Acute Coronary Syndromes (ACS)

Pharmacotherapeutics I

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ACS Objectives

- Determine diagnosis of UA, NSTEMI, or STEMI based on EKG changes and biomarker results
- Describe INITIAL treatments given to patients with prolonged chest pain indicative of ACS
- Determine which medications a patient should receive for early conservative therapy vs invasive strategy
- Compare and contrast P2Y12 inhibitors

ACS Objectives

- Identify appropriate oral antiplatelet regimens and doses
- Recognize situations when fibrinolytic therapy would be preferred over PCI and vice-versa
- List contraindications to fibrinolytic therapy
- Describe “other early therapies” given to patients with ACS, including routes of administration and when they should be administered

Epidemiology

Most common cause of CV death

Chest discomfort is the most common reason for E.D. visit ~ 7 million/year

STEMI – 7% death rate with fibrinolytics

NSTEMI - ~ 5% mortality in hospital

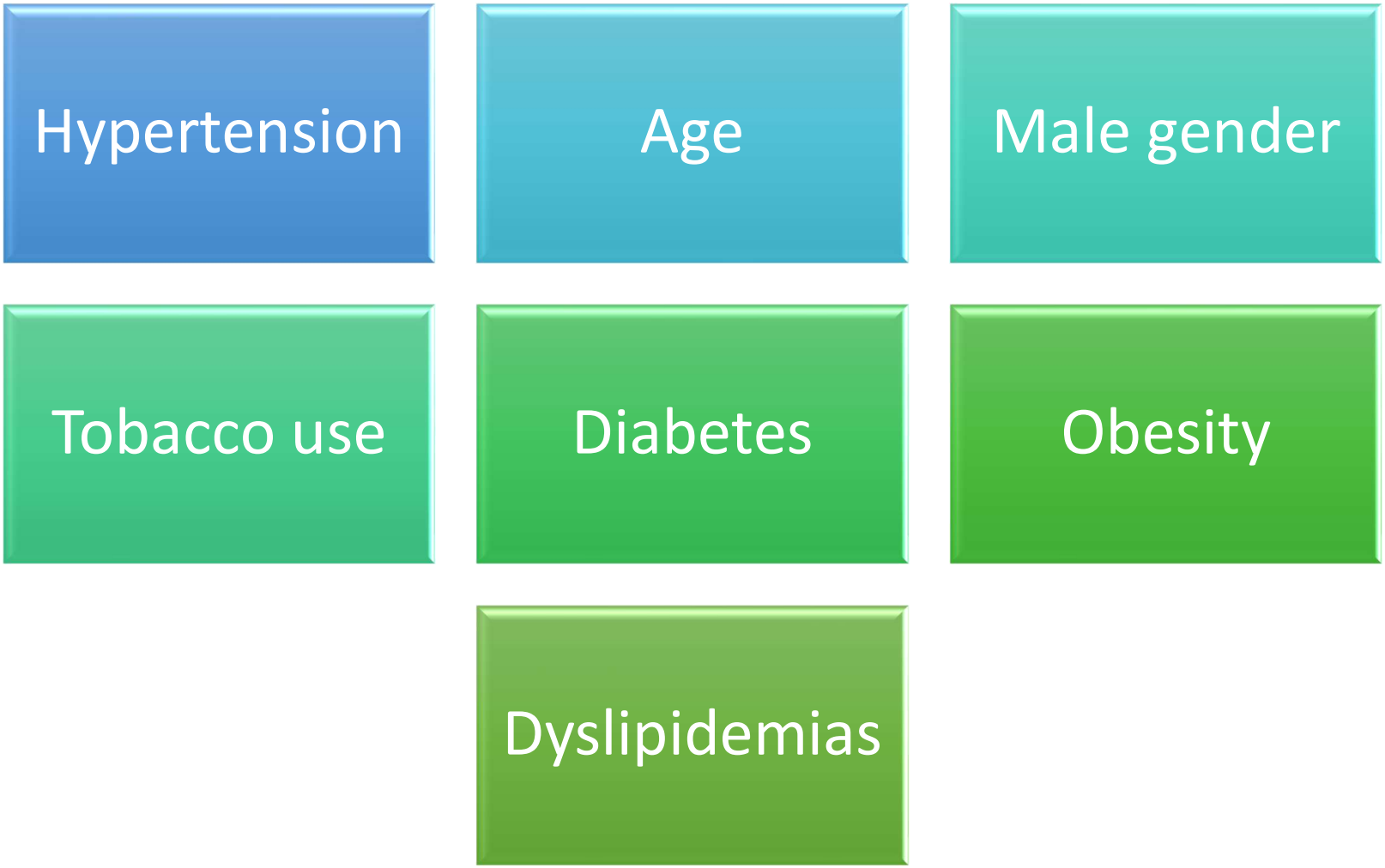
In hospital and 1 year mortality higher for women and elderly

~ 30% of patients develop HF in hospital

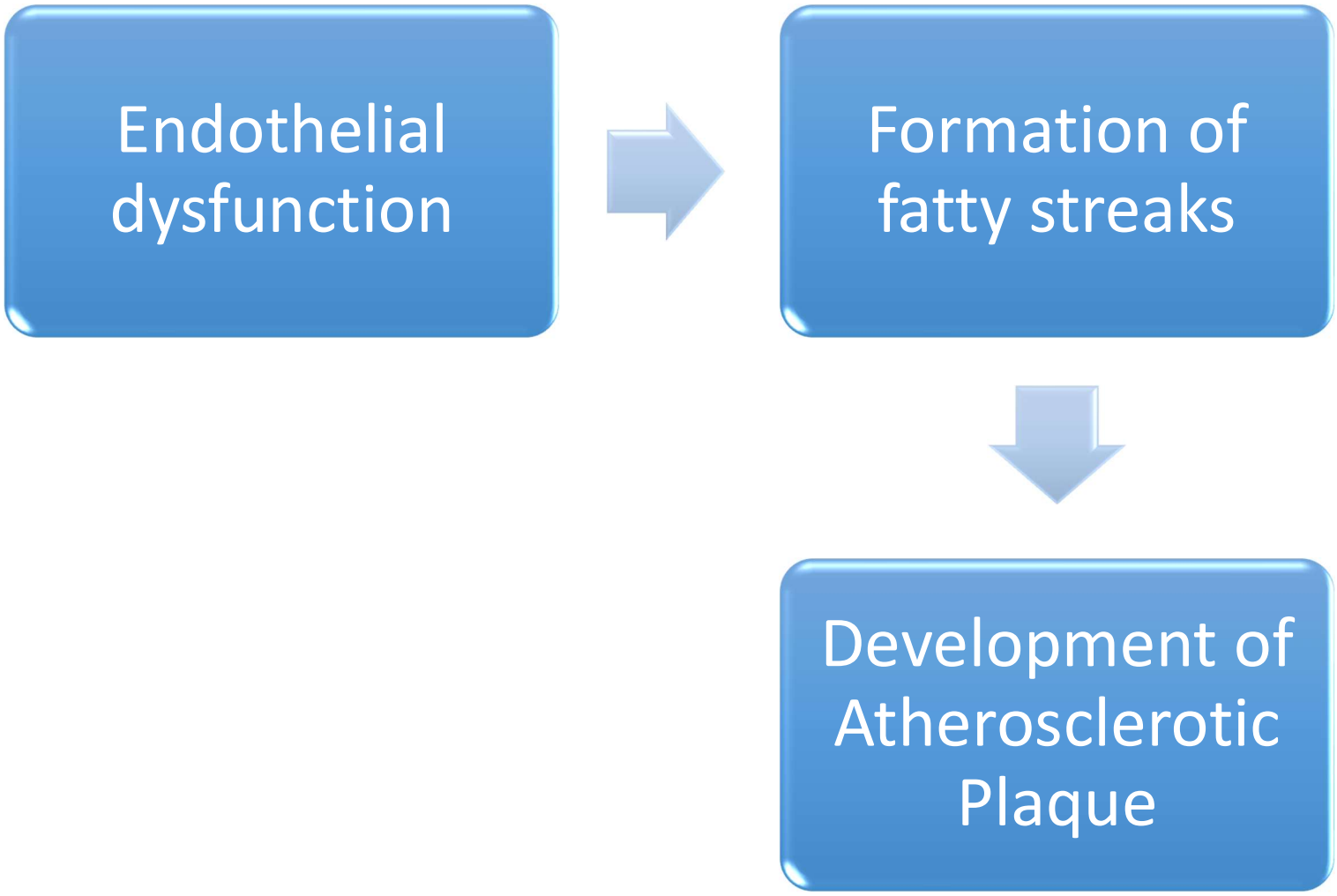
Etiology

- Atherosclerosis
- Cholesterol excess
- Inflammation plays key role
- Endothelial dysfunction

