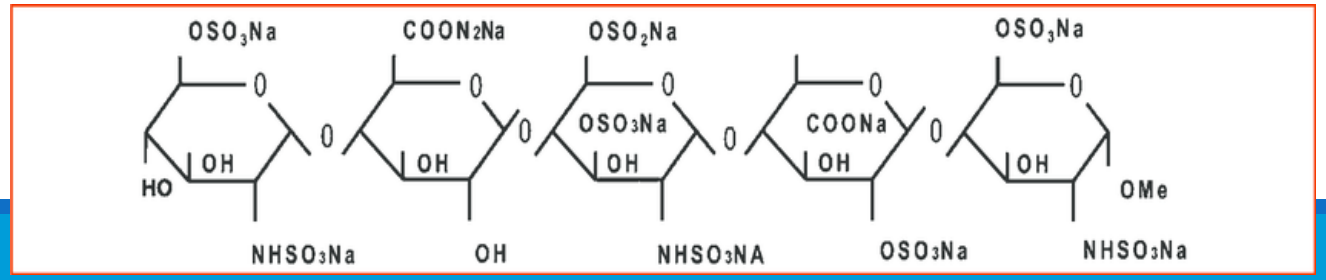
Antithrombotic therapy
Anticoagulants: **Fondaparinux**

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic reperfusion	Early invasive strategy	Ischemia-driven strategy
Fondaparinux	• No recommendation	• 2.5 mg IV first dose, followed by 2.5 mg SC daily for up to 8 days or hospital discharge	• 2.5 mg SC daily until PCI • At the time of PCI: • No GP IIb/IIIa: IV UFH 85 units/kg • With GP IIb/IIIa: IV UFH 60 units/kg	• 2.5 mg SC daily for up to 8 days or duration of hospitalization

Antithrombotic therapy
Anticoagulants: **Fondaparinux**

- MOA:
  - Pentasaccharide molecule that is needed to bind to and potentiate AT
  - Because of its small size, it can only inhibit factor Xa (no activity against factor IIa ‘thrombin’)





Antithrombotic therapy
Anticoagulants: **Fondaparinux**

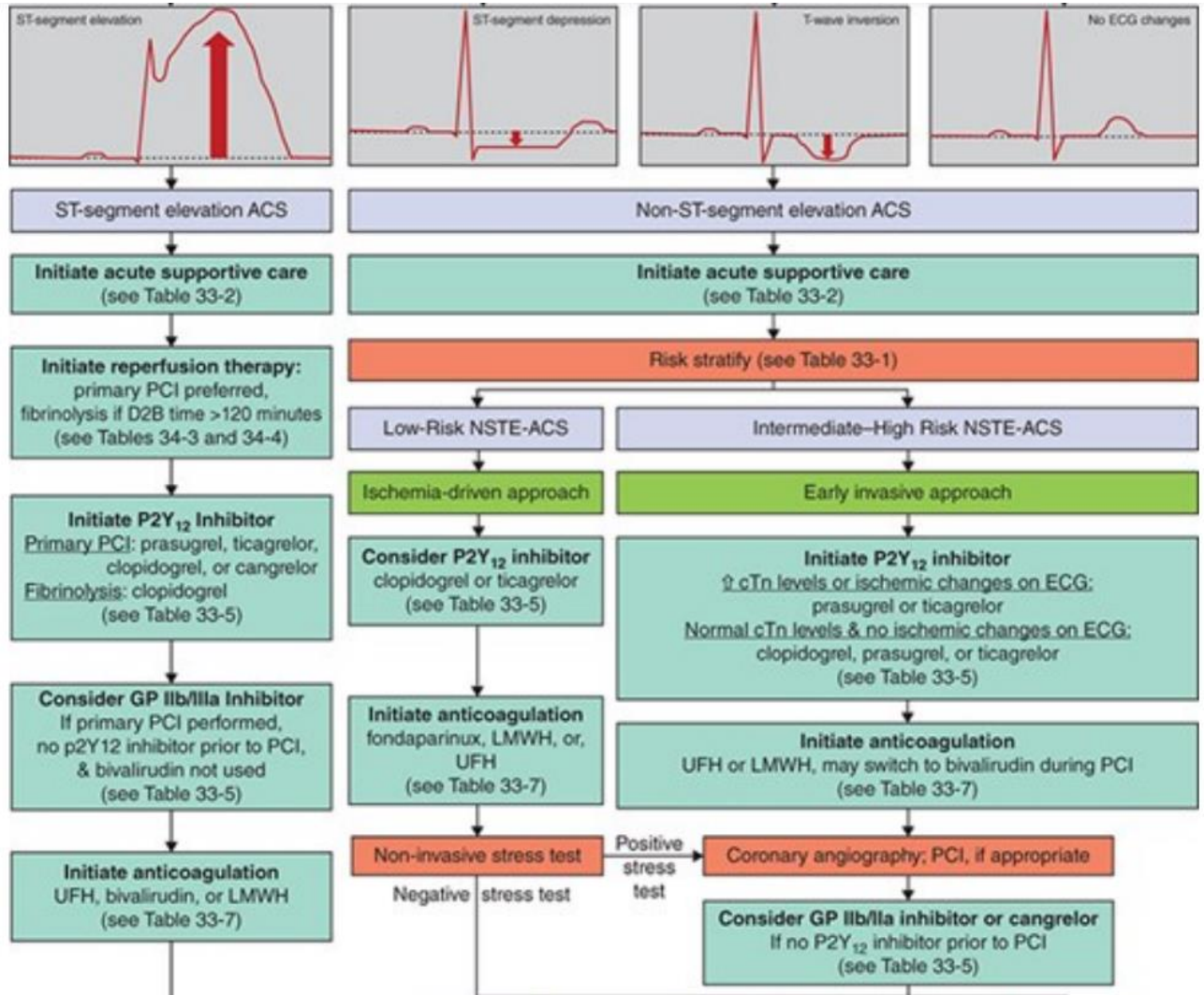
- Predicable anticoagulant response →
- No need for *routine* therapeutic monitoring

