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Siset Training Center:

CORSO TROMBOSI

Cremona, 19-23 settembre 2016

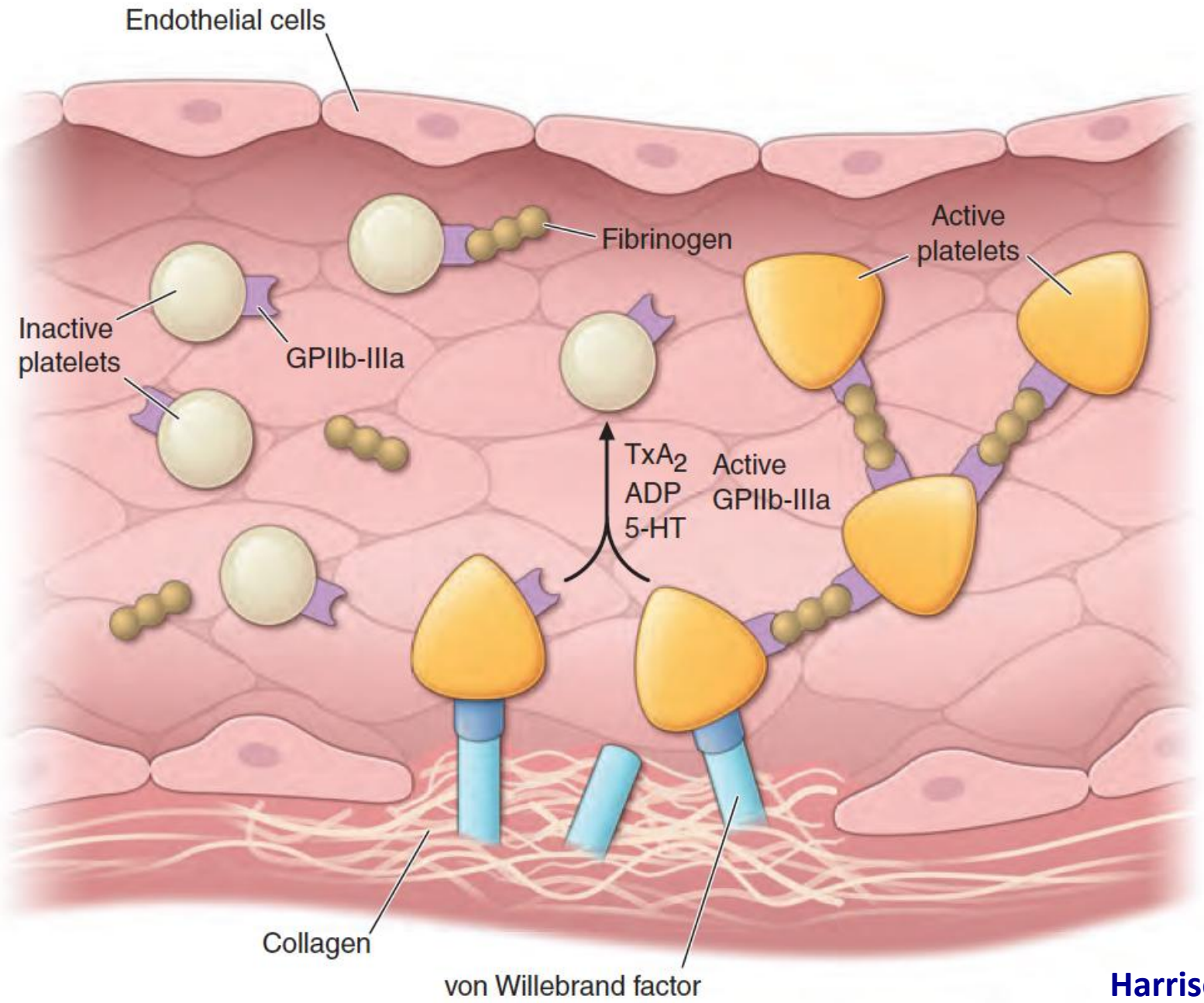
La Trombosi Arteriosa

Prof. Giovanni Davì

Medicina Interna

Chieti

Platelet activation and thrombosis



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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Platelet Activation and Atherothrombosis

Giovanni Davì, M.D., and Carlo Patrono, M.D.

- **Platelets** are essential for **primary hemostasis** and repair of the endothelium
- They also play a **key role** in the development of **acute coronary syndromes** and contribute to **cerebrovascular events**
- They participate in the process of **forming and extending atherosclerotic plaques**
- Atherosclerosis is a **chronic inflammatory process**, and **inflammation** is an important component of acute coronary syndromes

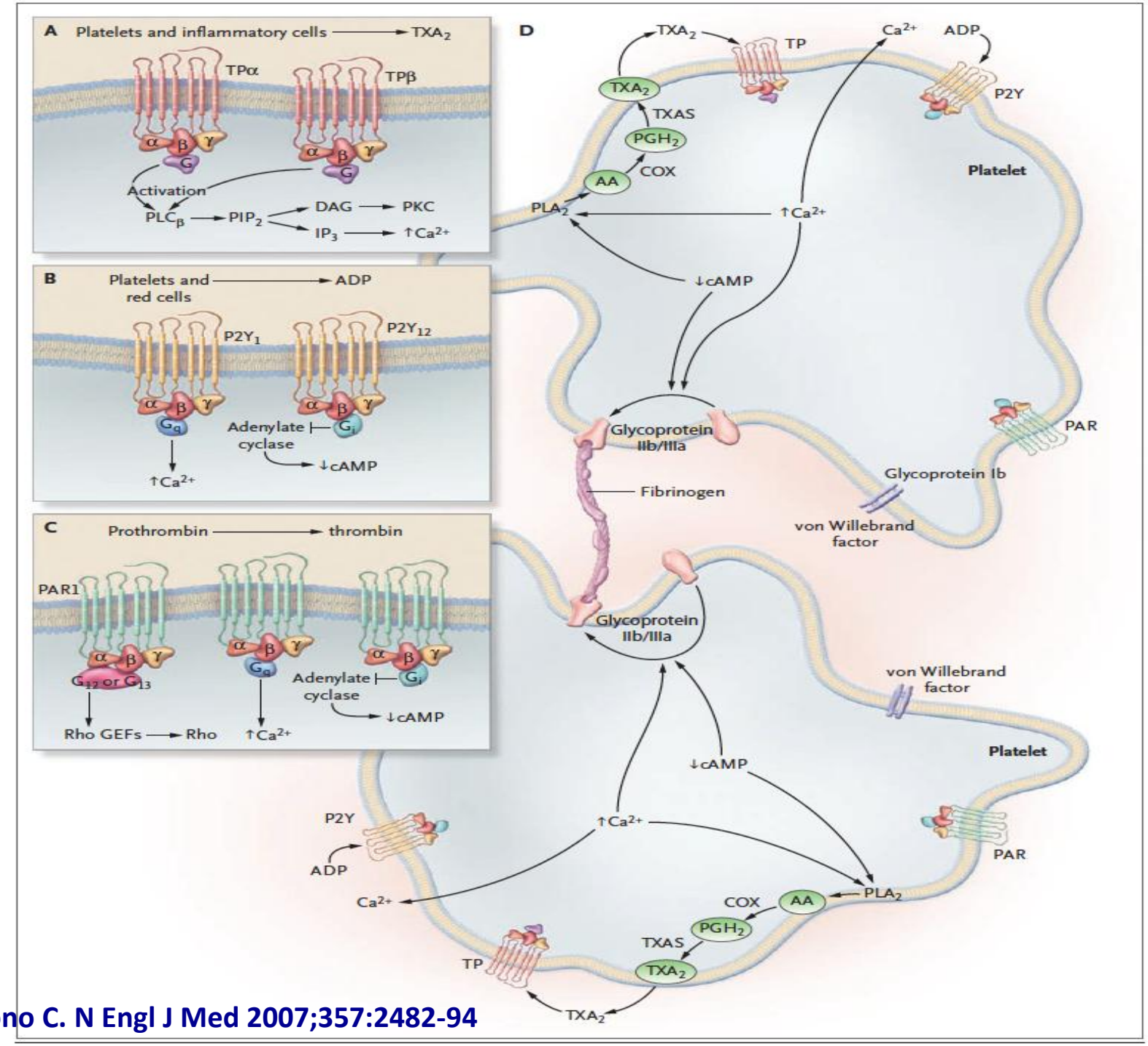
Davì G & Patrono C. N Engl J Med 2007;357:2482-94

Platelets circulate in an inactive form in the vasculature

Damage to the endothelium and/or external stimuli activates platelets that adhere to the exposed subendothelial von Willebrand factor and collagen

This adhesion leads to activation of the platelet, shape change, and the synthesis and release of thromboxane (TxA2), serotonin (5-HT), and adenosine diphosphate (ADP)

Platelet stimuli cause conformational change in the platelet integrin glycoprotein (GP) IIb/IIIa receptor, leading to the high affinity binding of fibrinogen and the formation of a stable **platelet thrombus**



Davì G & Patrono C. N Engl J Med 2007;357:2482-94

TABLE 142-1 HERITABLE CAUSES OF ARTERIAL AND VENOUS THROMBOSIS

A. Arterial Thrombosis

Platelet Receptors

- β3 and α2 integrins
- P_I A2 polymorphism
- Fc(gamma)RIIA
- GPIV T13254C polymorphism
- GPIb
- Thrombin receptor PAR1-5061 → D

Redox Enzymes

- Plasma glutathione peroxidase
- H2 promoter haplotype
- Endothelial nitric oxide synthase
- –786T/C, –922A/G, –1468T/A
- Paraoxonase
- –107T allele, 192R allele

Homocysteine

- Cystathionine β-synthase 833T → C
- 5,10-Methylene tetrahydrofolate reductase (MTHFR) 677C → T

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Arterial thrombus formation in cardiovascular disease

Giuseppe Lippi, Massimo Franchini and Giovanni Targher

- The **pathogenesis** of arterial thrombosis is complex and dynamic. Unlike venous thrombi, arterial thrombi typically form under conditions of high blood flow and are mainly composed of platelet aggregates, giving them the appearance of **'white clots'**
- Strong evidence suggests that arterial thrombi originate as a consequence of an injured atherosclerotic plaque, and that their formation involves the release of prothrombotic material (such as tissue factor), platelet aggregation, and platelet adhesion to the vascular wall

Nature Rev Cardiol 2011; 8: 502-512

Hemostasis is the host defense system aimed at preserving the integrity of the circulatory system in mammals. By necessity, hemostasis is a highly complex and tightly regulated process that involves blood cells (erythrocytes, platelets, and leukocytes), soluble plasma proteins, and the vessel wall. The **endothelium** is an inert surface that separates blood cells and soluble plasma proteins involved in blood coagulation and fibrinolysis from subendothelial vessel components.

Physiologically,

hemostasis is activated after injury of the vessel wall.

Exposure of the **subendothelial matrix** and activation of **endothelial cells** are the two most important events following vessel injury.

