Novel Anticoagulation Therapy in Acute Coronary Syndrome

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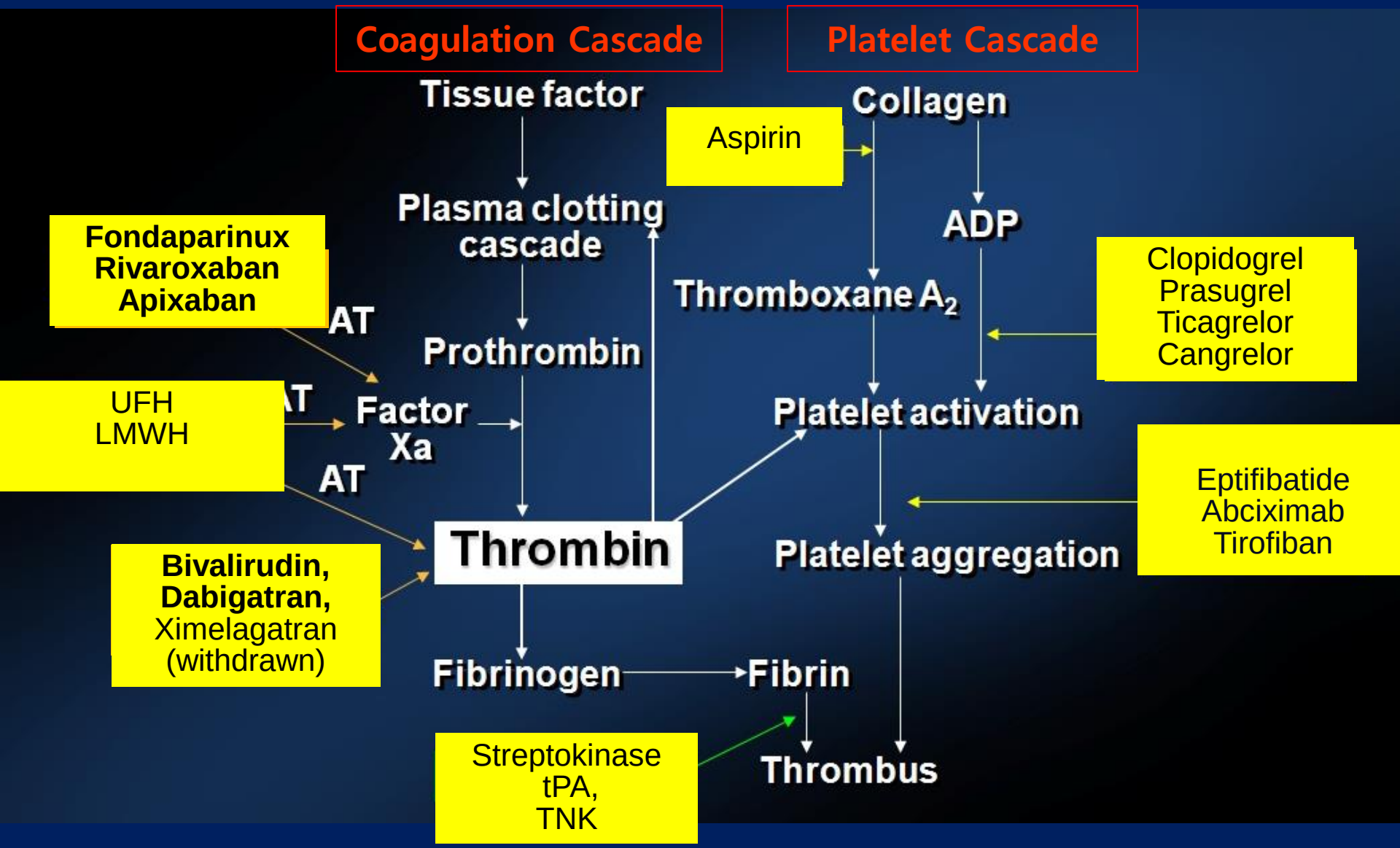
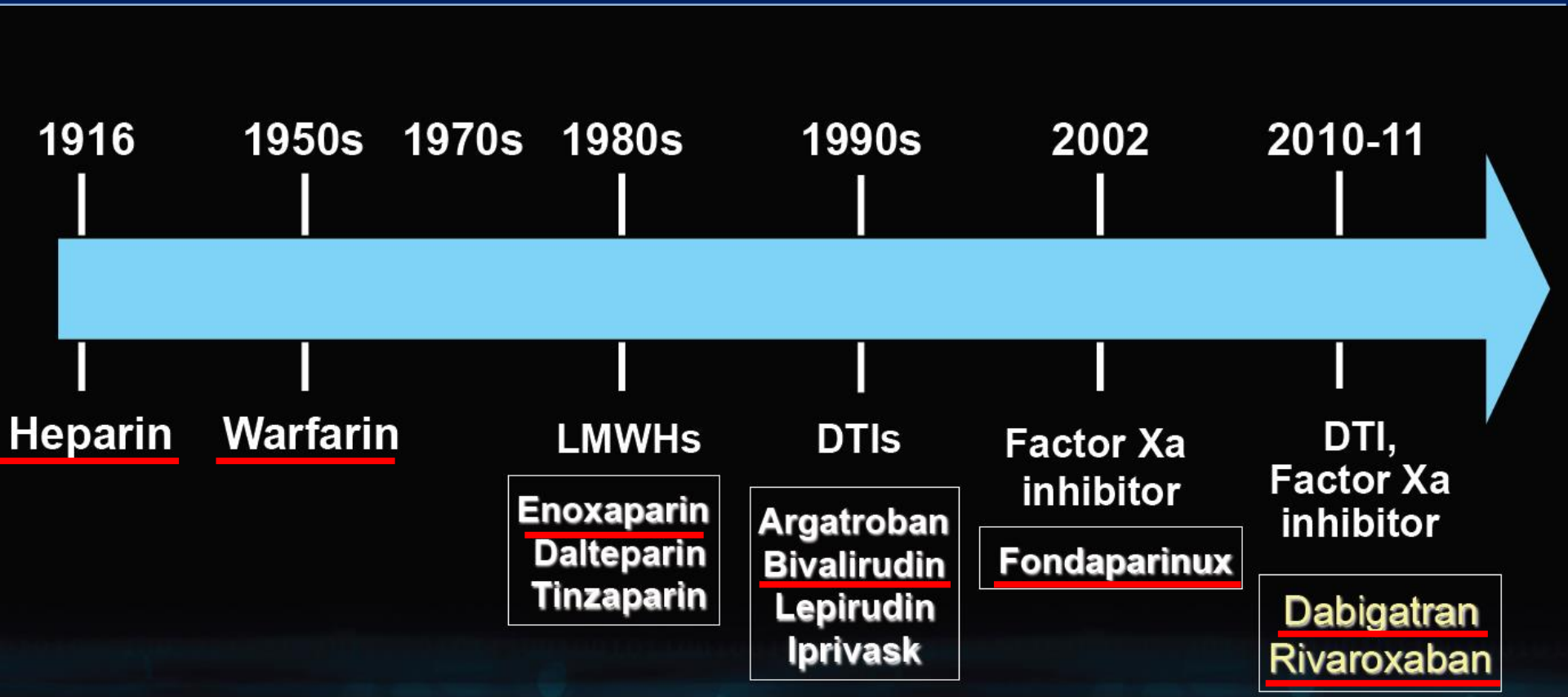
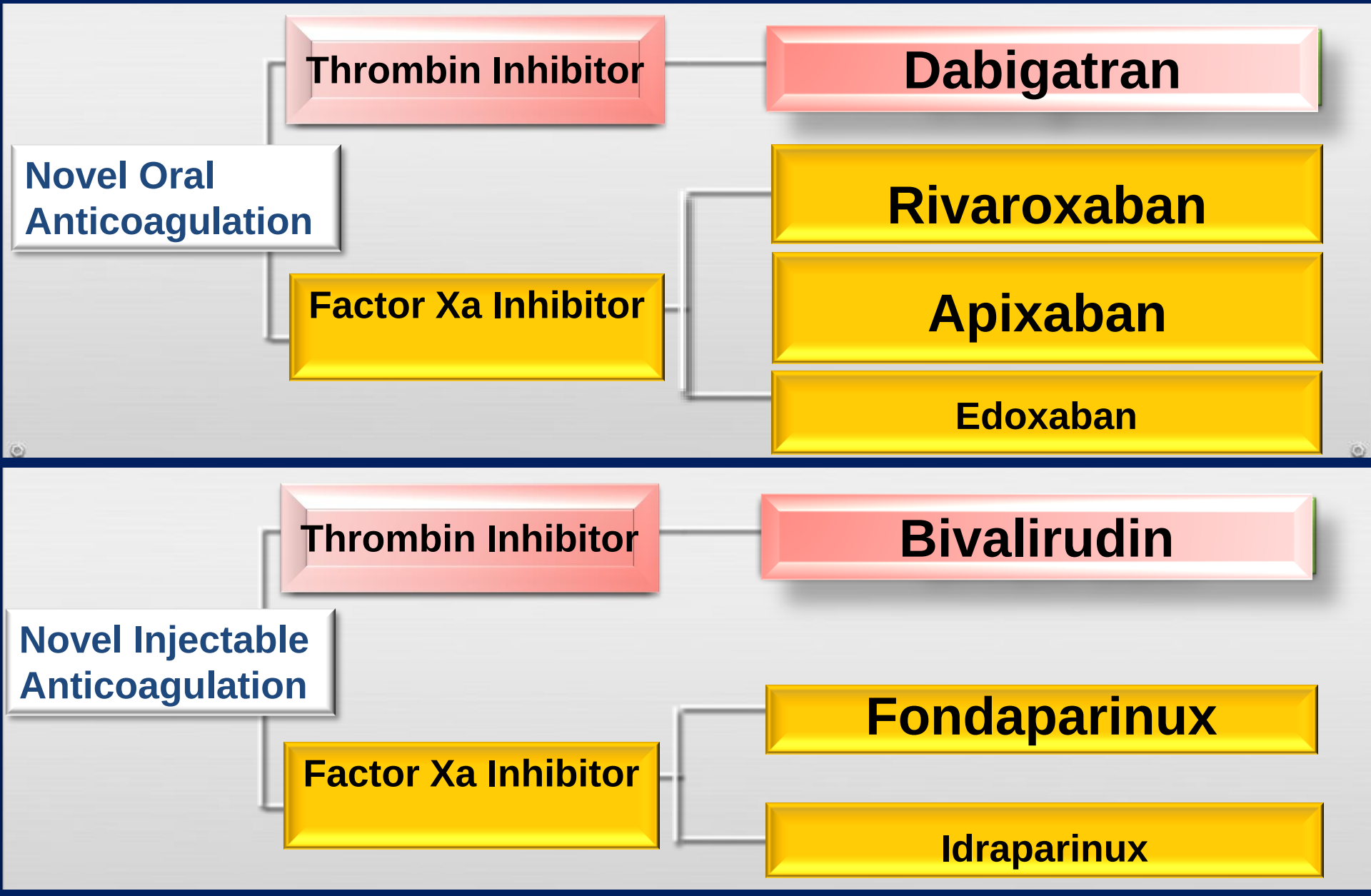
Thrombus Formation Cascade



Anticoagulation Drugs



New Anticoagulation Drug



What Is the Better Target?

Anti-Xa	Anti-IIa
Gatekeeper of the coagulation cascade	Final common pathway
Block thrombin generation	Block thrombin activity
Preserve hemostatic mechanisms	Block contact activation
	Block platelet activation

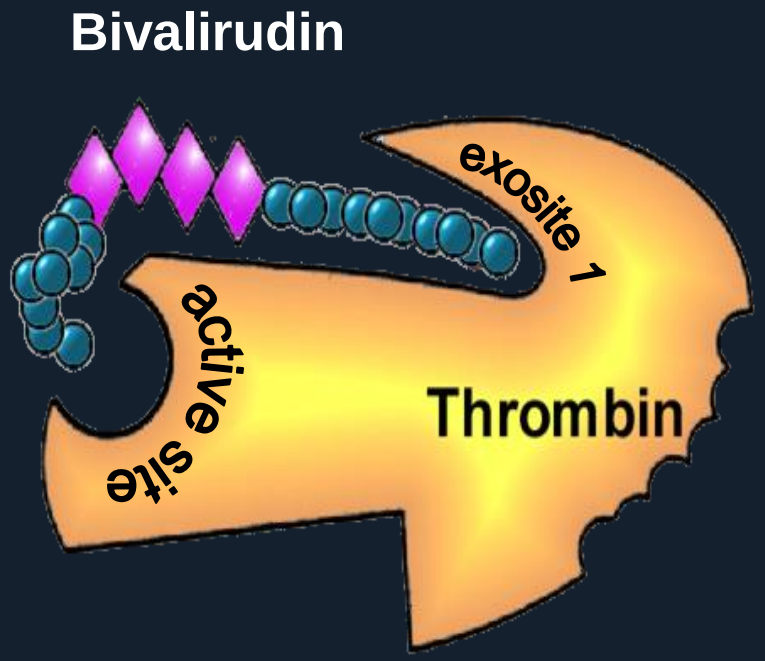
Trials Regarding Injectable Anticoagulation Agents

Limitations of Heparins

Attribute	UFH	Enox	Impact
Active moieties in substance	30-35%	40-60%	Unpredictable
Action independent of AT	No	No	Unpredictable
Non-specific protease binding	Yes	Partial	Unpredictable
Variable PK-PD	Yes	Less	Unpredictable
Inhibits fibrin-bound thrombin	No	No	Need ↑ dose
Activates/aggregates platelets	Yes	+/-	Need IIb/IIIa
$T_{0.5}$ in minutes	60-90’	270’	↑ Bleeding
PF-4 complexing & risk of HIT	Yes	Reduced	Very bad

Bivalirudin

Bivalent Synthetic Direct Thrombin Inhibitor



- Specifically inhibits
  - Fluid phase thrombin
  - Clot-bound thrombin
  - Thrombin-mediated platelet aggregation (blocks activation of PAR-1 and PAR-4 receptors
- Reversible
- $T_{0.5}$ 25 minutes

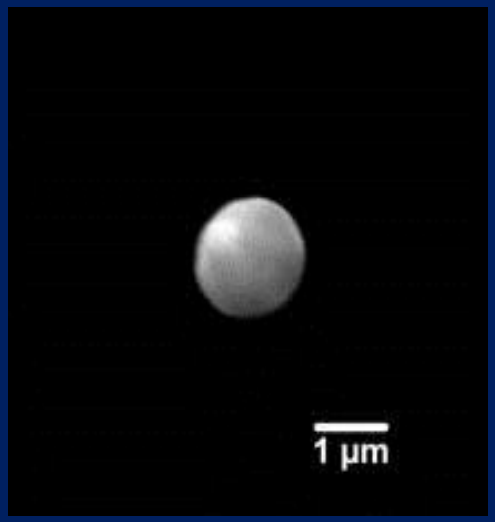
Topol EJ: Textbook of Interventional Cardiology

Overcoming Limitations of Heparins

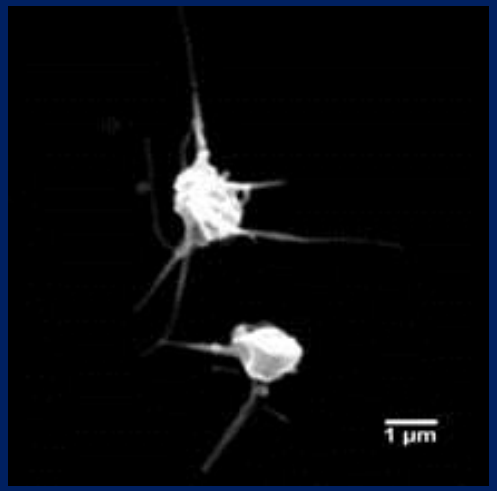
Attribute	UFH	Enox	Bivalirudin
Active moieties in substance	30–35%	40–60%	100%
Action independent of AT	No	No	Yes
Non-specific protease binding	Yes	Partial	No
Variable PK-PD	Yes	Less	No
Inhibits fibrin-bound thrombin	No	No	Yes
Activates/aggregates platelets	Yes	+/-	Inhibits
$T_{0.5}$ in minutes	60–90’	270’	25’
PF-4 complexing & risk of HIT	Yes	Reduced	No

Bivalirudin: No Platelet Activation

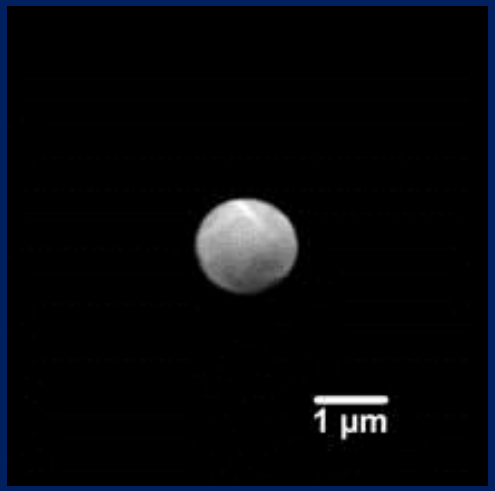
Direct platelet activation by UFH but not bivalirudin



Control platelets



Platelets treated with UFH

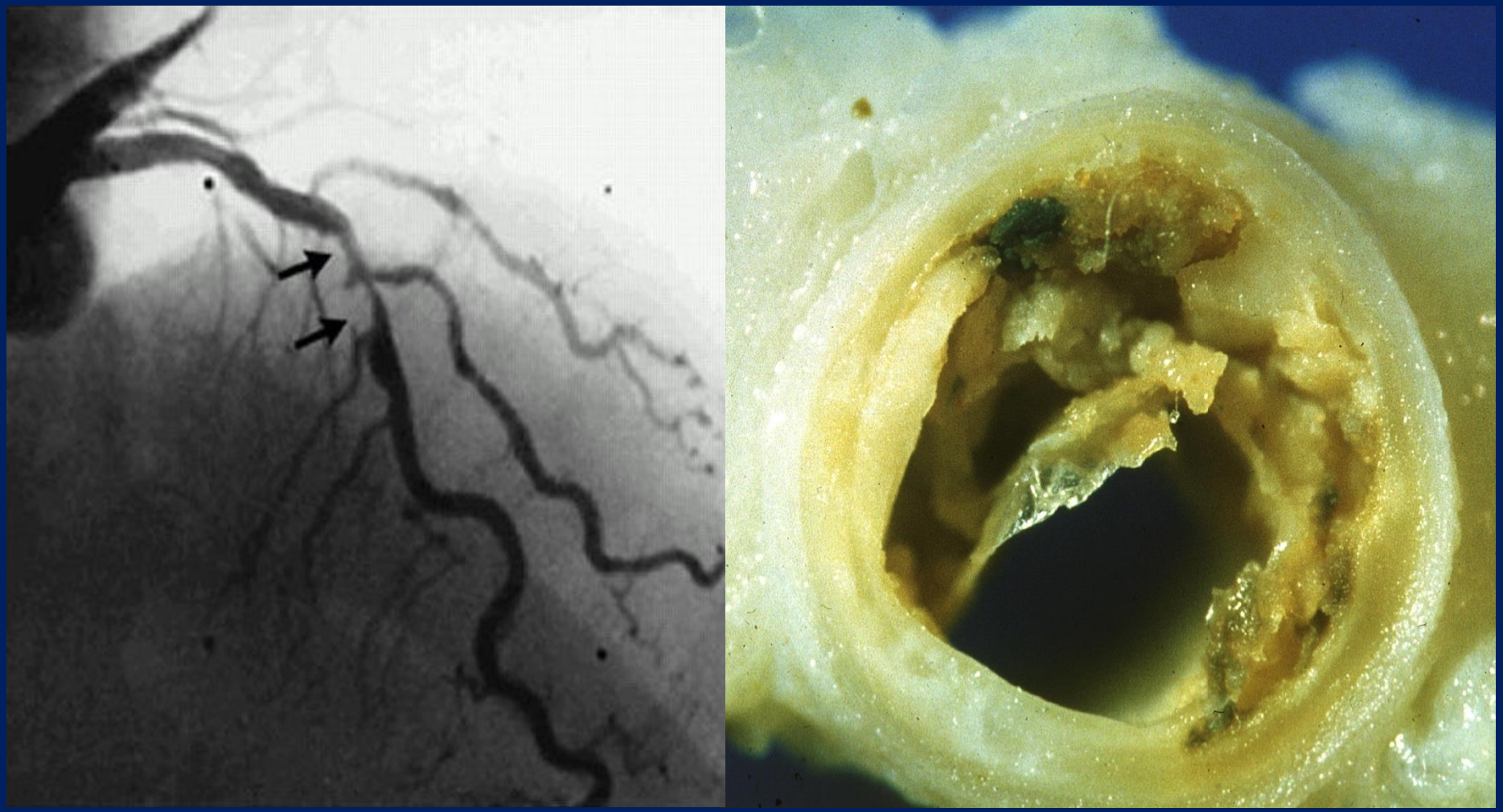


Platelets treated with Bivalirudin

Scanning electron micrographs were acquired at a magnification of 4,000x with the investigator blinded to treatment.

