

# Non-ST Elevation Myocardial Infarction (NSTEMI)

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**Associate Professor**

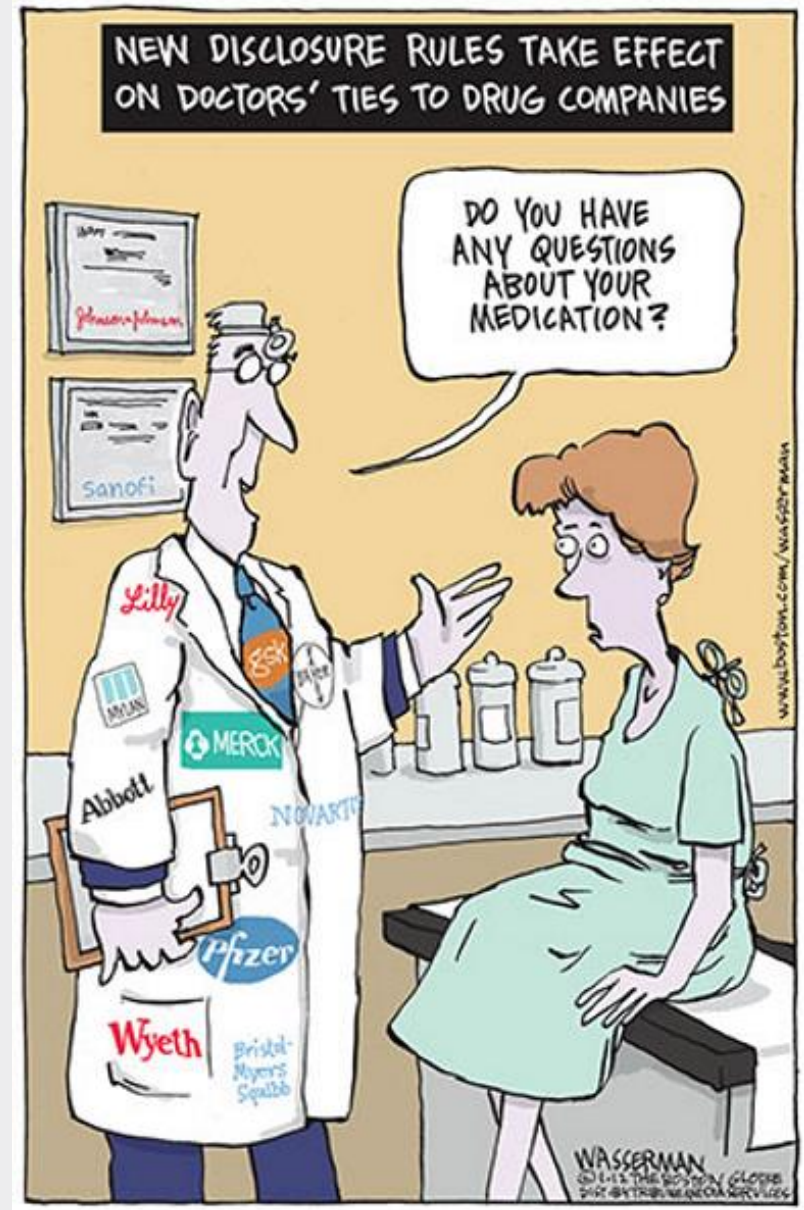
**Interventional Cardiology**

**Banner University Medical Center**

**University of Arizona College of Medicine Phoenix**

# DISCLOSURES

- Consultant Osprey Medical Pty, Ltd.
- Consultant Abiomed, Inc.

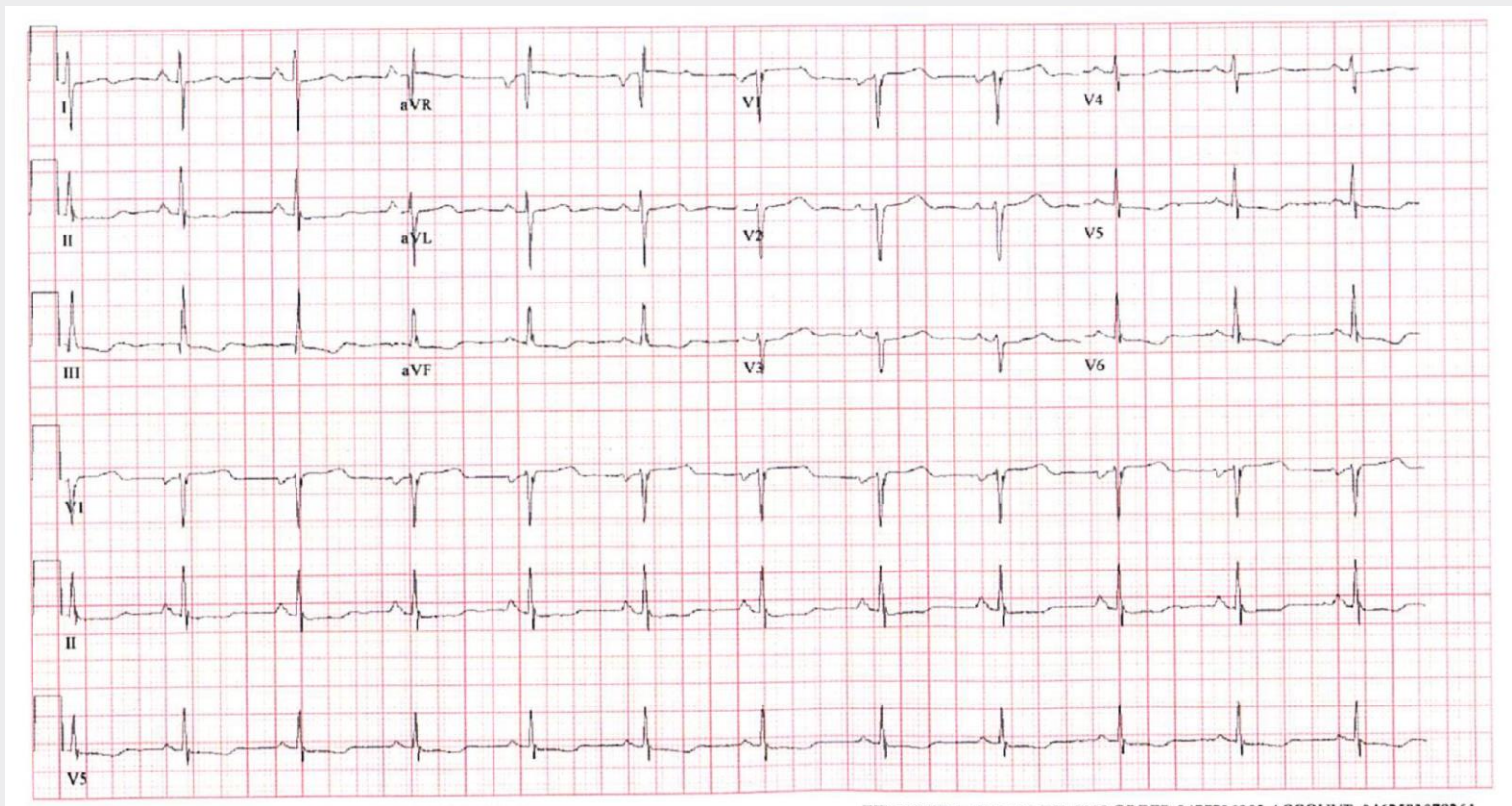


# CASE

54 year old female with HTN, HLD, DM, hypothyroidism, and obesity p/w chest pain and hypertensive urgency.

--CP 5/10, retrosternal pressure

--Initial troponin negative; second troponin elevated



# Question

The clinical presentation in the above case is consistent with which of the following syndromes:

- A) STEMI
- B) NSTEMI
- C) Unstable Angina
- D) Stable Angina
- E) Non-Cardiac Chest Pain

# Chest Pain Syndromes

## Acute Coronary Syndromes

STEMI  
NSTEMI  
UA

## Stable Angina

Chronic CAD

## Non-Cardiac Chest Pain

GERD  
Costochondritis

# ACS vs Stable Angina vs Non-Cardiac Chest Pain

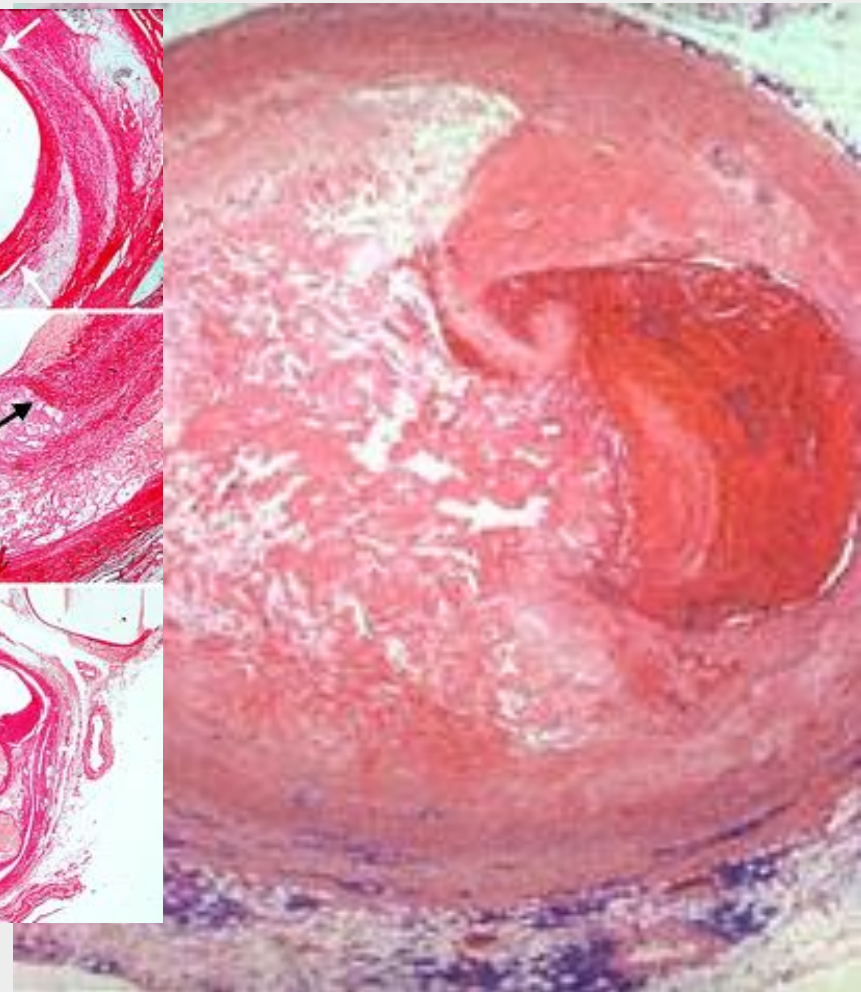
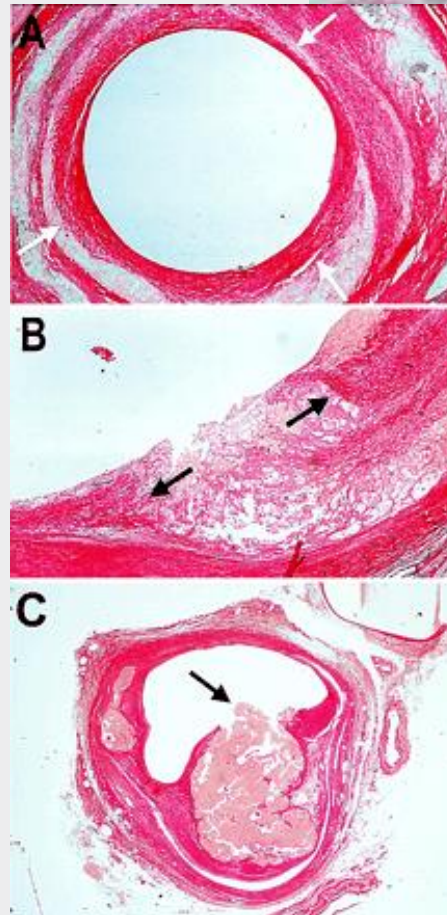
- ▶ History
  - ▶ Quality of pain
  - ▶ Risk factors
- ▶ Exam
  - ▶ Hypotension
  - ▶ Signs of heart failure
  - ▶ New murmur
- ▶ ECG
  - ▶ ST segment deviation
  - ▶ T wave inversions
- ▶ Cardiac Biomarkers
  - ▶ Elevated troponin



