Pathophysiology of Ischemia Heart Disease

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Classification of Ischemic Heart Disease

- Stable Ischemic Heart Disease (SIHD) also known as Chronic Coronary Syndrome (CCS)
- Acute Coronary Syndrome
  - Unstable Angina / NonSTEMI
  - ST elevation MI

PATHOPHYSIOLOGY of Acute Coronary Syndrome

- The pathogenesis of NSTE-ACS involves four processes operating singly or in various combinations:

(1) Disruption of an unstable atheromatous plaque, which may be driven at least in part by inflammation

(2) Coronary arterial vasoconstriction

(3) Gradual intraluminal narrowing of an epicardial coronary artery caused by progressive atherosclerosis or restenosis after stenting

(4) Oxygen supply-demand mismatch

PATHOPHYSIOLOGY of Acute Coronary Syndrome

- Our understanding of the complex interactions between these pathways continues to evolve.

- For example, recent studies have identified increased levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a risk factor for more severe atherosclerosis, a marker for vulnerable plaques, and a contributor to plaque destabilization resulting in ACS

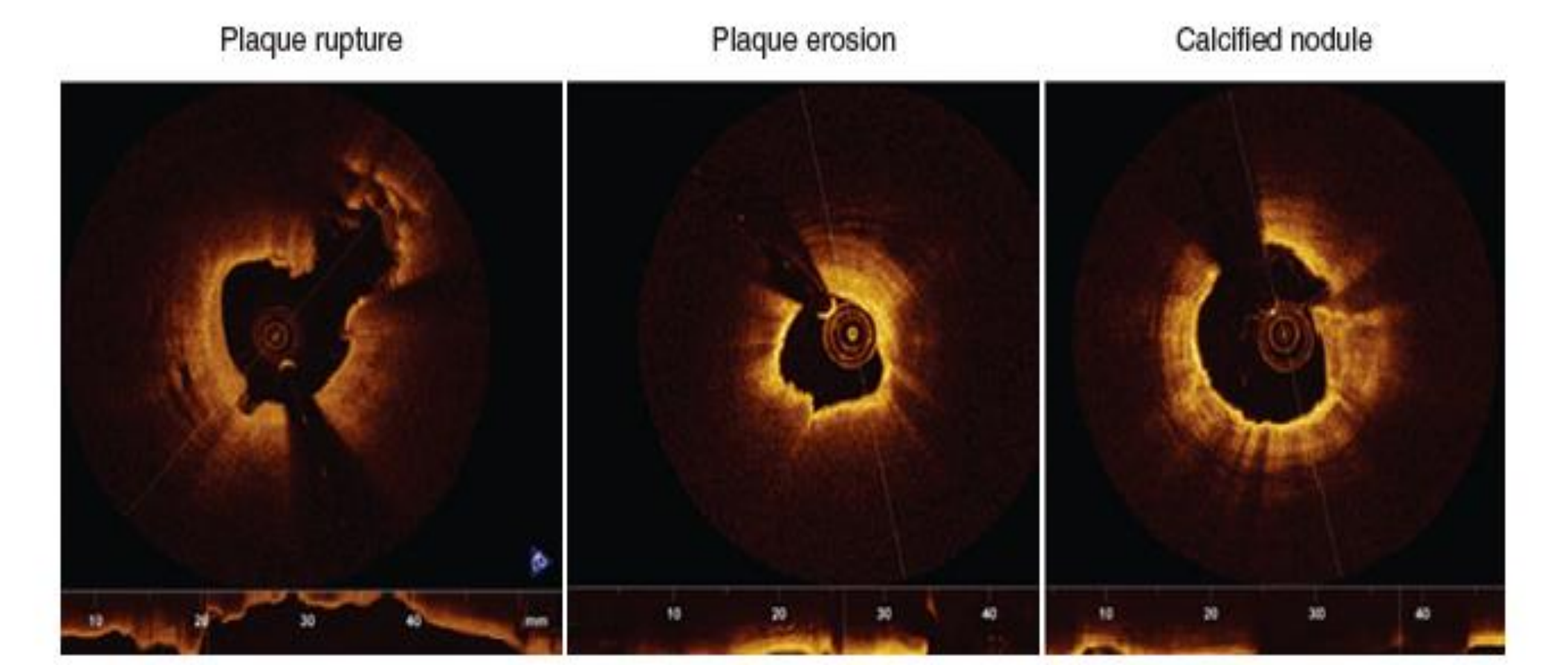
1. Forms of disruptions of coronary artery plaques

- Three forms of disruptions of coronary artery plaques can precipitate thrombosis:

1. Plaque rupture,
2. Plaque erosion,
3. Disruptive nodular calcification protruding into the lumen

- Plaque rupture remains the most common, but plaque erosion has become responsible for an increasing proportion of ACS events

Three forms of disruptions of coronary artery plaques



Differences in the main characteristics between plaque rupture and superficial erosion

TABLE 60.1 Main Characteristics of Plaque Rupture and Superficial Erosion

PLAQUE RUPTURE	PLAQUE EROSION
Lipid rich	Lipid poor
Collagen poor, thin fibrous cap	Proteoglycan and glycosaminoglycan rich
Interstitial collagen breakdown	Nonfibrillar collagen breakdown
Abundant inflammation	Few inflammatory cells
Smooth muscle cell apoptosis	Endothelial cell apoptosis
Macrophage predominance	Secondary neutrophil involvement
Male predominance	Female predominance
High level of low-density lipoprotein cholesterol	High level of triglycerides

Modified from Libby P, Pasterkamp G. Requiem for the "vulnerable plaque." Eur Heart J 2015;36:2984-87.

- Activation of the coagulation cascade and platelets play central roles in the formation of thrombus following plaque disruption

- The first step in thrombus formation is vascular injury that causes *adhesion* of platelets to the arterial wall via binding of platelet glycoprotein (GP) Ib to subendothelial von Willebrand factor.

- Exposure of platelets to subendothelial collagen and/or circulating thrombin causes platelet *activation*, which induces platelets to change shape and results in their degranulation with release of adenosine diphosphate (ADP) and thromboxane A2 (TxA2), which in turn cause further platelet activation and expression of platelet GP IIb/ IIIa.

- In parallel, tissue factor expressed within the lipid-rich core of atherosclerotic plaque, when exposed to circulating blood, activates the *coagulation cascade*. A complex of tissue factor and coagulation factors VIIa and Va leads to the formation of activated factor X (factor Xa), which in turn amplifies the production of activated factor IIa (thrombin). This cascade proceeds with thrombin-induced conversion of fibrinogen to fibrin.

    - The platelet and coagulation systems converge as thrombin also potently activates platelets. Platelet GP IIb/ IIIa binds circulating fibrinogen, thereby causing platelet aggregation and ultimately producing a platelet-fibrin thrombus, portions of which may embolize distally and cause myocardial necrosis.

