CVI SYMPOSIUM 2012

Acute Coronary Syndromes

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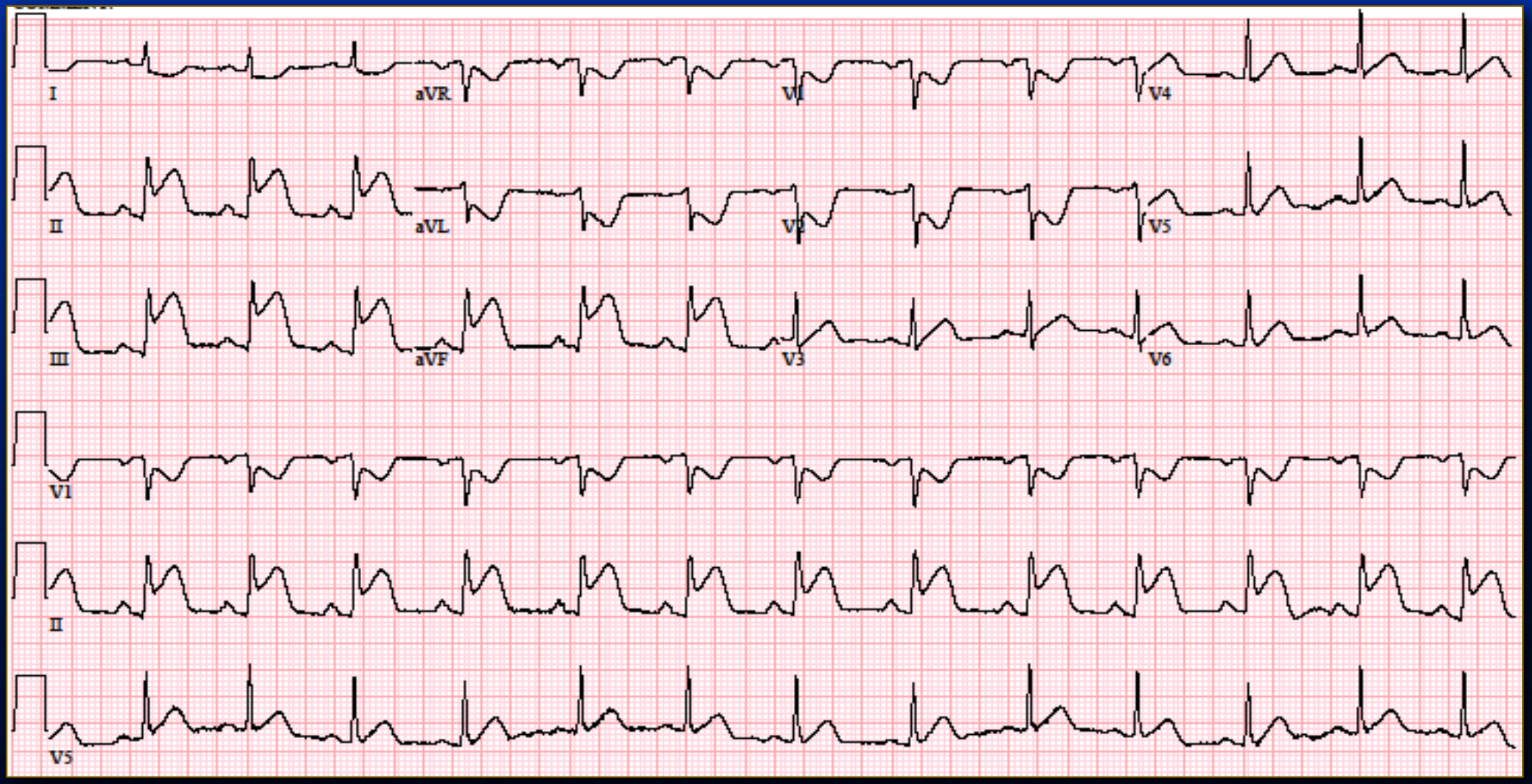
DISCLAIMER

ACS as seen by an Interventional Cardiologist

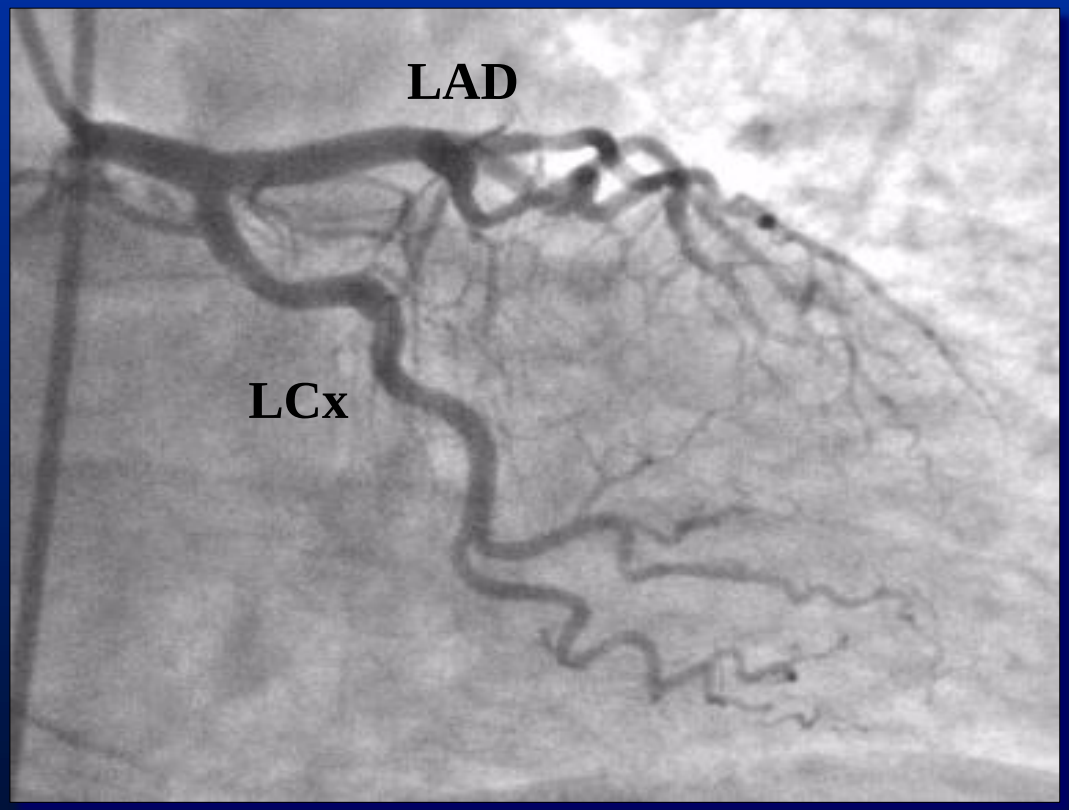
CAD

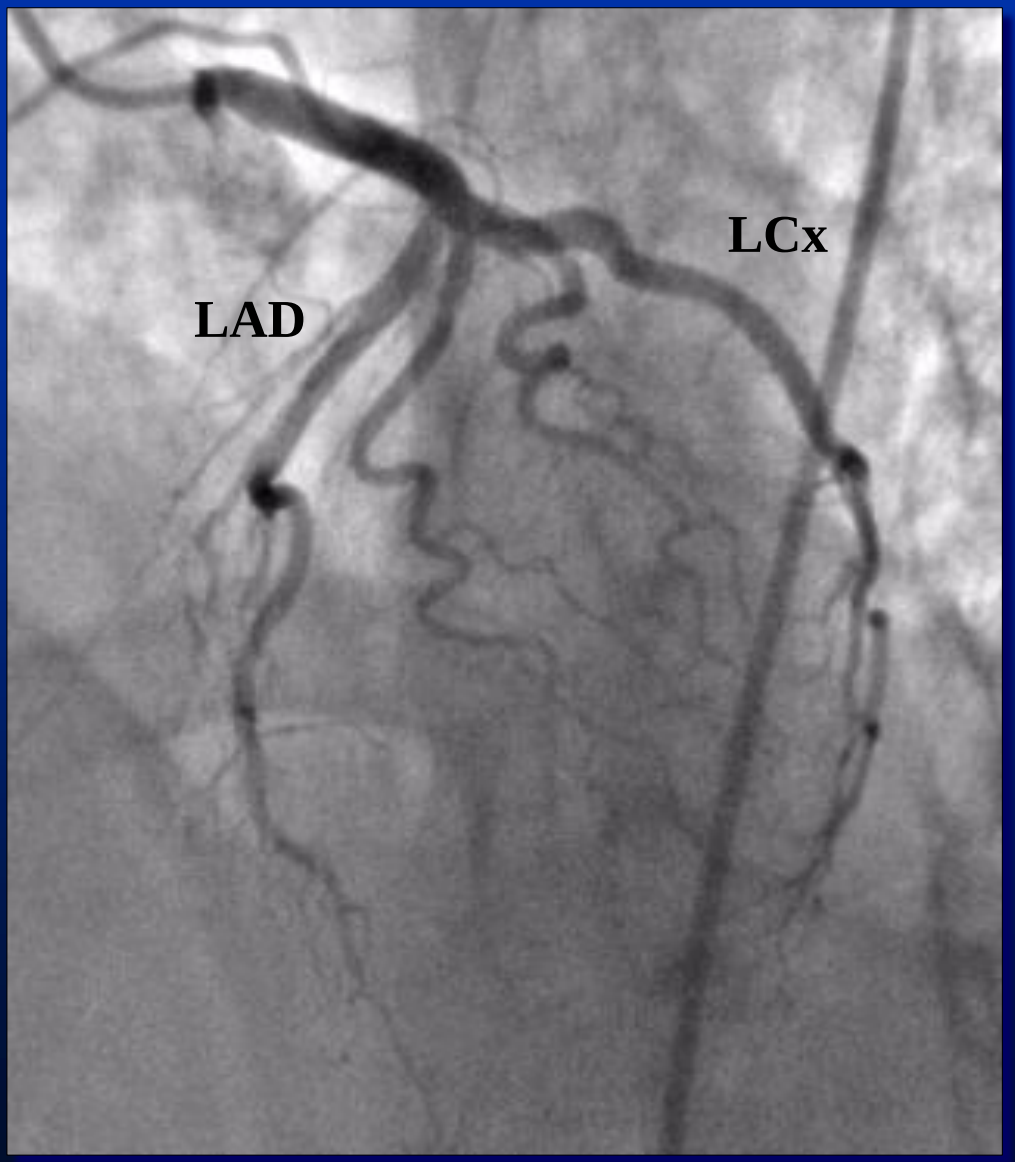
- Basic concepts
- Clinical Presentation / case examples
- Anatomic and physiological difference between stable and unstable syndromes
- Management
- Antiplatelet Therapy: Newly approved Prasugrel (Effient) and Ticagrelor (Brilinta)

46 yr old woman 1 ppd smoker with untreated dyslipidemia and FHx of CAD comes in at 7 PM with 2 hours of CP.



