

# **The Interplay of Bleeding Risk and Treatment Strategies in Elderly ACS/PCI patients**

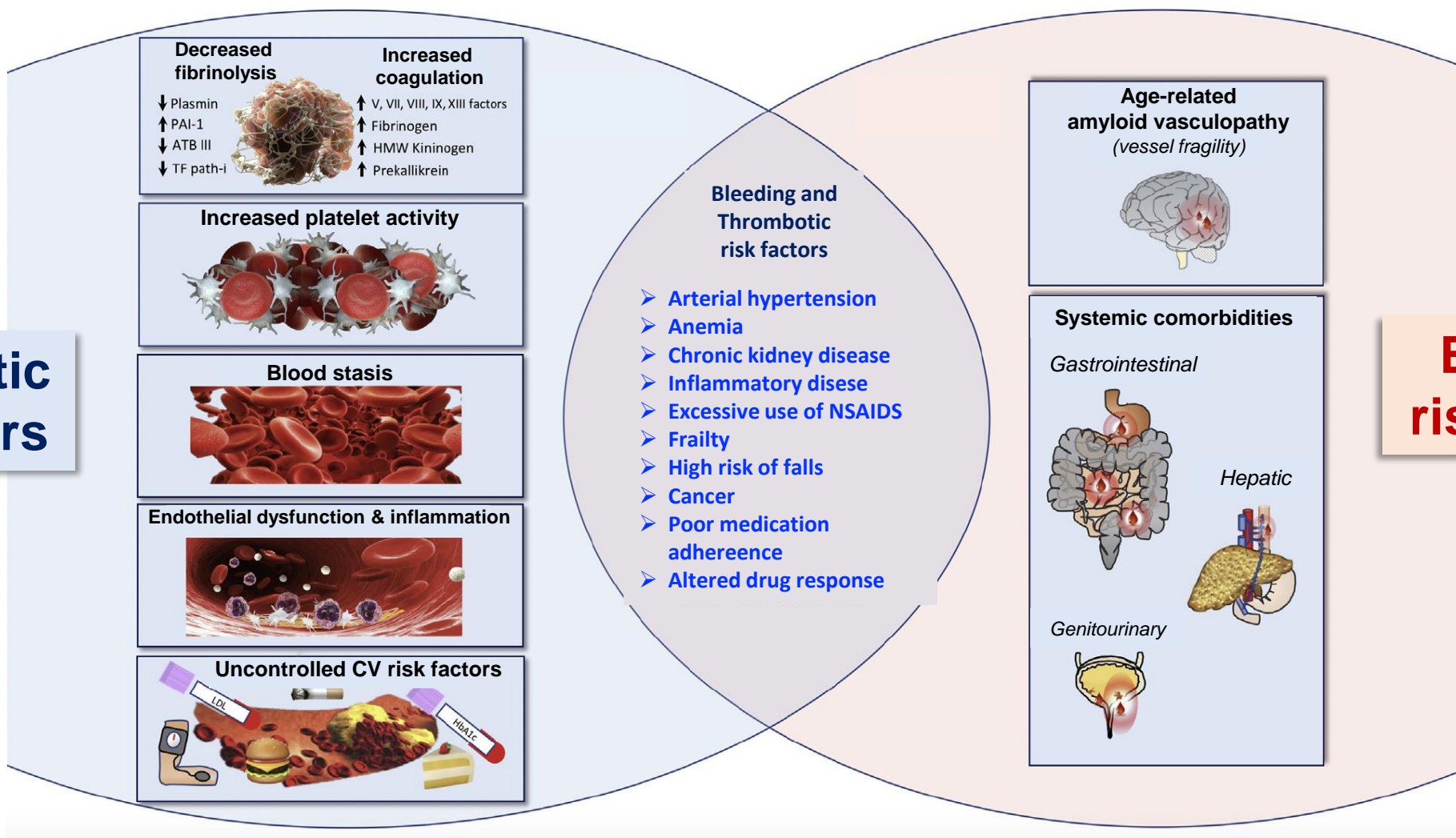
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# Disclosure

- I have nothing to disclose

# Risk Factors for Thrombotic and Bleeding Events in Elderly Patients





**PREdicting bleeding  
Complications In patients  
undergoing Stent  
implantation and  
subsEquent Dual Anti  
Platelet Therapy**

**VS.**



**ARC  
HBR**

**ARC-HBR  
Status**

**START  
EVALUATOR**

**MORE +**

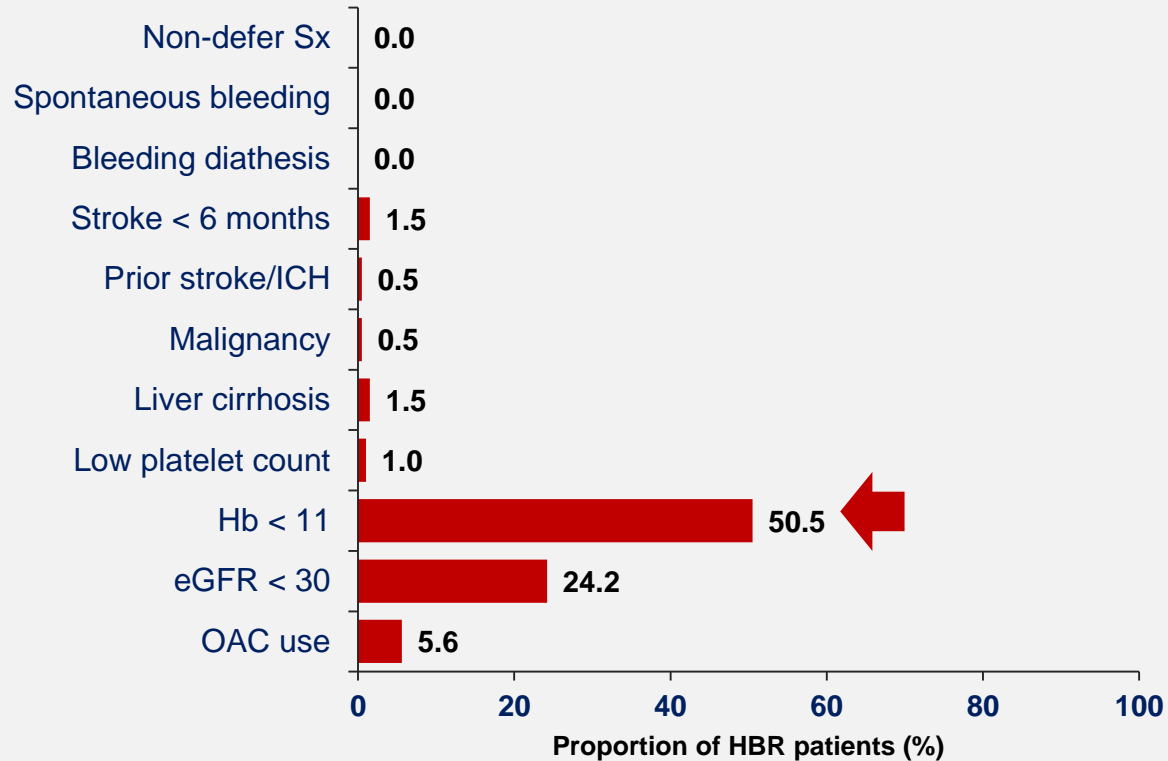
**Bleeding vs.  
thrombosis  
trade-off**

**START  
EVALUATOR**

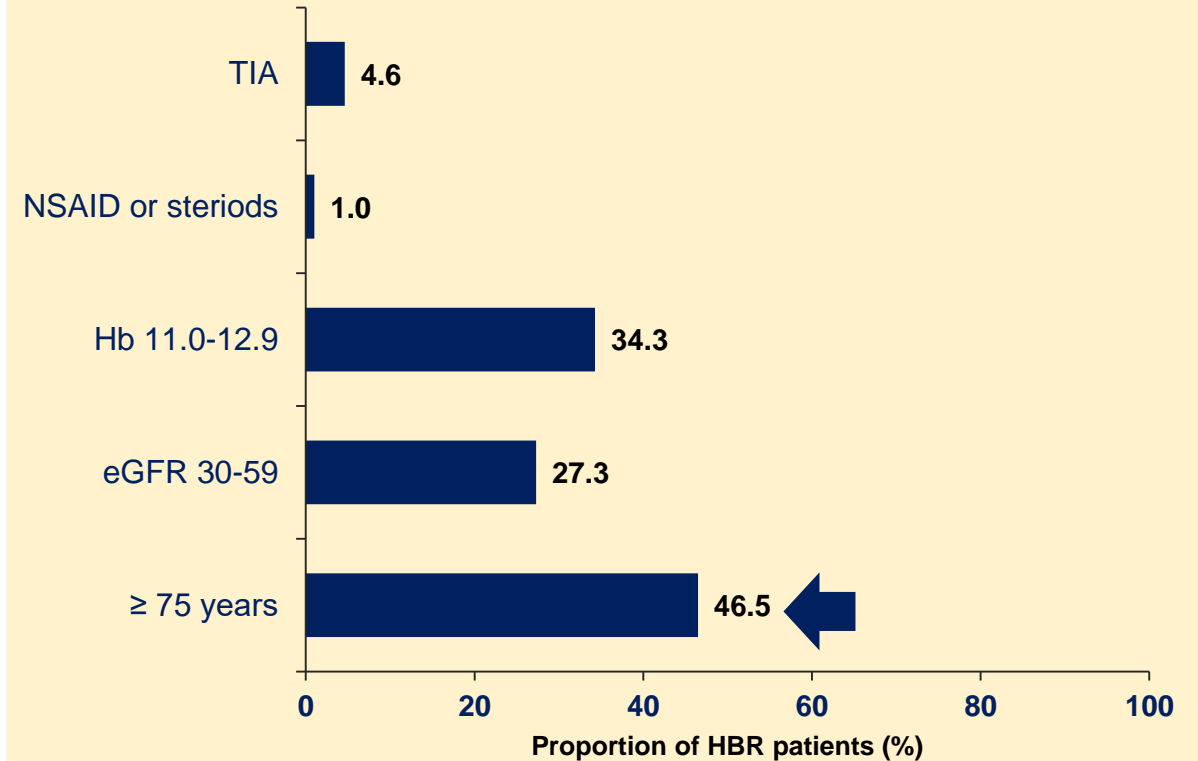
# Proportion of HBR patients by each ARC-HBR criterion

