Clinical Role of Platelet Function Testing: Short Overview of Recent European and American Expert Consensus Papers

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14 December I JCR 2013 I Busan, South Korea

CONFLICTS OF INTERESTS

- **CONSULTING/RESEARCH GRANTS:**
  - Verum Diagnostica

- **LECTURE FEES:**
  - Roche
  - Verum Diagnostica
  - DSI/Lilly
  - AstraZeneca
  - Krka
  - Bayer
  - Pfizer

BACKGROUND

European Heart Journal Advance Access published September 25, 2013

European Heart Journal
doi:10.1093/eurheartj/eht375

CURRENT OPINION

Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention

Dániel Aradi[1,*], Robert F. Storey[2], András Komócsi[3], Dietmar Trenk[4], Dietrich Gulba[5], Róbert Gábor Kiss[6], Steen Husted[7], Laurent Bonello[8], Dirk Sibbing[9], Jean-Philippe Collet[10], and Kurt Huber[11], on behalf of the Working Group on Thrombosis of the European Society of Cardiology

Aradi D et al. Eur Heart J. 2013 Sep 25. [Epub ahead of print]

BACKGROUND

Published online September 26, 2013

Accepted Manuscript

Consensus and Update on the Definition of On-Treatment Platelet Reactivity to ADP Associated with Ischemia and Bleeding

Udaya S. Tantry, PhD Laurent Bonello, MD, PhD Daniel Aradi, MD, PhD Matthew J. Price, MD Young-Hoon Jeong, MD, PhD Dominick J. Angiolillo, MD, PhD Gregg W. Stone, MD Nick Curzen, BM (hons), PhD Tobias Geisler, MD Jurrien ten Berg, MD, PhD Ajay Kirtane, MD, SM Jolanta Siller-Matula, MD, PhD Elisabeth Mahla, MD Richard C. Becker, MD Deepak L. Bhatt, MD, MPH Ron Waksman, MD Sunil V. Rao, MD Dimitrios Alexopoulos, MD Rossella Marcucci, MD, PhD Jean-Luc Reny, MD, PhD Dietmar Trenk, PhD Dirk Sibbing, MD Paul A. Gurbel, MD

GUIDELINE RECOMMENDATIONS

Clinical guideline recommendations regarding platelet function testing			
ESC guidelines on myocardial revascularization 2010	*Monitoring of antiplatelet response by platelet function assays is currently used for clinical research, but **not** in daily clinical practice.*	**III**	**C**
ESC NSTE-ACS guidelines 2011	*Platelet function testing **may be considered** in selected cases when clopidogrel is used. Several trials currently under way may clarify the impact of adapting therapy on the basis of the results of platelet reactivity assays, but, so far, the routine clinical use of platelet function tests in clopidogrel-treated patients with ACS cannot be recommended.*	**IIb**	**B**
ACC/AHA/SCAI PCI guidelines 2011	*Platelet function testing **may be considered** in patients at high risk for poor clinical outcomes. In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered. The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.*	**IIb**	**C**
ACCF/AHA UA/NSTEMI guidelines 2012	*Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on $P2Y_{12}$-receptor inhibitor therapy **may be considered** if results of testing may alter management.*	**IIb**	**B**
ESC STEMI guidelines 2012	*No specific recommendation.*	**-**	**-**
ACCF/AHA STEMI guidelines 2013	*The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain.*	**-**	**-**

Aradi D et al. Eur Heart J. 2013 Sep 25. [Epub ahead of print]

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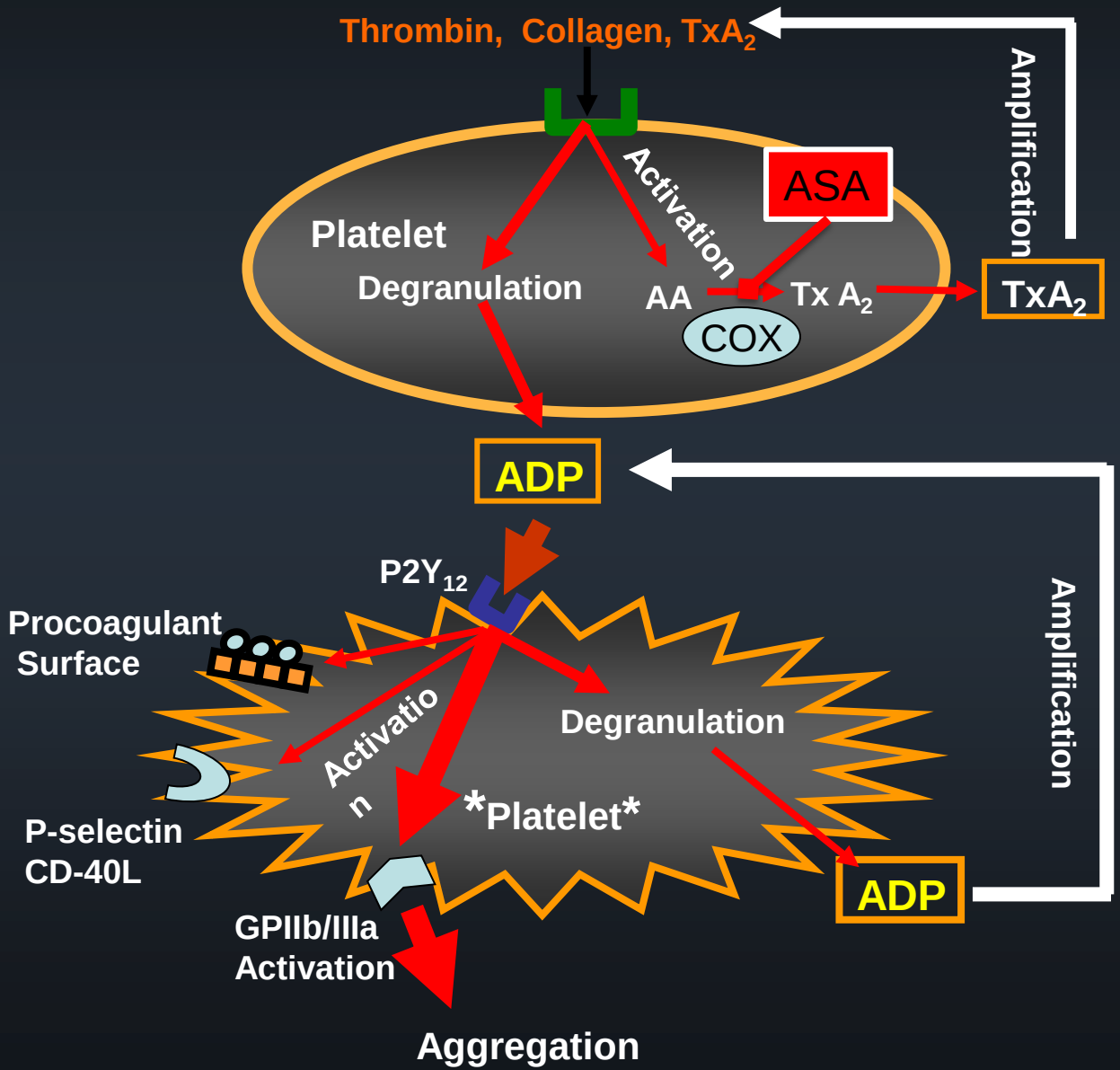
- What parameter should we measure?
- What device should we use?
- What should we do based on results?
- What patients should we measure?

