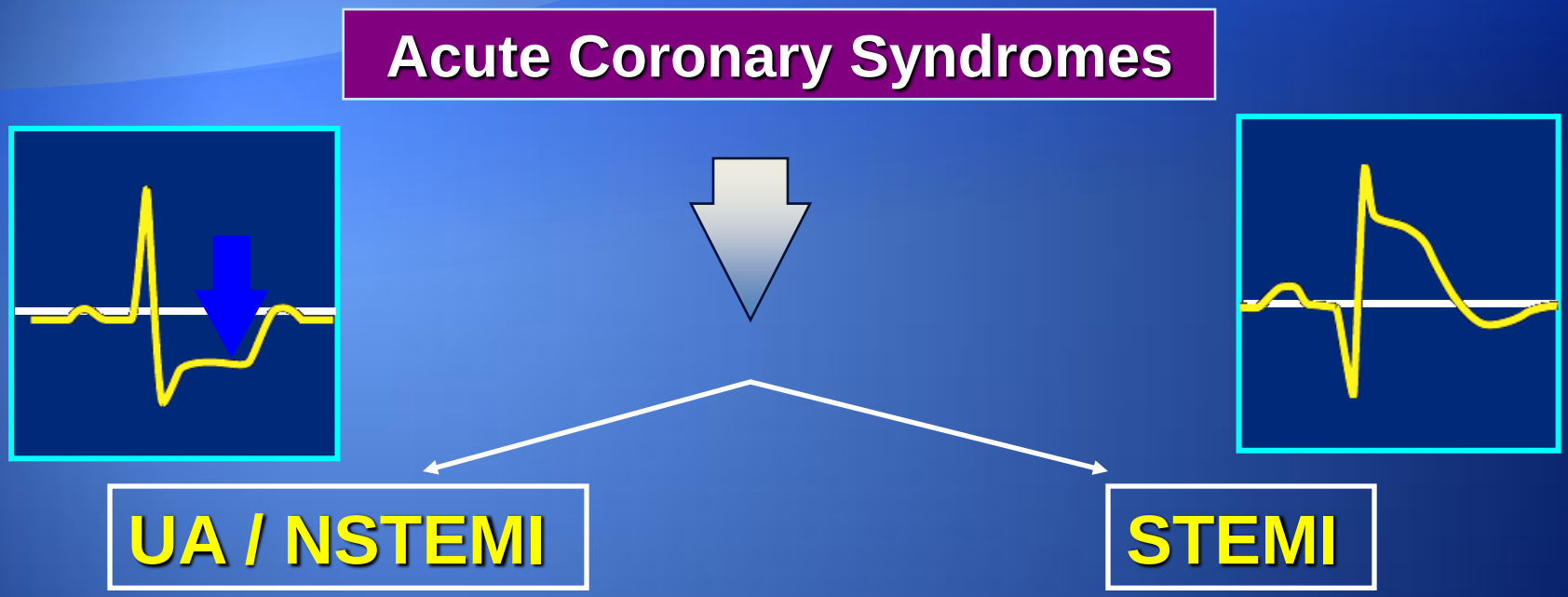
Acute MI

Therapy Update

Luis F. Tami, MD
Cath Lab Director
Memorial Regional Hospital

Aug 27, 2011

Acute Coronary Syndromes (ACS)



Heart Disease and Stroke Statistics – 2007 Update. Circulation 2007; 115:69-171.

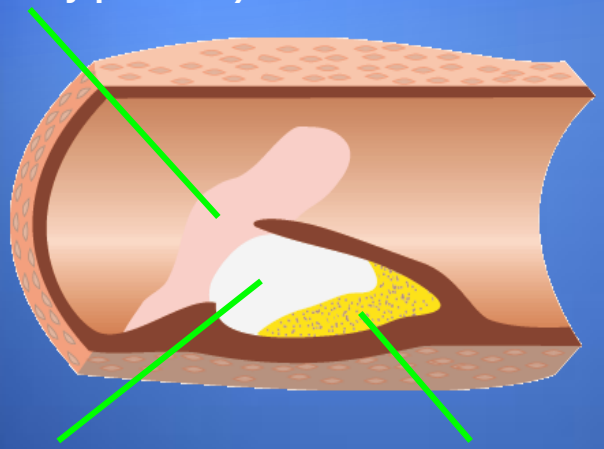
*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.

ACS: Pathology

Vulnerable Plaque

UA/NSTEMI

Partially-occlusive thrombus (primarily platelets)

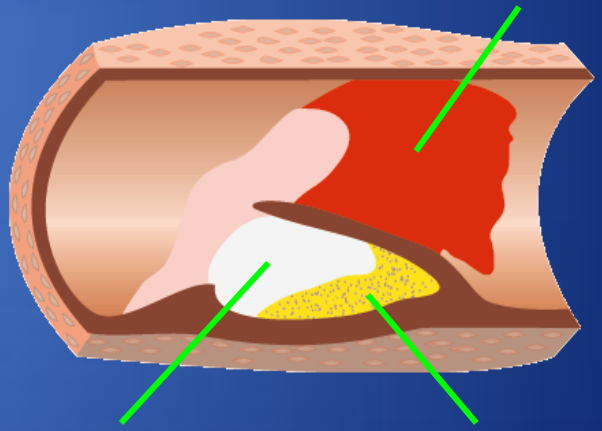


Intra-plaque thrombus (platelet dominated)

Plaque core

STEMI

occlusive thrombus (platelets, red blood cells, and fibrin)

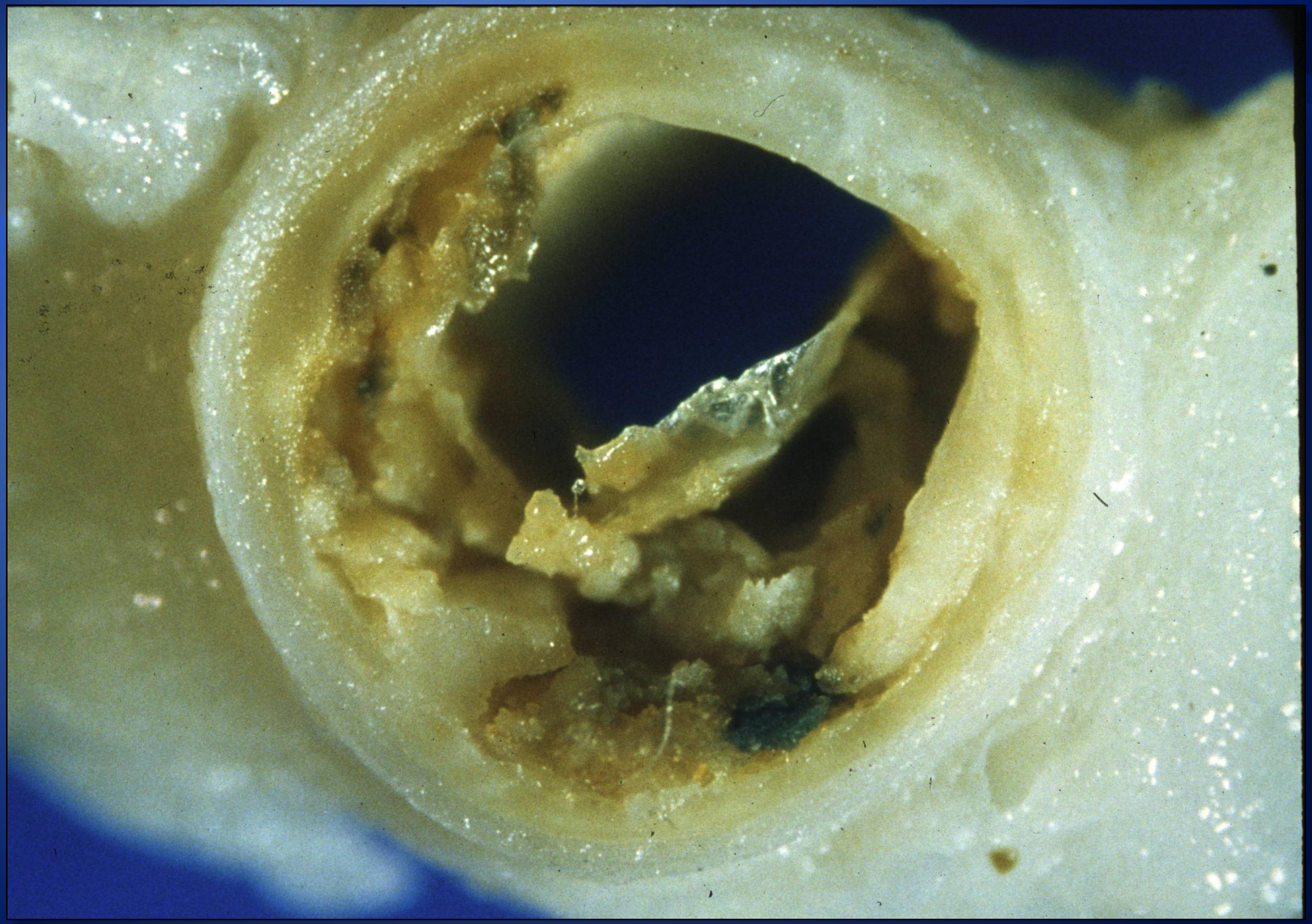


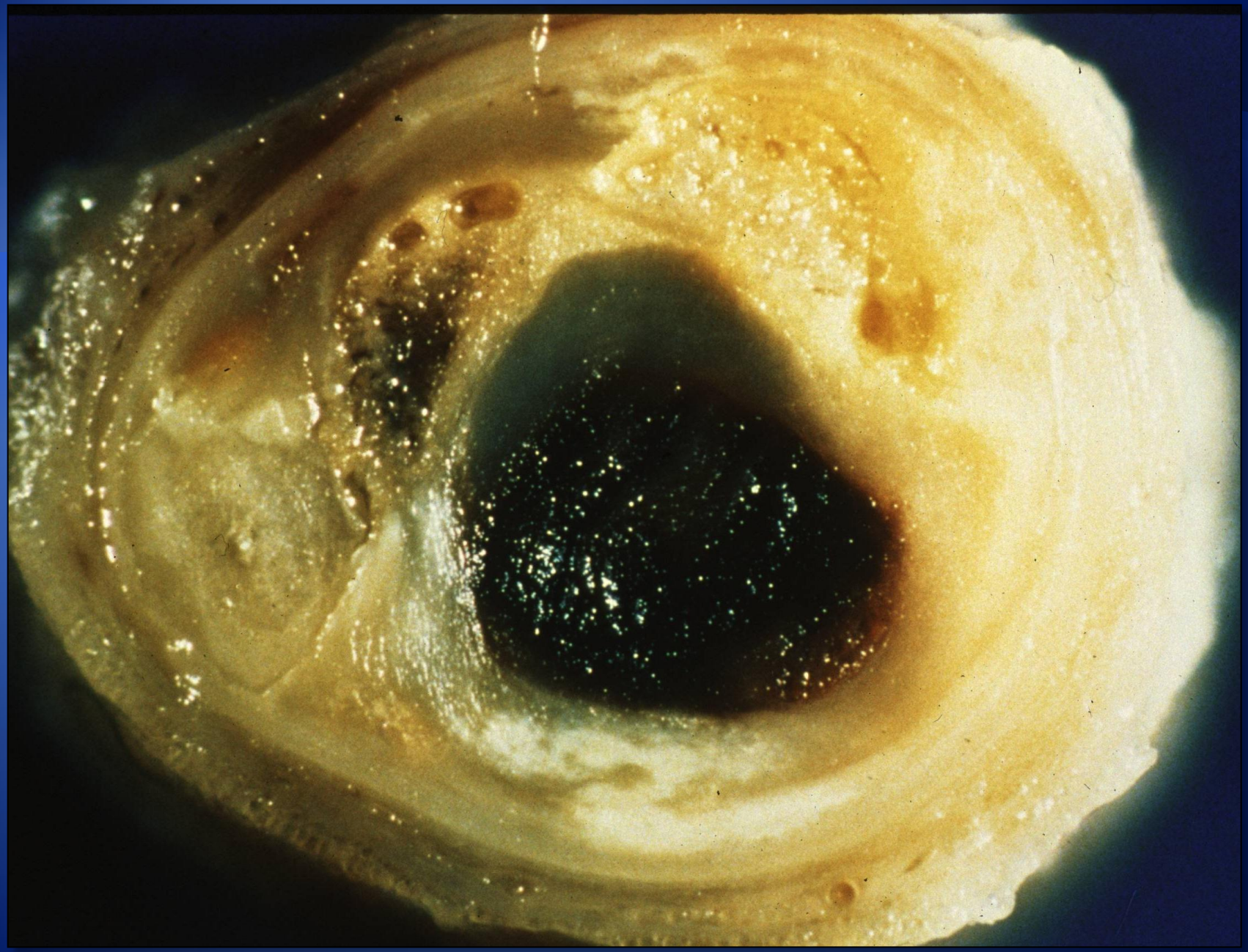
Intra-plaque thrombus (platelet dominated)

Plaque core

SUDDEN DEATH

Adapted from Davies MJ. *Circulation.* 1990; 82 (supl II): 30-46.



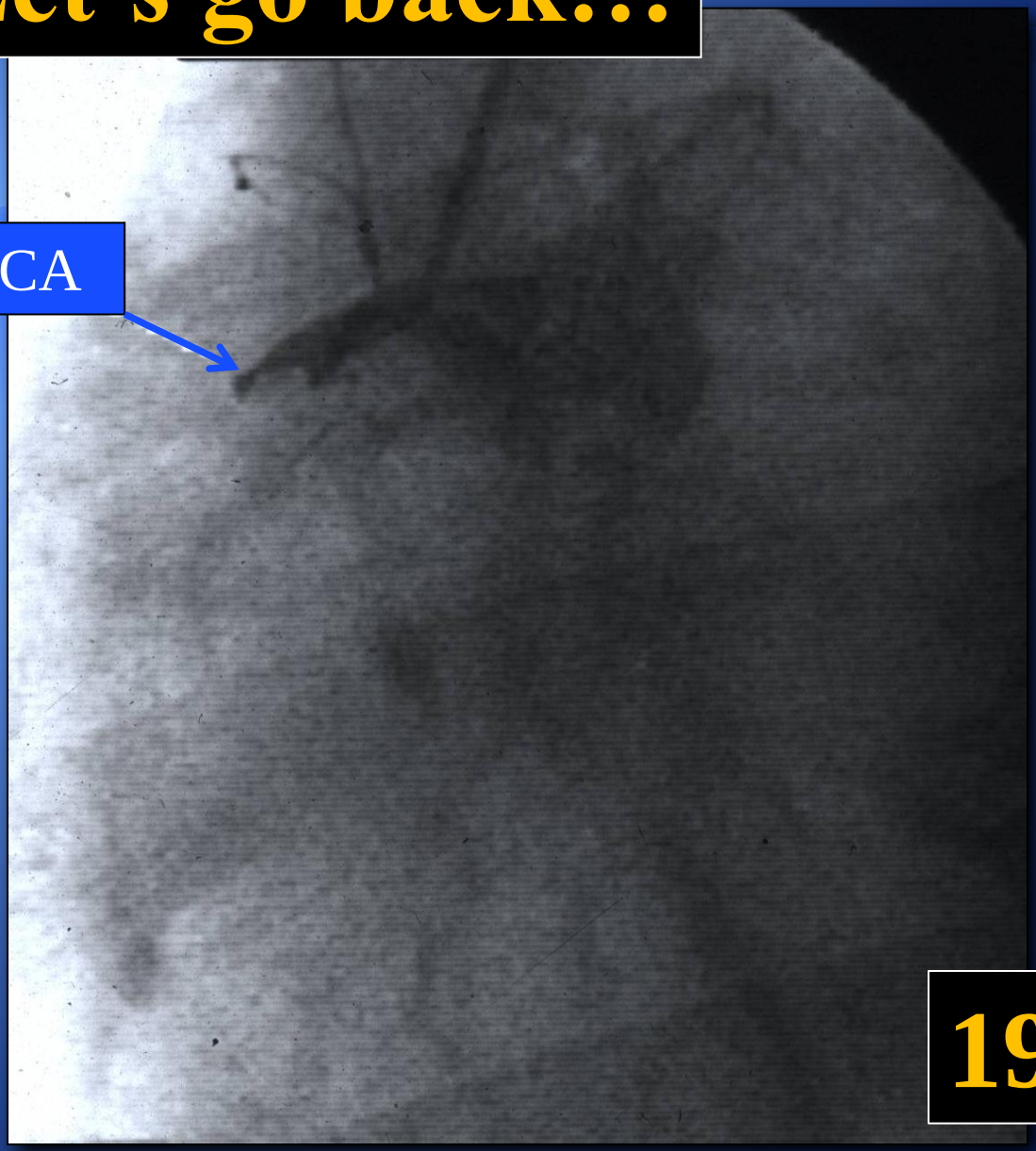


STEMI: IMMEDIATE REPERFUSION

"STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 min of first medical contact (D2B TIME)".