Chiang Mai University PCI database

## Major criteria



## Minor criteria

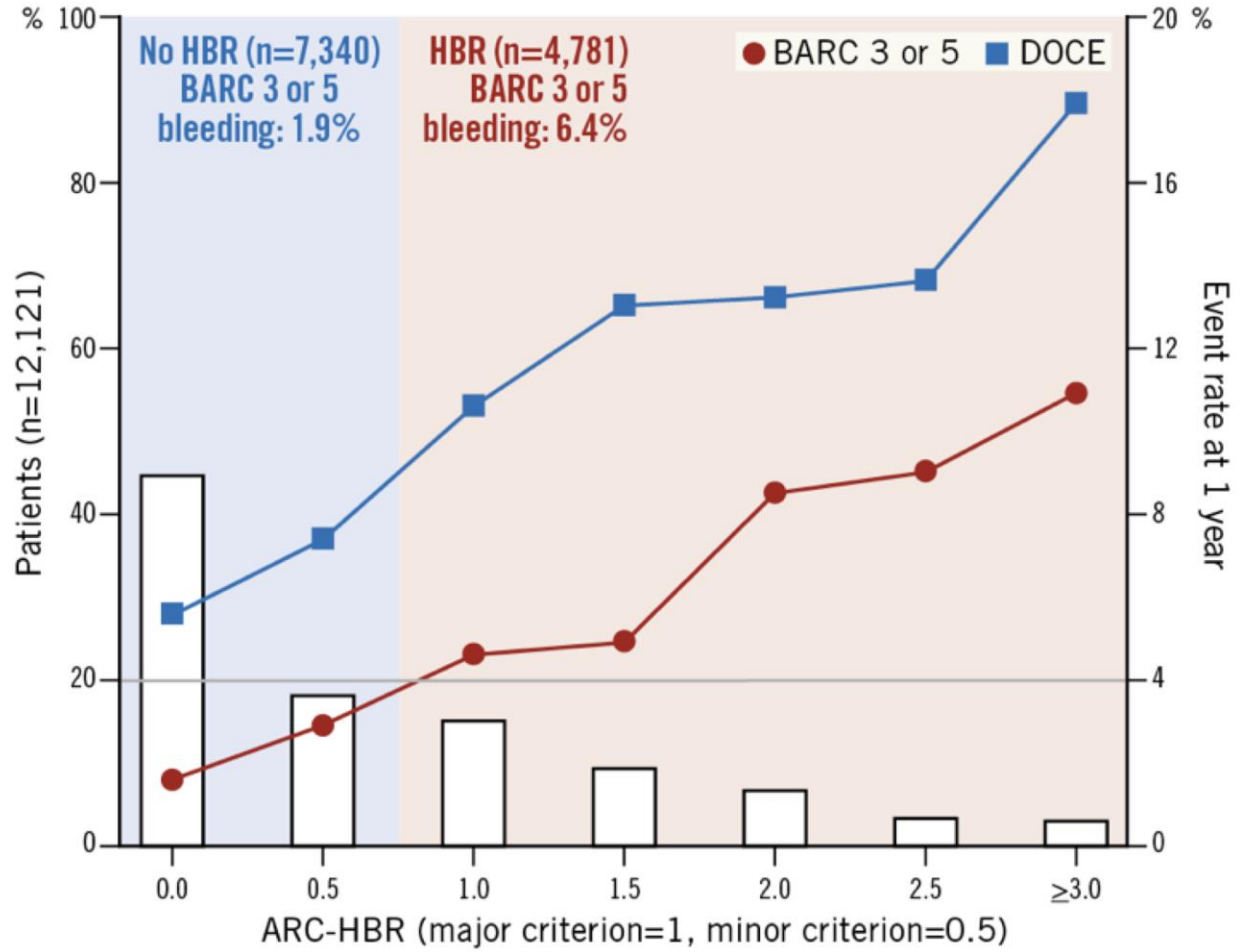
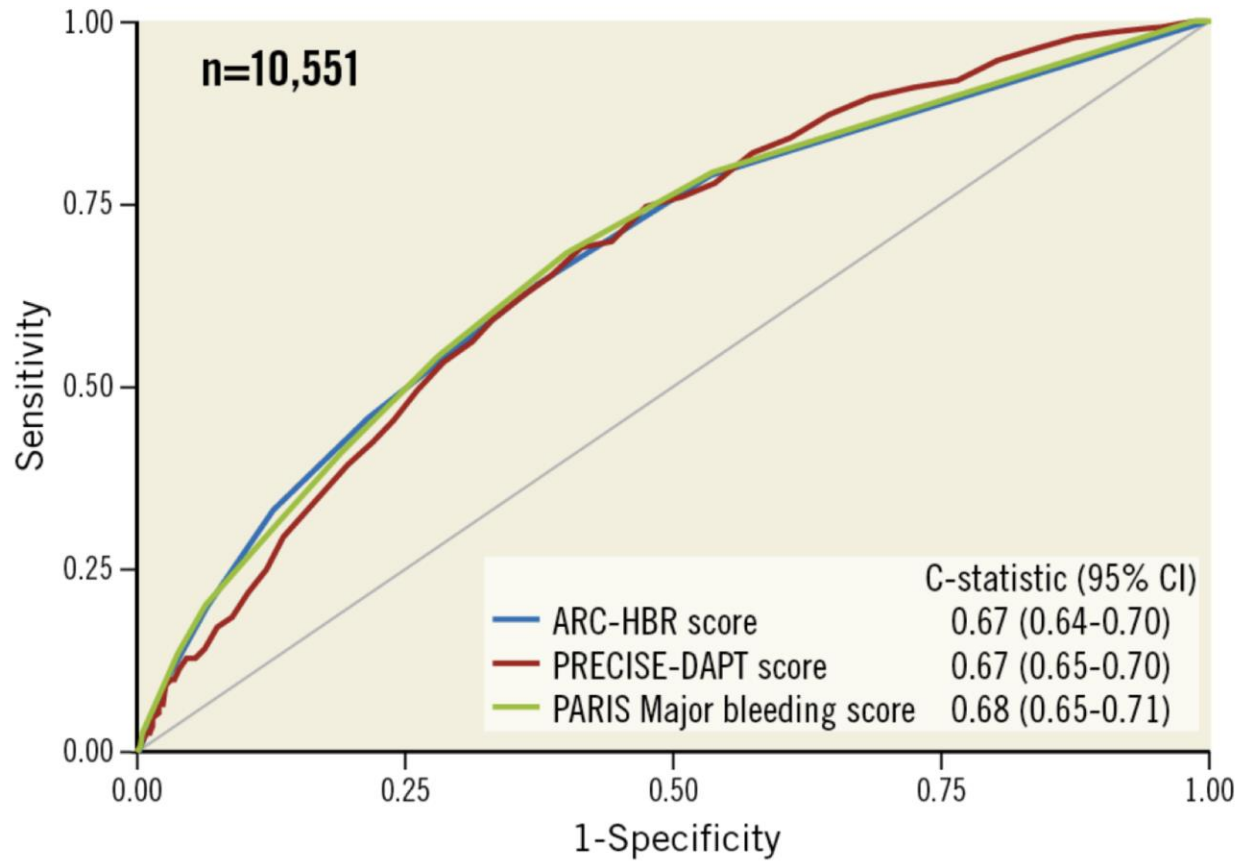




**CORONARY INTERVENTIONS**

# Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores

EuroIntervention 2020;16:371-379. DOI: 10.4244/EIJ-D-20-00052



Hemoglobin

Haemoglobin ? unit

g/dl  mmol/L

Age

Age (years)

WBC

White blood cells ? unit

u/mcL  10<sup>9</sup>/L

CrCl

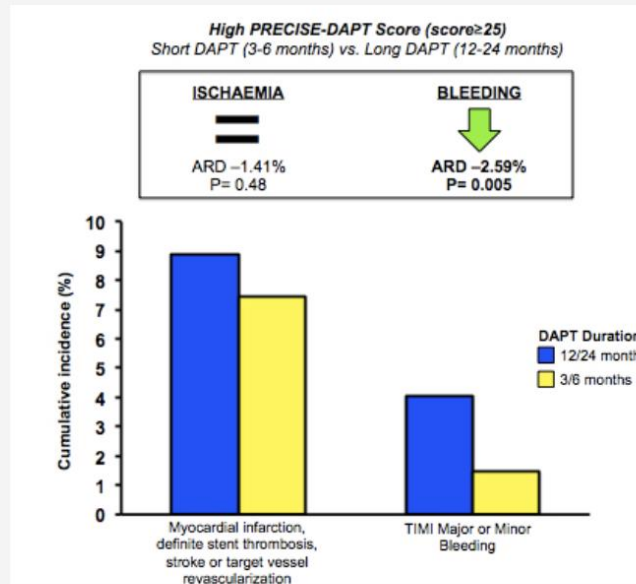
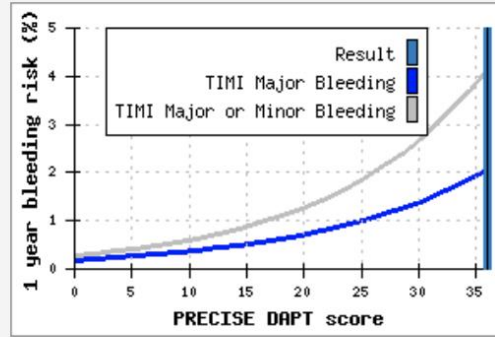
Creatinine Clearance (mL/min) ?

Prior bleeding

Prior Bleeding ?

CALCULATE

RESET



In patients with high PRECISE-DAPT score (Score ≥25) a short DAPT (3-6 months) as compared with a long DAPT (12-24 months) was associated with lower TIMI major and minor bleeding and similar rate of the composite ischemic endpoint.

RESULT:

Cluster of risk:

**HIGH**

Score Calculated

➔ **57**

12 months risk of TIMI major or minor Bleeding

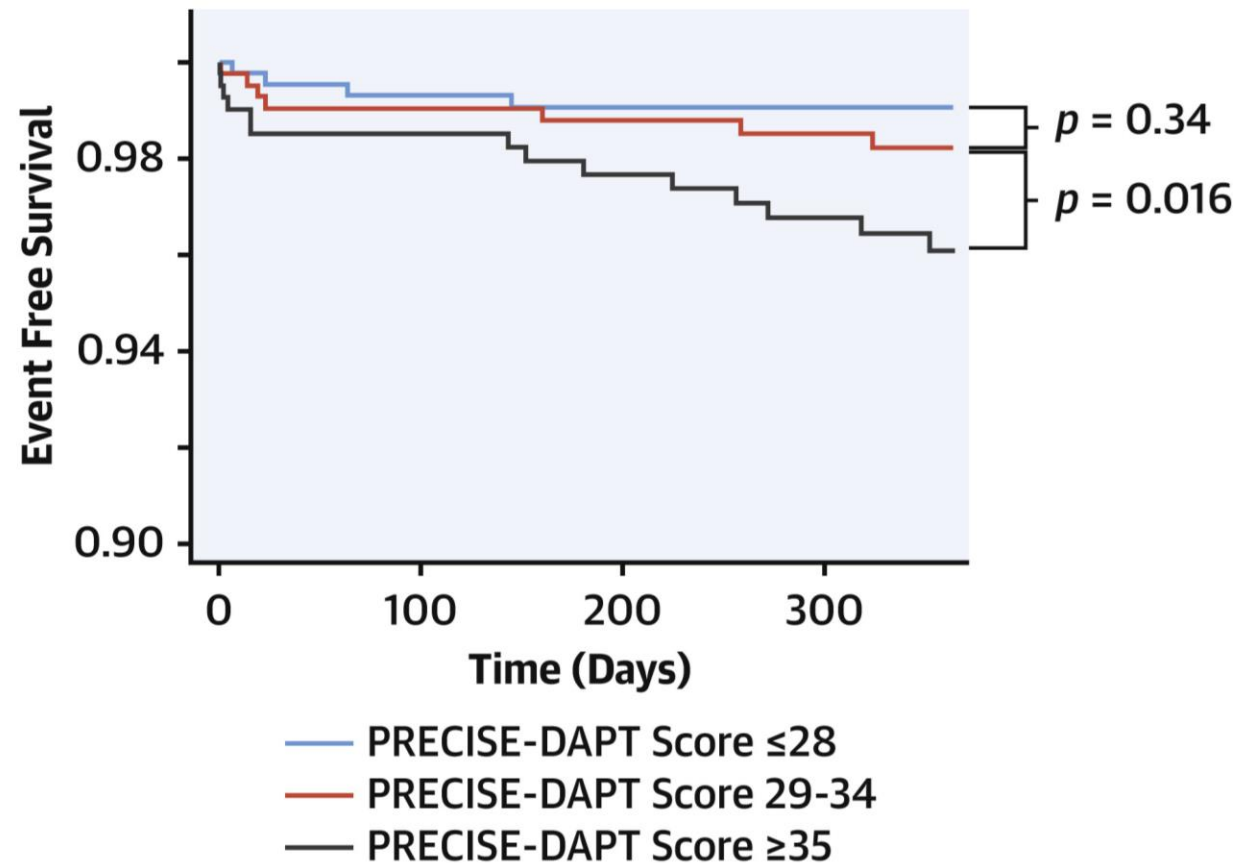
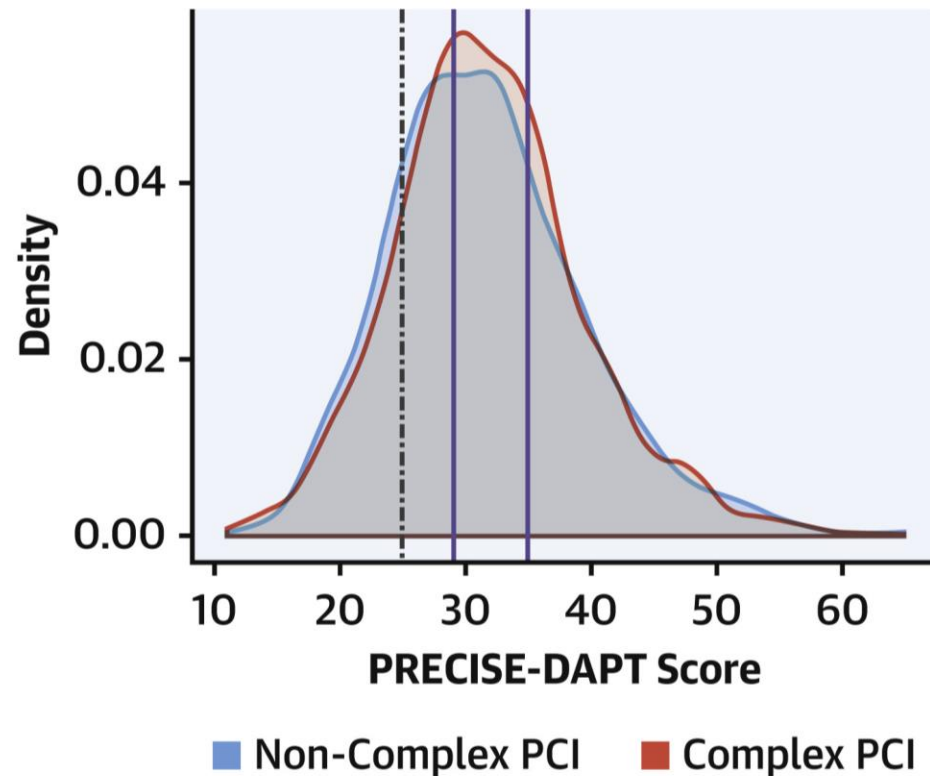
> 4.14%