Two consequences of endothelial activation are the expression of adhesion receptors, including intercellular adhesion molecule (ICAM) 1, ICAM2, ICAM3, vascular adhesion molecule, and platelet endothelial cell adhesion molecule on the endothelial cell membrane, and the release of Weibel/Palade bodies via exocytosis.

Alterations of the plasma membrane lipid bilayer result in the exposure of an endothelial surface to the blood flow that is rich in negatively charged phospholipids, which can bind coagulation factors and other hemostatic molecules (such as **tissue factor**), thereby promoting prothrombotic signaling. After release of tissue factor from injured endothelial cells, inactive blood coagulation proteins (zymogens) are sequentially converted into the corresponding active enzymes through a cascade of sequential, calcium-dependent enzymatic reactions. The rapid production of **thrombin** marks the initiation of thrombus formation.

- Notably, **arterial** and **venous thrombi** differ in their composition. **Arterial thrombi** are typically composed mainly of **platelet aggregates**, giving the appearance of **'white clots**'

- **Venous thrombi** largely consist of **fibrin** and **red blood cells** and are thereby identified as **'red clots**'. Although platelets accumulate at the 'head' of the venous thrombus, their incorporation gradually decreases and the clots become more 'red', because they are predominantly composed of fibrin and erythrocytes
- **Pathological thrombosis** occurs when the hemostatic pathway is so strongly activated that it exceeds the normal regulatory counterbalance by anticoagulant factors, which are supposed to limit and localize thrombus formation to the injured area

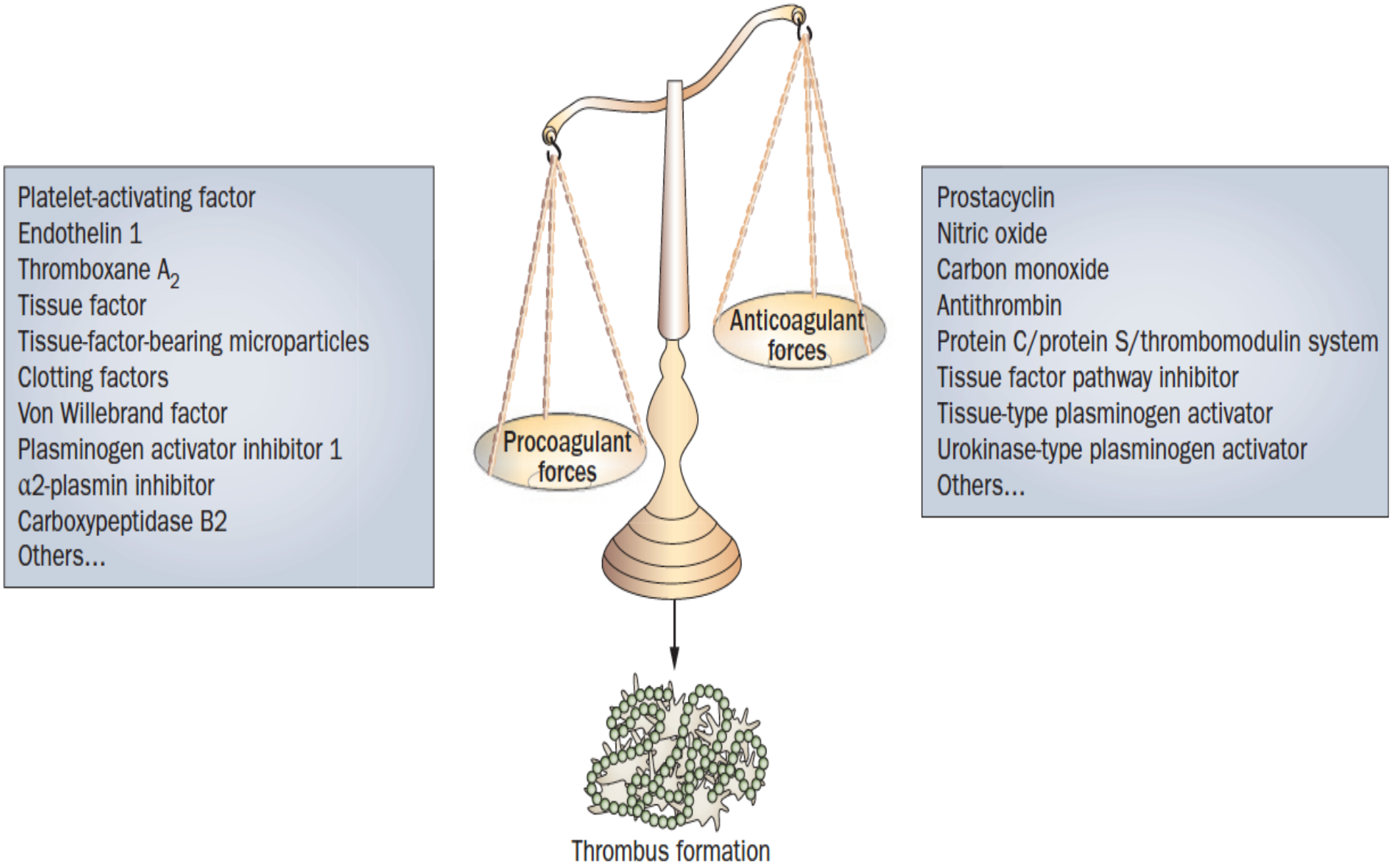
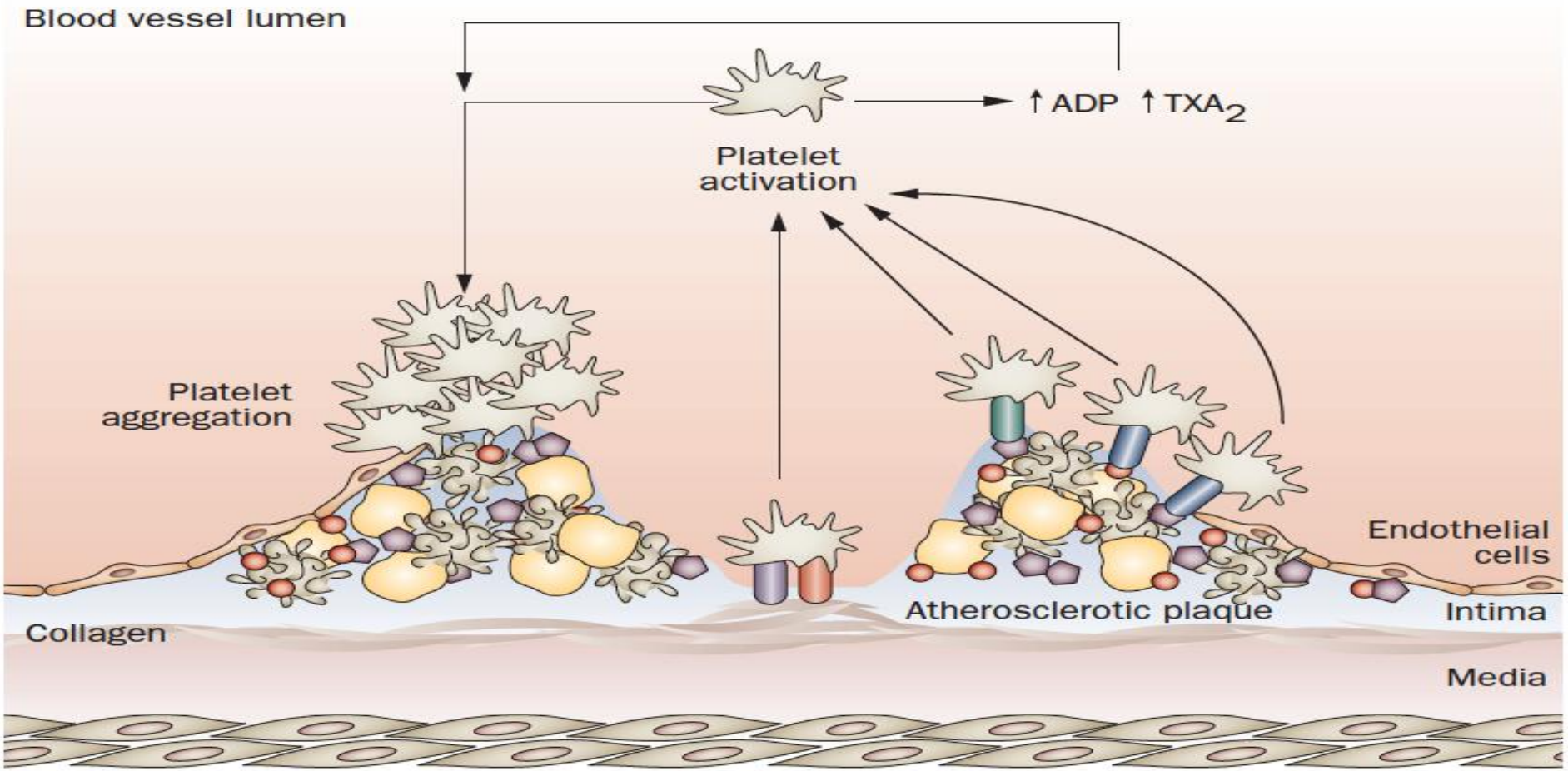


Figure 1 | An imbalance between prothrombotic and antithrombotic forces in the blood promotes the development of arterial thrombi.

