

***Rationale for **De-Escalation** of
Antiplatelet Therapy in East Asians
And De-Escalation with Prasugrel***

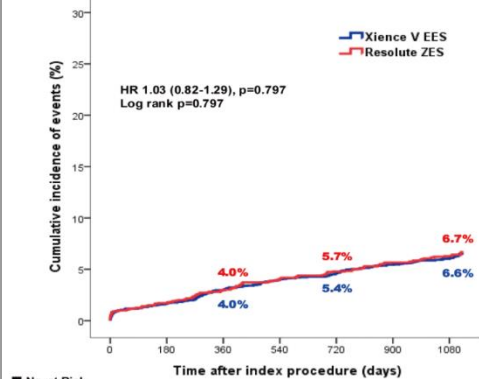
Kyung Woo Park, MD, PhD, MBA

Seoul National University Hospital, Seoul, Korea

Outcome differences?

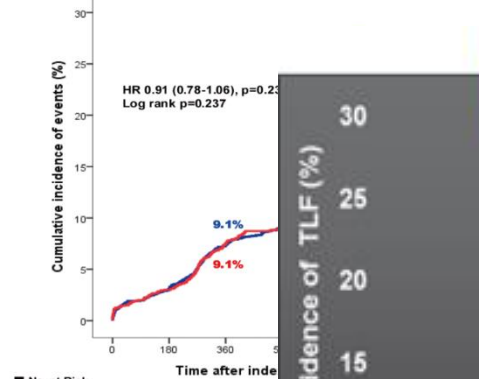
RESOLUTE vs. Xience V TLF at 3 years

A. Target Lesion Failure in Crude Population



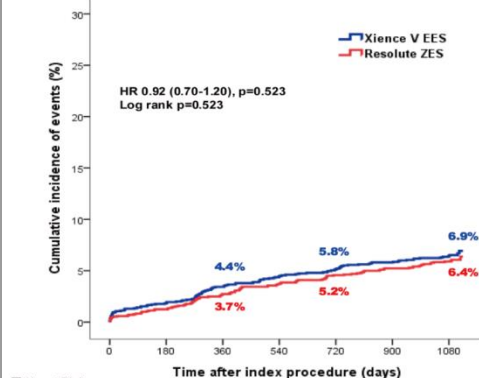
No. at Risk	Everolimus	Zotarolimus
3056	1998	1058
2989	1951	1038
2940	1920	1020
2901	1895	1006
2870	1877	993
2819	1850	969
2238	1456	782

B. Patient-Oriented Composite Events in Crude Population



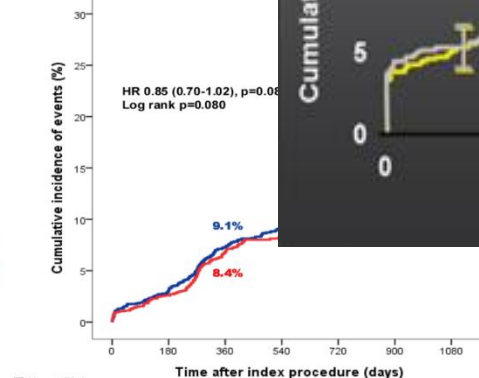
No. at Risk	Everolimus	Zotarolimus
3056	1998	1058
2963	1937	1026
2833	1848	985

C. Target Lesion Failure after Matching

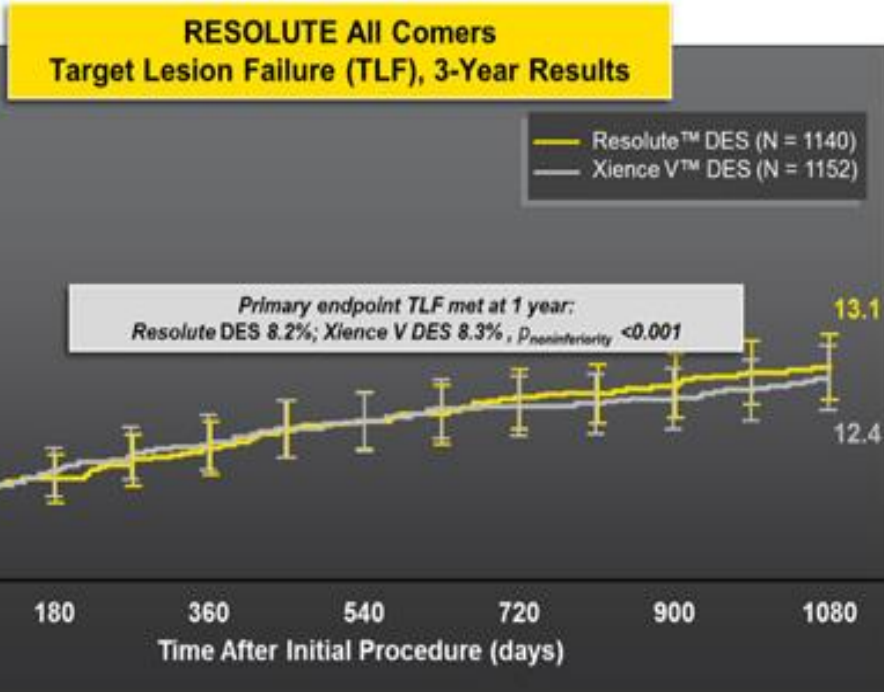


No. at Risk	Everolimus	Zotarolimus
1698	1698	0
1662	1666	0
1631	1637	0
1607	1617	0
1588	1599	0
1564	1578	0
1249	1241	0

D. Patient-Oriented Composite Outcome

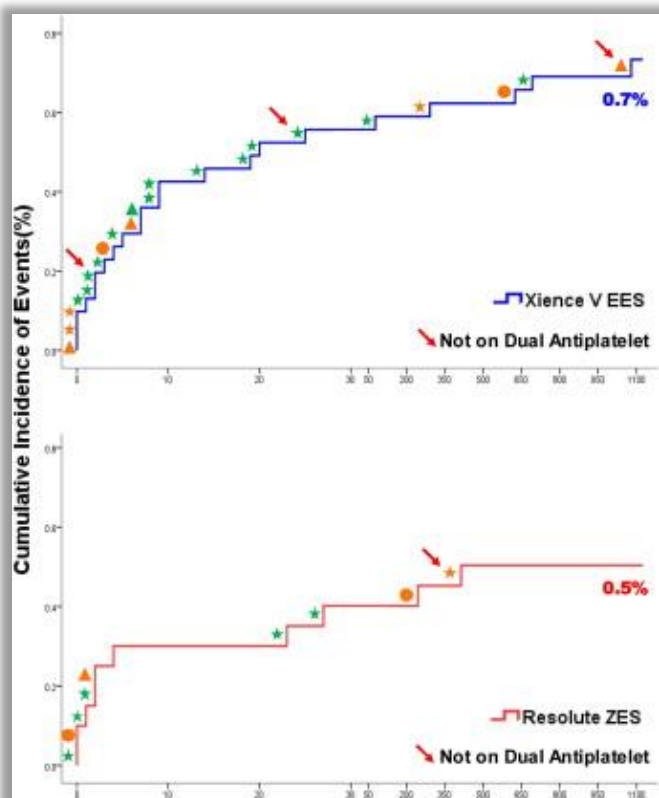


No. at Risk	Everolimus	Zotarolimus
1698	1698	0
1647	1653	0
1575	1582	0
1542	1554	0
1513	1532	0
1485	1509	0
1181	1190	0



Outcome differences?

RESOLUTE vs. Xience V ST at 3 years



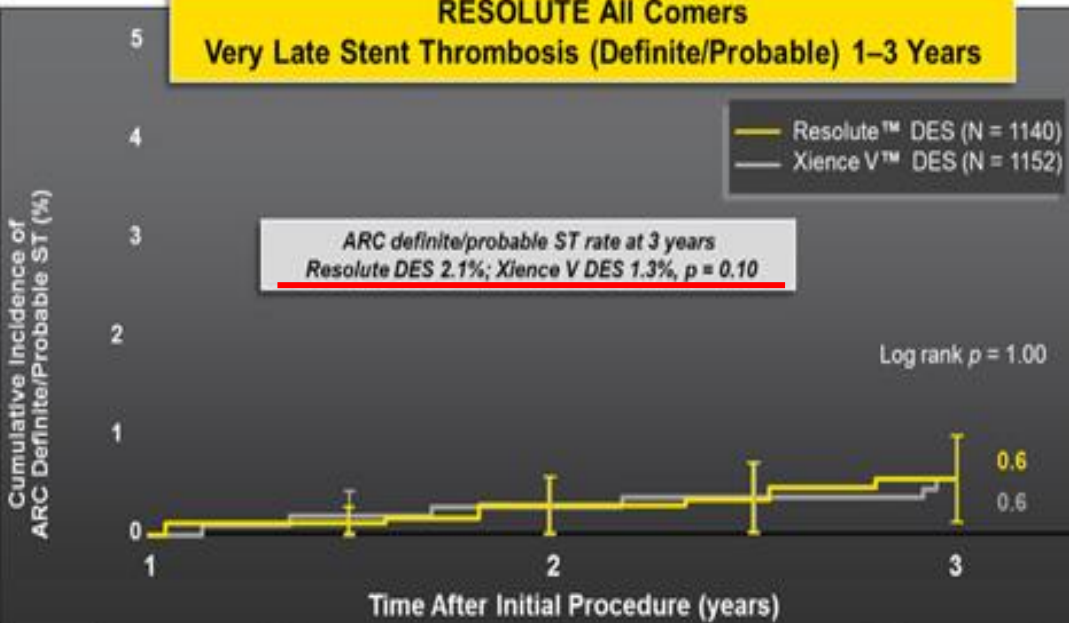
Definite Stent Thrombosis

- ★ Cardi
 - ▲ Myoc
 - Target
- Probab**
- ★ Cardi
 - ▲ Myoc
 - Target
- Cardi**

Cumulative Incidence of Definite or Probable ST (%)

	No. at Risk	Time after index procedure (days)						
EES	3056	2999	2975	2963	2926	2884	2290	
ZES	1998	1965	1943	1924	1912	1887	1488	