Risk Factors



Etiology



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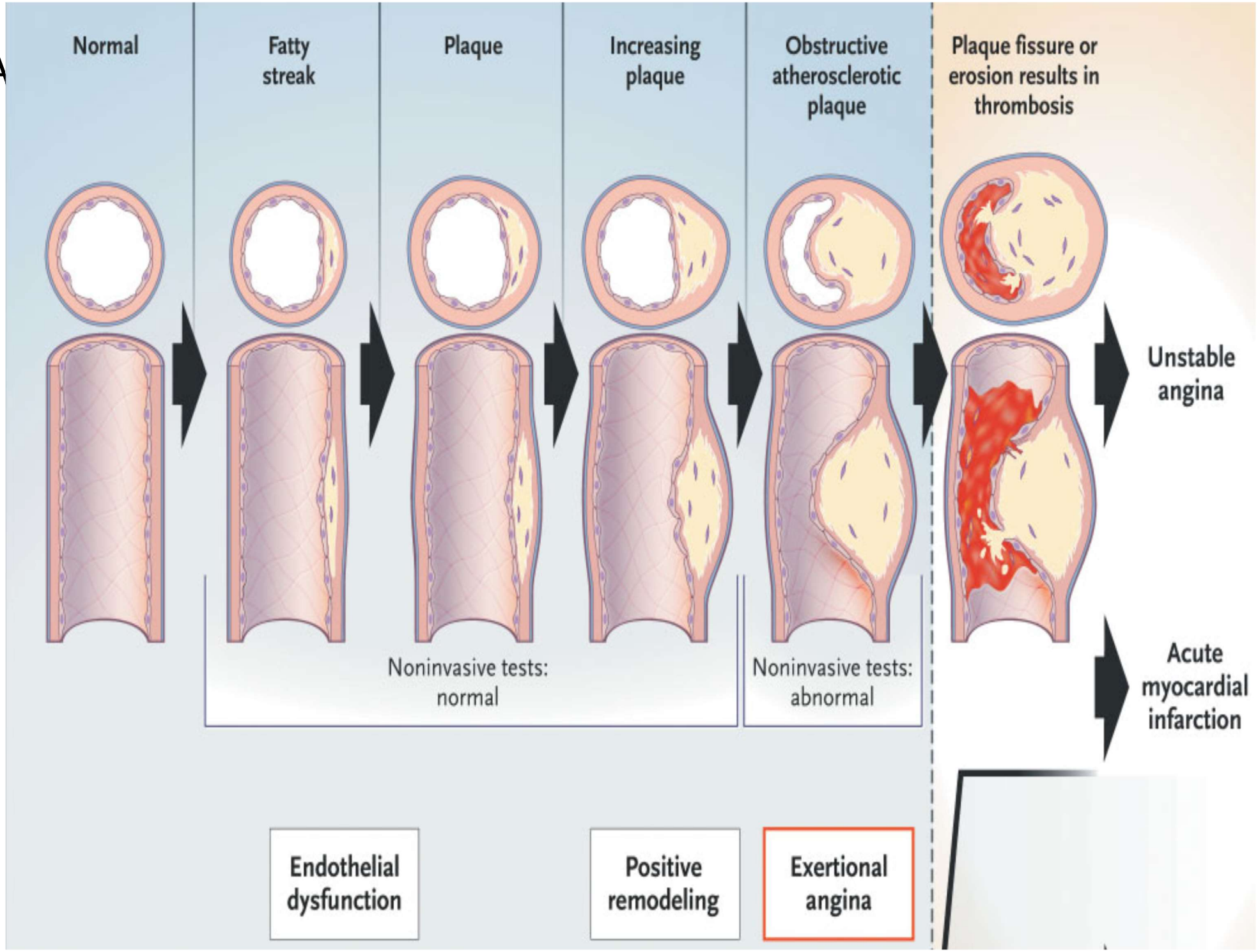
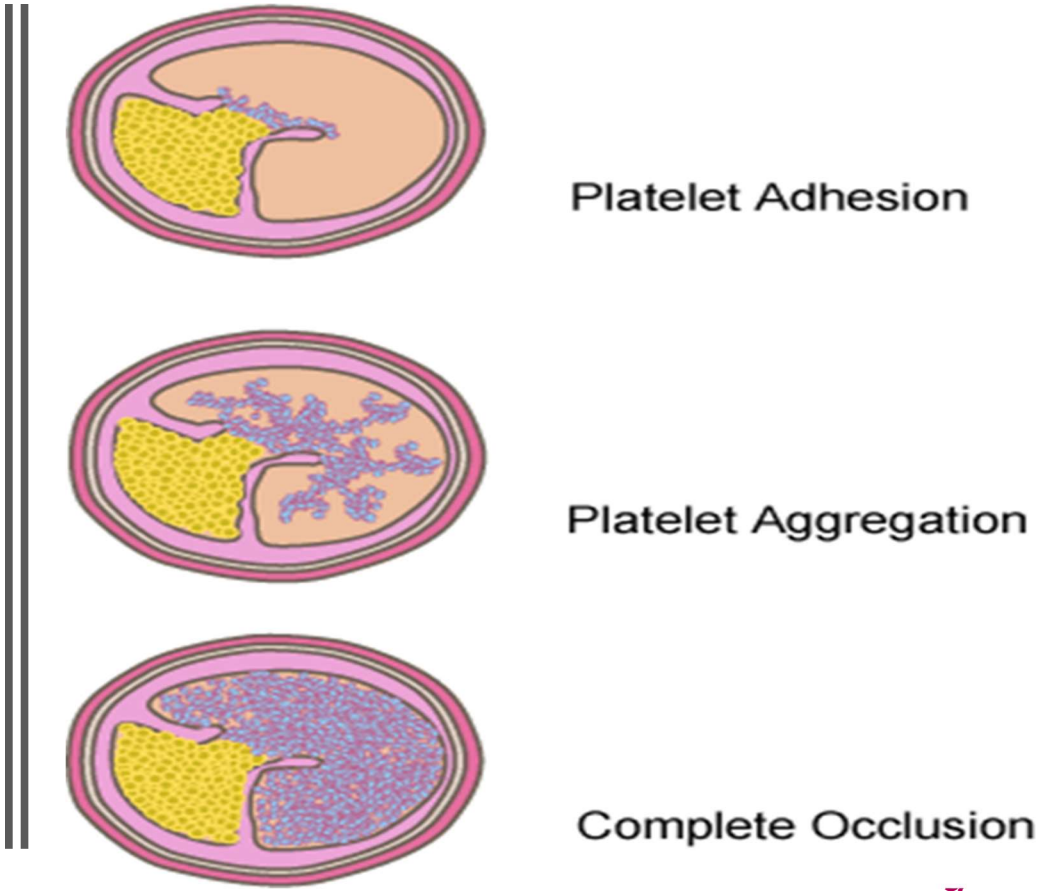
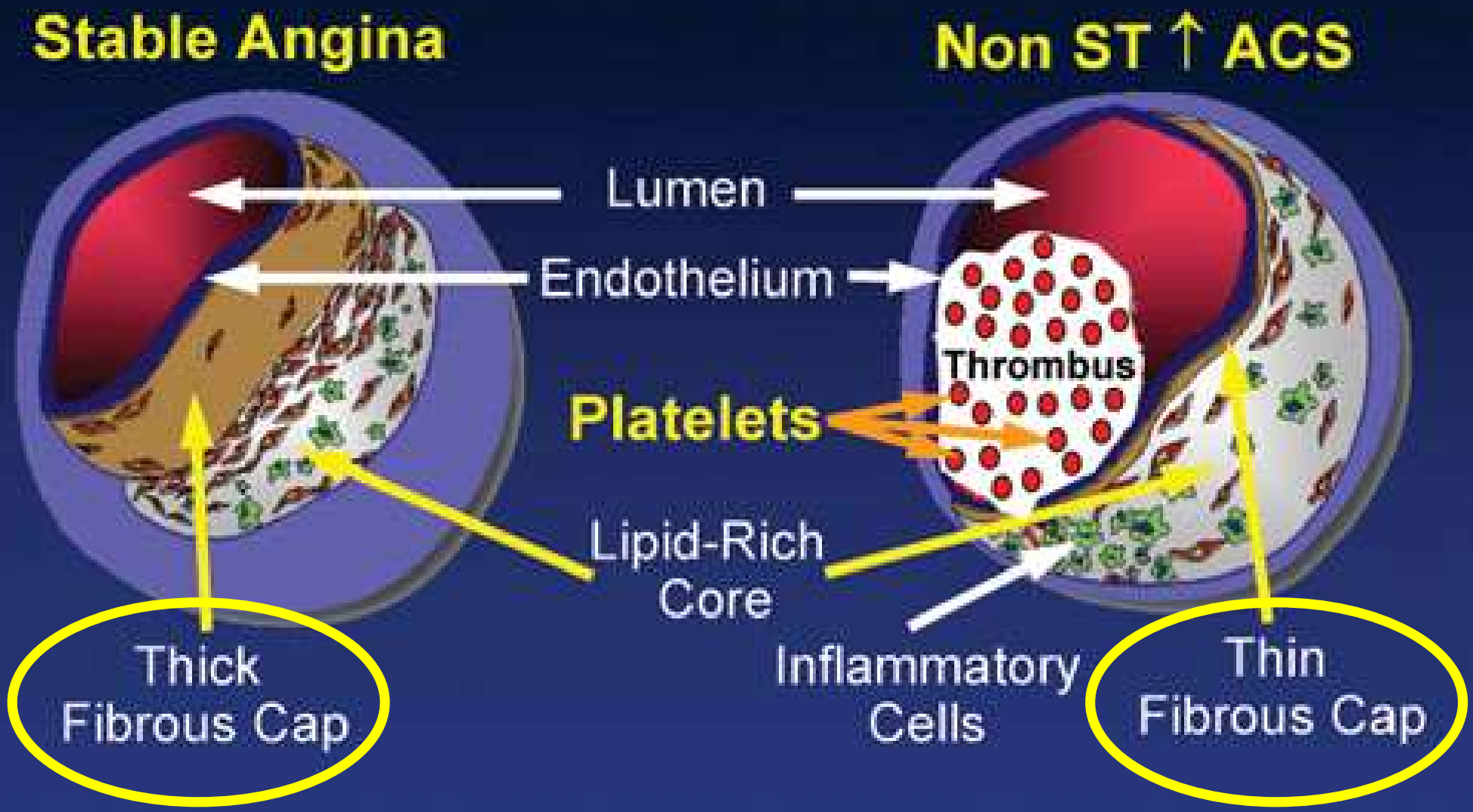


Etiology

Rupture
↓
Plt Adherence
↓
Plt Activation
↓
Plt Aggregation
↓
Activation of the clotting cascade

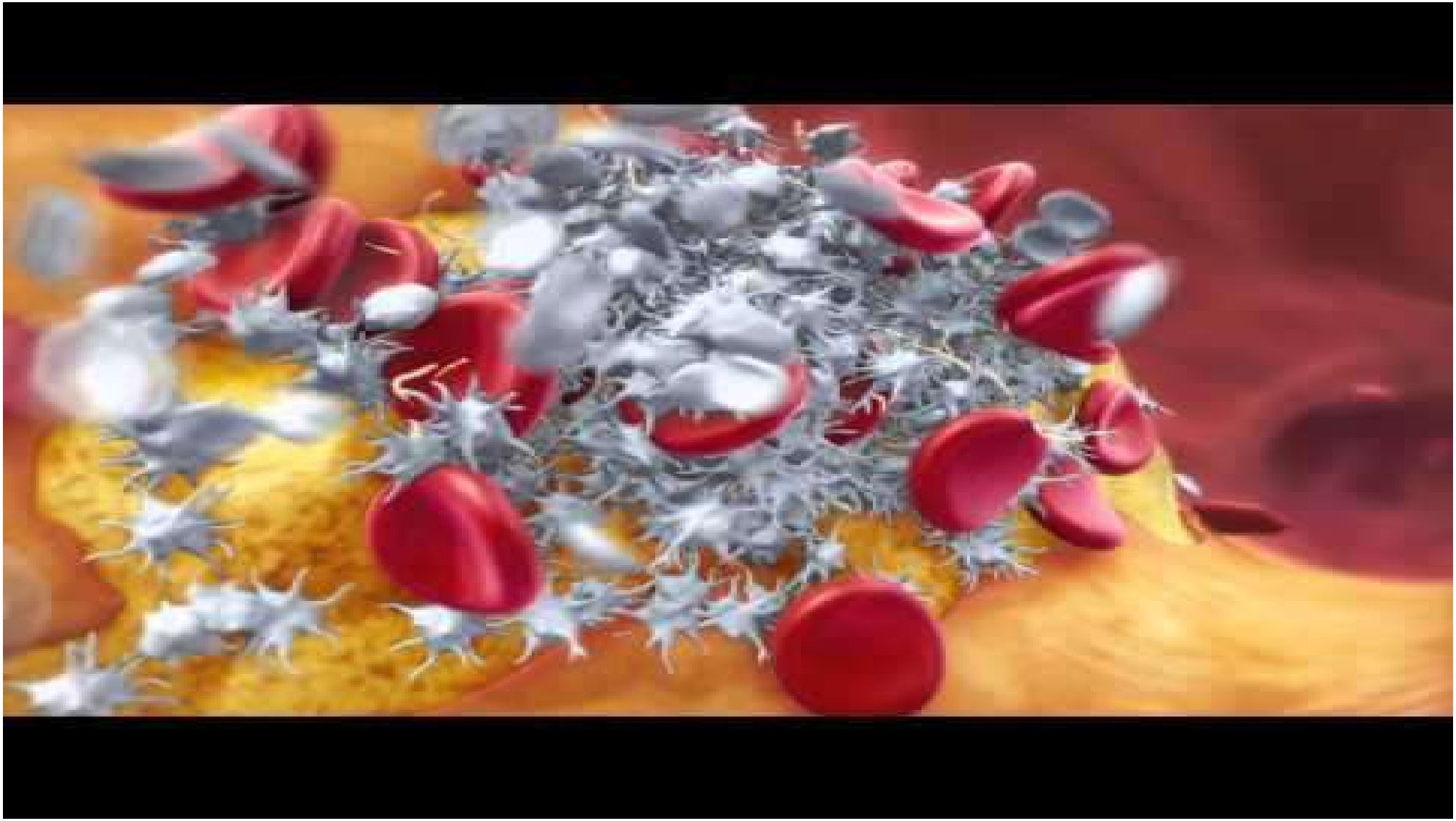


Types of Atherothrombotic Lesions Causing Coronary Artery Disease



MI = myocardial infarction.

Adapted with permission from Falk E, et al. *Circulation*. 1995;92:657-671.



Comparing White & Red Clots

White Clot

- Contains more platelets than fibrin
- Generally causes incomplete occlusion of coronary lumen
- More common in NSTEMI

Red Clot

- Contains more fibrin and red blood cells (RBCs) and smaller # plts compared to the “white clot”
- Generally completely occludes the vessel
- Most commonly STEMI

Acute Coronary Syndromes

Unstable Angina (UA)

Myocardial Infarction

- Non-ST segment elevation Myocardial Infarction (NSTEMI)
- ST segment elevation MI (STEMI)

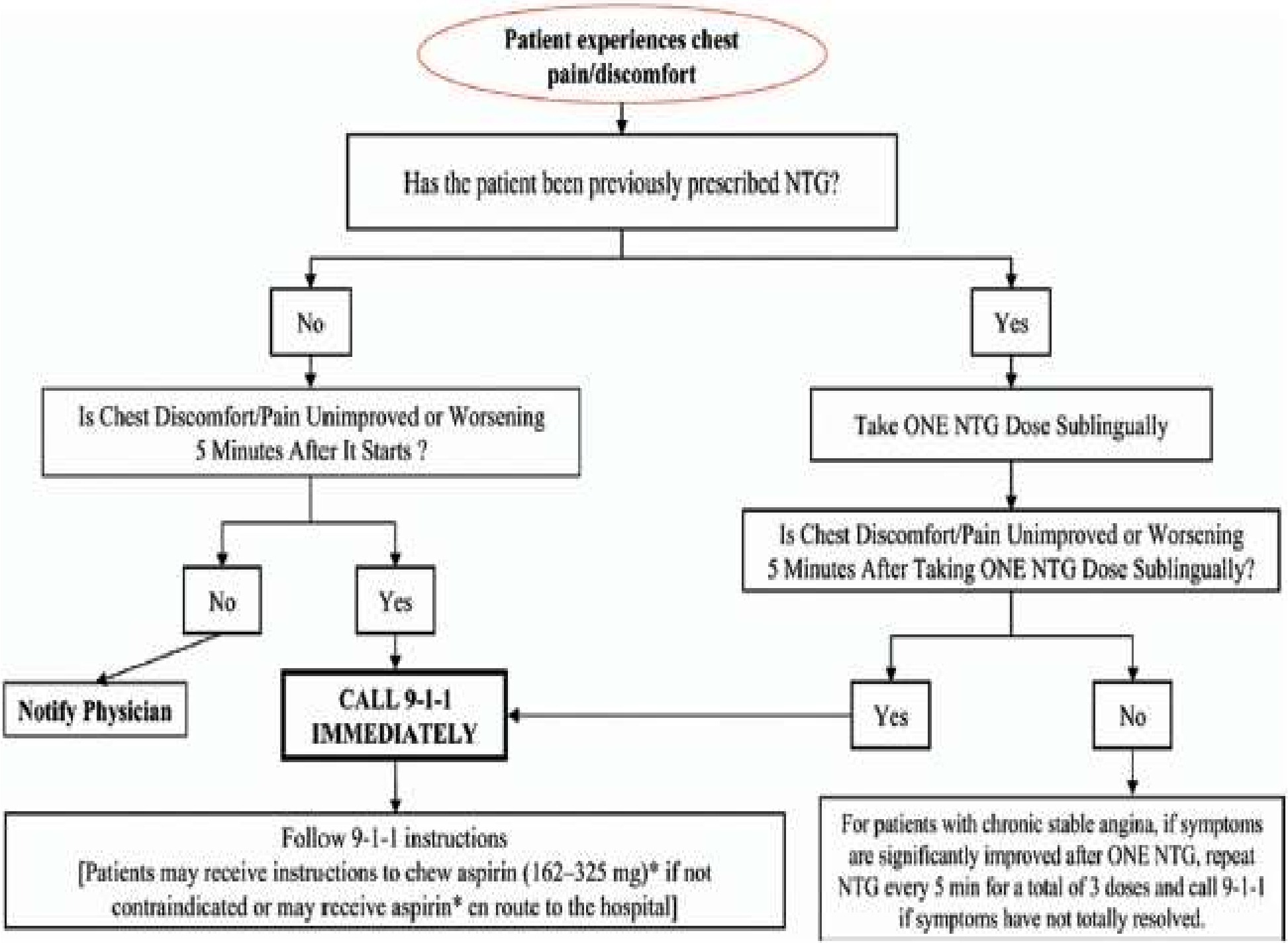
Patient Presentation

Midline, anterior chest discomfort described as crushing, burning, or a heavy pressure