Anand SX et al. *Am J Cardiol.* 2007;100:417-424.

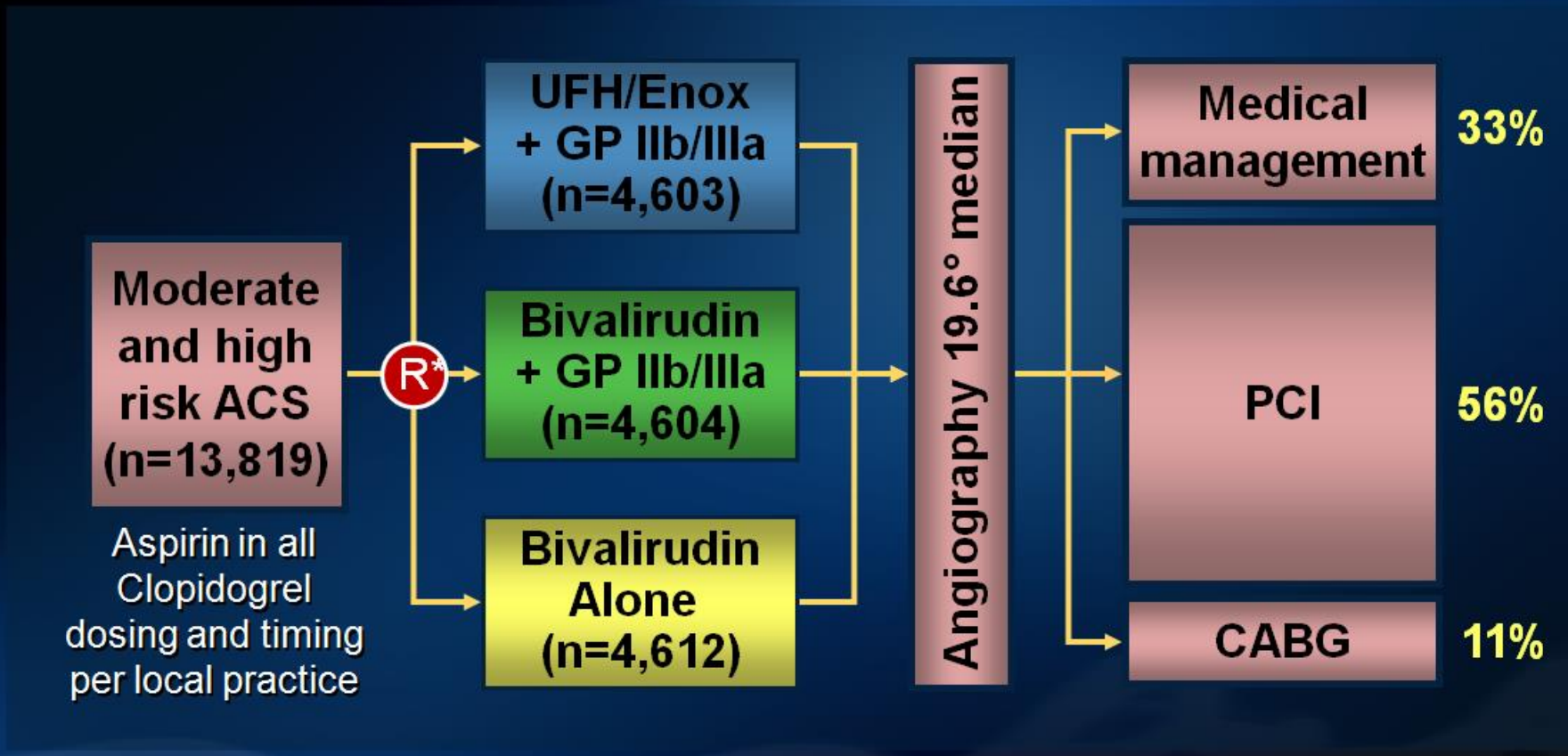
ACS: Pathophysiology



Ruptured plaque with sub-occlusive thrombus

ACUITY: First Randomization

Moderate and high risk unstable angina or NSTEMI undergoing an invasive strategy (N = 13,819)



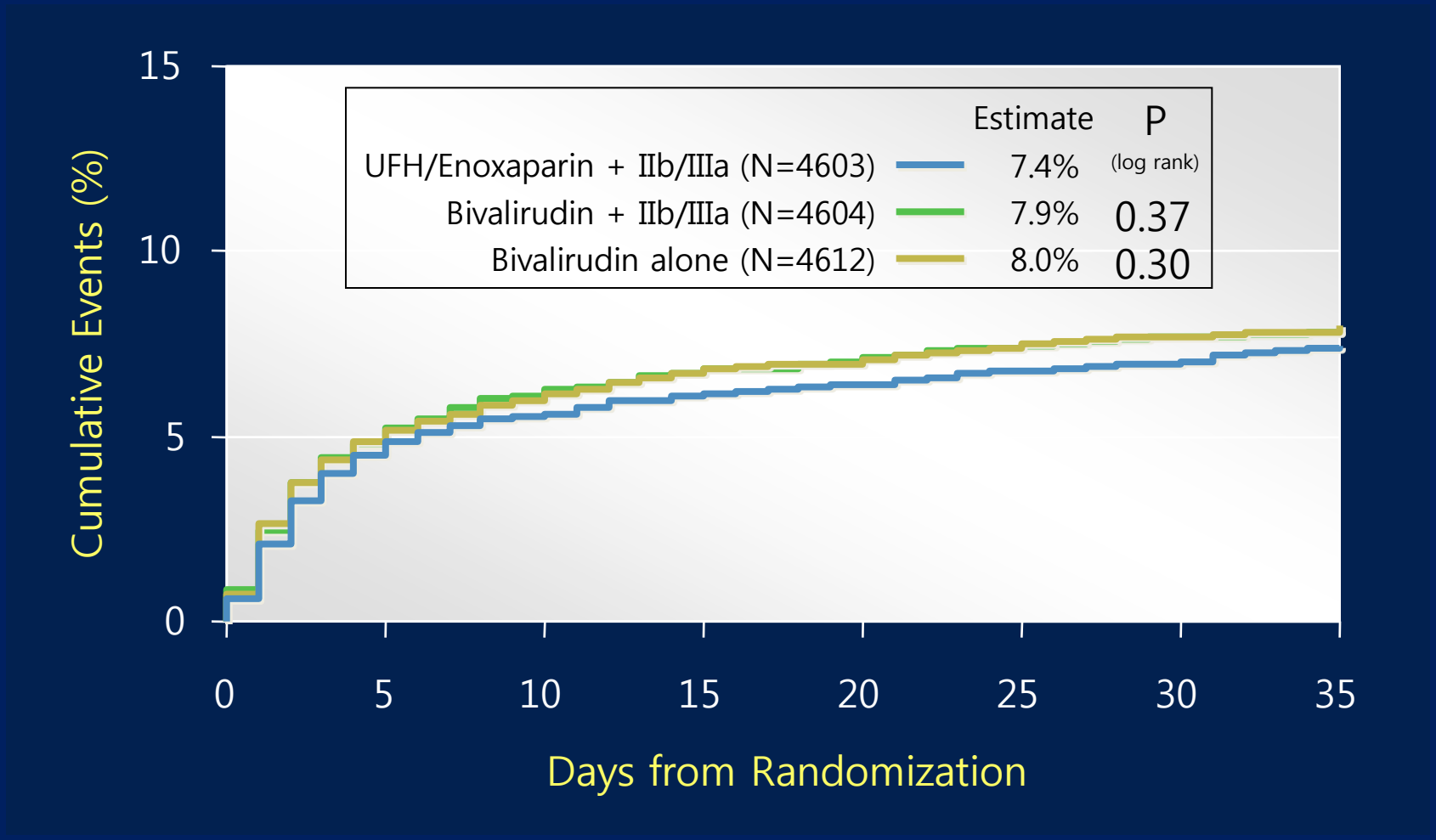
*Stratified by pre-angiography thienopyridine use or administration

Stone GW et al. NEJM 2006;355:2203-16

ACUITY

Ischemic Composite Endpoint

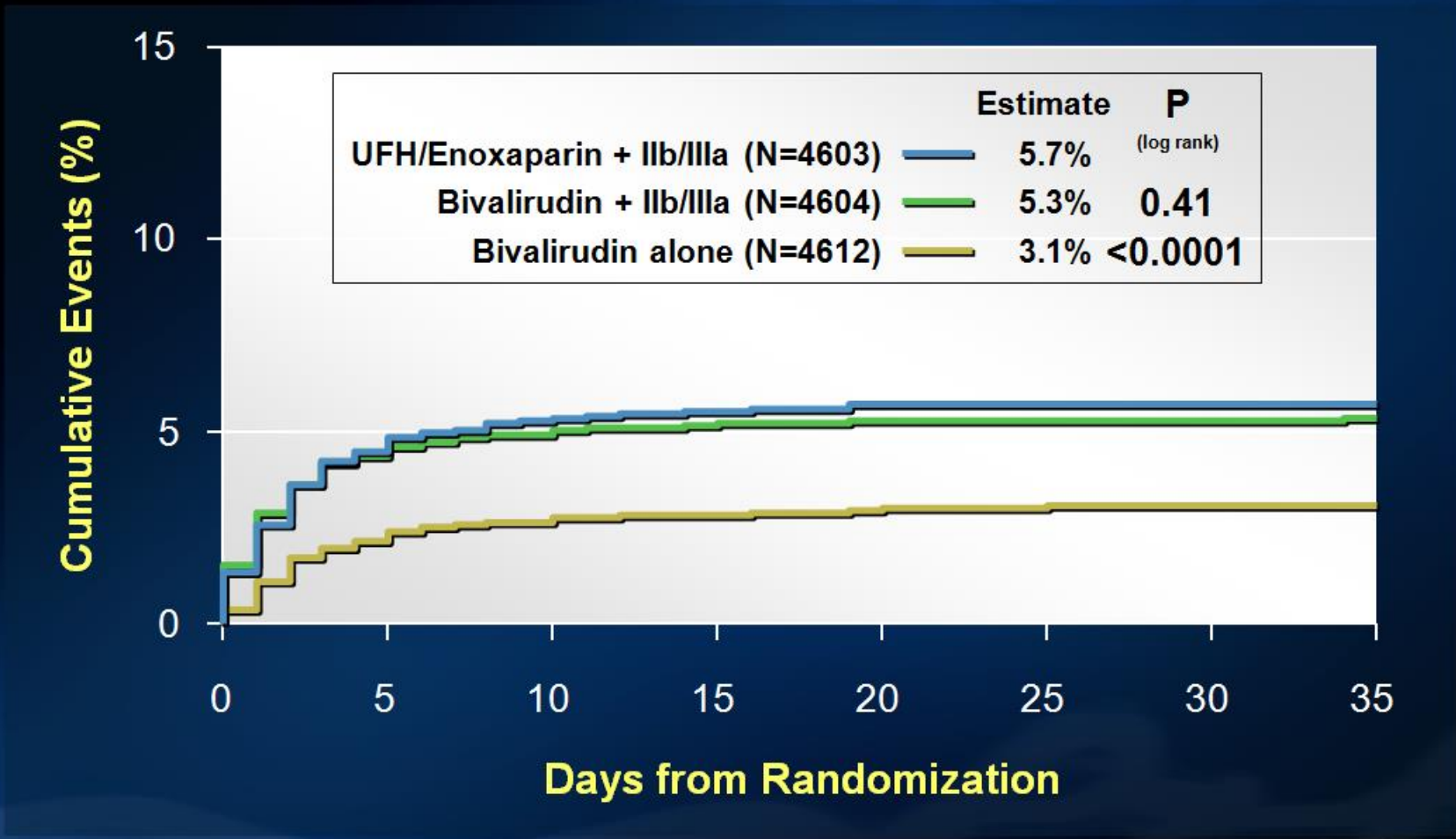
UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone



Stone GW et al. NEJM 2006;355:2203-16

Major Bleeding Endpoints

UFH/Enoxaparin + GPI vs. Bivalirudin + GPI vs. Bivalirudin Alone



Stone GW et al. NEJM 2006;355:2203-16

ACUITY

ISAR-REACT-4

1,721 Pts with NSTEMI (CK-MB or troponin+) undergoing PCI

Pre-treated with aspirin and 600 mg of clopidogrel

R

Double-blind
(double-dummy drug)