# Pathophysiology of ACS

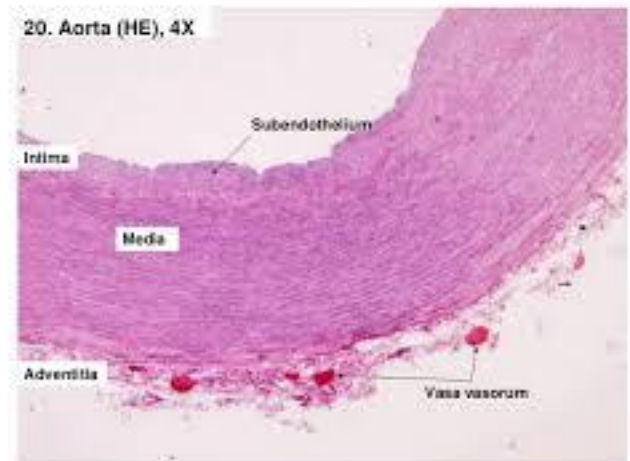
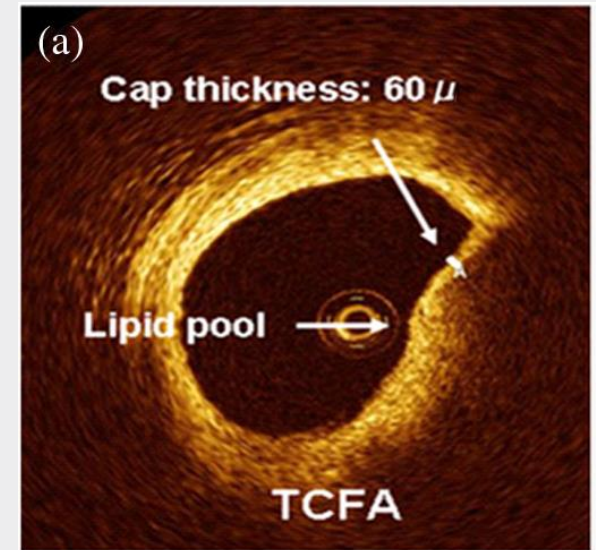
## Plaque Rupture

Disruption of fibrous cap with fissure resulting in hematoma or thrombus



## Vulnerability and Plaque Rupture

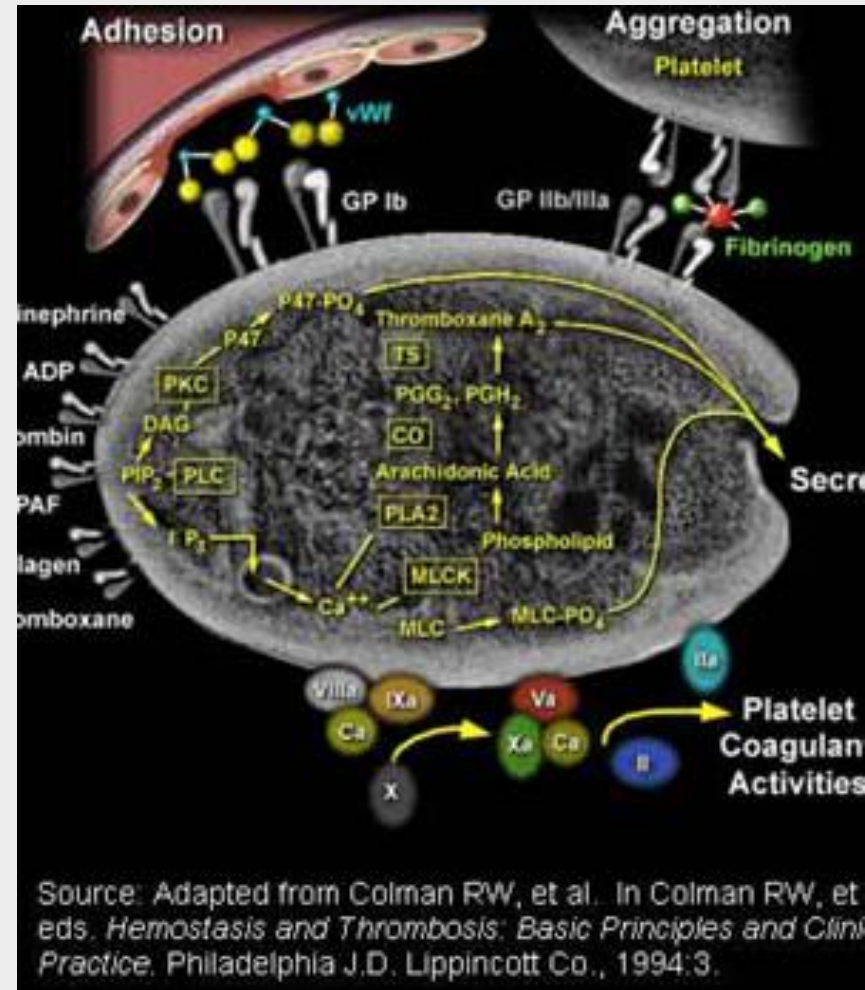
1. Thinner the fibrous cap  
greater likelihood of rupture
2. More macrophages (>25 per  
high-powered field), greater  
risk of rupture
3. 4-fold increase in vasa  
vasorum on ruptured plaques



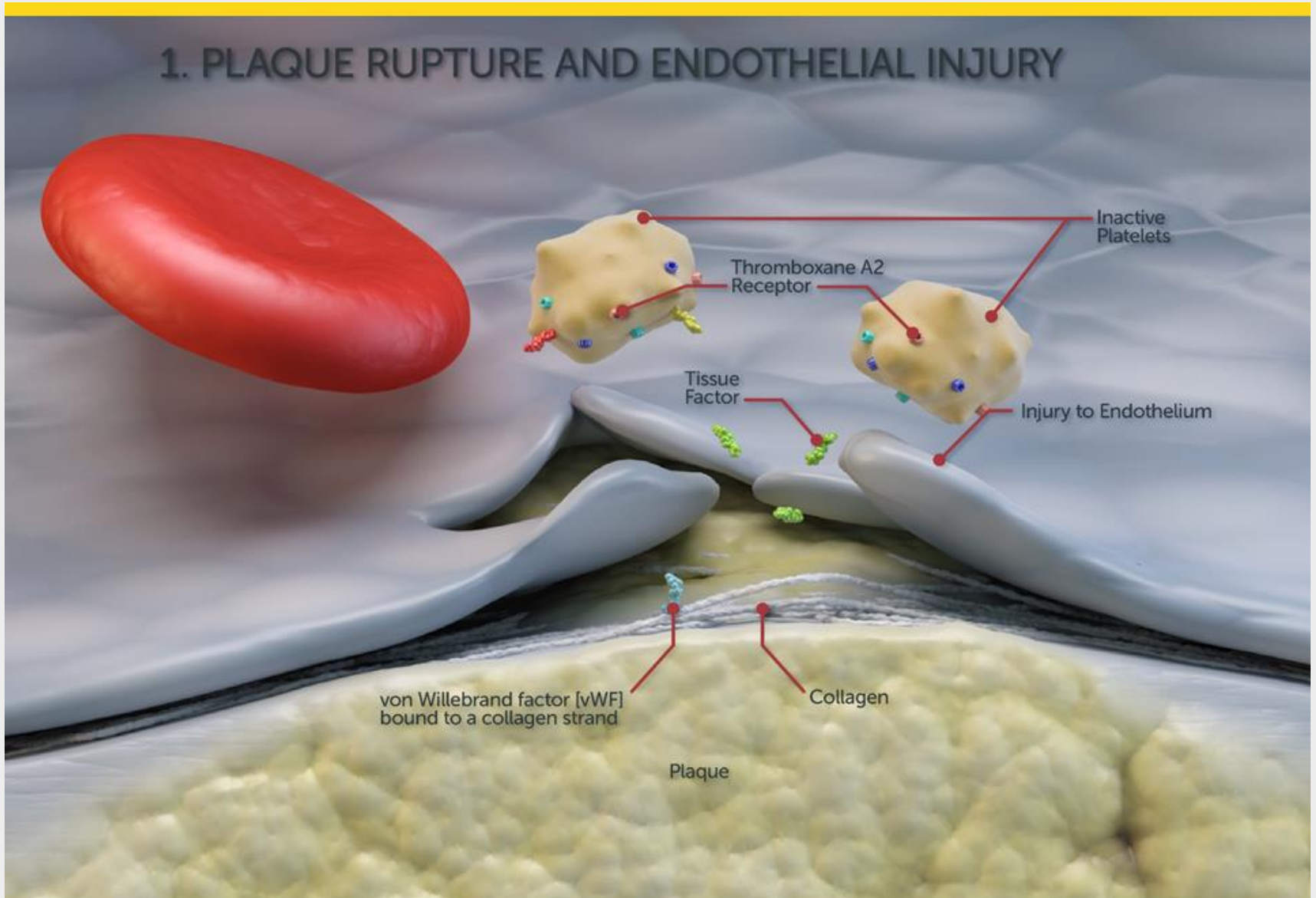


# Thrombosis

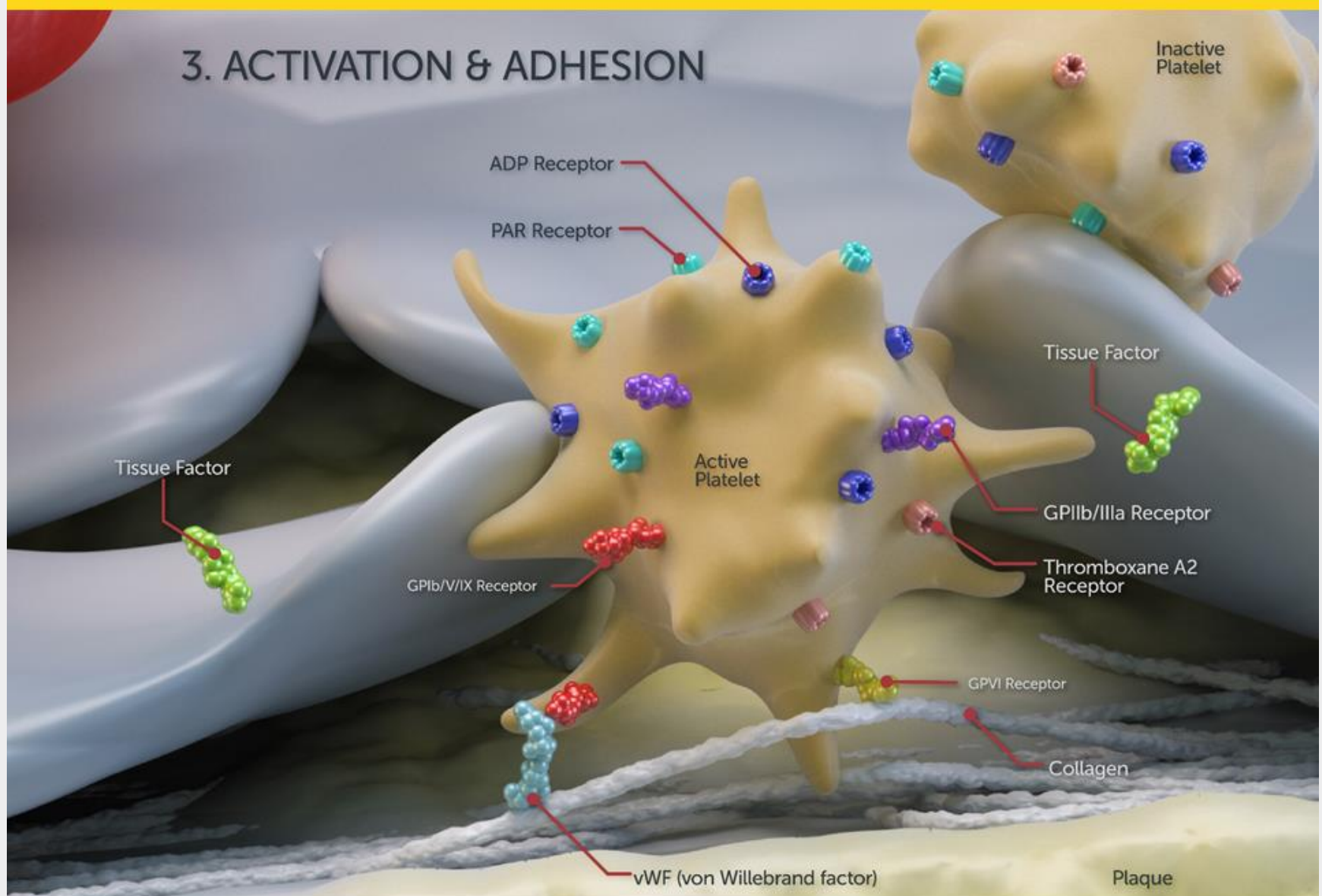
1. Disruption of fibrous cap exposes bloodstream to thrombogenic stimuli
2. Platelets activated by collagen and adhere to wall bound von Willebrand's factor
3. Results in activation of clotting cascade and formation of thrombus



