Bleeding and stent thrombosis on P2Y12-inhibitors

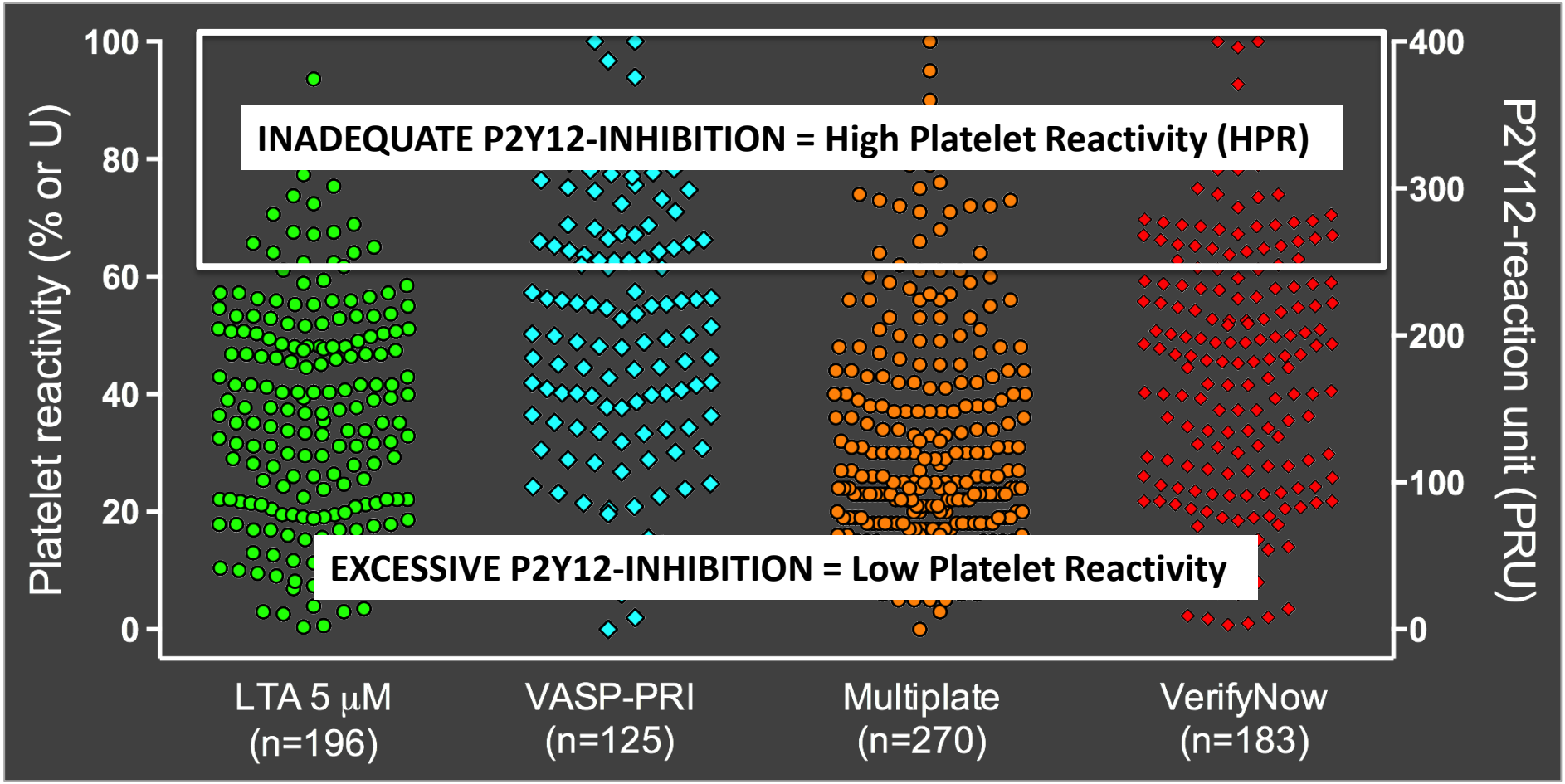
JCR© Joint meeting of Coronary Revascularization

Daniel Aradi MD PhD

Assistant Professor, Head of Thrombosis Research
Heart Center Balatonfüred and University of Semmelweis, Heart and Vascular Center
HUNGARY

11st December 2015 I JCR 2015 I Busan, South Korea

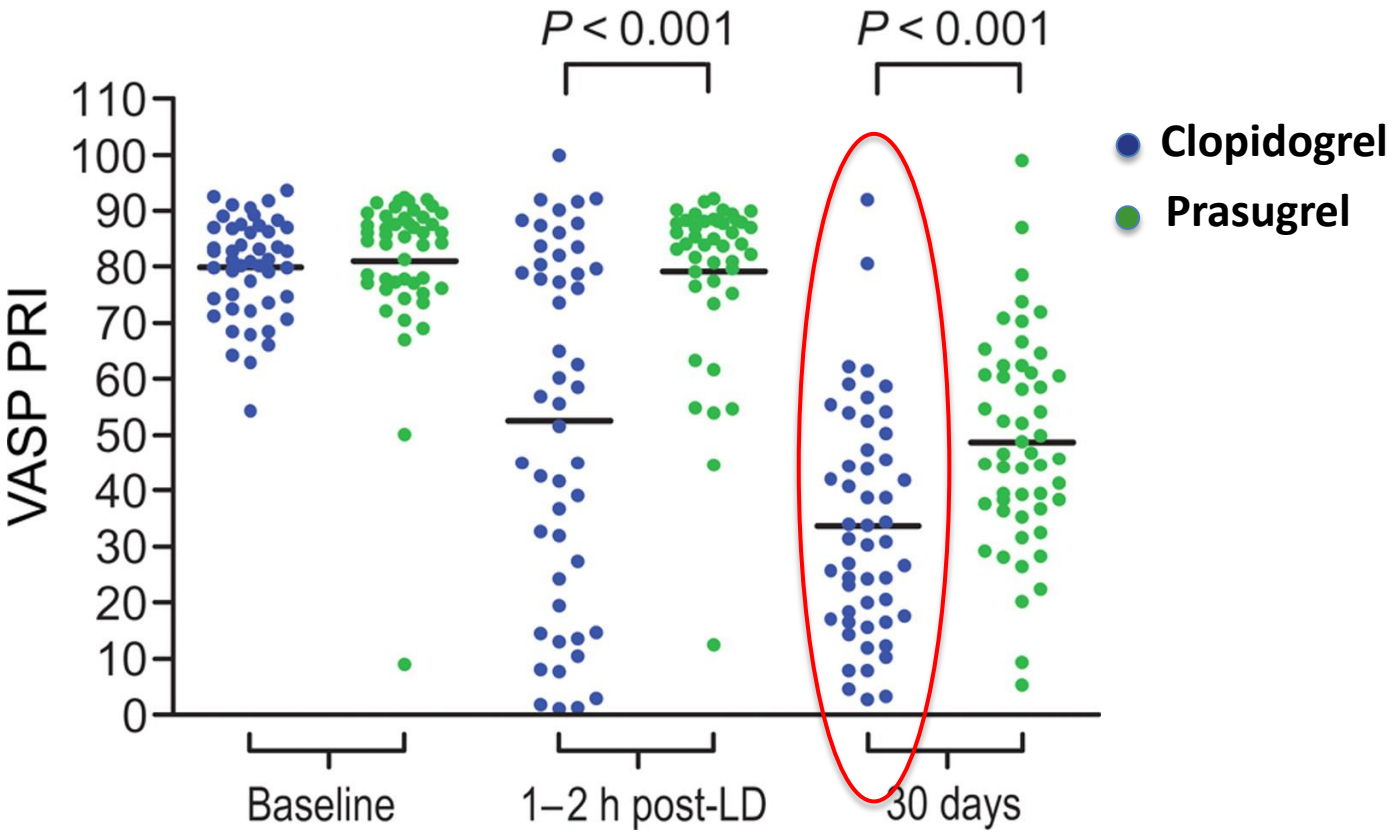
INTER-INDIVIDUAL VARIABILITY ON CLOPIDOGREL: UNPREDICTABLE $P2Y_{12}$-INHIBITION (n=774)



Aradi D et al. Eur Heart J. 2014:35;209-15.