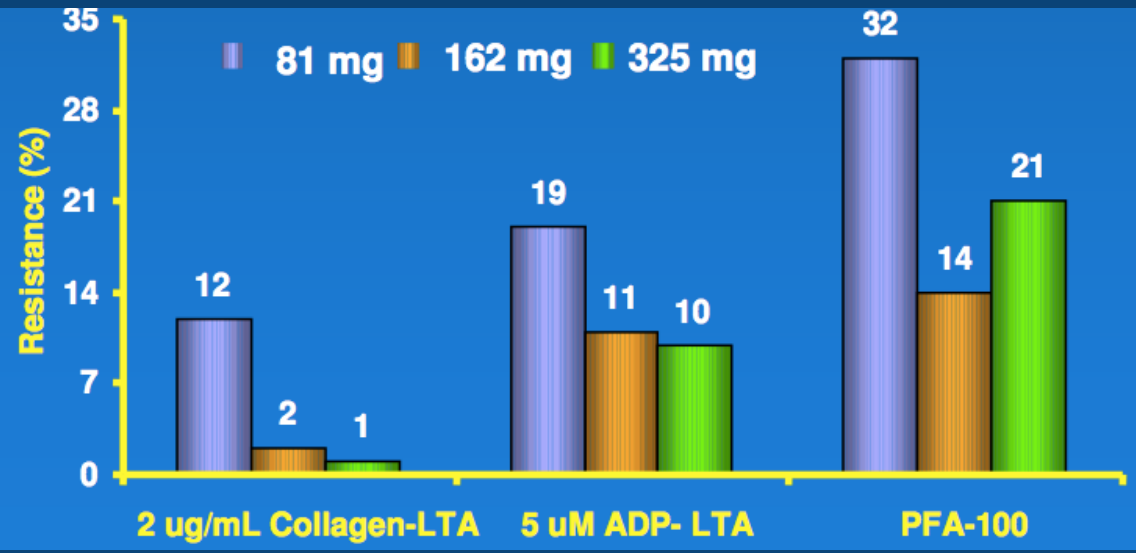
What parameter should we measure: ASA



PA Gurbel, modified

What parameter should we measure: ASA

Aspirin-Induced Platelet Effects- ASPECT Study

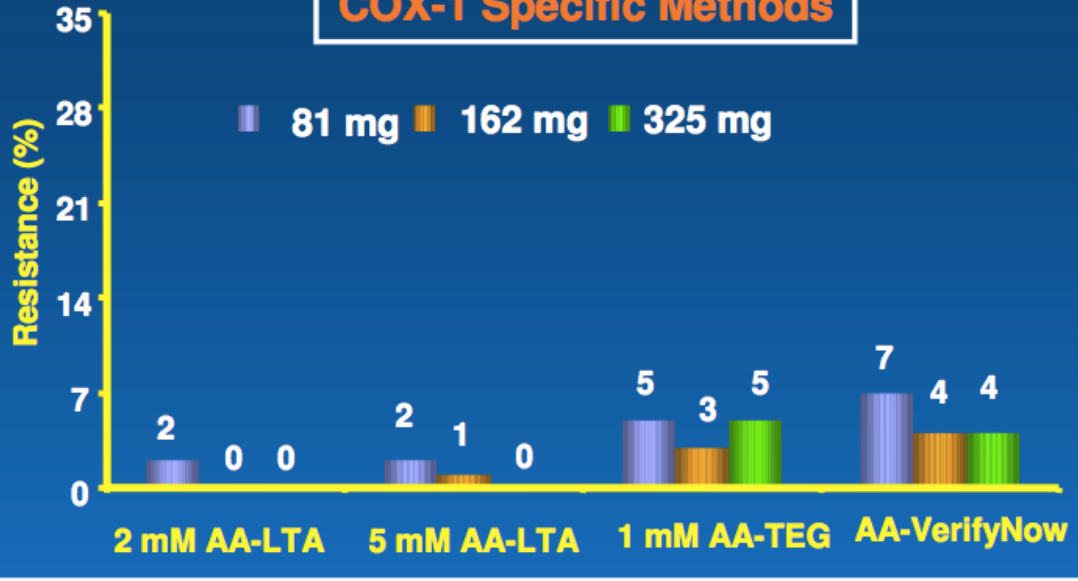


Definitions of "Resistance"

5 uM ADP- LTA	(>70% Agg)
2 ug/mL Collagen-LTA	(>70% Agg)
PFA-100	(<193 Secs)

(Gurbel PA et al. *Circulation*. 115: 3156-64, 2007)

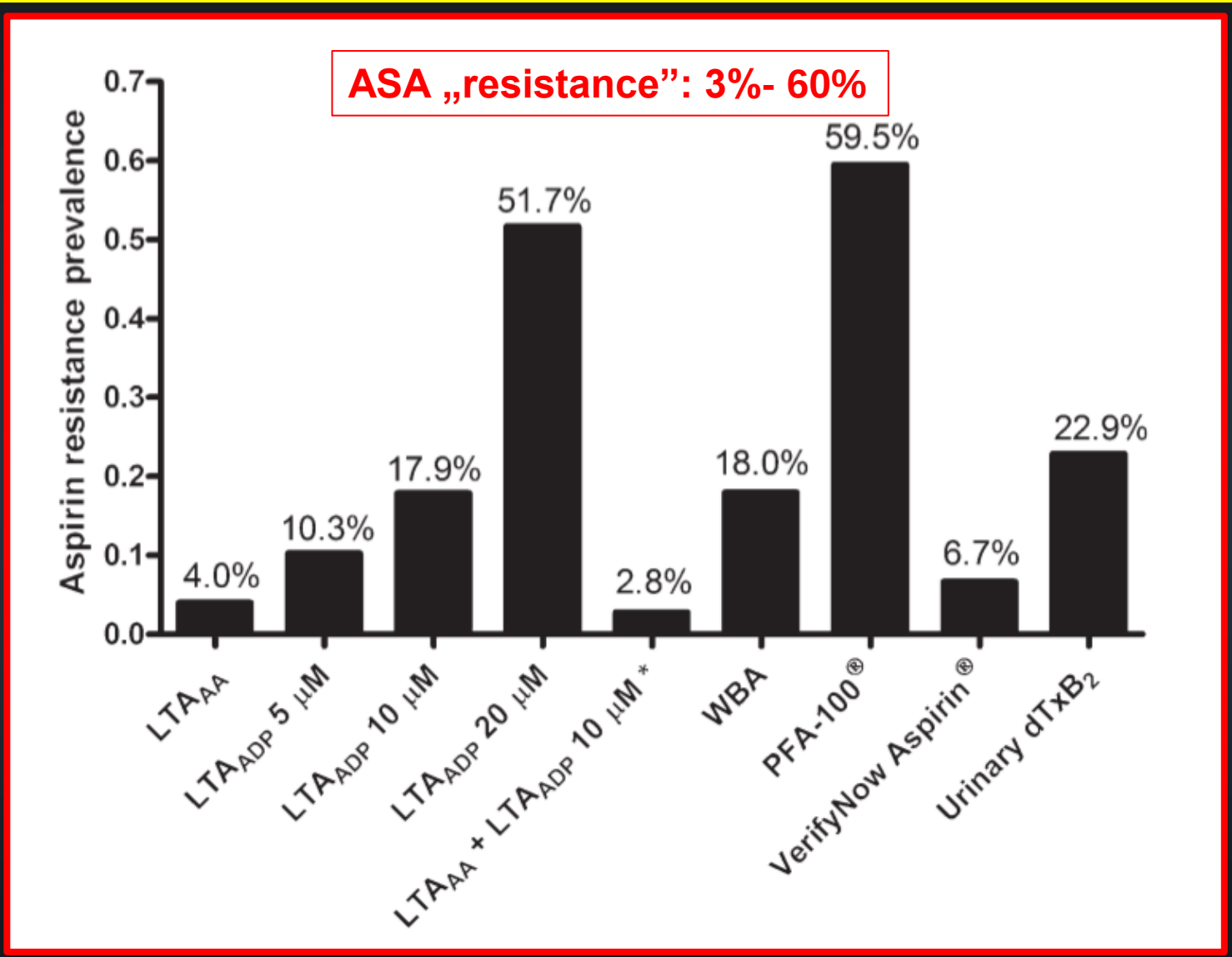
COX-1 Specific Methods



Definitions of "Resistance"