UFH + Abciximab

Bolus UFH 70 U/kg
Bolus Abcx 0.25 mg/kg + infusion 0.125 μg/kg/min x12h

N=861

Bivalirudin

Bolus 0.75 mg/kg + infusion 1.75 mg/kg/hr for duration of PCI

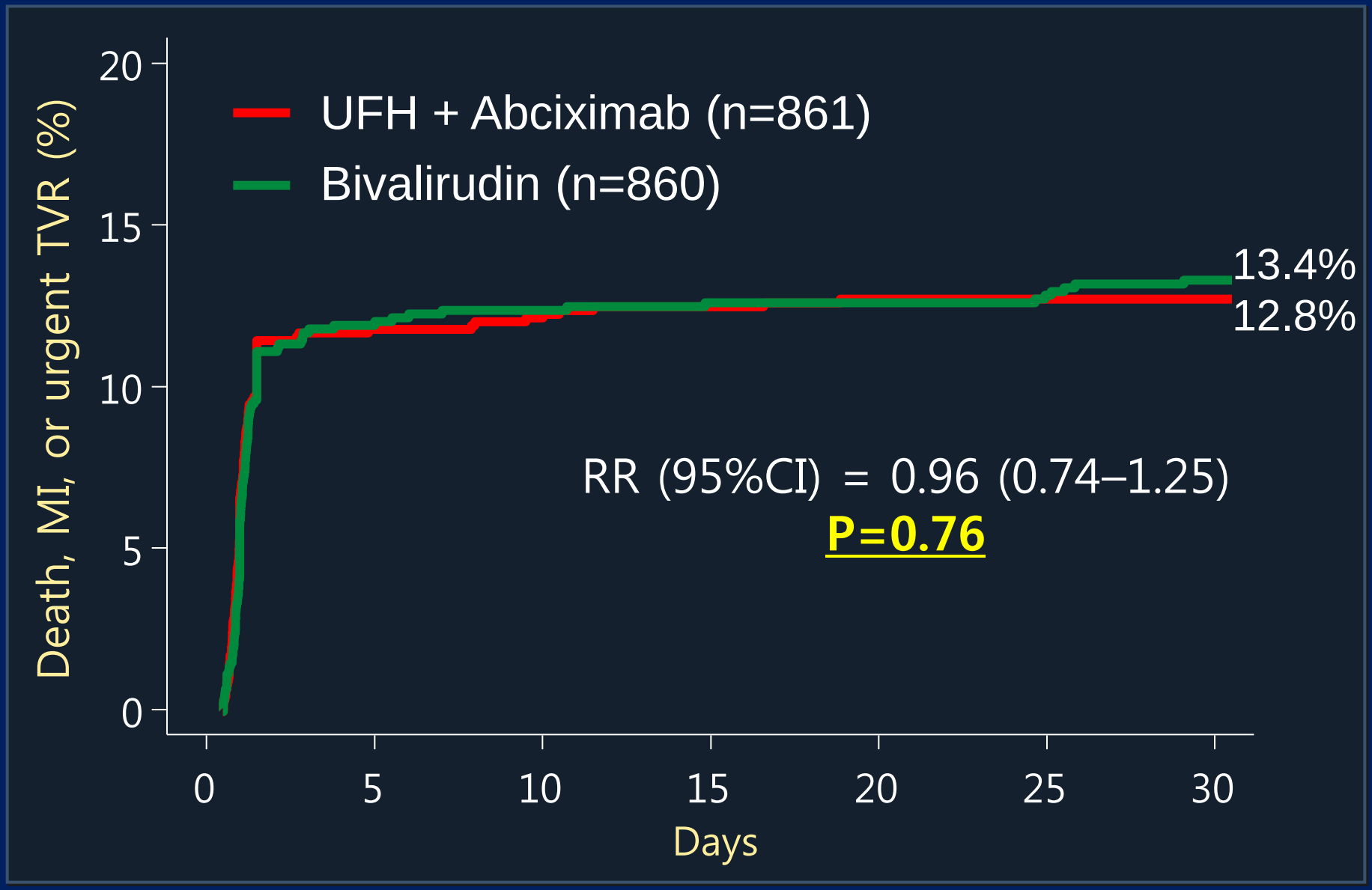
N=860

Primary endpoint = death, large MI, urgent TVR, or major bleeding at 30d

Powered for superiority of UFH/Abcx over bivalirudin

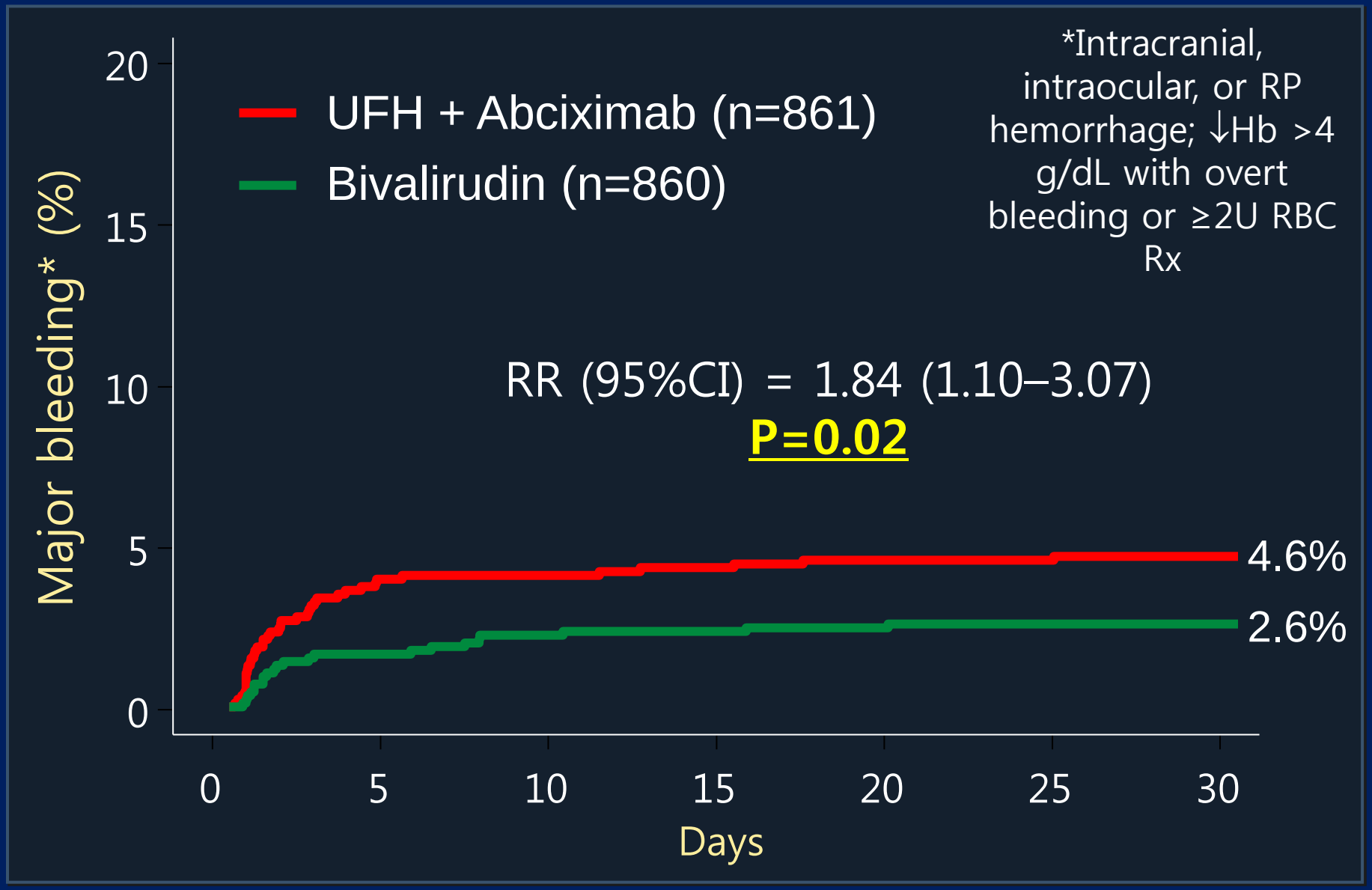
Kastrati A et al. NEJM 2011:365:1980-9

ISAR-REACT-4: Composite Ischemia



Kastrati A et al. NEJM 2011:365:1980-9

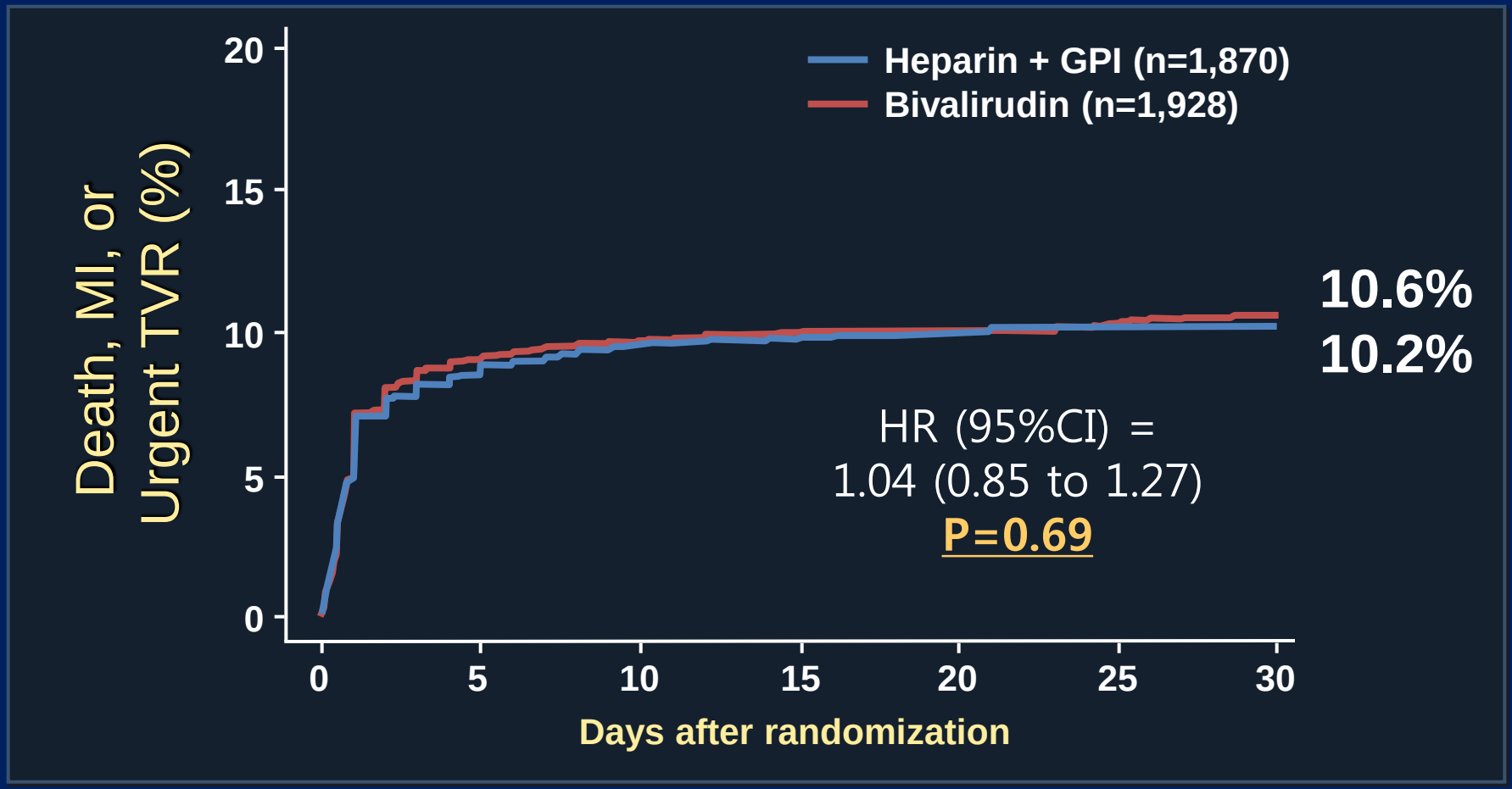
ISAR-REACT-4: Major Bleeding



Kastrati A et al. NEJM 2011:365:1980-9

ACUITY + ISAR-REACT-4: Pooled

3,798 clopidogrel-pre-treated pts with NSTEMI (troponin +) undergoing PCI randomized to bivalirudin vs. heparin + GPI



Kastrati, Stone et al. TCT 2012

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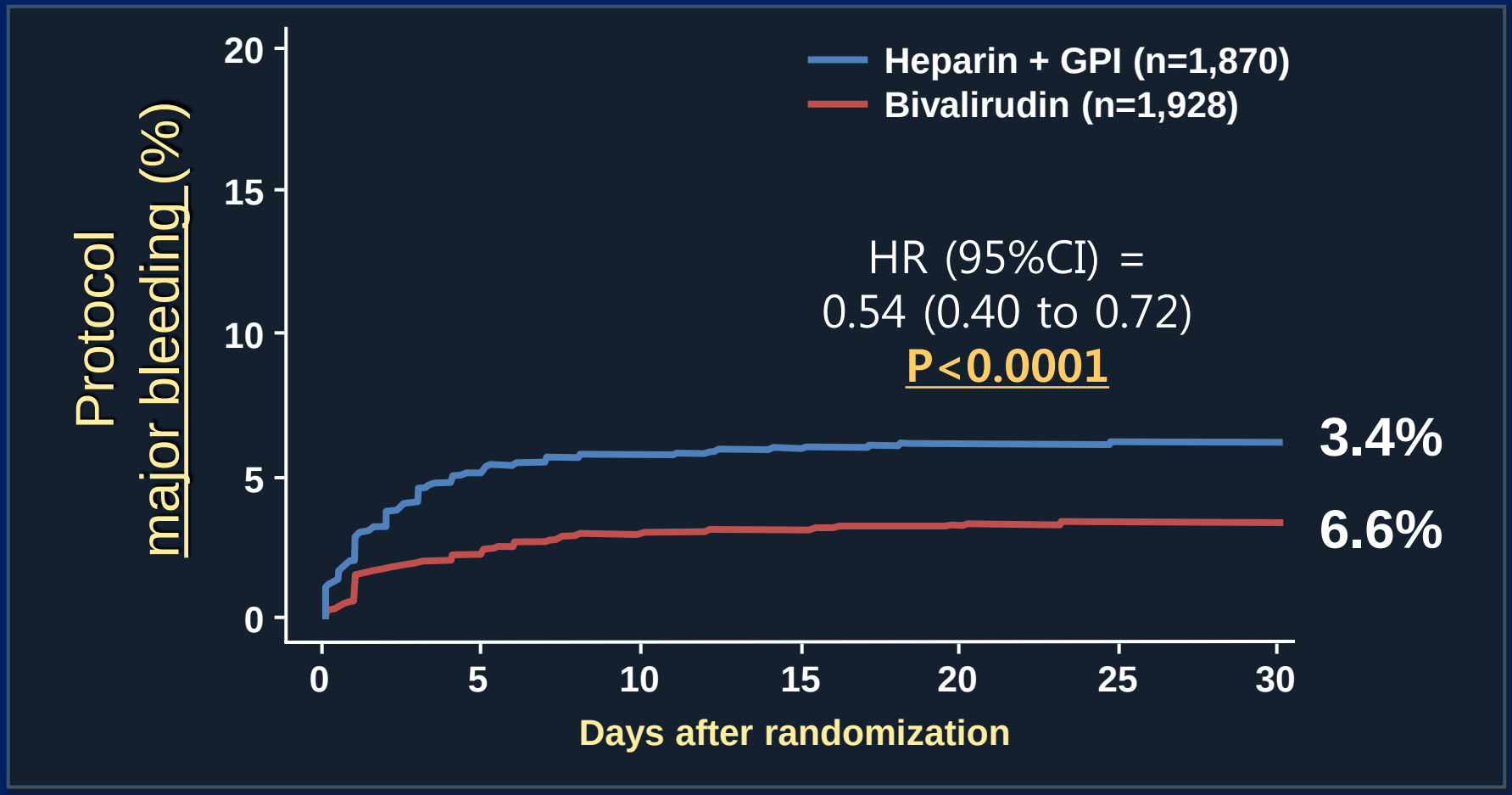
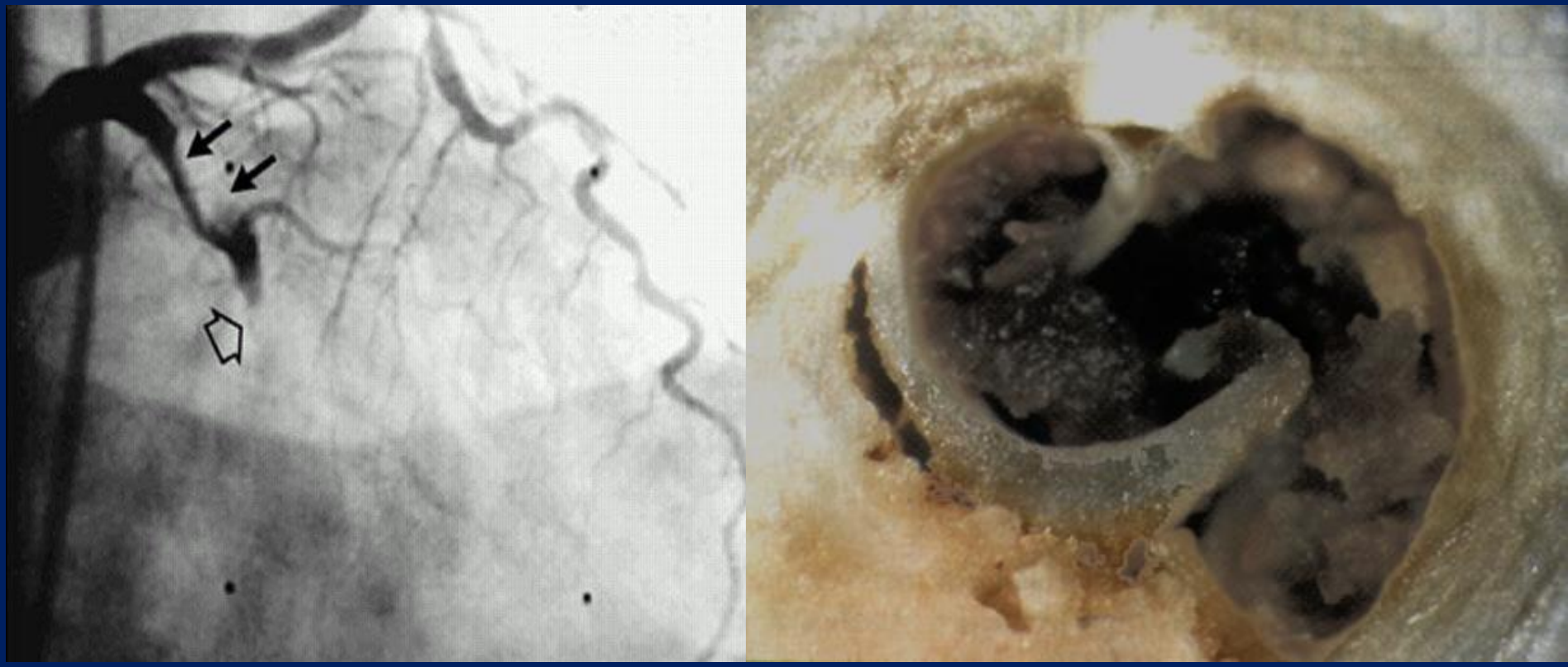


Kastrati, Stone et al. TCT 2012

AMI: Pathophysiology



Ruptured plaque with occlusive thrombus

HORIZON AMI

Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

R 1:1

- UFH + GP IIb/IIIa inhibitor (abciximab or eptifibatide)
- **Bivalirudin monotherapy (± provisional GP IIb/IIIa)**

