Role of NOAC in ACS

How to Select

Optimal Patients?

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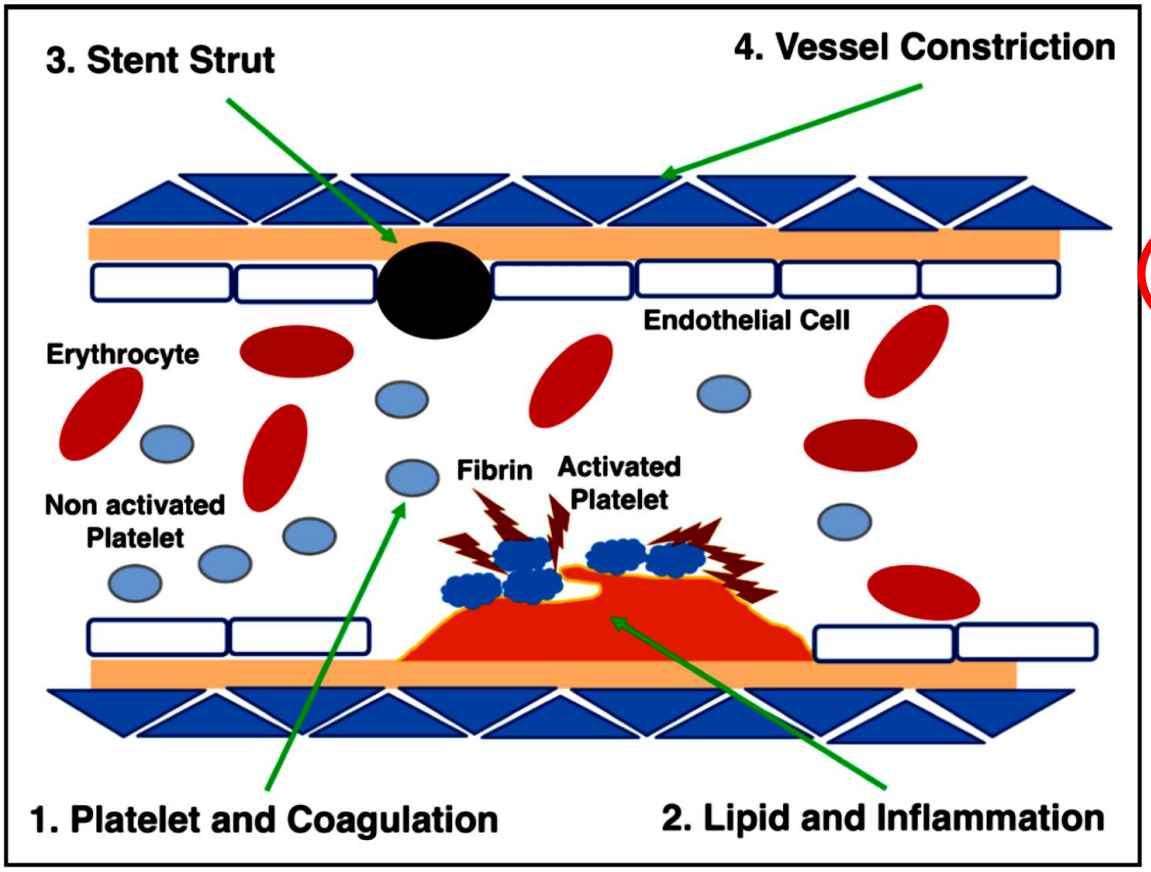
Next Project: Residual Risk Reduction in CV Disease



Platelet:

Prasugrel, Ticagrelor, Vorapaxar

Coagulation:

NOAC

Lipid:

PCSK9 inhibitor

(Evolucumab, Alirocumab)

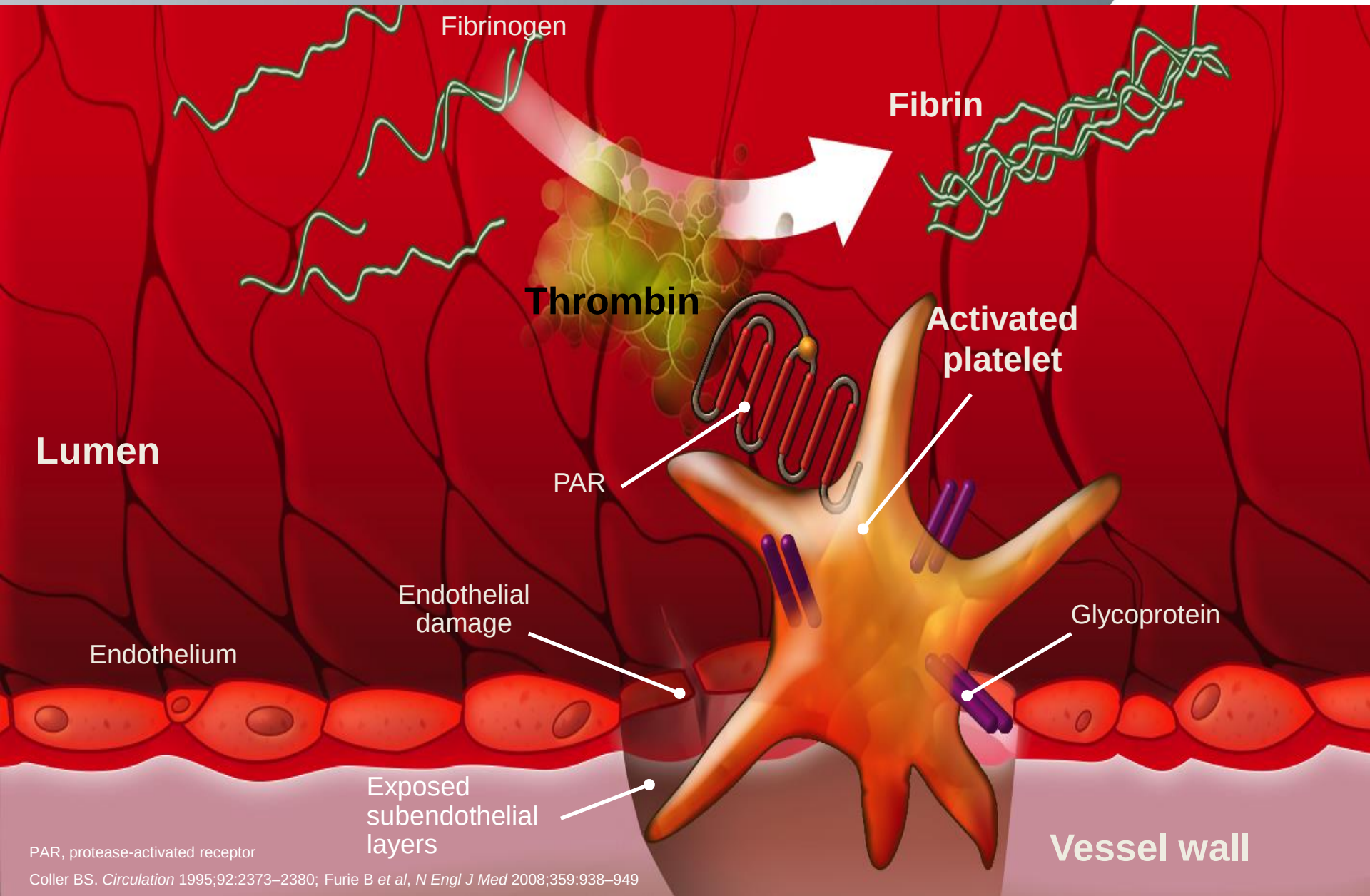
Inflammation:

IL-1 ß monoclonal antibody

(Canakinumab)

Yabushita H, Goto S. Circulation. 2018;137:563-6.