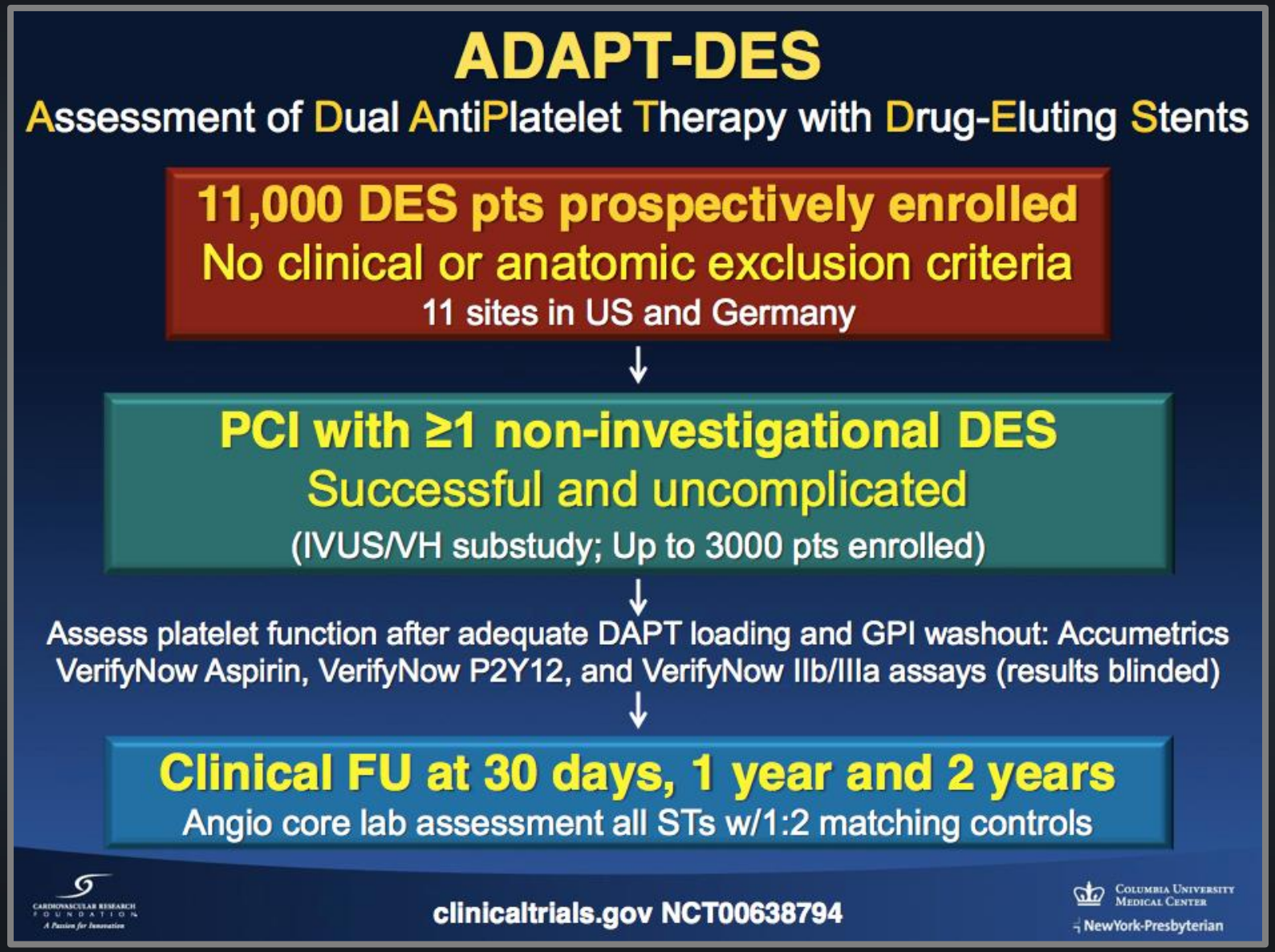
2 mM AA- LTA	(>20% Agg)
5 mM AA- LTA	(>20% Agg)
1 mM AA- TEG	(>50% Agg)
AA- VerifyNow	(>550 ARU)

What parameter should we measure: ASA



Lordkipanidzé M et al. Eur Heart J. 2007;28:1702-8.

What parameter should we measure: ASA



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

What parameter should we measure: ASA

ADAPT-DES: Relationship between VerifyNow platelet response to DAPT and subsequent 1-year def/prob stent thrombosis (n=8,583)

VerifyNow test	Def/prob ST (n=70)	No def/prob ST (n=8,513)	P
Aspirin ARU	426 ± 58	419 ± 55	0.30
- ARU ≥550	7.2%	5.6%	0.54

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

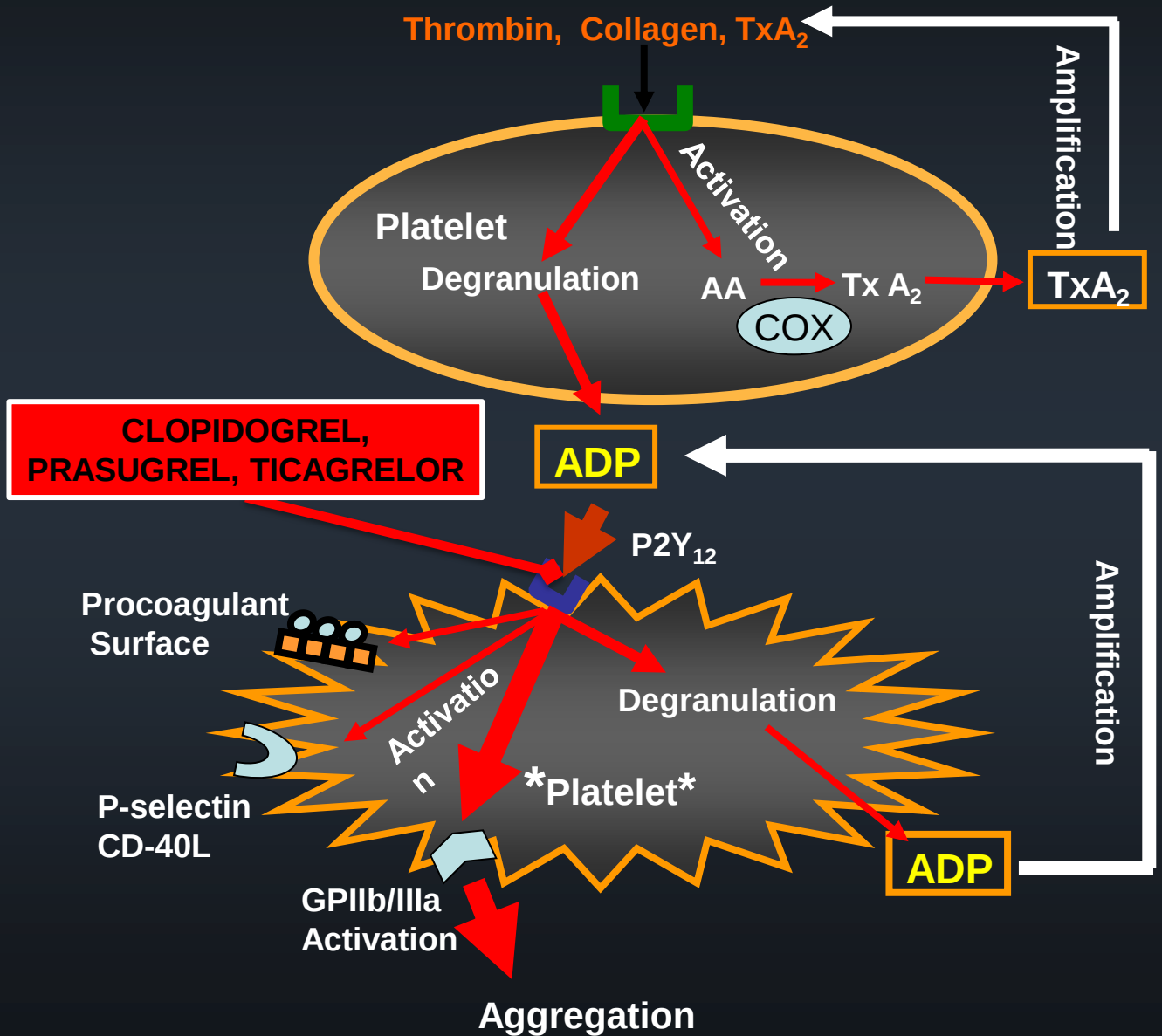
What parameter should we measure: ASA

Measuring the response to aspirin by platelet function testing is not recommended in patients after PCI.	**III**	**B**

- It is highly complicated to measure ASA effect specifically (serum TxA2), no point-of-care assays
- True aspirin “resistance” is very rare <5%
- Most assays that measure “aspirin response”, rather assess general platelet reactivity due to inflammation, hyperactivation (COX-1 independent pathways)
- ASA response is NOT a predictor of ischemic events, including ST

Aradi D et al. Eur Heart J. 2013 Sep 25. [Epub ahead of print]

