Mechanism of Plaque Rupture/Clot Formation and Drugs Considerations

Kevin R Kruse MD FACC

CRITICAL TOPICS IN SAVING LIVES IN NORTH CAROLINA
May 1, 2013

No Diclosures

Sequence of Atherosclerotic Changes

progressive

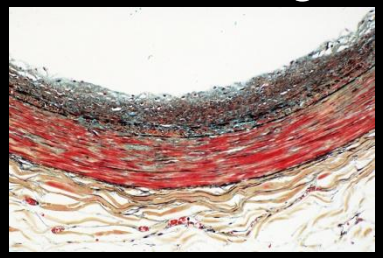
adaptive intimal thickening

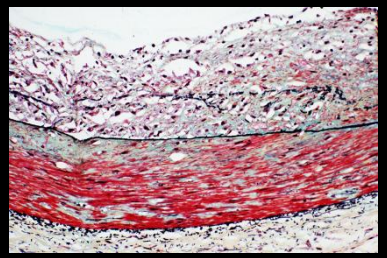
Intimal xanthoma

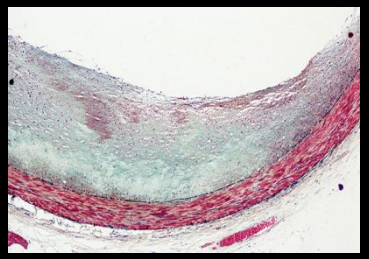
pathologic intimal thickening

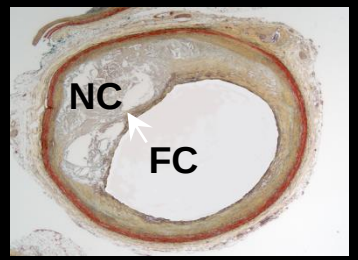
fibroatheroma

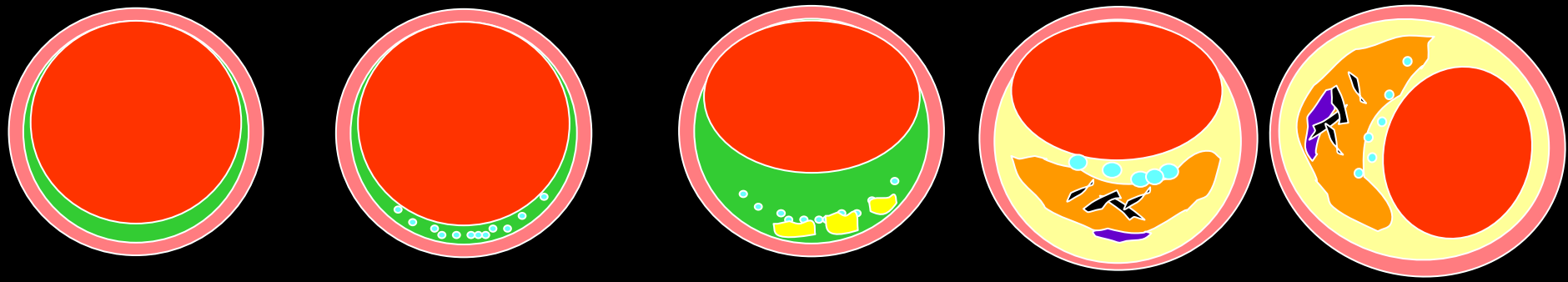
thin-cap fibroatheroma









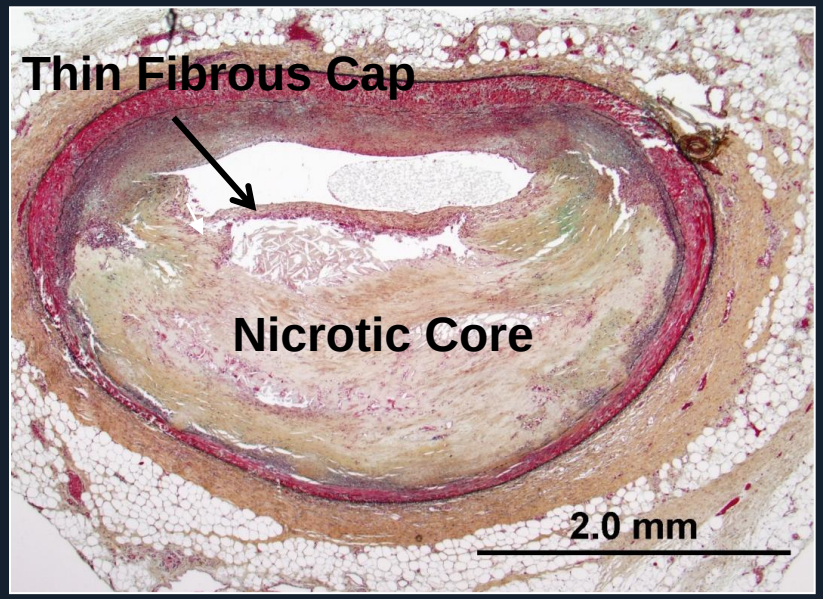


lipid pool

necrotic core

Virmani, Renu

Vulnerable Plaque

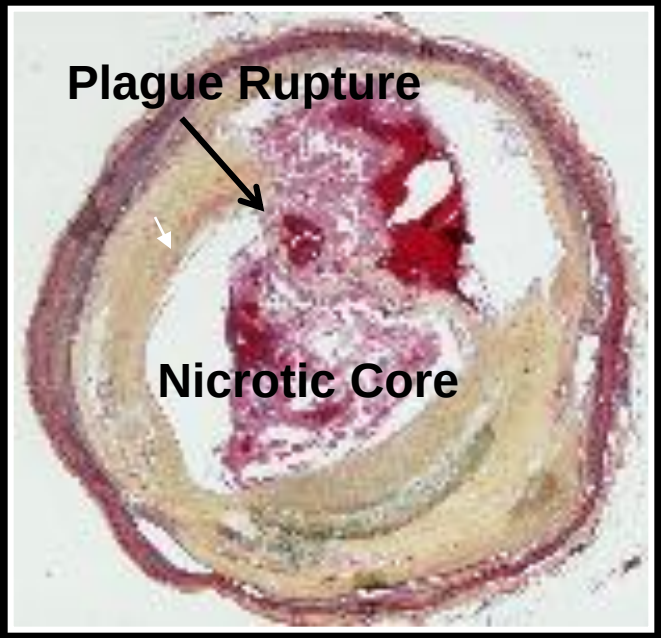


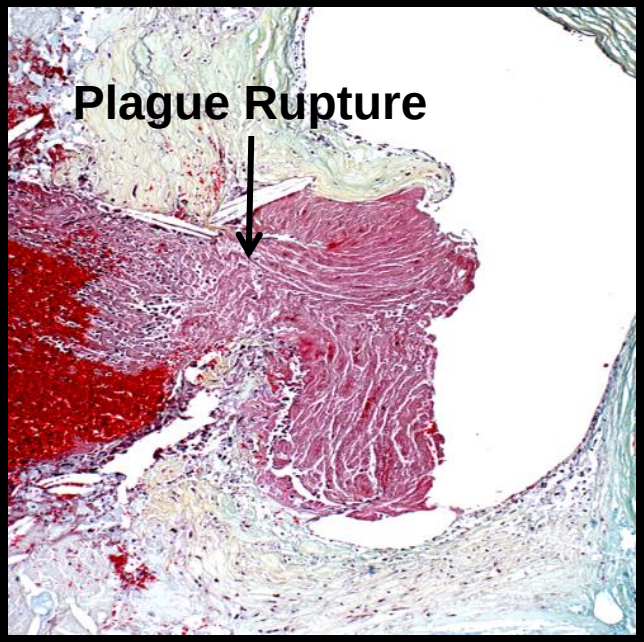
Thin Cap Fibro-Atheroma (TCFA)

- Presence of large necrotic core
- Thin fibrous cap (< 65 μm)
- Cap infiltrated by macrophages and lymphocytes
- Type I collagen with few or absent SMCs in cap

Virmani, Renu

PATHOGENSIS OF PLAQUE RUPTURE



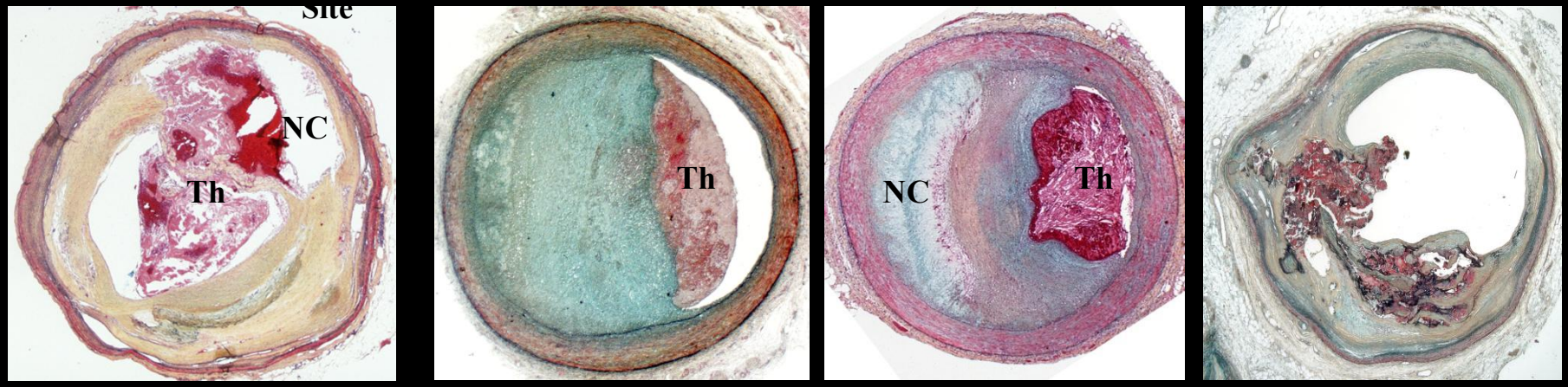


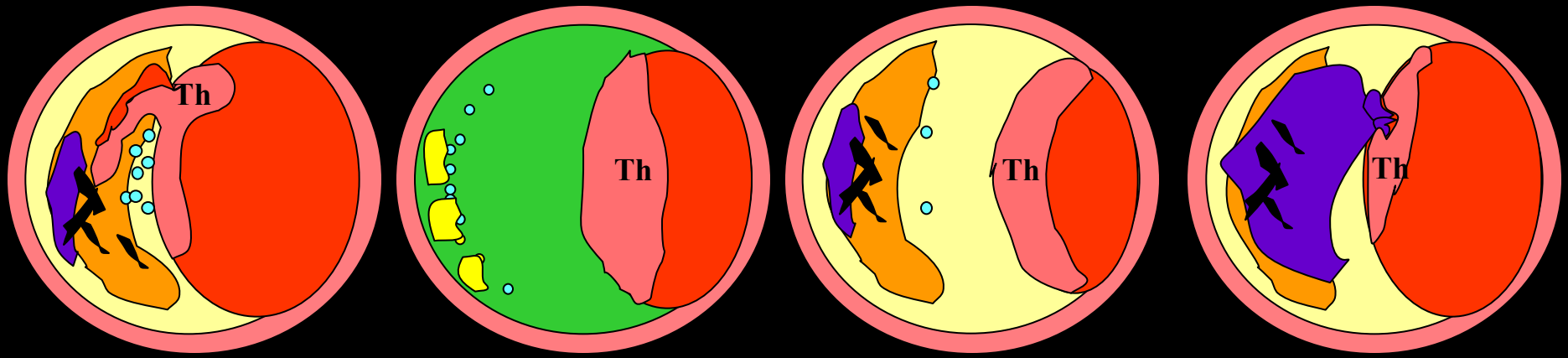
Plaque Rupture

- **Discontinuous fibrous cap**
- **Underlying necrotic core**
- **Luminal thrombus**

Causes of Coronary Thrombosis

Rupture | **Erosion** | **Calcified nodule**

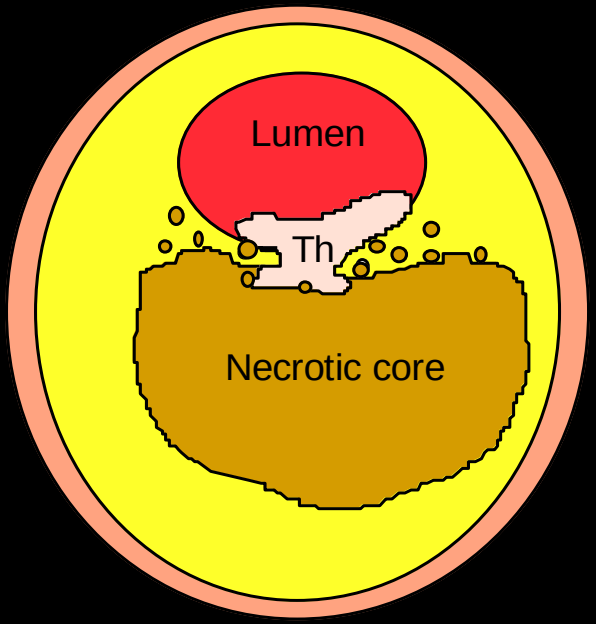




Virmani R, et al. Arterioscler Thromb Vasc Biol 2000;20:1262

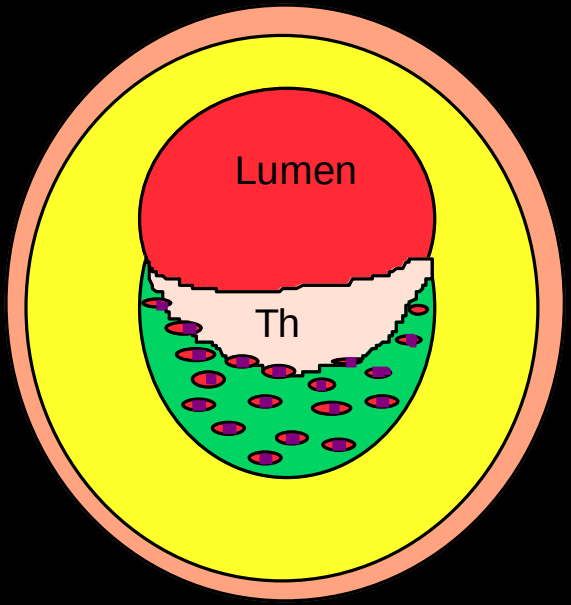
Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

Plaque rupture



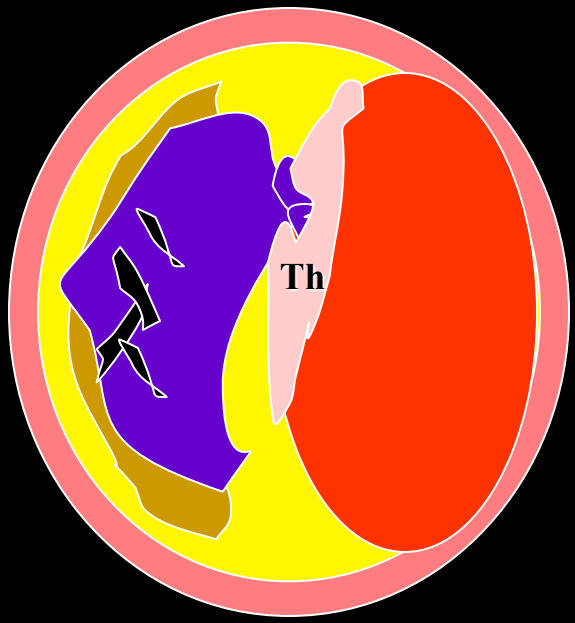
75% thrombi
M>F, Older
Eccentric = concentric
Greater % stenosis
Macs, T cells rich

Plaque erosion



15-20% thrombi
M=F, younger
Usually eccentric
Lesser % stenosis
SMC rich

Calcified nodule

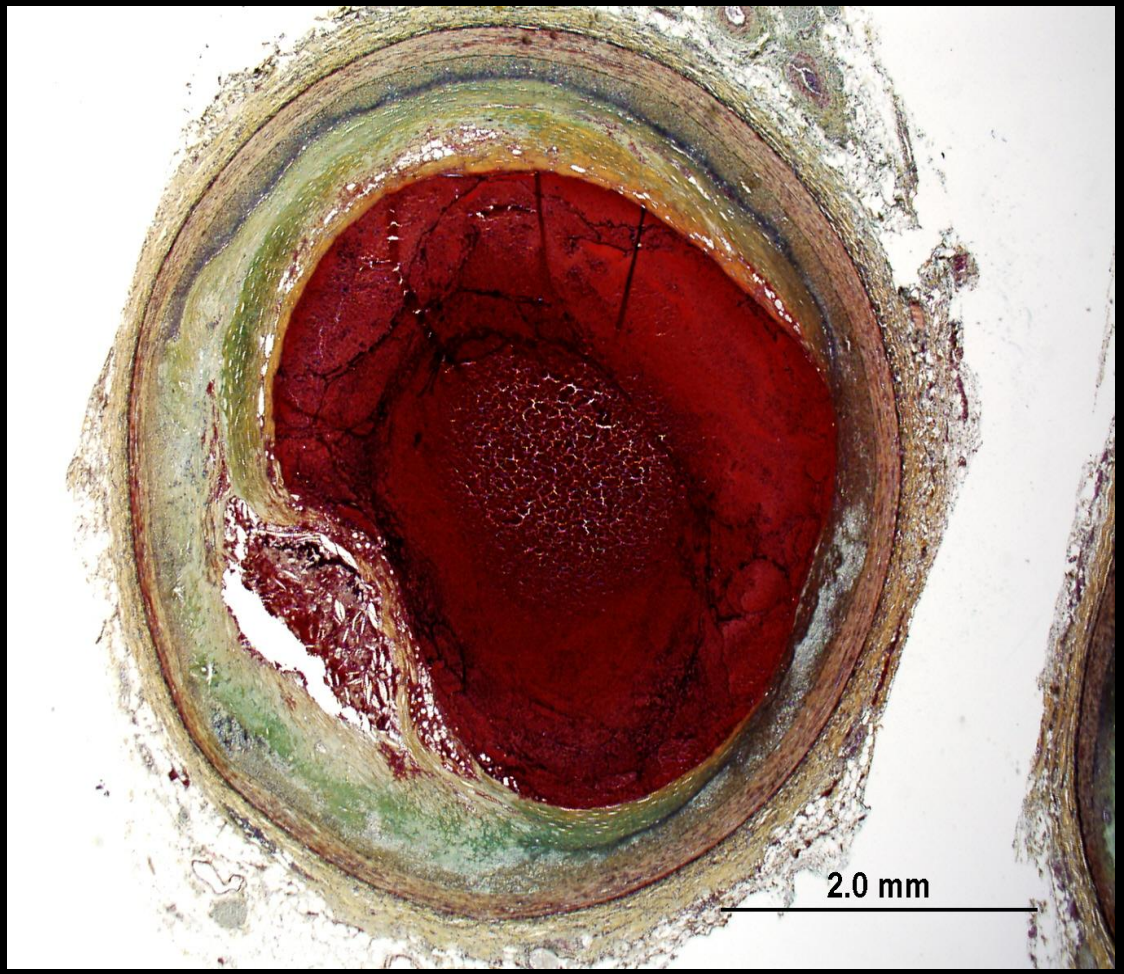


2-5% thrombi
M>F, Older
Usually eccentric
Stenosis variable
Ca^{++} rich

Virmani R, et al. Arterioscler Thromb Vasc Biol 2000;20:1262

Sanger Heart & Vascular Institute
Uncompromising Excellence. Commitment to Care.

