Non-ST Elevation Myocardial Infarction (NSTEMI)

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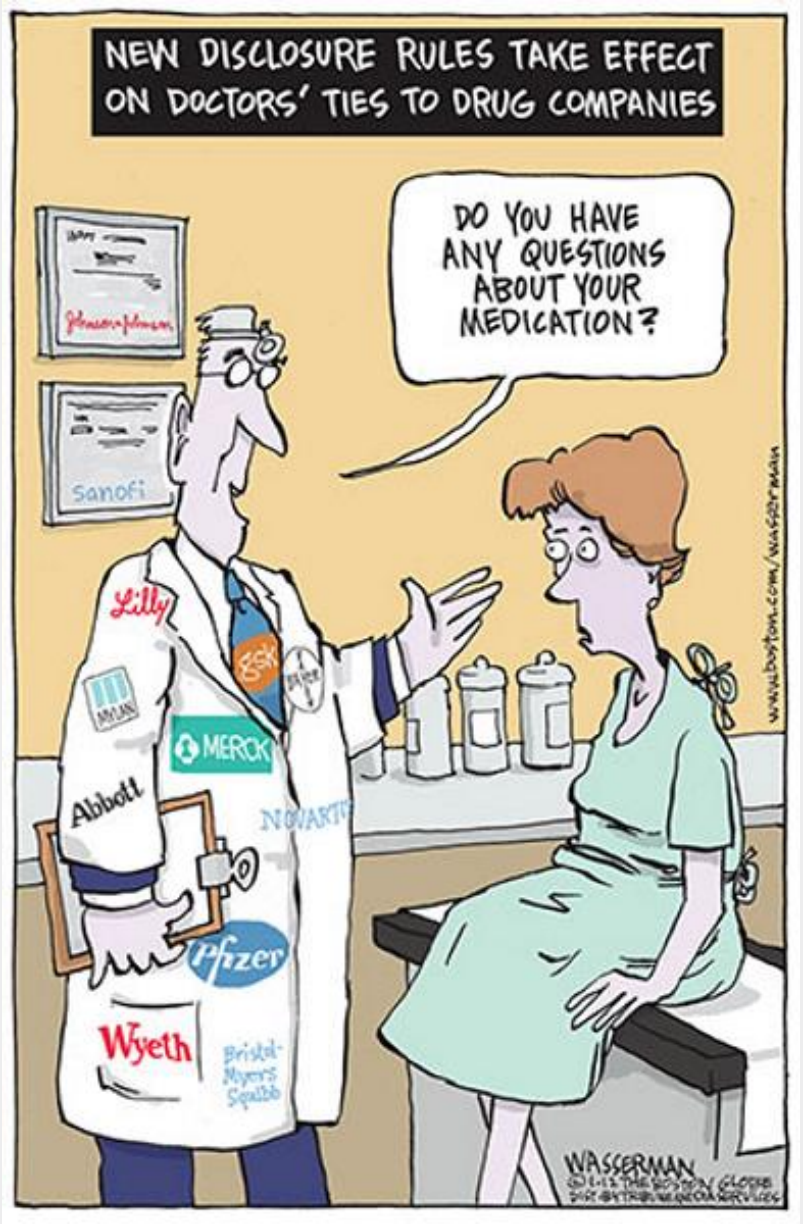
DISCLOSURES

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

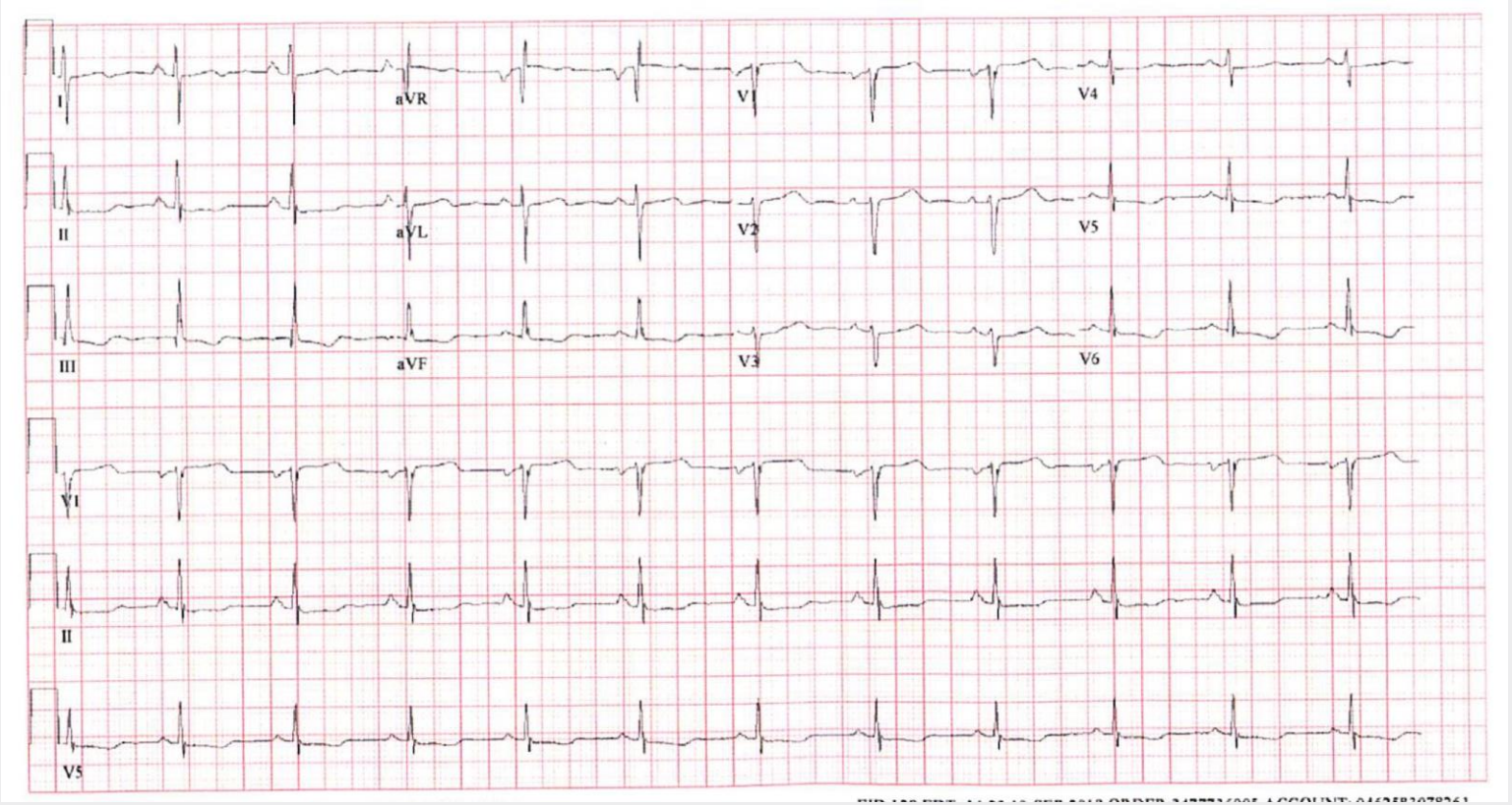


CASE

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

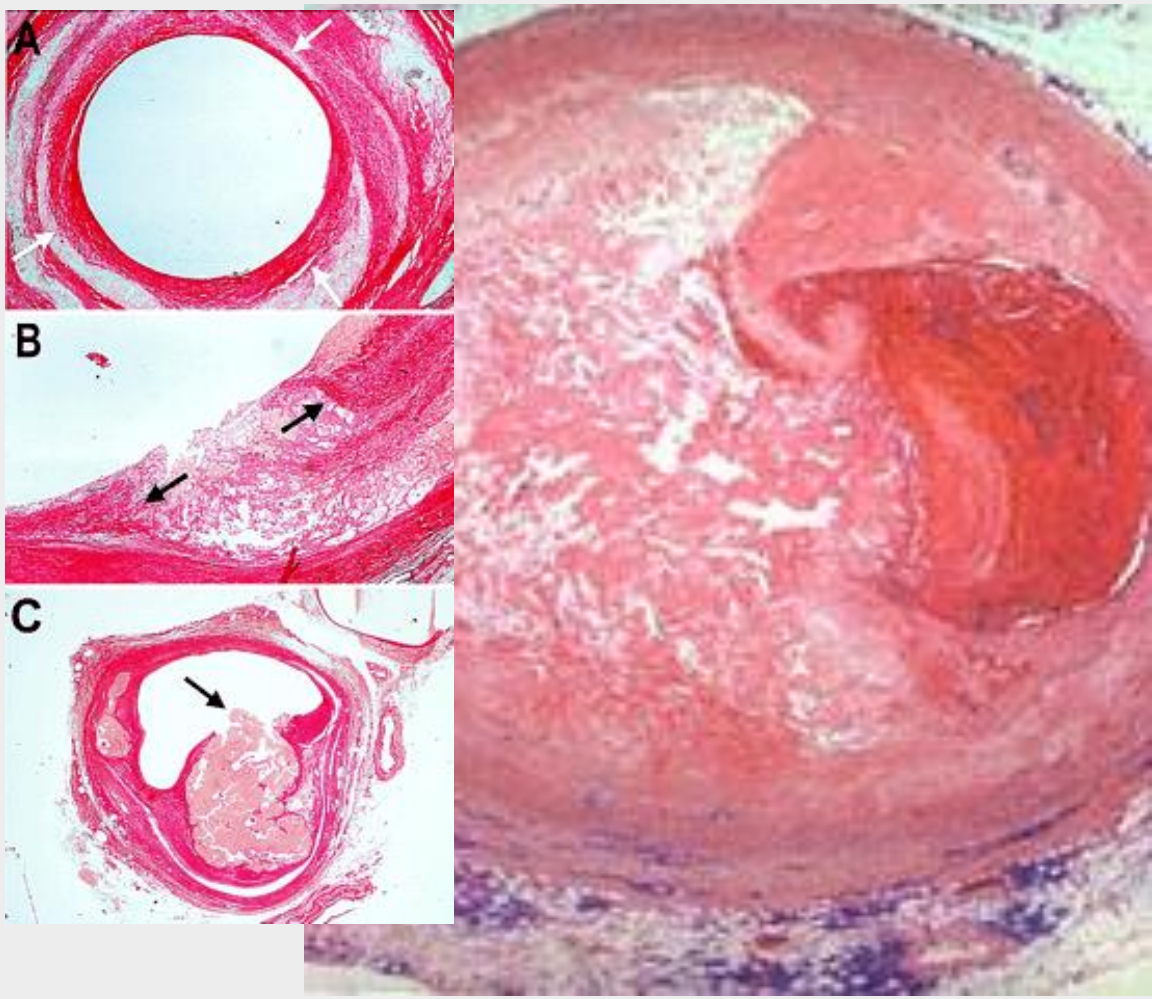
ACS vs Stable Angina vs Non-Cardiac Chest Pain

- 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

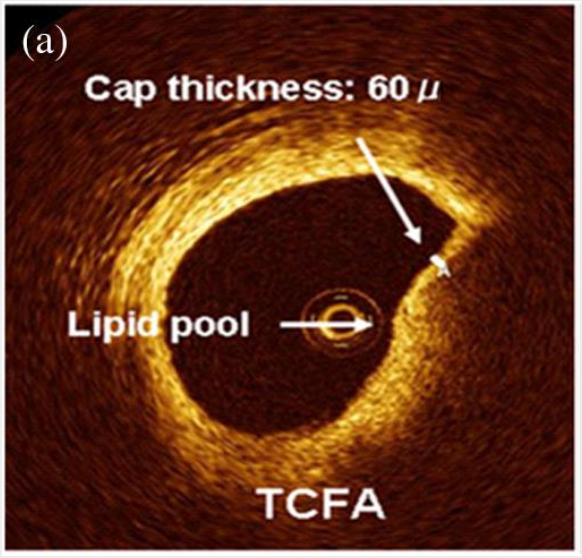
Plaque Rupture

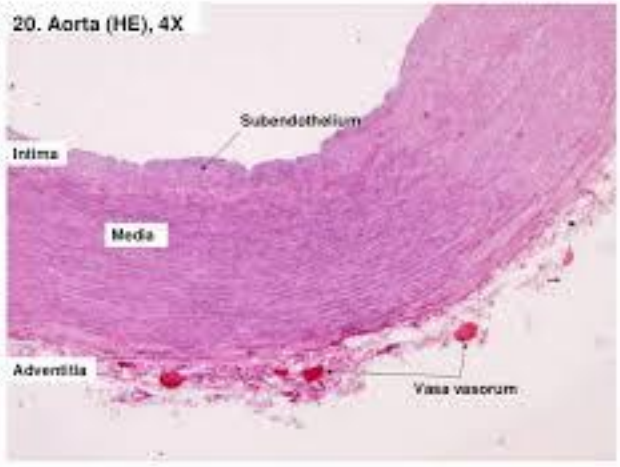
- Disruption of fibrous cap with fissure resulting in hematoma or thrombus