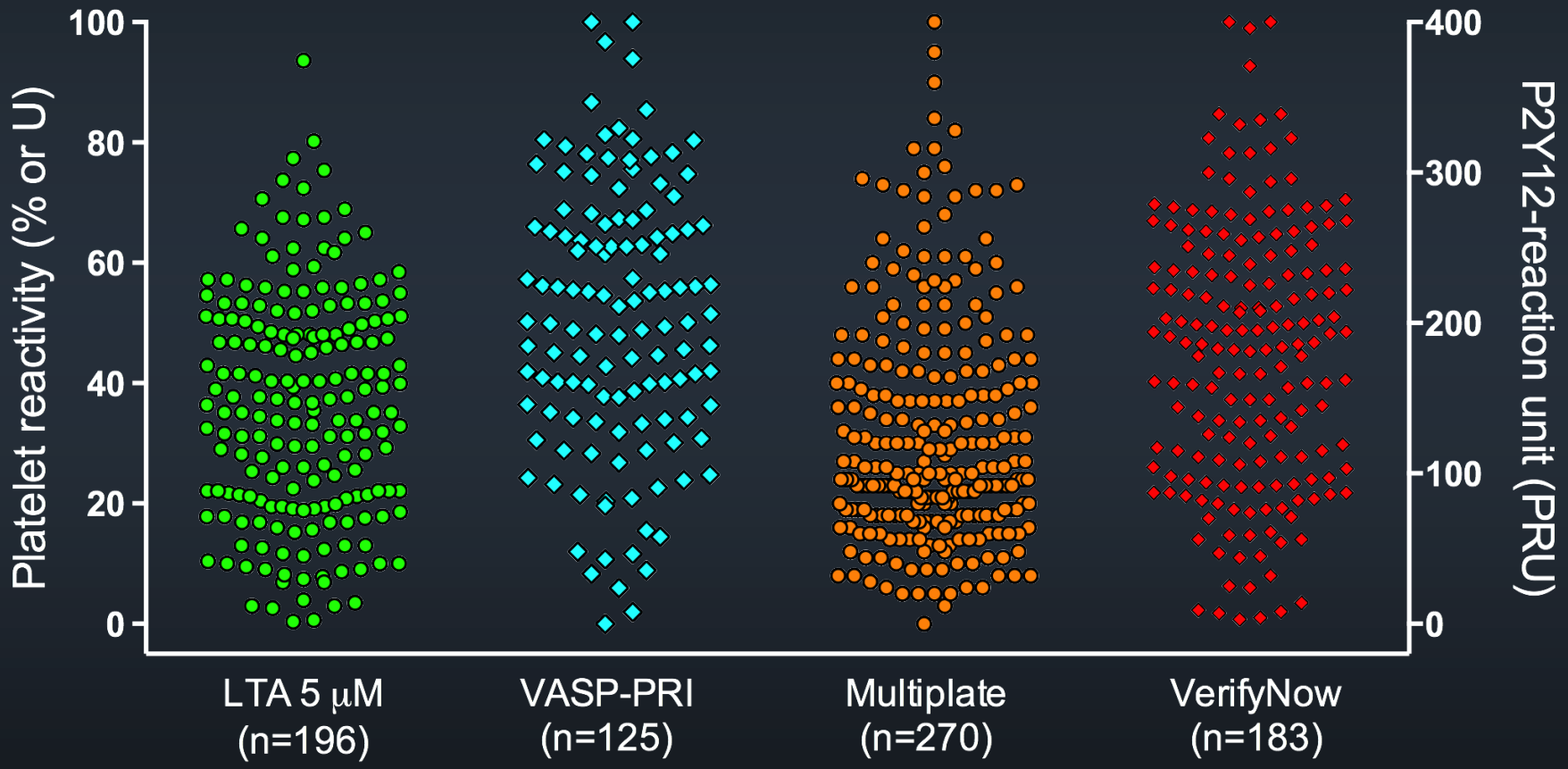
What parameter should we measure: $P2Y_{12}$ inhibitors



PA Gurbel, modified

What parameter should we measure: $P2Y_{12}$ inhibitors

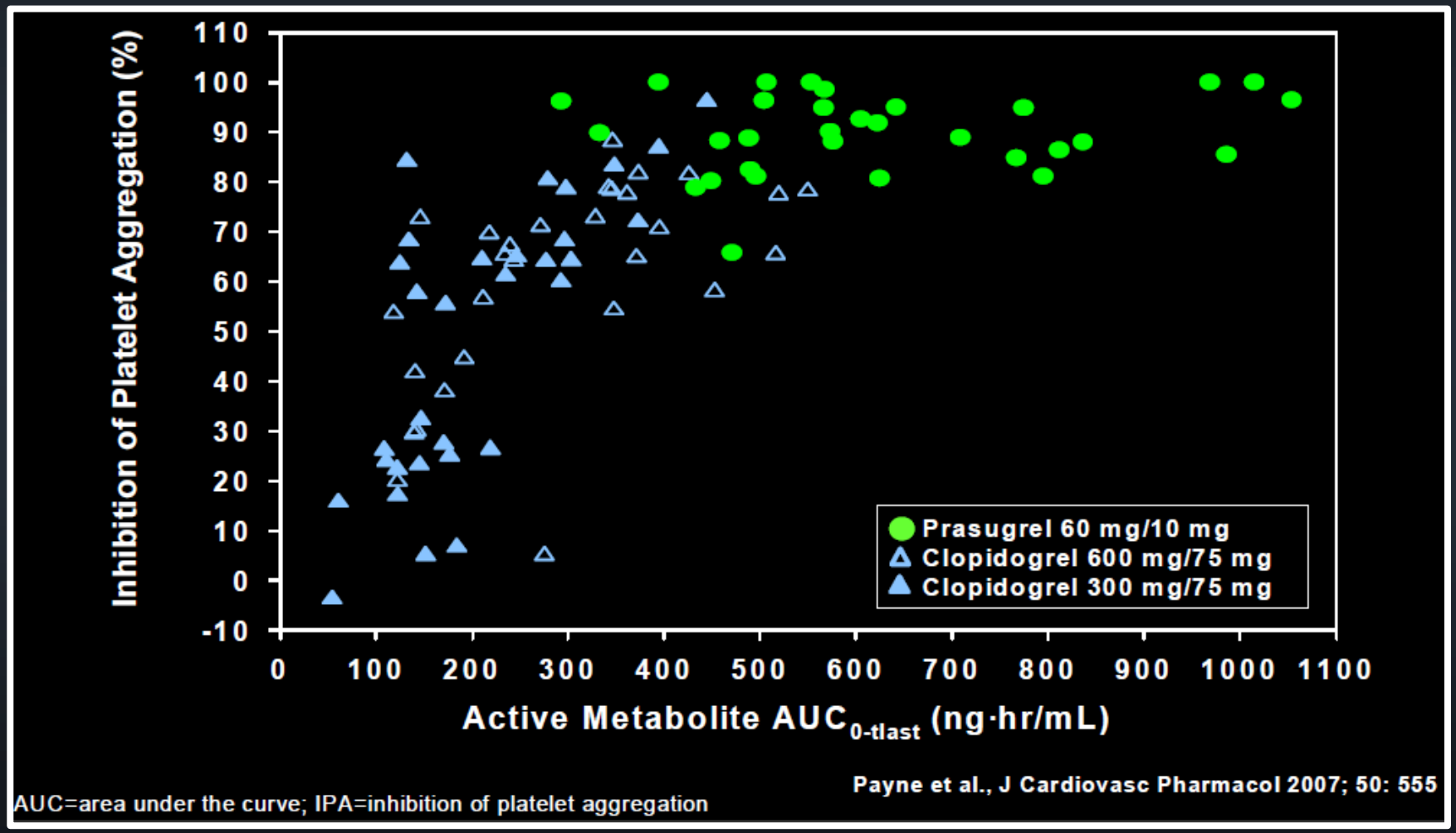
After 600 mg clopidogrel loading dose, in patients with stable angina undergoing PCI



Aradi D et al. Eur Heart J. 2013 Sep 25. [Epub ahead of print]

What parameter should we measure: $P2Y_{12}$ inhibitors

Good correlation between platelet function and active metabolite cc

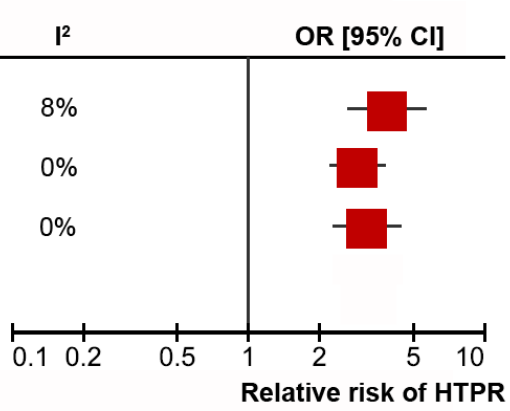


What parameter should we measure: $P2Y_{12}$ inhibitors

Meta-analysis on the clinical relevance of high on-clopidogrel platelet reactivity (HPR)