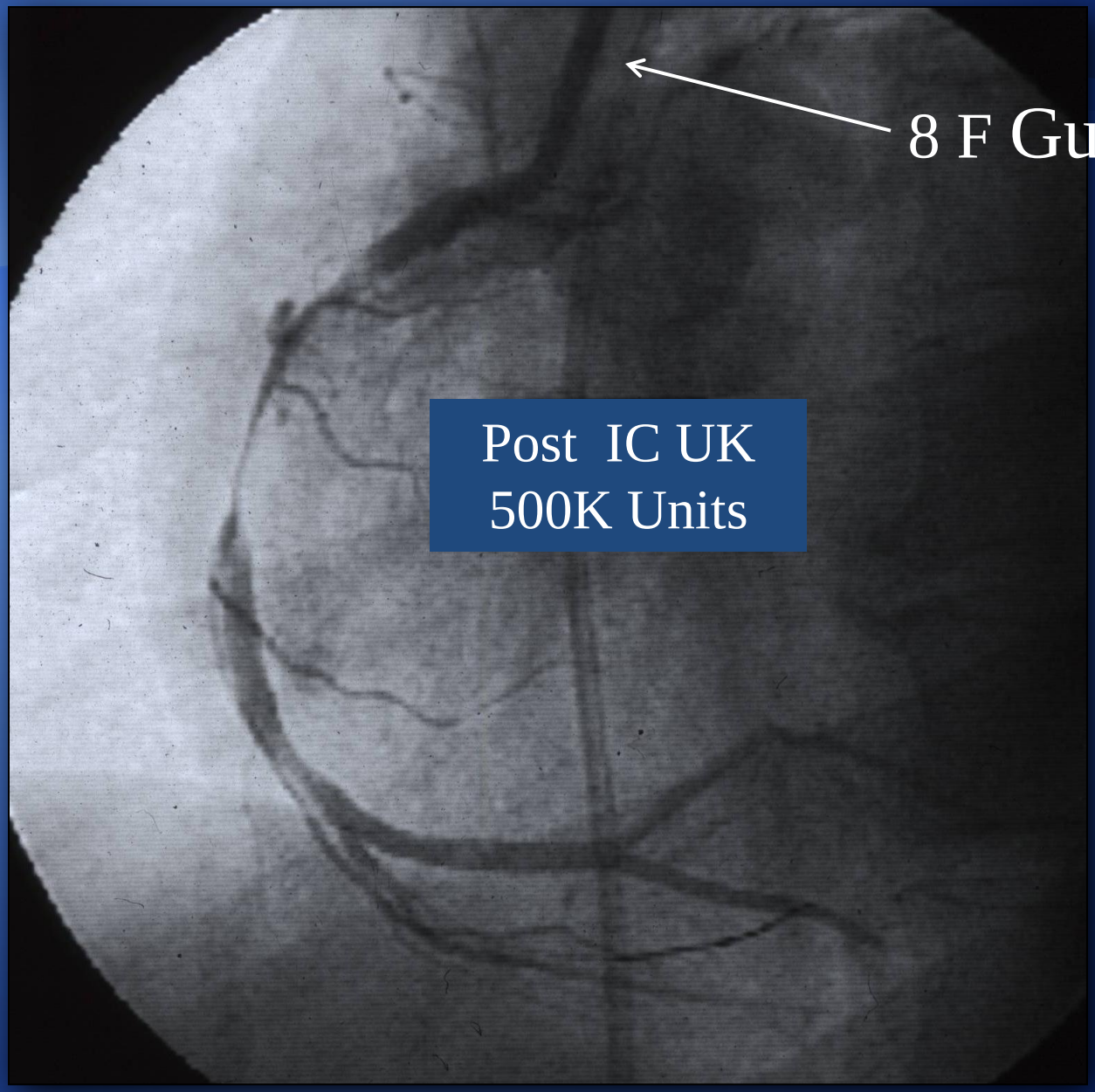
AHA/ACC 2009 STEMI/PCI Guidelines

Let's go back…



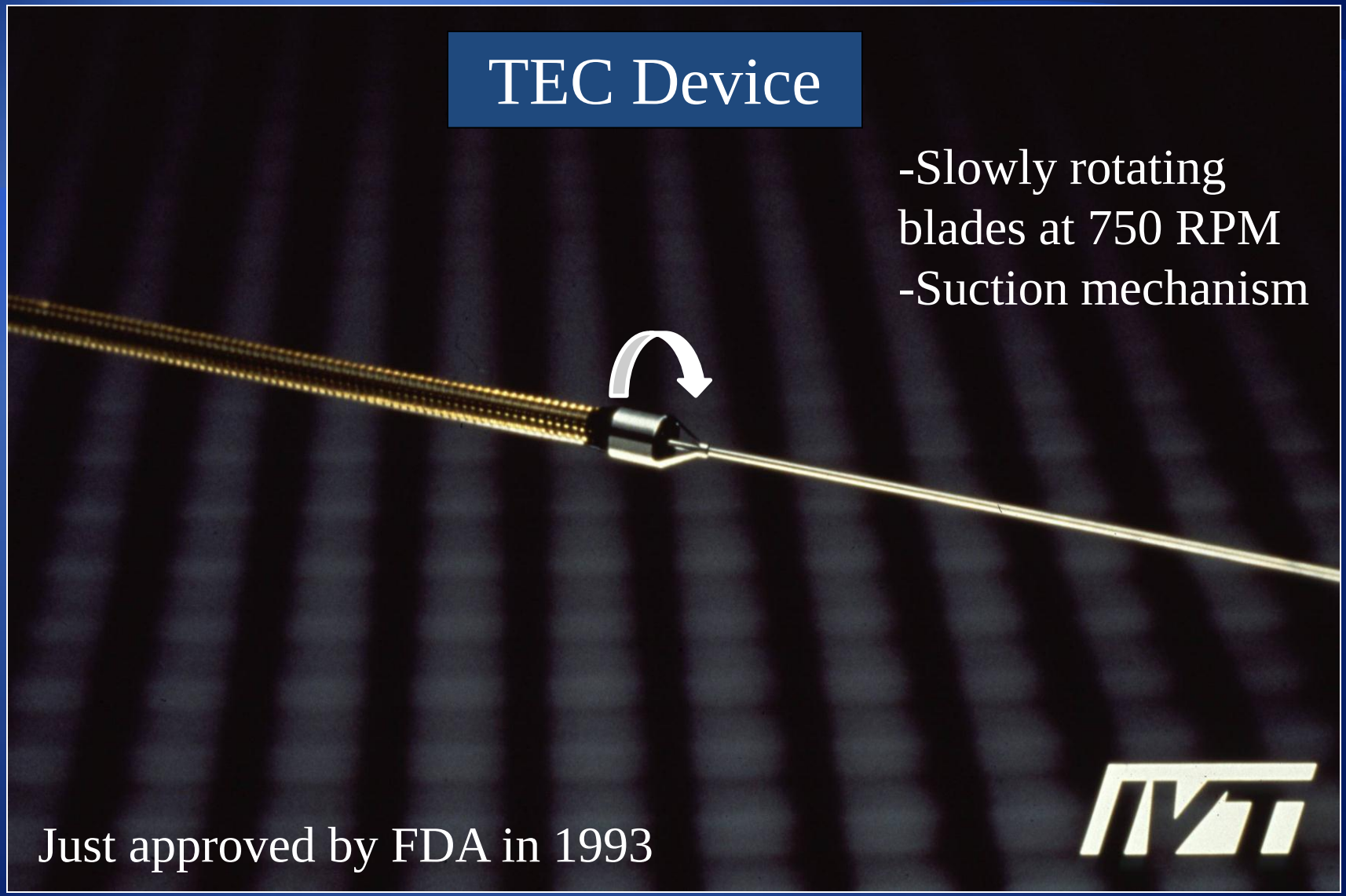
60 yr old obese female with an Inferior STEMI

1993

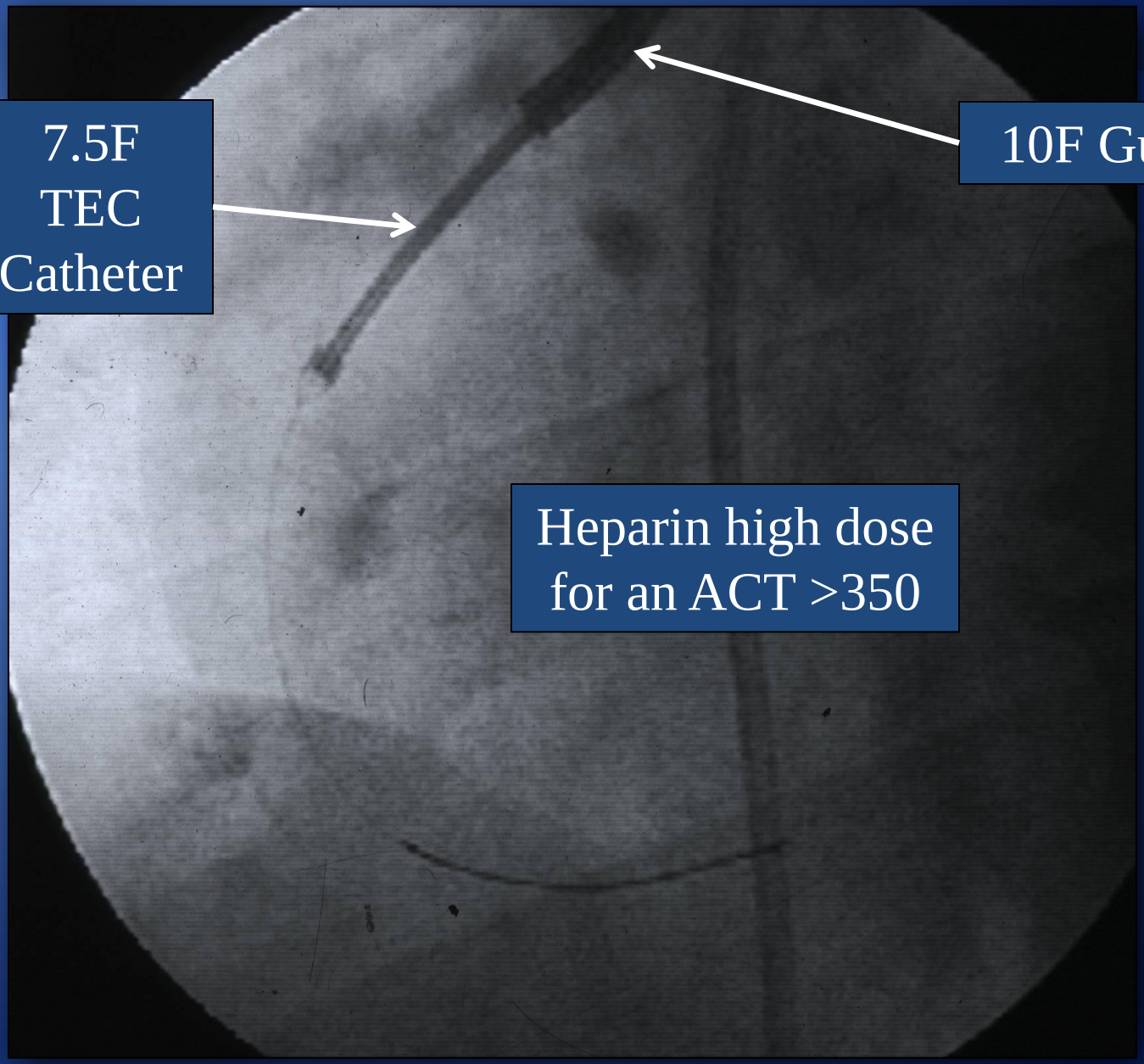

8 F Guide
Post IC UK
500K Units

TEC Device

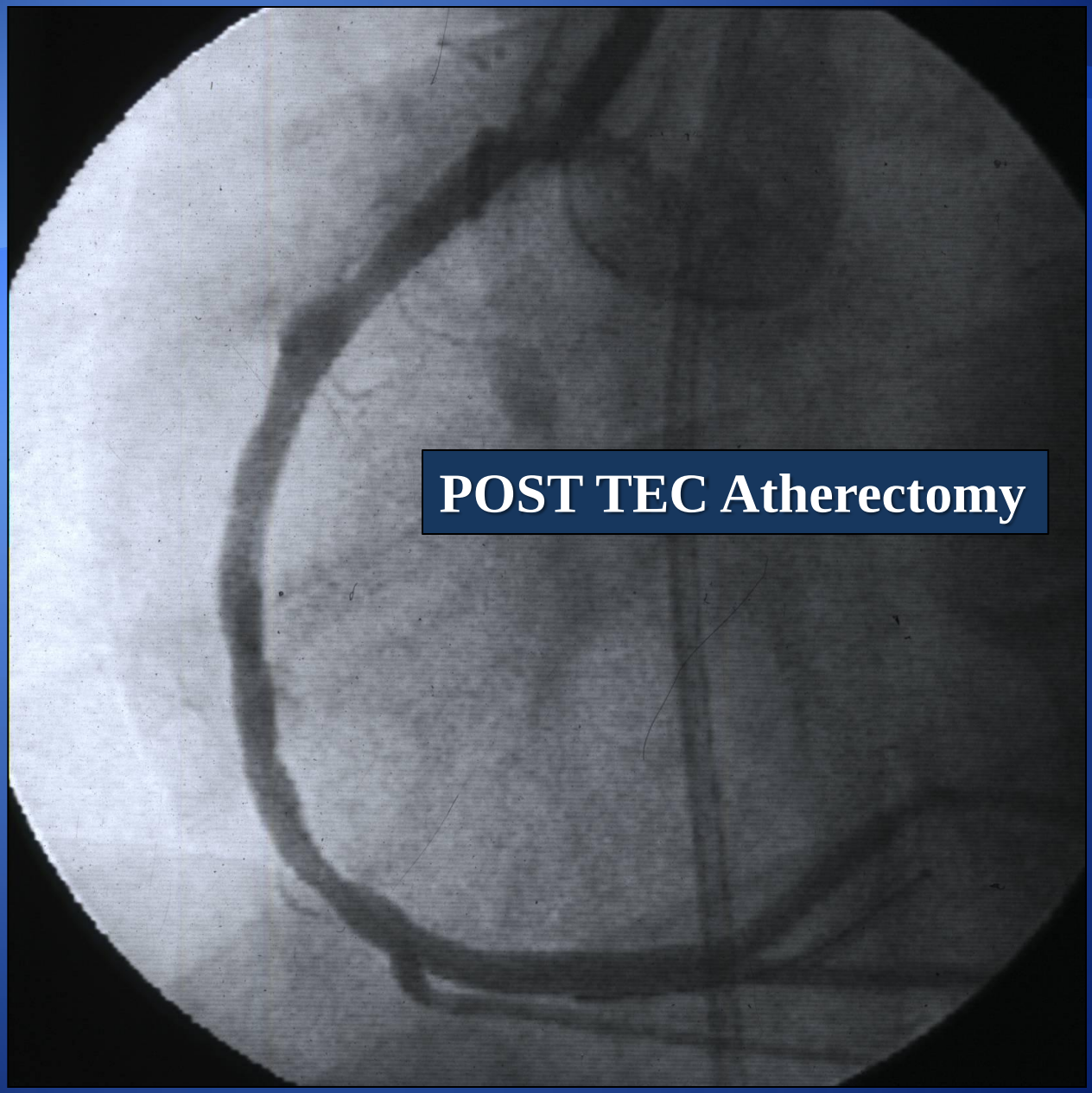
-Slowly rotating blades at 750 RPM
-Suction mechanism



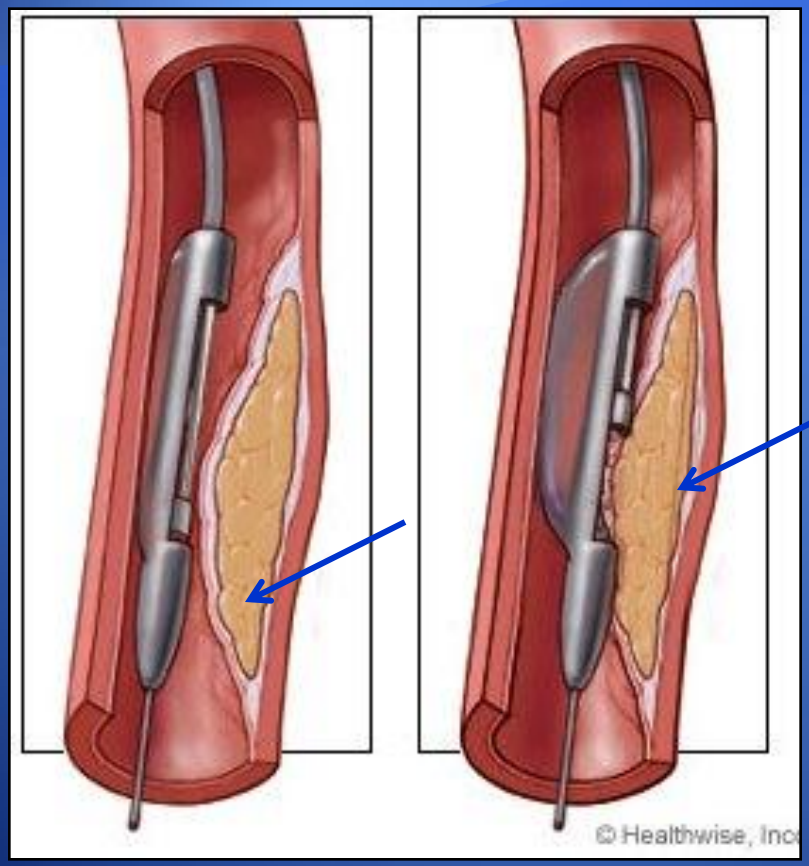
Just approved by FDA in 1993


7.5F
TEC
Catheter
10F Guide
Heparin high dose
for an ACT >350

TEC Aspirate


POST TEC Atherectomy

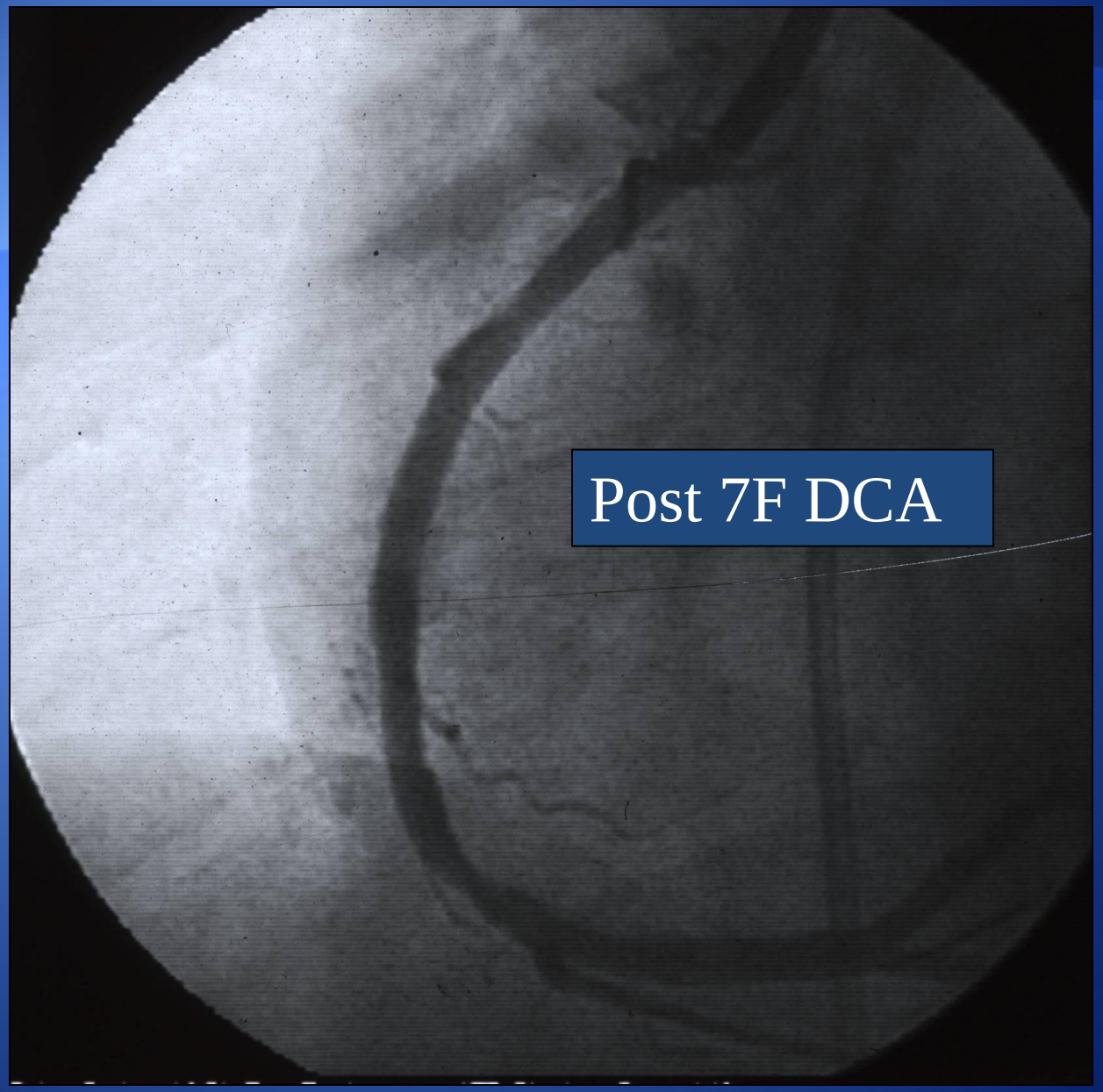
Directional Coronary Atherectomy (DCA)