LAD and LCx without significant obst. disease



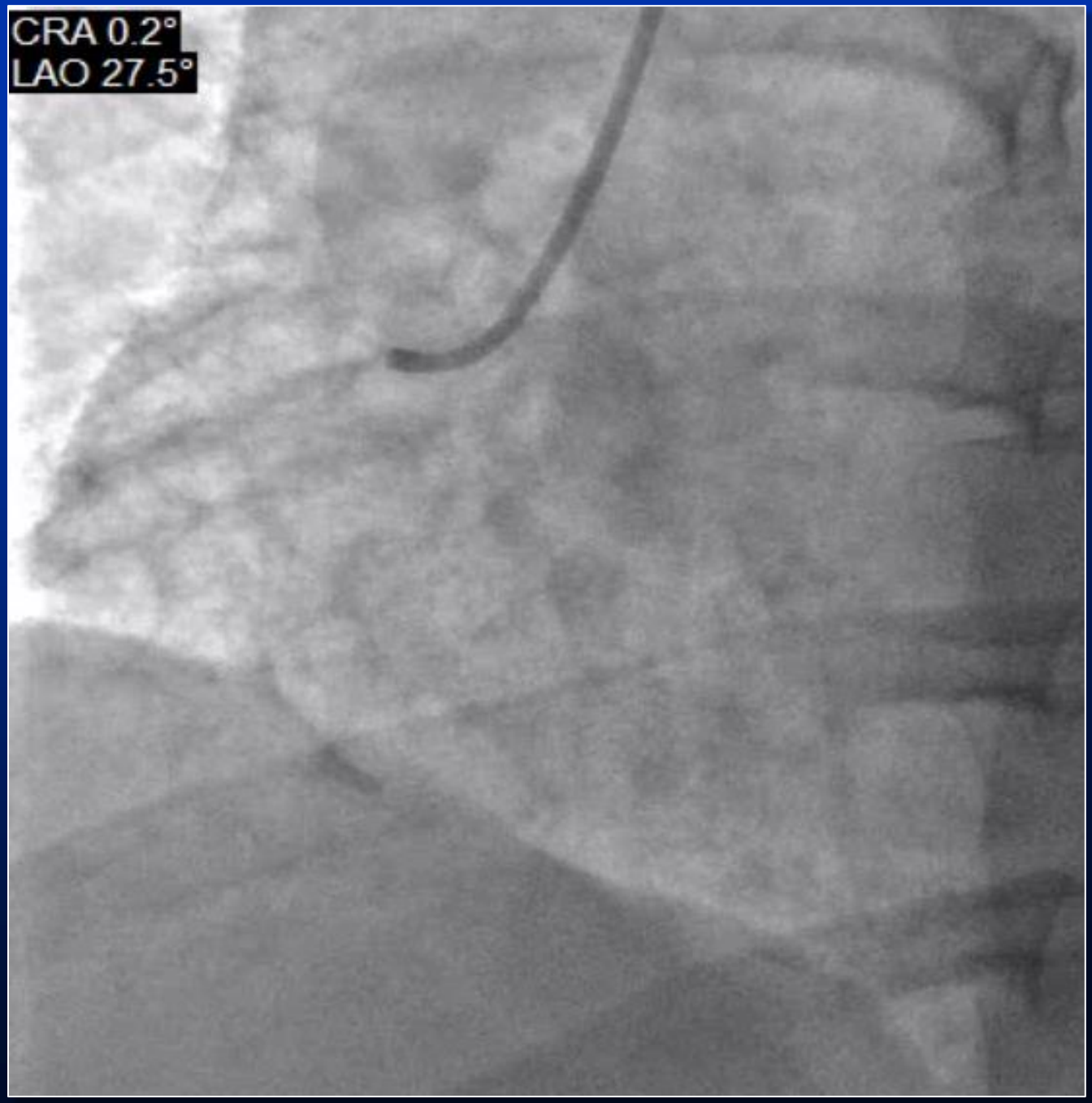


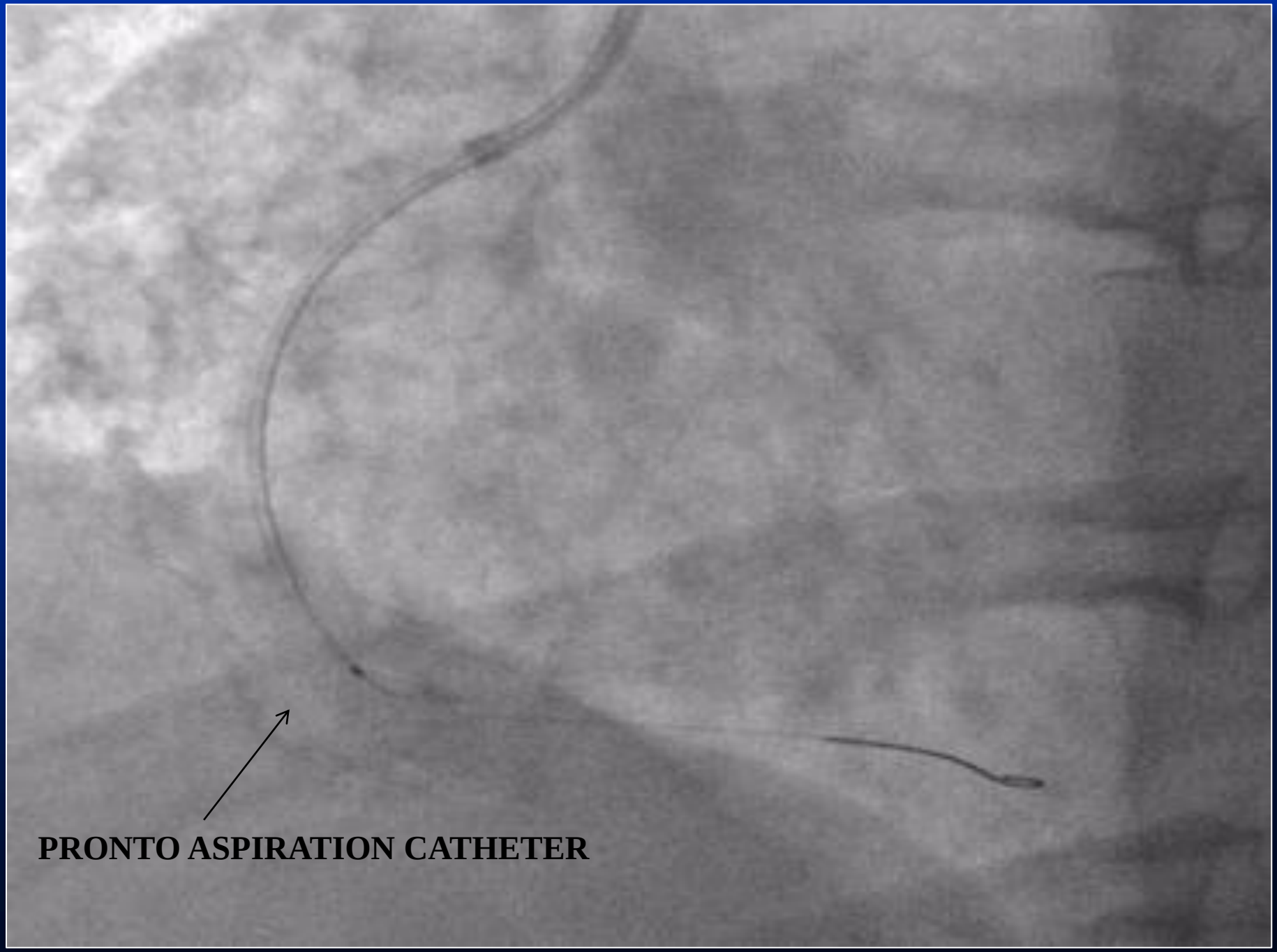
RCA

ASA/Plavix and heparin in ER

Reopro in CCL
Additional heparin

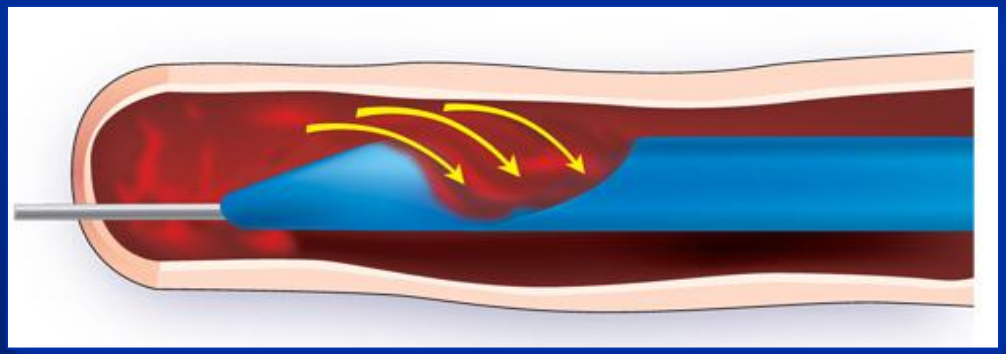
Aspiration Catheter

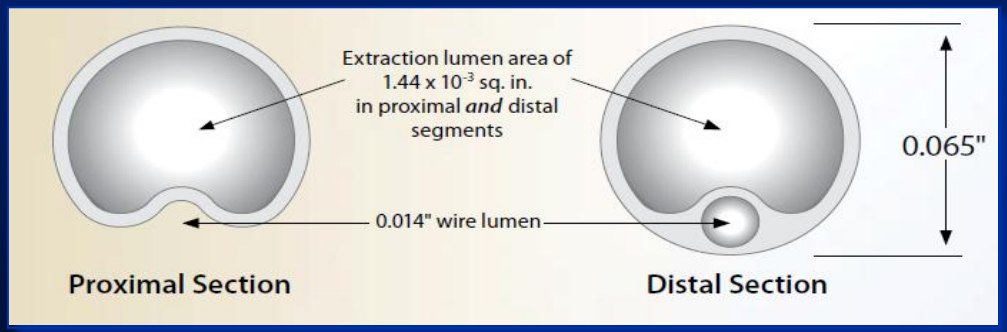


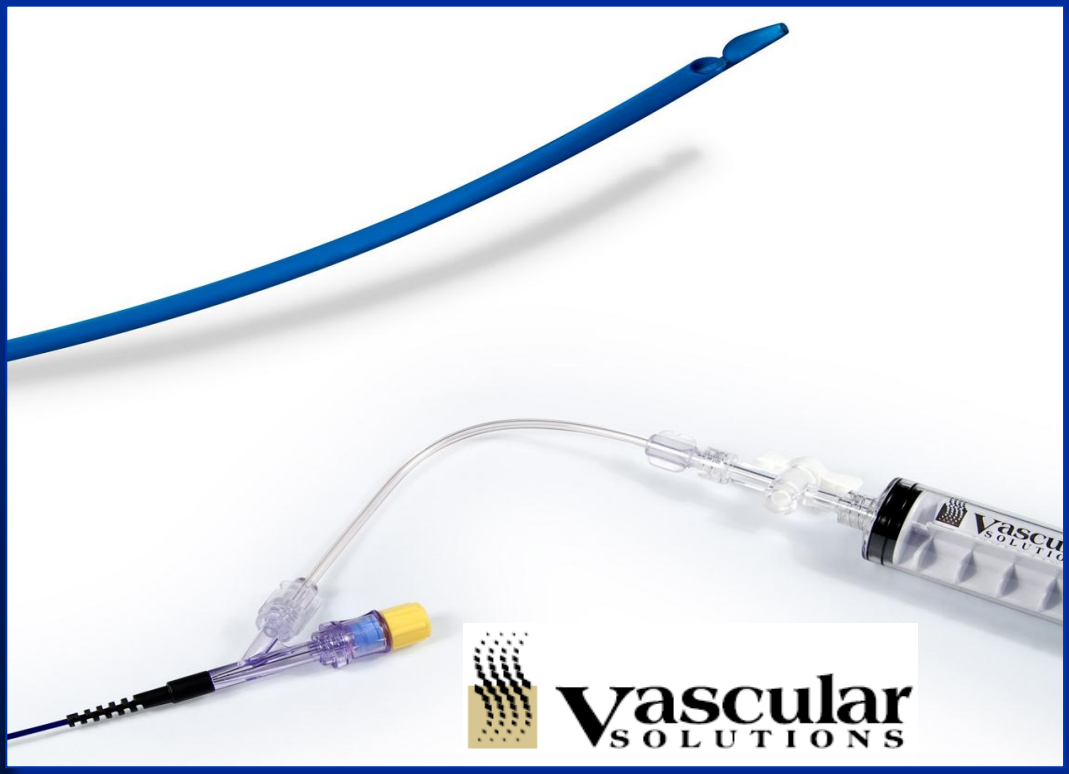

PRONTO ASPIRATION CATHETER

Pronto Aspiration Catheters

V3, V4, LP, 035” catheters



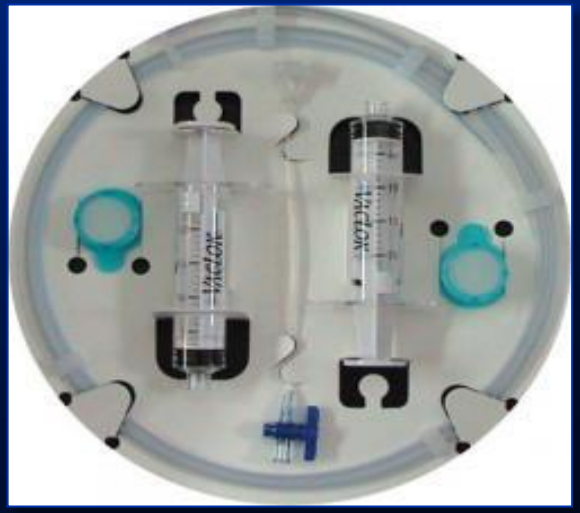




Aspiration Thrombectomy

Export AP ® Aspiration Catheter

Min 6 F Guide
0.070” Lumen
.014” wire
140 cm long

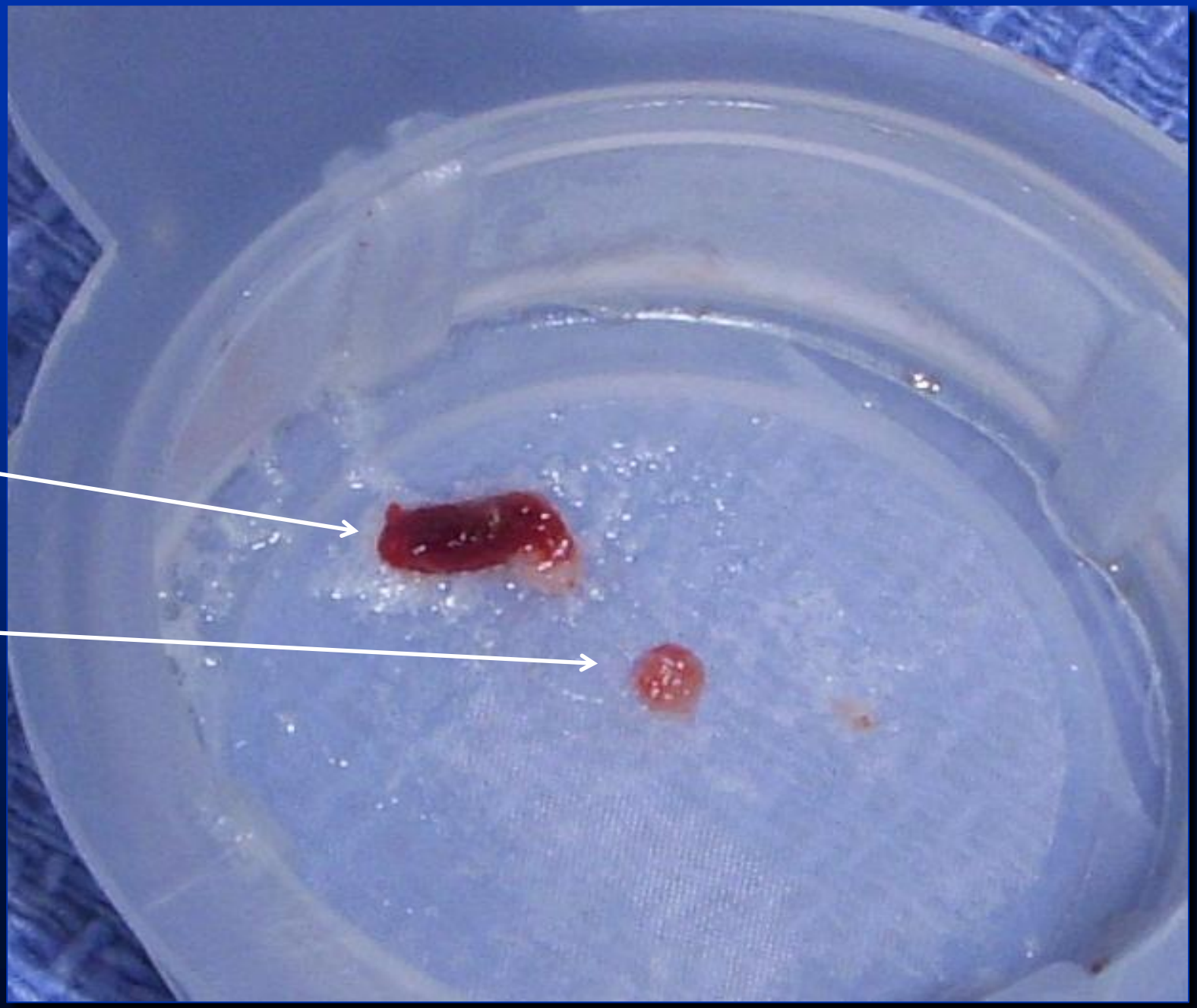


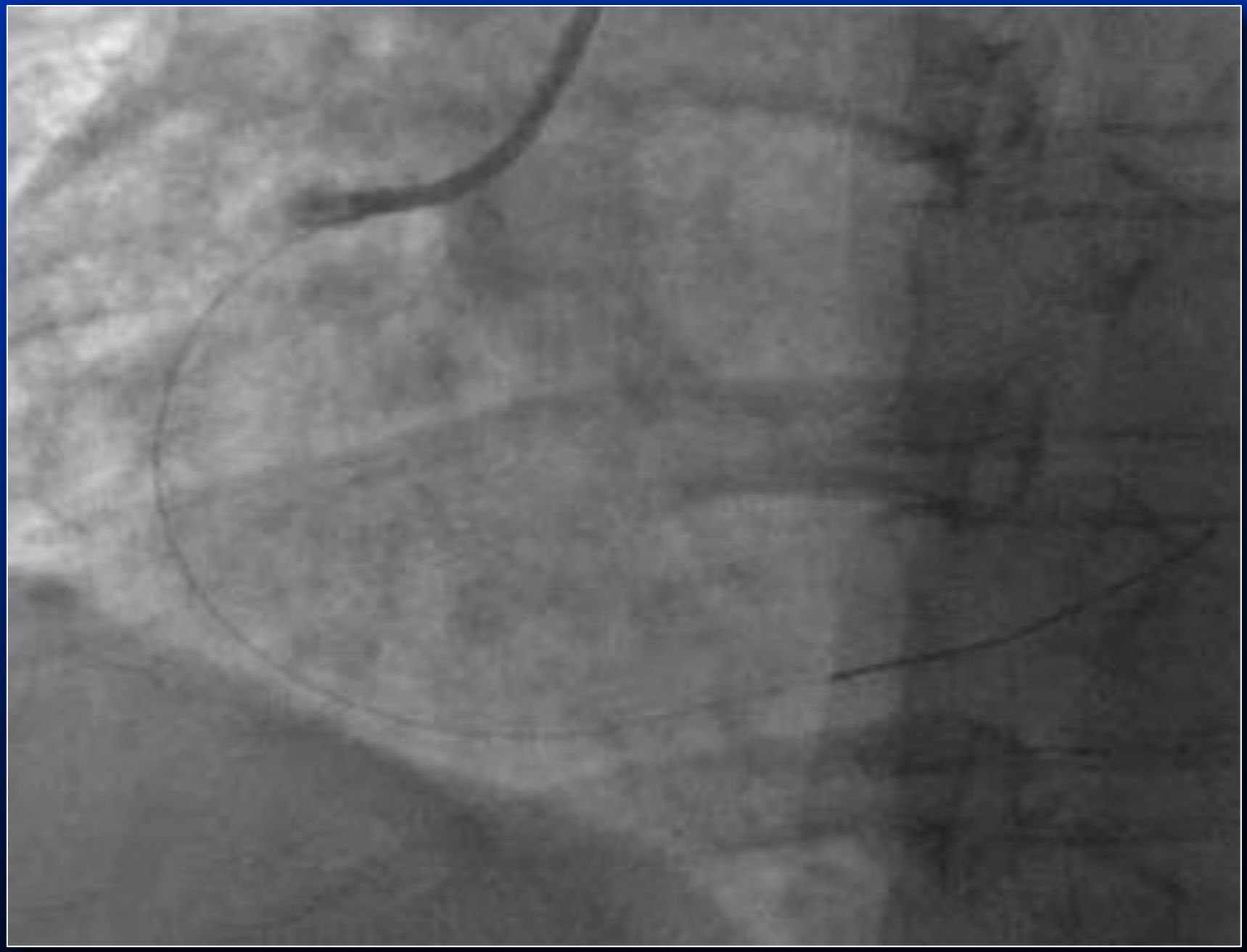
Medtronic

ASPIRATE

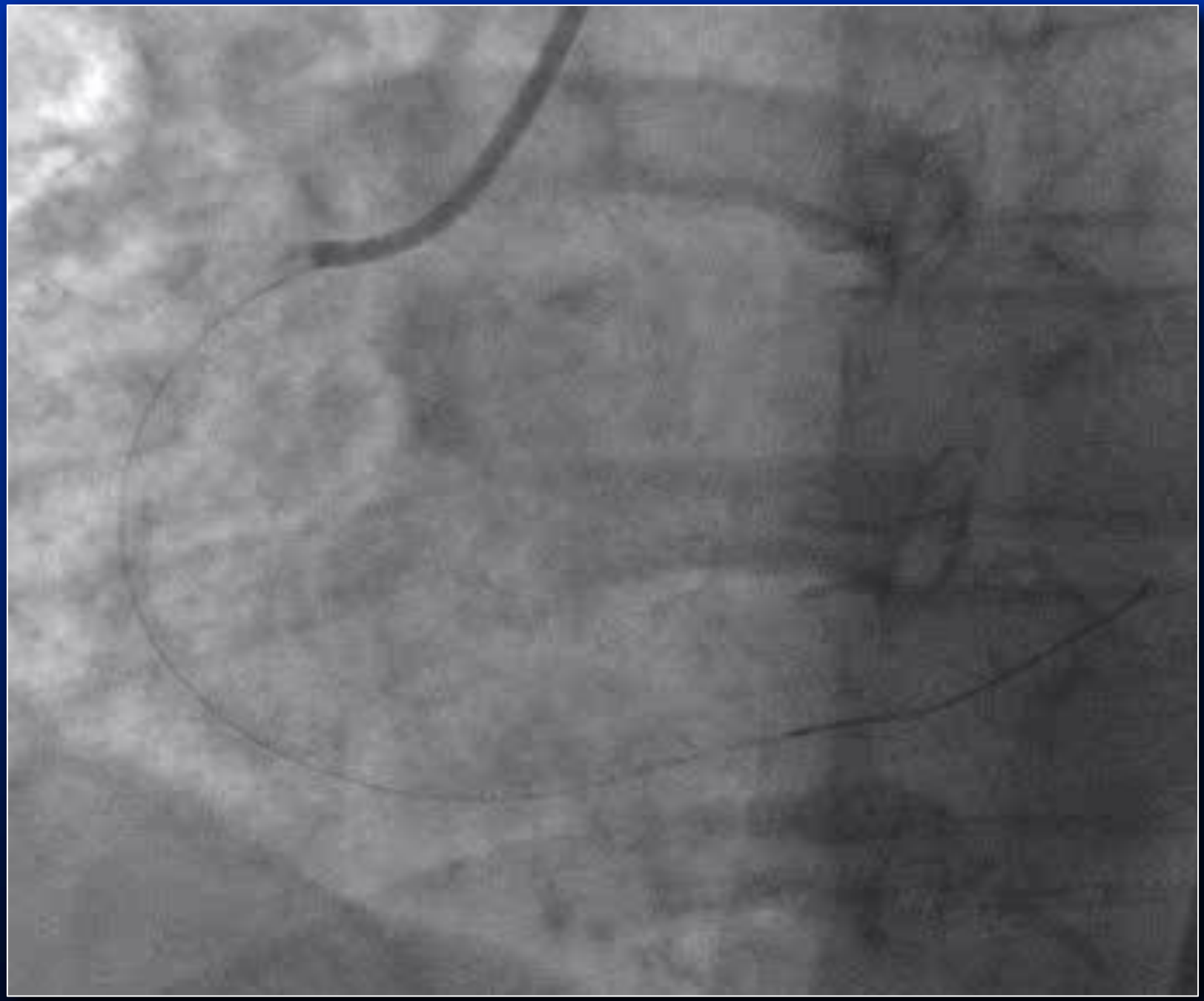
-Thrombus, white and red

-Atherosclerotic plaque

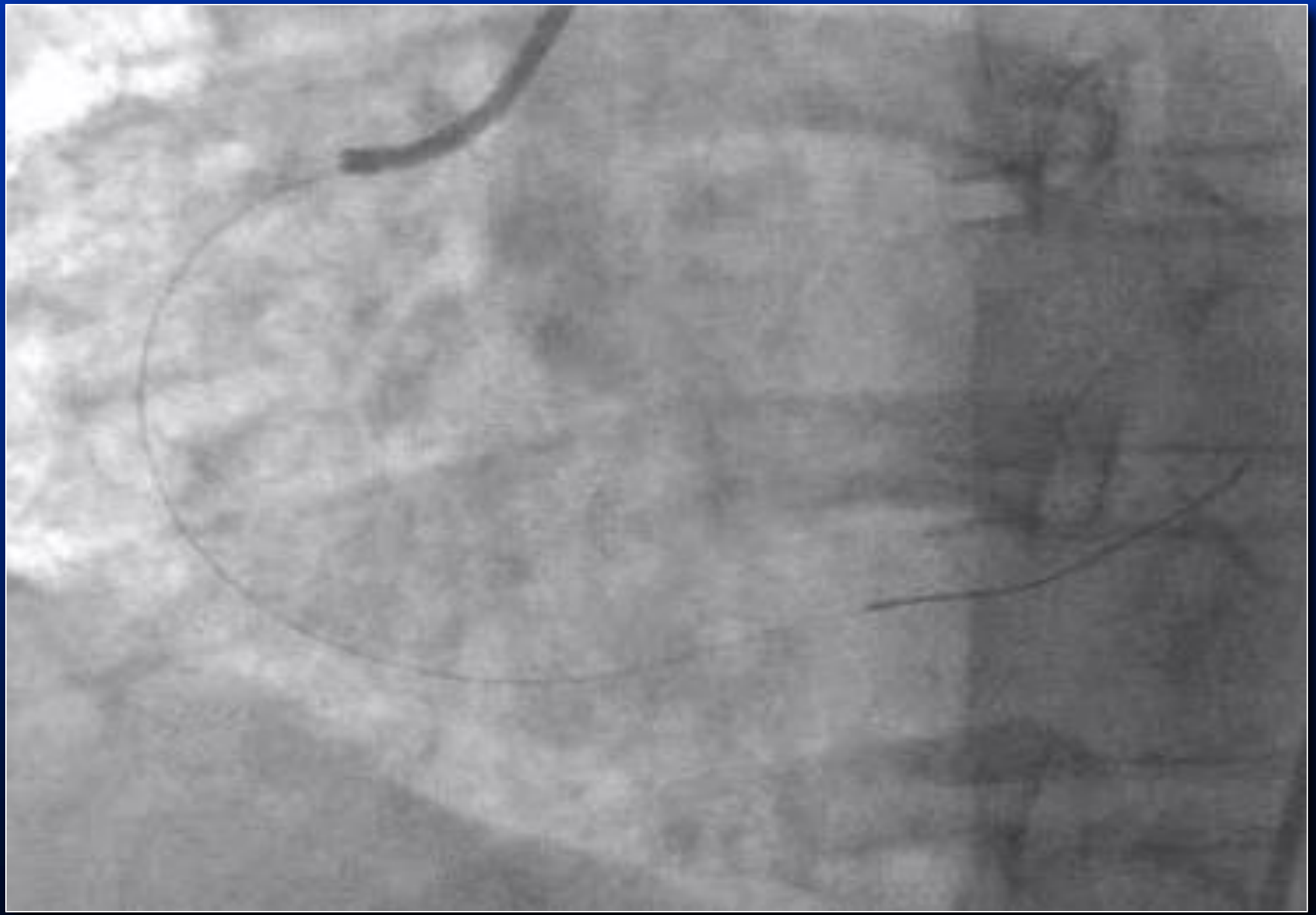




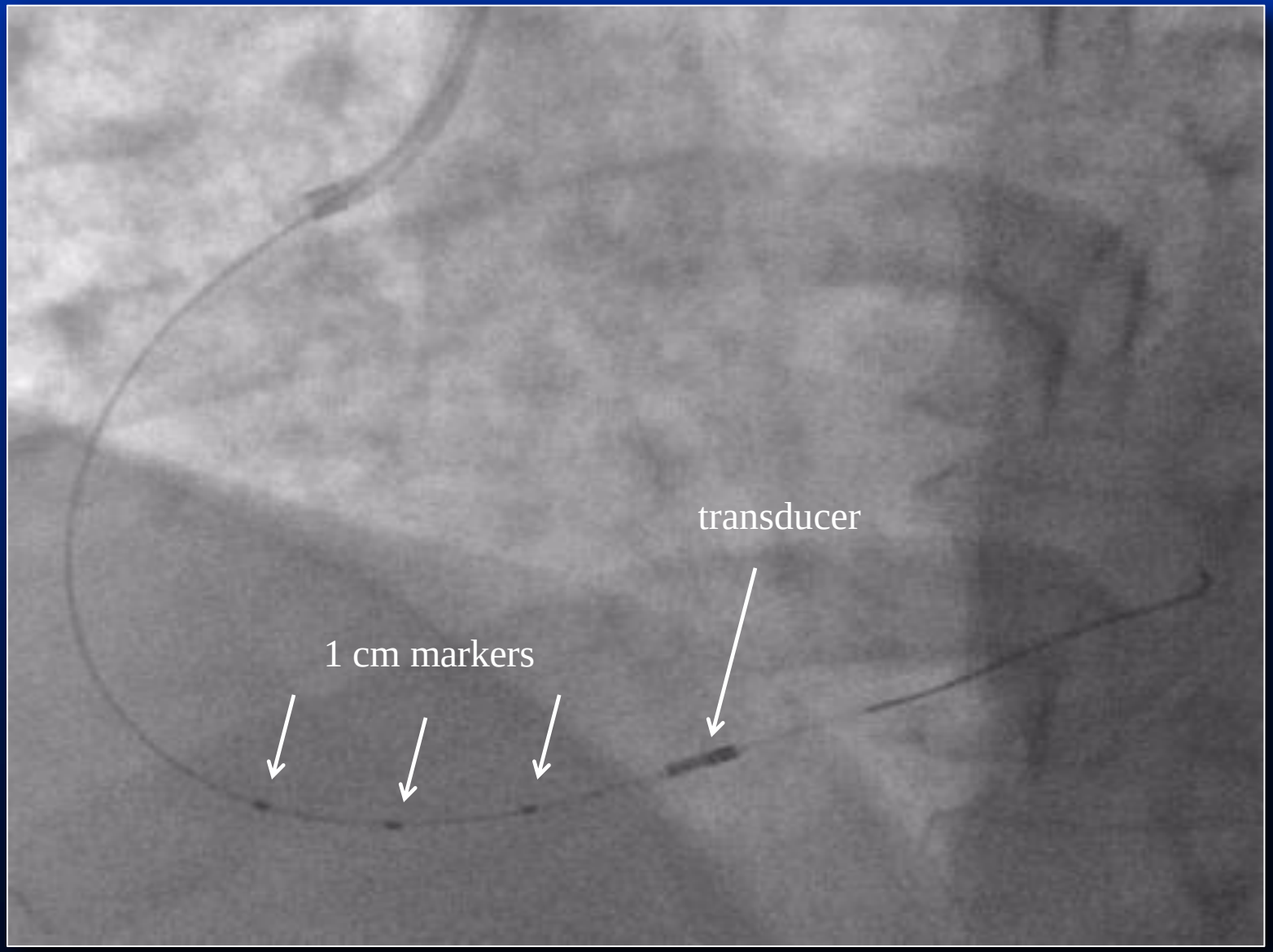
Coronary
SPASM

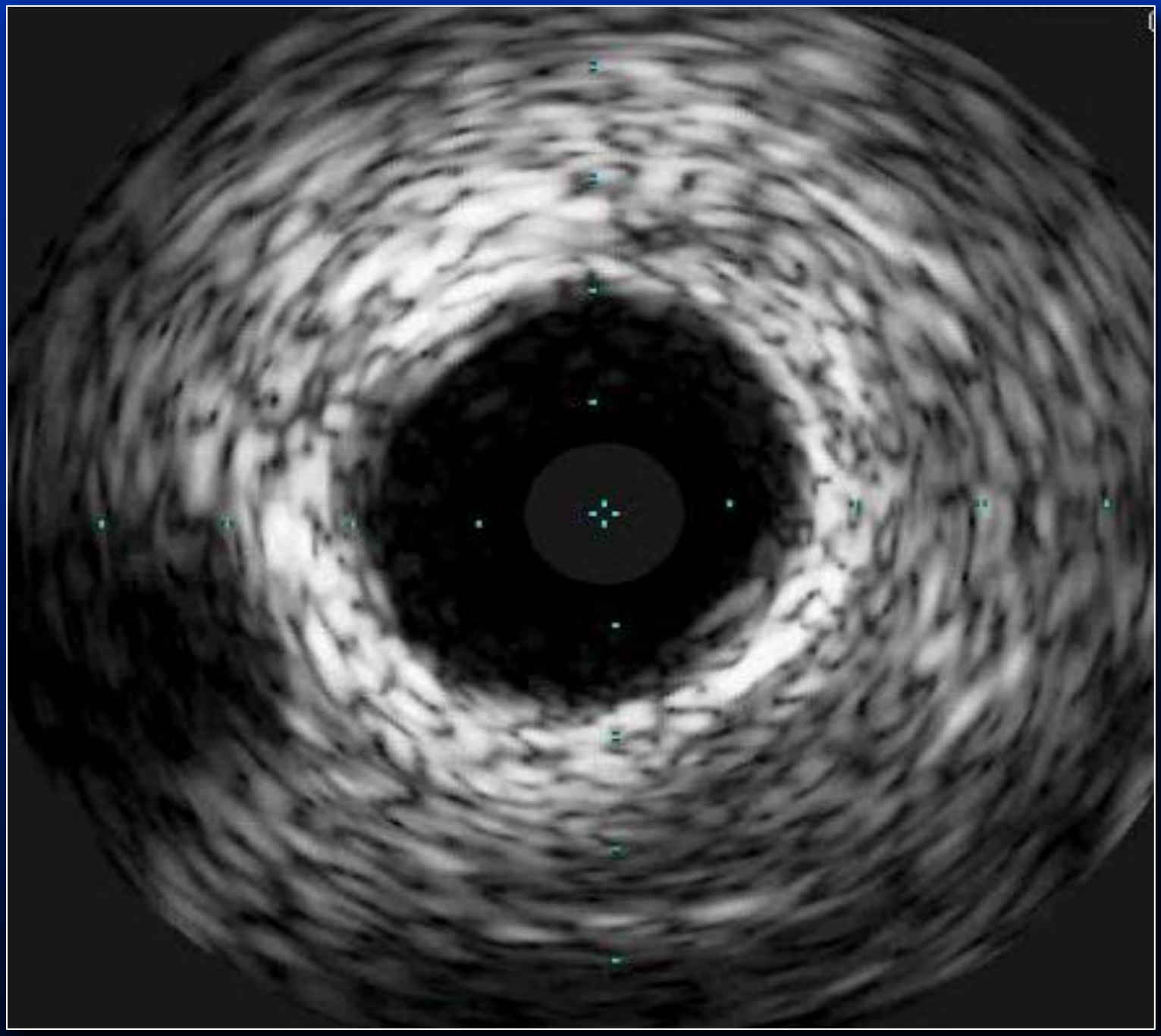


IC NTG

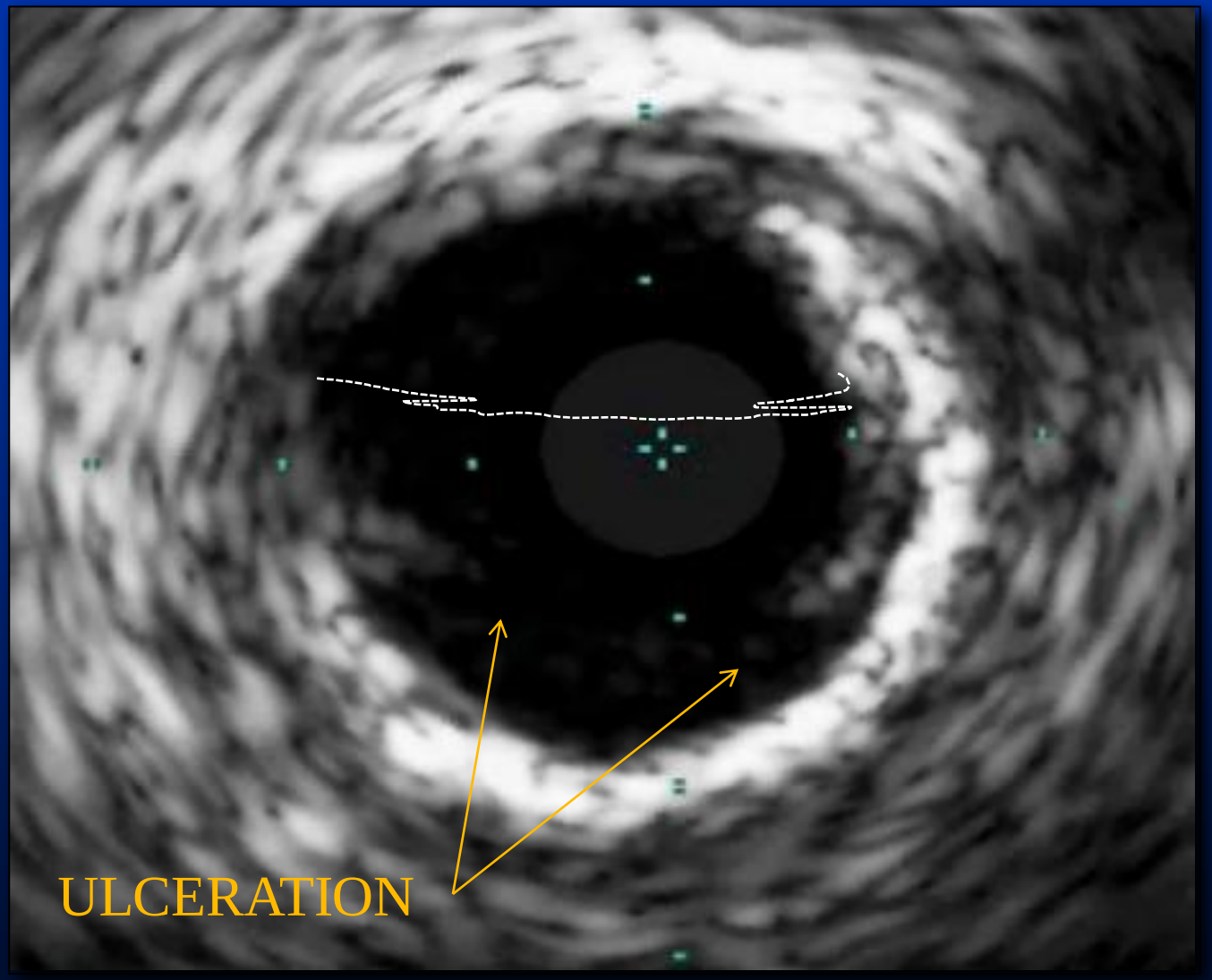


IntraVascular UltraSound (IVUS)