STEMI



Antithrombotic Therapy

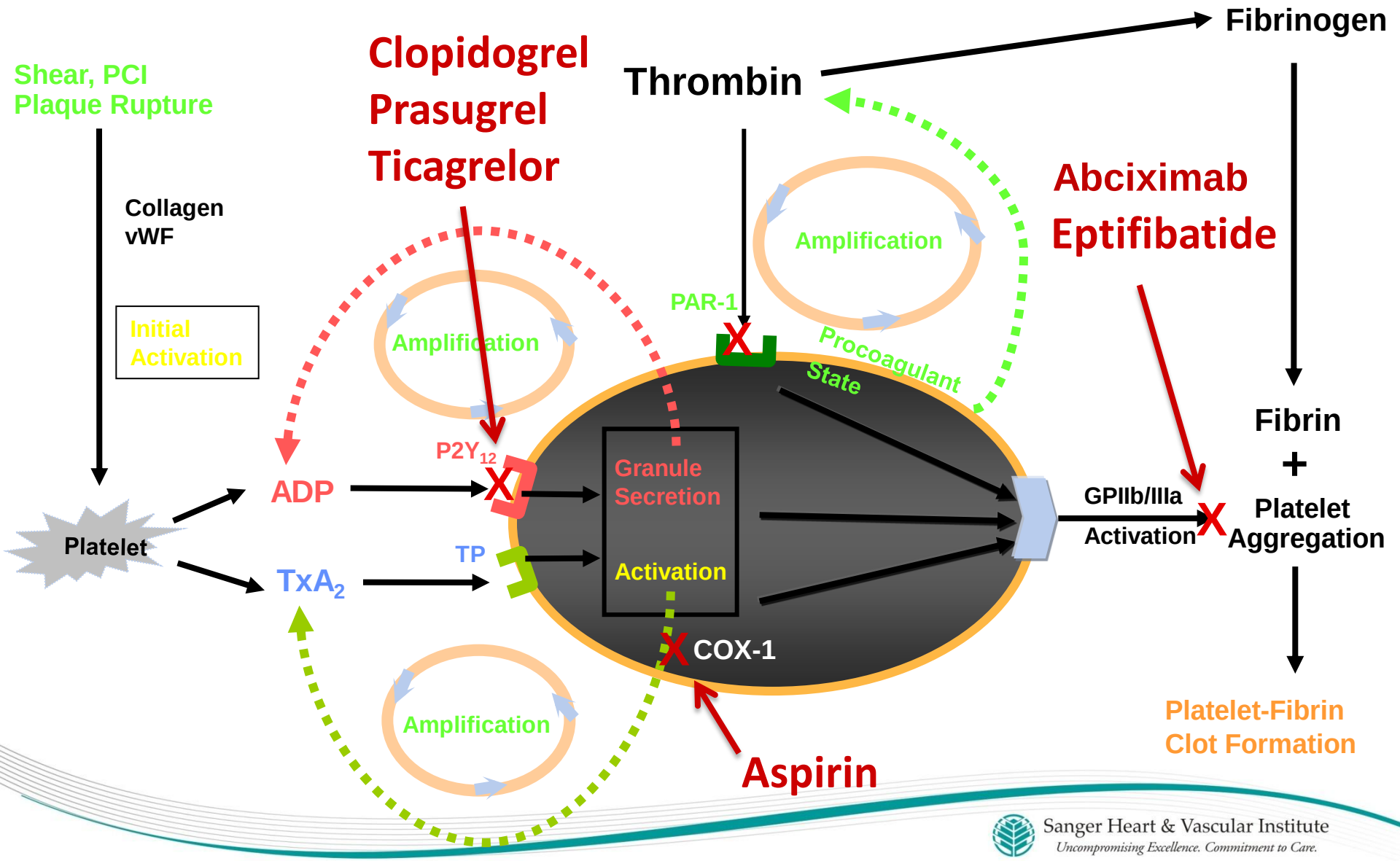
Antiplatelet Therapy

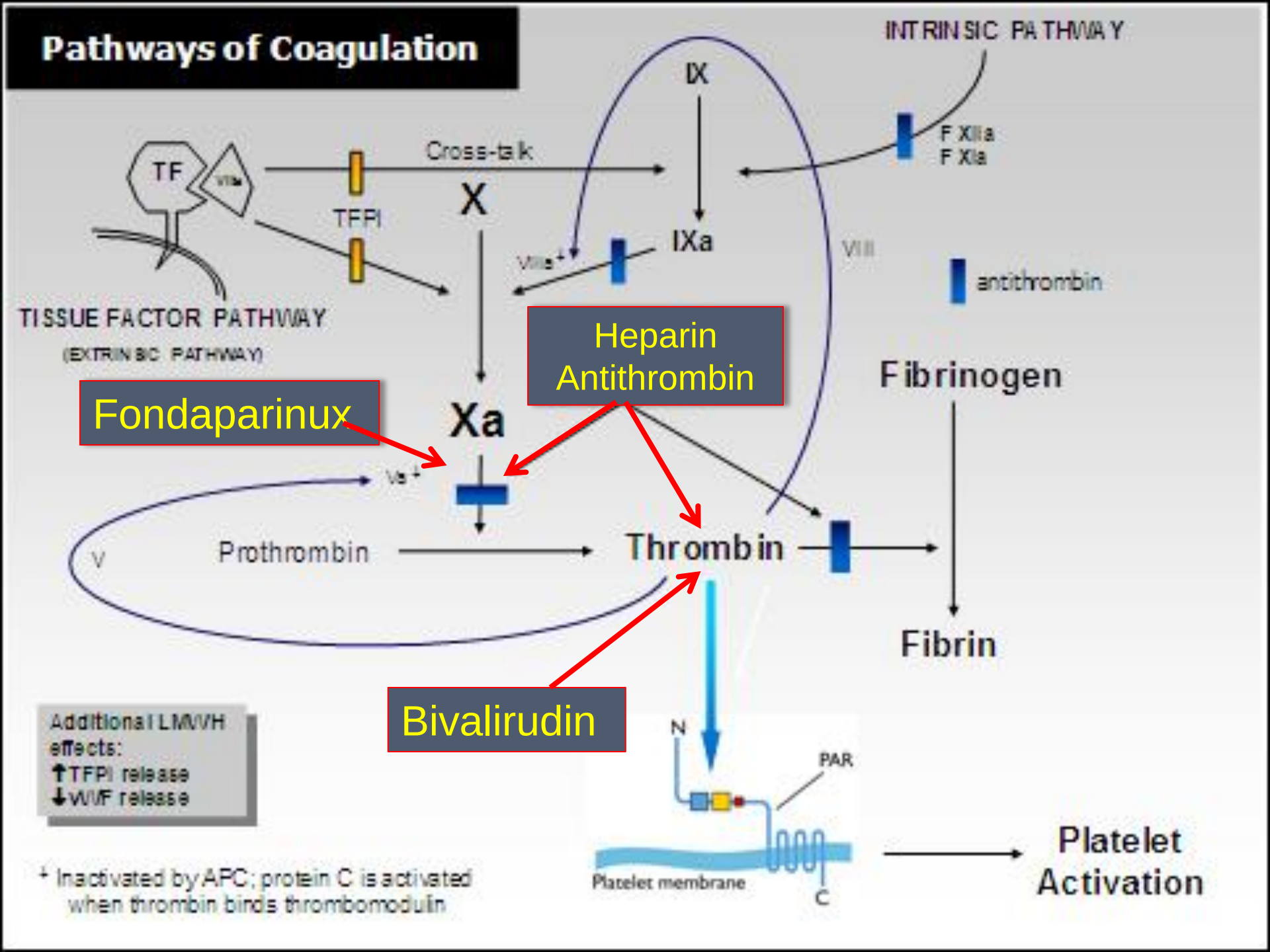
- Aspirin
- Platelet P2Y12 Receptor Blockers
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)
- GP IIb/IIIa Inhibitors
  - Abciximab (Reopro)
  - Tirofiban (Aggrastat)
  - Eptifibatide (Integrilin)
- PAR-1 Antagonists

Anticoagulant Therapy

- Heparin
- Low Molecular Weight Heparins
  - Enoxaparin (Lovenox)
  - Dalteparin (Fragmin)
- Synthetic Heparin Pentasaccharide
  - Fondaparinux (Arixtra)
- Direct Thrombin Inhibitors
  - Bivalirudin (Angiomax)
- Anti Xa Inhibitors
  - Rivaroxaban (Xarelto)

Site of Action of Antiplatelet Agents




Pathways of Coagulation
INTRINSIC PATHWAY
IX
F XIIa
F XIa
TF
VIIa
Cross-talk
X
TFPI
IXa
VIII
VIIIa+
antithrombin
TISSUE FACTOR PATHWAY
(EXTRINSIC PATHWAY)
Heparin
Antithrombin
Fondaparinux
Fibrinogen
Xa
Va+
V
Prothrombin
Thrombin
Fibrin
Bivalirudin
Additional LMWH effects:
↑TFPI release
↓vWF release
N
PAR
Platelet membrane
C
Platelet Activation
+ Inactivated by APC; protein C is activated when thrombin binds thrombomodulin

Case

- 50 year old male with history of hypertension, hypercholesterolemia, gout, hiatal hernia, tobacco abuse

- Presents with acute onset of substernal chest pain at 12:00 midnight radiating to left arm, jaw and ear with associated SOB and diaphoresis

[redacted] 6/30/2012 1:08:32 AM [redacted]
50 yrs Male ---/---

CABARRUS EMS 7
Department: CABARRUS
Room:
Operator:

Rate	81
PR	189
QRSd	85
QT	385
QTc	447

Axes

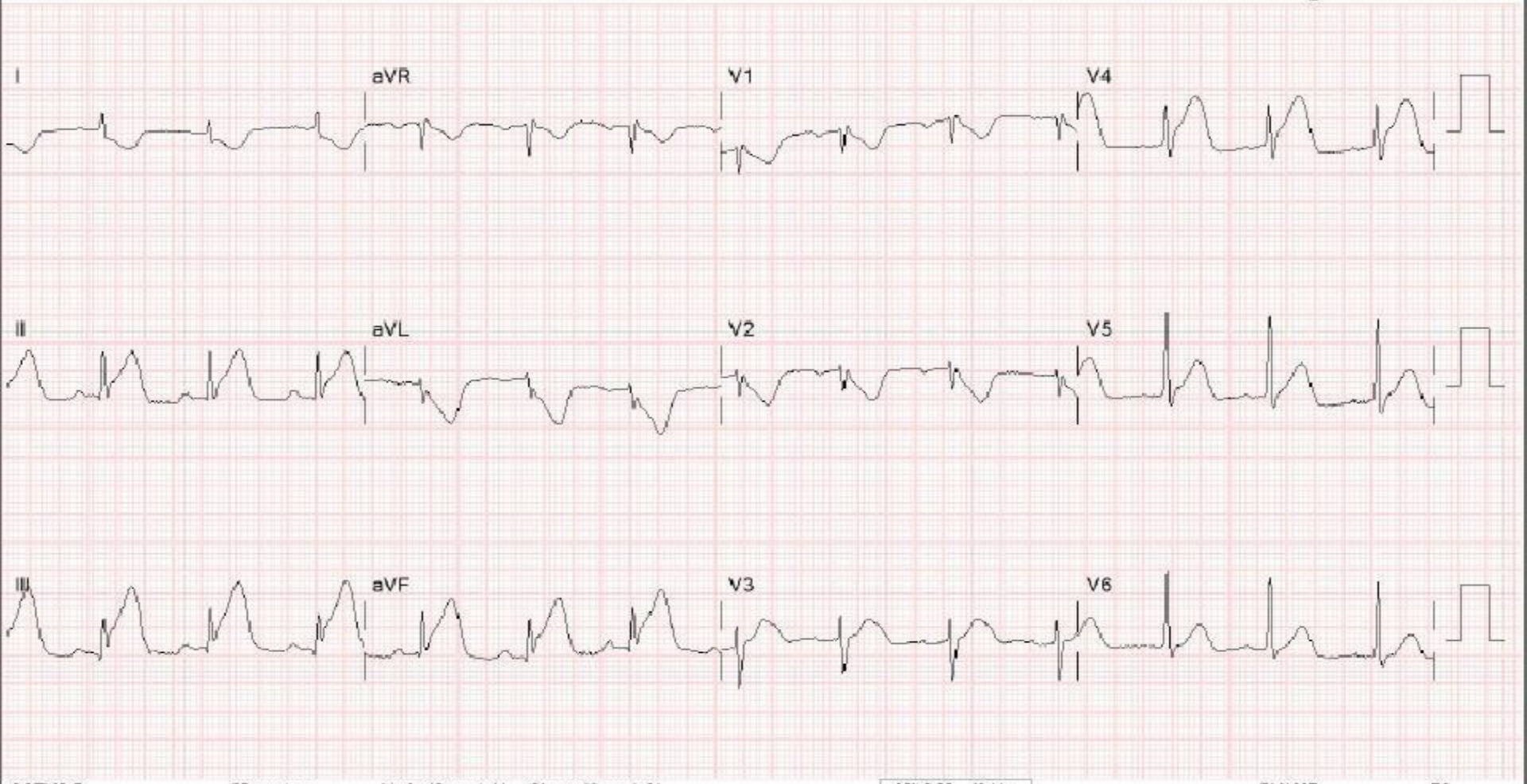
P	73
QRS	79
T	108

- Sinus rhythm ---------- normal P axis, V-rate 50-99
- Inferoposterior infarct, acute (RCA) ---------- ST>.1 inf, <-.1 ant
- Probable RV involvement, suggest recording right precordial leads
- >>> Acute MI <<<

Requested by:

- ABNORMAL ECG -

Unconfirmed diagnosis

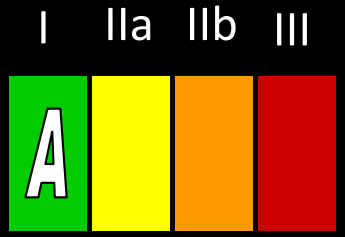


CCEMS-7 25 mm/sec Limb: 10 mm/mV Chest: 10 mm/mV 60~ 0.05 - 40 Hz PH100B P?

[redacted] 6/30/2012 1:08:32 AM [redacted]

CABARRUS EMS 7

ACC/AHA Guideline Recommendations for the Use of Aspirin

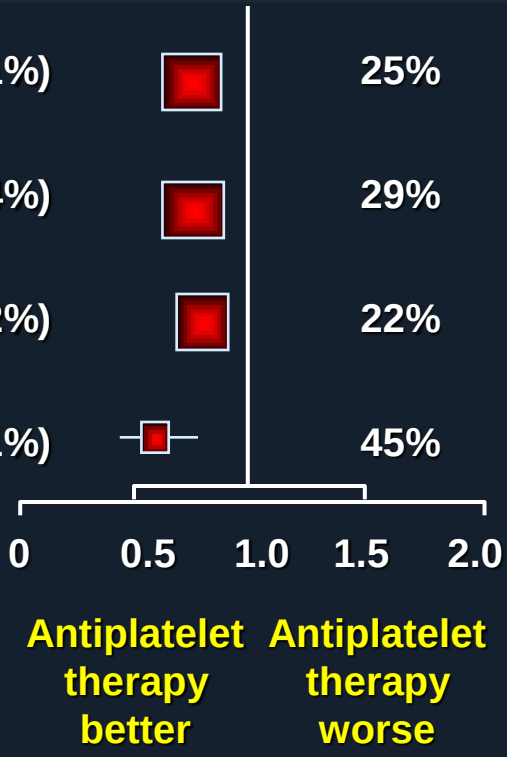


A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after STEMI to all patients without a true aspirin allergy.

Jneid, H, et al. *J Am Coll Cardiol*. 2012;60(7):645-681.

Anti-Platelet Therapy

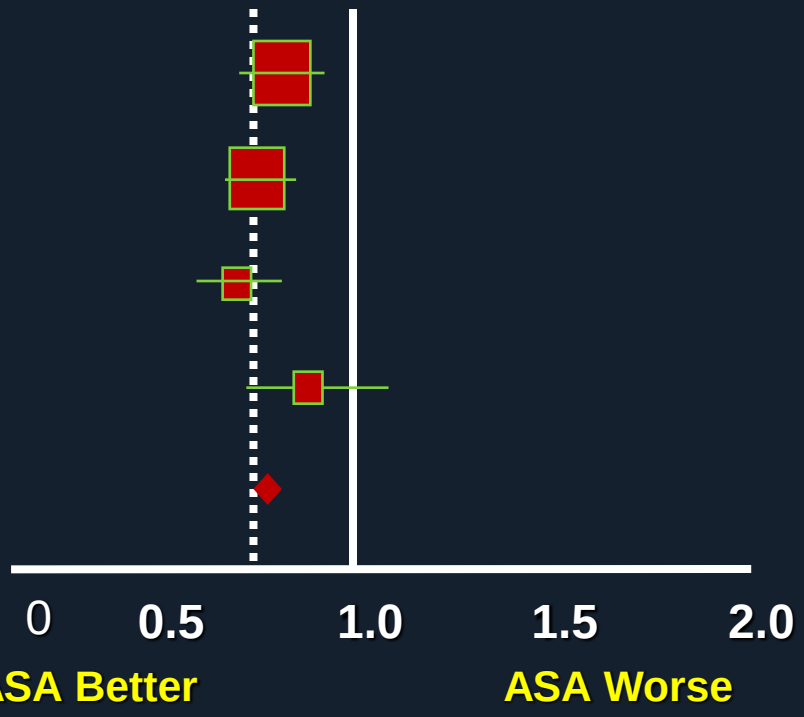
Category of trial	N of trials	MI, Stroke, or Vascular Death: Anti-platelet	MI, Stroke, or Vascular Death: Adjusted controls	Odds ratio & CI (Antiplatelet: Control)	% odds reduction (SD)
Prior MI	11	1330/9677 (13.7%)	1693/9914 (17.1%)		25%
Acute MI	9	992/9388 (10.6%)	1348/9385 (14.4%)		29%
Prior Stroke/TIA	18	1076/5837 (18.4%)	1301/5870 (22.2%)		22%
Unstable Angina	7	182/1991 (9.1%)	285/2027 (14.1%)		45%



Antiplatelet Trialists' Collaboration. *BMJ* 1994;308:81-106

Dose-dependence and Aspirin Efficacy

Aspirin Dose	# Trials	OR* (%)
500–1500 mg	34	19
160–325 mg	19	26
75–150 mg	12	32
<75 mg	3	13
Any aspirin	65	23

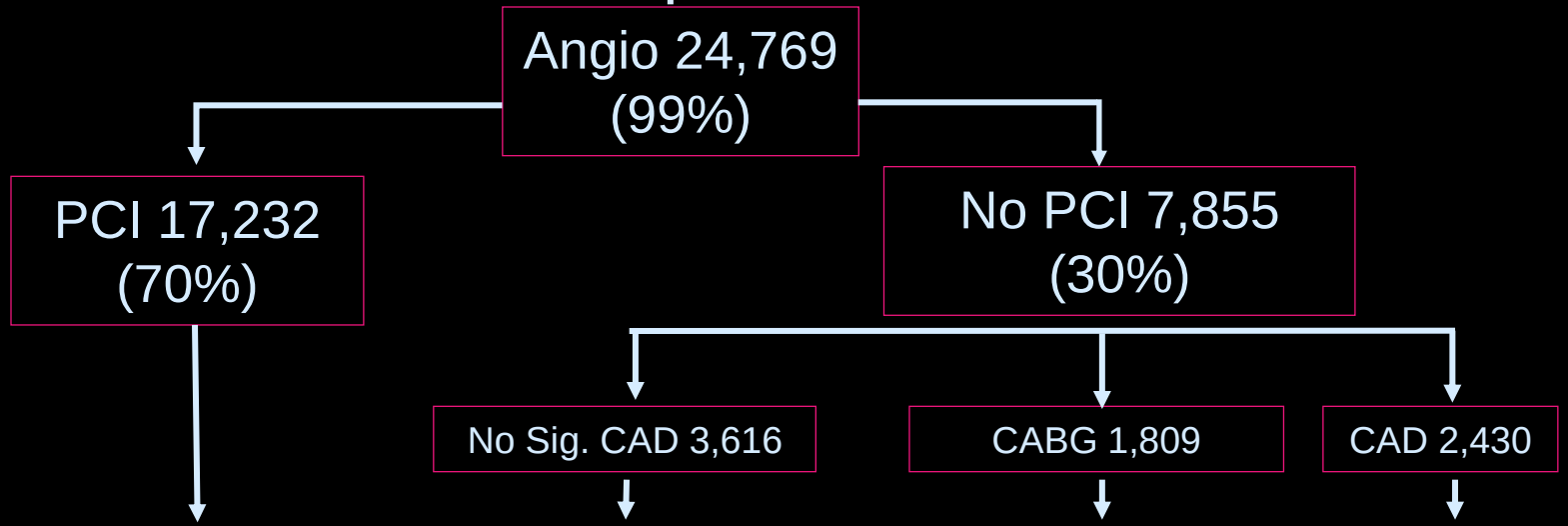


Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.