13 507 patients, 21 studies

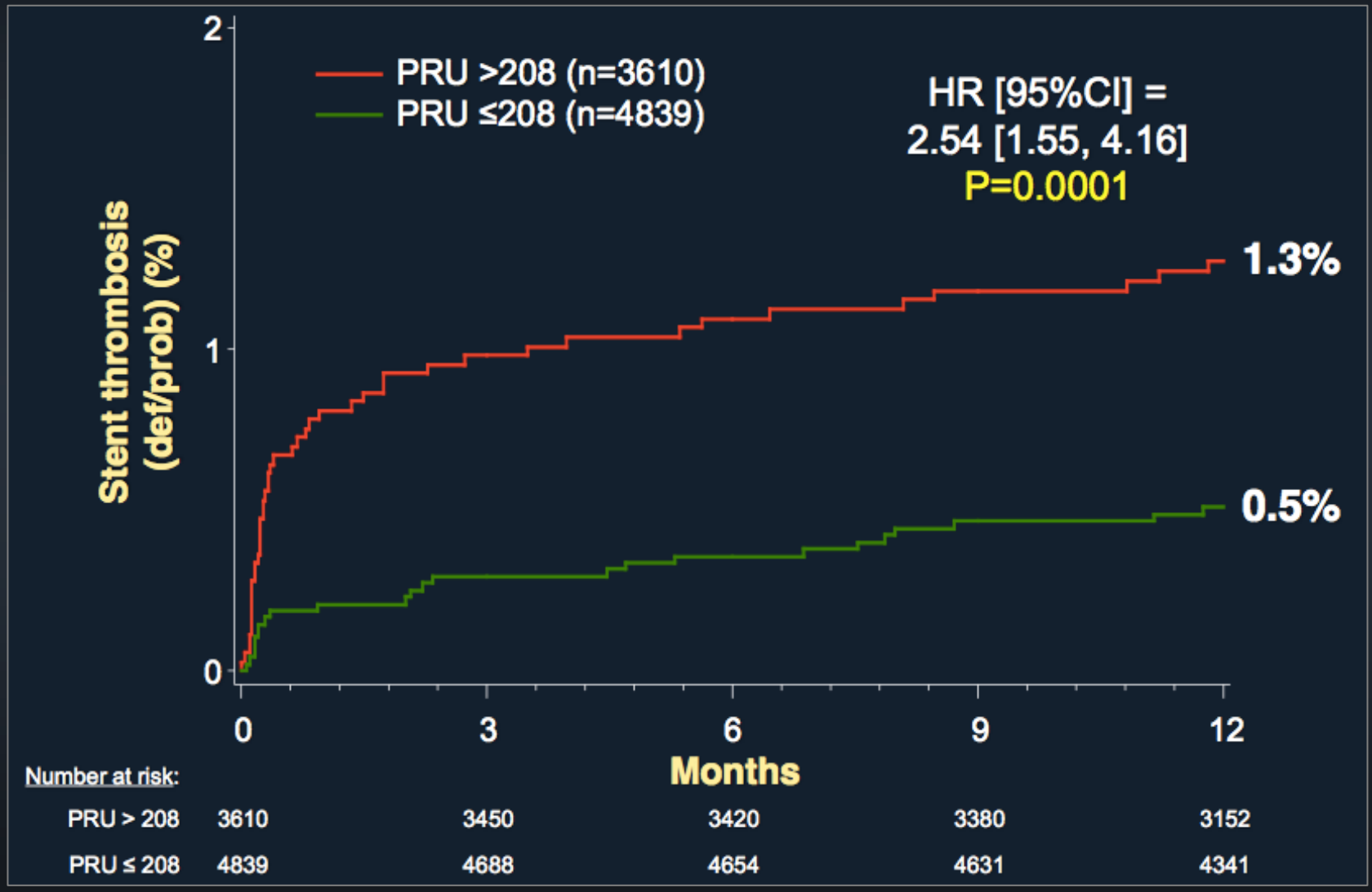
OUTCOME	HTPR	no HTPR	HTPR%	OR [95% CI]	Overall effect	I^2
DEF/PROB STENT THROMBOSIS	3371	5914	36.3%	3.95 [2.68 - 5.82]	p < 0.00001	8%
NON-FATAL MI	3421	5006	40.6%	2.90 [2.21 - 3.81]	p < 0.00001	0%
CV DEATH	3616	6135	37.1%	3.18 [2.29 - 4.42]	p < 0.00001	0%



Aradi et al. Am Heart J. 2010; 160: 543-51.

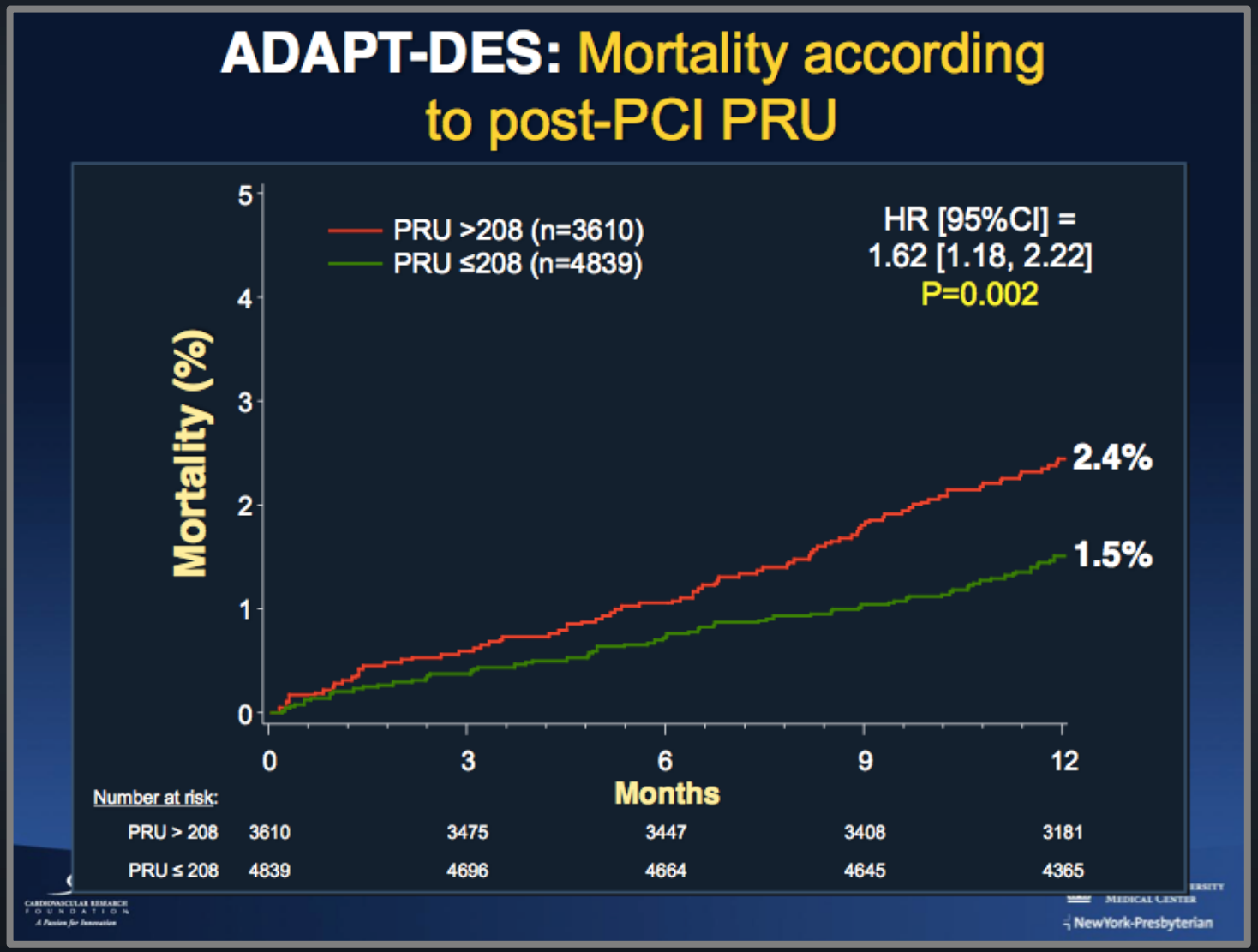
What parameter should we measure: $P2Y_{12}$ inhibitors

ADAPT-DES: DEFINITE / PROBABLE ST @ 1 year



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

What parameter should we measure: $P2Y_{12}$ inhibitors



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

What parameter should we measure: $P2Y_{12}$ inhibitors

In clopidogrel-treated patients, measuring ADP-dependent platelet reactivity with platelet function assays may be considered to predict the risk of ST.	**IIb**	**B**

- ADP-stimulated platelet reactivity is a good measure of the PD effect of $P2Y_{12}$-inhibitors
- High platelet reactivity (HPR) on clopidogrel varies around 20-30% according to the patients studied
- HPR on clopidogrel is a strong (HR>3.00) and independent predictor ($p<0.001$ in multivariate model) of ST
- ADP-stimulated platelet reactivity is not only a marker of $P2Y_{12}$-inhibitor effect, but also a integrator of patient comorbidities (age, STEMI, renal insuff., DM)

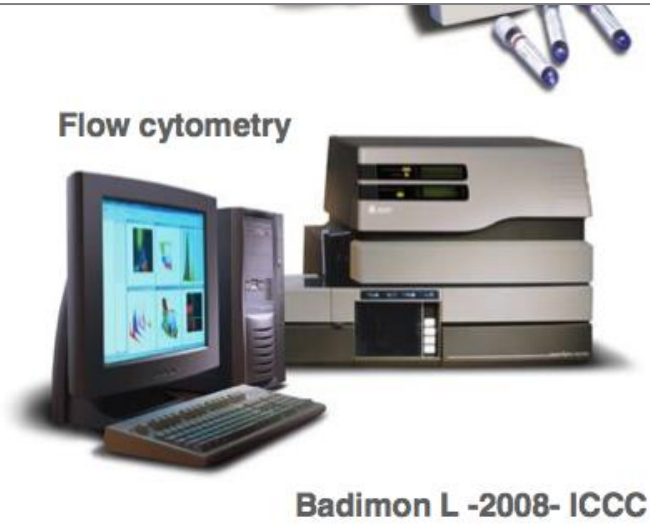
Aradi D et al. Eur Heart J. 2013 Sep 25. [Epub ahead of print]

WHAT DEVICE SHOULD WE USE?