Crucial Role of Thrombin on Thrombus Formation

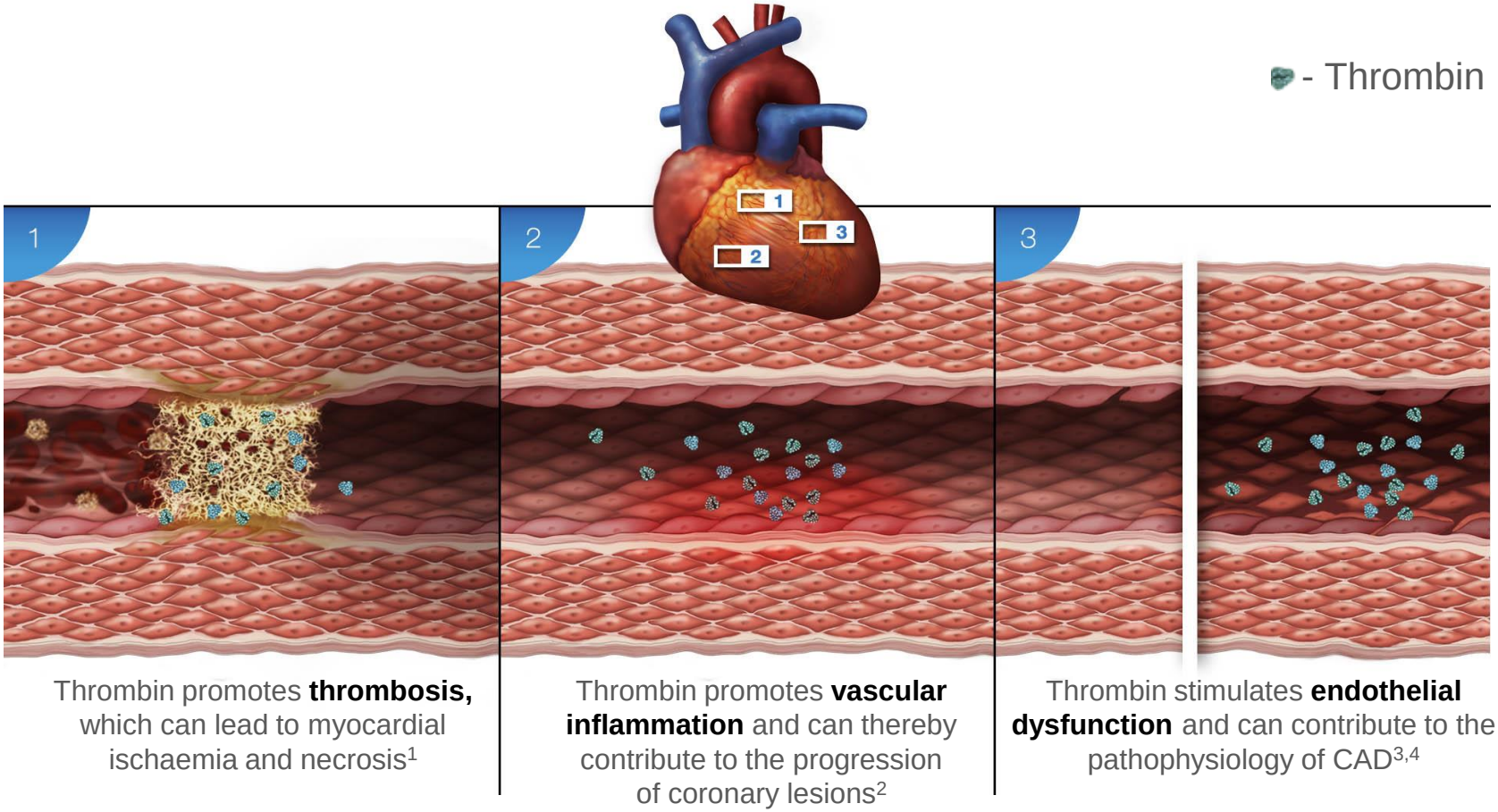


PAR, protease-activated receptor

Coller BS. *Circulation* 1995;92:2373–2380; Furie B *et al*, *N Engl J Med* 2008;359:938–949

Thrombin Involves in CV Pathophysiological Processes (Atherosclerosis + Thrombosis)

Thrombin promotes myocardial necrosis, inflammation and endothelial dysfunction



Thrombin promotes **thrombosis,** which can lead to myocardial ischaemia and necrosis[1]

Thrombin promotes **vascular inflammation** and can thereby contribute to the progression of coronary lesions[2]

Thrombin stimulates **endothelial dysfunction** and can contribute to the pathophysiology of CAD[3,4]

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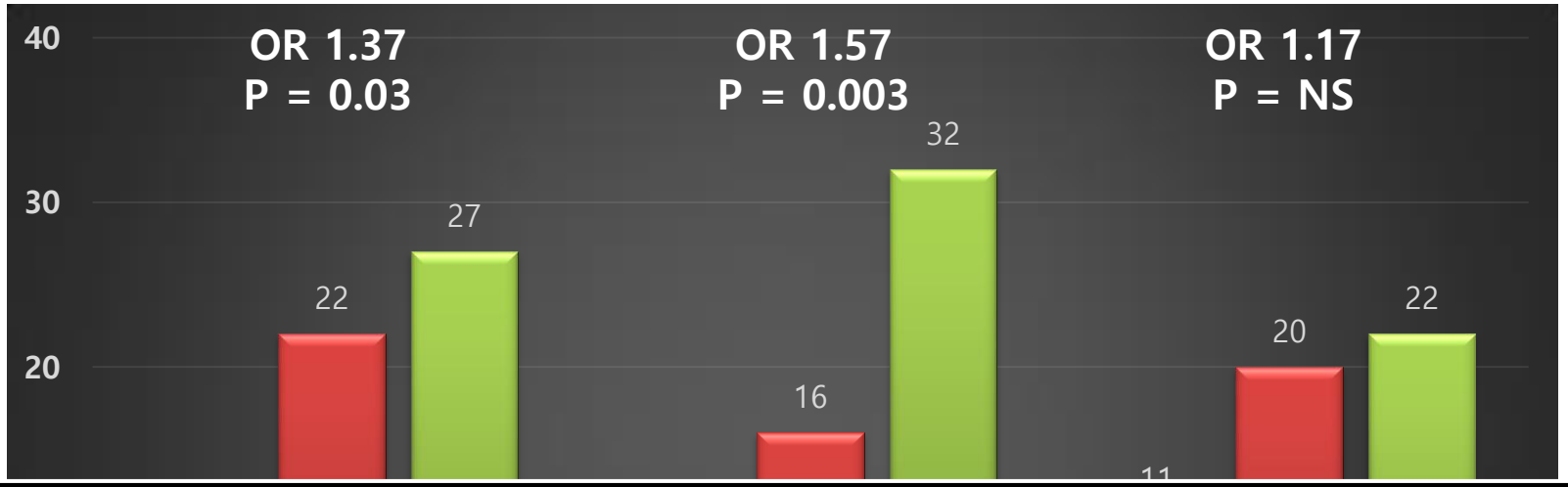
1. Hansen CH et al, Thromb J 2015;13:31; 2. Popović M et al, Mol Cell Biochem 2012;359:301–313;
3. Ming XF et al, Circulation 2004;110:3708–3714; 4. Choi BJ et al, Eur Heart J 2013;34:2047–2054

Coagulation & Cholesterol on CAD Occurrence

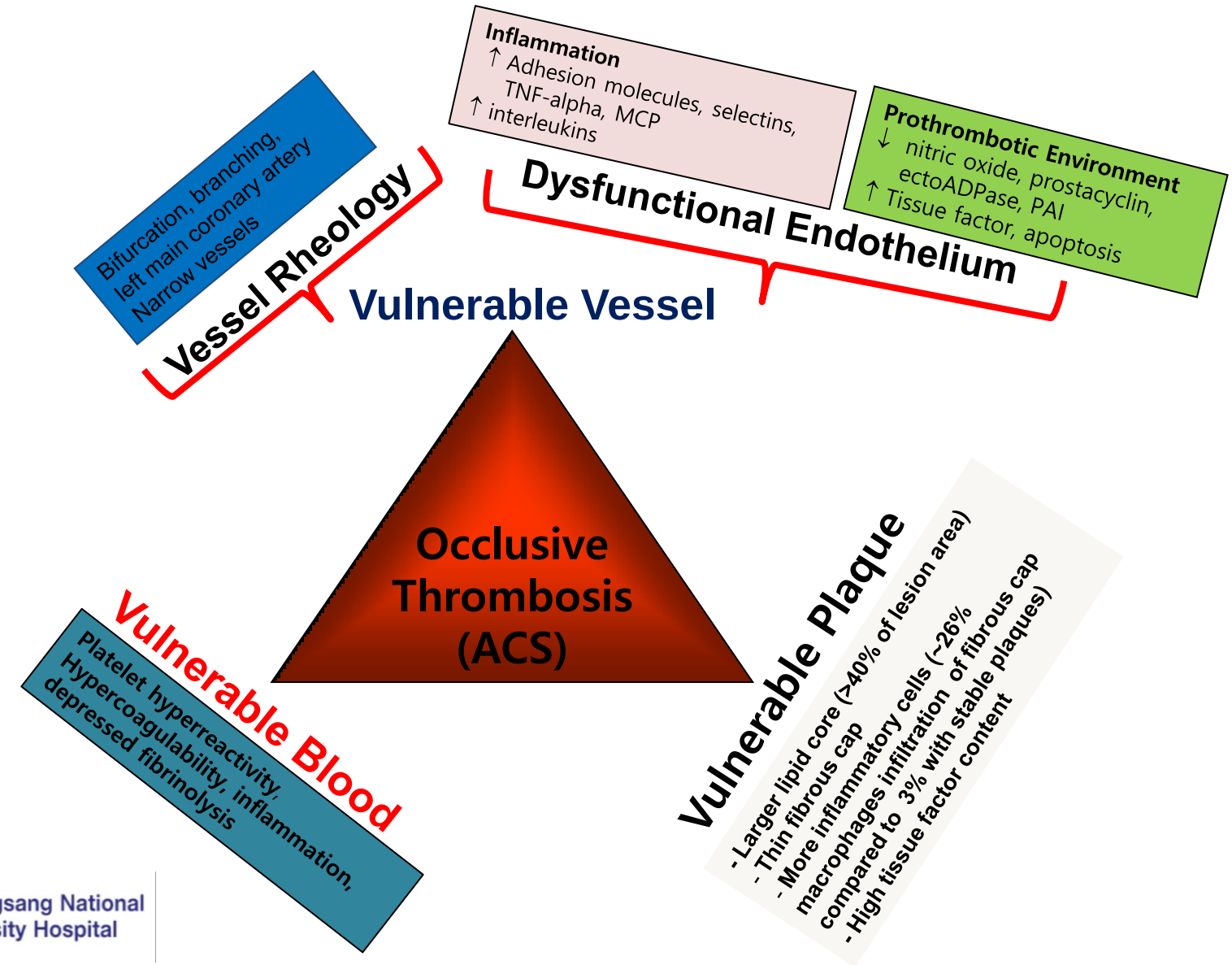
Northwick Park Heart Study (n=1511; healthy white men, 40-64 yo)

- UK registry, 10-year follow-up
- **Prevalence of 5-year CAD according to tertile distribution**



- **Role of "Coagulation pathway"**
  - **Progression of atherosclerosis**
  - **Occurrence of thrombotic event**
  - **Post-PCI atherothrombotic event recurrence**