## 1. PLAQUE RUPTURE AND ENDOTHELIAL INJURY



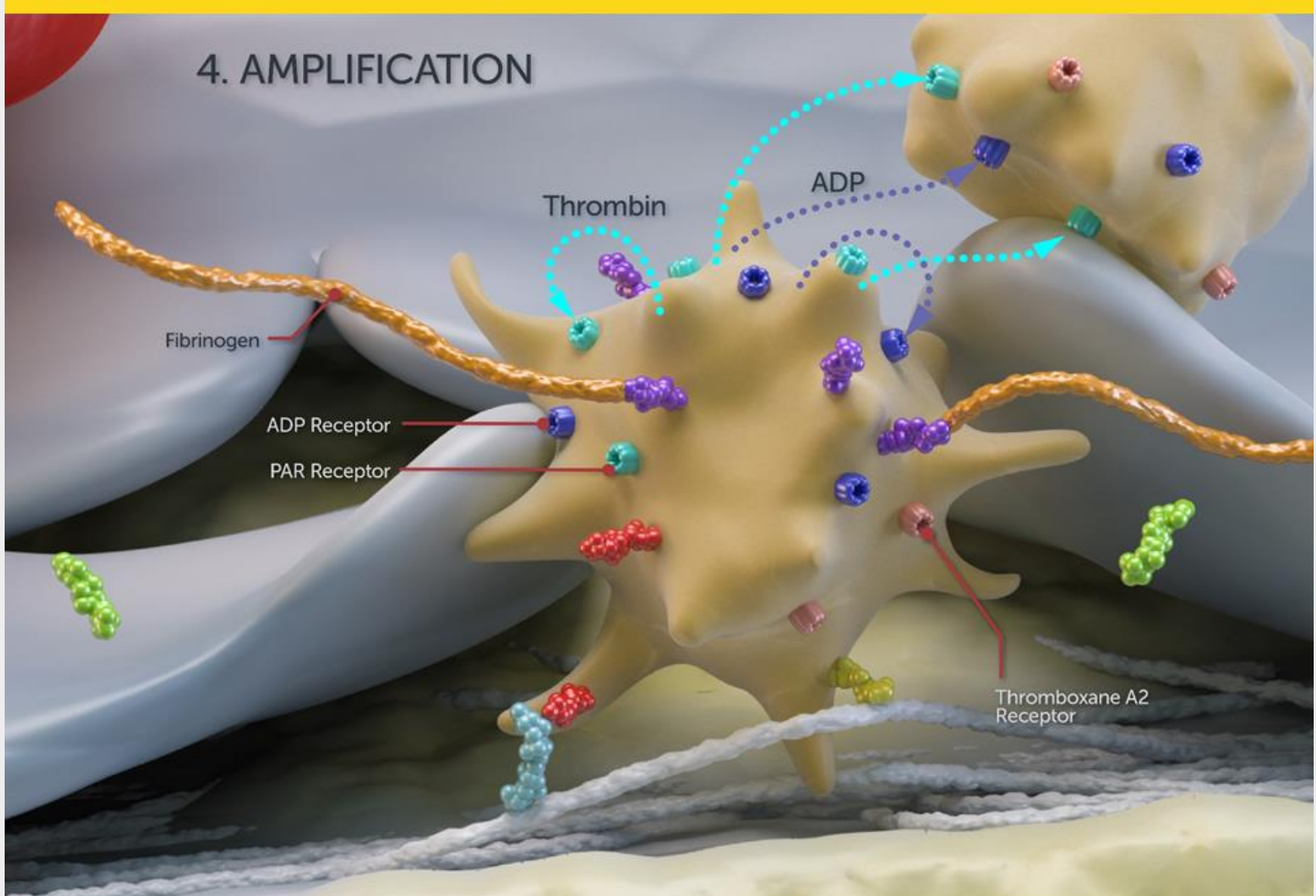
### 3. ACTIVATION & ADHESION



For illustrative purposes only.

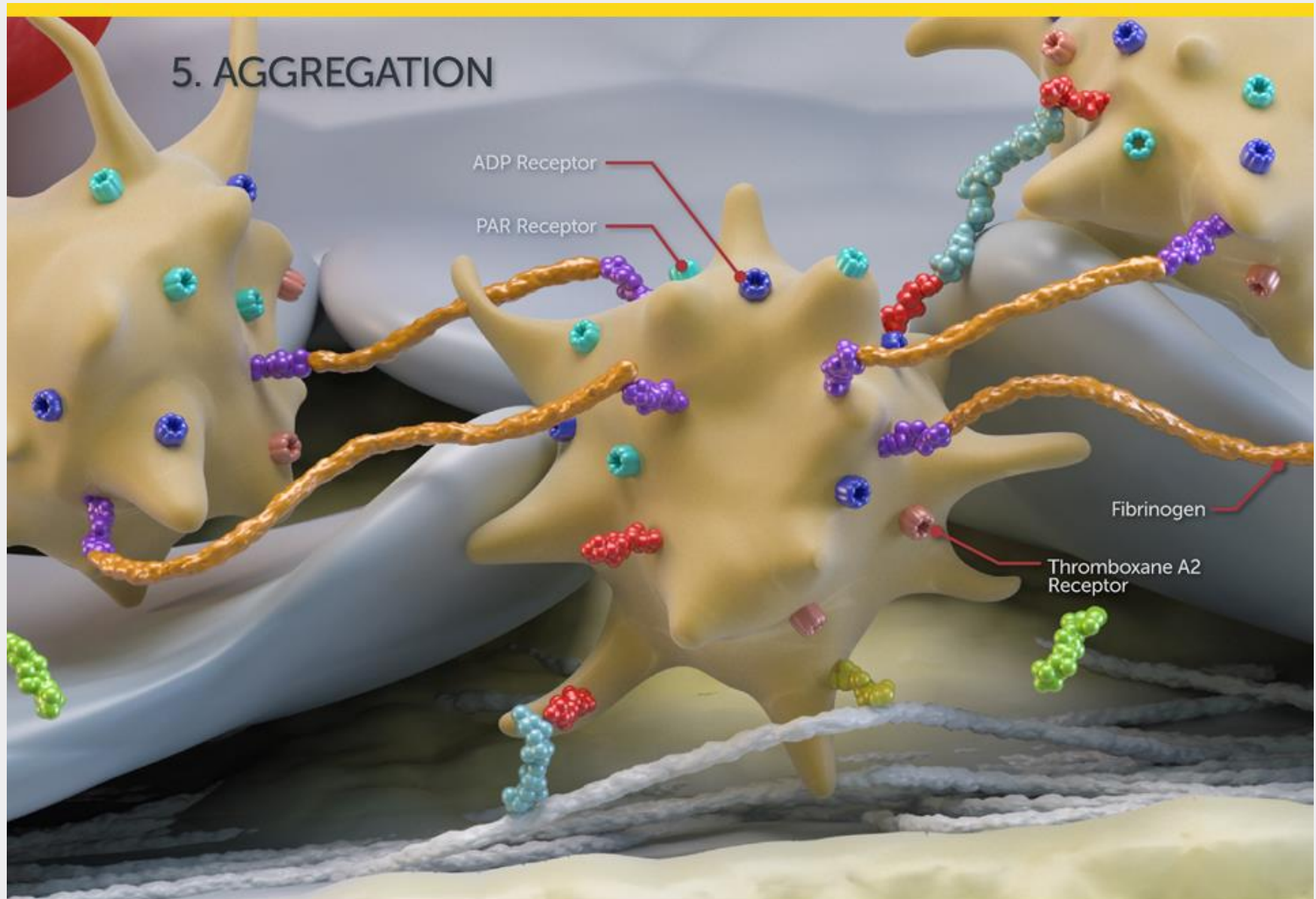


## 4. AMPLIFICATION



For illustrative purposes only.

## 5. AGGREGATION





## CLOT ARCHITECTURE: RATIONALE FOR DRUG TARGETS

### OUTER CORE

- Loosely packed
- Highly plasma permeable
- Little or no fibrin
- Modulated by  $P2Y_{12}$  inhibition

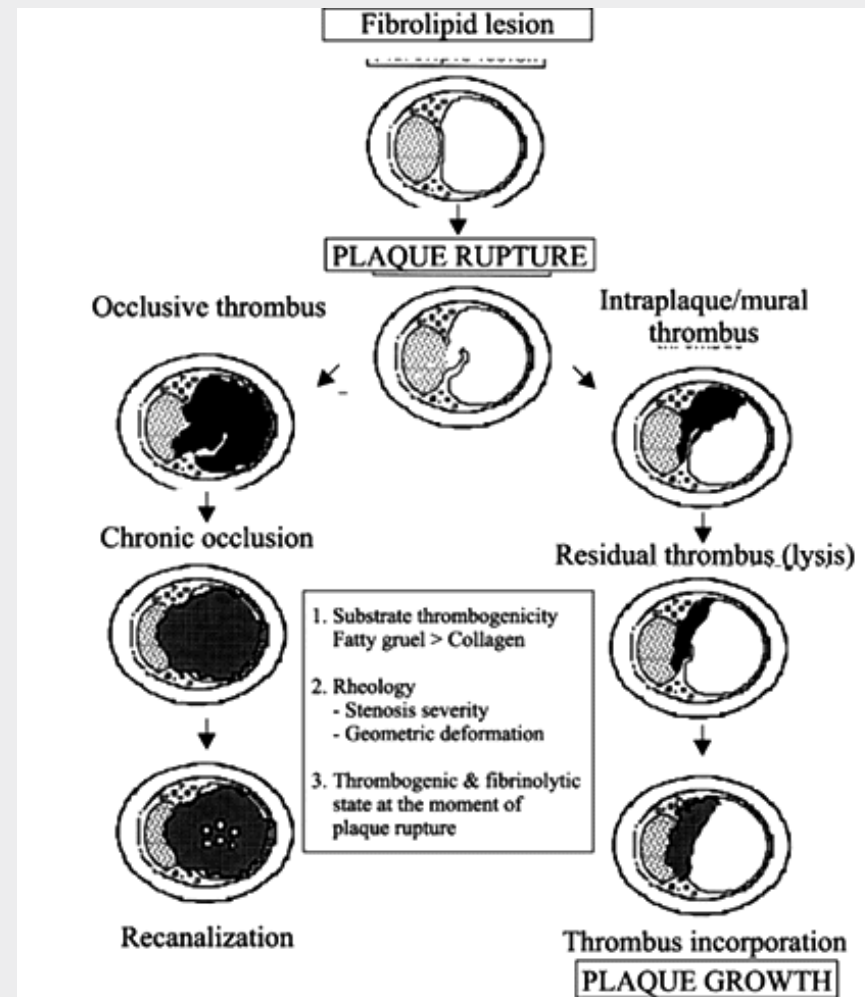
### INNER CORE

- Densely packed
- Restricted plasma entry
- Fibrin deposition at the base
- Thrombin dependent and expanded by ADP ( $P2Y_{12}$ )

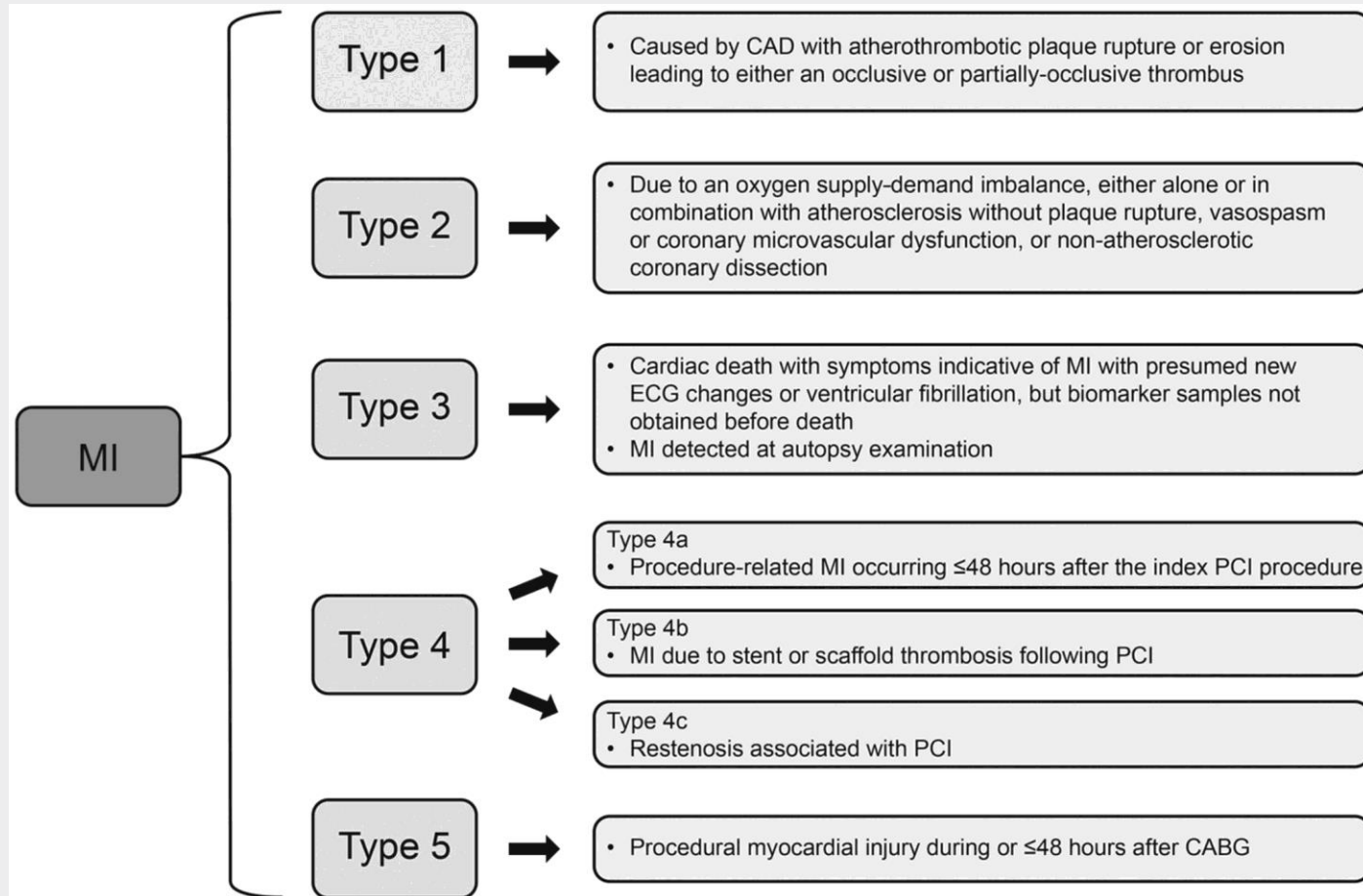


# Thrombosis

- ▶ Process of thrombotic occlusion dynamic
- ▶ Stuttering cycles of partial to near-total to total occlusion of arterial lumen
- ▶ Responsible for variability in clinical manifestation from sudden cardiac death, to STEMI, to NSTEMI, to UA