- Lower bleeding risk than UFH and LMWH
- Extremely rare cases of fondaparinux-induced thrombocytopenia
  - Reasonable to consider fondaparinux in patients with HIT history
  - Off-label use (second-line) for HIT treatment

- Long half-life; SC dose (2.5 mg) is given once daily

- <u>Renal function</u>:
  - Fondaparinux is excreted renally in significant amounts
  - Risk of accumulation with CrCl 30 - 60 mL/min (may not be problematic with the short duration of therapy in ACS)
  - Contraindicated with CrCl < 30 mL/min

Antithrombotic therapy
Anticoagulants: **Bivalirudin**



Bivalirudin is only used in ACS patients receiving PCI

Antithrombotic therapy
Anticoagulants: **Bivalirudin**

- IV agent
- Direct thrombin inhibitor (does not bind to AT)

Drug	STEMI		NSTE-ACS	
	Primary PCI	Fibrinolytic reperfusion	Early invasive strategy	Ischemia-driven strategy
Bivalirudin	• 0.75 mg/kg IV bolus, followed by 1.75 mg/kg/hr IV infusion until completion of PCI • CrCl less than 30 mL/min (0.5 mL/s): Reduce infusion to 1 mg/kg/hr	• No recommendation	• 0.10 mg/kg IV bolus, followed by 0.25 mg/kg/hr IV infusion continued until completion of PCI	• No recommendation

Secondary prevention of ischemic events

- Acute phase (initial 24 hours) of ACS:
  - Acute supportive care
  - Reperfusion
  - Antithrombotic therapy

- If ACS diagnosis is confirmed → Patients are considered to have ASCVD →
- Aggressive management to decrease the risk of recurrent MACE (mortality, HF, reinfarction, stroke)

- Secondary prevention strategies to reduce post-ACS MACE:
  - Anti-ischemic agents
  - Antiplatelet agents
  - Lipid-lowering agents
  - Antihypertensives

Secondary prevention of ischemic events

- Proton pump inhibitors:
  - Protect patients at high risk for GI bleeding from antithrombotic therapy
  - Consider in select patients
    - History of GI bleeding
    - Triple therapy with DAPT
    - Oral anticoagulant with or without a history of GI bleeding

- NSAIDs:
  - All patients should refrain from chronic use of NSAIDs with high COX-2 selectivity
  - COX-2 selective agents are associated with increased risk of cerebrovascular and cardiovascular events