Mechanism of ACS: ↑ Virchow's Triad Activity



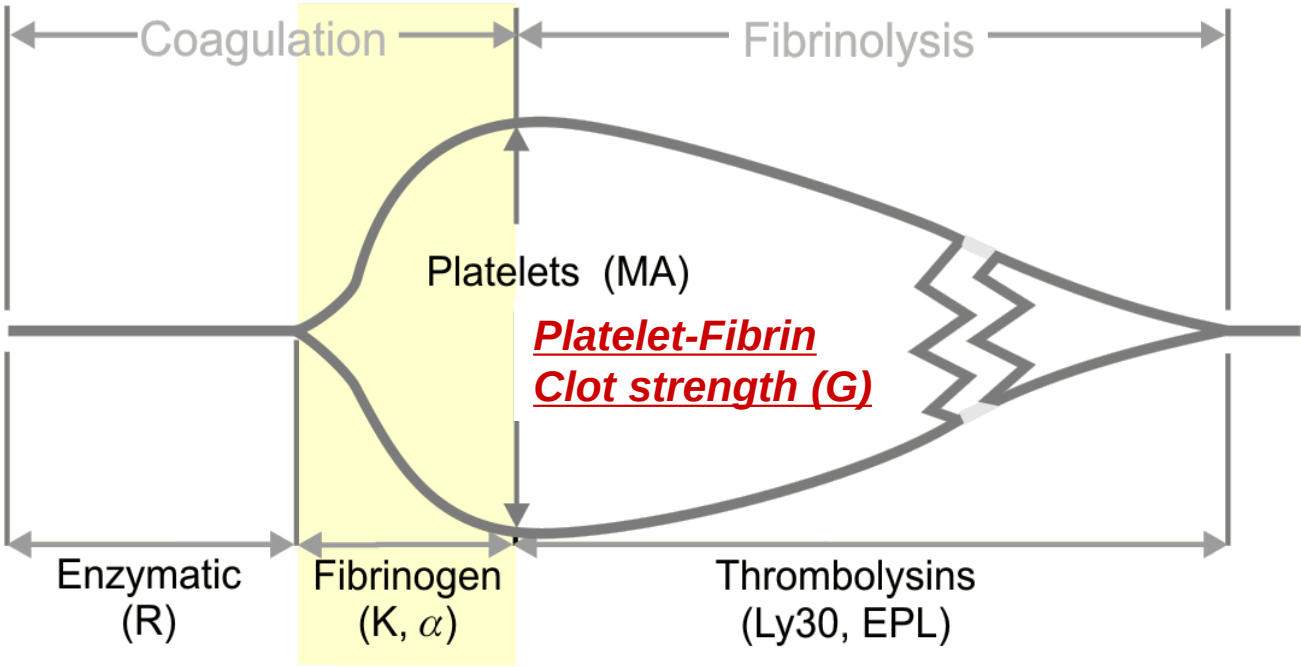
Hypercoagulable Status in CAD Cohorts

? Benefit of adjunctive anticoagulant in CAD patients

- **Arrhythmia: AF/Aflutter**
- **ACS (STEMI > NSTE-ACS)**
- **High atheroma burden: PAD, complex lesion**
- **Low ejection fraction (e.g. EF < 40%)**
- **LV thrombus w/ aneurysm**
- **Severe SEC**
- **Mechanical valve**
- **…**

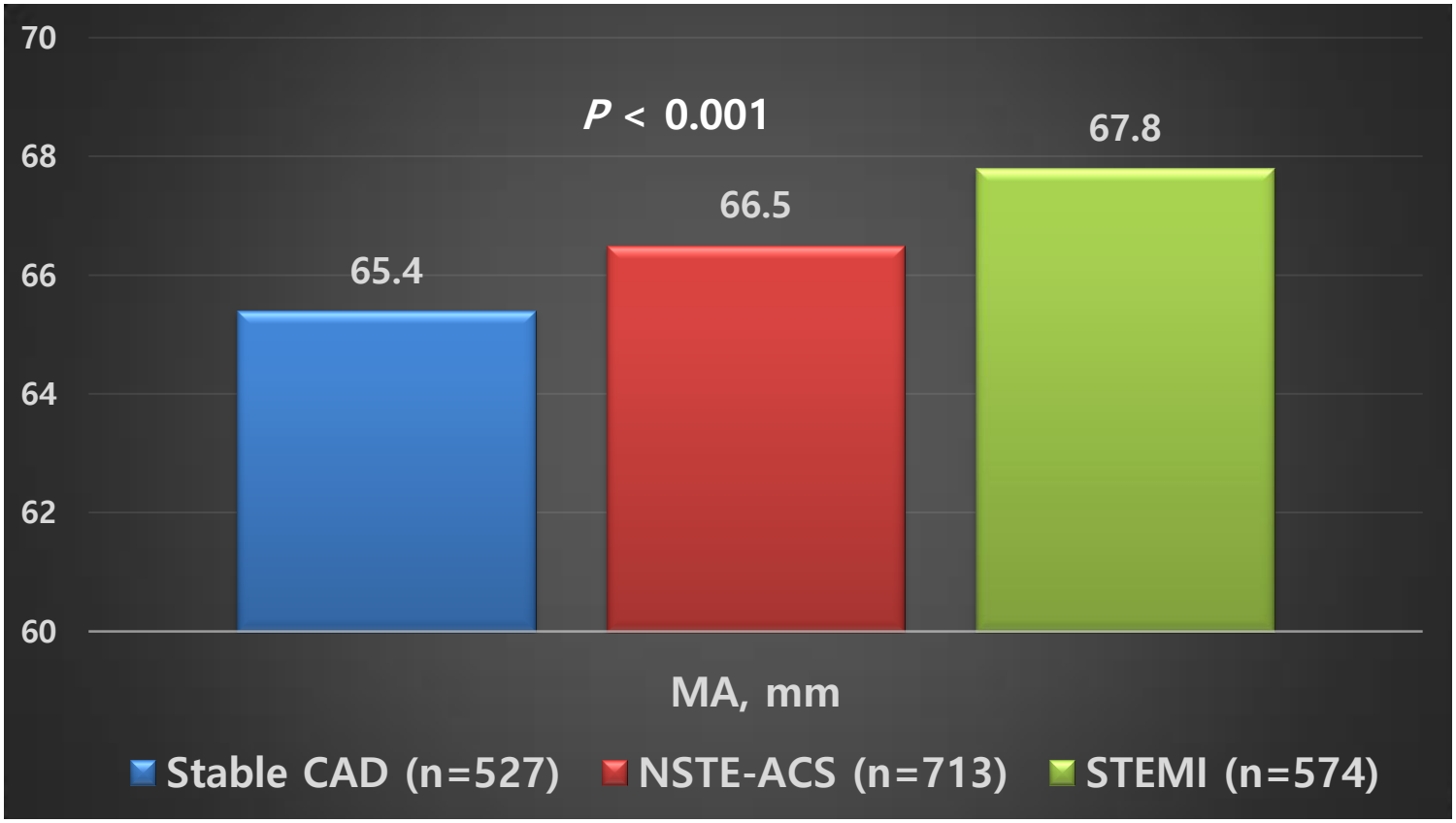
Thromboelastography (TEG®) System

- **Physiologic whole blood test**
- **Use: hematologic disorder, surgery, trauma, burn…**
- **Measures global hemostasis**
  - **From clot initiation to clot lysis**
  - **Net effect of components**



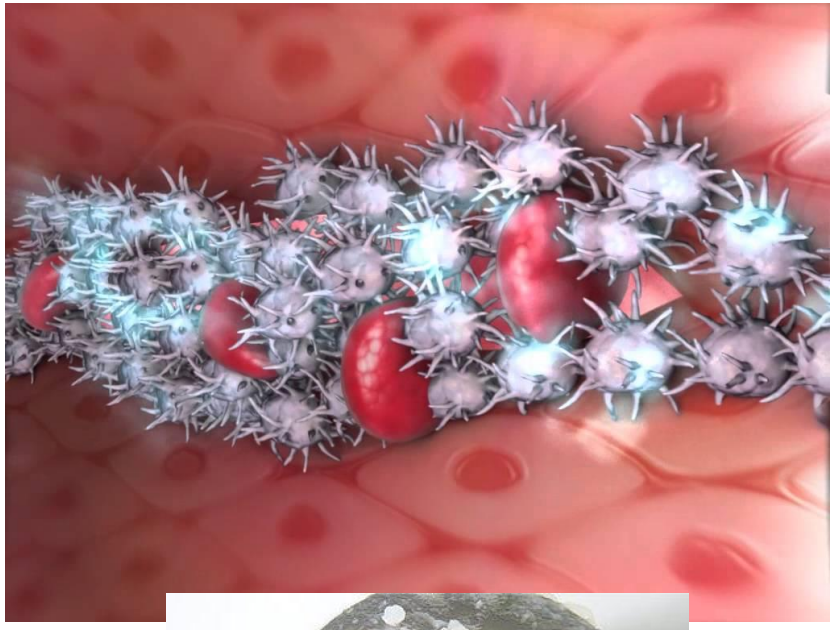
Hypercoagulable Status by Disease Entity

GNUH registry: PCI-treated patients (n = 1,814 w/ TEG)



$MA_{thrombin}$ ≥ 68mm	Stable CAD	NSTE-ACS	STEMI	*P* Value
Prevalence	38.0%	44.2%	51.6%	< 0.001

Atherothrombotic Events:
How Much by Platelet vs. Coagulation Pathway?



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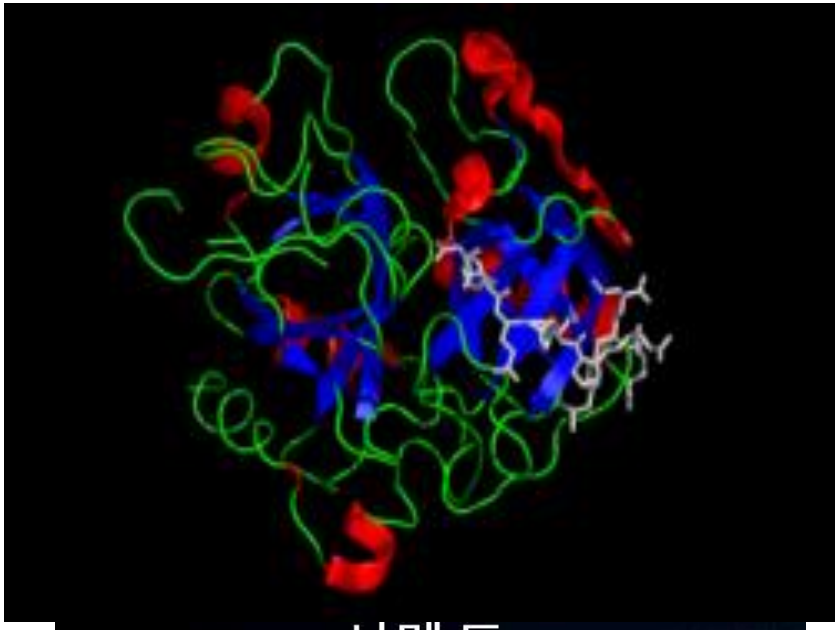