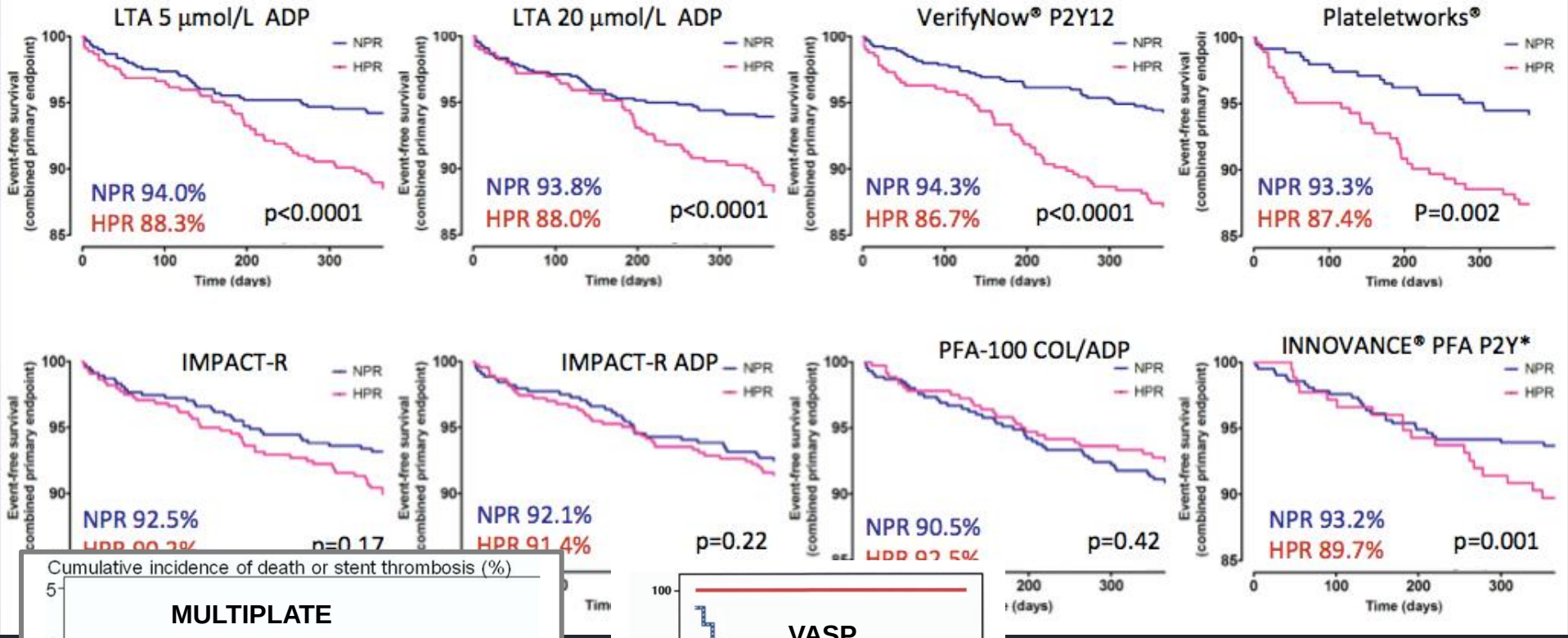
Methods for platelet function assessment

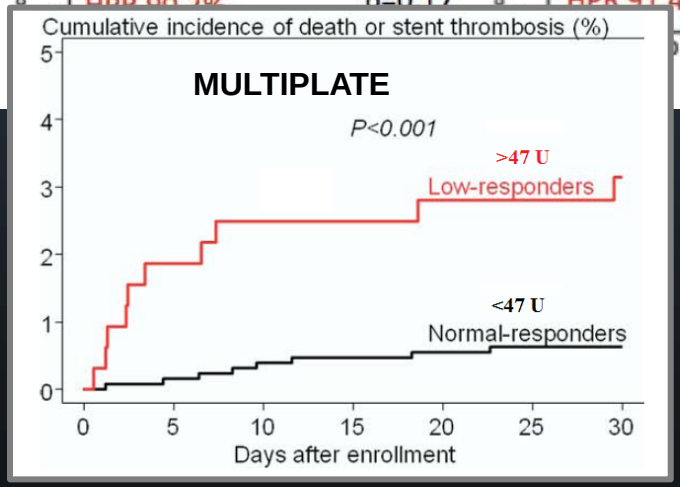
3 MAJOR CRITERIA:

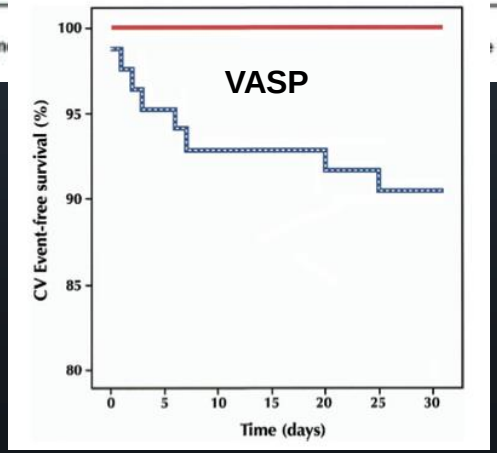
- Predict clinical outcomes? (ST and bleeding)
- Standardized? (universal cutoffs may be applied)
- Point-of-care, easy-to use, bedside available?



WHAT DEVICE SHOULD WE USE?







Breet et al. JAMA. 2010;303:754-62.
Sibbing et al. JACC 2009;53:849-56.
Bonello JACC 2008;51:1404-11.

WHAT DEVICE SHOULD WE USE?

Methods for platelet function assessment

VerifyNow™

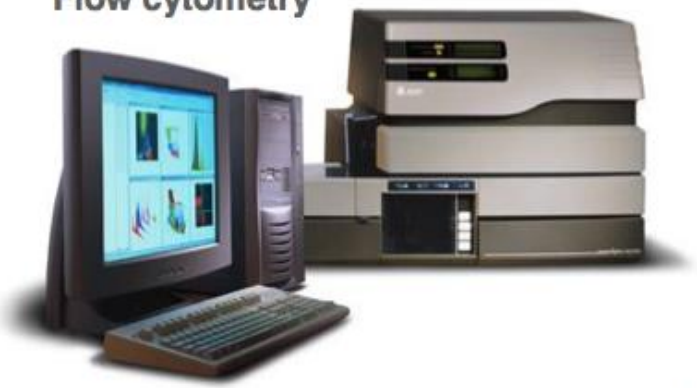
VERIFYNOW:
Predict clinical outcomes? ✔
Standardized? ✔
Easy-to-use? ✔

LTA:
Predict clinical outcomes? ✔
Standardized? ✖
Easy-to-use? ✖

Born aggregation

VASP:
Predict clinical outcomes? ✔
Standardized? ✔
Easy-to-use? ✖

Flow cytometry



Multiplate®

MULTIPLATE:
Predict clinical outcomes? ✔
Standardized? ✔
Easy-to-use? ✔

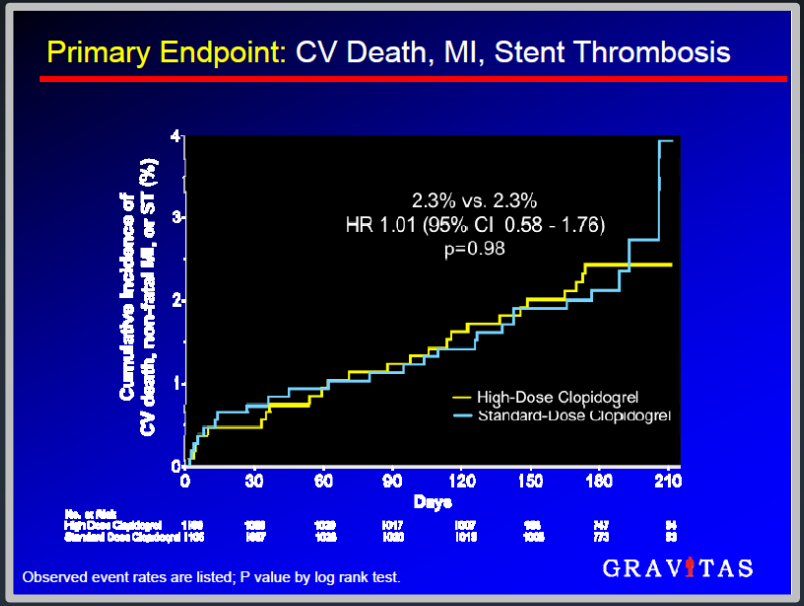
Badimon L -2008- ICCC

WHAT DEVICE SHOULD WE USE?