Emergent angiography, followed by triage to…

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

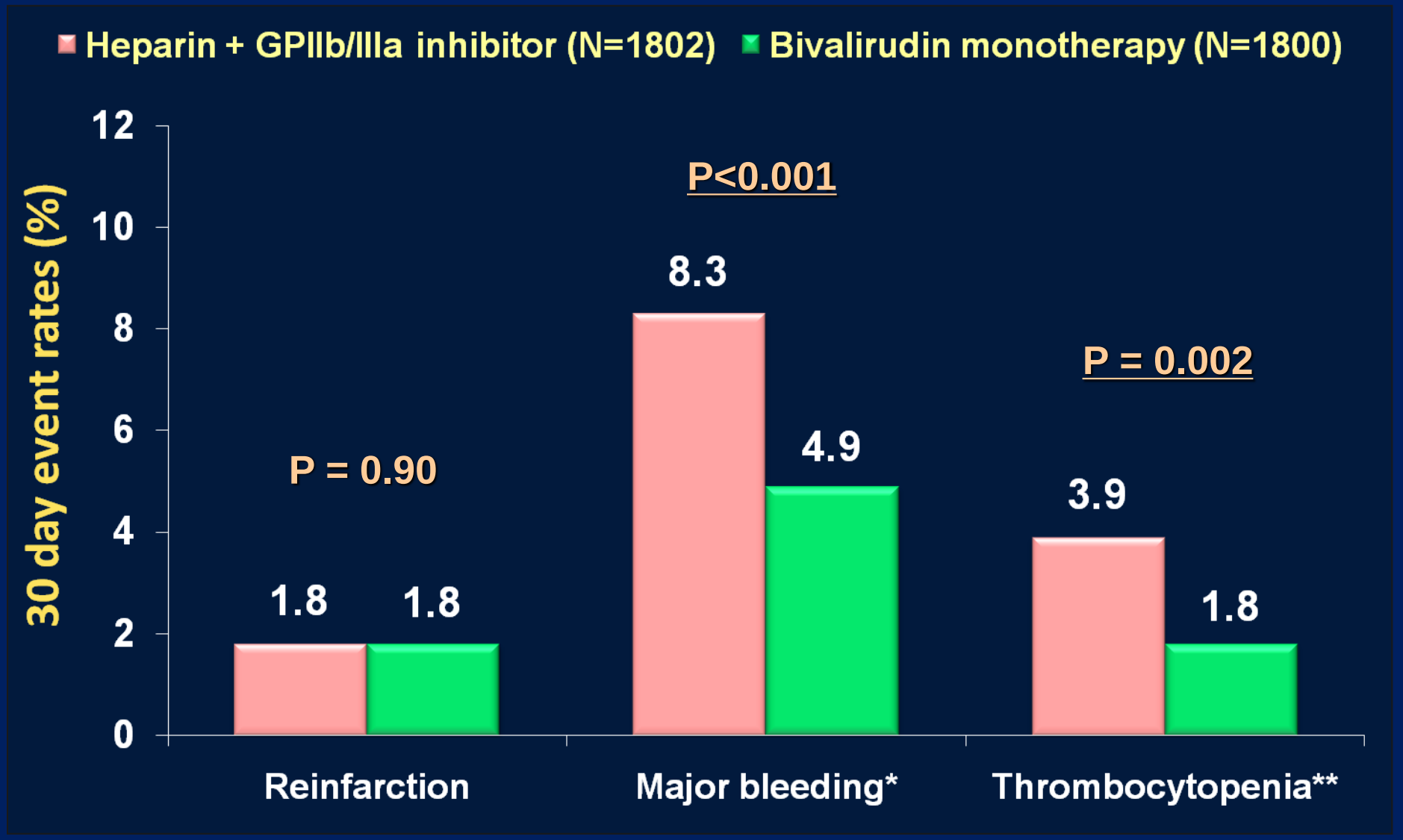
R 3:1

- Paclitaxel-eluting TAXUS stent
- Bare metal EXPRESS stent

Clinical FU at 30d, 6 mo, 1 yr, and then yearly through 3 yrs; Angio FU at 13 mo

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

HORIZONS: 30 Day Adverse Events

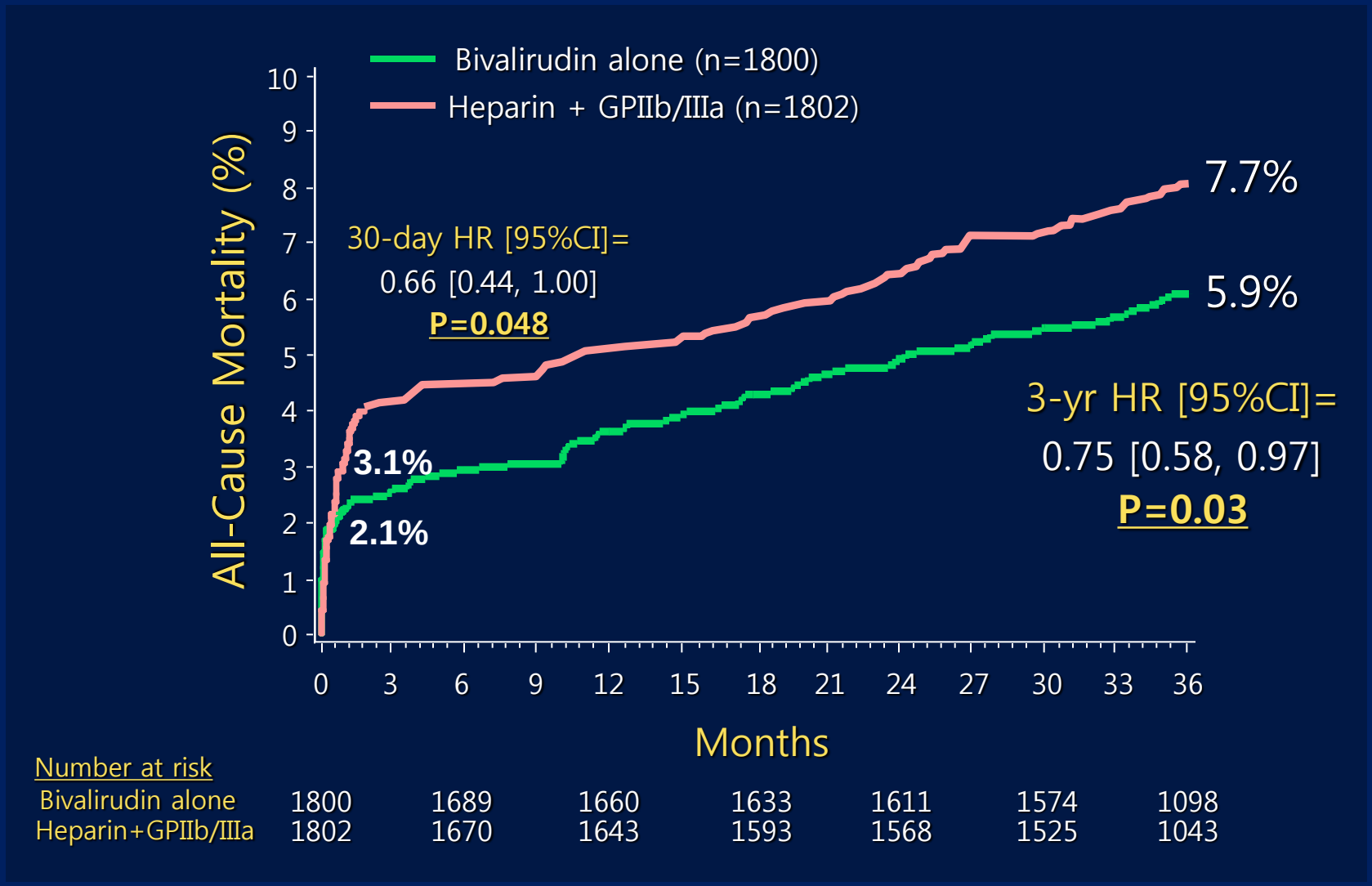


*Not related to CABG

** Plat cnt <100,000 cells/mm^3

Stone GW et al. NEJM 2008;358:2218-30

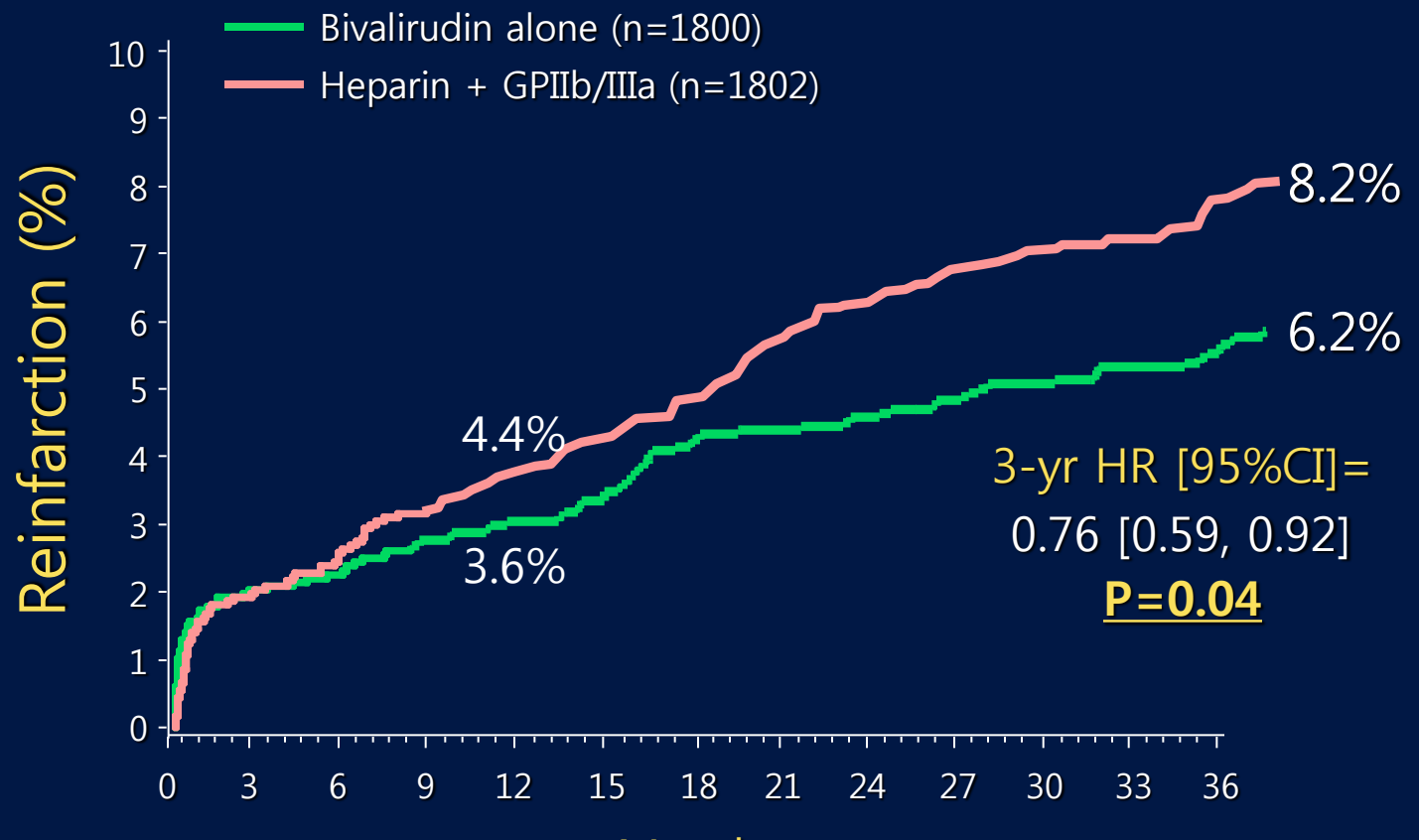
HORIZONS: 3-Year All-Cause Mortality



Stone GW et al. NEJM 2008;358:2218-30

Stone GW et al. Lancet 2011;377:2193-204

HORIZONS: 3-Year Reinfarction



Number at risk

Bivalirudin alone	1800	1643	1605	1560	1536	1494	1032
Heparin+GPIIb/IIIa	1802	1623	1581	1513	1474	1425	965

Stone GW et al. Lancet 2011;377:2193-204

But Bivalirudin costs too much!

To Summarize Bivalirudin

- Bivalirudin compared with UFH plus GPI significantly reduced both access site and non access site bleeding.
- The ACUITY and ISAR-REACT-4 trials supports the superiority of Bivalirudin compared to LMWH/UFH + GPI.
- Bivalirudin showed reduced mortality with reduced bleeding especially in high risk patients in HORIZONS-AMI:

  - Bivalirudin reduced the rate of cardiac death in the diabetic group at 30 days (2.1 vs. 5.5%, P=0.04) and 1 year (2.5 vs. 7.1%, P=0.01).

Segie Z, et al. *Current Opinion,* 2012

ACC/AHA Guidelines on Bivalirudin Use

- PCI in STEMI and NSTE-ACS
- Patients with HIT or HITTS

ESC/EACTS Guidelines on Myocardial Revascularization

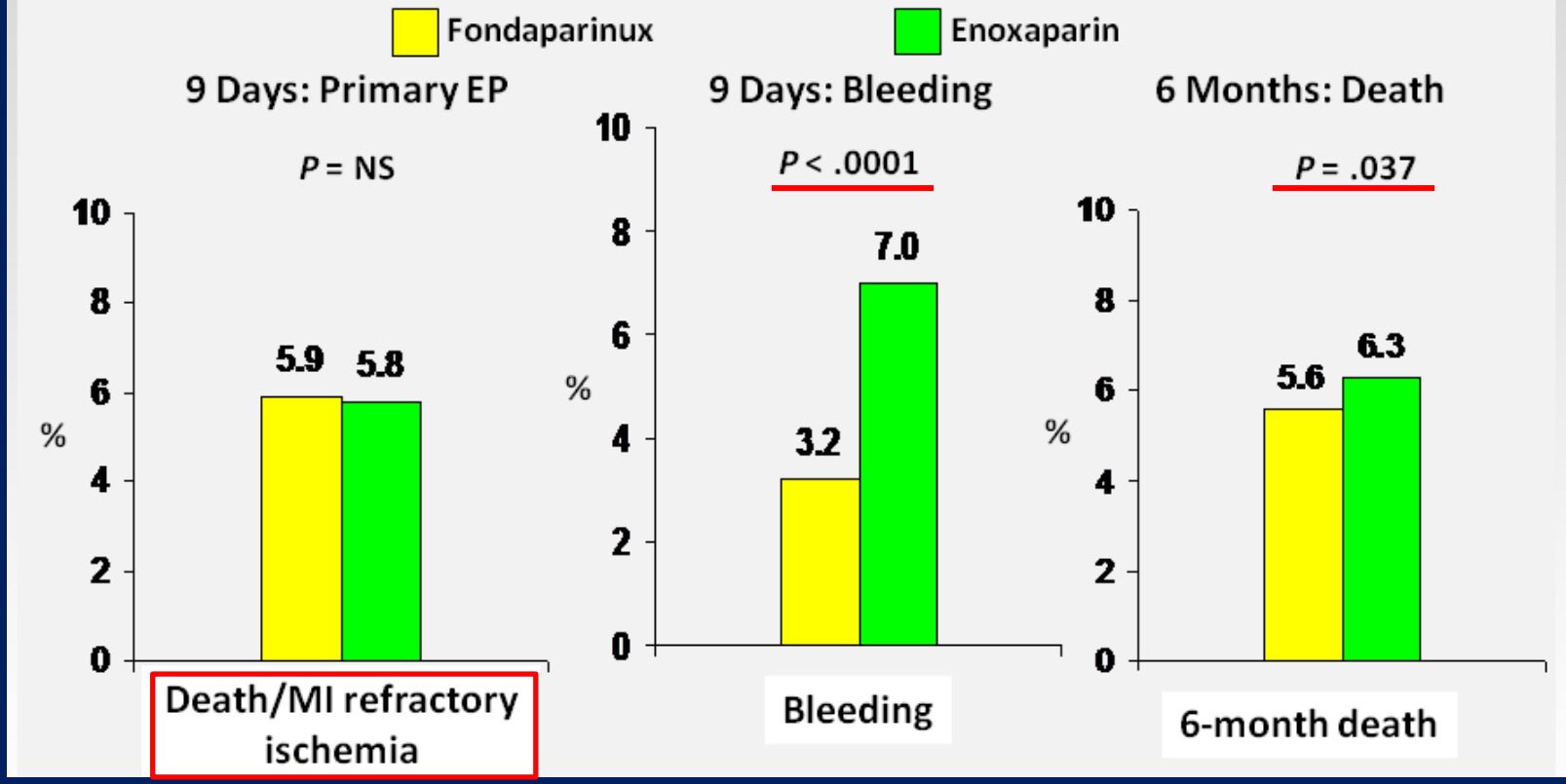
- PCI in STEMI and NSTE-ACS

Circulation and JACC 2005, 2007, 2009, 2011
EHJ 2010

Fondaparinux: OASIS-5

(Bleeding & Death)

20,078 patients with NSTE-ACS < 24 hours, 40% PCI, 97% aspirin, 67% clopidogrel, 1 x 2.5 mg/day fondaparinux subcutaneously vs 2 x 1 mg/kg/day enoxaparin subcutaneously for max 8 days



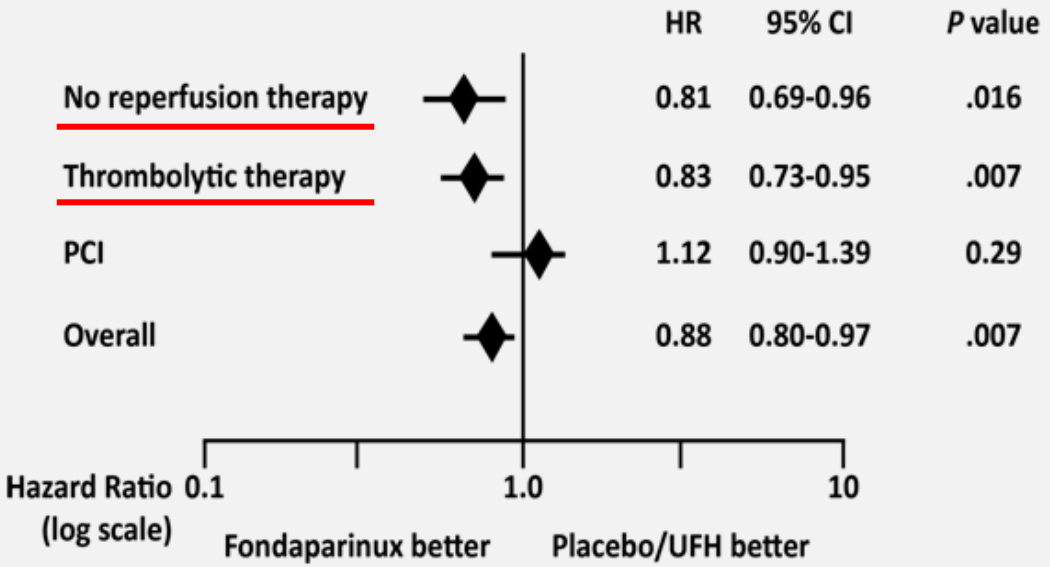
OASIS-5 Investigators. *N Engl J Med* 2006;354:1464-1476.

Fondaparinux: OASIS-6

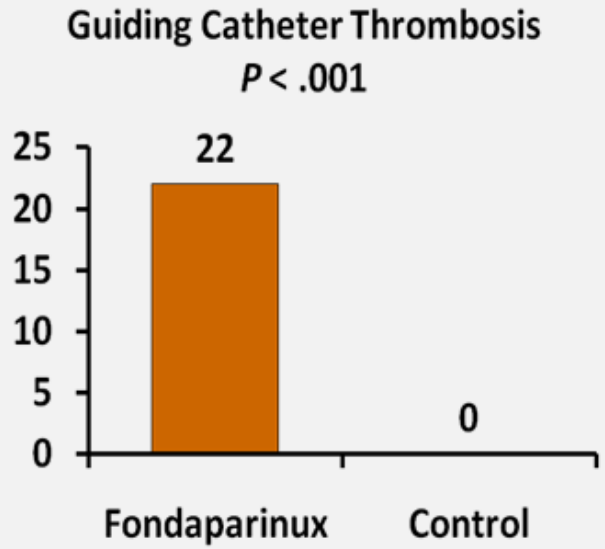
STEMI < 12 hours (n = 12,092), 96% aspirin, 58% clopidogrel or ticlopidine, PCI (n = 3789), thrombolysis (n = 5486), or conservative (n = 2869) fondaparinux vs placebo + UFH or placebo only

Outcome according to reperfusion strategy

Death/Reinfarction/Stroke/Severe Bleeding



Wire thrombi



UFH = unfractionated heparin

OASIS-6 Investigators. JAMA 2006;295:1519-1530.

To Summarize Fondaparinux

- Reduces bleeding vs. enoxaparin
- Reduces mortality vs. enoxaparin
- Similar to enoxaparin in reducing the risk of ischemic events at 9 days
- ↑ Catheter-related thrombosis in PCI patients

2011 ESC Guidelines for NSTEMI

Fondaparinux (2.5 mg subcutaneously daily) is recommended as having the most favourable efficacy-safety profile with respect to anticoagulation.	I	A
If the initial anticoagulant is fondaparinux, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GPIIb/IIIa receptor inhibitors) should be added at the time of PCI.	I	B
Enoxaparin (1 mg/kg twice daily) is recommended when fondaparinux is not available.	I	B
If fondaparinux or enoxaparin are not available, UFH with a target aPTT of 50-70 s or other LMWHs at the specific recommended doses are indicated.	I	C

2012 ACC/AHA Guidelines for NSTEMI

If fondaparinux is used during PCI, it must be co-administered with another anticoagulant with Factor IIa activity (ex. UFH).