Vulnerability and Plaque Rupture

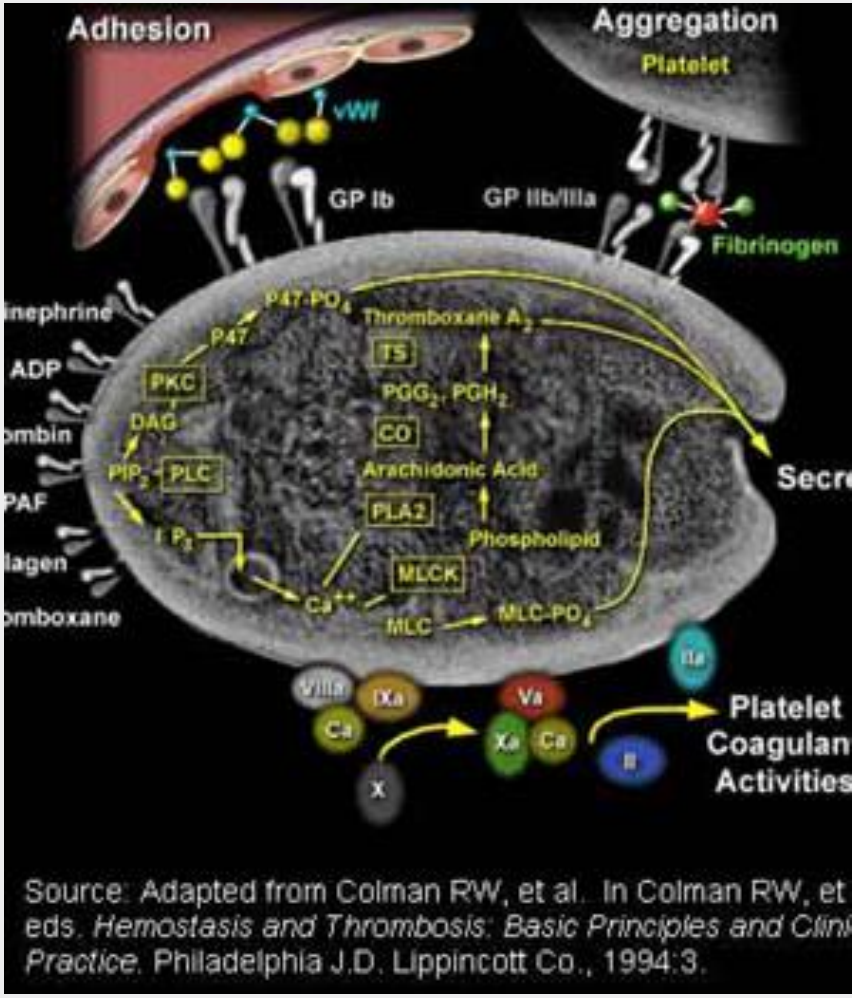
1. Thinner the fibrous cap greater likelihood of rupture
2. More macrophages (>25 per high-powered field), greater risk of rupture
3. 4-fold increase in vasa vasorum on ruptured plaques

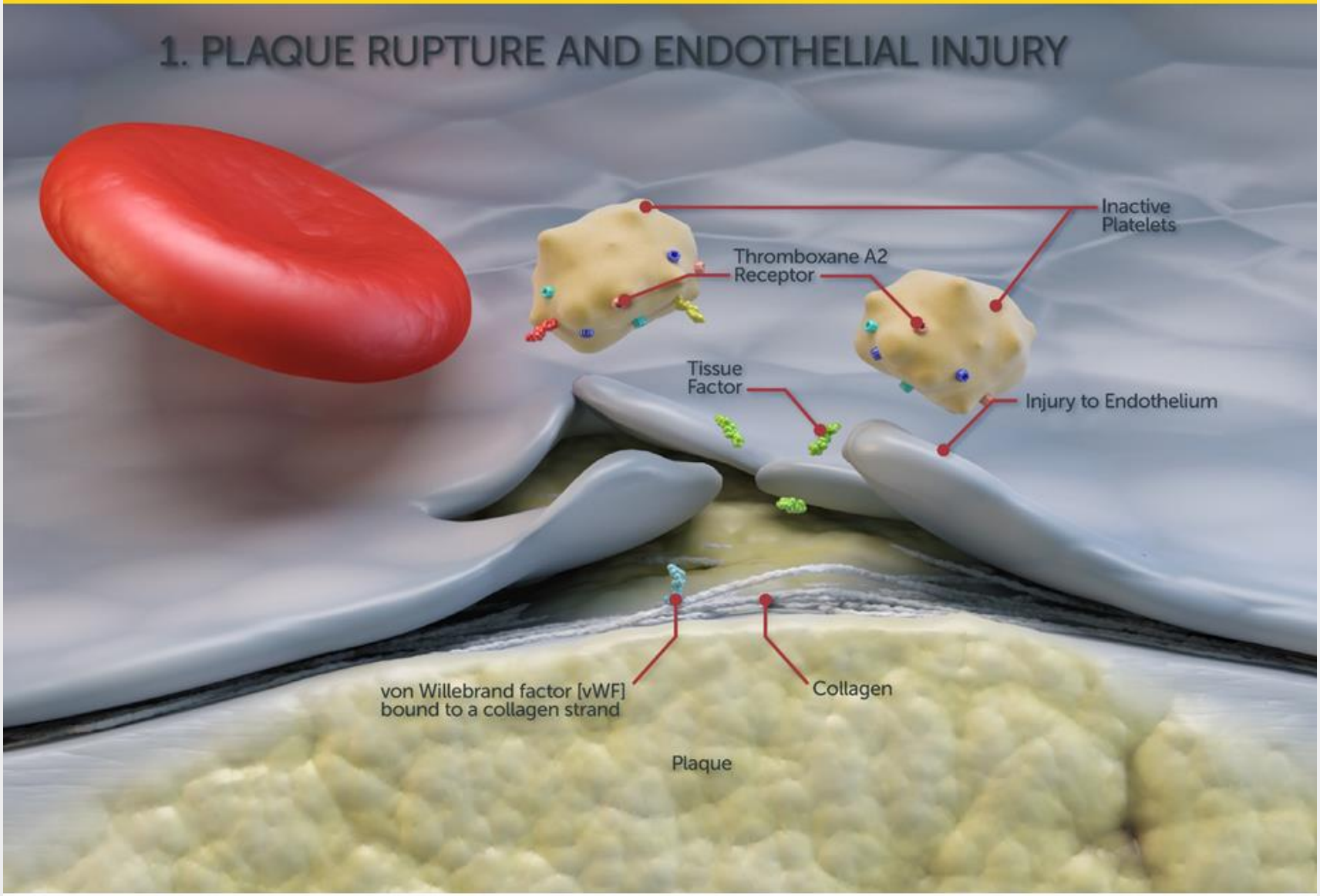




Thrombosis

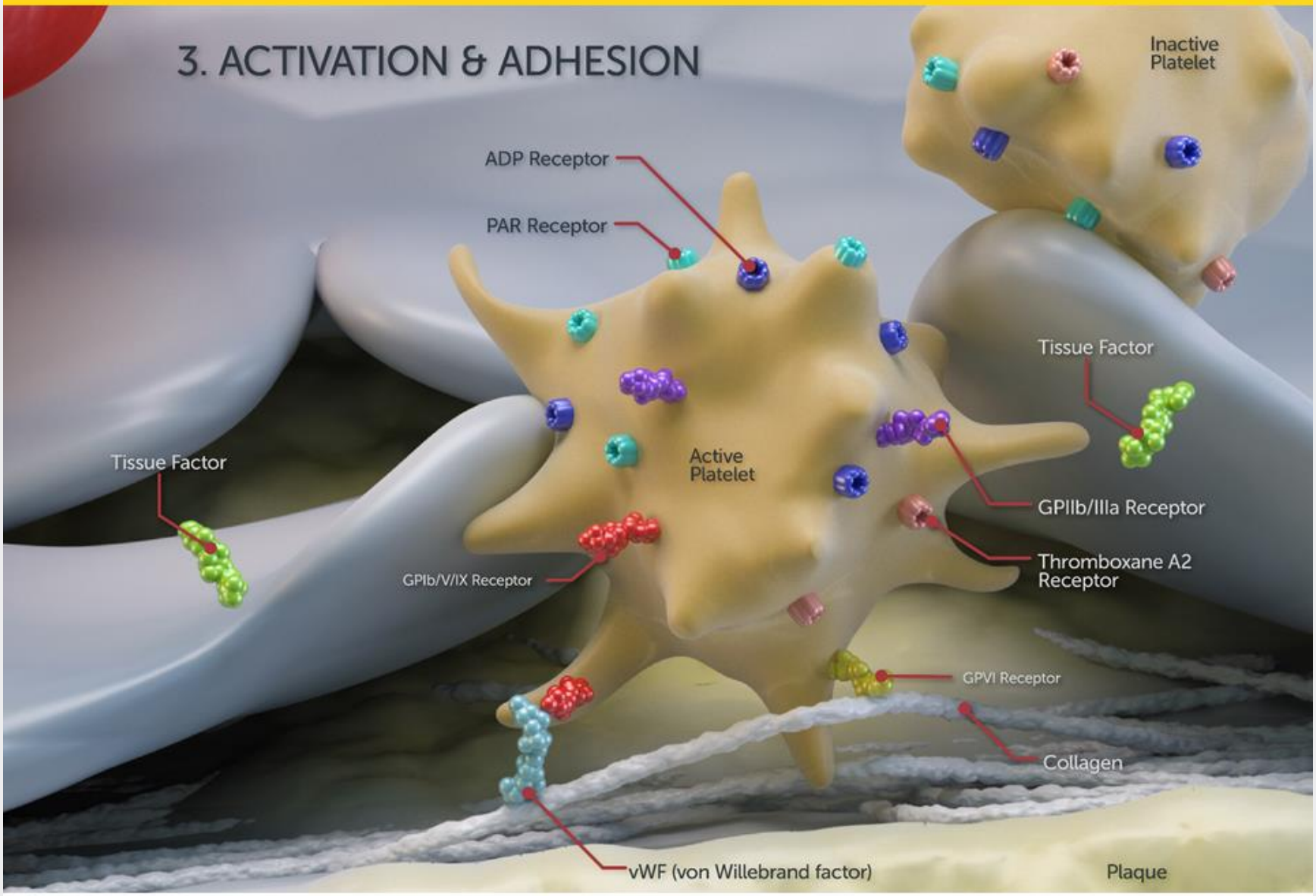
1. Disruption of fibrous cap exposes bloodstream to thrombogenic stimuli
2. Platelets activated by collagen and adhere to wall bound von Willebrand's factor
3. Results in activation of clotting cascade and formation of thrombus





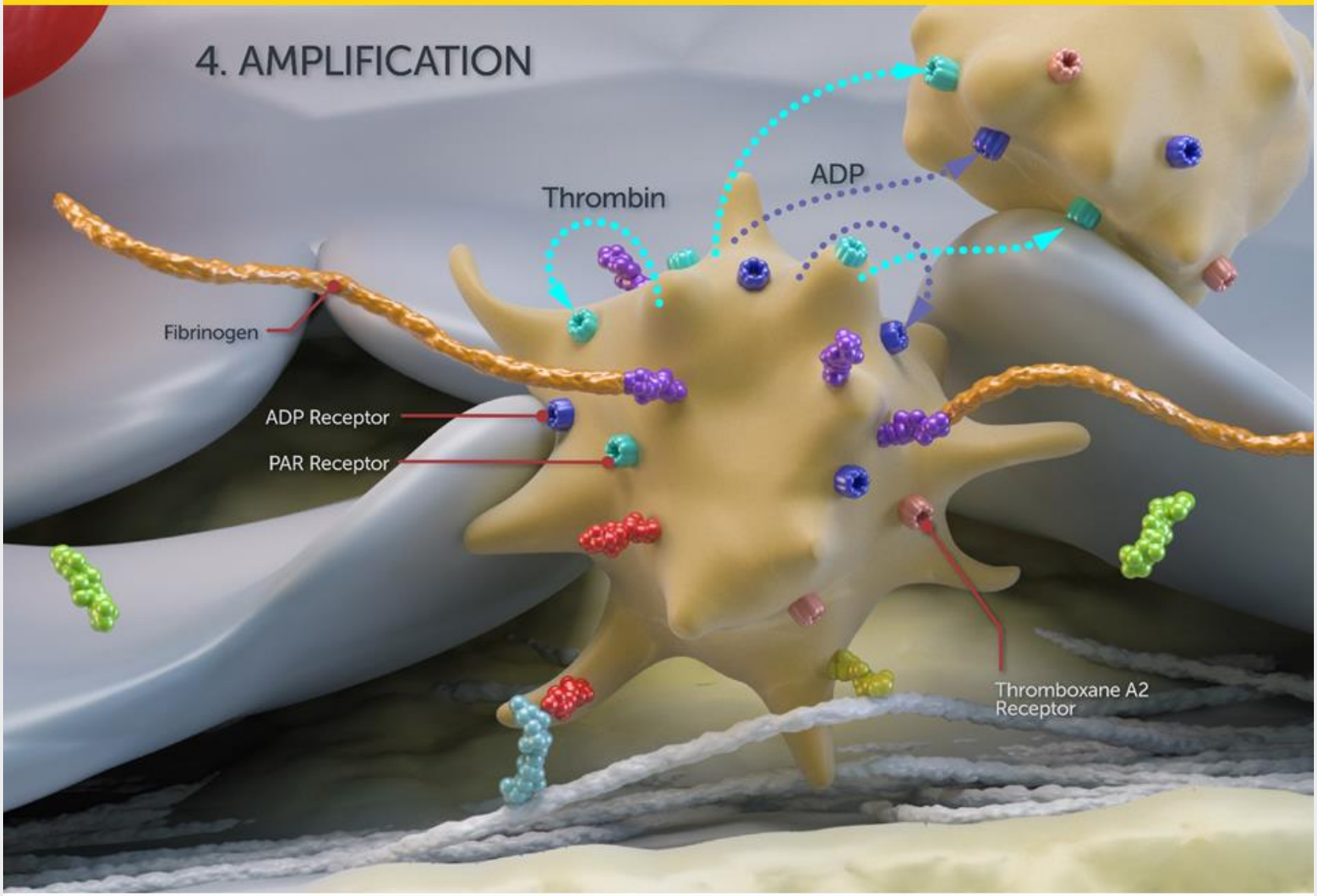
For illustrative purposes only.

