Tailored Antiplatelet Therapy: Frustrated But Not Gone

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Uses of Platelet Function Testing

DIAGNOSTIC TEST

Outcome has happened

- Is there evidence of a $P2Y_{12}$ antagonist effect?

PROGNOSTIC TEST

Outcome has not yet occurred

- What is the risk of a CV event?

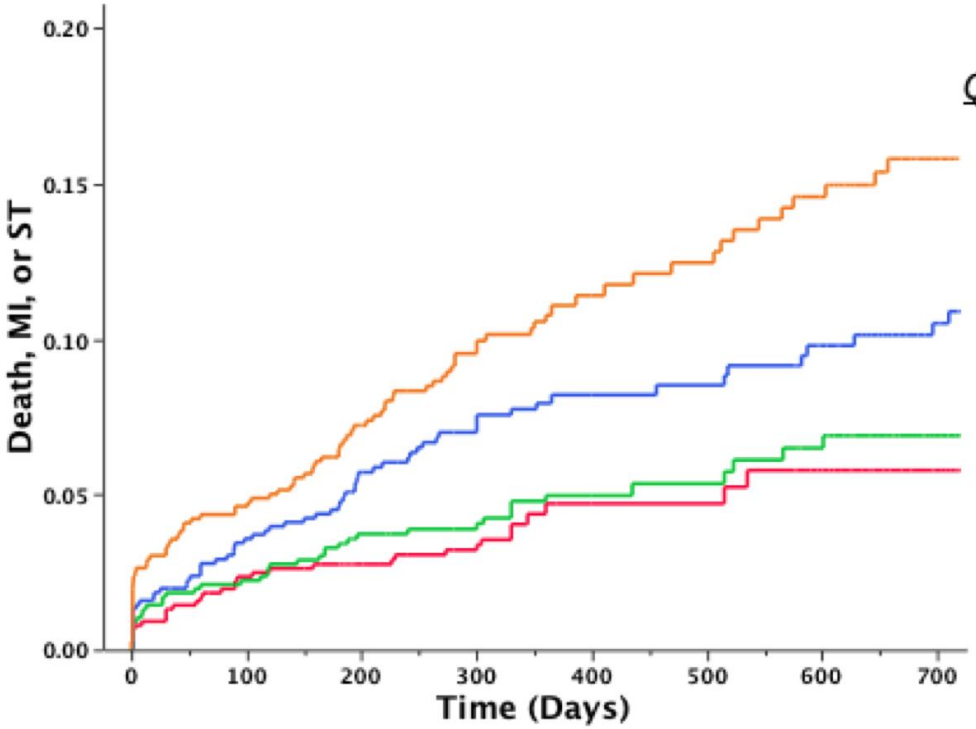
Assessment of diagnostic and prognostic utility differ!!

What We Talk About When We Talk About Risk

Type of use	Measure Description	Examples
Diagnostic Testing		
	Test [illegible]acteristics	Sensitivity and spec[illegible]y Positiv[illegible] [illegible]ictive value
	Disc[illegible] Likelihood ratio	ROC curve ([illegible]stic)
Risk Prediction		
	Association	Odds ratio Hazard ratio Relative risk
	Discrimination	ROC curve (AUC, c-statistic)
	Calibration	Hosmer-Lemeshow goodness of fit
	Reclassification	Net reclassification improvement

Pletcher MJ et al Circulation 2011;123:1116-24

On-Clopidogrel Platelet Reactivity & Ischemic Events Post-PCI: A Patient-Level Meta-Analysis