??%

??%

ADAPT-DES

Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents

11,000 DES pts prospectively enrolled

No clinical or anatomic exclusion criteria

11 sites in US and Germany

↓

PCI with ≥ 1 non-investigational DES

Successful and uncomplicated

(IVUS/VH substudy; Up to 3000 pts enrolled)

↓

Assess platelet function after adequate DAPT loading and GPI washout: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded)

↓

Clinical FU at 30 days, 1 year and 2 years

Angio core lab assessment all STs w/1:2 matching controls

CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

clinicaltrials.gov NCT00638794

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

ADAPT-DES: Multivariable propensity score

Adjusted risk of **VerifyNow PRU >208 (Clopidogrel)** for subsequent 1-year adverse events (n=8,583)

Event	Adj HR [95%CI]	P value
ST, def/prob	2.49 [1.43, 4.31]	0.001
- Definite	3.05 [1.62, 5.75]	0.0006
MI	1.42 [1.09, 1.86]	0.01
Major bleeding	0.73 [0.61, 0.89]	0.002
Death, all-cause	1.20 [0.85, 1.70]	0.30

Variables in model: age, gender, diabetes, hypertension, hyperlipidemia, current smoking, prior MI, CKD, stable vs NSTEMI vs STEMI, hemoglobin, WBC, platelet count, creatinine clearance, MVD, premature DAPT discontinuation within 6 months, PRU >208 (forced in), ARU >550 (forced in)

ADAPT-DES: Multivariable propensity score

Adjusted risk of **VerifyNow ARU >550 (Aspirin)** for subsequent 1-year adverse events (n=8,583)

Event	Adj HR[95%CI]	P value
ST, def/prob	1.46 [0.58, 3.64]	0.42
- Definite	1.60 [0.57, 4.48]	0.37
MI	0.81 [0.46, 1.42]	0.46
Major bleeding	0.65 [0.43, 0.99]	0.04
Death, all-cause	1.42 [0.83, 2.43]	0.20

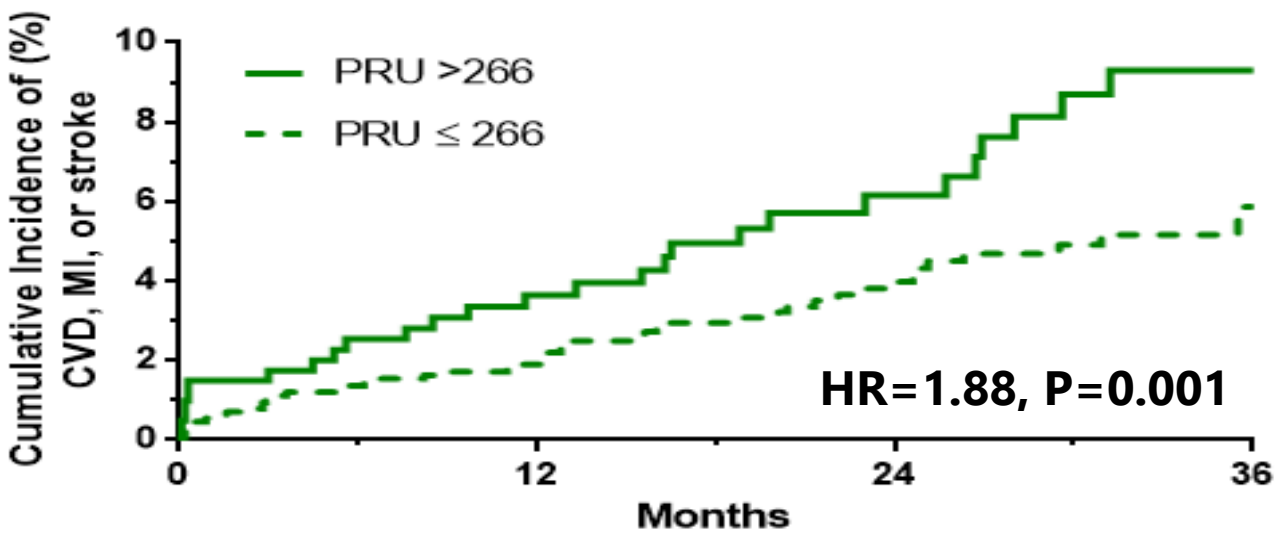
Variables in model: age, gender, diabetes, hypertension, hyperlipidemia, current smoking, prior MI, CKD, stable vs NSTEMI vs STEMI, hemoglobin, WBC, platelet count, creatinine clearance, MVD, premature DAPT discontinuation within 6 months, PRU >208 (forced in), ARU >550 (forced in)

Thrombin-induced Clot Strength and Platelet Reactivity for Prediction of Post-PCI MACE (GNUH Cohort)

F/U duration after index PCI (n = 1,702): 23 [13 – 36] months

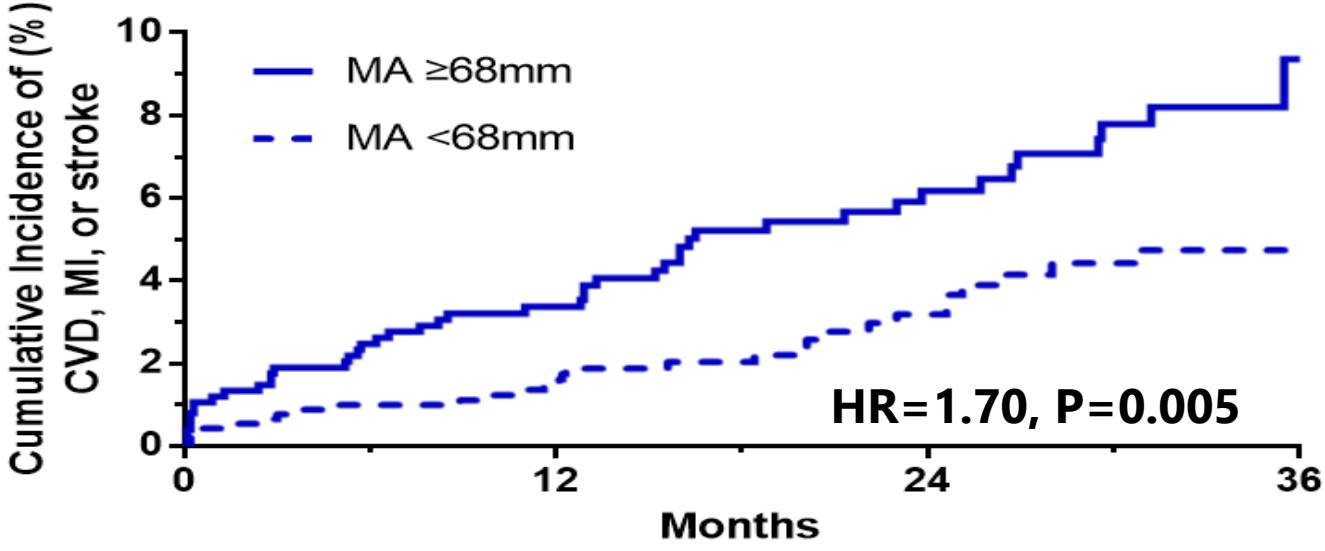
Platelet reactivity

(A)



Coagulation system

(B)



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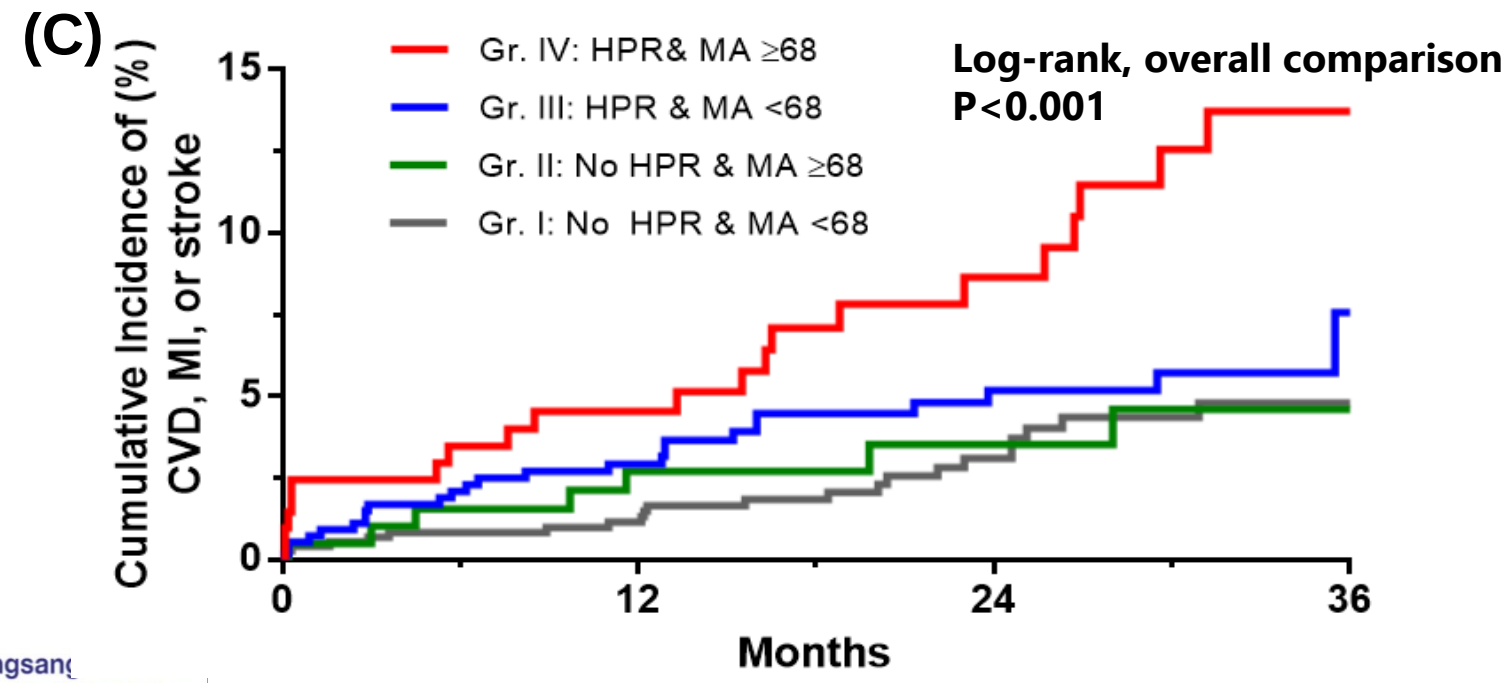
GNUH registry. Ahn JH, Jeong YH, et al. ACC 2018