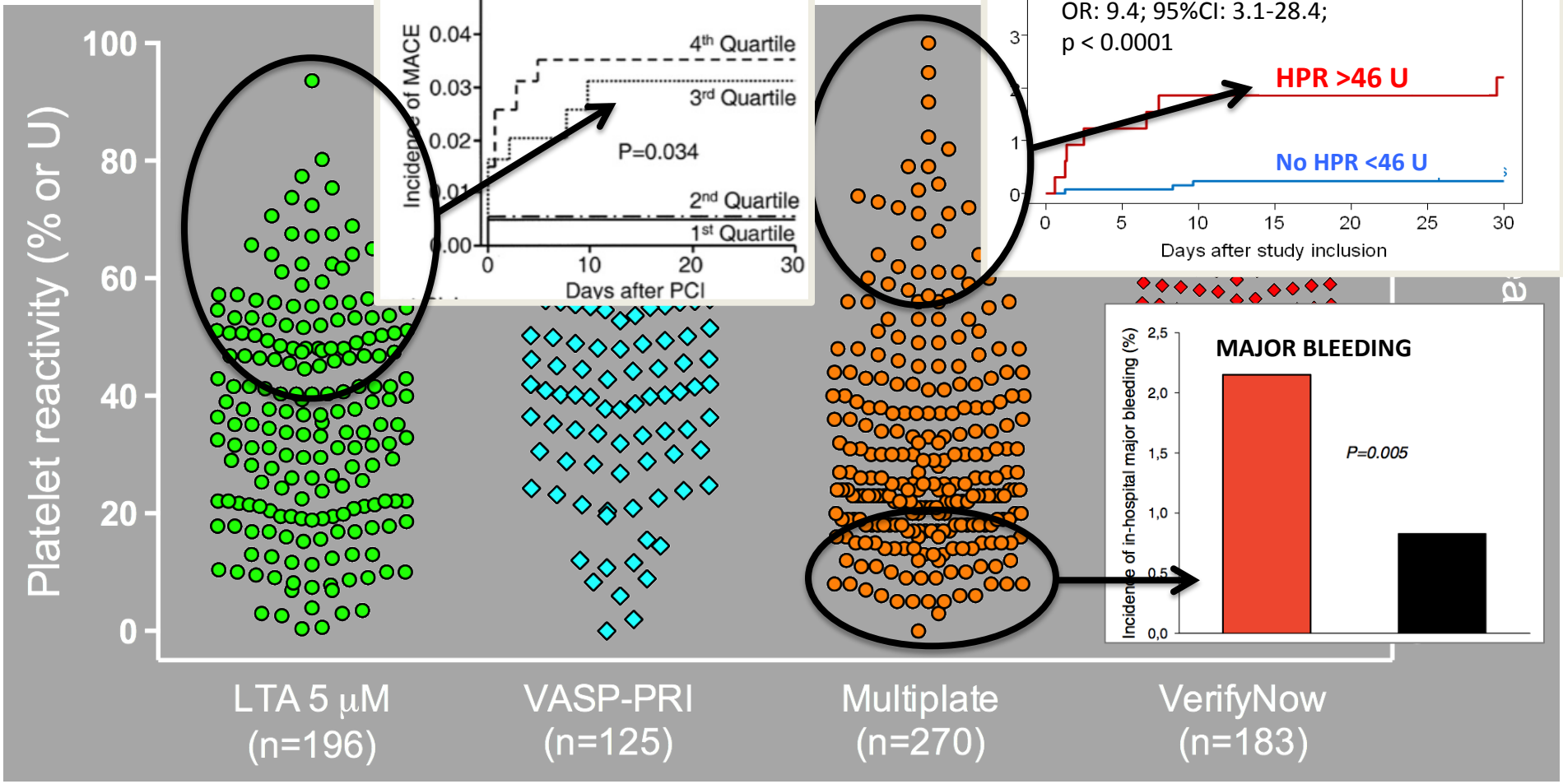
INTER-INDIVIDUAL VARIABILITY ON CLOPIDOGREL & PRASUGREL

TIMI38 PFT SUBSTUDY



Michelson AD et al. Eur Heart J. 2009;30:1753-63.

RISK ASSESSMENT:
BASED ON PLATELET FUNCTION TESTING: PLATELET REACTIVITY



Hochholczer, Trenk et al. JACC 2006;48:1742-50.
Aradi D et al. Eur Heart J. 2014:35;209-15.

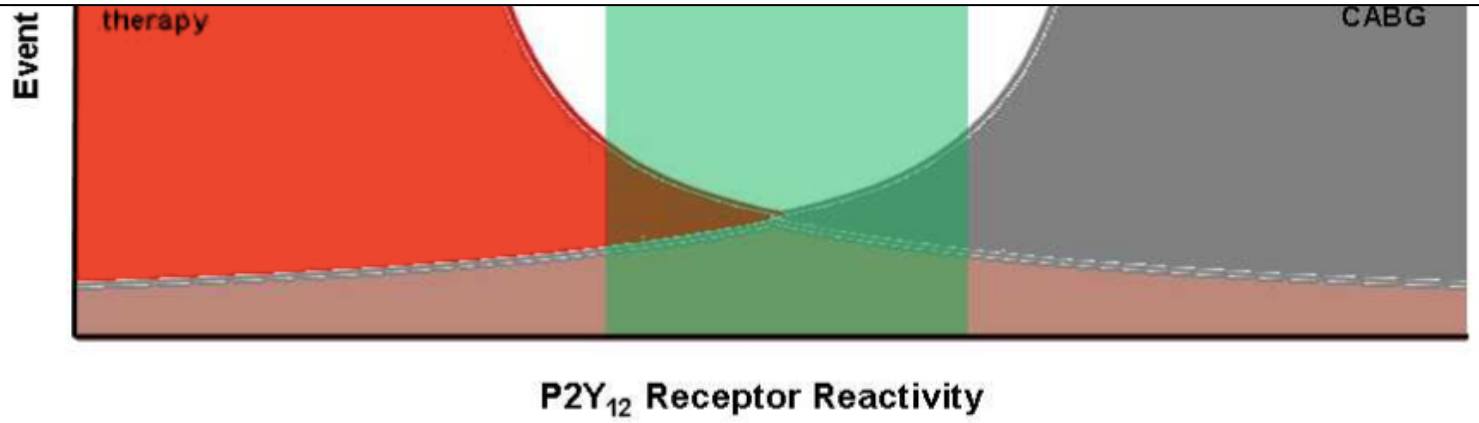
Sibbing D et al. JACC 2009;**53**:849-856.
Sibbing D et al. JTH 2010.

EXPERT POSITION PAPER ON PFT AFTER PCI

<85	VerifyNow-PRU	>208
<16%	VASP-PRI	>50%
<19	MEA-AU*min	>46
<31	TEG- MA_{ADP} (mm)	>47

- **The therapeutic window is not well established**
- **Cutoffs to define HPR and LP are heterogeneous**

RECOMMENDATION PRELIMINARY?



Tantry, Bonello, Aradi et al. JACC 2013.

AIMS

We sought to determine the prognostic value of

- **low (LPR)**
- **optimal (OPR) or**
- **high platelet reactivity (HPR)**

in patients after PCI receiving $P2Y_{12}$-inhibitor treatment by applying **pre-defined** **cut-off criteria** for 3 standardized platelet function assays:

- **VerifyNOW,**
- **Multiplate and**
- **VASP.**

METHODS: PATIENT-LEVEL ANALYSIS

- Studies published before January 2015, reporting the association between platelet reactivity, ST and major bleeding were searched

- Only standardized platelet function assays were allowed (LTA excluded)

- Based on the best available evidence (exploratory studies, n=3) platelet reactivity categories were defined as:

- **VerifyNow:** LPR: <95 PRU, OPR: 95-208 PRU, HPR: >208 PRU *(ADAPT DES, Stone, 2013)*
- **Multiplate:** LPR: <19 U, OPR: 19-46 U, HPR: >46 U *(ISAR, Sibbing, 2010)*
- **VASP:** LPR <16 PRI, OPR: 16-50 PRI, HPR: >50%. *(Bonello, 2012)*

- External validation: authors were contacted to re-evaluate the original results with the new, standardized cutoff points

- **ENDPOINTS:** Definite or probable ST, major bleeding (study defined) and mortality were evaluated at the longest follow-up available.

EAST-ASIAN PARADOX: Exclusion criterion

Relationship between VerifyNow and Post-PCI Outcome

Korea: ROC curve analysis for HPR (total n = 3,844)

Study	Cohort	EP	Cutoff
ACCEL-LOADING-ACS (Randomized)[1]	NSTE-ACS (n=218); emergent PCI	1-mo MACE	PRU ≥ 289 % inhibition ≤ 12%
Zhang et al. (Registry)[2]	NSTE-ACS (n=228); emergent PCI	1-mo MACE	PRU > 272
Ko et al. (Registry)[3]	All comer (n=222); PCI	1-mo MACE	PRU ≥ 275
CILON-T (Randomized)[4]	All comer (n=960); DES implantation	6-mo MACE	PRU ≥ 252.5
Ahn et al.	All comer (n=1226);	12-mo	Non-AMI: no cutoff

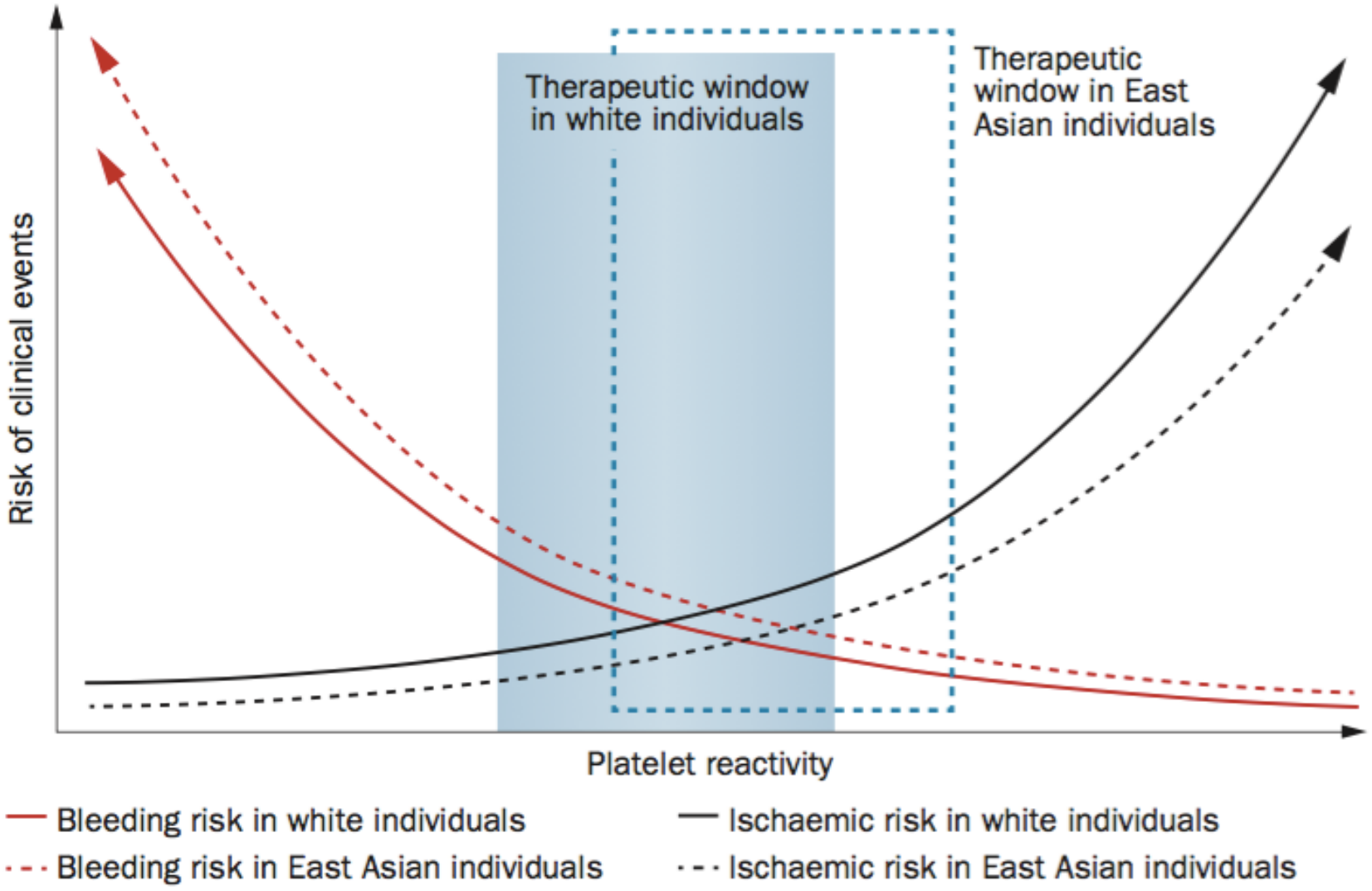
Different cutoff of HPR between races

PRU: Western (208~235) vs. Korean (253~289)

"Influence of different thrombogenecity"

Jeong YH. JCR 2013

EAST-ASIAN PARADOX



Levine, Jeong et al. Nat Rev Cardiol 2014.