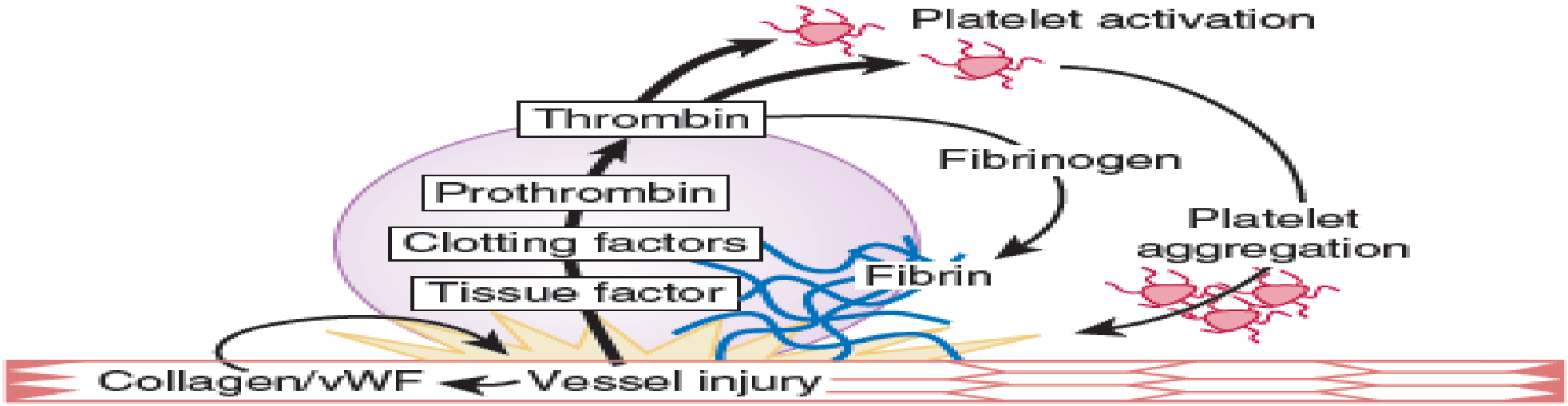
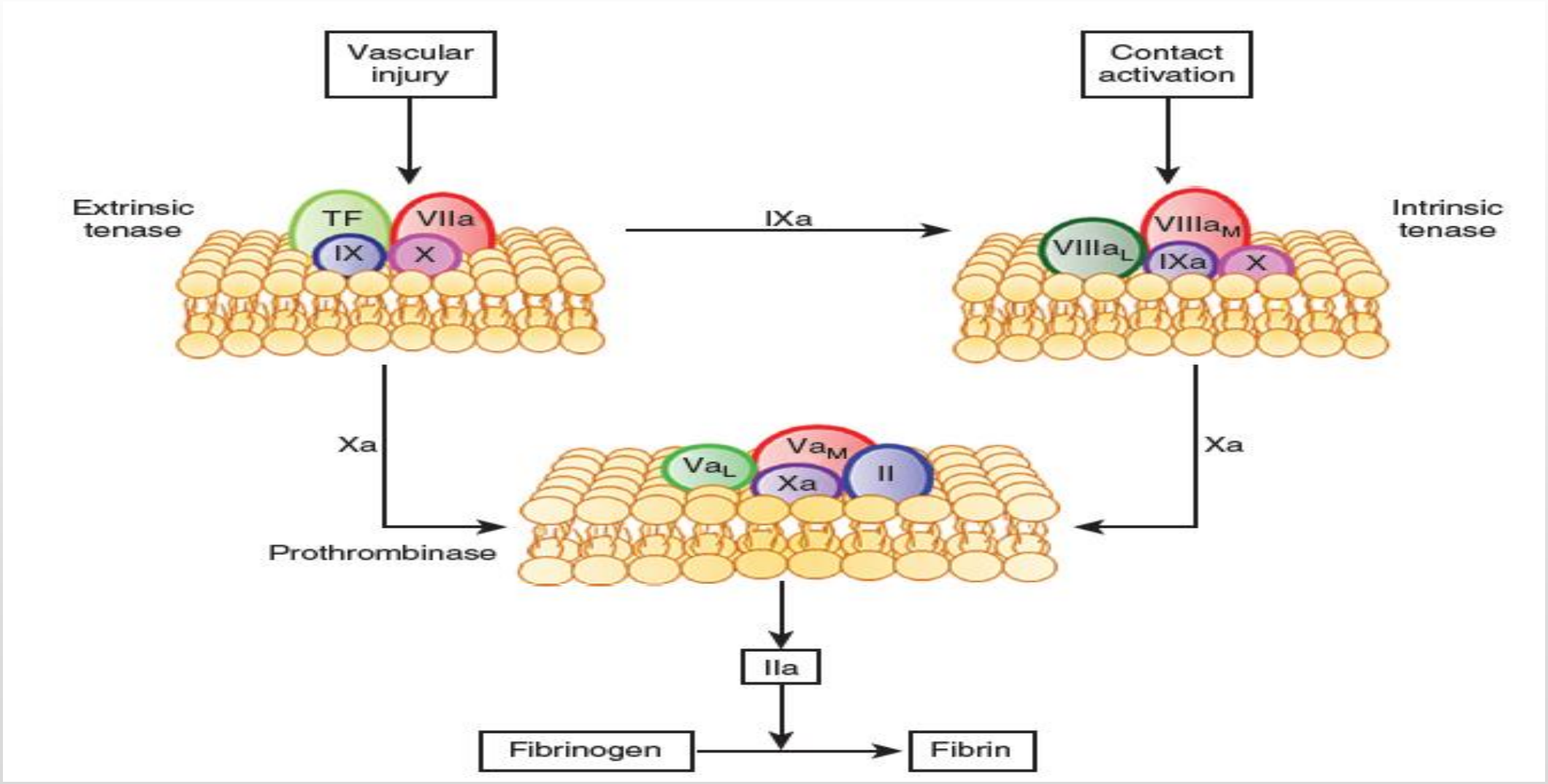
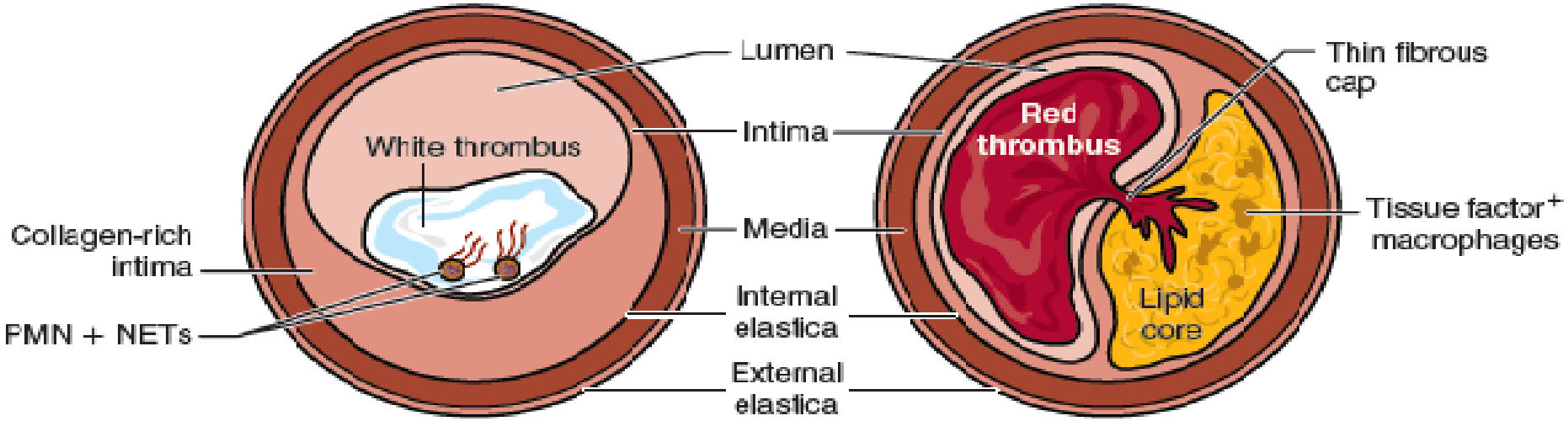