12 months risk of TIMI Major Bleeding

> 2.06%

# A cut-off of the PRECISE-DAPT score $\geq 25$ may be too low for elderly patients?

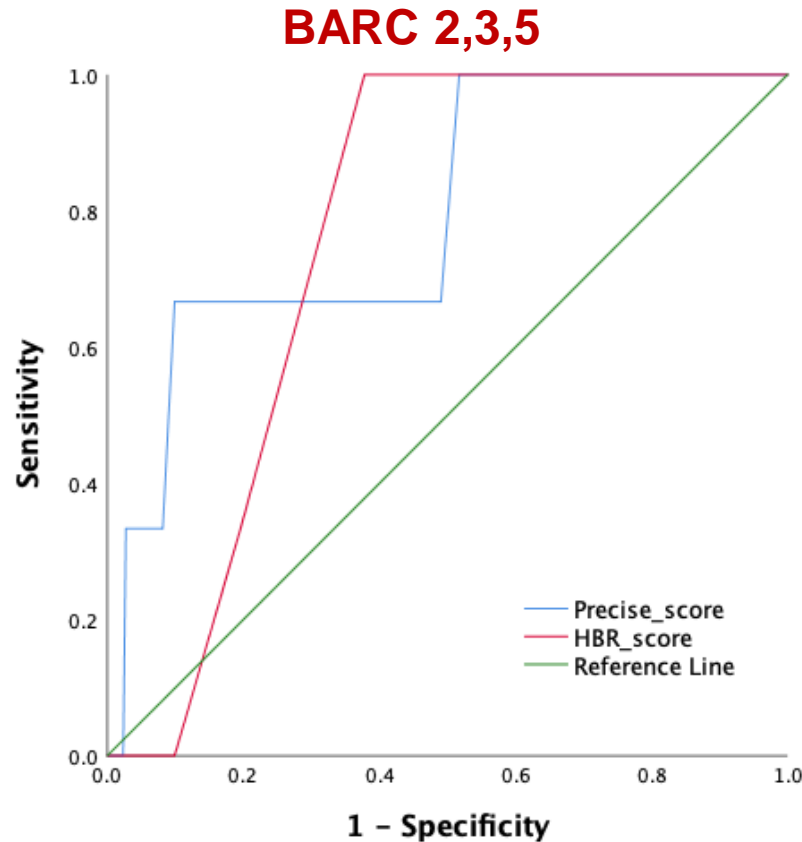
1,443 patients age  $\geq 75$  years with acute coronary syndromes (ACS) undergoing invasive management Patient  $> 74$  years, AMI undergoing PCI were randomized to either prasugrel 5 mg or clopidogrel 75 mg complex PCI (3) was performed in 605 patients (42%)



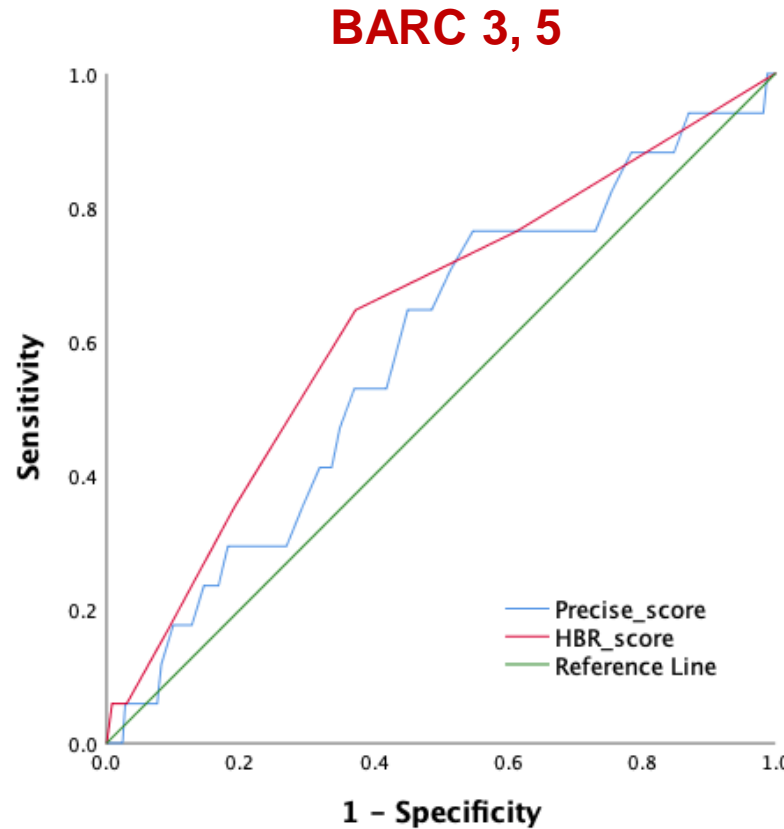


# ROC between ARC-HBR and PRECISE-DAPT

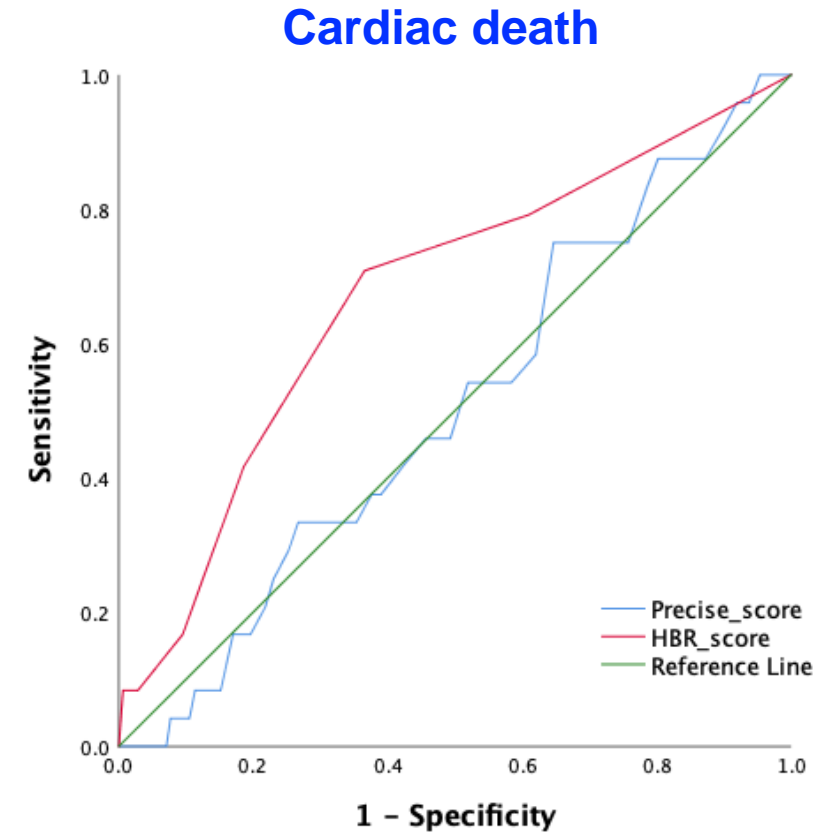
- The ARC-HBR criteria demonstrates a better discrimination of cardiac death than PRECISE-DAPT in Thai patients.
  - Due to small size of the patients and single center study, the results should be cautiously interpreted.



score	AUC	P-value
PRECISE-DAPT	0.794	0.079
HBR score	0.760	0.121

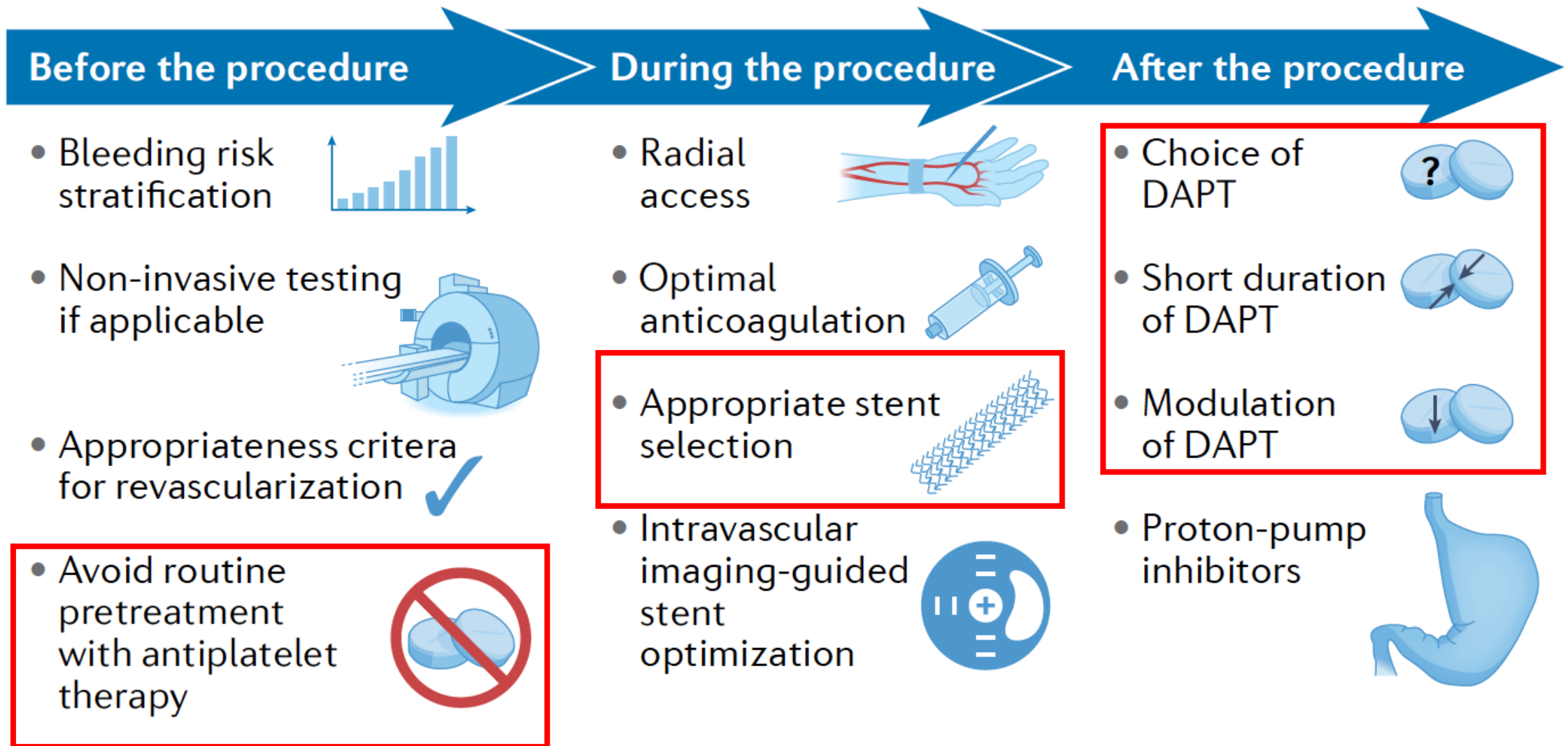


score	AUC	P-value
PRECISE-DAPT	0.585	0.232
HBR score	0.636	0.056



score	AUC	P-value
PRECISE-DAPT	0.505	0.928
<b>HBR score</b>	<b>0.671</b>	<b>0.005</b>