Risk of MACE According to Risk Stratification

Combined groups		Events	Unadjusted HR (95% CI)	P	Adjusted HR† (95% CI)	p
I	No HPR & MA <68	38/742 (5.1%)	1 [Reference]		1 [Reference]	
II	No HPR & MA ≥68	35/551 (6.4%)	1.66 (1.04 – 2.65)	0.033	1.48 (0.91 – 2.50)	0.111
III	HPR & MA <68	22/201 (11.8%)	1.84 (1.09 – 3.11)	0.024	1.59 (0.91 – 2.79)	0.104
IV	HPR & MA ≥68	25/208 (12.2%)	3.02 (1.81 – 5.04)	<0.001	**2.54 (1.45 – 4.43)**	**0.001**



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GNUH registry. Ahn JH, Jeong YH, et al. ACC 2018

No Net Benefit of TAPT (ASP + CLPD + NOAC) in ACS Patients

Main issues of combination therapy are Bleeding & Ischemic risk

Single antiplatelet therapy

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor

Vitamin K antagonist

- Warfarin

Dual antiplatelet therapy

- **Aspirin + Clopidogrel**
- Aspirin + Prasugrel
- Aspirin + Ticagrelor

Non-Vitamin K antagonist

- **Rivaroxaban**
- Dabigatran
- **Apixaban**
- Edoxaban

Triple antithrombotic therapy (TAPT): Unfavorable risk-benefit ratio (APPRAISE 2, ATLAS ACS 2)

Triple Therapy in ACS:

ASP + Clopidogrel + *Standard-dose NOAC*

APPRAISE-2

Recent (≤7days) Acute Coronary Syndrome

(STEMI or NSTE-ACS)

At Least 2 Additional Risk-Factors

N=10,800

- Aspirin
- Other antiplatelet therapy

Randomize 1:1

Double blind

Apixaban 5 mg BID

CrCl<40 ml/min 2.5 mg BID

Placebo

Primary Outcome: CV Death, MI, Ischemic Stroke

Safety: TIMI Major Bleeding

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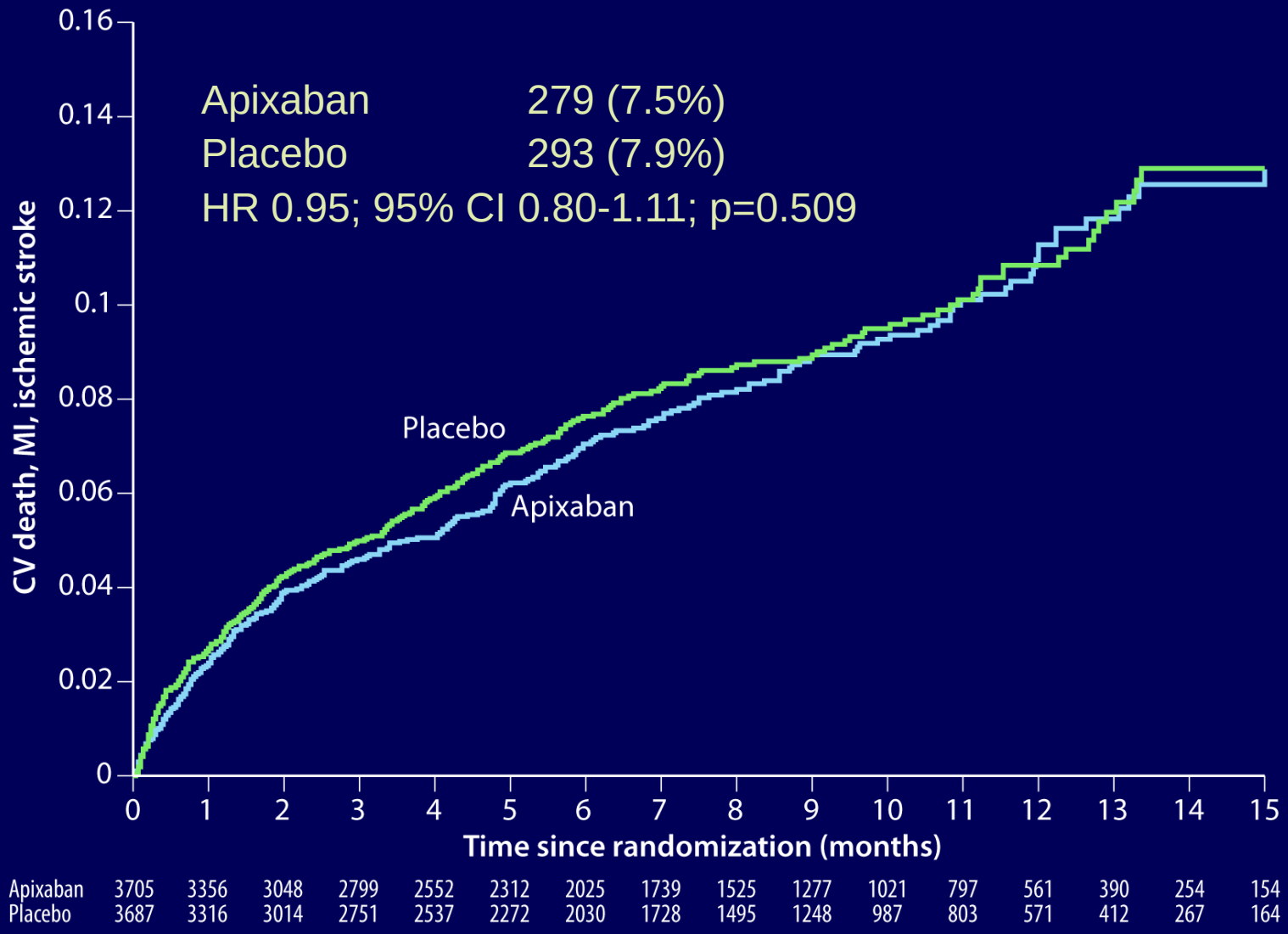
Primary Outcome

CV Death, MI, Ischemic Stroke



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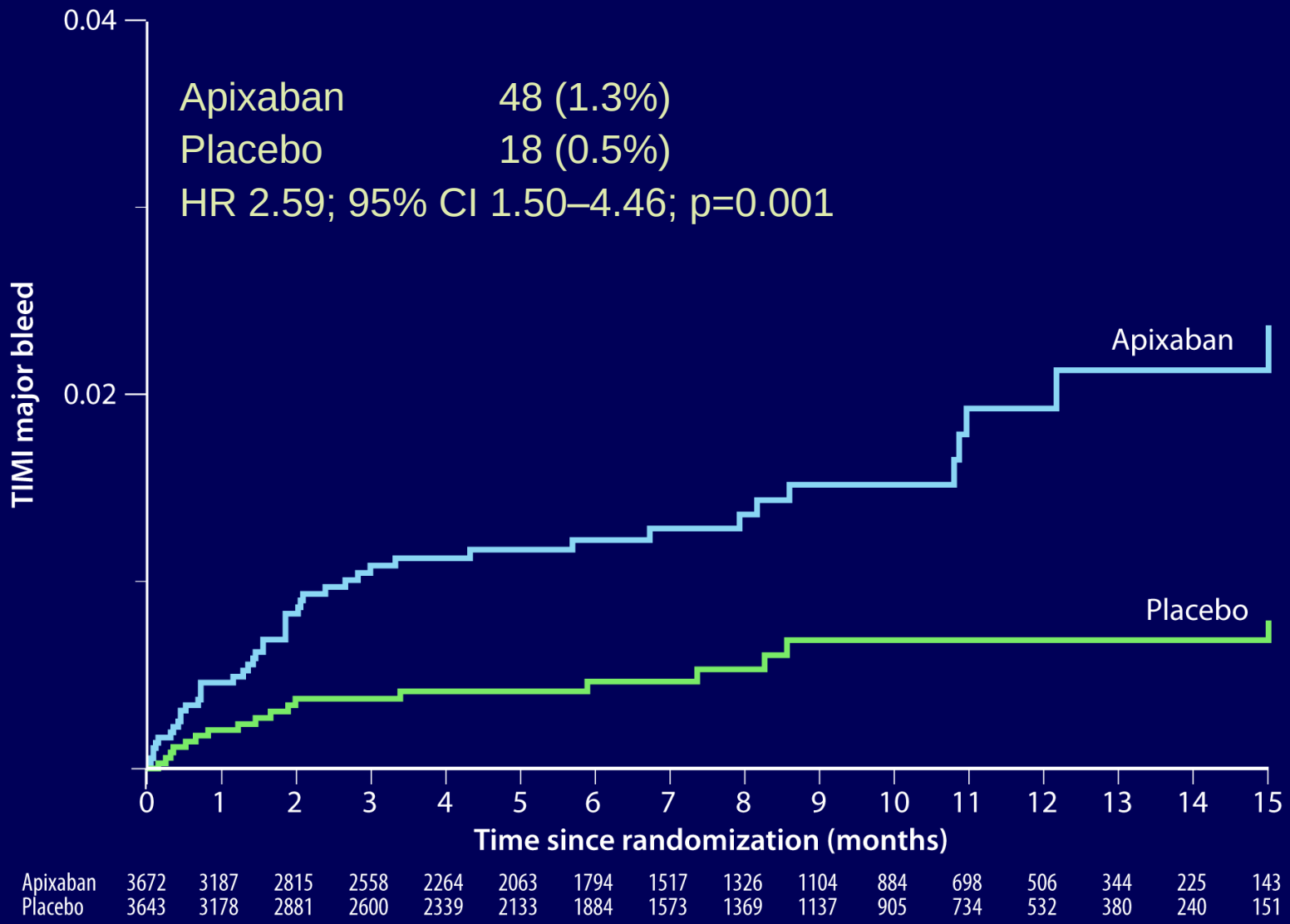
TIMI Major Bleeding