Yousuf O, Bhatt D. *Nat Rev Cardiol*. 2011;8(10):547-559.



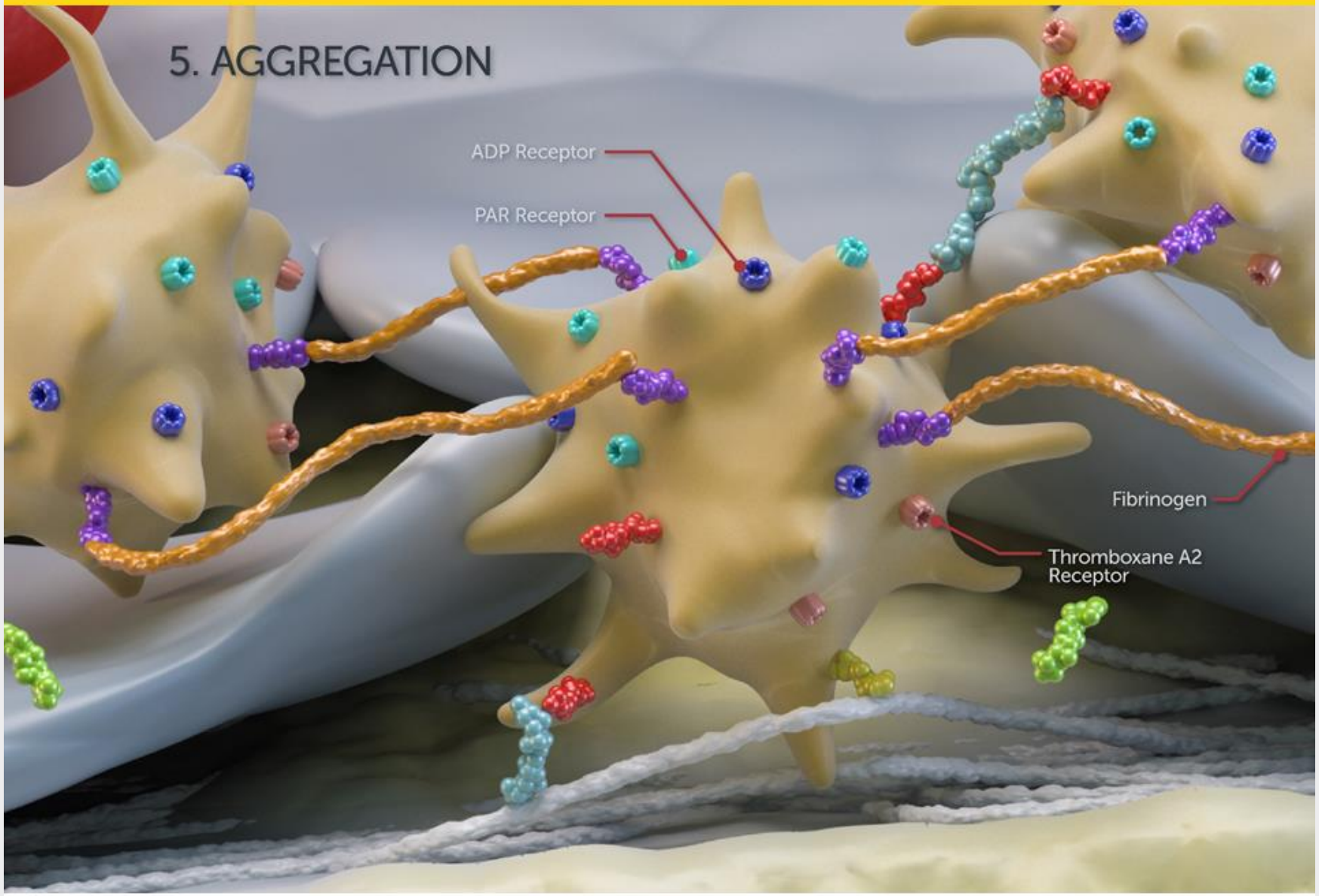
For illustrative purposes only.

1. Coughlin SR. *Nature*. 2000;407(6801):258-264. 2. Monroe DM, Hoffman M. *Arterioscler Thromb Vasc Biol*. 2006;26(1):41-48.



For illustrative purposes only.

Monroe DM, Hoffman M. *Arterioscler Thromb Vasc Biol*. 2006;26(1):41-48.



For illustrative purposes only.

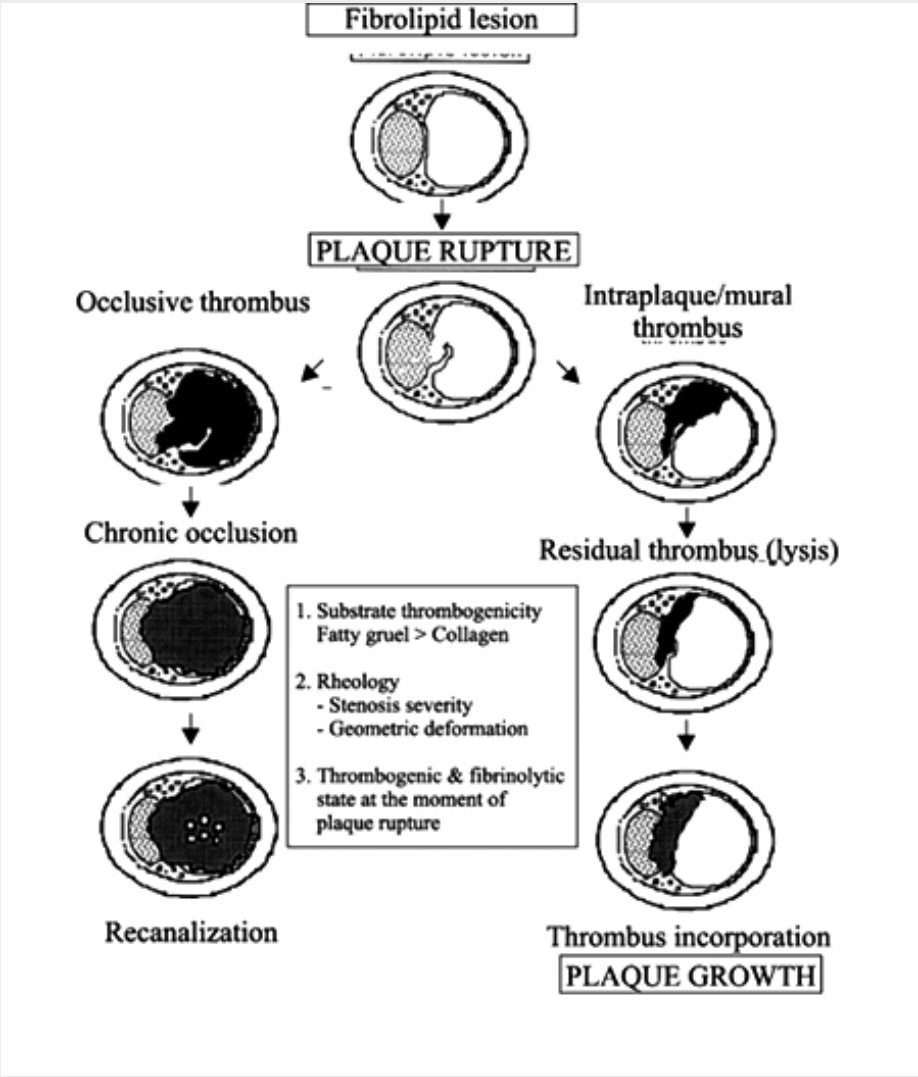
Jackson SP. *Blood*. 2007;109(12):5087-5095.

For illustrative purposes only.

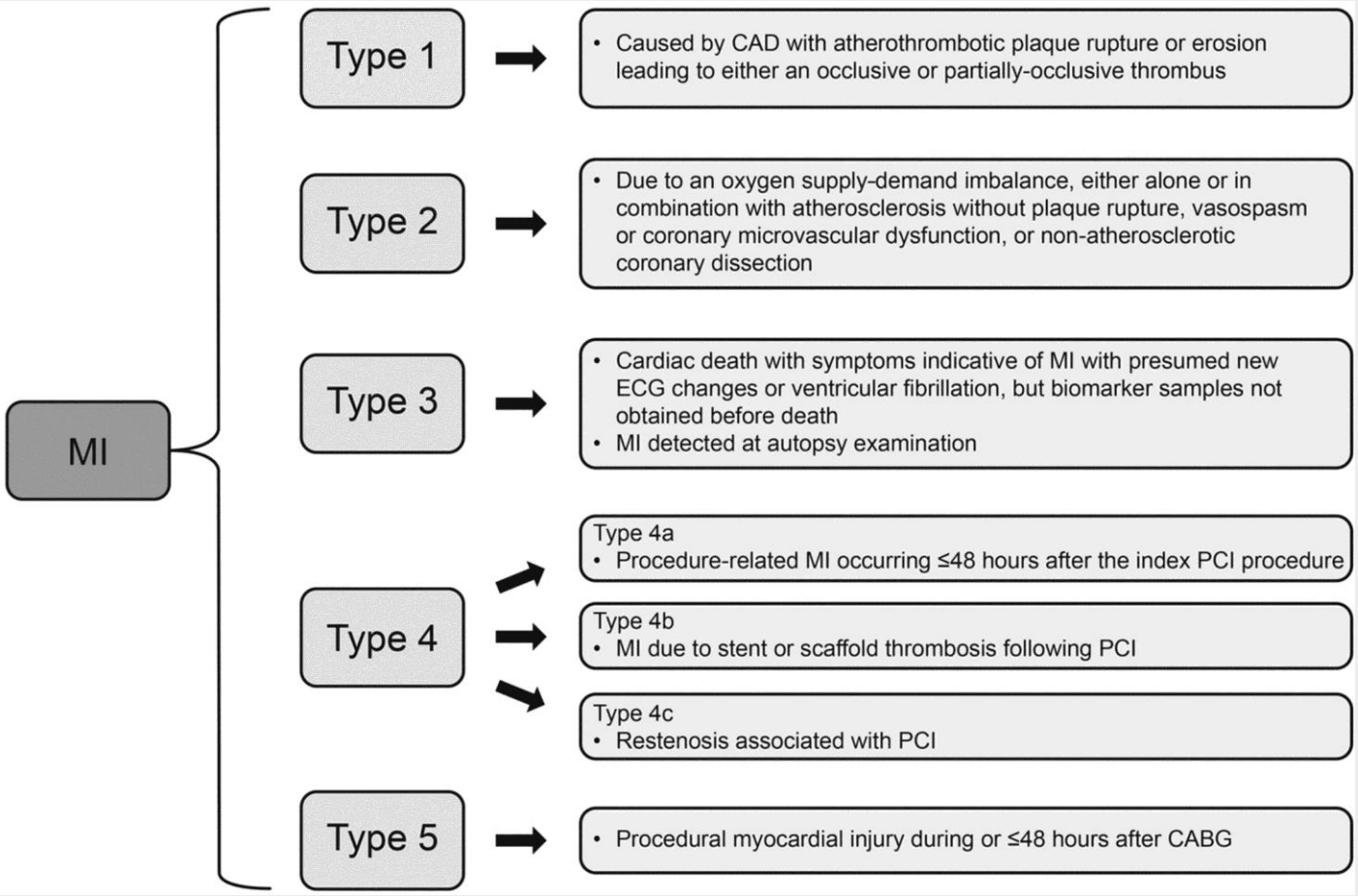
Stalker TJ, Traxler EA, Wu J, et al. *Blood*. 2013;121(10):1875-1885.