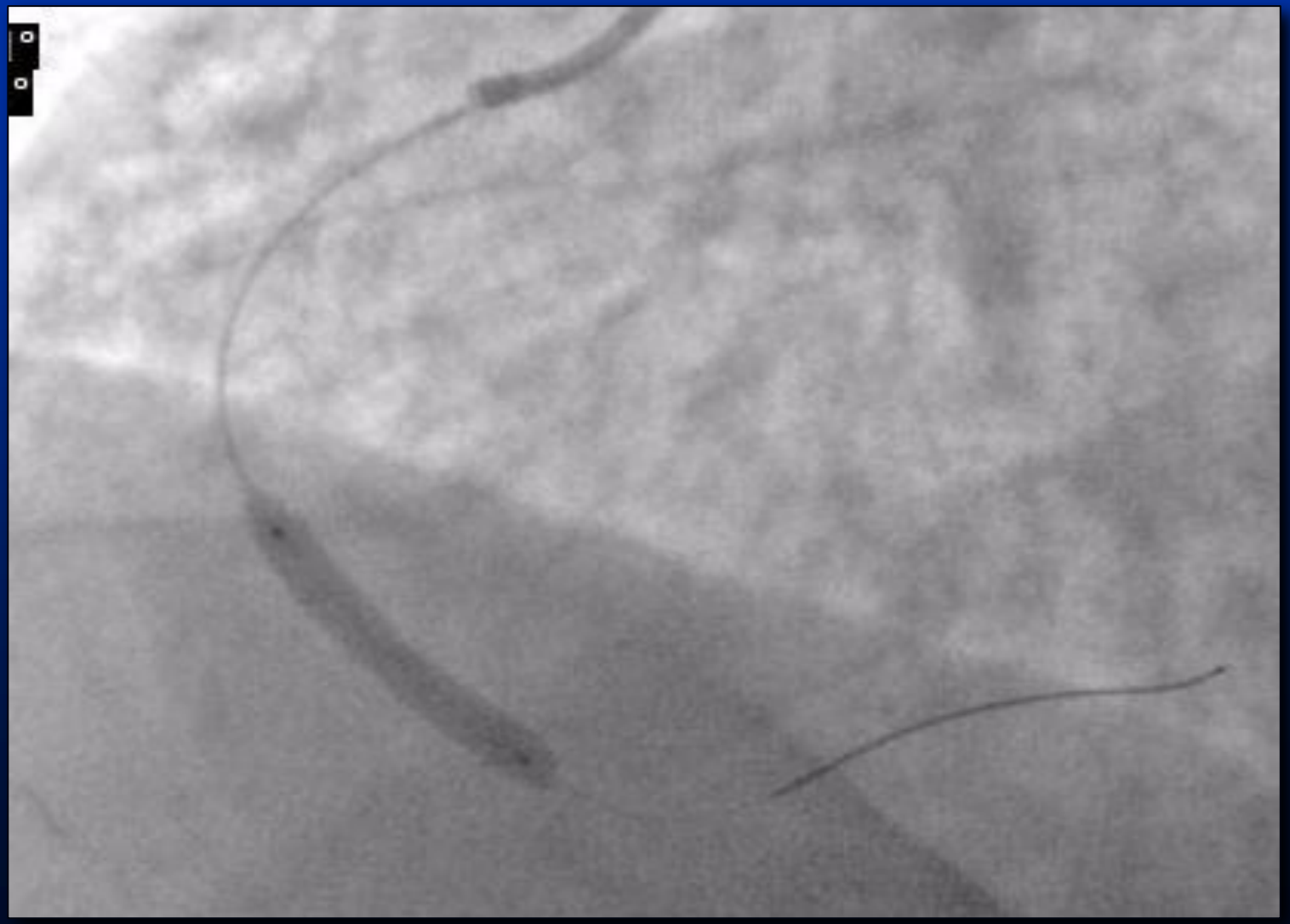


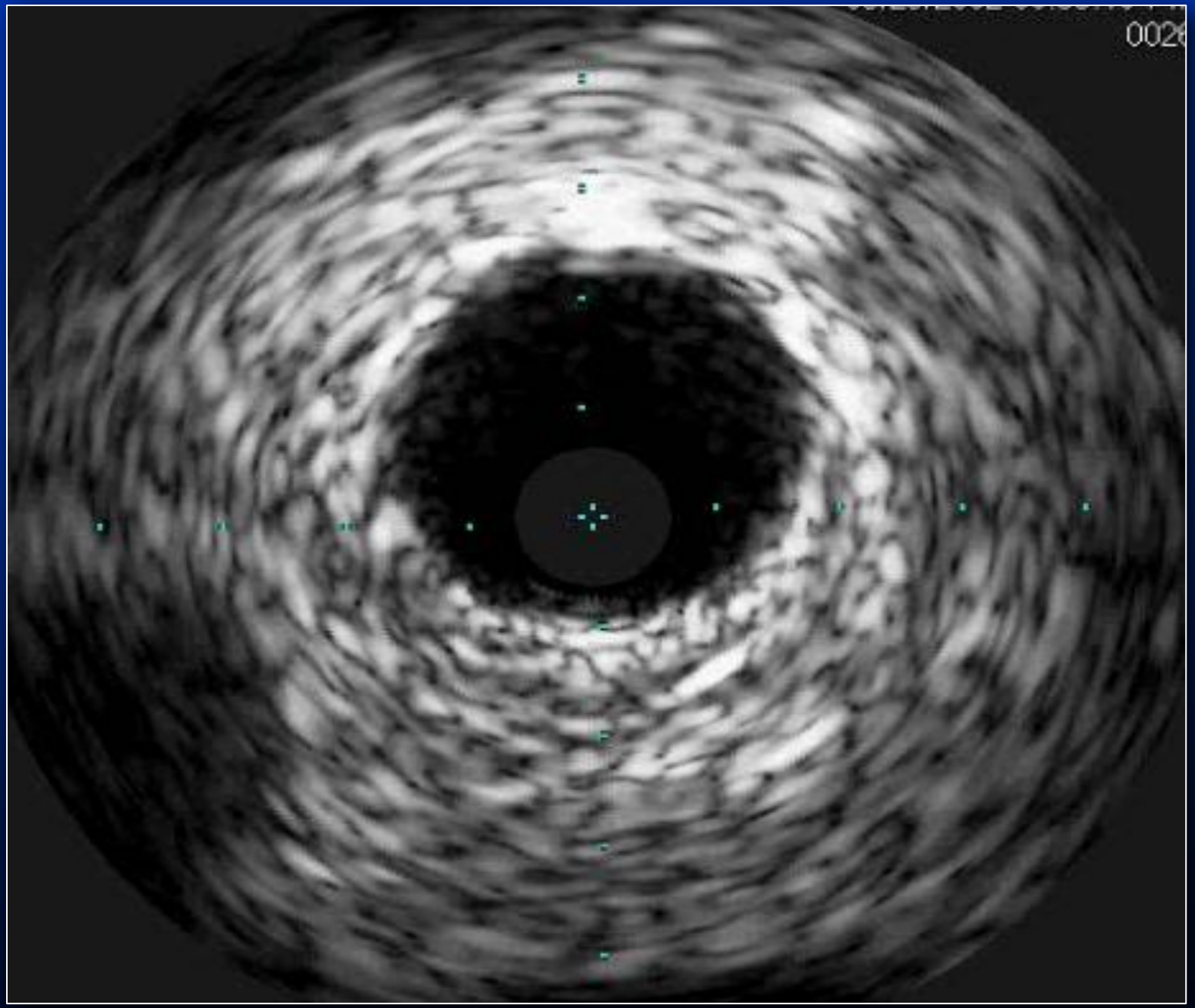


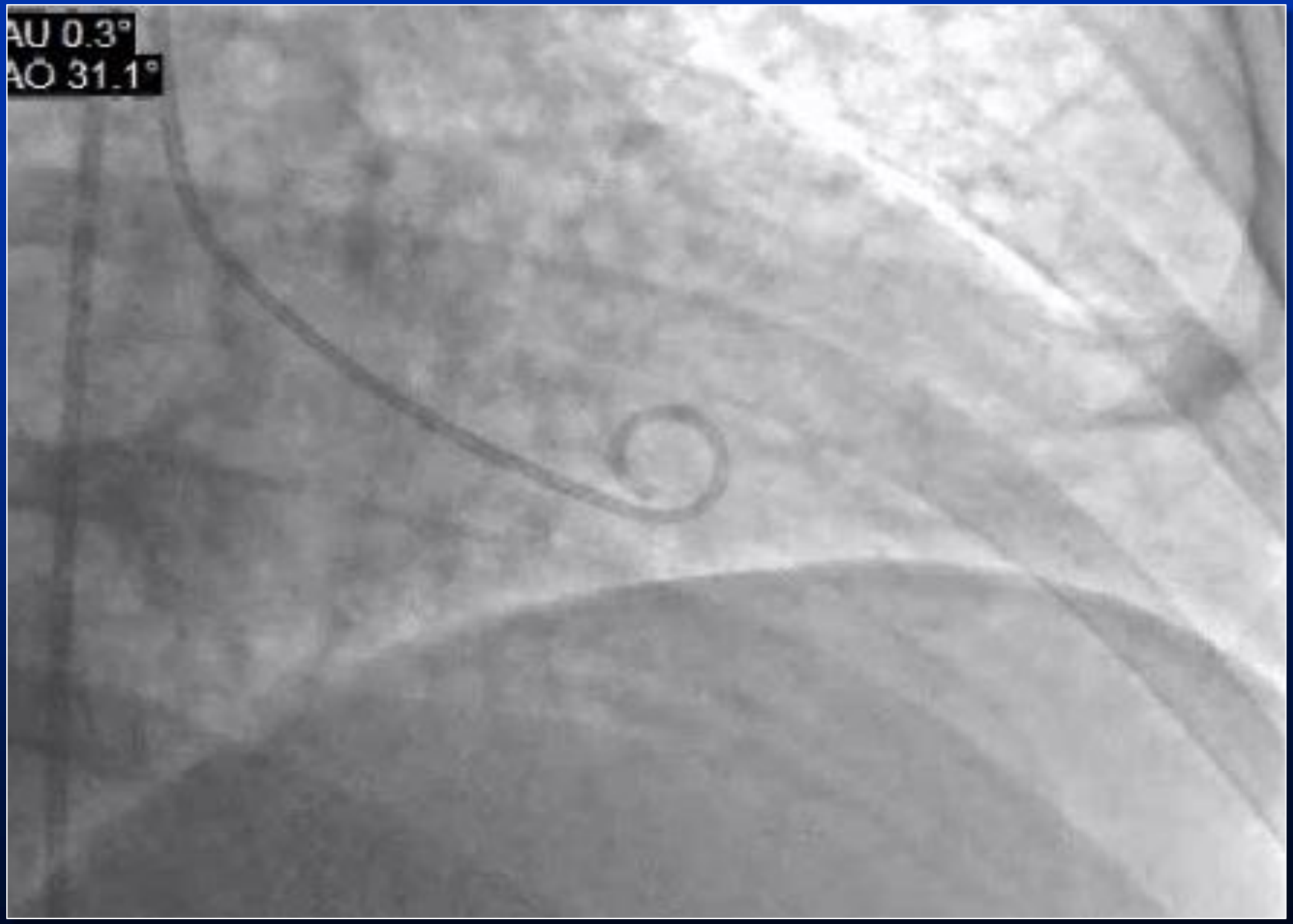
Ruptured Plaque



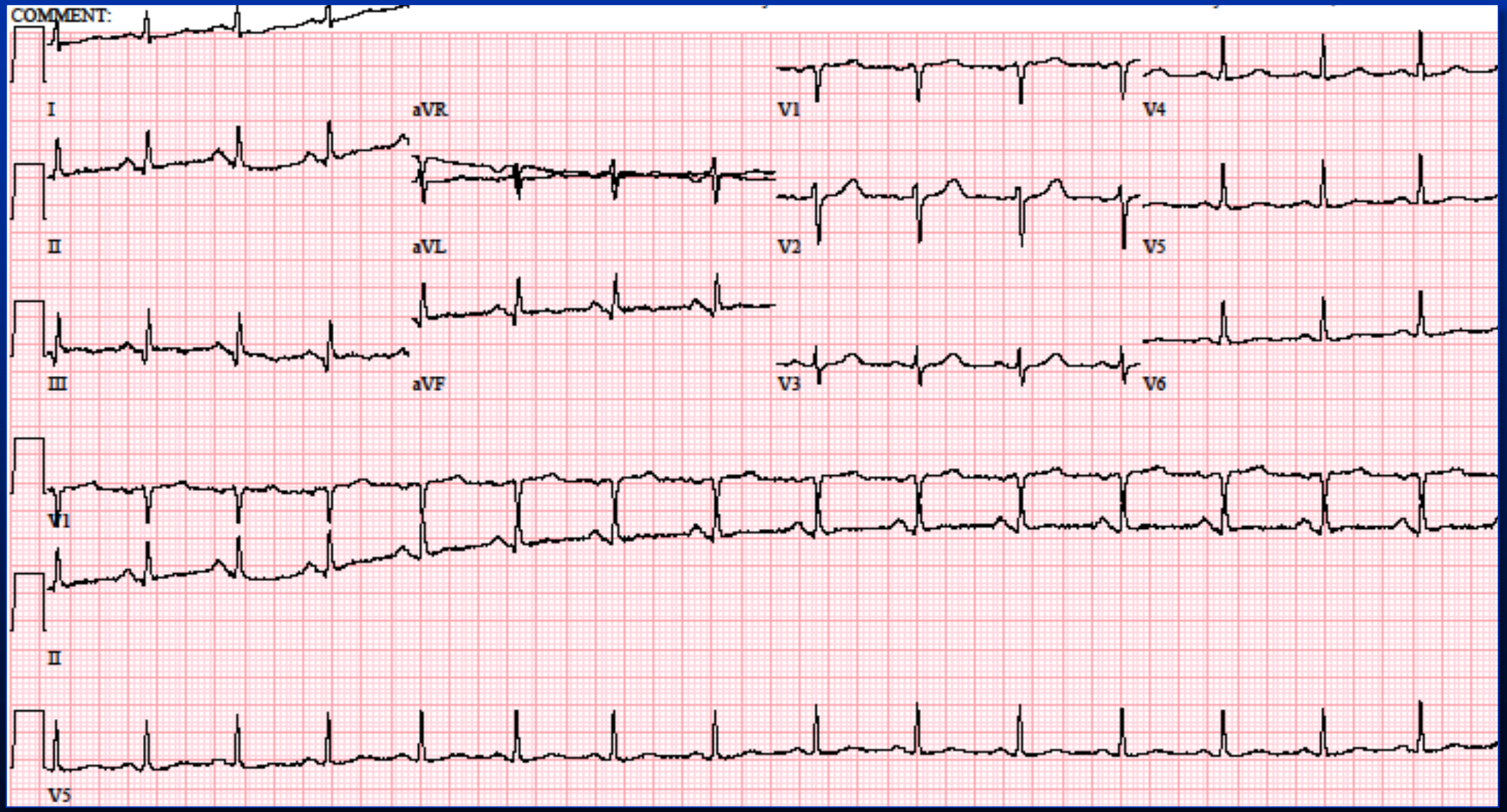
Xience DES 3.5x 23 mm






AU 0.3°
AO 31.1°

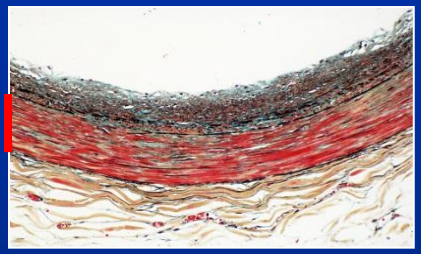
EKG at 10 PM on arrival to ICU. Pain free.



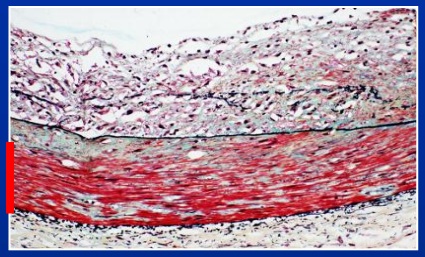
Completely different situation from stable, chronic CAD

Human Coronary Atherosclerosis Development

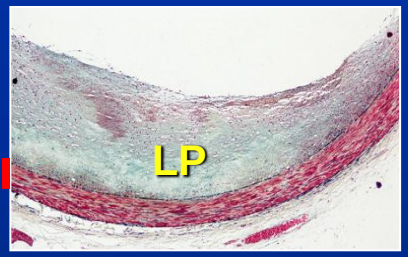
Adaptive Intimal Thickening



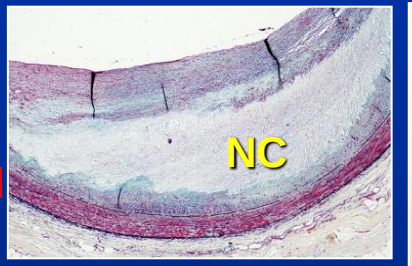
Intimal Xanthoma



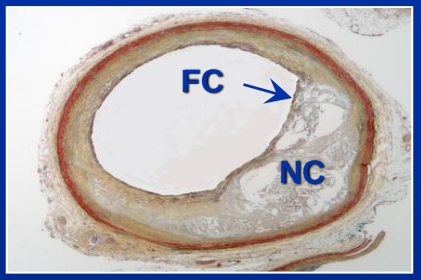
Pathologic Intimal Thickening

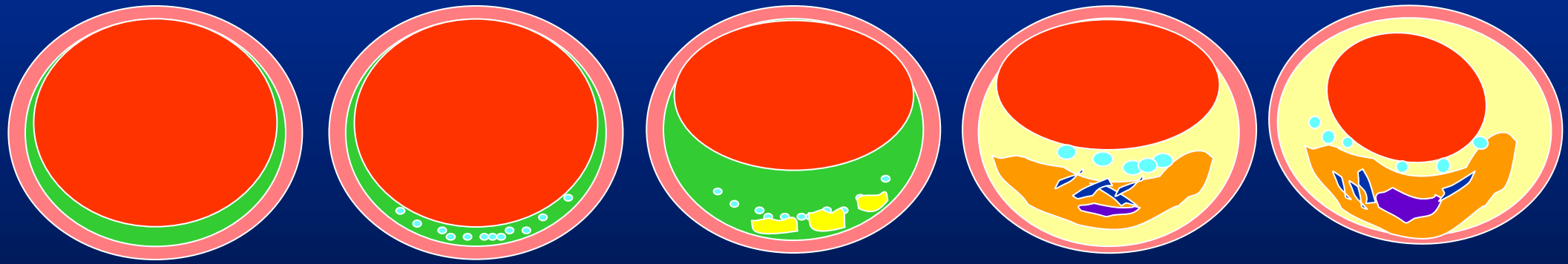


Fibrous Cap Atheroma



Thin-Cap Fibroatheroma





- Smooth muscle cells
- Macrophage foam cells
- Extracellular lipid
- Cholesterol clefts
- Necrotic core
- Calcified plaque
- Hemorrhage
- Thrombus
- Healed thrombus
- Collagen

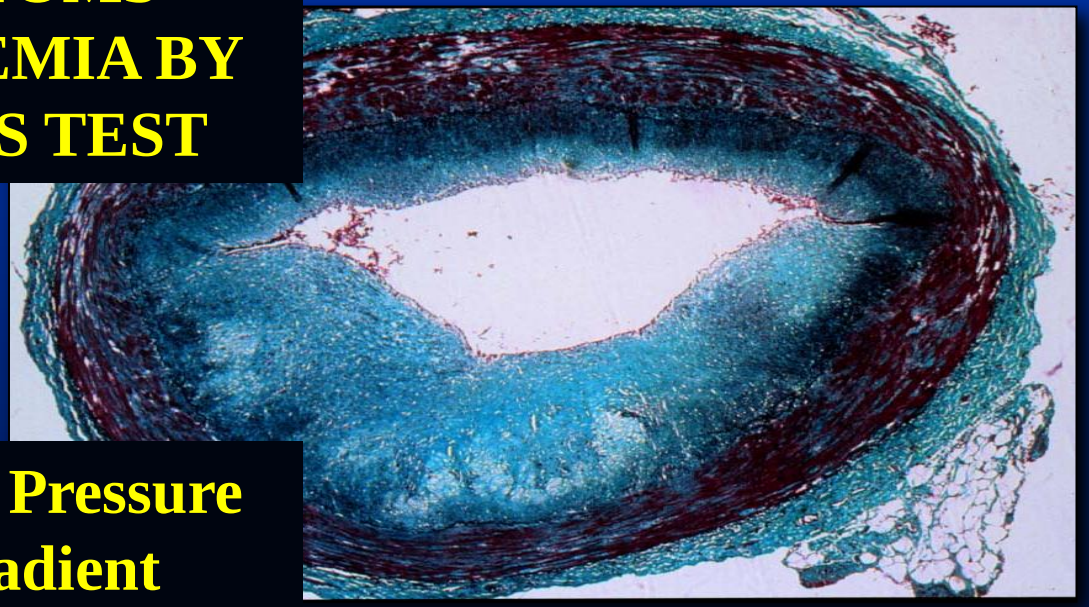
FC = Fibrous cap
LP = Lipid pool
NC = Necrotic core