# Type 1 vs Type 2 MI



## Question

An 84 year old man with a history of HTN, HLD, DM, CAD, CHF, Afib, & CKD presents with active hematochezia with dull chest pressure and is found to have a Hgb of 6g/dl, a mildly elevated troponin, and diffuse ST-depressions on EKG. Appropriate initial therapy would be:

- A) Loading with aspirin, ticagrelor, & heparin
- B) Loading with aspirin, ticagrelor, heparin, & eptifibatide
- C) Urgent cardiac catheterization
- D) Addressing acute anemia and source of bleeding
- E) Outpatient management of anemia

# Epidemiology/Prevalence/Prognosis

- NSTEMI accounts for 60-70% of all MI hospitalizations
- Roughly 70-90% of all NSTEMI are Type 1 NSTEMI
- Among all NSTEMI in-hospital mortality ranges from 5.2%-13.1%
- 30-day mortality from NSTEMI ranges from 7.6%-17%
- NSTEMI mortality rates have improved over time



## Initial Assessment

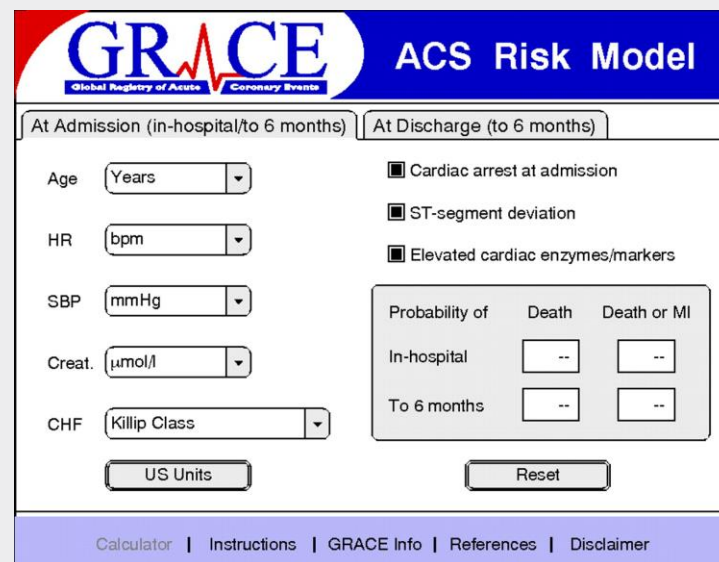
--Risk stratification tools such as the Global Registry of Acute Cardiac Events (GRACE) risk score and the Thrombolysis in Myocardial Infarction (TIMI) risk score can be utilized to assess both the acute and long-term likelihood of a further ischemic event following an NSTEMI

--Assessment of acute risk guides initial evaluation and selection of care facility, such as a coronary care unit, and the choice of appropriate pharmacotherapy, and guides decision-making regarding invasive revascularization procedures

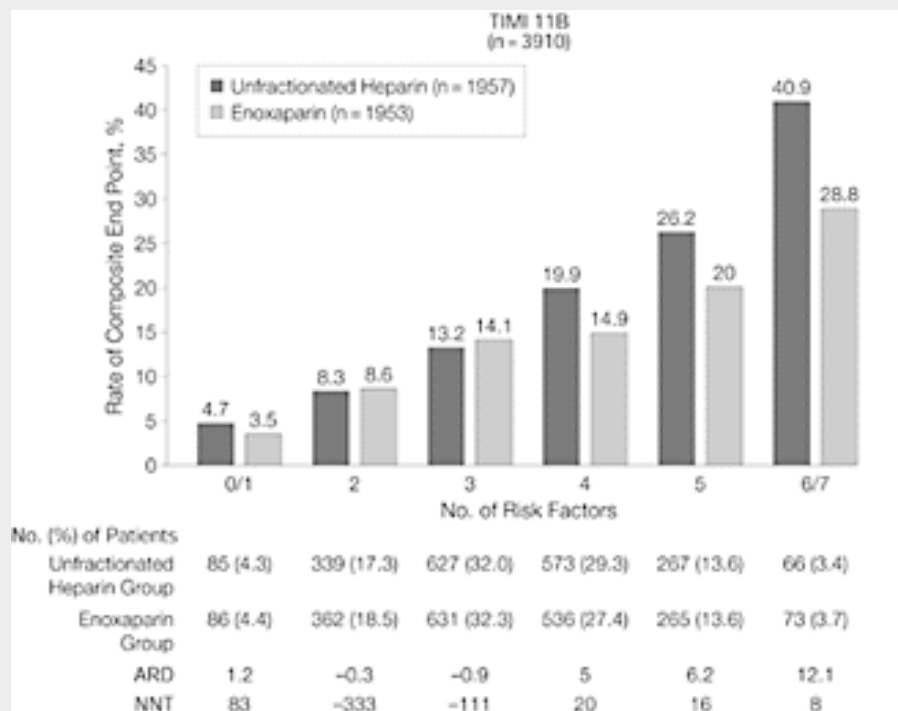
### TIMI UA/NSTEMI RISK SCORE

1) Age $\geq 65$	1 point
2) $\geq 3$ risk factors for CAD	1 point
3) Use of ASA (last 7 days)	1 point
4) Known CAD (prior stenosis $\geq 50\%$ )	1 point
5) $>1$ episode rest angina in $<24$ h	1 point
6) ST-segment deviation	1 point
7) Elevated cardiac markers	1 point

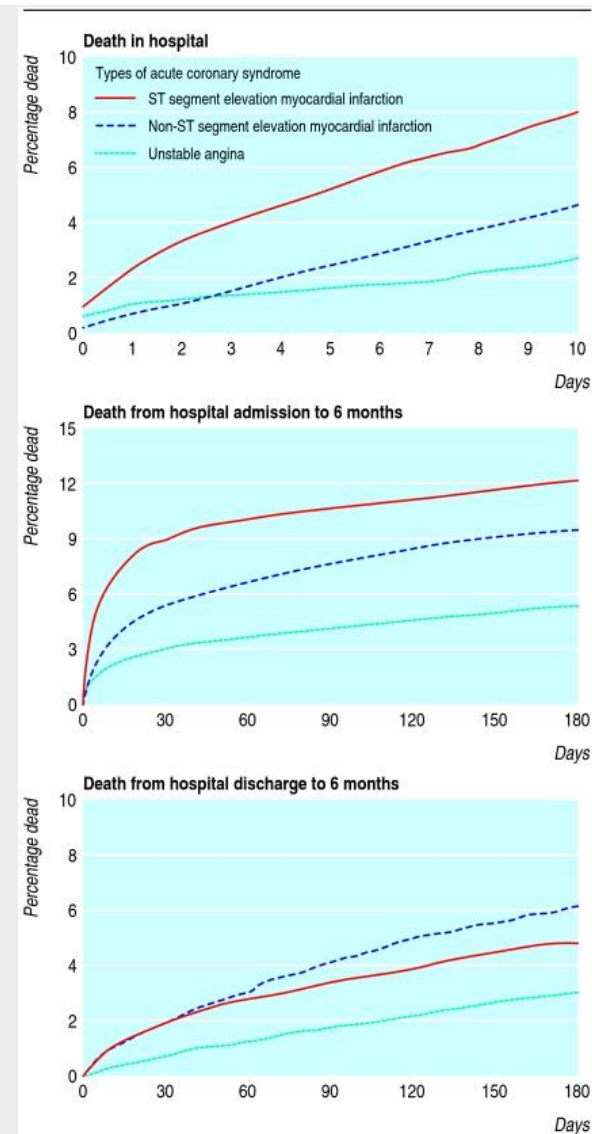
doi:10.1371/journal.pone.0007947.t001



The image shows the GRACE ACS Risk Model calculator interface. It features a blue header with the GRACE logo and the text 'ACS Risk Model'. Below the header, there are two tabs: 'At Admission (in-hospital/to 6 months)' and 'At Discharge (to 6 months)'. The 'At Admission' tab is selected. The form includes input fields for Age (Years), HR (bpm), SBP (mmHg), Creat. ( $\mu\text{mol/l}$ ), and CHF (Killip Class). There are checkboxes for 'Cardiac arrest at admission', 'ST-segment deviation', and 'Elevated cardiac enzymes/markers'. A table shows the 'Probability of' 'Death' and 'Death or MI' for 'In-hospital' and 'To 6 months' outcomes, with values represented by dashes. There are 'US Units' and 'Reset' buttons at the bottom. A footer bar contains links for 'Calculator', 'Instructions', 'GRACE Info', 'References', and 'Disclaimer'.



Antman EM, Cohen M, Bernink PJLM, et al. The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI: A Method for Prognostication and Therapeutic Decision Making. *JAMA*. 2000;284(7):835–842. doi:10.1001/jama.284.7.835



Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006 Nov 25;333(7578):1091. doi: 10.1136/bmj.38985.646481.55. Epub 2006 Oct 10. PMID: 17032691; PMCID: PMC1661748.

# TREATMENT

1. STEMI
2. NSTEMI
3. UA



# MANAGEMENT

## 1. Early Invasive Strategy

1. Coronary angiography within 24-48h with angiographically directed revascularization
2. Aggressive antiplatelet & antithrombin therapy

## 2. Early Conservative Strategy

1. Observation followed by noninvasive evaluation
2. Medical therapy

## Question

A 69-year-old man is evaluated at the hospital for four episodes of chest pain at rest in the past 24 hours. Medical history is significant for hyperlipidemia, hypertension, tobacco use, and previous transient ischemic attack. Medications are aspirin, hydrochlorothiazide, atorvastatin, and ramipril. On physical examination, vital signs are normal. The remainder of the examination is unremarkable. Laboratory studies are notable for normal serum troponin levels. An ECG demonstrates 2-mm ST-segment depressions in leads V4 through V6. Metoprolol, nitrates, clopidogrel, and heparin are initiated.

**Which of the following is the most appropriate management?**

1. Adenosine nuclear stress testing
2. Coronary CT angiography
3. Exercise stress electrocardiography
4. Urgent angiography



## Question

A 55-year-old woman is evaluated in the hospital for a single 10-minute episode of chest pain at rest, which occurred 1 hour before presentation. Medical history is significant for hypertension and hyperlipidemia. Medications are hydrochlorothiazide, ramipril, and pravastatin. On physical examination, vital signs are normal. The remainder of the examination is unremarkable. Laboratory studies are notable for normal serum troponin levels. An ECG demonstrates 1-mm ST-segment depressions in leads V4 through V6. Aspirin and metoprolol are initiated.