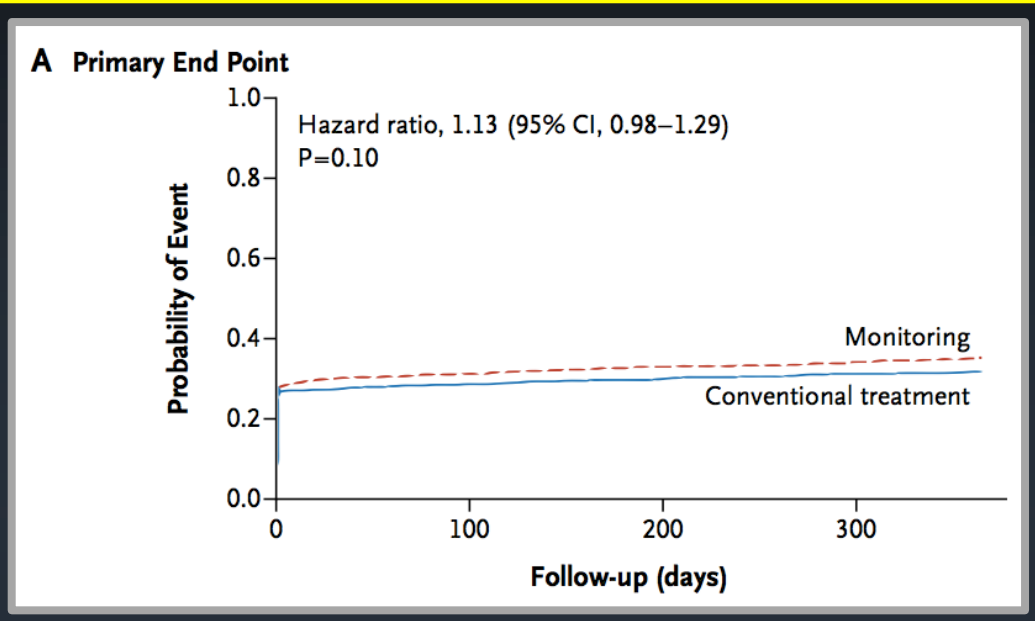
Based on the currently available evidence, the recommended assays for monitoring platelet inhibition during $P2Y_{12}$-inhibitors are the VerifyNow P2Y12 assay, the Multiplate device with the ADP kit and the VASP assay.	**IIa**	**B**
Although the optimal thresholds to define a higher risk for thrombotic events may depend on the clinical situation and are still under investigation, available evidence suggests 208 PRU with the VerifyNow, 46 U with the Multiplate assay and 50% with the VASP assay.	**IIb**	**B**
LTA is only recommended when no standardized assays are available.	**III**	**B**

Aradi et al. Eur Heart J. 2013 Sep 25. E-pub ahead of print.

WHAT PATIENTS SHOULD WE MEASURE?
WHAT SHOULD WE DO BASED ON RESULTS?



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



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

Summary of primary and secondary CEC-adjudicated efficacy endpoints

	Prasugrel N=212	Clopidogrel N=211	p HR (95% CI)
Days on study treatment(median)	174	174	-
Primary composite efficacy EP: **CV death or MI**	0	1 (0.5%)	-
Key secondary efficacy EPs:			
MI	0	1 (0.5%)	-
Rehospitalization for cardiac ischemic event	2 (0.9%)	4 (1.9%)	0.992 0.99 (0.14-7.03)
Urgent TVR	2 (0.9%)	1 (0.5%)	-
Definite ST	0	0	-
Stroke	0	1 (0.5%)	-
CV death	0	0	-
All cause death	0	1 (0.5%)	-

Trenk D et al. J Am Coll Cardiol 2012;59:2159-64.

WHAT PATIENTS SHOULD WE MEASURE? WHAT SHOULD WE DO BASED ON RESULTS?

	GRAVITAS	ARCTIC	TRIGGER PCI
n (study population)	2,214	2,440	423
Patient risk profile			
AMI (%)	10%	27%	0%
STEMI (%)	0.4%	0%	0%
Shock (%)	0%	0%	0%
All-cause mortality	0.8%	2%	0%
Intervention			
High-dose clopidogrel	100%	80%	-
High-dose ASA	-	45%	-
Prasugrel	-	12%	100%
PFT Assay	VerifyNow	VerifyNow	VerifyNow
Results			
1° Endpoint	2.3% vs. 2.3%	31.1% vs. 34.6%	0.0% vs. 0.5%

Price MJ et al. JAMA 2011; 305: 1097-105.
Collet et al. N Engl J Med. 2012;367:2100-9.
Trenk D et al. J Am Coll Cardiol 2012;59:2159-64.

WHAT PATIENTS SHOULD WE MEASURE? WHAT SHOULD WE DO BASED ON RESULTS?

…..NO RANDOMIZED STUDY ON THE USE OF PLATELET FUNCTION TESTING IN HIGH-RISK ACS PATIENTS APPLYING PRASUGREL/TICAGRELOR IN HPR SUBJECTS

In patients with acute coronary syndrome undergoing PCI, prasugrel and ticagrelor should be the preferred choices over clopidogrel unless contraindications exist and routine platelet function testing is not recommended.	**III**	**B**
In stable angina patients after uncomplicated PCI, standard-dose clopidogrel should be preferred and routine platelet function testing is not recommended.	**III**	**B**

BUT: there is a REGISTRY….

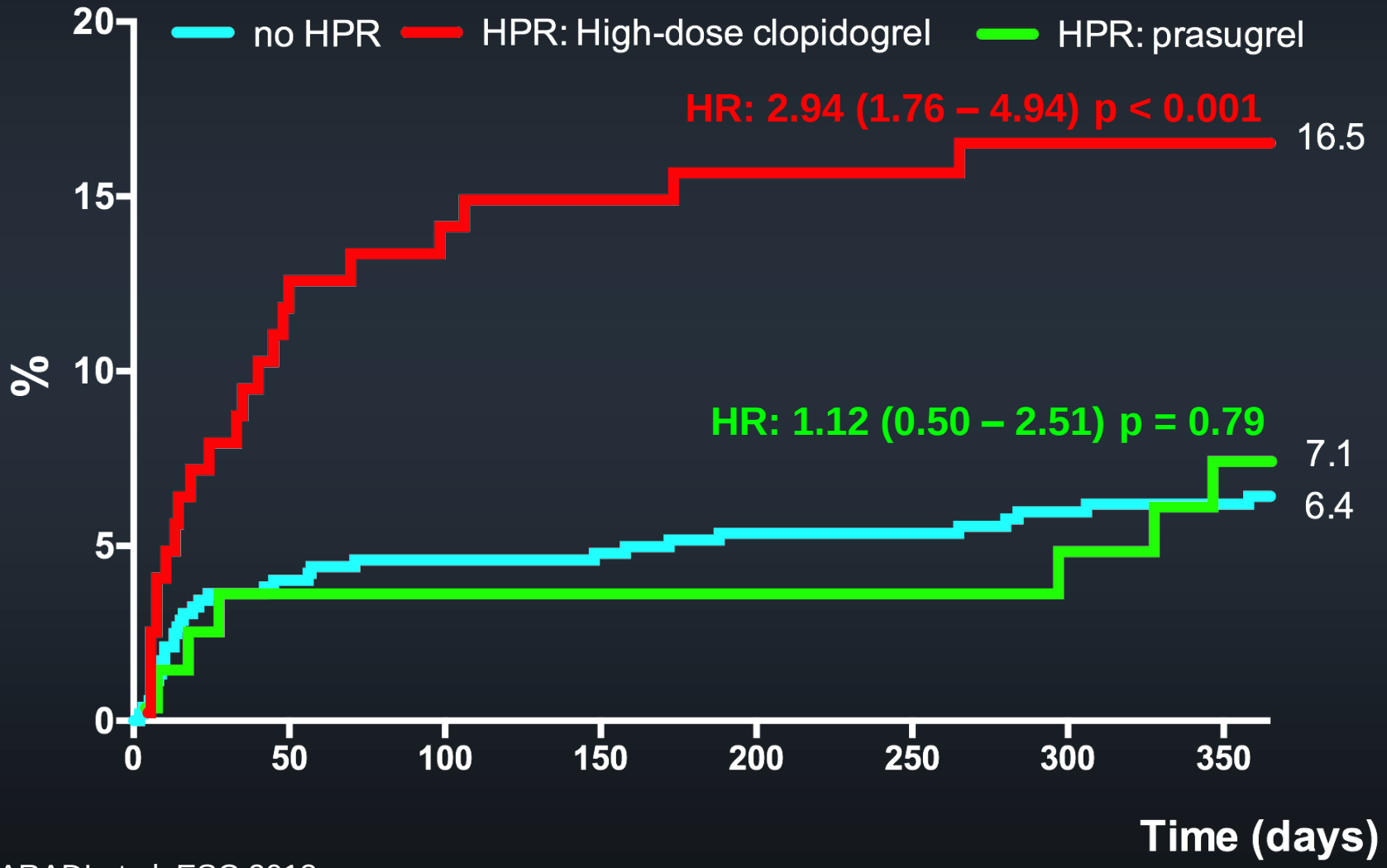
Aradi et al. Eur Heart J. 2013 Sep 25. E-pub ahead of print.