APPRAISE-2



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ASP + Clopidogrel + *Low-dose NOAC* in ACS

ATLAS ACS 2 TIMI 51

Recent ACS: STEMI, NSTEMI, UA
Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
n=5,176	n=5,174	n=5,176

PRIMARY ENDPOINTS:

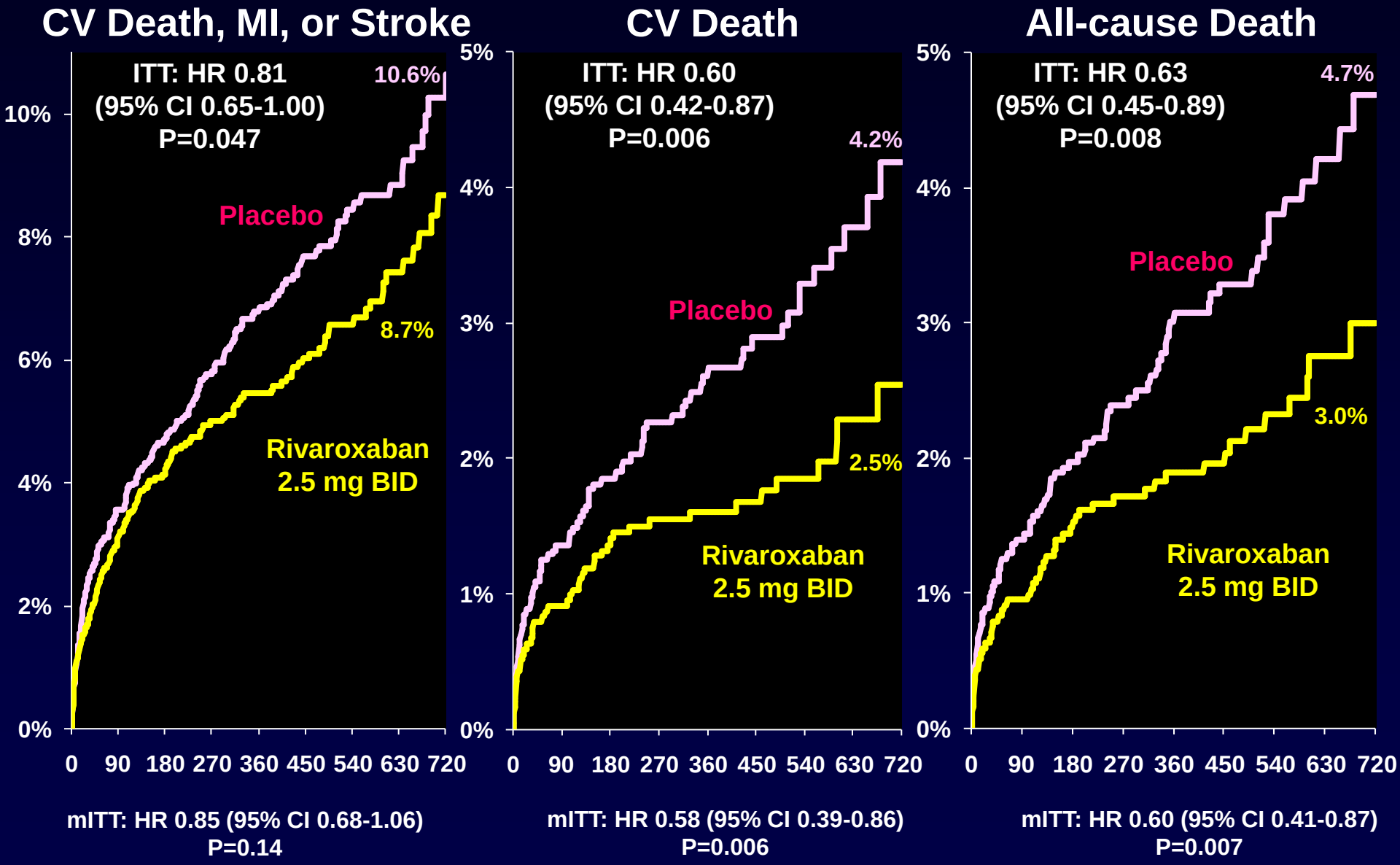
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

SAFETY: TIMI major bleeding not associated with CABG

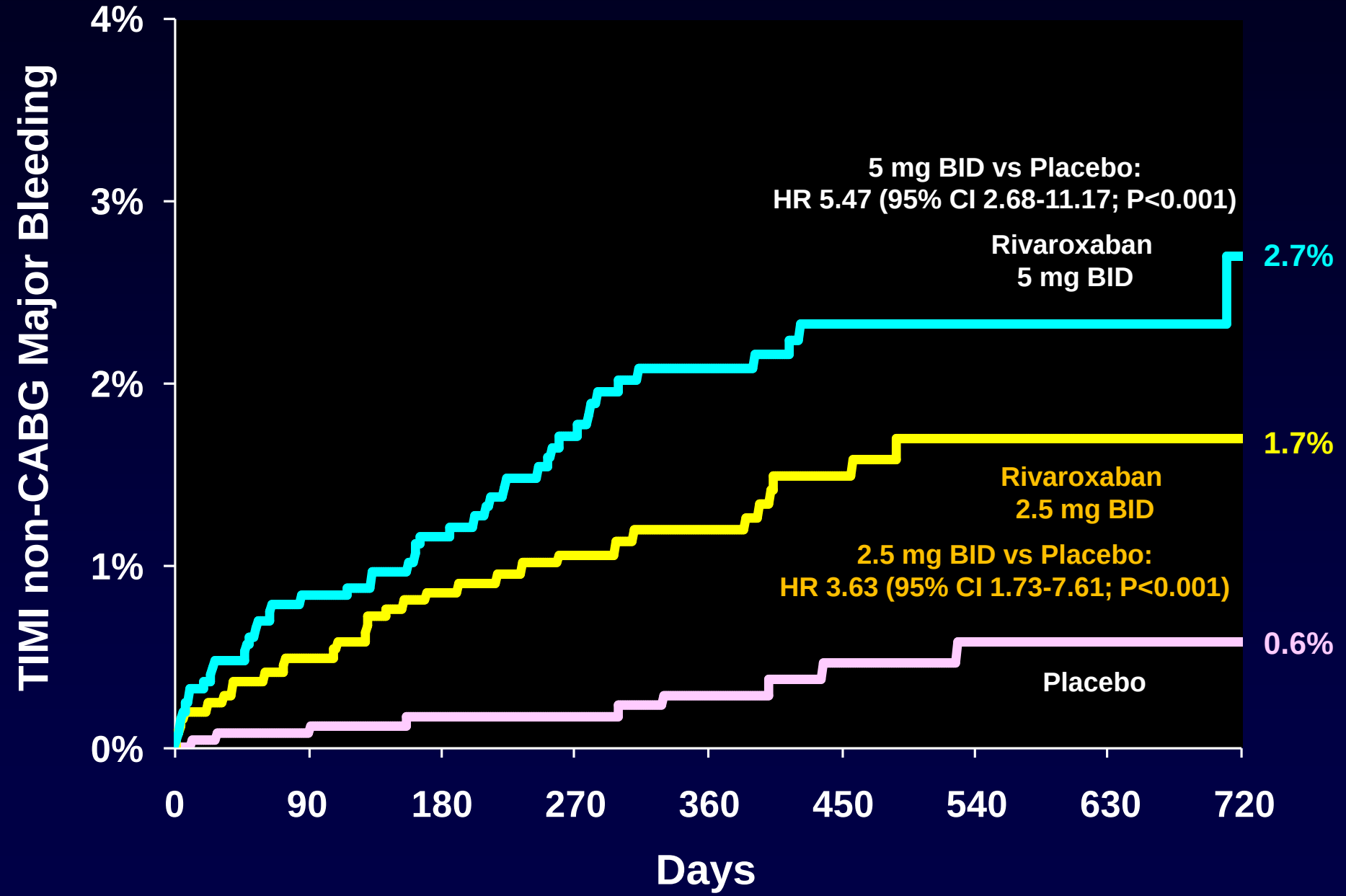
Event driven trial with 1,002 primary efficacy events