**Which of the following is the most appropriate management?**

1. Amlodipine
2. Enoxaparin and eptifibatide
3. Exercise stress testing
4. Urgent angiography

# Initial Medical Therapy

## ■ Antiplatelet Therapy

- ▶ Aspirin 325 chewed
- ▶ Clopidogrel 600 mg/Ticagrelor 180 mg
- ▶ Avoid Glycoprotein IIb/IIIa inhibitors

## ■ Antithrombin Therapy

- ▶ Unfractionated heparin
- ▶ Avoid low molecular weight heparin (Enoxaparin)
- ▶ Avoid Direct thrombin inhibitors (Bivalirudin) except in HIT

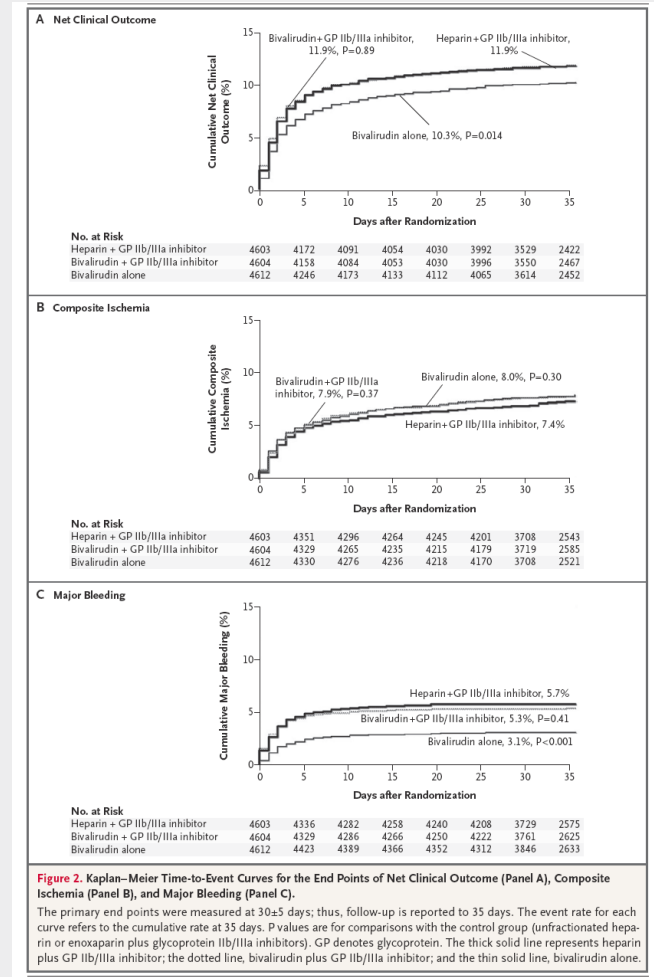
## ■ Anti-Anginal Therapy

- ▶ Beta Blockers (PO in higher risk patients based on COMMIT trial)
- ▶ Nitrates
- ▶ Avoid hypotension

# ACUITY Trial

(Acute Catheterization and Urgent Intervention Triage Strategy)

- 13,819 patients with NSTEMI randomizing patients to one of three antithrombotic regimens prior to angiography
  - Heparin/Enoxaparin + GP IIb/IIIa receptor antagonist
  - Bivalirudin + GP IIb/IIIa receptor antagonist
  - Bivalirudin
- Either heparin or bivalirudin + GP IIb/IIIa showed similar rates of ischemia and bleeding
- Bivalirudin without GP IIb/IIIa showed similar rates of ischemia but significantly less bleeding



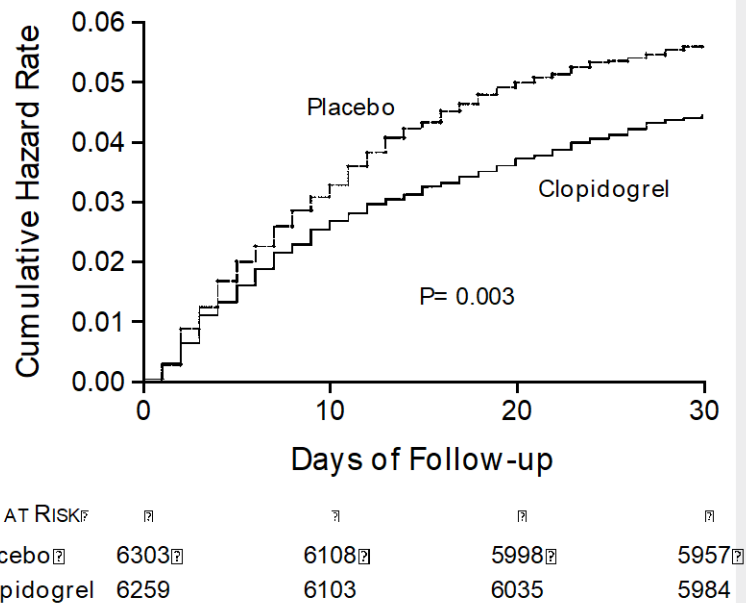
# CURE TRIAL

(Clopidogrel in Unstable angina to prevent Recurrent Events)

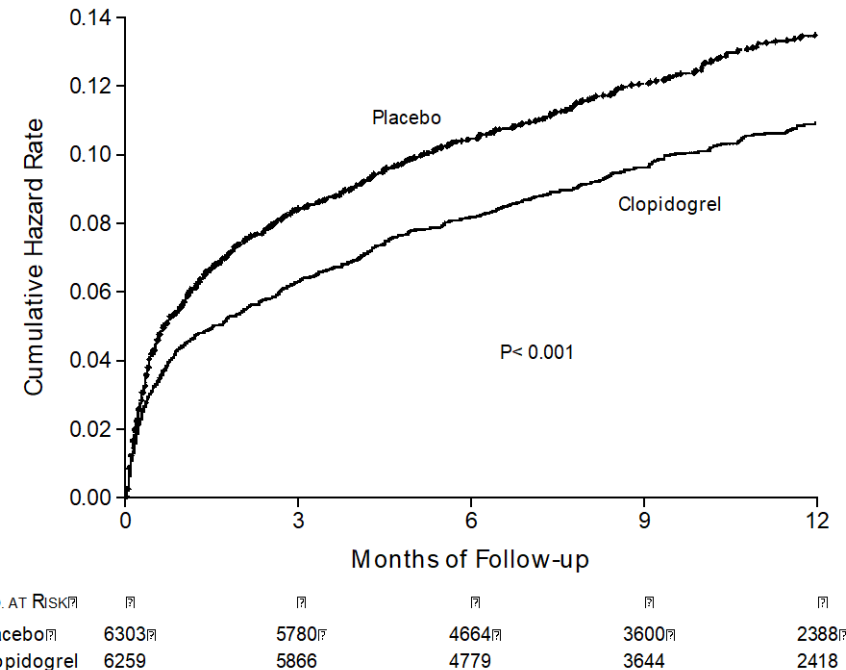
1. Randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of dual anti-platelet therapy vs. aspirin alone in patients with ACS absent ST-segment elevations
2. 12,562 patients randomized to receive clopidogrel 300 mg x 1 followed by 75 mg daily + aspirin (6,259 patients) vs. placebo + aspirin (6,303 patients)
3. Primary outcome measure was composite of death from cardiovascular causes, nonfatal MI, or stroke
4. Primary outcome occurred in 582 of 6259 patients in treatment group (9.3%) as compared to 719 of 6303 patients in the placebo group (11.4%)
5. Significantly fewer MIs in treatment group (116 vs 193)
6. Treatment group showed benefit both early and late

# CURE TRIAL

(Clopidogrel in Unstable angina to prevent Recurrent Events)



**Figure 2.** Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the First 30 Days after Randomization. The results demonstrate the early effect of clopidogrel.



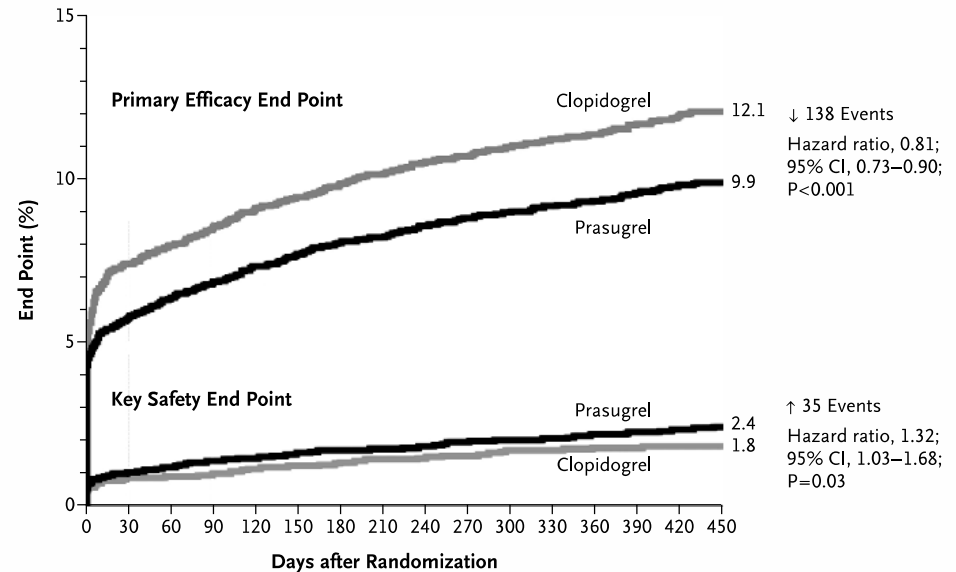
**Figure 1.** Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study. The results demonstrate the sustained effect of clopidogrel.



# TRITON-TIMI 38

1. Prasugrel vs Clopidogrel
2. 13,608 patients with ACS
3. Primary efficacy endpoint composite of death from CV causes, nonfatal MI, nonfatal stroke
4. Primary safety endpoint major bleeding

A



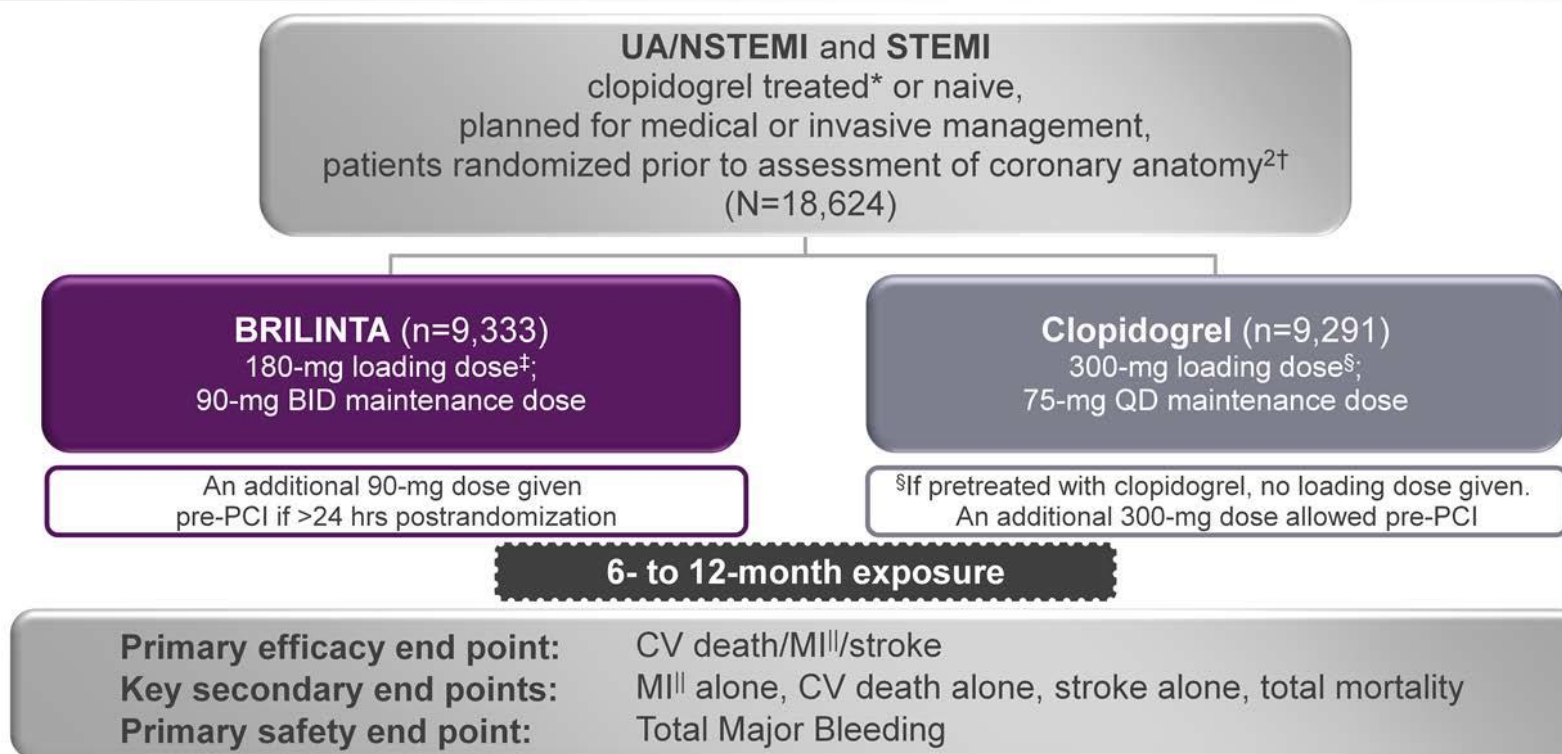
No. at Risk							
Clopidogrel	6795	6169	6036	5835	5043	4369	3017
Prasugrel	6813	6305	6177	5951	5119	4445	3085

Age ≥75 yr, body weight <60 kg, or history of stroke or TIA

Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	198/1320 (16.1)	199/1347 (16.0)	1.02 (0.84–1.24)	0.83
Non-CABG-related TIMI major bleeding	52/1305 (4.3)	38/1328 (3.3)	1.42 (0.93–2.15)	0.10