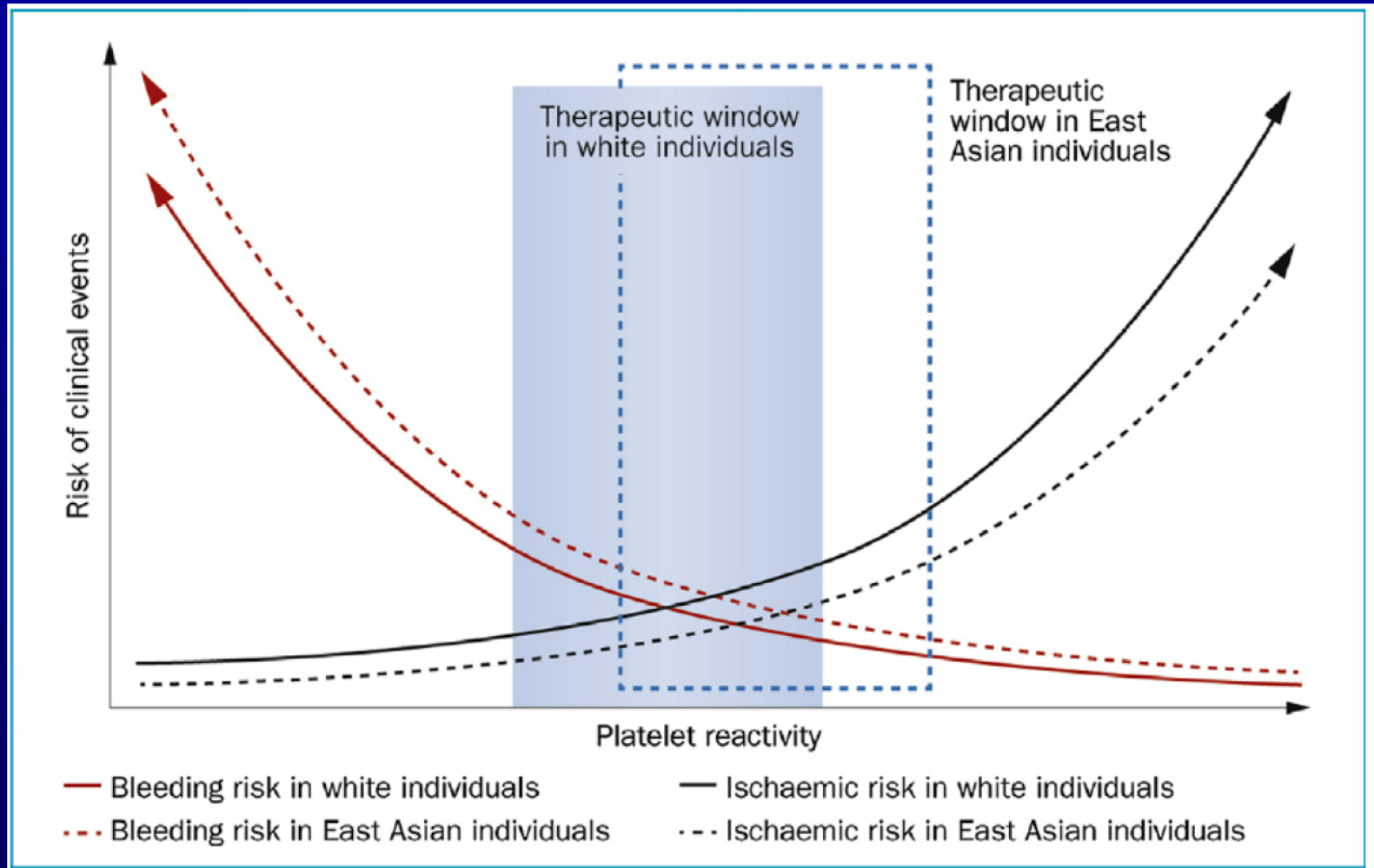
RESOLUTE All Comers Very Late Stent Thrombosis (Definite/Probable) 1-3 Years



Why might there be differences in response to antiplatelet therapy between Westerners and East Asians?

1. Because the genetics of drug metabolism may be different
2. Because BMI and volume of distribution may be different
3. Because the relative tradeoff “sweet spot” between ischemia & bleeding may be different

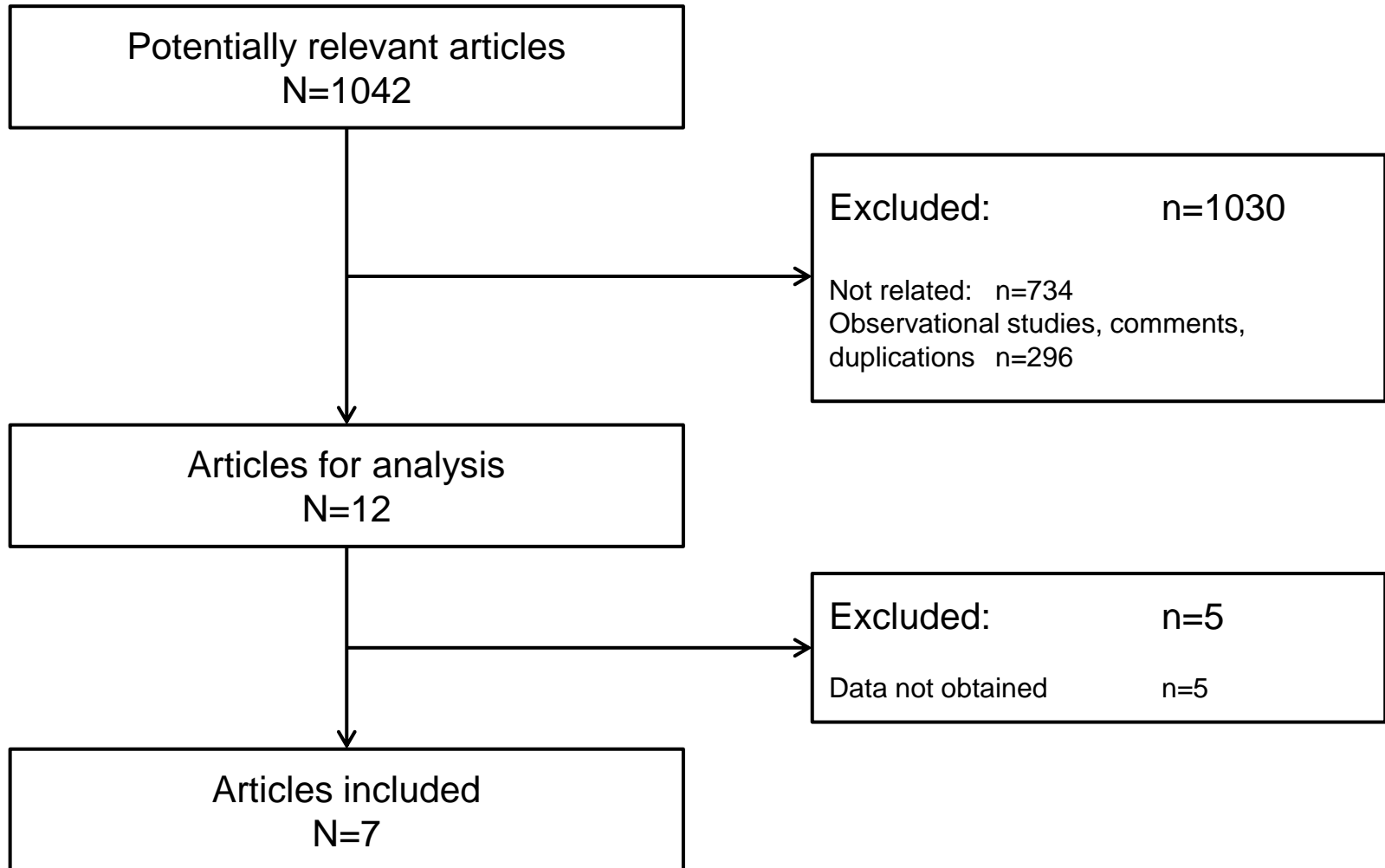
Postulated differences in the optimal 'therapeutic window' of platelet reactivity between white and East Asian pts



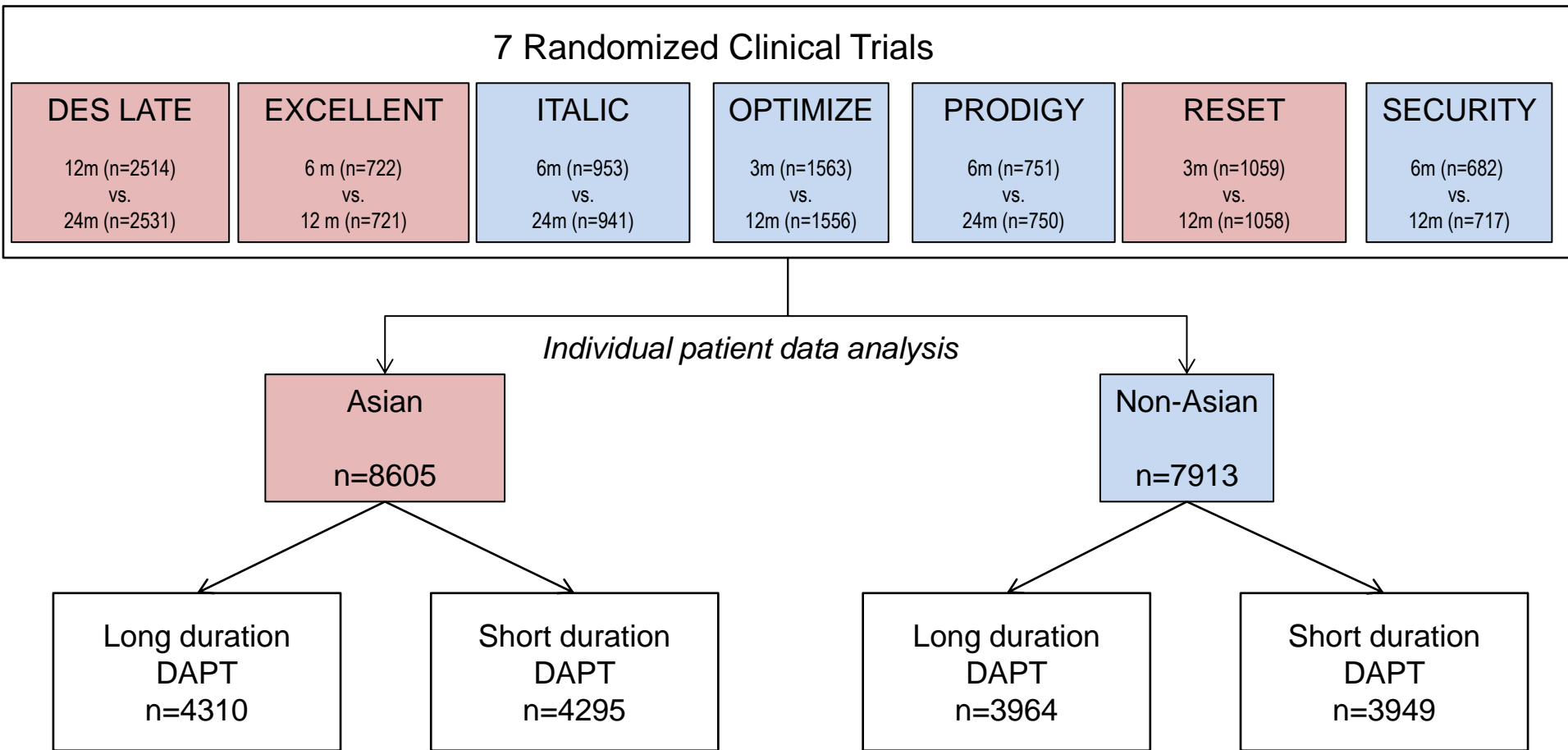
Levine GN et al. Glob Heart. 2014;9:457-67



Patient Level Meta-Analysis



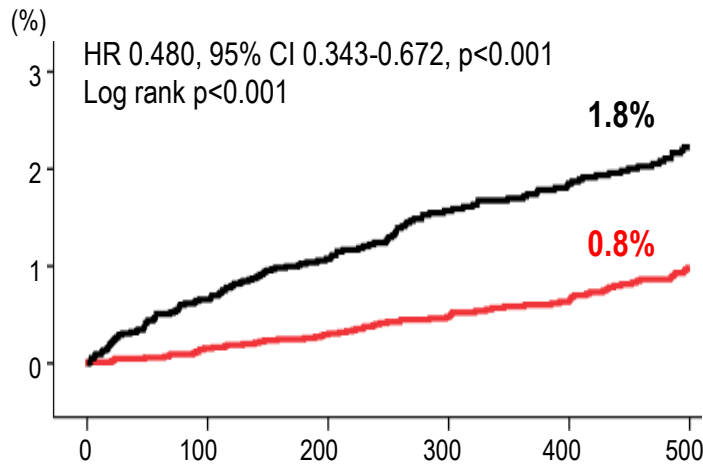
Patient Level Meta-Analysis (7 RCTs)



Disparity in ischemia and bleeding risk (according to ethnicity)

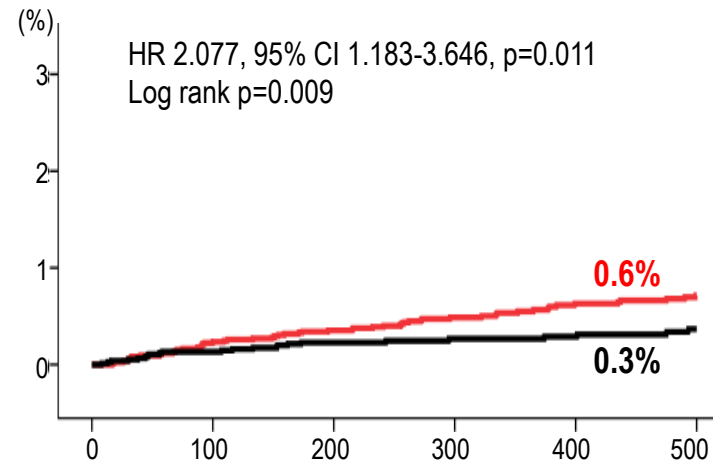
Asian
Non-Asians

A. Ischemic outcomes



No at risk					
Asian	8504	8453	8400	6615	6090
Non-Asian	7564	7344	5369	4671	4510

