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

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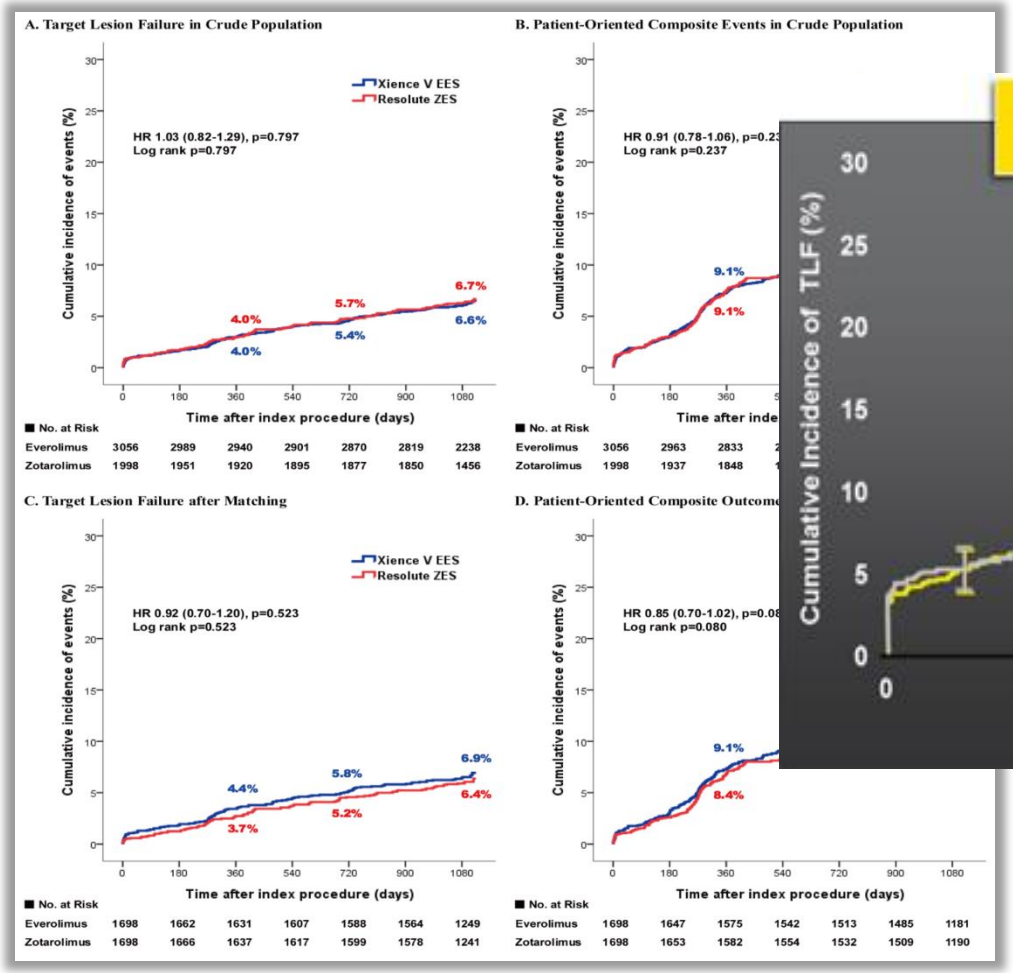
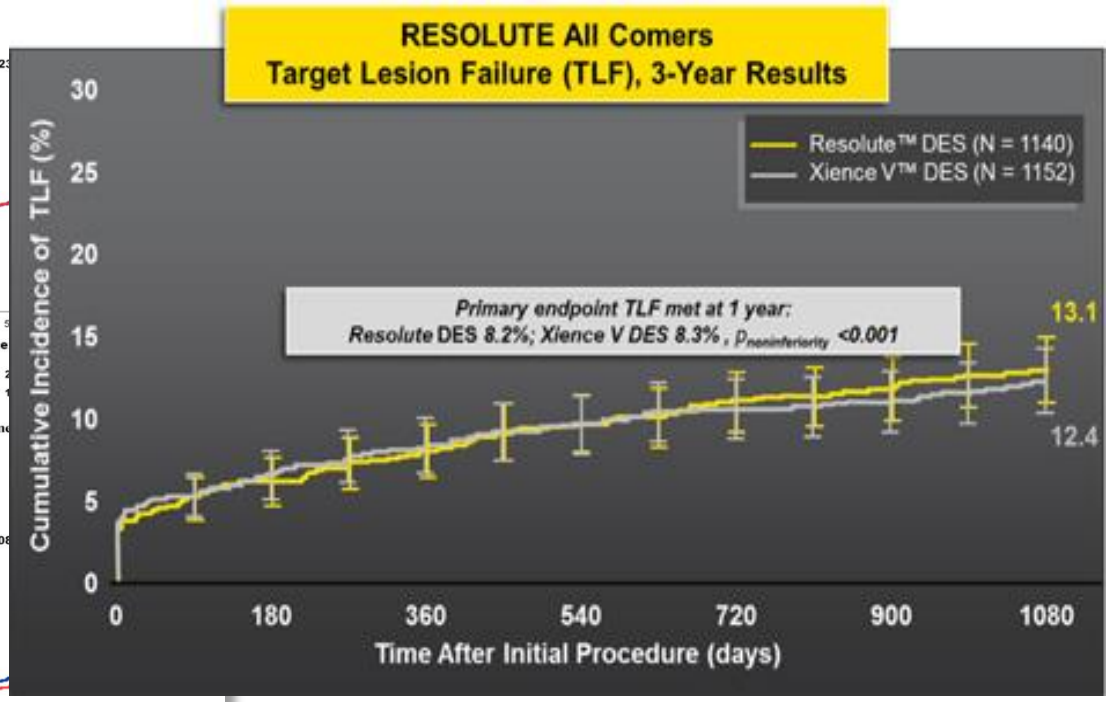
Outcome differences?

RESOLUTE vs. Xience V TLF at 3 years

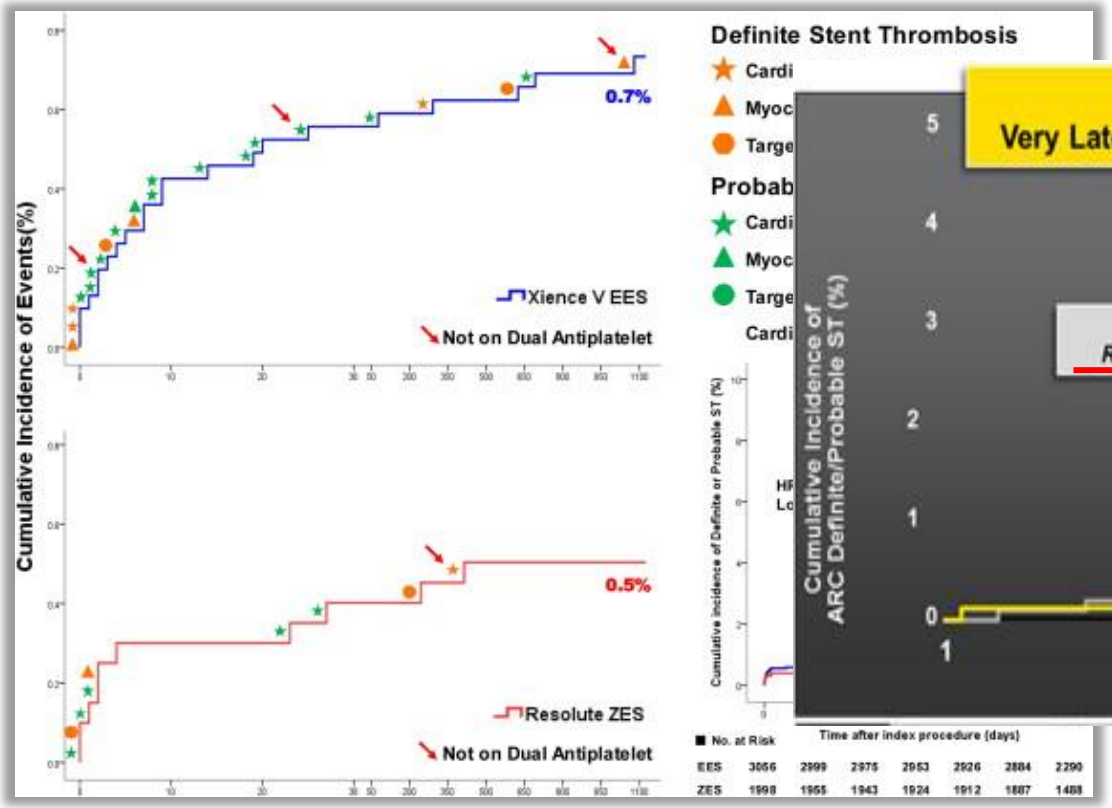


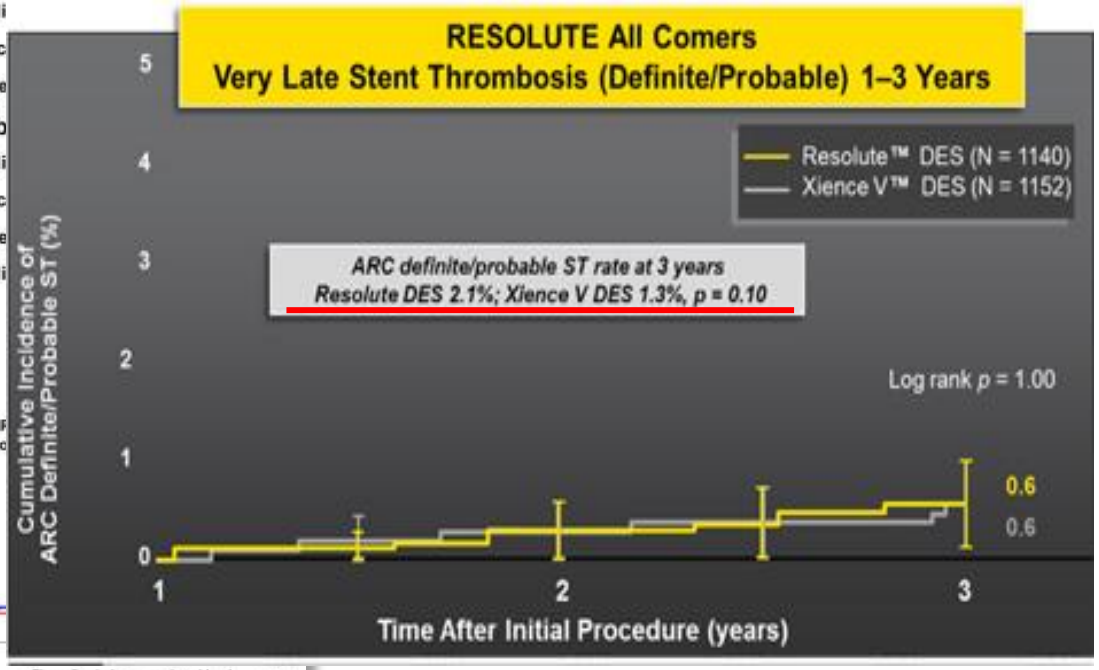


Park KW, Kim HS et al. JACC 2013
Park KW, Kim HS et al. AJC 2014

Outcome differences?