2012 ESC Guidelines for STEMI

Fondaparinux is <u>not recommended for primary PCI</u>

Trials Regarding Oral Anticoagulation Agents

New Oral Anticoagulants

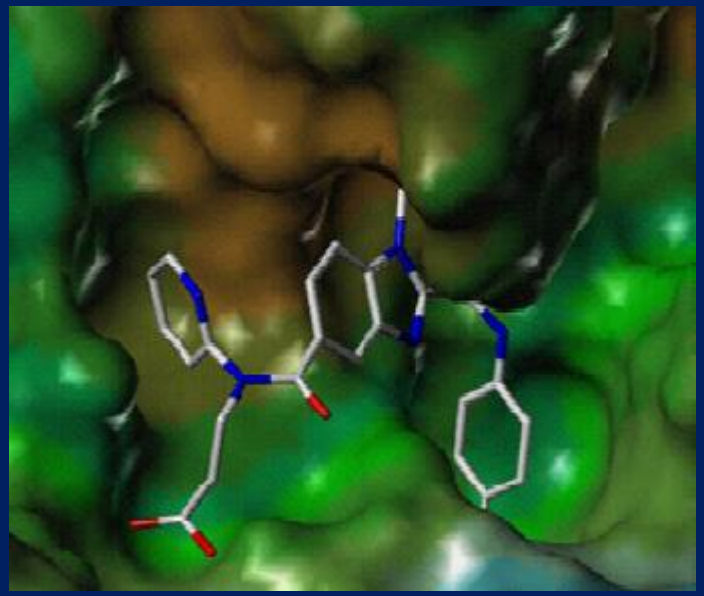
Comparative Pharmacology

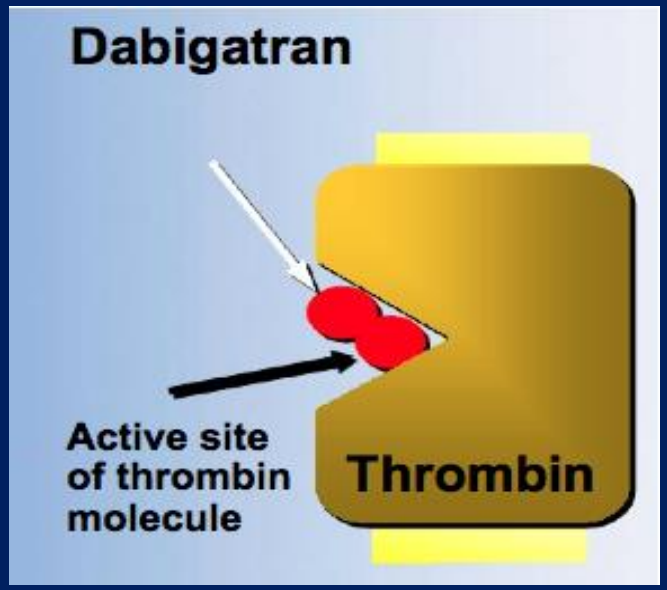
Characteristic	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Bioavailability (%)	80	60	50	6
Dosing	Once a day (Twice a day)	Twice a day	Once a day	Twice a day (Once a day)
Half-life (hours)	7-11	12	9-11	12-14
Renal excretion (%)	33 (66)	25	35	80
Monitoring	No	No	No	No
Interactions	3A4/Pgp	3A4	3A4/Pgp	Pgp

Pgp=P-glycoprotein

Dabigatran

- Oral prodrug
- Potent, competitive inhibitor of thrombin
- Half life 12 ~17 hours





Dabigatran

- 80% excreted by kidneys: contraindication in patients with renal failure.
- Drugs that inhibit P-glycoprotein (Amiodarone, Quinidine, Verapamil, Diltiazem) can increase the plasma levels of dabigatran by reducing the clearance of dabigatran

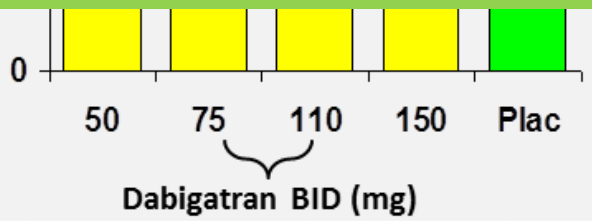
Dabigatran ACS Phase II (RE-DEEM trial)

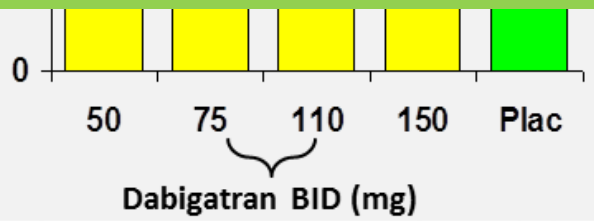
- Dose-finding study of dabigatran BID vs. placebo on top of DAPT after NSTEMI or STEMI (n=1891), PCI done between 52.2%~58.4%
- Primary endpoint: major or clinically relevant minor bleeding within 6 months

Primary Endpoint:
Major and Clinically Relevant Minor Bleeding*

Death, MI, Nonhemorrhagic Stroke

"The net clinical benefit of dabigatran, balancing the reduction of thromboembolic events vs. the increased risk of bleeding, can only be appropriately evaluated in a large-scale, adequately powered phase 3 study, for which there is currently no final decision."





*ISTH criteria: fatal, critical organ, hemoglobin drop 2 g/dL, ≥ 2 U transfusion

Oldgren J, et al. Eur Heart J 2011;32:2781-2789.

Randomized, Open Label Study of Dabigatran Etexilate in Elective Percutaneous Coronary Intervention

This study has been completed.

Sponsor:
Boehringer Ingelheim Pharmaceuticals

Information provided by (Responsible Party):
Boehringer Ingelheim Pharmaceuticals

ClinicalTrials.gov Identifier:
NCT00818753

First received: January 7, 2009
Last updated: May 18, 2012
Last verified: May 2012
History of Changes

Purpose

To assess whether two doses of dabigatran etexilate (110 mg twice daily (b.i.d) and 150 mg twice daily (b.i.d)) as compared to unfractionated heparin (UFH), both in addition to a standard dual antiplatelet regimen, provide sufficient anticoagulation in the setting of elective percutaneous coronary intervention (PCI).

Condition	Intervention	Phase
Heart Catheterization	Drug: dabigatran 110 mg Drug: dabigatran 150 mg Drug: unfractionated heparin	Phase 2

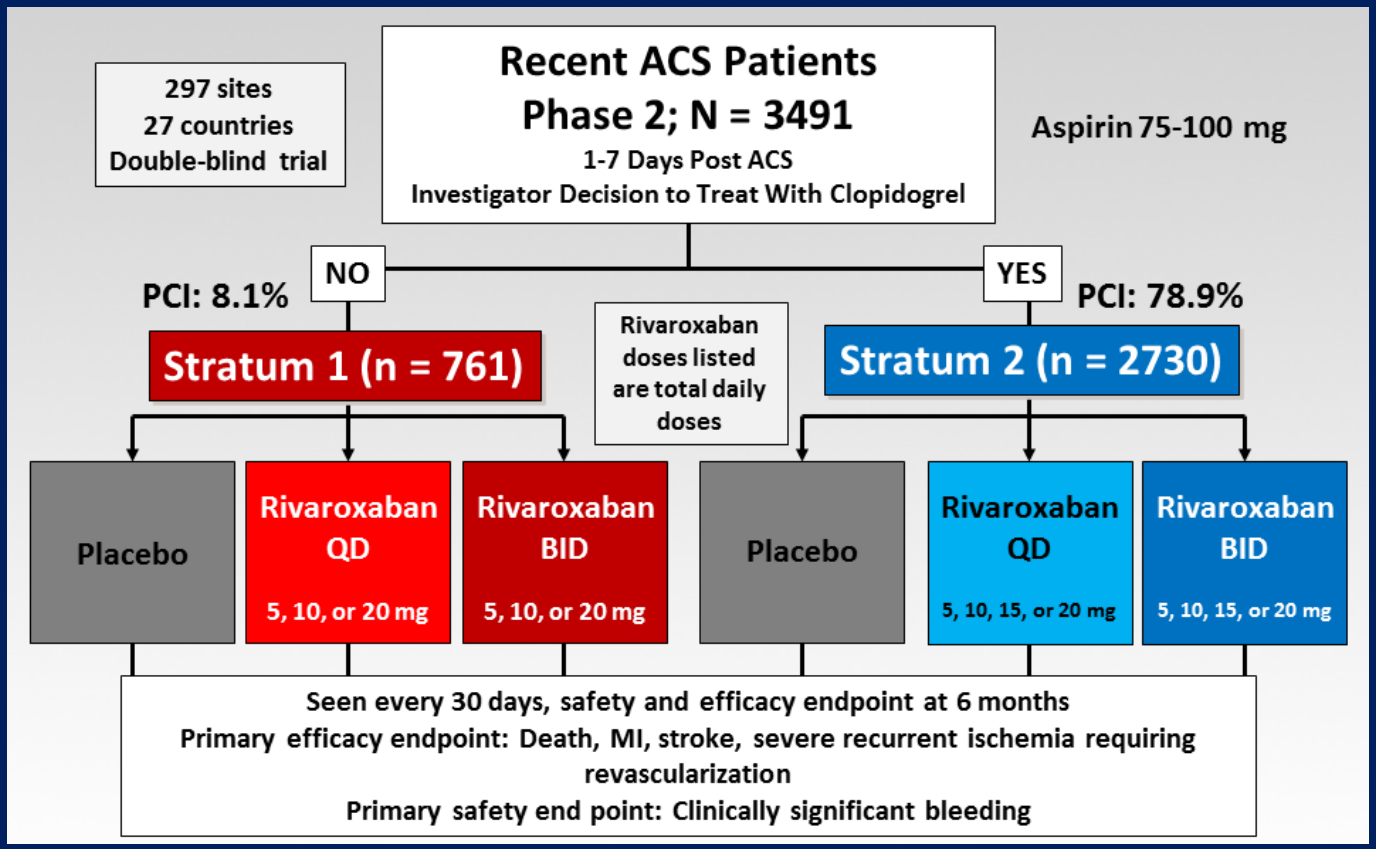
Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label

Rivaroxaban

- An oral, direct Factor Xa inhibitor
- Binding reversibly to its active site.
- Half-life of 7–11 h, and 67% is renally cleared.
- Substrate for P-glycoprotein and metabolized via CYP3A4 → co- administration of potent inhibitors of P-glycoprotein and CYP3A4, such as ketoconazole, should be avoided.

Rivaroxaban in ACS
(ATLAS-ACS TIMI 46)

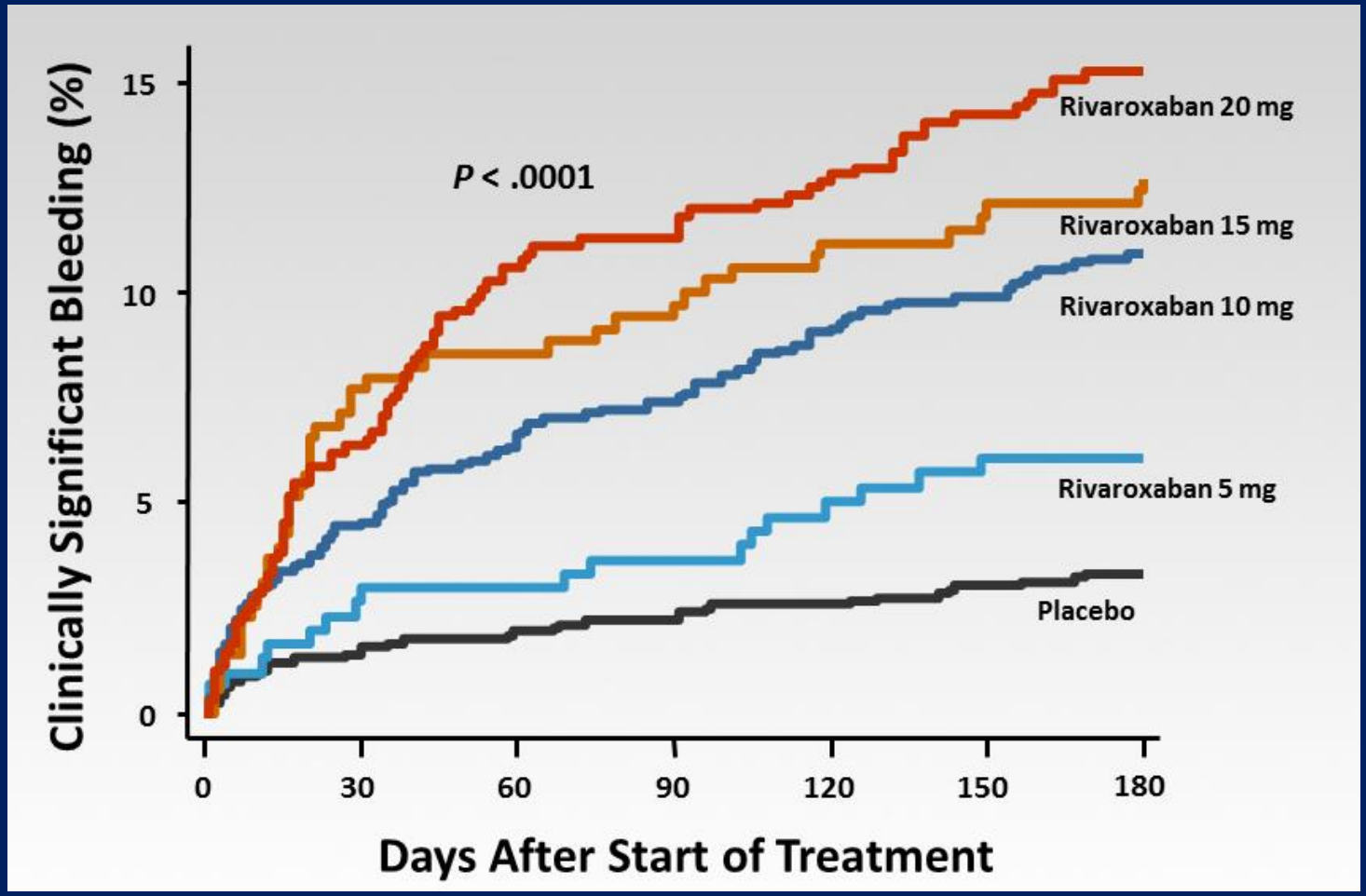
- 3,491 patients after ACS randomized
- The primary safety endpoint was clinically significant bleeding
- The primary efficacy endpoint was death, MI, stroke, or severe recurrent ischemia requiring revascularization during 6 months.



Mega JL et al. Lancet. 2009;374:29-38

Rivaroxaban in ACS
(ATLAS-ACS TIMI 46)

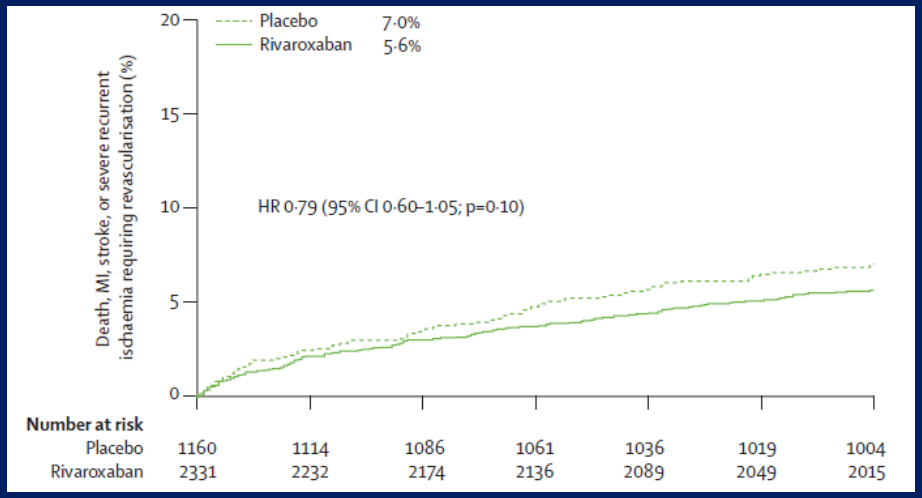
- Clinically significant bleeding (TIMI major, TIMI minor, or requiring medical attention) across doses

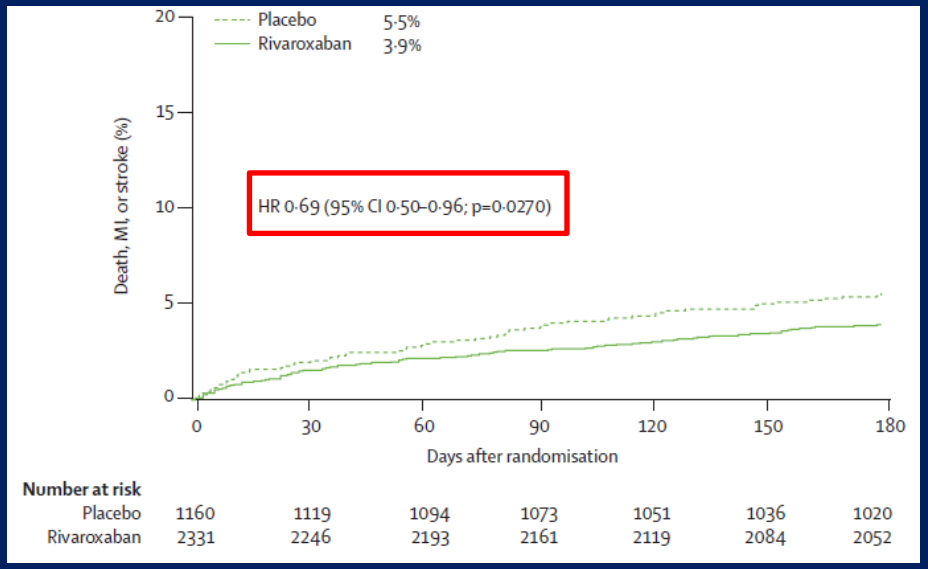


Mega JL et al. Lancet. 2009;374:29-38

Rivaroxaban in ACS
(ATLAS-ACS TIMI 46)