Within first 24 hours

Initiate aspirin, β-blocker, statin as early as possible if no contraindication exists

Length of therapy: aspirin and statin indefinitely; β-blocker therapy for at least 1 year & up to 3 years or more in patients with normal ejection fraction; indefinitely in LVEF ≤40%

Prior to hospital discharge

Medication reconciliation should include:

- DAPT with aspirin and $P2Y_{12}$ inhibitor
- Statin therapy if not already initiated
- β-Blocker therapy if not already initiated
- Consider ACE inhibitor (or ARB) in all patients; strongest evidence if LVEF ≤40% (indefinite), anterior MI (for 3 months)
- Consider AA if LVEF ≤40%& HF symptoms or DM, & no CI
- SL NTG as needed
- Discontinue NSAIDs

At 1 month follow-up

Emphasize adherence with guideline-directed medical therapies

Consider statin, β-blocker ACE inhibitor (or ARB), AA if indicated & not already initiated

Check lipid panel and add ezetimibe ± PCSK9 inhibitor if LDL-C >70 mg/dL, according to shared decision making between provider and patient

At 12 months follow-up

Emphasize adherence with guideline-directed medical therapies

Evaluate for continuation of $P2Y_{12}$ inhibitor beyond 1 year therapy (ie, DAPT score, lower dose ticagrelor, etc.)

Evaluate for continued β-blocker therapy beyond 1-3 years (consider LVEF & angina symptom control)

Lifestyle modifications for all patients including cardiac rehabilitation, weight management, smoking cessation, blood pressure control, glucose control, and influenza vaccination

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Aspirin	All patients without contraindications	•Hypersensitivity to aspirin or NSAID •History of asthma, rhinitis, and nasal polyps •History of upper GI bleeding •Bleeding disorder/active bleeding	•81 mg once daily	•Dyspepsia, GI bleeding
$P2Y_{12}$ inhibitors	All patients without contraindications	•Thienopyridine hypersensitivity •Bleeding disorder/active bleeding •Previous intracranial hemorrhage •Prasugrel: prior TIA or stroke •Ticagrelor: aspirin doses greater than 100 mg daily; strong CYP3A4 inhibitors or inducers	•Clopidogrel 75 mg once daily •Prasugrel 10 mg once daily; weight less than 60 kg: 5 mg daily •Ticagrelor 90 mg twice daily	•Bleeding, rash; Ticagrelor: dyspnea, ventricular pauses, bradycardia

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
β-Blockers	All patients without contraindications	•Signs of heart failure •Low cardiac output state •High-grade AV block •Active asthma or reactive airway disease	•Carvedilol 6.25 mg twice daily; target dose (in patients with HFrEF): 25 mg twice daily as tolerated •Metoprolol 25-50 mg every 6-12 hours for 2-3 days, then once (metoprolol succinate) or twice daily (metoprolol tartrate); target dose (in patients with HFrEF): 200 mg daily •Continue therapy for at least 1-3 years, indefinitely in patients with concomitant HFrEF •Other β-blockers may be considered; in patients with HFrEF, use either metoprolol succinate, carvedilol, or bisoprolol	•Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Statins	All patients without contraindications	•Active liver disease •Pregnancy •Breastfeeding •Concomitant use of fibrate	•Atorvastatin 80 mg daily •Rosuvastatin 20-40 mg daily	•GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity
Non-statin therapies	Patients with very high-risk ASCVD (eg, post-ACS) with LDL-C greater than 70 mg/dL on maximally tolerated statin therapy (Ezetimibe first; then PCSK-9 inhibitor if LDL goal not achieved)	•Hypersensitivity •Simvastatin/ezetimibe: strong CYP3A4 inhibitors	•Ezetimibe 10 mg daily •Simvastatin 40 mg/ezetimibe 10 mg •Alirocumab 75 mg SC every 2 weeks or 300 mg SC every 4 weeks •Evolocumab 140 mg SC every 2 weeks or 420 mg SC monthly	•Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain •Alirocumab: injection site pain, hypersensitivity