Mega et al, N Engl J Med 2012; 366:9-19

EFFICACY ENDPOINTS: 2.5 mg BID



PRIMARY SAFETY ENDPOINT



Benefit of Low-dose NOAC vs. ASP + $P2Y_{12}$ inhibitor in ACS Patients

Main issues of combination therapy are Bleeding & Ischemic risk

Single antiplatelet therapy

- **Aspirin**
- **Clopidogrel**
- **Prasugrel**
- **Ticagrelor**

Vitamin K antagonist

- **Warfarin**

Dual antiplatelet therapy

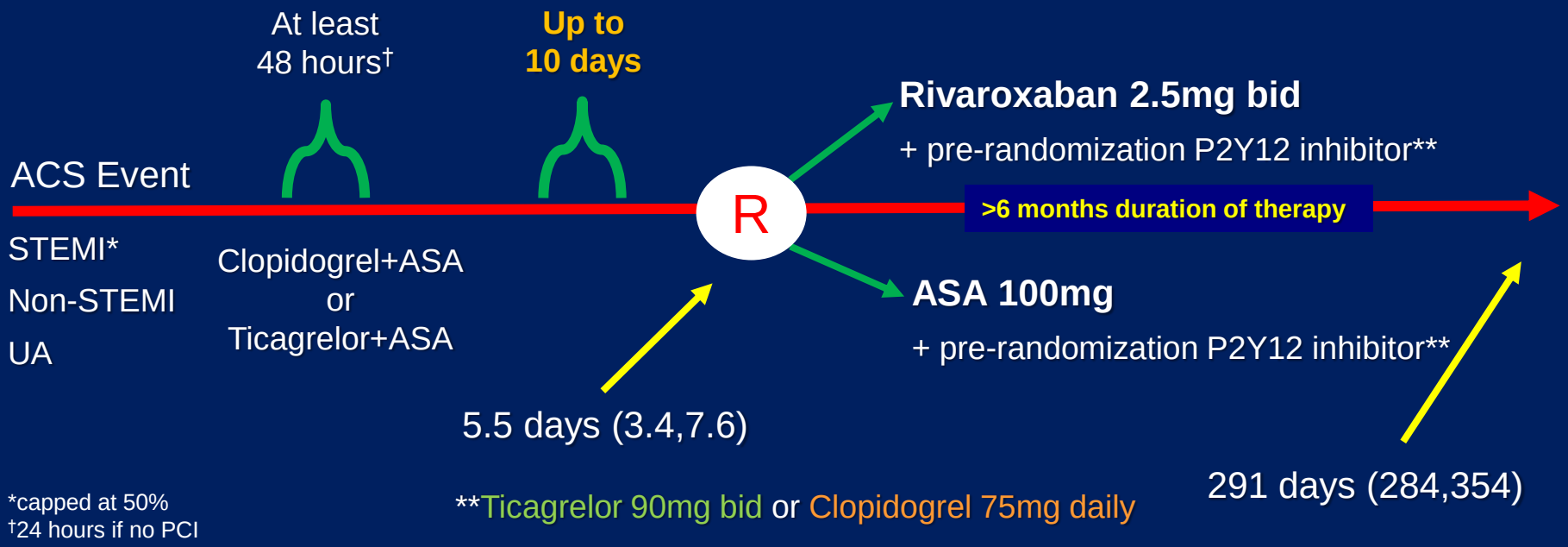
- **Aspirin + Clopidogrel**
- **Aspirin + Prasugrel**
- **Aspirin + Ticagrelor**

Non-Vitamin K antagonist

- **Rivaroxaban**
- **Dabigatran**
- **Apixaban**
- **Edoxaban**

ASP vs. Low-dose NOAC + P2Y12 Inh in ACS

3037 patients randomized after having been started on DAPT
Adherence to P2Y12 therapy 95% during study period, 6.5% switched P2Y12 therapy



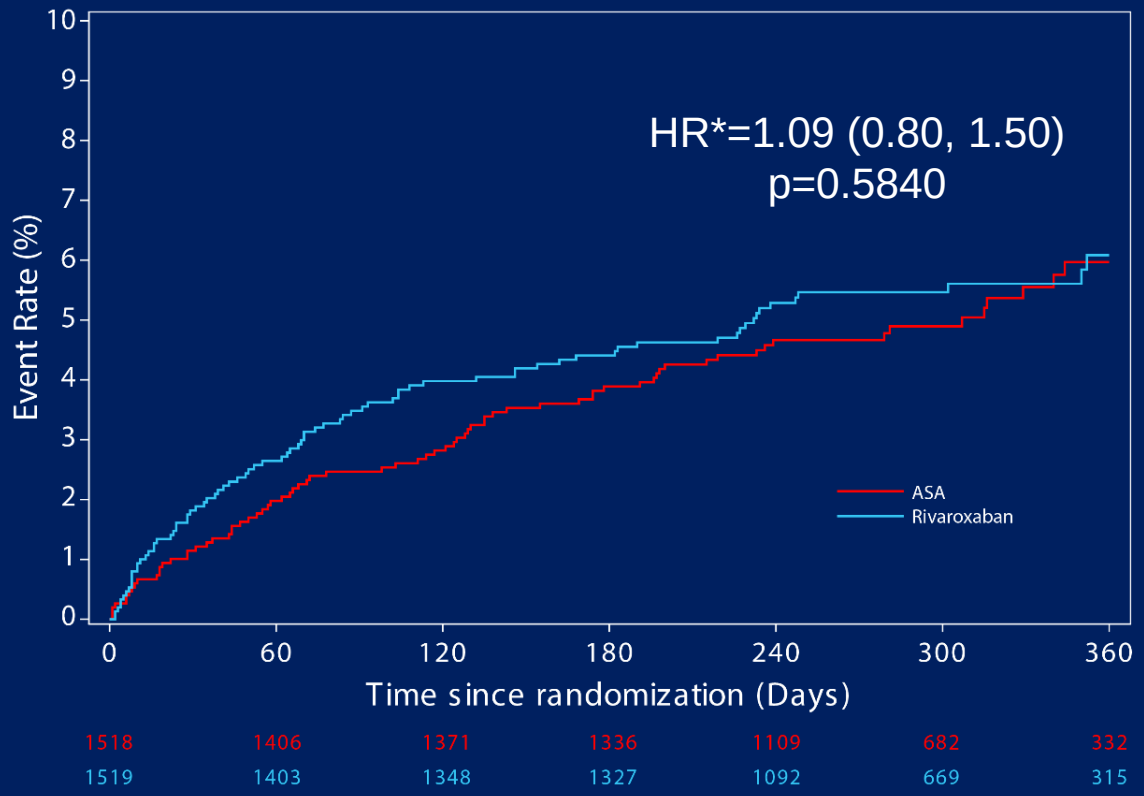
*capped at 50%
†24 hours if no PCI

**Ticagrelor 90mg bid or Clopidogrel 75mg daily

Ohman EM, et al, Lancet. 2017;389:1799-1808.

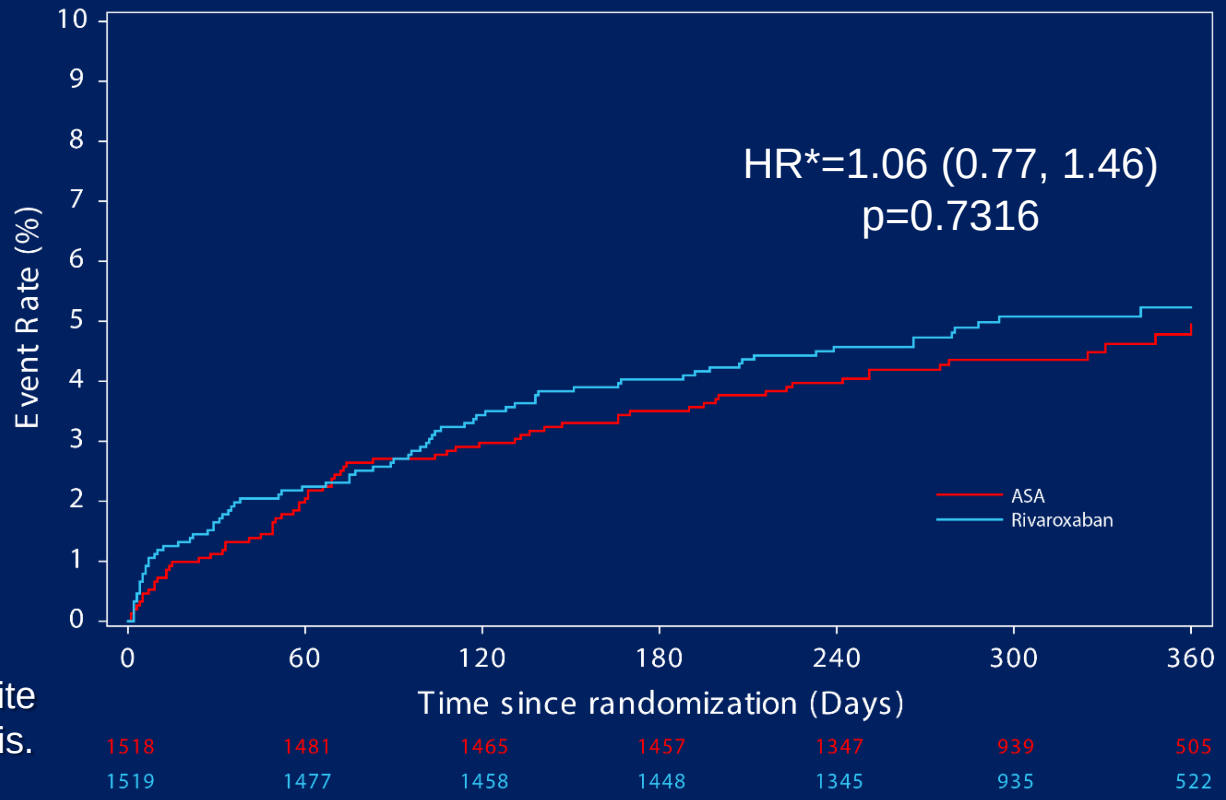
Primary EP: TIMI Non-CABG Clinically Significant Bleeding

Non-CABG major, minor, or requiring medical attention



*Hazard Ratio (95%CI)

Exploratory Composite Ischemic Endpoint

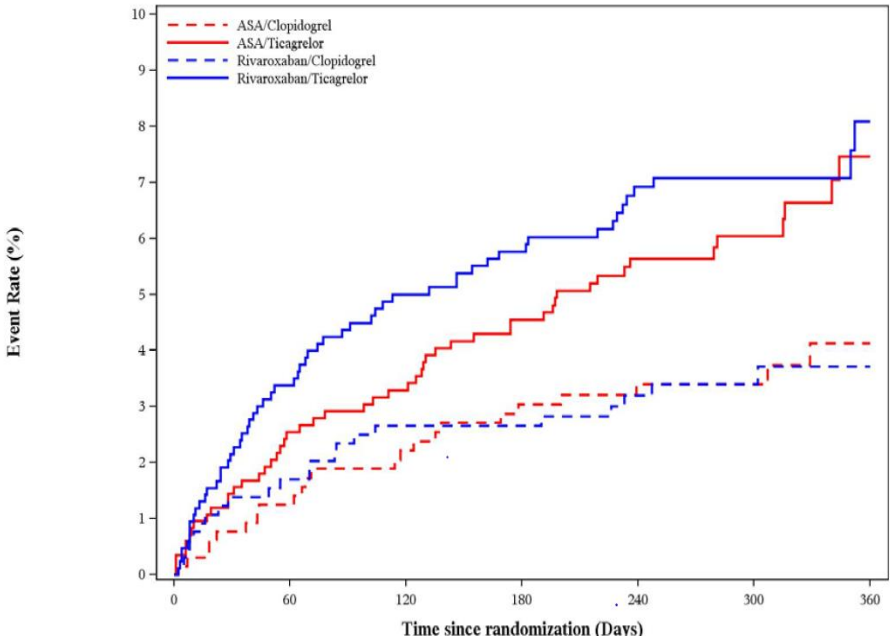


CV death, MI, stroke, or definite stent thrombosis.