EAST-ASIAN PARADOX

Korean dinner

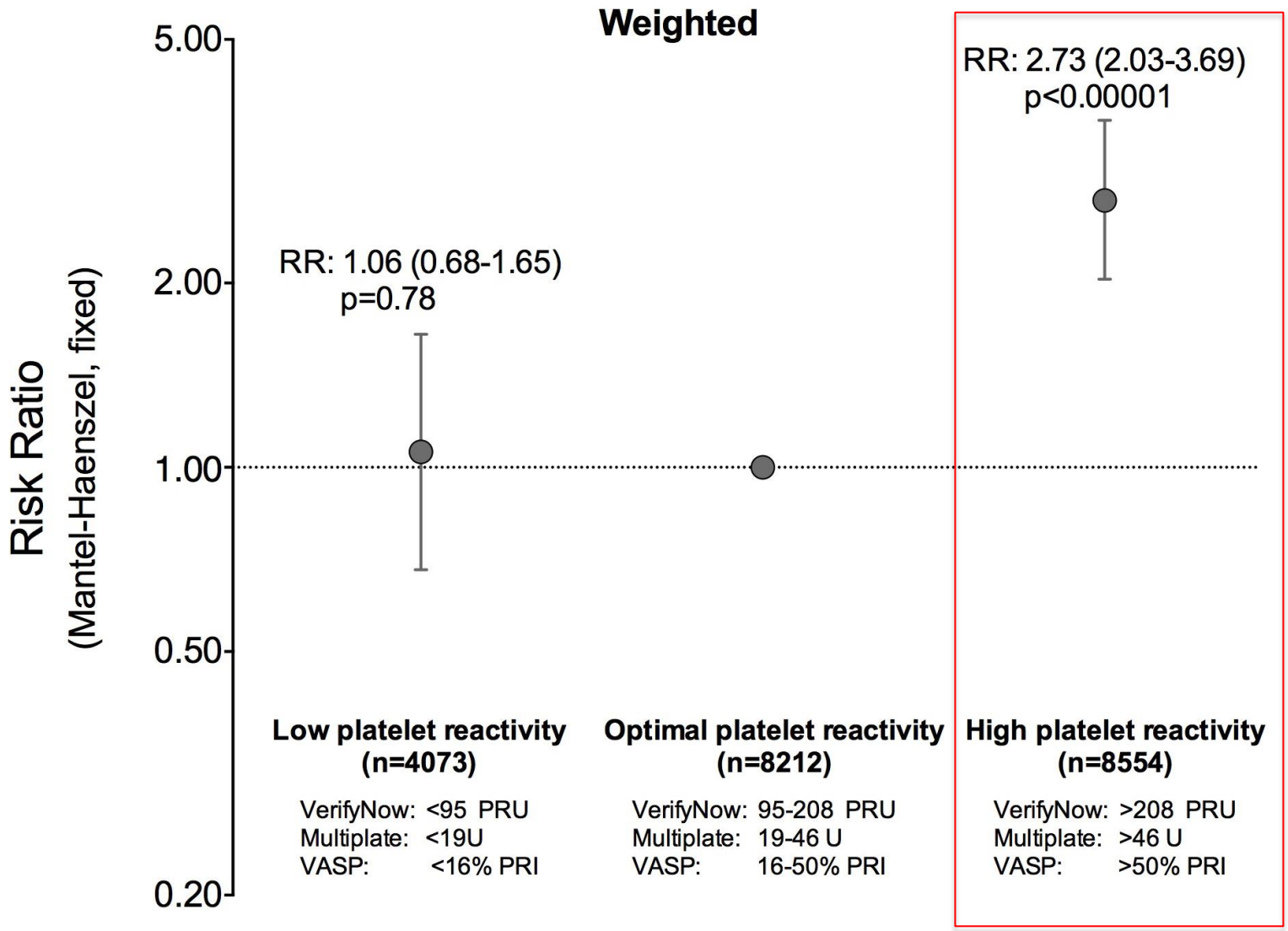
Hungarian dinner

RESULTS:
17 studies of 20,839 pts

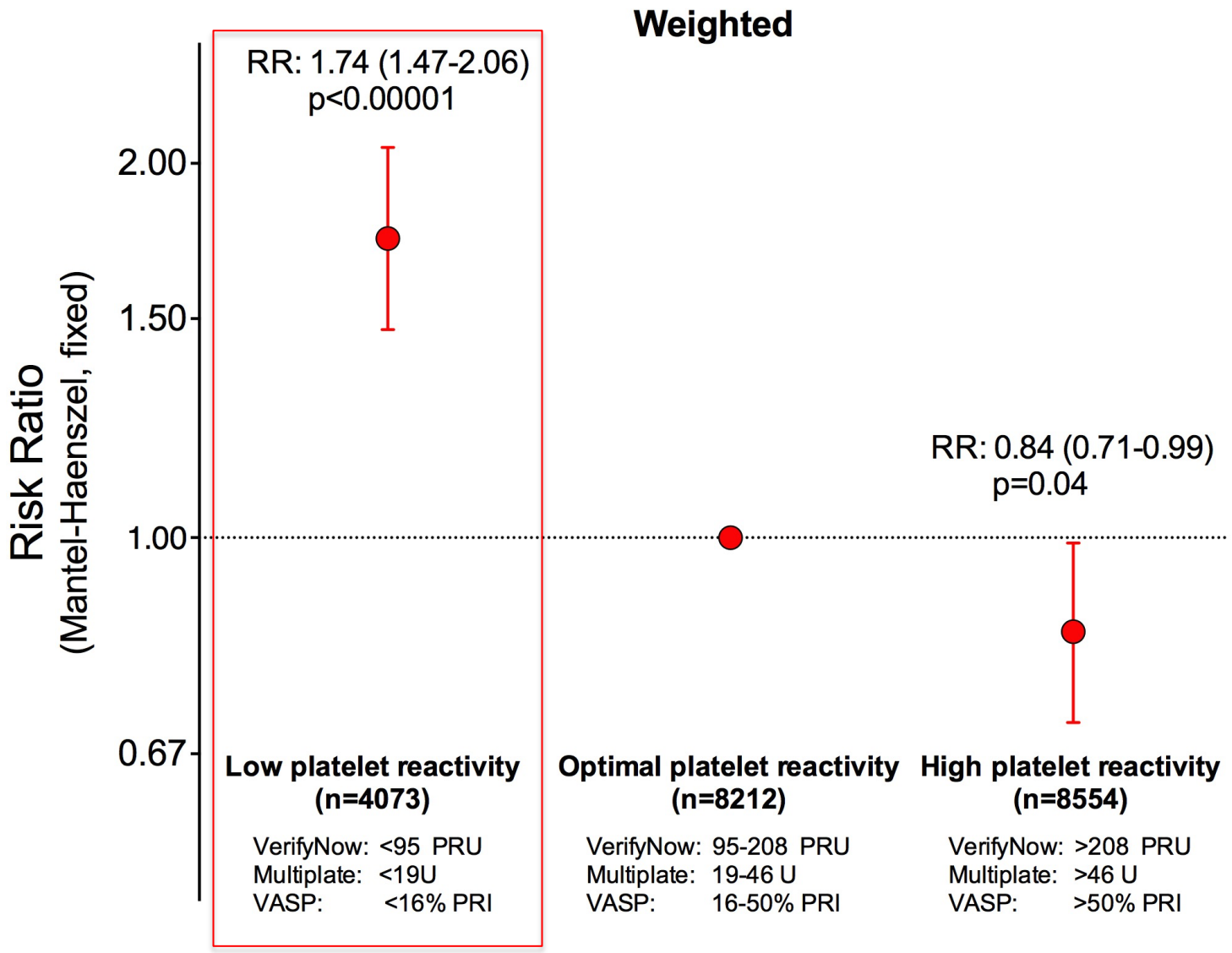
First author	Acronym	Year	*n*	Expl study	Device	$P2Y_{12}$-inhibitor	Definition of bleeding	HPR (%)	LPR (%)	Age (mean)	Female gender (%)	DM (%)	ACS (%)	DES (%)	Median length of follow-up (months)
Bonello[15]	–	2012	301	Yes	VASP	Prasugrel	TIMI major	25.2	27.9	68	11	23	100	53	12
Breet[19]	POPular	2010	1052	No	VerifyNow	Clopidogrel	TIMI major	53.3	7.8	64	25	18	0	64	12
Campo[20]	–	2011	300	No	VerifyNow	Clopidogrel	TIMI major + minor	20.7	27.0	66	23	24	61	71	17
Cuisset[22]	POBA	2013	1542	No	VASP	Clopidogrel, prasugrel	BARC type ≥ 2	30.0	8.5	64	20	30	100	58	6
Freynhofer[17]	WILMAA	2011	300	No	VASP	Clopidogrel	TIMI major	75.0	3.3	62	32	27	64	65	7
Mangiacapra[23]	ARMYDA-PROVE	2012	732	No	VerifyNow	Clopidogrel	TIMI major	48.1	7.1	66	27	30	0	27	1
Marcucci[27]	–	2009	683	No	VerifyNow	Clopidogrel	TIMI major	45.1	15.8	69	24	26	100	18	12
Morel[24]	–	2011	433	No	VASP	Clopidogrel	TIMI major	6.9	57.3	65	25	37	76	45	9
Patti[26]	ARMYDA-PRO	2008	160	No	VerifyNow	Clopidogrel	TIMI major	59.4	4.4	66	19	34	54	26	1
Patti[25]	ARMYDA-BLEEDING	2011	310	No	VerifyNow	Clopidogrel	TIMI major	59.4	4.2	67	22	37	32	25	1
Palmerini[28]	GEPRESS	2014	978	No	VASP	Clopidogrel	BARC type ≥2	48.9	7.7	67	24	27	100	59	12
Price[9]	GRAVITAS	2011	1692[a]	No	VerifyNow	Clopidogrel	GUSTO mod/severe	70.0	8.0	63	30	41	15	100	5.7
Sibbing[13]	ISAR	2010	2533	Yes	Multiplate	Clopidogrel	TIMI major	16.9	38.5	68	24	29	12	100	1
Sibbing[21]	ISAR-REACT 4	2012	564	No	Multiplate	Clopidogrel	TIMI major	36.3	27.0	68	22	31	100	100	1
Siller-Matula[18]	MADONNA	2012	395[a]	No	Multiplate	Clopidogrel	TIMI major	36.2	28.4	64	24	34	37	91	1
Siller-Matula[16]	PEGASUS PCI	2012	416	No	Multiplate	Clopidogrel	TIMI major	36.3	28.6	64	24	32	34	99	12
Stone[12]	ADAPT-DES	2013	8,448	Yes	VerifyNow	Clopidogrel	ADAPT-defined	42.7	20.0	64	26	32	52	100	12