# Bleeding avoidance strategies in PCI



# High Bleeding Risk Trial Design

## Randomized drug trials

WOEST  
ISAR-TRIPLE  
PIONEER-AF PCI  
RE-DUAL PCI  
AUGUSTUS  
ENTRUST-AF PCI  
SAFE-A  
COBRA reduce  
Background Rx: PCI

MASTER DAPT  
TARGET SAFE  
Background Rx:  
DP-DES, BP-DES

## Randomized device trials

LEADERS FREE  
ZEUS-HBR  
SENIOR\*  
ONYX ONE  
DEBUT  
BIOFLOW-DAPT<sup>†</sup>  
COMPARE 60/80<sup>†</sup>

Background Rx:  
1-month DAPT  
DAPT shortening

## Randomized strategy trials

COBRA REDUCE  
Patients chronic  
needs for OAC

*Randomized device +  
DAPT duration*

## Single-arm studies

LEADERS FREE II  
EVOLVE Short DAPT  
ONYX ONE Clear  
XIENCE 90 Short DAPT  
XIENCE 28 GLOBAL  
POEM  
MODEL U-SES

Background Rx:  
1-month or  
3-month DAPT  
DAPT shortening

\*ACS 6-M DAPT; RED: trial in AF patients; BLUE: DAPT 3 months; BLACK: DAPT 1 month; †on-going trial

# Trials of stent for patients at HBR on 1-M DAPT

Trial	Stent	HBR Patients (n)	Control arm	BARC 3-5 bleeding @ 1 Year Study vs. Control	1 outcomes Study vs. Control	Results
<b>LEADER FREE (2015)</b>	SS BioFreedom	2466	<b>BMS Gazelle</b>	7.2% vs. 7.3% 1.7 HBR/pt	CD/MI/def or prob ST at 390 days 9.4% vs. 12.9% <sup>#,##</sup>	PF DCS was superior to BMS
<b>ZEUS-HBR (2016)</b>	Endeavor ZES	828	<b>BMS</b>	3.5% vs. 5.0%	D, MI, TVR (MACE) at 12 months 22.6% vs. 29% <sup>##</sup>	E-ZES provides superior efficacy and safety as compared to BMS
<b>LEADERS FREE II (2019)</b>	SS BioFreedom	1203	<b>LF BMS</b>	7.2% vs. 7.2% 1.7 HBR/pt	1 efficacy EP: TLR 1 Y 7.2% vs. 9.2% 1 safety EP: CD, MI 1 Y 9.3% vs. 12.4%	superior 365-day clinical safety and effectiveness of DCS versus BMS
<b>ONYX ONE* (2020)</b>	ONYX ZES	1996	<b>SS BioFreedom</b>	4.9% vs. 4.4% 1.6 HBR/pt	CD/MI/def or prob ST at 1 Y : 17.1% vs. 16.9% <sup>#</sup>	ZES was noninferior to use of PF DCS
<b>ONYX ONE CLEAR (2020)</b>	ONYX ZES	1506	Performance goal 9.7%	4.0% 1.6 HBR/pt	CD/MI/def or prob ST at 1 Y 7% vs. 9.7%	Onyx ONE Clear met its primary endpoint
<b>XIENCE Global 28 (2020)</b>	Xience EES	960	Xience V Propensity score matching	BARC 2-5 4.9% vs. 5.9%, P=0.19 BARC 3-5 2.2 vs. 4.5%, p=0.01	All-cause death or all MI at 6 months <sup>#</sup> 3.5% vs. 4.3%	non-inferior ischemic outcomes
<b>MASTER DAPT (2021)</b>	Ultimaster Abbreviated 1-M DAPT	4434	<b>Ultimaster Non-abbreviated DAPT</b>	BARC 3-5 2.3% vs. 2.5%	Three ranked 1 EP: NACE 7.5% vs. 7.7; HR 0.97 (0.78-1.20) MACE 6.1% vs. 5.9; HR 1.02 (0.80-1.30) major or CRNMB 6.4% vs. 9.2% (0.68 (0.55-0.85))	<ul style="list-style-type: none"> <li>Non-inferior NACE and MACE between abbre vs. non-abbrev</li> <li>Abbreviated DAPT has a lower incidence of bleeding</li> </ul>

<sup>##</sup> test for non inferiority, <sup>##</sup> test for superiority

# Algorithm for antithrombotic therapy in NTE-ACS patients

Anticoagulation for PCI



## NSTE-ACS

UFH OR Enoxaparin OR Bivalirudin

Bleeding Risk

LOW HIGH VERY HIGH

Treatment duration

1 month  
3 months  
6 months  
12 months

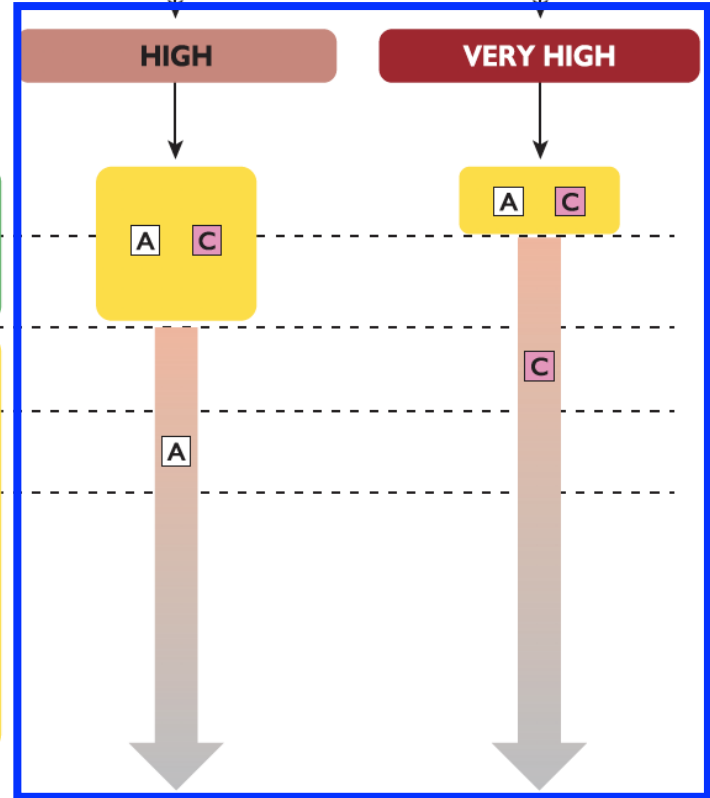
Antithrombotic drugs

- A** = Aspirin
- C** = Clopidogrel
- P** = Prasugrel
- R** = Rivaroxaban
- T** = Ticagrelor

**A R**  
DAT<sup>c</sup>  
>12 months

**A T**  
OR  
**A P**<sup>b</sup> **A C**<sup>b</sup>  
DAPT<sup>c</sup>  
>12 months

Ischaemic Risk



*Very HBR is defined as recent bleeding in the past month and/or not deferrable planned surgery.*

# High bleeding risk & High thrombotic risk in one patient

*83 YO woman presented with NSTEMI, denied CABG*

*Known case DM type II on medication, Hx of NSTEMI 2019, eGFR 35 ml/min, Hb 10.5 mg/dL*



**Bleeding risk assessment:** 1 major (Hb), 2 minor (age, eGFR)

**Thrombotic risk assessment:** DM, history of MI, multivessel CAD, CKD, 3 stents (ZES), 3 lesions, stent length > 60 mm, LM stenting

# High Thrombotic risk (class IIa): *Complex CAD and at least 1 criterion*

## Risk enhancers

- Diabetes mellitus requiring medication
- History of recurrent MI
- Any multivessel CAD
- Polyvascular disease (CAD plus PAD)
- Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD
- Concomitant systemic inflammatory disease (e.g HIV, SLE, chronic arthritis)
- CKD with eGFR 15-59 mL/min/1.73 m<sup>2</sup>

## Technical aspects

- At least 3 stents implanted
- At least 3 lesion treated
- Total stent length > 60 mm
- History of complex revascularization
  - Left main
  - bifurcation with ≥ 2 stents implanted
  - Chronic total occlusion
  - stenting of last patent vessel
- History of stent thrombosis on antiplatelet treatment

# Tailor management of HBR patients

6,641 patients for developing ARC-HBR trade-off model

## Increased risk of both MI and/or ST and major bleeding

- Anemia
- Kidney insufficiency
- Current smoking
- Complex PCI procedure

## Increased only BARC 3 to 5 bleeding

- Age  $\geq 65$  years
- COPD
- Liver disease, cancer or planned surgery
- OAC at discharge

## Increased only MI and Stent thrombosis

- DM treated with insulin or oral med
- STEMI or NSTEMI
- Use of BMS

Predictor	BARC types 3-5 bleeding		MI and/or ST	
	HR (95% CI)	P value	HR (95% CI)	P value
Aged $\geq 65$ y	1.50 (1.08-2.08)	.01	NA	NA
Diabetes (requiring treatment with either insulin or oral medication)	NA	NA	1.56 (1.26-1.93)	<.001
Prior MI	NA	NA	1.89 (1.52-2.35)	<.001
Liver disease, cancer, or surgery <sup>a</sup>	1.63 (1.27-2.09)	.0001	NA	NA
COPD	1.39 (1.05-1.83)	.02	NA	NA
Current smoker	1.47 (1.08-1.99)	.01	1.48 (1.09-2.01)	.009
NSTEMI or STEMI presentation	NA	NA	1.82 (1.46-2.25)	<.001
Hemoglobin, g/dL				
$\geq 13$	1 [Reference]		1 [Reference]	
11-12.9	1.69 (1.30-2.20)	<.001	1.27 (0.99-1.63)	.005
<11	3.99 (3.06-5.20)		1.50 (1.12-1.99)	
eGFR, mL/min				
$\geq 60$	1 [Reference]		1 [Reference]	
30-59	0.99 (0.79-1.24)	.02	1.30 (1.03-1.66)	.001
<30	1.43 (1.04-1.96)		1.69 (1.20-2.37)	
Complex procedure <sup>b</sup>	1.32 (1.07-1.61)	.008	1.50 (1.21-1.85)	<.001
Bare metal stent <sup>c</sup>	NA	NA	1.53 (1.23-1.89)	<.001
OAC at discharge	2.00 (1.62-2.48)	<.001	NA	NA
C statistic	0.68	NA	0.69	NA







Validation: ARC-HBR ONYX-ONE 0.74







0.74



### Bleeding vs. thrombosis trade-off

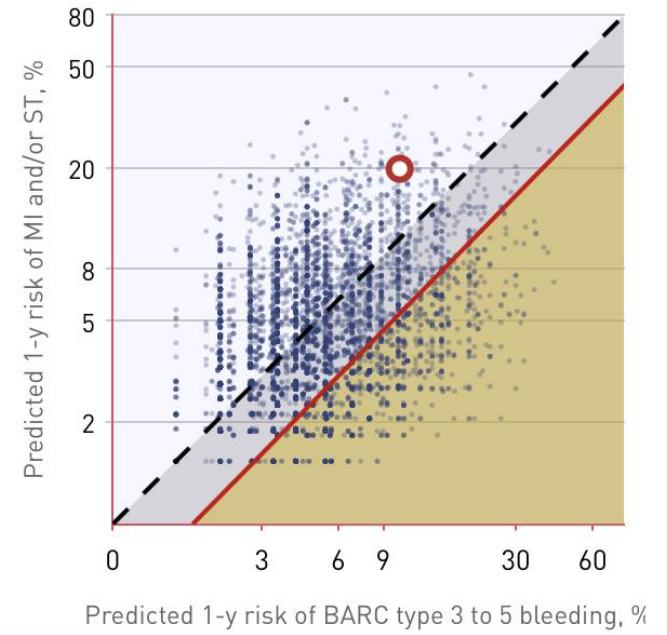
Select all criteria that you believe are either definitely or possibly satisfied.