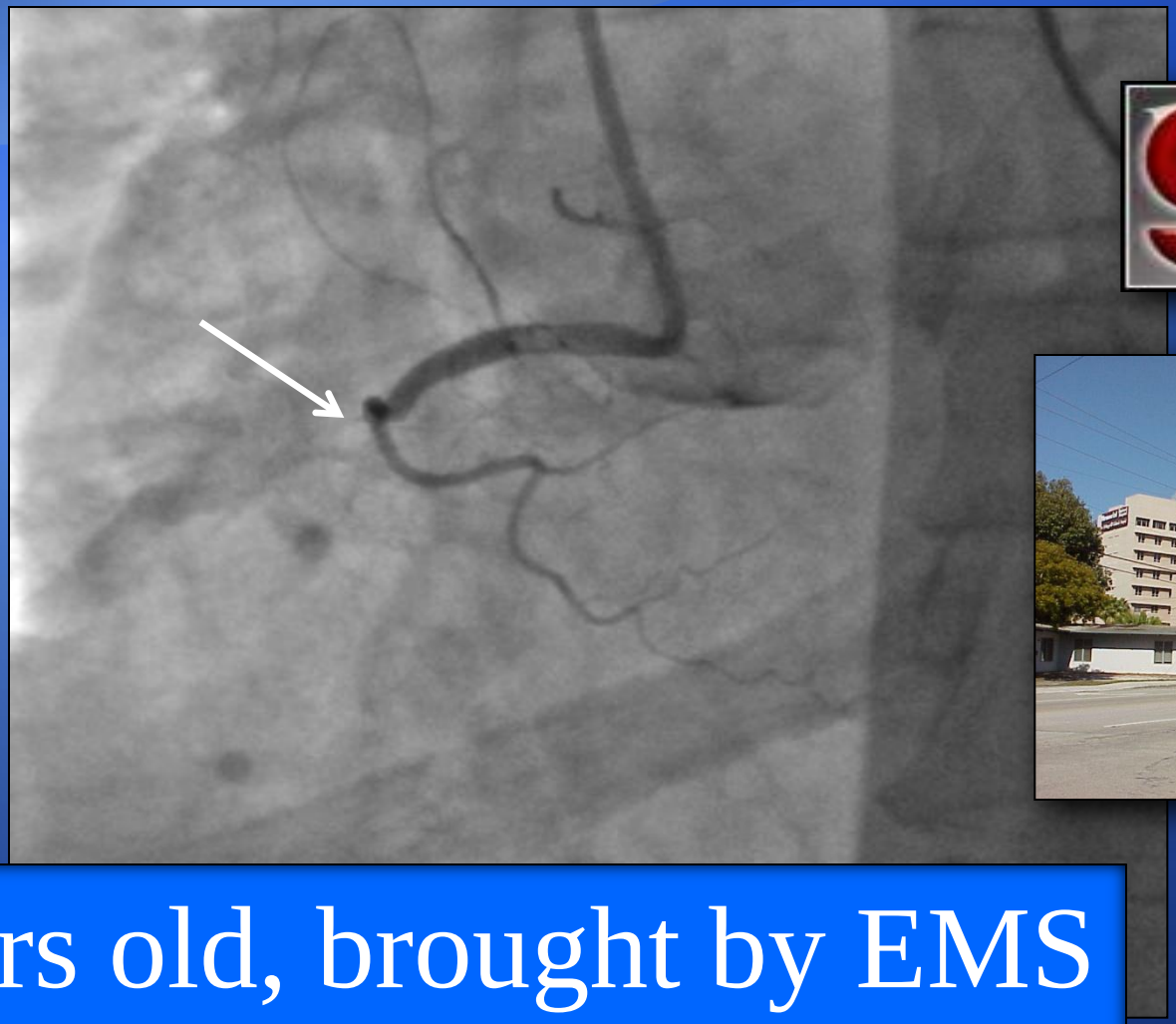
Side window
Blade rotates at 2,000 rpm

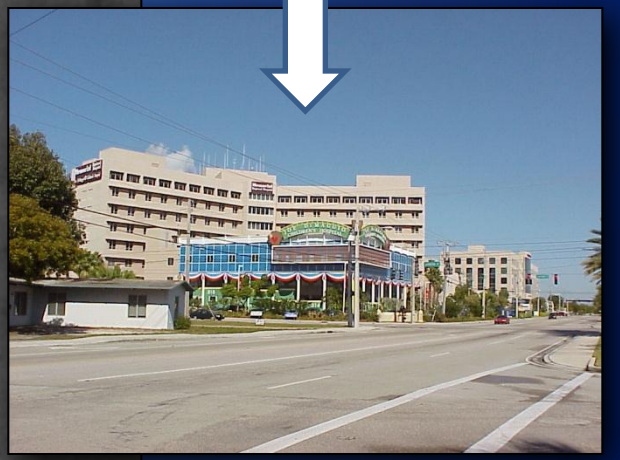
Approved by FDA in 1992

DCA Specimen

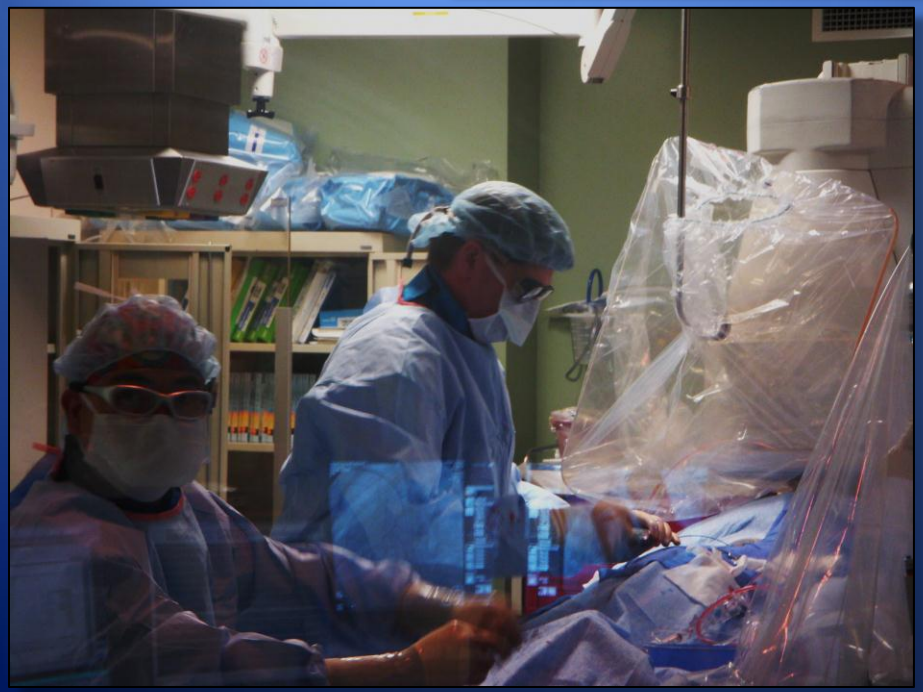

Post 7F DCA

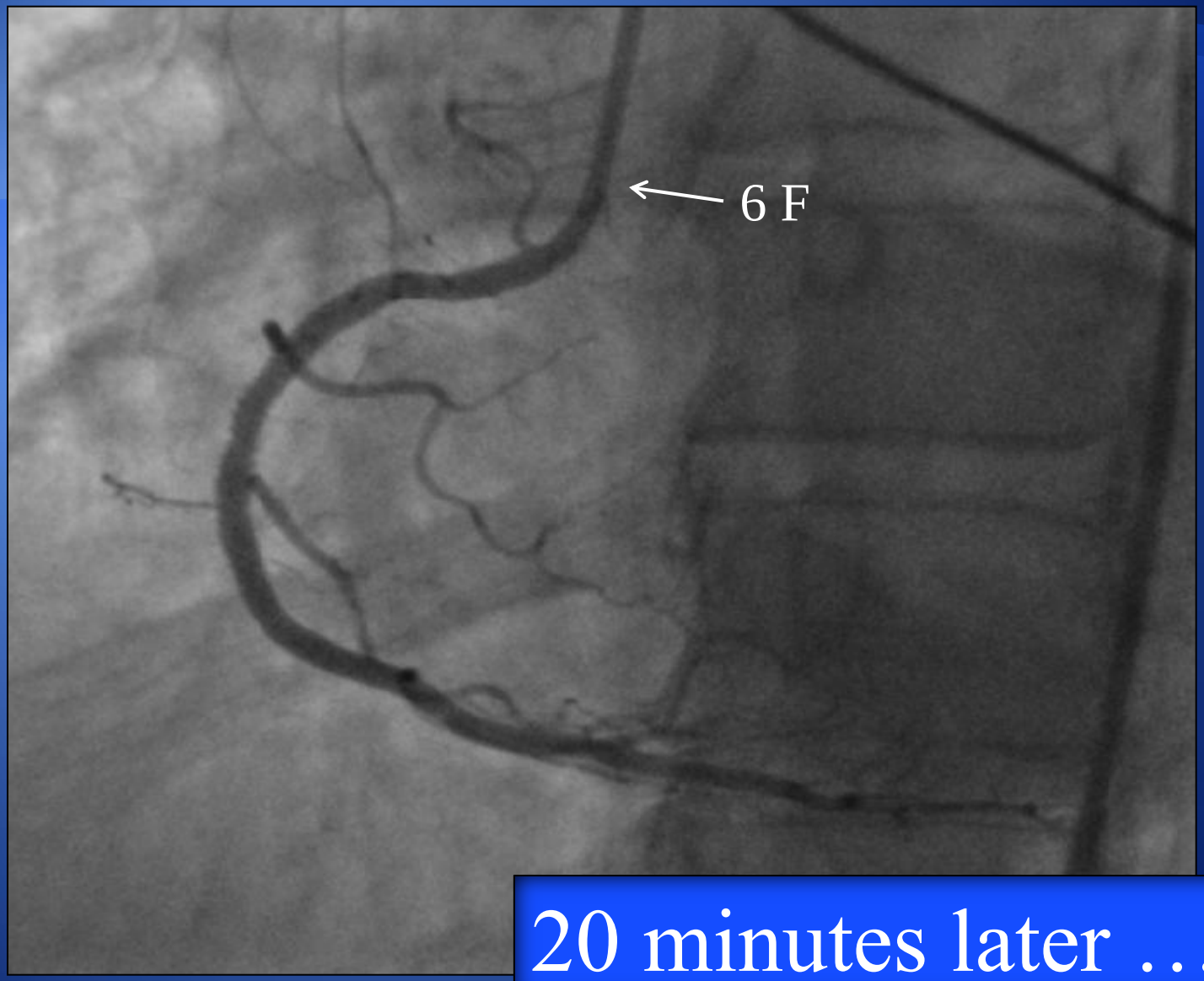
TODAY…..





73 yrs old, brought by EMS
Inferior STEMI…



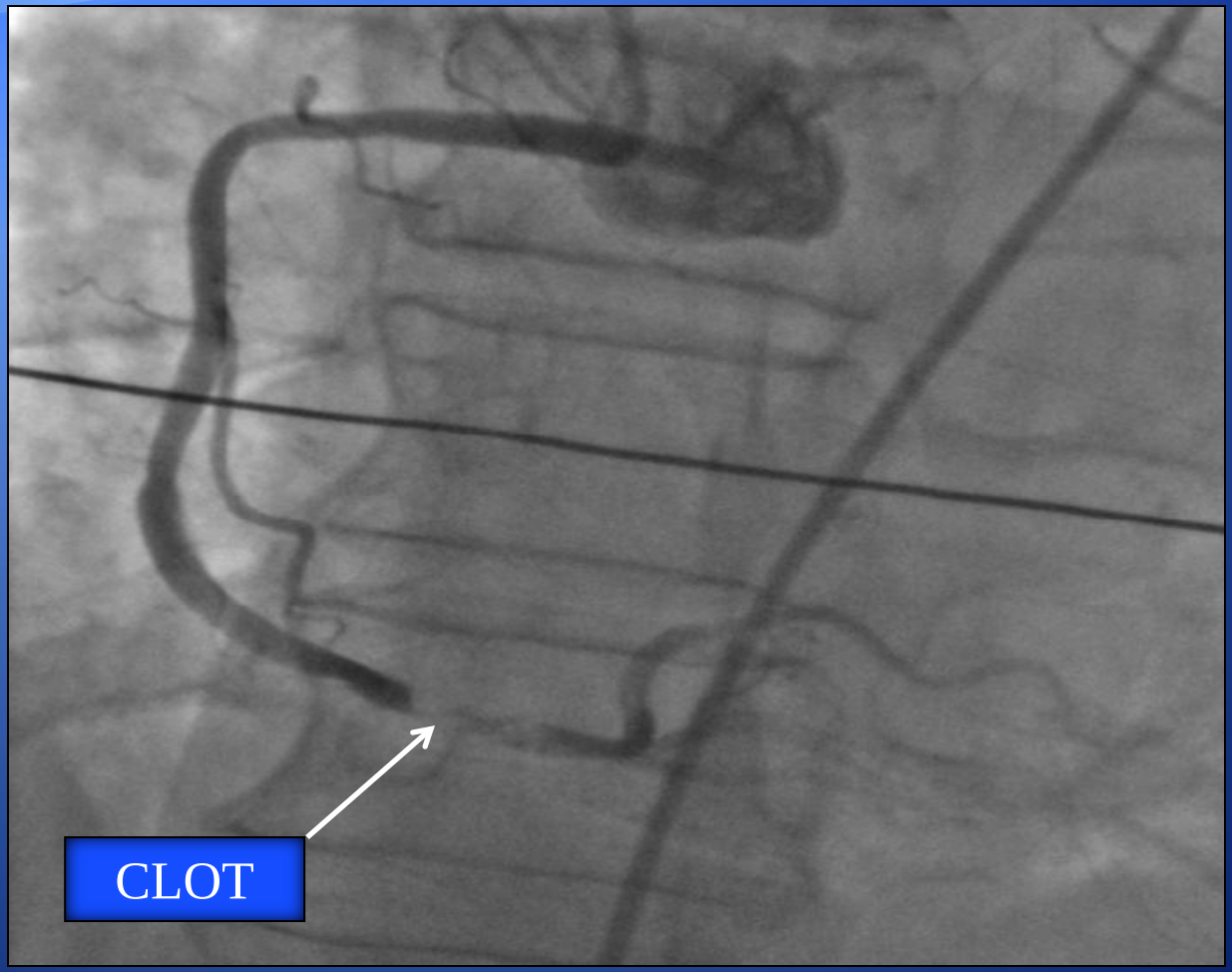


20 minutes later …..

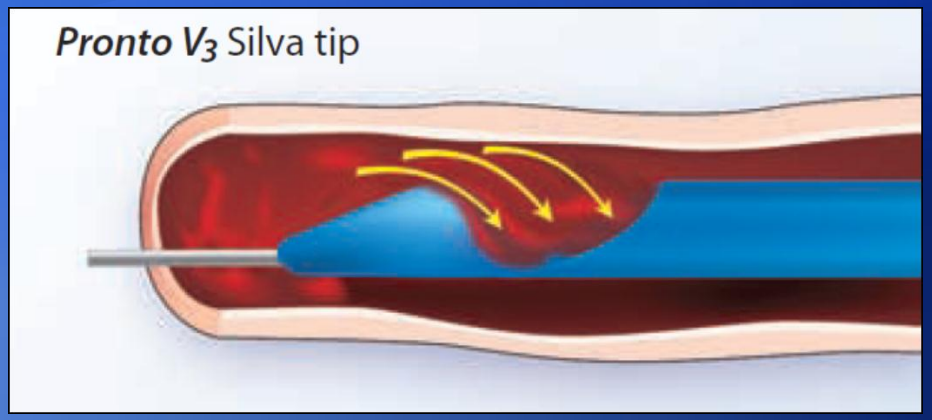
Post Interventional Call 1993

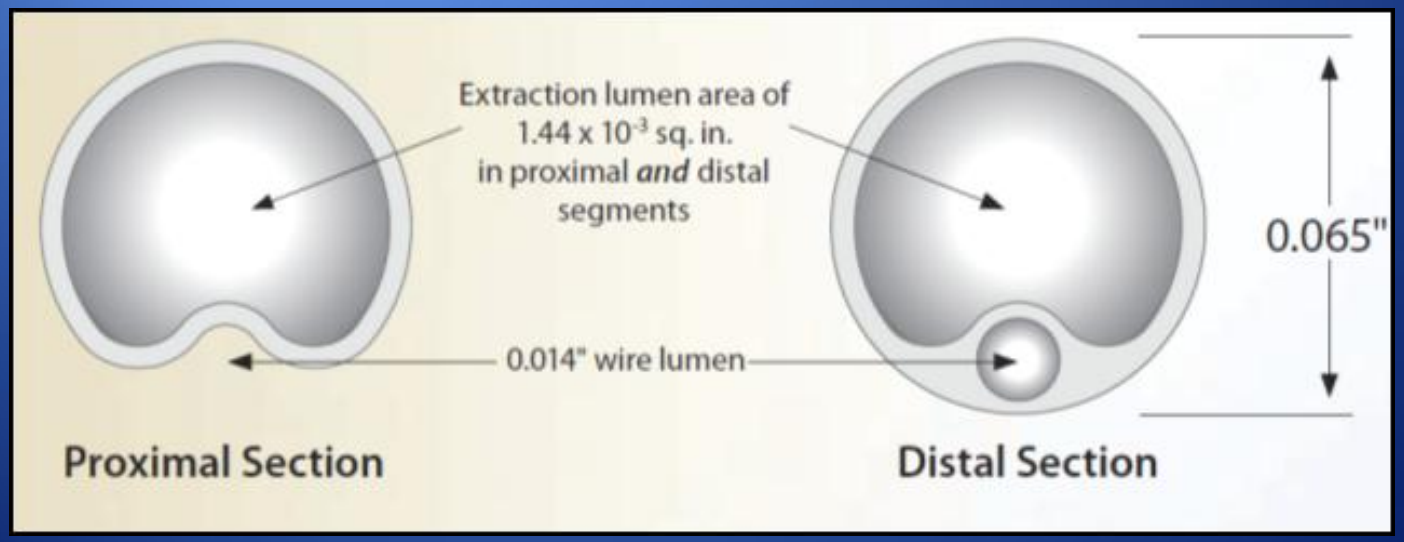
Post Call in 2011

67 yrs old, Miami-Dade EMS, D2B 43 minutes

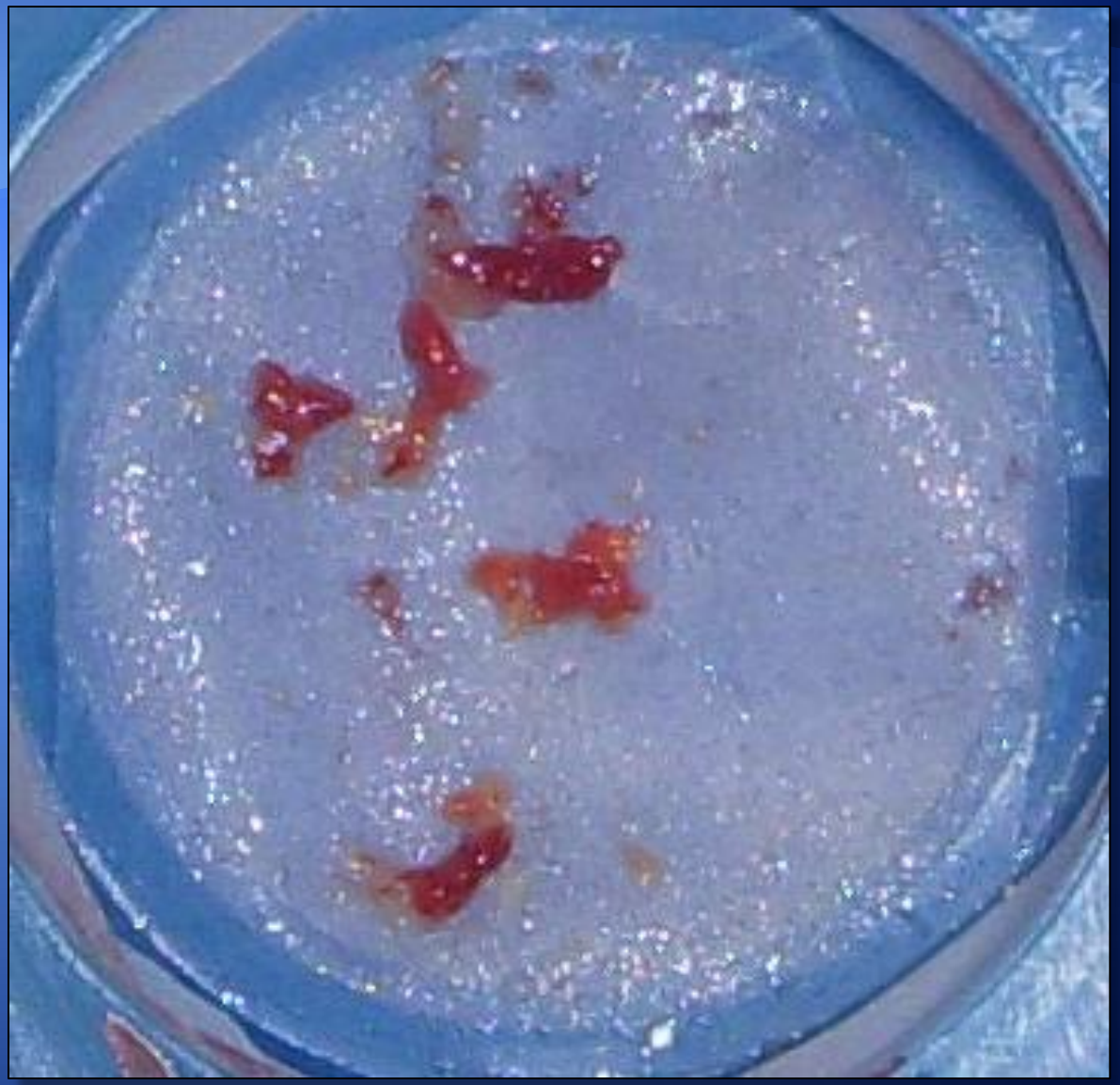


Pronto Extraction Catheter

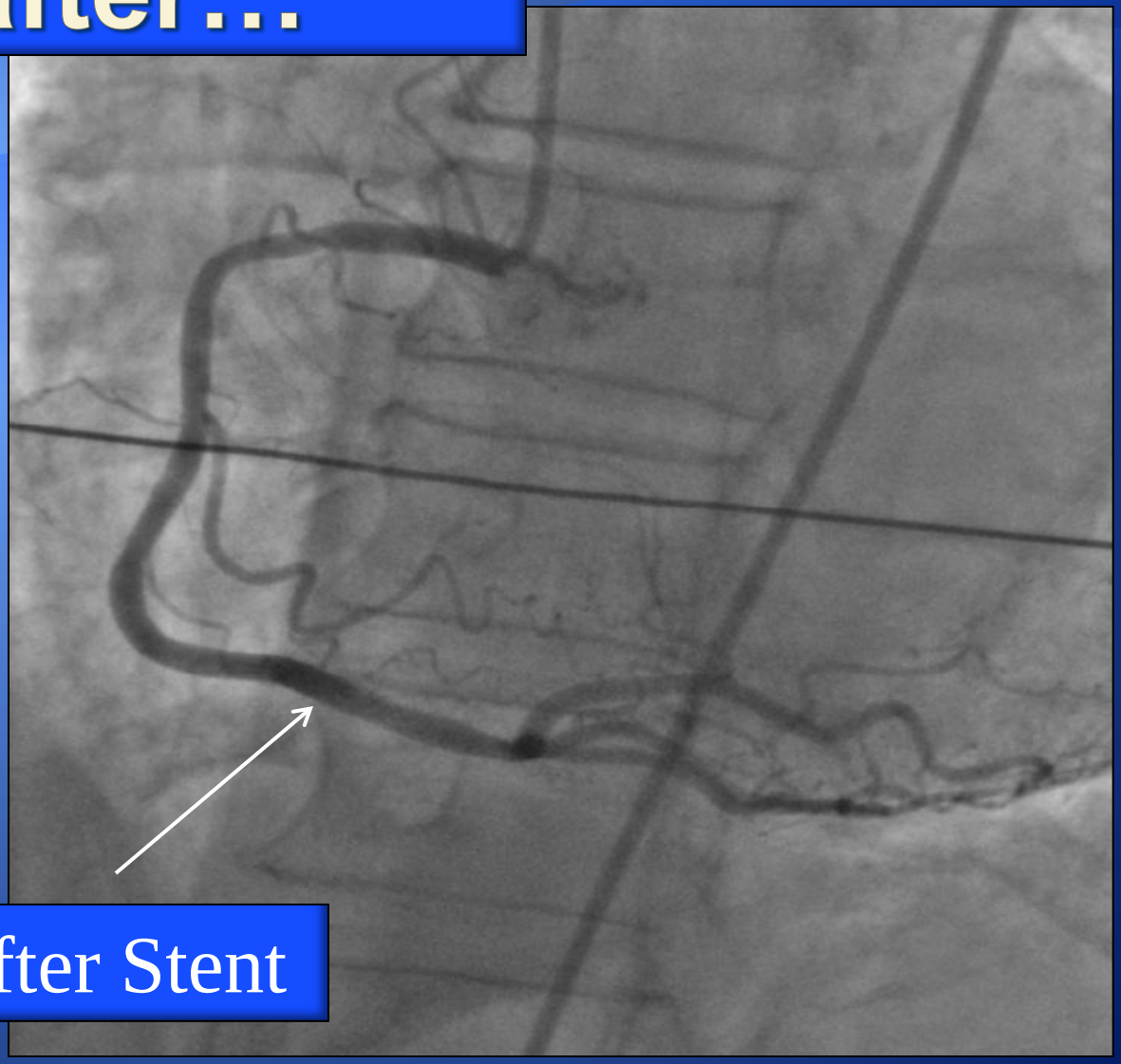




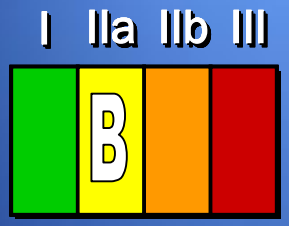
Aspirate with thrombus of different age and atherosclerotic material