- At rest
- Severe new onset
- Increasing angina at least 20 min in duration

Pain may radiate to shoulder, down left arm, to the back, or to the jaw

N/V, diaphoresis, SOB may accompany the chest pain



Diagnosis

Clinical presentation

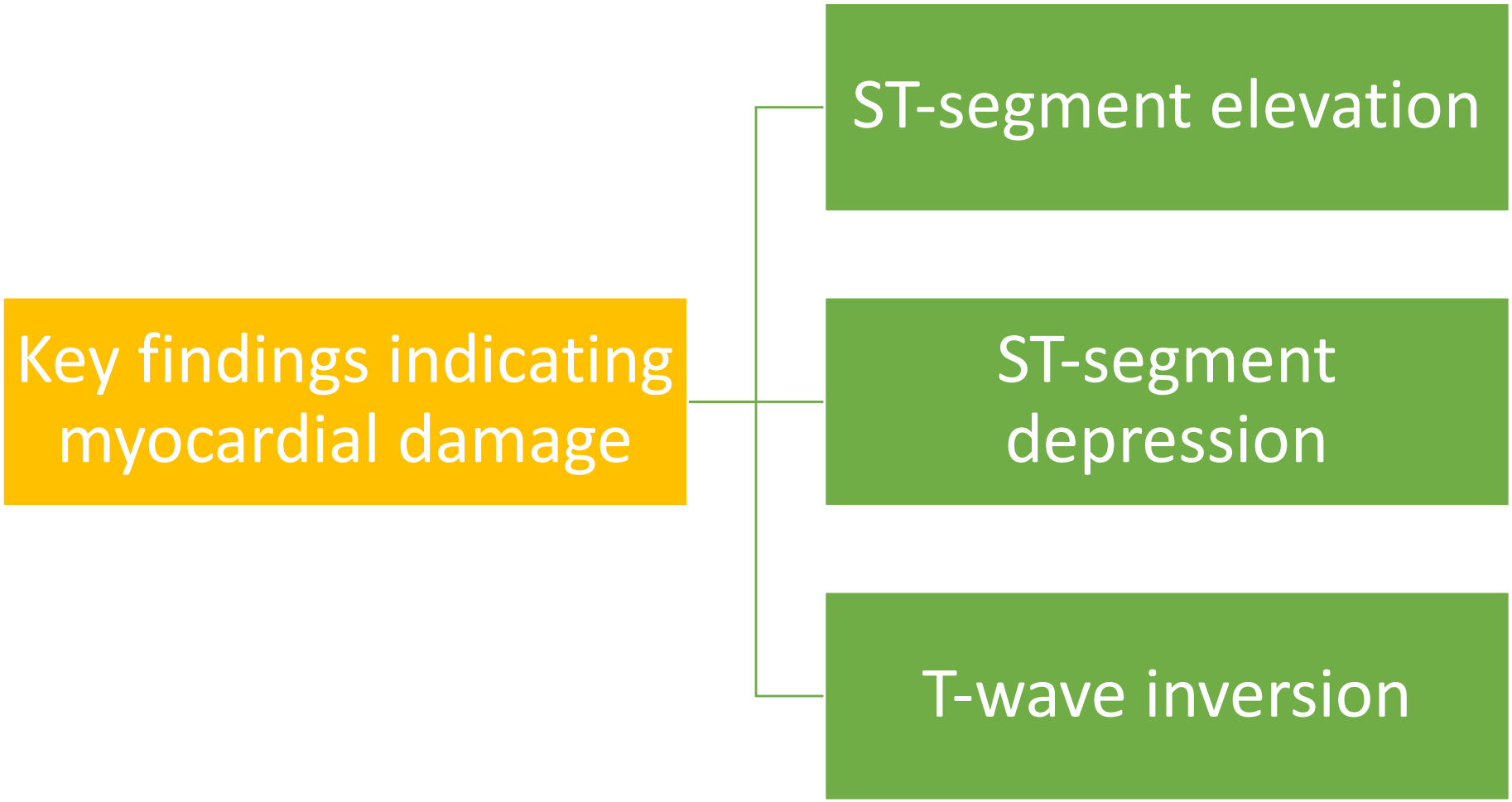
- **Unstable Angina**
  - 10 - 20 minutes
  - may or may not be relieved by NTG
- **Myocardial Infarction**
  - > 30 minutes
  - unrelieved by rest or NTG

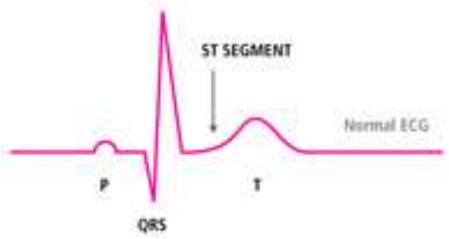
EKG

- ST elevation or depression, T wave changes

Cardiac biomarkers

ECG

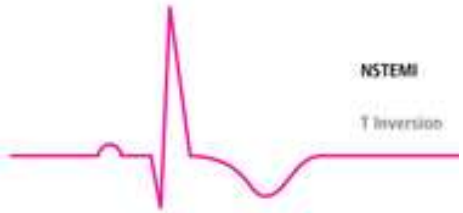




NORMAL EKG

STEMI

NSTEMI



NSTEMI

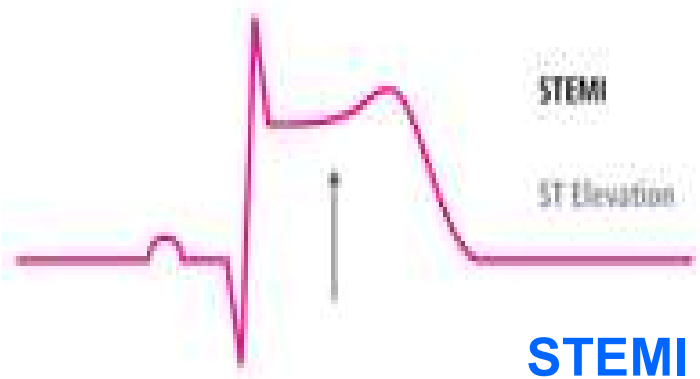
EKG Variances in ACS

Chest Discomfort ≥ 20 min

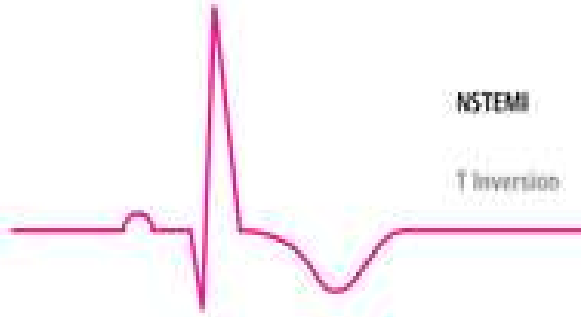
EKG:Obtain & interpret within 10 min (Ambulance; Emergency Dept)

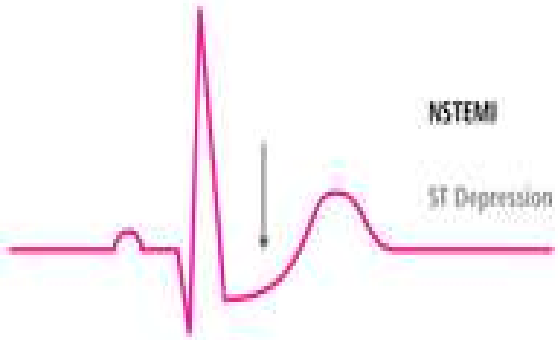
ST-segment Elevation

No ST-segment Elevation



STEMI





Comparison of ACSs

	Unstable Angina	NSTE ACS	STE ACS
Symptoms present	+	+	+
ECG changes	None	ST segment depression, T wave inversion, or no changes	ST segment elevation
Biochemical marker	No changes	Increased troponins & CK MB	Increased troponins & CK MB

Adapted from DiPiro, Acute Coronary Syndromes

UA versus NSTEMI

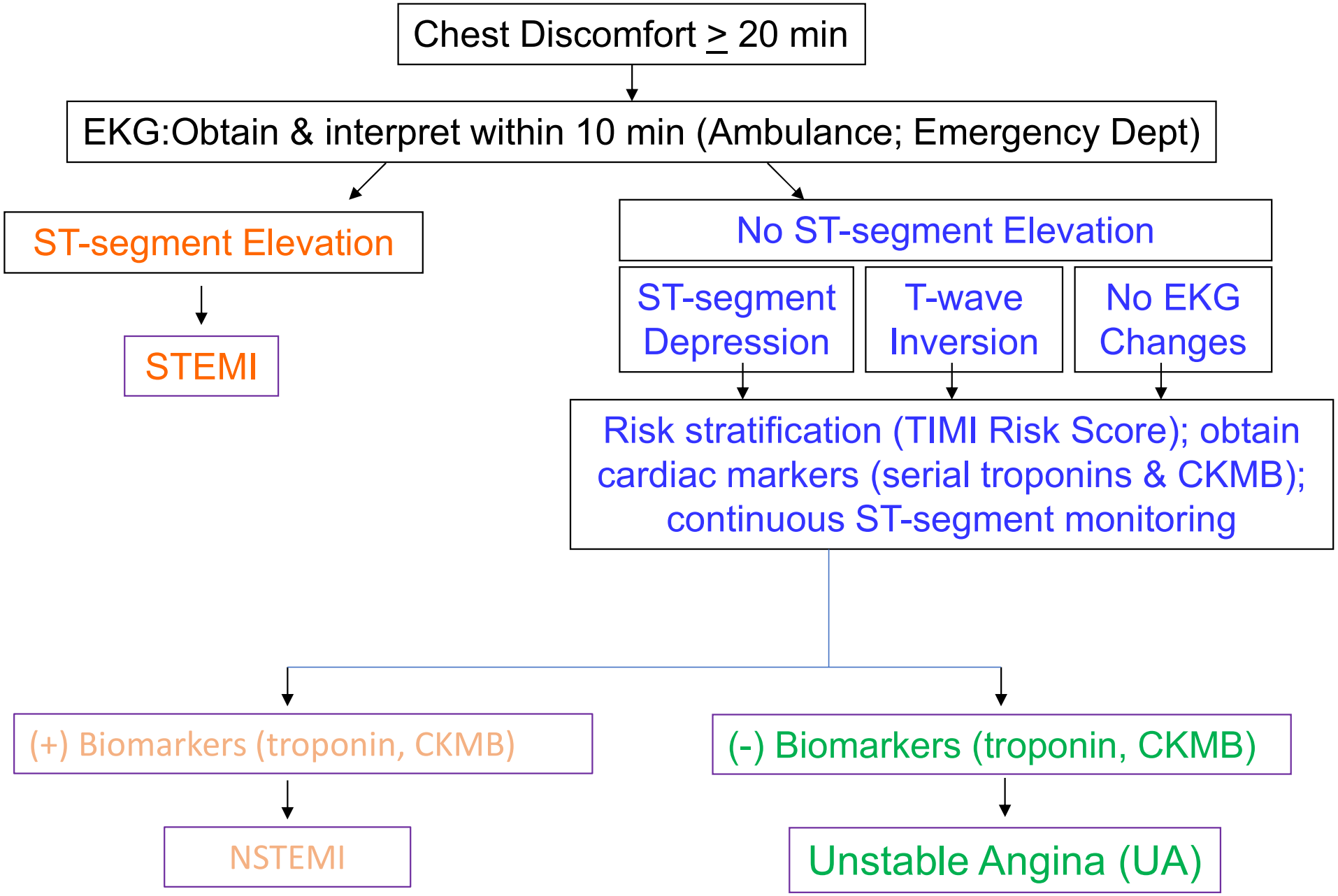
Difficult to differentiate NSTEMI from UA early in hospital presentation