RESOLUTE vs. Xience V ST at 3 years





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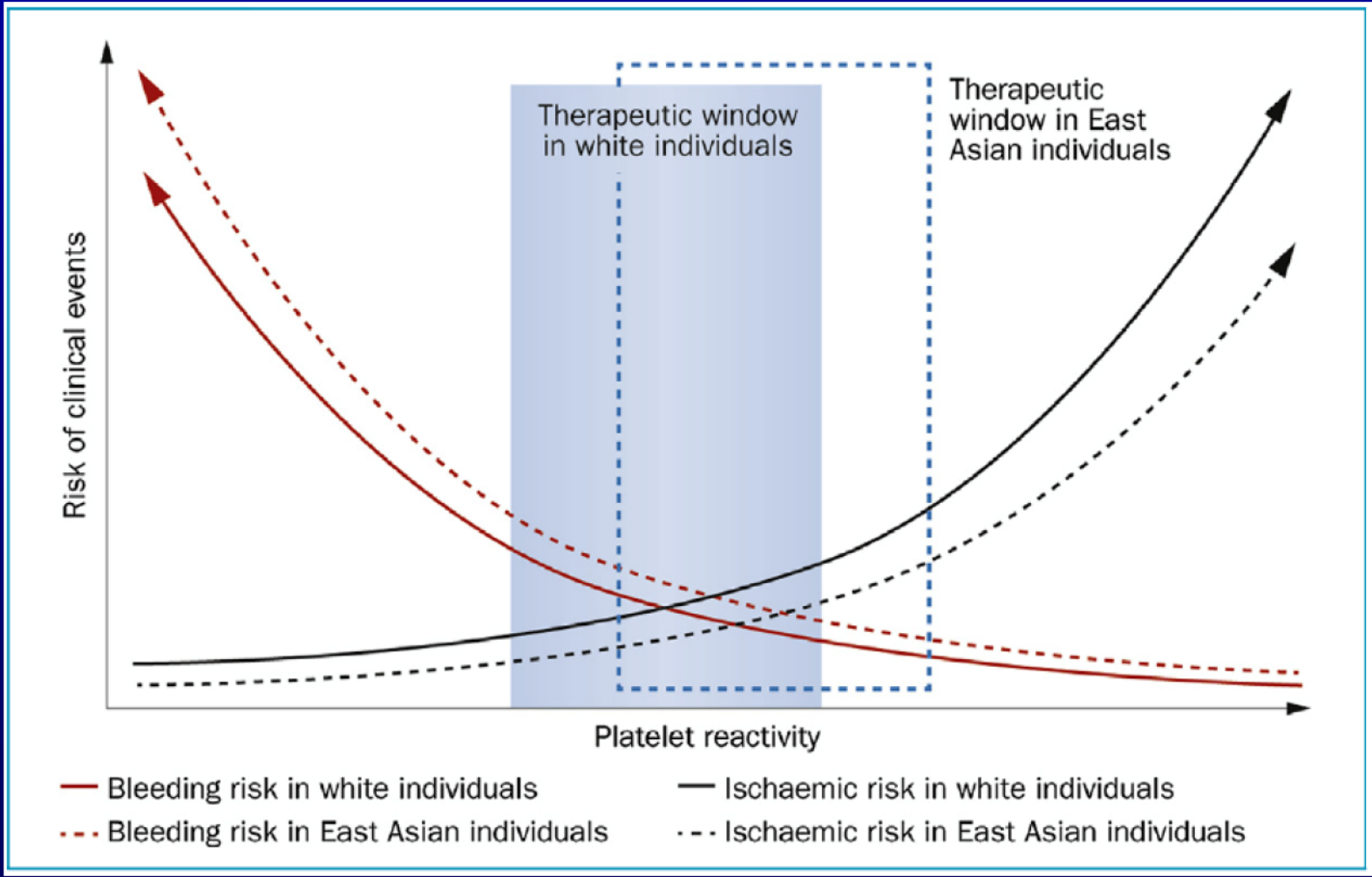
Why might there be differences in response to antiplatelet therapy between Westerners and East Asians?

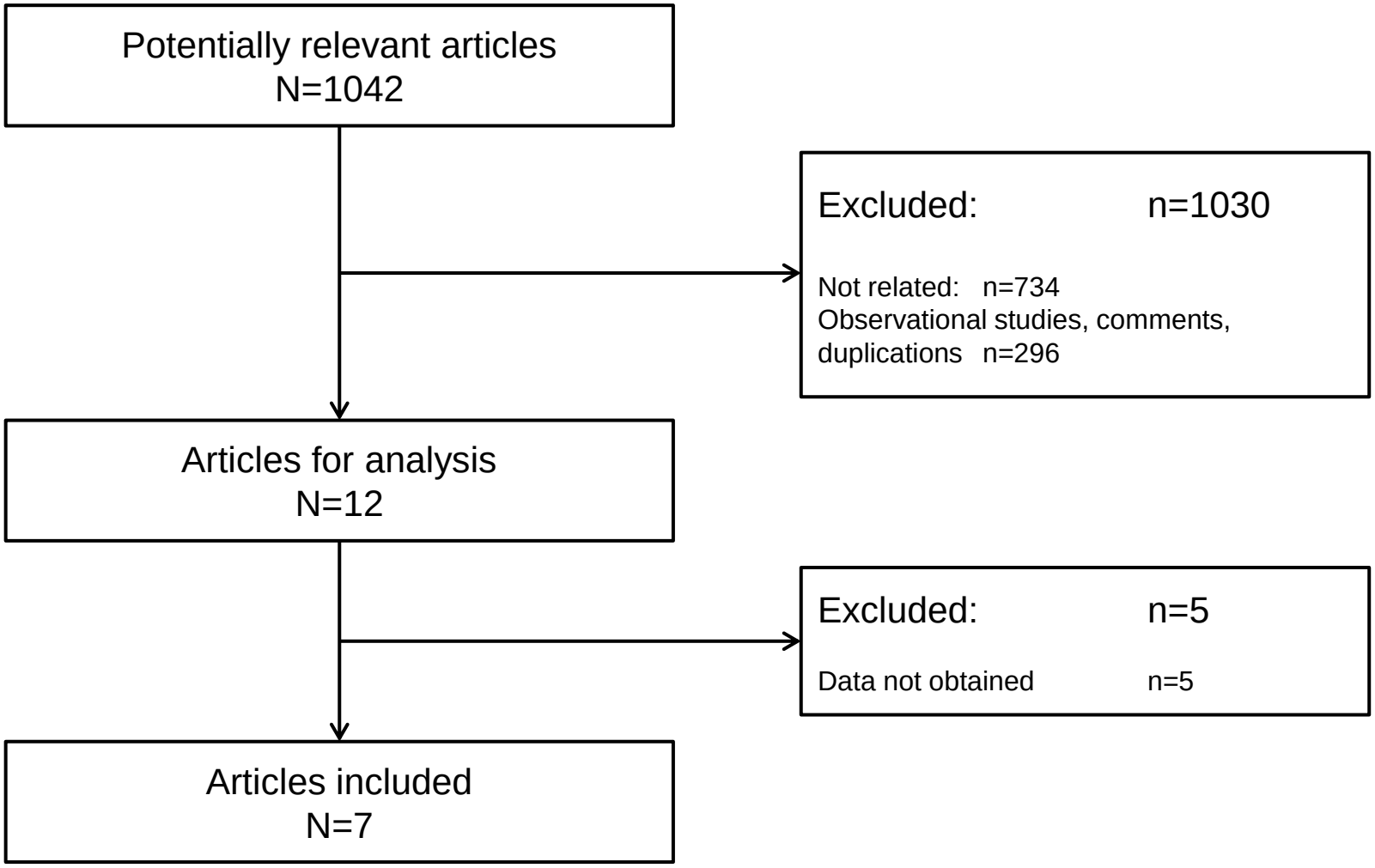
1. **Because the *genetics of drug metabolism* may be different**
2. **Because *BMI and volume of distribution* may be different**
3. **Because *the relative tradeoff "sweet spot" between ischemia & bleeding* may be different**

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



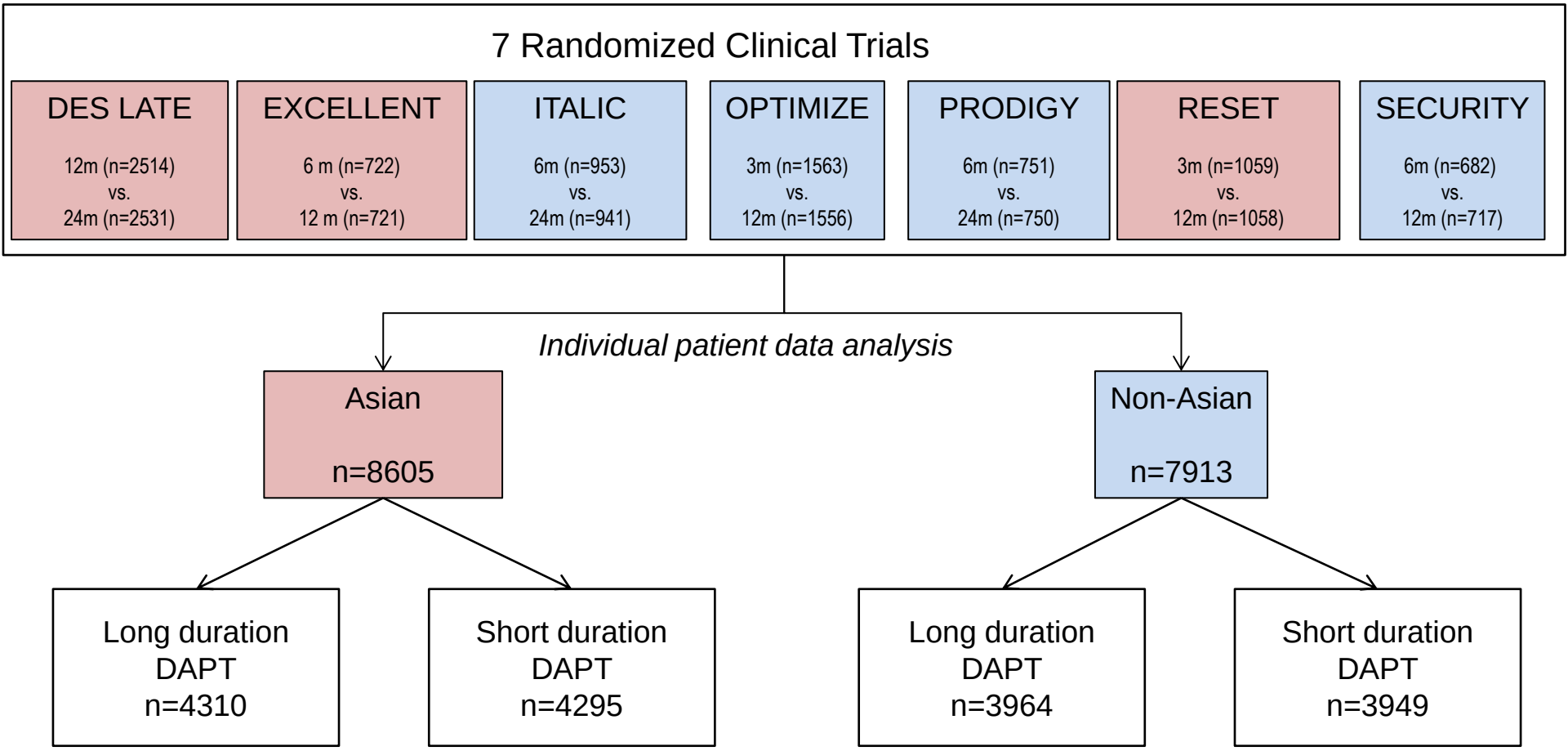
Levine GN et al. Glob Heart. 2014;9:457-67

Patient Level Meta-Analysis



Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

Patient Level Meta-Analysis (7 RCTs)

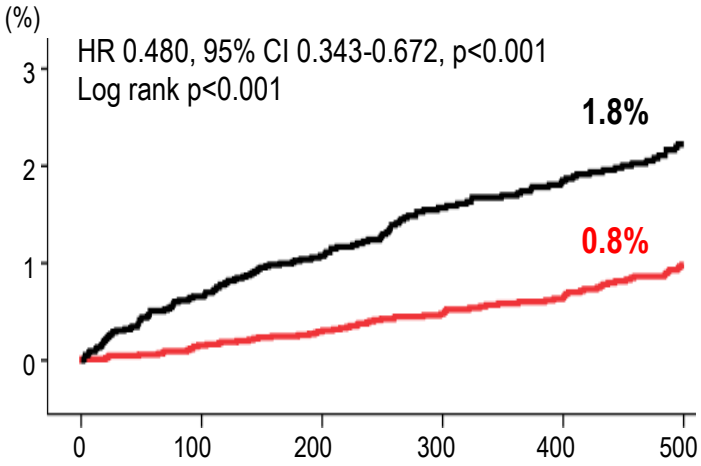


Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

Disparity in ischemia and bleeding risk
(according to ethnicity)