Stable Coronary Artery Disease

Pathologic intimal thickening

STENT ONLY IF…

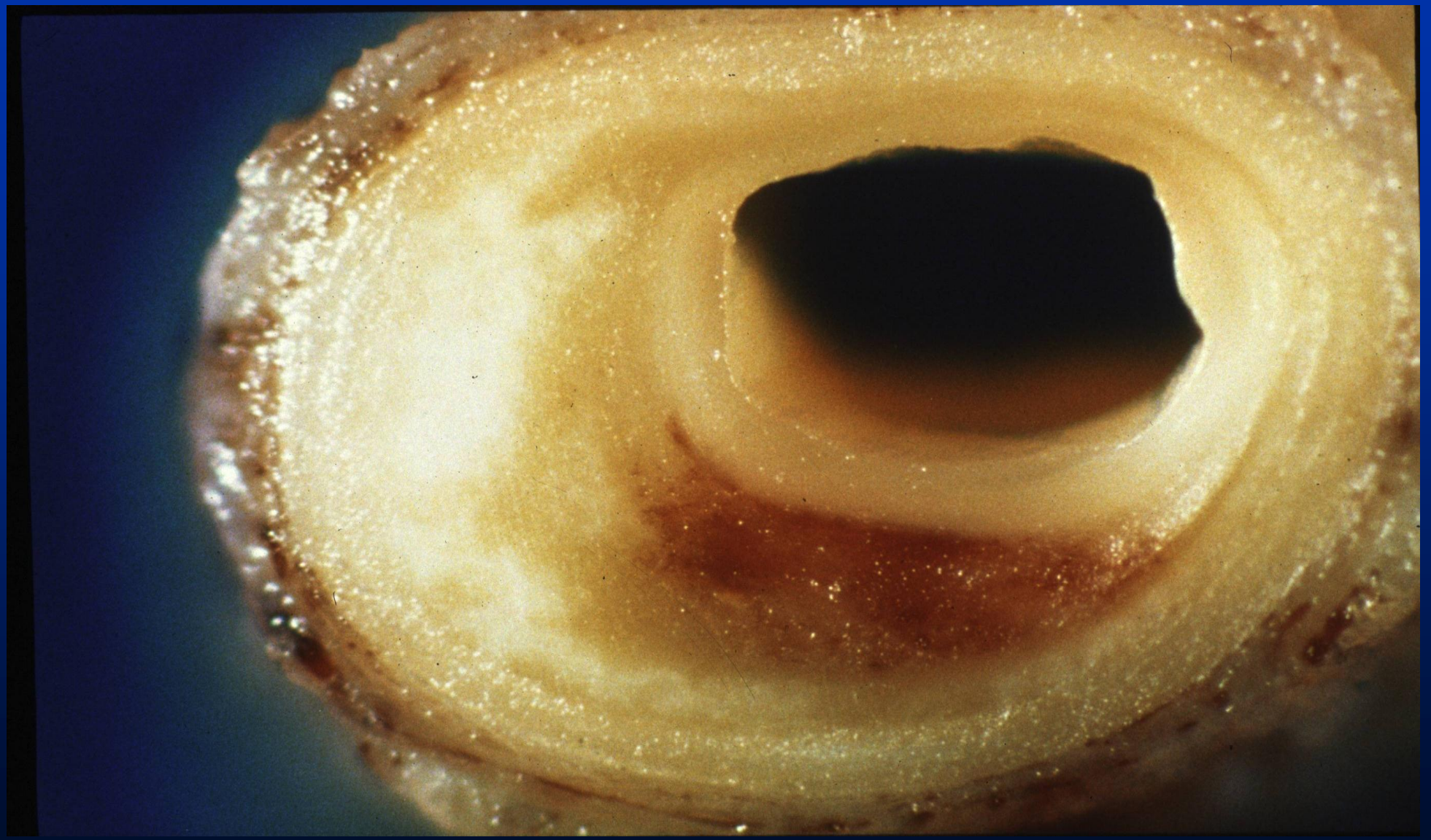
- **-CLASS III SYMPTOMS**
- **-ISCHEMIA BY STRESS TEST**
- **FFR: Pressure gradient**



WHY?

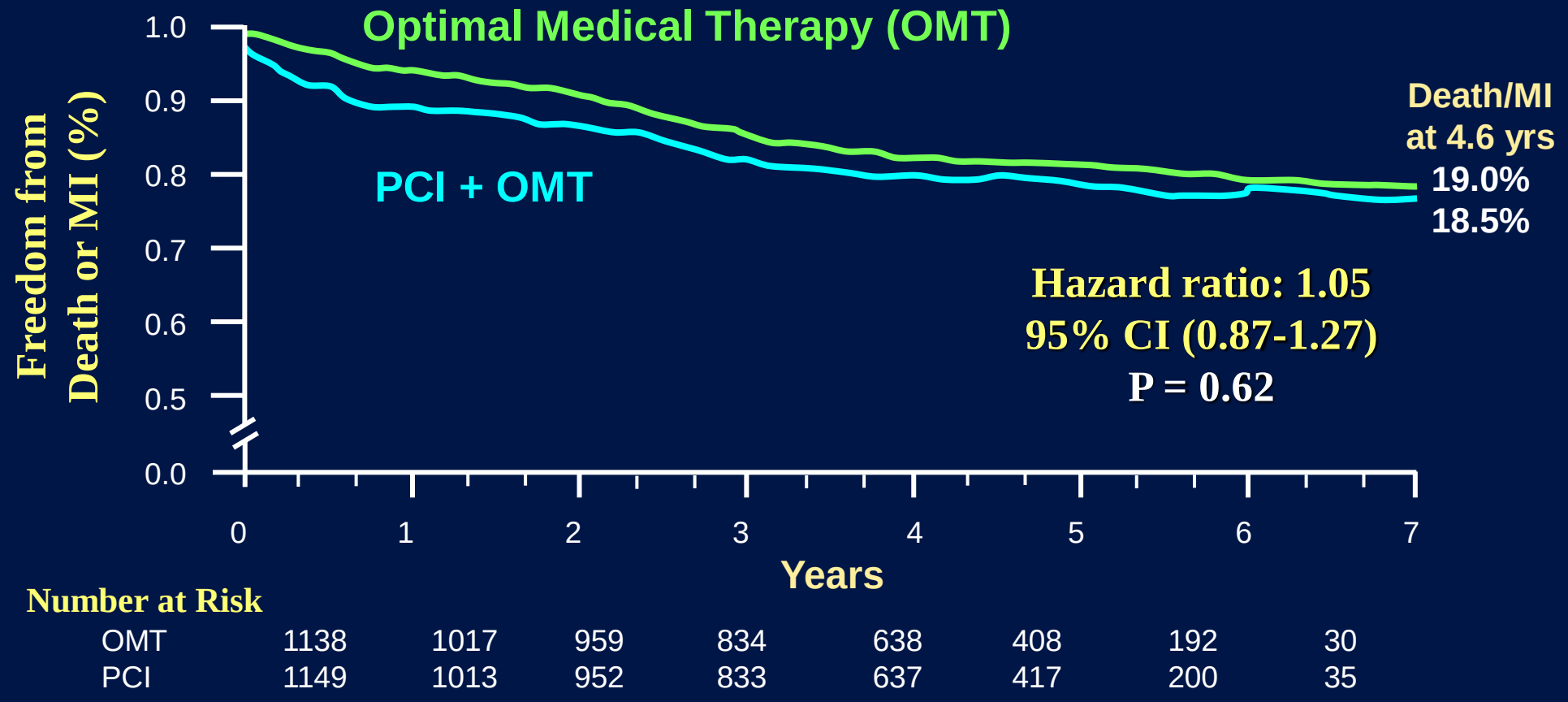
PCI in stable CAD decreases the frequency of angina and improves exercise performance, without reducing death or MI

Can you judge “unnecessary stenting”?



PCI in Stable CAD: COURAGE

Median FU 4.6 years



2,287 SIHD ***STABLE*** patients randomized to PCI+OMT vs. OMT

Boden WE et al. NEJM 2007;356:1503-16

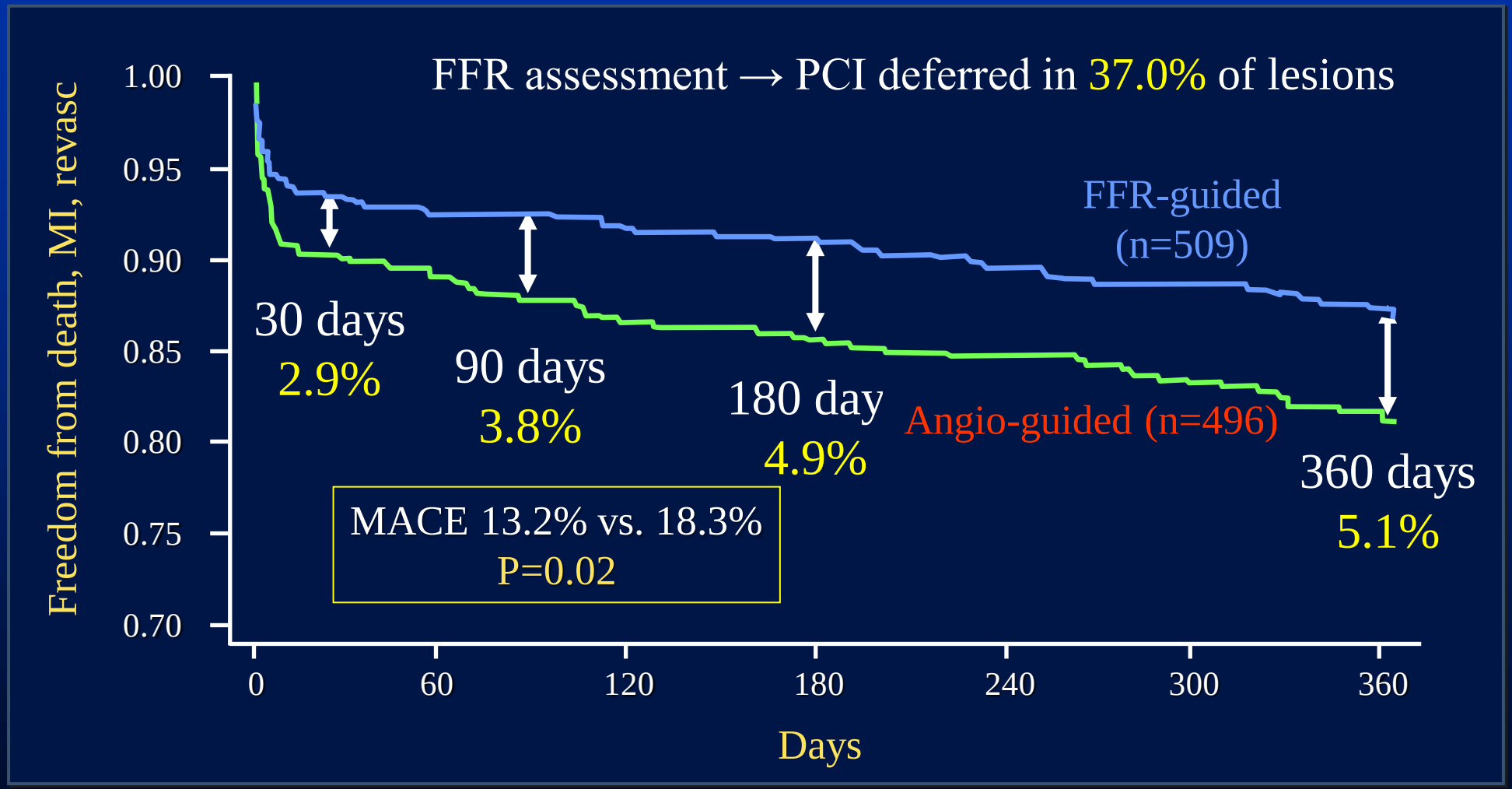
TAKE HOME MESSAGE #1:

"IN MOST STABLE CAD PATIENTS: INITIAL TRIAL OF MEDICAL THERAPY IS INDICATED PRIOR TO CATH AND PCI".

*13 RCTs in 7,605 patients

FAME: Primary Endpoint

1005 pts with MVD undergoing PCI with DES were randomized to FFR-guided vs. angio-guided intervention



Tonino **PAL et al. NEJM 2009;360:213–24**

TAKE HOME MESSAGE #2 :

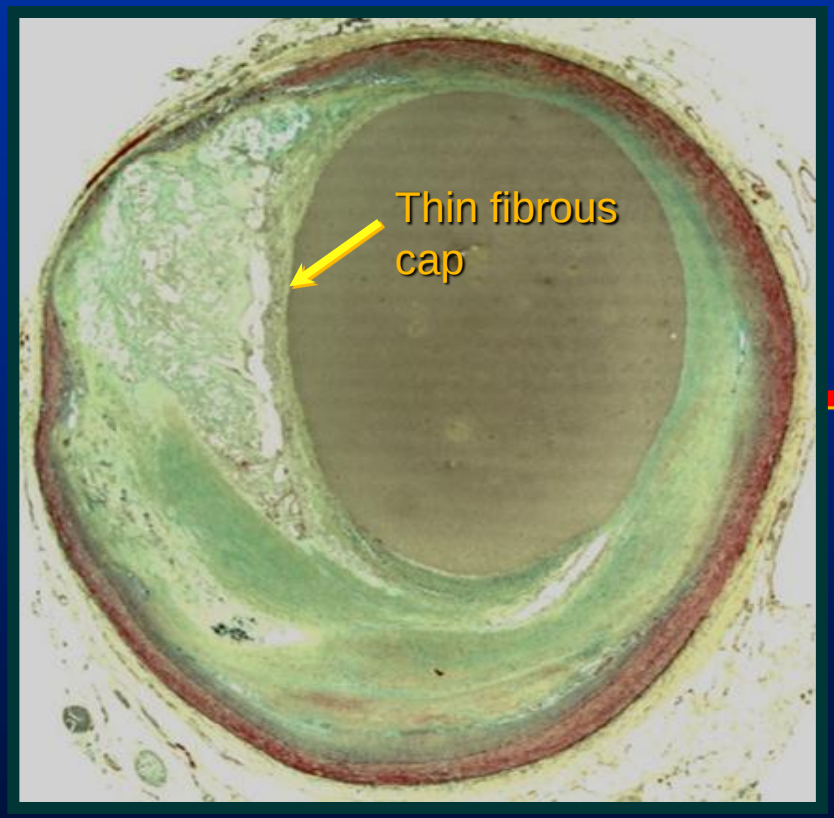
IN STABLE CAD PATIENTS UNDERGOING CARDIAC CATHERIZATION, REVASCULARIZATION SHOULD BE DONE ONLY IN ISCHEMIA-PRODUCING LESIONS

*13 RCTs in 7,605 patients

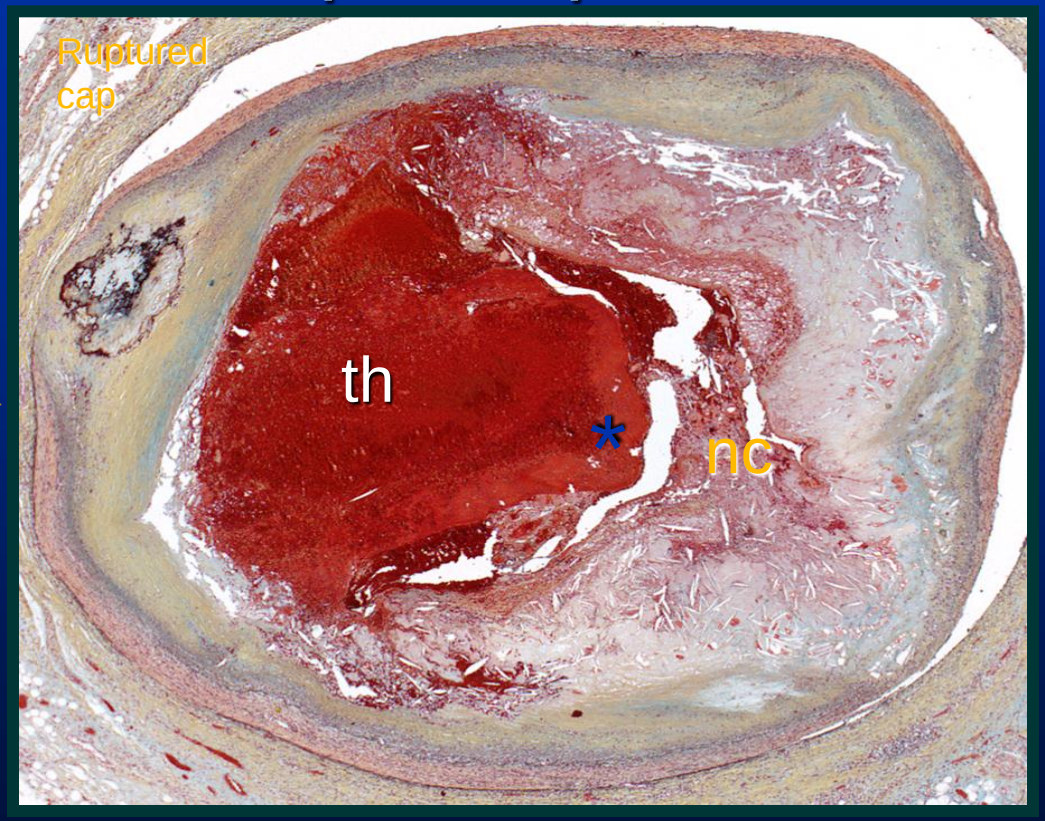
UNSTABLE CORONARY SYNDROMES
OR
“ACUTE CORONARY SYNDROMES”

Thin Cap Fibroatheroma (TCFA) is the Precursor Lesion of Plaque Rupture

TCFA



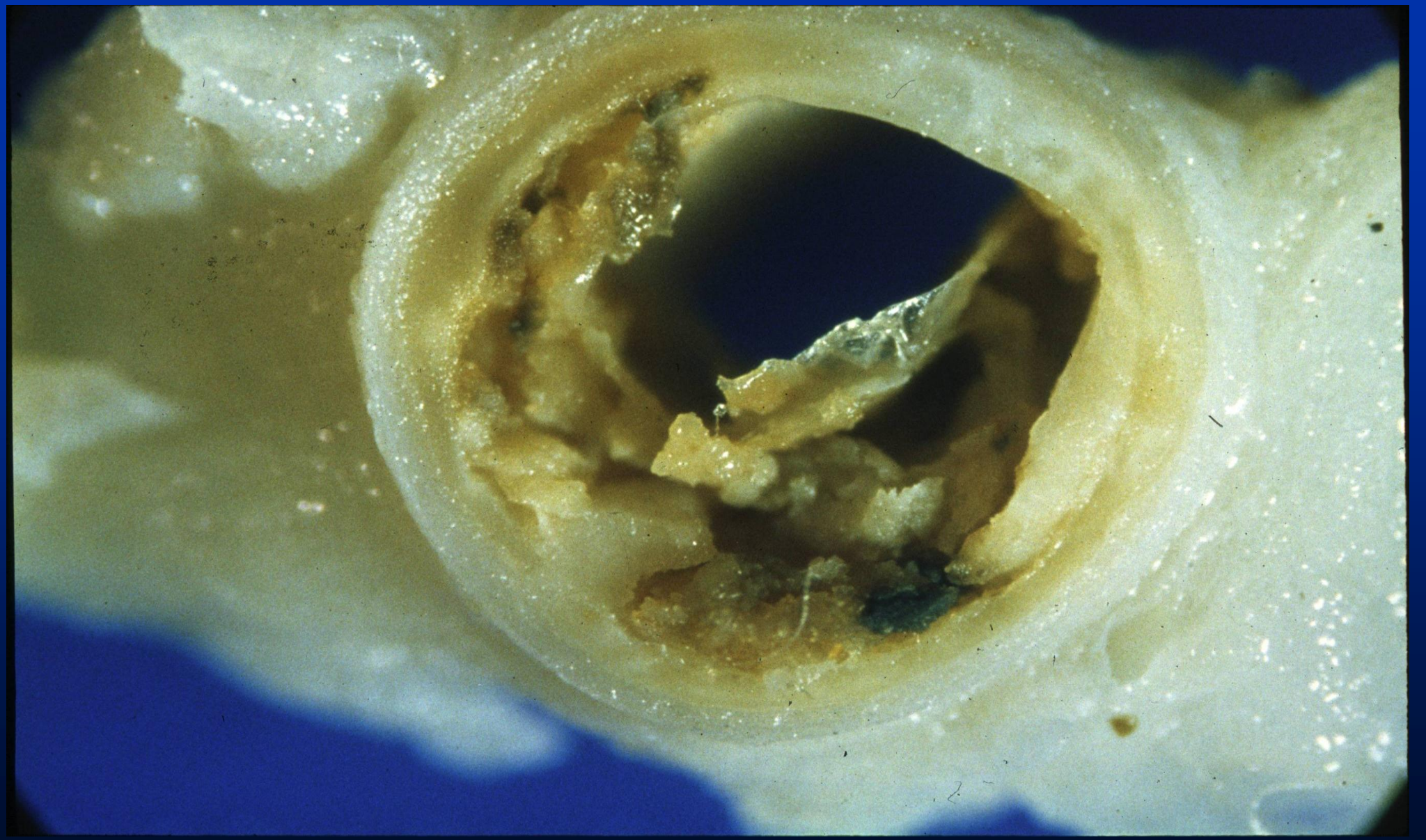
Plaque Rupture

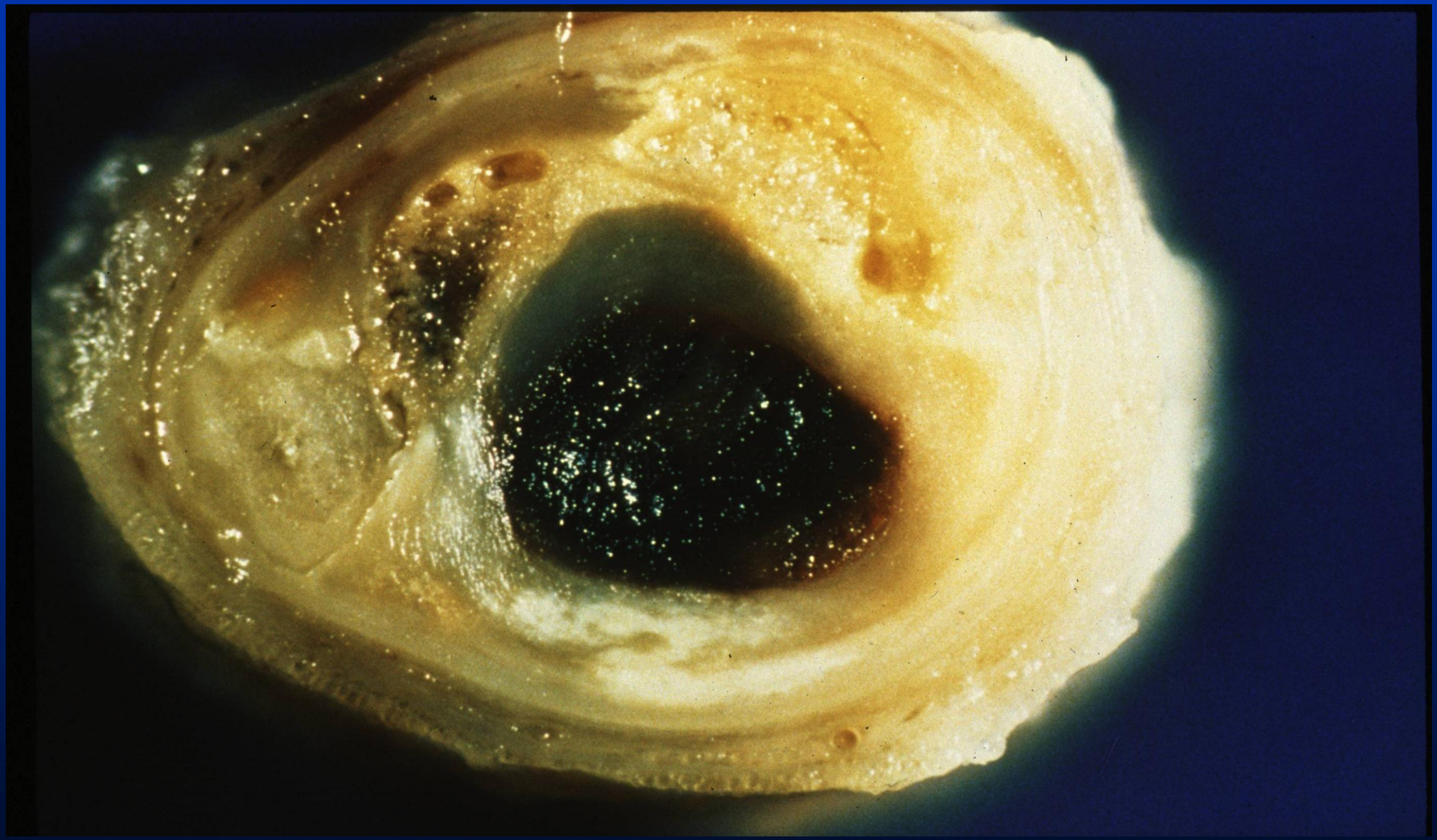


TCFA =

- Lipid rich necrotic core
- Thin fibrous cap (<65 um)