FIGURE 93.3 Central role of thrombin in thrombogenesis. Vascular injury simultaneously triggers platelet adhesion and activation, as well as activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (vWF), onto which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. Coagulation, which is triggered by tissue factor exposed at the site of injury and enhanced by assembly of clotting factor complexes on the activated platelet surface, results in thrombin generation. Thrombin not only converts fibrinogen to fibrin but also serves as a potent platelet agonist. When platelets are activated, glycoprotein (GP) IIb/IIIa on their surfaces undergoes a conformational change that endows it with the capacity to ligate fibrinogen and mediate platelet aggregation. Fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus.


Vascular injury
Contact activation
Extrinsic tenase
TF
VIIa
IX
X
IXa
Intrinsic tenase
VIIIa$_M$
VIIIa$_L$
IXa
X
Xa
Xa
Va$_M$
Va$_L$
Xa
II
Prothrombinase
IIa
Fibrinogen
Fibrin

Coronary Artery Cross Sections



Thrombosis due to erosion

- Fibrous cap thick and intact
- "White" fibrin-rich thrombus
- Collagen trigger
- Smooth muscle cells prominent
- Often sessile, nonocclusive thrombus
- Usually less remodeled outward
- Neutrophil extracellular traps (NETs) involved
- More frequent in non-STEMI?

Thrombosis due to rupture

- Thin fibrous cap with fissure
- "Red" fibrin-rich thrombus
- Tissue factor trigger
- Macrophages prominent
- Often occlusive thrombus
- Usually expansively remodeled
- Less NET involvement?
- More frequently causes STEMI?

- Four observations support the central role of coronary artery thrombosis in the pathogenesis of ACS:

(1) Autopsy findings of thrombi in the coronary arteries typically localized to a ruptured or eroded atherosclerotic plaque,

(2) Visualization by optical coherence tomography or computed tomographic angiography (CTA) of plaque ulceration and/or irregularities in the fibrous cap of atherosclerotic plaque, consistent with plaque rupture and thrombus formation;

(3) Elevation of serum markers of platelet activity, thrombin generation, and fibrin formation;

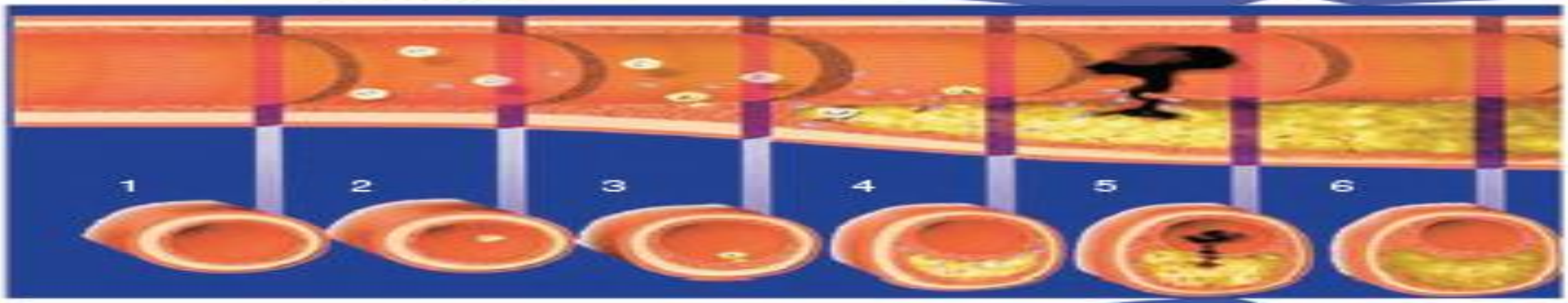
(4) Improvement in clinical outcome with antiplatelet and anticoagulant therapies.