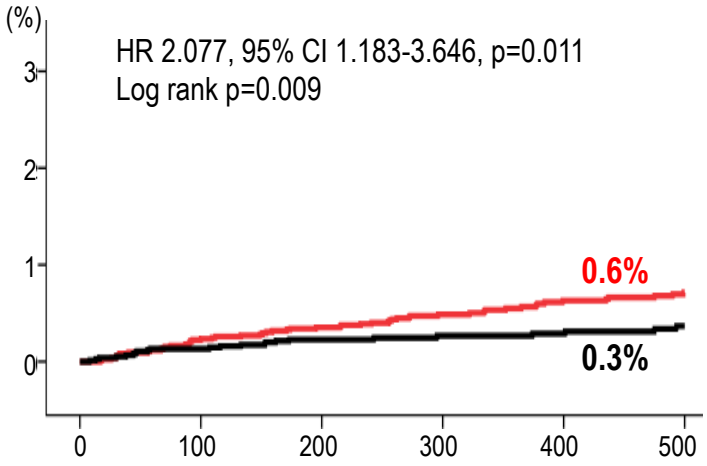
Asian
Non-Asians

A. Ischemic outcomes



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

B. Bleeding outcomes



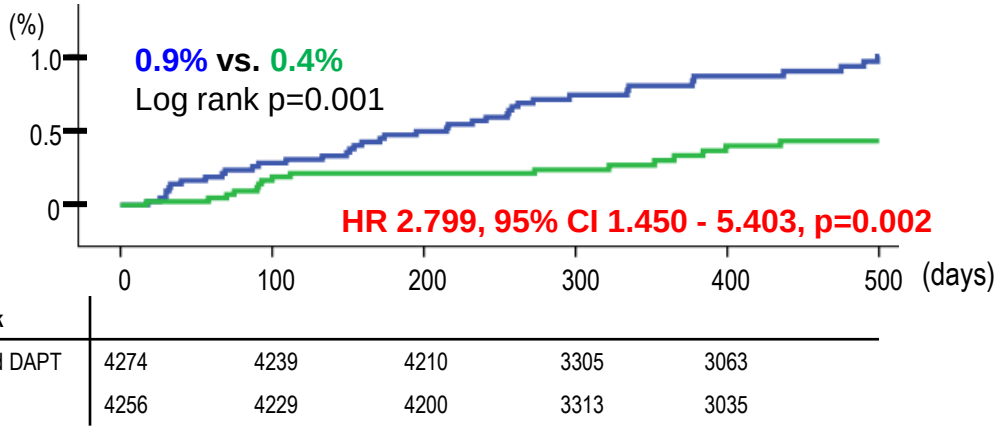
No at risk					
Asian	8530	8468	8410	6618	6098
Non-Asian	7676	7439	5437	4727	4570

Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

Bleeding Outcomes: Prolonged DAPT vs. SAPT

Significant increased risk of bleeding in only Asians

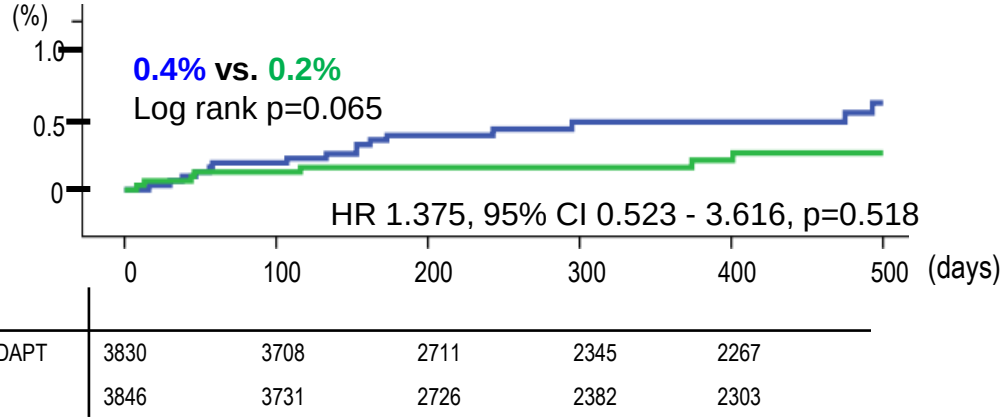
3.B Asians



No at risk					
Prolonged DAPT	4274	4239	4210	3305	3063
SAPT	4256	4229	4200	3313	3035

Prolonged DAPT
SAPT

3.C Non-Asians

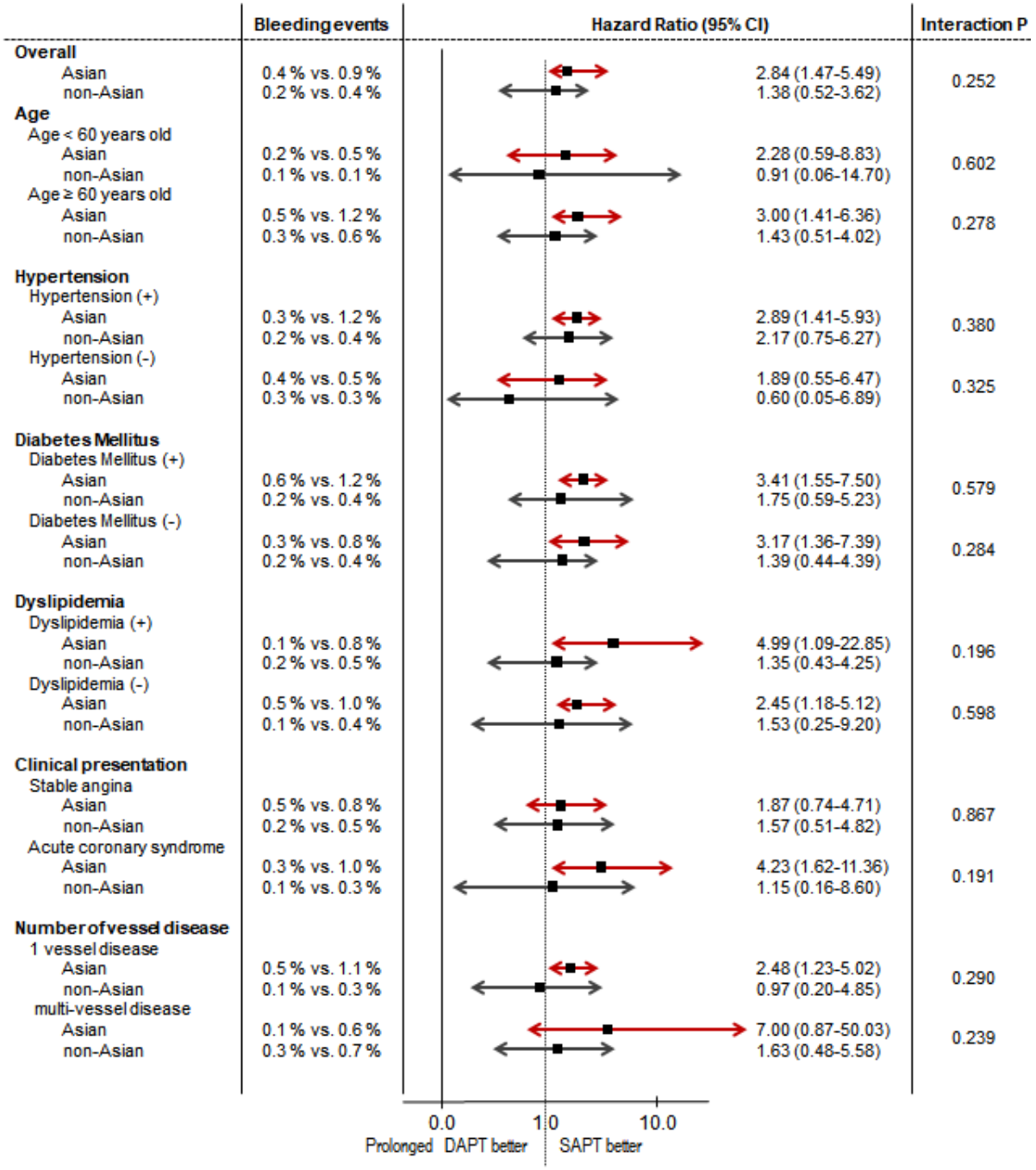


No at risk					
Prolonged DAPT	3830	3708	2711	2345	2267
SAPT	3846	3731	2726	2382	2303

Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

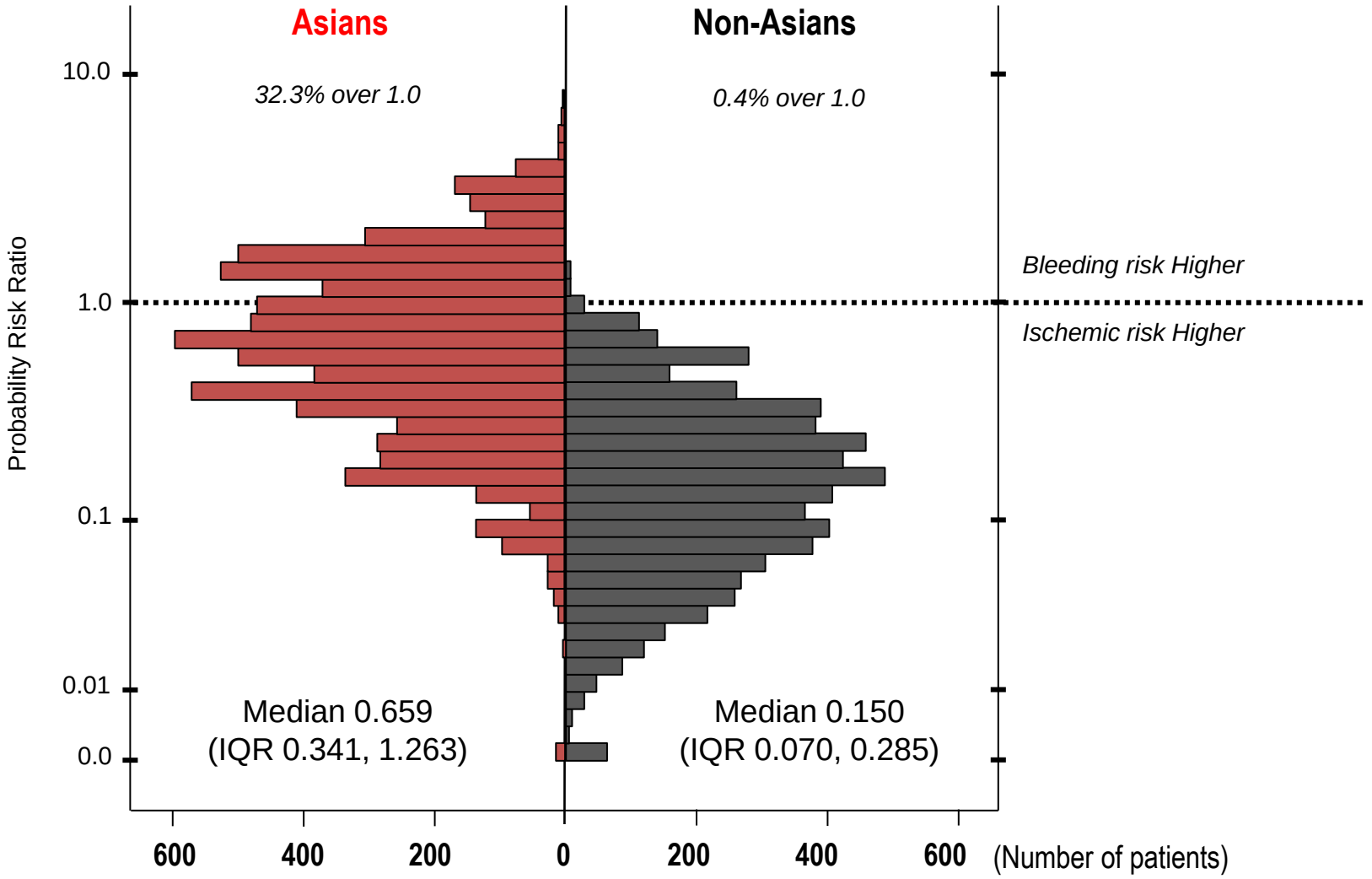
Subgroup analysis of bleeding outcomes

Asian
Non-Asians



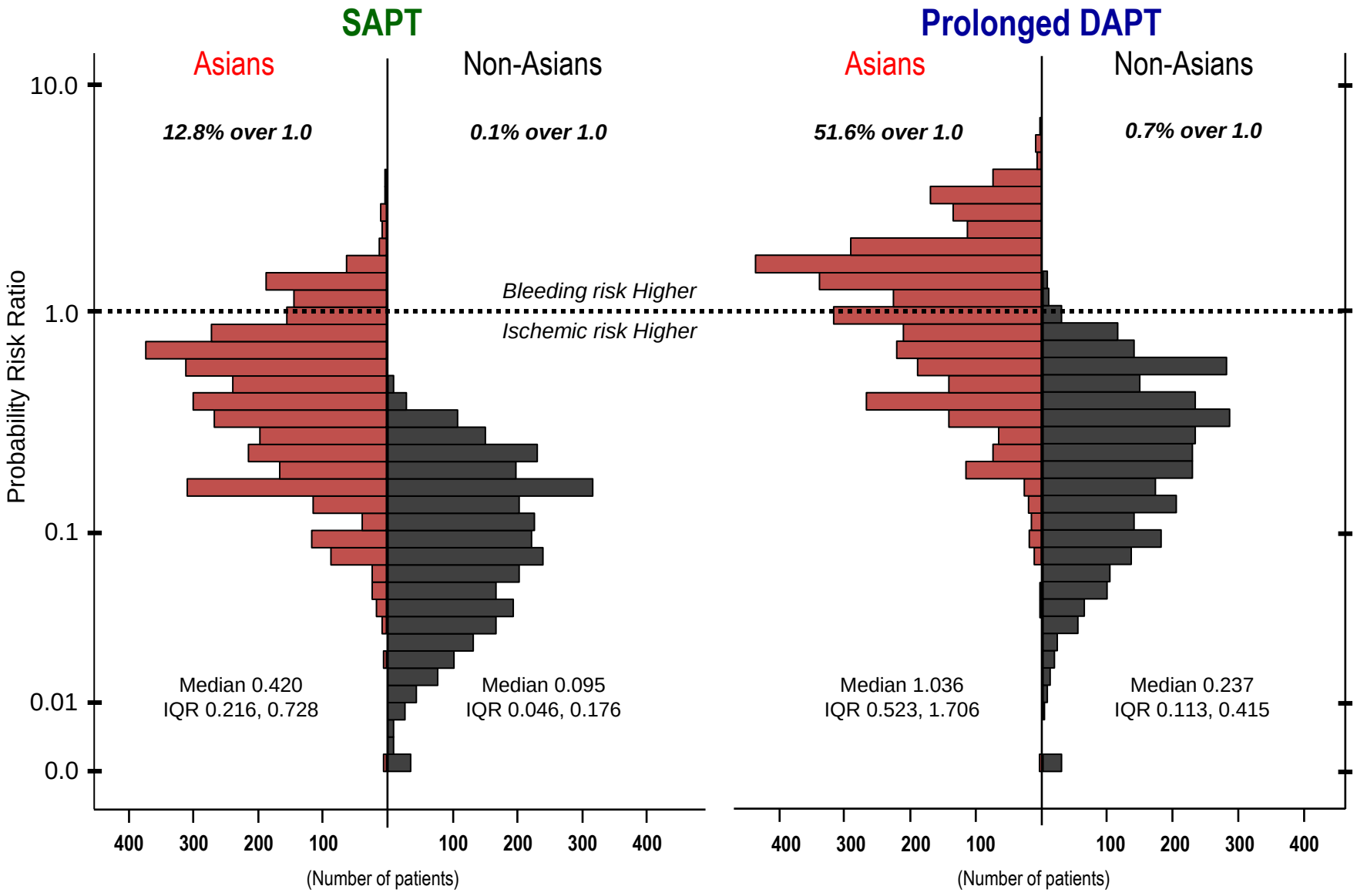
Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

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



Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

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



Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

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%)

Kang JH, Park KW, Kim HS et al. Thrombosis and Hemostasis 2018

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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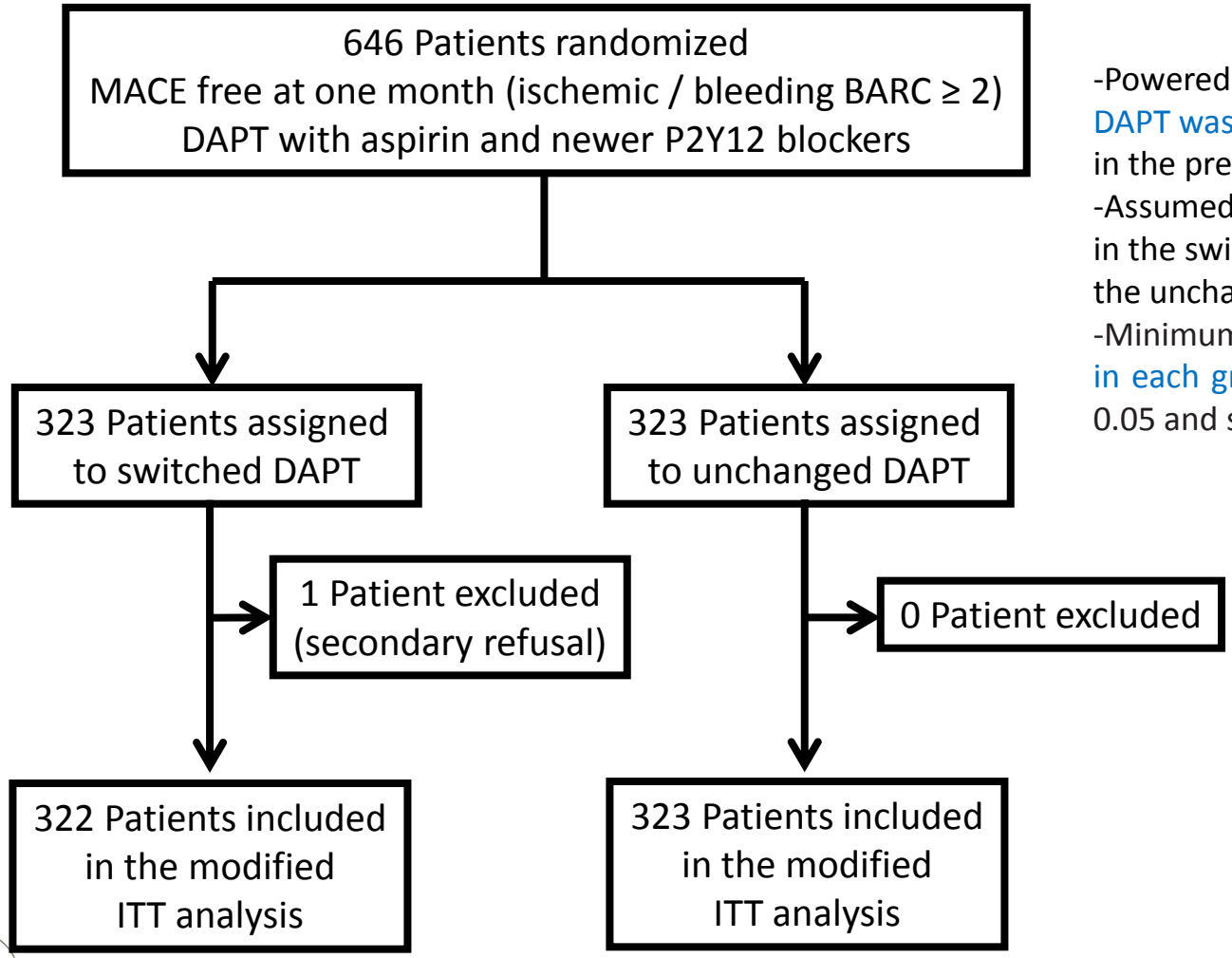
TOPIC Trial