Study Design

25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)
✓ Planned Early (<24 h) Invasive Management with intended PCI

Randomized to receive (2 X 2 factorial):
CLOPIDOGREL: Double-dose vs Standard dose
ASA: High Dose (300-325 mg/d) vs Low dose (75-100 mg/d)



Efficacy Outcomes: CV Death, MI or stroke at day 30
Stent Thrombosis at day 30

CURRENT

ASA Dose Comparison
Primary Outcome and Bleeding

	ASA 75-100 mg	ASA 300-325 mg	HR	95% CI	P
CV Death/MI/Stroke					
PCI (2N=17,232)	4.2	4.1	0.98	0.84-1.13	0.76
No PCI (2N=7855)	4.7	4.4	0.92	0.75-1.14	0.44
Overall (2N=25,087)	4.4	4.2	0.96	0.85-1.08	0.47
Stent Thrombosis	2.1	1.9	0.91	0.73-1.12	0.37
TIMI Major Bleed	1.03	0.97	0.94	0.73-1.21	0.71
CURRENT Major Bleed	2.3	2.3	0.99	0.84-1.17	0.90
CURRENT Severe Bleed	1.7	1.7	1.00	0.83-1.21	1.00

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups

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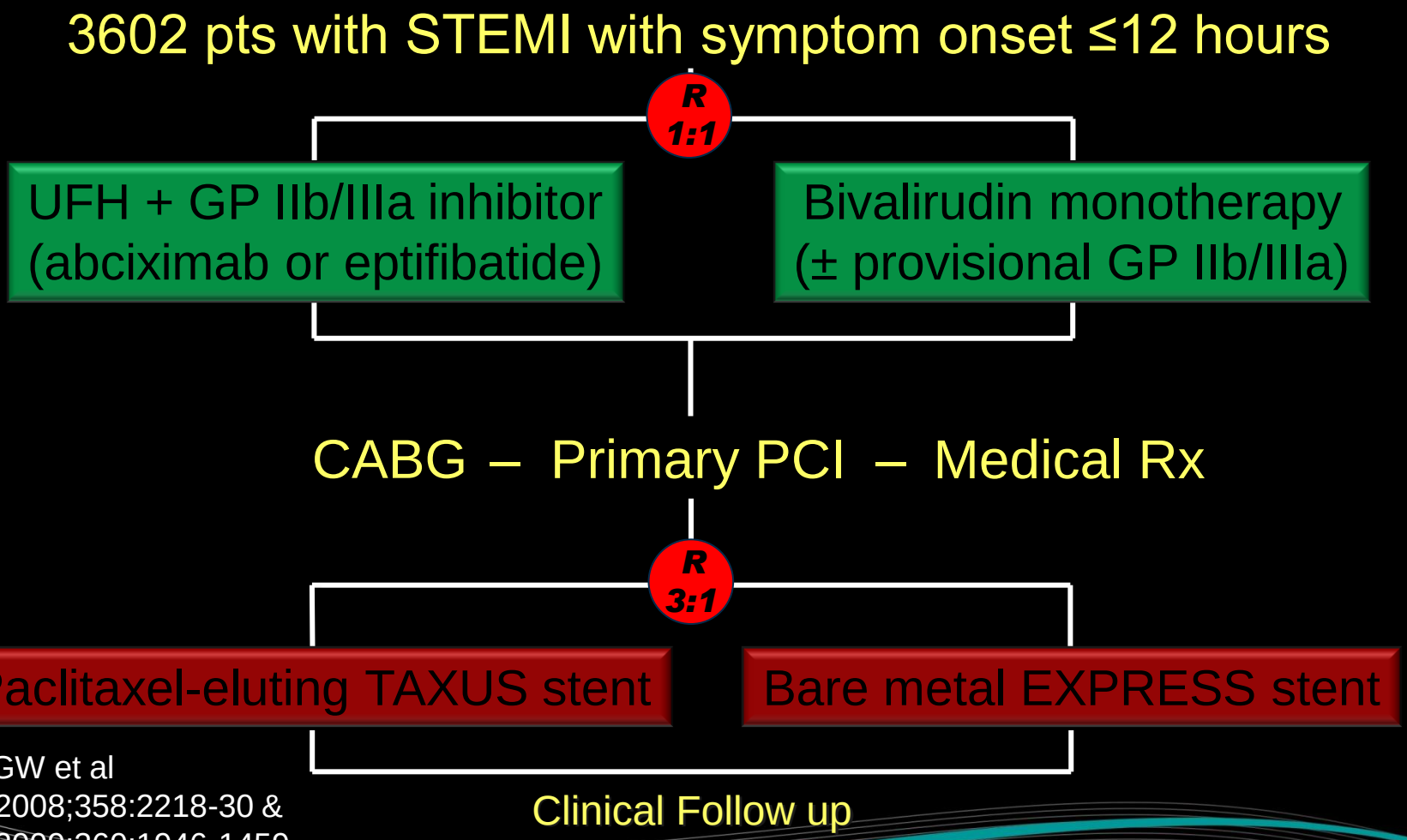
HORIZONS AMI

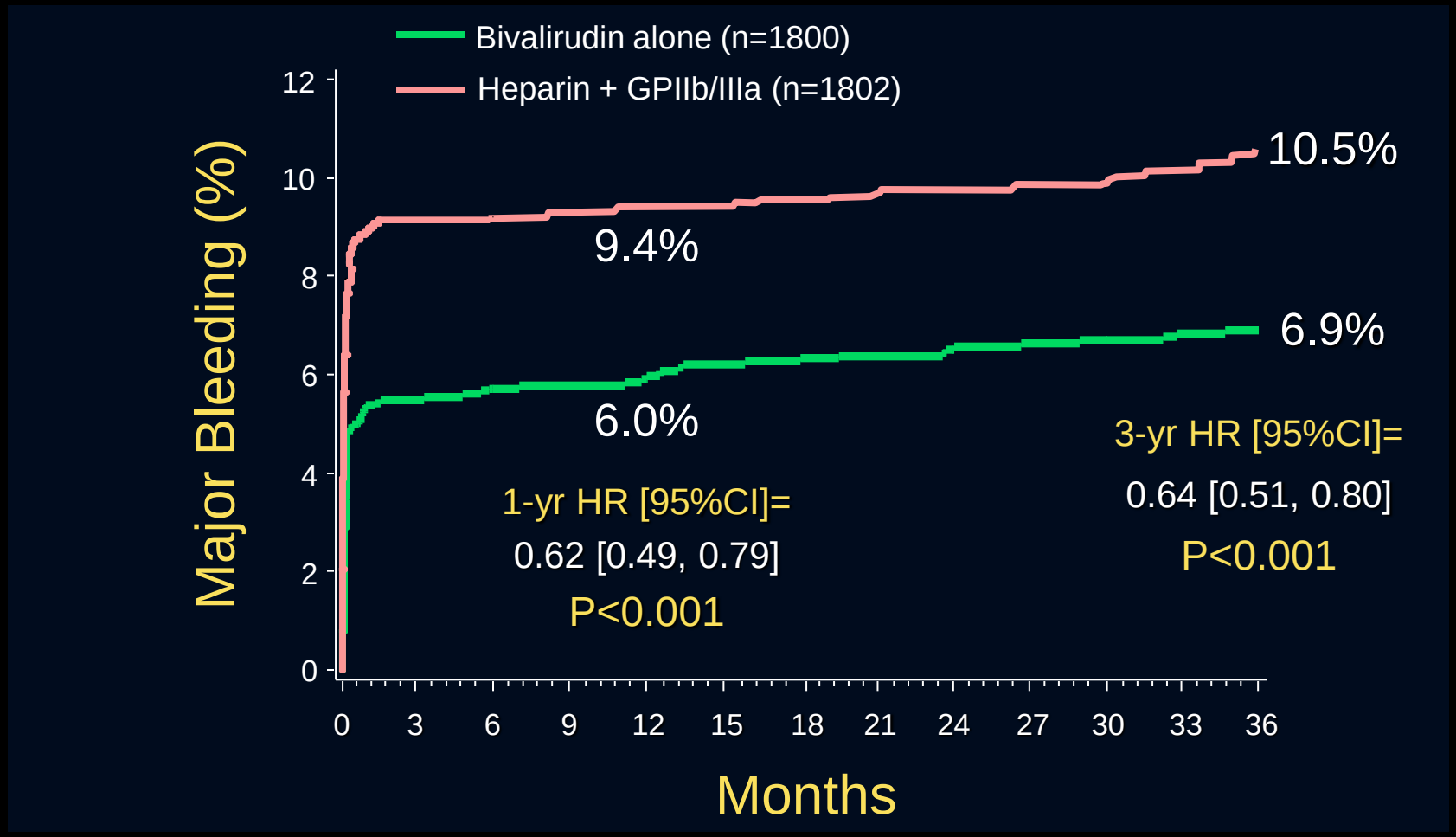
Harmonizing Outcomes with Revascularization and Stents in AMI



Stone GW et al
NEJM 2008;358:2218-30 &
NEJM 2009;360:1946-1459

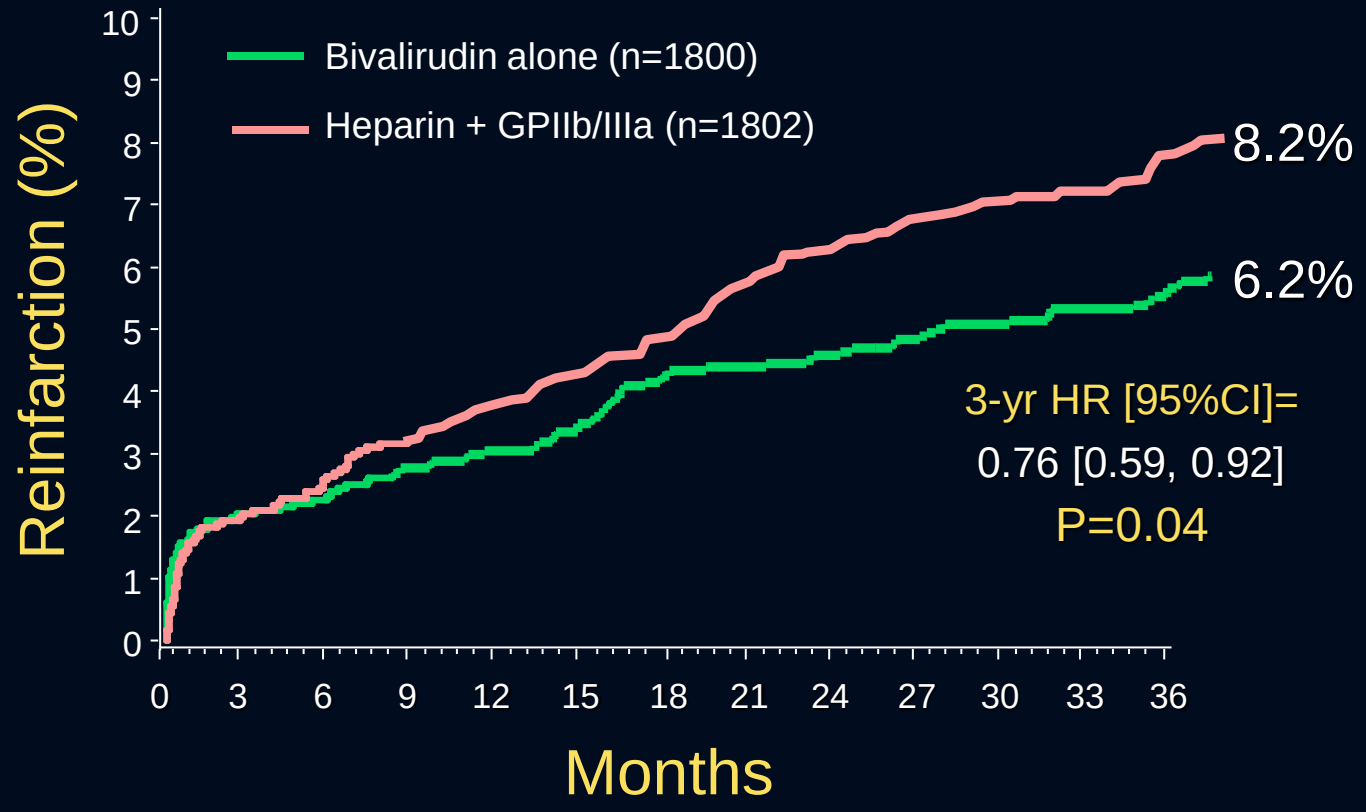
Three-Year Major Bleeding

HORIZONS AMI



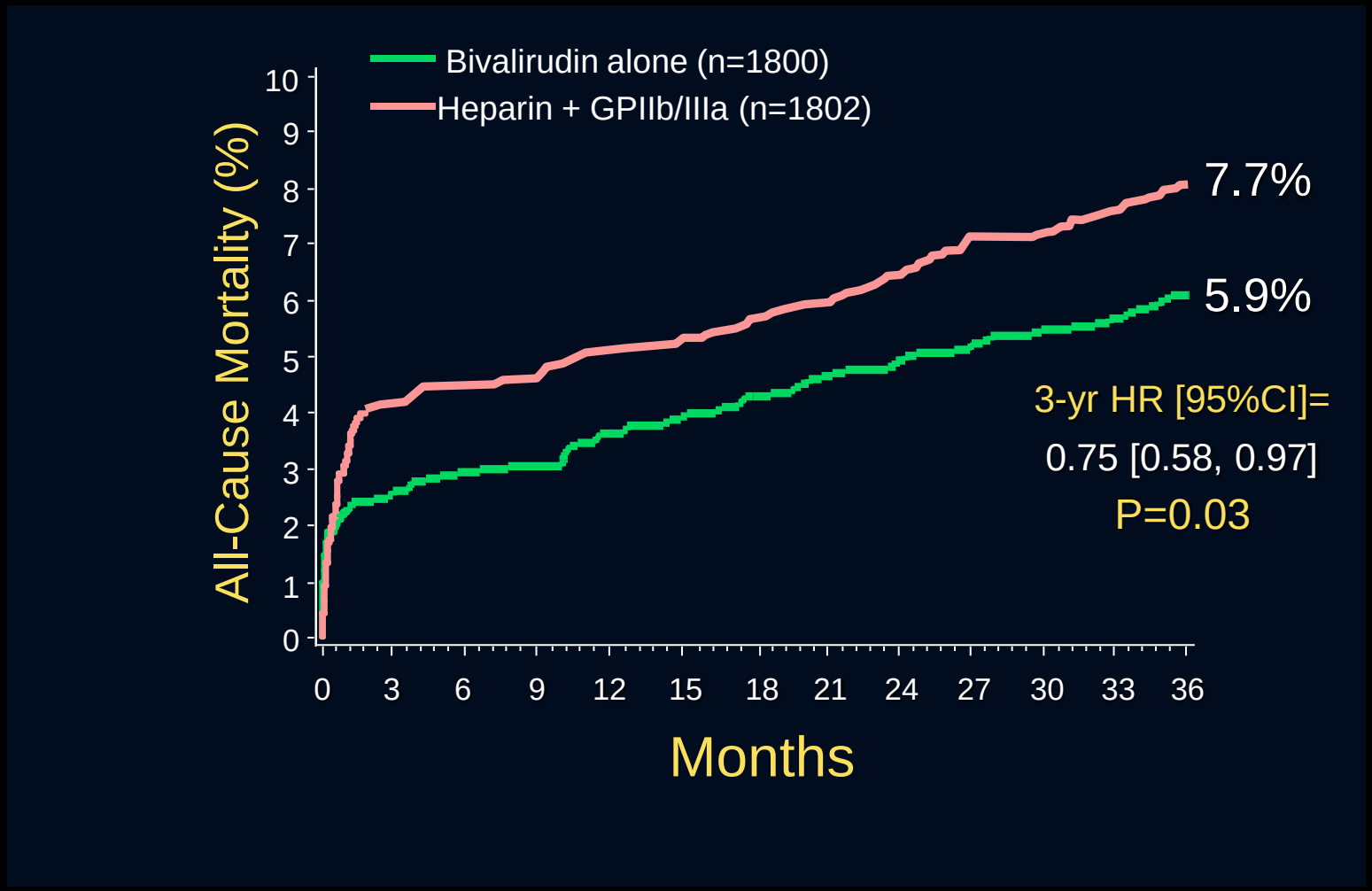
* Intracranial intraocular, retroperitoneal, access site bleed requiring intervention/surgery, hematoma ≥5 cm, hgb ↓ ≥3g/dL with or ≥4g/dL w/o overt source; reoperation for bleeding; or blood product transfusion