-  **Age ≥ 65**
-  **Diabetes**
-  **Prior MI**
-  **Liver disease, cancer or surgery**
-  **COPD**
-  **Current smoker**

-  **NSTEMI or STEMI presentation**
-  **Anemia**
-  **Estimated GFR**
-  **Complex procedure**
-  **Bare metal stent**
-  **OAC at discharge**

Estimated BARC 3-5 bleeding risk after PCI (day 3-365) = 10.44%  
 Estimated risk of MI and or ST (day 3-365) = 19.85%  
 The patients is in the blue zone: the risk of MI/ST is greater than the risk of bleeding

**19.85% MI /ST**  
**10.44% BARC 3-5**



# DAPT strategies in elderly with ACS

*the risk of bleeding in the elderly can be mitigated by strategies*

## Standard of care

12 M  
A+C

12 M  
A+T

12 M  
A+P

## Bleeding reduction strategies

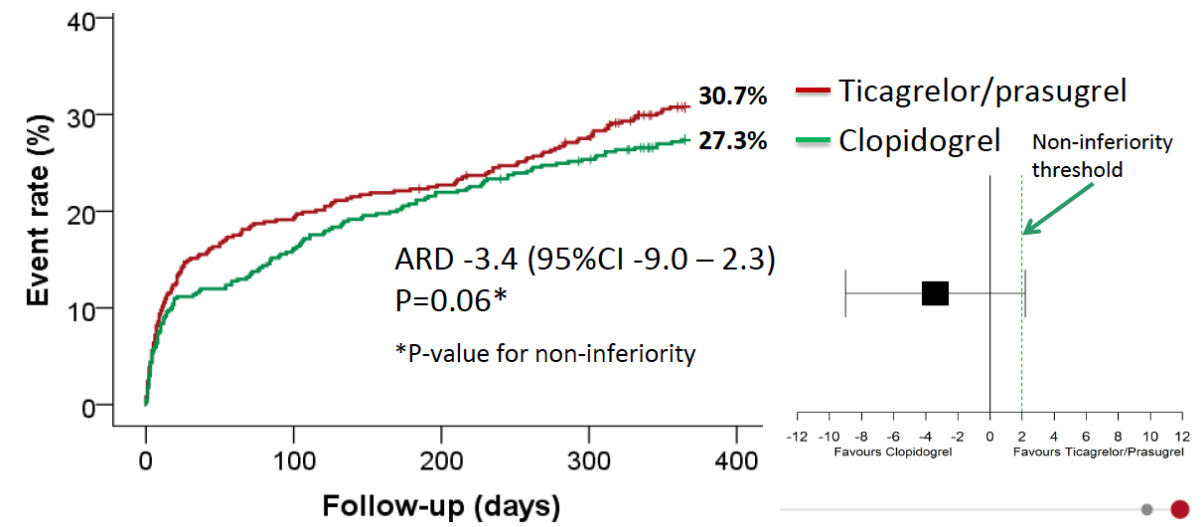
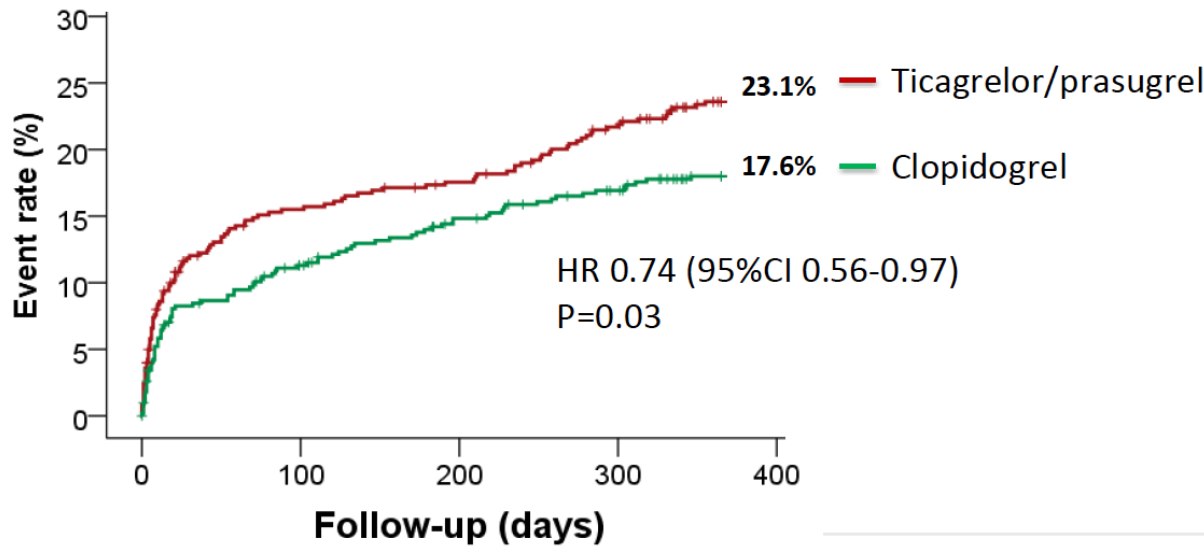
- **1.Short DAPT:** 1-, 3- or 6-month DAPT then aspirin (MASTER-DAPT)
- **2.P2Y12i monotherapy after brief DAPT:** 3-month DAPT then single P2Y12i i.e ticagrelor or clopidogrel (TWILIGHT, TICO, STOPDAPT-2)
- **3.P2Y12i de-escalation**

# POPular Age

## Clopidogrel (n=500) vs. Ticagrelor or Prasugrel (n=502) in NSTEMI ≥ 70 years old

**Primary bleeding outcome:**  
PLATO major or minor bleeding

**Co-Primary net clinical benefit:**  
All death, MI, stroke, major and minor bleeding



- Mean age 77 yr
- OAC 20%
- 95% of T/P arm received ticagrelor (n=475)

**clopidogrel was associated with a significant 6% absolute reduction in bleeding events compared to standard treatment with ticagrelor or prasugrel and was non-inferior for ischemic events.**

# Ticagrelor vs. Clopidogrel in elderly patients with ACS

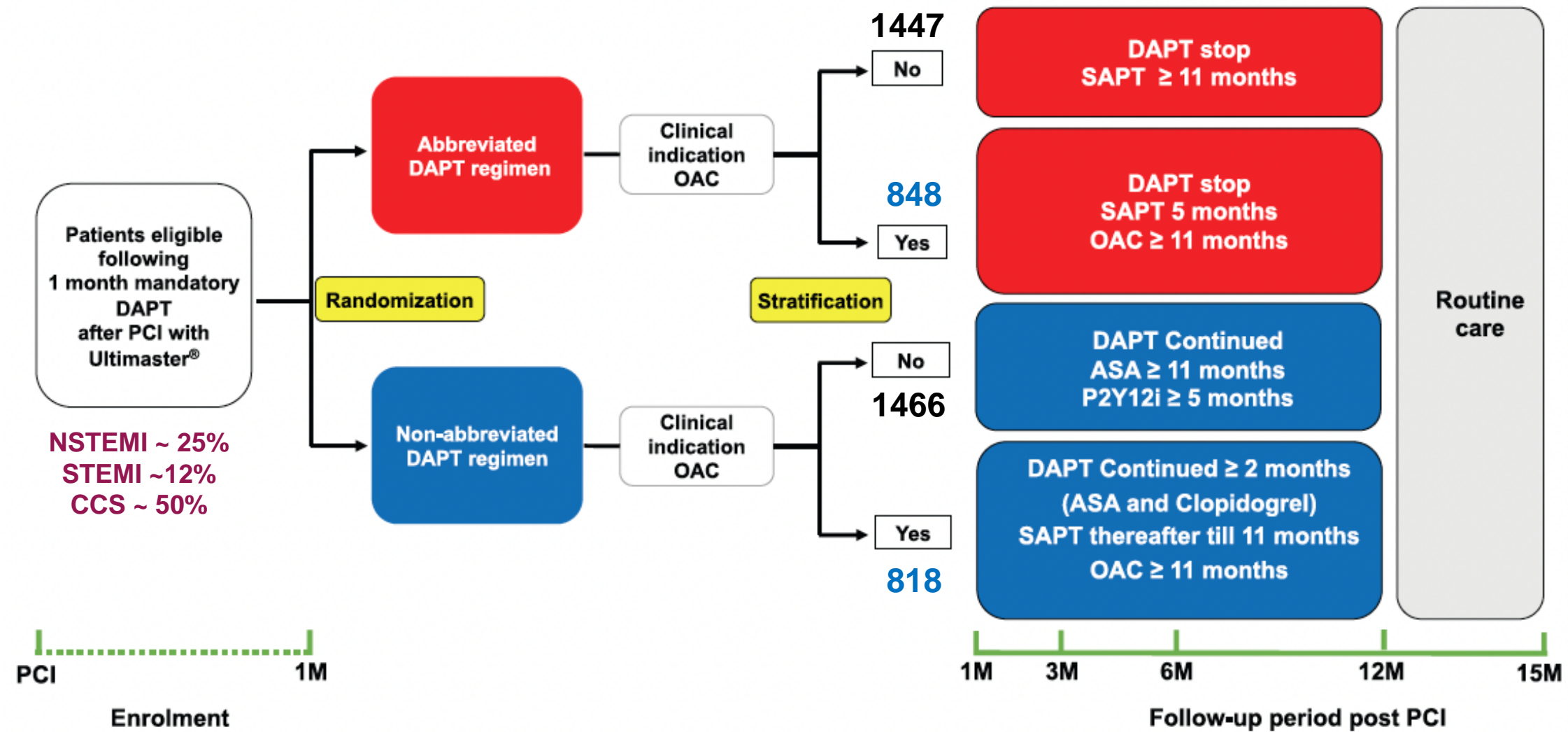
*Insights From the SWEDEHEART Registry, n=15,005*

	Clopidogrel			Ticagrelor			IPTW-adjusted cause-specific hazard ratio (95% CI)*	IPTW-adjusted competing risk hazard ratio (95% CI)*
	N events	Mean±SD/ median follow-up time	Incidence rate (per 100 person-years)	N events	Mean±SD/ median follow-up time	Incidence rate (per 100 person-years)		
Stroke, MI, death	2230	296±121/365	32.8	844	297±117/365	18.7	0.97 (0.88–1.06)	—
Stroke, MI, death, readmission for bleeding	2427	290±125/365	37.4	1058	288±123/365	24.2	1.03 (0.94–1.12)	—
MI	1048	300±119/365	13.9	360	300±115/365	7.5	0.80 (0.70–0.92)	0.78 (0.68–0.90)
Stroke	277	318±104/365	3.44	155	308±108/365	2.32	0.72 (0.56–0.93)	0.70 (0.54–0.91)
Death	1344	322±99/365	18.1	511	311±105/365	10.8	1.17 (1.03–1.32)	—
Readmission for bleeding	388	314±107/365	4.86	333	300±114/365	6.90	1.48 (1.25–1.76)	1.45 (1.23–1.72)