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

N=3,041

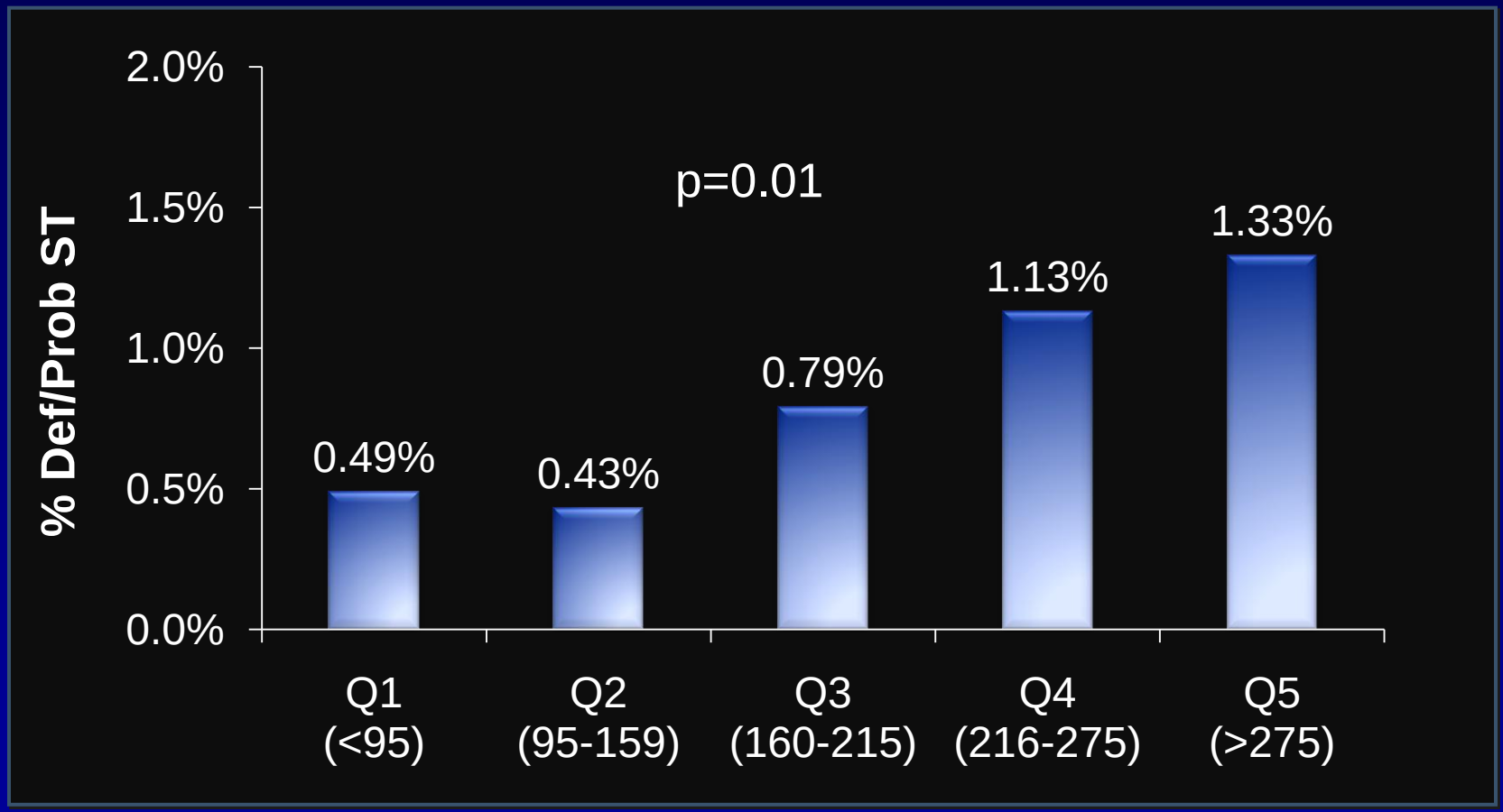
No. at risk

Q1	765	639	179	169
Q2	761	611	249	237
Q3	757	595	294	271