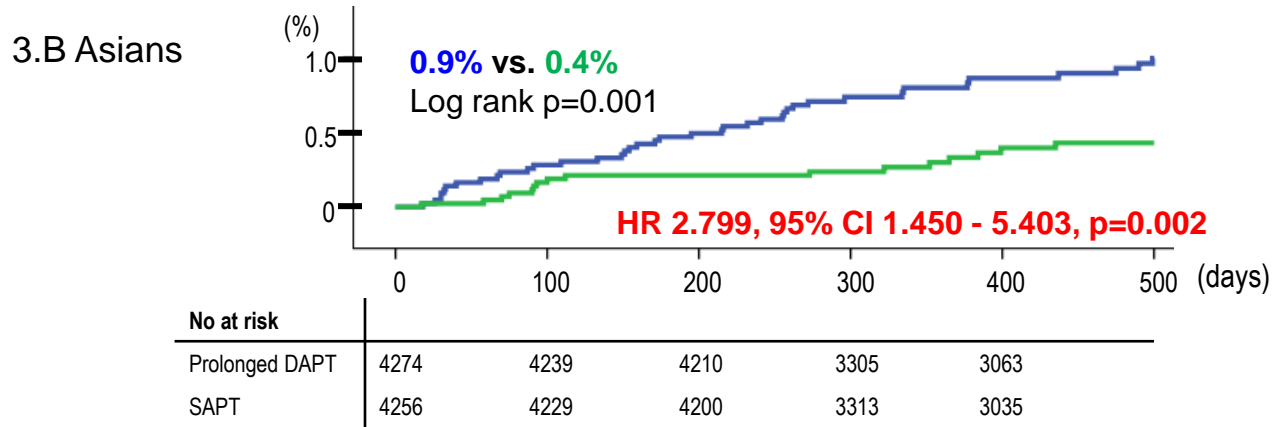
B. Bleeding outcomes



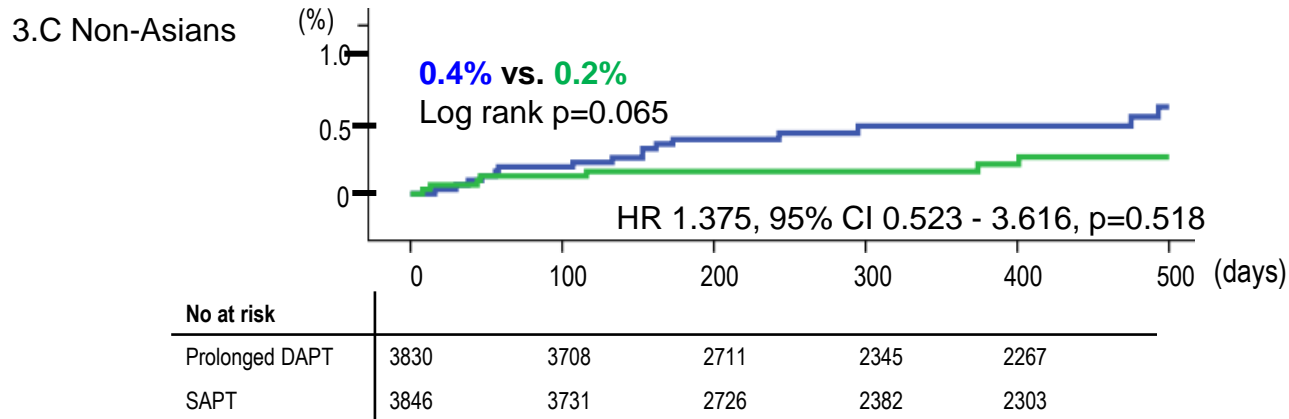
No at risk					
Asian	8530	8468	8410	6618	6098
Non-Asian	7676	7439	5437	4727	4570