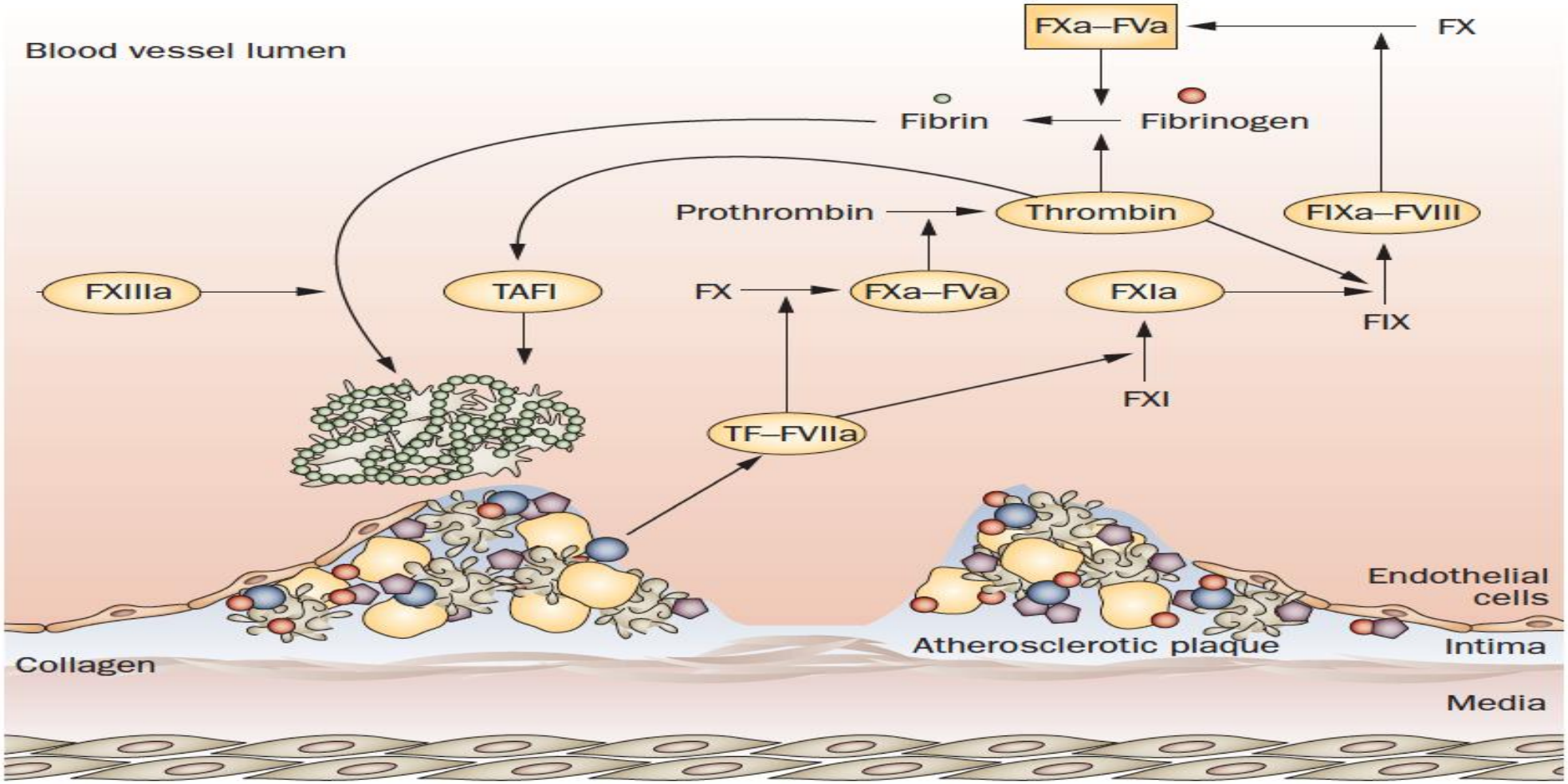
Nature Rev Cardiol 2011; 8: 502-512

Platelet activation and aggregation in the context of arterial thrombus formation



Nature Rev Cardiol 2011; 8: 502-512

The activation of blood coagulation in arterial thrombus formation



Nature Rev Cardiol 2011; 8: 502-512

The **vascular endothelium** controls platelet reactivity by means of three pathways:

- **arachidonic acid–prostacyclin** pathway
- **L –arginine–nitric oxide** pathway
- **endothelial ectoadenosine diphosphatase** (ecto-ADPase) pathway

- Activated platelets can also influence the progression of plaque formation by releasing adhesive ligands, such as P-selectin, that become expressed on the platelet membrane and mediate platelet–endothelium interactions
  - Signaling by **P-selectin** stimulates monocytes and macrophages to produce chemoattractants or growth factors
- Moreover, engagement by P-selectin of the P-selectin glycoprotein ligand 1 on the monocyte surface initiates the formation of platelet–monocyteaggregates and outside-in signaling that induces the transcription of COX-2

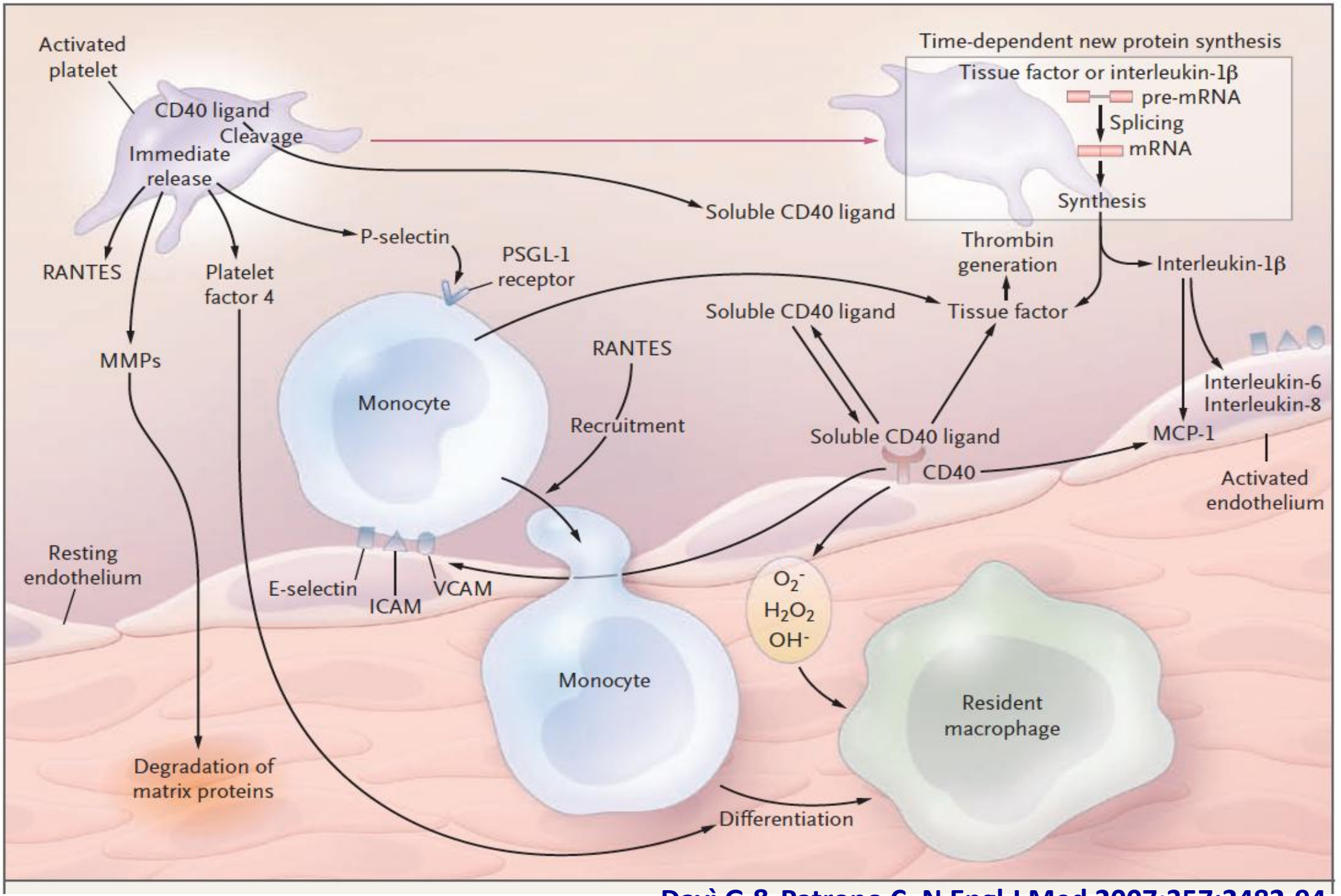
Platelet-Derived Mediators of Inflammation

- Activated platelets release inflammatory and mitogenic mediators into the local microenvironment

- Thereby altering the chemotactic and adhesive properties of endothelial cells. These platelet induced alterations of endothelial-cell function support the chemotaxis, adhesion, and transmigration of monocytes to the site of inflammation

- **CD40** ligand released from platelets induces inflammatory responses in the endothelium

- CD40 ligand released from platelets induces inflammatory responses in the endothelium
- This ligand, originally identified on activated T cells, is a trimeric transmembrane protein in the tumor necrosis factor family. CD40 ligand is stored in the cytoplasm of resting platelets and rapidly appears on the surface after platelet activation
- On the platelet membrane, the CD40 ligand undergoes cleavage over a period of minutes or hours, generating a functional soluble fragment
- Platelet derived CD40 ligand can induce endothelial cells to produce reactive oxygen species, adhesion molecules, chemokines, and tissue factor, all of which are components of an inflammatory response



Davì G & Patrono C. N Engl J Med 2007;357:2482-94

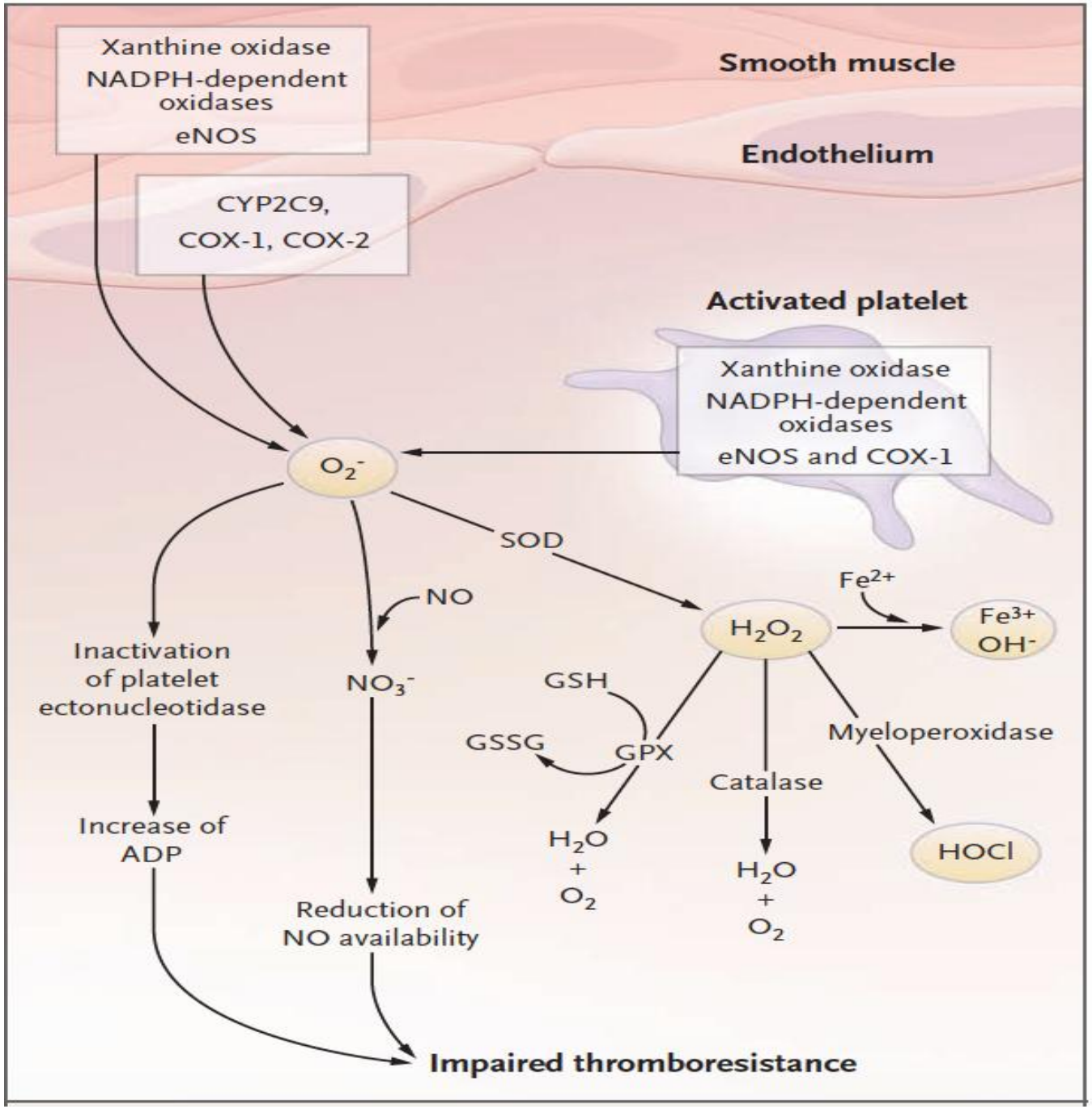
- Moreover, several cardiovascular risk factors, including cigarette smoking, hypertension, hypercholesterolemia and type 2 diabetes mellitus