- VerifyNow: 64%, Multiplate: 19%, VASP: 17%.
- LPR: 20%, OPR: 39%, HPR: 41%.
- Clopidogrel: 97%, Prasugrel: 3%, Ticagrelor: 0%.
- Median ACS rate: 53% (0-100%).
- Median length of follow-up: 8.5 months (1-17).
- Median DES rate: 64% (18-100%).

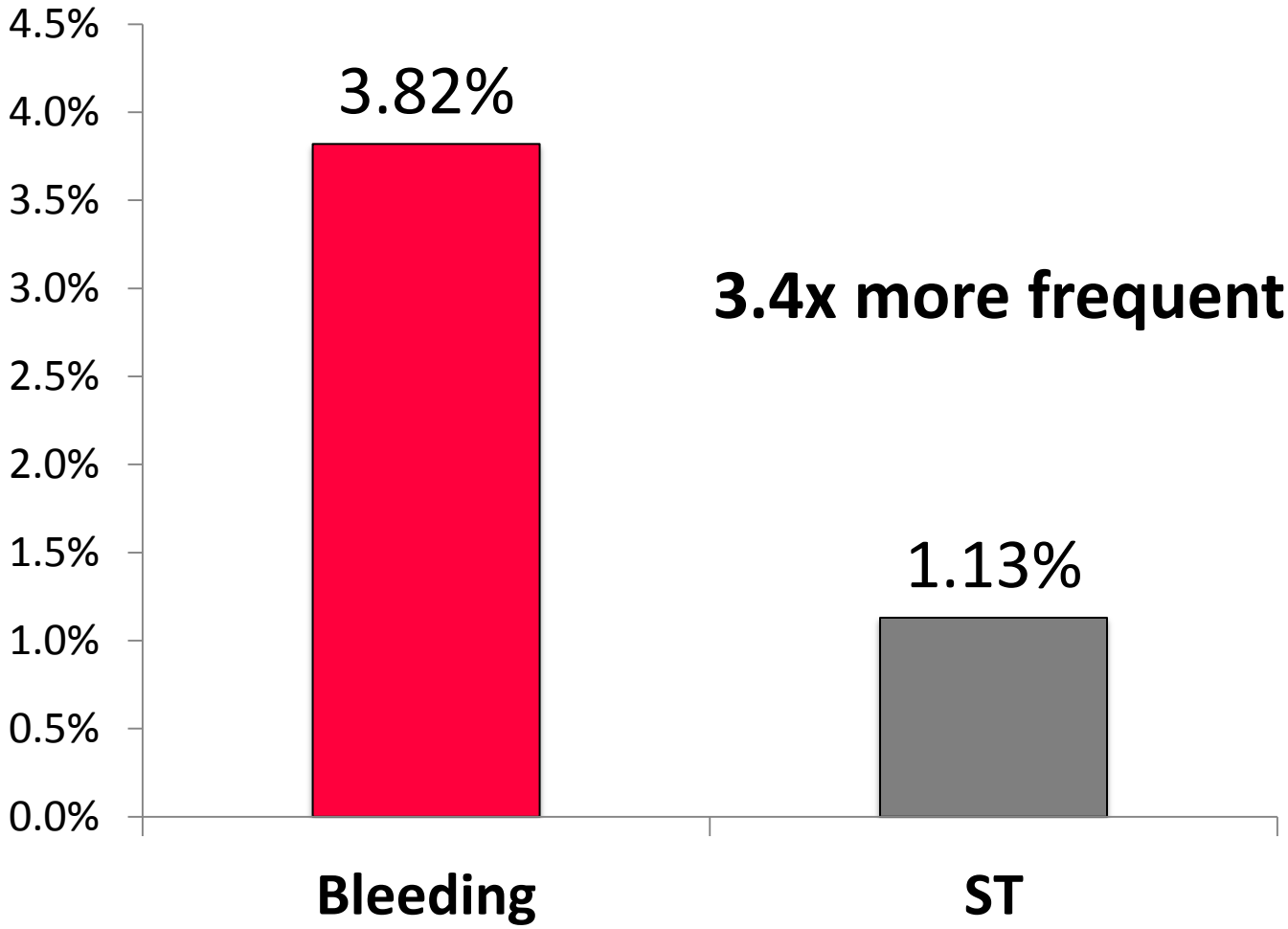
RESULTS: relative risk for ST



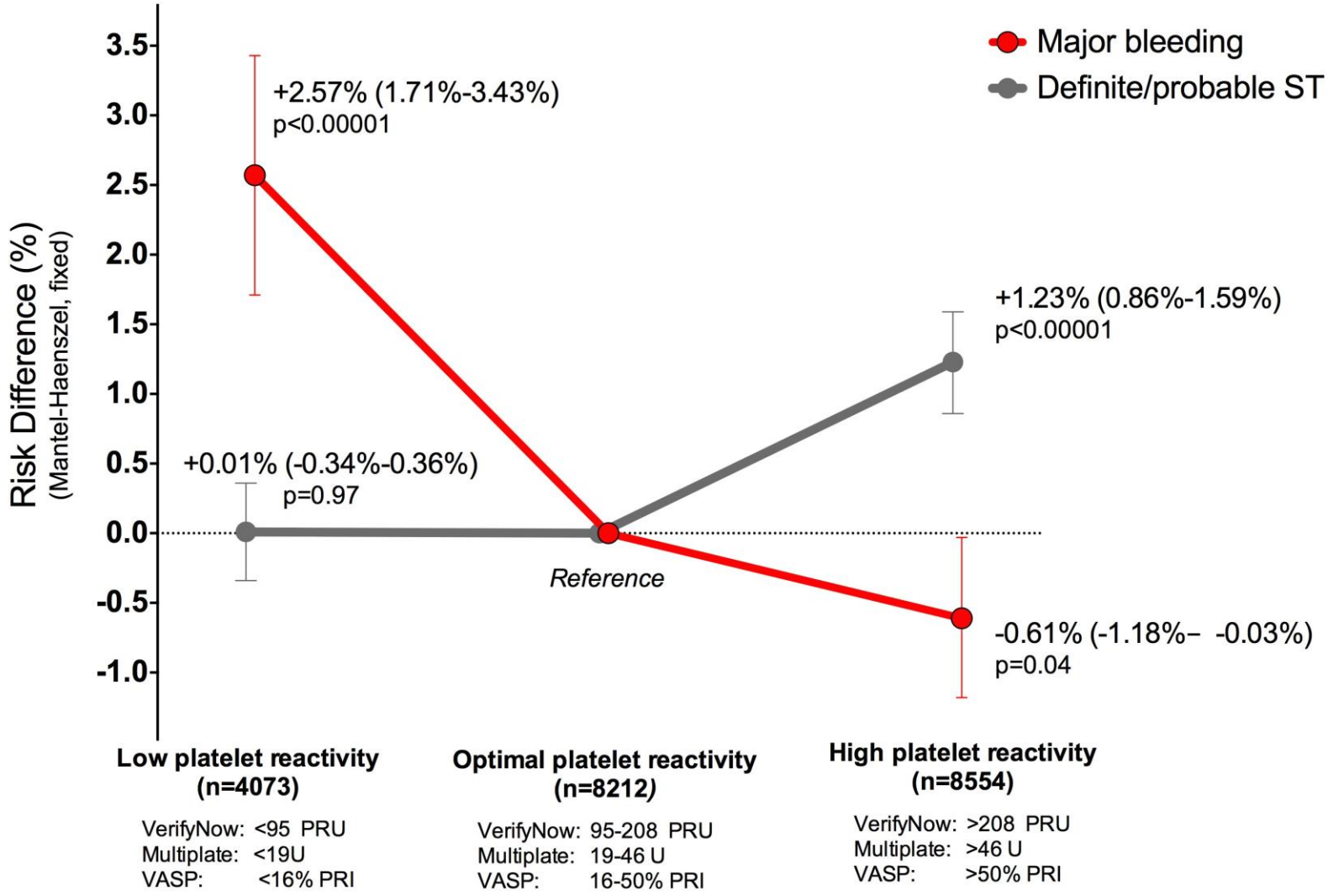
RESULTS: relative risk for MAJOR BLEEDING