Bleeding Outcomes: Prolonged DAPT vs. SAPT

Significant increased risk of bleeding in only Asians

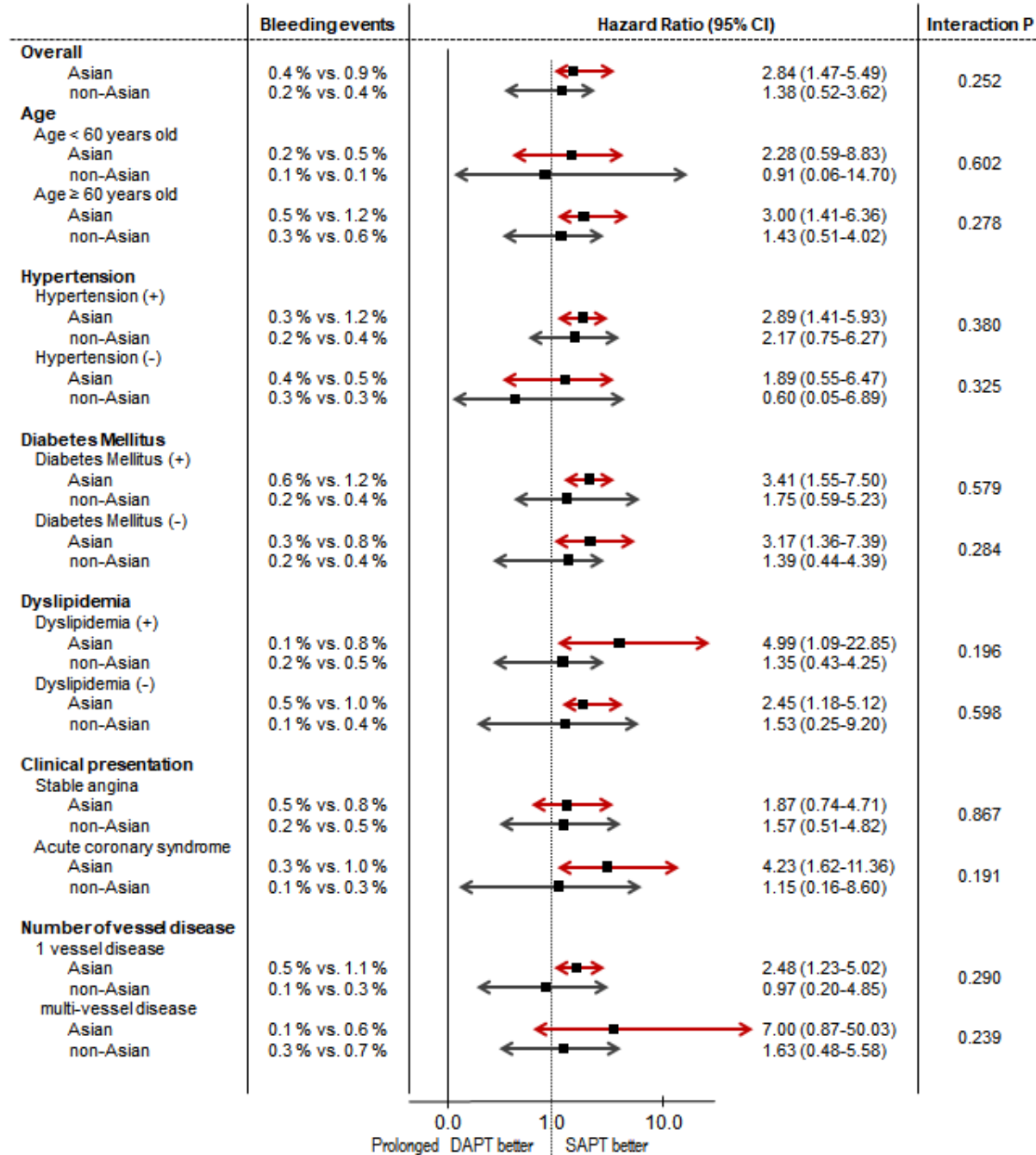


Prolonged DAPT
SAPT

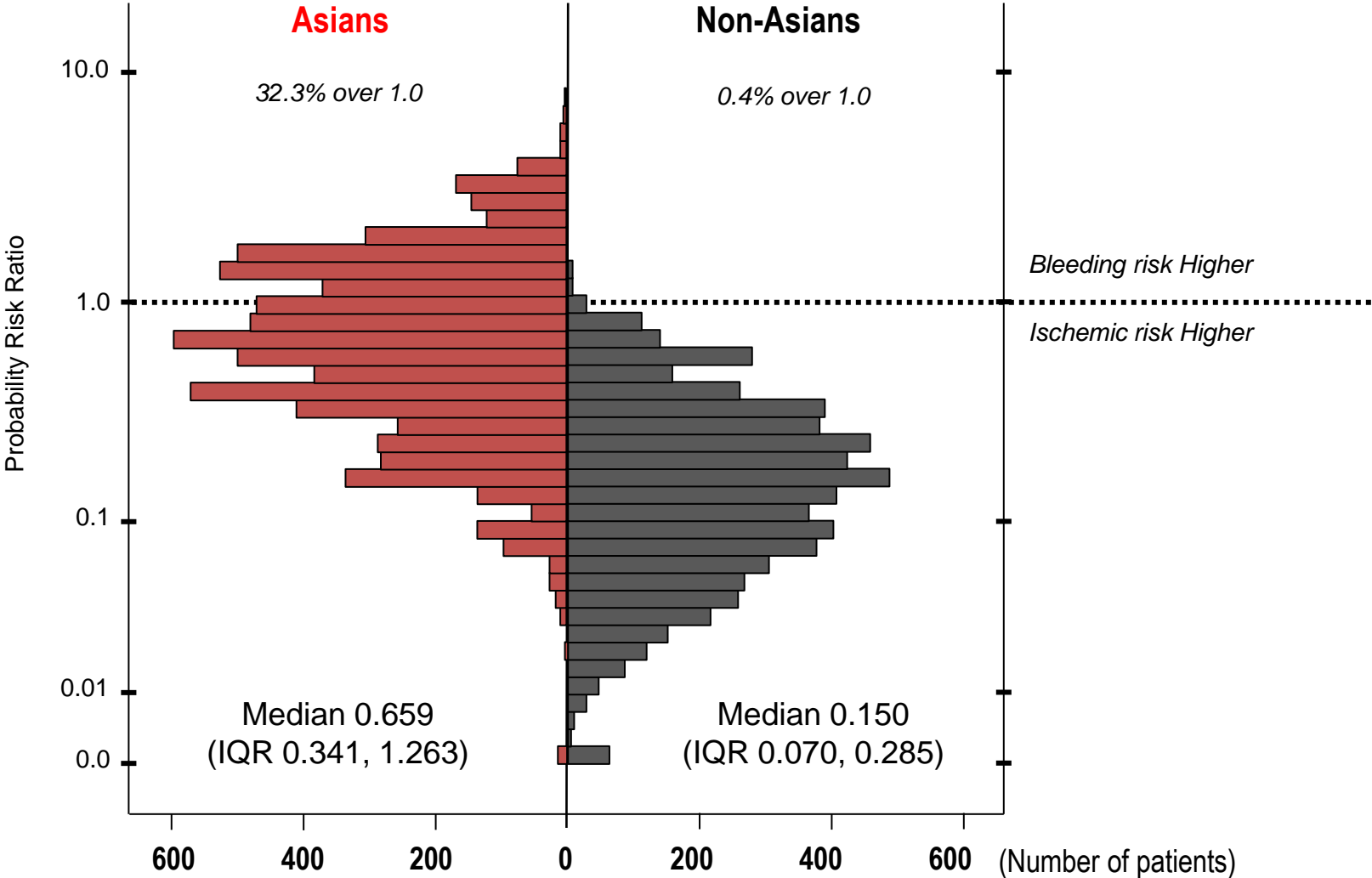


Subgroup analysis of bleeding outcomes

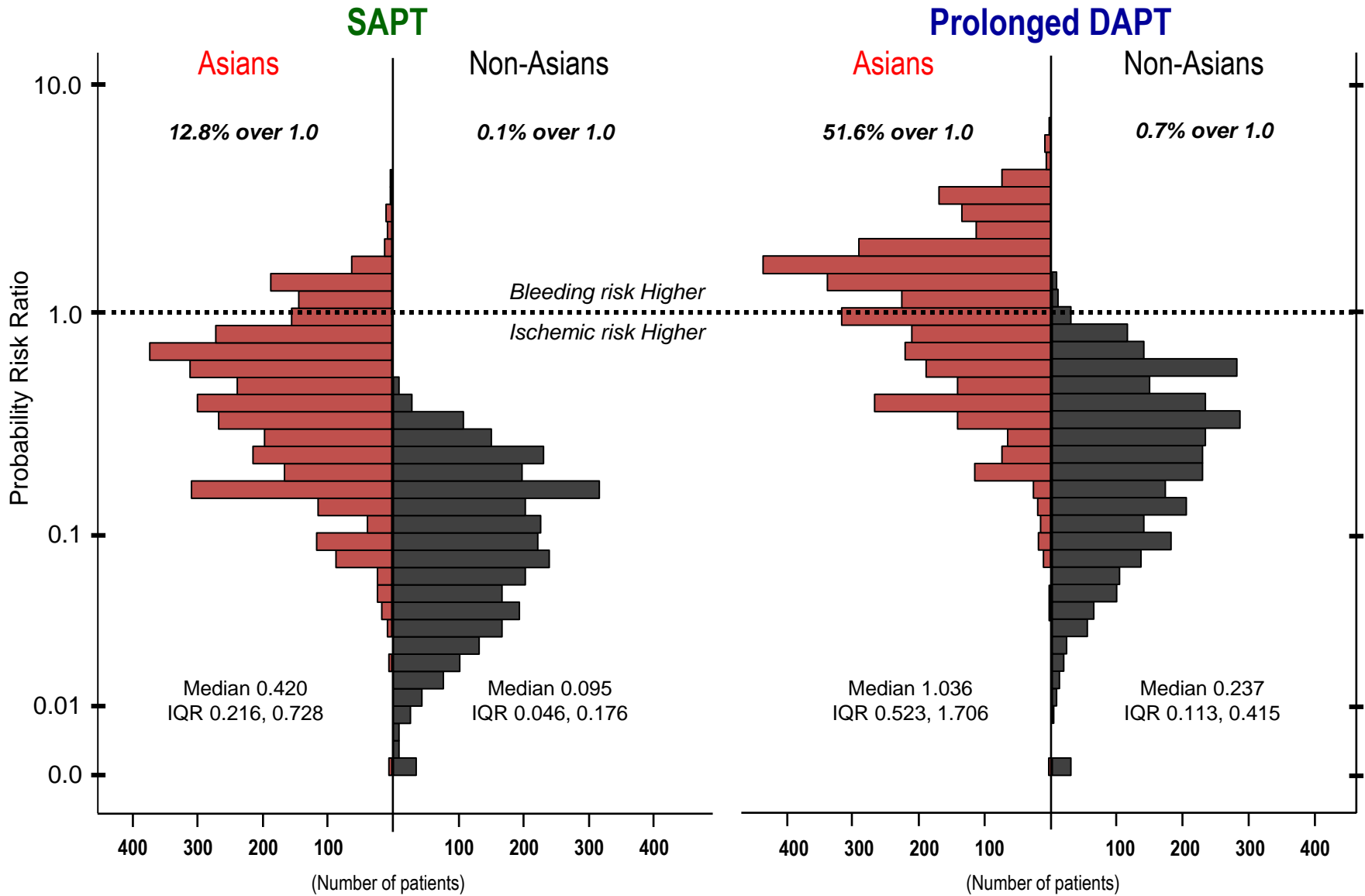
Asian
Non-Asians



Probability Risk Ratio of Bleeding to Ischemia (I): All Patients



Probability Risk Ratio of Bleeding to Ischemia (II): DAPT duration



Estimated hypothetical cumulative event incidence : by DAPT duration and ethnicity

	Total population		Asians		Non-Asians	
	Ischemic events	Bleeding events	Ischemic events	Bleeding events	Ischemic events	Bleeding events
Prolonged DAPT	1.01% (0.67%, 1.70%)	0.65% (0.19%, 1.54%)	0.79% (0.58%, 1.08%)	1.21% (0.58%, 2.33%)	1.56% (0.96%, 3.06%)	0.19% (0.01%, 0.60%)
SAPT	1.06% (0.71%, 1.78%)	0.30% (0.10%, 0.65%)	0.85% (0.62%, 1.16%)	0.43% (0.21%, 0.84%)	1.60% (0.98%, 3.13%)	0.14% (0.01%, 0.43%)
Predicted net event rate*	-0.05% (-0.07%, -0.03%)	0.29% (0.06%, 0.86%)	-0.05% (-0.07%, -0.03%)	0.77% (0.37%, 1.49%)	-0.03% (-0.07%, -0.02%)	0.05% (0.00%, 0.16%)

**So, in fact, we may need to lower the
intensity of antiplatelet agents (“de-escalate”)
in East Asians**

How can we “de-escalate” with Prasugrel

1. Universal de-escalation → “shut-up & de-escalate” (닥줄)

change drug or change dose

2. Selective de-escalation → “test & de-escalate” (검줄)

what test? PFT based vs. Genetic based

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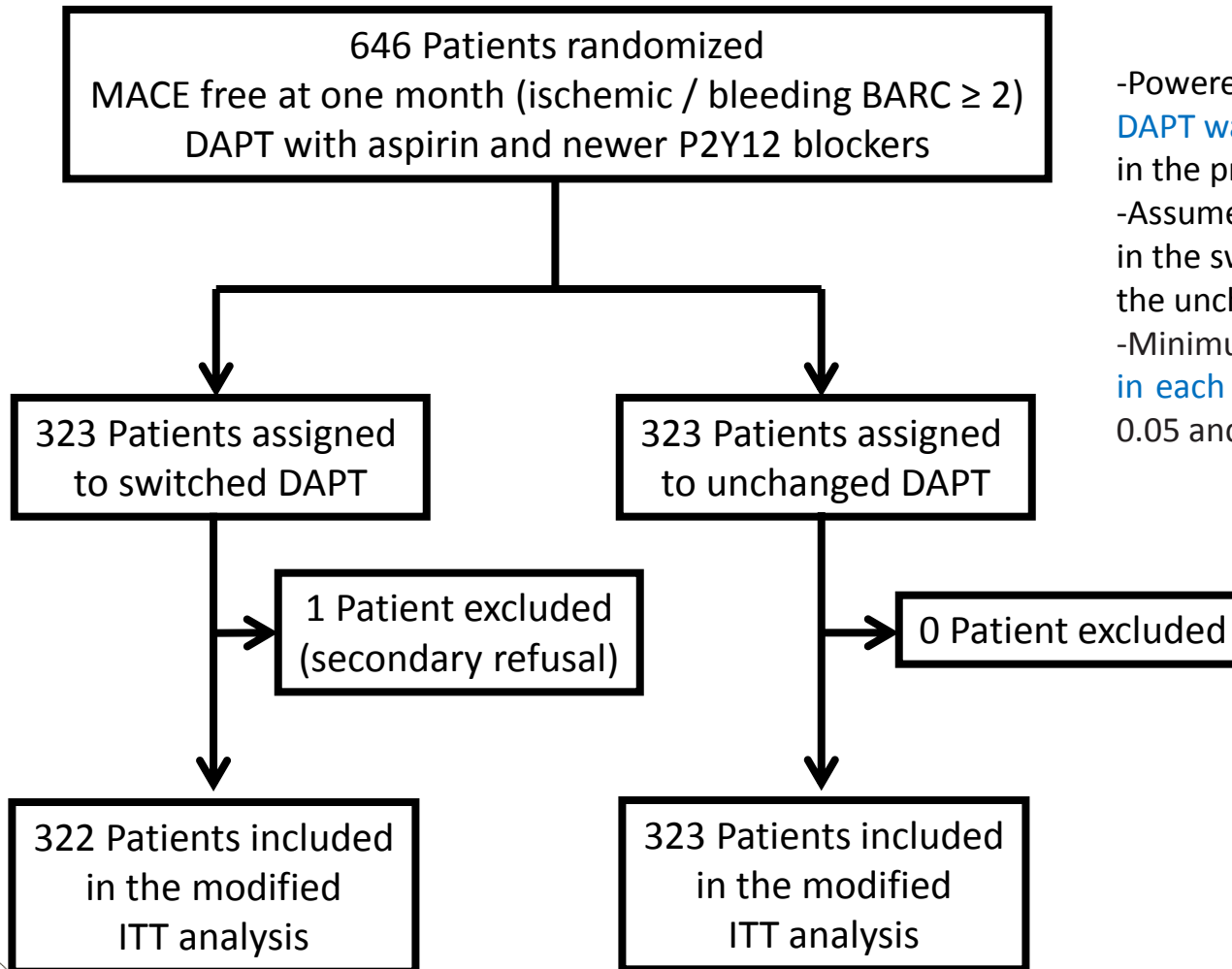
change drug or change dose

2. Selective de-escalation → “test & de-escalate” (검줄)

what test? PFT based vs. Genetic based



Flow chart



-Powered to assess whether **switched DAPT was better than unchanged DAPT** in the prevention of the PEP.

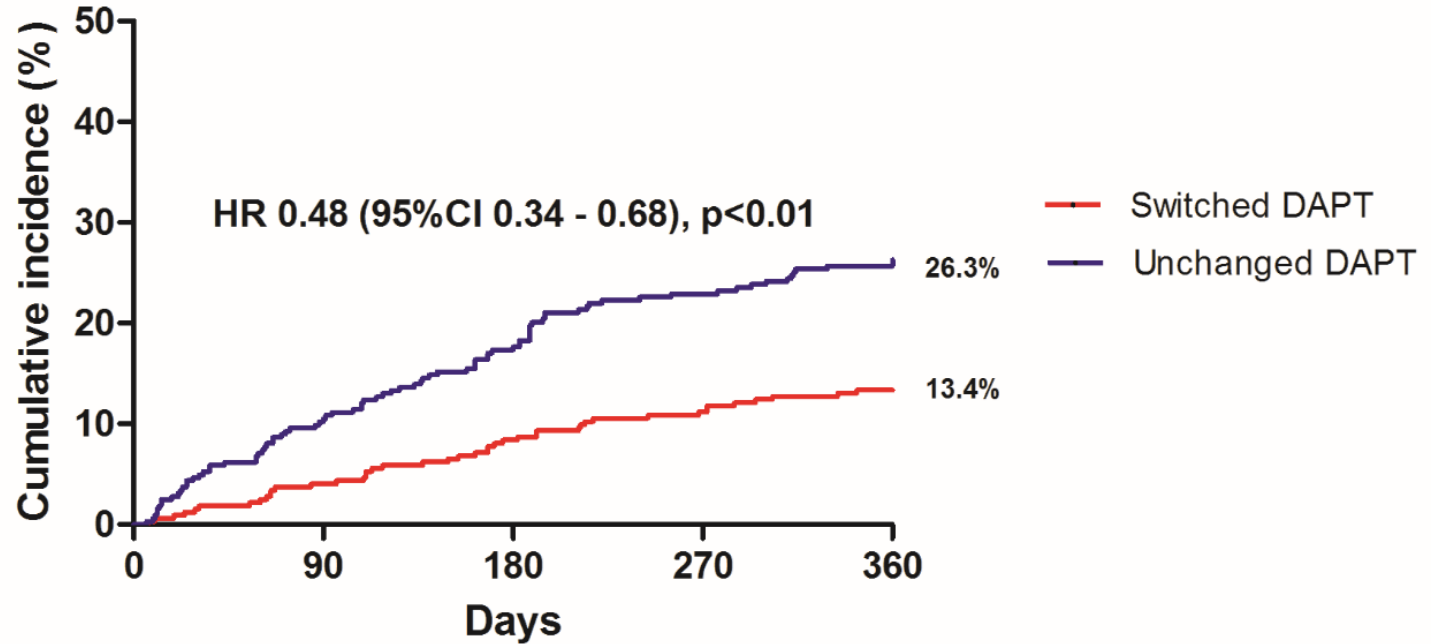
-Assumed 10% occurrence rate of PEP in the switched DAPT group and 18% in the unchanged DAPT group at 1yr.