- Primary and Secondary Efficacy Endpoints





Mega JL et al. Lancet. 2009;374:29-38

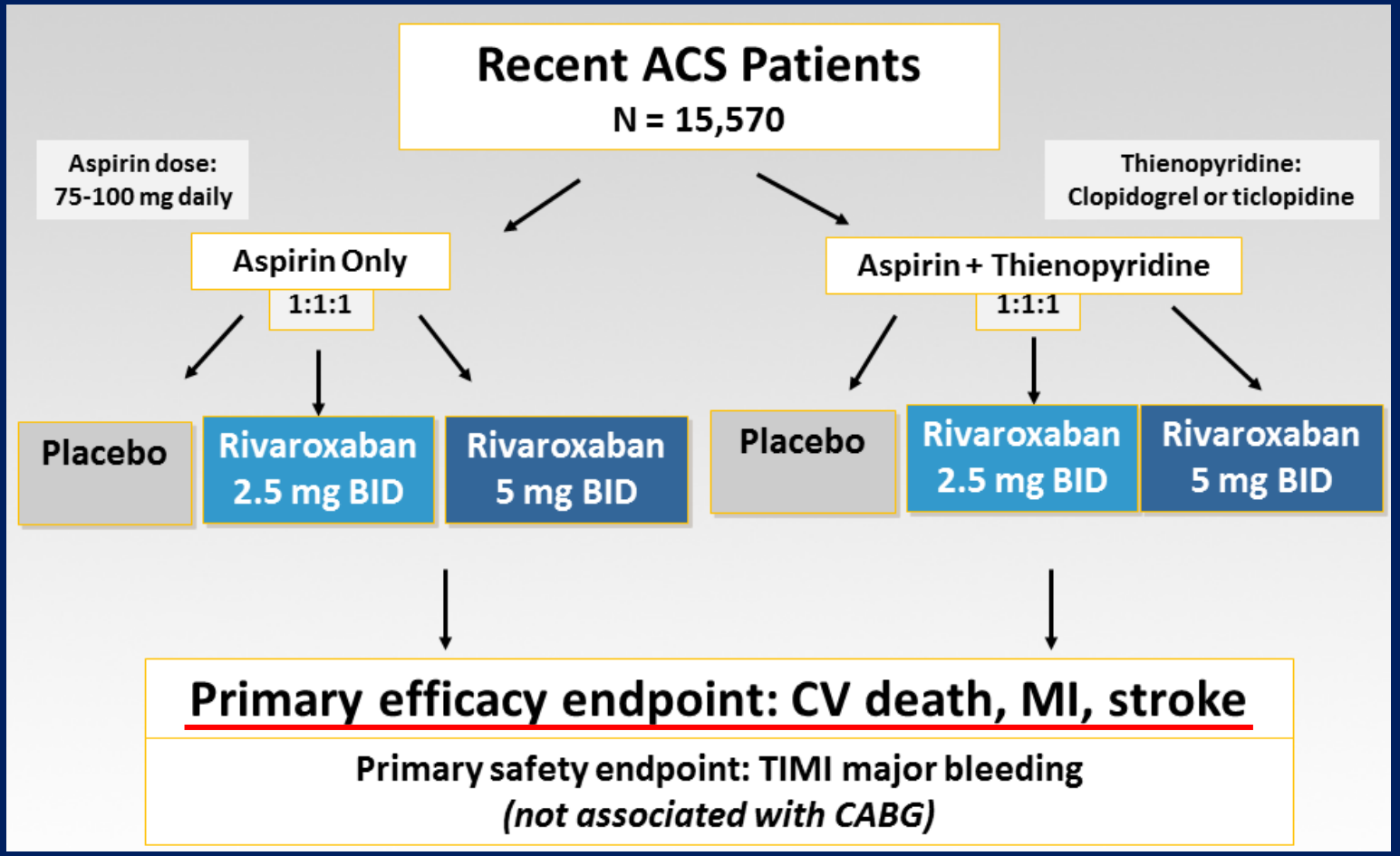
ATLAS-ACS TIMI 46

- The use of rivaroxaban in patients with ACS increased bleeding in a dose-dependent manner and might reduce major ischemic outcomes.
- On the basis of these observations → a phase III study of low-dose rivaroxaban as adjunctive therapy in ACS patients (ATLAS ACS 2 TIMI 51).

Mega JL et al. Lancet. 2009;374:29-38

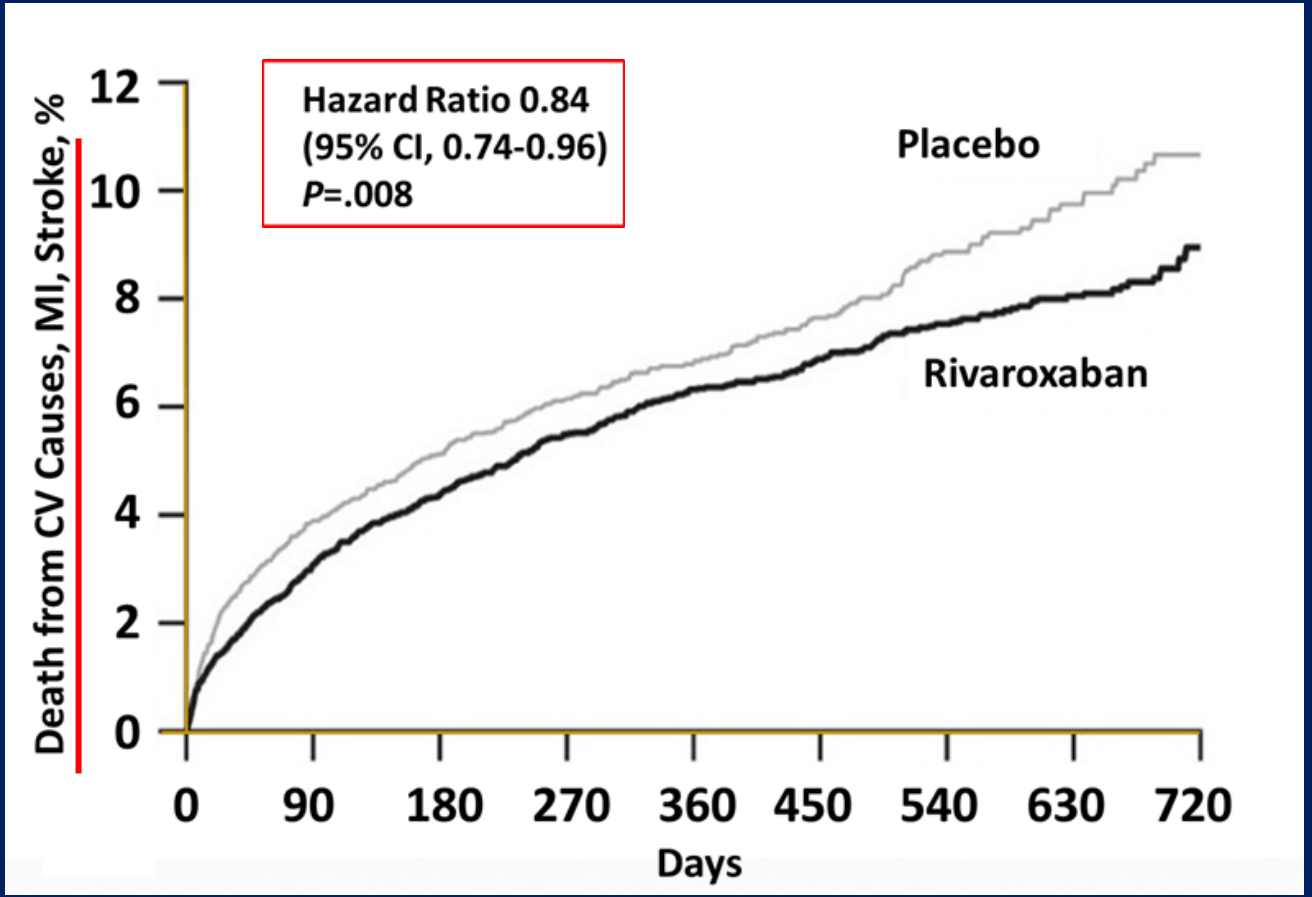
Rivaroxaban in ACS
(ATLAS-ACS TIMI 51)

15,570 patients with ACS randomized to rivaroxaban 2.5 or 5mg BID vs. placebo on top of DAPT (>92.6%) for 13~31 months, PCI done in about 60%



Gibson CM et al. Am Heart J. 2011;161:815-821

Rivaroxaban in ACS
(ATLAS-ACS TIMI 51)



N Engl J Med. 2012; 366:9-19.

ATLAS-ACS TIMI 51
(Rivaroxaban 2.5mg BID vs. Placebo)

	Rivaroxaban %	Placebo %		
	2.5 mg BID n = 5114	n = 5113	Hazard ratio (95% CI)	*P* value
Primary outcome	9.1	10.7	0.84 (0.72-0.97)	.02
Secondary outcome	2.7	4.1	0. 66 (0.51-0.86)	.002
Major non-CABG bleeding	1.8	0.6	3.46 (2.08-5.77)	.001
ICH	0.4	0.2	2.83 (1.02-7.86)	.04
Fatal bleeding	0.1	0.2	0.67 (0.24-1.89)	.45

Primary outcome: death from CV causes, stroke
Secondary outcome: death from any cause, MI, stroke

Mega JL et al. N Engl J Med. 2011 Nov 13

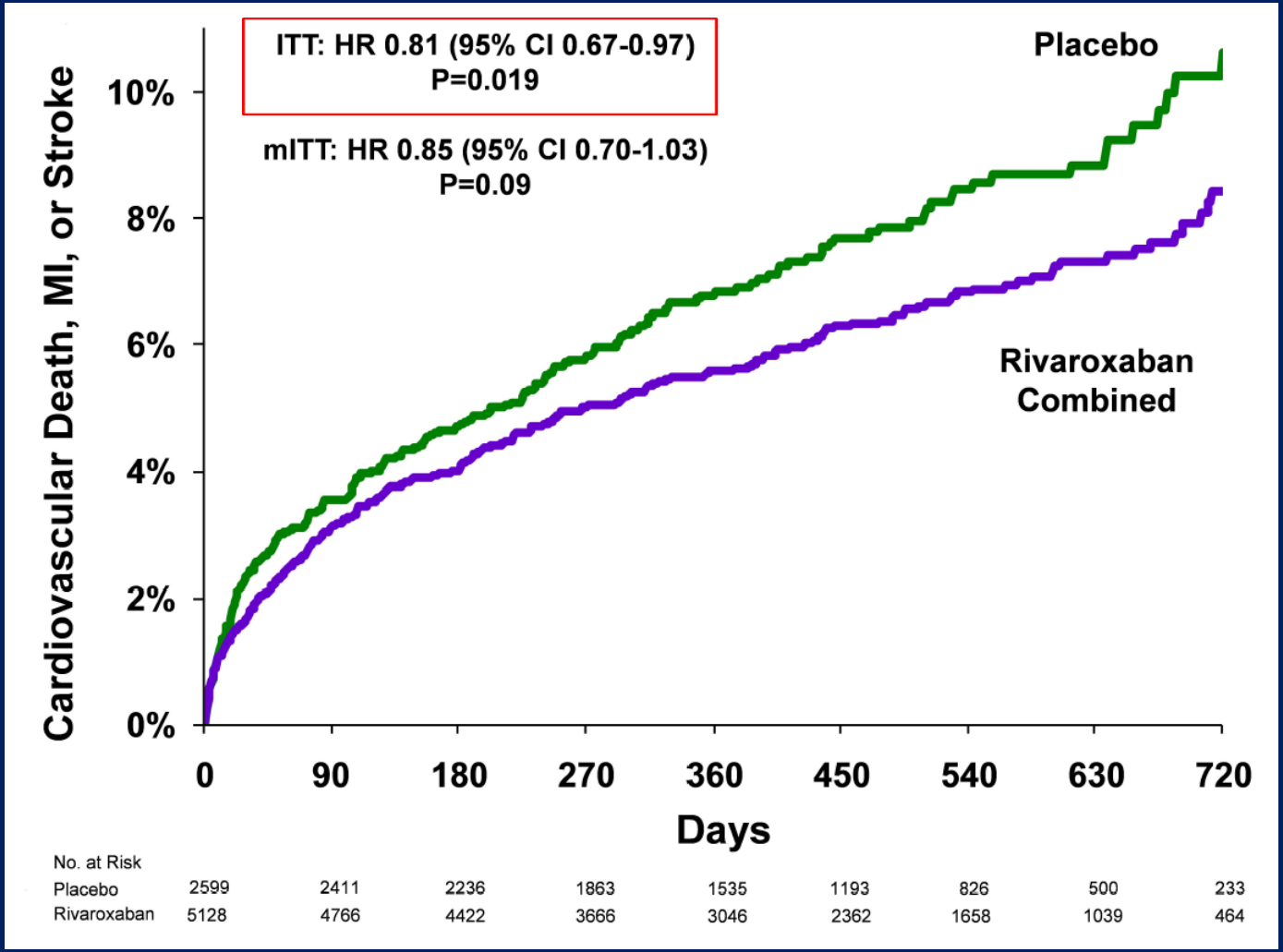
ATLAS-ACS TIMI 51
(Rivaroxaban 5mg BID vs. Placebo)

	Rivaroxaban %	Placebo %		
	5 mg BID n = 5115	n = 5113	Hazard ratio (95% CI)	*P* value
Primary outcome	8.8	10.7	0.85 (0.73-0.98)	.03
Secondary outcome	4.0	4.1	0.94 (0.75-1.20)	.63
Major non-CABG bleeding	2.4	0.6	4.47 (2.71-7.36)	<.001
ICH	0.7	0.2	3.74 (1.39-10.07)	.005
Fatal bleeding	0.4	0.2	1.72 (0.75-3.92)	.20

Primary outcome: death from CV causes, stroke
Secondary outcome: death from any cause, MI, stroke

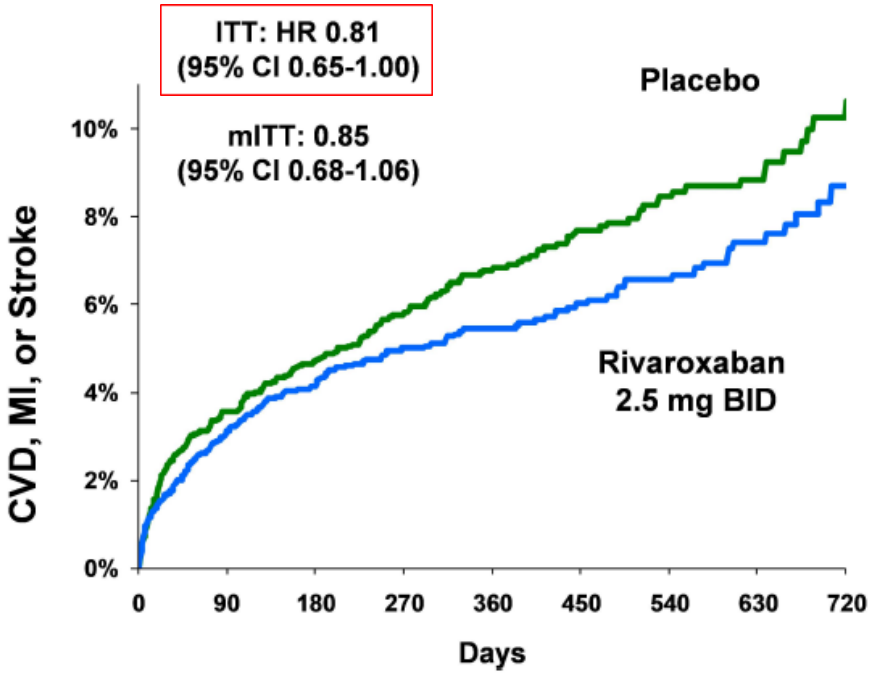
Mega JL et al. N Engl J Med. 2011 Nov 13

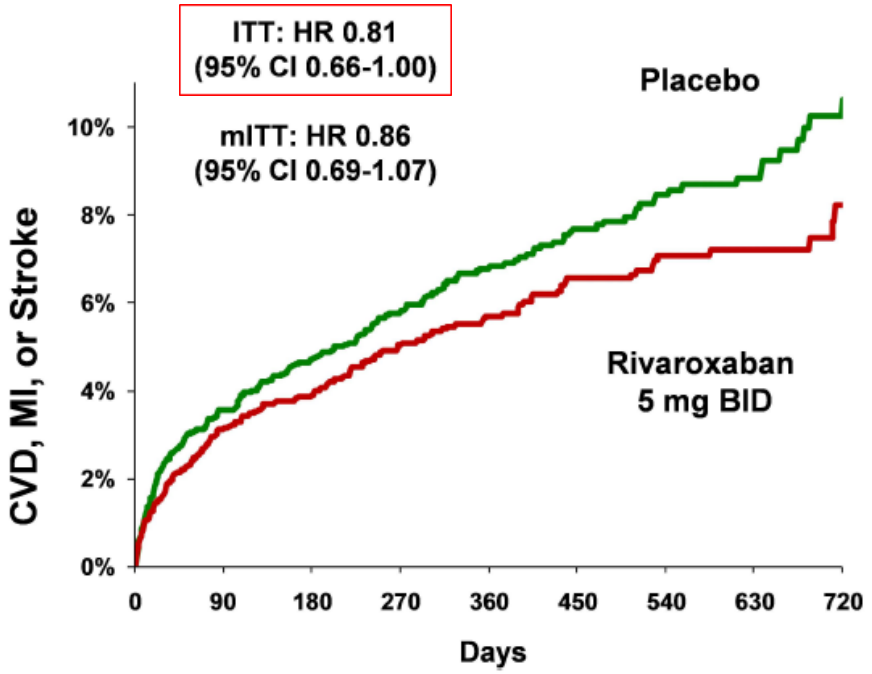
ATLAS-ACS TIMI 51
(STEMI subgroup)



Mega JL et al. JACC 2013

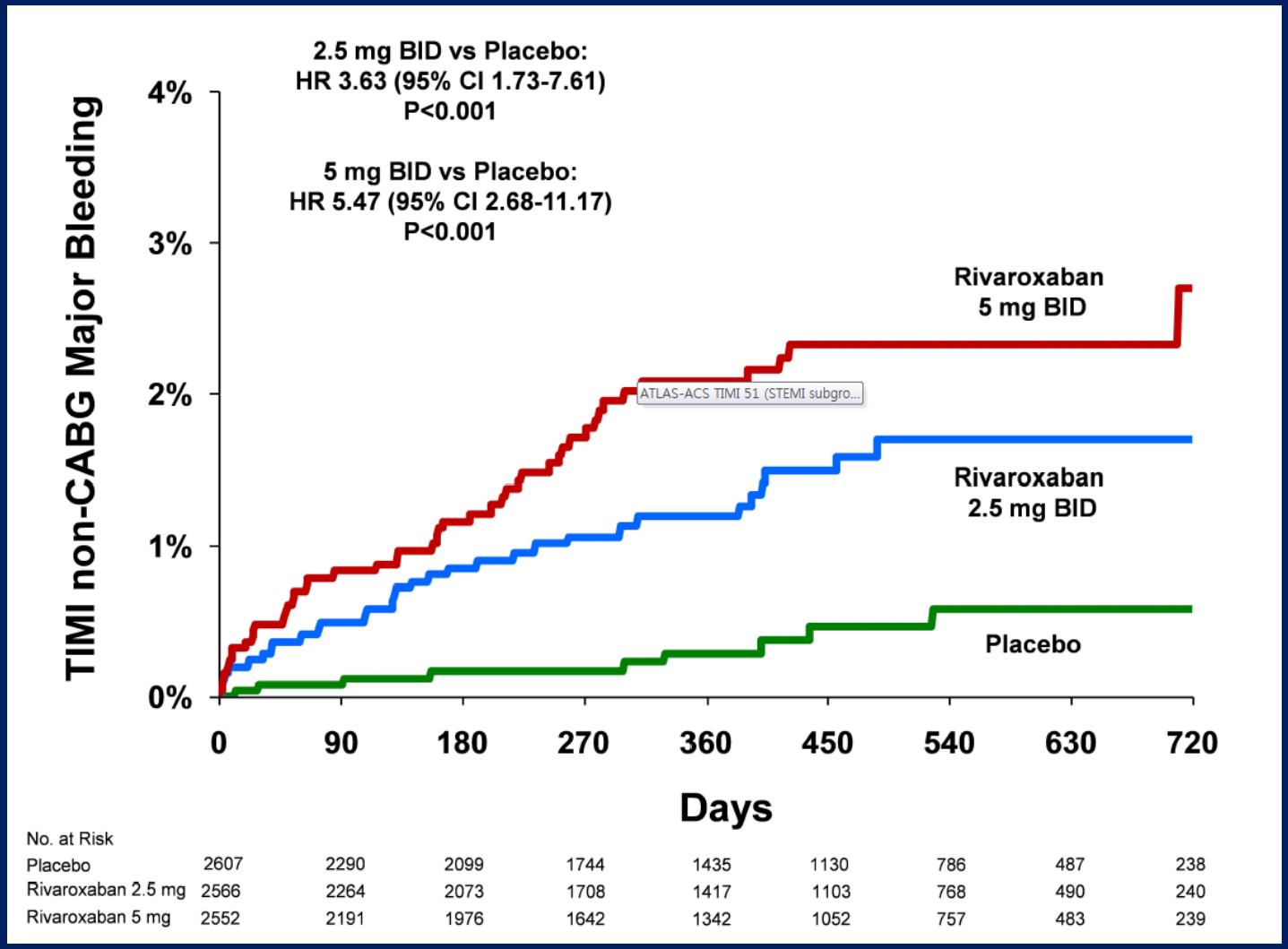
ATLAS-ACS TIMI 51
(STEMI subgroup)





Mega JL et al. JACC 2013

ATLAS-ACS TIMI 51
(STEMI subgroup)



Mega JL et al. JACC 2013

To Summarize ATLAS-ACS TIMI 51

- In patients with ACS, rivaroxaban reduced the risk of the composite end point of death from CV causes, MI, or stroke.
- Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.
- Same findings in STEMI subgroups.