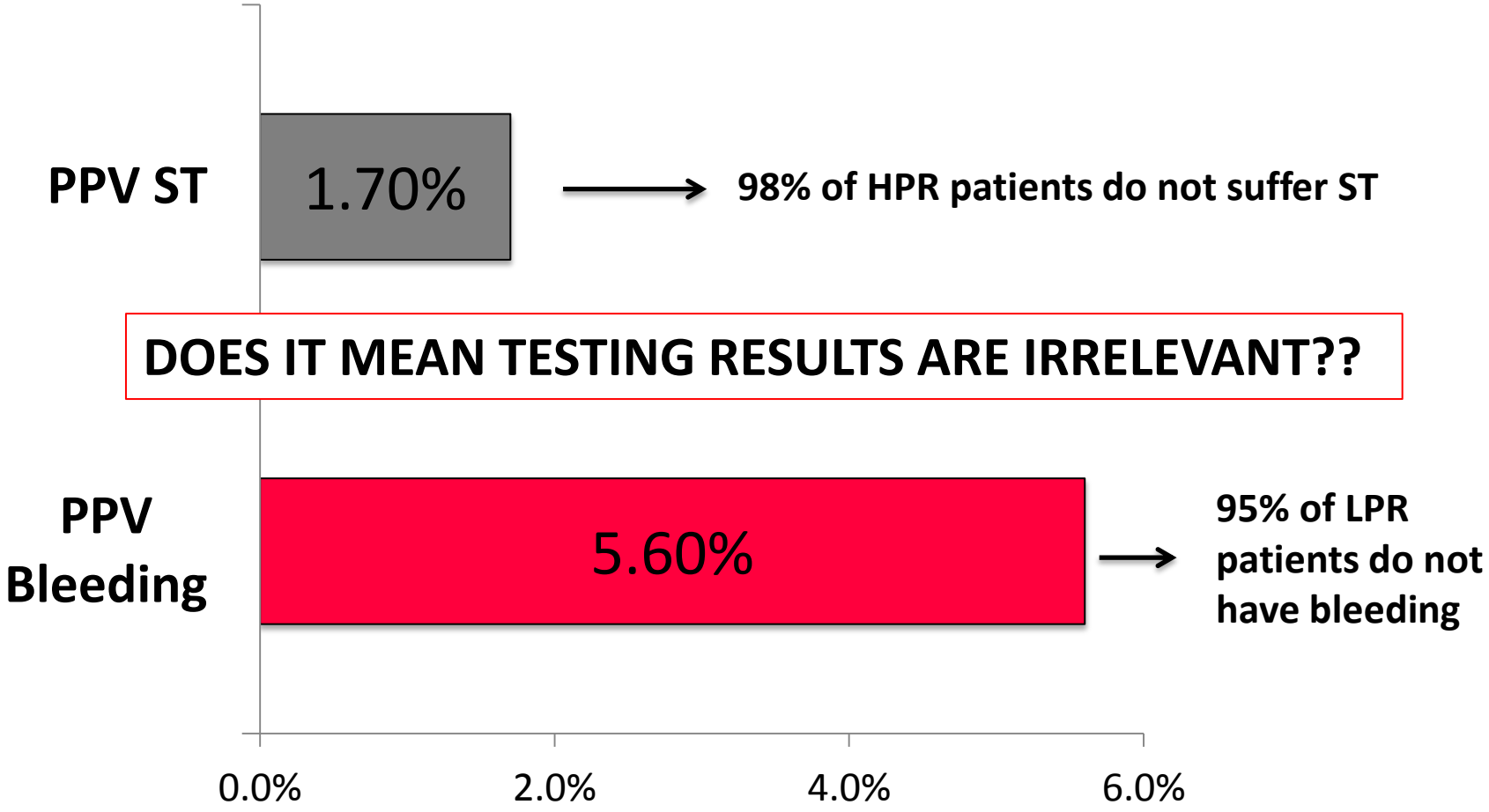
RESULTS: absolute risks of MAJOR BLEEDING and ST



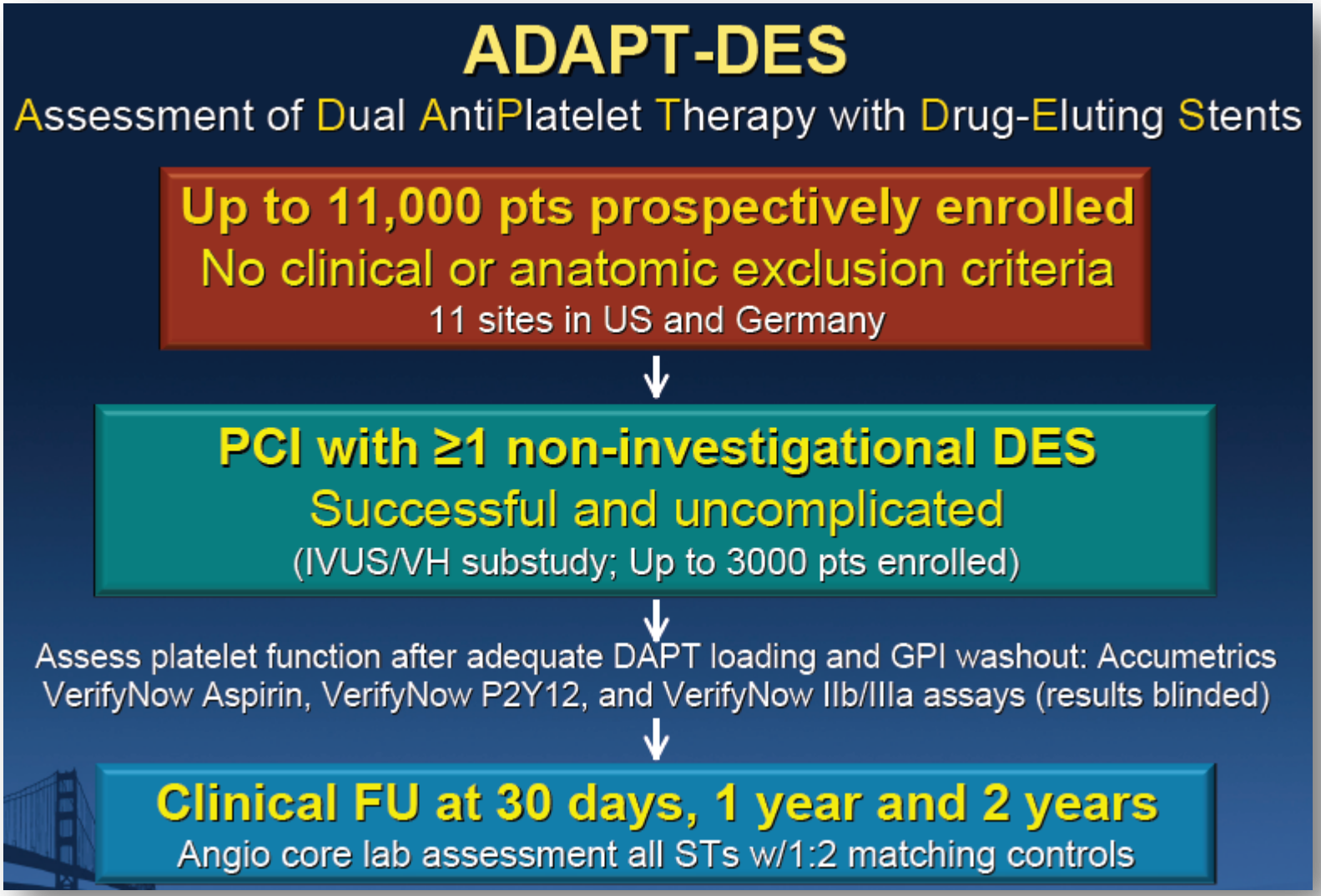
RESULTS: absolute risk for ST & BLEEDING