-Minimum sample size of **319 patients in each group** to achieve an α level of 0.05 and statistical power of 0.80



Primary Endpoint

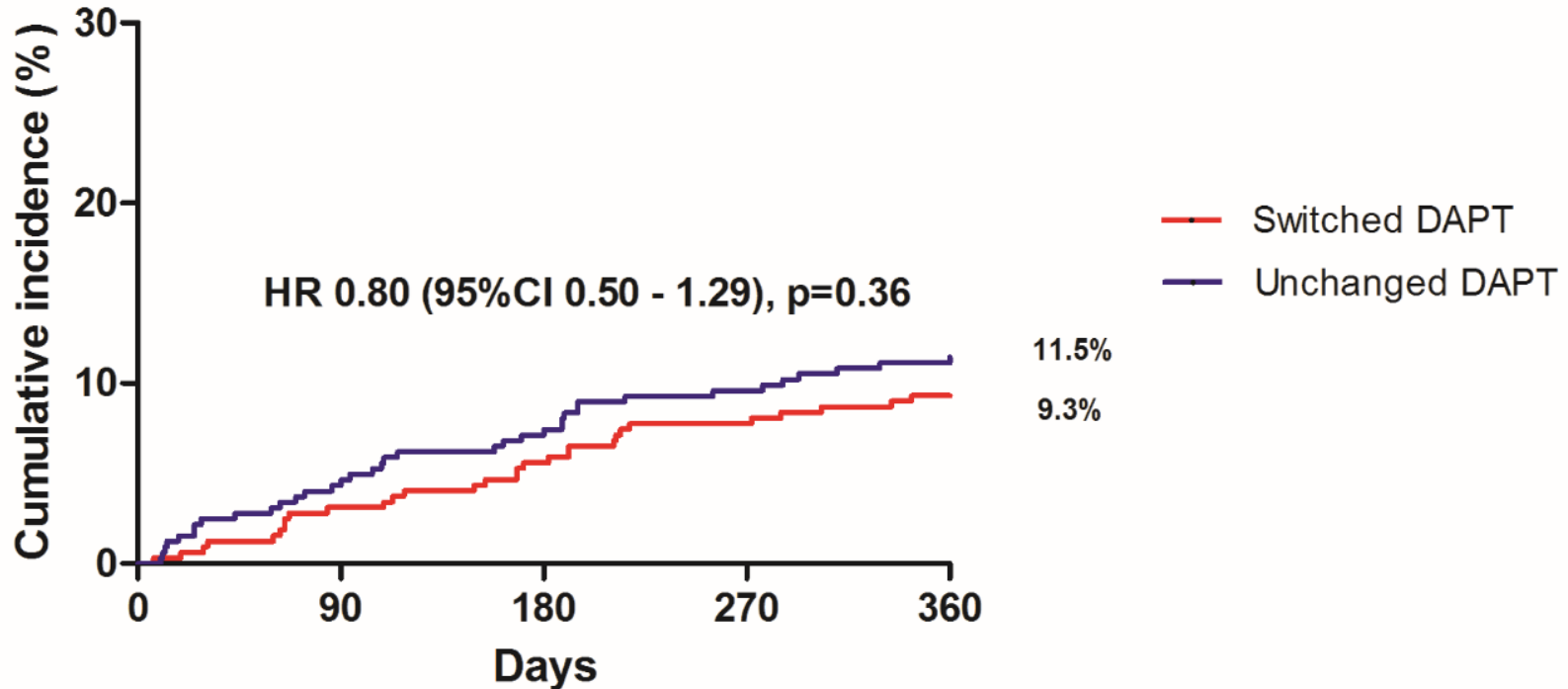
Death, Urgent revasc., Stroke, BARC ≥ 2



Better Prognosis with switched DAPT

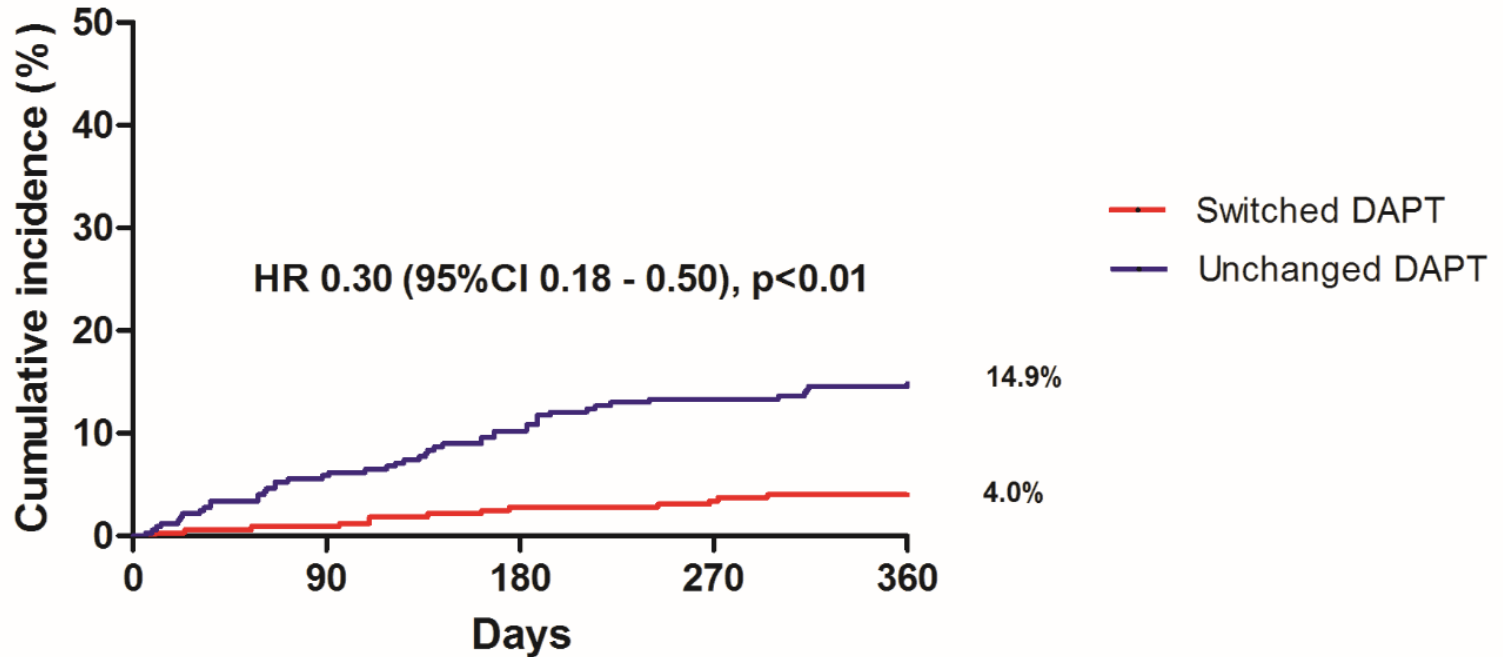


Any ischemic endpoint



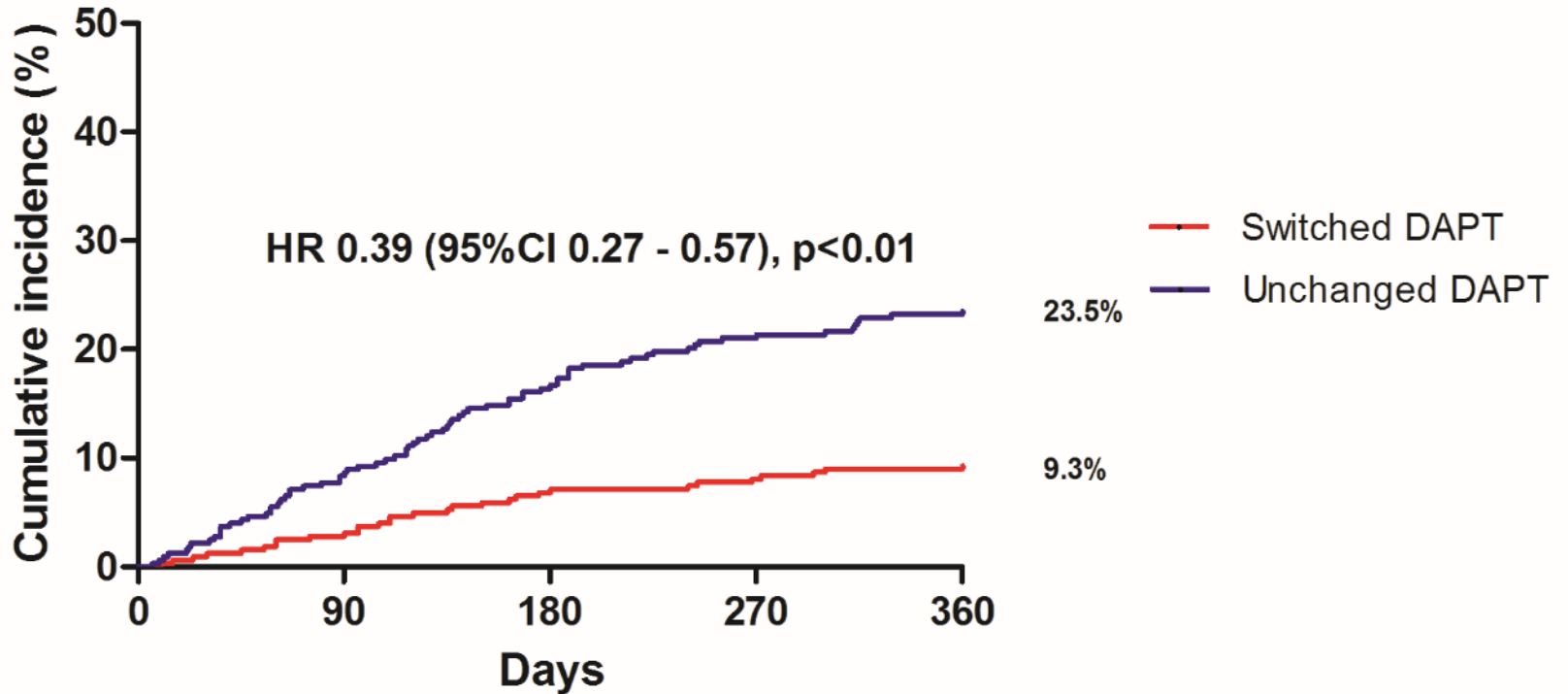
No difference for ischemic events

BARC bleedings ≥ 2



Higher Rate of BARC bleeding ≥ 2 with Unchanged DAPT

All BARC Bleedings



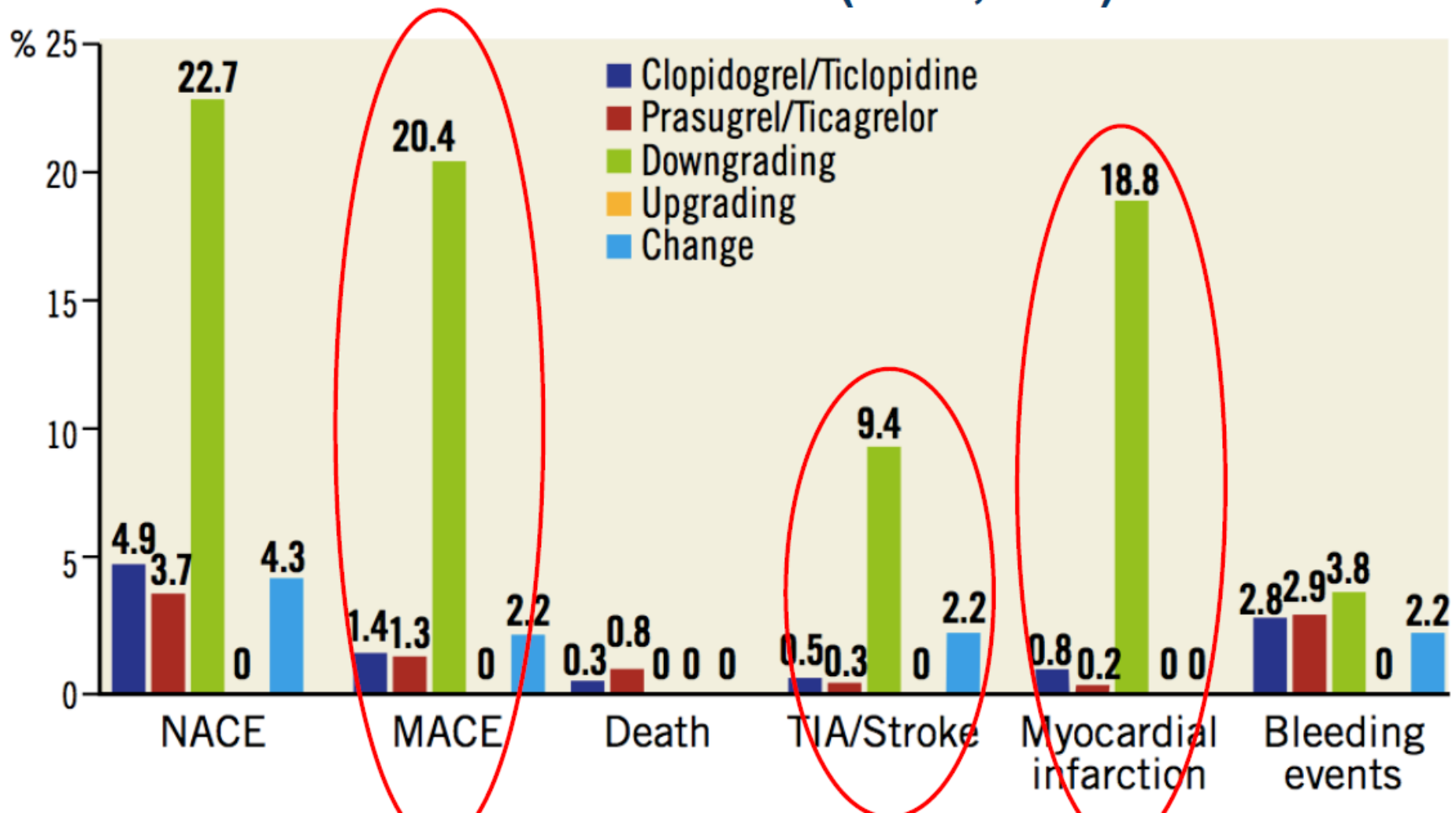
Higher Rate of all BARC bleeding with Unchanged DAPT



In patients without adverse event 1 month after stented ACS, a **switched DAPT** is superior to an **unchanged DAPT** strategy. (Results driven mostly by preventing bleeding events without any significant increased risk of ischemic events)

CONTRA

SCOPE REGISTRY (n= 1, 363)



De Luca et al. Eurointervention 2017