- All them are associated with platelet activation and increased release of the CD40 ligand

- The combination of hyperinsulinemia and hyperglycemia up-regulates the release of platelet CD40 ligand and monocyte-derived tissue factor

Reactive Oxygen Species and Platelet Activation

The enhanced release of reactive oxygen species (e.g., O2−) from the vessel wall (where endothelial and smooth-muscle cells express a variety of enzymes that generate these species) indirectly affects the activation of platelets because the species scavenge nitric oxide



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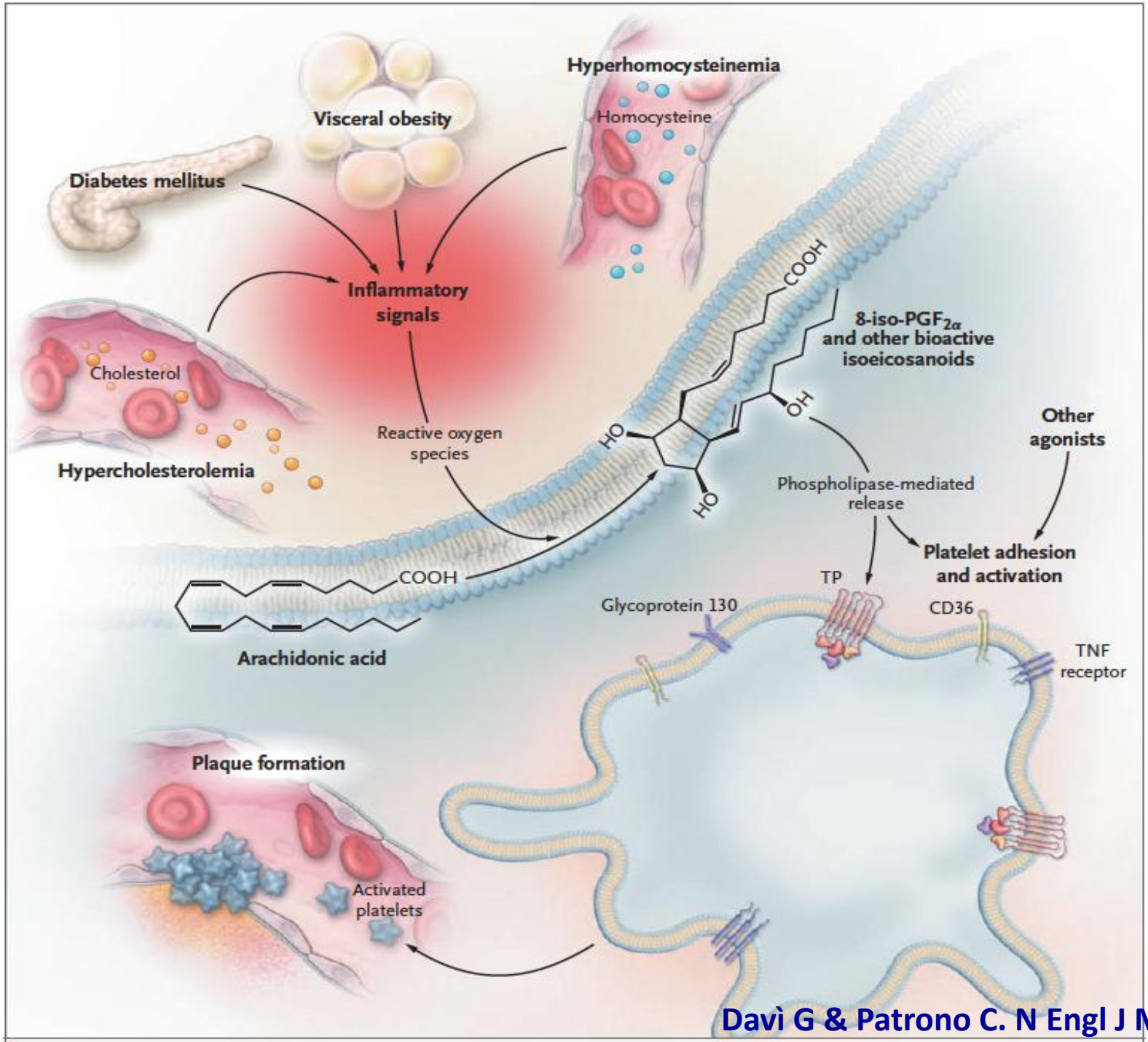


Davì G & Patrono C. N Engl J Med 2007;357:2482-94

Platelet Activation in **Acute Coronary Syndromes**

- Repeated, transient increases in the excretion of **thromboxane metabolites** have been described in patients with **acute coronary syndromes**

- The episodic nature of platelet activation is consistent with the concept of coronary thrombosis as a dynamic process, in which repeated episodes of thrombus formation and fragmentation occur over a disrupted plaque

- The consistent finding of a 50% reduction in the risk of myocardial infarction or death from vascular causes among patients with unstable angina who take aspirin24 highlights the importance of thromboxane A_2 as a platelet-mediated mechanism of the growth and stabilization of an intraluminal coronary thrombus

Review

Updates on Acute Coronary Syndrome
A Review

Alon Eisen, MD; Robert P. Giugliano, MD, SM; Eugene Braunwald, MD

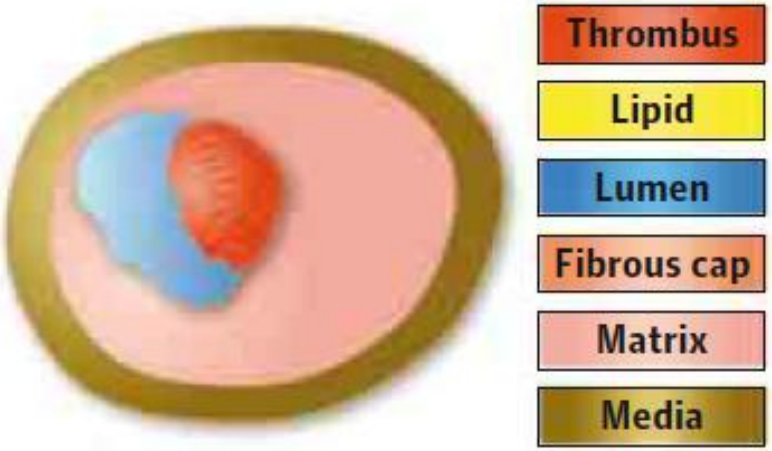
- Acute coronary syndrome (ACS), the acute manifestation of ischemic heart disease, remains a major cause of morbidity and mortality worldwide and is responsible for more than 1 million hospital admissions in the United States annually

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

- While **plaque rupture** is the most frequent cause of coronary thrombosis, studies with optical coherence tomography demonstrate that **superficial plaque erosion** is more common than previously thought

- **High-sensitivity troponin** assays and cardiac computed tomographic angiography are being increasingly used in diagnosis and risk stratification of patients with suspected ACS

Main Characteristics of Superficial erosion and Plaque Rupture as Causes of Thrombosis in Acute Coronary Syndrome



Plaque erosion	Plaque rupture
Lipid poor	Lipid rich
Proteoglycan and glycosaminoglycan rich	Collagen poor, thin fibrous cap
Nonfibrillar collagen breakdown	Interstitial collagen breakdown
Few inflammatory cells	Abundant inflammation
Endothelial cell apoptosis	Smooth muscle cell apoptosis
Secondary neutrophil involvement	Macrophage predominance
Female predominance	Male predominance
High triglycerides	High LDL

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

- A study using optical coherence tomography in 126 patients with

ACS showed that **plaque erosion** accounted for 31% of all cases

- Patients with **plaque erosion** presented more frequently with **NSTE-ACS** than patients with plaque rupture (61.5% vs 29.1%,P = .008)

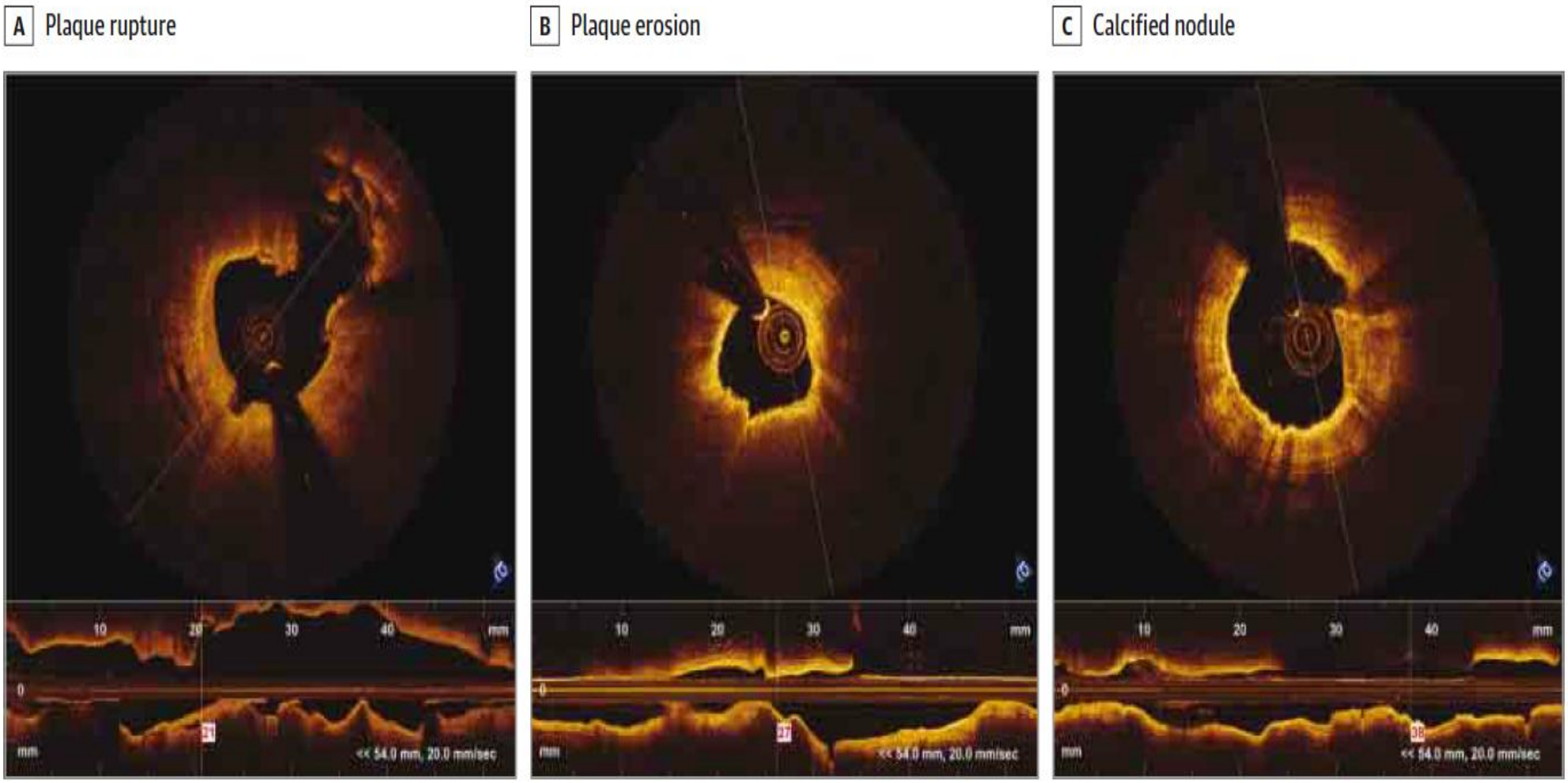
- In another study in 112 patients with **STEMI** who underwent percutaneous coronary intervention (PCI), both optical coherence tomography and intravascular ultrasound evaluated the culprit plaque morphology after aspiration thrombectomy