Secondary prevention of ischemic events

- Statins:
  - Lower LDL-C and stabilize atherosclerotic plaques
  - Following MI, statins provide ~ 1% reduction in ASCVD event per 1% reduction in LDL-C
  - Survival benefit observed after ~ 4 months of treatment
  - High-intensity statin for all ACS patients, even if normal LDL-C at baseline
  - May consider moderate-intensity statin if intolerant to high-intensity (> 75 yrs, drug interactions…)
  - Goal: 50% reduction in LDL-C from baseline
  - Lipid panel profile 4 to 6 weeks after initiation of therapy

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
ACE inhibitors	All patients without contraindications	•Hypotension •Renal failure •Hyperkalemia	•Lisinopril 2.5-5 mg daily; target dose: 10-40 mg daily •Enalapril 2.5-5 mg twice daily; target dose: 10-20 mg twice daily •Captopril 6.25-12.5 mg three times daily; target dose: 25-50 mg three times daily •Ramipril 2.5 mg twice daily; target dose: 5 mg twice daily •Trandolapril 0.5-1 mg daily; target dose: 4 mg daily	•Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema
ARBs	Patients intolerant to ACE inhibitors	•Hypotension •Renal failure •Hyperkalemia	•Valsartan 20 mg twice daily; target dose: 160 mg twice daily	•Hypotension, hyperuricemia, hyperkalemia, worsening renal function

Secondary prevention of ischemic events

- ACE inhibitors:
  - Following MI, ACEIs lower MACE through preventing adverse cardiac remodeling
  - Strongest evidence in LVD (LVEF ≤ 40%) or HF symptoms in the early phase of ACS
  - MI and concomitant HFrEF, HTN, DM, or CKD: *Recommended* to provide ACEI
  - MI without these comorbidities: *Reasonable* to provide ACEI
  - Monitor renal function, K levels, and BP 1 - 2 weeks following drug initiation and dose adjustments
  - Angioedema and chronic cough occur infrequently with ARBs

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Aldosterone antagonists	Patients with LVEF 40% (0.40) or less and either DM or symptoms of HF treated with both an ACE inhibitor (or ARB) and β-blocker	•Elevated serum creatinine: • Men: 2.5 mg/dL or greater • Women: 2.0 mg/dL or greater •CrCl 30 mL/min or less •Serum potassium 5.0 mEq/L or greater	•Eplerenone 25 mg daily; target dose: 50 mg daily •Spironolactone 12.5-25 mg daily; target dose: 25-50 mg daily	•Hyperkalemia, worsening renal function

Secondary prevention of ischemic events

- Aldosterone receptor antagonists:
  - Following MI, ARAs lower MACE through attenuating aldosterone hemodynamic effects and adverse cardiac remodeling
  - **Spironolactone**
    - Non-specific steroid hormone receptor antagonist
    - Binds progesterone and androgen receptors
    - May cause gynecomastia, breast pain, and sexual dysfunction (impotence) in men
    - May cause menstrual irregularities in women
  - **Eplerenone**
    - Selective for the mineralocorticoid receptor (aldosterone); causing fewer adverse effects
  - Monitor K and renal function 3 days and 1 week after drug initiation or dose titration; then monthly for the first 3 months; and then every 3 months

Secondary prevention of ischemic events

Drug	Indication in ACS Patients	Contraindication/Caution	Dose (All doses are oral unless indicated)	Adverse Effects
Nitroglycerin	All patients without contraindications	•Hypotension •Avoid if recent PDE5 inhibitor use • Avanafil: within 12 hours • Sildenafil: within 24 hours • Vardenafil: within 24 hours • Tadalafil: within 48 hours	•SL: 0.3-0.4 mg every 5 minutes, up to 3 doses PRN	•Flushing, headache, hypotension, tachycardia

Chronic long-acting nitrate therapy does not reduce MACE following ACS

Its role is typically limited to the prevention of recurrent symptoms of angina

Secondary prevention of ischemic events
Duration of DAPT

- Long duration of DAPT is indicated for patients with:
  - High ischemic risk, &
  - Low bleeding risk

- Generally, ischemic risk post-ACS is high →
- DAPT (ASA + $P2Y_{12}$ inhibitor) is indicated for most patients for at least 12 months to reduce MACE
  - Regardless of the initial management strategy 'medical management or revascularization'