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



Clinical Cardiology, Volume: 43, Issue: 3, Pages: 242-250, First published: 10 January 2020, DOI: (10.1002/clc.23308)

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 aspiring, 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

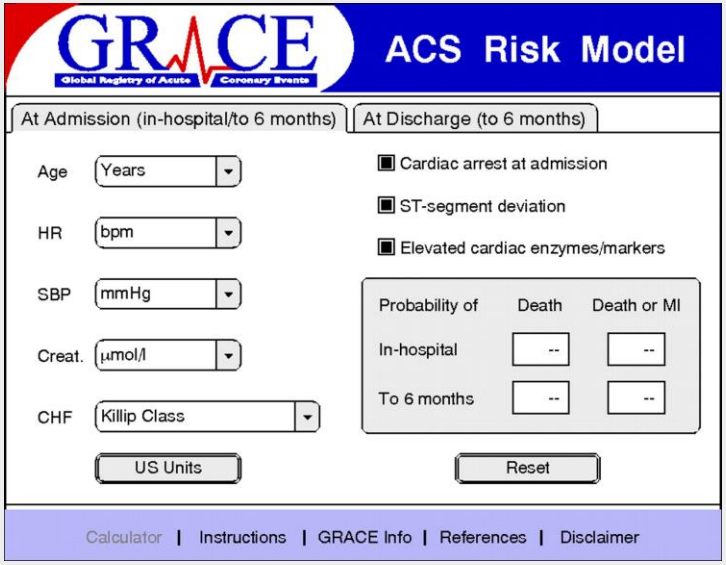
Initial Assessment

--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 ≥65	1 point
2) ≥3 risk factors for CAD	1 point
3) Use of ASA (last 7 days)	1 point
4) Known CAD (prior stenosis ≥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



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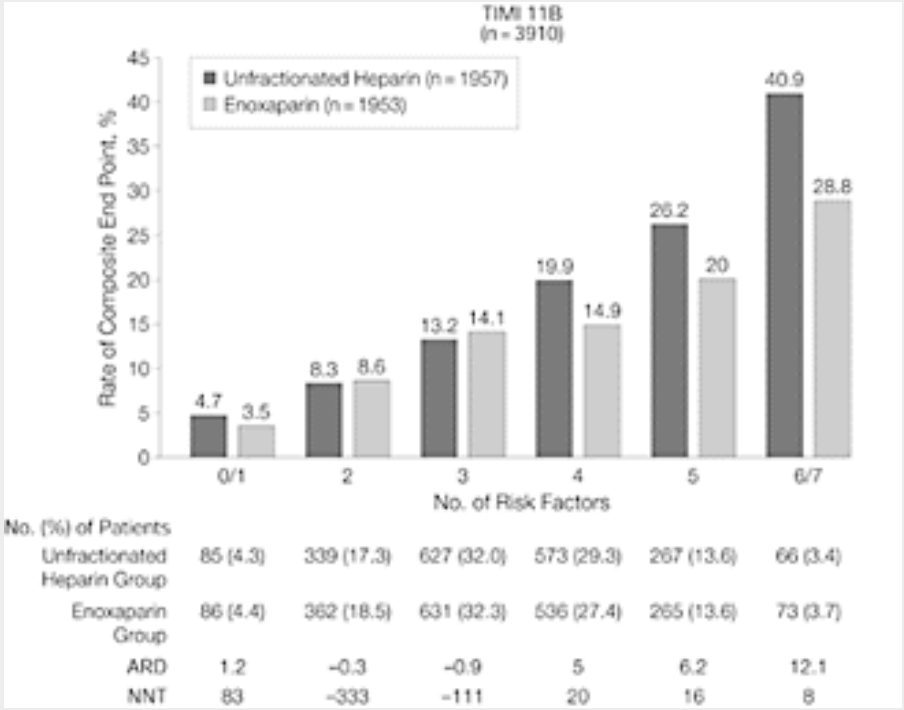
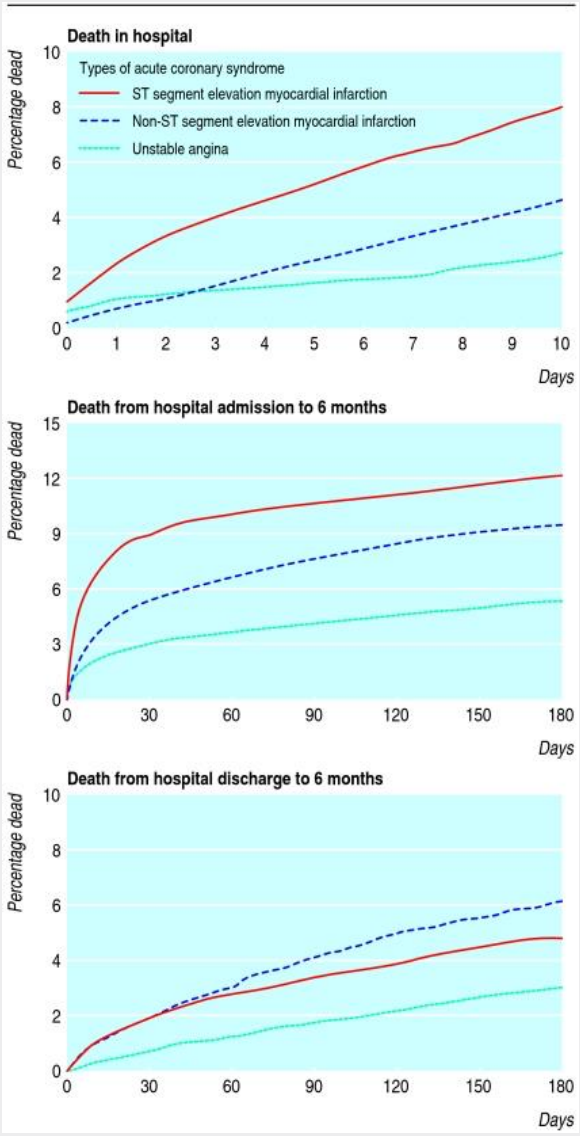


No. (%) of Patients						
Unfractionated Heparin Group	85 (4.3)	339 (17.3)	627 (32.0)	573 (29.3)	267 (13.6)	66 (3.4)
Enoxaparin Group	86 (4.4)	362 (18.5)	631 (32.3)	536 (27.4)	265 (13.6)	73 (3.7)
ARD	1.2	−0.3	−0.9	5	6.2	12.1
NNT	83	−333	−111	20	16	8

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

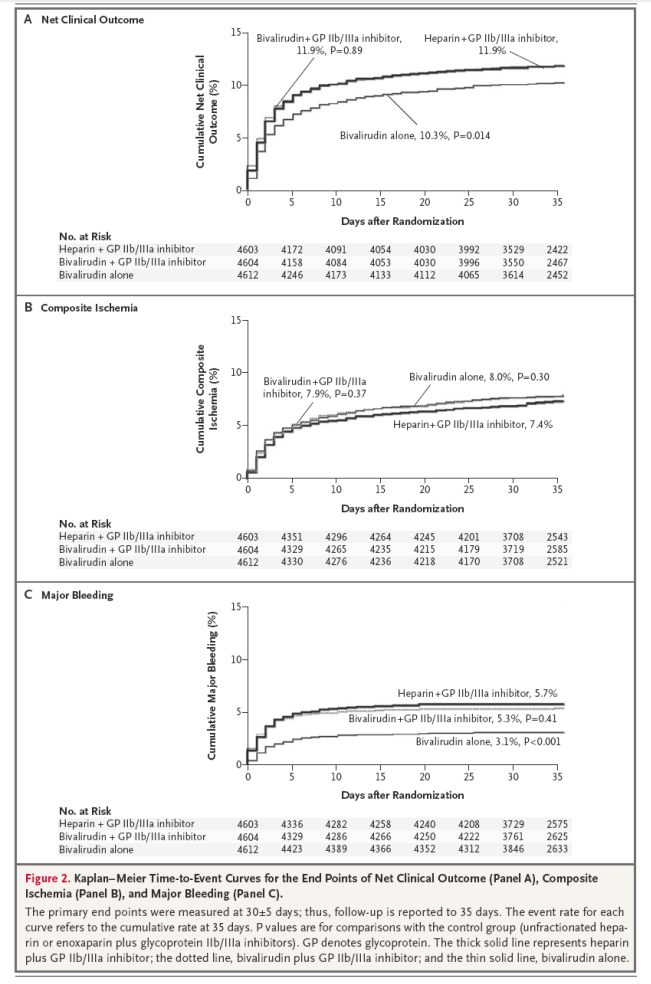


Figure 2. Kaplan–Meier Time-to-Event Curves for the End Points of Net Clinical Outcome (Panel A), Composite Ischemia (Panel B), and Major Bleeding (Panel C).

The primary end points were measured at 30±5 days; thus, follow-up is reported to 35 days. The event rate for each curve refers to the cumulative rate at 35 days. P values are for comparisons with the control group (unfractionated heparin or enoxaparin plus glycoprotein IIb/IIIa inhibitors). GP denotes glycoprotein. The thick solid line represents heparin plus GP IIb/IIIa inhibitor; the dotted line, bivalirudin plus GP IIb/IIIa inhibitor; and the thin solid line, bivalirudin alone.

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

Yusuf S on behalf of CURE Trial Investigators. Effects of Clopidogrel in Addition in Patient with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med* 2001; 345: 494-502.

CURE TRIAL

(Clopidogrel in Unstable angina to prevent Recurrent Events)

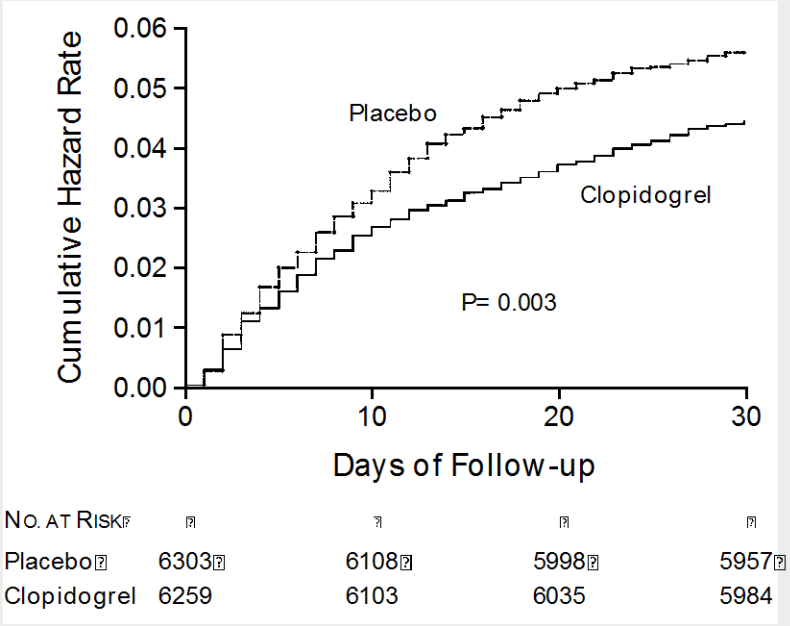


Figure 2. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the First 30 Days after Randomization. The results demonstrate the early effect of clopidogrel.

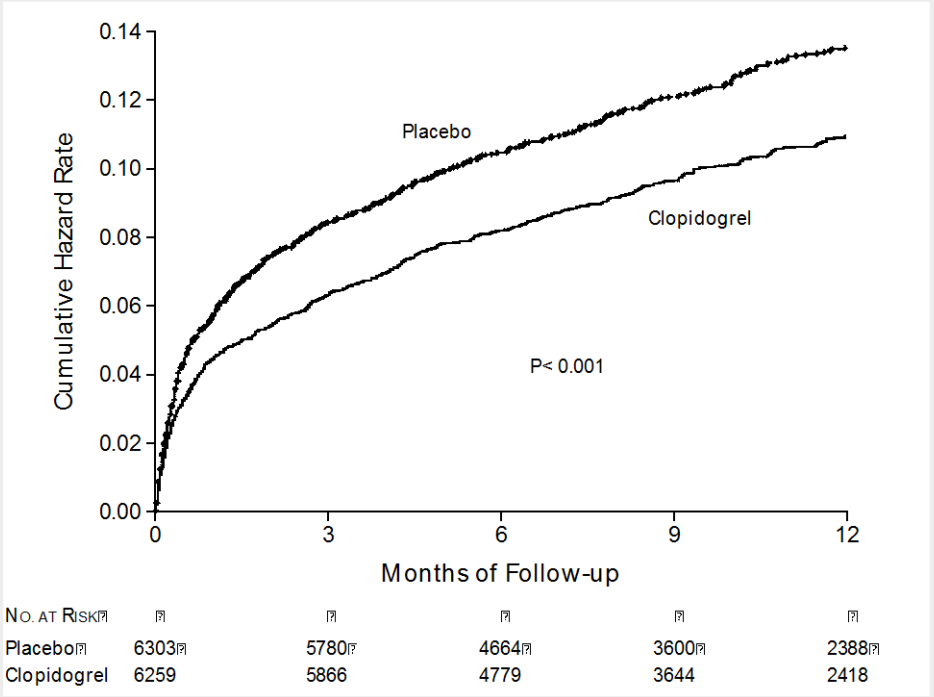
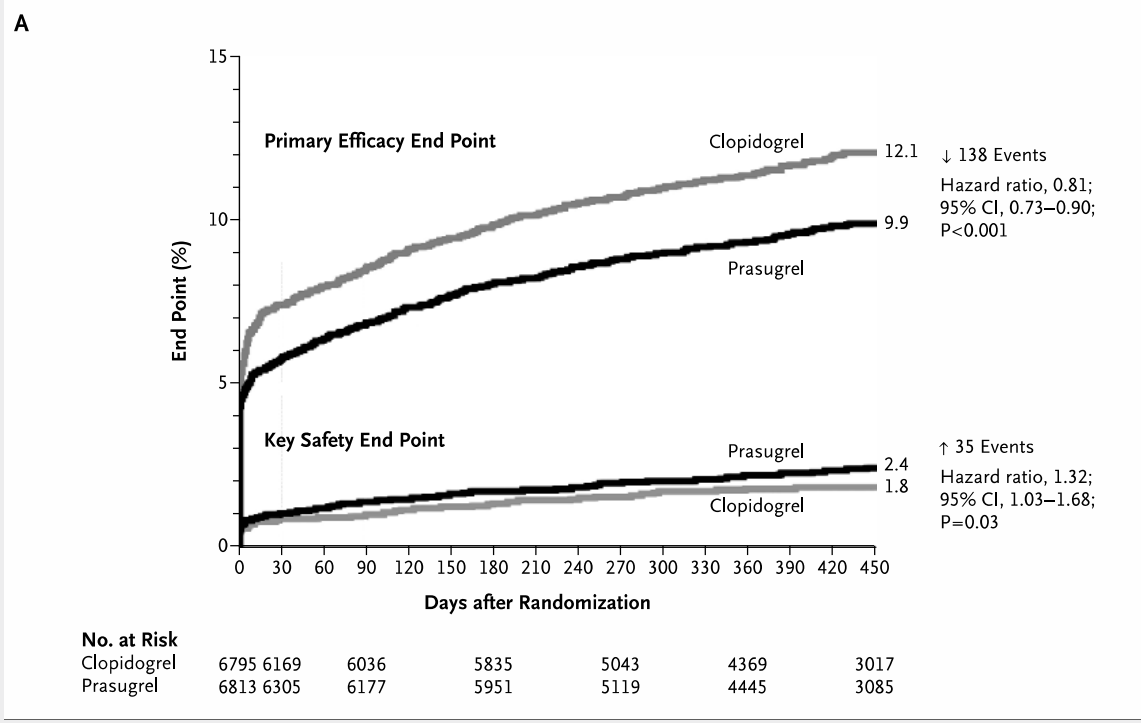


Figure 1. Cumulative Hazard Rates for the First Primary Outcome (Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Stroke) during the 12 Months of the Study. The results demonstrate the sustained effect of clopidogrel.