# PLATO Trial

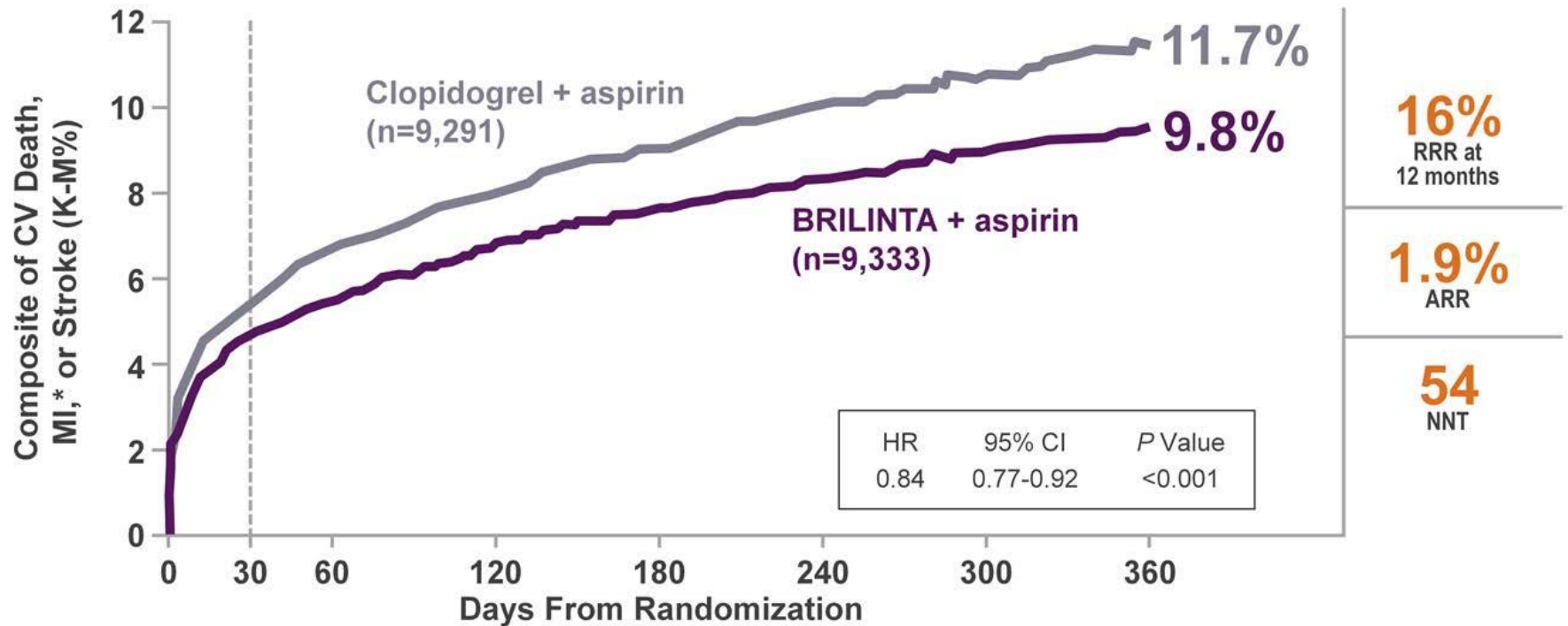
## The PLATO Trial Design<sup>1</sup>



- BRILINTA and clopidogrel were both given in combination with aspirin and other standard therapy

# PLATO Trial

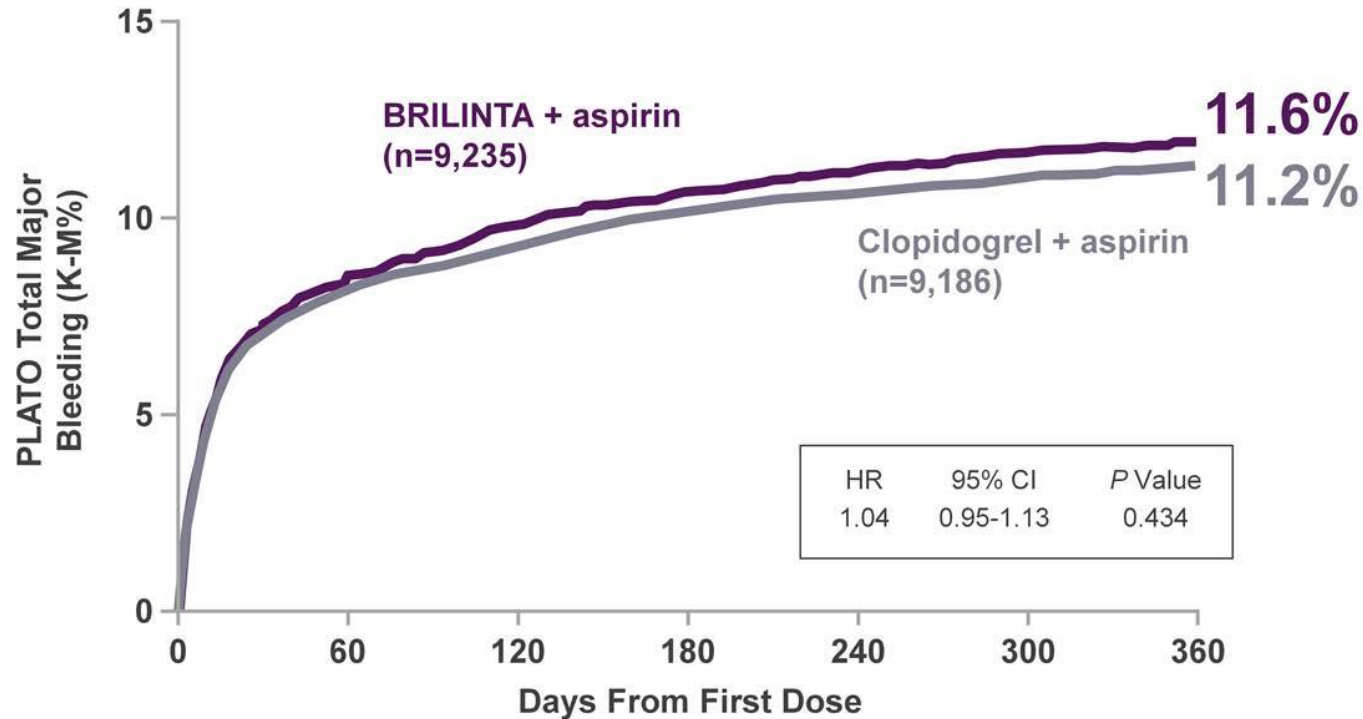
## PLATO Primary Efficacy End Point: Composite of CV Death, MI,\* or Stroke at 12 Months<sup>1</sup>



- Difference in treatments was driven by CV death and MI\* with no difference in stroke<sup>1</sup>

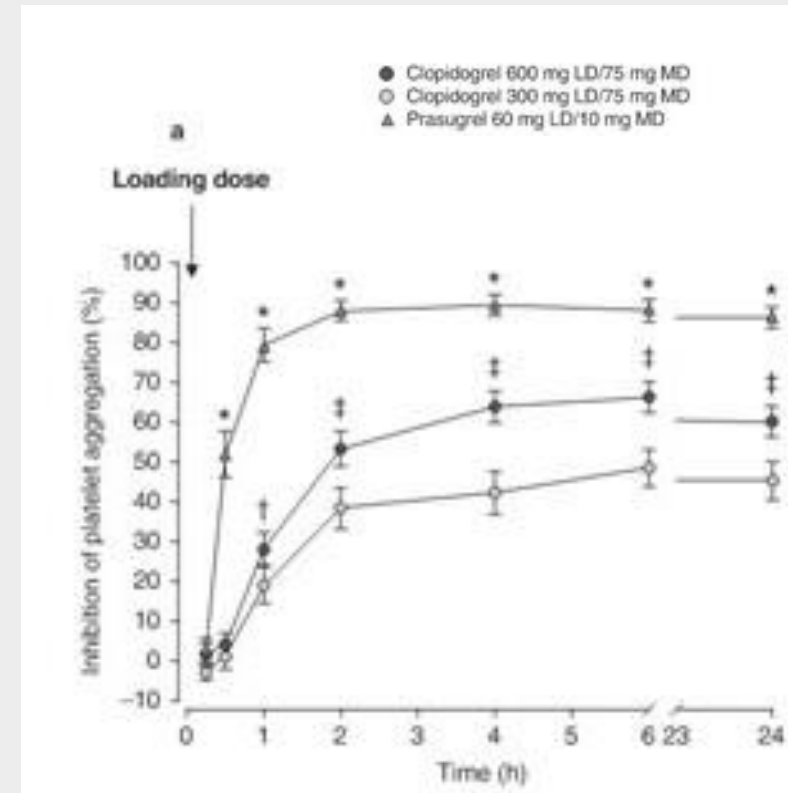
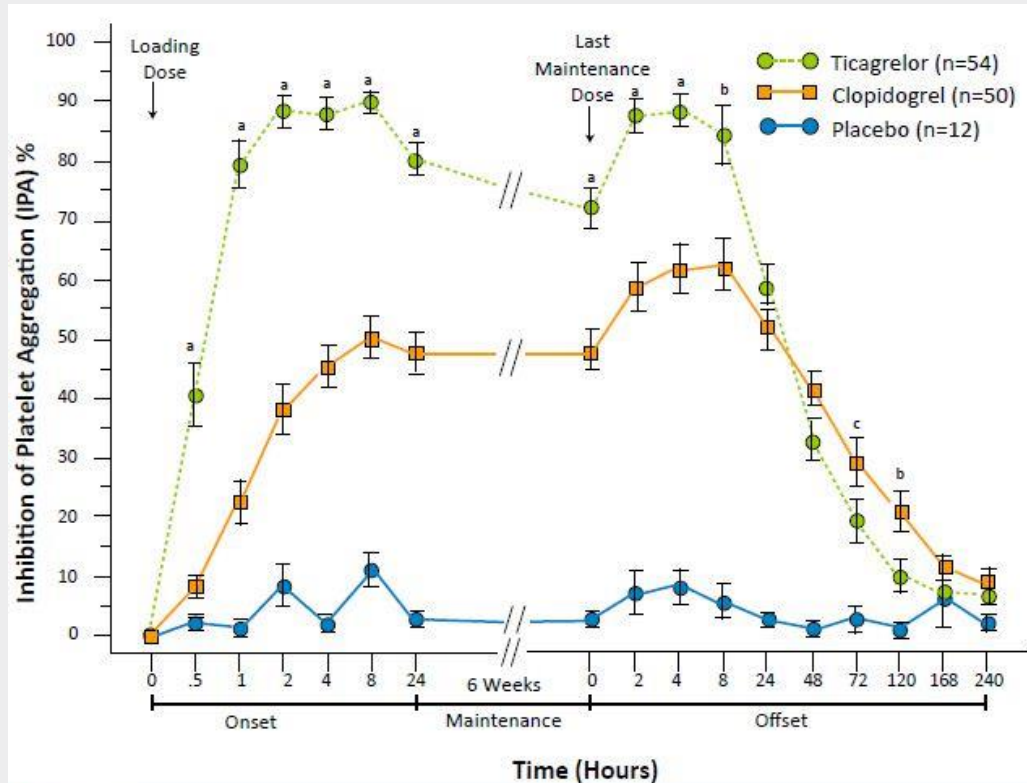
# PLATO Trial

PLATO Primary Safety End Point: Total Major Bleeding at 12 Months



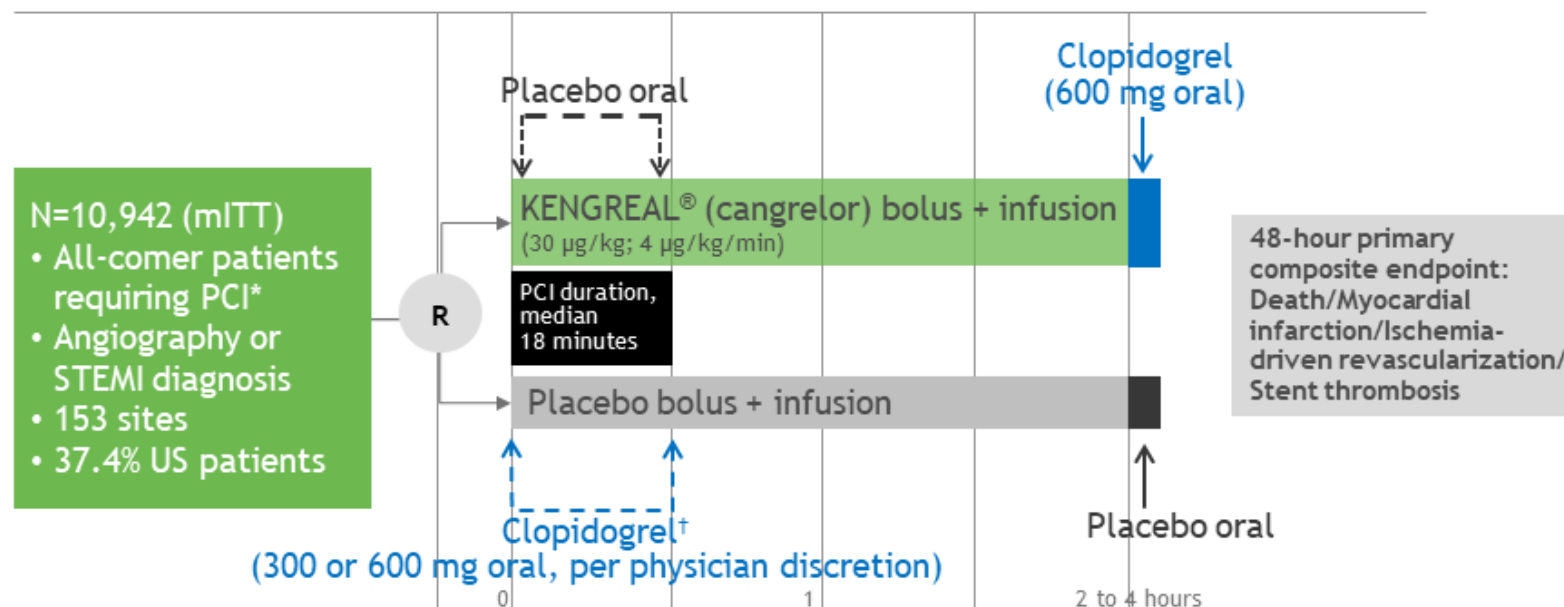
- No baseline demographic factor altered the relative risk of Total Major Bleeding with BRILINTA compared to clopidogrel
- In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding

# PHARMACOKINETICS



# CHAMPION PHOENIX: Pivotal phase III trial

## Study schematic<sup>1,2</sup>



KENGREAL bolus was administered prior to start of PCI. Clopidogrel 300 mg or 600 mg was administered shortly before or shortly afterwards in patients randomized to clopidogrel. The protocol also called for clopidogrel (75 mg) to be administered during the first 48 hours.