Q4	758	588	252	224

Non-ACS pts with high reactivity : HR 2.47 (1.79–3.40), P<0.0001

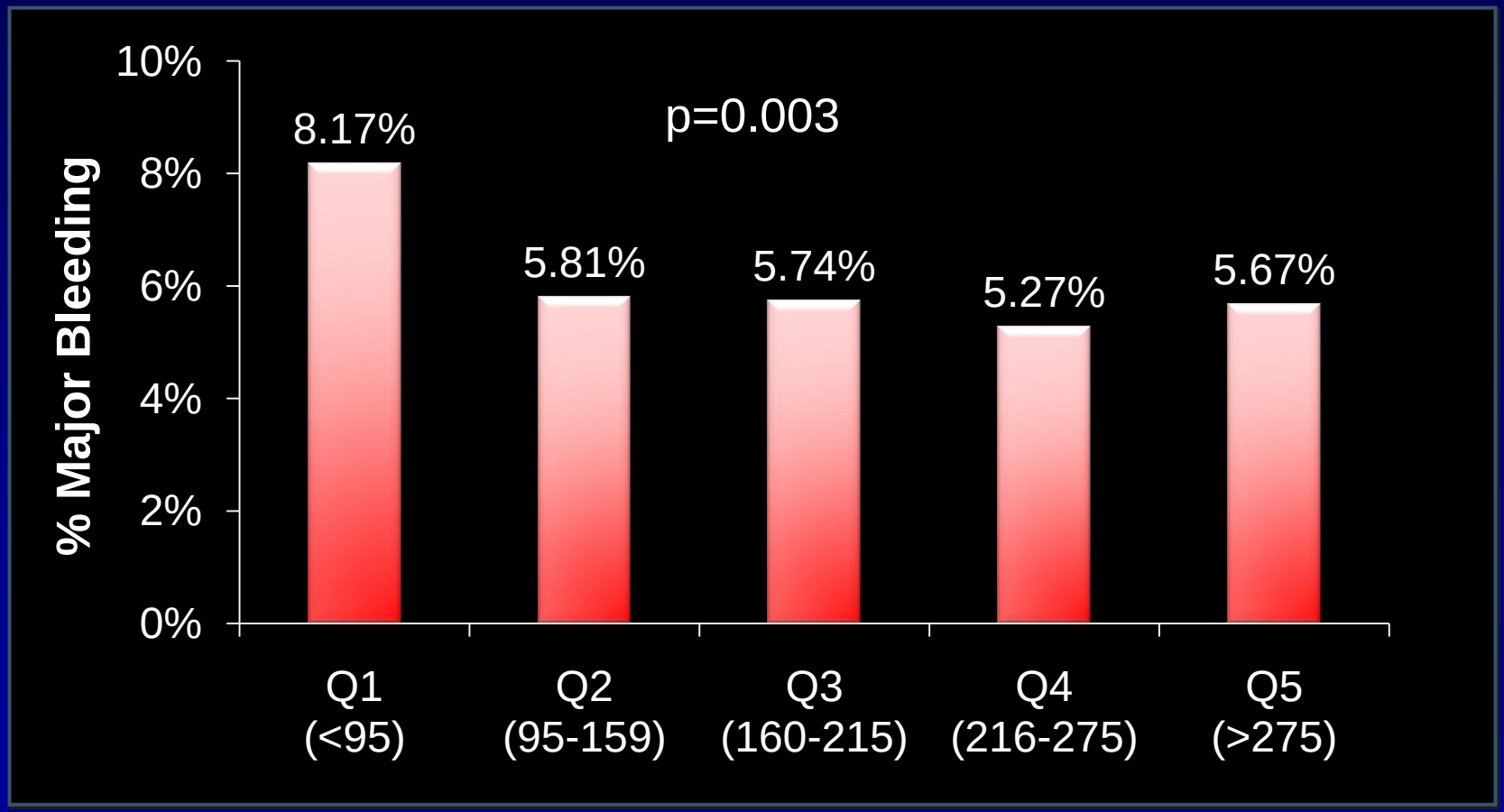
ADAPT DES at 1 Year: Def/Prob ST by PRU Quintiles