Yusuf S on behalf of CURE Trial Investigators. Effects of Clopidogrel in Addition in Patient with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med* 2001; 345: 494-502.

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

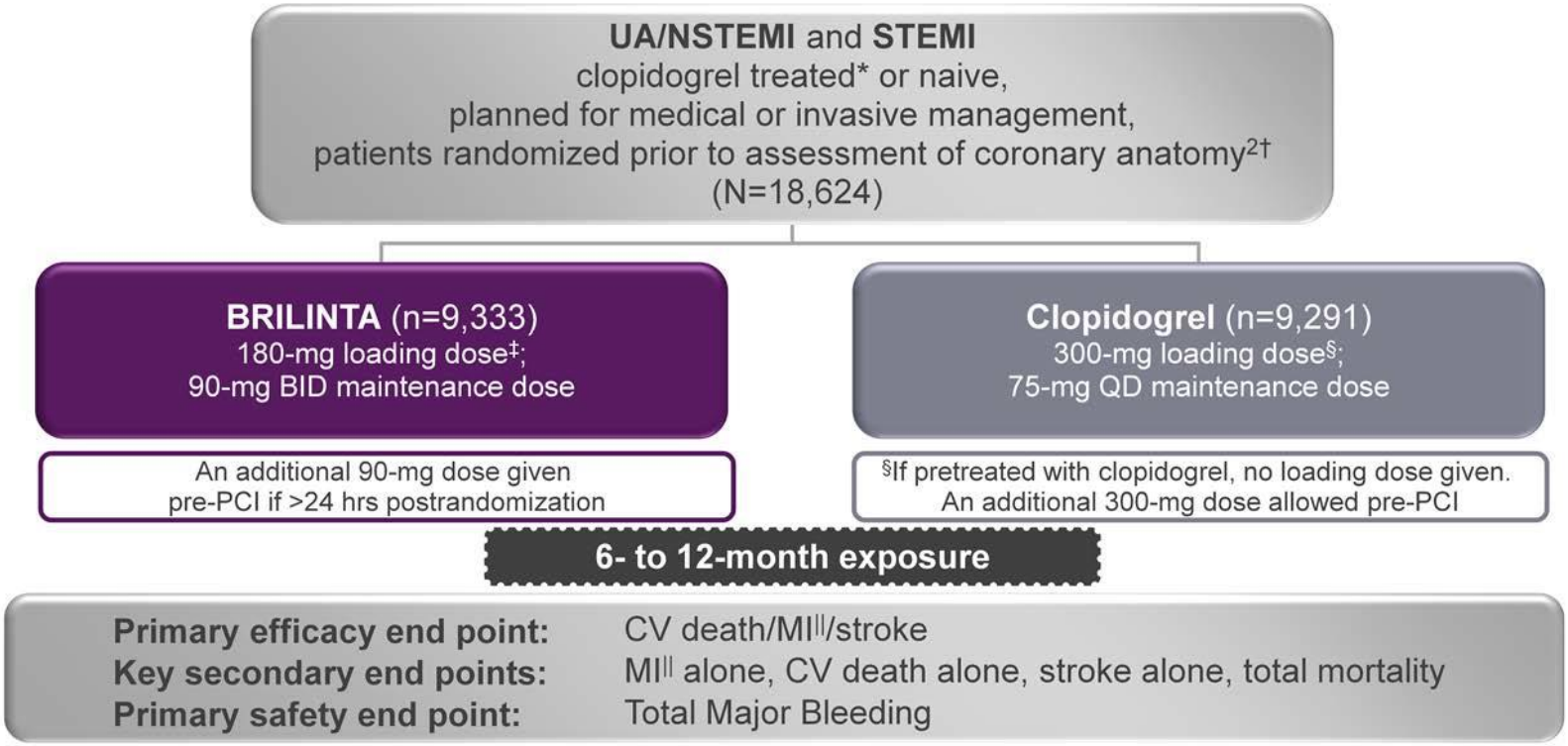


Age ≥75 yr, body weight <60 kg, or history of stroke or TIA				
Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)	198/1320 (16.1)	199/1347 (16.0)	1.02 (0.84–1.24)	0.83
Non–CABG-related TIMI major bleeding	52/1305 (4.3)	38/1328 (3.3)	1.42 (0.93–2.15)	0.10

Wiviott SD et al. Prasugrel vs Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2007; 357: 2001-15.

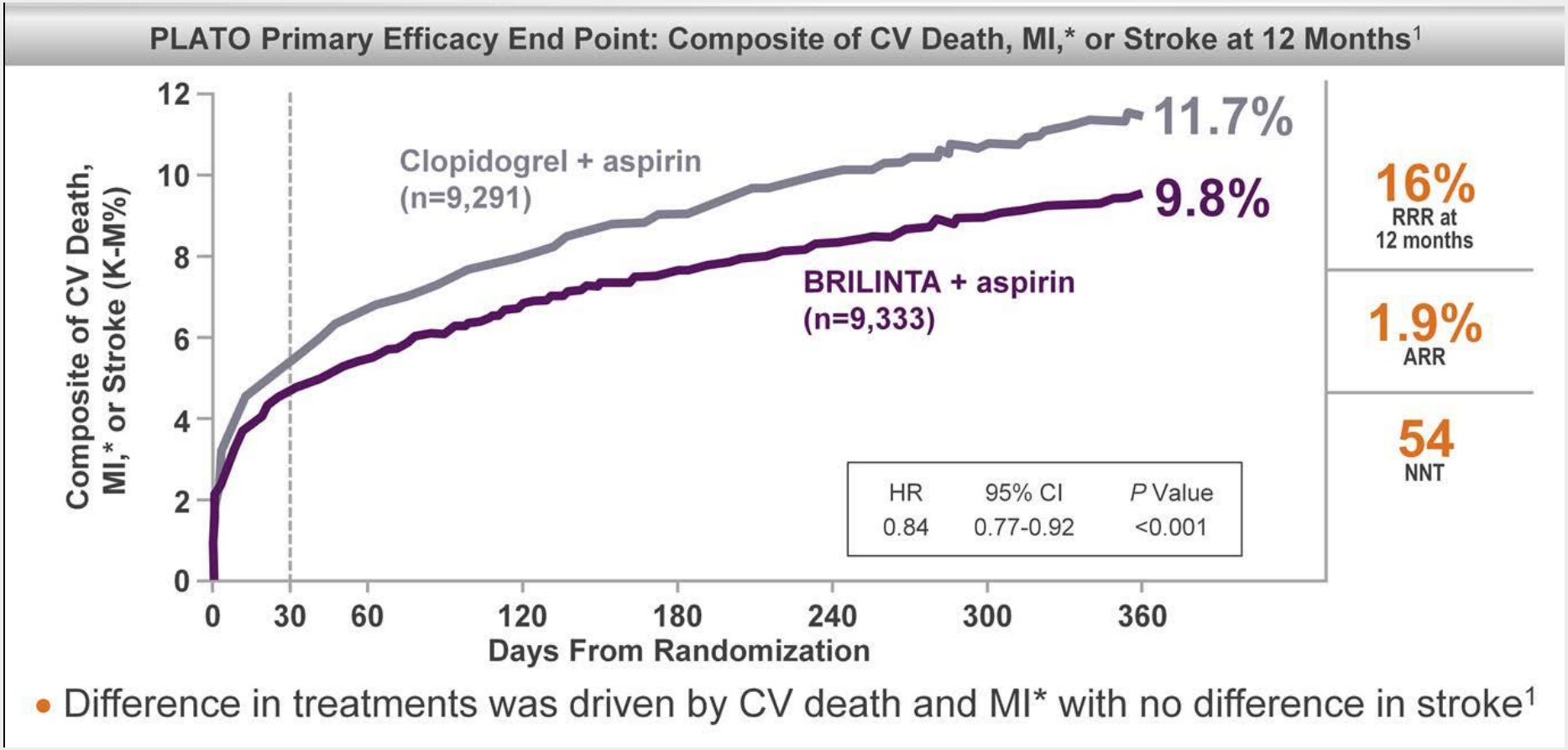
PLATO Trial

The PLATO Trial Design[1]



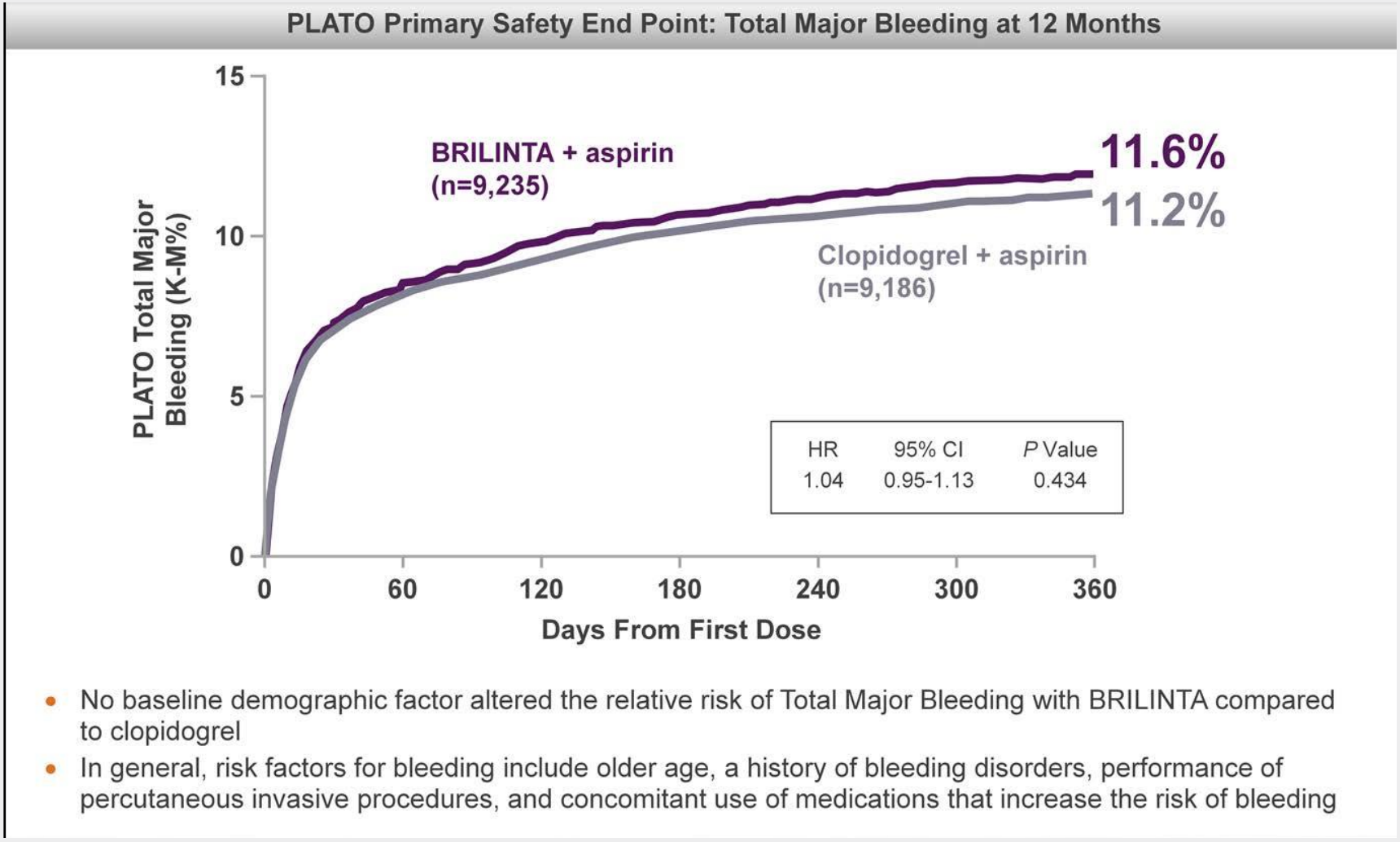
- BRILINTA and clopidogrel were both given in combination with aspirin and other standard therapy