Soon after…

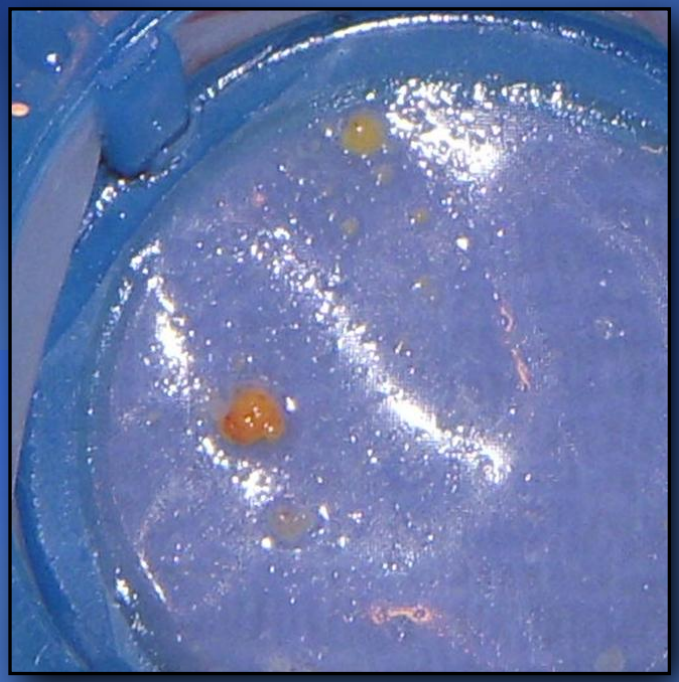


Thrombus Aspiration During PCI for STEMI

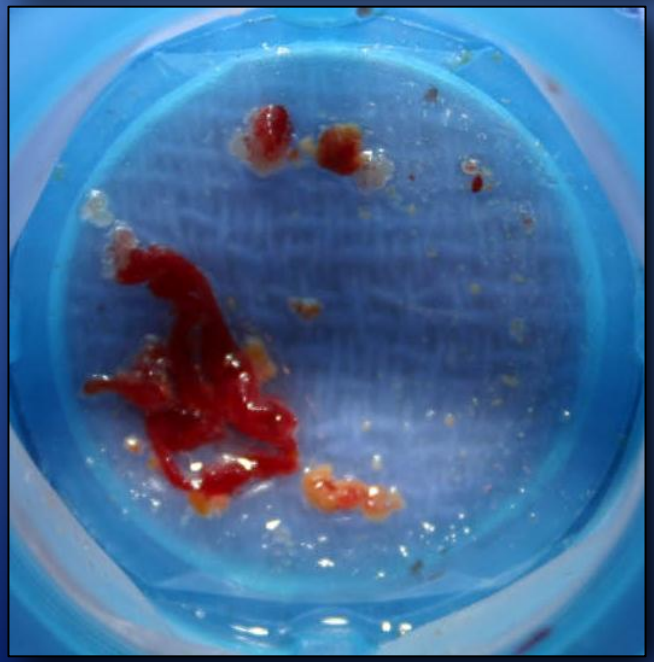


Aspiration thrombectomy is reasonable for patients undergoing primary PCI

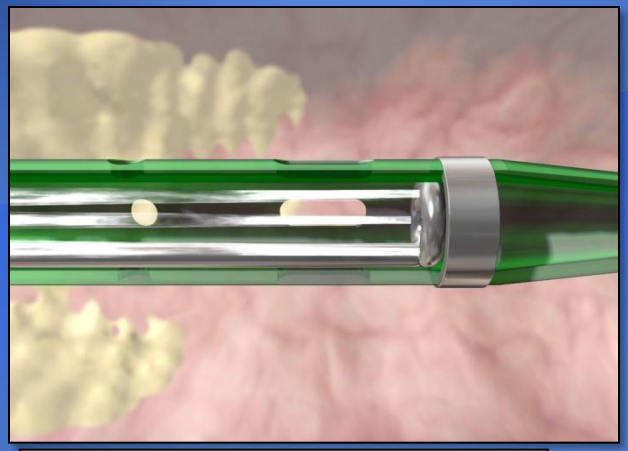
AHA/ACC 2009 STEMI/PCI Guidelines

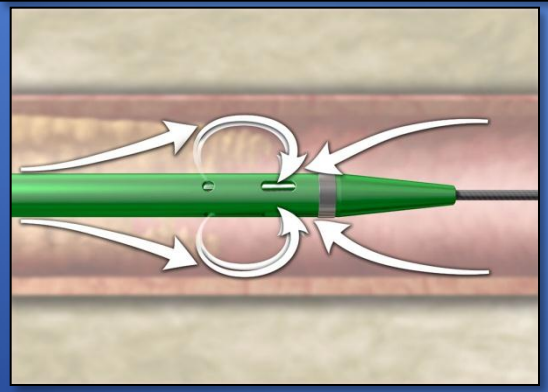


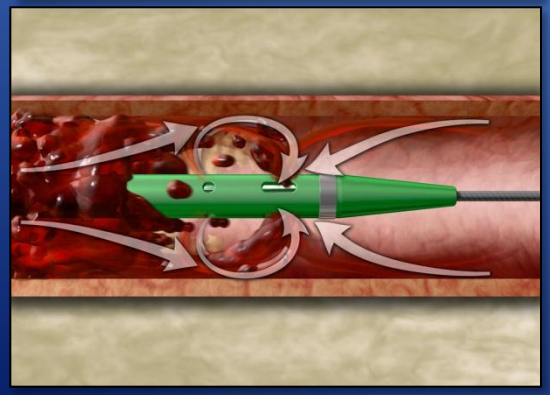

07/14/2005



AngioJet® System XMI Catheter







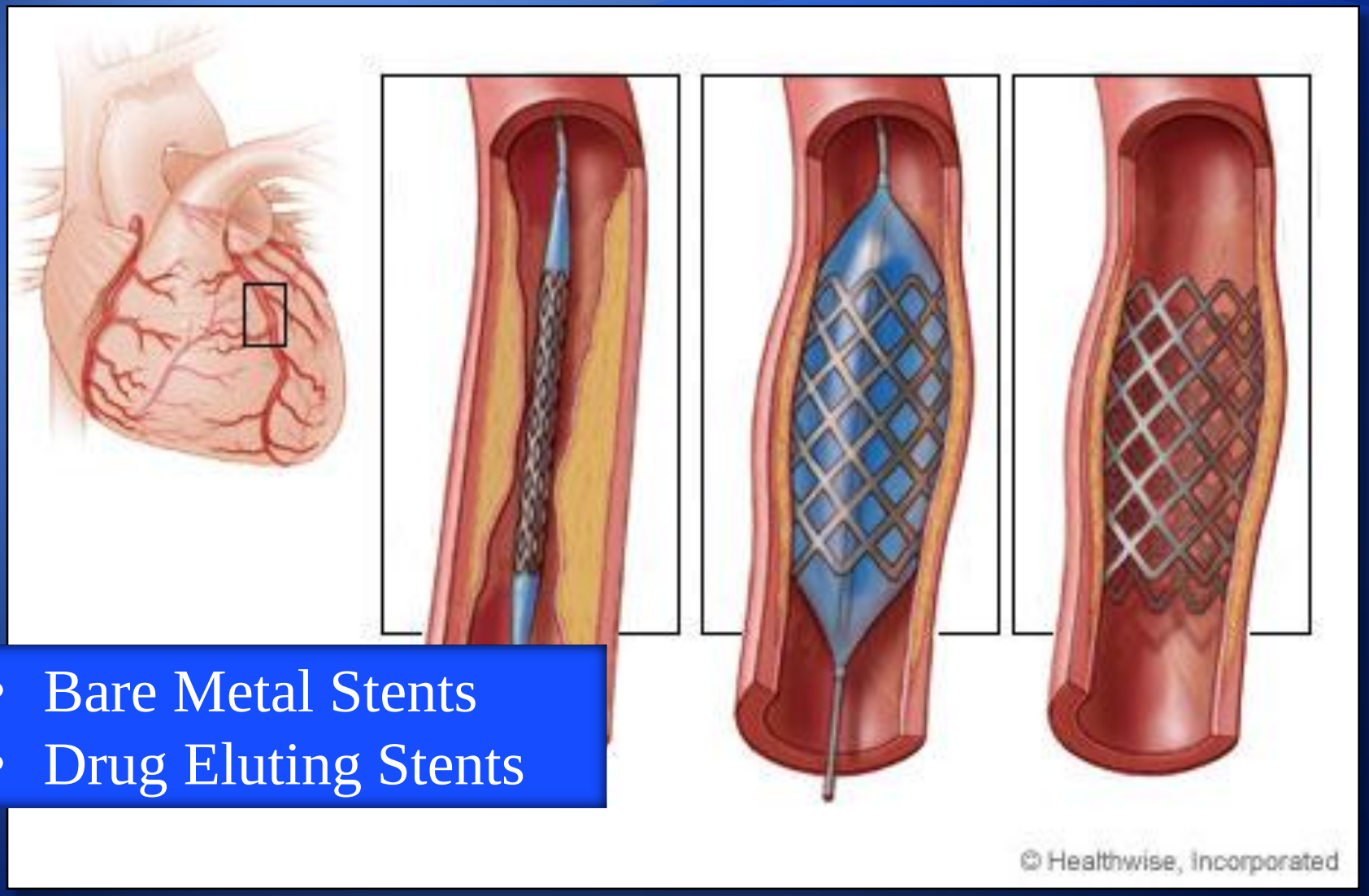
The Bernoulli Effect explains the relationship between velocity and pressure.

"Where velocity is greatest, the pressure is lowest"

Three Saline jets travel backwards at 390 mph to create a low pressure zone causing a vacuum effect.

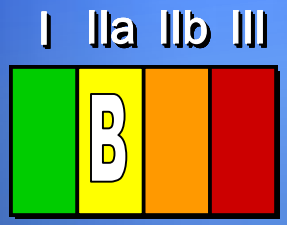
Thrombus is drawn into the catheter where it is fragmented by the jets and evacuated from the body.

Coronary Stenting



- Bare Metal Stents
- Drug Eluting Stents

Use of stents in STEMI

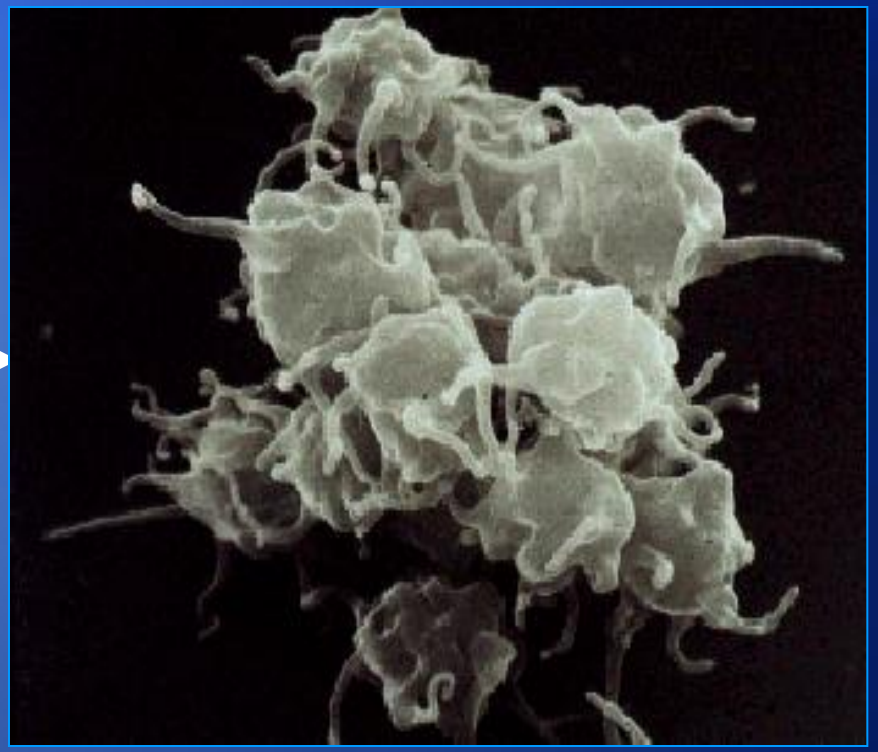


It is reasonable to use a drug-eluting stent as an alternative to a bare-metal stent for primary PCI in STEMI

* Consideration for the use of stents (DES or BMS) in STEMI should include COMPLIANCE with prolonged dual antiplatelet therapy, the BLEEDING RISK in patients on chronic oral anticoagulation, and the possibility that the patient may NEED FOR SURGERY during the ensuing year

AHA/ACC 2009 STEMI/PCI Guidelines

Platelets: Central Role

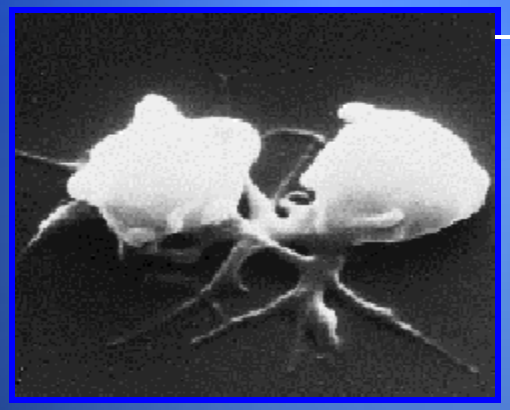


Smooth discoid shape of <u>resting</u> platelets

Spiny spheric shape of <u>activated</u> platelets

Platelets: An Hemostatic and Inflammatory Cell

Inflammatory Modulators Produced by Activated Platelets

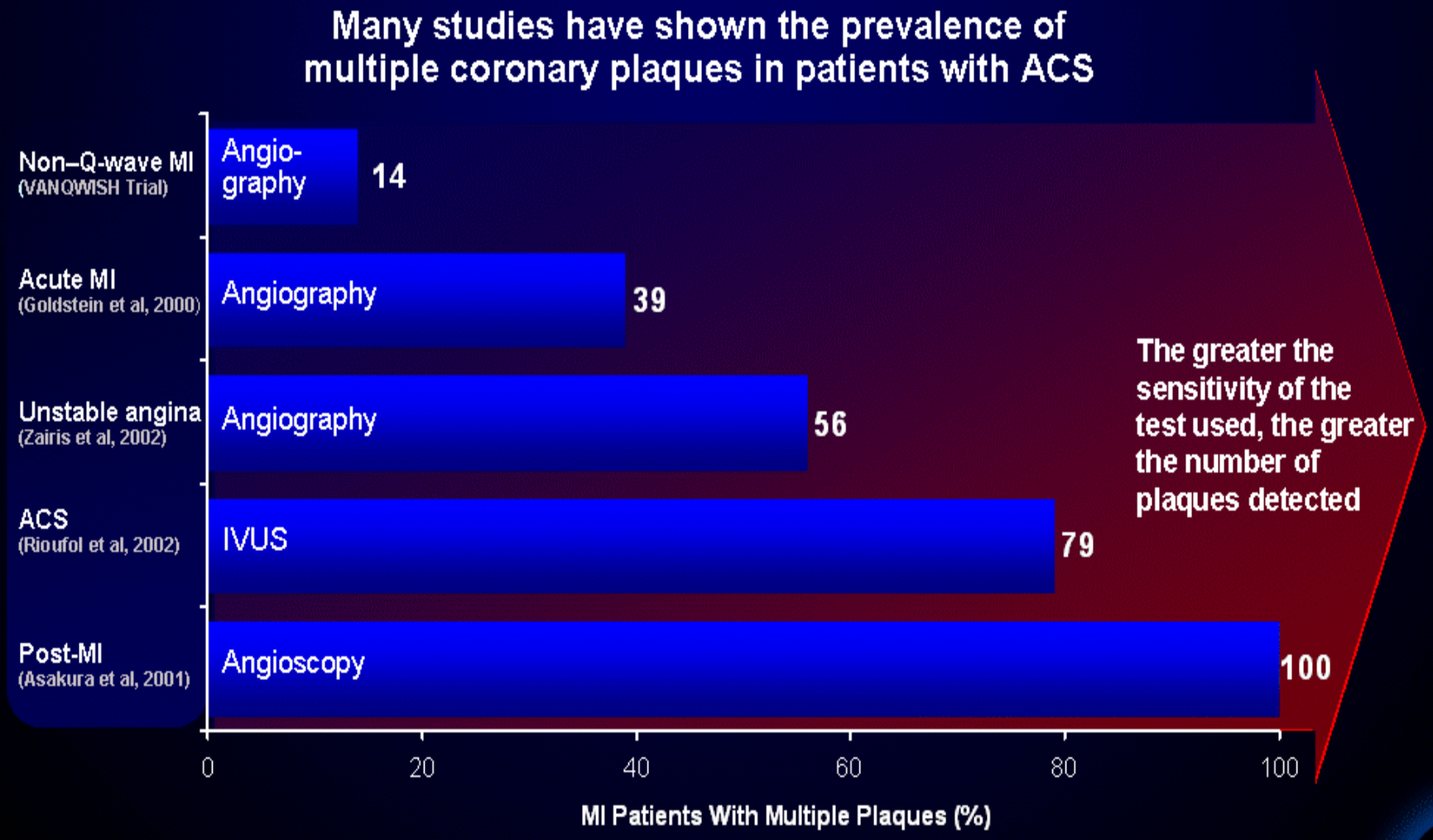


- Platelet-derived growth factor
- Platelet factor 4
- CD 154 (CD40L)
- RANTES*
- Thrombospondin
- Transforming growth factor-β
- Nitric oxide

*Regulated on activation, normal T-cell-expressed and -secreted.

Libby P et al. Circulation. 2001:103:1718-1720.

Patients With MI Have Evidence of Multiple Plaques

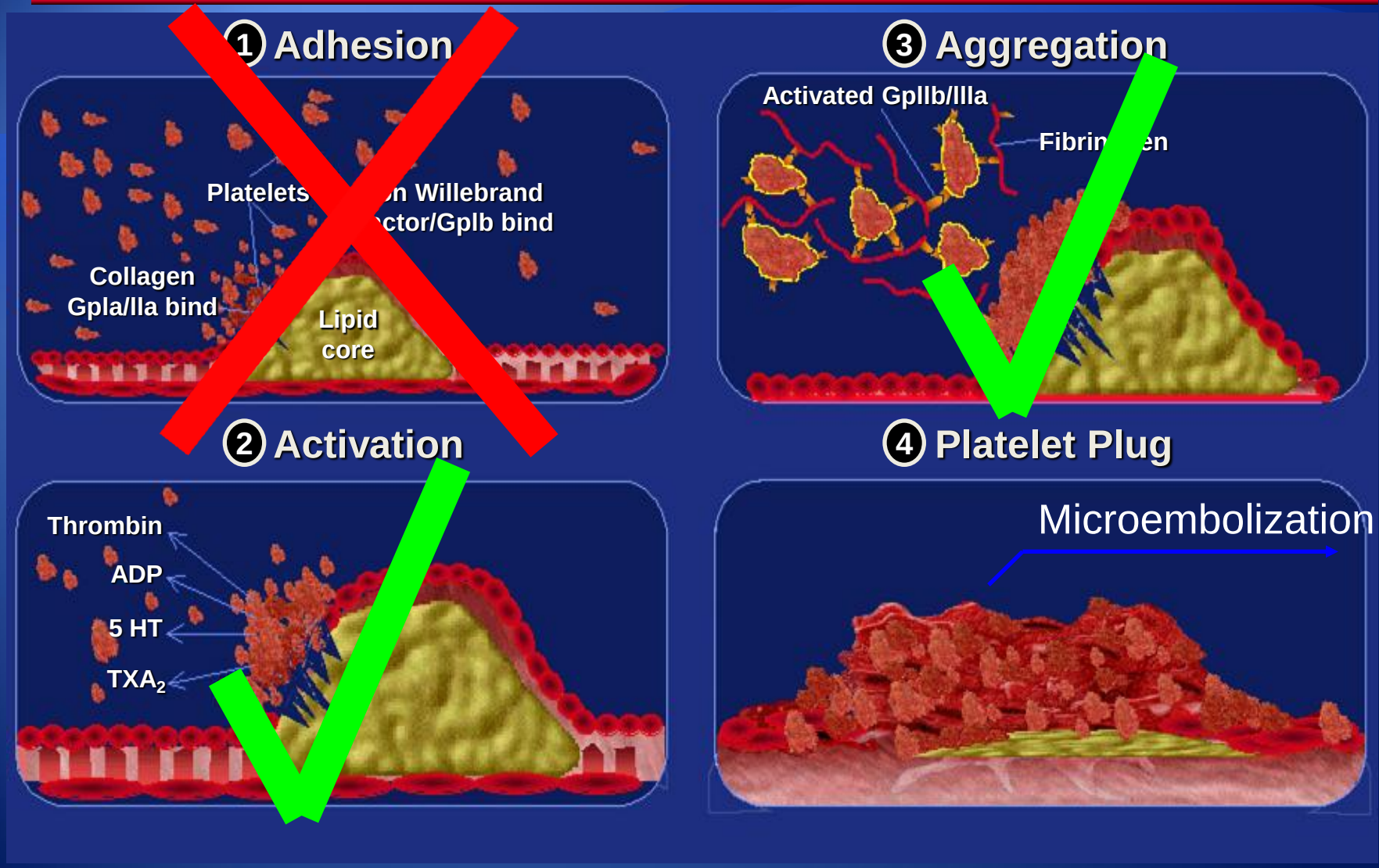


Bhatt DL. *J Invasive Cardiol*. 2003;15(suppl B):3B-10B.