Positive Predictive Value for ST & Bleeding



CLINICAL PREDICTIVE VALUE OF HPR & LPR

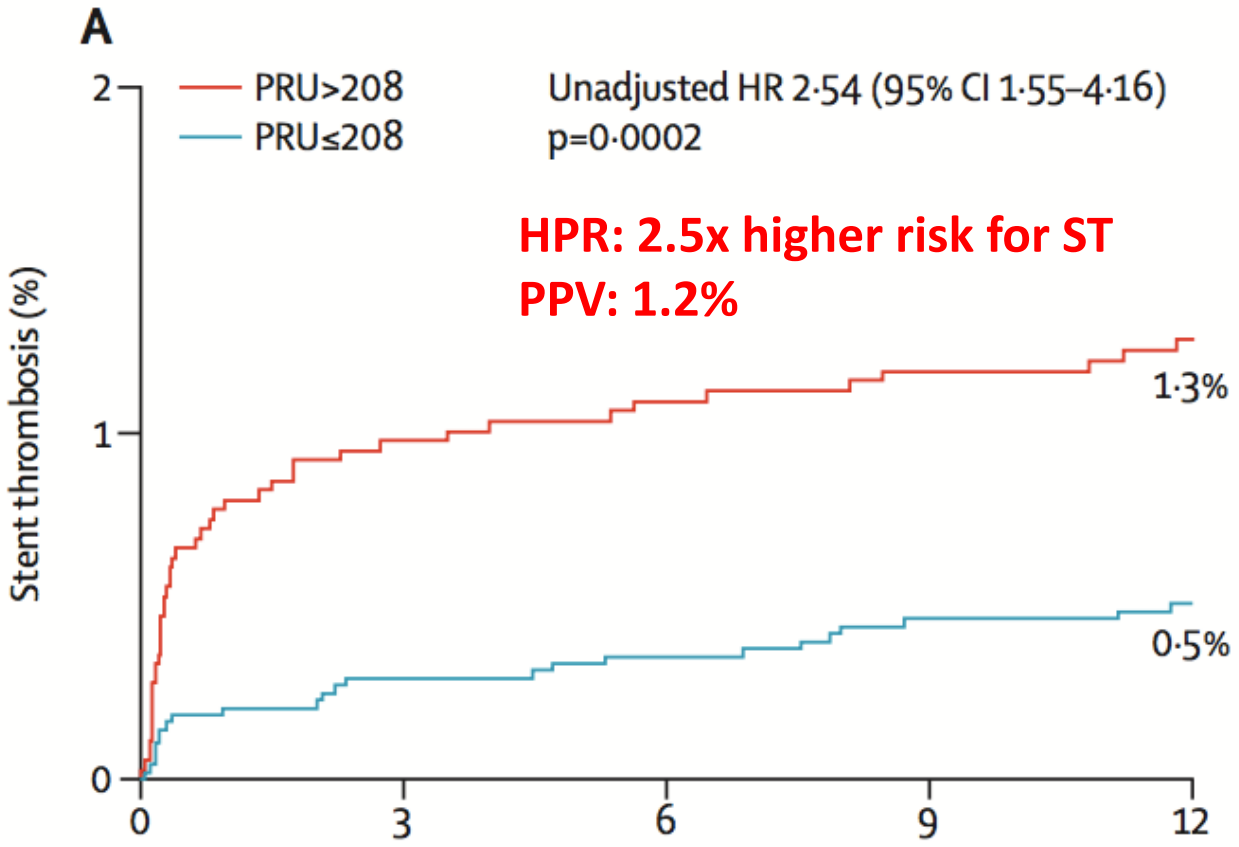


Stone et al. Lancet, 2013;382:614-23.

CLINICAL PREDICTIVE VALUE OF HPR & LPR

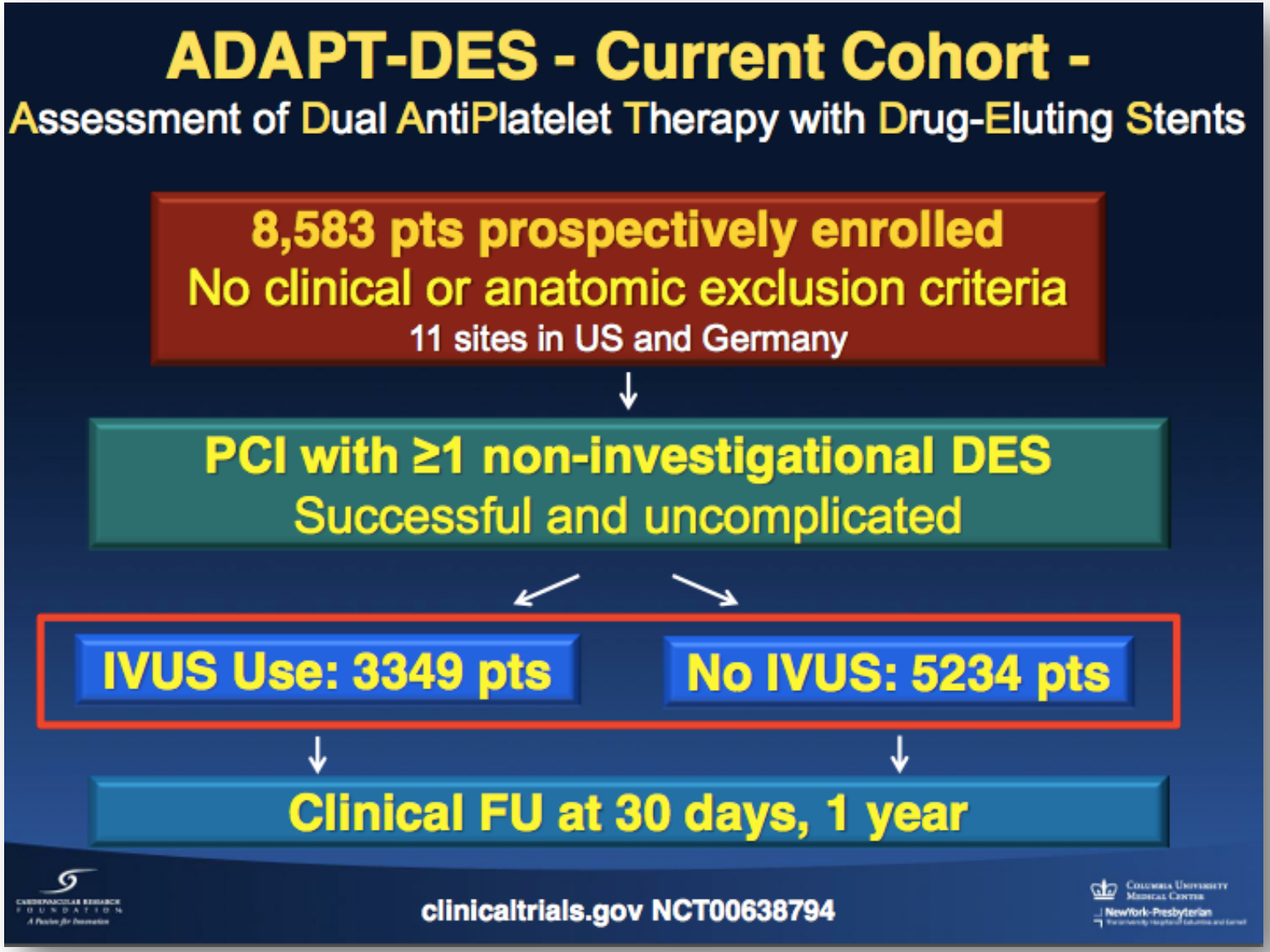
ADAPT DES REGISTRY (n=8,449 pts)

STENT THROMBOSIS at 1 year



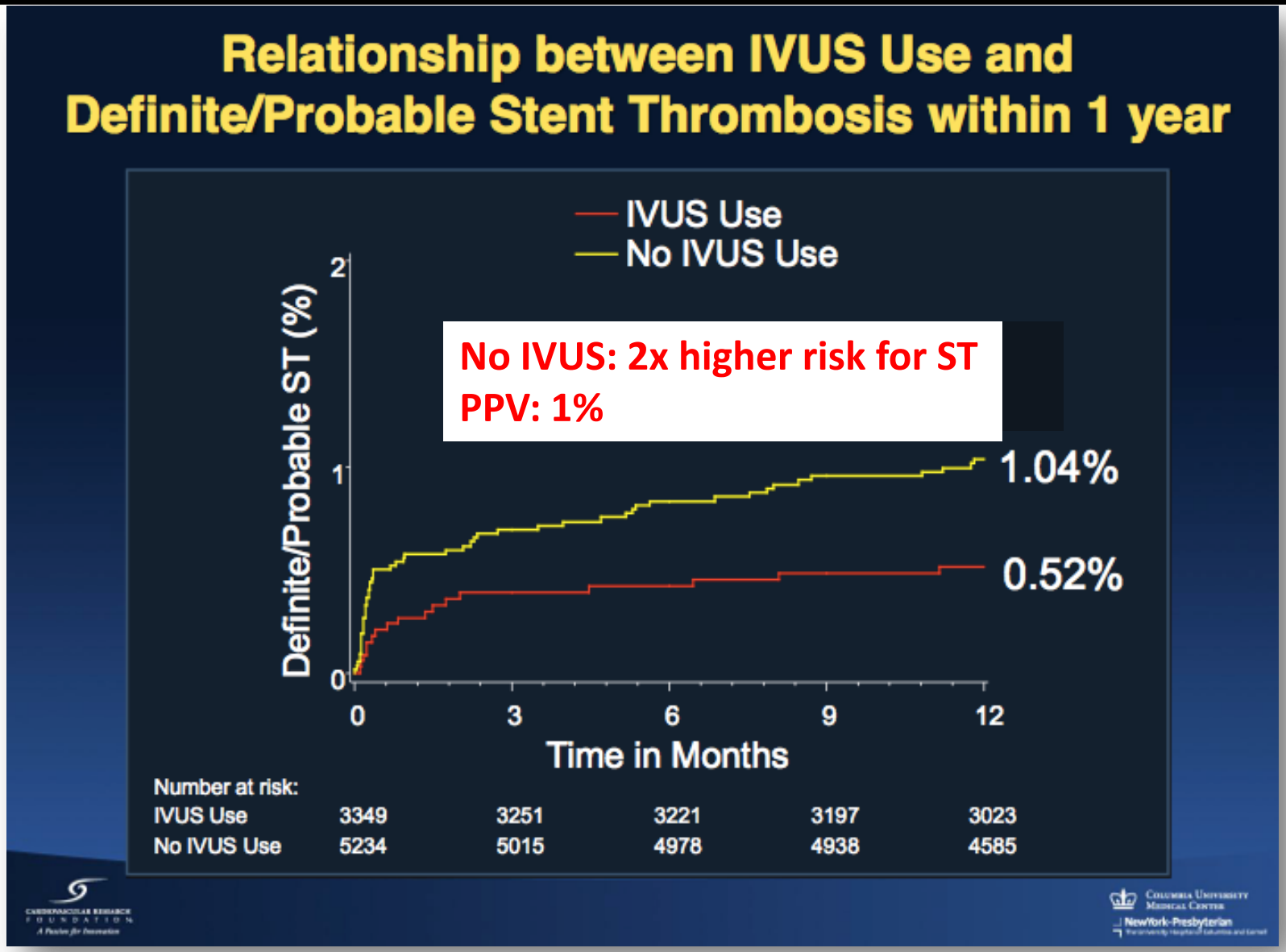
Stone et al. Lancet, 2013;382:614-23.