Plaque rupture was demonstrated in 64% of the patients, plaque

erosion in 27% of the patients, and calcified nodule in 8% of the patients

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Representative Optical Coherence Tomography Images of Underlying Plaque Morphologies in ST-Segment Elevation Myocardial Infarction



JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

- **Biomarkers** as **hsTn** assays became increasingly available in recent years, several studies examined their clinical implications

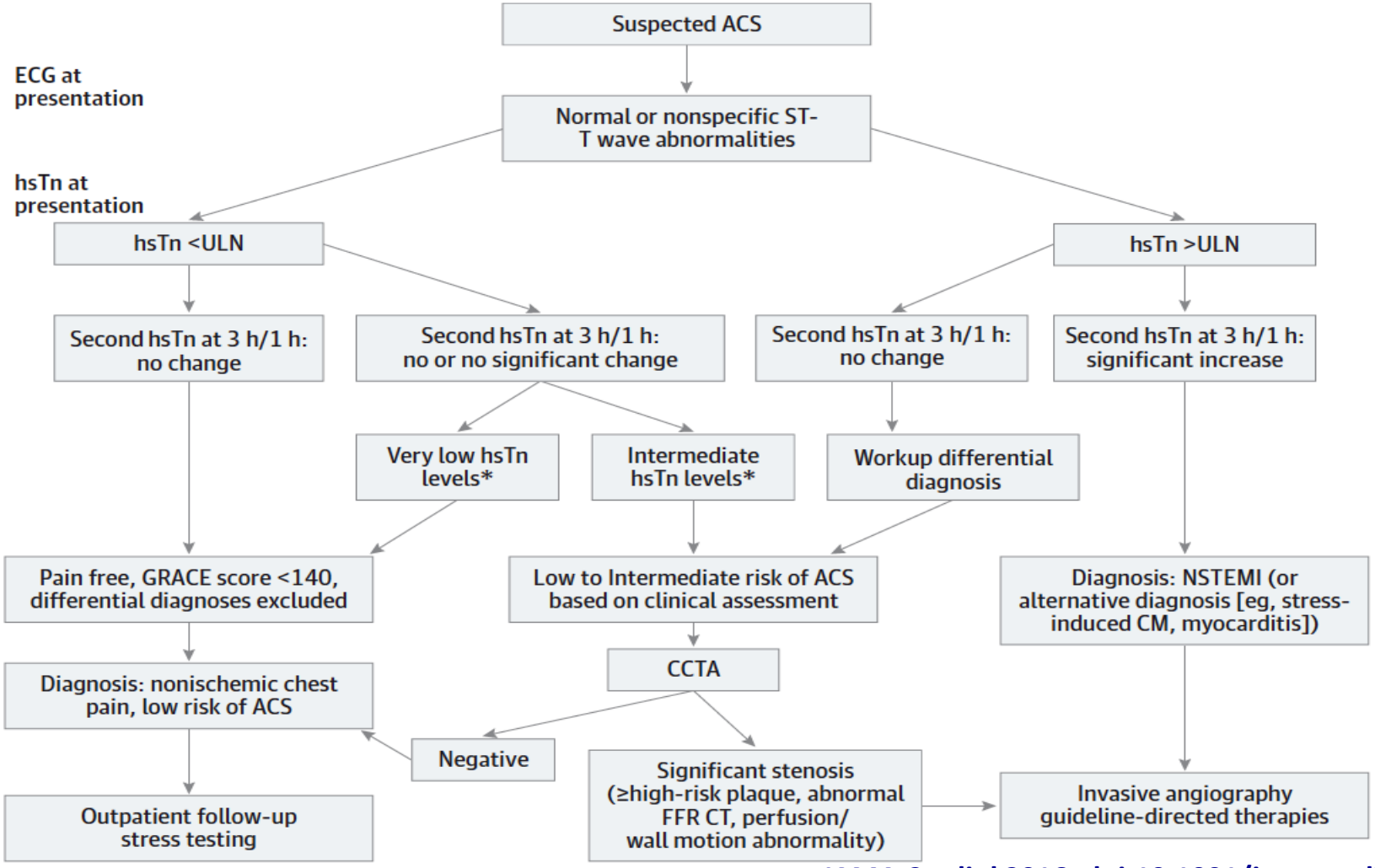
- Data from 48 594 patients who were admitted for suspected ACS in the SWEDEHEART Registry demonstrated that almost 90% of patients had a **detectable hsTnT level** on admission

- Using hsTn to rule out an MI in patients presenting with chest pain in the emergency department has become increasingly common

- Patients with chest pain but undetectable hsTnT levels and an electrocardiogram without signs of ischemia (n = 14 636) were shown to be at minimal risk of MI or death within 30 days (**negative predictive value for MI,99.8%**)

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Suggested Algorithm for the Use of High-Sensitivity Troponin Assays and Coronary Computed Tomographic Angiography in the Evaluation of Patients With Suspected Acute Coronary Syndrome (ACS) in the Emergency Department



JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

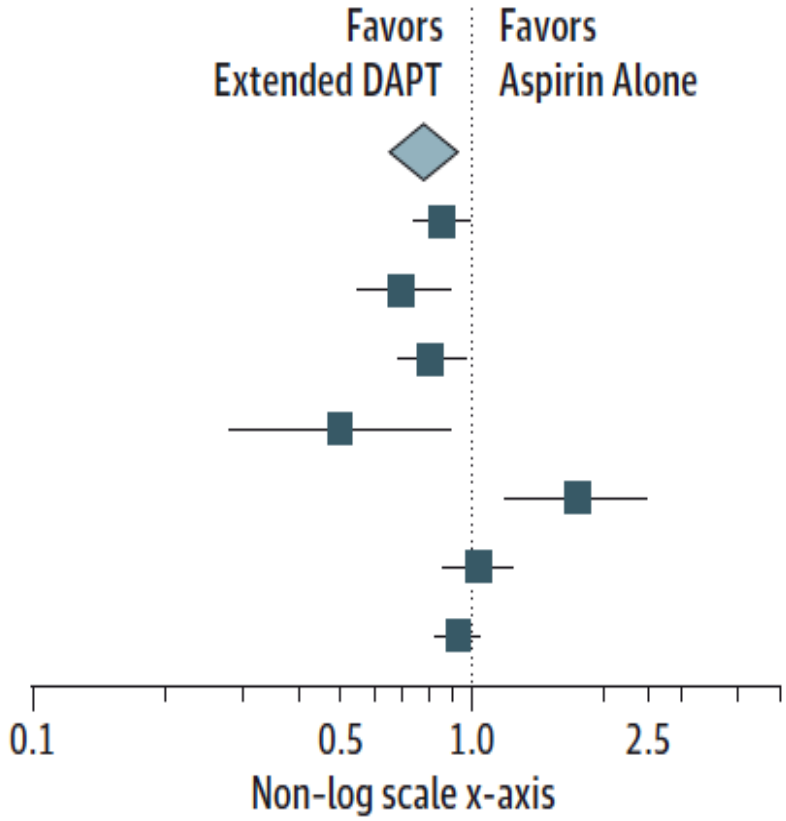
- New data from long-term **dual antiplatelet therapy** studies and investigations of anticoagulants provide important insights into the balance between ischemic and bleeding risks

- The added benefit of **percutaneous coronary intervention** in non–infarct-related arteries in patients with ST-segment elevation myocardial infarction has been demonstrated in randomized trials, and the radial approach has become the standard of care in patients with ACS undergoing angiography

- Promising old and new adjunctive therapies, such as pretreatment with β-blockers, ezetimibe, and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, are discussed

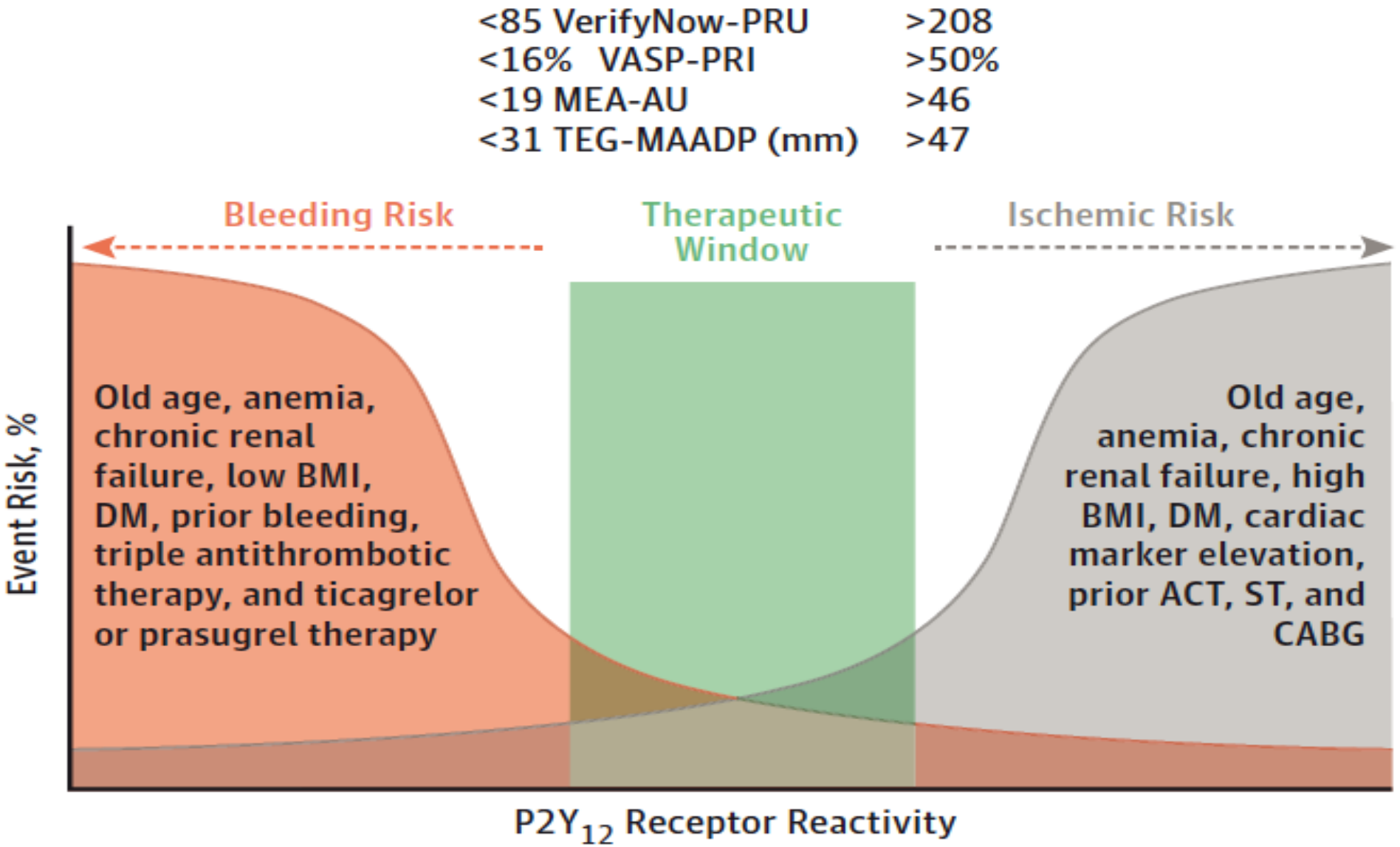
Figure 4. Risk of Individual Cardiovascular and Bleeding End Points Comparing Extended Dual Antiplatelet Therapy (DAPT) vs Aspirin Alone in a Meta-analysis of 6 Trials in 33 435 Patients With a Prior Myocardial Infarction