ACS/PCI:

High Platelet Reactivity State

Acute Coronary Syndrome: Role of Platelets



DRUG THERAPY

UPDATE

Antiplatelet Therapy in ACS

Aspirin

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine

Clopidogrel

Prasugrel

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine

Clopidogrel

Prasugrel

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine

Clopidogrel

Prasugrel

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel

Prasugrel

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel: Approved in 1997

Prasugrel

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel: Approved in 1997

Prasugrel: Approved in 2009

-Non-thienopyridine: Ticagrelor

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel: Approved in 1997

Prasugrel: Approved in 2009

-Non-thienopyridine: Ticagrelor: Approved July 2011

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel: Approved in 1997

Prasugrel: Approved in 2009

-Non-thienopyridine: Ticagrelor: Approved July 2011

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Approved in 1996

Antiplatelet Therapy in ACS

Aspirin: Approved by FDA since 1985 for ACS

P2Y12 Inhibitors:

-Thienopyridines:

Ticlopidine: Approved in 1991 for PCI

Clopidogrel: Approved in 1997

Prasugrel: Approved in 2009

-Non-thienopyridine: Ticagrelor: Approved July 2011

GpIIb/IIIa Inhibitors: Reopro/Integrelin/Aggrastat

Approved in 1998

Platelet Aggregation: VerifyNow™

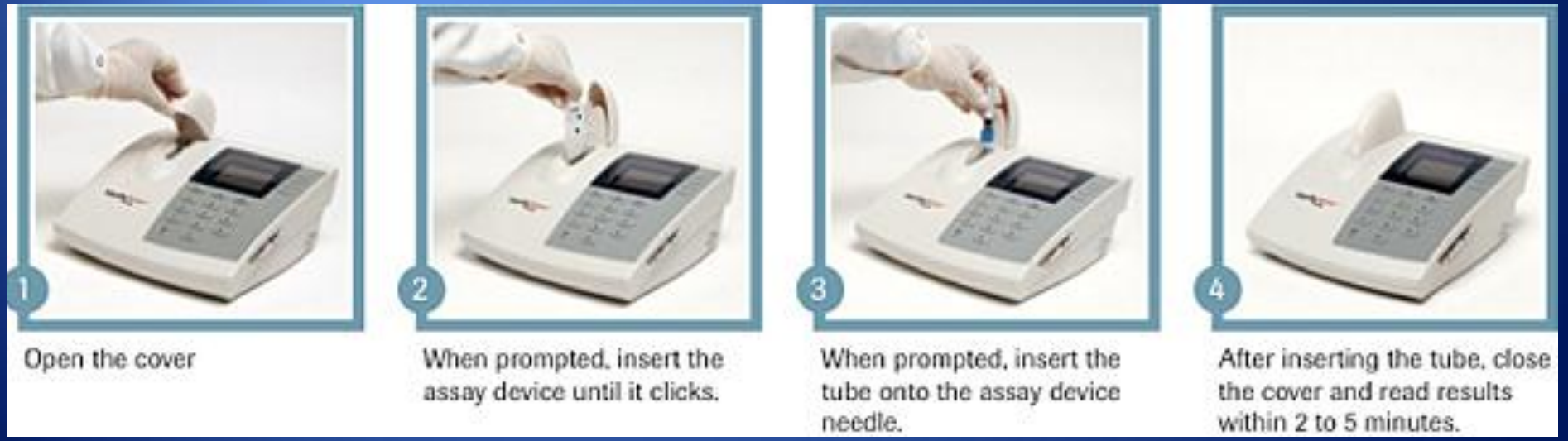
ASPIRIN

P2Y12

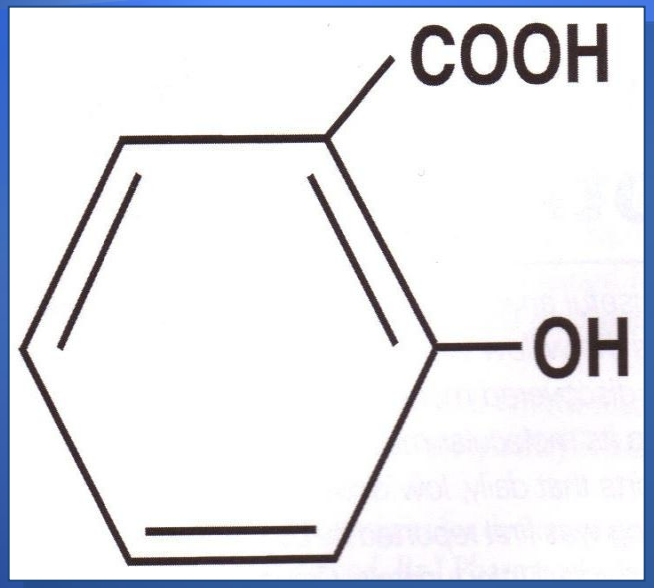
IIb/IIIa Inh.

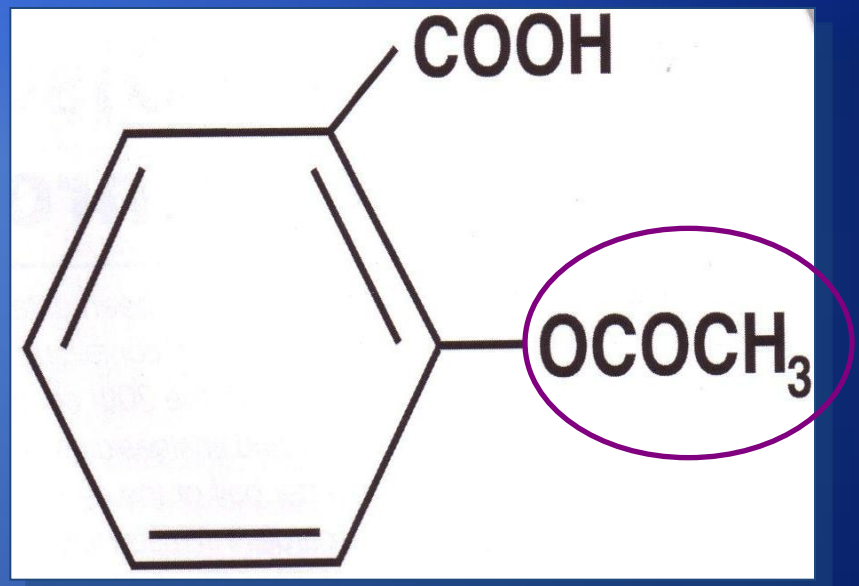
Easy to Use

- Whole blood, small sample volume.
- No sample preparation
- Results in 2-5 minutes
- Point of care device: CATH LAB AND CENTRAL LAB



From Willow bark and other plants



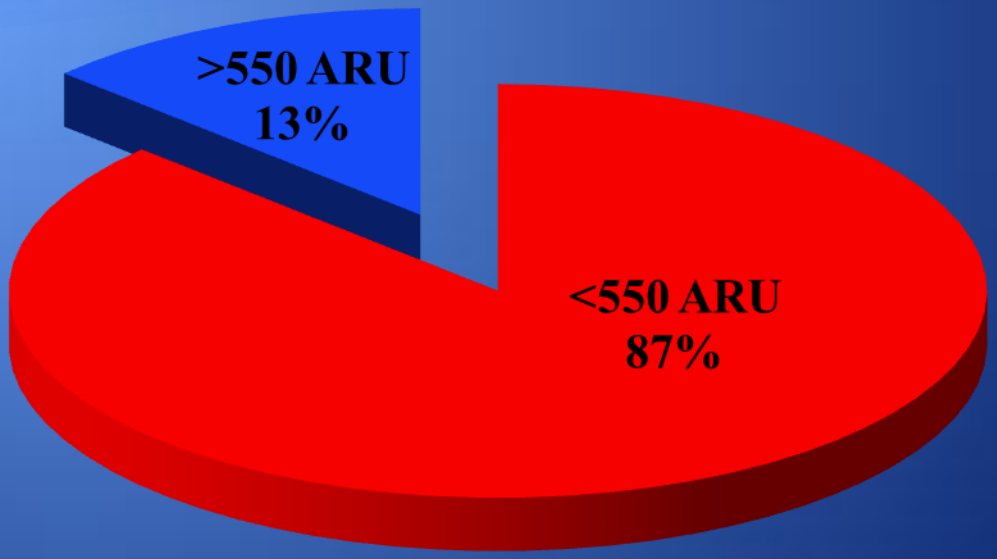


SALICYLIC ACID ⟶ **ACETYLSALICYLIC ACID (ASPIRIN)**

Bayer Lab in 1897

VerifyNow Aspirin Platelet Function Test

MRH Mar - Apr 2009 (N=94)



CLOPIDOGREL (PLAVIX)

1. *Going generic soon!*

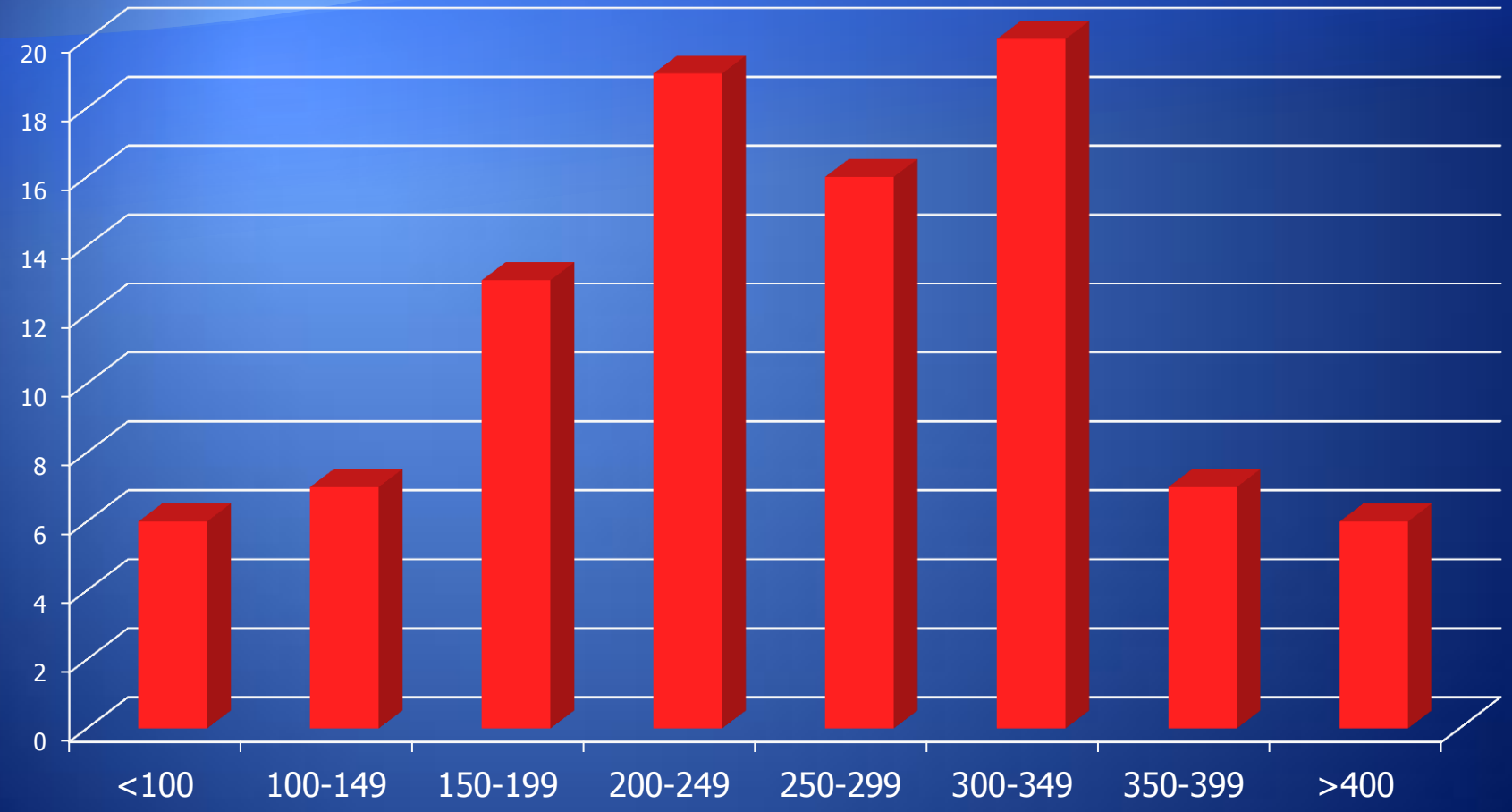
   BMS / SA will loose the exclusivity to market Plavix on May 17, 2012