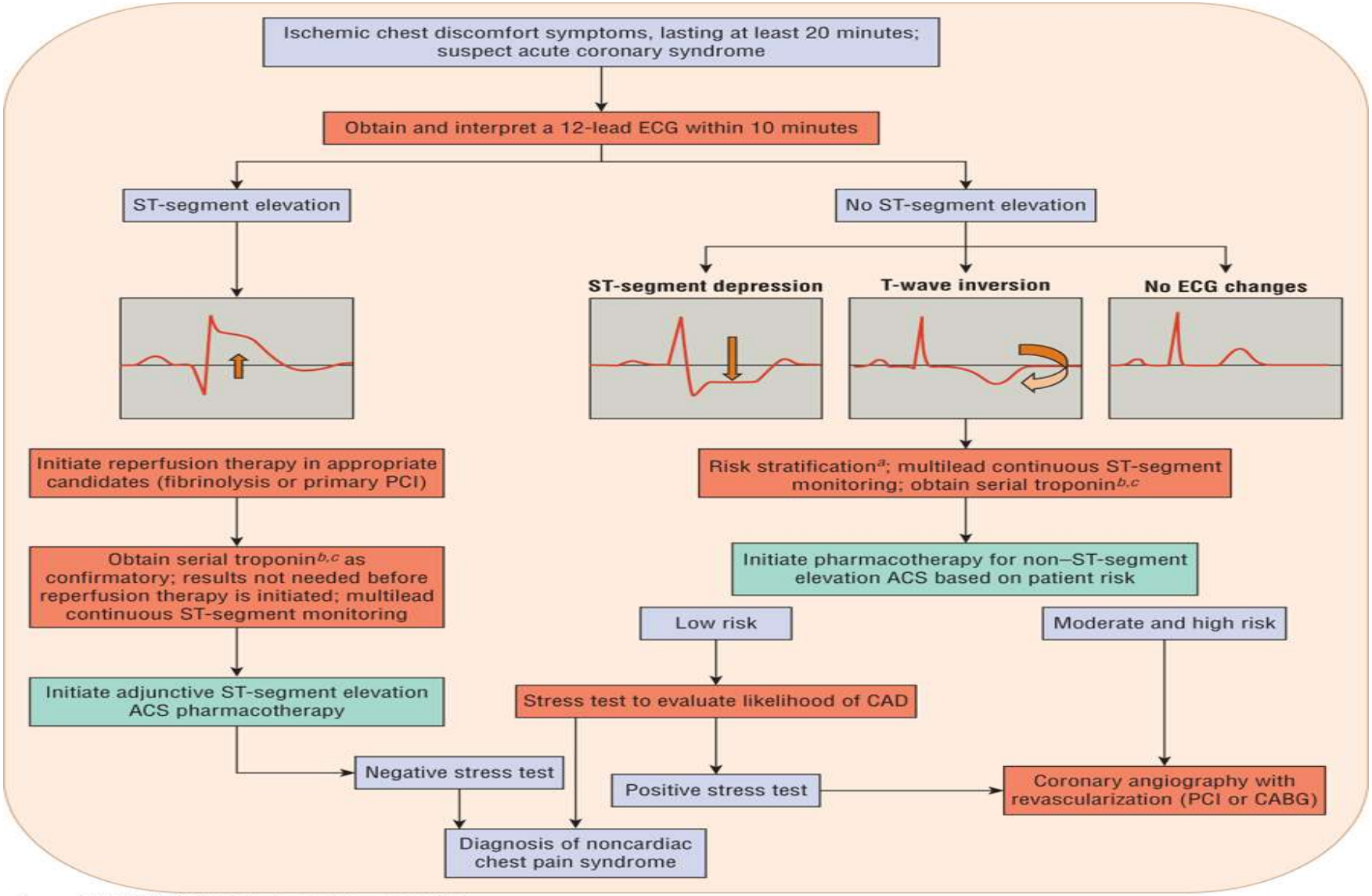
Very similar in terms of clinical symptoms & pathophysiology

Overall risk is higher in patients w/ NSTEMI than in those w/ UA; more favorable prognosis with UA

Cardiac biomarkers may be useful

- UA: normal troponin or CK MB
- NSTEMI: ↑ troponin, ↑ CK MB





Evaluation of the acute coronary syndrome patient. [a]As described in Table 17-1. [b]"Positive": Above the myocardial infarction decision limit. [c]"Negative": Below the myocardial infarction decision limit. (ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; PCI, percutaneous coronary intervention.) (Used with permission from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson MM, Chant C, Cheng JWM, et al., eds. Pharmacotherapy Self-Assessment Program. Book 1: Cardiology, 7th ed. Lenexa, KS: American College of Clinical Pharmacy, 2010.)

Cardiac Biomarkers
Creatine Kinase Myocardial Bands (CK-MB)

40% of the creatine kinase present in myocardial tissue

Peaks roughly same time as troponin, but returns to normal/baseline more quickly

- Not helpful for late diagnosis of acute MI (if patient waits a long time to seek medical attention)
- If levels rise again after declining, may suggest infarct extension

Cardiac Biomarkers
Troponin I (or T)

Components of contractile apparatus of myocardial cells and expressed almost exclusively in the heart

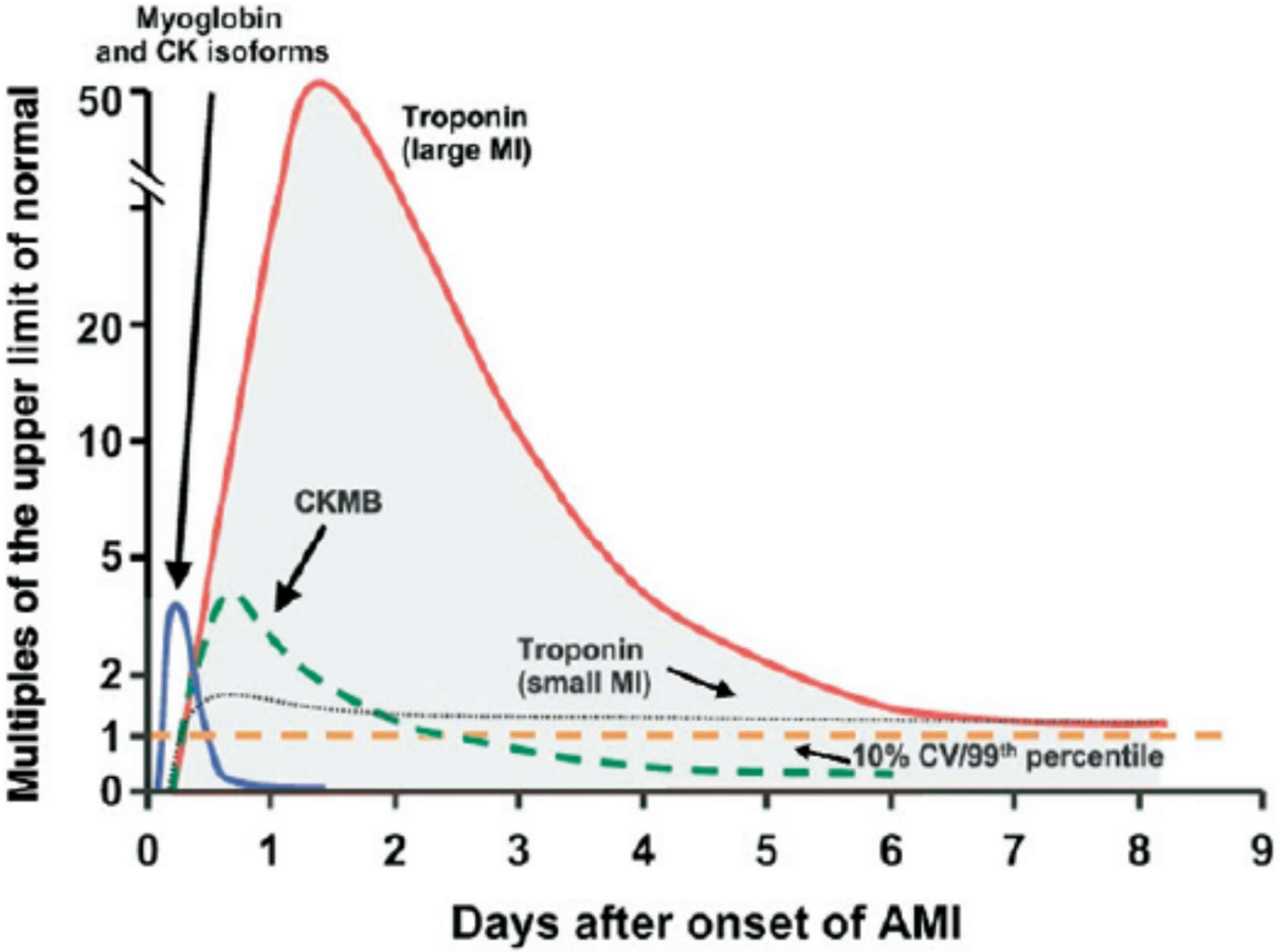
Reflect injury leading to necrosis

High myocardial tissue sensitivity & high clinical sensitivity

(+) = value exceeding 99th percentile of normal reference population (upper reference limit, URL)

Drawn on first assessment and repeat in 3-6 hrs

For diagnosis, need to have a rise and/or fall with at least one (+) value



Goals of Treatment

Restore
- Restore blood flow to the infarct-related area to prevent infarct expansion (MI) or complete occlusion and MI (UA)

Prevent
- Prevent death and other MI complications
  - Cardiogenic shock, LV/RV failure, Arrhythmias, Pericarditis, Valvular dysfunction

Prevent
- Prevent coronary artery re-occlusion w/ re-infarction

Relieve
- Relieve ischemic chest discomfort

Resolve
- Resolve ST-segment and T-wave changes on EKG

Early Treatment "MONA plus B" or "MONA-B" Acronym, not in this order

Morphine	Oxygen	Nitroglycerin
Aspirin	plus	B- Beta blocker

Early Management

Morphine

- Pain relief, Symptoms not relieved after 3 doses of SL NTG
- 1-5 mg IV q 5-30 min prn for unrelieved chest pain despite nitroglycerin/maximally tolerated anti-ischemic medications (or if symptoms recur)
- Causes vasodilation, Reduces cardiac oxygen demand, Relieve anxiety
- Contraindications:
  - Hypotension
  - Respiratory depression
  - Confusion

Early Management

Oxygen

- For oxygen saturation (O2 sat) < 90%
- OR
- Respiratory distress
- OR
- High risk features for hypoxemia

Nitroglycerin

0.4 mg SL tab (or spray) x 3 doses to relieve acute CP

- If pain unrelieved after ONE dose, CALL 911

Contraindications:

- Within 24 hours of sildenafil or vardenafil use; 48 hours of tadalafil use
- SBP < 90 mmHg or > 30 mmHg below baseline, marked bradycardia or tachycardia, right ventricular infarction

Candidates for IV NTG

If chest pain persists after 3 doses of SL NTG, IV may be indicated for 24 hours after relief of ischemia

Persistent ischemia

Heart failure symptoms

Hypertension

Dose: 5-10 mcg/min IV infusion (max rate 200 mcg/min)

- Titrate to effect or limiting side-effects (headache)
- Watch SBP!

Aspirin

The preferred antiplatelet agent in the treatment of choice in all subsets of ACS

Chew and swallow NON-Enteric coated aspirin 162-325 mg x 1 dose

- May give 4 x 81 mg chewable tablets (324 mg)

Reduces the incidence of recurrent MI and death

If ALLERGY or considerable GI intolerance, give clopidogrel instead

The most frequent side effects of aspirin are dyspepsia and nausea

counseled about the risk of bleeding, especially GI bleeding

Beta Blocker

Oral BB preferred: Metoprolol 25-50mg PO BID, up titrated as tolerated

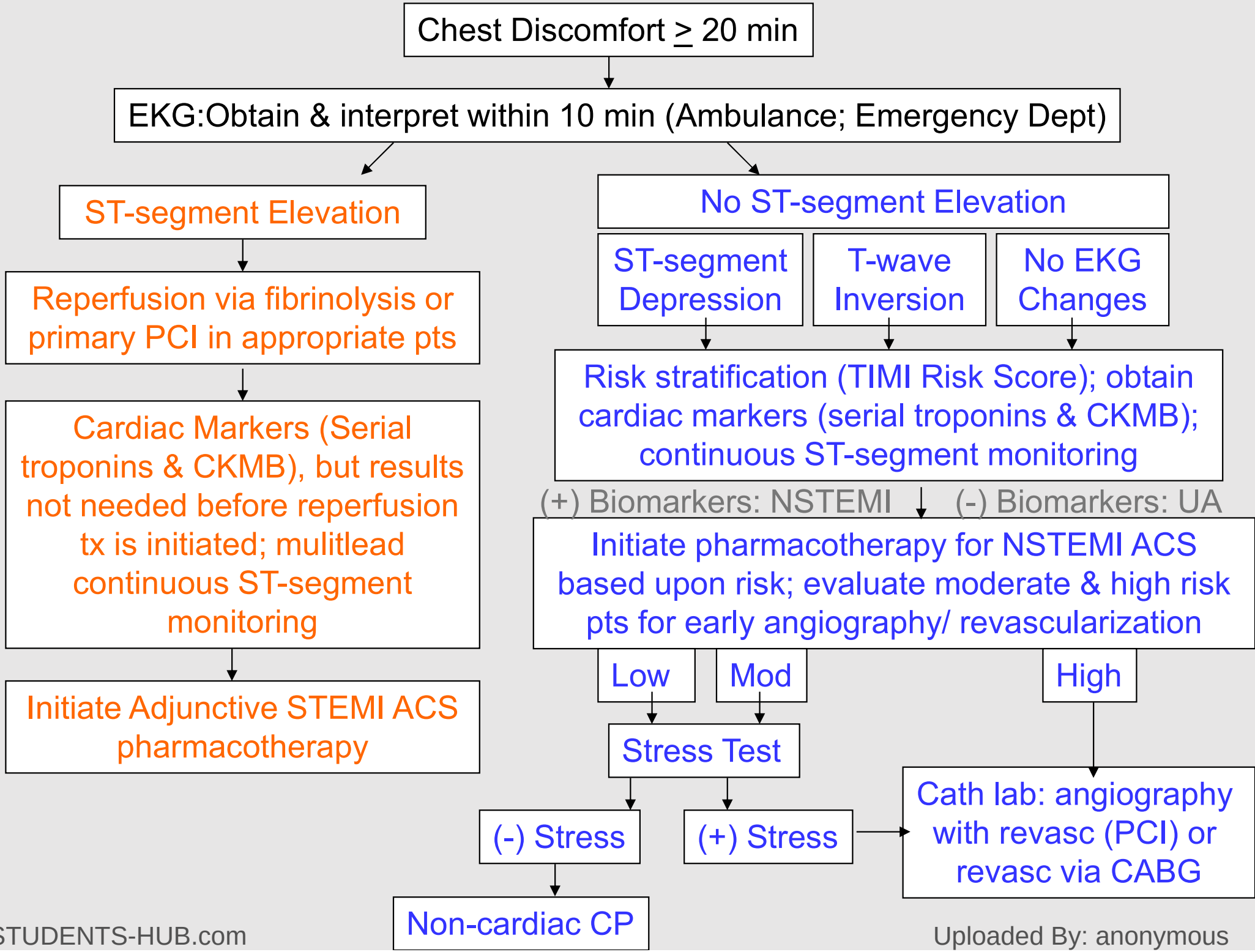
IV route reasonable if hypertensive or ongoing ischemia (otherwise can increase risk of shock): Metoprolol 5 mg IV q 5 min x 3 doses; titrate to HR and BP