Source	Risk Ratio (95% CI)	*P* Value
Major adverse cardiovascular events	0.78 (0.67-0.90)	.001
Cardiovascular death	0.85 (0.74-0.98)	.03
Myocardial infarction	0.70 (0.55-0.88)	.003
Stroke	0.81 (0.68-0.97)	.02
Stent thrombosis (definite/probable)	0.50 (0.28-0.89)	.02
Major bleeding	1.73 (1.19-2.50)	.004
Noncardiovascular death	1.03 (0.86-1.23)	.76
All-cause death	0.92 (0.83-1.03)	.13



JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Therapeutic Window Concept for P2Y12 Receptor Reactivity



JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Key Changes to the North American and European Non–ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) Practice Guidelines

Source	Key Changes
Amsterdam et al,[62] 2014	1. An ischemia-guided strategy is recommended for patients at low risk (TIMI score 0-1 or GRACE score <109). 2. Either clopidogrel or ticagrelor can be used initially with either an early invasive or ischemia-guided strategy (COR I, LOE B). Ticagrelor may be preferred over clopidogrel as the initial treatment (COR IIa, LOE B). In patients treated with ticagrelor, the preferred aspirin maintenance dosage is 81 mg/d. 3. Use prasugrel only in patients receiving coronary stents (COR I, LOE B). 4. Bivalirudin is preferred over UFH* + GP IIb/IIIa in patients undergoing PCI who are at high risk of bleeding (COR IIa, LOE B). 5. There is no benefit of early invasive strategy in women with low-risk features (COR III). 6. In patients with possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD, it is reasonable to initially perform (without serial ECGs and troponins) coronary CT angiography to assess coronary artery anatomy (COR IIa, LOE A).

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Key Changes to the North American and European Non–ST Segment Elevation Acute Coronary Syndrome (NSTE-ACS) Practice Guidelines

Roffi et al,[63] 2016	1. The transradial approach for vascular access is recommended for coronary angiography and PCI (COR I, LOE A). 2. There is a new algorithm for NSTEMI rule in and rule out based on high-sensitivity cardiac troponin assessment at presentation and at 1 h (COR I, LOE B). 3. It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known (COR III, LOE B). 4. While a 1-y duration of dual antiplatelet therapy in patients with NSTE-ACS is recommended based on individual patient ischemic and bleeding risk profiles, dual antiplatelet therapy duration may be shortened (ie, 3-6 mo) or extended (ie, up to 30 mo) in selected patients if required (COR IIb). 5. A new-generation, drug-eluting stent may be considered over a bare-metal stent even if short dual antiplatelet therapy is planned because of increased bleeding risk (COR IIb, LOE B) or in patients treated with oral anticoagulants (COR IIa, LOE B). 6. In patients undergoing PCI, uninterrupted therapeutic anticoagulation with VKAs or NOACs should be considered during the periprocedural phase (COR IIa, LOE C). 7. Direction for managing antiplatelet therapy in patients who are treated with chronic oral anticoagulants is based on the $CHADS_2$-VASc and HAS-BLED scores.

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Key Points in Acute Myocardial Infarction (MI) in Women

Key Point	Description
Pathophysiology	• Plaque rupture is the most common cause of acute MI in both sexes. • There is a greater role of microvascular disease and non-obstructive coronary artery disease in women. • There is an increased prevalence of plaque erosion, particularly in younger women. • Spontaneous coronary artery dissection is a very rare cause of acute MI that occurs more frequently in women.
Risk factors	• Several risk factors in women increase the risk of acute MI more so than in men, including hypertension, diabetes mellitus type 2, depression, and other psychosocial risk factors. • Depression is more prevalent in women and increases a woman's risk for cardiac death or MI by ≥50%, particularly in young and middle-aged women. • Smoking is the most important preventable cause of MI in women.

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

Key Points in Acute Myocardial Infarction (MI) in Women

Clinical presentation	• First presentation of acute MI is at an older age compared with men. • Women are more commonly seen with atypical chest pain and angina-equivalent symptoms (eg, dyspnea, palpitations, fatigue, weakness, or indigestion). • Women are more likely to have high-risk features at presentation. • There is a median delay of 2-5 h in presentation with acute MI.
Treatment	• Women are more likely to be undertreated in NSTE-ACS and in STEMI. • Women have increased bleeding risk in acute MI. • Cardiac rehabilitation is underused and underprescribed.
Outcome	• There has been a significant decline in CV death and MI overall in women in the last decade. However, this decline is absent in younger women. • The annual rate of CV death in women after MI is still greater than that in men. • There are higher rates of readmission and recurrent ischemic events in women in the first year after ACS.

JAMA Cardiol 2016; doi:10.1001/jamacardio.2016.2049

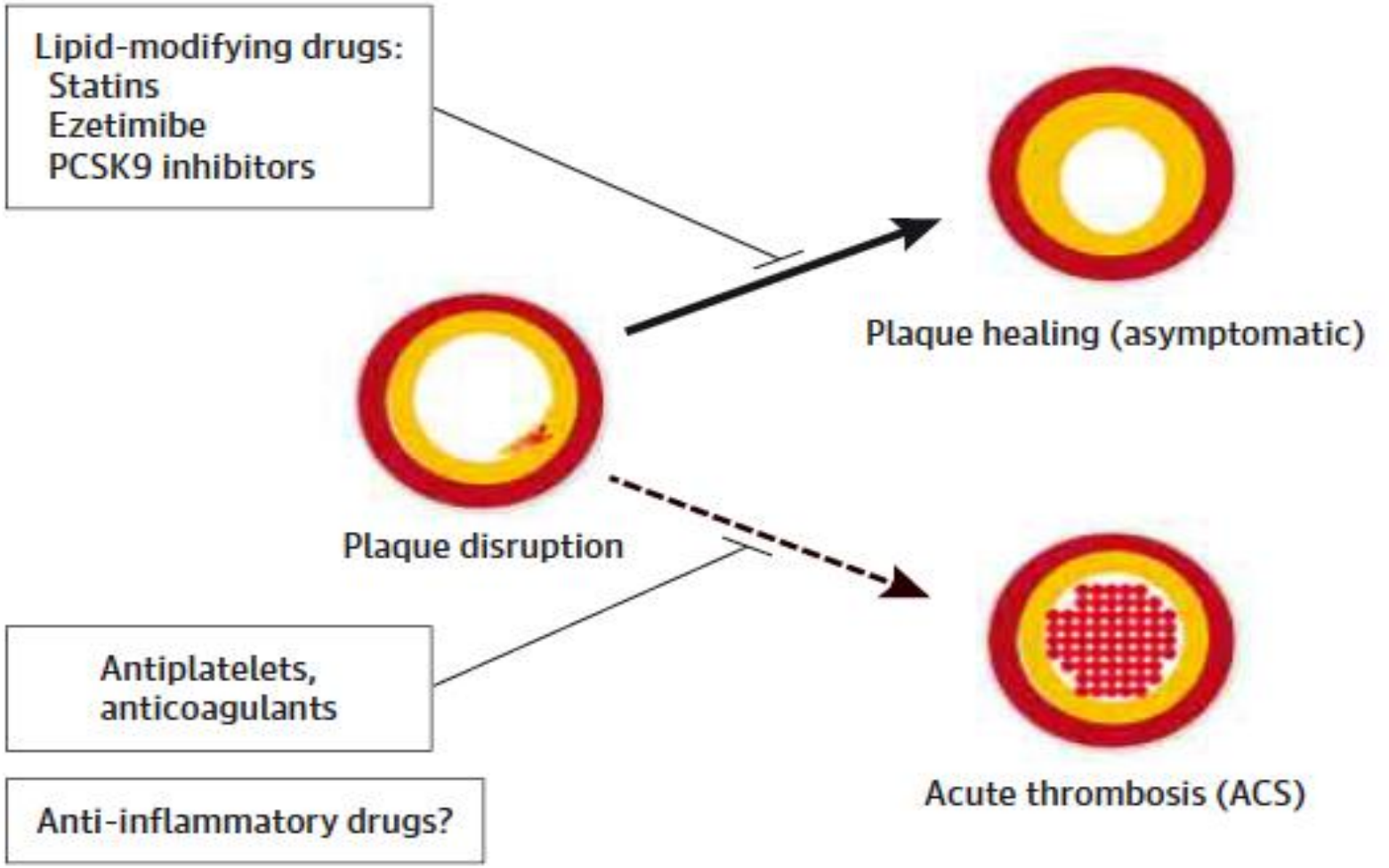
Key Unanswered Questions in Acute Coronary Syndrome (ACS)

Key Unanswered Question	Description
Pathophysiology	• Will superficial plaque erosion continue to rise to become the dominant pathophysiology of ACS? • Should patients be treated differently based on their underlying pathophysiology of ACS? • What are the critical determinants that cause one vulnerable plaque to cause a clinical event but another vulnerable plaque to be silent and heal?
Diagnosis	• What will be the role of concomitant use of coronary computed tomographic angiography and high-sensitivity troponin assays in evaluating patients with suspected ACS? • Will shorter rule-out algorithms with high-sensitivity troponin assays improve patients' outcomes? • What is the role of genetic testing to individualize treatment and improve patients' outcomes?
Acute treatment	• To what extent can the total ischemic time be reduced further in patients with STEMI? • What are the therapeutic targets of reperfusion injury? How can microvascular circulation after primary PCI be improved? • What is the preferred antithrombotic regimen during PCI? • What is the optimal timing for administering high-potency statins? • What is the optimal timing and dosing for administering β-blockers? Will β-blockers given before primary PCI improve patients' clinical outcomes? • What is the optimal timing of oral antiplatelet administration in patients with NSTE-ACS who are intended for an invasive strategy? • What is the role of platelet function testing during the acute phase of STEMI? • What are the indications for and timing of revascularization of obstructed non–infarct-related arteries? • What is the role of FFR-guided PCI in patients with NSTE-ACS? • What are the contemporary benefits of CABG vs PCI in patients with ACS and multivessel disease? • Will novel pharmacological and mechanical circulatory support strategies improve survival in patients with cardiogenic shock after STEMI? • What is the desired hemoglobin level in patients with ACS, and what is the optimal timing for blood transfusion?