2. *Variability of Effect*
3. *Double dose*

Bristol-Myers Squibb Company
sanofi aventis

P2Y12 Reactivity on Clopidogrel

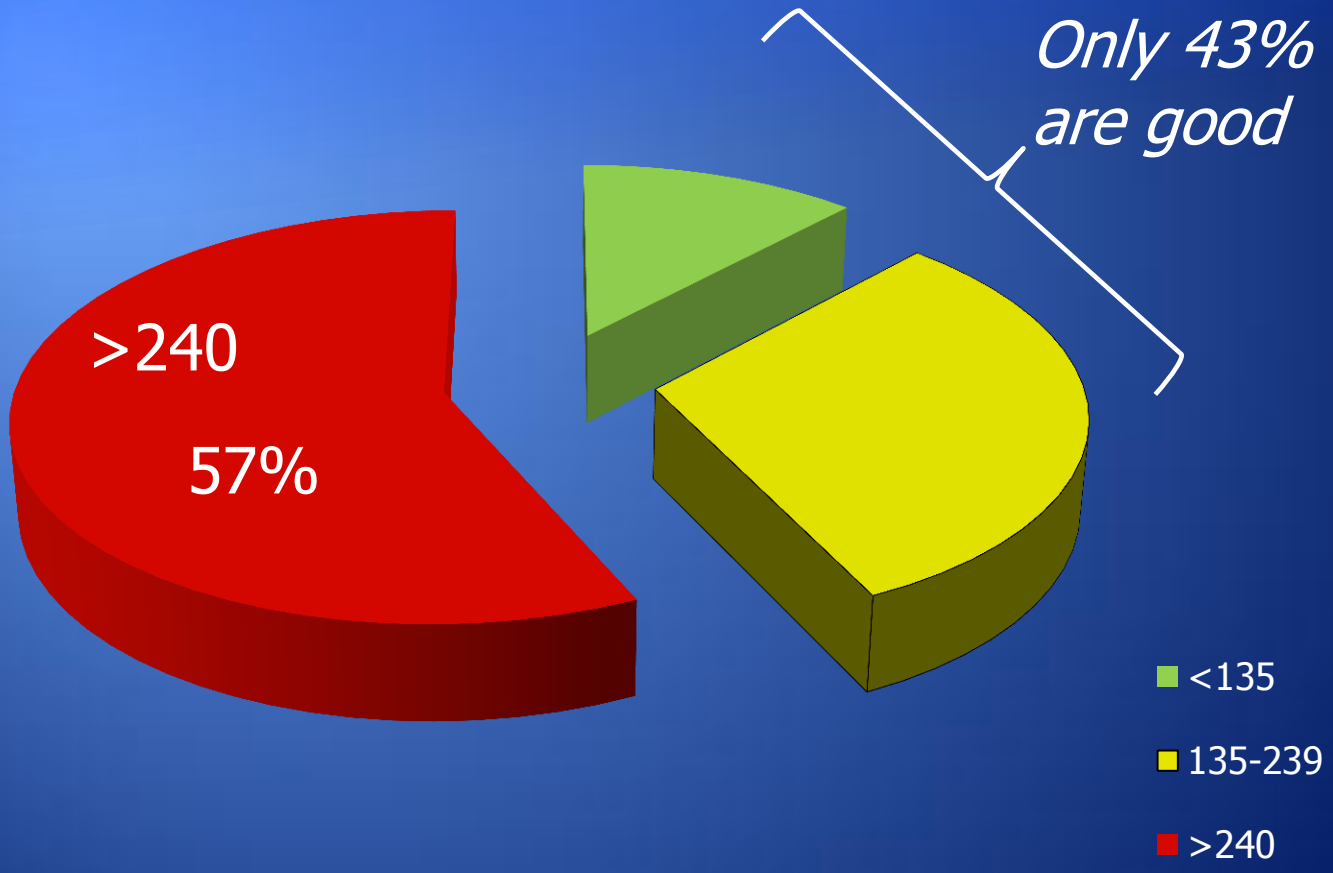
MRH, Mar-Apr 2009, n=94



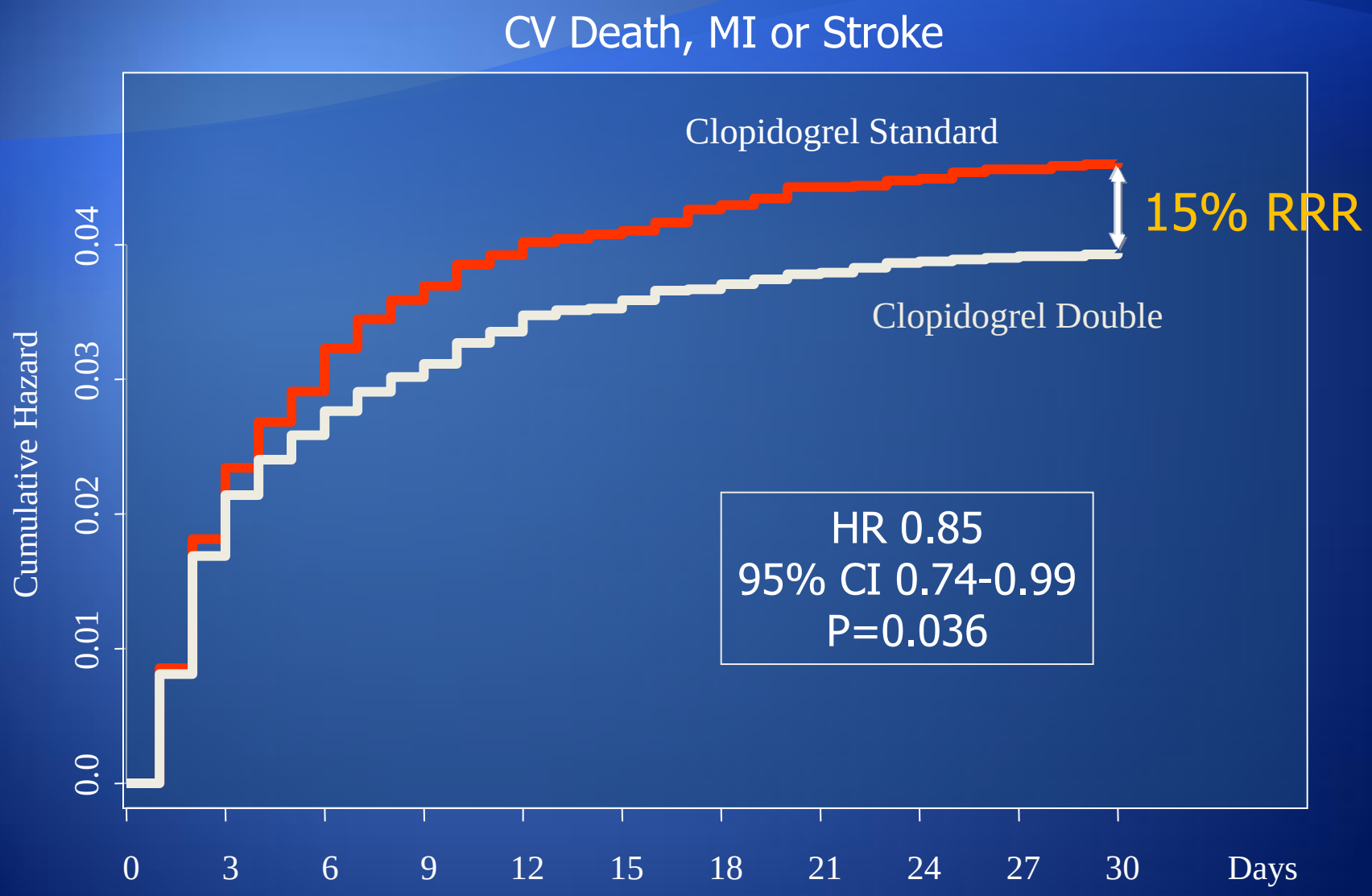
PRU using Verify*Now*

VerifyNow P2Y12 Inhibition

PRU GOAL < 240

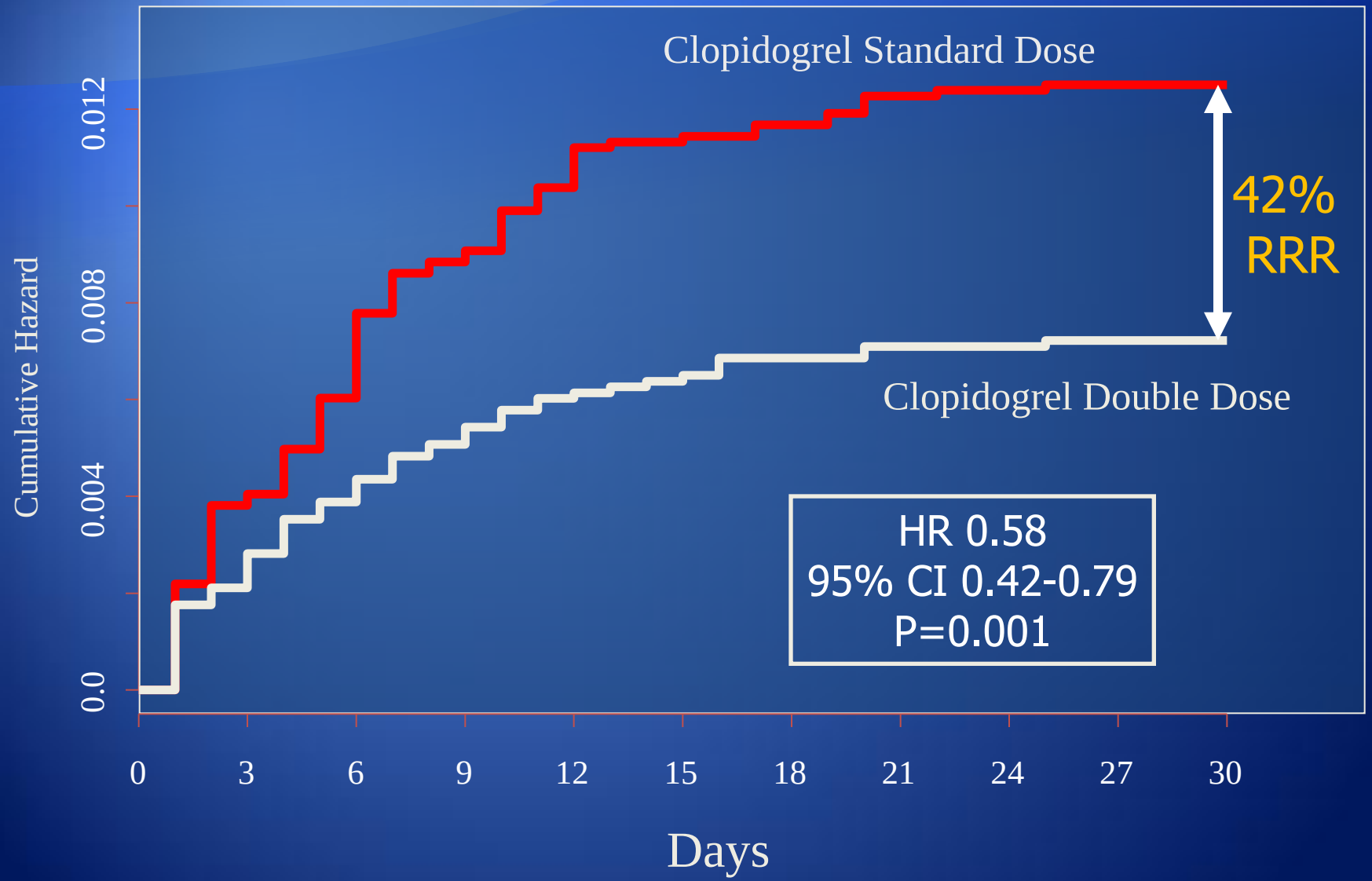


Clopidogrel: Double vs Standard Dose Primary Outcome: PCI Patients



The CURRENT-OASIS. N Engl J Med 2010; 363:930-942

Clopidogrel: Double vs Standard Dose
Definite Stent Thrombosis (Angio confirmed)

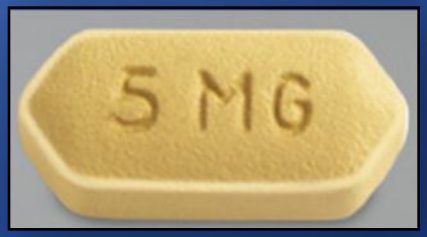


PRASUGREL (EFFIENT)

1. A Cath Lab Drug
2. Efficacy and safety (TRITON)

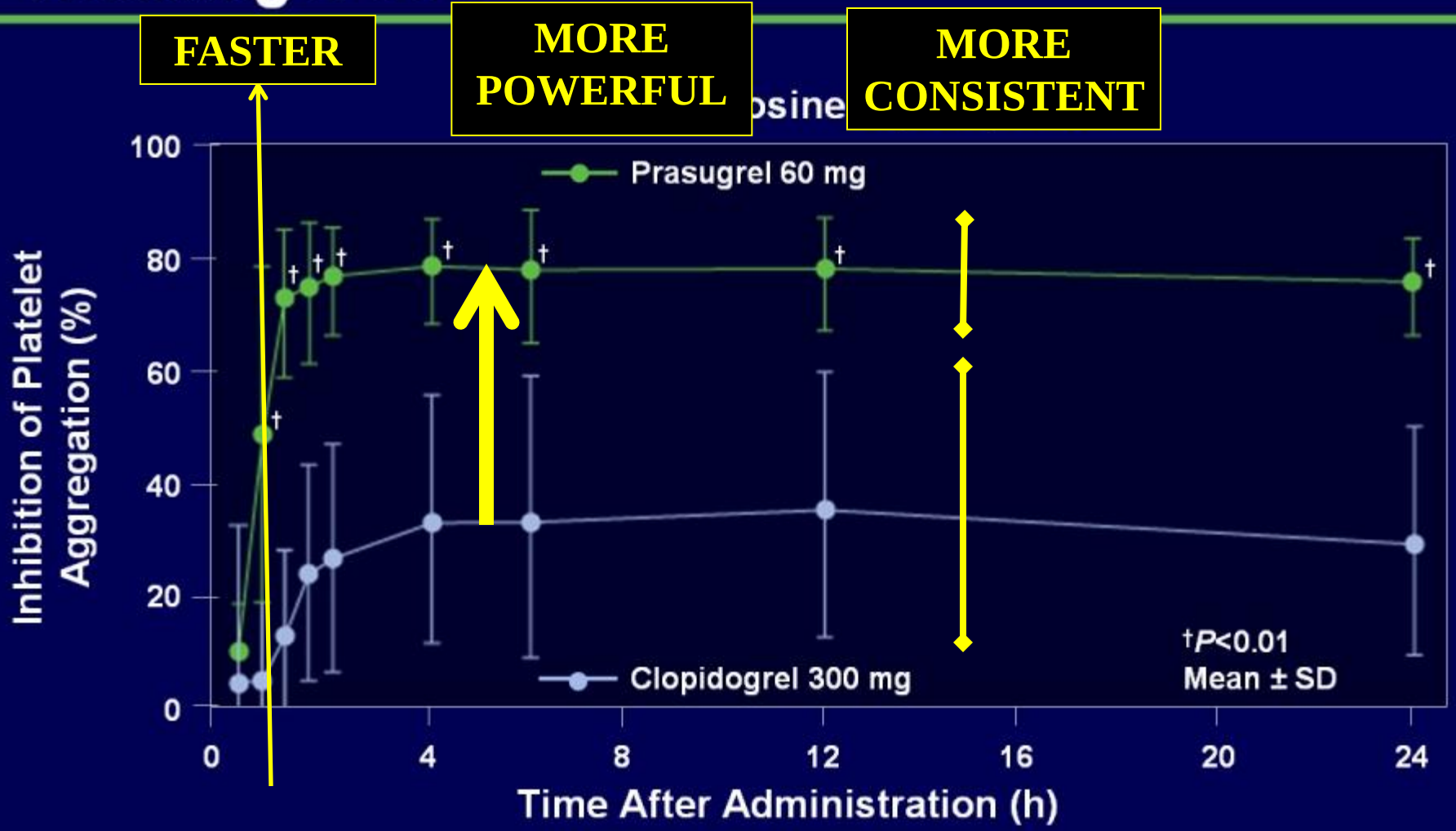
DOSE:

DOSE FOR PATIENTS ≤60 Kg



Daiichi-Sankyo Lilly

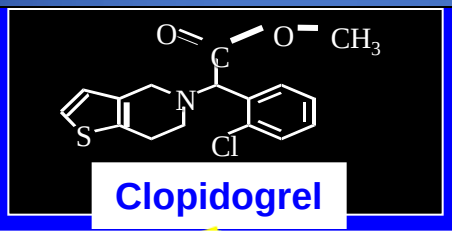
IPA: Prasugrel and Clopidogrel Loading Dose



The relationship between IPA and clinical activity has not been established.

1. Brandt JT et al. *Am Heart J*. 2007;153:66.e9-16.
2. Effient Full Prescribing Information.

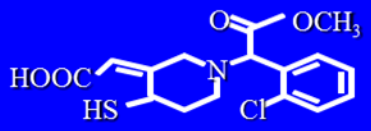
Thienopyridines: Equipotent Active Metabolite



Clopidogrel

85% I
Metal

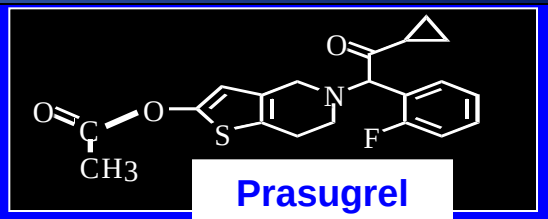
RESPONSE VARIABILITY



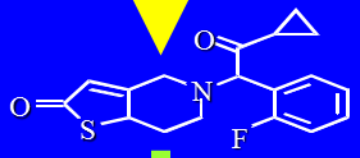
Active Metabolite

Pro-drugs

Hydrolysis (Esterases)



Prasugrel



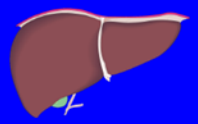
CYPs:

3A

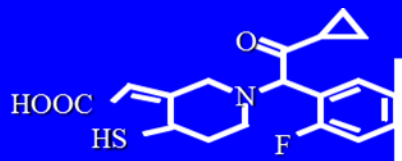
2B6

2C9

2C19



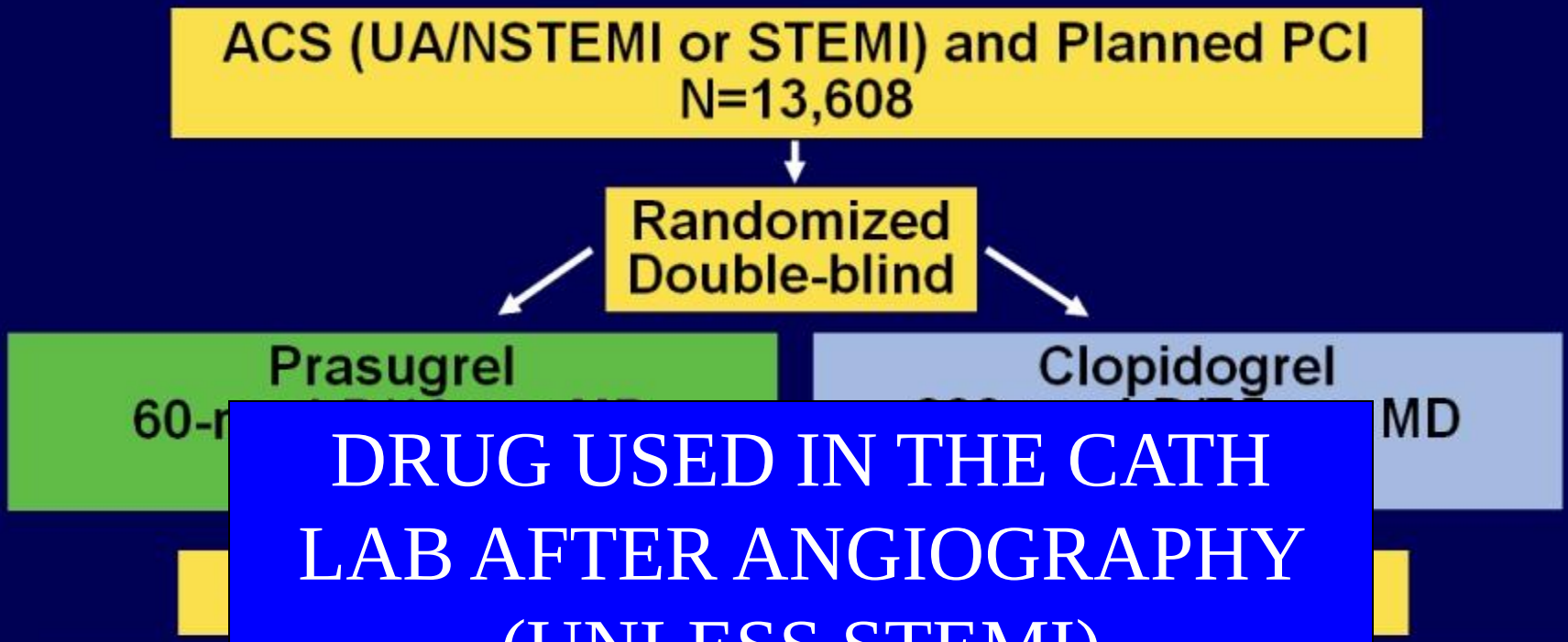
Oxidation (Cytochrome P450)



Active Metabolite

Mega JL, NEJM 2008 and Mega JL Circ 2009

TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN With Prasugrel (TRITON)-TIMI 38



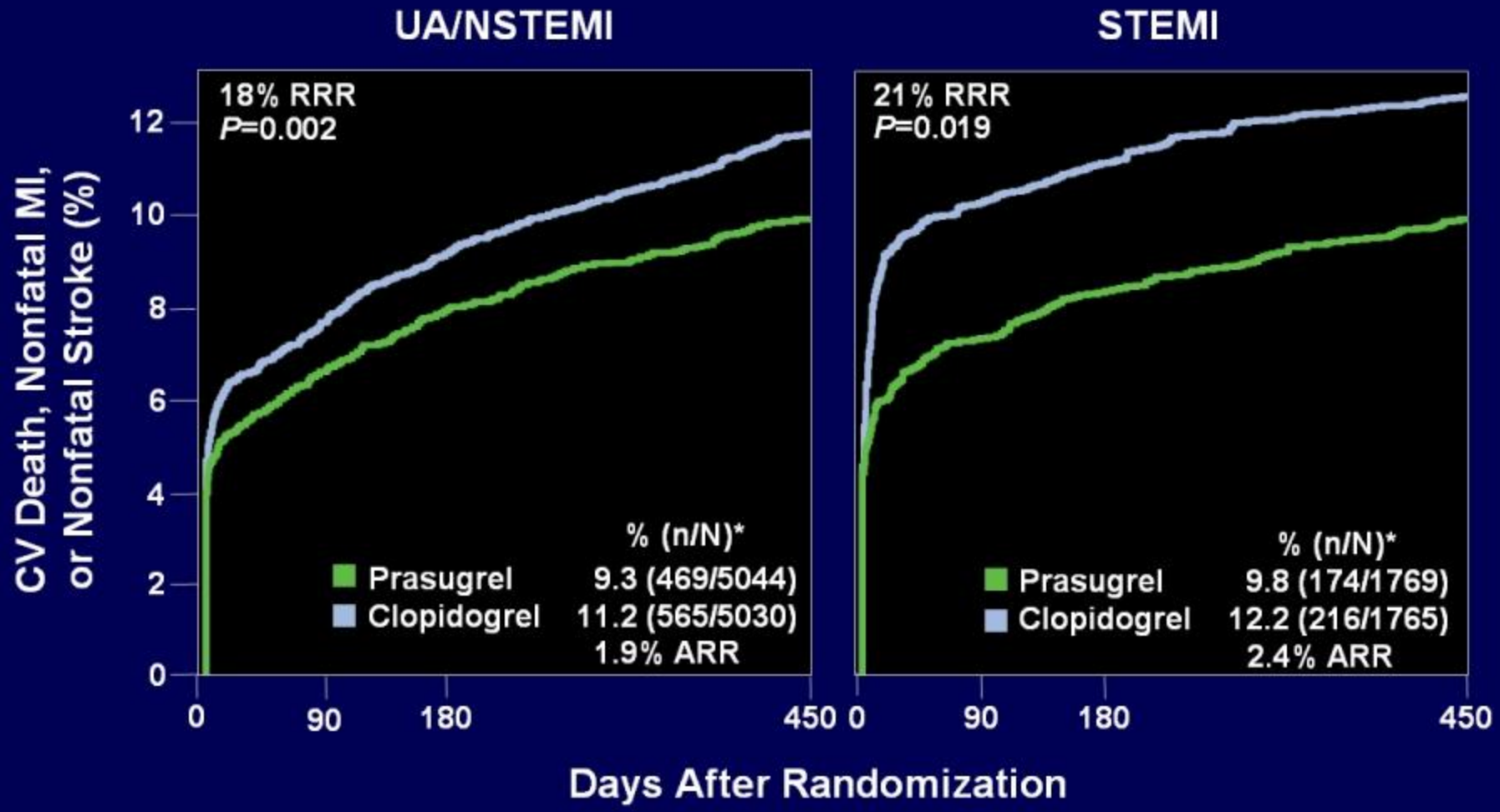
DRUG USED IN THE CATH LAB AFTER ANGIOGRAPHY (UNLESS STEMI)

- Prim
  - Composite CV death, nonfatal MI, or nonfatal stroke
- Safety endpoints:
  - TIMI major or minor bleeding

Administration of the clopidogrel LD in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS.

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

Primary Endpoint Events at End of Trial: UA/NSTEMI and STEMI Patients

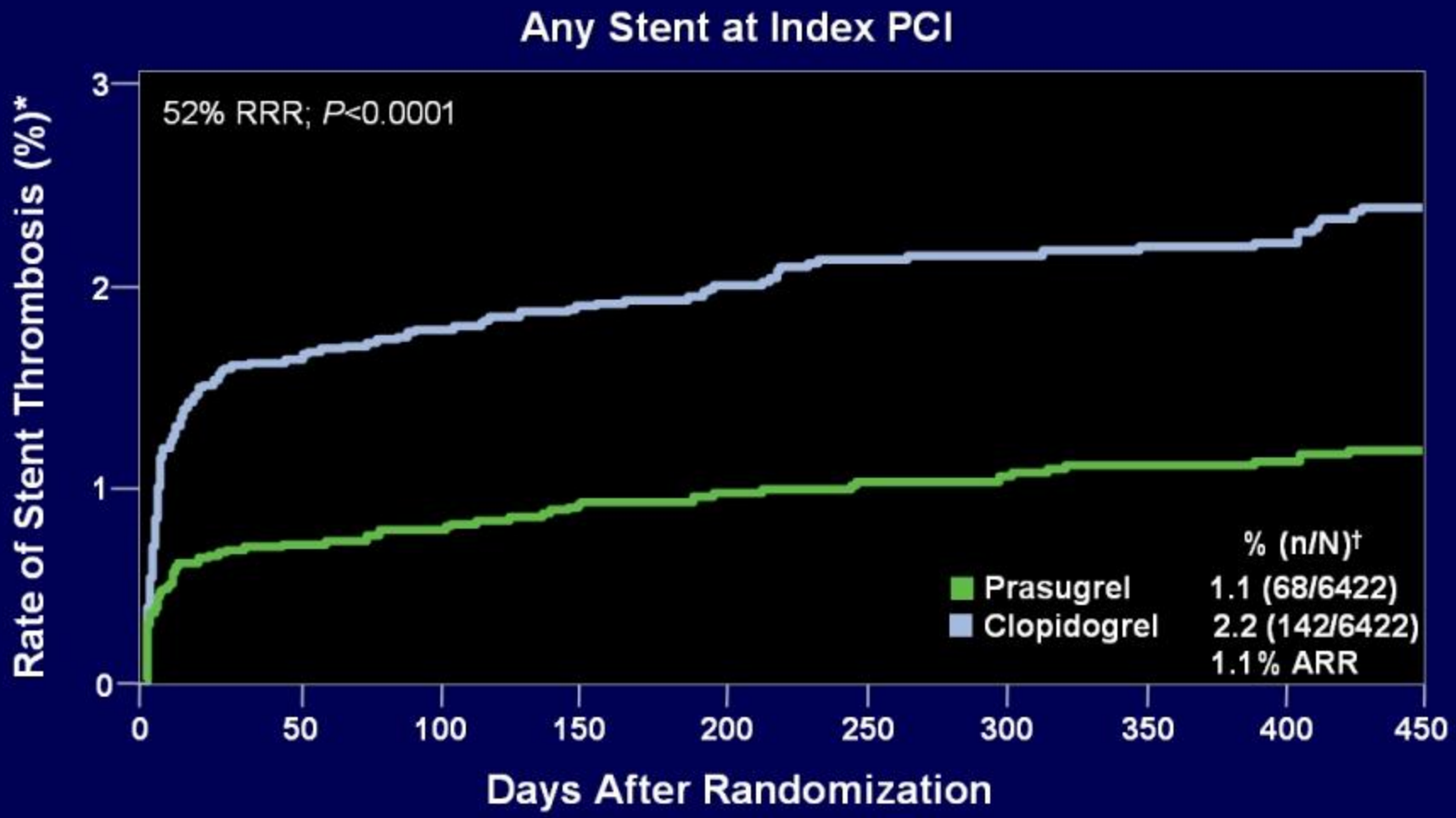


*Observed data.