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what test? PFT based vs. Genetic based

A-MATCH Trial [Korea]

ACS patients (UA, NSTEMI and STEMI) undergoing uneventful PCI

Prasugrel: 60mg LD and 10mg/d MD (Clopidogrel naïve patients)

GPIIb/IIIa inhibitor use permitted (Tirofiban/Eptifibatide bailout)

Pre-discharge VerifyNow Assessment during Prasugrel 10 mg/d MD (3-5days)

1:1:1 Randomization

10 mg/d Prasugrel
(n=85)

5 mg/d Prasugrel
(n=85)

Fixed-dose group

Phenotype group (n=85)

PRU \leq 94

No: 10mg/d
Prasugrel

Yes: 5mg/d
Prasugrel

Exclusion (n=0)

Exclusion (n=2)

Exclusion (n=3)

VerifyNow Assessment at 1 month

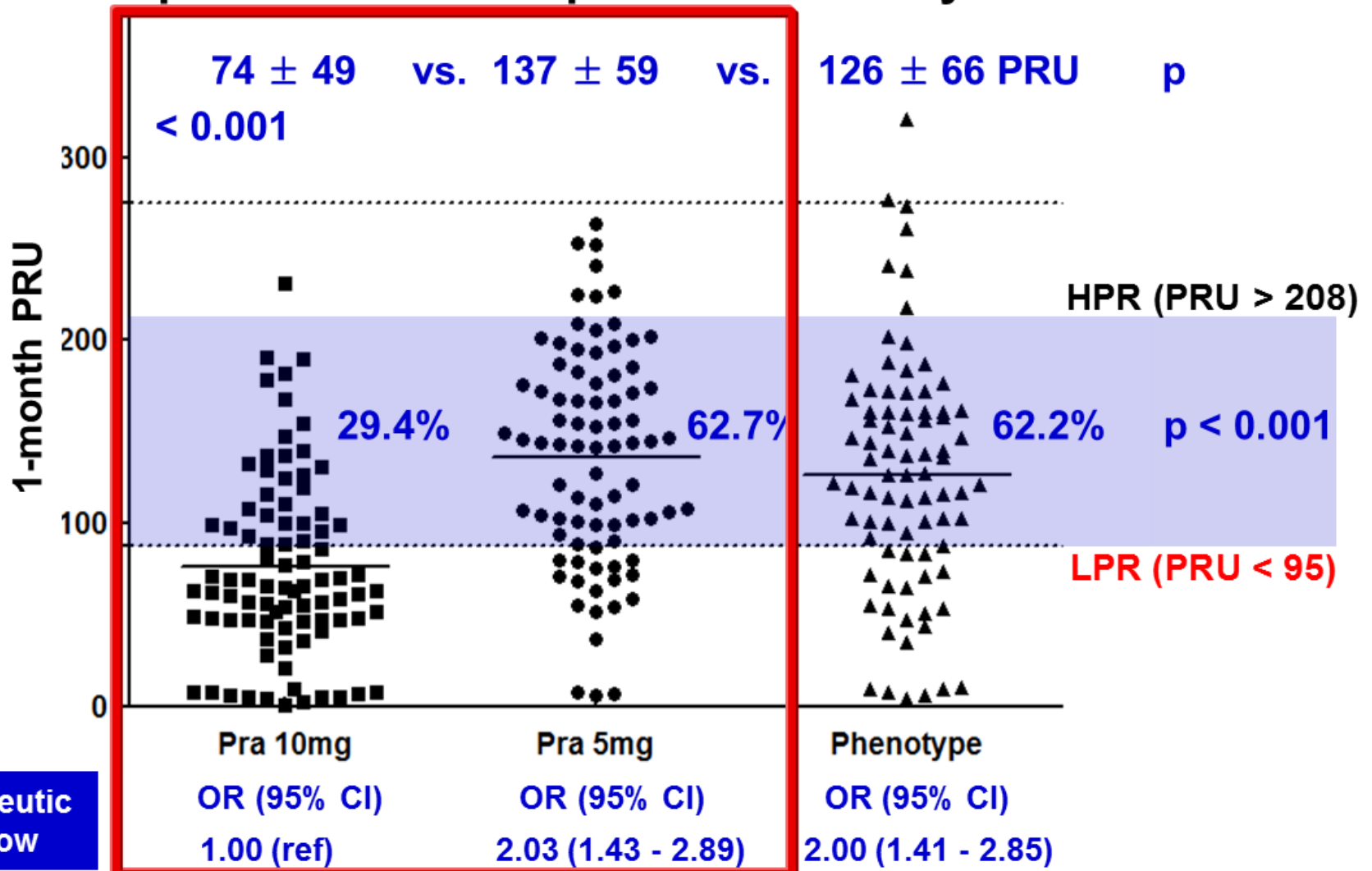
Clinical Follow-up & BARC bleeding questionnaire at 1 month

Primary EP: Percentage to meet the therapeutic zone ($95 \leq \text{PRU} \leq 208$) at 1 month

Primary End Point

Jeong YH, et al. ESC 2015

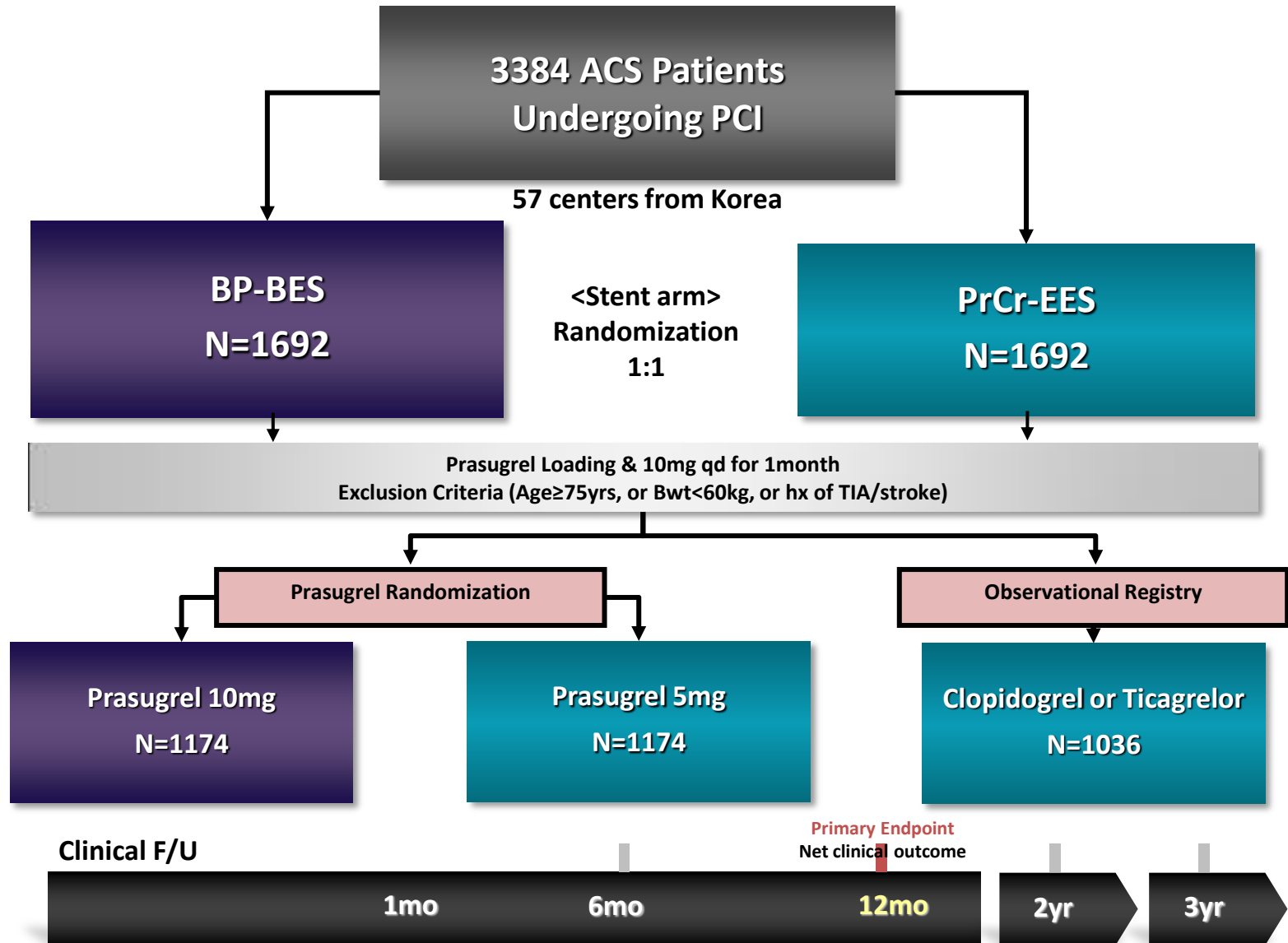
Therapeutic window of platelet reactivity in Westerners