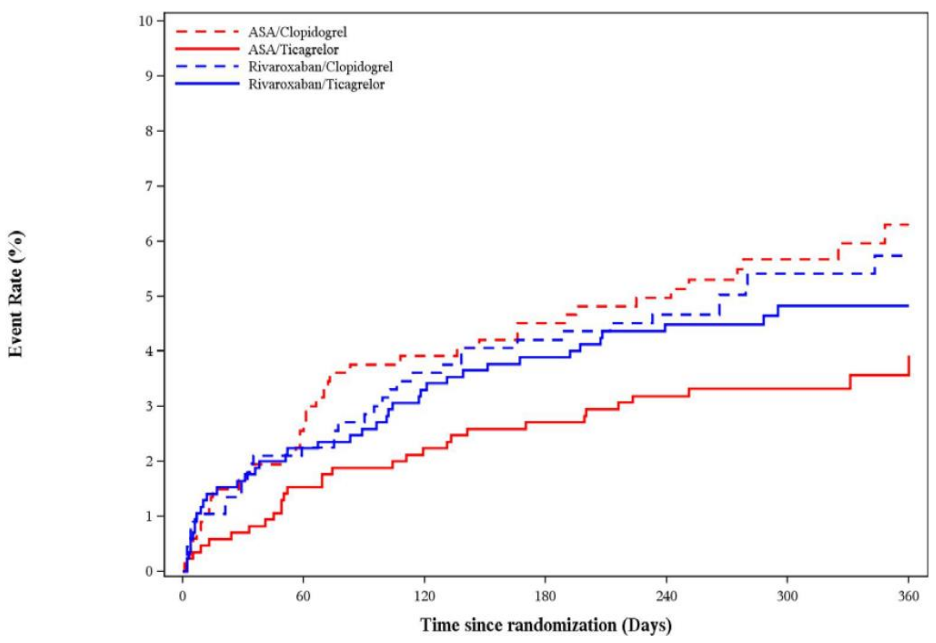
*Hazard Ratio (95%CI)

Clinical Outcomes According to the Regimens

Major bleeding



MACE



	TIMI significant bleeding	CV death, MI, stroke, or definite ST	*Net events*
ASP + CLPD	**3.5%**	5.9%	9.4%
Riva + CLPD	**3.3%**	5.4%	**8.7%**
ASP + TICA	6.0%	**3.9%**	9.9%
Riva + TICA	**6.8%**	4.7%	**11.5%**

?Best Combo in High-risk CAD patients: Gentle Platelet + Coagulation Inhibition

Inlet versus Outlet

Coagulation		Platelet
Rivaroxaban Apixaban Edoxaban	Xa	$P2Y_{12}R$	Clopidogrel Prasugrel Ticagrelor
Ximelagatran Dabigatran	IIa	IIbIIIa	Orbofiban Sibrafiban Xemilofiban

"Balance between Efficacy and Safety" is most important

Benefit of APT +/- NOAC : STEMI vs. NSTE-ACS

Meta-analysis (6 RCTs, n = 29,667)

Table 1. Main Features of the Studies Included in the Meta-analysis

Source	Design	Study Population			Anticoagulant Dosages	Follow-up, mo
		Overall	DOAC Group	Control Group		
APPRAISE	RCT (phase II)	1715	1104	611	Apixaban, 2.5 mg BID, 10 mg QD	6
APPRAISE 2	RCT (phase III)	7392	3705	3687	Apixaban, 5 mg BID	8
APPRAISE J	RCT (phase II)	150	99	51	Apixaban, 2.5 mg BID, 10 mg QD	6
ATLAS ACS TIMI 46	RCT (phase II)	3491	2331	1160	Rivaroxaban, 5, 10, 15, and 20 mg QD	6
ATLAS ACS 2 TIMI 51	RCT (phase III)	15 526	10 350	5176	Rivaroxaban, 2.5 and 5 mg BID	13
REDEEM	RCT (phase II)	1861	1490	371	Dabigatran, 50, 75, and 110, 150 mg BID	6

Table 2. Baseline Clinical Features in the Studies Included in the Meta-analysis

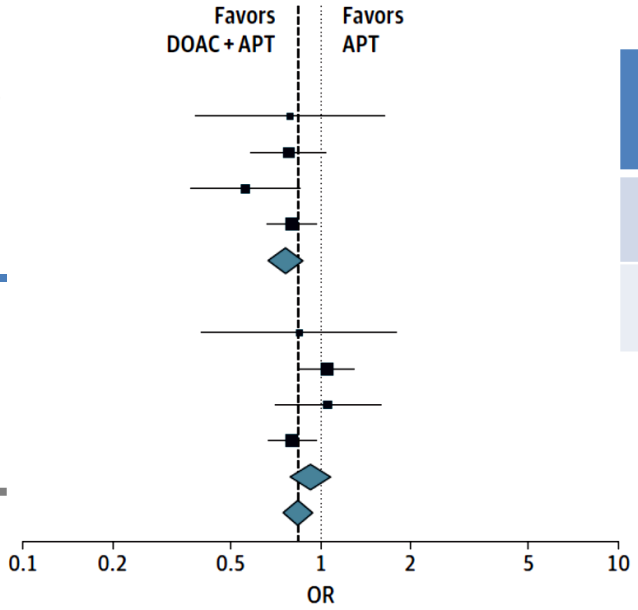
Source	Age, y	% Male	% DM	% STEMI	% NSTEMI	% Unstable Angina	% DAPT	% PCI	% Prior Stroke
APPRAISE	61	75	22	62.9	29.5	7.6	75.5	65	4
APPRAISE 2	67	69	48	39.6	41.6	18.1	81	44	10
APPRAISE J	64.6	87	40	75.5	15.2	9.3	97.4	99	4
ATLAS ACS TIMI 46	57.4	77	19	52.2	29.9	18.0	78.2	64	NA
ATLAS ACS 2 TIMI 51	61.7	75	32	50.4	25.6	24.0	93	57	NA
REDEEM	61.8	60	31	60	40	-	99.2	55	NA

Chiarito M, et al. JAMA Cardiol. 2018;3:234-41.

Benefit of APT +/- NOAC: STEMI vs. NSTE-ACS

A Efficacy: CV death, MI, or stroke

	OR (95% CI)
STEMI	
APPRAISE	0.79 (0.38-1.64)
APPRAISE 2	0.78 (0.59-1.04)
ATLAS ACS TIMI 46	0.56 (0.37-0.85)
ATLAS ACS 2 TIMI 51	0.80 (0.66-0.96)
Subtotal: I-2 = 0.0% (*P* = .49; *P* < .001)	0.76 (0.66-0.88)
NSTE-ACS	
APPRAISE	0.85 (0.40-1.80)
APPRAISE 2	1.05 (0.85-1.30)
ATLAS ACS TIMI 46	1.06 (0.70-1.60)
ATLAS ACS 2 TIMI 51	0.80 (0.67-0.96)
Subtotal: I-2 = 27.2% (*P* = .25; *P* = .36)	0.92 (0.78-1.09)
Overall: I-2 = 29.1% (*P* = .20; *P* < .001)	0.84 (0.74-0.95)

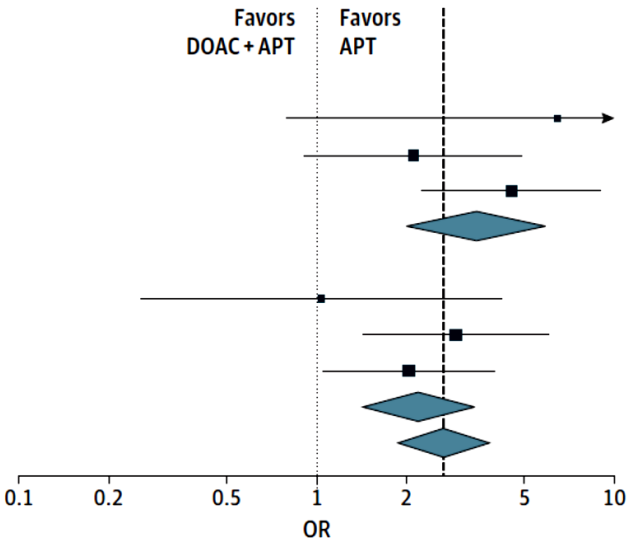


	NNT	NNH
STEMI	**63**	**96**
NSTE-ACS	**130**	**137**

NOAC + APT might represent an attractive option for STEMI patients.

B Safety: major bleeding

	OR (95% CI)
STEMI	
APPRAISE	6.44 (0.79-52.59)
APPRAISE 2	2.11 (0.91-4.90)
ATLAS ACS TIMI 51	4.53 (2.27-9.03)
Subtotal: I-2 = 11.0% (*P* = .33; *P* < .001)	3.45 (1.95-6.09)
NSTE-ACS	
APPRAISE	1.03 (0.25-4.18)
APPRAISE 2	2.93 (1.42-6.02)
ATLAS ACS 2 TIMI 51	2.04 (1.05-3.96)
Subtotal: I-2 = 0.00% (*P* = .41; *P* < .001)	2.19 (1.38-3.48)
Overall: I-2 = 12.2% (*P* = .34; *P* < .001)	2.67 (1.83-3.89)



Conversely,
In patients with NSTE-ACS, the risk-benefit profile of NOAC appears unfavorable.

Perspectives: NOAC in ACS patients

1. Role of coagulation pathway:

Atheroma progression and occurrence of thrombotic event

2. Hypercoagulable milieu in ACS (STEMI > NSTE-ACS):

Net clinical benefit of NOAC in STEMI > NSTE-ACS

3. ?Best Combo in high-risk ACS patients after acute phase:

Gentle Platelet ($P2Y_{12}$ Inh > ASP) + Coagulation Inhibition

4. Precision medicine of *"personalized antithrombotic Tx":*

NOAC for high $MA_{Thrombin}$, potent $P2Y_{12}$ inhibitor for HPR…

I HAVE A DREAM by Martin Luther King, Jr (1929-1968)

We have a dream of "precision antithrombotic medicine"