β1-Blockade ↓ (HR), ↓myocardial contractility, ↓(BP) →decreasing myocardial oxygen demand

↓ myocardial ischemia, reinfarction, & frequency of complex ventricular dysrhythmias

Contraindications: HYPOtension, low output state, signs of HF, risk factors for cardiogenic shock, plus other CI (AV block, bradycardia, etc)

NSTEMI / UA



Treatment of NSTE-ACS

Two categories of NSTE-ACS:

Non-ST elevation myocardial infarction (NSTE ACS)	Unstable angina (UA)

Treatment of each is largely the same

Treatment of NSTE-ACS

1

Step 1 – Early Treatment

2

Step 2 – Decide on a Strategy

- Early Invasive
- Early Conservative

NSTEMI: TIMI Risk Score
Helps predict risk of death or MI within 14 days

TIMI Risk Score: Non-ST-elevation ACS	
Past Medical History	**Clinical Presentation**
Age ≥65 years	ST-segment depression (≥0.5 mm)
≥3 risk factors for CAD: Hypercholesterolemia HTN DM Smoking Family history of premature CHD	≥2 episodes of chest discomfort within the past 24 hours
	Positive biochemical marker for infarction
Known CAD (≥50% stenosis of coronary artery)	**One point for each section**
Use of aspirin within the past 7 days	

Using the TIMI Risk Score		
Assign one point for each of seven findings, then calculate the total risk score		
High Risk	**Medium Risk**	**Low Risk**
5-7 points	3-4 points	0-2 points

Invasive vs. Conservative Strategy

Generally Preferred Strategy	Patient Characteristics
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Elevated cardiac biomarkers (TnT or TnI) New or presumably new ST-segment depression Signs or symptoms of HF or new or worsening mitral regurgitation High-risk findings from noninvasive testing Hemodynamic instability Sustained ventricular tachycardia PCI within 6 mo Prior CABG High-risk score (eg, TIMI, GRACE) Mild to moderate renal dysfunction Diabetes mellitus Reduced LV function (LVEF $<$40%)
Conservative	Low-risk score (eg, TIMI, GRACE) Patient or physician preference in the absence of high-risk features

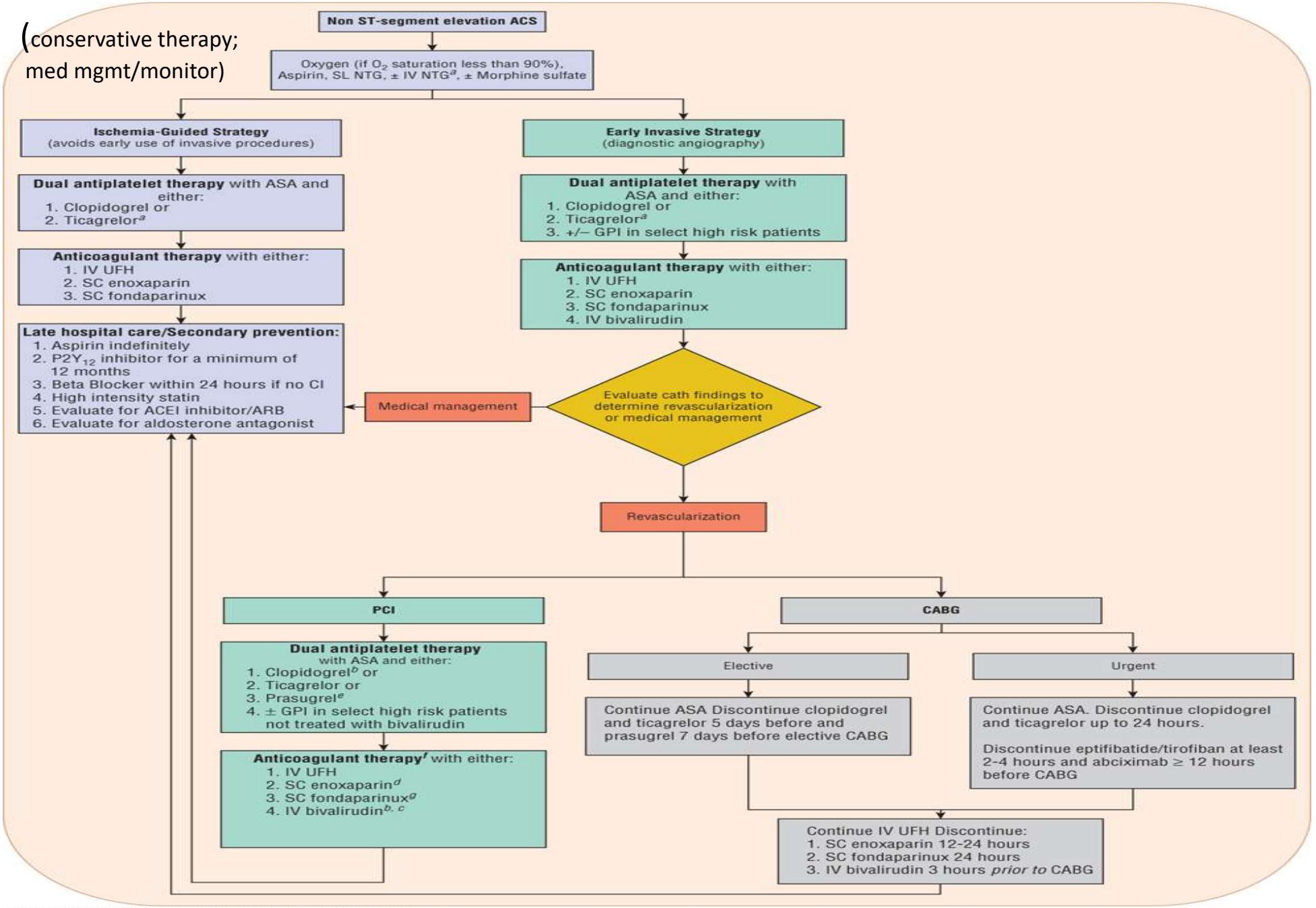
NSTEMI/UA Management

Critically unstable patients

- Urgent cardiac catheterization
- Transfer to facility with catheterization
  - If catheterization unavailable

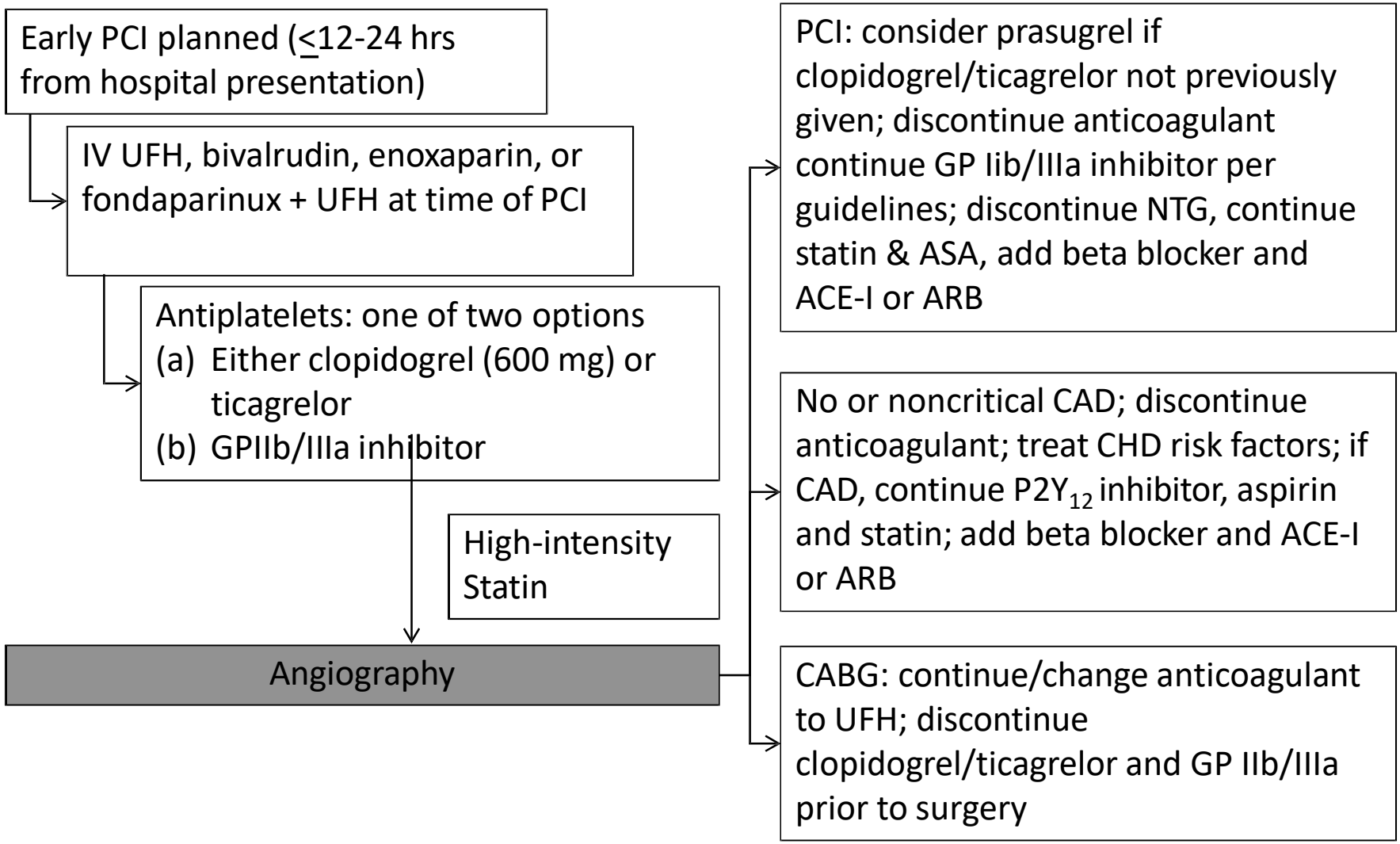
Fibrinolytics are **NOT** used for UA or NSTEMI

(conservative therapy; med mgmt/monitor)

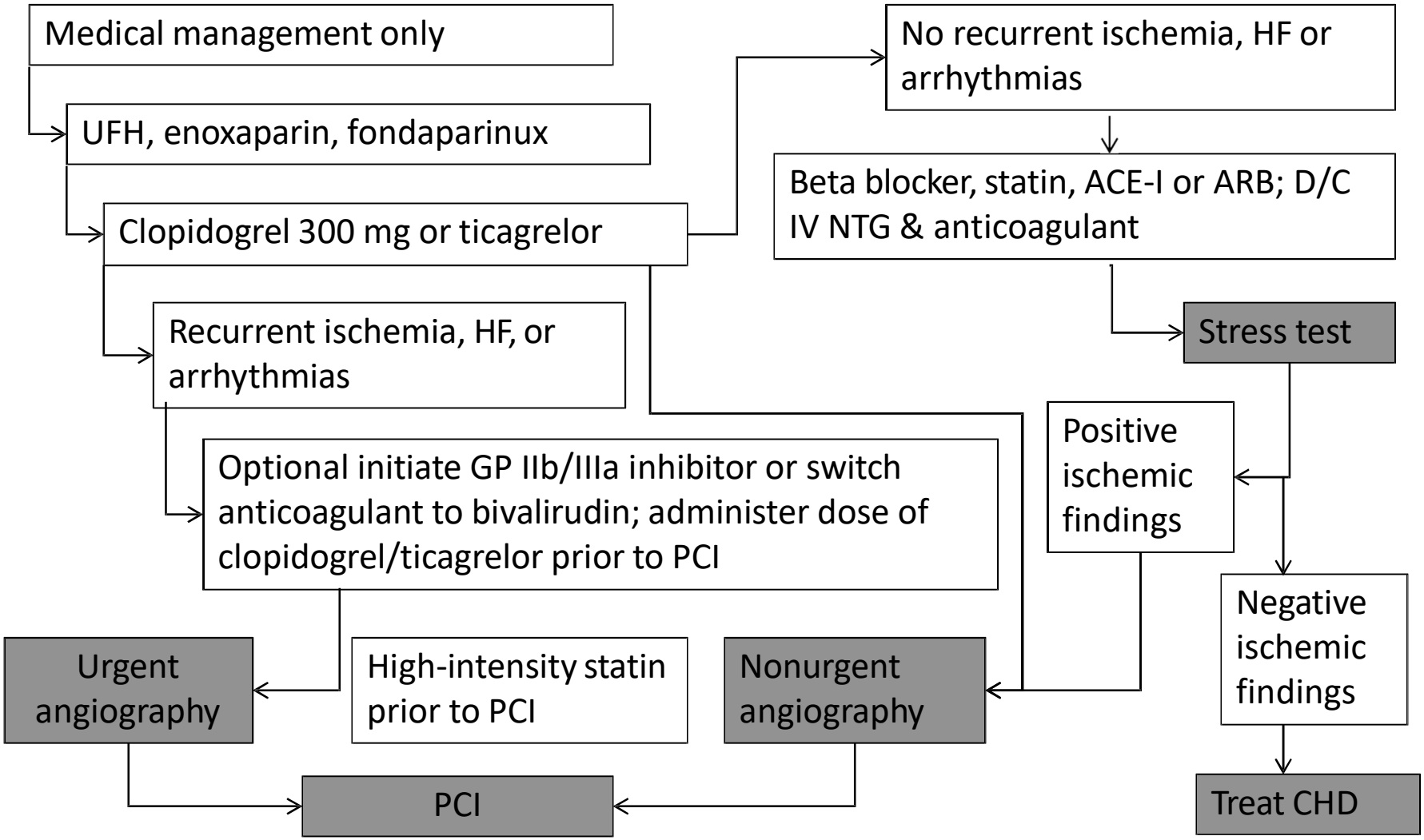


Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic Approach, 10th Edition, www.accesspharmacy.com