8,449 PCI pts with VerifyNow PRU after clopidogrel loading



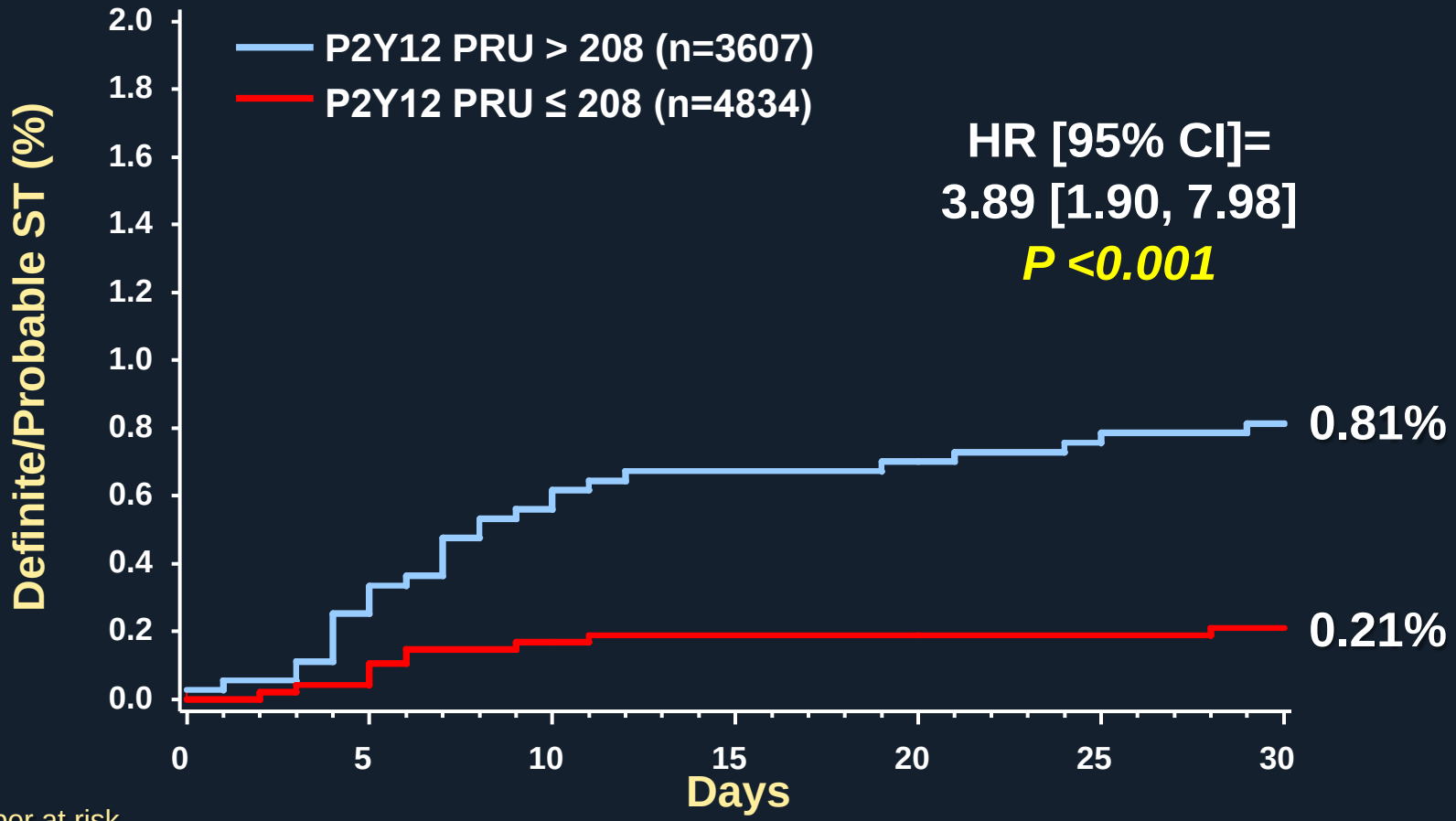
ADAPT DES at 1 Year: Bleeding by PRU Quintiles