\*P2Y<sub>12</sub> inhibitor naïve.

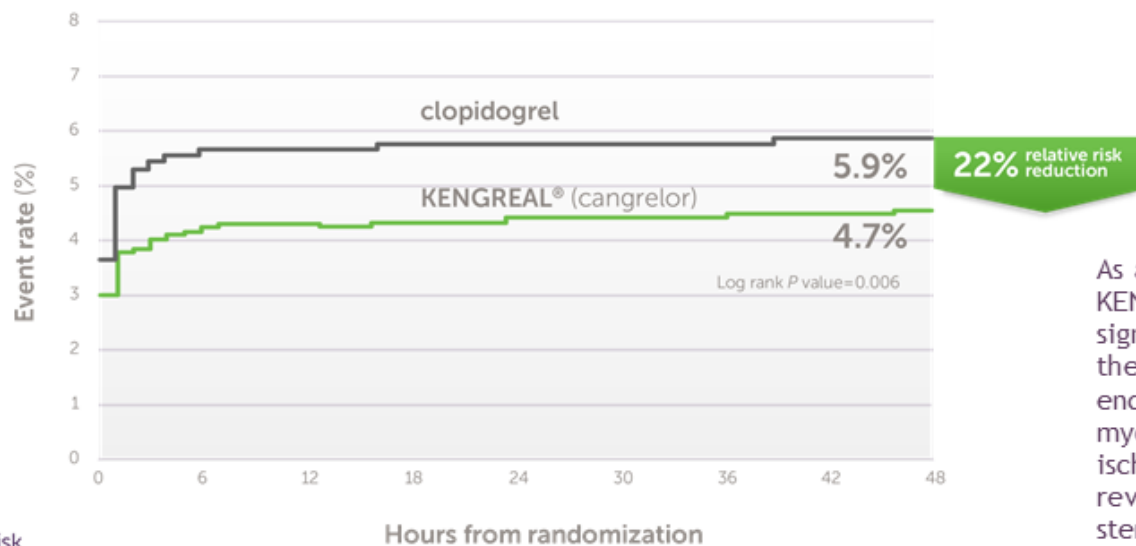
†Administration (dose and timing) of loading dose of clopidogrel was at the operator's discretion.

mITT=modified intent-to-treat; R=randomization.



## 22% relative risk reduction in periprocedural thrombotic events<sup>1,2</sup>

CHAMPION PHOENIX primary composite endpoint (death/MI/IDR/stent thrombosis at 48 hours) in an all-comer PCI patient population



Patients at risk

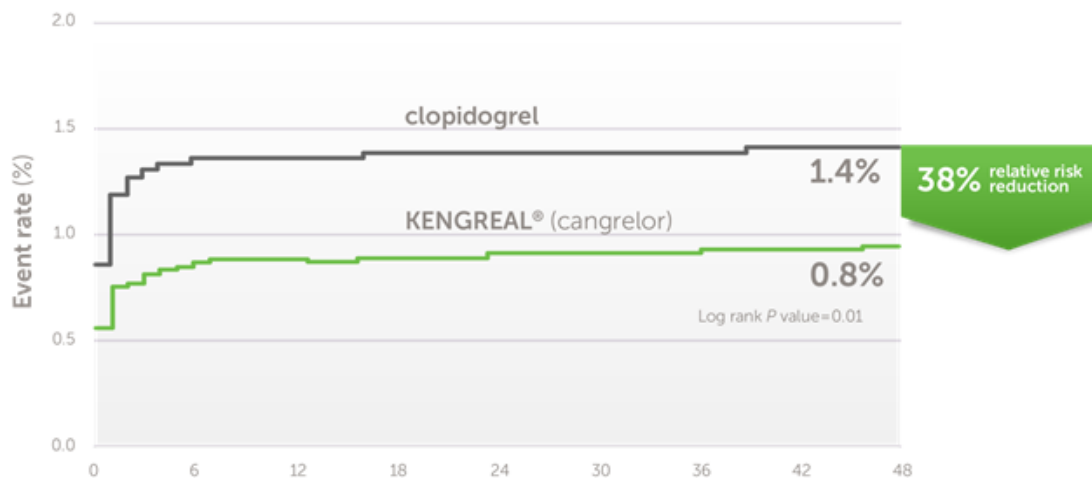
KENGREAL:	5472	5233	5229	5225	5223	5221	5220	5217	5213
Clopidogrel:	5470	5162	5159	5155	5152	5151	5151	5147	5147

As an adjunct to PCI, KENGREAL® (cangrelor) significantly reduced the primary composite endpoint of death, myocardial infarction, ischemia-driven revascularization, and stent thrombosis events at 48 hours.

1. KENGREAL® (cangrelor) Prescribing Information. 2016. 2. Bhatt DL, Stone GW, Mahaffey KW, et al. *N Engl J Med*. 2013;368(14):1303-1313.

## 38% relative risk reduction in key secondary endpoint of stent thrombosis<sup>1,2</sup>

### Stent thrombosis at 48 hours in an mITT patient population



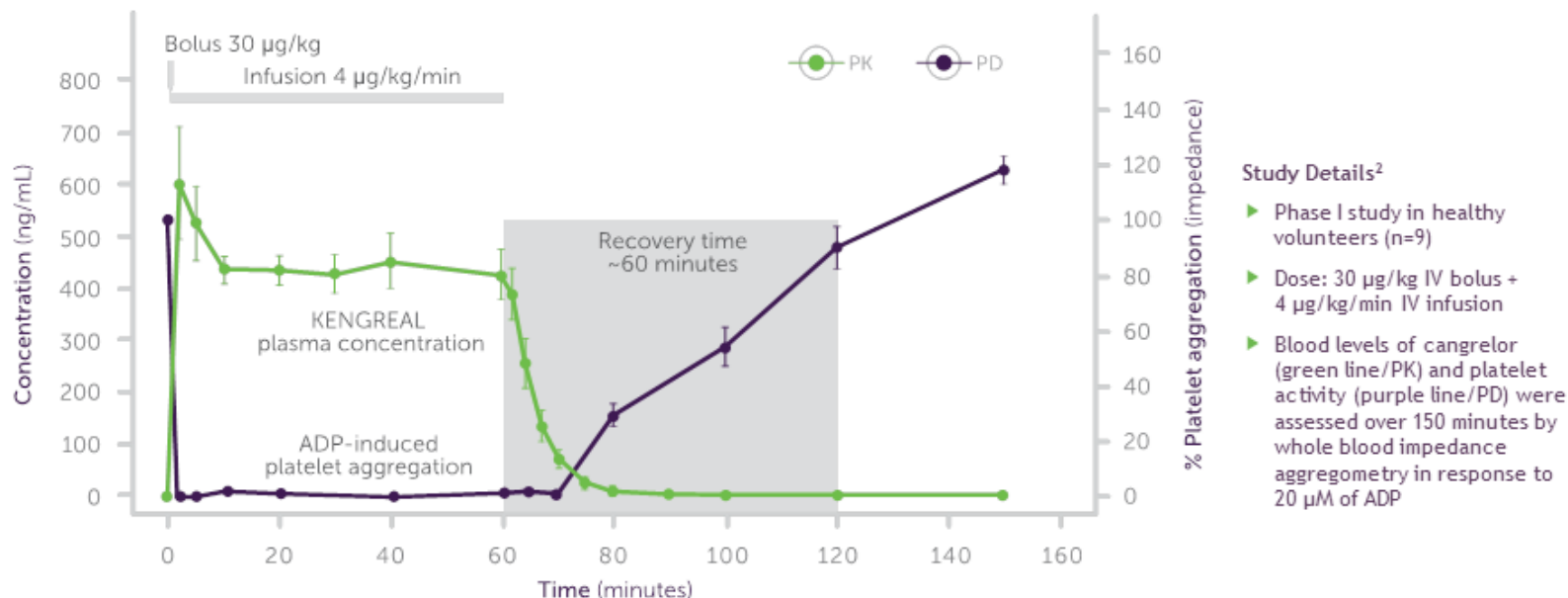
Patients at risk

	0	6	12	18	24	30	36	42	48
KENGREAL:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

1. KENGREAL® (cangrelor) Prescribing Information. 2016. 2. Bhatt DL, Stone GW, Mahaffey KW, et al. *N Engl J Med*. 2013;368(14):1303-1313.



## KENGREAL® (cangrelor) pharmacology<sup>1,2</sup> (cont'd)



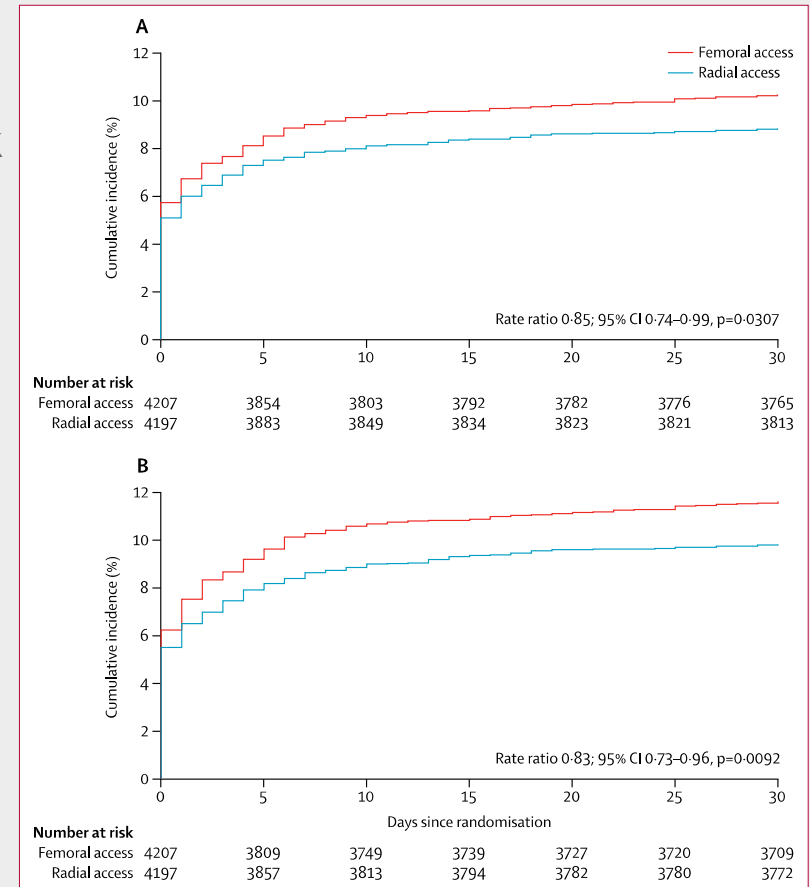
- ▶ >98% inhibition of platelet aggregation in whole blood impedance aggregometry<sup>3</sup>

# RADIAL ACCESS



# RADIAL ACCESS

1. Multiple trials now show lower bleeding risk & lower mortality with radial vs femoral access in ACS
2. MATRIX trial randomized 8,404 patient with STEMI or NSTEMI to radial vs femoral access
3. Primary endpoint MACE (death, MI, stroke) + major bleeding