1. Effient Full Prescribing Information.
2. Data on file: #EFF20091204a. DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Rates of Stent Thrombosis Over Time: Prasugrel Compared With Clopidogrel



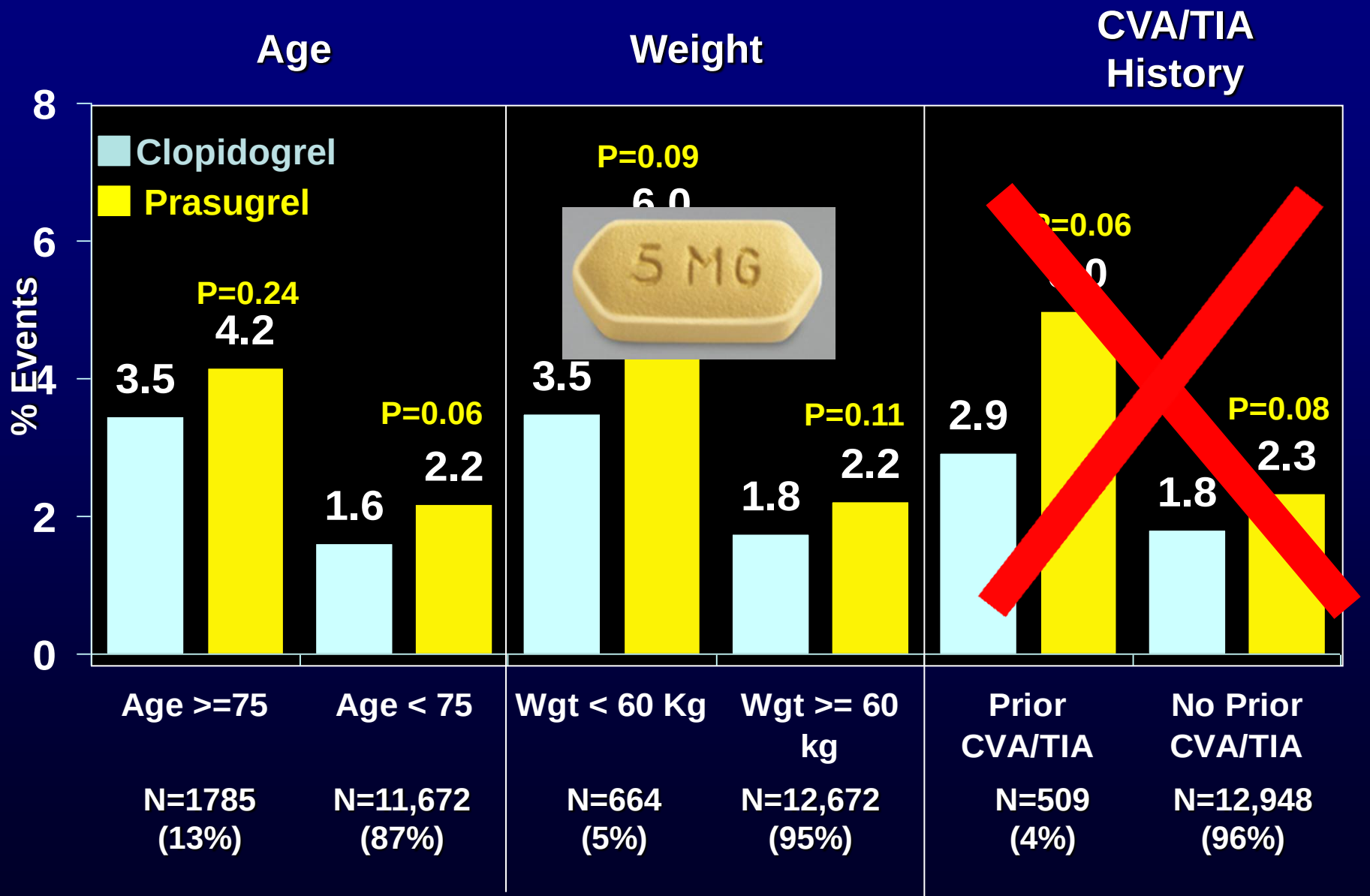
*Stent thrombosis defined as Academic Research Consortium definite or probable. †Observed data.

1. Wiviott et al. *Lancet*. 2008;371(9621):1353-1363.
2. Data on file: #EFF20091204b. DSI/Lilly.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

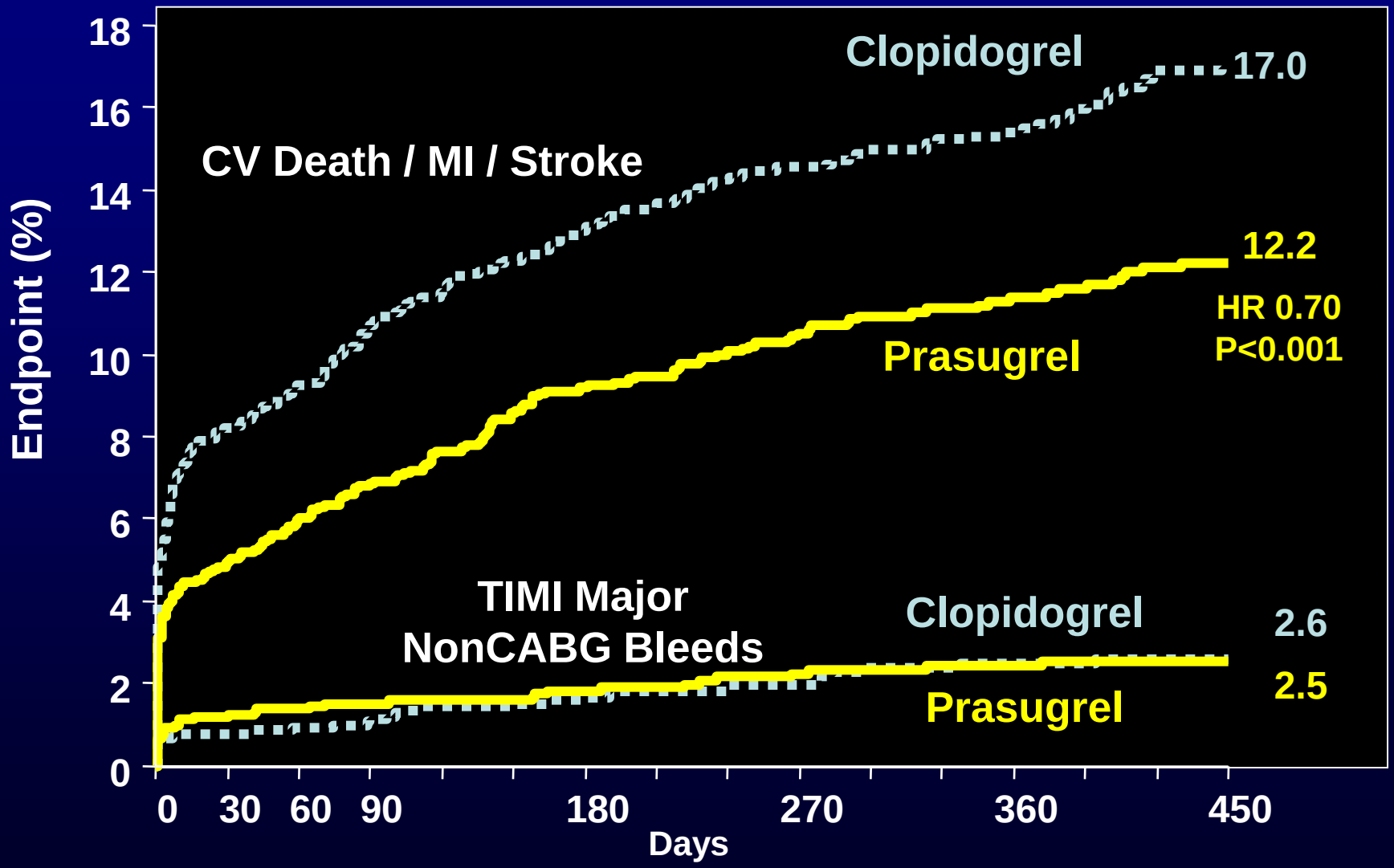
TRITON TIMI-38

TIMI Major Non-CABG Bleeds
Subgroups

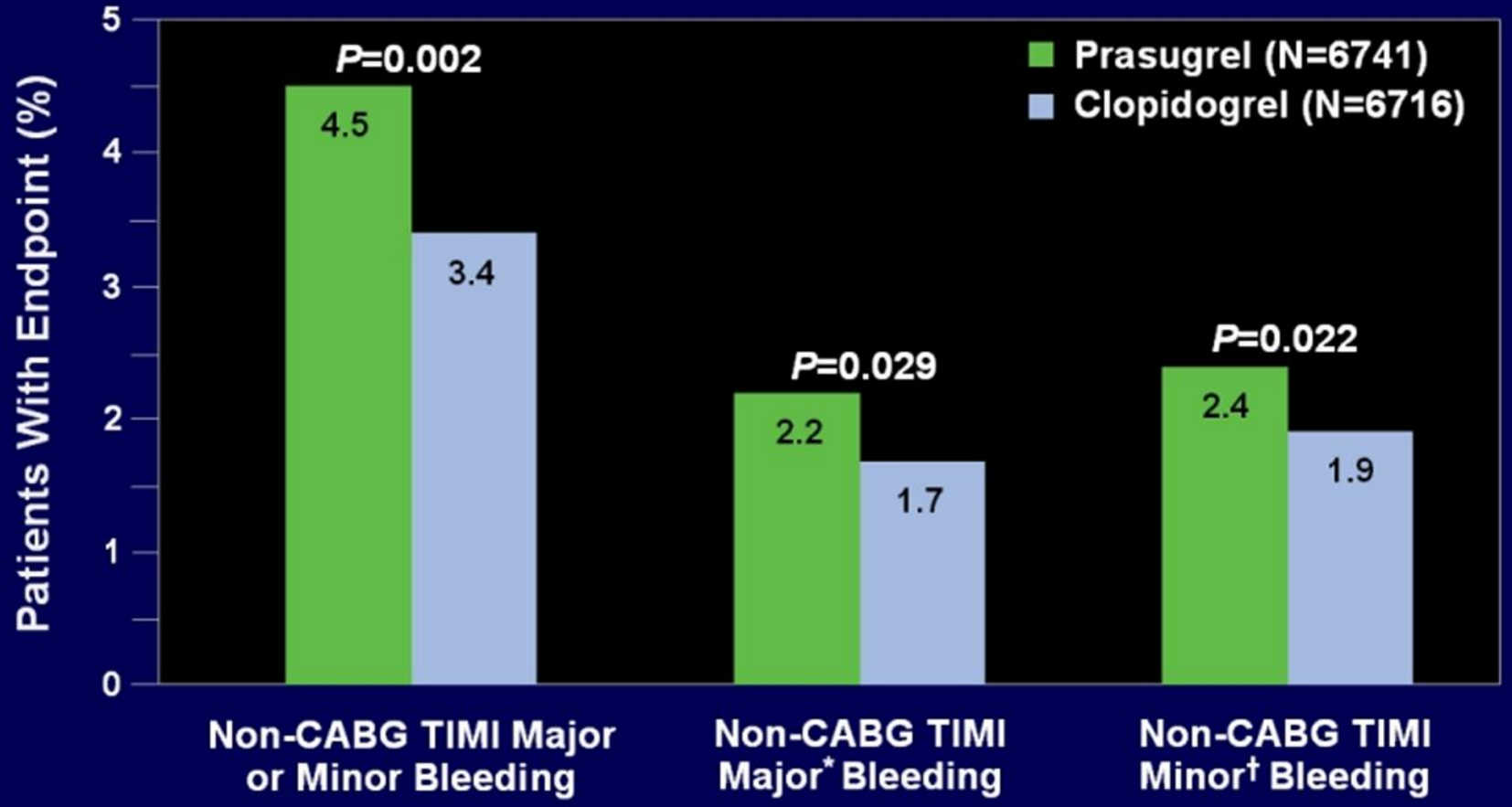


TRÎTON TIMI·38

Diabetic Subgroup
N=3146



Non-CABG TIMI Major or Minor Bleeding



*Any intracranial hemorrhage or any clinically overt bleeding associated with a fall in hemoglobin ≥5 g/dL. †Clinically overt bleeding associated with a fall in hemoglobin of ≥3 g/dL but <5 g/dL.

Effient Full Prescribing Information.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

TICAGRELOR (BRILINTA)

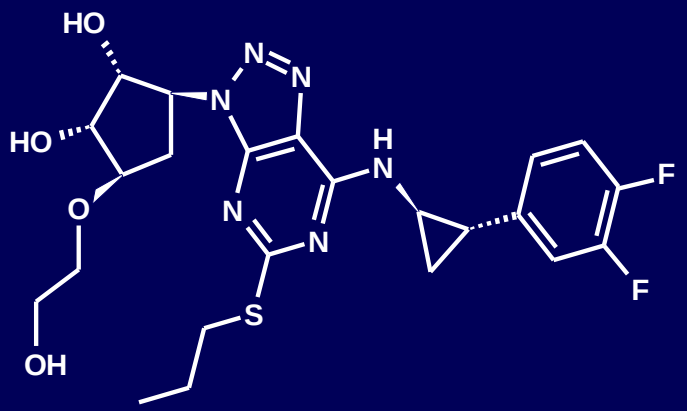
Just Approved in July 2011

1. It is an ER and Cath Lab Drug
2. Mechanism of action
3. DATA (PLATO): Safety advantage

DOSE: 90 mg BID

AstraZeneca

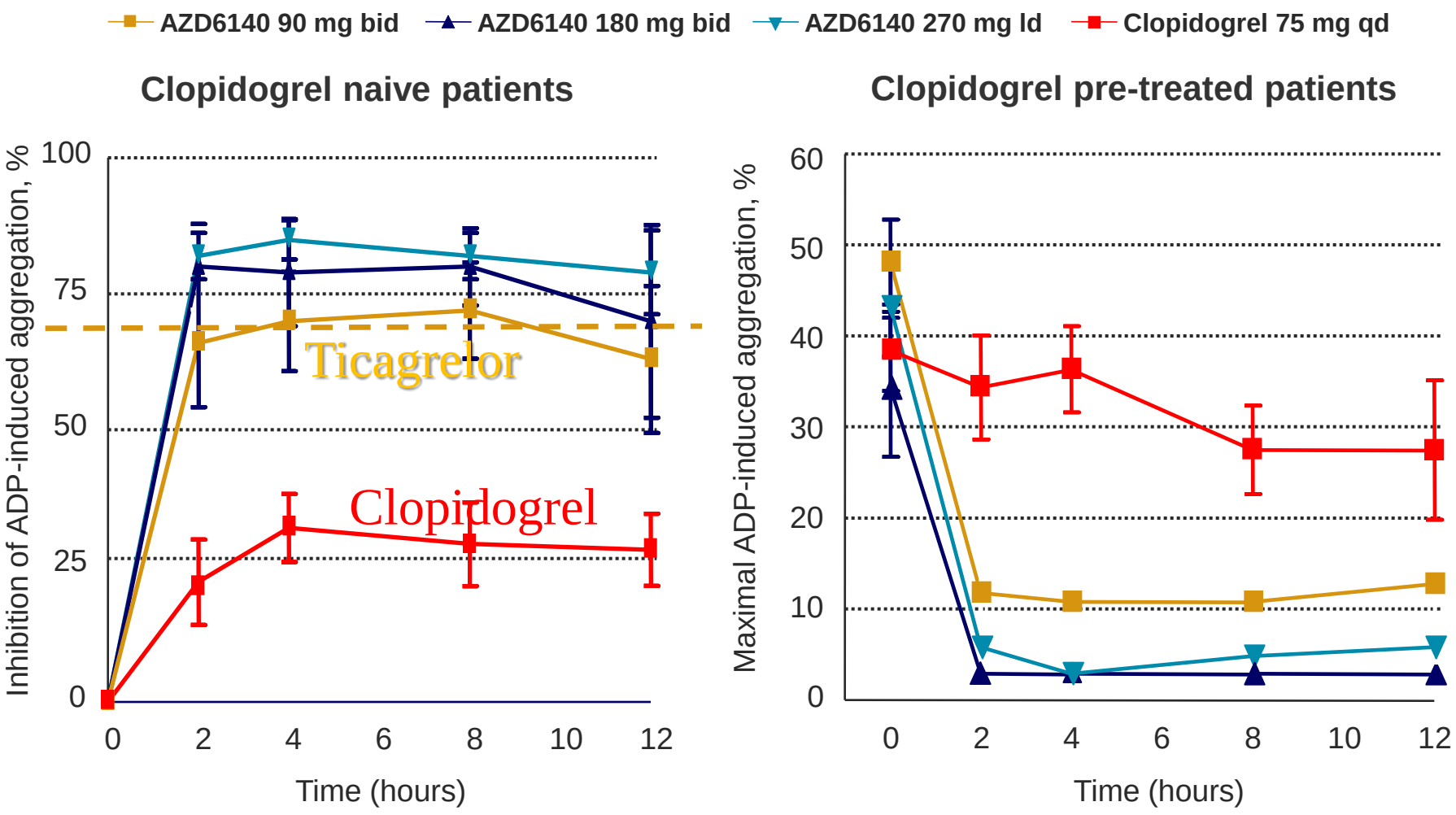
Ticagrelor (BRILINTA): an oral reversible $P2Y_{12}$ antagonist



Ticagrelor is not a thienopyridine

- **Not a Pro-drug: Direct , rapid and powerful P2Y12 inhibitor**
  - It 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
  - Functional recovery of all circulating platelets within approx 48 hrs

DISPERSE2 platelet function substudy: more rapid, greater and more consistent IPA with ticagrelor



IPA = inhibition of platelet aggregation; ld = loading dose

Storey R et al. *J Am Coll Cardiol.* 2007;50:1852–1860

PLATO study design

PLATO

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)

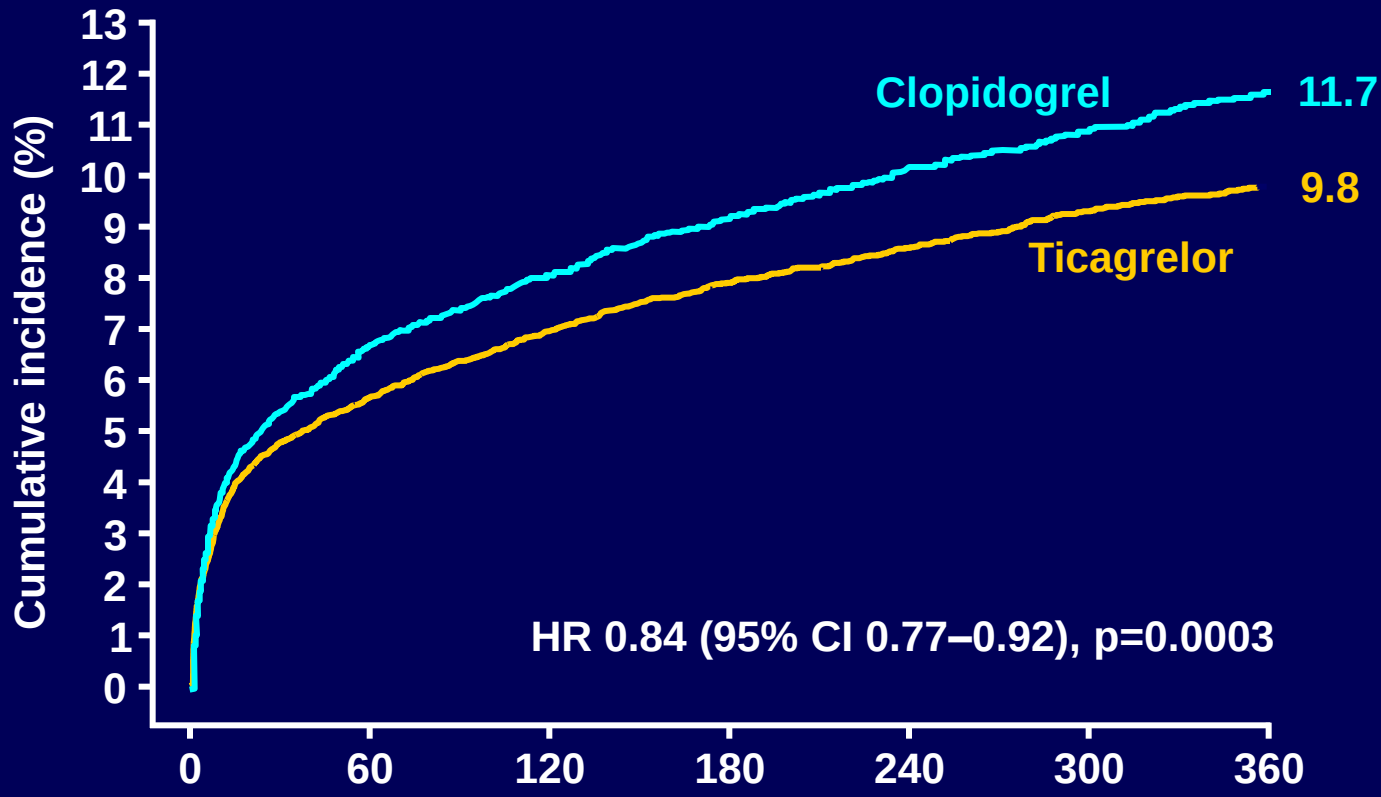
Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