PLATO Trial



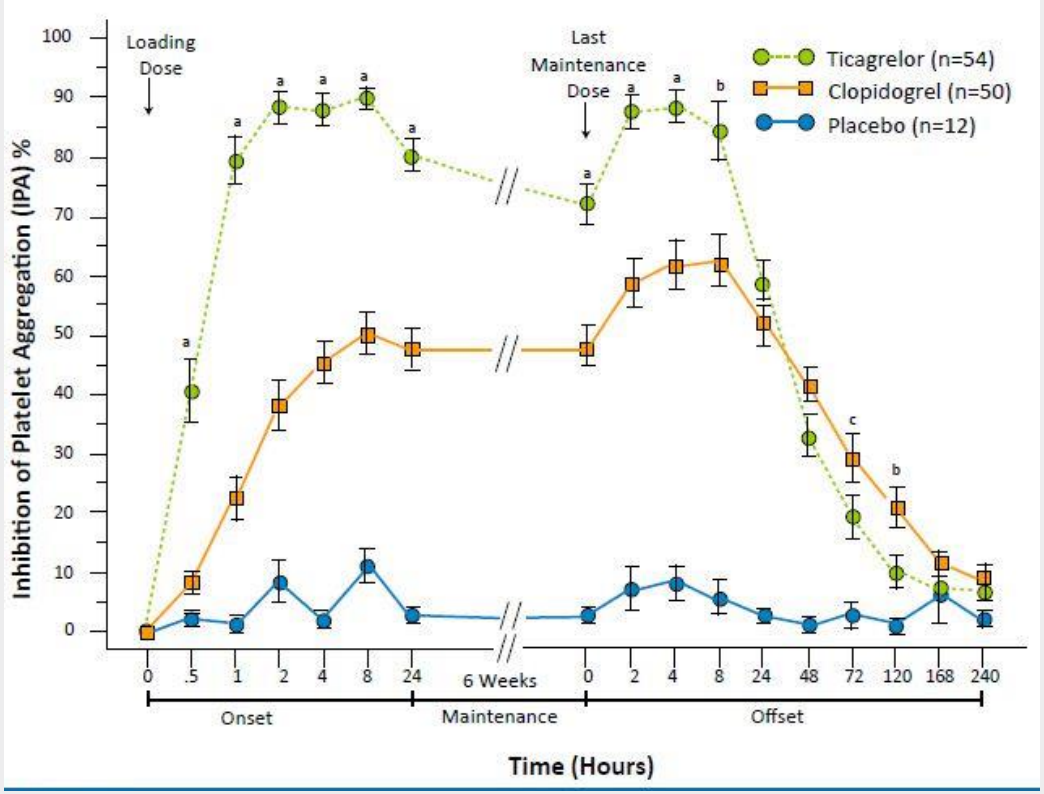
- Difference in treatments was driven by CV death and MI* with no difference in stroke[1]

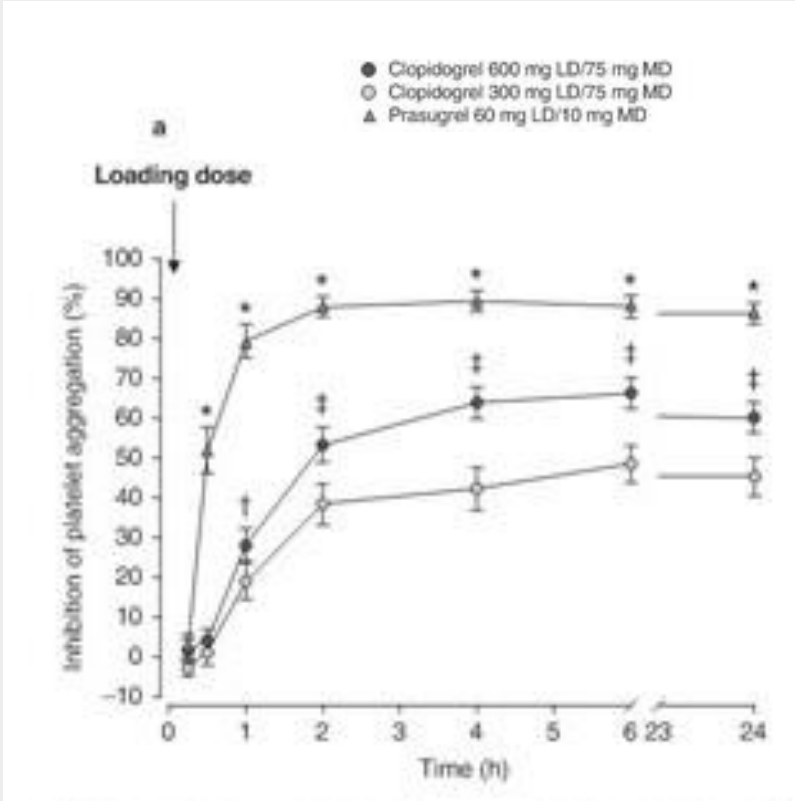
PLATO Trial



- 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

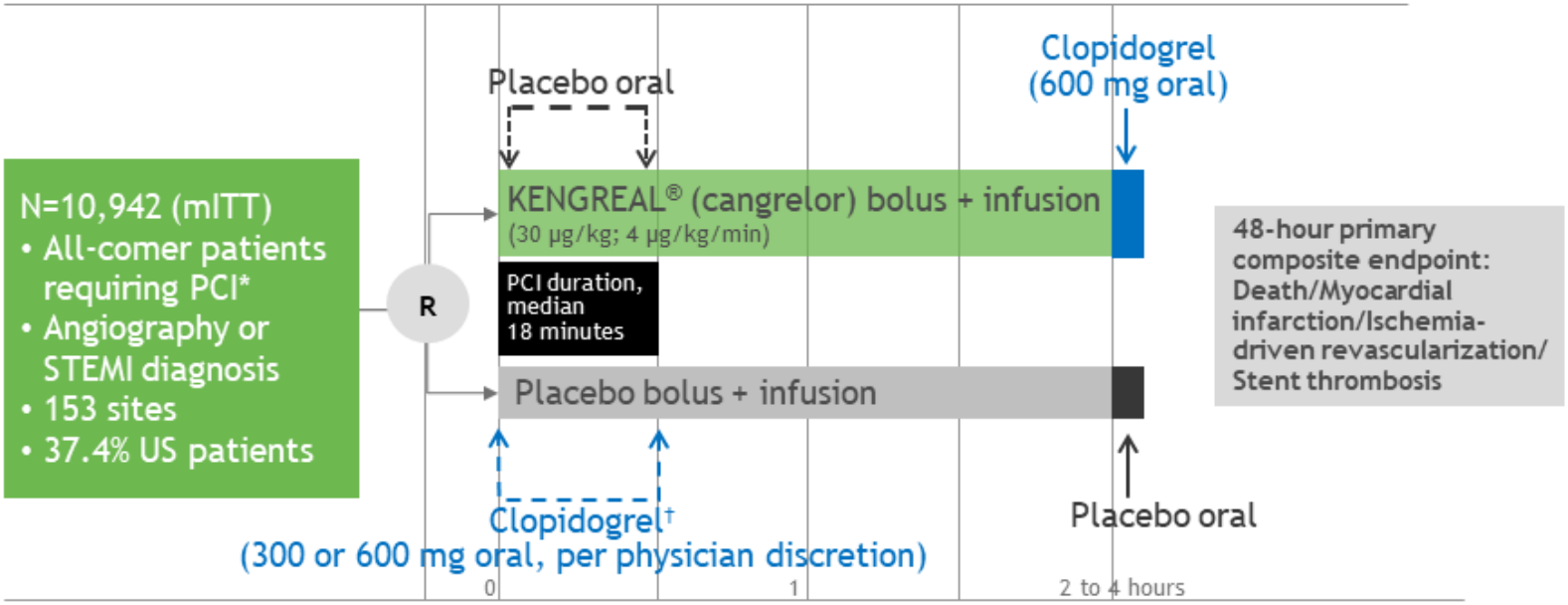
PHARMACOKINETICS





CHAMPION PHOENIX: Pivotal phase III trial

Study schematic[1,2]



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.

*$P2Y_{12}$ inhibitor naïve.

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

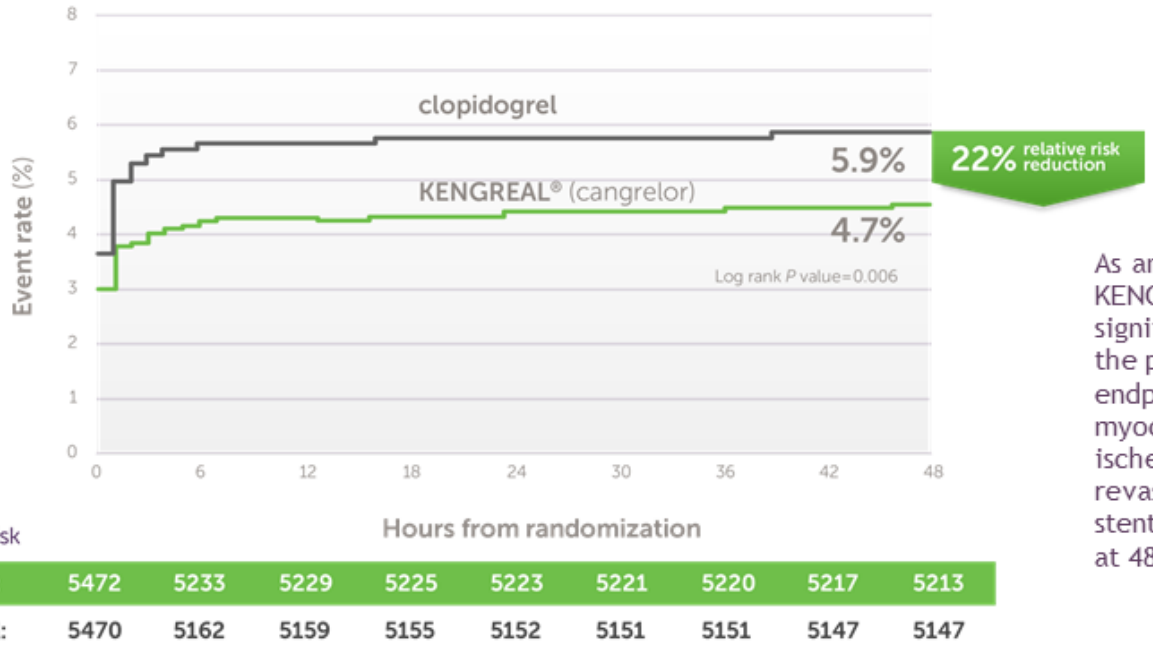
mITT=modified intent-to-treat; R=randomization.

1. Bhatt DL, Stone GW, Mahaffey KW, et al. *N Engl J Med.* 2013;368(suppl):1-15. 2. Bhatt DL, Stone GW, Mahaffey KW, et al. *N Engl J Med.* 2013;368(14):1303-1313.

KENGREAL® (cangrelor) for injection

22% relative risk reduction in periprocedural thrombotic events[1,2]

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

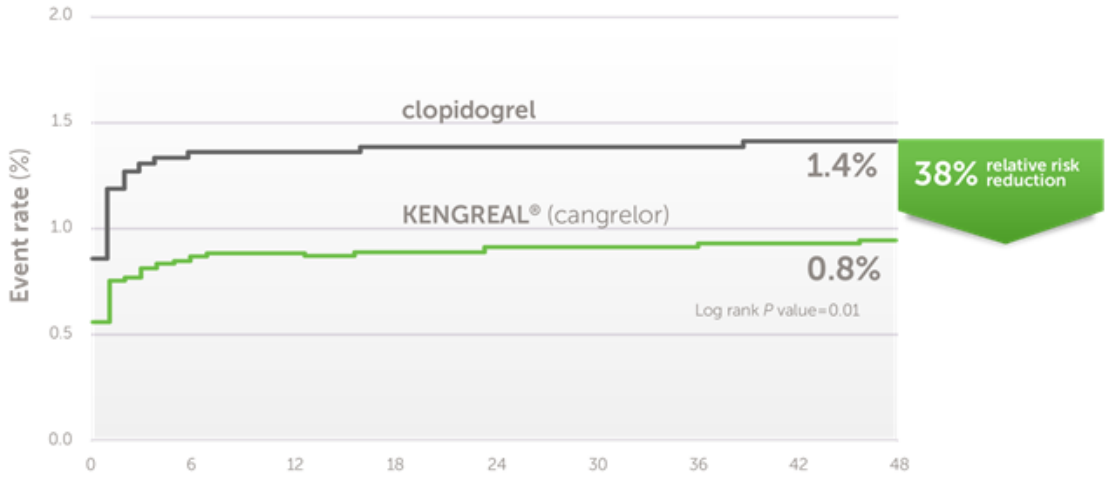
As an adjunct to PCI, KENGREAL® (cangrelor) significantly reduced the primary composite endpoint of death, myocardial infarction, ischemia-driven revascularization, and stent thrombosis events at 48 hours.