- Cap = type 1 collagen with few SMC and infiltrated by M and Lymph

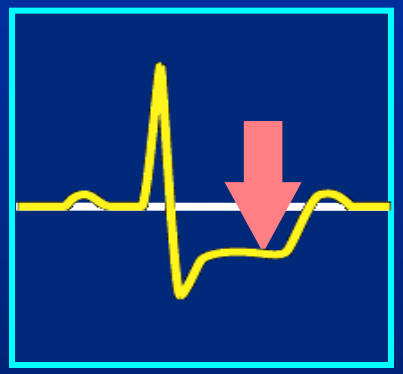




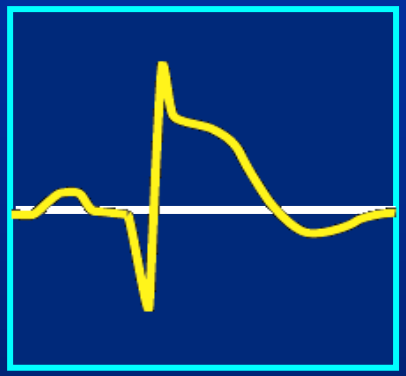
ACS

CLINICAL PRESENTATION

Acute Coronary Syndromes (ACS)



Acute Coronary Syndromes



UA/NSTEMI

STEMI

1.42 million
admissions per year

0.41 million
admissions per year

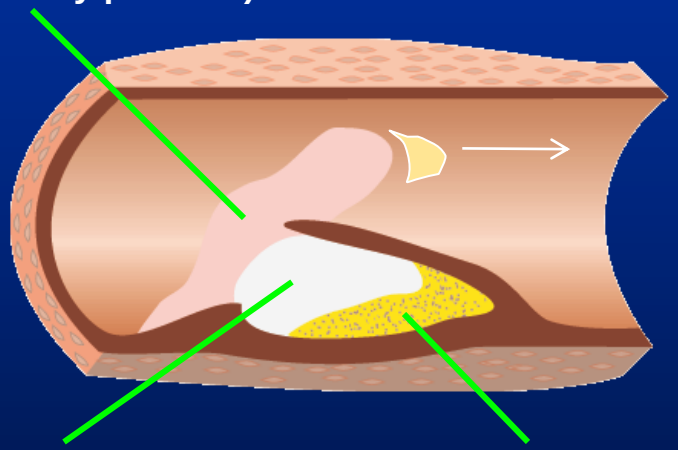
National Hospital Discharge Survey 1998. National Center for Health Statistics/Centers for Disease Control and Prevention. Series 13, No.14. September 2000.

Clinical Manifestations of Arterial Thrombosis

Vulnerable Plaque

UA/NSTEMI

Partially-occlusive thrombus (primarily platelets)

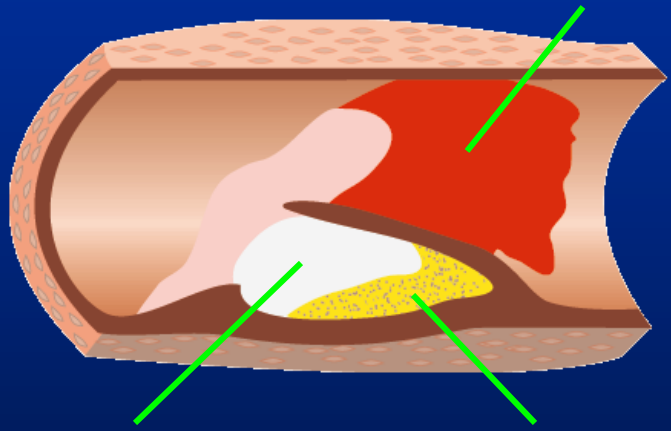


Intra-plaque thrombus (platelet dominated)

Plaque core

STEMI

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



Intra-plaque thrombus (platelet dominated)

Plaque core

SUDDEN DEATH

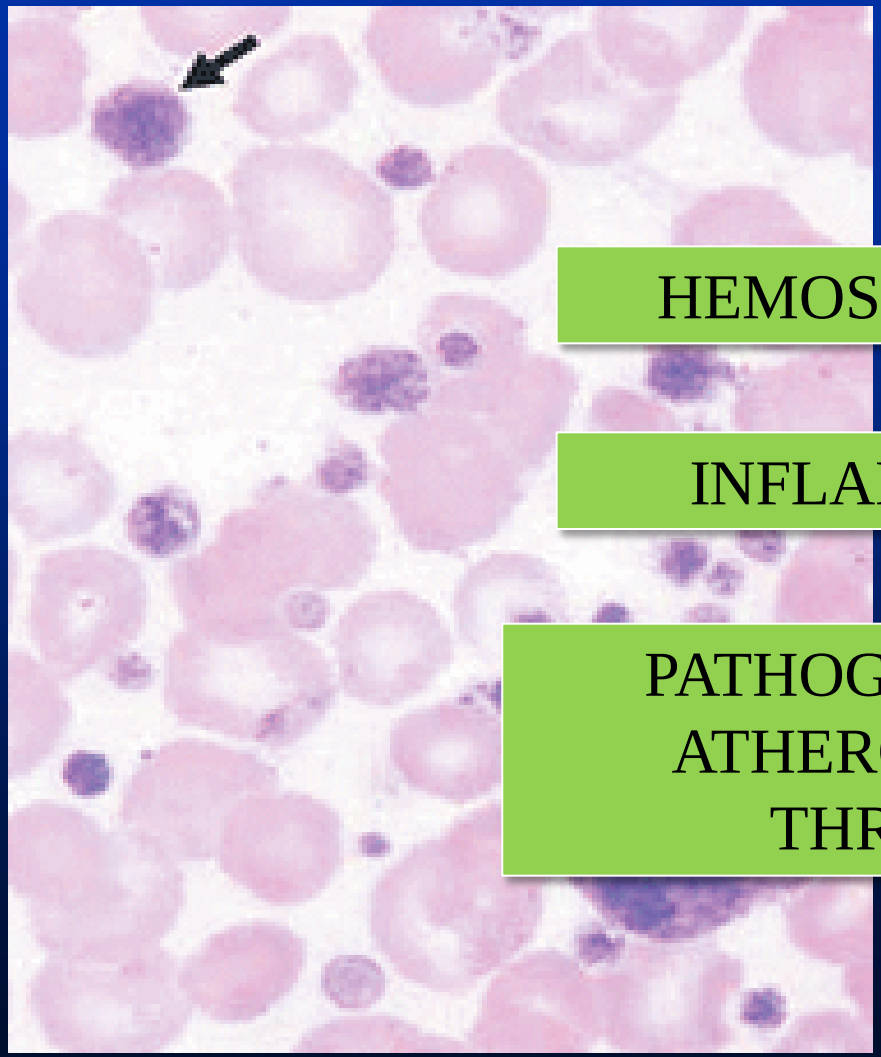
Adapted from Davies MJ. *Circulation.* 1990; 82 (supl II): 30-46.

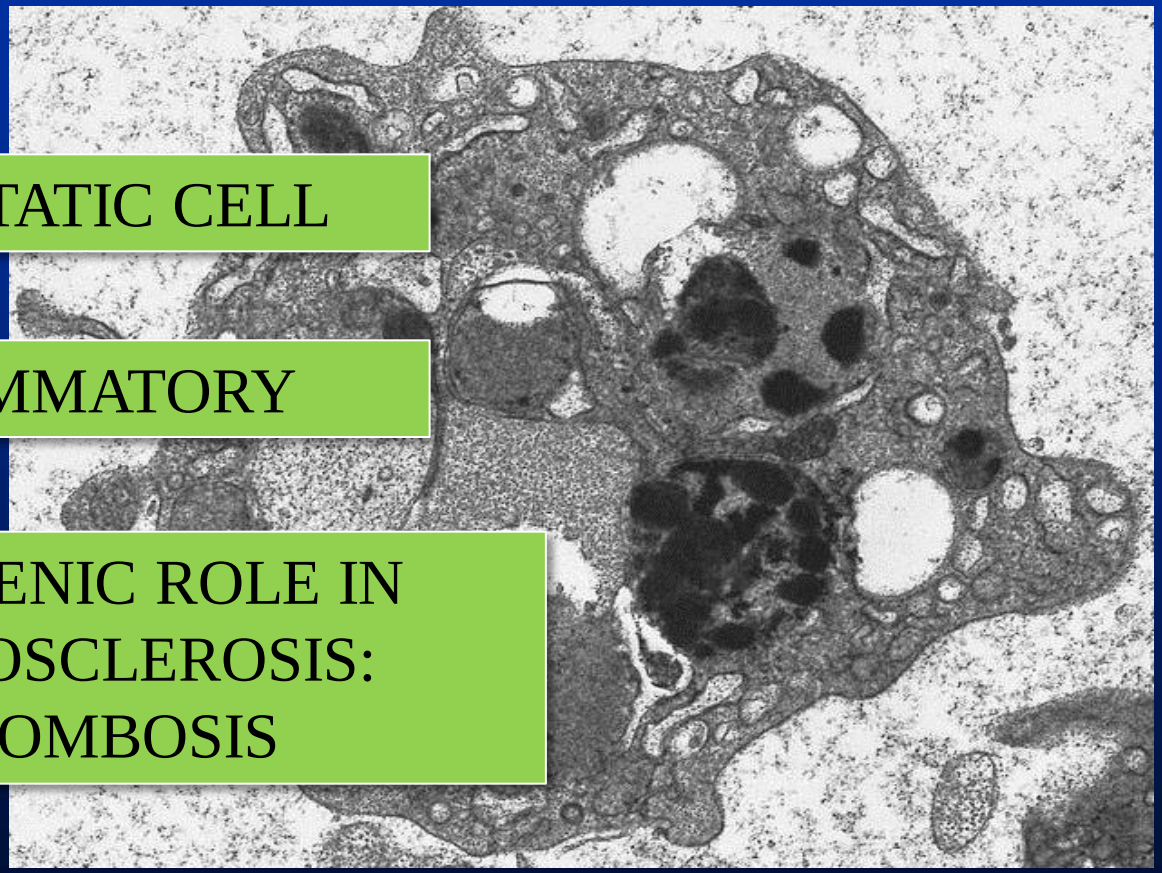
Prevalence of Multiple Coronary Plaques in Patients With Acute Coronary Syndrome

Study	Diagnostic technique	Patients with multiple plaques (%)
Non-Q-wave MI[1]	Angiography	48/350 (14%)
Acute MI[2]	Angiography	100/253 (39%)
Unstable angina[3]	Angiography	128/228 (56%)
ACS[4]	IVUS	19/24 (79%)
Post-MI[5]	Angioscopy	20/20 (100%)

1. Kerensky R. *JACC*. 2002;39:9:1456-1462.
2. Goldstein AR. et al. *N Engl J Med.* 2000; 343:915-922.
3. Zairis M. *Atherosclerosis.* 2002;164:355-359.
4. Rioufol G. *Circulation*. 2002;106:804-808.
5. Asakura M. *JACC*. 2001;37:5:1284-1288.

PLATELET



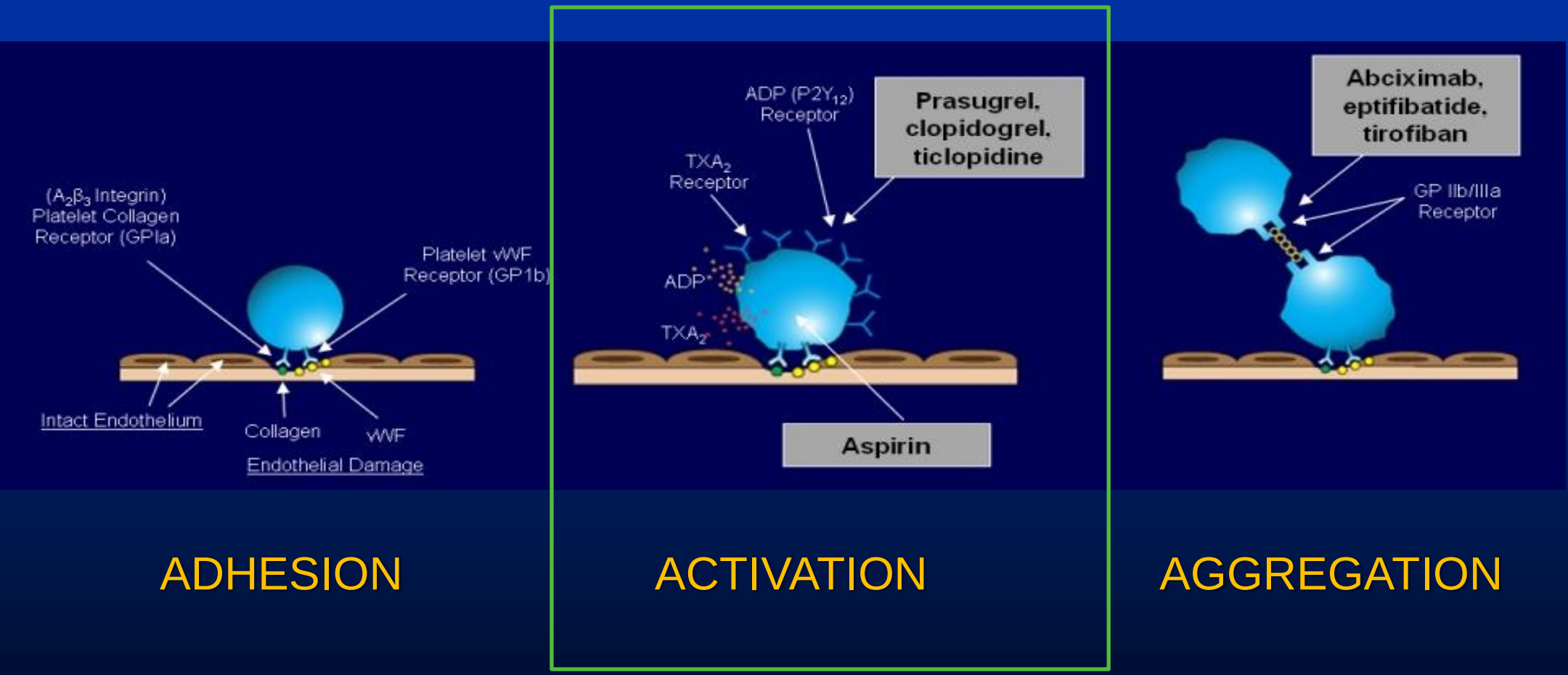


HEMOSTATIC CELL

INFLAMMATORY

PATHOGENIC ROLE IN ATHEROSCLEROSIS: THROMBOSIS

PLATELET MEDIATED THROMBOSIS

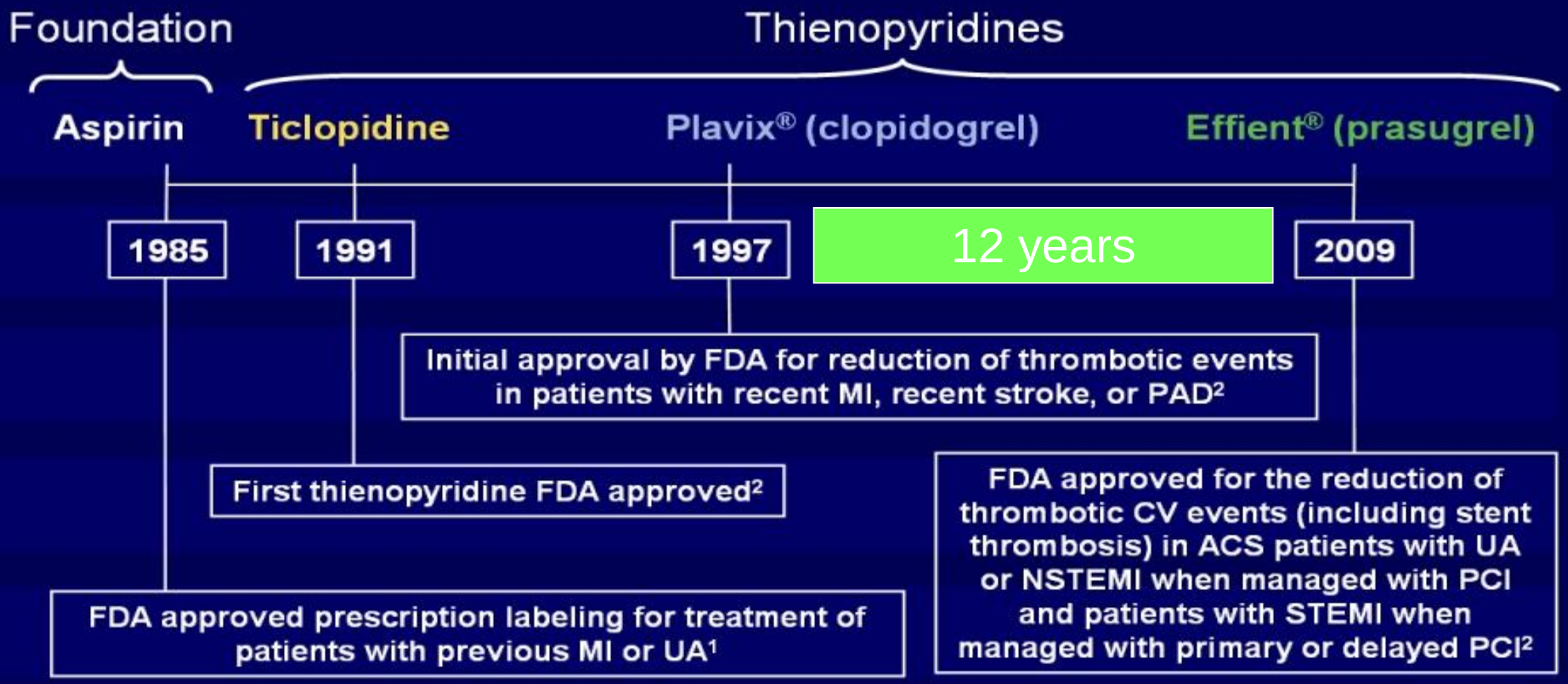


ADHESION

ACTIVATION

AGGREGATION

Evolution of Oral Antiplatelet Therapy



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® Effient and the Effient logo are registered trademarks of Eli Lilly and Company.

1. Aspirin for heart patients. *FDA Drug Bull.* 1985;15:34-36.
2. FDA/Center for Drug Evaluation and Research. FDA Approved Drug Products. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 13, 2009.

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

Antiplatelet Trialists' Collaboration

Meta-analysis of Antiplatelet Agents

Overview of 174 randomized trials
in 100,000 individuals

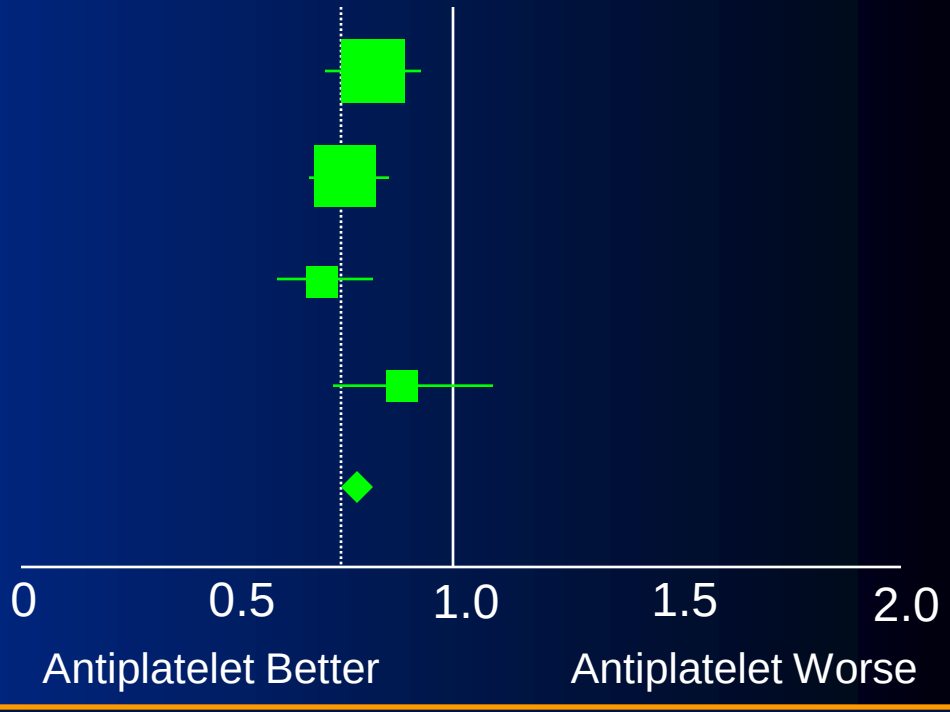
	Reduction of CV Events*
Aspirin vs Placebo	25%
Dipyridamole vs Placebo	16%
Ticlopidine vs Placebo	33%
Ticlopidine vs Aspirin	10%
DP + Aspirin vs Aspirin	- 1%

*Events = MI, stroke, or vascular death

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

Efficacy of Aspirin Doses on Vascular Events in High Risk Patients

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

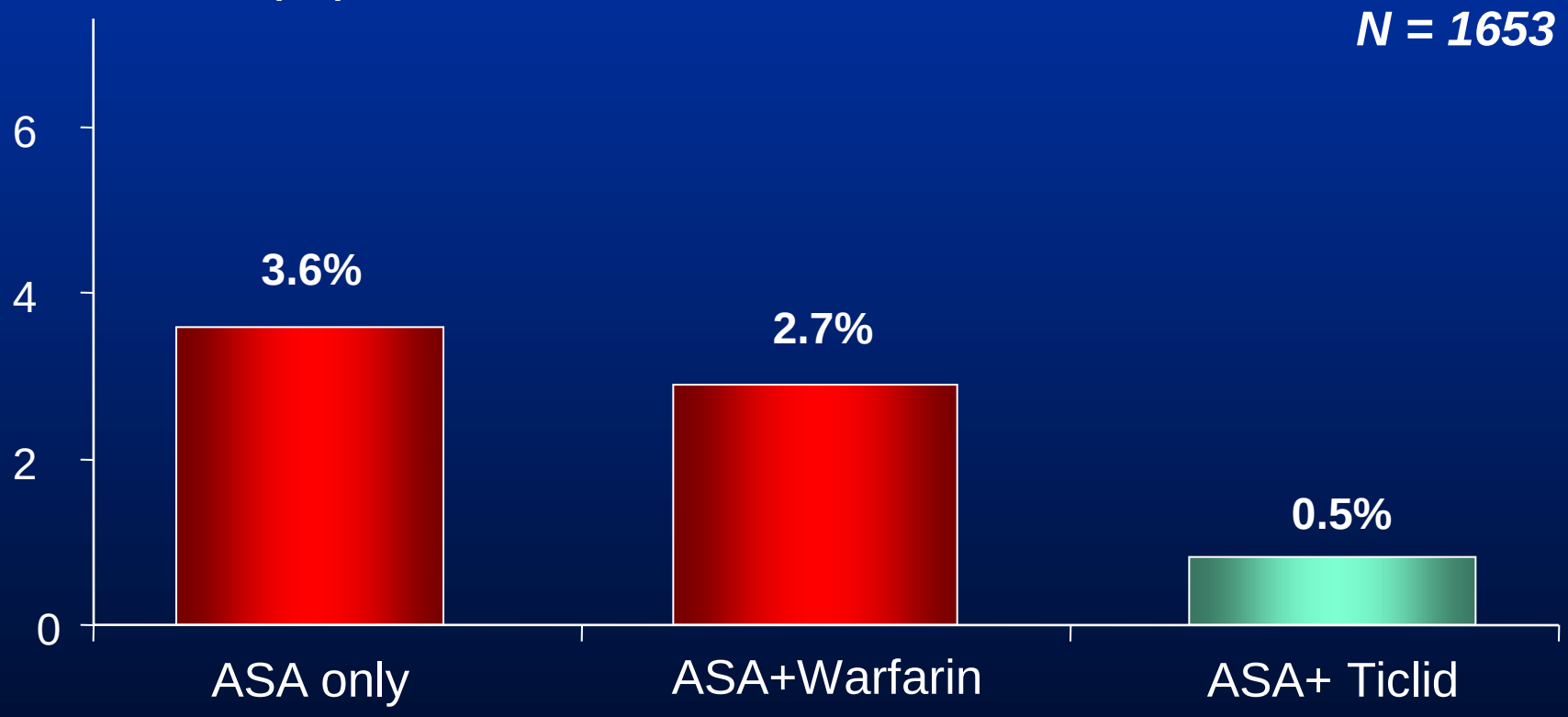


*Odds reduction.
Treatment effect $P < 0.0001$.