Three-Year Reinfarction



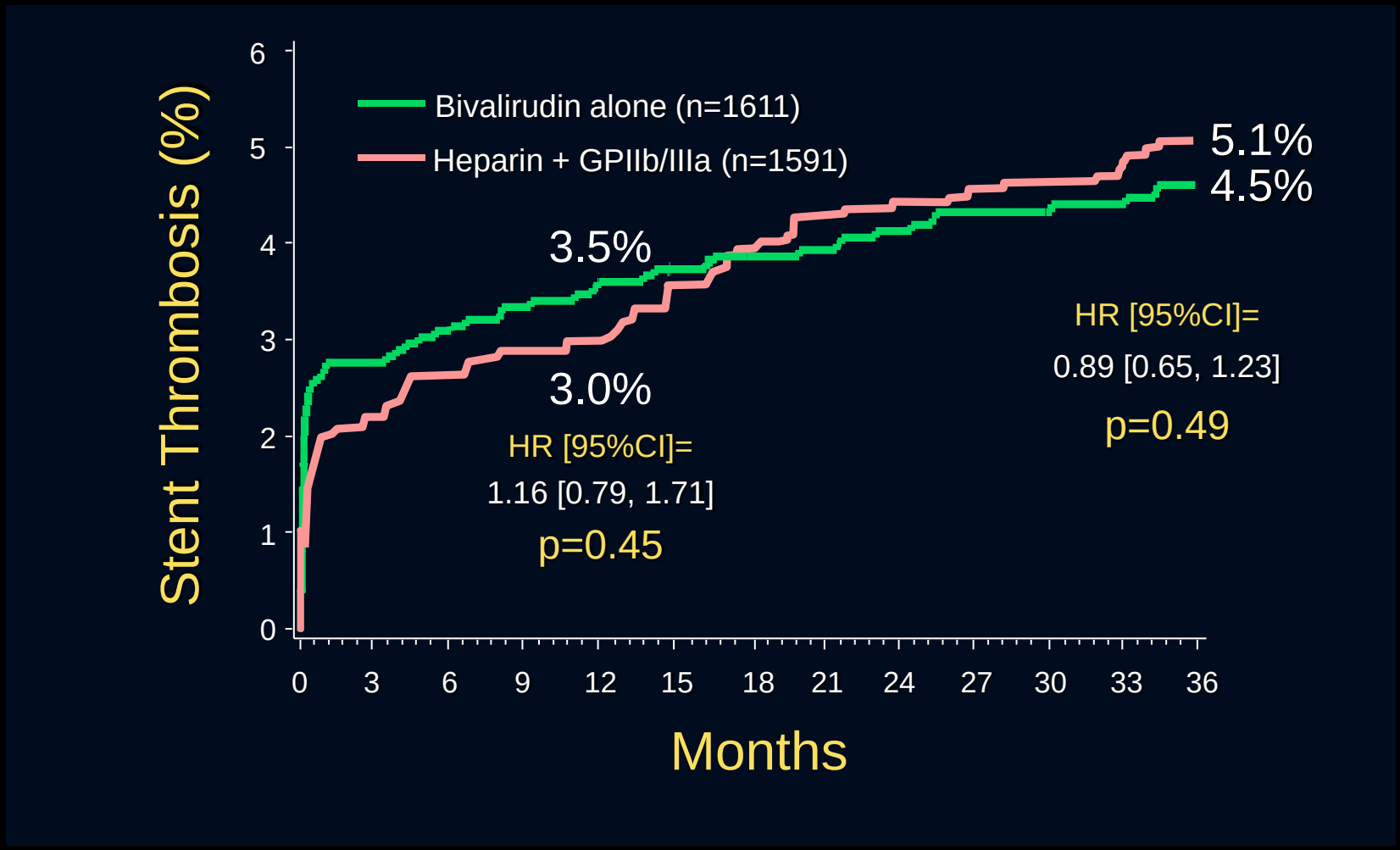
HORIZONS AMI

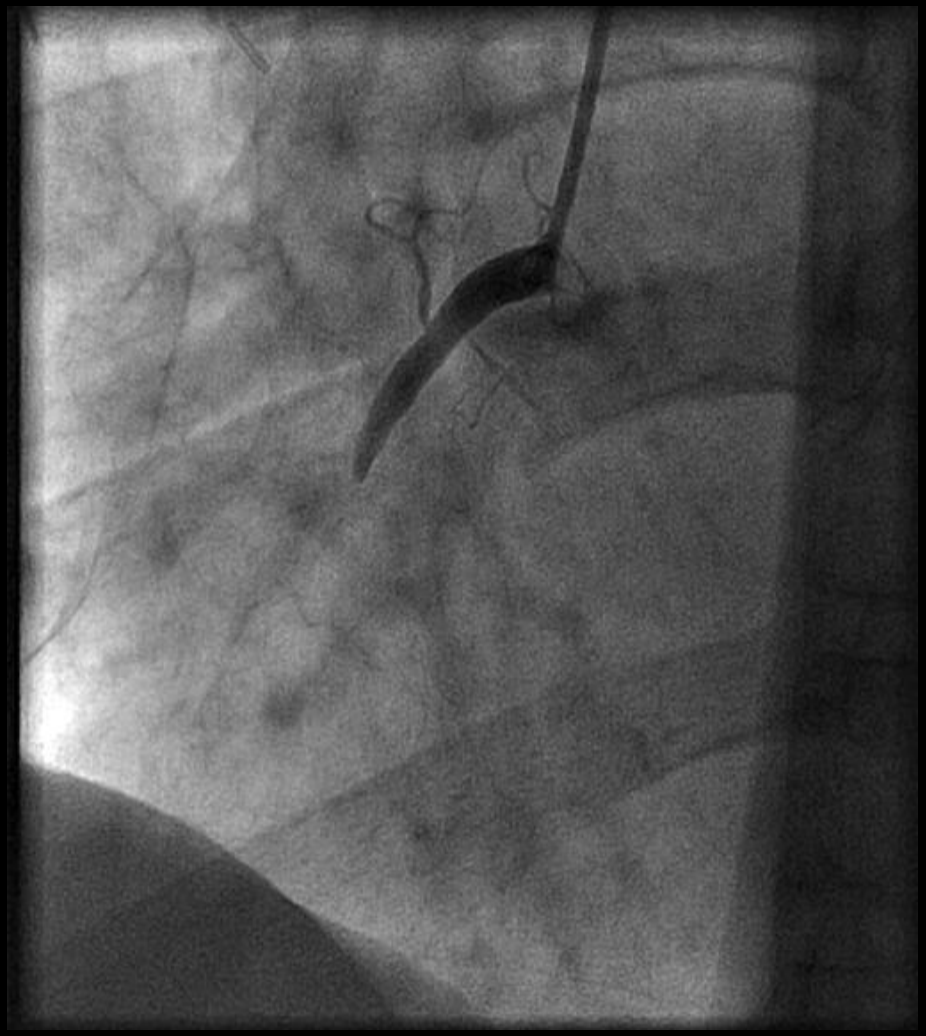
Three-Year All-Cause Mortality



Three-Year Stent Thrombosis (ARC Definite/Probable)

HORIZONS AMI



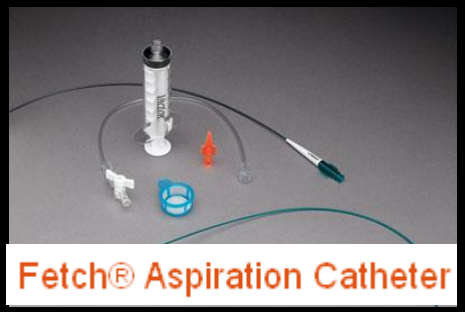


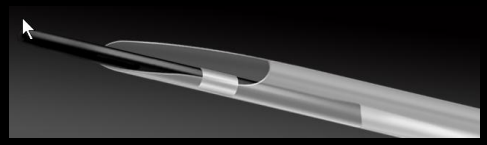
THROMBECTOMY

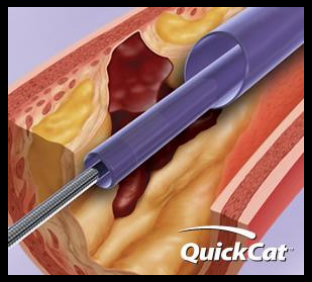
Mechanical

Rheolytic thrombectomy (AngioJet)

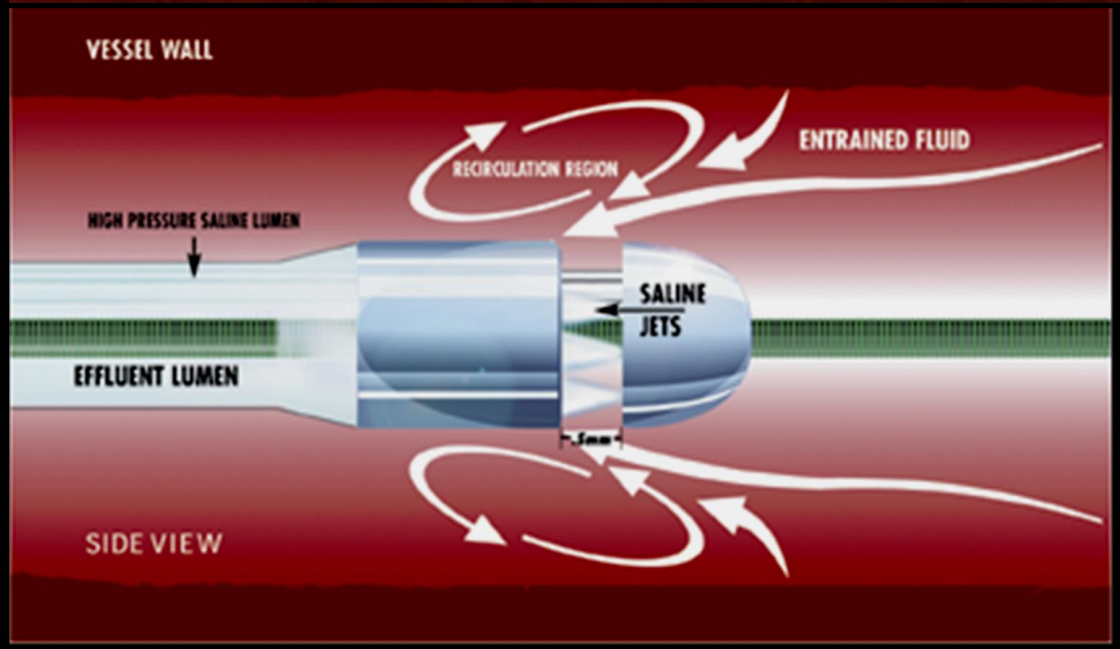
Aspiration







AngioJet Rheolytic Thrombectomy



AiMI Trial: Study Design

Transmural anterior MI or large inferior MI undergoing emergent PCI within 12 hours of symptom onset.

Rheolytic Thrombectomy using the Possis Angiojet XMI device n=240

Primary PCI Control

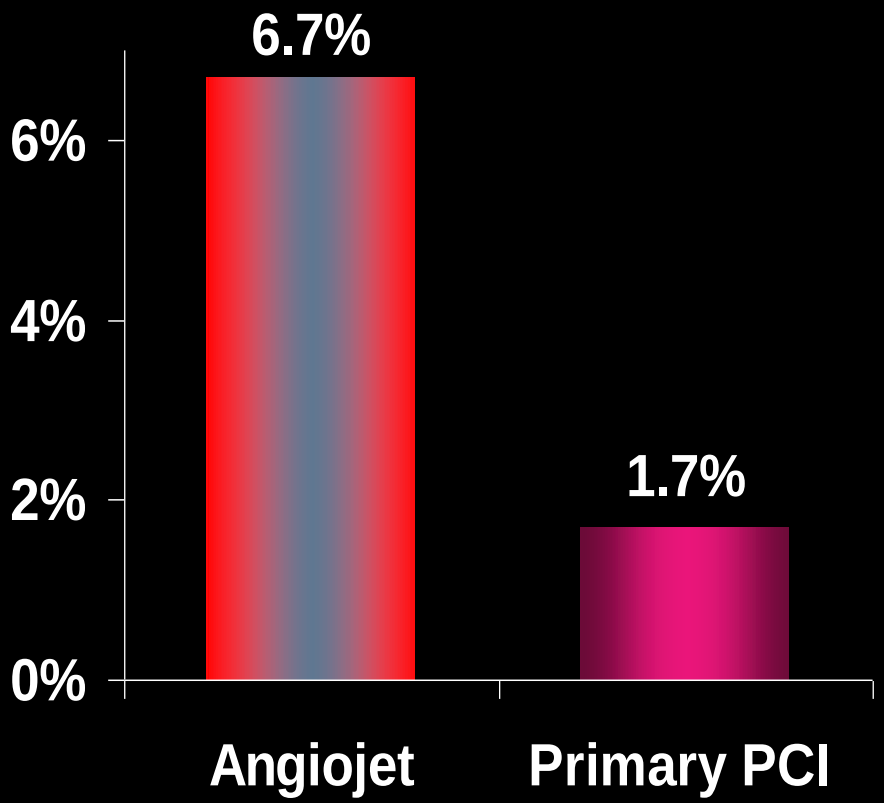
n=240

J Am Coll Cardiol 2006;48:244–52

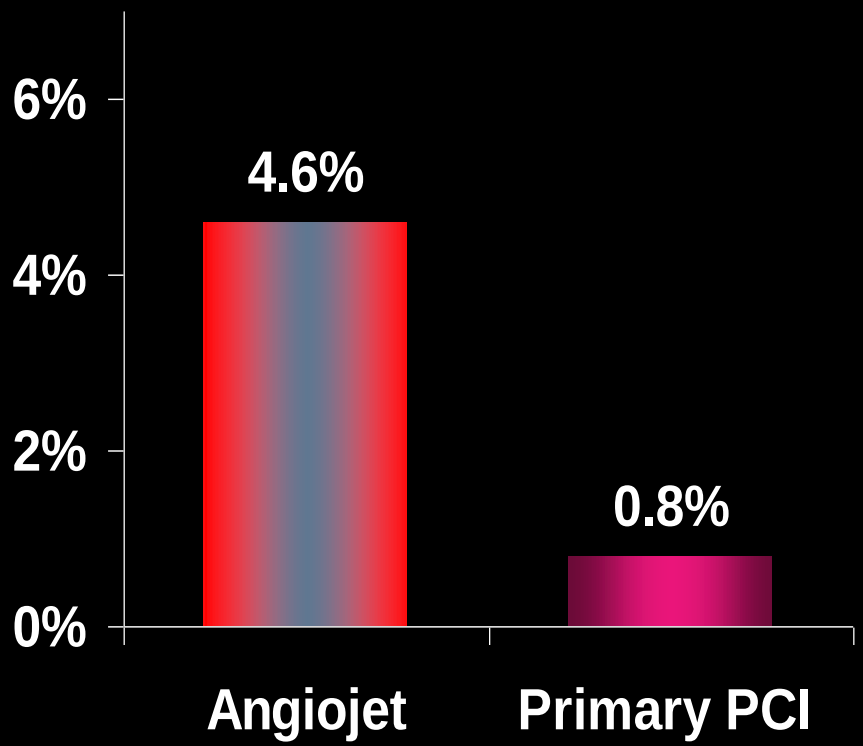
- **Primary Endpoint: Final infarct size at 14-28 days, as measured by Tc-99m sestamibi SPECT imaging**
- **Secondary Endpoint: ST segment resolution, post-procedure TIMI flow, corrected TIMI frame count, TIMI myocardial perfusion grade, MACE (death, new Q wave MI, stroke, target lesion revascularization), ejection fraction and procedural complications**

AiMI Trial: 30 Day Endpoints

Rate of MACE in Patients Undergoing Thrombectomy
p=0.01



Rate of Mortality in Patients Undergoing Thrombectomy
p=0.01



J Am Coll Cardiol 2006;48:244–52

JETSTENT Study Design

Pts with STEMI admitted within 12 hours from symptom onset

- Lysis
- Stroke < 30 days
- Surgery < 6 weeks
- Pre-stented IRA

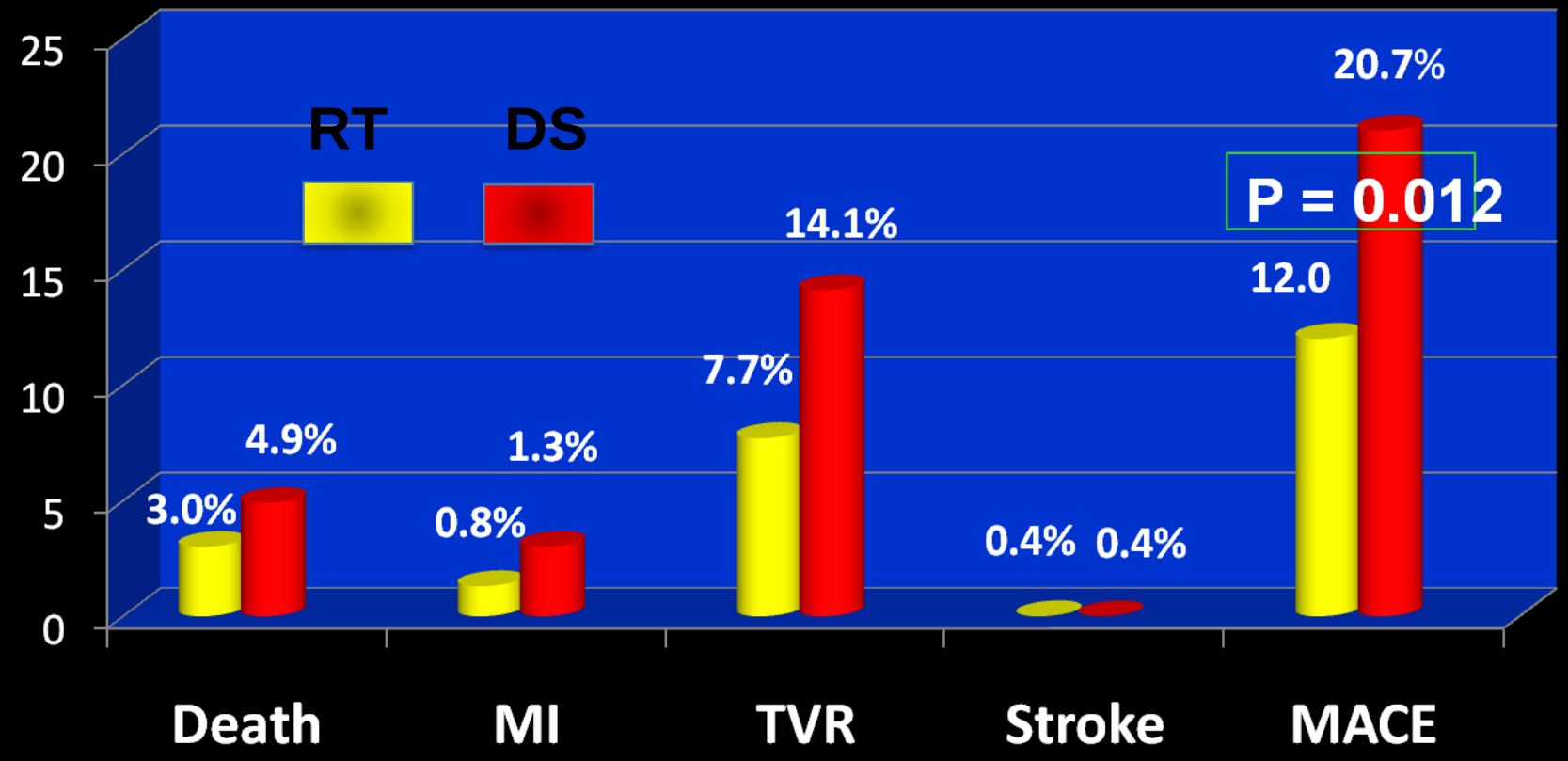
After angiography and IRA wiring: thrombus grade 3 to 5
Randomization 1:1

N = 500

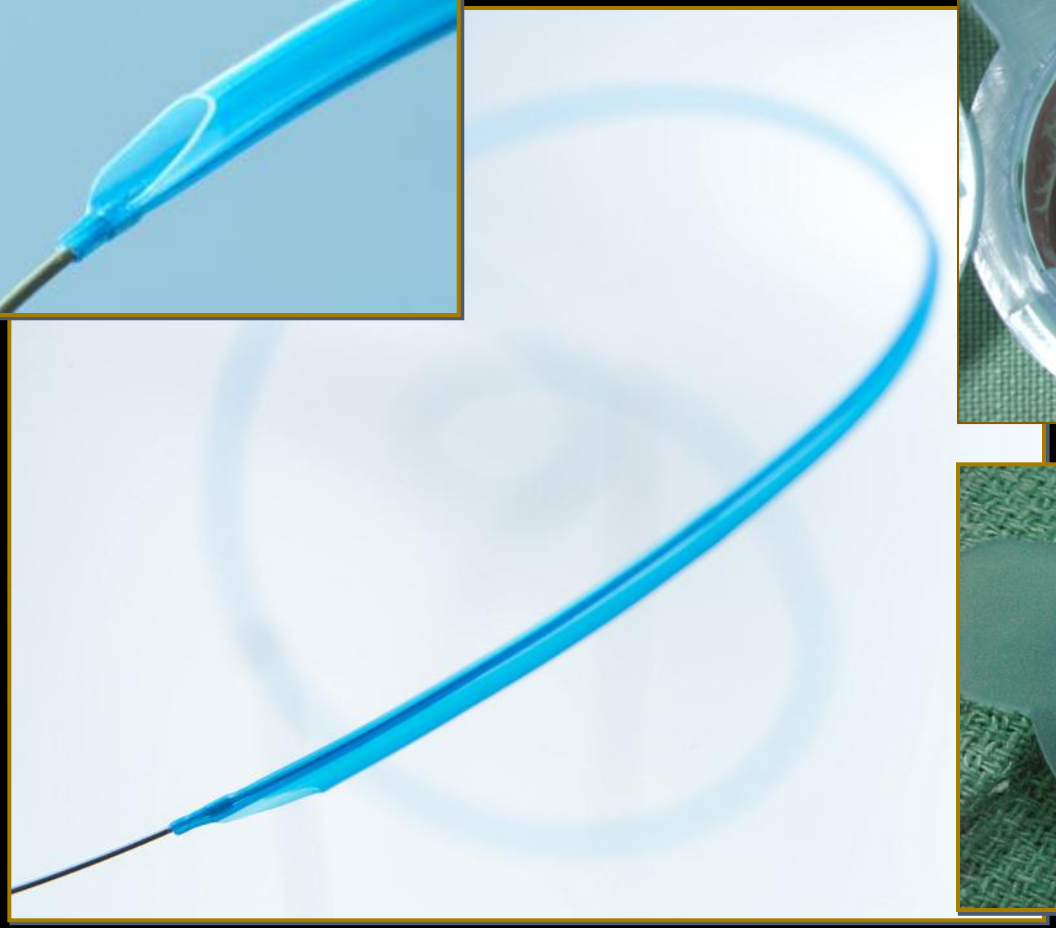
Direct Stenting (DS)