CLINICAL PREDICTIVE VALUE OF HPR & LPR



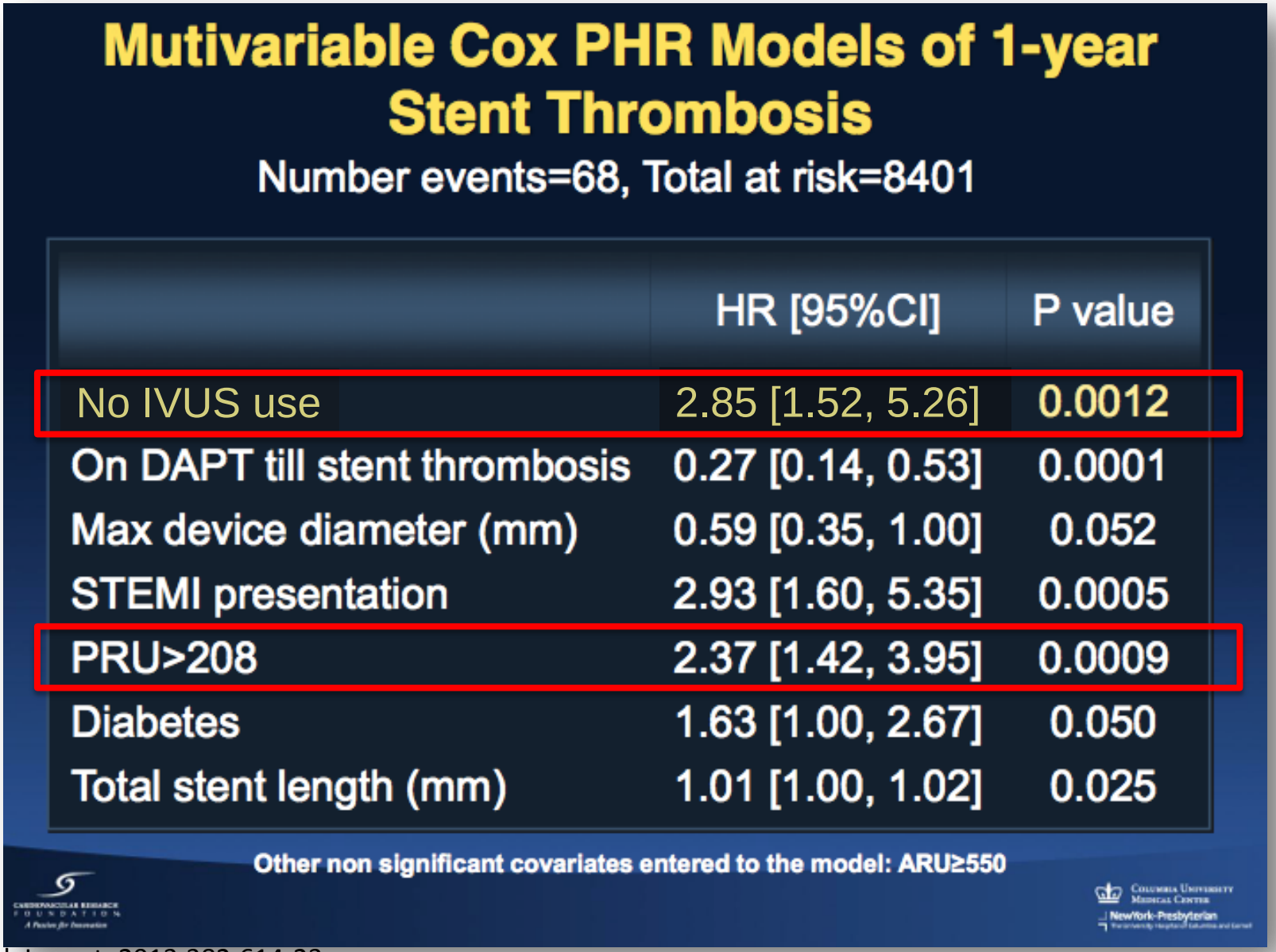
Stone et al. Lancet, 2013;382:614-23.

CLINICAL PREDICTIVE VALUE OF HPR & LPR



Stone et al. Lancet, 2013;382:614-23.

CLINICAL PREDICTIVE VALUE OF HPR & LPR



Stone et al. Lancet, 2013;382:614-23.

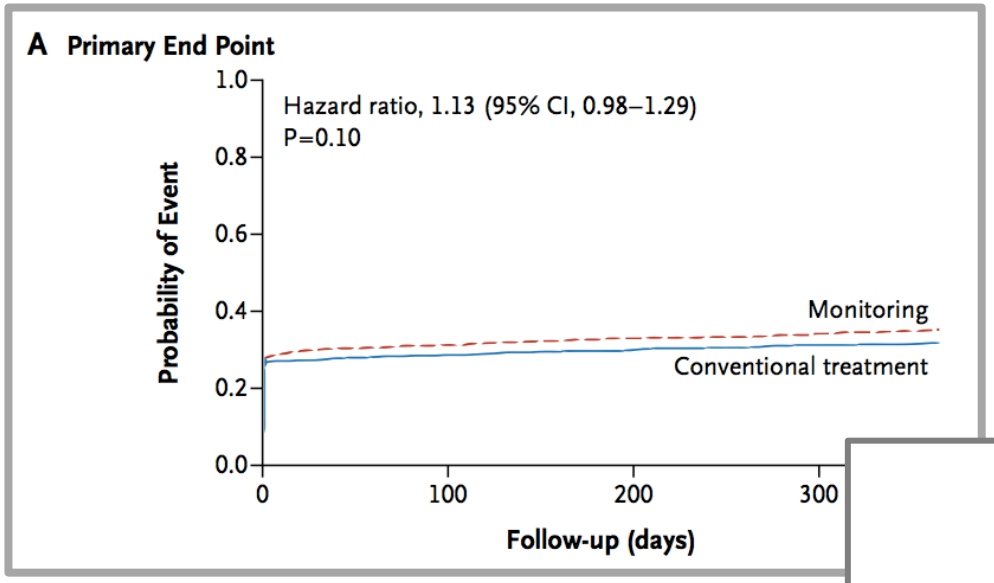
GUIDELINES:
ESC 2014 MYOCARDIAL REVASCULARIZATION

SELECTIVE Testing:	Platelet function testing or genetic testing may be considered in specific high-risk situations (e.g. history of stent thrombosis; compliance issue; suspicion of resistance; high bleeding risk).	IIb	C	
ROUTINE Testing:	Routine platelet function testing or genetic testing (clopidogrel and ASA) to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A	778,892

Windecker S et al. Eur Heart J. 2014 Aug 29. [Epub ahead of print]

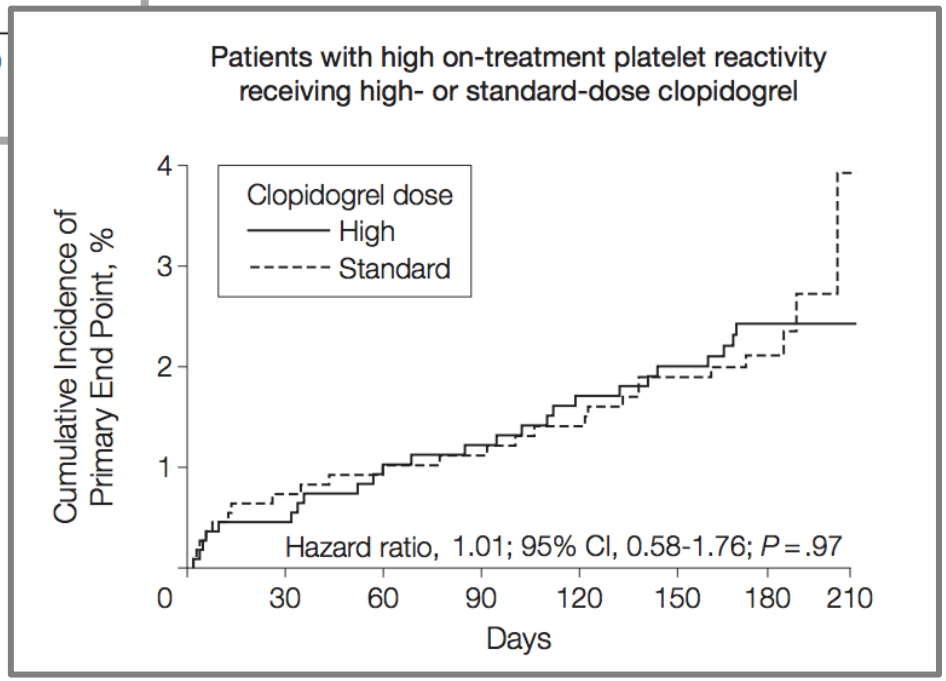
NEUTRAL RCTs

ARCTIC STUDY



Collet et al. N Engl J Med. 2012;367:2100-9.

GRAVITAS STUDY



Price MJ et al. JAMA 2011; 305: 1097-105.

LIMITATIONS OF AVAILABLE RCT-s

- Inappropriate cutoff
  - GRAVITAS: 230 PRU, ARCTIC: 235 PRU
- Low risk of patients, low event rates
  - GRAVITAS: 2.3% vs. 5% predicted
- Suboptimal effect of 150 mg clopidogrel
- No/low use of prasugrel/ticagrelor to overcome HPR
  - GRAVITAS: 0%, ARCTIC: 12%