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

KENGREAL® (cangrelor) for injection

38% relative risk reduction in key secondary endpoint of stent thrombosis[1,2]

Stent thrombosis at 48 hours in an mITT patient population

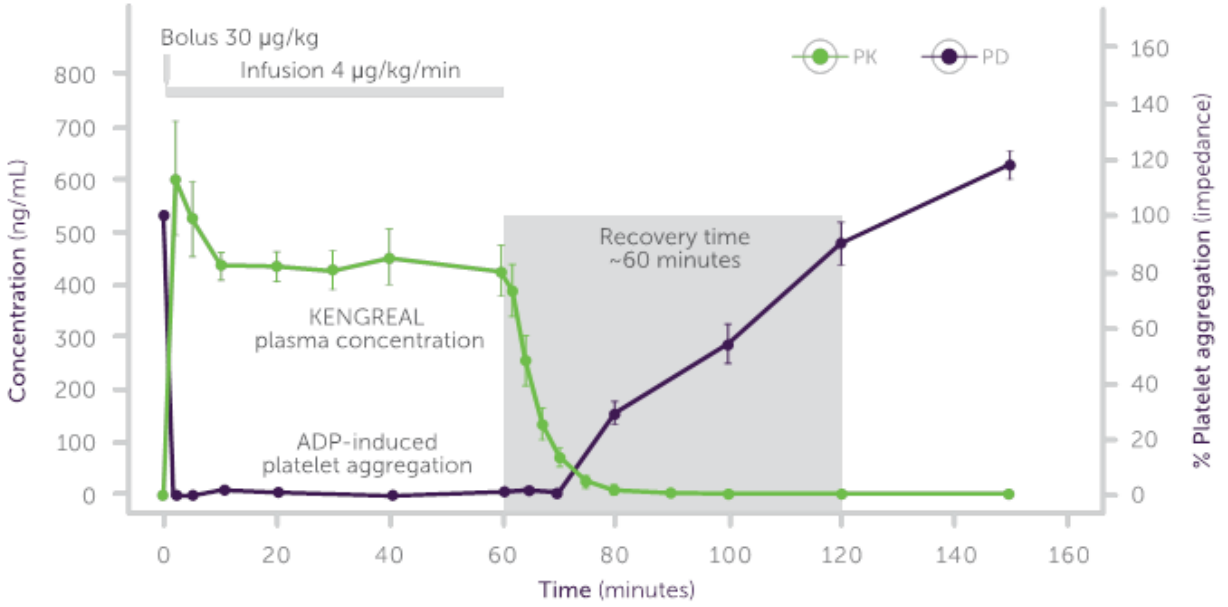


Patients at risk									
KENGREAL:	5472	5426	5421	5419	5419	5418	5417	5416	5414
Clopidogrel:	5470	5392	5389	5388	5386	5385	5385	5383	5383

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) for injection

KENGREAL® (cangrelor) pharmacology[1,2] (cont'd)



Study Details[2]

- Phase I study in healthy volunteers (n=9)
- Dose: 30 µg/kg IV bolus + 4 µg/kg/min IV infusion
- Blood levels of cangrelor (green line/PK) and platelet activity (purple line/PD) were assessed over 150 minutes by whole blood impedance aggregometry in response to 20 µM of ADP

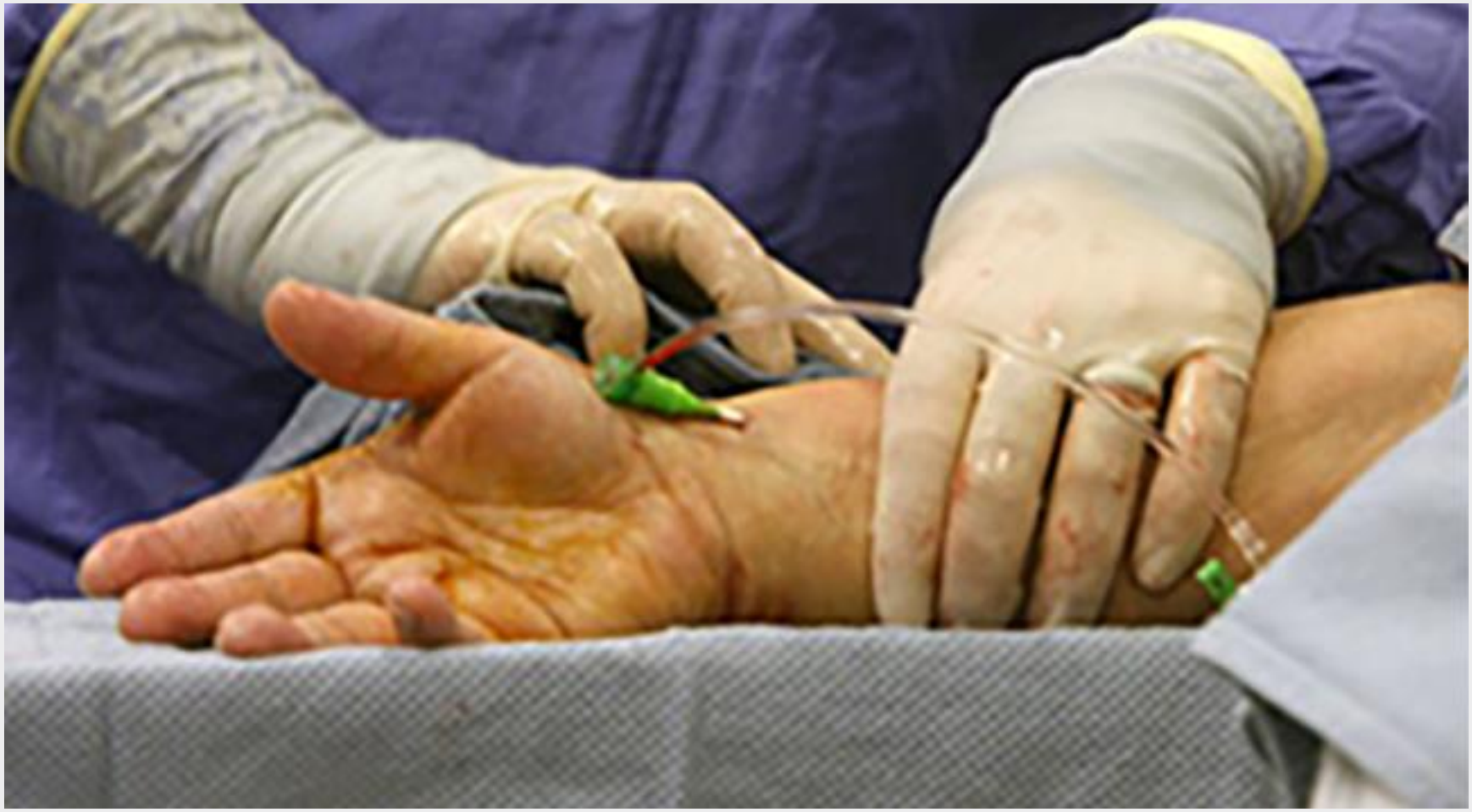
- >98% inhibition of platelet aggregation in whole blood impedance aggregometry[3]

1. KENGREAL® (cangrelor) Prescribing Information. 2016. 2. Akers WS, Oh JJ, Oestreich JH, et al. *J Clin Pharmacol.* 2010;50(1):27-35. 3. Data on file. Chiesi USA, Inc.

KENGREAL (cangrelor) for injection

Banner University Medicine

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

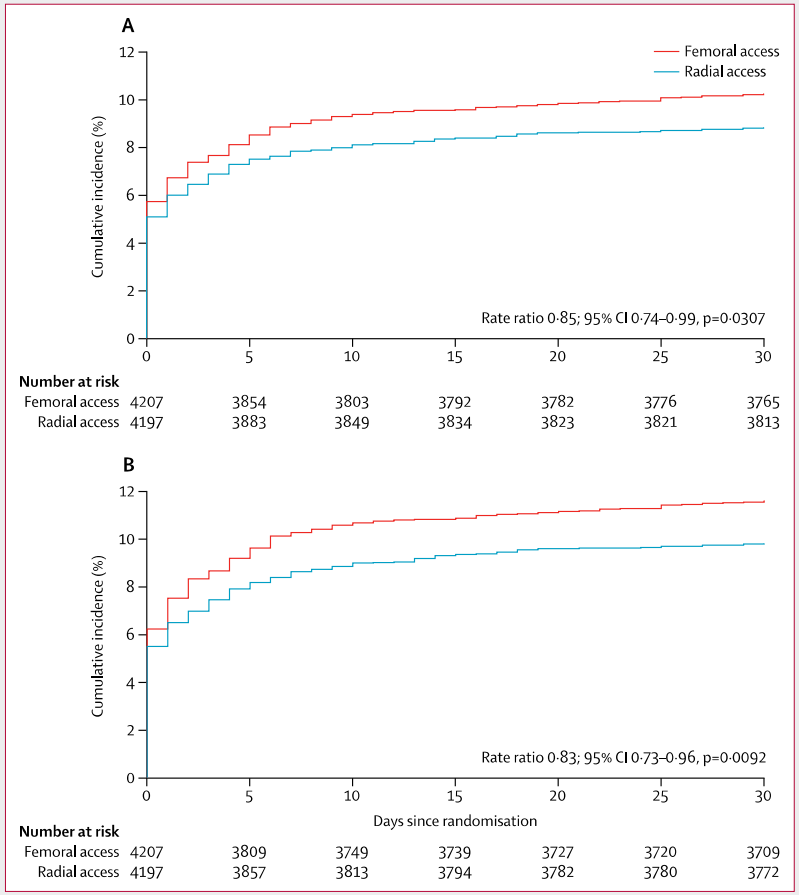


***Figure 2*: Coprimary composite outcomes at 30 days**
(A) All-cause mortality, myocardial infarction, or stroke, and (B) all-cause mortality, myocardial infarction, stroke, or Bleeding Academic Research Consortium 3 or 5 bleeding.

Valgimigli M et al. Radial versus Femoral Access in Patients with Acute Coronary Syndromes Undergoing Invasive Management: A Randomized Multicentre Trial. *Lancet* 385: 2465-75.

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:

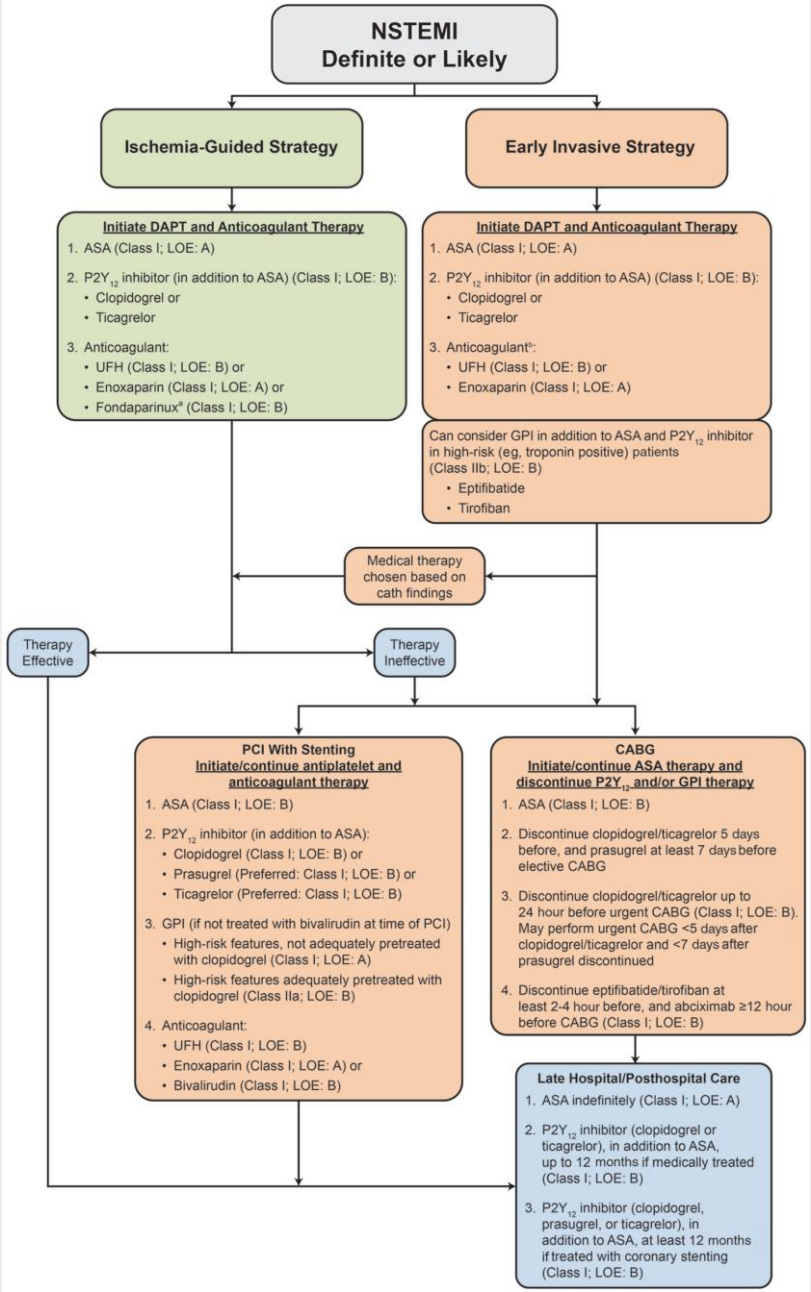
A) Loading with aspirin, prasugrel, and unfractionated heparin