Step 2: Early Invasive Strategy



Step 2: Early Conservative Strategy



Anticoagulants

Added on to anti-platelet therapy

Prevent clot formation or any already present clots from getting bigger

Anticoagulants

Heparins

- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
  - Eg. Enoxaparin, Dalteparin

Factor Xa inhibitors

- Fondaparinux
- Rivaroxaban

Direct thrombin inhibitors

- Bivalirudin: reversible binding

Anticoagulants

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Choice of Anticoagulant

Early invasive strategy:	• UFH, , Bivalirudin, Enoxaparin, Fondaparinux + UFH at PCI
Early conservative - no angiography/PCI planned:	• UFH, Enoxaparin, Fondaparinux
High bleeding risk:	• Fondaparinux • Bivalirudin (in PCI)
Undergoing CABG:	• UFH

Unfractionated Heparin (UFH)

MOA: Binds antithrombin & inhibits clotting factors Xa & IIa (thrombin)

IV bolus followed by infusion, adjust according to aPTT or antifactor Xa levels

- ACT 200-250 (with IIb/IIIa), 250-350 (w/o IIb/IIIa)
- aPTT 1.5-2.5 times control for NSTE ACS
  - Draw first aPPT 3 hours after fibrinolytics (in STE ACS)

Can be used in patients with renal dysfunction

Discontinue immediately after PCI

Unfractionated Heparin (UFH)

STE ACS

- W/ Fibrinolytics
  - Initial bolus = 60 units/kg IV (max 4000 units)
  - Infusion = 12 units/kg/hr initially (max 1000 units/hr)
- W/O Fibrinolytics
  - Bolus = 50 – 70 units/kg with GP IIb/IIIa
  - Bolus = 70 – 100 units/kg with out GP IIb/IIIa
  - Supplemental boluses to maintain ACT

NSTE ACS dosing (PCI):

- Initial bolus = 60 units/kg IV (max 4000 units)
- Infusion = 12 units/kg/hr initially (max 1000 units/hr)

Enoxaparin

MOA: Binds antithrombin, inhibits factors Xa & IIa

Shorter chain length compared to UFH

- More predictable effects

Dose: 1 mg/kg SQ every 12 hrs

- CrCL 15-30 mL/min = 1 mg/kg Q24 hrs
- Continue for duration of hospitalization (Max 8 days), or discontinue immediately after PCI if performed

Fondaparinux

MOA: Inhibits factor Xa

- Less likely to cause HIT than UFH and LMWH

OASIS-5

- Fondaparinux 2.5 mg/day vs. Enoxaparin 1 mg/kg Q12 hours in NSTE ACS
- Less major bleeding and lower 30-day mortality
- Limitation: Patients undergoing PCI

Dose: 2.5 mg SQ daily

- Continue until hospital discharge (max 8 days)

Should not give as the sole anticoagulant in PCI

Bivalirudin – Direct Thrombin Inhibitor

NSTE ACS

- Option in patients undergoing planned early angiography & revascularization

Dose: 0.1 mg/kg IV bolus, then 0.25 mg/kg/hr

PCI dosing: 0.75 mg/kg bolus, then 1.75 mg/kg per h

- Discontinue after PCI (may continue up to 4 hours later)

Inhibit clot-bound & circulating thrombin

Does not bind plasma proteins

- More predictable response than UFH

Antiplatelet activity

Usually for pts with high risk of bleeding

$P2Y_{12}$ Inhibitors

Oral

- Clopidogrel (Plavix)
- Prasugrel (Effient)
- Ticagrelor (Brilinta)
- Cangrelor (Kengreal)

Intravenous

- For PCI (in cath lab) for pts not treated with a P2Y12 inhibitor OR a GPIIbIIIa inhibitor
- ↓ the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis

P2Y12 Inhibitors

Block P2Y12 component of ADP receptors on the surface of the platelet

Prevents activation of the GPIIbIIIa receptor complex

Reduces platelet aggregation

Clopidogrel

MOA: Blocks ADP2Y12 receptors on platelets

- Prevents activation & aggregation of platelets
- Prevents fibrin binding
- Prodrug

Alternative for patients with ASA allergy (Class 1)

NSTE ACS:

- Stent - recommended for most patients in combination with ASA for at least 12 months (Class 1)
- No stent - recommended for up to 12 months (Class 1)

Clopidogrel

Dosing:

- 300 to 600 mg PO loading dose, followed by 75 mg PO daily

Duration of therapy depends on whether stents are placed and which type of stent

- Medically managed: 1 – 12 months (risk/benefit)
- Bare metal stent placed: 12 months (risk/benefit)
- Drug-eluting stent: 12 months to indefinite (risk/benefit)

Should be given indefinitely if ASA-allergic (replacing ASA

Candidates for Clopidogrel

Used in patients unlikely to initially undergo CABG

- Non-interventional approach
- Only PCI planned
- Good adherence candidate

If CABG planned

- Must be stopped ≥5 days prior
- Preferably be stopped ≥7 days prior

Contraindications:

- Hypersensitivity
- Active bleeding
- Severe bleeding risk

Prasugrel (EFFIENT)

MOA: Blocks ADP2Y12 receptors on platelets

- Metabolized by different CYP enzymes from clopidogrel
  - Limited interactions with CYP 450
- Fast onset of action

Indicated for NSTE ACS in patients undergoing PCI

- May only be administered once coronary anatomy is known
- Given at time of PCI rather than before

Not to be used in patients undergoing CABG

- Increases bleeding risk
- Must D/C ≥7 days before if CABG is performed

Prasugrel (EFFIENT)

Dosing:

- 60 mg loading dose, then 10 mg/day in patients ≥60 kg
- 60 mg loading dose, then 5 mg/day in patients <60 kg
- Same duration of therapy as Clopidogrel

Contraindications:

- Active major bleeding
- History of stroke/TIA
- ≥75 years old (unless DM or history of MI)

Ticagrelor (BRILINTA)

MOA: Reversibly Blocks ADP2Y12 receptors on platelets

- Prevents activation & aggregation of platelets
- Prevents fibrin binding

NSTE ACS:

- FDA approval - In conjunction with ASA for secondary prevention of thrombotic events in patients managed medically, with PCI or via CABG
- Stent – combination with ASA recommended for most patients for up to 12 months

Ticagrelor (BRILINTA)

- Dosing: 180 mg PO loading dose, followed by 90 mg PO BID
- Duration of therapy is similar to clopidogrel
- Option for ASA-allergic patients
- AE: bleeding, hyperuricemia, bradycardia, ventricular pauses > 3 sec & dyspnea
- Contraindications: severe hepatic impairment, h/o intracranial hemorrhage & active bleeding

CLOPIDOGREL	PRASUGREL	TICAGRELOR
Prodrug	Prodrug	Active
Thienopyridine	Thienopyridine	Cyclopentyltriazolopyrimidine
Irreversible plt inhibition	Irreversible plt inhibition	Reversible plt inhibition
Delay in several hrs before max antiplatelet effect seen	Faster onset and greater antiplatelet effect (vs. clopidogrel)	Faster onset and greater antiplatelet effect (vs. clopidogrel)
Platelet inhibition: ~ 30-45%	Platelet inhibition: ~60-70%	Platelet inhibition: ~50-60%
Maintenance dose (MD): 75 mg PO daily	MD: 10 mg PO daily Consider 5 mg PO daily in pts weighing < 60 kg	MD: 90 mg PO BID
Contraindicated with active pathological bleeding Avoid concurrent CYP2C19 inhibitors Less effective in CYP2C19 poor metabolizers	Contraindicated in history of stroke or TIA Efficacy/benefit in pts age ≥ 75 is uncertain	Avoid use if prior intracranial hemorrhage Must only be used with aspirin 81 mg PO daily May cause dyspnea – usually transient
Hold before **surgery: 5 days**	Hold before **surgery: 7** days	Hold before surgery: 5 days

InhibitoP2Y12 Inhibitor Dosing – UA/NSTEMI

	Conservative (ex: can't get to cath lab)	**Invasive (PCI)**
Clopidogrel	LD: 300 mg x 1 on presentation MD: 75 mg daily x 1 yr	LD: 600 mg x 1 **ASAP** OR at time of PCI MD: 75 mg daily x 1 yr
Prasugrel	LD: N/A Not to be used prior to knowing anatomy, which can't be determined without invasive strategy	LD: 60 mg x 1 ONCE ANATOMY IS KNOWN MD: 10 mg daily **x 1 yr** Consider 5 mg daily if pt weighs less than 60 kg or is age 75 or greater AVOID in pts with prior stroke or TIA
Ticagrelor	LD: 180 mg x 1 on presentation MD: 90 mg PO **BID** x 1 yr Note: aspirin maintenence dose is 81 mg daily when used with ticagrelor	LD: 180 mg x 1 **ASAP** OR at time of PCI MD: 90 mg PO **BID** x 1 yr Note: aspirin maintenence dose is 81 mg daily when used with ticagrelor AVOID in pts with prior intracranial hemorrhage

Glycoprotein IIb/IIIa Inhibitors

MOA:

- Inhibit GP IIbIIIa receptor, final common pathway of platelet aggregation

Place in therapy

- Cardiac Catheterization and reperfusion(NSTE-ACS PCI or STEMI primary PCI)

Safety/Monitoring

- Bleeding risk
- Retroperitoneal, pulmonary, GI and/or GU bleeding
- Monitor for bleeding
- Especially the arterial access site
- Acute, profound thrombocytopenia
  - Within 24 hours of initiation
- Monitor: Monitor
  - CBC and for s/sx bleeding

Glycoprotein IIb/IIIa Inhibitors

Contraindication:

- Active bleeding, thrombocytopenia, prior stroke, renal dialysis

Products

- Tirofiban - Aggrastat®
- Eptifibitide - Integrilin®
- Abciximab - ReoPro®

Early/Primary Invasive Strategy

Understanding the cath lab (STEMI OR NSTEMI)

<<<< BEFORE CATH LAB >>>>

Anticoagulant

UFH, enoxaparin

(or bivalirudin or fondaparinux)

PLUS

Antiplatelets

P2Y12 inhibitor

(not always given before angiography because if pt ends up needing CABG,

would have to wait 5-7 days before taking pt to surgery to reduce risk of bleeding)

OR

GPIIbIIIa inhibitor (used precath for higher risk patients; otherwise initiated in cath lab for high risk features)

(Can give both P2Y12 inhibitors and GPIIbIIIa inhibitors for certain high risk patients)

↓

Early/Primary Invasive Strategy
(Cath lab/PCI)

Understanding the cath lab (STEMI OR NSTEMI)

<<<< CATH STARTS >>>>

Angiography done to determine coronary anatomy. Once angiography is done, further management will be determined by what is found. There are essentially three pathways

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(usually severe CAD), then cath is over

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-Continue use of anticoagulant until surgery
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(balloon angioplasty or stent placement with either bare metal or drug eluting stent)

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Medical management

(cath is over; medical therapy, aka no surgery or PCI)

-Give P2Y12 loading dose if not already done
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ALL PATHWAYS:
See "other early therapies for ACS" and "secondary prevention" slides