8,449 PCI pts with VerifyNow PRU after clopidogrel loading



ADAPT-DES: Relationship Between VerifyNow P2Y12 PRU and Stent Thrombosis within 30 Days

Definite or probable stent thrombosis



Number at risk

>208 PRU	3607	3540	3534	3482
≤208 PRU	4834	4754	4752	4686

ADAPT-DES: Multivariable (Cox PHR) models of 30-day stent thrombosis stratified by propensity quintiles

Definite stent thrombosis

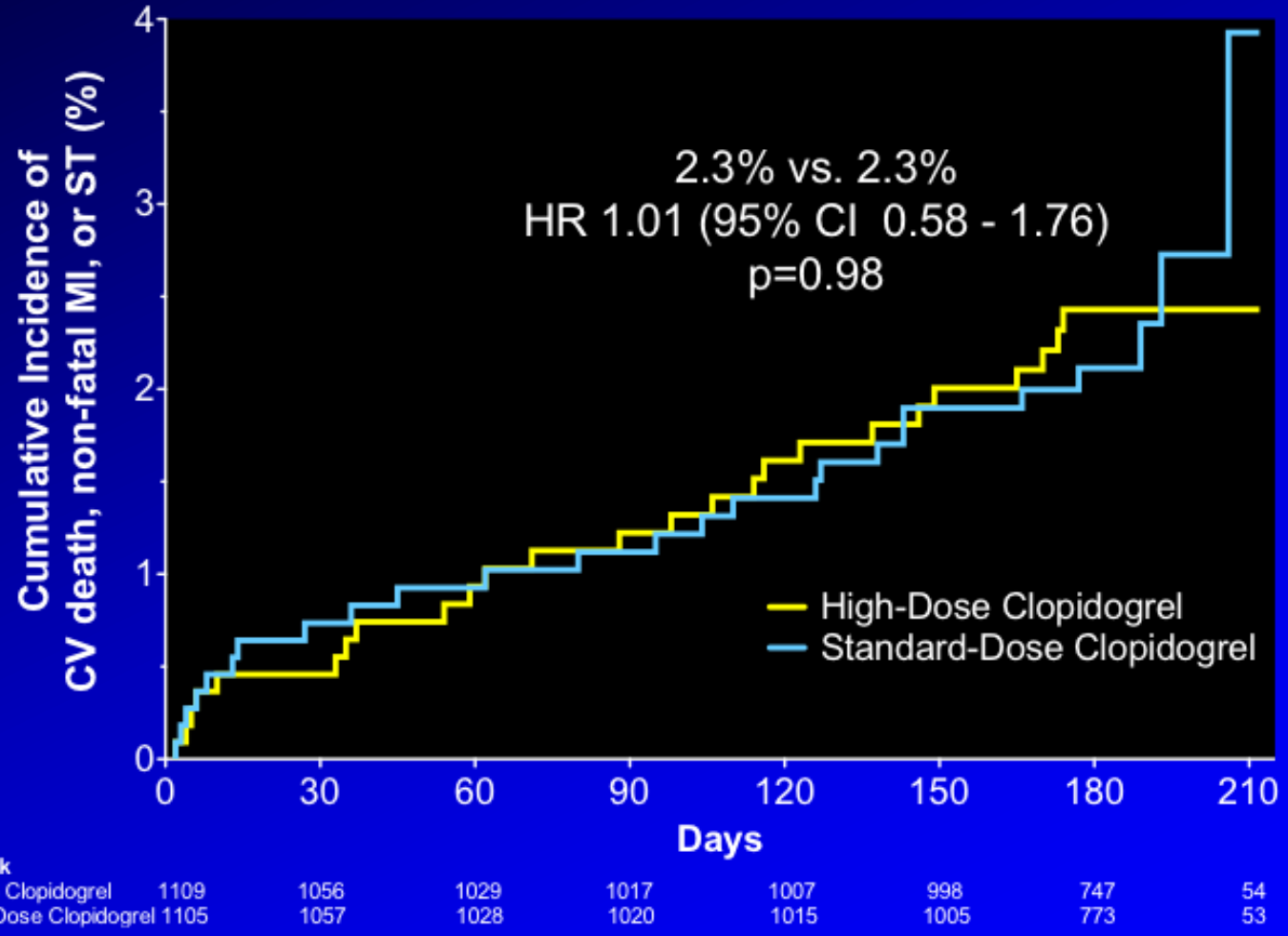
VerifyNow test P2Y12	N at risk	N events	Adj. HR* [95%CI]	P value	Attributable events	Attributable percent
P2Y12 PRU >208†	8439	27	5.36 [1.89, 15.21]	0.002	17.9 [10.4, 20.6]	66.3% [38.3%, 76.1%]
P2Y12 PRU ≥230†	8439	27	4.46 [1.80, 11.03]	0.001	14.7 [8.5, 17.3]	54.6% [31.4%, 64.0%]