- Patient education about:
  - Benefits/Risks associated with DAPT therapy
  - Importance of maintaining adherence with DAPT long-term therapy

Secondary prevention of ischemic events
Duration of DAPT

- Short duration of DAPT is indicated for patients with:
  - Low ischemic risk, &
  - High bleeding risk

- Suggested DAPT durations in patients with high bleeding risk:
  - 6 months of DAPT; followed by ASA monotherapy
  - 1 - 3 months of DAPT; followed by $P2Y_{12}$ monotherapy
  - 14 days of DAPT (minimum recommended duration) for STEMI patients treated with fibrinolysis

Secondary prevention of ischemic events
Duration of DAPT: **DAPT risk score**

- Aids in making decisions regarding prolonging DAPT *beyond* 12 months
- Score range (-2 – 10)
- Higher scores indicate higher thrombotic/ischemic risk
  - A score of ≥ 2 favors prolonged DAPT
- Lower scores indicate higher bleeding risk
  - A score of < 2 favors discontinuing DAPT

Points	+2	+1	–1	–2
Clinical variables	•CHF or LVEF less than 30% (0.30) •Saphenous vein graft PCI	•Current tobacco user •DM •NSTEMI or STEMI at presentation •Prior MI or PCI •Stent diameter less than 3 mm •Paclitaxel-eluting stent	Age 65-74 years	Age ≥75 years

Secondary prevention of ischemic events
Duration of DAPT: **DAPT risk score**

- Issues with the DAPT score:
  - Not appropriate for determining DAPT duration shorter than 12 months
  - Studied only in patients who had PCI with intracoronary stenting for either ACS or SIHD
  - Studied only in patients receiving clopidogrel and prasugrel (ticagrelor was not studied)

- Continued use of DAPT with ticagrelor *beyond* 12 months after ACS can be considered:
  - In the first 12 months; use the standard dose of ticagrelor (90 mg BID)
  - Beyond 12 months; use low dose of ticagrelor (60 mg BID)
    - To reduce risk of bleeding

Evaluation of therapeutic outcomes
Short-term

- Symptoms evaluation
  - To confirm restoration of blood flow and relief of ischemia after revascularization (resolution of symptoms quickly)
- ECG evaluation
  - To confirm restoration of blood flow and relief of ischemia after revascularization (resolution of ECG changes)
- cTn evaluation
  - cTn levels may remain elevated for several days (at least 5 days) after MI
  - cTn levels should peak within 12 - 24 hours and then decline steadily once ischemia is relieved
- MACE complications (HF, arrhythmias…)
- Whether evidence-based therapies that reduce MACE have been initiated

Evaluation of therapeutic outcomes Long-term

- Functional capacity:
  - Enhancing quality of life (QoL)
  - Returning to activities of daily living (ADL)

- MACE risk reduction:
  - Control of CAD risk factors (lifestyle…)
  - Appropriate use of and adherence to medications that reduce MACE (at each healthcare encounter)

- Need for escalation or de-escalation:
  - Escalation: e.g. adding additional ACS therapies; increasing their doses
  - De-escalation: e.g. D/C $P2Y_{12}$ inhibitor after 12 months; D/C BB after 1-3 years in a post-MI patient with normal LVEF

- Adverse effects from ACS pharmacotherapy:
  - Mainly HoTN and bleeding
  - May need to D/C medication until the symptoms have resolved
  - Clinical signs of bleeding: bloody stools, melena, hematuria, hematemesis, bruising, oozing from puncture sites

Evaluation of therapeutic outcomes
Medication adherence/counseling

- Assess:
  - Health literacy level
  - Barriers to adherence
  - Access to medications
  - Understanding of instructions

- Provide written and verbal instructions about:
  - Purpose of each medication
  - Changes to previous medication regimen
  - Optimal time to take each medication
  - New allergies or medication intolerances
  - Need for a timely prescription fill after discharge
  - Anticipated duration of therapy
  - Consequences of nonadherence
  - Common/serious adverse reactions that may develop
  - Drug-drug and drug-food interactions