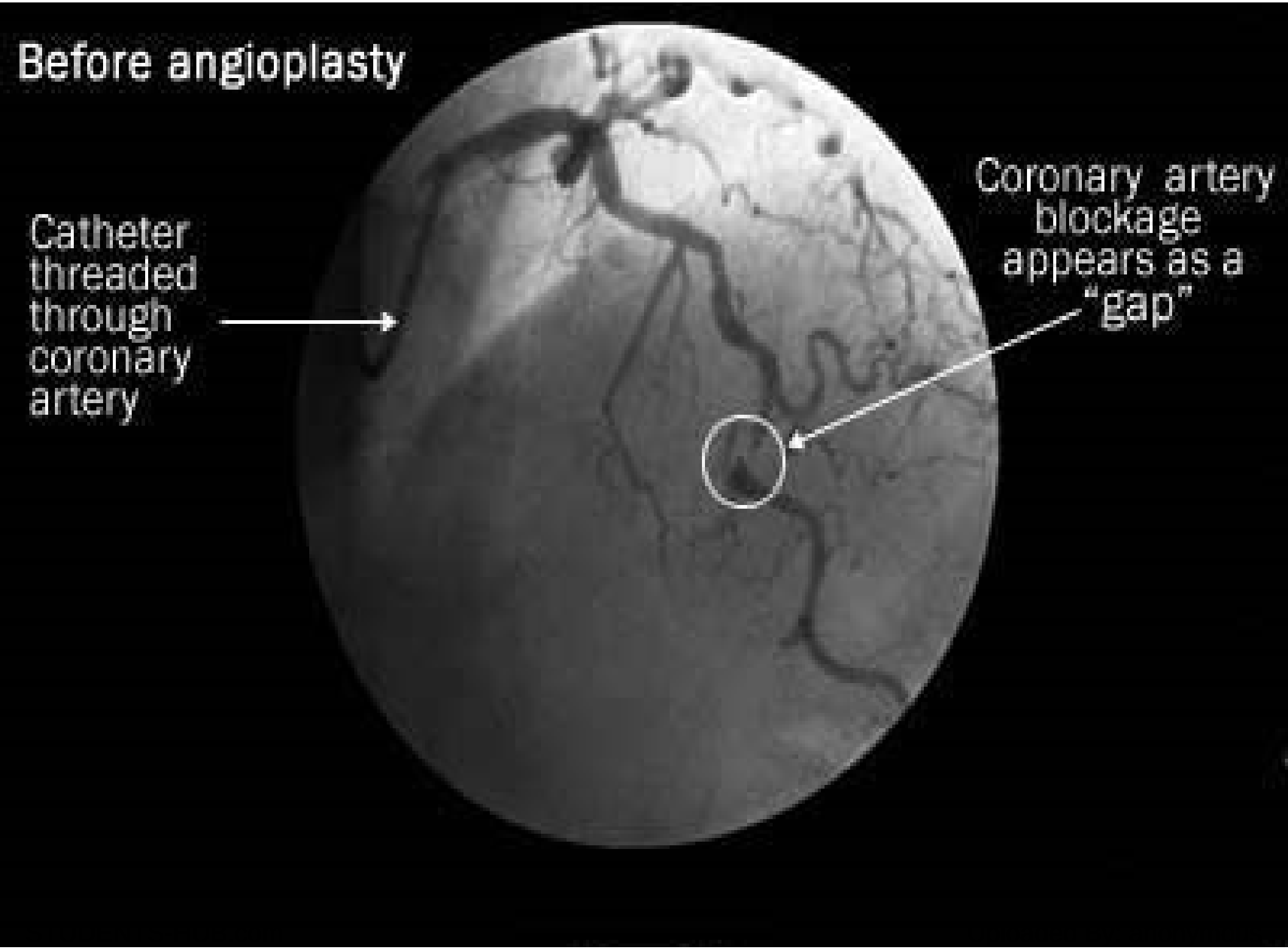
INVASIVE STRATEGY (Cath lab/PCI)

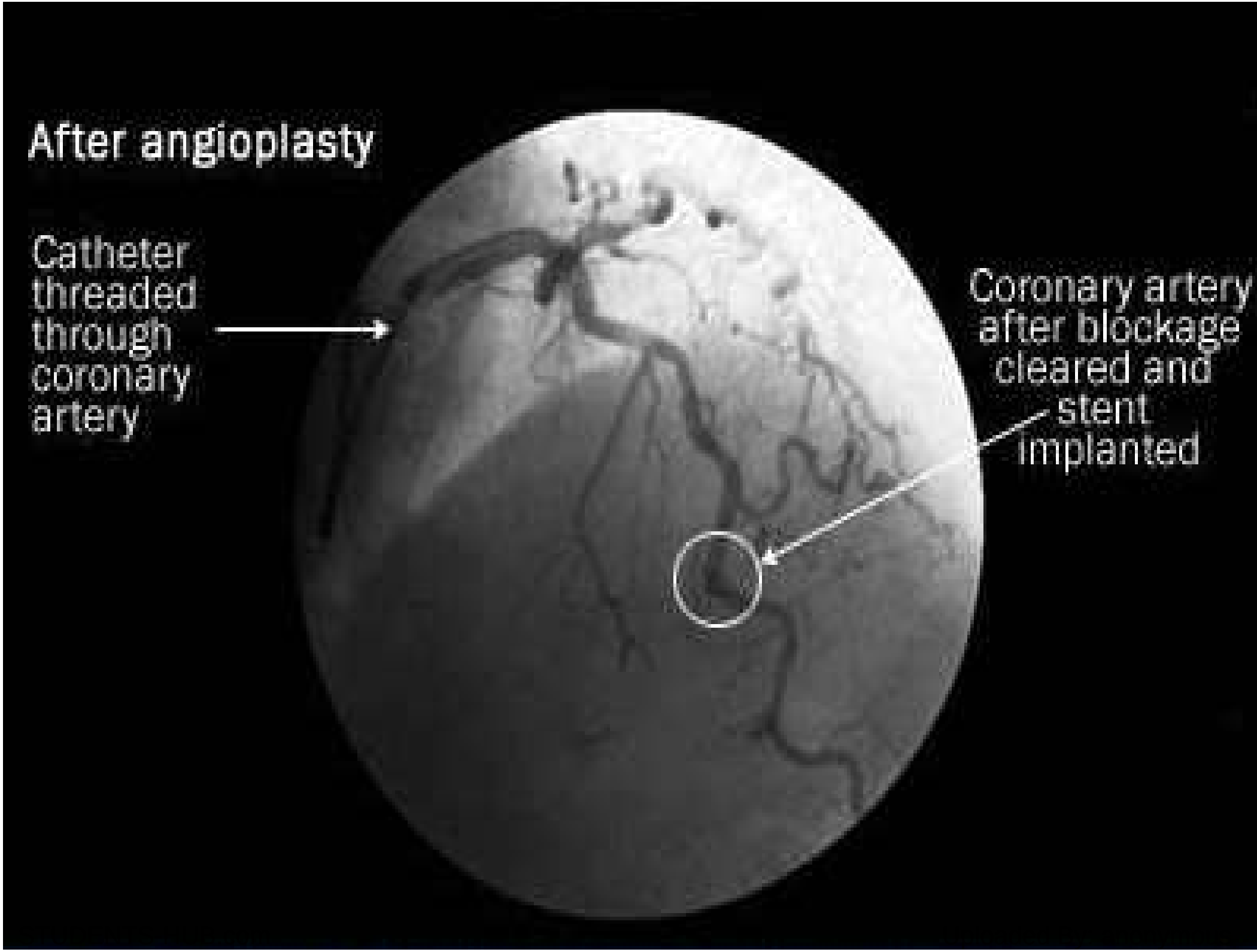
Revascularization (FYI)

LOS = length of stay

PTCA (percutaneous transluminal coronary angioplasty) or PCI (percutaneous coronary intervention)		
1 or 2 vessel disease and unstable angina	LOS: 24 – 36 hrs; Recovery 2-5 days	Angina: 30 % in 6 months – may repeat

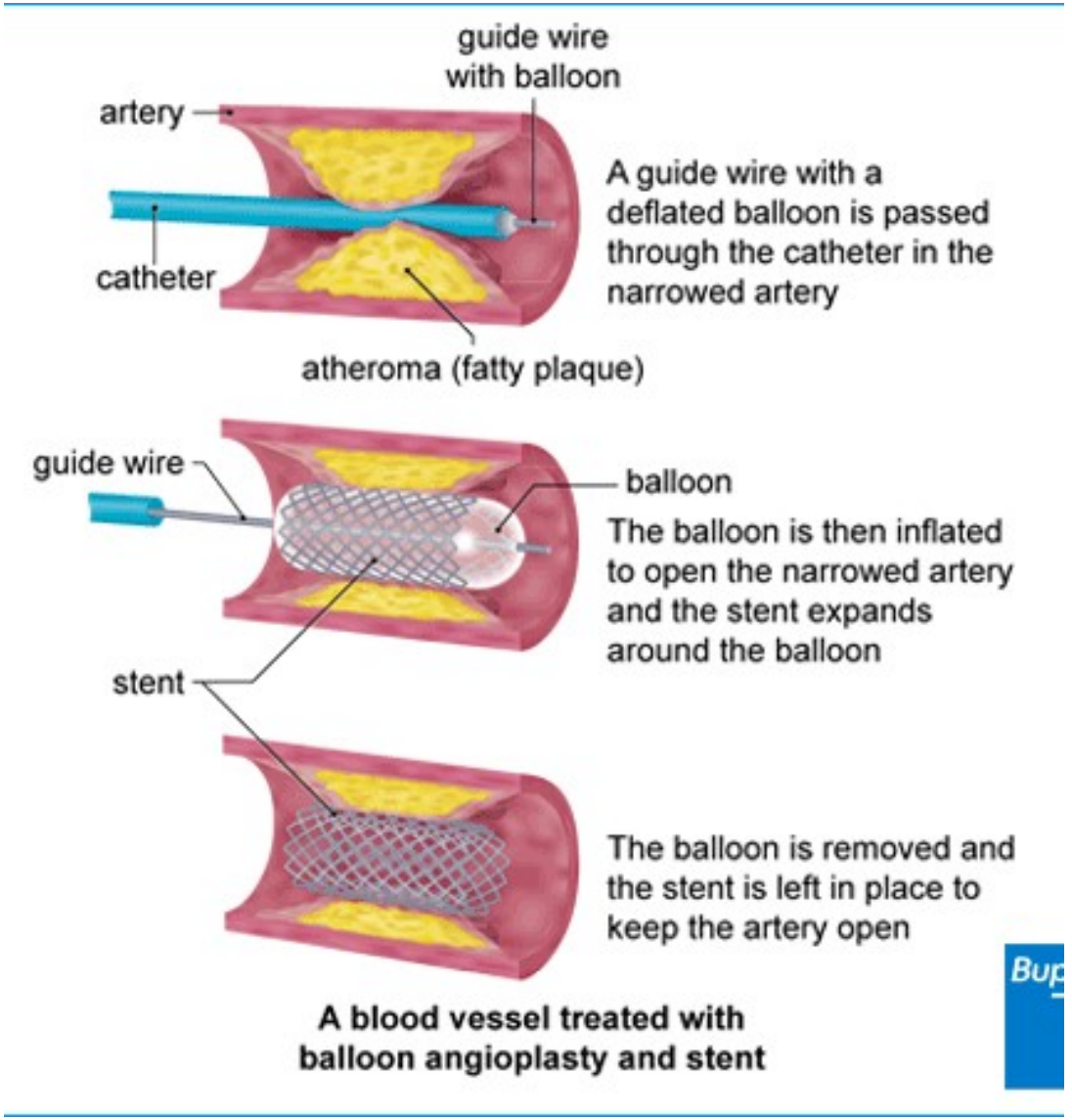
CABG (coronary artery bypass grafting)		
Left coronary stenosis, 2 or 3 vessel disease	LOS: 7-10 days; Recovery 2-3 months	Angina: 10 % in 1 year, then 5 % per year


Before angioplasty
Catheter threaded through coronary artery
Coronary artery blockage appears as a "gap"


After angioplasty
Catheter threaded through coronary artery
Coronary artery after blockage cleared and stent implanted

PCI (percutaneous coronary intervention)

- Procedure to open blocked or narrowed coronary arteries
- Done during the left cardiac catheterization
- Balloon angioplasty alone or with stent placement



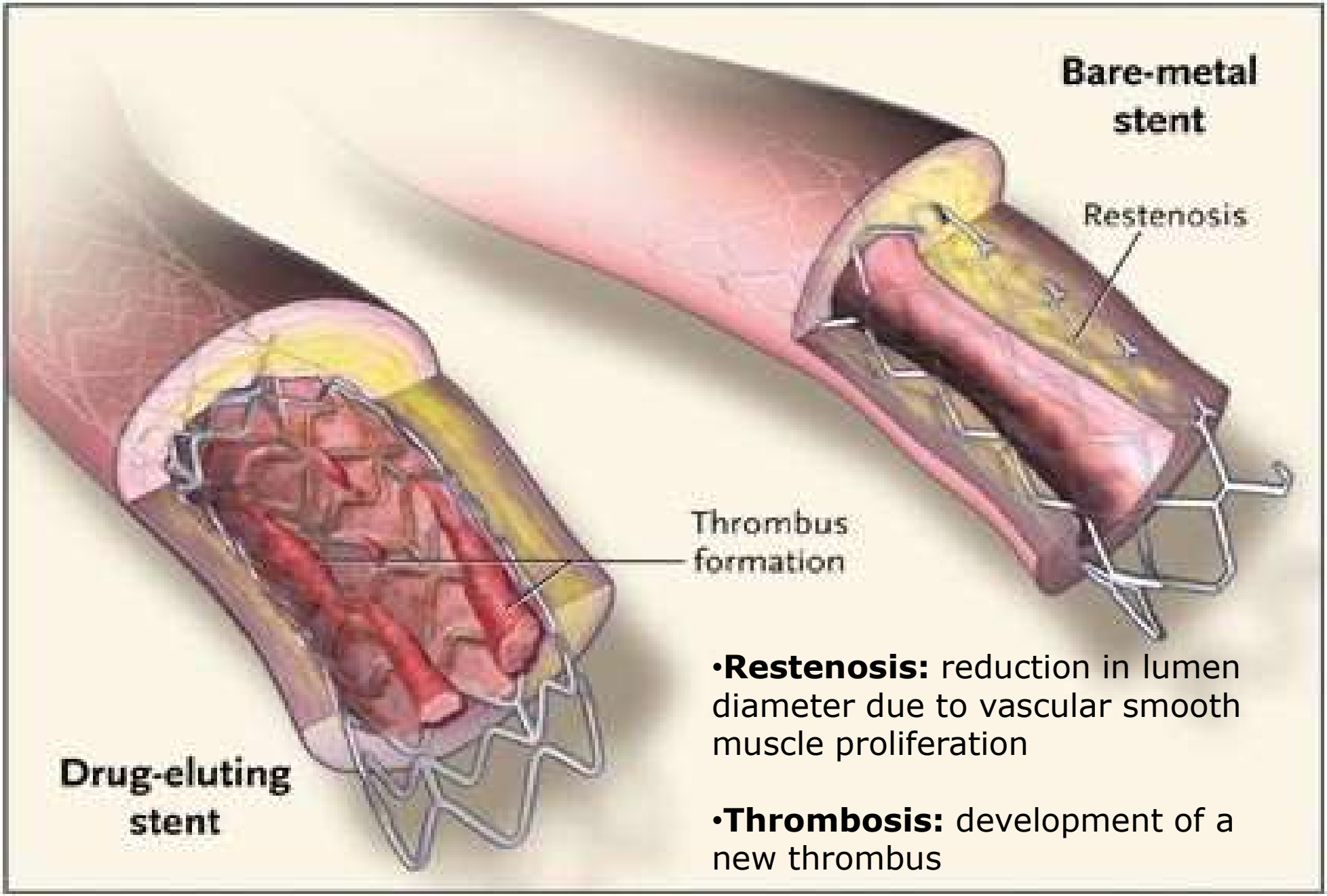
http://www.radiology.ucsf.ed

After stent placement

Regardless of STEMI or NSTEMI

Bare Metal Stents (BMS) & Drug Eluting Stents (DES)