Adapted with permission from the BMJ Publishing Group. Antithrombotic Trialists' Collaboration. *BMJ.* 2002;324:71-86.

Antiplatelet Therapy in Reducing Ischemic Events after Coronary Stenting : STARS

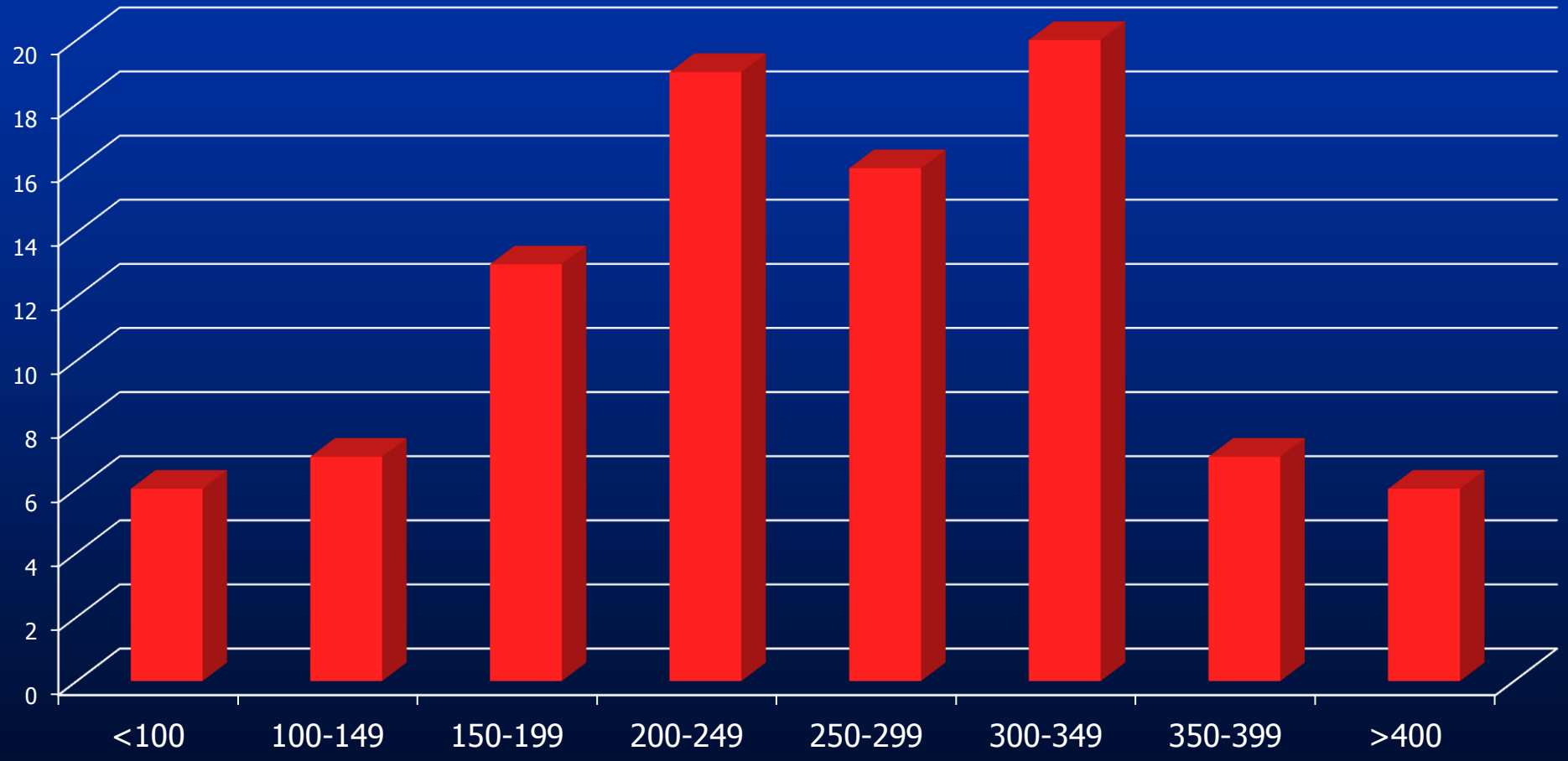
Event rate: Death, MI, CABG or Reintervention (%)



Leon M et al. *N Engl J Med*. 1998.

P2Y12 Reactivity on Clopidogrel:

PRU (n=94)

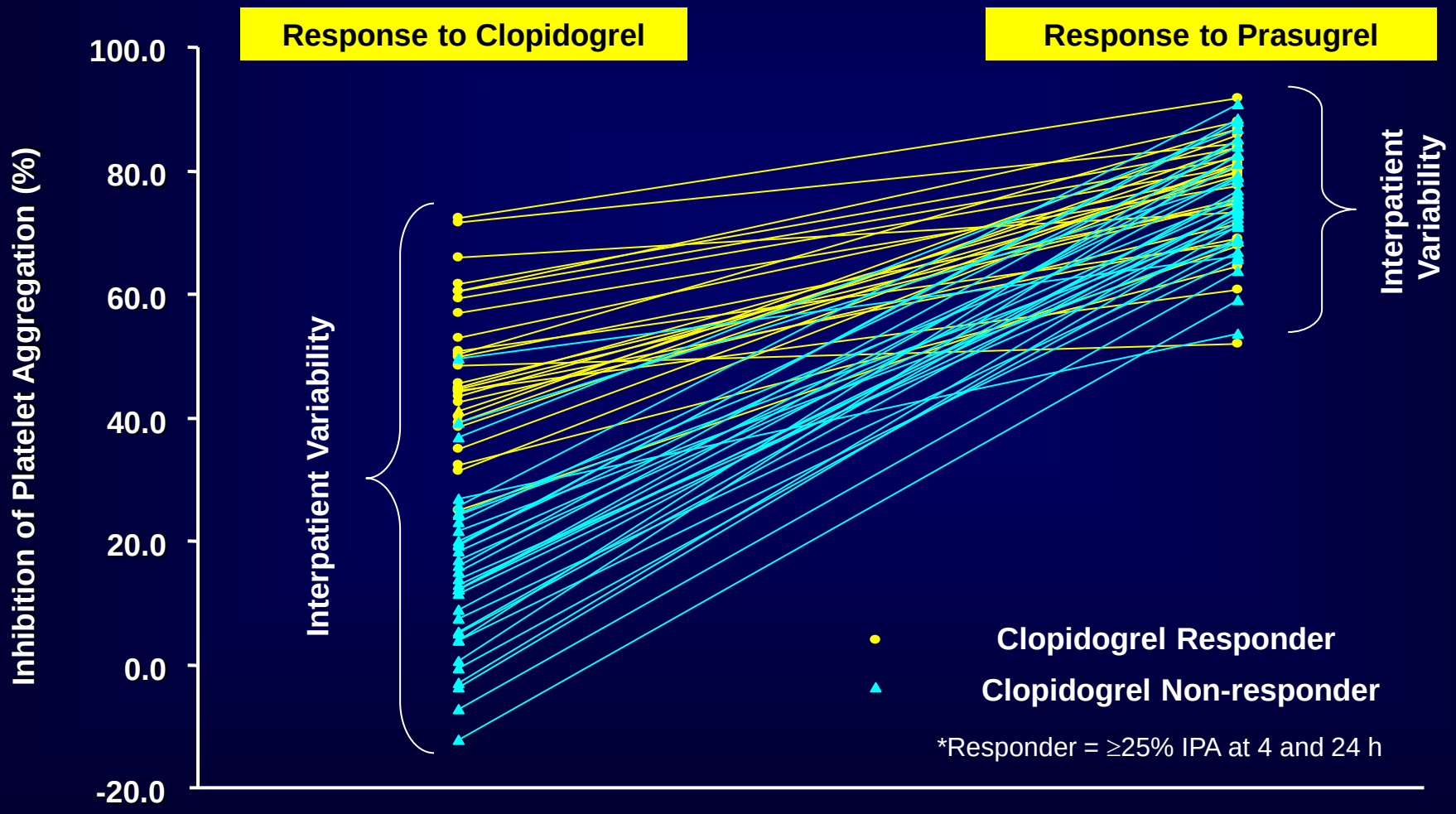


PRU using Verify*Now*

Inhibition of Platelet Aggregation:

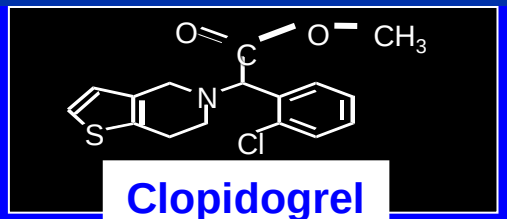
Clopidogrel(PLAVIX) Vs. Prasugrel (EFFIENT)

Healthy Volunteers at 24 Hours, N=68



Brandt JT et al., *Am Heart J* 2007;153:e9-e16.

Thienopyridines: Equipotent Active Metabolite



Clopidogrel

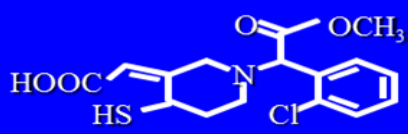
85% Inactive Metabolites

Oxidation (Cytochrome P450)

CYPs:
1A2
2C19
2B6

Oxidation (Cytochrome P450)

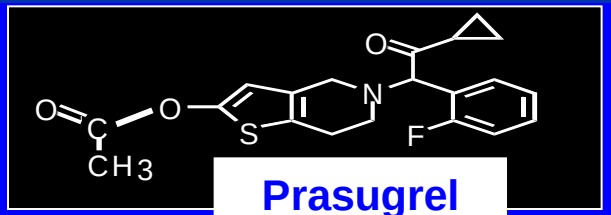
CYPs:
3A
2C19
2C9
2B6



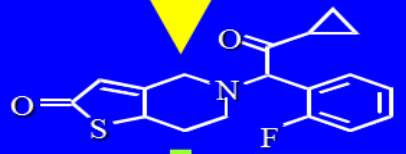
Active Metabolite

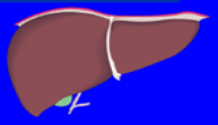
Pro-drugs

Hydrolysis (Esterases)



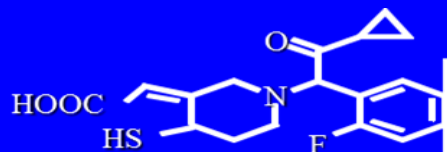
Prasugrel





Oxidation (Cytochrome P450)

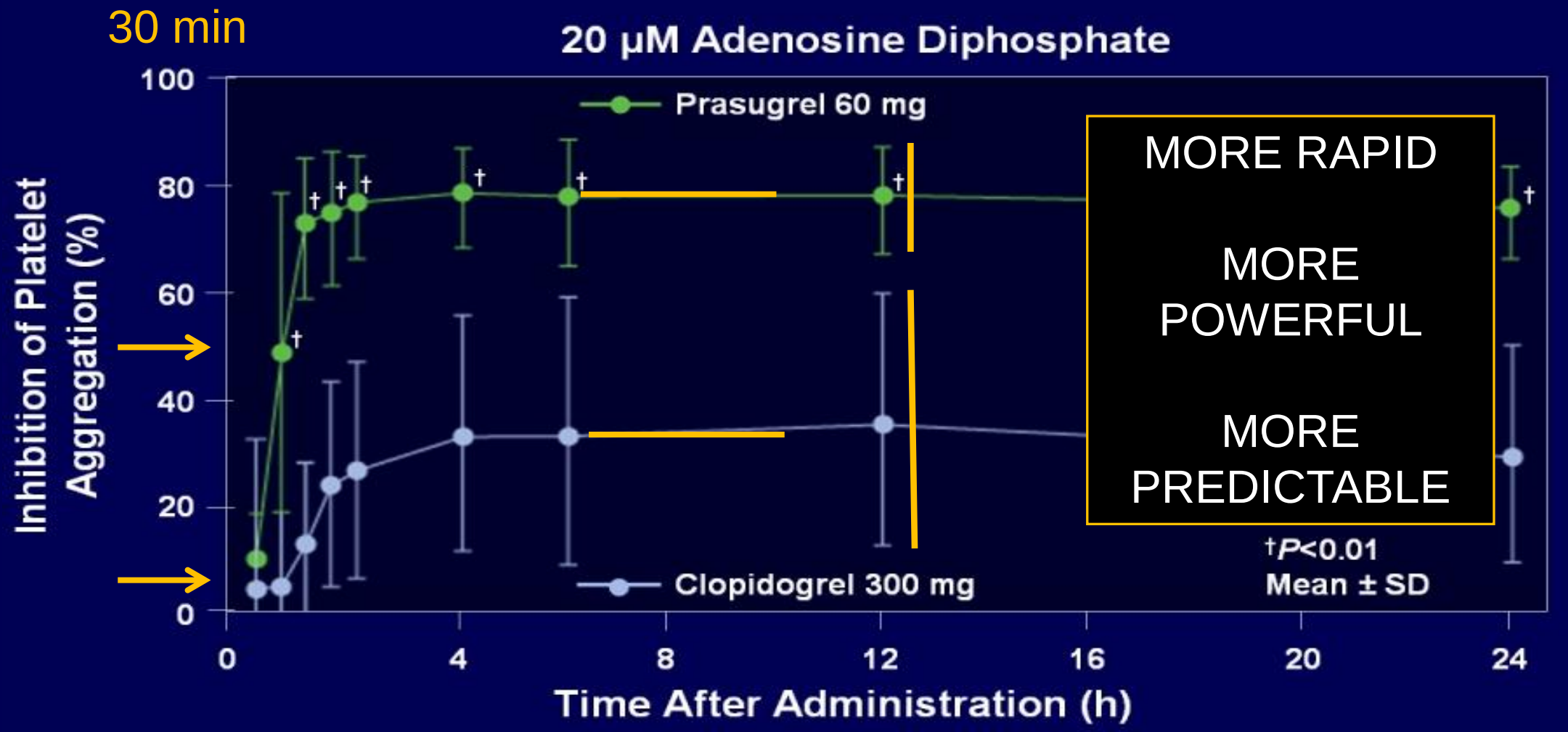
CYPs:
3A
2B6
2C9
2C19



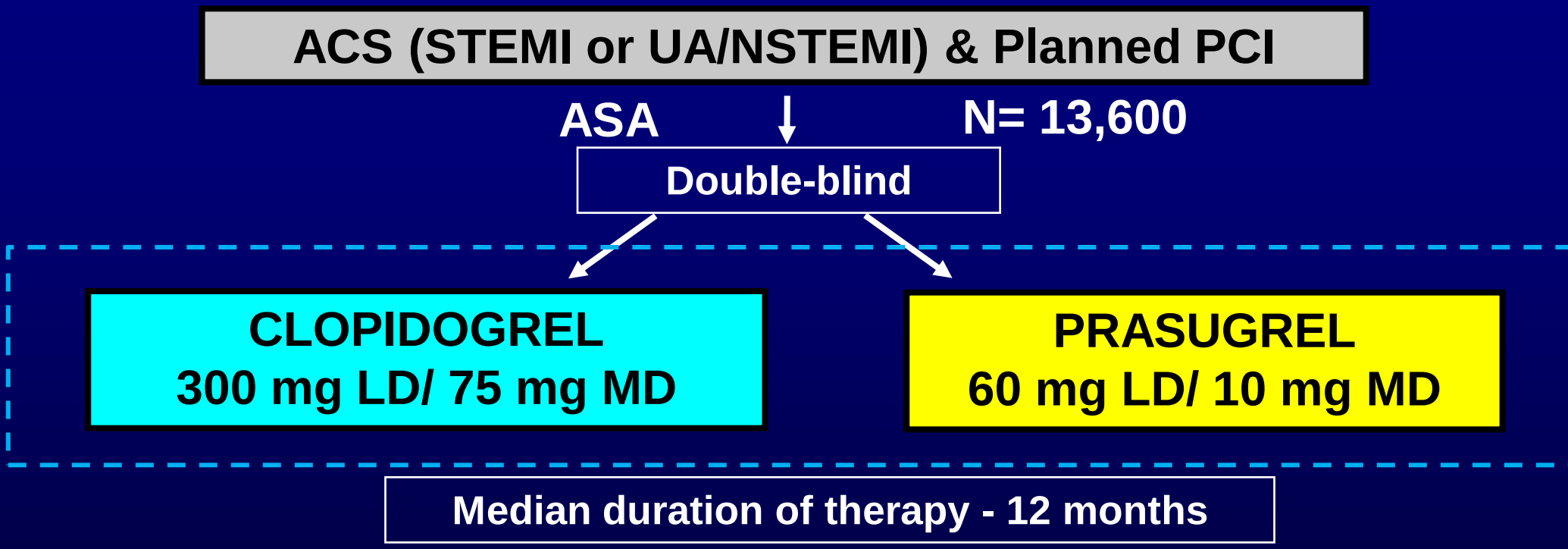
Active Metabolite

Mega JL, NEJM 2008 and Mega JL Circ 2009

PLATELET INHIBITION



TIMI-38 Study Design

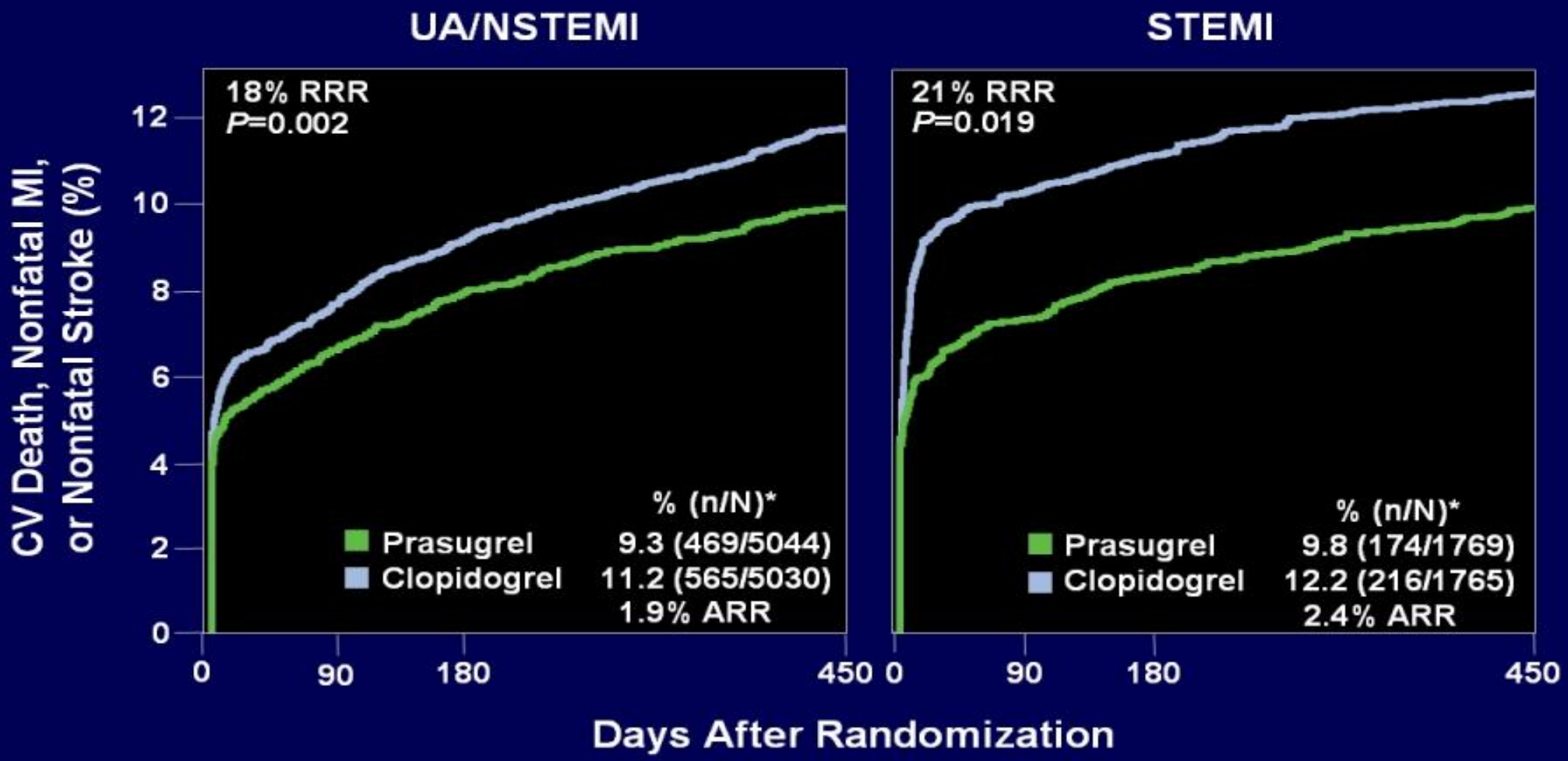


CV death, MI, Stroke

Stent Thrombosis

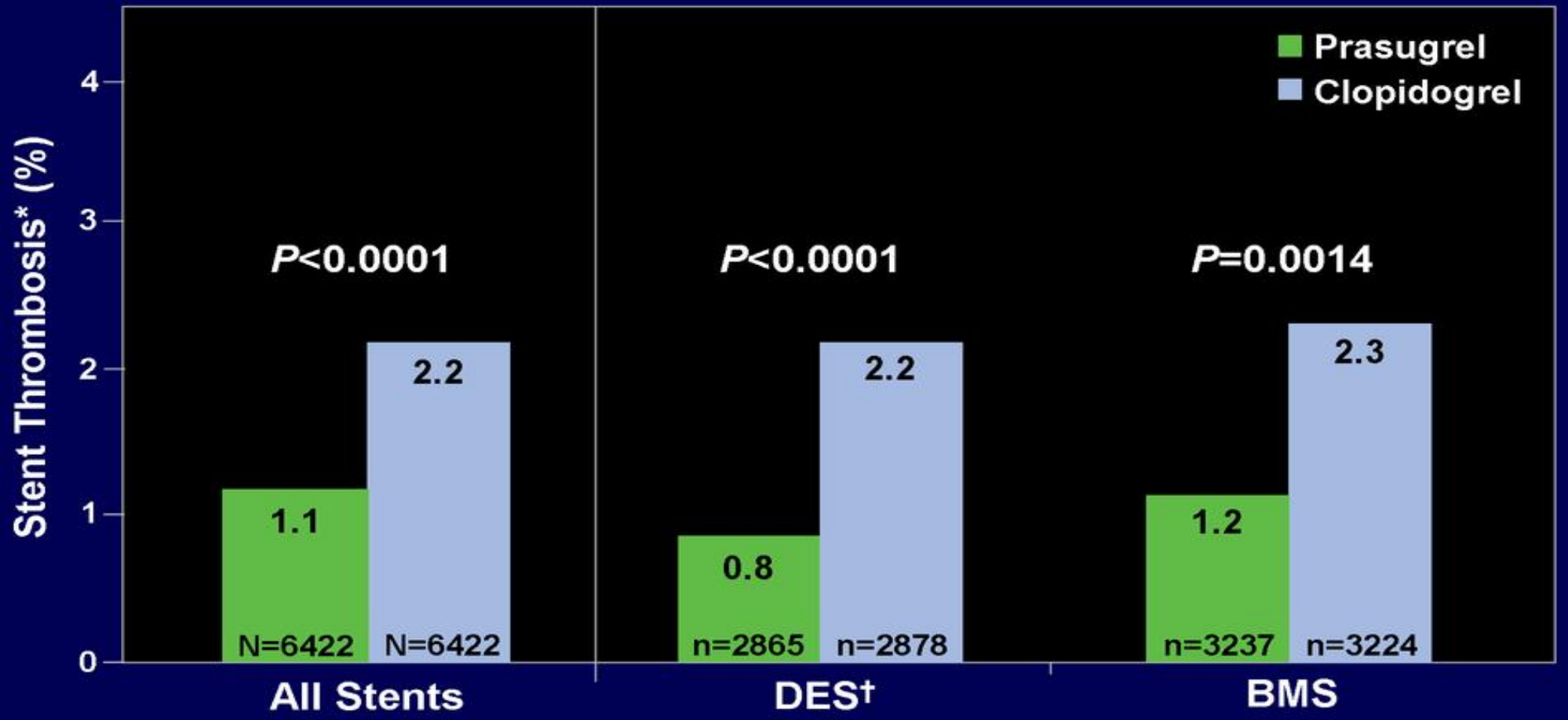
Safety endpoints: ***TIMI major bleeds, Life-threatening bleeds***