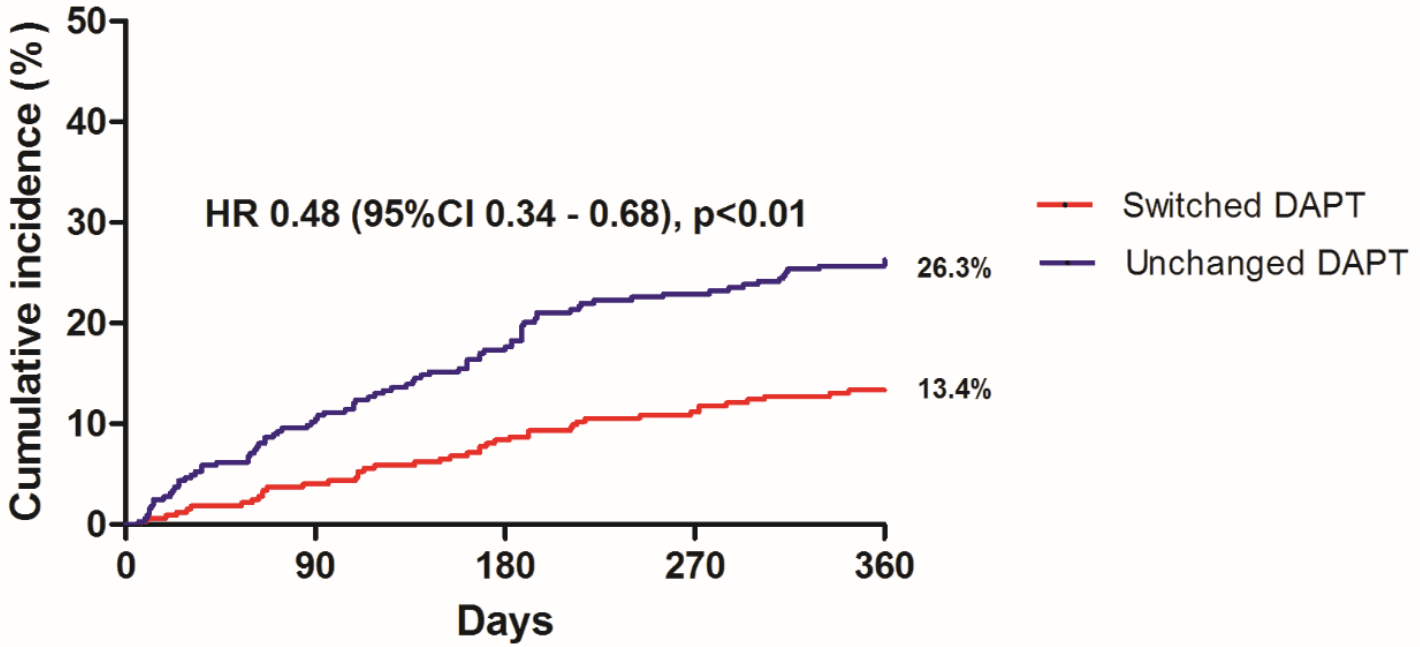
Flow chart



-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

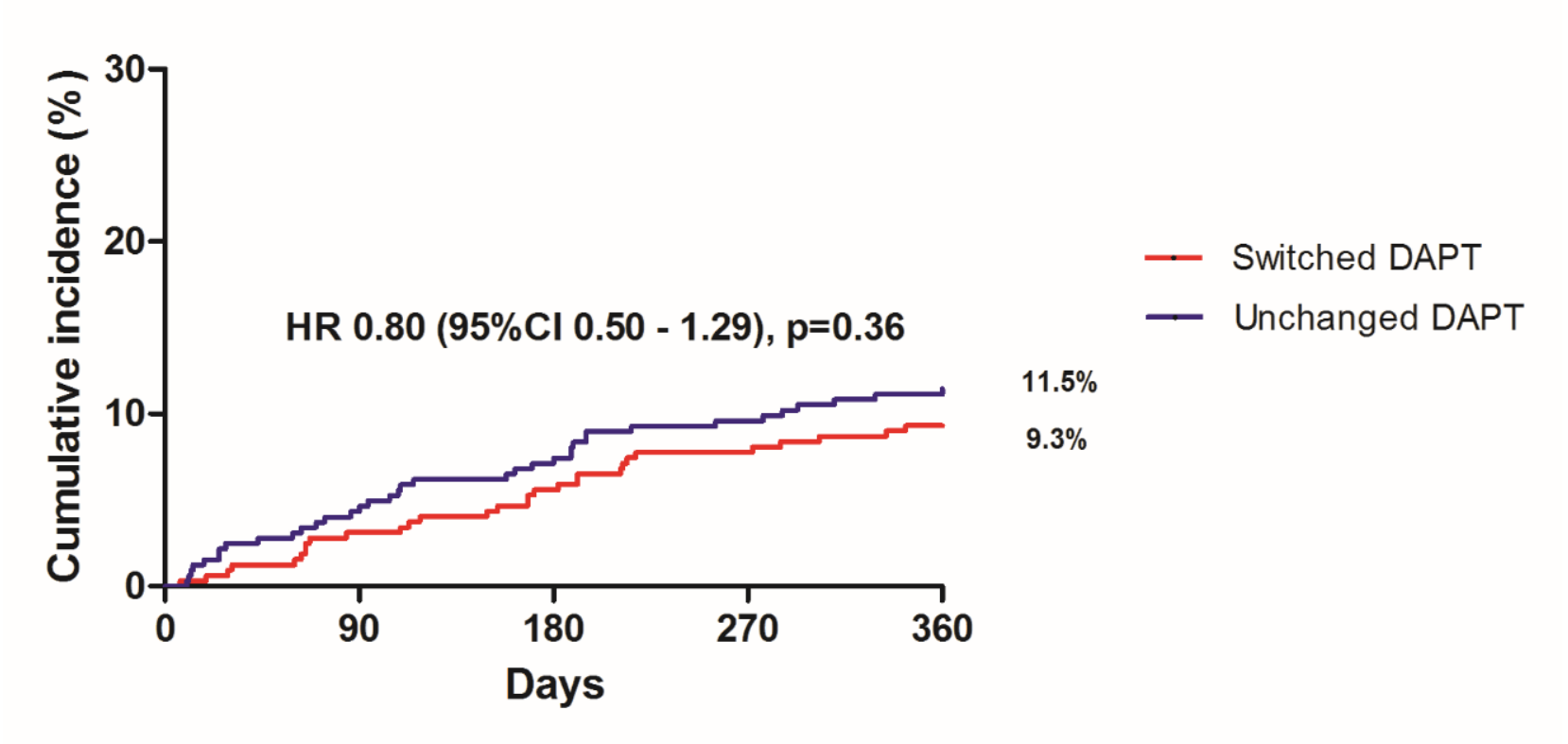
Primary Endpoint

Death, Urgent revasc., Stroke, BARC ≥ 2



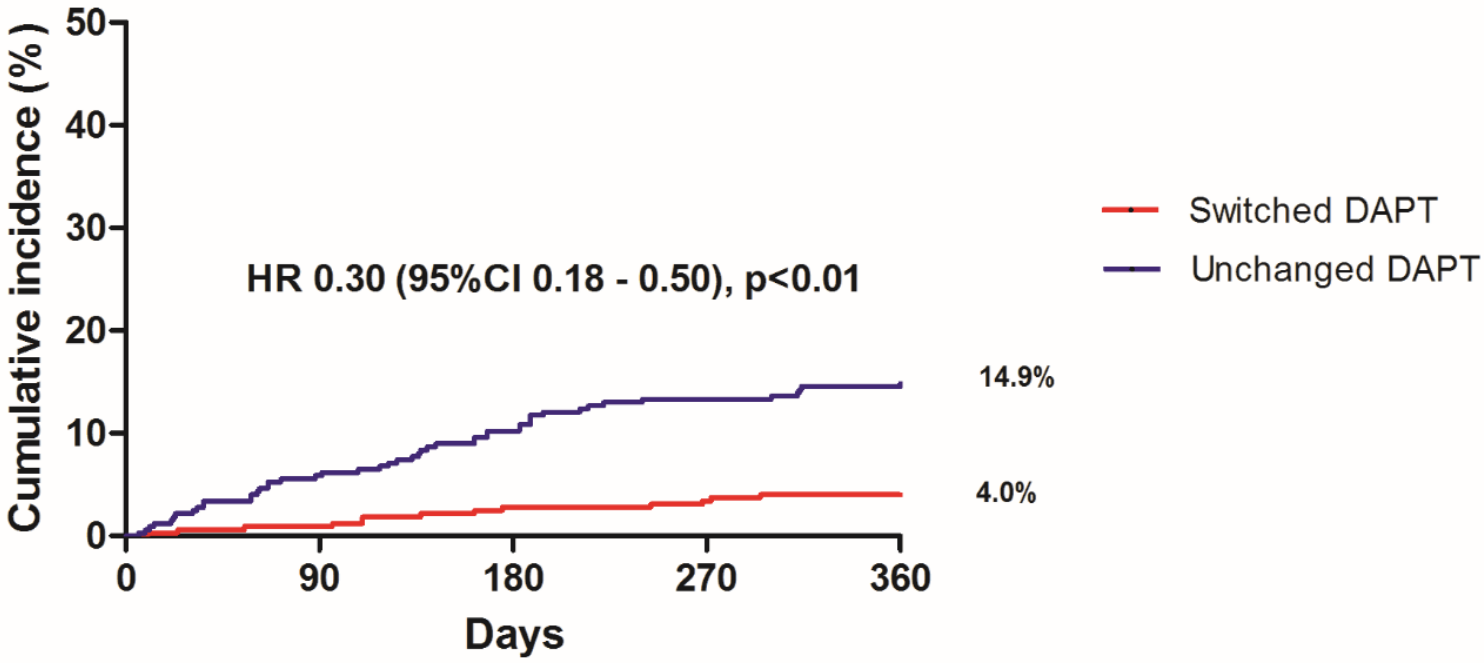
Better Prognosis with switched DAPT

Any ischemic endpoint



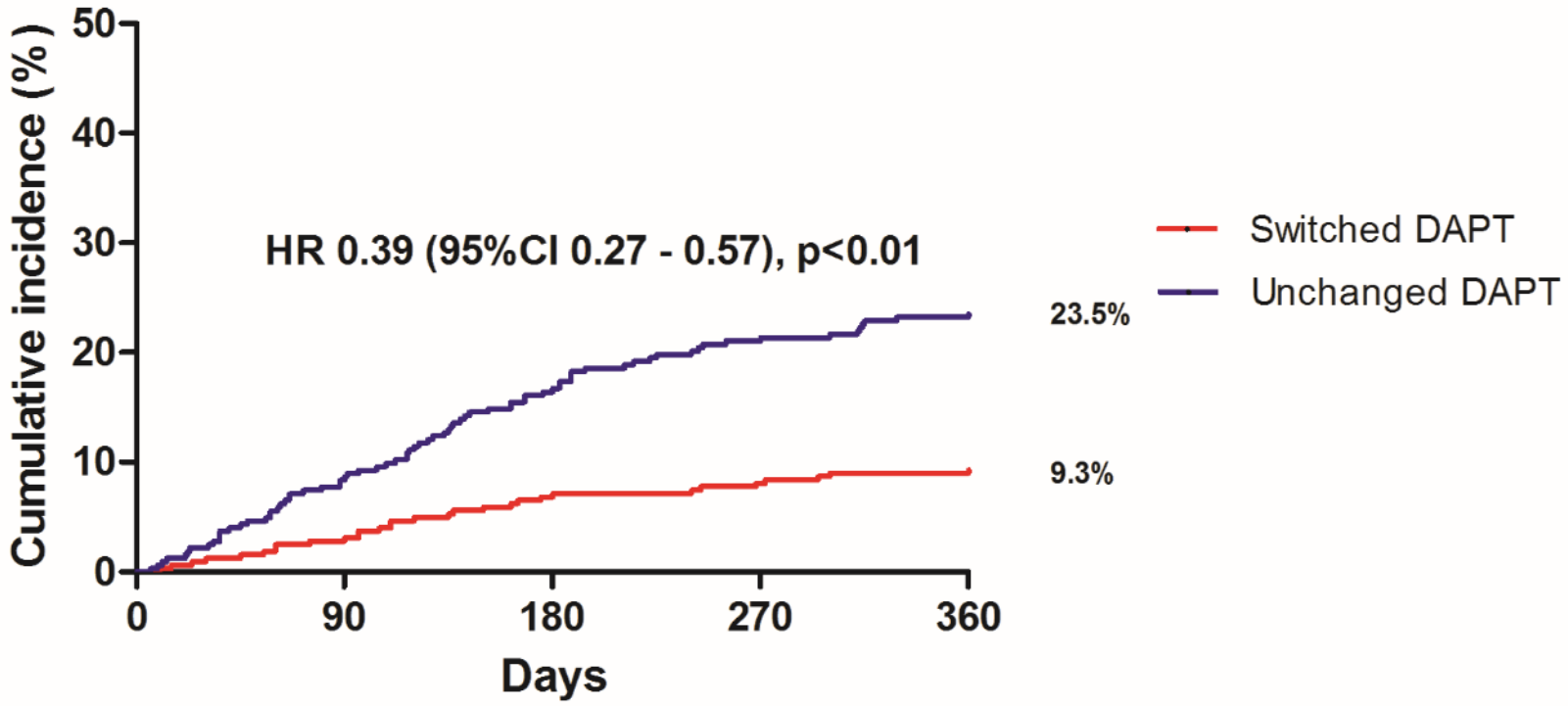
No difference for ischemic events

BARC bleedings ≥ 2



Higher Rate of BARC bleeding ≥ 2 with Unchanged DAPT

All BARC Bleedings

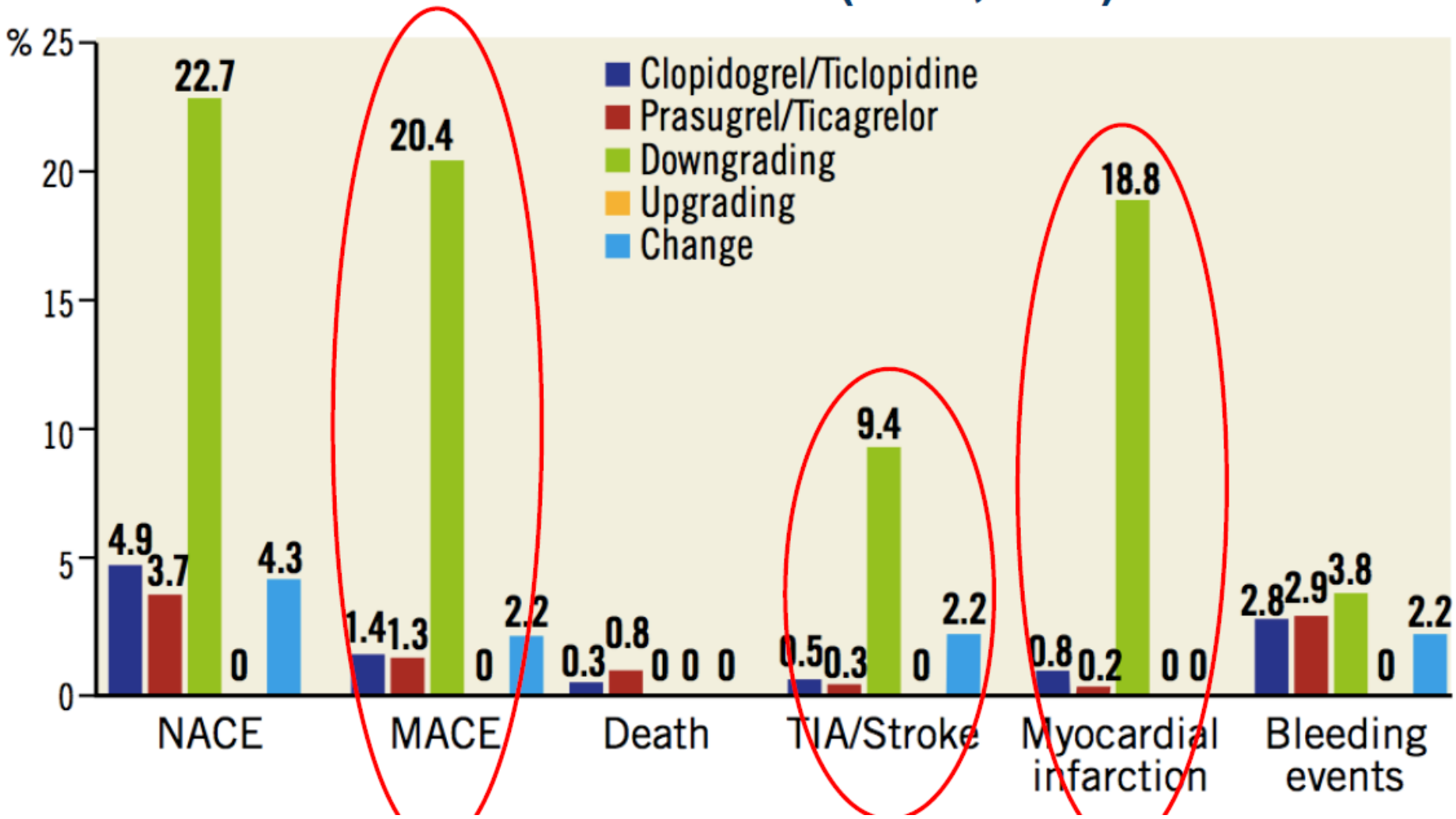


Higher Rate of all BARC bleeding with Unchanged DAPT

Conclusion

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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   change drug or **change dose**