- Require dual antiplatelet therapy (DAPT)
  - Aspirin 75 – 325 mg PO daily (continued indefinitely) plus
  - P2Y12 inhibitor
    - Clopidogrel 75mg PO daily
    - Prasugrel 10 mg PO daily
    - Ticagrelor 90 mg PO BID** (no Aspirin doses >100 mg!)
      - P2Y12 inhibitor generally continued for a year, but will also depend on pt bleeding risk/occurrence of bleeding



- **Restenosis:** reduction in lumen diameter due to vascular smooth muscle proliferation
- **Thrombosis:** development of a new thrombus

Source: N Engl J Med. 2006;355(19):1949-52

Bare Metal vs. Drug Eluting Stents

Bare Metal Stent (BMS)	Drug Eluting Stent (DES)
▪ Endothelial cells grow over stent faster (~30 days) ▪Restenosis is primary problem	▪ Contain immunosuppressants (ex: everoliumus, zotarolimus) to prevent proliferation of vascular smooth muscle to help prevent restenosis ▪ Prevent/delay the growth of endothelial cells over the stent → less restenosis ▪ Stent (foreign body) exposed longer duration since endothelial cells don't grow over stent ▪ Higher risk of thrombosis due to exposed stent, which can narrow or occlude stent lumen

STEMI

Strategy for STEMI: PCI vs Lytics

PCI is preferable, mortality benefit depending on time

EMS transfer to PCI-capable hospital for primary PCI is the recommended triage strategy for pts with STEMI, with first medical contact (FMC)-to-device time system goal 0f ≤ 90 minutes

If initially seen/taken to non-PCI capable hospital

- Transfer to PCI-capable hospital is recommended with first medical contact (FMC)-to-device time system goal of ≤ 120 minutes

When Fibrinolytics are Preferred

Early presentation –

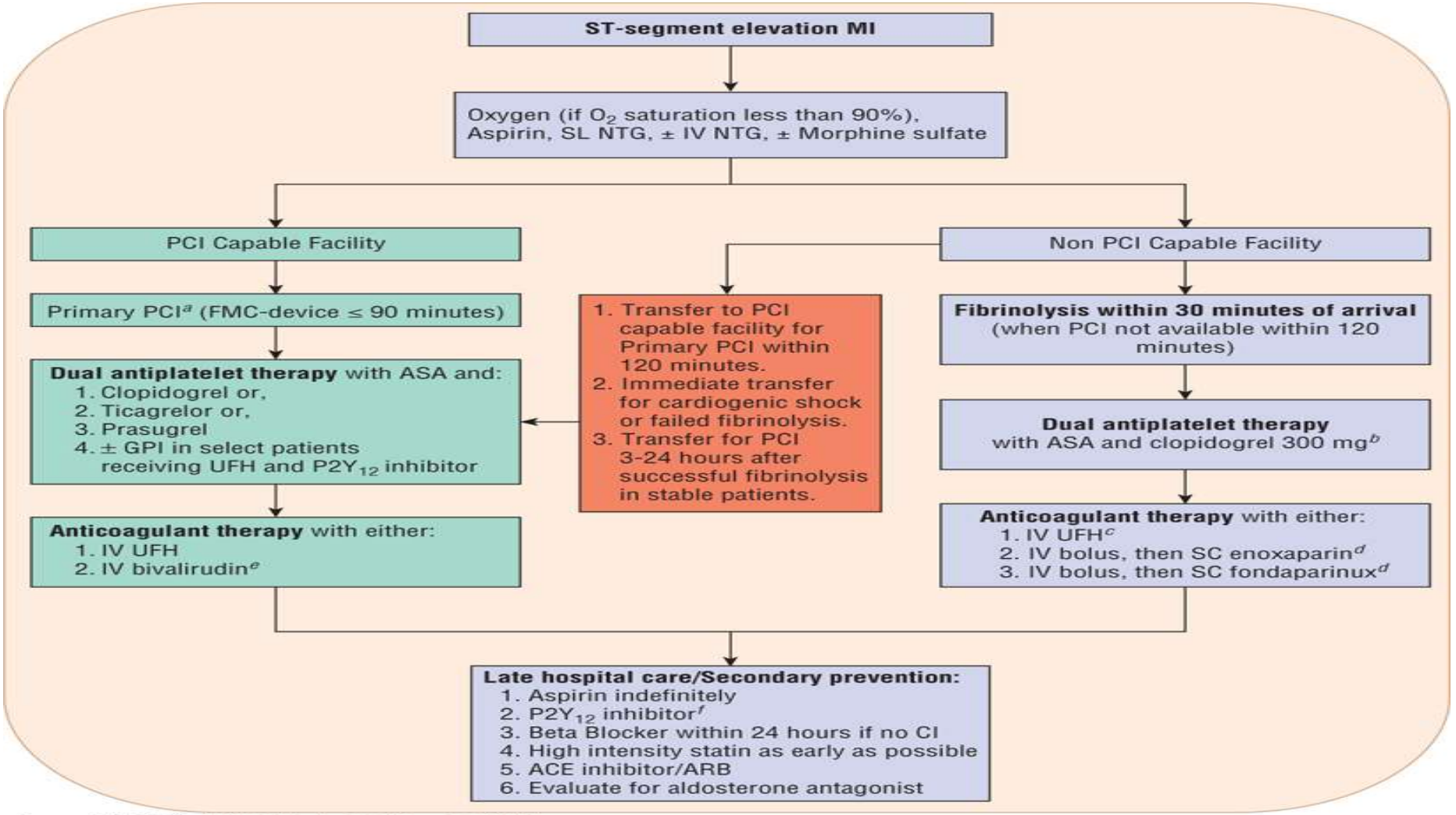
- Less than or equal to 12 hours from onset of sx
  - PCI is preferred if presenting within 12-24 hrs from symptom onset

AND

- **Anticipated first medical contact (FMC)-to-device system time > 120 min** because of unavoidable delays
  - Prolonged transport
  - Lab occupied/not available
  - Lack of access to skilled PCI lab

If fibrinolytics are going to be given, should be within 30 minutes of hospital arrival

- "Door-to-needle time" of < 30 minutes



Initial pharmacotherapy for ST-segment elevation myocardial infarction. [a]Options after coronary angiography also include medical management alone or CABG surgery. [b]Clopidogrel preferred $P2Y^{12}$ inhibitor when fibrinolytic therapy is utilized. No loading dose recommended if age older than 75 years. [c]Given for up to 48 hours or until revascularization. [d]Given for the duration of hospitalization, up to 8 days or until revascularization. [e]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin (bolus plus infusion). [f]In patients with STEMI receiving a fibrinolytic or who do not receive reperfusion therapy, administer clopidogrel for at least 14 days and ideally up to 1 year. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CI, contraindication; FMC, first medical contact; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; MI, myocardial infarction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.) (Reproduced with permission from Rogers KC, de Denus S, Finks SW. Chapter 8. Acute Coronary Syndromes. In: Chisholm-Burns MA, Schwinghammer TL Wells BG, et al, eds. Pharmacotherapy: Principles and Practice. 4th ed. New York: McGraw-Hill Companies; 2016.)

Fibrinolytics

Fibrinolytics

Thrombolytic agents are plasminogen activators Convert the plasminogen to plasmin

Plasmin degrades fibrin, fibrinogen, prothrombin, and factors V and VII

Indication

- Ischemic chest discomfort at least 20 minutes in duration but 12 hours or less since symptom onset and
- ST-segment elevation of at least two contiguous leads of ≥2 mm in men and ≥1.5 mm in women in leads V2-V3 and/or of ≥1 mm in other leads, or new or presumed new left bundle-branch block
- Ongoing ischemic chest discomfort at least 20 minutes in duration 12-24 hours since symptom onset and ST-segment elevation of at least 1 mm in height in two or more contiguous leads

Fibrinolytics
Absolute Contraindications

- Any prior ICH
- Known structural cerebrovascular lesion
- Known malignant intracranial neoplasm
- Ischemic stroke within 3 months
- Except acute ischemic stroke within 3 hours
- Suspected aortic dissection
- Active bleeding or bleeding diathesis

Relative CI to Fibrinolysis

- Pregnancy
- History of chronic, severe, poorly controlled hypertension
- Severe uncontrolled hypertension on presentation
- SBP >180 mm Hg or DBP >110 mm Hg
- Traumatic or prolonged (> 10 min) resuscitation or major surgery (within < 3 weeks)
- Recent internal bleeding (within 2 to 4 weeks)

Relative CI to Fibrinolysis

- Current use of anticoagulants
- Higher the INR = Higher risk of bleeding (warfarin)
- Active peptic ulcer
- History of prior ischemic stroke (>3 months), dementia, or known intracranial pathology not covered in absolute CI
- Streptokinase: Exposure (> 5 days) or prior allergic reaction
- Known intracranial neoplasm

Fibrinolytics

Agent	Fibrin Specificity	Patency Rate (90 min TIMI 2 or 3 flow)	Dose
Tenecteplase (TNKase™)	++++	85%	≈0.5 mg/kg single bolus over 5 sec; max dose of 50 mg < 60 kg: 30 mg ≥ 60 to < 70 kg: 35 mg ≥70 to < 80 kg: 40 mg ≥ 80 to < 90 kg: 45 mg ≥ 90 kg: 50 mg
Reteplase (Retavase®)	++	84%	10 units IV over 2 minutes, then repeat 10 unit bolus 30 min later
Alteplase (Activase®)	++	73-84%	15-mg bolus + 0.75 mg/kg for 30 min (max 50 mg), then 0.5 mg/kg (max 35 mg) over next 60 min) Total dose not to exceed 100 mg

STEMI

Fibrinolytics

- Option only for STEMI, NOT UA/NSTEMI!!

Anticoagulants

- Heparin
- LMWH

Antiplatelets

- Aspirin
- Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta)
- Glycoprotein IIb/IIIa receptor blockers
  - Eptifibatide, tirofiban, abciximab

Invasive Strategy Preferred

Skilled PCI lab available with O.R. avail

- FMC-to-device system time ≤ 90 min

High Risk from STEMI

- Cardiogenic shock

Contraindications to "lytic"

- Increased risk of bleeding
- ICH

Late presentation

- Onset of sx > 12 hours

Diagnosis of STEMI in doubt

Early/Primary Invasive Strategy

Understanding the cath lab (STEMI OR NSTEMI)

<<<< BEFORE CATH LAB >>>>

Anticoagulant

UFH, enoxaparin

(or bivalirudin or fondaparinux)

PLUS

Antiplatelets

P2Y12 inhibitor

(not always given before angiography because if pt ends up needing CABG,

would have to wait 5-7 days before taking pt to surgery to reduce risk of bleeding)

OR

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ALL PATHWAYS:
See "other early therapies for ACS" and "secondary prevention" slides

When is PCI needed after fibrinolytics?

- Failed reperfusion or reocclusion after fibrinolytics
- Cardiogenic shock or acute severe HF that develops after initial presentation
- Spontaneous or easily provoked myocardial ischemia
- Intermediate or high risk findings on pre-discharge noninvasive ischemia testing
- Stable pts after fibrinolysis, before discharge, and ideally between 3 and 24 hrs

Other Early Therapies for ACS

Other Early Therapies for ACS

Aspirin

- Regardless of stent or medical therapy
- 75 mg -325 mg PO daily

Sublingual nitroglycerin

- Tablet: 0.3 or 0.4 mg SL X 1 dose
- Spray: 0.4 mg/spray – onto or under tongue
- If no relief after one dose, call 911
- Repeat q 5 min up to 3 doses

Other Early Therapies for ACS

Statins

- High-intensity
- Mortality data for starting statins early while in house (start in first 24 hrs)

ACEI

- Especially with HF, LVEF < 40%, Type 2 DM, CKD, or STEMI with anterior location but can be considered for all pts without CI
  - Orally in 1st 24 hours with STEMI
  - IV contraindicated due to risk of hypotension
  - Contraindicated if pt is HYPOtensive
- May use ARB if ACEI is intolerable

Other Early Therapies for ACS

Non-DHP CCB

- If continuing or frequently recurring ischemia WITH CI to BB therapy OR BB & nitrates used optimally
  - No change in morbidity/mortality – more for sx relief
- Contraindications: clinically significant LV dysfunction, second or third degree heart block without pacemaker, increased risk for cardiogenic shock

Aldosterone Antagonist

- IF already on therapeutic doses of BB and ACEI
  - plus
- EF < 40%
- Symptomatic Heart failure
- DM
- Avoid with significant renal dysfunction (CrCl < 30 mL/min; SCr > 2.5 mg/dL in men or > 2 mg/dL in women) or hyperkalemia (K > 5 mEq/L)

Long-term Goals

Control modifiable risk factors

Prevent systolic heart failure

Prevent recurrent MI and stroke

Prevent death

Secondary Prevention

- Statins (high-intensity)
- P2Y12 inhibitors
- Aspirin
- Beta Blockers
- ACE Inhibitors
- Add Aldosterone Antagonist