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



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

Stent Thrombosis Rates at End of Study



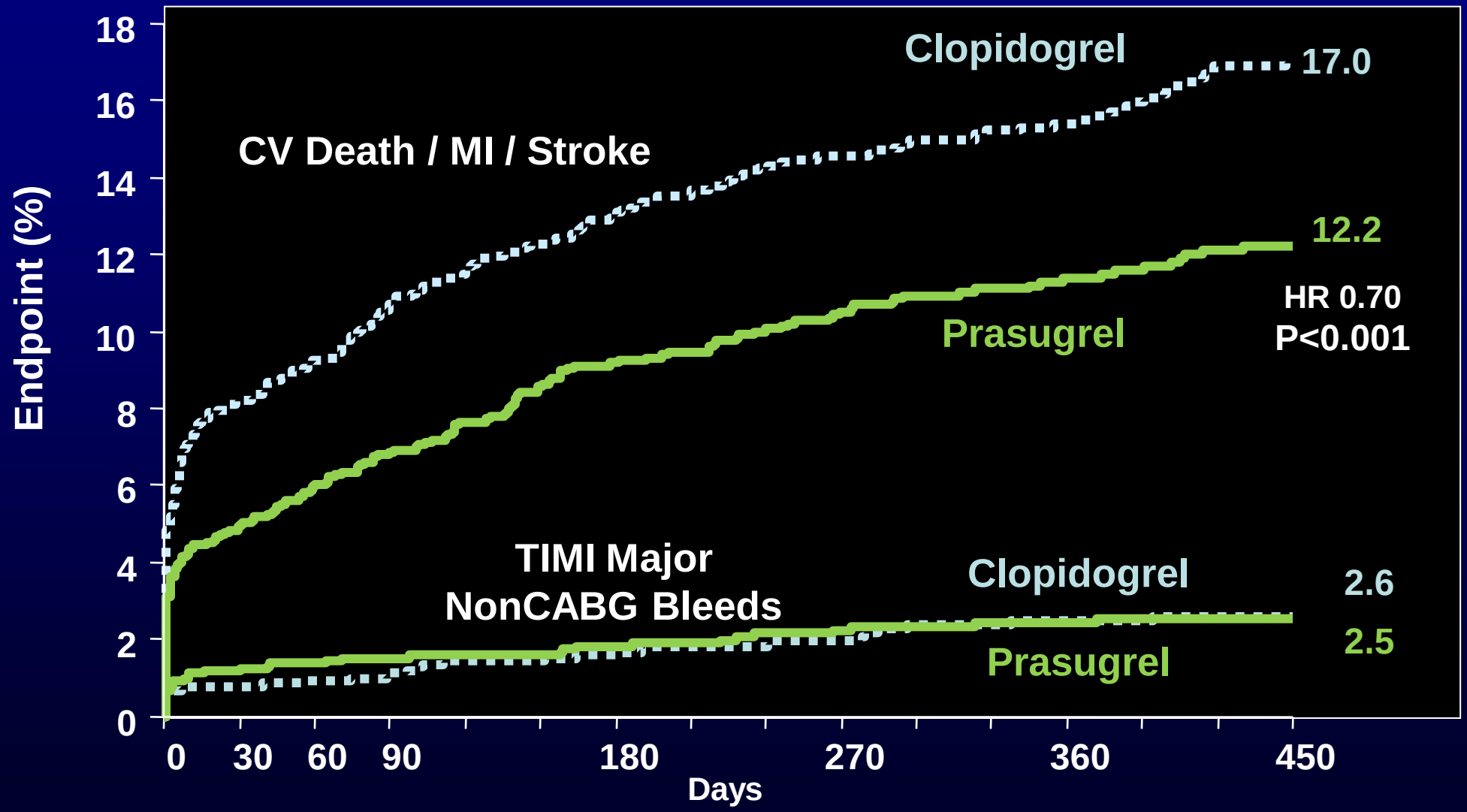
*Stent thrombosis defined as Academic Research Consortium definite or probable. †Patients having more than one type of stent are not included in DES.

Data on file: #EFF20091204b, DSI/Lilly.

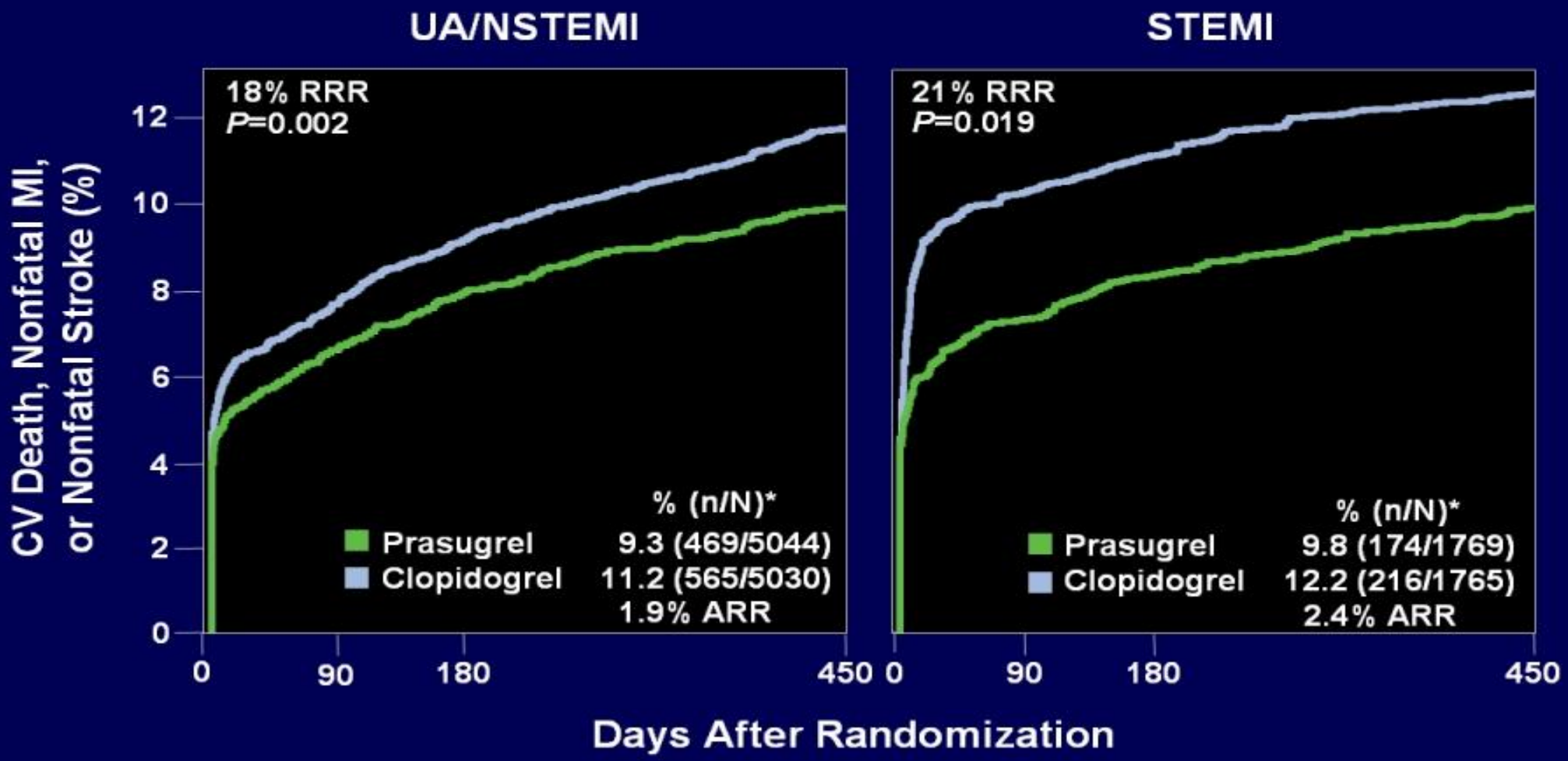
Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Diabetic Subgroup

N=3146

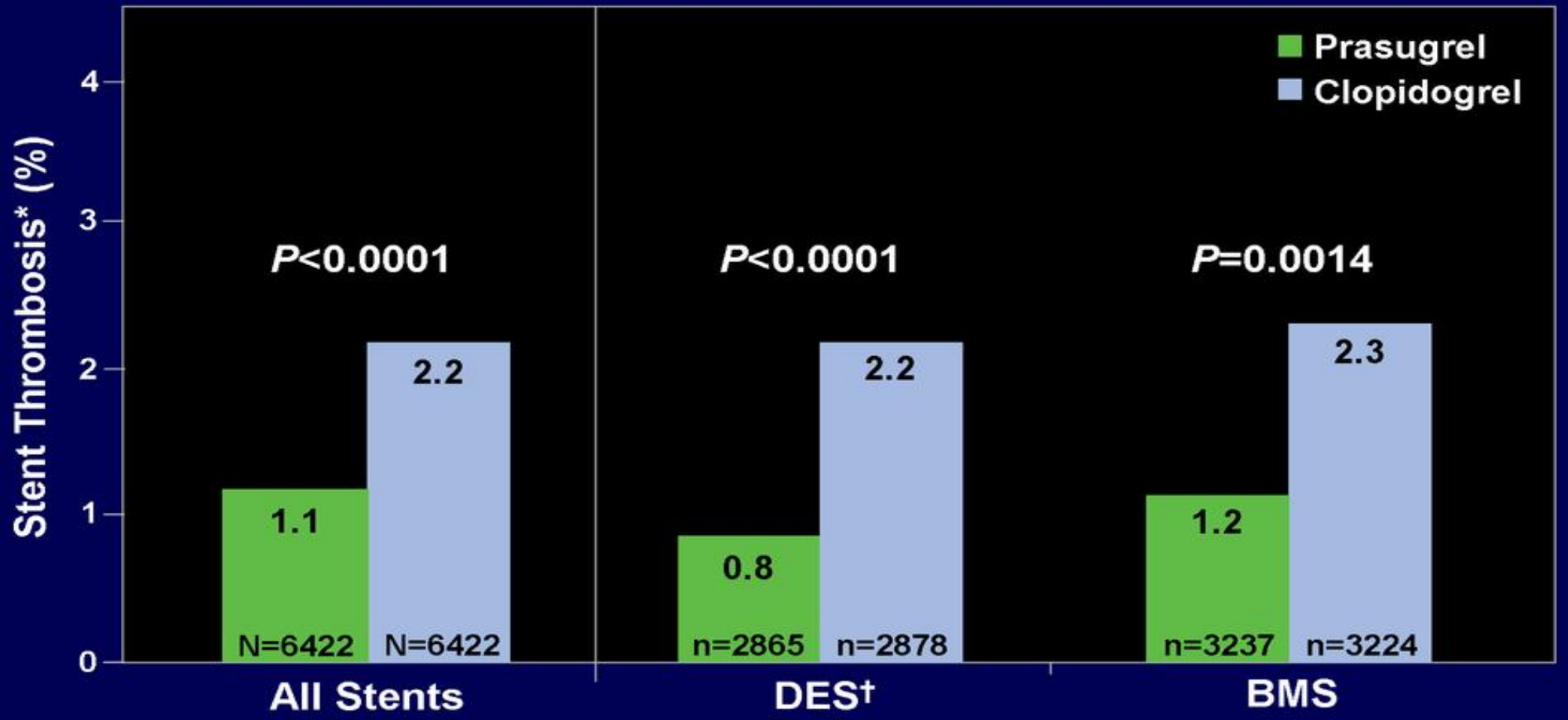


Primary Endpoint Events at End of Trial: UA/NSTEMI and STEMI Patients



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

Stent Thrombosis Rates at End of Study



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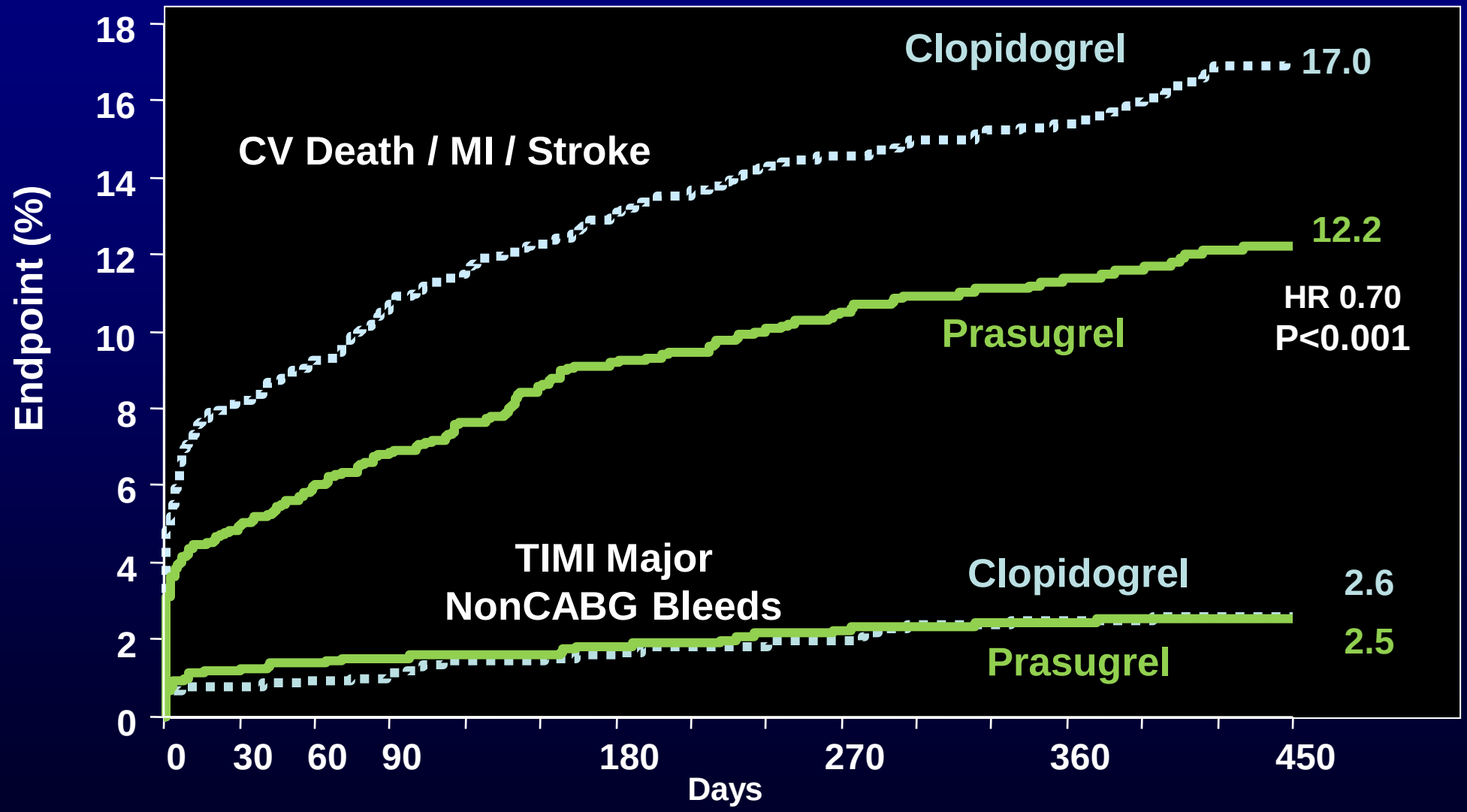
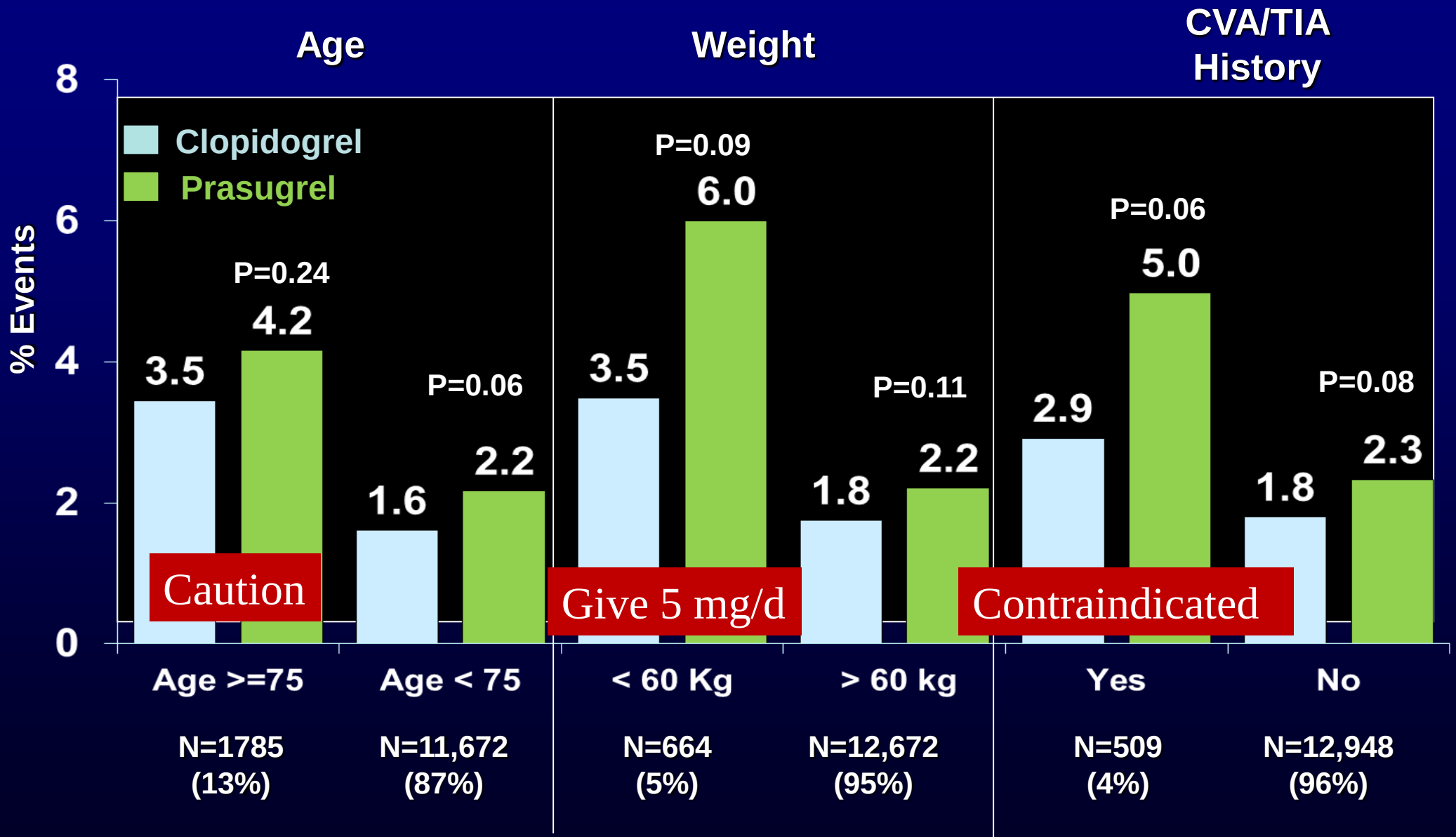
Diabetic Subgroup