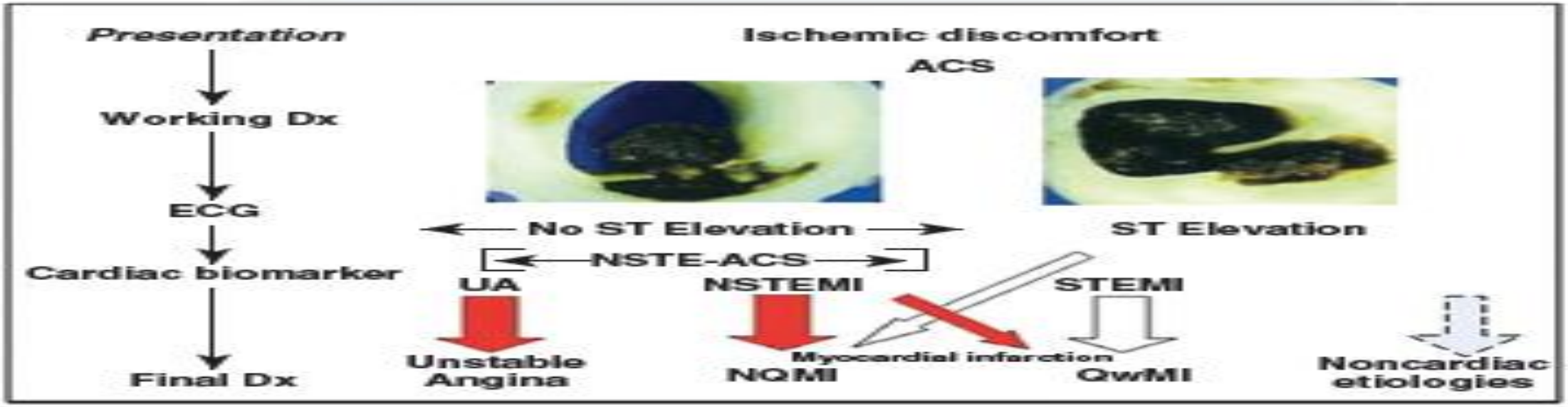
Onset of NSTE-ACS
- Initial recognition and management by first responders or ED personnel
- Risk stratification
- Immediate management

Hospital Management
- Medication
- Conservative versus ischemia-guided strategy
- Special groups
- Preparation for discharge

Management prior to NSTE-ACS

Secondary prevention/ Long-term management





2. Coronary arterial vasoconstriction

- Vasoconstriction causing dynamic obstruction of coronary arterial flow may result from;

✓ Spasm of the epicardial coronary arteries (Prinzmetal angina)

or

✓ Constriction of small, intramural muscular coronary arteries

- Constriction of small, intramural muscular coronary arteries may result from

➢ Vasoconstrictors released by platelets,

➢ Endothelial dysfunction (cardiac syndrome X),

➢ Adrenergic stimuli,

➢ Cold,

➢ Cocaine, or amphetamines

More than one of these mechanisms may operate simultaneously.

4. Increased Myocardial Oxygen Requirements / Decreased Oxygen Supply

- *Demand angina*, the myocardial O2 requirement increases in the presence of a constant and usually restricted O2 supply. It results from;

➢ Physiologic response to exertion, emotional duress, or mental stress.

➢ Mental and emotional stress

➢ The combination of physical exertion and emotion in association with sexual activity

➢ Other precipitants of angina include physical exertion after a heavy meal and the excessive metabolic demands imposed by chills, fever, thyrotoxicosis, tachycardia from any cause, uncontrolled hypertension, exposure to the cold, and hypoglycemia

- As with unstable angina, chronic stable angina may be caused by transient reductions in O2 supply, a condition sometimes termed *supply angina.*

➢ They often complain of a circadian variation in angina that is more common in the morning. Angina on exertion and sometimes even at rest may be precipitated by cold temperature, emotion, and mental stress.