PFT-GUIDED ANTIPLATELET THERAPY

	GRAVITAS	ARCTIC	TRIGGER PCI	PÉCS REGISTRY
n (study population)	2,214	2,440	423	741
Patient risk profile				
AMI (%)	10%	27%	0%	84%
STEMI (%)	0.4%	0%	0%	48%
Shock (%)	0%	0%	0%	4.5%
All-cause mortality	0.8%	2%	0%	8.2%
Intervention				
High-dose clopidogrel	100%	80%	-	58%
High-dose ASA	-	45%	-	-
Prasugrel	-	12%	100%	42%
PFT Assay	VerifyNow	VerifyNow	VerifyNow	Multiplate

Price MJ et al. JAMA 2011; 305: 1097-105.
Collet et al. N Engl J Med. 2012;367:2100-9.
Trenk D et al. J Am Coll Cardiol 2012;59:2159-64.

CLINICAL RESULTS:
MORTALITY OR STENT THROMBOSIS



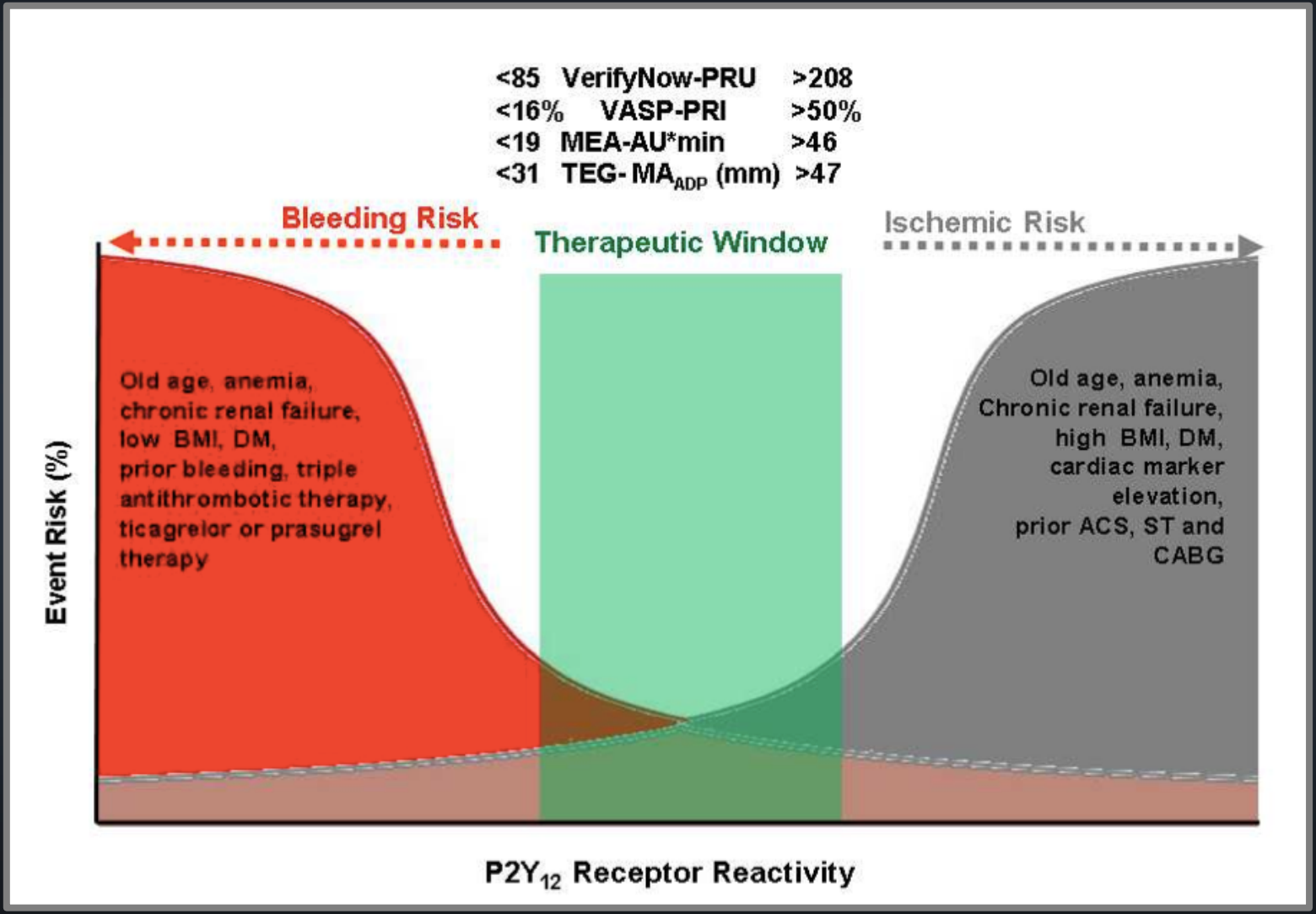
ARADI et al. ESC 2013.

WHAT PATIENTS SHOULD WE MEASURE? WHAT SHOULD WE DO BASED ON RESULTS?

In patients with acute coronary syndrome undergoing PCI, prasugrel and ticagrelor should be the preferred choices over clopidogrel unless contraindications exist and routine platelet function testing is not recommended.	III	B
In stable angina patients after uncomplicated PCI, standard-dose clopidogrel should be preferred and routine platelet function testing is not recommended.	III	B
Where the availability of prasugrel and ticagrelor is restricted or limited to certain indications, platelet function testing may be considered to identify patients with HPR, who are at heightened risk for thrombotic complications on clopidogrel and require a potent P2Y12- inhibitor (prasugrel or ticagrelor).	IIb	C
Administration of high-dose clopidogrel in ACS patients with HPR is not recommended.	III	B

Aradi et al. Eur Heart J. 2013 Sep 25. E-pub ahead of print.

THERAPEUTIC WINDOW: CONSENSUS DOCS



Tantry US, ...Aradi D, et al. JACC 2013. Sept. 26.

CONCLUSIONS: KEY TAKE-HOME MESSAGES

- ASA testing is not recommended
- HPR during $P2Y_{12}$-inhibitors is a strong predictor of ST
- LPR during $P2Y_{12}$-inhibitor Rx may predict major bleeding

- VerifyNow, VASP, Multiplate are recommended assays
- LTA downgraded due to lack of standardization

- When evaluating the clinical impact of platelet function assays, PROGNOSITIC (HR, OR, NRI) rather than DIAGNOSTIC tests (ROC, PPV, NPV) are recommended

CONCLUSIONS: KEY ELEMENTS

- In ACS, prasugrel and ticagrelor are recommended in routine, routine PFT is not recommended
- If prasugrel/ticagrelor are not available or in case of planned clopidogrel treatment in ACS, PFT to test platelet reactivity to ADP may be considered
- Patients with HPR should be switched to prasugrel/ticagrelor, high-dose clopidogrel is not recommended

- In stable angina patients, clopidogrel is recommended and routine PFT is not recommended
- In stable angina patients after ST while being compliant to clopidogrel or who are at high risk for ST may be tested with a PFT

THANK YOU FOR YOUR KIND ATTENTION!