Therapeutic window

HOST III-REDUCE POLYTECH ACS Trial

PI: HS Kim (Seoul National University Hospital) Prospective, open label, randomized multi-center trial



Prasugrel arm comparison

Assumption: 8% vs. 7%
Noninferiority design
Noninferiority margin: 2.5%
Sampling ratio: 1:1
Alpha: 1-sided 2.5%
Power 75%
2348 pts needed

3,429 ACS Patients
Undergoing PCI
Prasugrel(2,348) + Observation(1,081)

Prasugrel 10mg daily for 1month

Maintain Prasugrel 10mg
N=1,174

<Prasugrel arm>
Randomization
1:1

Maintain Prasugrel 5mg
N=1,174



Composite of
Any death, MI, ST,
repeat revascularization,
stroke, bleeding (BARC≥2)

How can we “de-escalate” with Prasugrel

1. Universal de-escalation → “shut-up & de-escalate” (닥줄)

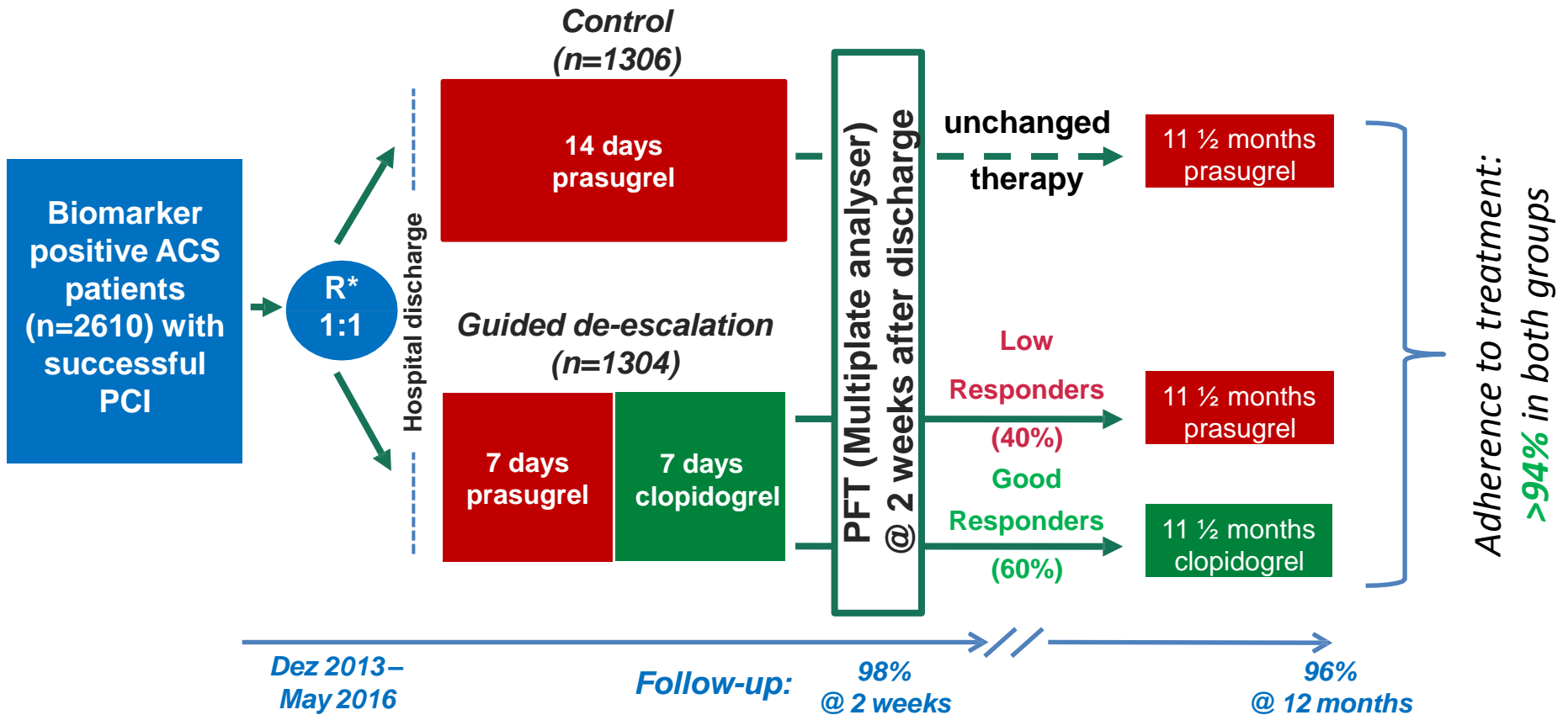
change drug or change dose

2. Selective de-escalation → “test & de-escalate” (검줄)

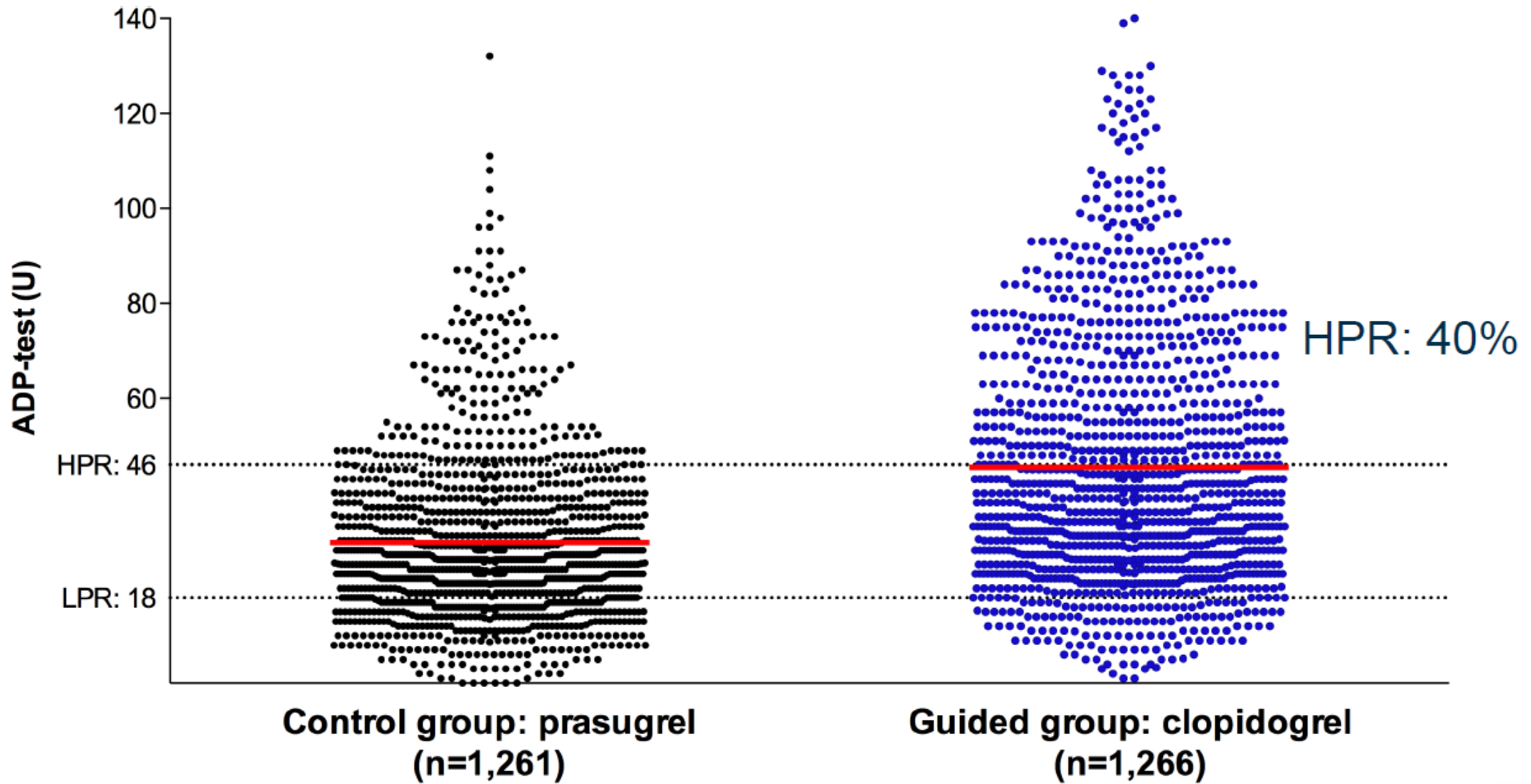
what test? PFT based vs. Genetic based

TROPICAL-ACS Trial

Study patients & follow-up data

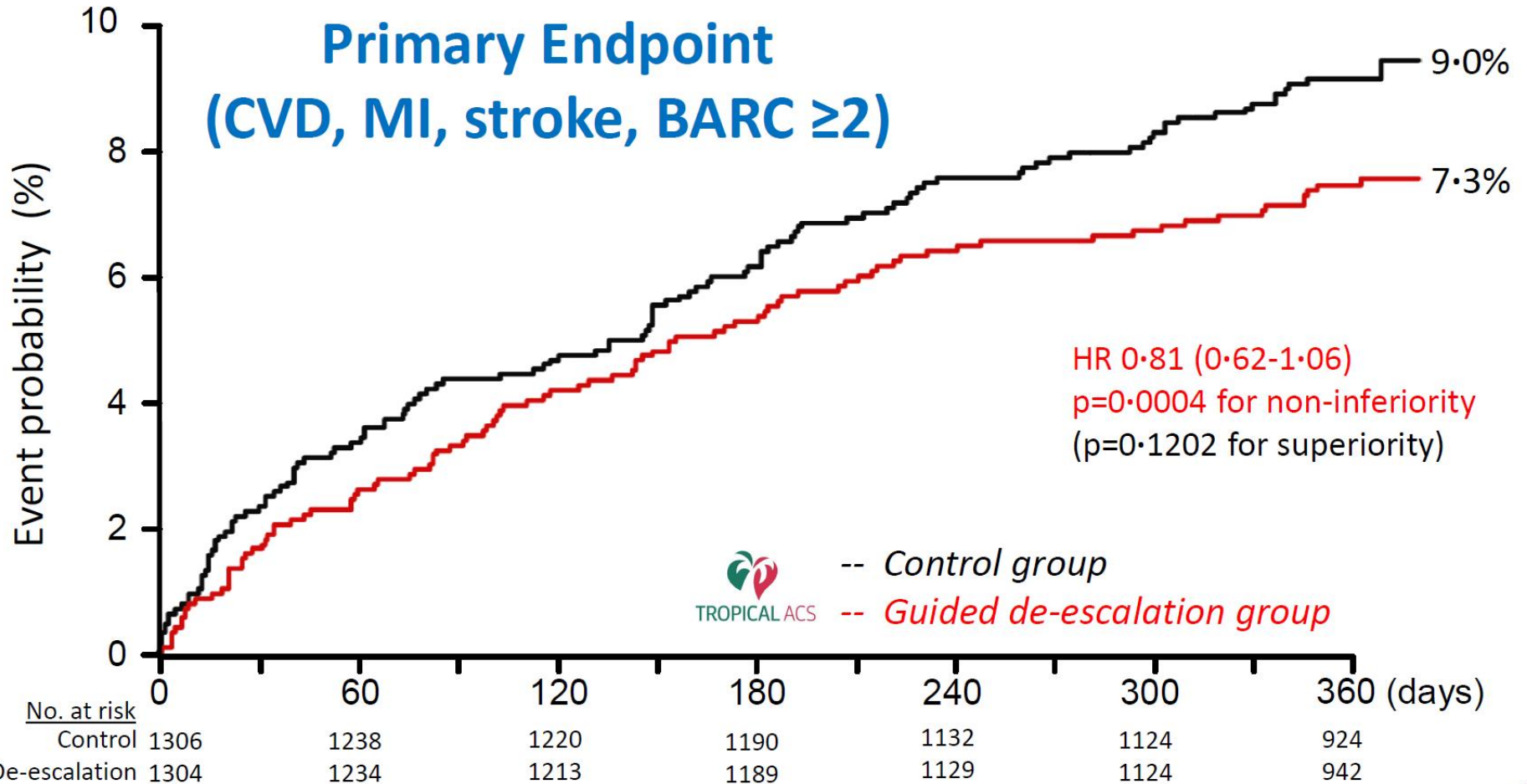


TROPICAL ACS PFT RESULTS



TROPICAL-ACS Results

**Primary Endpoint
(CVD, MI, stroke, BARC ≥ 2)**

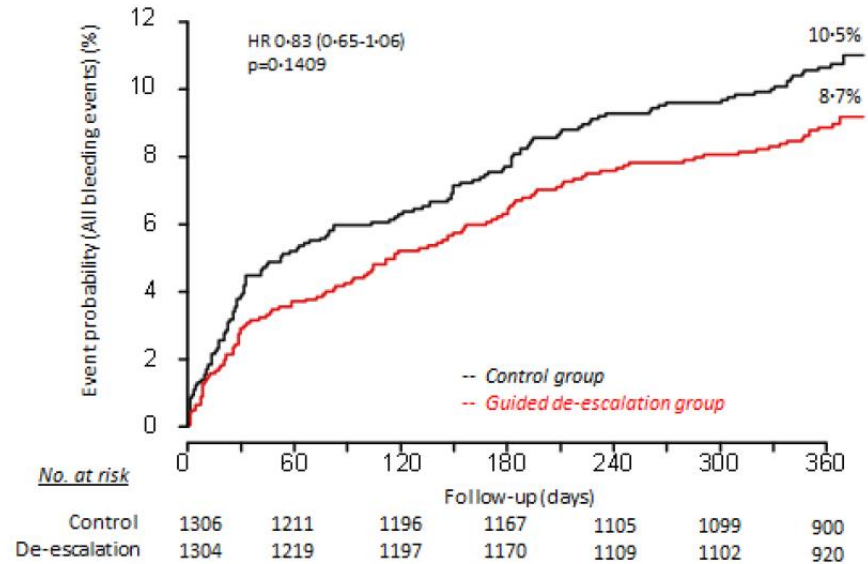
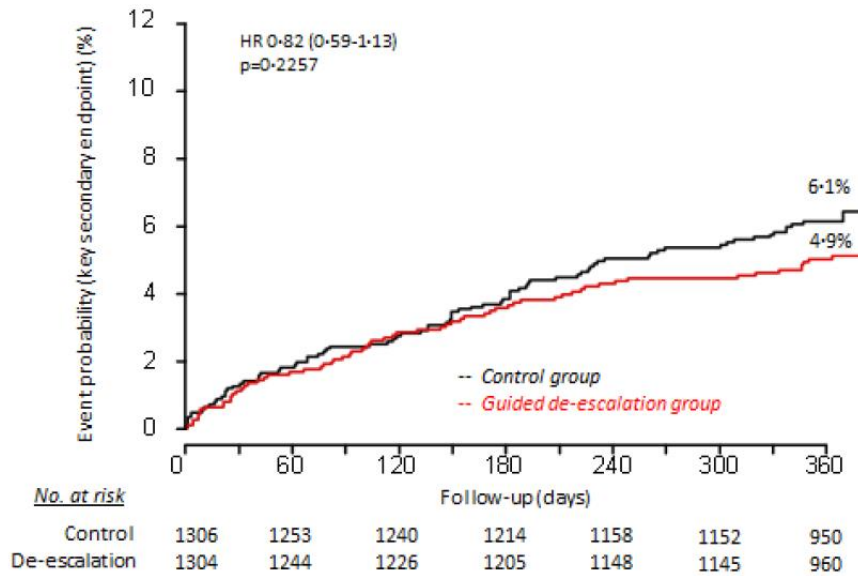


TROPICAL-ACS Results



Key Secondary endpoint Bleeding BARC ≥ 2

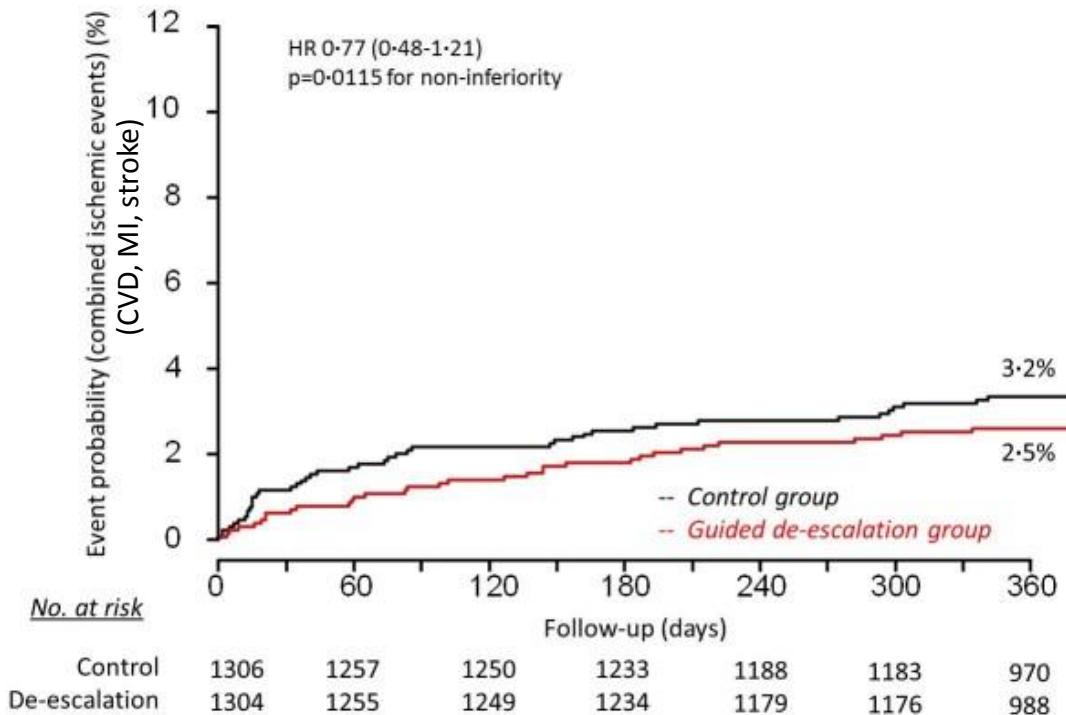
All bleeding events (BARC 1 to 5)



TROPICAL-ACS Results



Ischemic events at 12 months follow-up

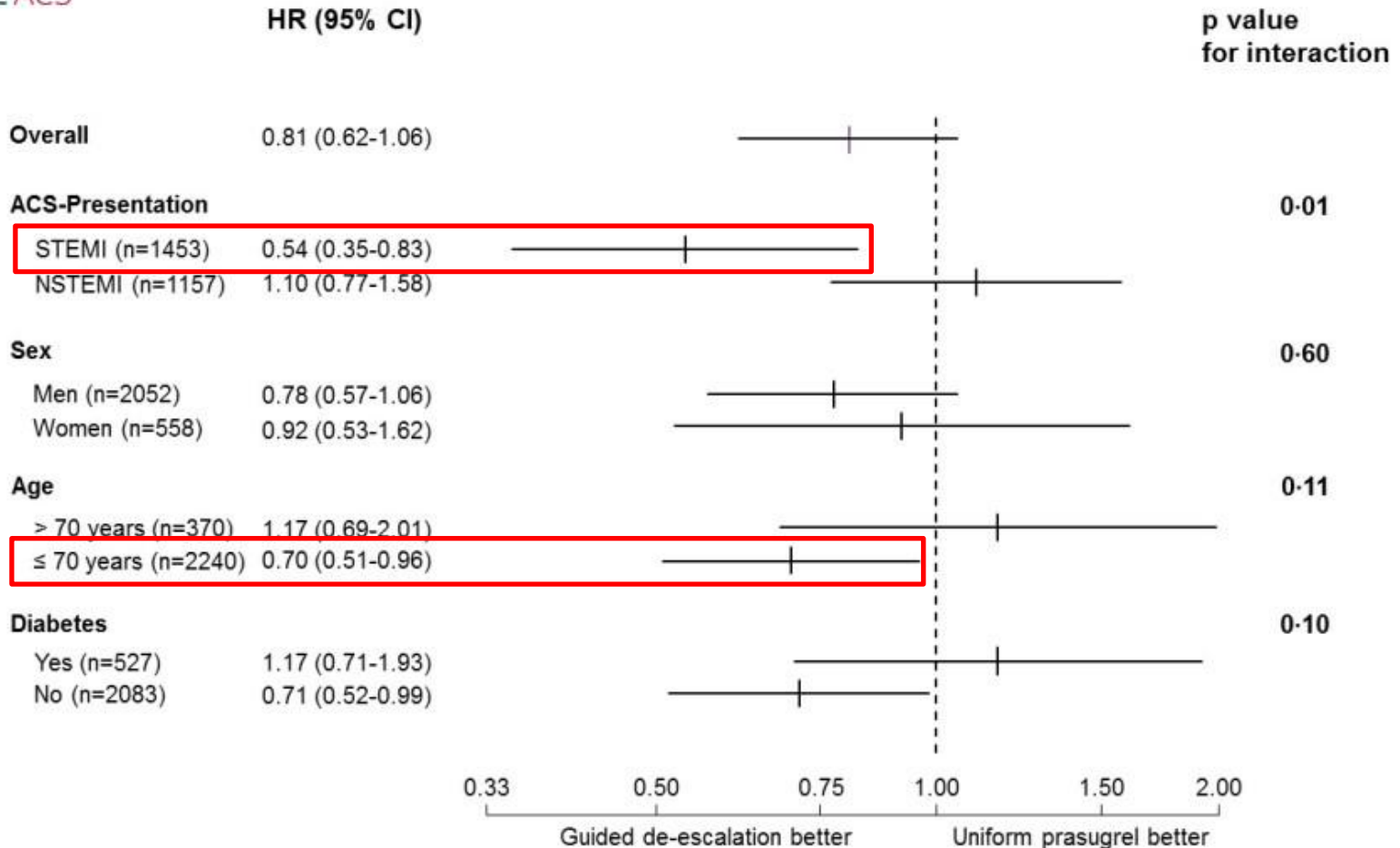


- All-cause mortality: 12 events (1%) in control vs. 11 (1%) in guided de-escalation group, p=0.85