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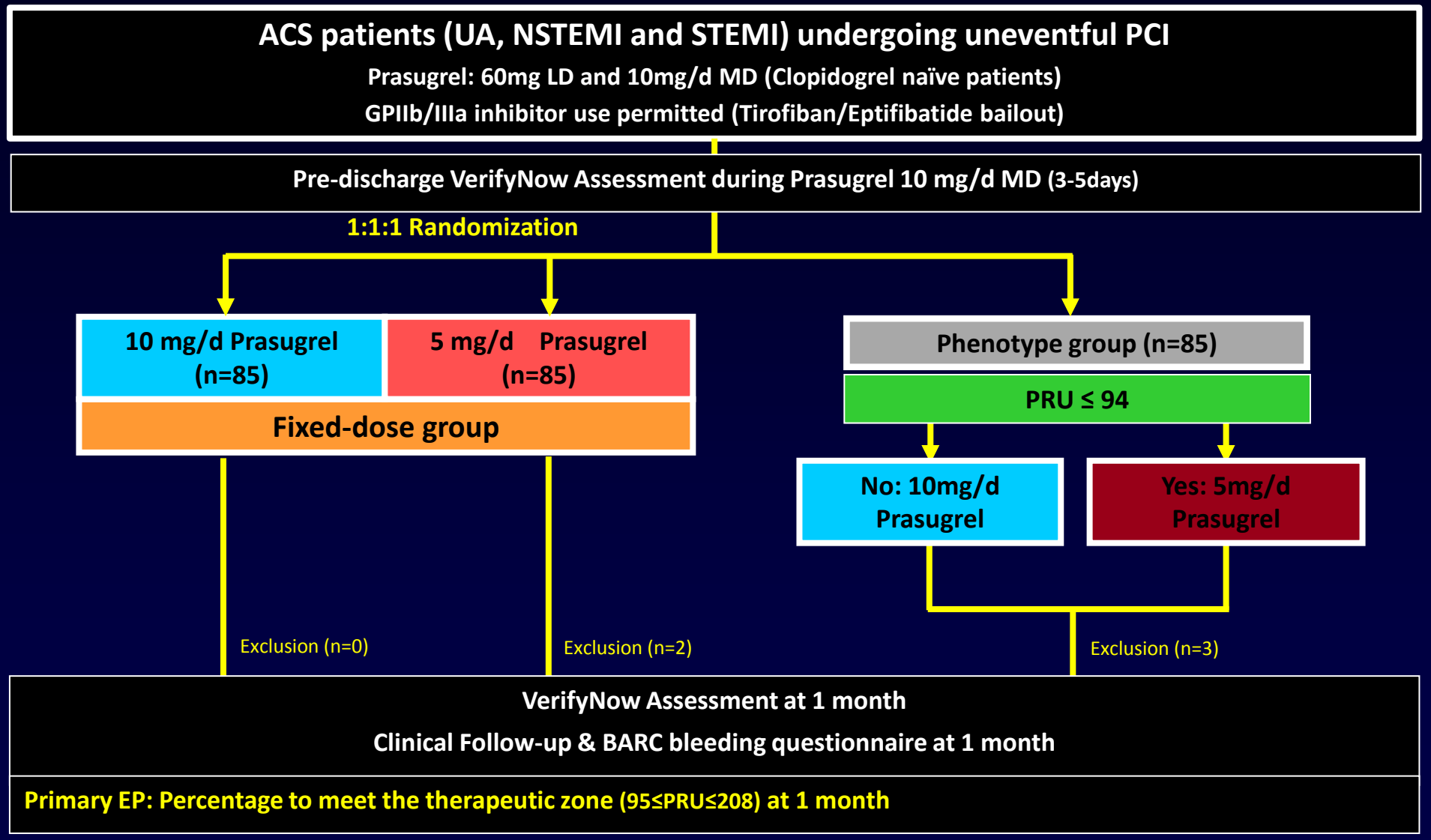
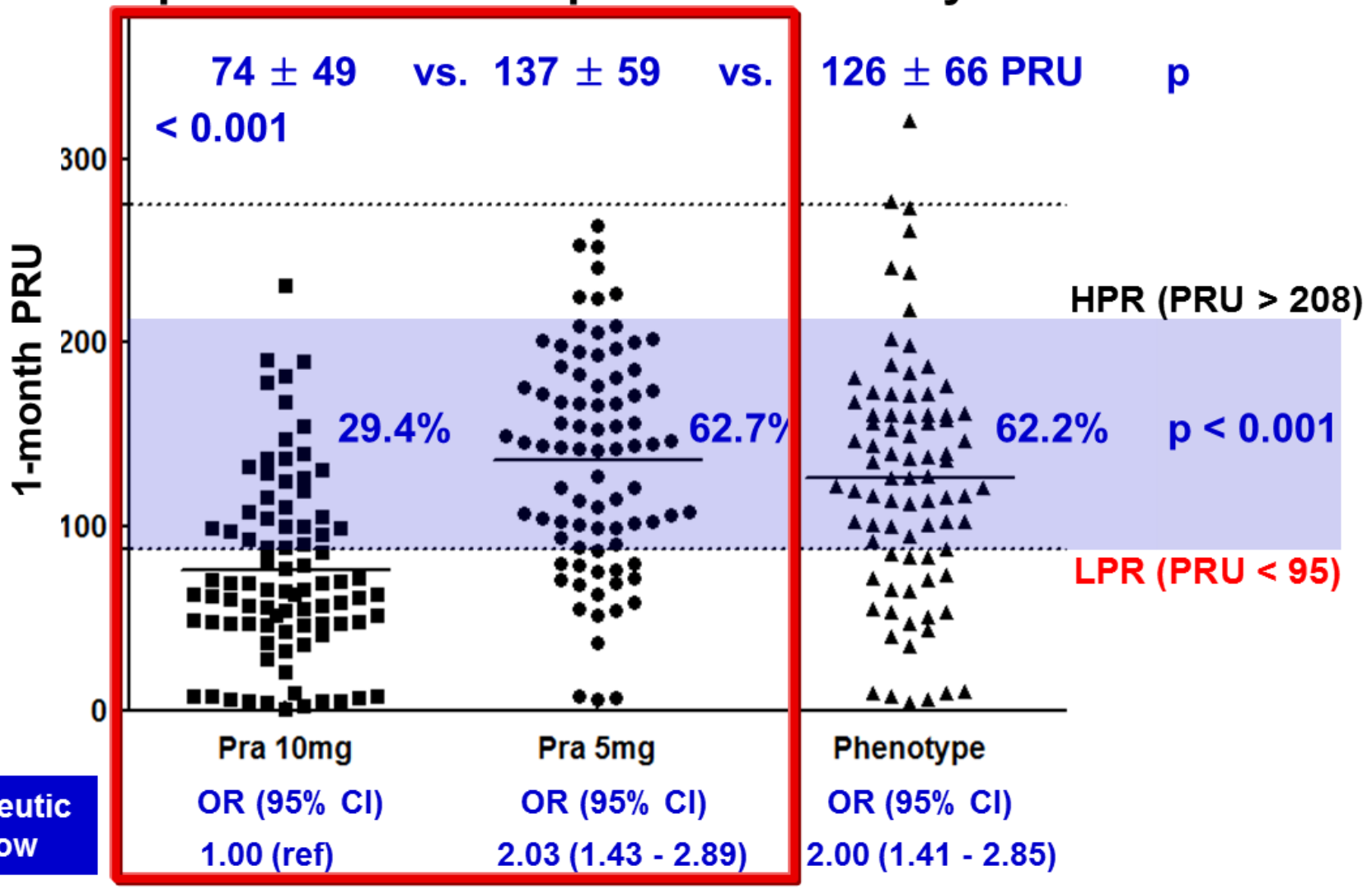
A-MATCH Trial [Korea]



Primary End Point

Jeong YH, et al. ESC 2015

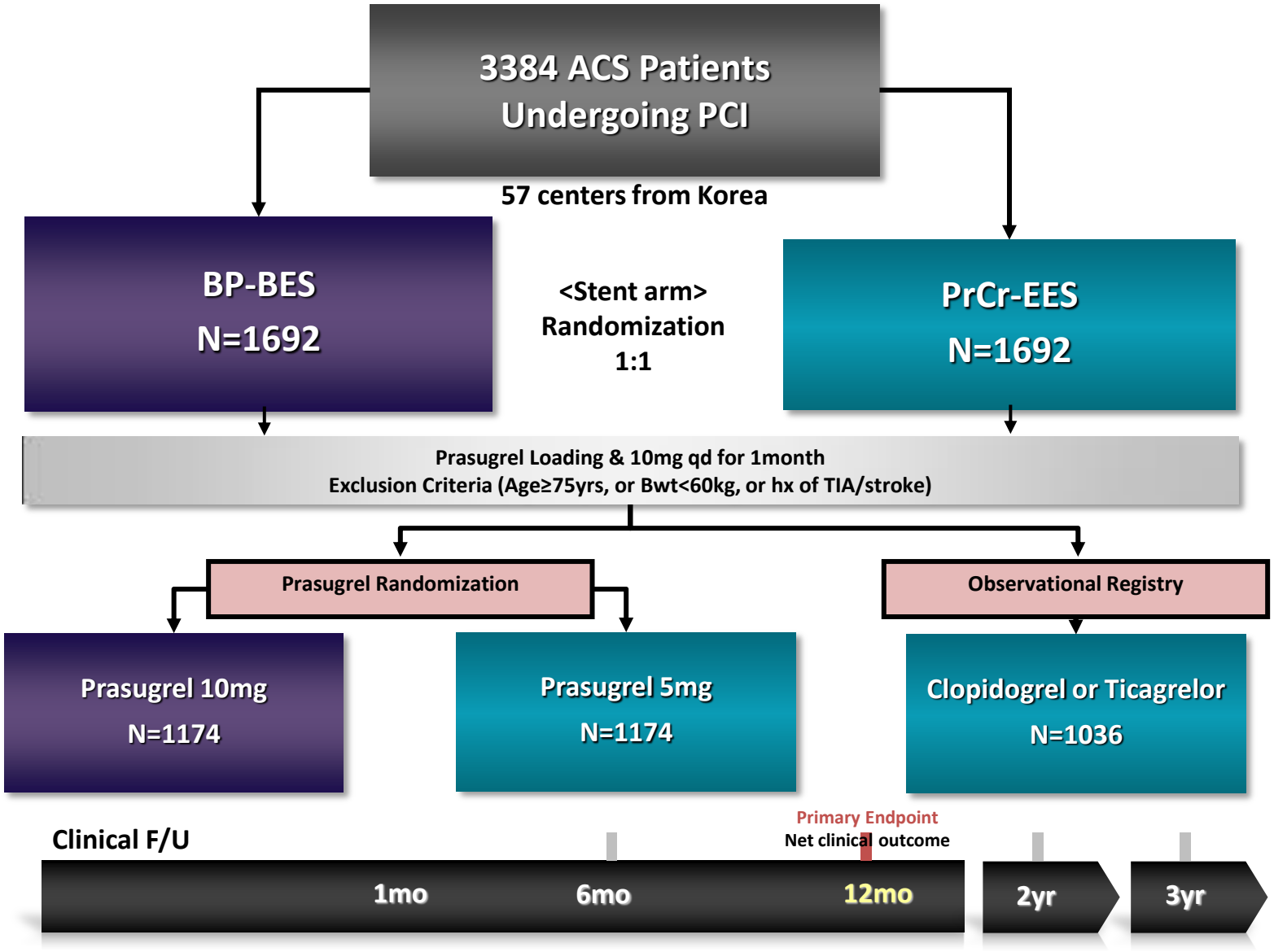
Therapeutic window of platelet reactivity in Westerners