Mega JL et al. N Engl J Med. 2011 Nov 13

2012 ESC Guidelines (STEMI)

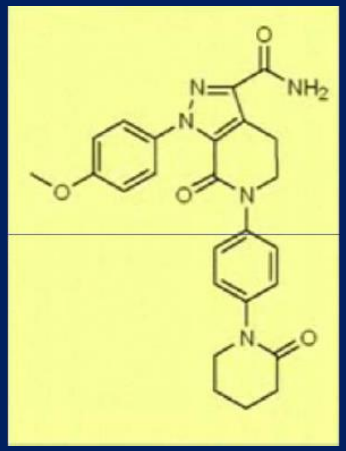
Routine therapies in the acute, subacute, and long-term phase of STEMI

	Class	Level
In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg BID) may be considered if the patient is at low bleeding risk.	IIb	B

- On March 2013:

Rivaroxaban gets **ACS indication** recommendation from European regulators

Apixaban

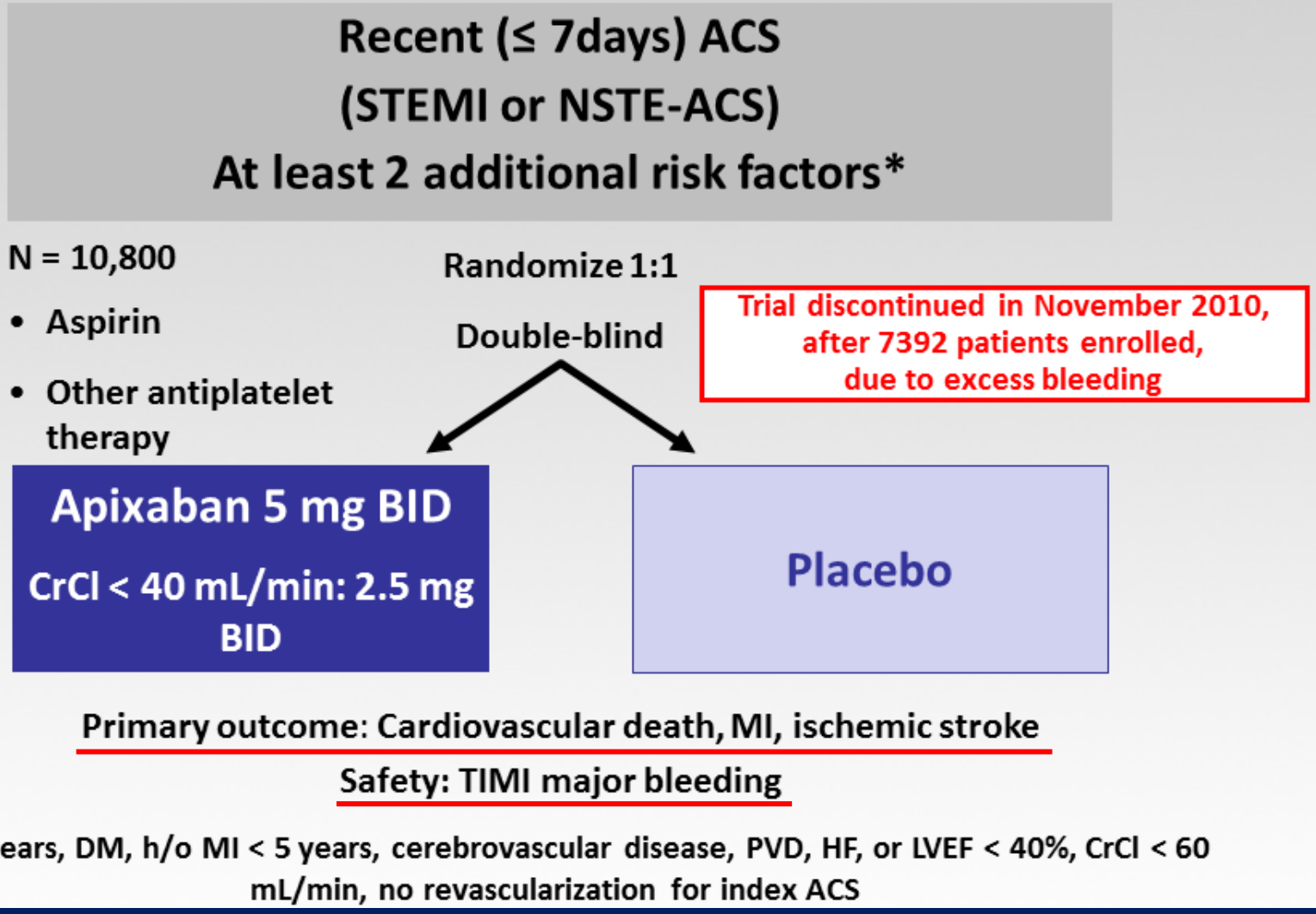


- Oral direct Factor Xa Inhibitor
- Half-life :12 h
- 25% of the drug is cleared by kidney.
- Metabolized via the CYP3A4 system

  → coadministration of potent inhibitors of the enzyme, including some HIV protease inhibitors, macrolide antibiotics, and azole antifungals, should be avoided.

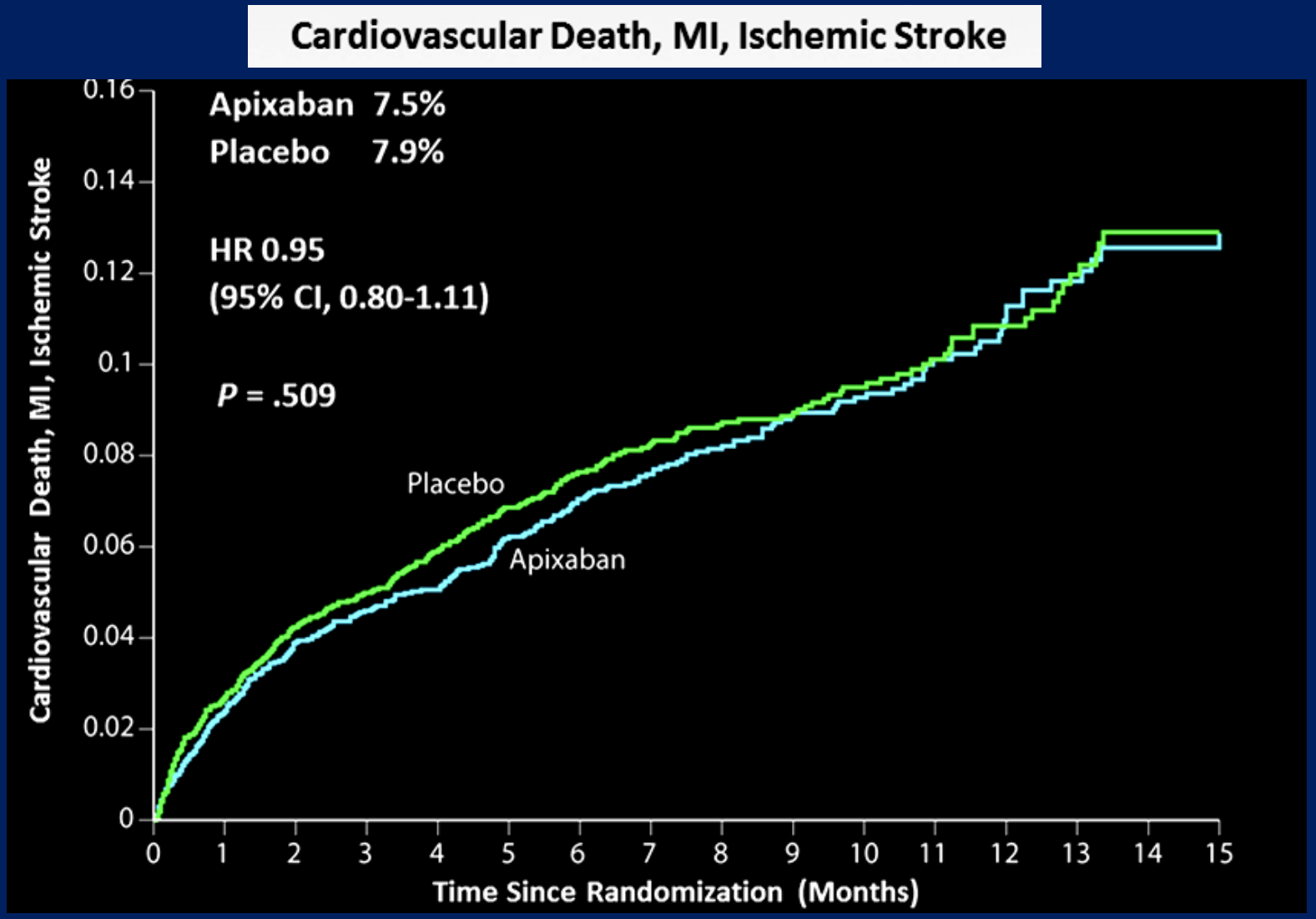
Apixaban in ACS (APPRAISE II)

PCI in about 44%



Alexander JH et al. New Eng J Med 2011: 365:699-708

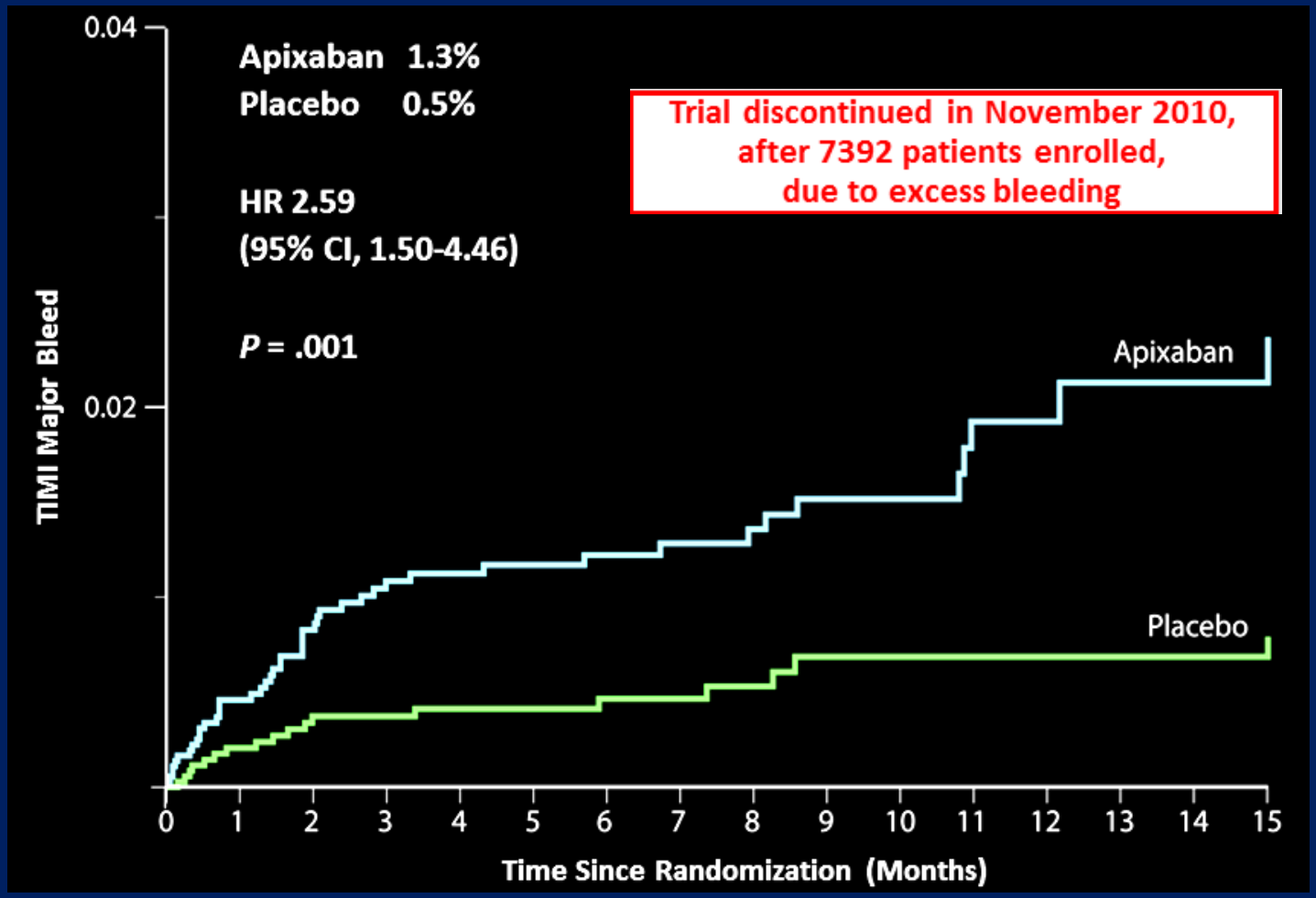
Apixaban in ACS (APPRAISE II)



Alexander JH et al. New Eng J Med 2011: 365:699-708

Apixaban in ACS (APPRAISE II)

TIMI Major Bleeding



Alexander JH et al. New Eng J Med 2011: 365:699-708

Potential Advantages of New Oral Anticoagulants

- High specificity
- Predictable pharmacokinetics
- Good efficacy and tolerability balance
- Fixed daily dose (once- or twice-daily)
- No monitoring or dose adjustment requirement
- Rapid onset of action
- Fewer drug and food interactions

Halperin JL. J Cardiovasc Med 2009:10:610-615

Unresolved Issues with New Oral Anticoagulants

- No established methods of monitoring
- No known therapeutic ranges
- Lack of an antidote (difficulty in the management of bleeding)
- Long-term safety
- No head-to-head comparisons of new agents

Ideal Anticoagulation Drug

1. Potent antithrombotic effect
2. Rapid onset and offset (availability of an antidote)
3. Predictable pharmacodynamic profile,
   making monitoring unnecessary
4. No interaction with adjunctive medications
5. Low risk and cost
6. Easy to administer

Summary

1. Bivalirudin: Approved for ACS patients undergoing PCI
   - Reduced 3-year cardiac mortality in STEMI pts after PCI.
   - Reduced CV events with lower bleeding in NSTEMI pts after PCI.
   - BUT too expensive and not available in Korea!
2. Fondaparinux:
   - Not recommended for ACS pts undergoing PCI
3. Dabigatran:
   - Reduced CV events with increased bleeding in AMI pts.
   - Still need more data in PCI pts!
4. Rivaroxaban: Approved for ACS patients in Europe
   - Reduced CV events with increased bleeding in ACS pts.
5. Apixaban:
   - No reduction in CV events with increased bleeding in ACS pts.
   - Too early for PCI pts!

Conclusions

- Novel injectable anticoagulant

  → **Bivalirudin**, which is not available in Korea and more expensive than heparin, could be a good alternative option in ACS pts undergoing PCI.