F/U 6–12-months

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

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

PLATO



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

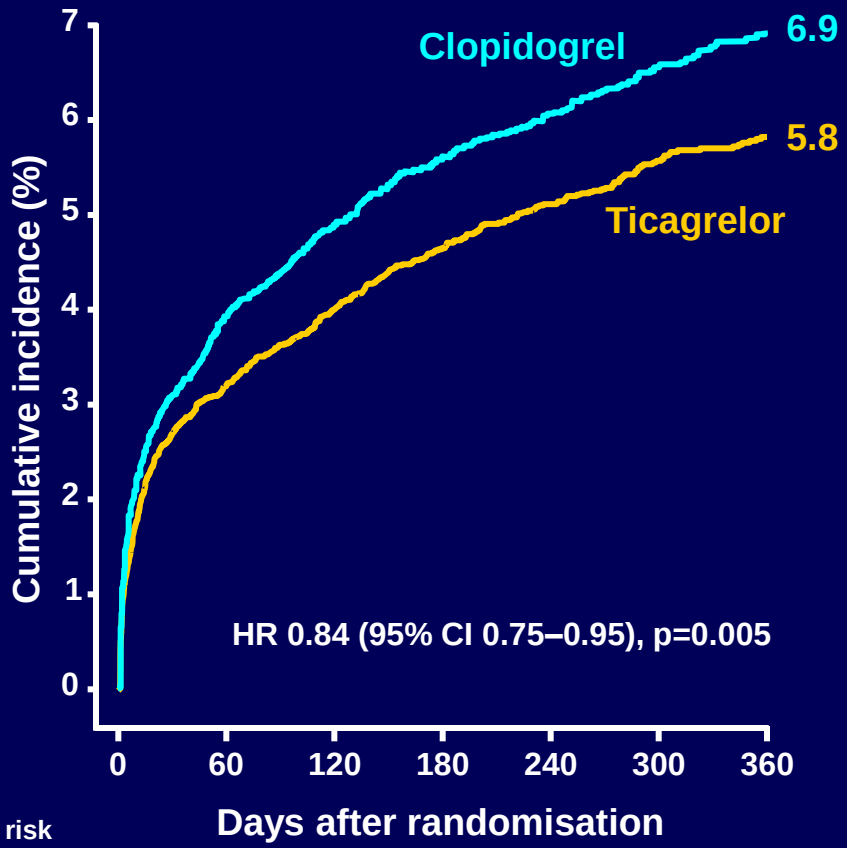
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

Secondary efficacy endpoints over time

PLATO

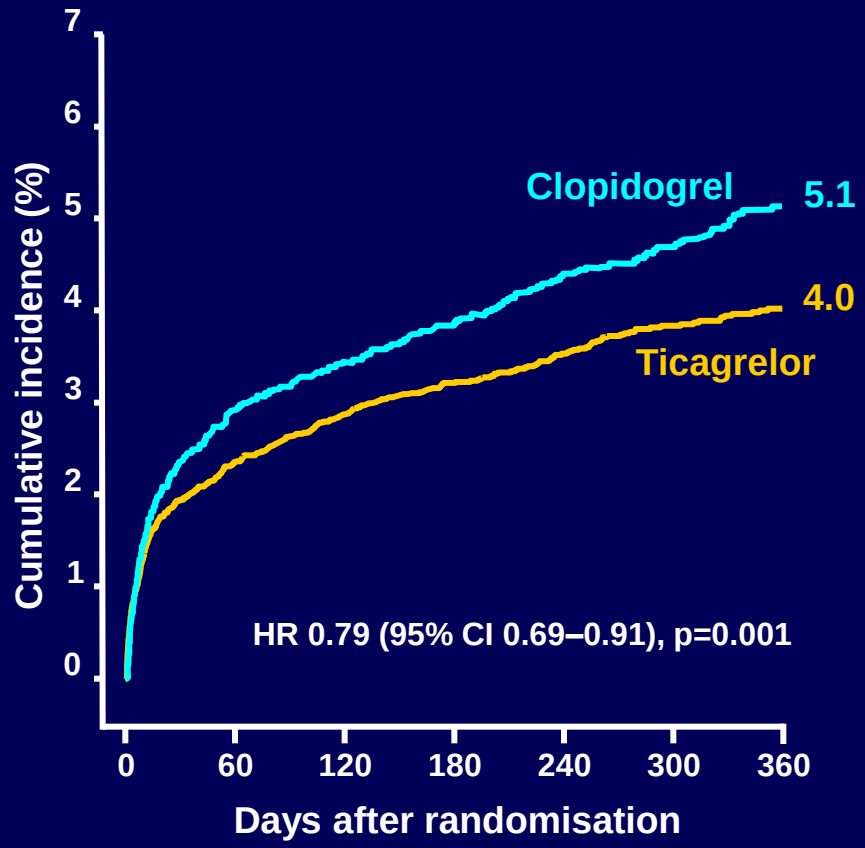
Myocardial infarction



No. at risk

Ticagrelor	9,333	8,678	8,520	8,279	6,796	5,210	4,191
Clopidogrel	9,291	8,560	8,405	8,177	6,703	5,136	4,109

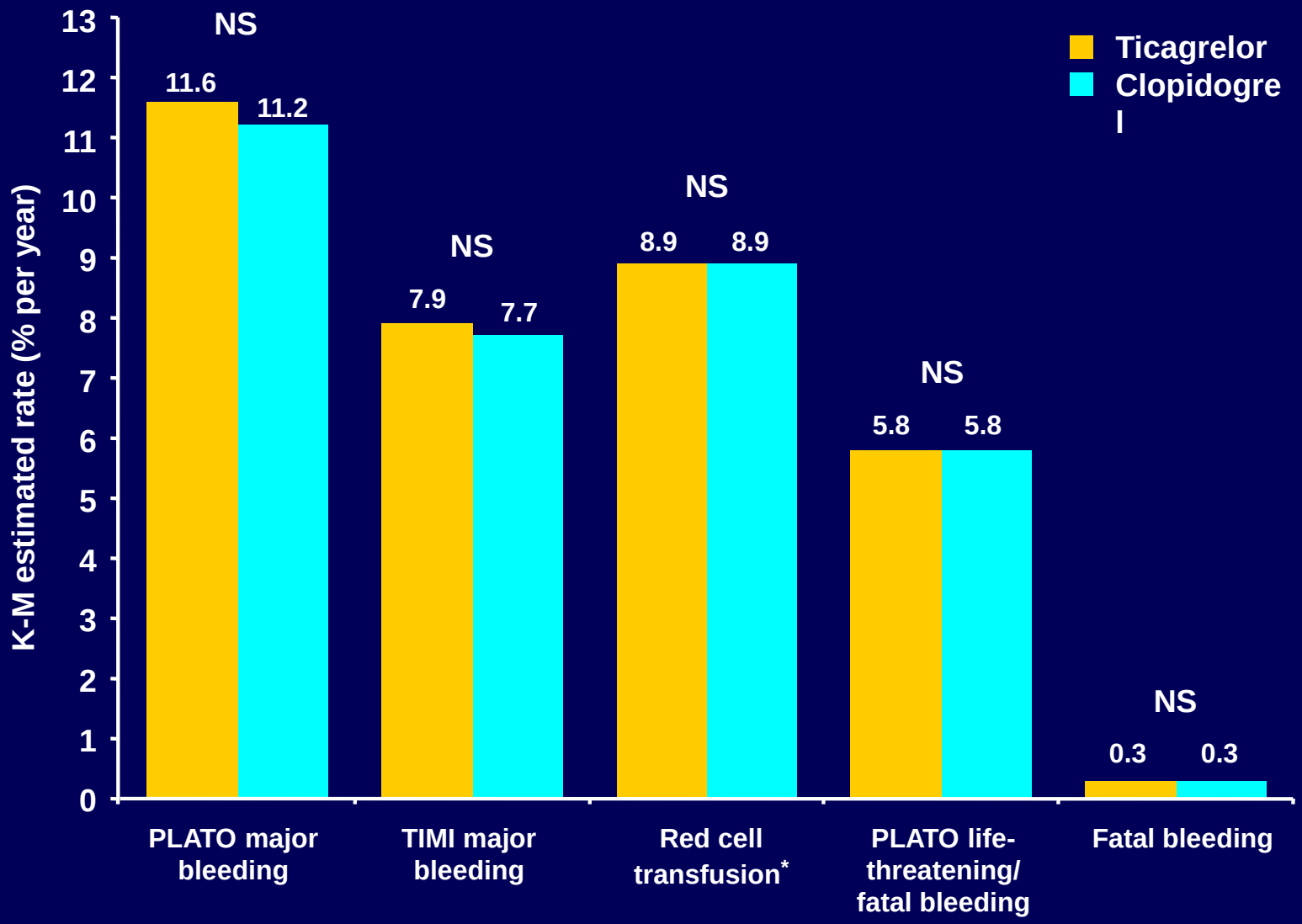
Cardiovascular death



	9,333	8,294	8,822	8,626	7119	5,482	4,419
	9,291	8,865	8,780	8,589	7079	5,441	4,364

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

Total major bleeding



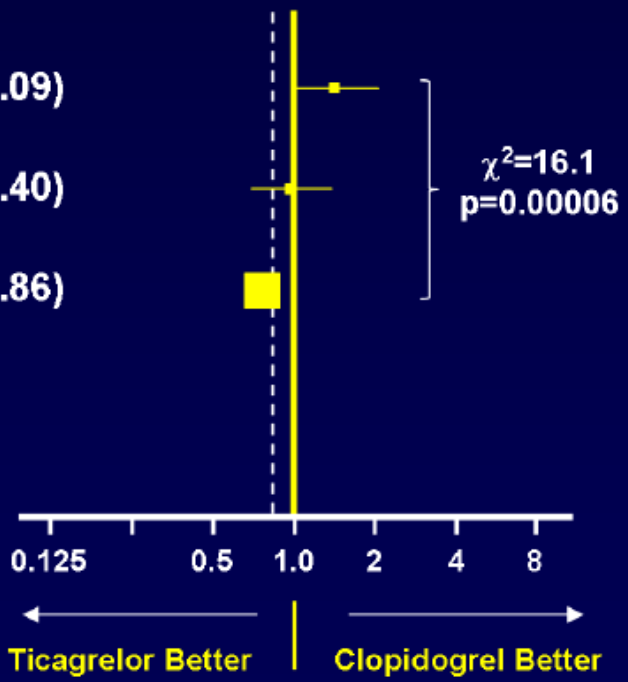
Major bleeding and major or minor bleeding according to TIMI criteria refer to non-adjudicated events analysed with the use of a statistically programmed analysis in accordance with definition described in Wiviott SD et al. NEJM 2007;357:2001–15;
*Proportion of patients (%); NS = not significant

Adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

Interaction of Treatment Effect with ASA Dose

Does it explain difference between US and OUS?

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)



Conclusion

- **TICAGRELOR is a reversible, more intense $P2Y_{12}$ receptor inhibitor than clopidogrel and if given x 1 year in a broad population with ST- and non-ST-elevation ACS provides :**
  - **Reduction in myocardial infarction and stent thrombosis**
  - **Reduction in cardiovascular and total mortality**
  - **No change in the overall risk of major bleeding**

PLATO Invasive

TCT LBCT Session – Thrusday 11:00 am

DAPT*: Take home message

ALL ACS patients (regardless how are they treated) :

Add P2Y12 to ASA: EARLY (esp. plavix) and AT LEAST FOR 1 year

ALL PCI patients (ACS and elective):

EARLY (Plavix >6 hrs prior to PCI) and AT LEAST FOR 1 YEAR

*DAPT: ASA + PLAVIX, EFFIENT OR BRILINTA

ANTICOAGUAGULATION:

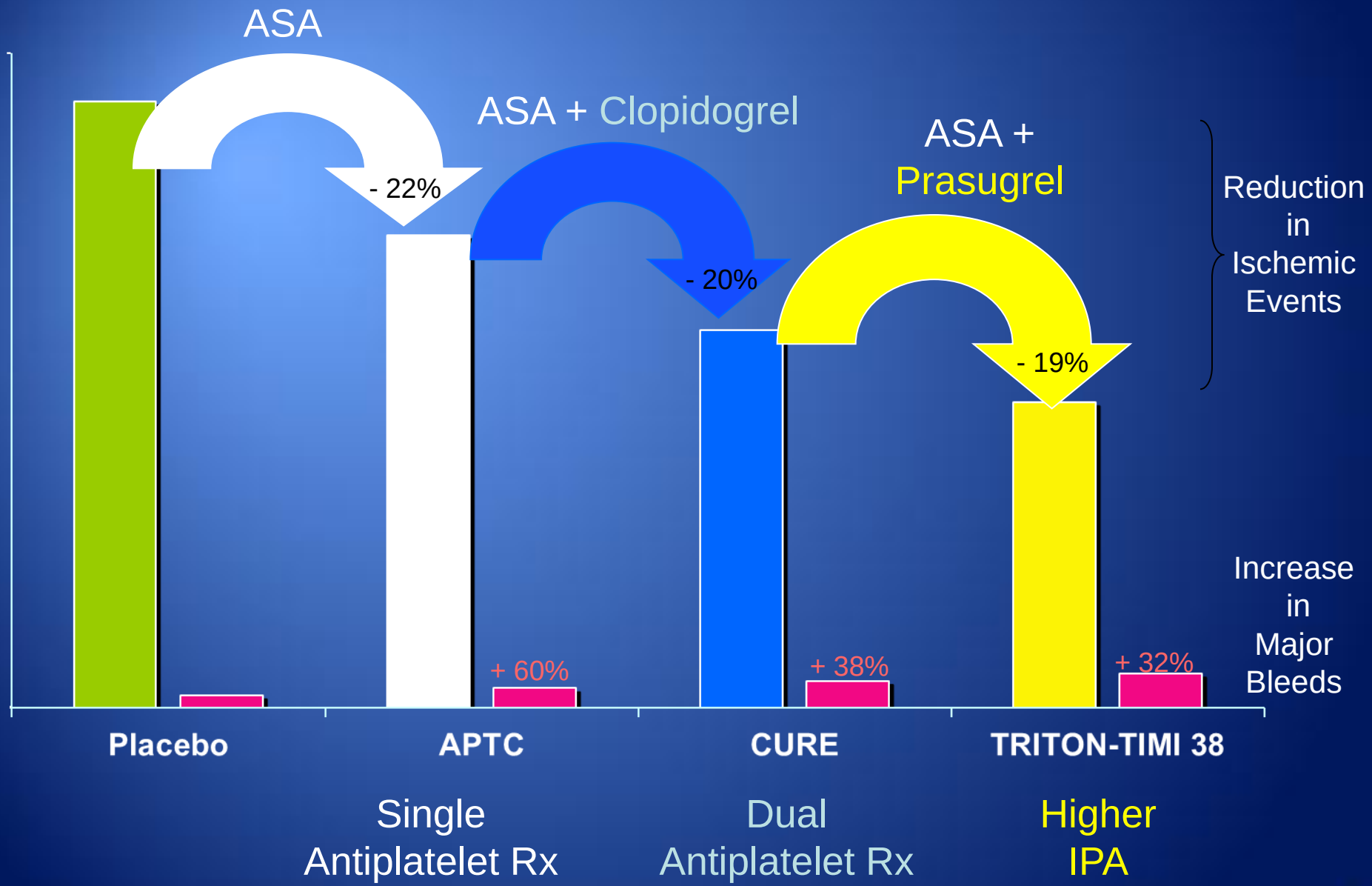
Heparin

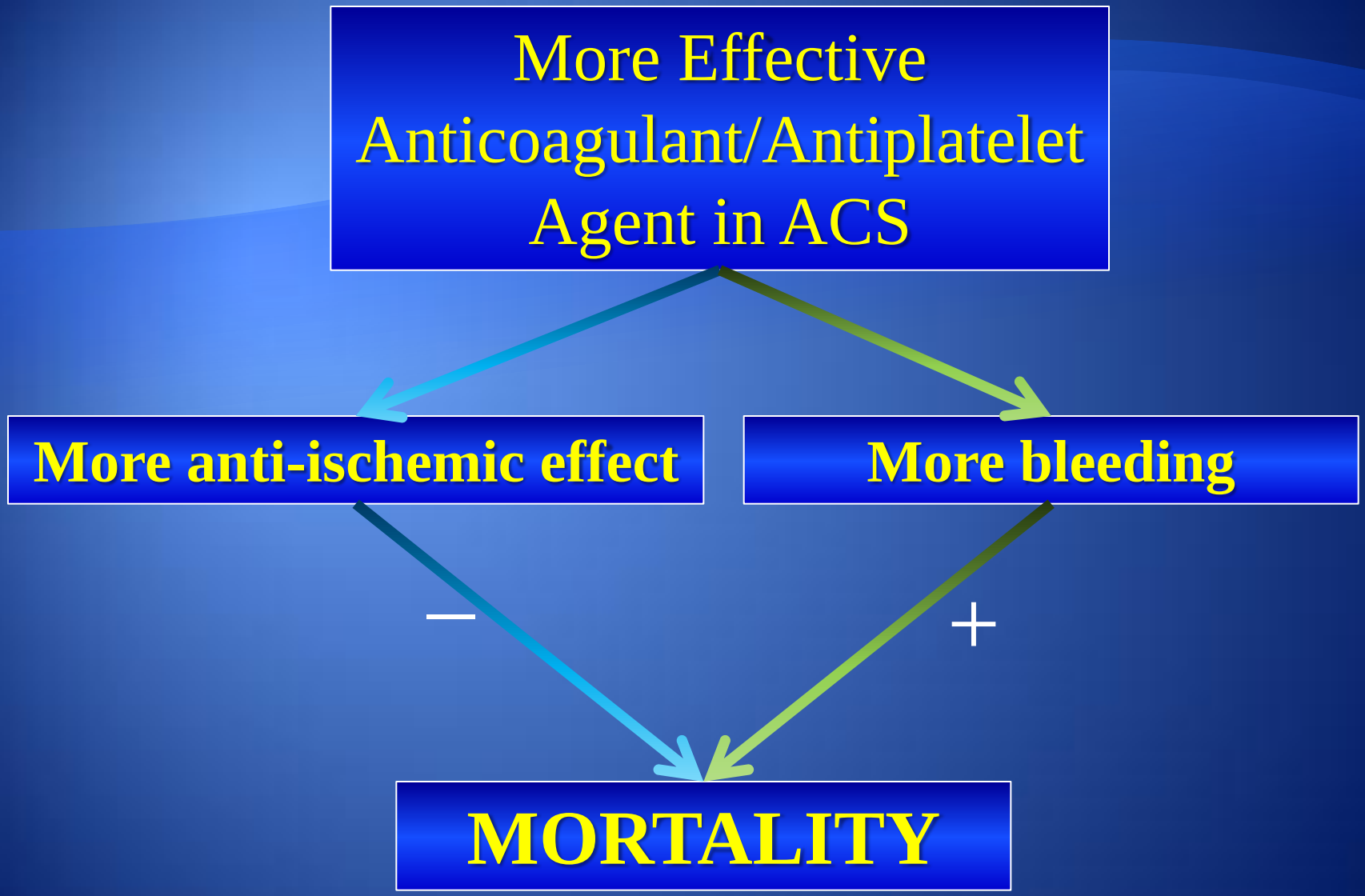
Bivalirudin (Angiomax)

Heparin + Gp IIb/IIIa


9
8
7
15cm

Oral Antiplatelet Therapy in ACS




More Effective Anticoagulant/Antiplatelet Agent in ACS
More anti-ischemic effect
More bleeding
–
+
MORTALITY

EFFIENT
Vs.
Plavix

More anti-ischemic effect

More bleeding

–

+

NO DIFFERENCE in MORTALITY

ANGIOMAX
Vs
Heparin and IIb/IIIa Inh

Similar anti-ischemic effect

Less bleeding

LESS CARDIAC MORTALITY

Brilinta
Vs
Plavix

More anti-ischemic effect

Similar bleeding

–

0

LESS MORTALITY

SELECTION OF AGENTS