Rheolytic Thrombectomy +DS

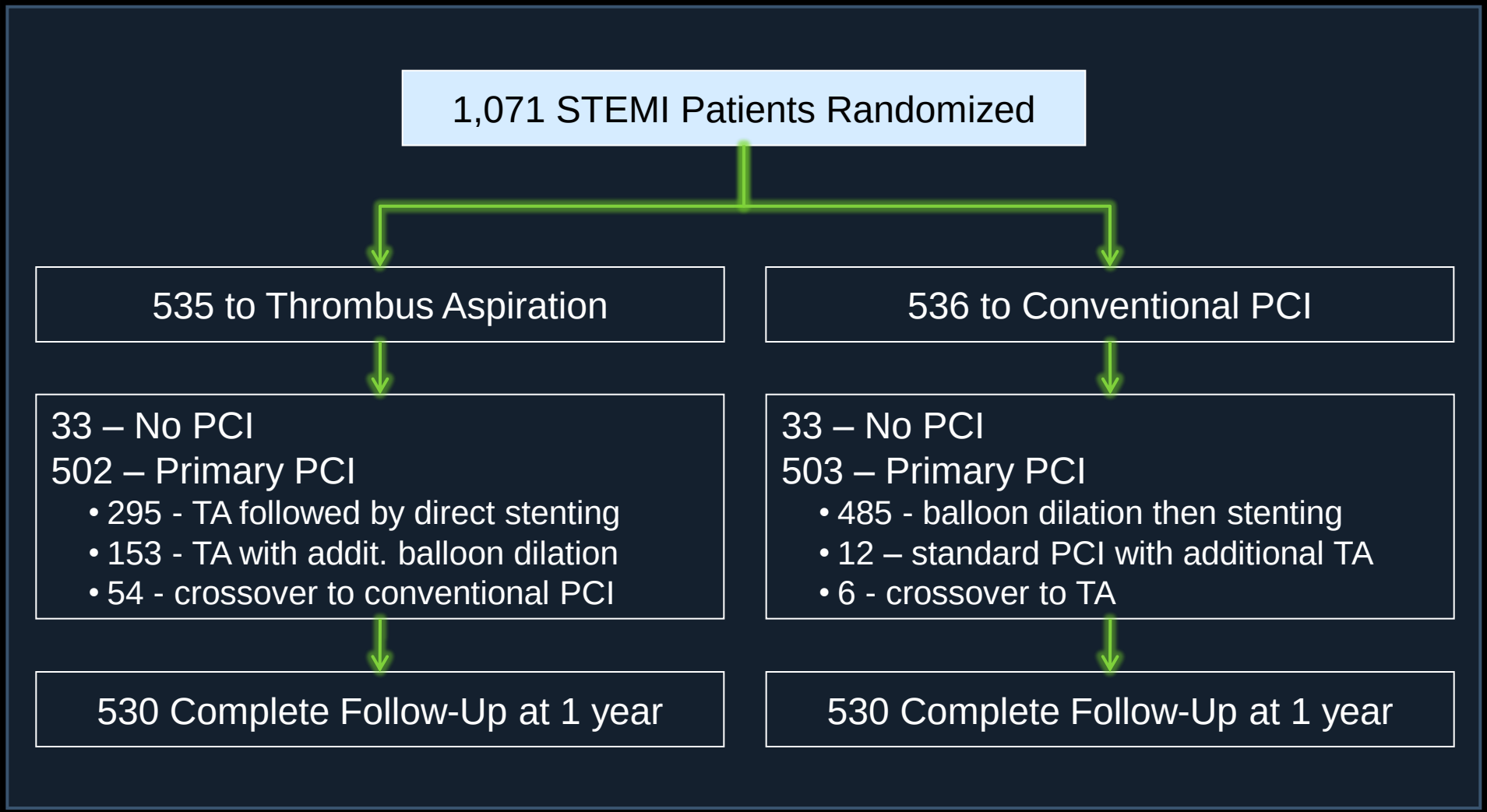
6-Month Outcome



Aspiration Catheter

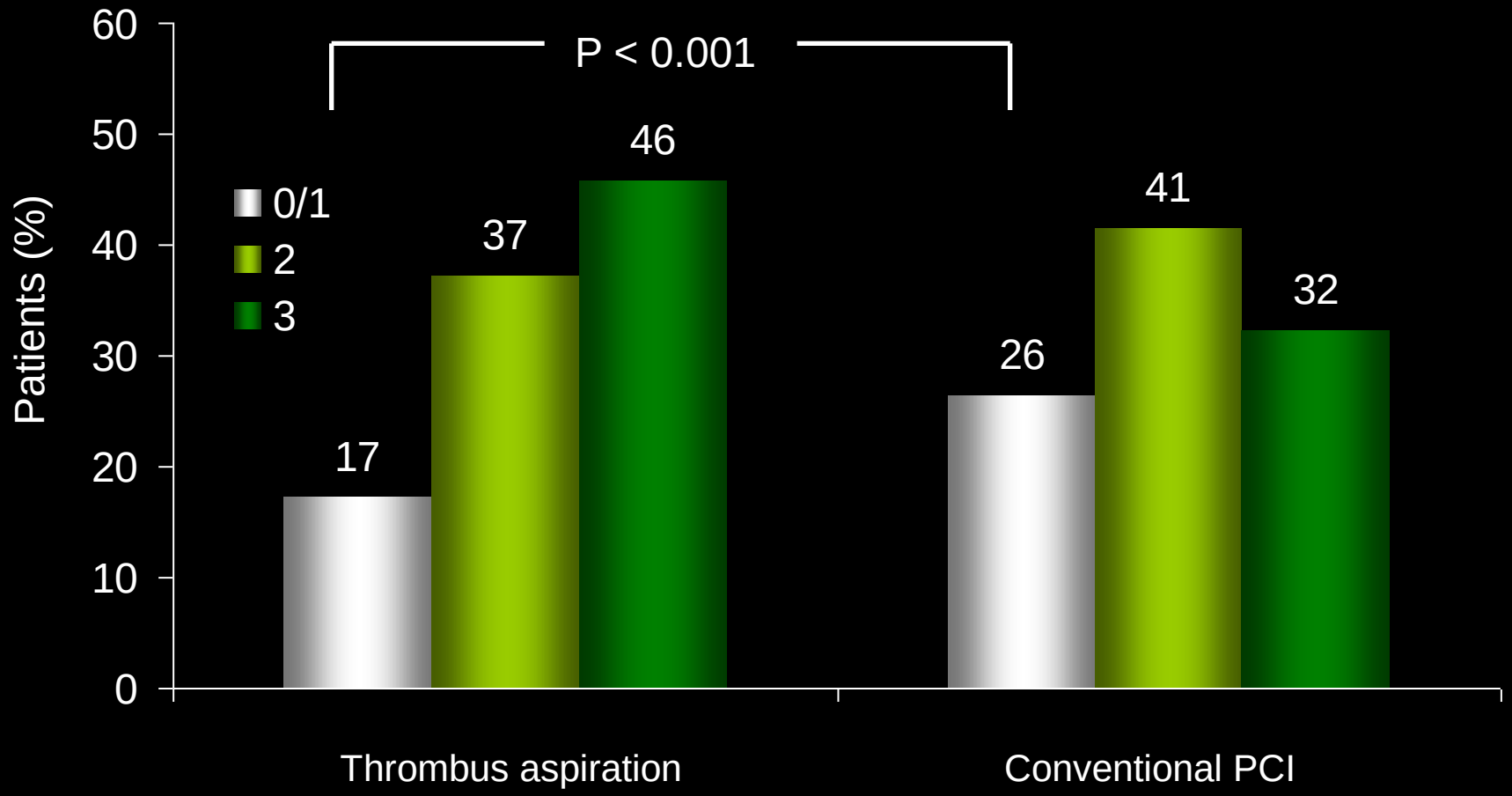


TAPAS: Study Design



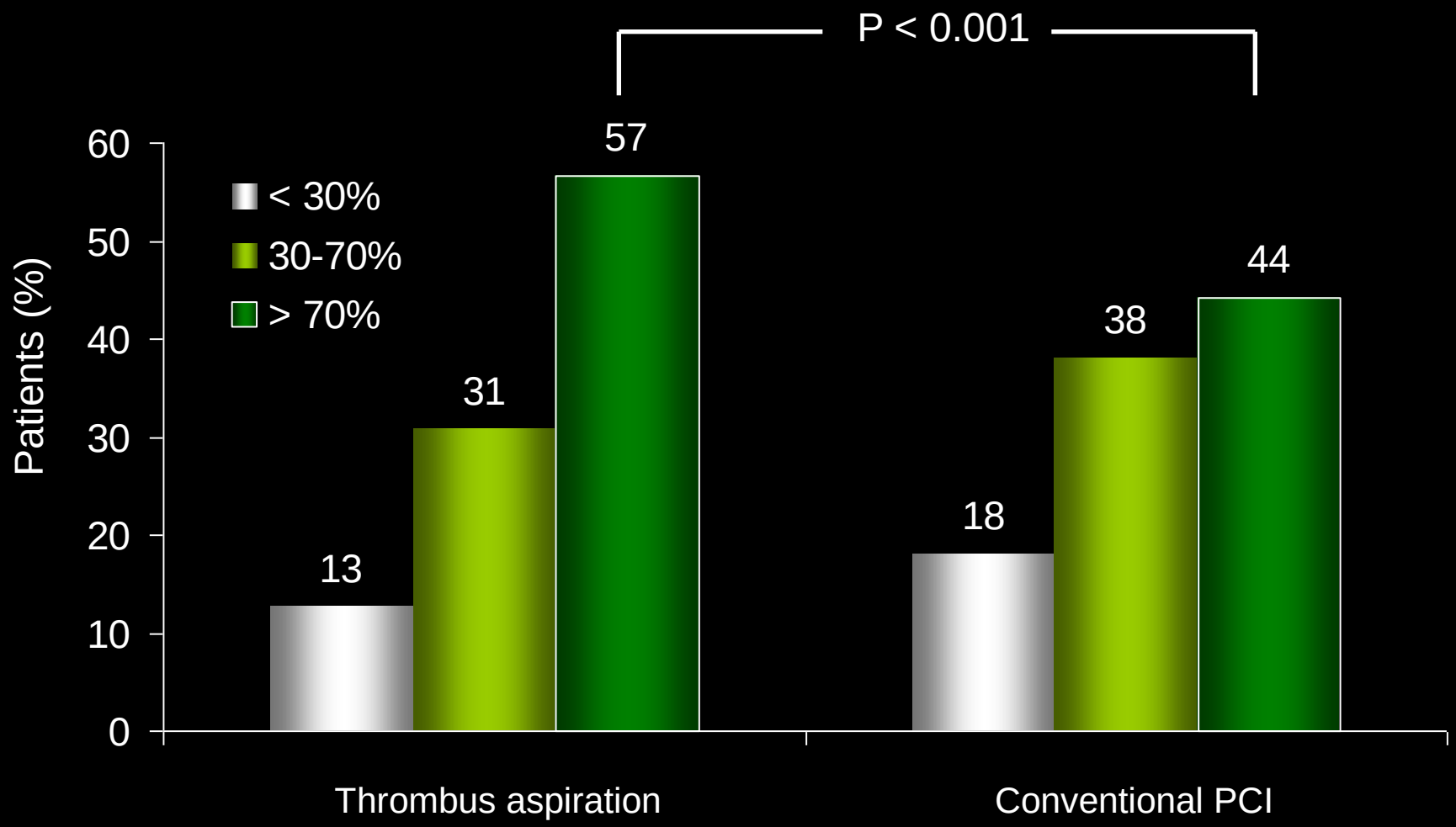
Svilaas T et al. Am Heart J 2006

Primary endpoint: Myocardial blush grade



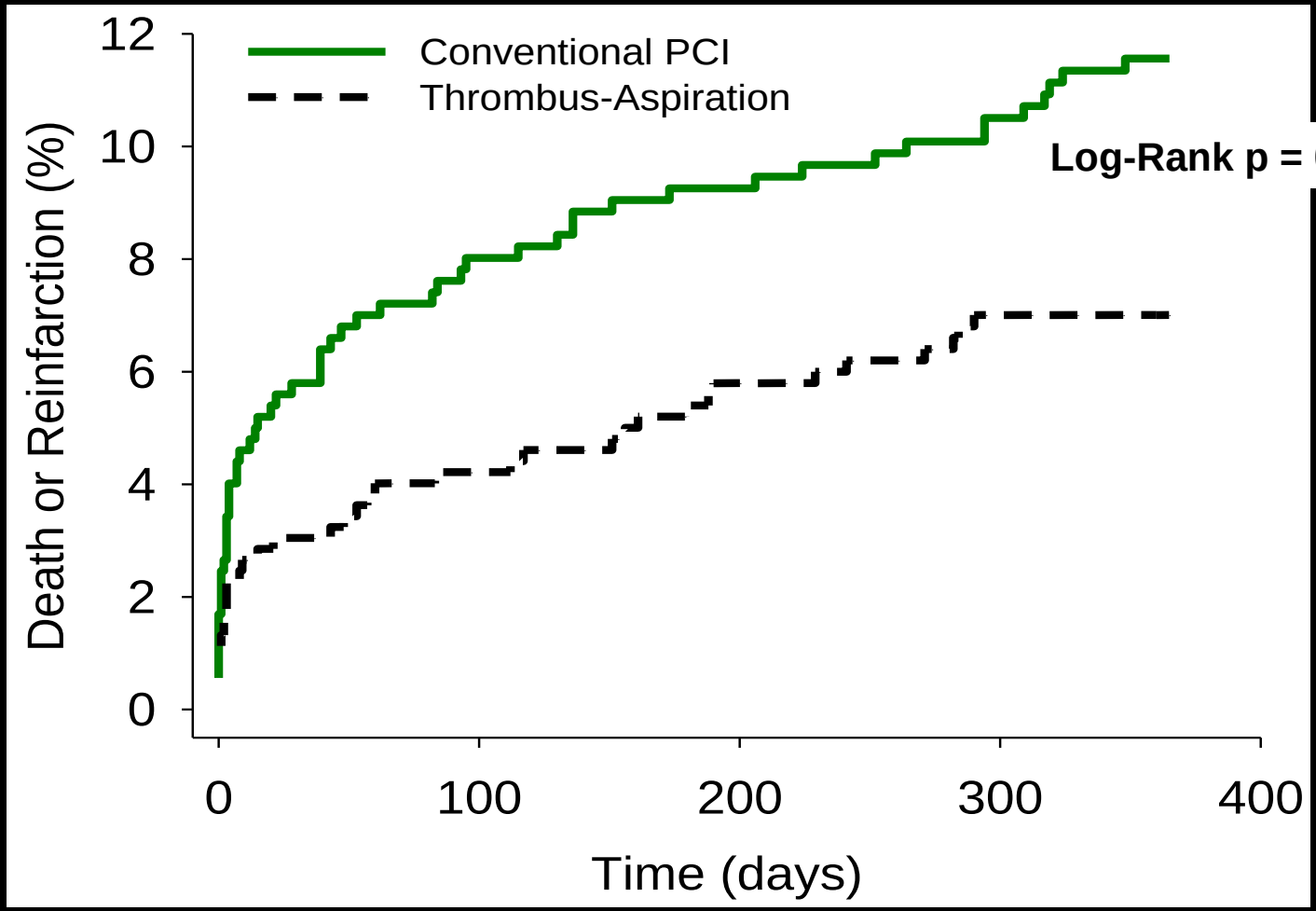
Svilaas T et al. NEJM 2008;358:557 - FZ 2008-8