Key Unanswered Questions in Acute Coronary Syndrome (ACS)

Chronic treatment	• What is the optimal duration and regimen of antiplatelet therapy after ACS, and how does this differ if an oral anticoagulant is needed? • Will newer-generation stents allow shortening of the duration of antiplatelet therapy after ACS? • Can dual antiplatelet therapy after ACS be replaced by a single potent $P2Y_{12}$ inhibitor? • What is the role of PCSK9 inhibitors in patients admitted with ACS?
Prognosis and secondary prevention	• Can we improve prediction of the risk of sudden cardiac death after ACS and identify who might benefit more from prevention strategies? • Can left ventricular remodeling be reduced by the angiotensin receptor blocker–neprilysin inhibitor? Will this translate into improved survival? • How can the rate of recurrent ischemic cardiovascular events after ACS be further reduced? • What is the role of cardiac regenerative medicine in patients with left ventricular dysfunction after MI?

Nature of the Disrupted Plaque and Possible Targets for Current and Future Therapies



ACS indicates acute coronary syndrome; PCSK9, proprotein convertase subtilisin kexin type 9.

Platelet Activation in **Acute Ischemic Stroke**

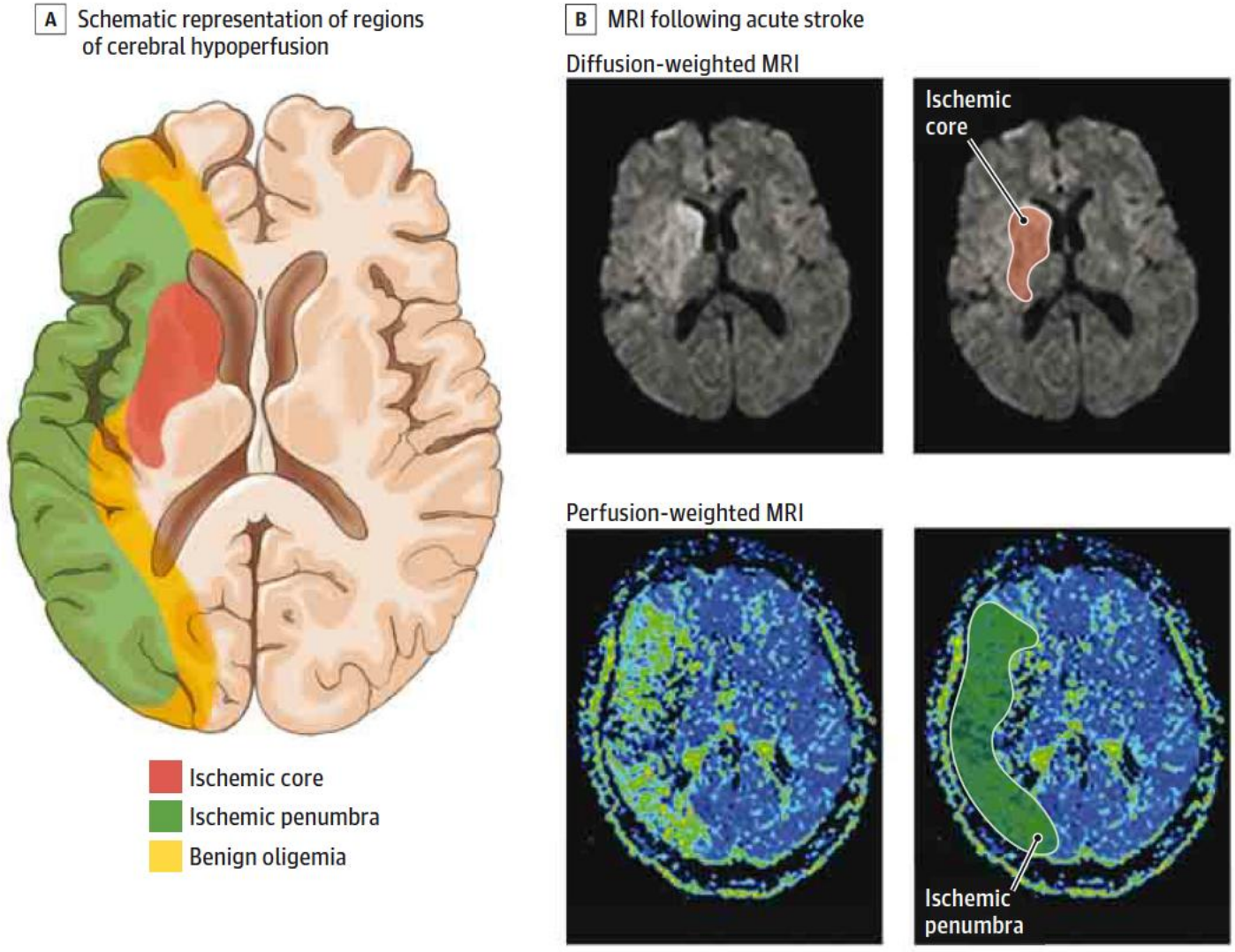
- **Platelet activation** is also important in patients with ischemic stroke, as suggested by biochemical measurements and trials of platelet inhibitors

- Episodic increases in **thromboxane biosynthesis** have been described in the acute phase of ischemic stroke, though with a lower frequency and shorter duration than in acute coronary syndromes

- This difference may reflect the heterogeneity of the mechanisms responsible for ischemic stroke — a thrombosis in a large artery accounts for only a fraction of the ischemic events

- The effect of **aspirin therapy**, started within 48 hours after the onset of symptoms of an acute ischemic stroke, on short-term rates of death and nonfatal outcomes is correspondingly smaller than the benefit seen in the acute phase of myocardial infarction

Regions of Cerebral Hypoperfusion Following Acute Ischemic Stroke



JAMA 2015; 313: 1451-1462

Common Signs of Acute Stroke and Tests Used in Ischemic Stroke Diagnostic Evaluation

Examination Findings Suggestive of Acute Stroke

Aphasia

Hemiparesis

Hemisensory loss

Hemineglect

Visual field deficit

Gaze deviation and eye movement abnormalities

Dysarthria

Gait instability and incoordination

Diagnostic Tests to Establish Diagnosis and Cause of Acute Stroke

Magnetic resonance imaging or computed tomography of the brain to evaluate for ischemia and exclude hemorrhage

Computed tomography or magnetic resonance angiogram to evaluate for intracranial or extracranial stenosis or occlusion

Echocardiogram to evaluate for cardioembolic source (ie, thrombus)

Telemetry and extended outpatient cardiac monitoring to evaluate for arrhythmias (ie, atrial fibrillation)

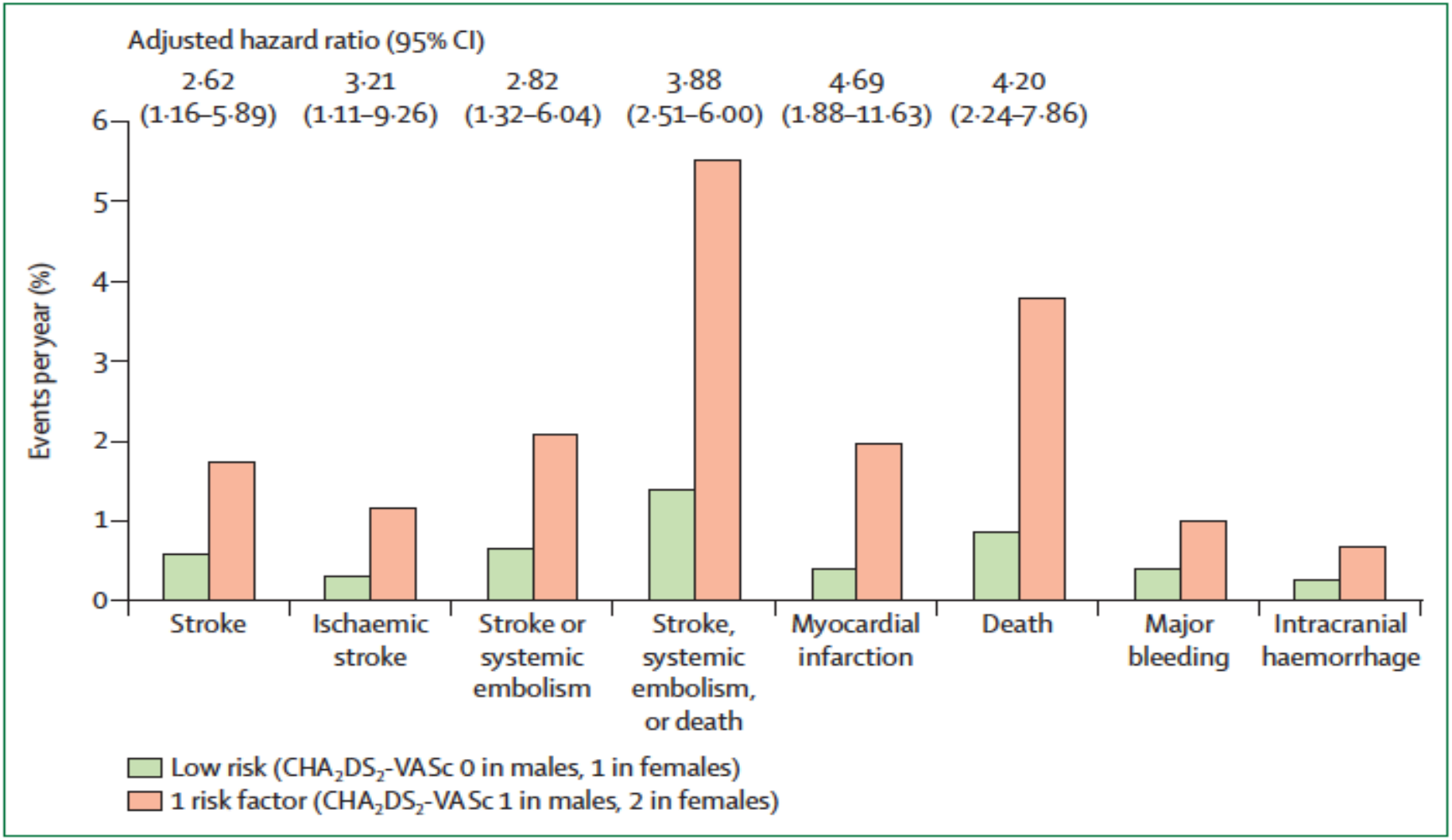
Lipid panel to evaluate for hyperlipidemia