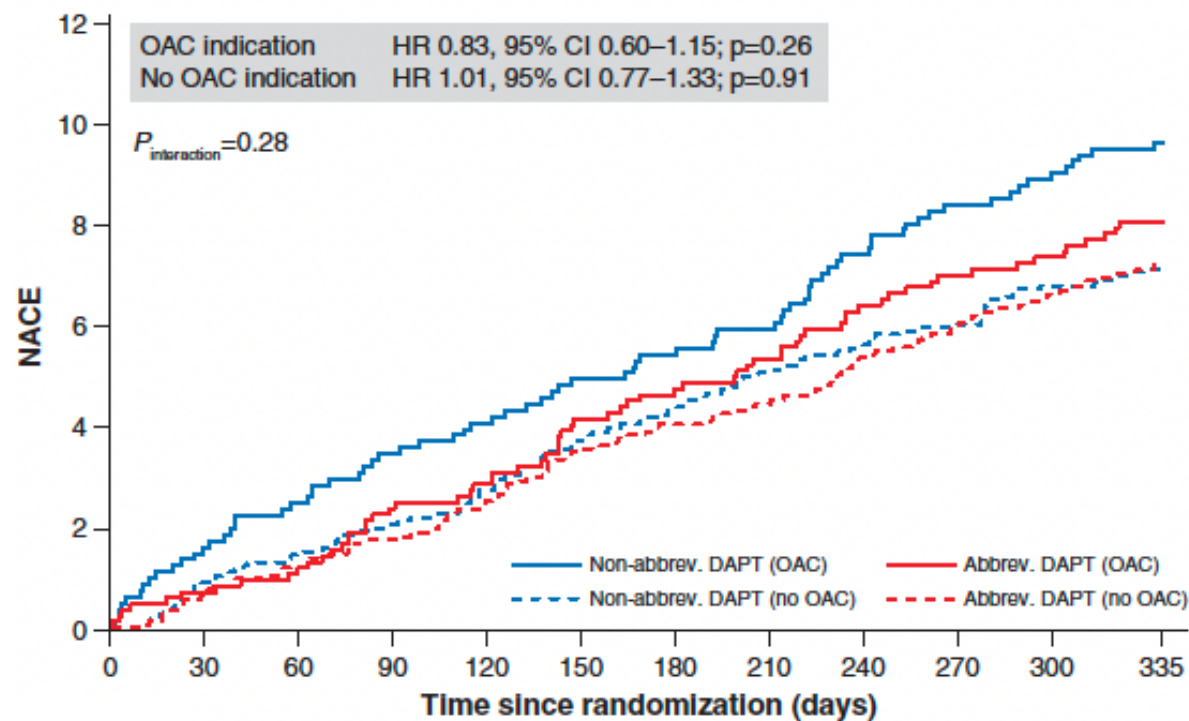
- different benefit-risk ratio between ticagrelor and clopidogrel in elderly patients
- Ticagrelor vs. Clopidogrel : **17% ↑ risk of death, 48% ↑ risk of bleeding**  
**20% ↓ risk of new MI, 28% ↓ risk of stroke**
- Ticagrelor should be used with caution among patients ≥ 80 years

# MASTER-DAPT: Schematic trial design

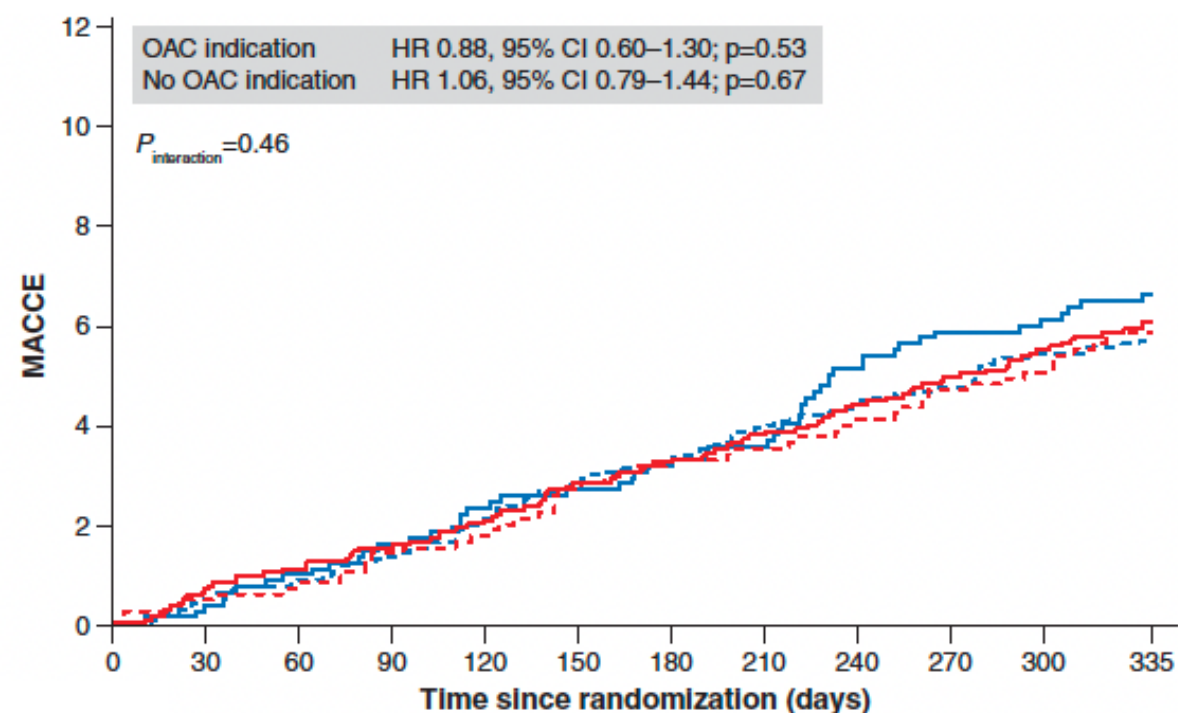


# Kaplan-Meier curves of NACE and MACCE at 11 months after randomization: MASTER-DAPT

## net adverse clinical outcomes (NACE)



## major adverse cardiac and cerebral events (MACCE)



NACE and MACCE did not differ with **abbreviated** vs. **non-abbreviated** APT regimens in patients with OAC indication or without OAC indication

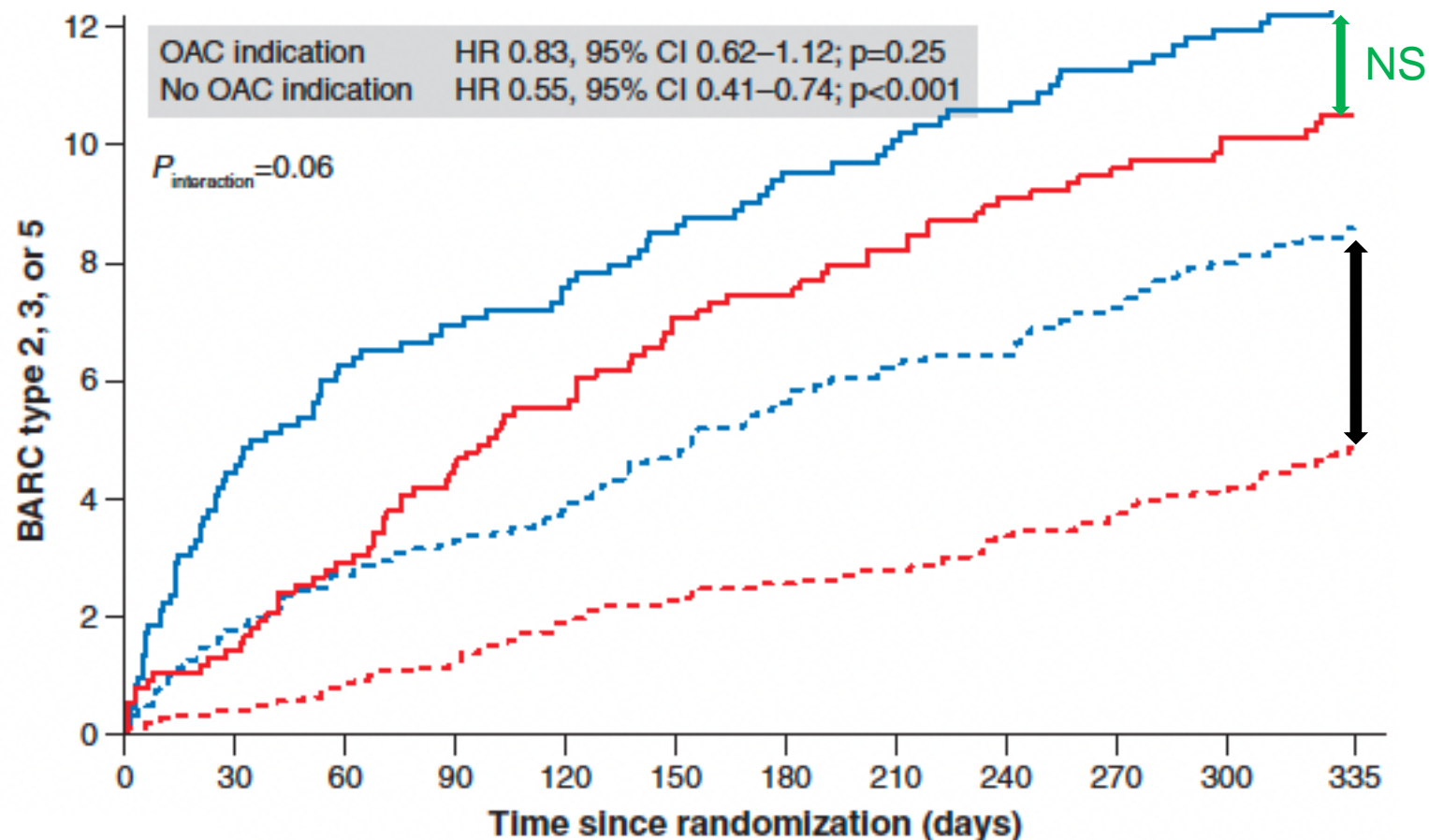
# Kaplan-Meier curves of major or clinically relevant non-major bleeding at 11 months after randomization : MASTER-DAPT

## Findings:

- BARC 2, 3, or 5 bleeding did not significantly differ in patients with OAC indication
- BARC was lower with abbreviated APT in patients without OAC indication



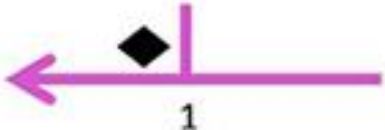

## What Are the Clinical Implications?

- DAPT beyond 1 month in patients with or without an indication for OAC has no benefit and only increases bleeding risk.



# STOPDAPT-2 ACS

*1-month DAPT followed by clopidogrel monotherapy in ACS*

Population	Intervention	Control	Outcomes	Time
4136 pts. with ACS	1-month DAPT	12-month DAPT	Bleeding	1 year
<ul style="list-style-type: none"> <li>• Mean age 67</li> <li>• 79% male</li> <li>• 30% diabetes</li> <li>• 56% STEMI</li> </ul>	 <p>1-month DAPT</p>		<p>HR 0.46, CI95% 0.23-0.94</p>  <p>1-month DAPT better</p>	<p>Primary analysis at 1 year post ACS</p>
	<ul style="list-style-type: none"> <li>• 85% radial approach</li> <li>• 97% IVUS or OCT</li> </ul>		<p>11 months Clopidogrel alone</p> 	





# Twilight: Study Design

## Enrollment Period

3 Months

High-Risk PCI Patients  
(N=9006)

N = 7119

Not Randomized  
(N=1887)

Ticagrelor + Aspirin  
(Open label)