ST-segment elevation resolution



Svilaas T et al. NEJM 2008;358-557 - FZ 2008-9

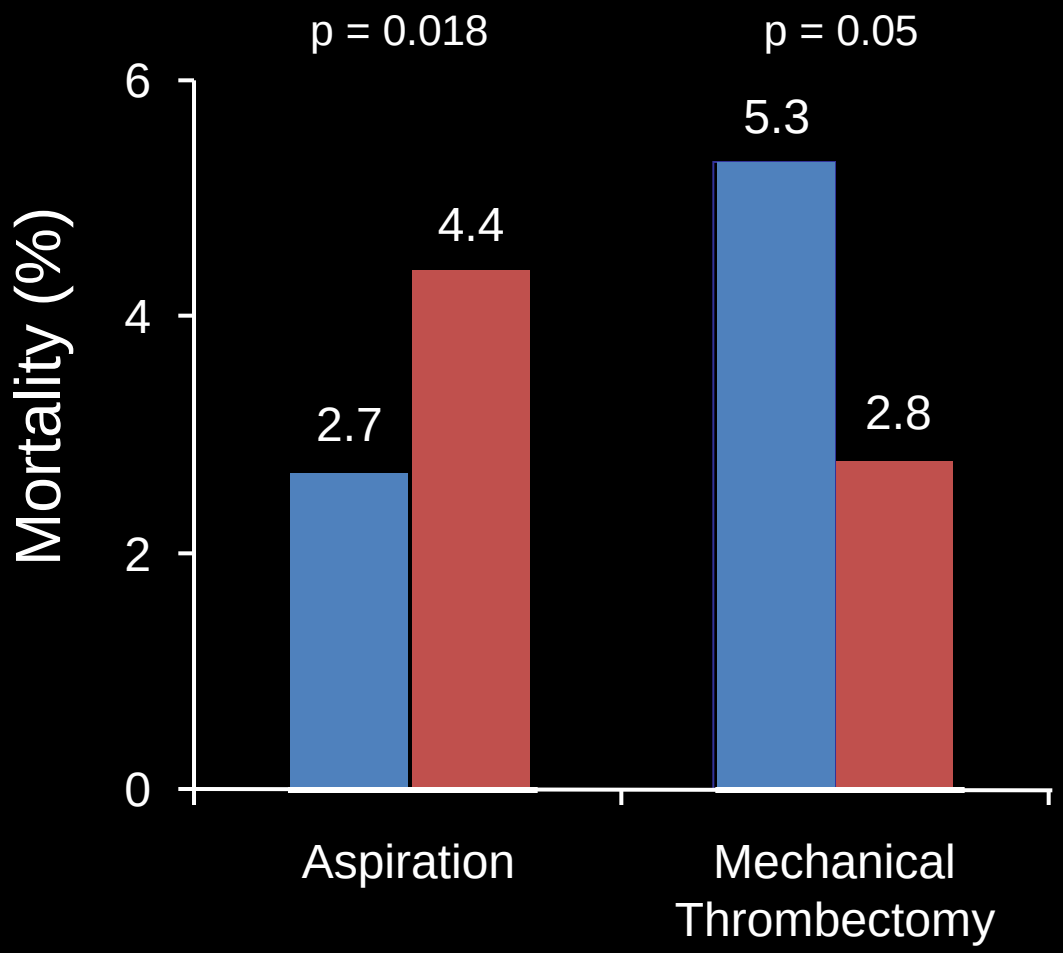
Mortality or non-fatal MI at 1 year



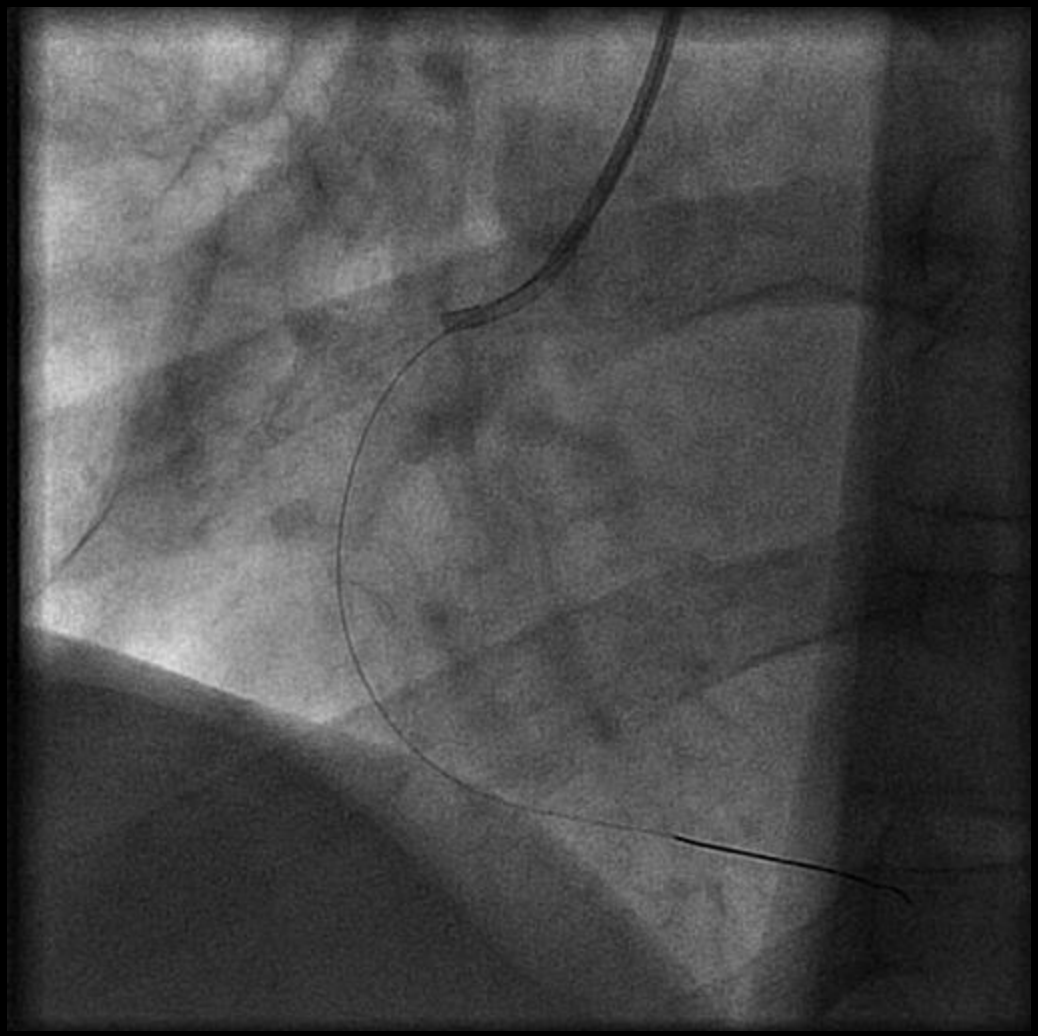
Svilaas T et al. NEJM 2008;358-557 - FZ 2008-9

Meta-analysis of Thrombectomy on Mortality

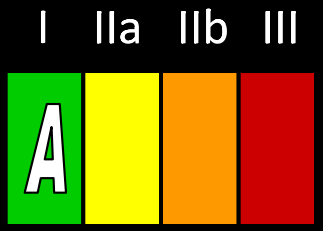
30 Studies, 6415 patients, weighted mean FU of 5 months



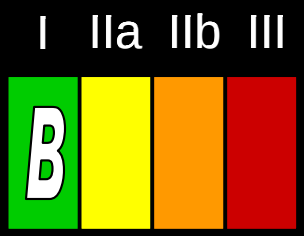
Bavry AA et al, Eur Heart J 2008; 29: 2989-3001



ACC/AHA Guideline Recommendations



A loading dose of $P2Y_{12}$ antagonist is recommended for STEMI patients for whom PCI is planned (given as early as possible).



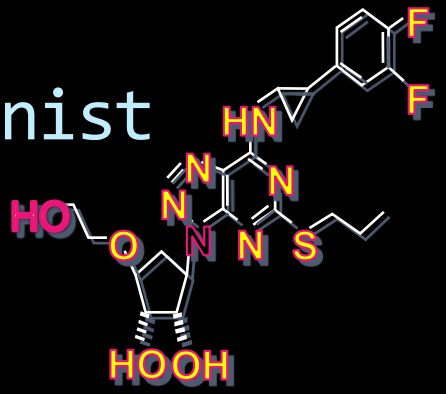
Possible regimens

- Clopidogrel 600 mg — If prior fibrinolytic Rx, then 300 mg
- Prasugrel 60 mg — Contraindicated in pts with prior TIA/CVA: Class III LOE: B; Generally not recommended in pts ≥75 y of age; Consider using a 5 mg maintenance dose in pts weighing <60 kg)
- Ticagrelor 180 mg — Maintenance aspirin 81mg PO Daily

Jneid, H, et al. *J Am Coll Cardiol*. 2012;60(7):645-681.

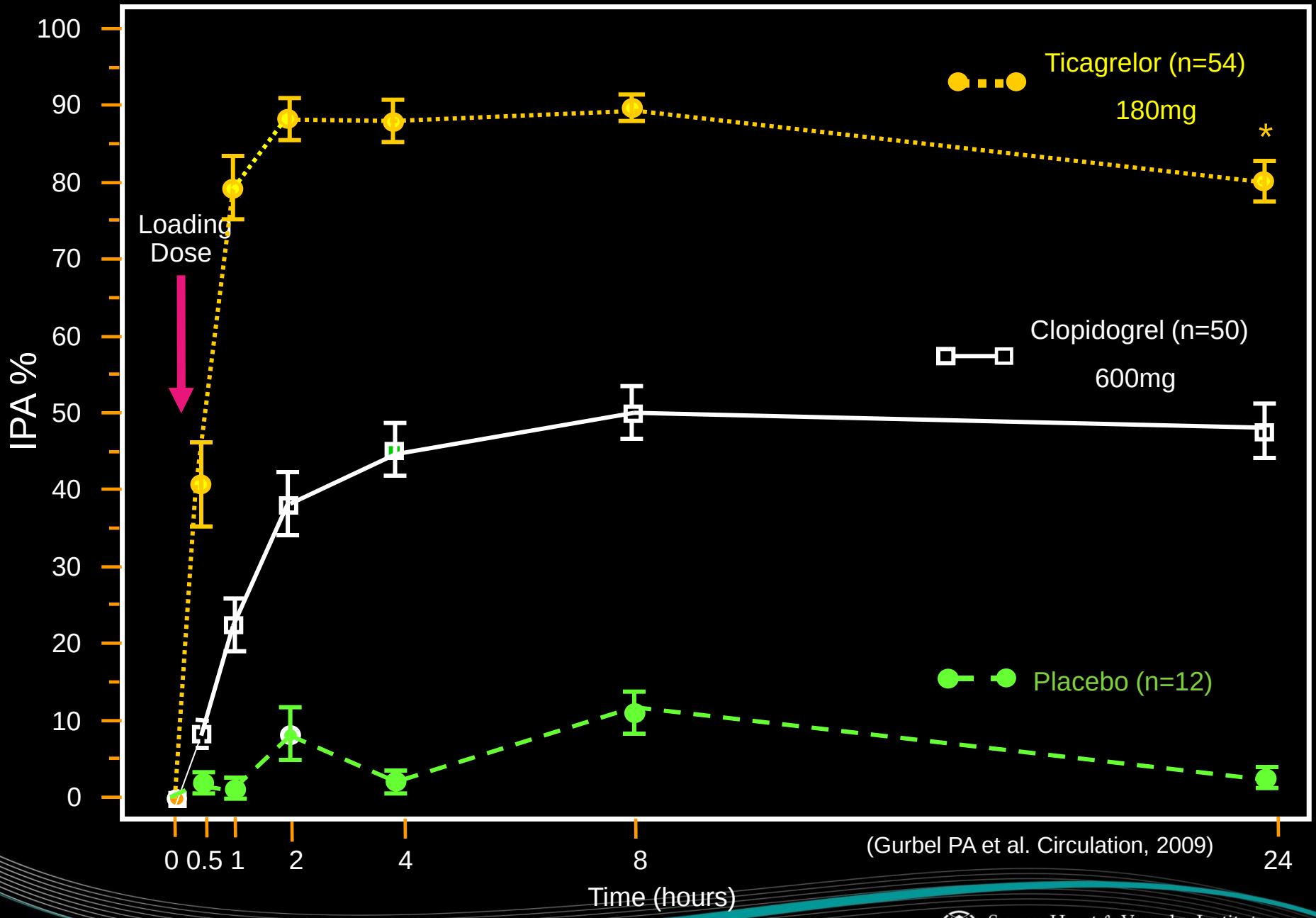
Ticagrelor:

An oral reversible $P2Y_{12}$ antagonist



- Direct acting
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Hold 5 days prior to surgical procedures

Onset of platelet inhibition



PLATO Trial-Study Design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel

If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

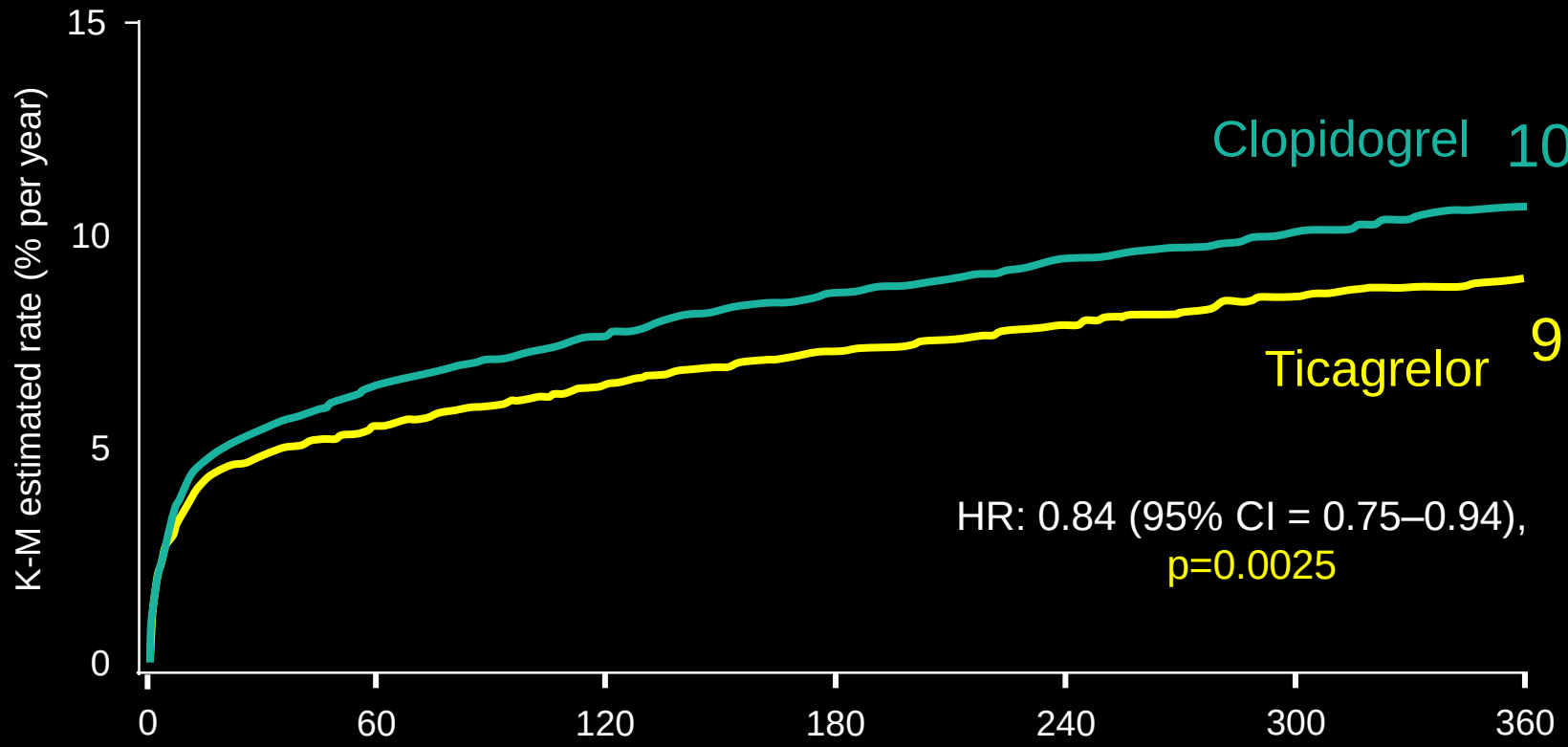
Ticagrelor

180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

PLATO Trial-Primary Endpoint:
CV death, MI or stroke

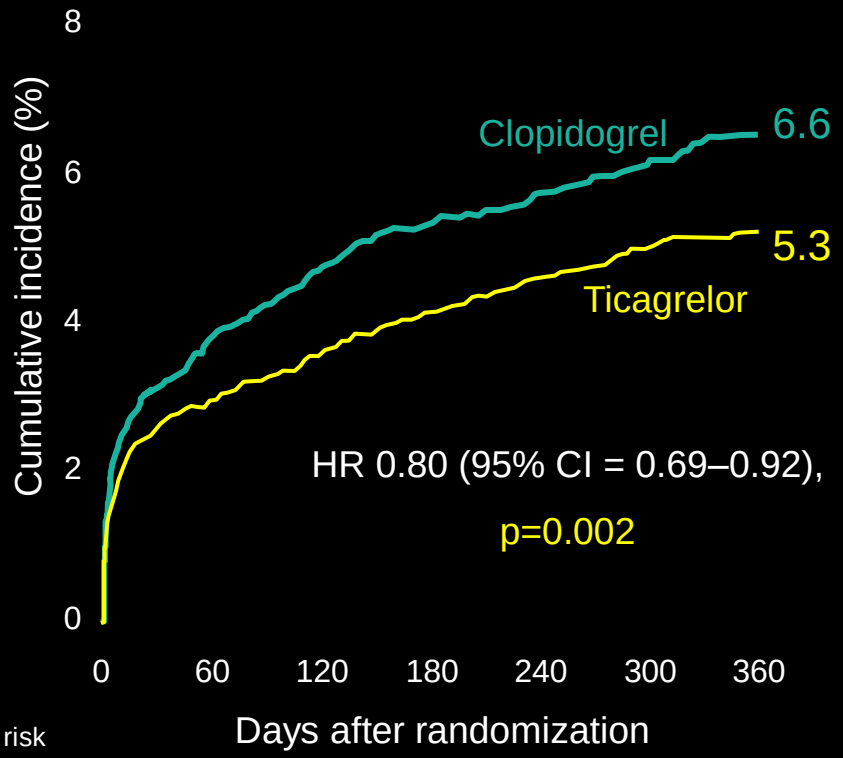


No. at risk							
Ticagrelor	6,732	6,236	6,134	5,972	4,889	3,735	3,048
Clopidogrel	6,676	6,129	6,034	5,881	4,815	3,680	2,965

N Engl J Med 2009; 361:1045-1057

PLATO Trial

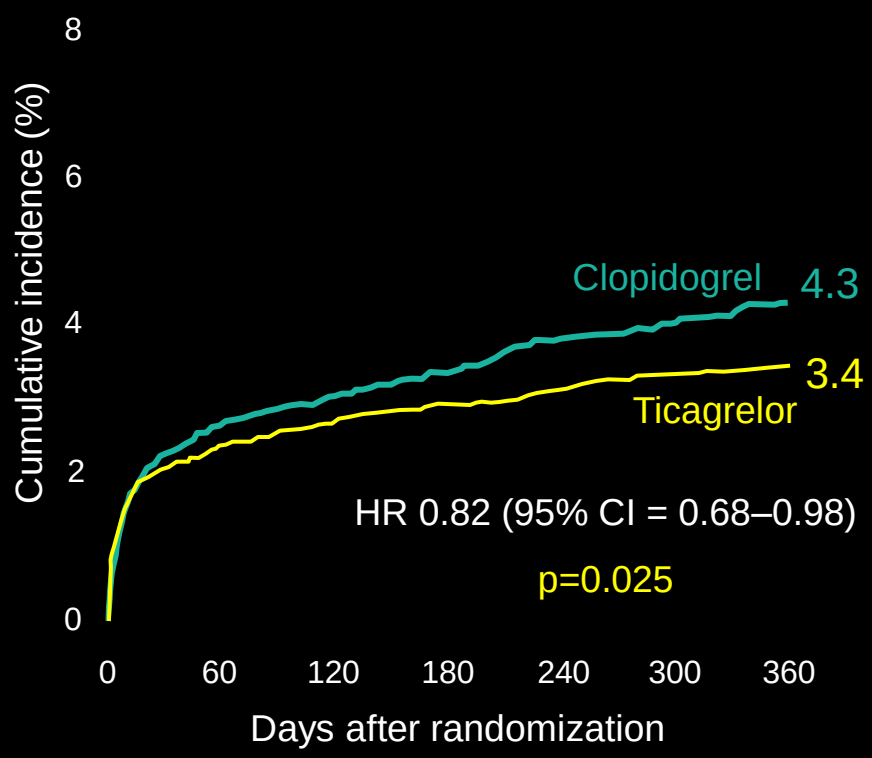
Myocardial infarction



No. at risk

Ticagrelor	6,732	6,268	6,173	6,010	4,924	3,766	3,078
Clopidogrel	6,676	6,157	6,062	5,917	4,849	3,706	2,987

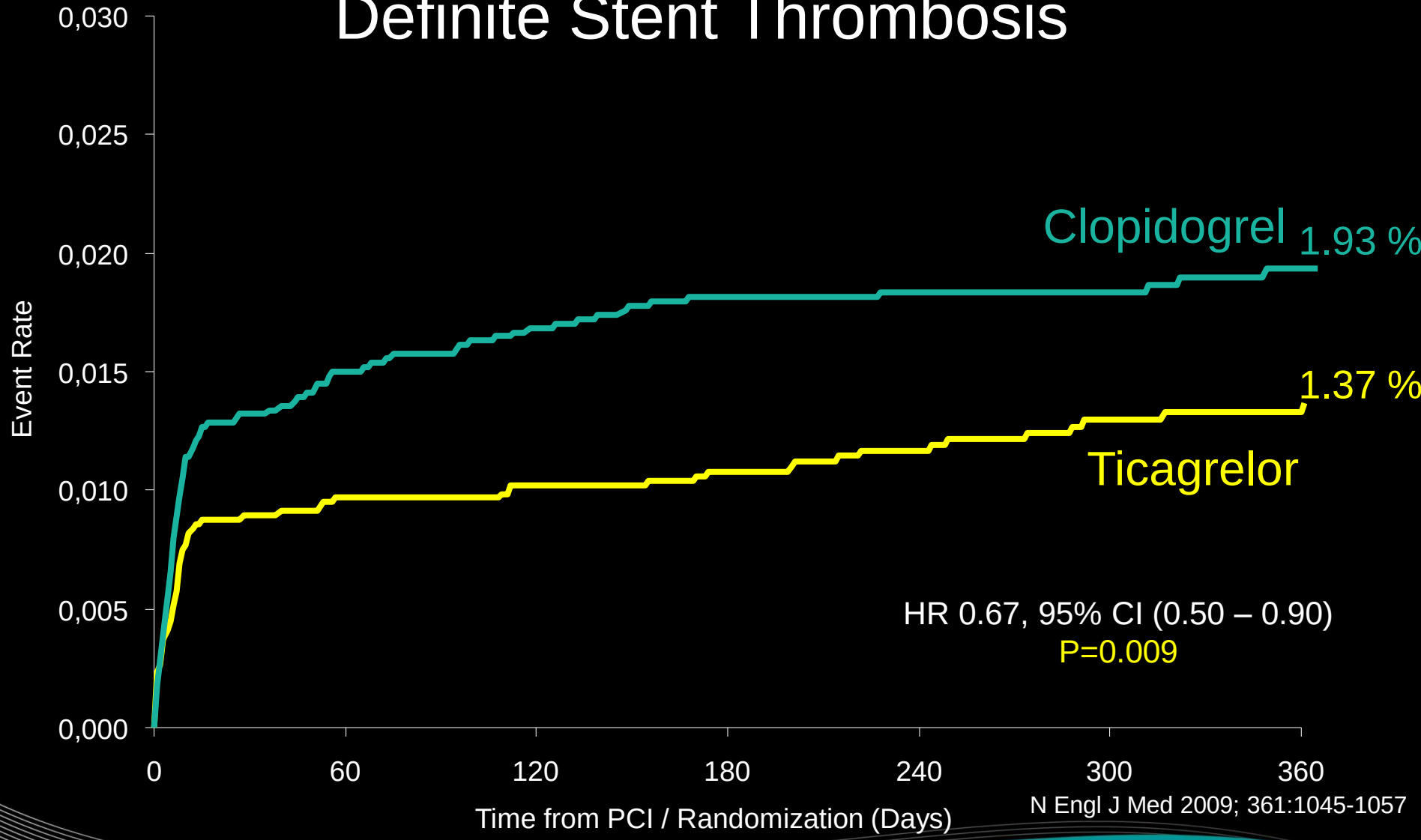
Cardiovascular death



	6,732	6,439	6,375	6,241	5,141	3,591	3,233
	6,676	6,376	6,332	6,209	5,114	3,917	3,164