Therapeutic window

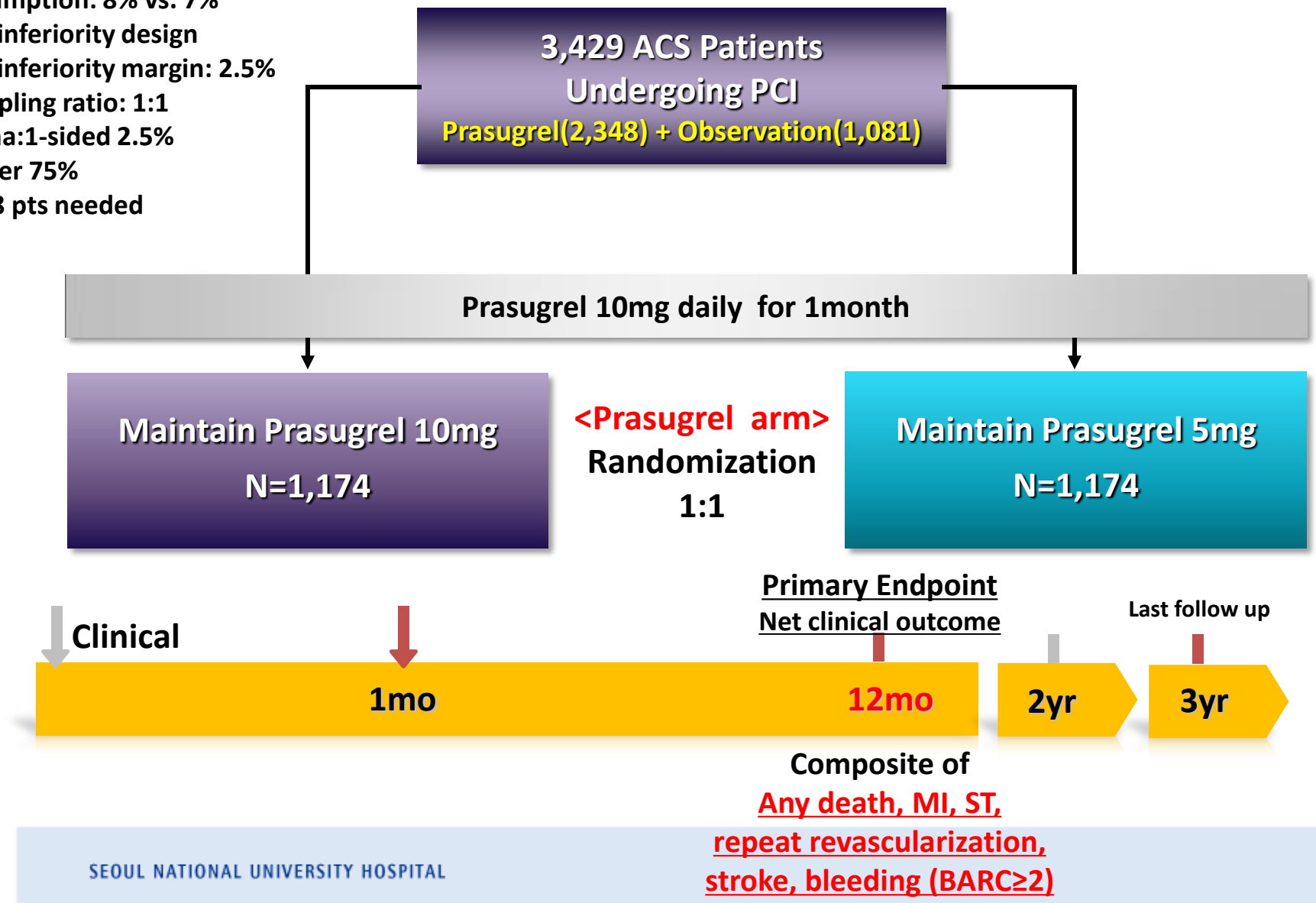
HOST III-REDUCE POLYTECH ACS Trial

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



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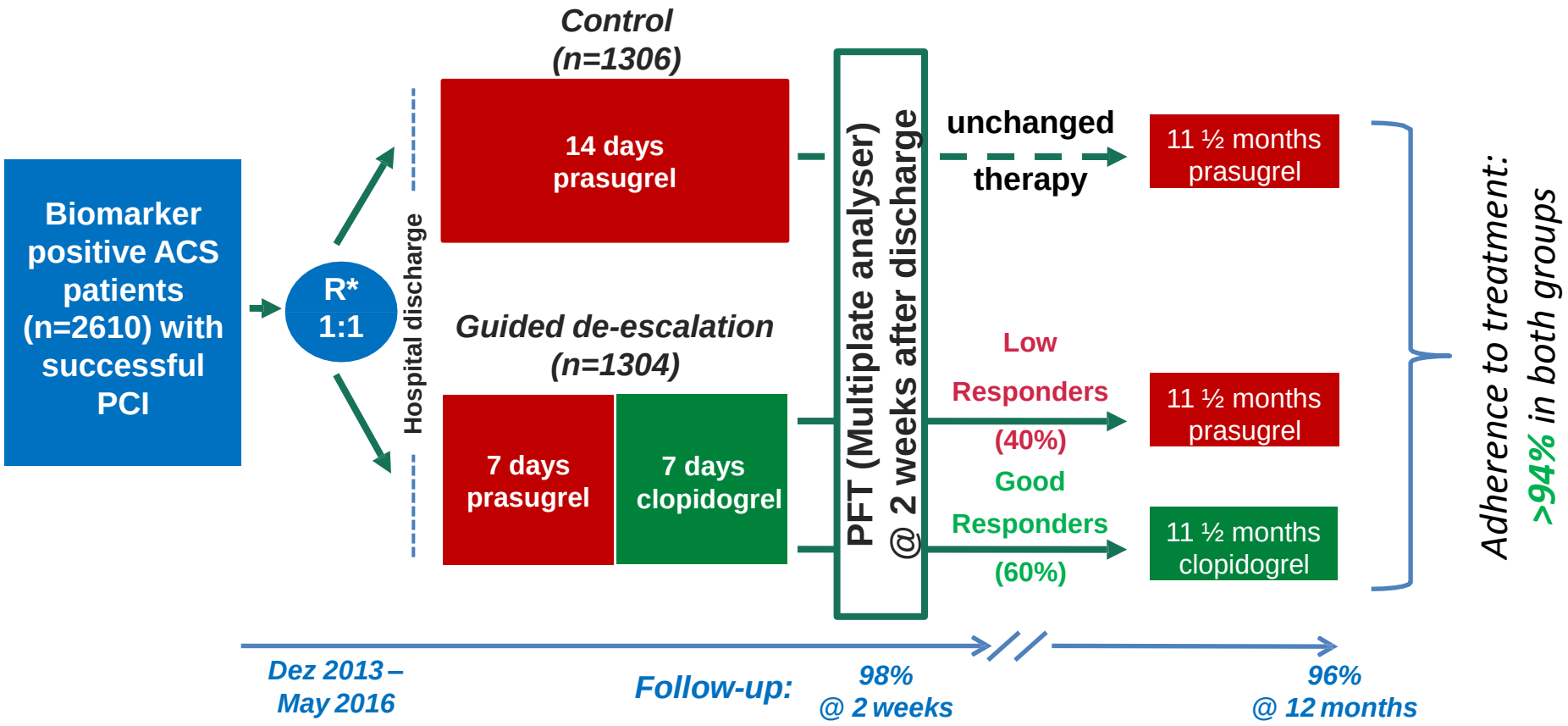
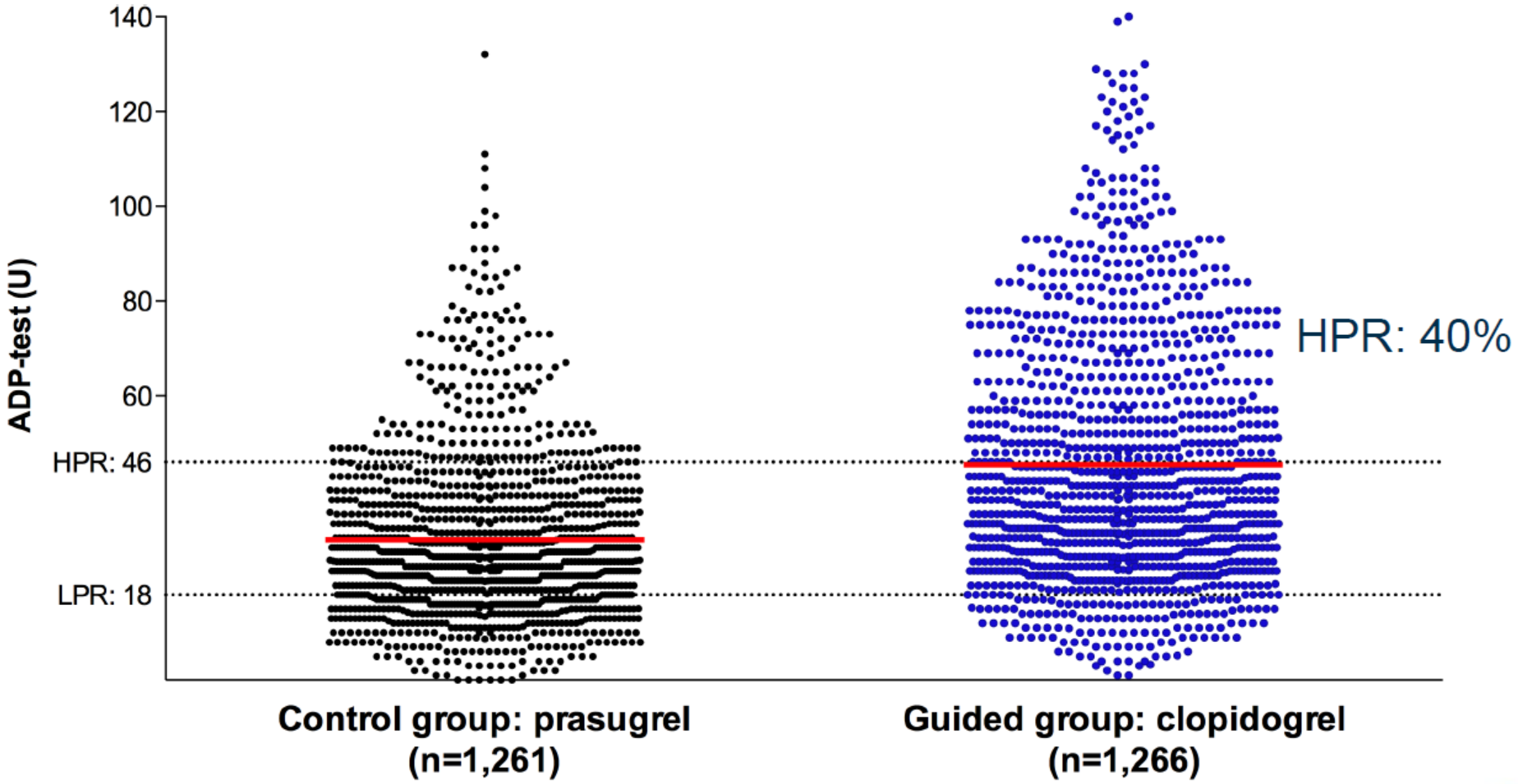
TROPICAL-ACS Trial