B) Loading with aspirin, clopidogrel, and unfractionated heparin

C) Loading with ticagrelor, enoxaparin, & eptafibitide

D) Loading with prasugrel, enoxaparin, & fondaparinux

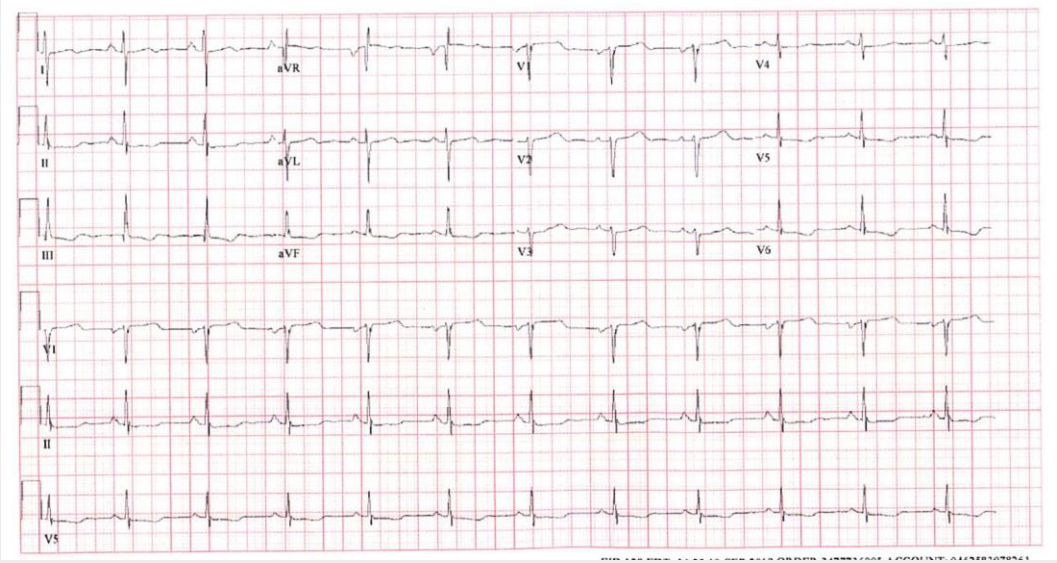
E) Loading with aspirin, ticagrelor, enoxaparin, & cangrelor



Clinical Cardiology, Volume: 43, Issue: 3, Pages: 242-250, First published: 10 January 2020, DOI: (10.1002/clc.23308)

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

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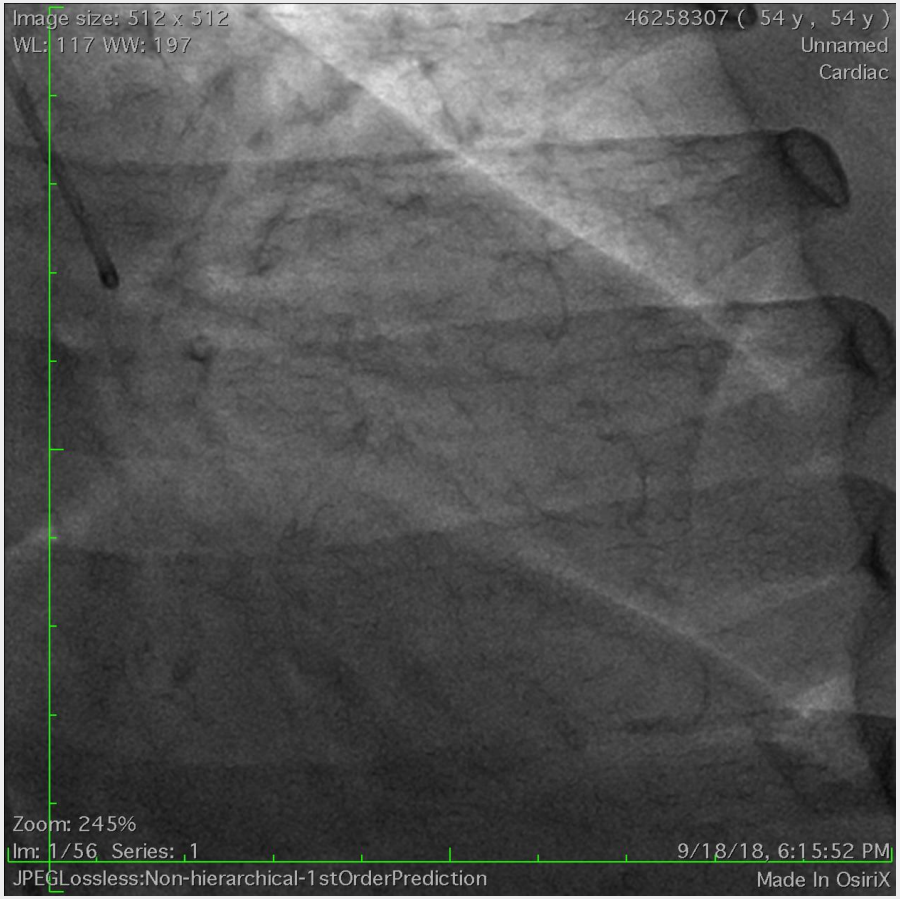
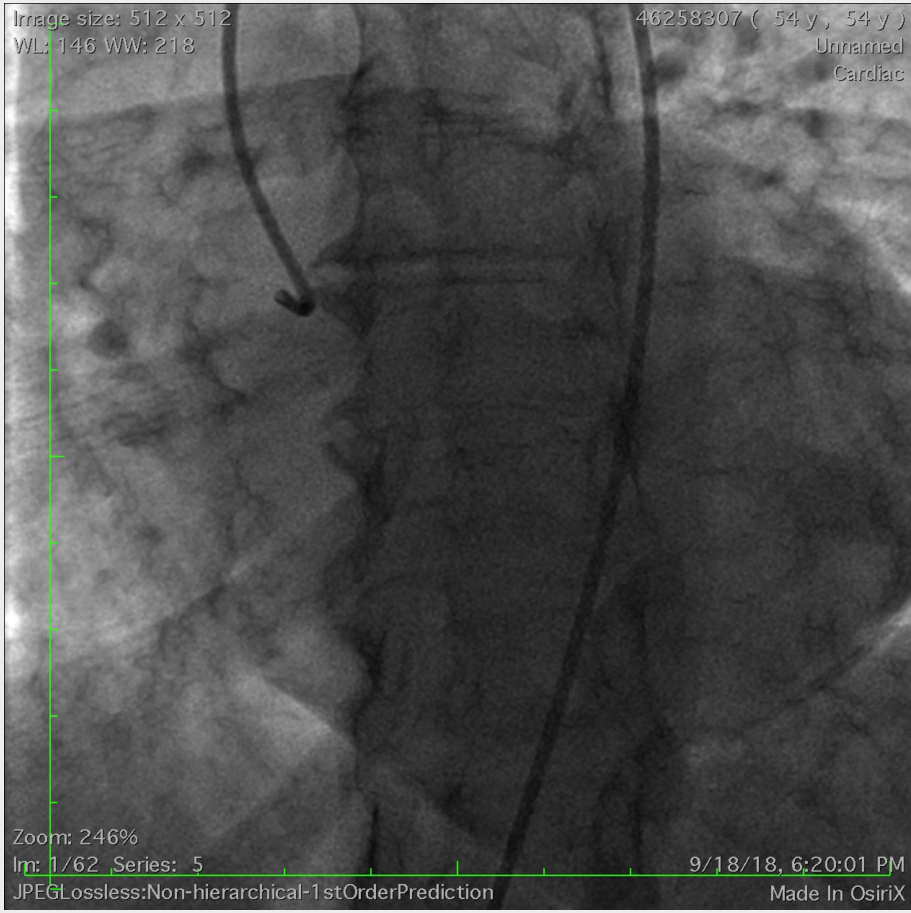
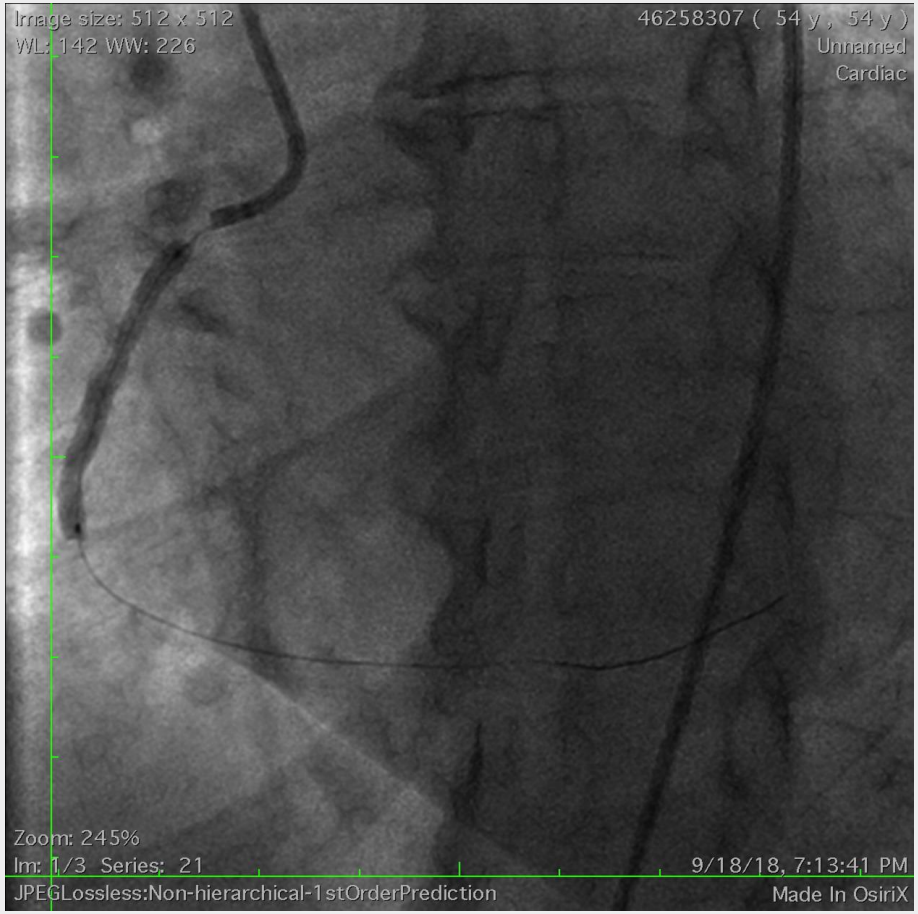
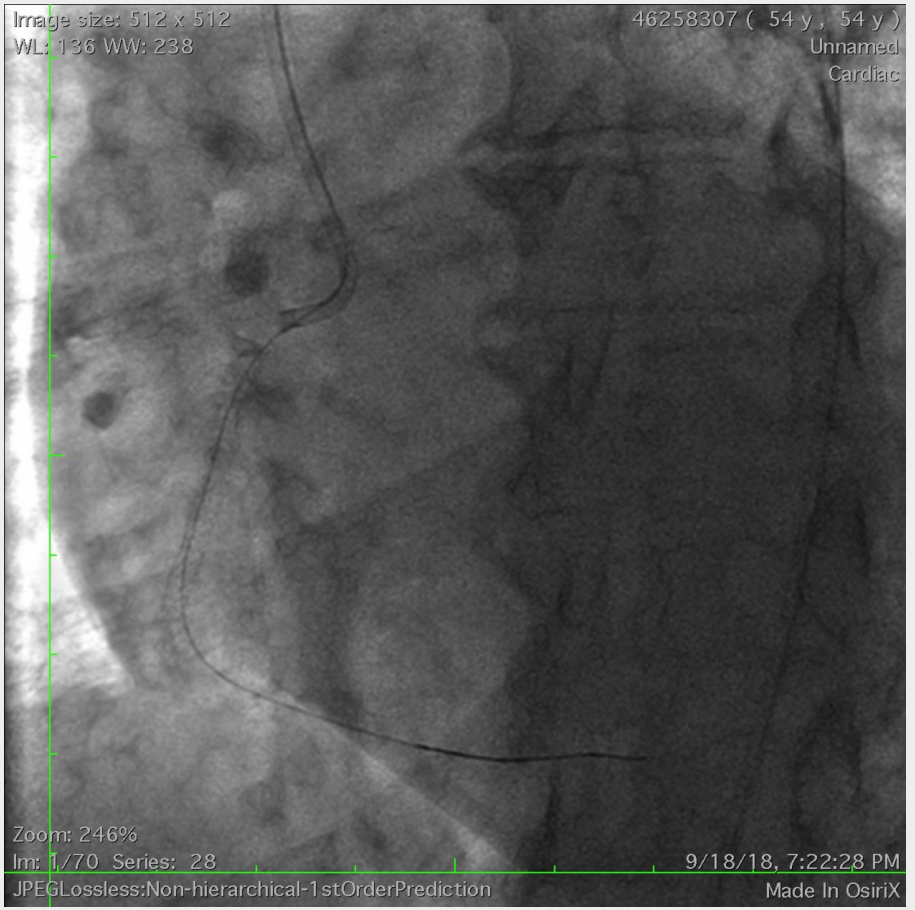




Banner University Medicine





Thank you!

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