- Definite ST: 3 events (0.2%) in control vs. 2 (0.2%) in guided de-escalation group, p=0.66

TROPICAL-ACS Results



Subgroup Analyses (primary endpoint)



How can we “de-escalate” with Prasugrel

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change drug or change dose

2. Selective de-escalation → “test & de-escalate” (검줄)

what test? PFT based vs. Genetic based

Genetic testing based de-escalation

- 1. TAILOR PCI Trial: 5270 pts randomized to conventional arm vs. CYP2C19 genotype based arm (prospective vs. retrospective genotyping): escalation rather than a de-escalation therapy**
- 2. POPular GENetics Trial: 2700 pts (ACS) randomized to conventional newer antiplatelets vs. genetic testing within 48hrs: de-escalation to clopidogrel in *1/*1**

Summary

- 1. The optimal antiplatelet therapy should be a balancing act between risk of ischemia and risk of bleeding.**
- 2. East Asians may have different relative tradeoff “sweet spot” between ischemia and bleeding → higher risk of bleeding with less risk of ischemia.**
- 3. Therefore, de-escalation therapy may be a suitable therapeutic option for East Asian patients.**
- 4. Unguided universal de-escalation to clopidogrel has conflicting results. Dose reduction makes more sense and HOST-RP ACS trial will answer this question.**
- 5. Guided tx using PFT maybe feasible, but no evidence of definite clinical gain.**
- 6. Guided tx using genetic testing will be tested in the POPular GENetics Trial.**

**THANK YOU FOR
YOUR ATTENTION!**