## Randomization Period

12 Months

Ticagrelor + Aspirin

1064 (17.2%) met the  
ARC-HBR criteria  
ACS 62%

STEMI is excluded

Ticagrelor + Placebo

## Observation Period

3 Months

Standard of Care

Standard of Care



3 M



4 M



9 M



15 M

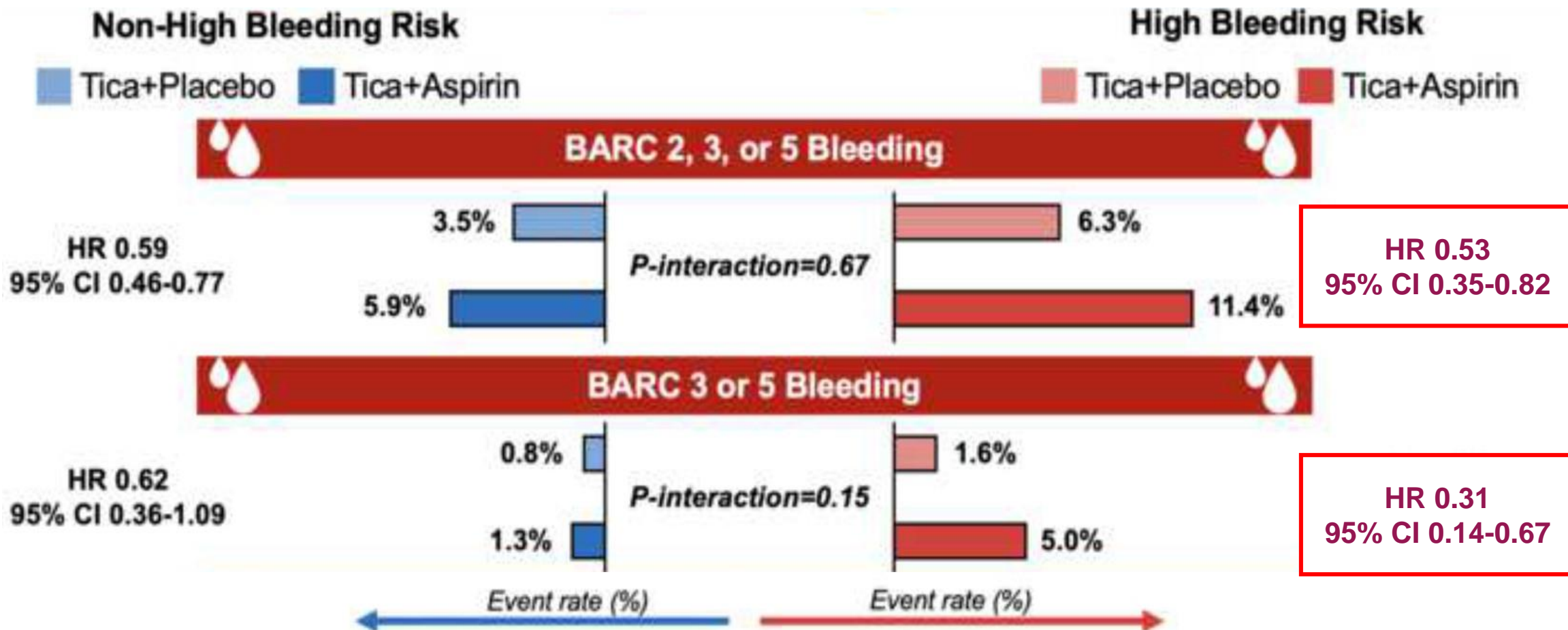


18 M

TCTAP

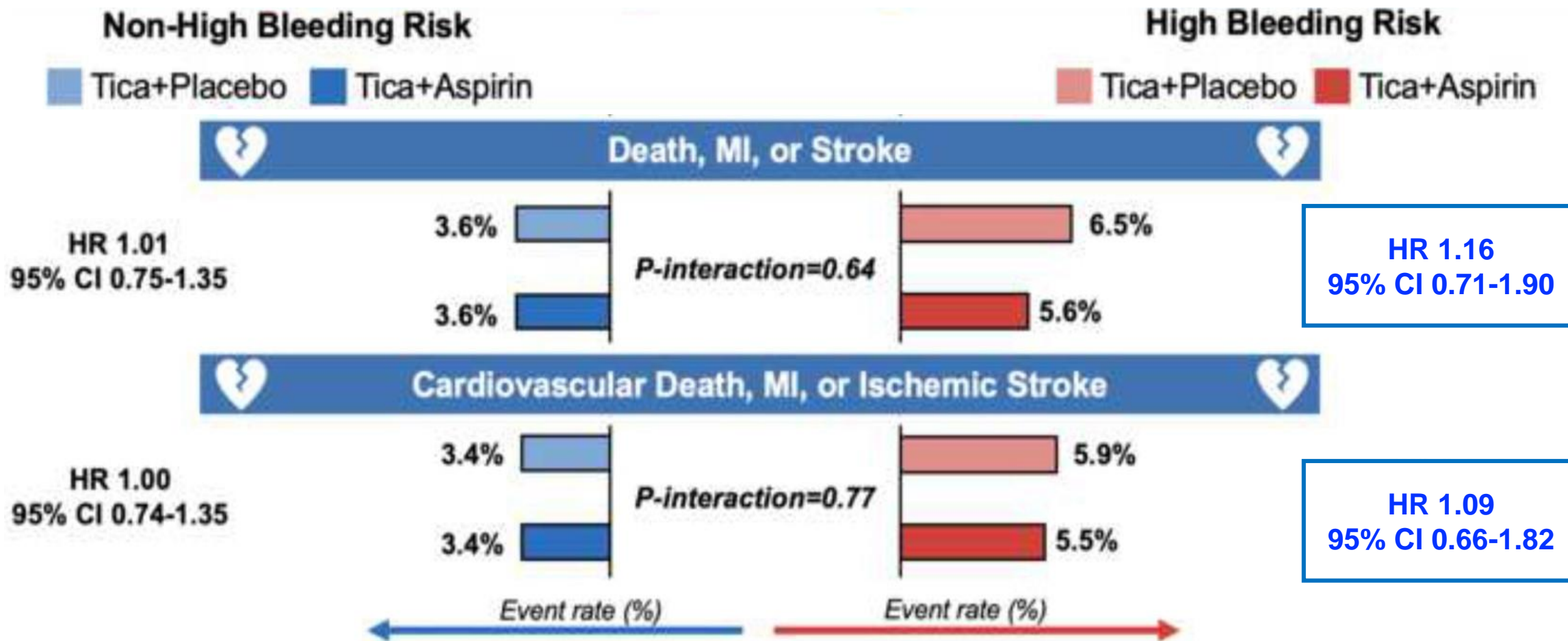
# Ticagrelor Monotherapy After 3-month DAPT in Patients at High Bleeding Risk Undergoing PCI

*A Prospective Analysis of the TWILIGHT Trial*



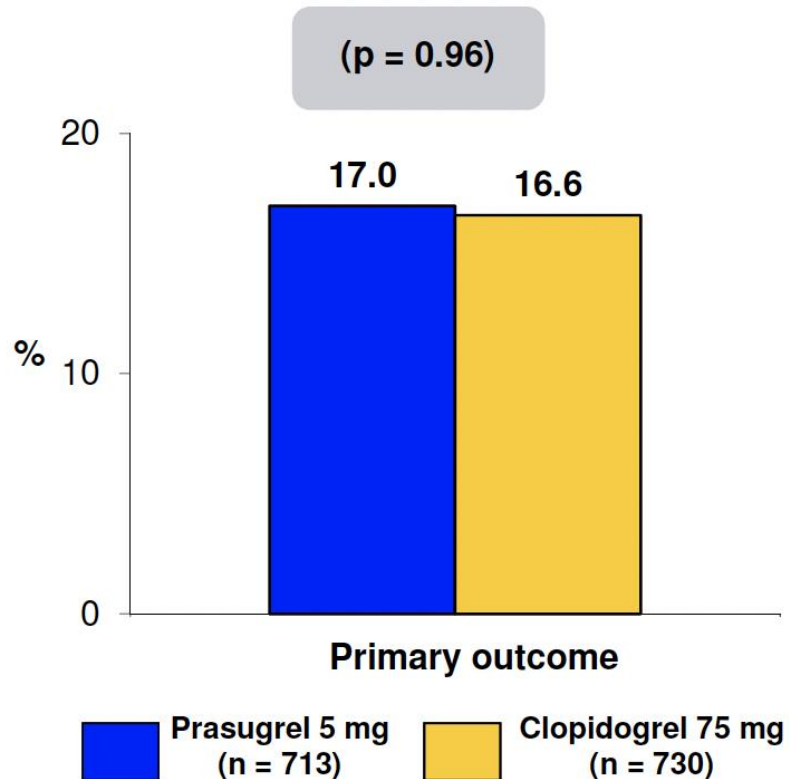
# Ticagrelor Monotherapy After 3-month DAPT in Patients at High Bleeding Risk Undergoing PCI

*A Prospective Analysis of the TWILIGHT Trial*



# ELDERLY ACS trial

**Trial design:** Patients >74 years of age presenting with AMI and undergoing PCI were randomized in a 1:1 fashion to either prasugrel 5 mg daily or clopidogrel 75 mg daily. Patients were followed for 12.1 months.



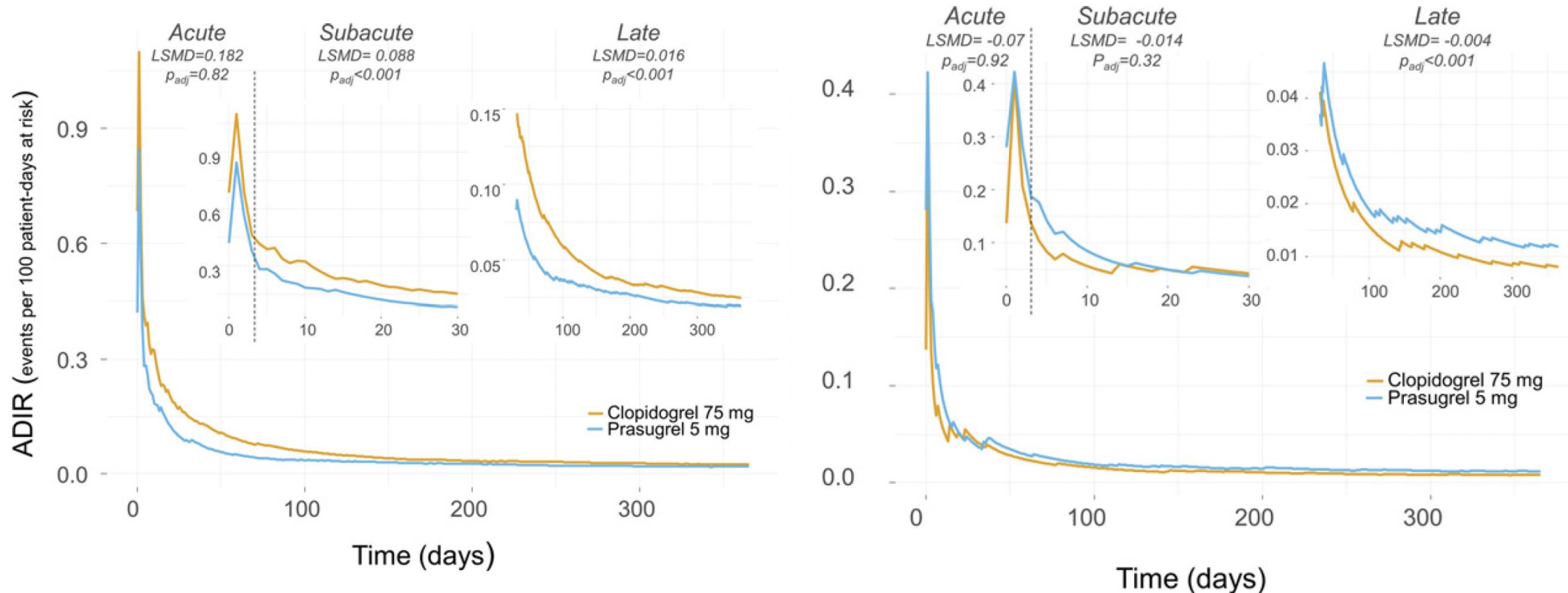
## Results

- Primary endpoint: Death/MI/stroke/CV rehospitalization/bleeding: prasugrel vs. clopidogrel: 17.0% vs. 16.6%,  $p = 0.96$
- Stent thrombosis: 0.7% vs. 1.9%,  $p = 0.06$
- All BARC 2, 3, 5 bleeding: 4.1% vs. 2.7%,  $p = 0.18$

## Conclusions

- Half-dose prasugrel is not superior to regular-dose clopidogrel in reducing ischemic events among elderly (age >74 years; mean 80.6 years) patients undergoing PCI for ACS
- The trial was terminated early due to futility

# Post-hoc analysis of ELDERLY ACS trial



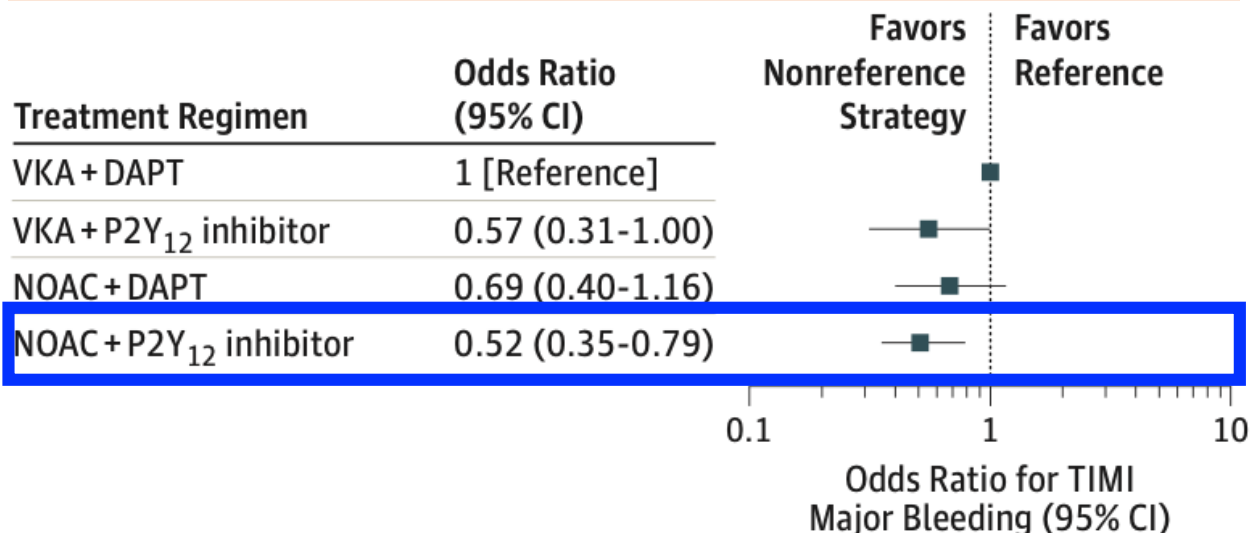
- Prasugrel 5 mg was significantly superior to clopidogrel in reducing thrombotic events in the first month after ACS, whereas clopidogrel was superior to prasugrel 5 mg in reducing late bleedings (31–365 days).