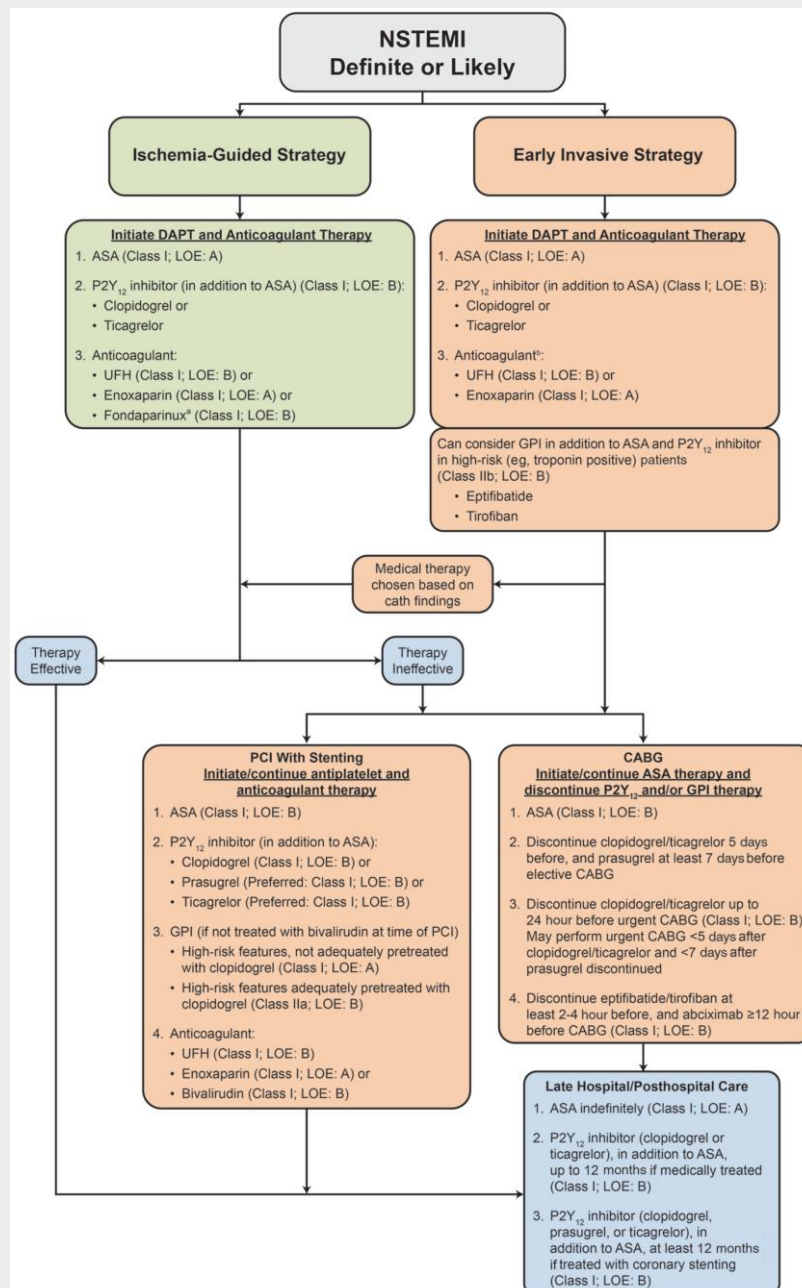
**Figure 2: Coprimary composite outcomes at 30 days**  
(A) All-cause mortality, myocardial infarction, or stroke, and (B) all-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding.

## Question

A 78 year old woman with a history of HTN, HLD, and prior CVA presents with retrosternal chest pain 7/10, with lateral ST-depressions on EKG, and elevated troponin that is exponentially rising on serial testing. She weights 59 kg. Appropriate initial medical therapy would be:

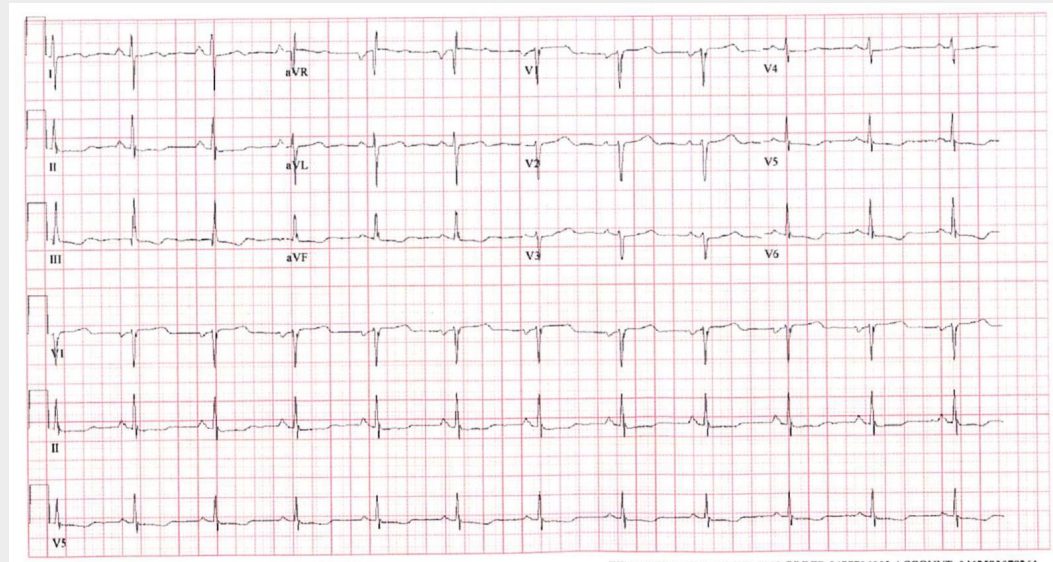
- A) Loading with aspirin, prasugrel, and unfractionated heparin
- B) Loading with aspirin, clopidogrel, and unfractionated heparin
- C) Loading with ticagrelor, enoxaparin, & eptafibitide
- D) Loading with prasugrel, enoxaparin, & fondaparinux
- E) Loading with aspirin, ticagrelor, enoxaparin, & cangrelor



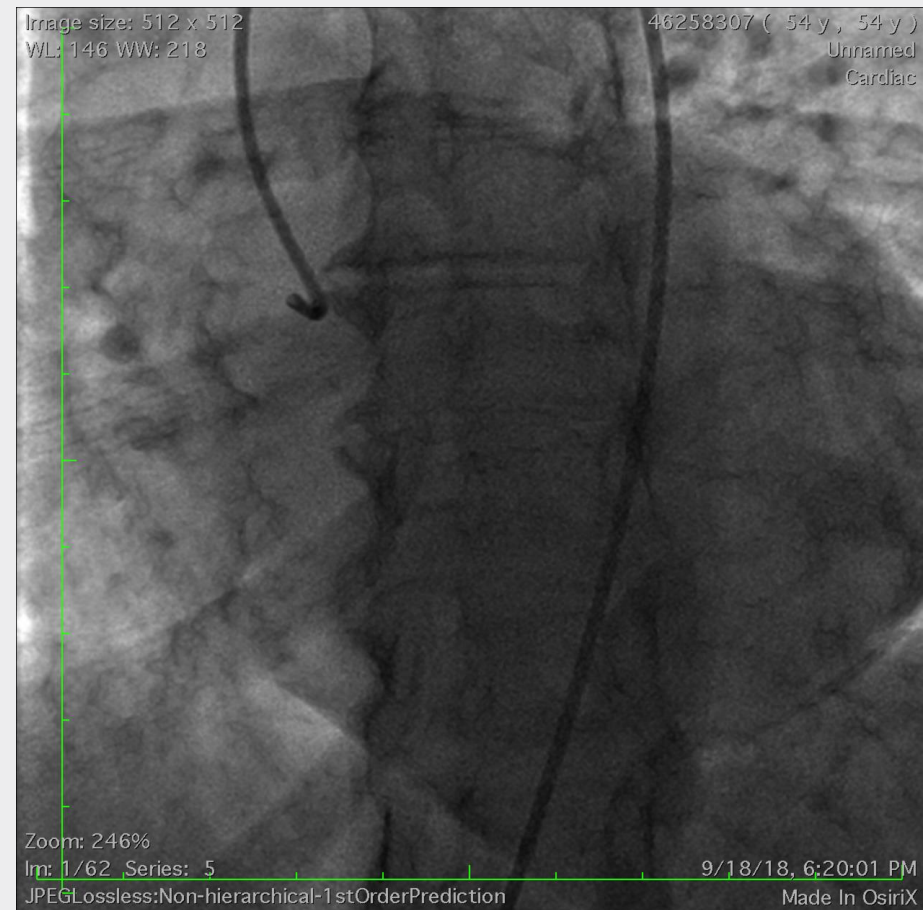
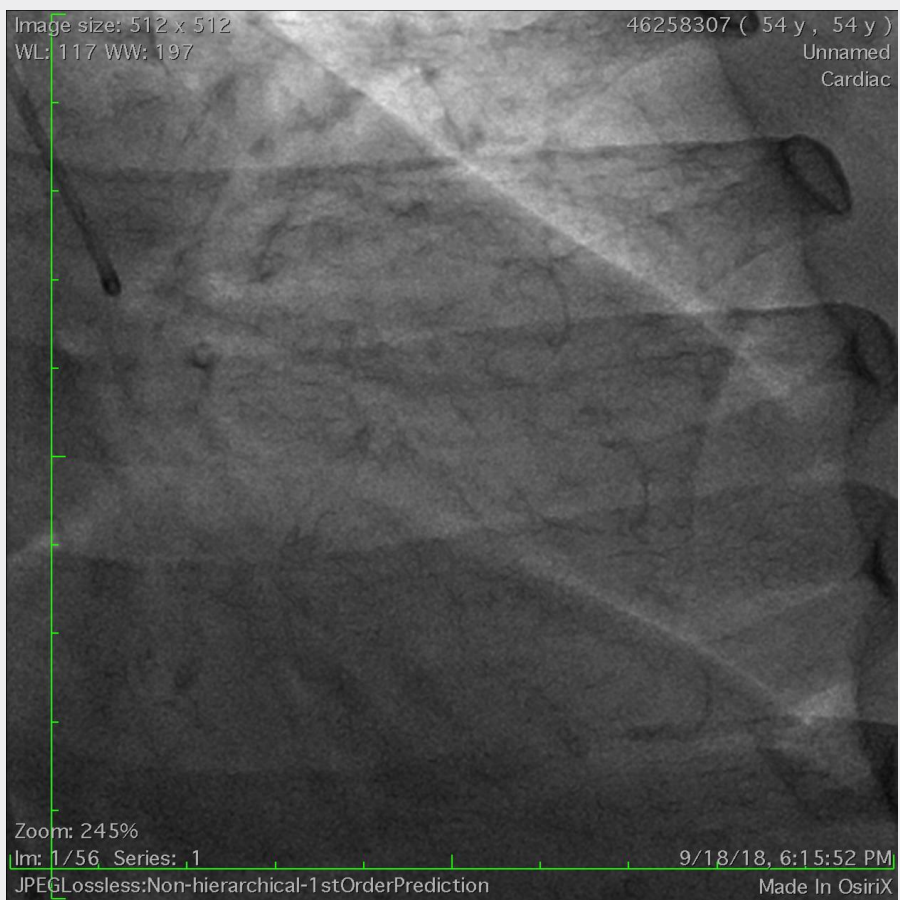


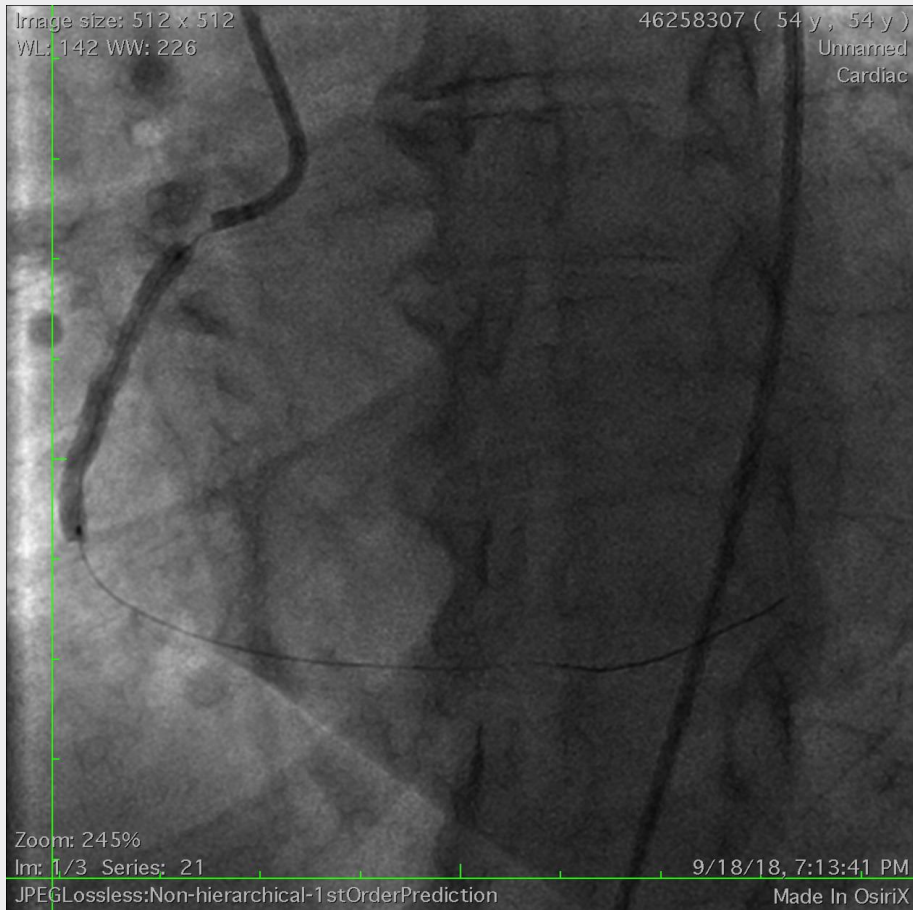
## CASE

54 year old female with HTN, HLD, DM, hypothyroidism, and obesity p/w chest pain and hypertensive urgency



- NSTEMI
- Early Invasive Strategy
- Aspirin, Ticagrelor
- Heparin
- PCI







# Thank you!



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