Hemoglobin A_{1c} to evaluate for diabetes mellitus

In select patients, consider inflammatory markers, hypercoagulable workup, ultrasound of the lower extremities, lumbar puncture, and blood cultures

JAMA 2015; 313: 1451-1462

Risk of stroke with a single additional risk factor



Lancet 2016; 388: 806-817

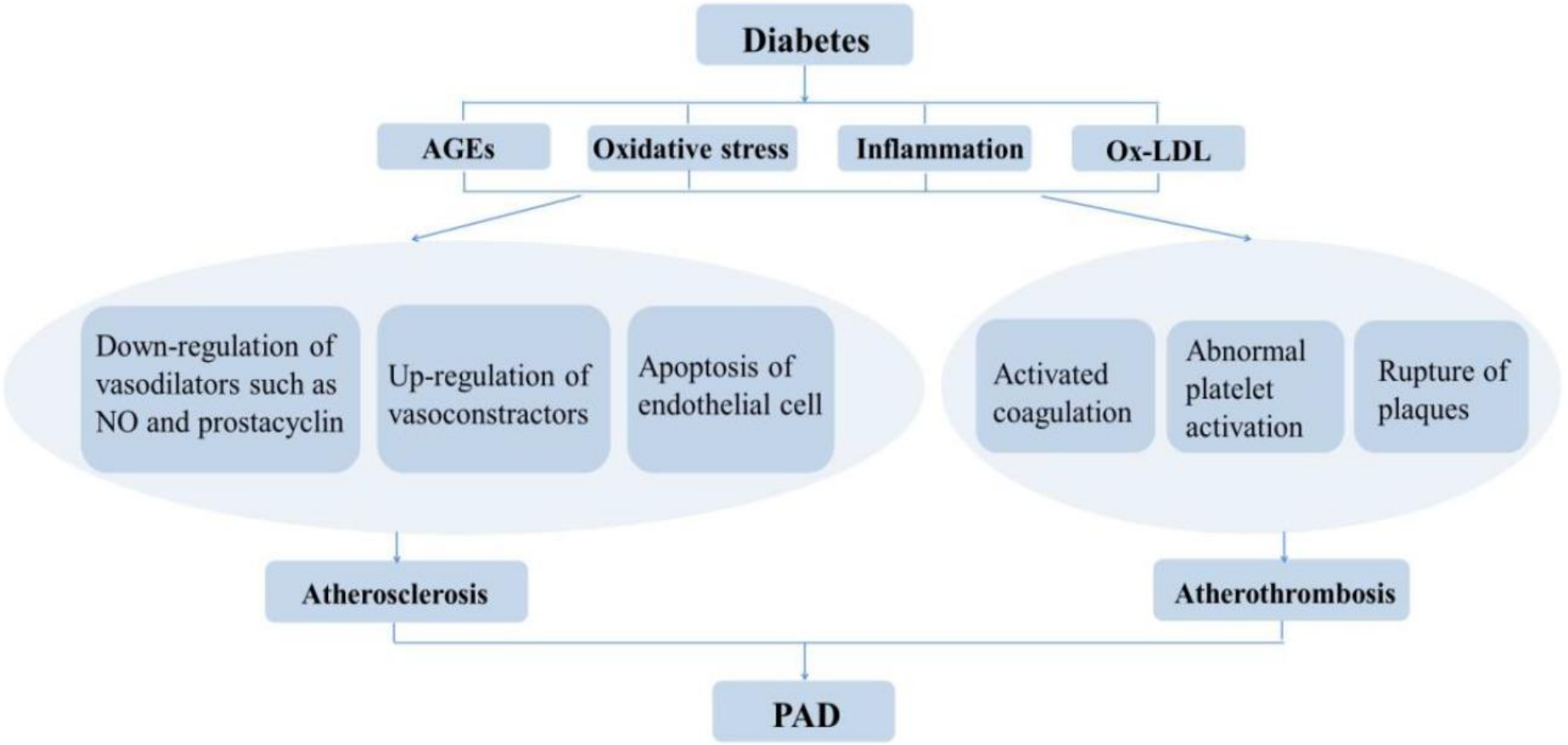
Platelet activation in **Peripheral artery Disease (PAD)**

- Peripheral arterial disease (PAD) often refers to progressive narrowing and blockade of peripheral arteries, especially the lower extremity arteries

- The **risk factors** for developing PAD include smoking, diabetes mellitus (DM), obesity, high blood pressure, high cholesterol, aging and a family history of peripheral artery disease, heart disease and stroke

- DM is a major risk factor for PAD. PAD in diabetic patients progresses rapidly and is more diffuse and affects distal limb arteries, such as tibial and peroneal arteries compared with non-diabetic PAD

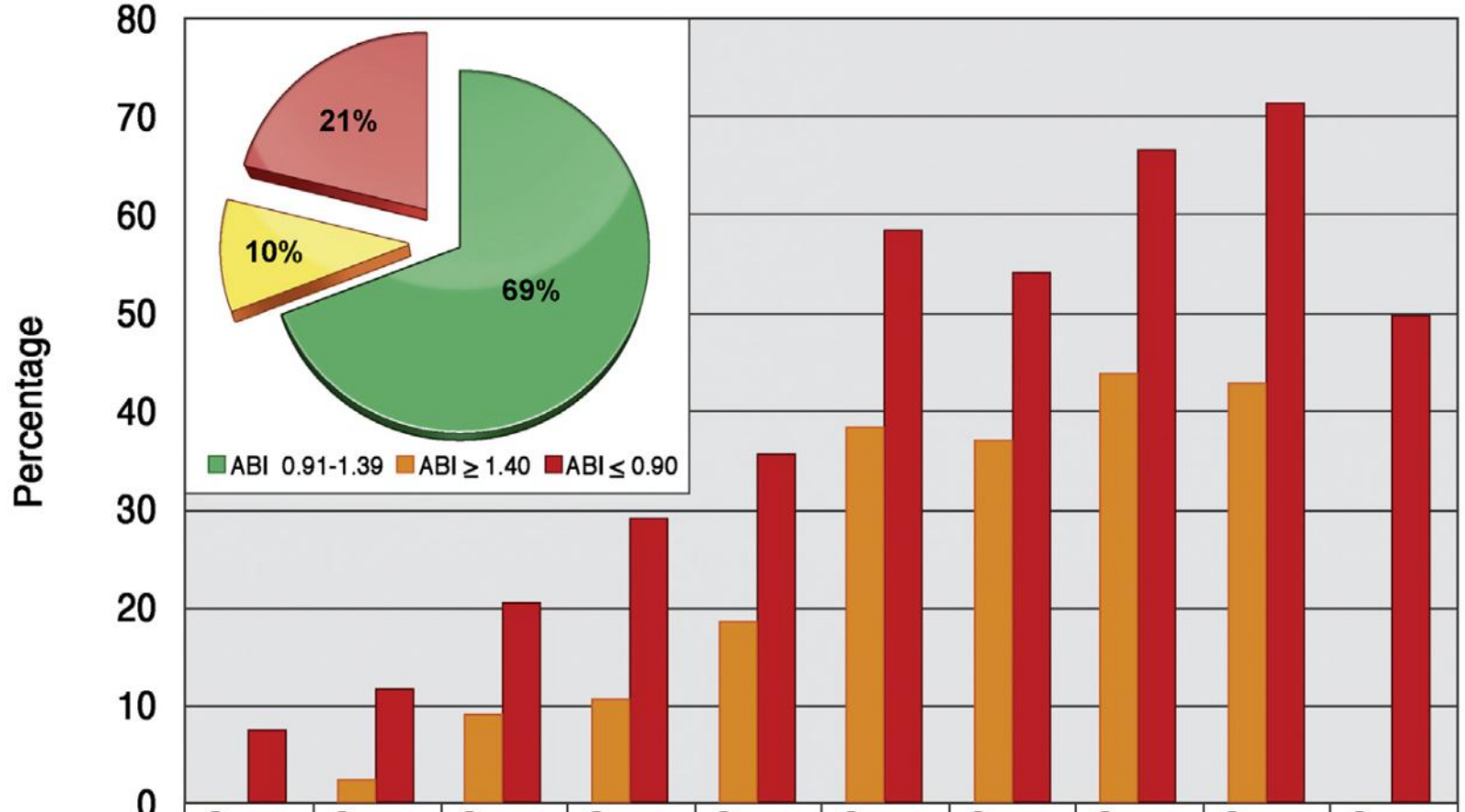
The pathophysiological characteristics of PAD in DM



J Diabetes 2016; doi: 10.1111/1753-0407.12474.

Prevalence of Peripheral Artery Disease by Abnormal Ankle-Brachial Index in Atrial Fibrillation Implications for Risk and Therapy

ABI Distribution of Any Category and CHA2DS2-VASc Score Including ABI 0.90



	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5	Score 6	Score 7	Score 8	Score 9
VASc	0	2.56	9.19	10.79	18.65	38.49	37.14	43.94	42.86	0
VASc + ABI	7.69	11.97	20.73	29.26	35.73	58.58	54.29	66.67	71.43	50

Violi F, Davì G, Hiatt W, et al. J Am Coll Cardiol 2013;62:2255-6

Triggers, targets and treatments for thrombosis

Nature 2008

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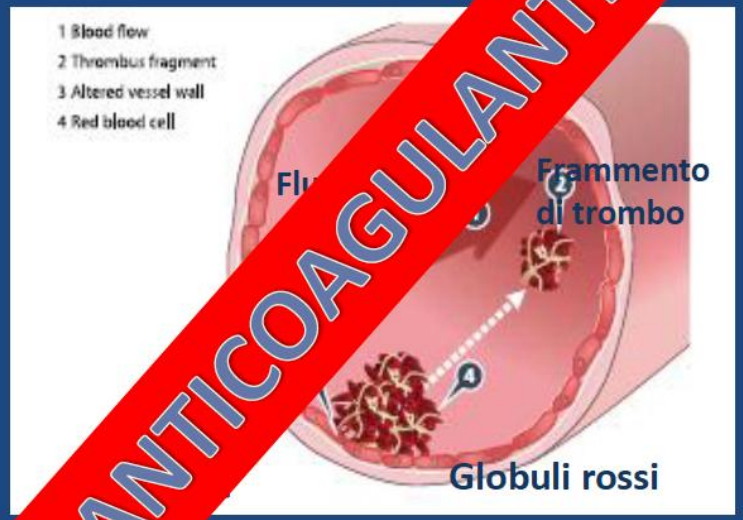
TROMBOSI VENOSA



ANTICOAGULANTI

Stasi, ***ipercoagulabilità***, danno endoteliale

TROMBOSI ARTERIOSA

ANTIAGGREGANTI

- Rottura placca
- Esposizione core lipidico
- Attivazione piastrinica