# Optimal Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

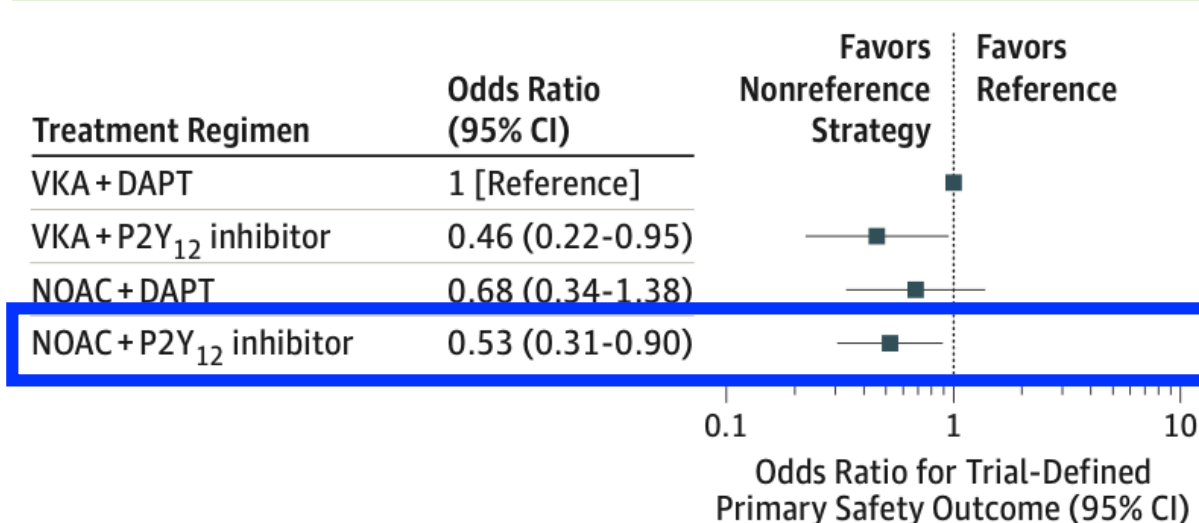
## An Updated Network Meta-analysis

Five randomized studies were included (N = 11 542; WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI).

### Primary safety outcome: TIMI major bleeding

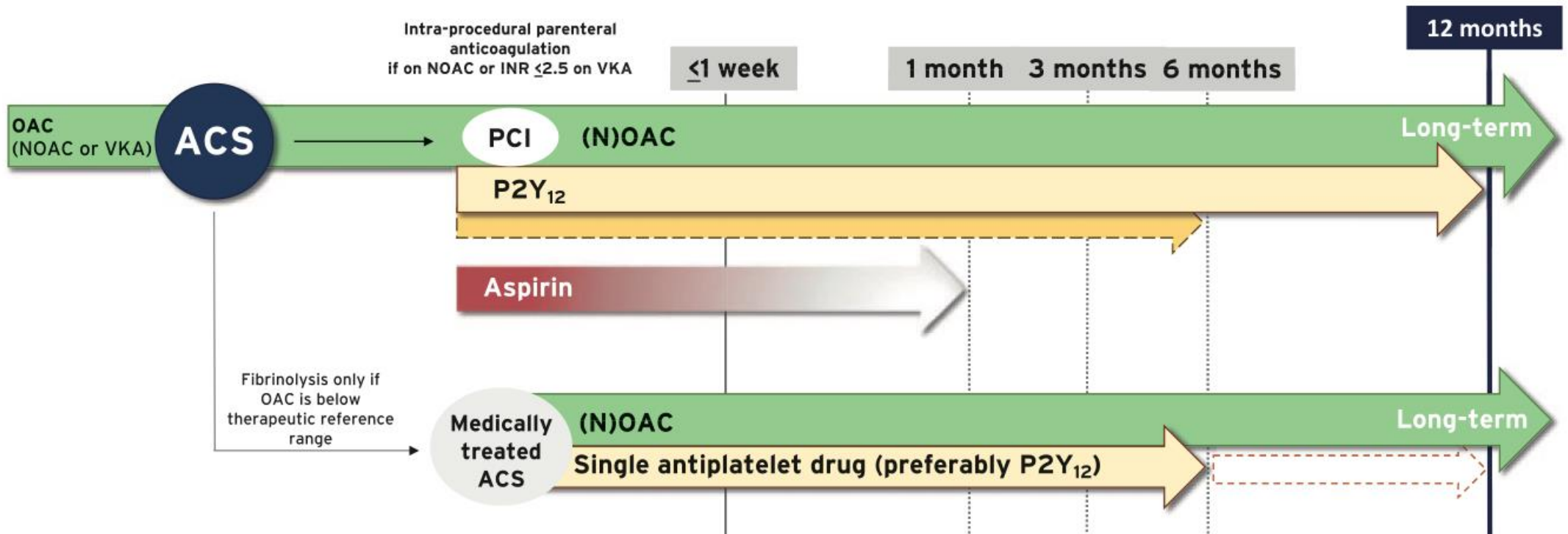


### Primary efficacy outcome: Trial-defined MACE



- An antithrombotic regimen of **VKA plus DAPT should generally be avoided**
- **NOAC plus a P2Y12 inhibitor without aspirin may be the most favorable treatment option**

# Post-procedural management of patients with AF and ACS/PCI



## Recommendations for AF patients with ACS







In AF patients with ACS undergoing an uncomplicated PCI, early cessation ( $\leq 1$  week) of aspirin and continuation of dual therapy with an OAC and a P2Y<sub>12</sub> inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis<sup>d</sup> is low or if concerns about bleeding risk<sup>e</sup> prevail over concerns about risk of stent thrombosis,<sup>d</sup> irrespective of the type of stent used.<sup>1090,1092–1095</sup>

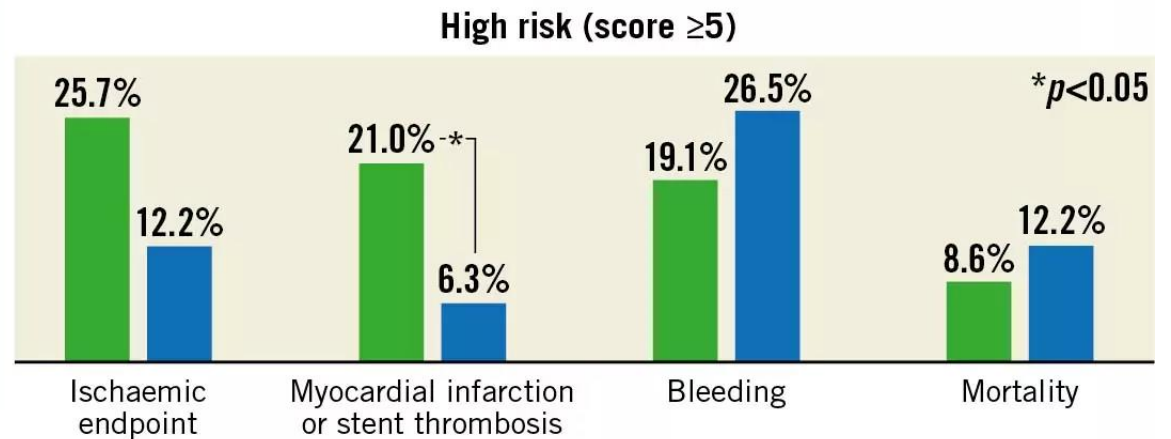
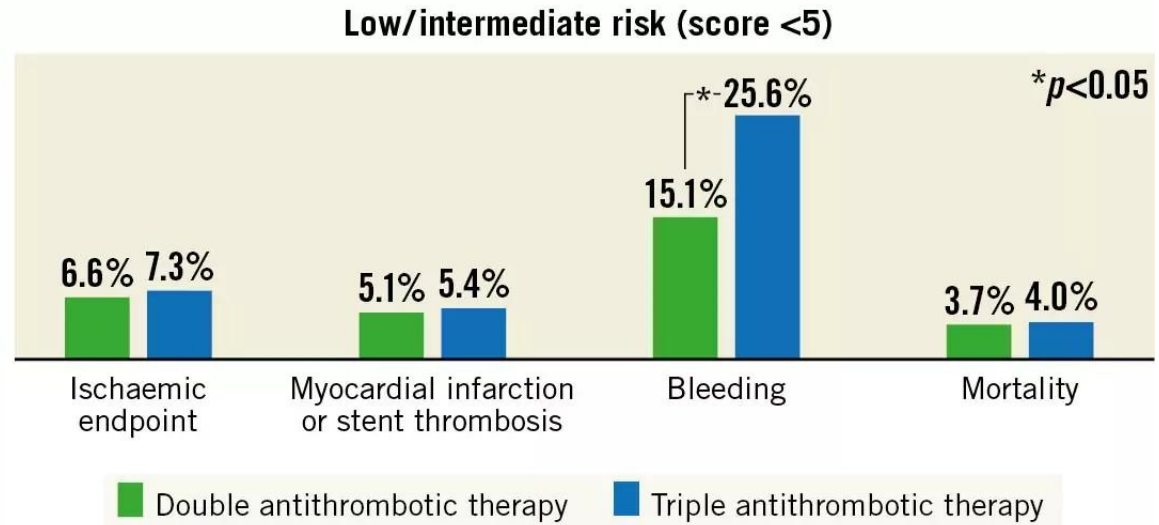
Triple therapy with aspirin, clopidogrel, and an OAC<sup>f</sup> for longer than 1 week after an ACS should be considered when risk of stent thrombosis<sup>d</sup> outweighs the bleeding risk,<sup>e</sup> with the total duration ( $\leq 1$  month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge.

<b>I</b>	<b>A</b>
<b>IIa</b>	<b>C</b>

# A novel risk score to identify the need for TAT

post hoc analysis of the RE-DUAL PCI trial, significant reduction in MI/ST with TAT in patients with a risk score >5

Thrombotic risk in AF-PCI patients		
Feature		Score
	LVEF <30%	+3
	LVEF 30-50%	+1
	3-vessel disease	+2
	MI as indication for index PCI	+2
	History of peripheral artery disease	+2
	Platelet count $\geq 400 \times 10^9/L$	+3
	eGFR $\geq 90$ ml/min	-1





# Conclusion

- Elderly patients with ACS are at higher risk of both atherothrombotic events and bleeding.
- Risk assessment is important, elderly ACS patients should be evaluated for ARC-HBR criteria before the procedure.
- A case-by-case decision based not only on the assessment of the bleeding risk but also of the ischaemic risk.
- The risk of bleeding in the elderly can be mitigated by DAPT strategies.
- HBR trade-off model would help for DAPT strategies in HBR patients.
- Short duration of DAPT as default strategies in elderly patients