N Engl J Med 2009; 361:1045-1057

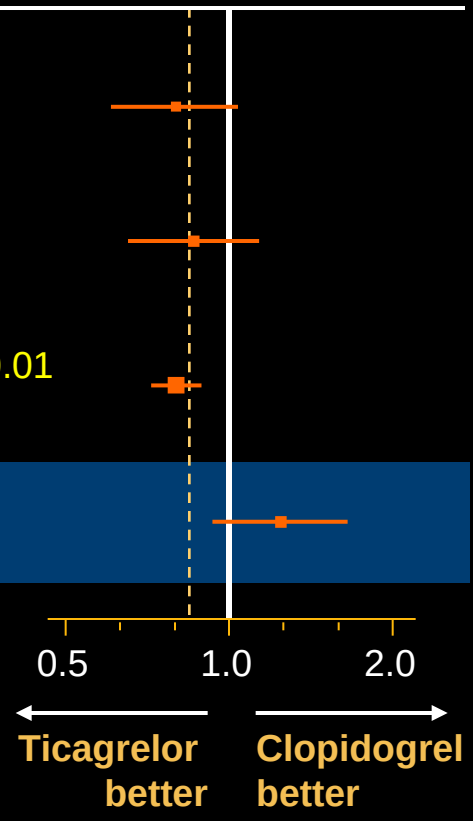
PLATO Trial:
Definite Stent Thrombosis



N Engl J Med 2009; 361:1045-1057

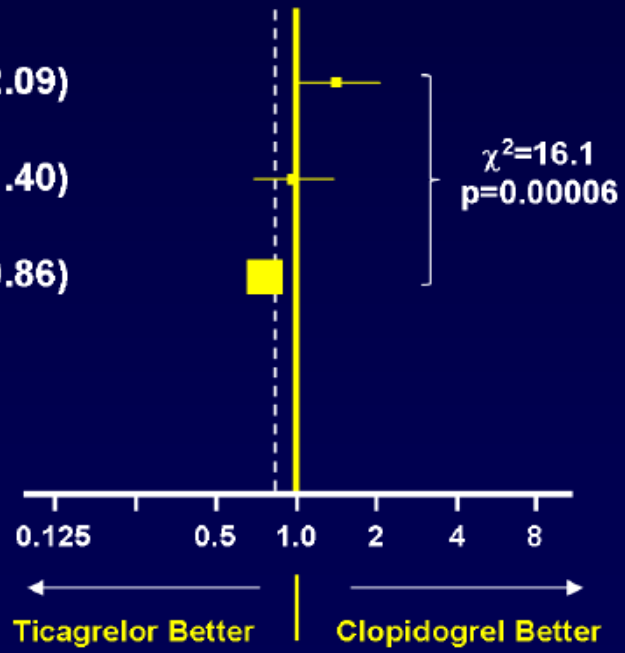
Geographic Regions
CV Death, MI, Stroke

Geographic region	Total patients	KM at month 12 Tic	KM at month 12 Clop	HR (95% CI)	Interaction p-values
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	
Central America / South America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe / Middle East / Africa	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



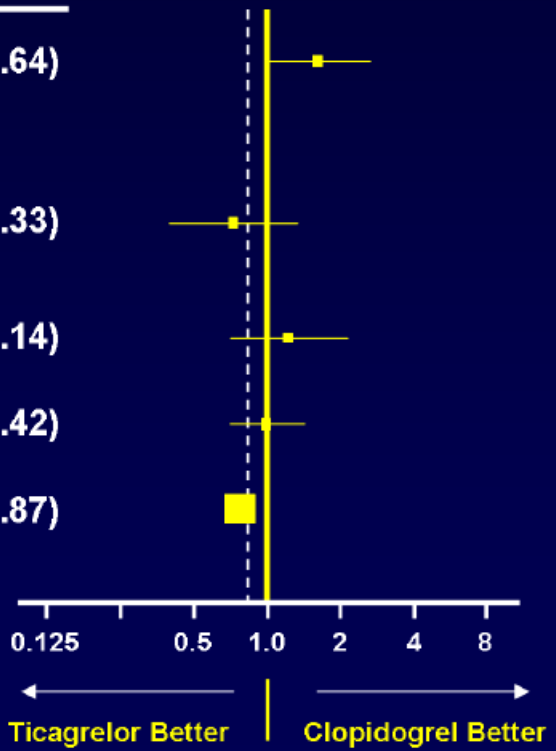
Interaction of Treatment Effect with ASA Dose

ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
Overall					
≥300	464	68	492	50	1.45 (1.01, 2.09)
>100 – <300	525	64	527	65	0.99 (0.70, 1.40)
≤100	7733	565	7706	723	0.77 (0.69, 0.86)

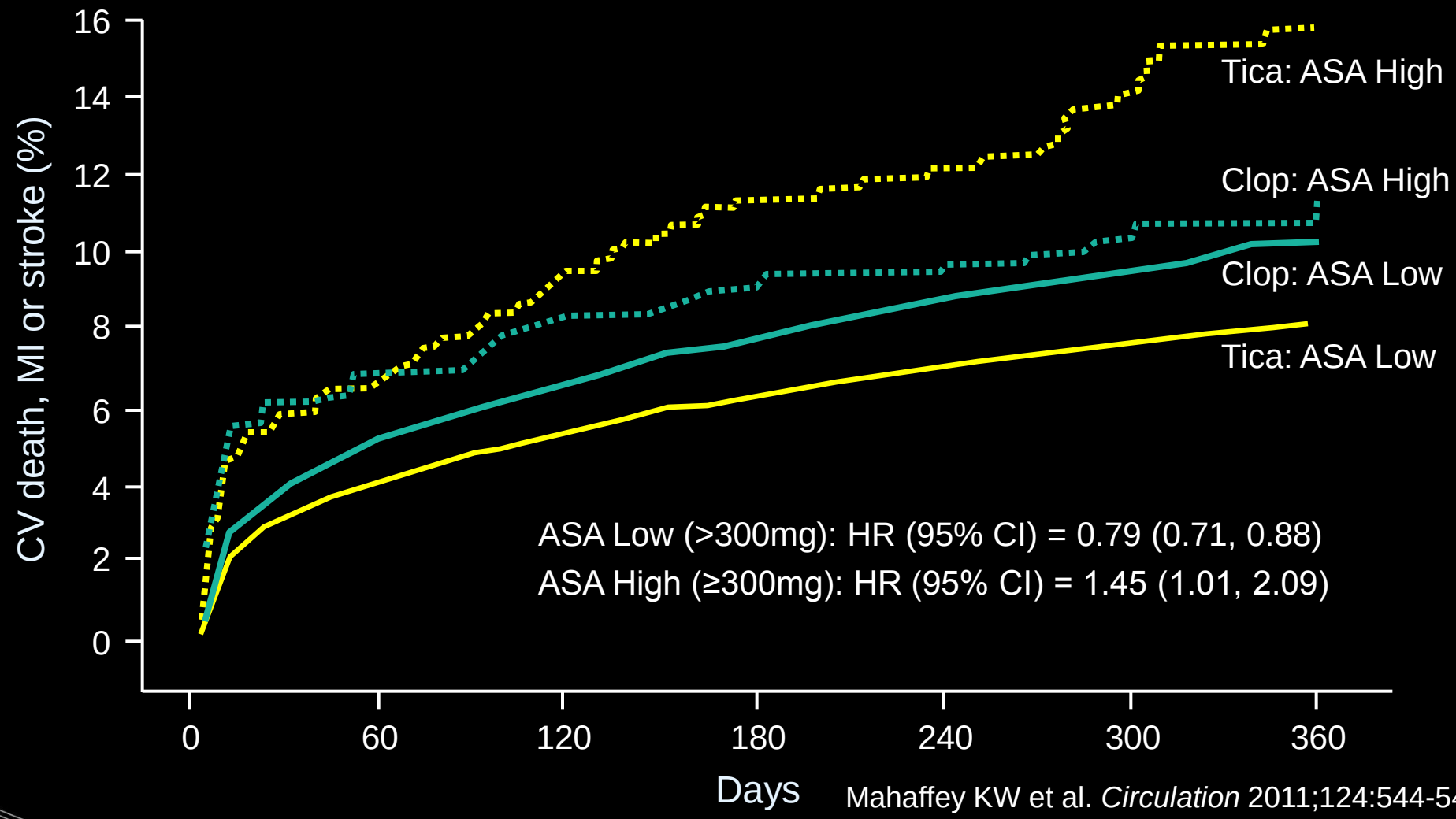


Similar Effect of ASA Maintenance Dose In Both U.S. and Non-U.S.

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100 – <300	22	2	16	2	
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100 – <300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)

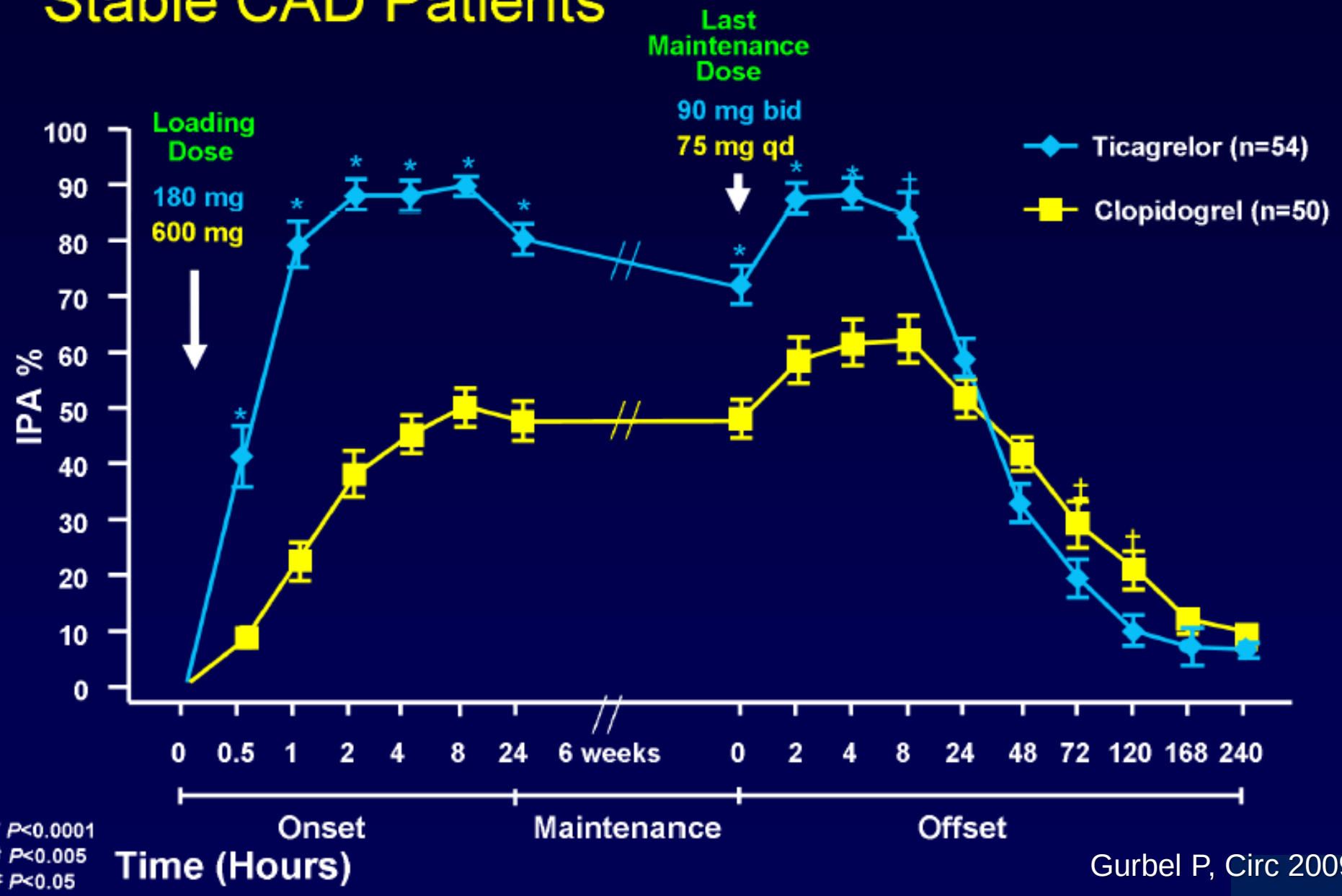


PLATO Trial : Interaction Between Treatment Effect and ASA Maintenance Dose



Mahaffey KW et al. *Circulation* 2011;124:544-54

ONSET/OFFSET: Pharmacodynamics in Stable CAD Patients



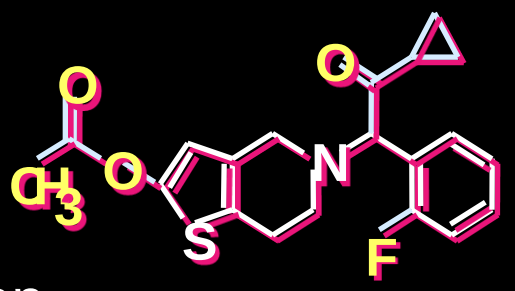
Gurbel P, Circ 2009

Summary of Ticagrelor

- Advantages
  - Rapid onset on action
  - Better clinical outcomes than clopidogrel
  - Can be given to all patients
  - Shorter offset of effect
- Disadvantages
  - Trial data from North American patients
  - Requires ASA 81mg Daily
  - Twice a day dosing
  - Associated with dyspnea and pauses

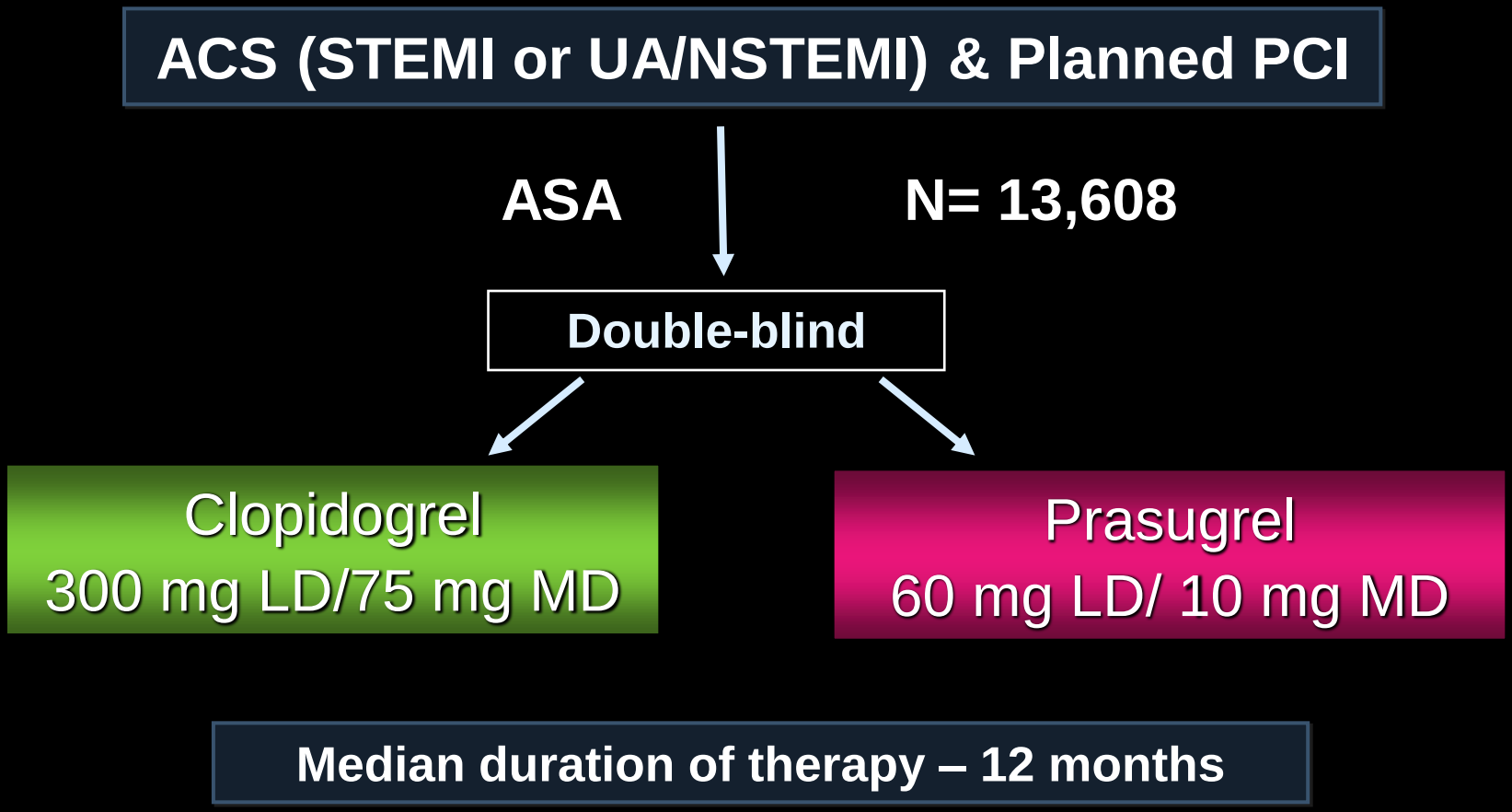
Prasugrel:

An oral irreversible $P2Y_{12}$ antagonist

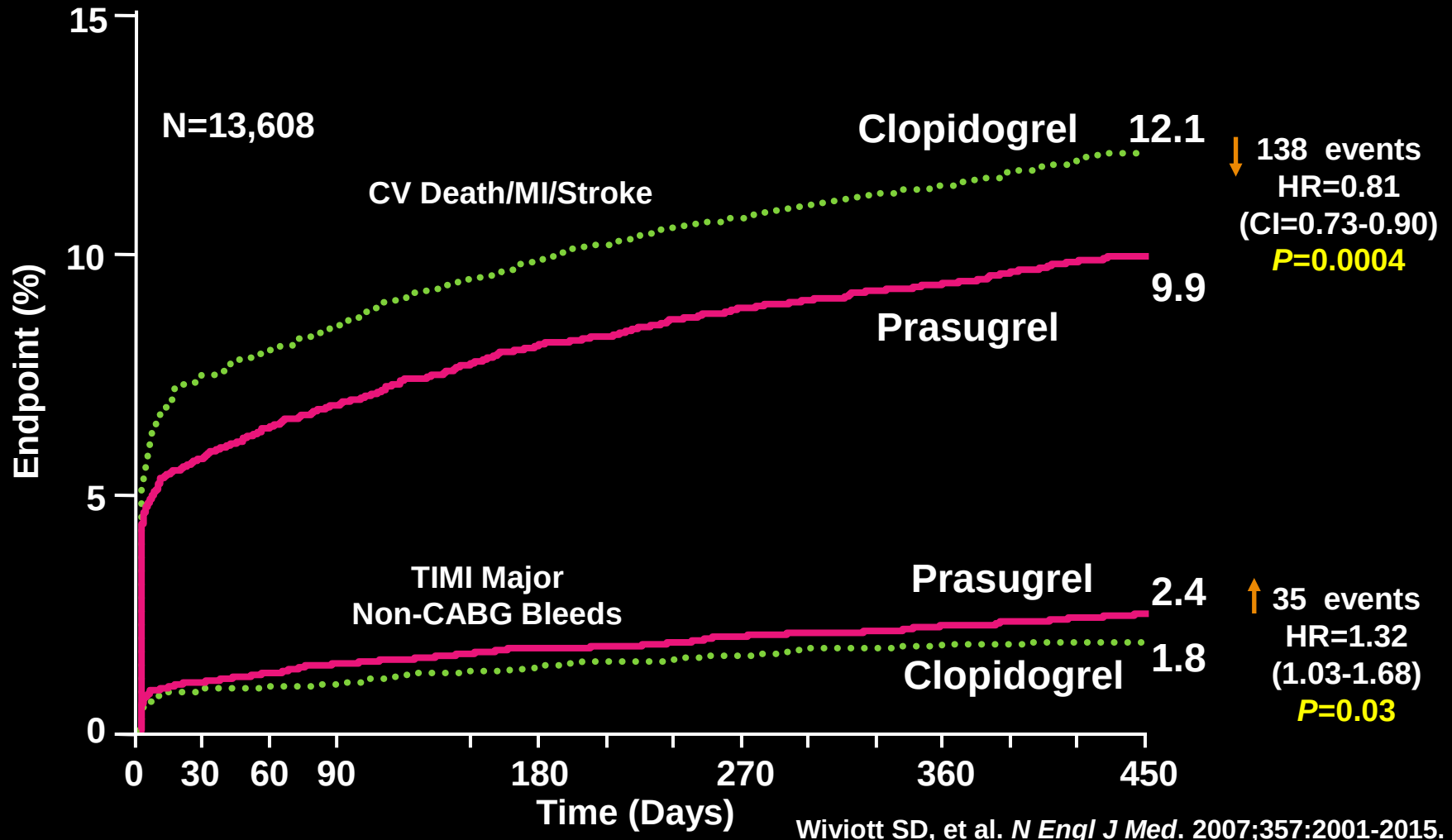


- Not direct acting
  - Prodrug; does require metabolic activation
  - Rapid onset of inhibitory effect on the $P2Y_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel
- Irreversibly bound
  - Longer offset of effect than clopidogrel
  - Hold 7 to 10 days prior to surgical procedures

TRITON TIMI 38-Study Design

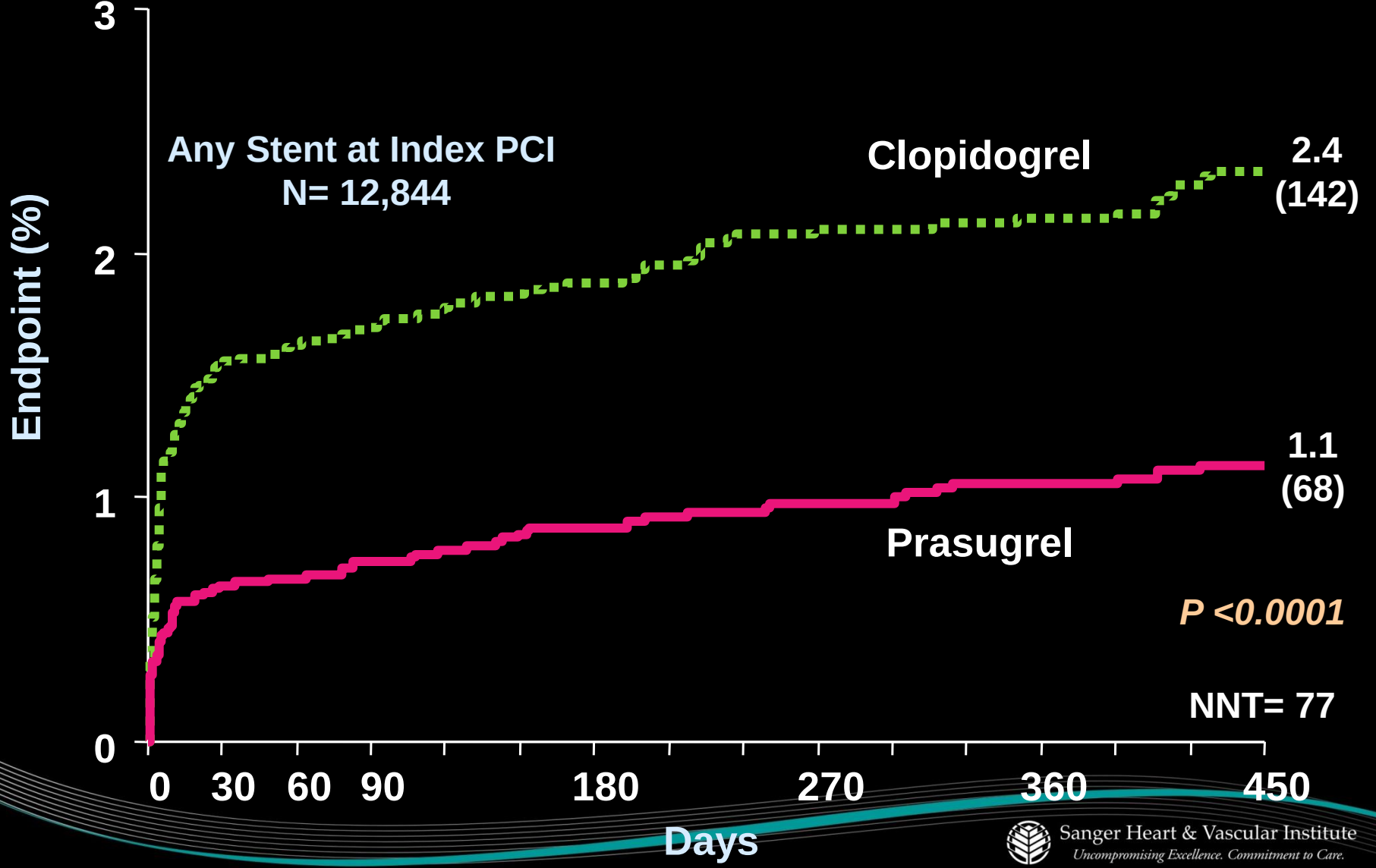


TRITON-TIMI 38: Balance of Efficacy and Safety



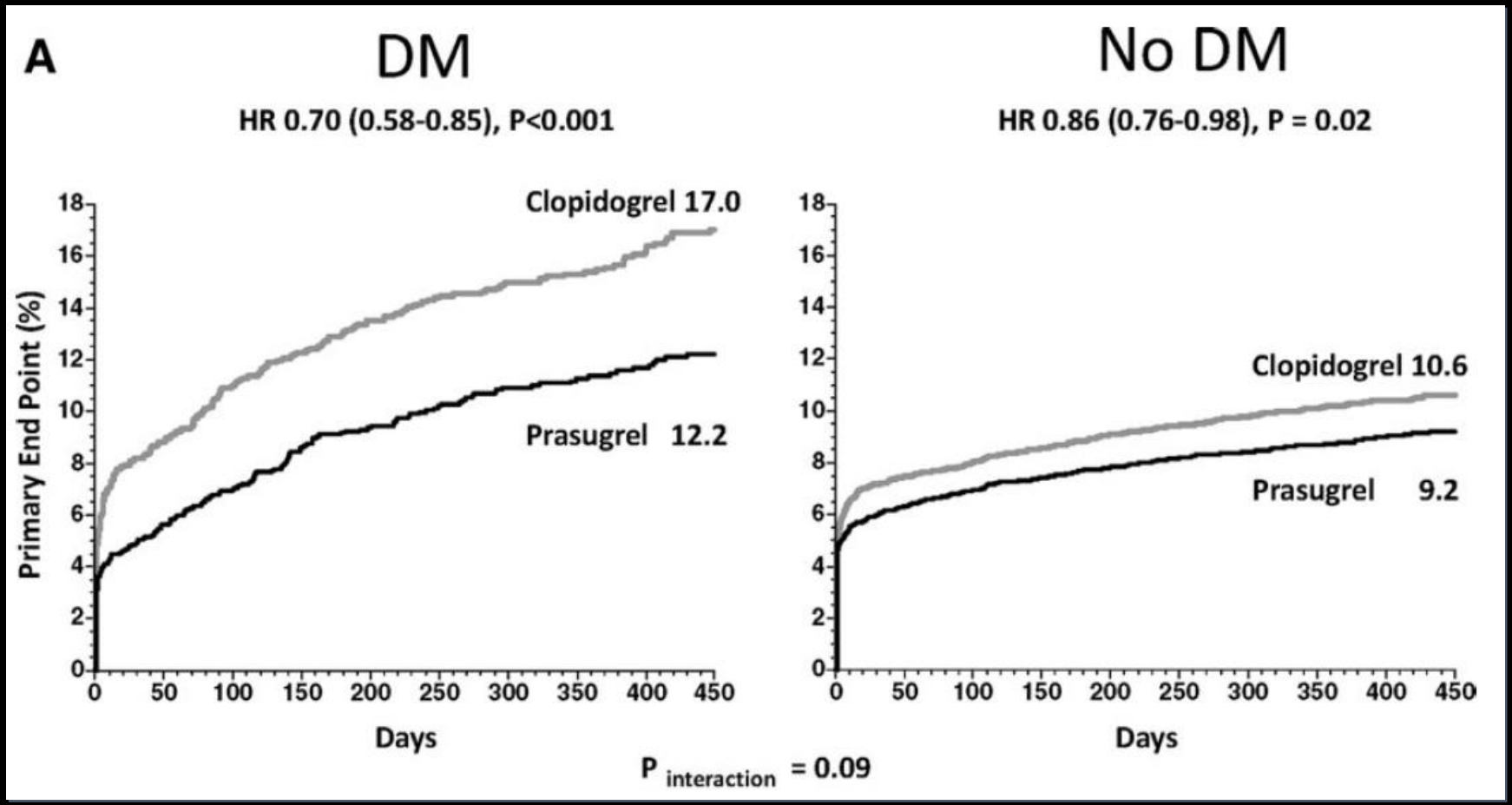
Wiviott SD, et al. *N Engl J Med*. 2007;357:2001-2015.

Stent Thrombosis (ARC Definite + Probable)



Sanger Heart & Vascular Institute
Uncompromising Excellence. Commitment to Care.

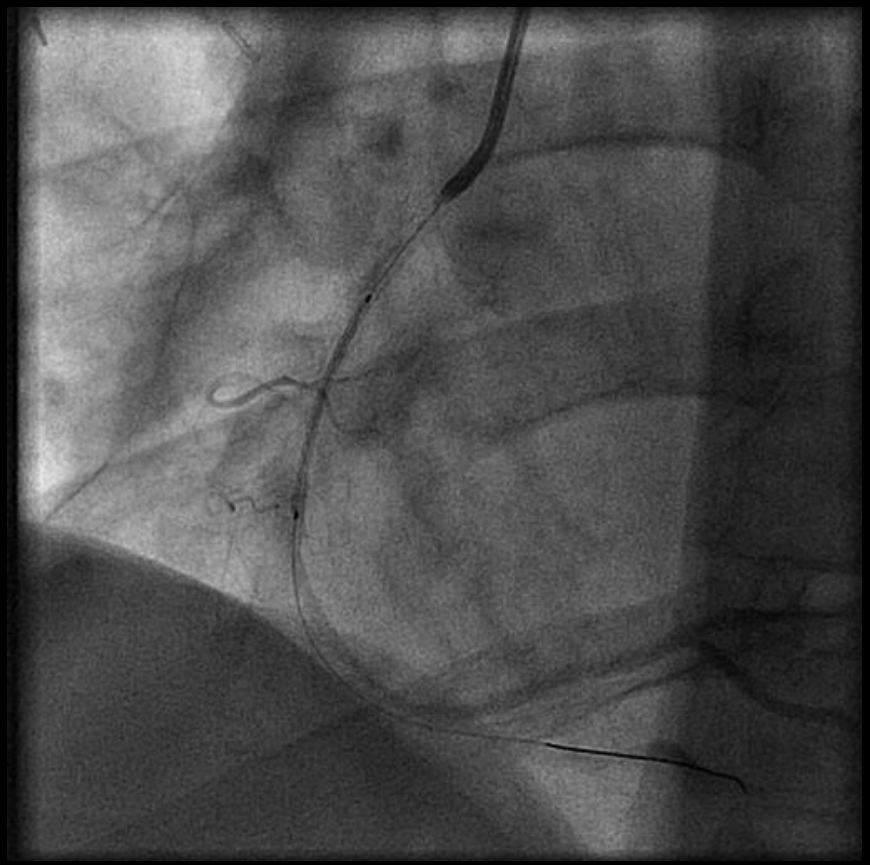
TRITON TIMI 38 Trial:
Outcomes in Patients with Diabetes
Death, MI or Stroke at 1 year

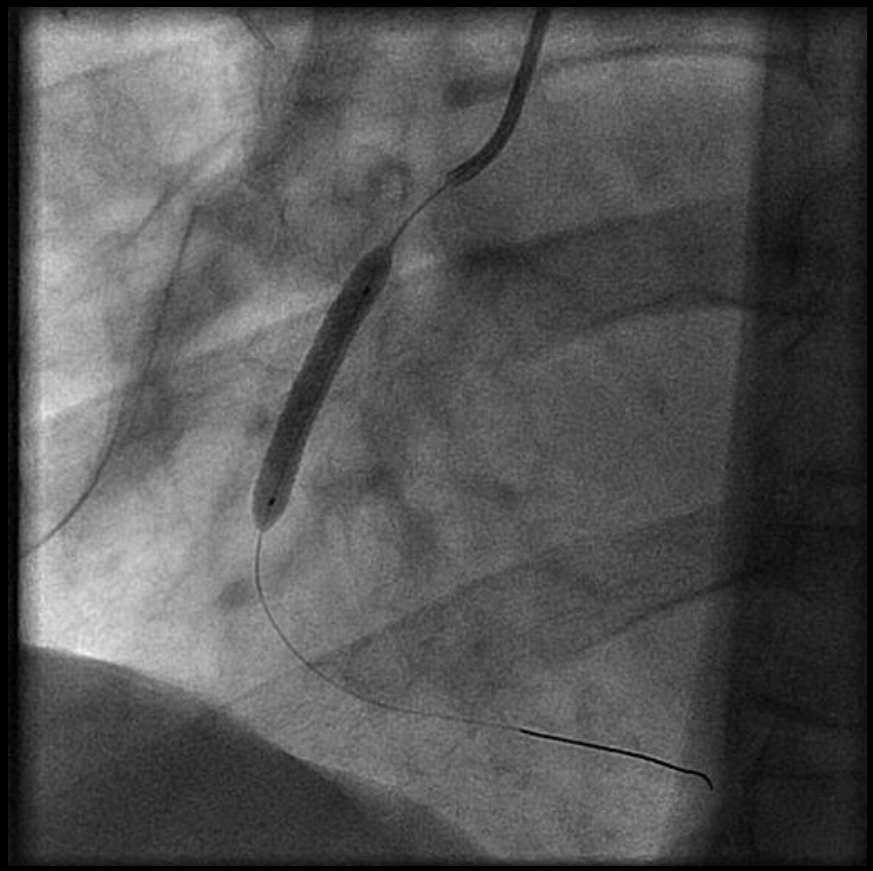


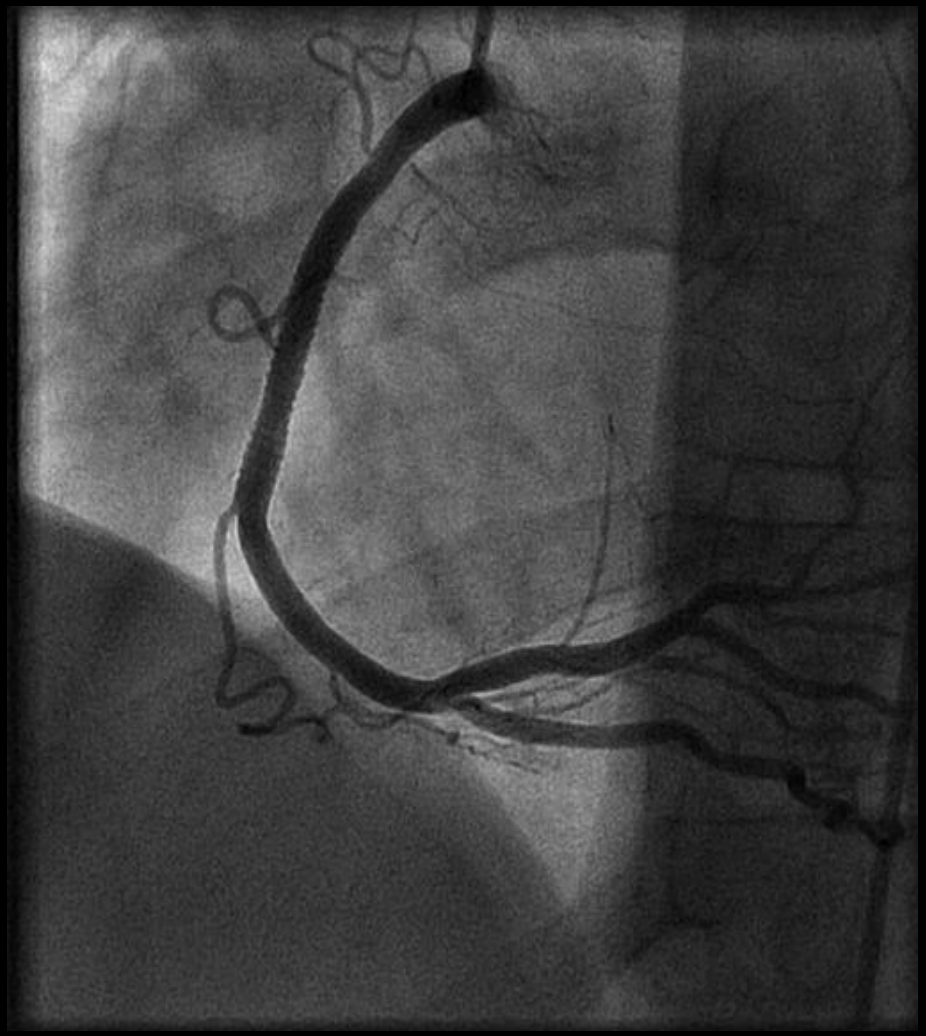
Wiviott, Circ 2008

Summary of Prasugrel

- Advantages
  - Rapid onset on action
  - Better clinical outcomes than clopidogrel
  - Once a day dosing regimen
  - Improved efficacy in diabetic patients
- Disadvantages
  - Black Box warning: History of TIA/CVA, Age >75 and Weight <60kg
  - Longer offset of effect
  - More life threatening bleeds







Antithrombotic Therapy in STEMI Patients: 2013

- Aspirin 325mg load on arrival then 81mg Daily indefinitely
- Atorvastatin 80mg PO
- IV Bivalirudin per protocol
- Aspiration Thrombectomy as indicated
- Ticagrelor 180mg load then 90mg BID for 12 months or Prasugrel 60mg load then 10mg Daily for 12 months