Target both patients and family caregivers

Schedule follow-up within 1 - 2 weeks after discharge

Therapeutic Drug Monitoring of Pharmacotherapy for ACS

Drug	Adverse Effects	Monitoring
Fibrinolytics	Bleeding (ICH)	Clinical signs of bleeding[a]; baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily; mental status every 2 hours for signs of ICH
Aspirin	Dyspepsia, GI bleeding	Clinical signs of bleeding[a]; GI upset; Hgb, Hct, and platelet count at baseline & every 6 months
$P2Y_{12}$ inhibitors	Bleeding, rash	Clinical signs of bleeding[a]; evidence of rash; Hgb, Hct, platelet count at baseline and every 6 months
	Ticagrelor: dyspnea, ventricular pauses, bradycardia	Ticagrelor: dyspnea, heart rate, telemetry during hospitalization
Glycoprotein IIb/IIIa inhibitors	Bleeding, thrombocytopenia (can be profound with abciximab)	Clinical signs of bleeding[a]; Hgb, Hct, and platelet count at baseline, 2 hours, then daily
		Eptifibatide and tirofiban: serum creatinine at baseline then daily
Anticoagulants	Bleeding	Clinical signs of bleeding[a]; baseline aPTT, INR; Hgb, Hct, platelet count at baseline then daily
	Unfractionated heparin and LMWH: heparin-induced thrombocytopenia	Unfractionated heparin: aPTT every 6 hours until two consecutive aPTT values are at goal, then every 24 hours; ACT during PCI
		Enoxaparin, bivalirudin, and fondaparinux: serum creatinine at baseline then daily
		Enoxaparin: may consider steady-state anti-Xa levels in special populations
β-Blockers	Hypotension, heart failure, bradycardia, cardiogenic shock, AV block, exacerbation of asthma or reactive airway disease	Continuous telemetry (while hospitalized); blood pressure, heart rate, signs and symptoms of heart failure; monitor every 5 minutes before each IV bolus dose; monitor every shift while hospitalized then at each healthcare encounter after discharge
Nitroglycerin	Flushing, headache, hypotension, tachycardia	Blood pressure and heart rate; monitor every 5-15 minutes following dosage adjustment of intravenous nitroglycerin then every 1-2 hours; monitor every 5 minutes following administration of short-acting nitroglycerin
Morphine	Hypotension, respiratory depression, sedation, hypersensitivity	Blood pressure, heart rate, respiratory rate, sedation level 5 minutes after administration then every 1-2 hours for 4 hours after the last dose
Calcium channel blockers	Hypotension	Blood pressure, heart rate, every shift while hospitalized then at each healthcare encounter after discharge
	Verapamil and diltiazem: heart failure, cardiogenic shock, bradycardia, AV block	Verapamil and diltiazem: continuous telemetry (while hospitalized); signs and symptoms of heart failure every shift while hospitalized then at each healthcare encounter after discharge
Statins	GI discomfort, arthralgia, myalgia, musculoskeletal pain, hepatotoxicity	Liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatotoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
Nonstatin therapies	Ezetimibe and combination: GI discomfort, arthralgia, myalgia, musculoskeletal pain	Simvastatin/ezetimibe: liver function tests at baseline (prior to discharge) and if signs or symptoms of hepatoxicity develop; creatinine kinase if severe myalgia or musculoskeletal symptoms occur; LDL-C at baseline, 4-12 weeks after initiation or dose adjustment, then every 3-12 months
	PCSK9 inhibitors: injection site pain, hypersensitivity, nasopharyngitis	PCSK9 inhibitors: LDL-C at baseline and 4-8 weeks after initiation or dose adjustment; evaluation of injection site if injection site pain develops, signs and symptoms of hypersensitivity with each healthcare encounter
ACE inhibitors	Hypotension, hyperuricemia, hyperkalemia, worsening renal function, chronic cough, angioedema	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months; signs and symptoms of angioedema or cough with each healthcare encounter
ARBs	Hypotension, hyperuricemia, hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, 1-2 weeks after initiation, then every 6-12 months
Aldosterone antagonist	Hyperkalemia, worsening renal function	Blood pressure every shift while hospitalized, 1-2 weeks after initiation or dose adjustment, then with each healthcare encounter; serum creatinine and potassium at baseline, after initiation or dose adjustment: at 3 days, 1 week, monthly for 3 months, then every 3 months