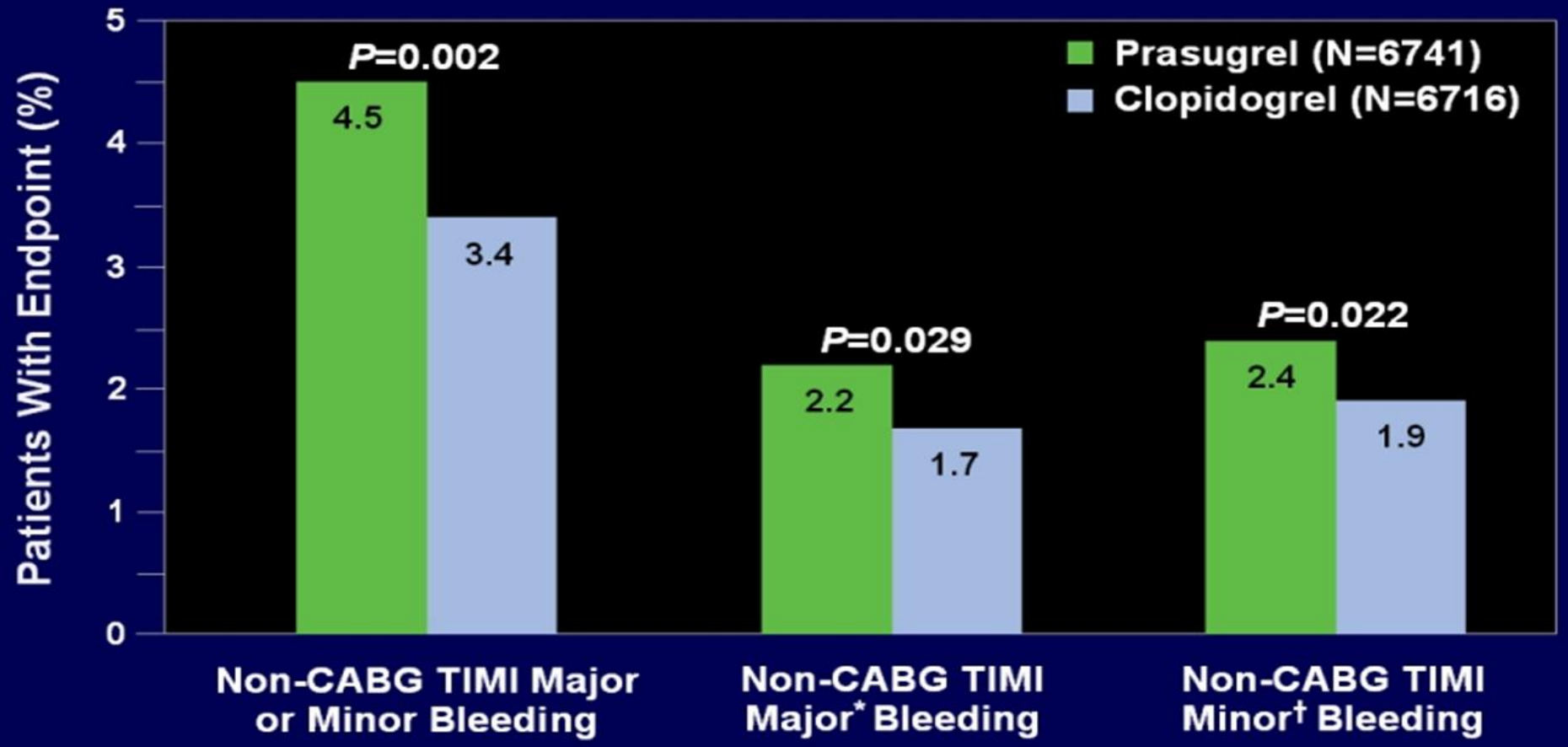
N=3146



TIMI Major Non-CABG Bleeds
Subgroups



Non-CABG TIMI Major or Minor Bleeding



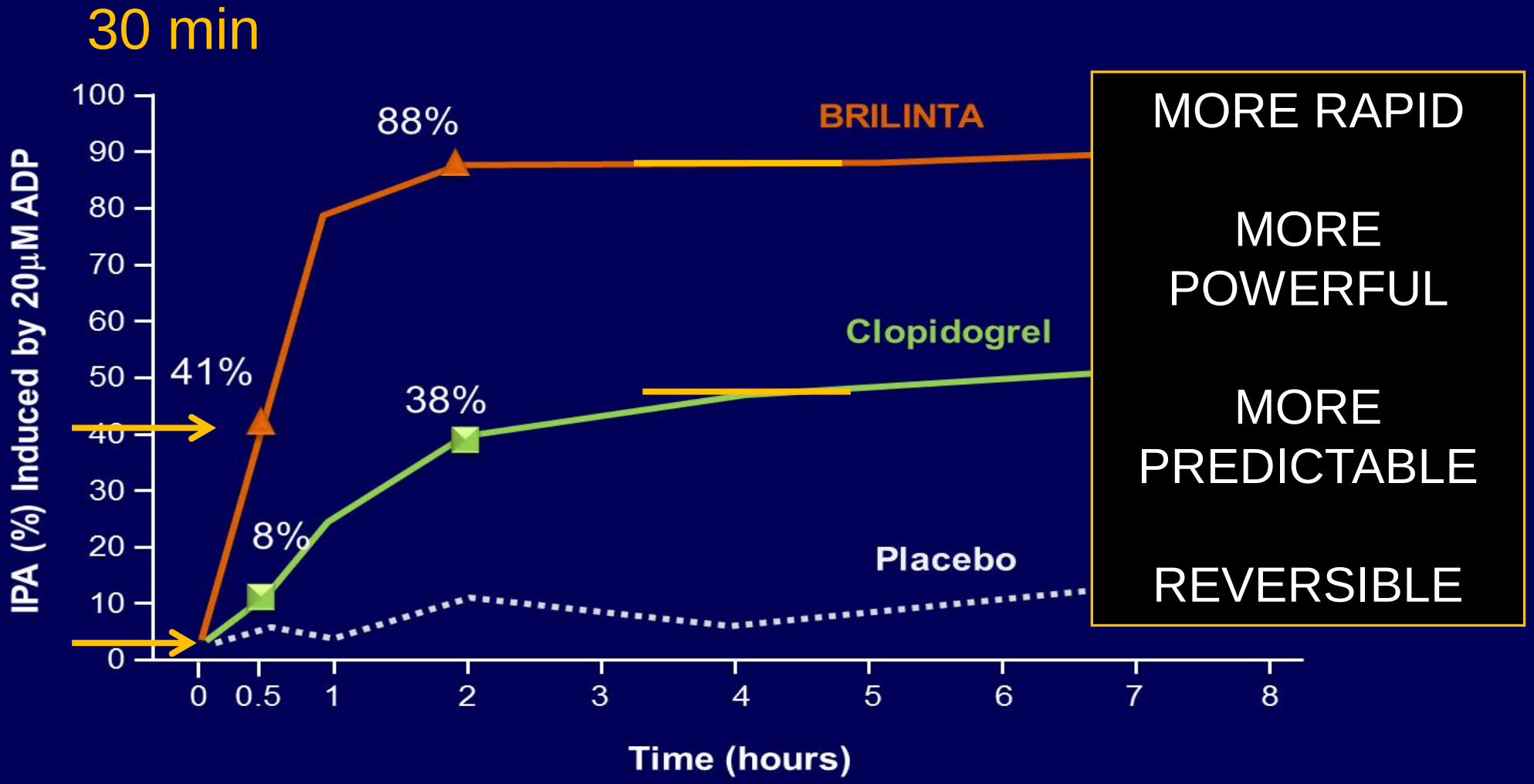
*Any intracranial hemorrhage or any clinically overt bleeding associated with a fall in hemoglobin ≥5 g/dL. †Clinically overt bleeding associated with a fall in hemoglobin of ≥3 g/dL but <5 g/dL.

Effient Full Prescribing Information.

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

HOW ABOUT BRILINTA (TICAGRELOR) ?

IPA Is Rapid With BRILINTA[1,2]

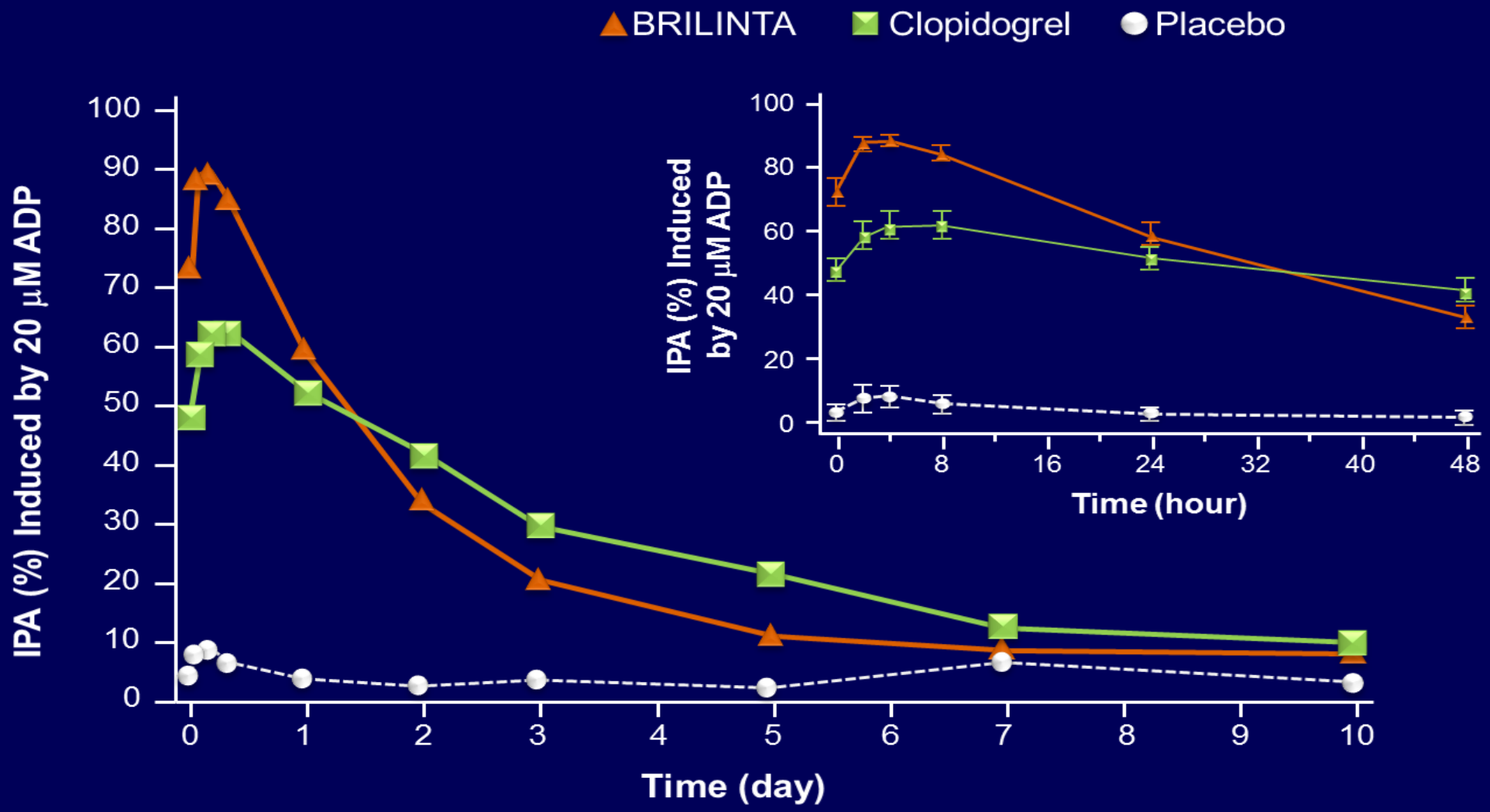


- It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel

IPA=inhibition of platelet aggregation.

1. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE; 2. Gurbel et al. *Circulation*. 2009;120(25):2577-2585.

BRILINTA Offset of IPA Over Time



- It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel

BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

PLATO STUDY DESIGN

NSTE-USA (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
(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)

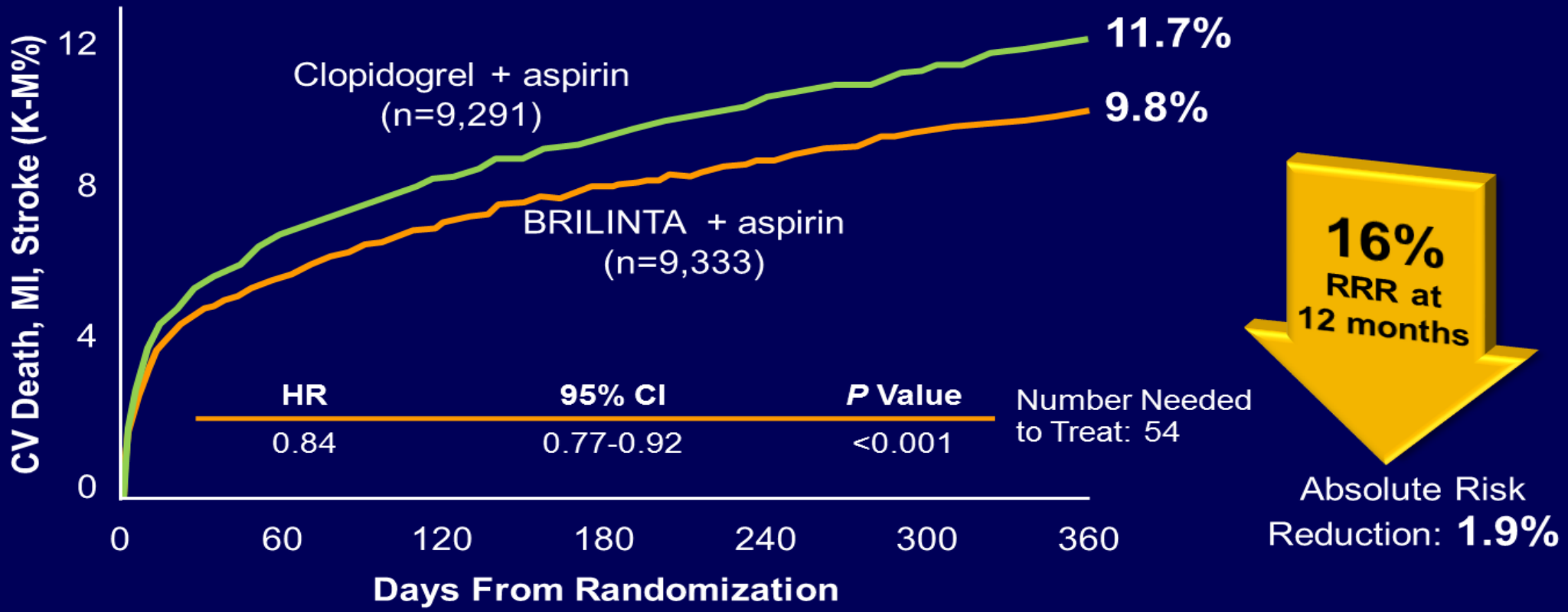
Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-months FU

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

Patients could be included whether the intend was to manage patient invasively or medically

Primary Outcome of the PLATO Trial: Time to First Occurrence of CV Death, MI, or Stroke at 12 Months

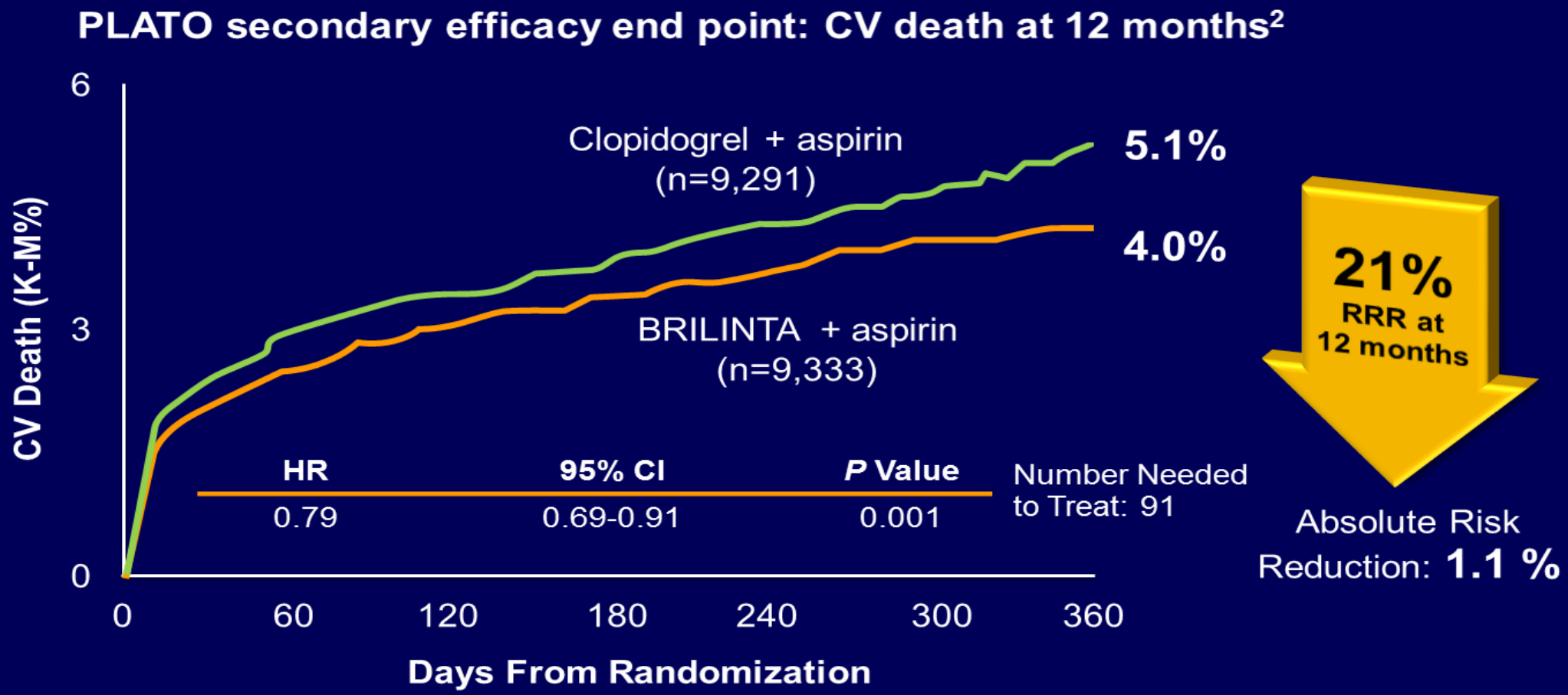


- Difference in treatments was driven by CV death and MI with no difference in stroke
- The curves separate by day 30 (RRR 12%) and continued to diverge throughout the 12-month treatment period (RRR 16%)
- BRILINTA and clopidogrel were studied with aspirin and other standard therapies

RRR=relative risk reduction; K-M=Kaplan-Meier; HR=hazard ratio; CI=confidence interval.

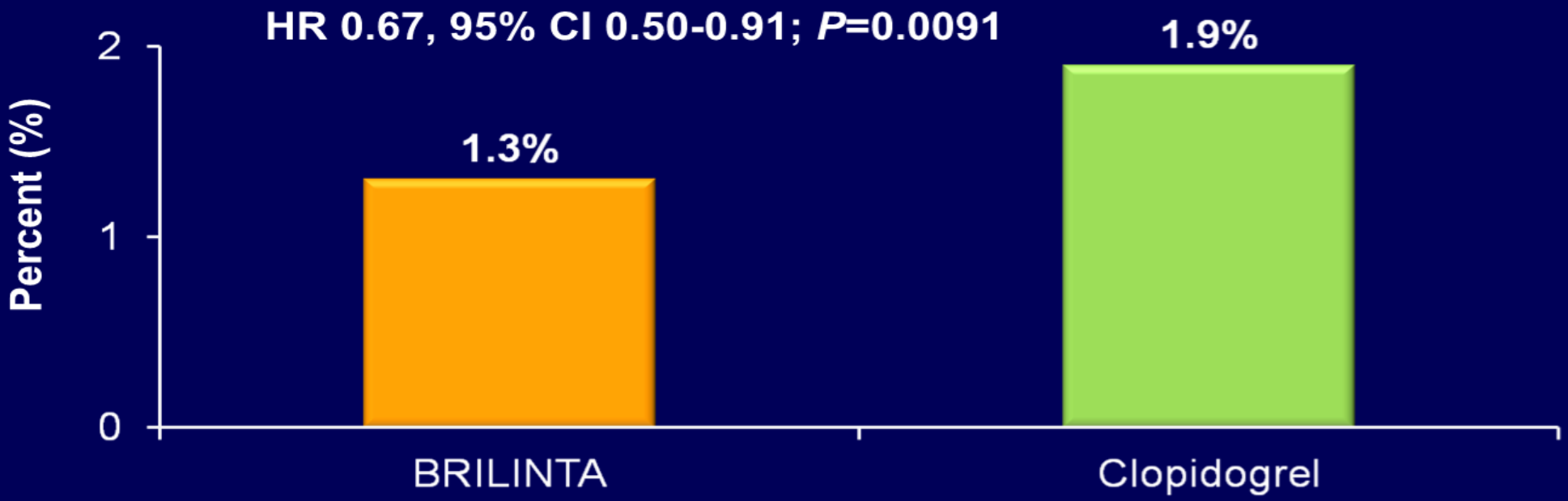
BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

BRILINTA: The First and Only Oral Antiplatelet FDA-Approved to Significantly Reduce CV Death vs Clopidogrel[1]



1. Data on file, 1343803, AstraZeneca, LP; 2. Wallentin et al for the PLATO Investigators. Supplementary appendix, *N Engl J Med.* 2009; 361(11):1045-1057. Available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0904327/suppl_file/nejm_wallentin_1045sa1.pdf. Accessed October 19, 2011; 3. Wallentin et al. *N Engl J Med.* 2009;361(11):1045-1057.

In the PLATO Trial, Definite Stent Thrombosis[a] Was Lower With BRILINTA



- 11,289 patients with PCI received a stent during PLATO[1]
- The results were similar for drug-eluting and bare-metal stents[1]

[a]Utilizing the Academic Research Consortium (ARC) definition of definite stent thrombosis, which requires angiographic or pathological confirmation.[2,3]

1. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE; 2. Cutlip et al. *Circulation.* 2007;115(17):2344-2351; 3. Wallentin et al. *N Engl J Med.* 2009;361(11):1045-1057.

PLATO Overall and Non–CABG-related Bleeding Rates

Overall and Non–CABG-related Bleeding Rates (K-M%)	BRILINTA + Aspirin (n=9,235)	Clopidogrel + Aspirin (n=9,186)
Total Major Bleeding	11.6	11.2
Non–CABG-related Bleeding		
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

- About half of the bleeding events were in the first 30 days
- No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared with 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 (eg, anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDs])

BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

PLATO: Bradycardia-related Events

All Patients[1]	BRILINTA (n=9,235)	Clopidogrel (n=9,186)
Bradycardia-related event, n (%)		
Pacemaker insertion	82 (0.9)	79 (0.9)
Syncope	100 (1.1)	76 (0.8)
Bradycardia	409 (4.4)	372 (4.0)
Heart block	67 (0.7)	66 (0.7)

- In a Holter substudy of about 3,000 patients, ventricular pauses ≥3 seconds occurred in 6% of BRILINTA-treated patients vs 3.5% of clopidogrel-treated patients in the acute phase and 2.2% and 1.6% after 1 month respectively[2]
- There were no differences in adverse clinical consequences (ie, pacemaker insertion, syncope, bradycardia, and heart block)[1]
- In clinical studies, BRILINTA has been shown to increase the occurence of Holter-detected bradyarrhythmias. PLATO excluded patients at increased risk of bradycardic events. Consider the risks and benefits of treatment[2]

1. Wallentin et al. *N Engl J Med*. 2009;361(11):1045-1057; 2. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE.

PLATO: Dyspnea

Dyspnea[a] in PLATO Trial[1,2]	BRILINTA	Clopidogrel
Incidence of dyspnea adverse events (%)	13.8	7.8
Patients who discontinued treatment due to dyspnea (%)	0.9	0.1

- BRILINTA-associated dyspnea was mostly mild to moderate and often resolved during continued treatment[1]
- Most episodes lasted less than a week[2]
- No effect on pulmonary function after one month or after at least 6 months of chronic treatment[1]

[a]Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturna.

1. BRILINTA Prescribing Information. AstraZeneca, LP. Wilmington, DE; 2. Wallentin et al. *N Engl J Med*. 2009;361(11):1045-1057.

TAKE HOME MESSAGES

Both Brilinta and Effient are more effective than Plavix in ACS patients in terms of reduction in MI, stent thrombosis, especially in diabetics (Effient) . Brilinta reduced CV mortality in a more wide spectrum patient population

Both are fast, more powerful and consistent than plavix. Whereas Effient is a cath lab drug, Brilinta is also indicated in post CABG or medically treated patients

Brilinta is reversible inhibitor and has not been compared head to head with Effient.

Effient is contraindicated in patients with TIA and stroke

Brilinta should be used with 81 mg/d of aspirin. Higher doses negate any beneficial anti-ischemic effect (mechanism remains unknown)