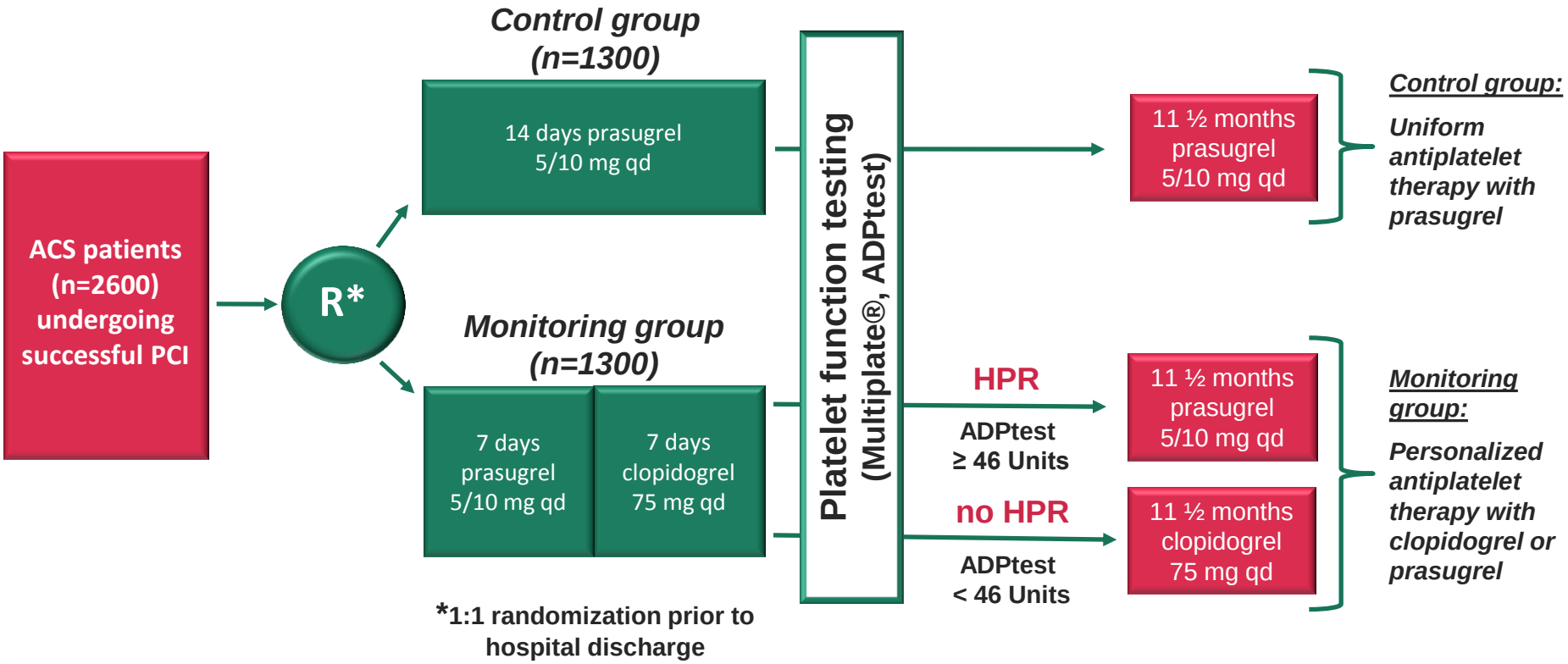
Collet et al. N Engl J Med. 2012;367:2100-9.

Price MJ et al. JAMA 2011; 305: 1097-105.

TROPICAL ACS TRIAL

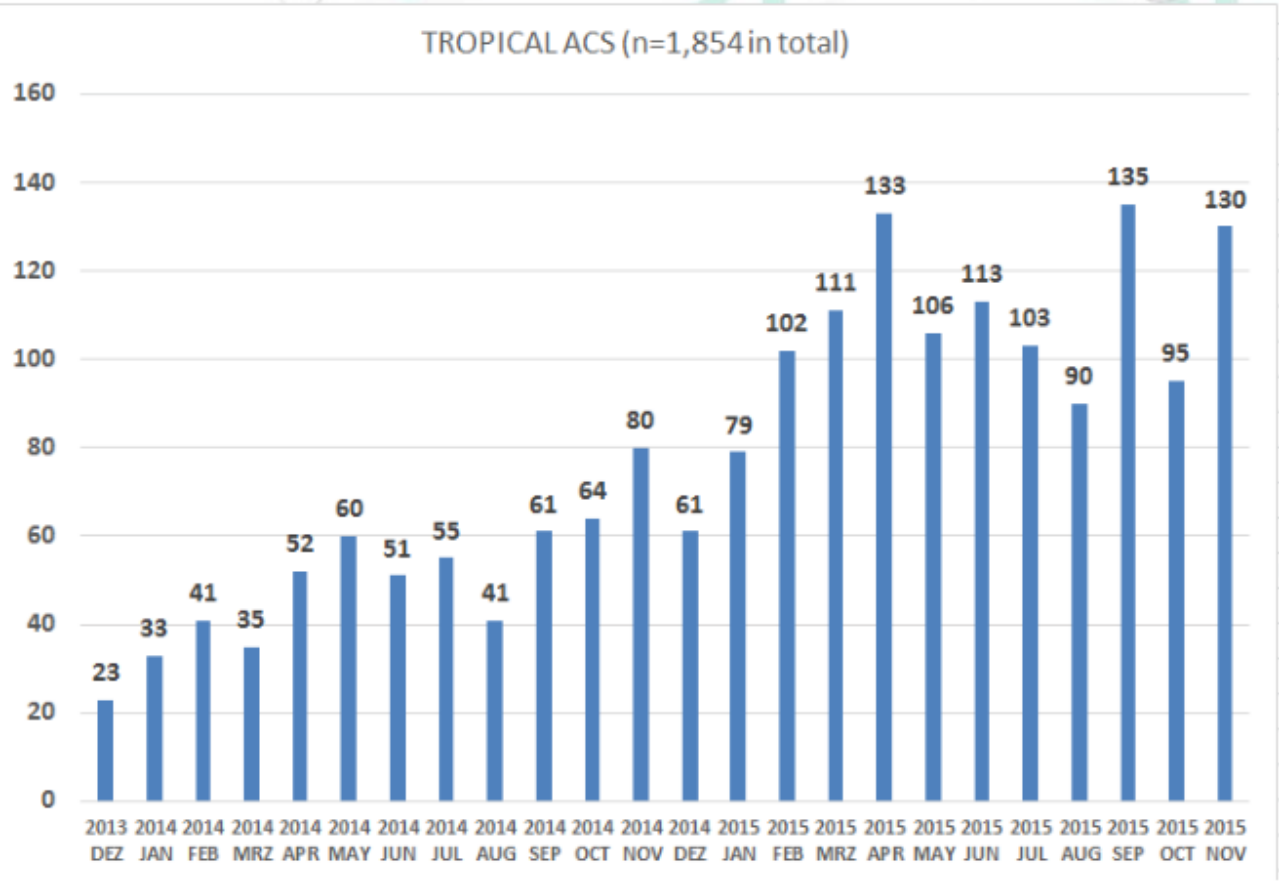
TROPICAL ACS

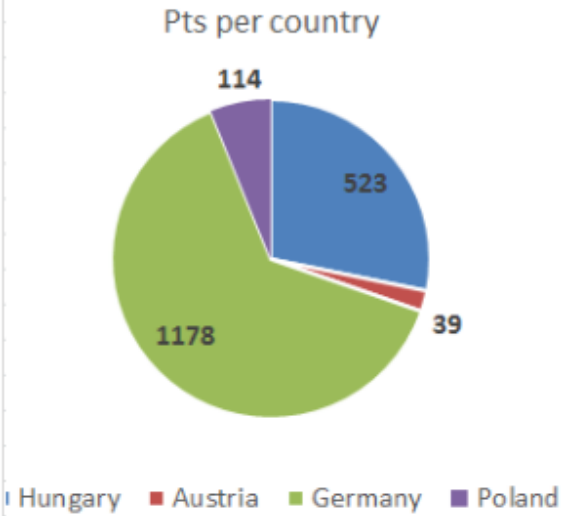
TESTING **R**ESP**O**NSIVENESS TO **P**LATELET **I**NHIBITION ON **C**HRONIC **A**NTIPLATE**L**ET TREATMENT FOR **A**CUTE **C**ORONARY **S**YNDROMES **(TROPICAL-ACS)** TRIAL



TROPICAL ACS TRIAL: ≈1900/2600 enrolled

Enrolment statistics:





RESULTS AVAILABLE: Spring 2017

CONCLUSIONS

In PCI-treated patients on thienopyridines from the Western populations:

- **HPR** is associated with a 2.7-fold higher risk for stent thrombosis
- **LPR** is associated with a 1.7-fold higher risk for major bleeding
- **OPR** seems to be a secure zone to prevent both complications

- Low PPV for ST and Bleeding relates mostly to the low prevalence of events

= Platelet reactivity is a valuable tool for *risk stratification* after PCI

CONCLUSIONS

- Whether modifying Rx to target an optimal range of platelet reactivity (OPR) is superior to conventional treatment needs to be validated in further clinical trials

= Routine *therapy adjustments* based on PFT are preliminary
= May be considered in selected patients at high risk of events or after complications

- Ongoing studies such as TROPICAL ACS may tackle limitations of prior RCTs and may bring new results to the field soon

THANK YOU FOR YOUR KIND ATTENTION!

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CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Bleeding and stent thrombosis on $P2Y_{12}$-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention

Dániel Aradi[1]*, Ajay Kirtane[2†], Laurent Bonello[3†], Paul A. Gurbel[4], Udaya S. Tantry[4], Kurt Huber[5], Matthias K. Freynhofer[5], Jurrien ten Berg[6], Paul Janssen[6], Dominick J. Angiolillo[7], Jolanta M. Siller-Matula[8], Rossella Marcucci[9], Giuseppe Patti[10], Fabio Mangiacapra[10], Marco Valgimigli[11], Olivier Morel[12], Tullio Palmerini[13], Matthew J. Price[14], Thomas Cuisset[15], Adnan Kastrati[16,17,18], Gregg W. Stone[2‡], and Dirk Sibbing[18,19‡]

BACKUP SLIDES

RESULTS: interaction analyzes

	Subgroup	LPR: n/N	no LPR: n/N	Risk Ratio 95%CI	MAJOR BLEEDING	Test for interaction
	Overall			**1.82 (1.57-2.12)**		
1.	VerifyNow	172/2167	461/11210	1.64 (1.38-1.94)		
	Multiplate	32/1358	20/2550	2.98 (1.73-5.14)		0.02
	VASP	26/548	86/3006	2.62 (1.74-3.94)		
2.	Exploratory studies	164/2748	404/8532	1.52 (1.27-1.82)		<0.01
	Validation studies	66/1325	163/8234	3.32 (2.46-4.47)		
3.	ADAPT-DES	140/1690	388/6758	1.44 (1.20-1.74)		<0.01
	Excl. ADAPT-DES	90/2383	179/10008	3.13 (2.38-4.10)		
4.	Clopidogrel	210/3909	549/16242	1.71 (1.46-2.00)		<0.01
	Prasugrel	20/164	18/524	3.97 (2.18-7.24