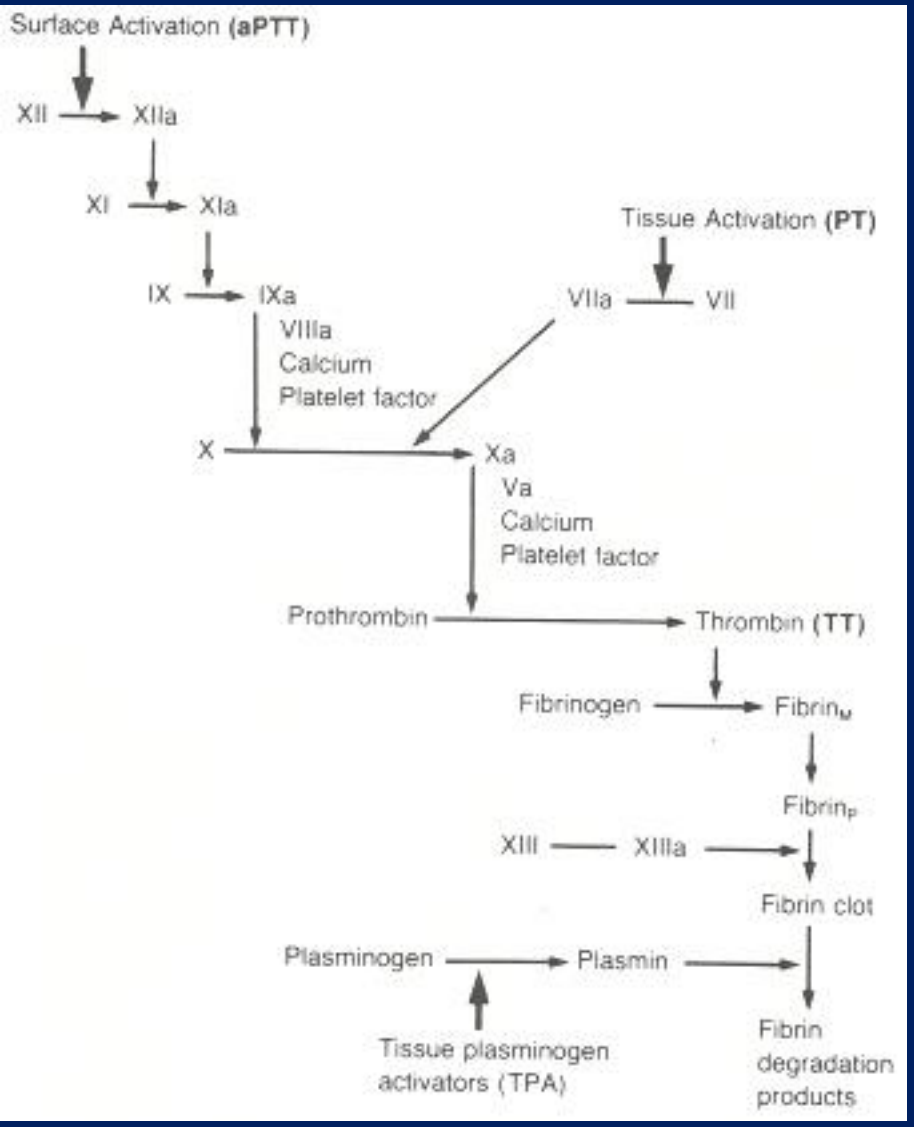
- Novel oral anticoagulant

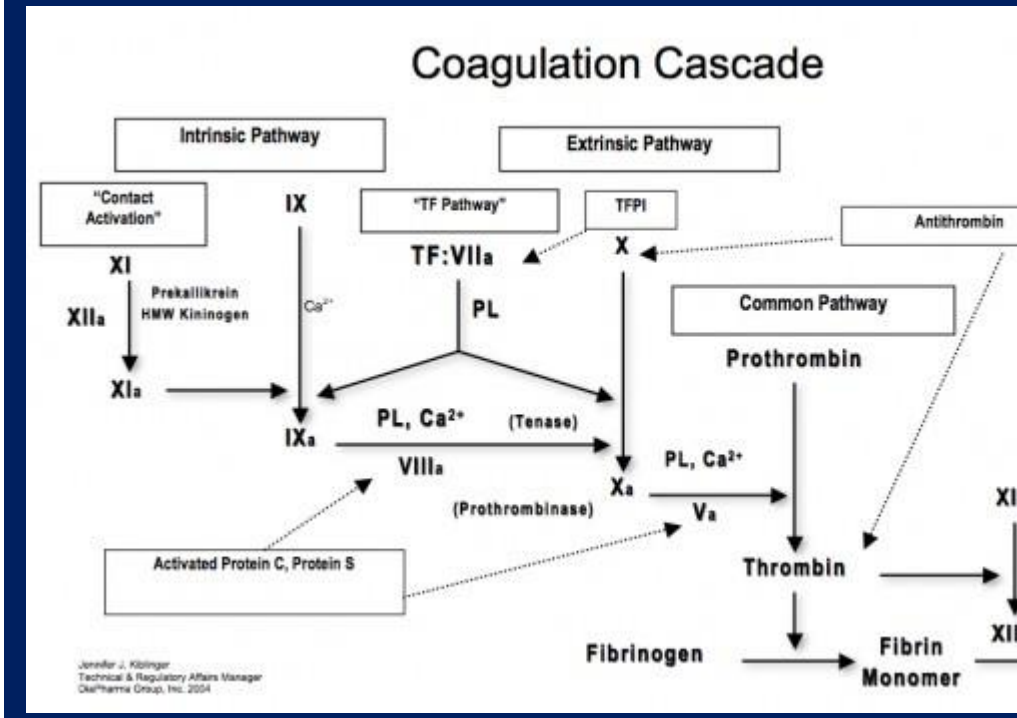
  → **Rivaroxaban** which is approved only in Europe for ACS could be used to decrease CV events.

  → Apixaban and dabigatran need more data in ACS.

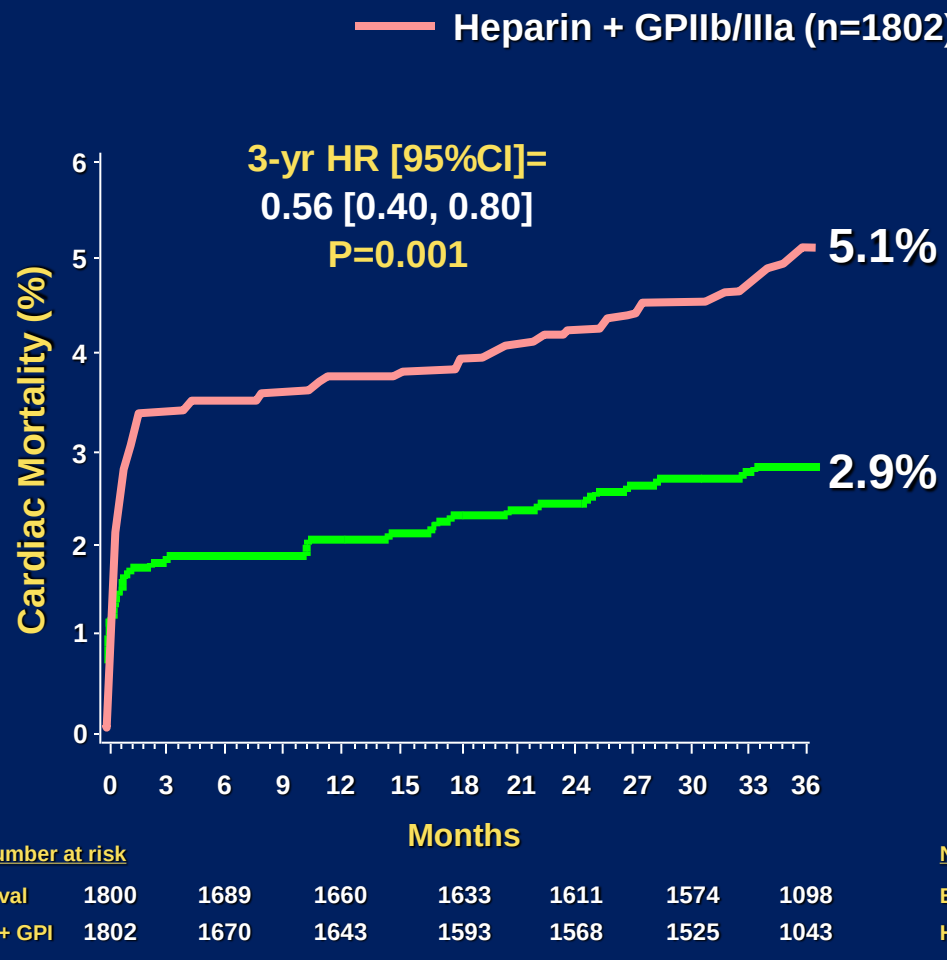
- No data yet on new anticoagulants + prasugrel or ticagrelor.

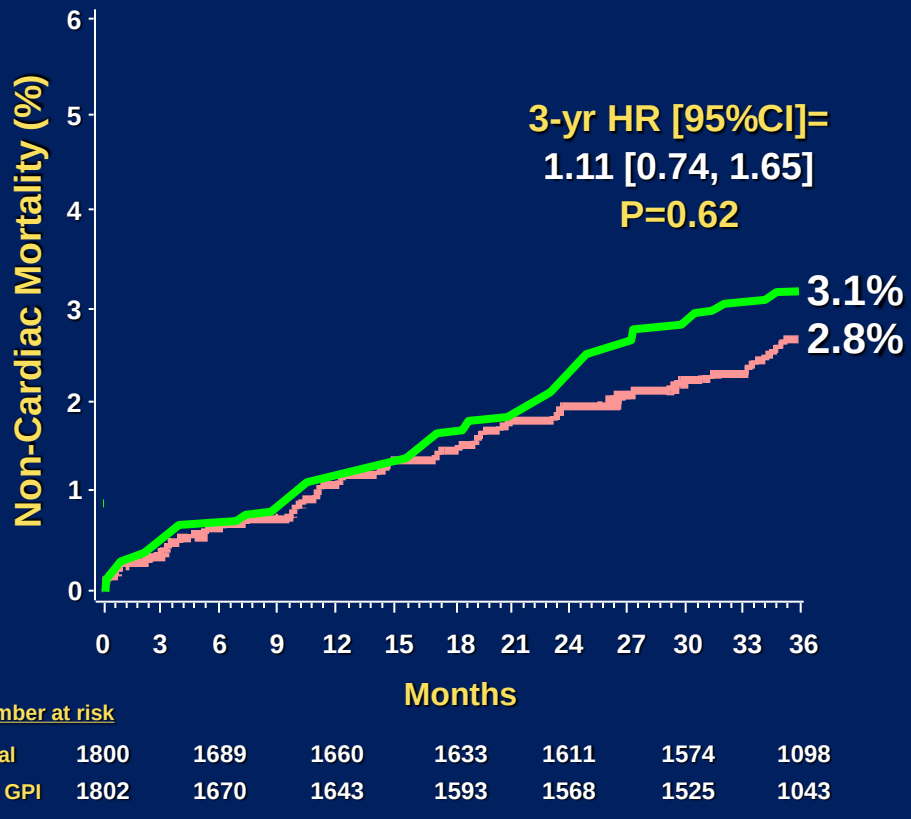
Thank You For Your Attention!


Surface Activation (aPTT)
XII
XIIa
XI
XIa
IX
IXa
VIIIa
Calcium
Platelet factor
Tissue Activation (PT)
VIIa
VII
X
Xa
Va
Calcium
Platelet factor
Prothrombin
Thrombin (TT)
Fibrinogen
Fibrin$_M$
Fibrin$_P$
XIII
XIIIa
Fibrin clot
Plasminogen
Plasmin
Tissue plasminogen activators (TPA)
Fibrin degradation products


Coagulation Cascade
Intrinsic Pathway
Extrinsic Pathway
"Contact Activation"
IX
"TF Pathway"
TFPI
Antithrombin
XI
TF:VIIa
X
XIIa
Prekallikrein
HMW Kininogen
Ca2+
PL
Common Pathway
Prothrombin
XIa
PL, Ca2+
(Tenase)
IXa
VIIIa
PL, Ca2+
Xa
(Prothrombinase)
Va
Activated Protein C, Protein S
Thrombin
Fibrinogen
Fibrin Monomer
Jennifer J. Kitzinger
Technical & Regulatory Affairs Manager
DadPharma Group, Inc. 2004

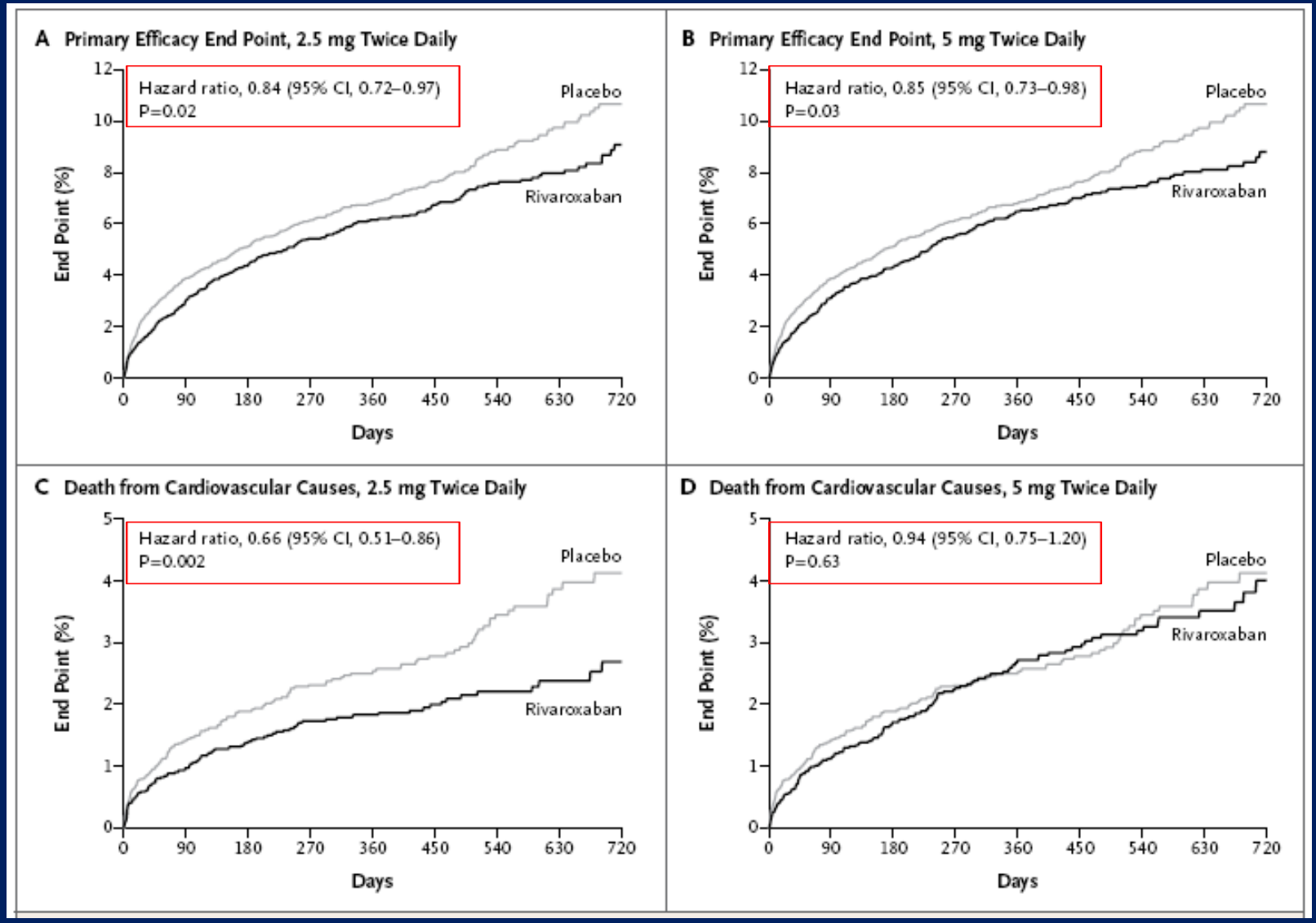
3-Year Mortality: Cardiac and Non Cardiac





Stone GW et al. Lancet 2011;377:2193-204

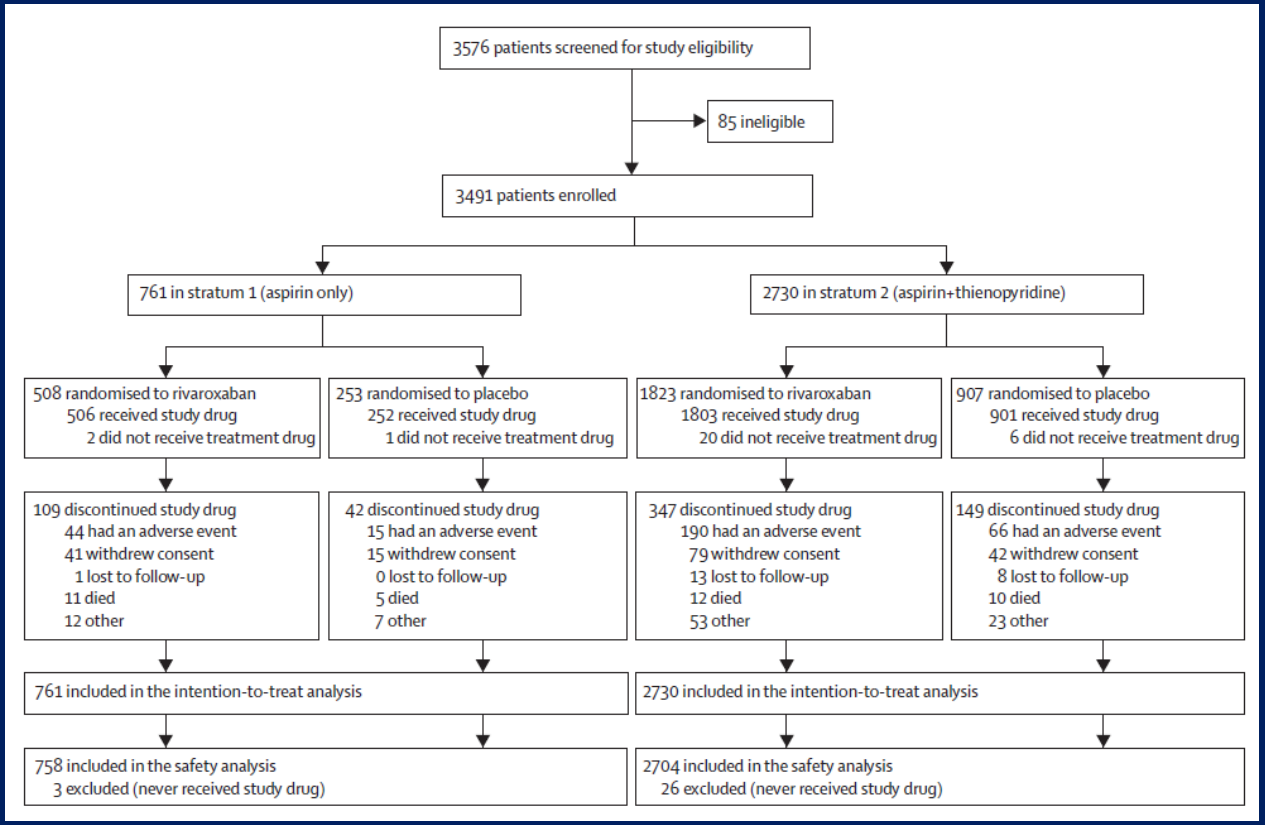
Rivaroxaban in ACS
(ATLAS-ACS 2 TIMI 51)



N Engl J Med. 2012; 366:9-19.

Rivaroxaban in ACS
(ATLAS-ACS TIMI 46)

- 3,491 patients after ACS randomized, PCI between 63.3%~ 64.2%
- The primary safety endpoint was clinically significant bleeding
- The primary efficacy endpoint was death, MI, stroke, or severe recurrent ischemia requiring revascularization during 6 months.



Mega JL et al. Lancet. 2009;374:29-38