Study patients & follow-up data

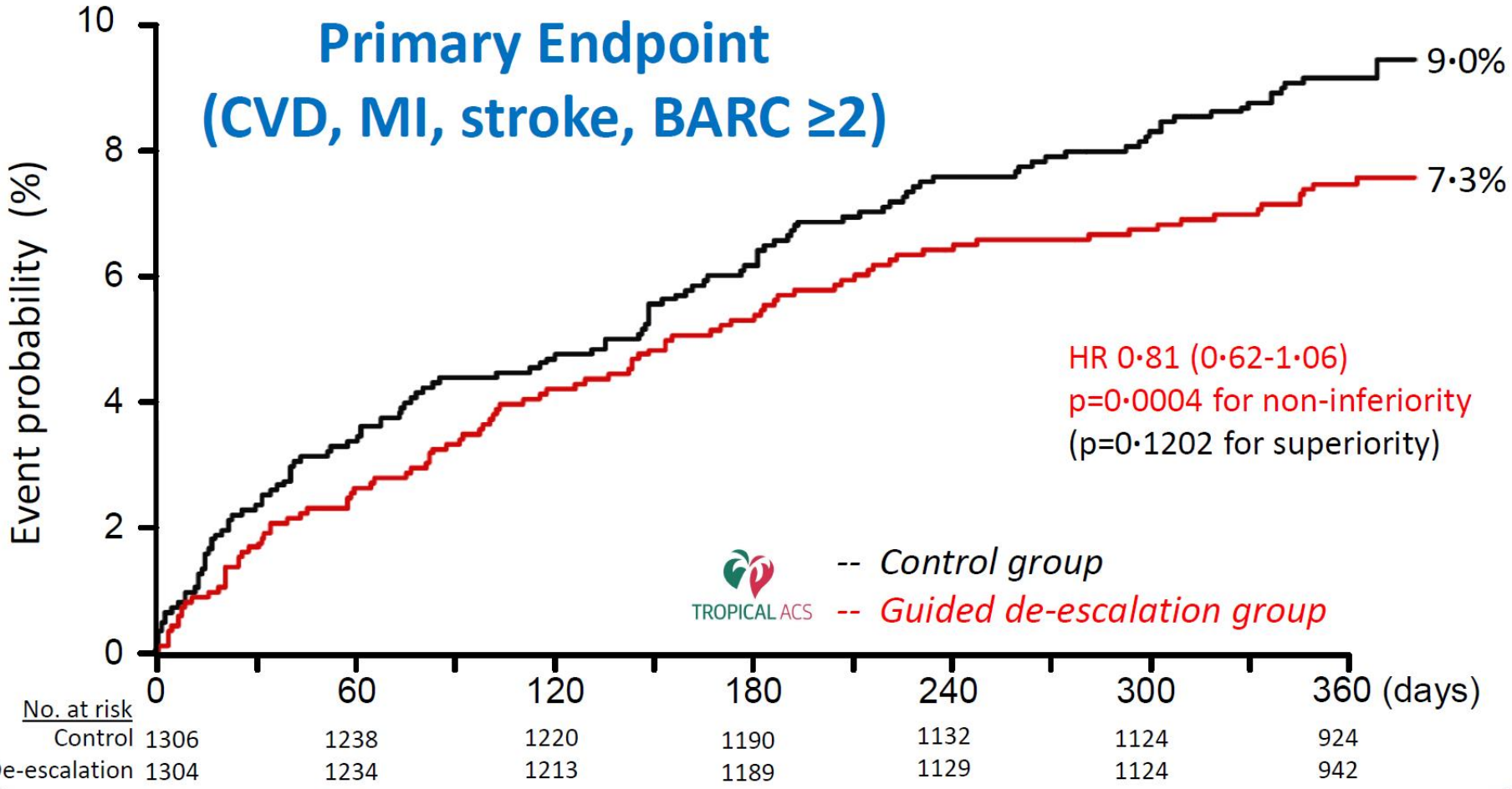


Sibbing et al., Lancet 2017

TROPICAL ACS PFT RESULTS



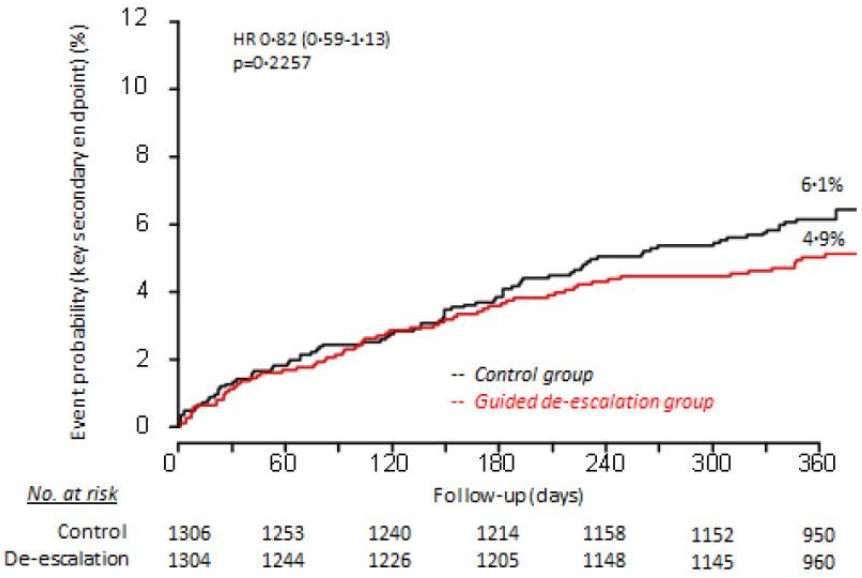
TROPICAL-ACS Results



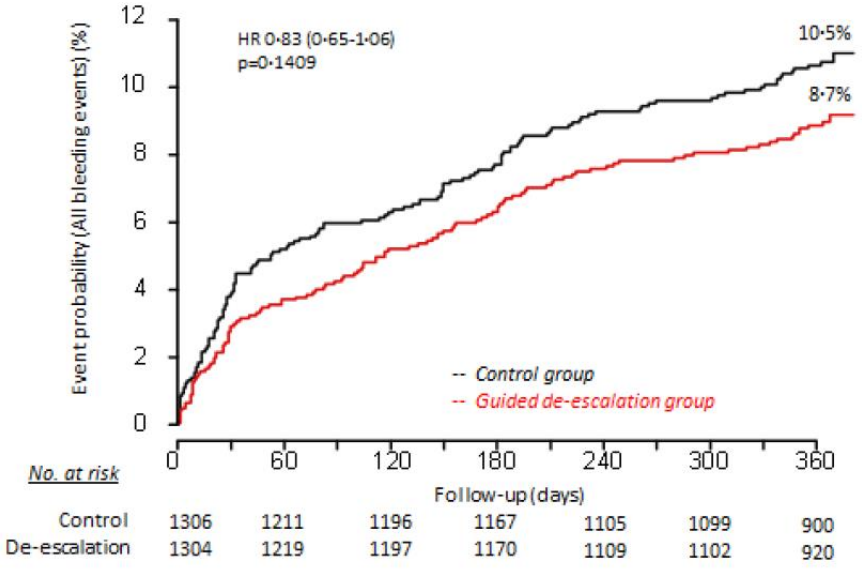
TROPICAL-ACS Results

TROPICAL ACS

Key Secondary endpoint
Bleeding BARC ≥2



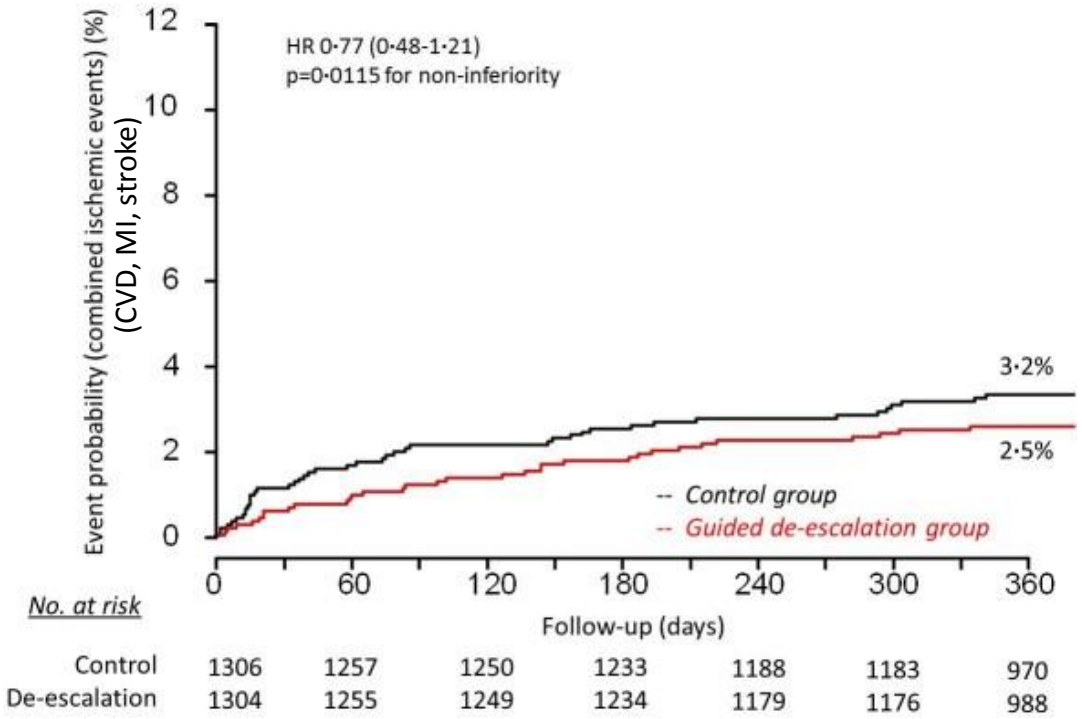
All bleeding events (BARC 1 to 5)



TROPICAL-ACS Results

TROPICAL ACS

Ischemic events at 12 months follow-up

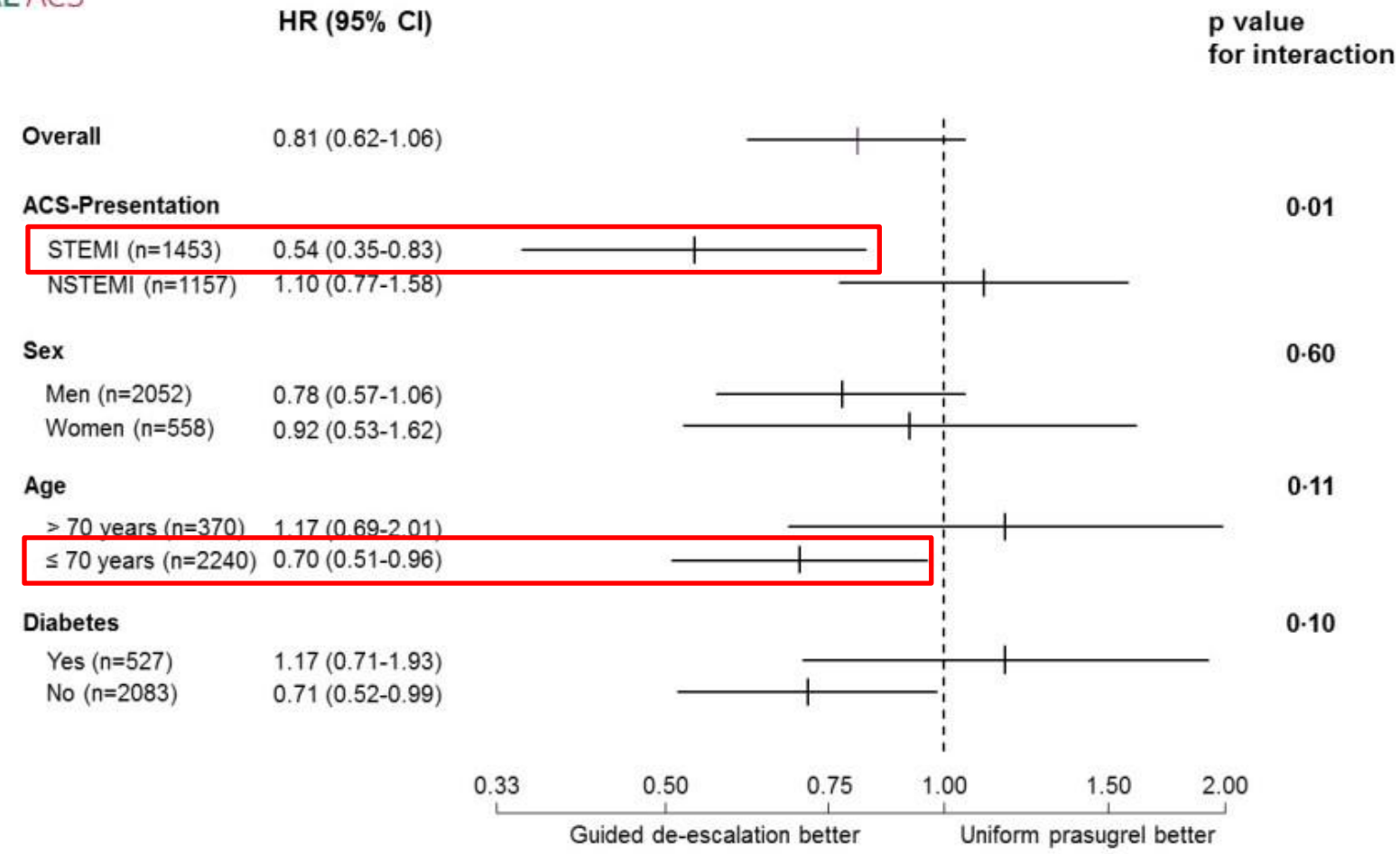


- All-cause mortality: 12 events (1%) in control vs. 11 (1%) in guided de-escalation group, p=0.85
- Definite ST: 3 events (0.2%) in control vs. 2 (0.2%) in guided de-escalation group, p=0.66

TROPICAL-ACS Results

TROPICAL ACS

Subgroup Analyses (primary endpoint)



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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!