***Adjusted for non-ACS vs NSTEMI vs STEMI, diabetes vs no diabetes, and stent length**
Model c-statistics = 0.753, 0.721, 0.722

†Pre-specified measures

Primary Endpoint: CV Death, MI, Stent Thrombosis

Only 10% of patients with +TnI



Observed event rates are listed; P value by log rank test.

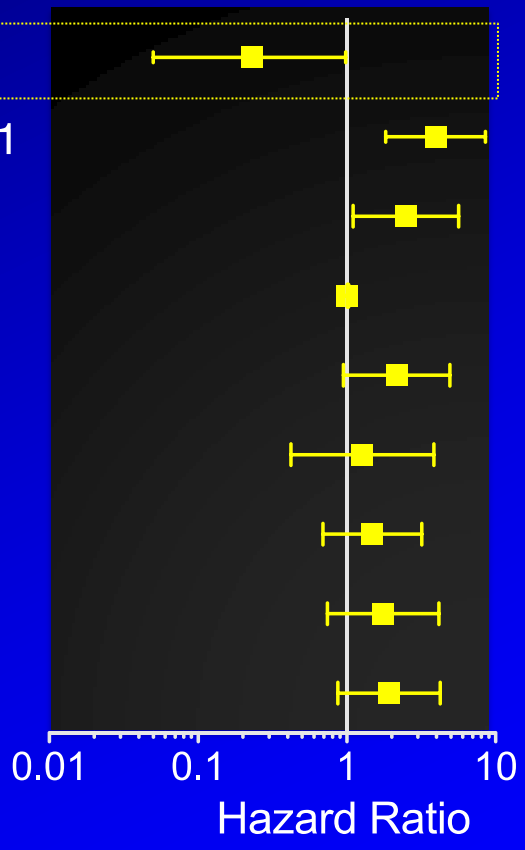
Price MJ et al, JAMA. 2011;305(11):1097-1105

GRAVITAS

GRAVITAS: Lower Reactivity Over Course of Trial Associated with Reduced With CV Death, MI, ST at 60 days

N=2796

	HR [95% CI]	P
PRU <208	0.23 [0.05, 0.98]	0.047
ACS	3.95 [1.83, 8.53]	<0.001
Diabetes	2.49 [1.10, 5.64]	0.028
Stent Length (per mm)	1.01 [1.01, 1.02]	0.003
Prior MI	2.16 [0.94, 4.93]	0.068
Beta Blocker	1.27 [0.42, 3.85]	0.668
CrCl <60	1.48 [0.69, 3.18]	0.668
Prior PCI	1.76 [0.74, 4.16]	0.201
Prior CABG	1.92 [0.87, 4.23]	0.108

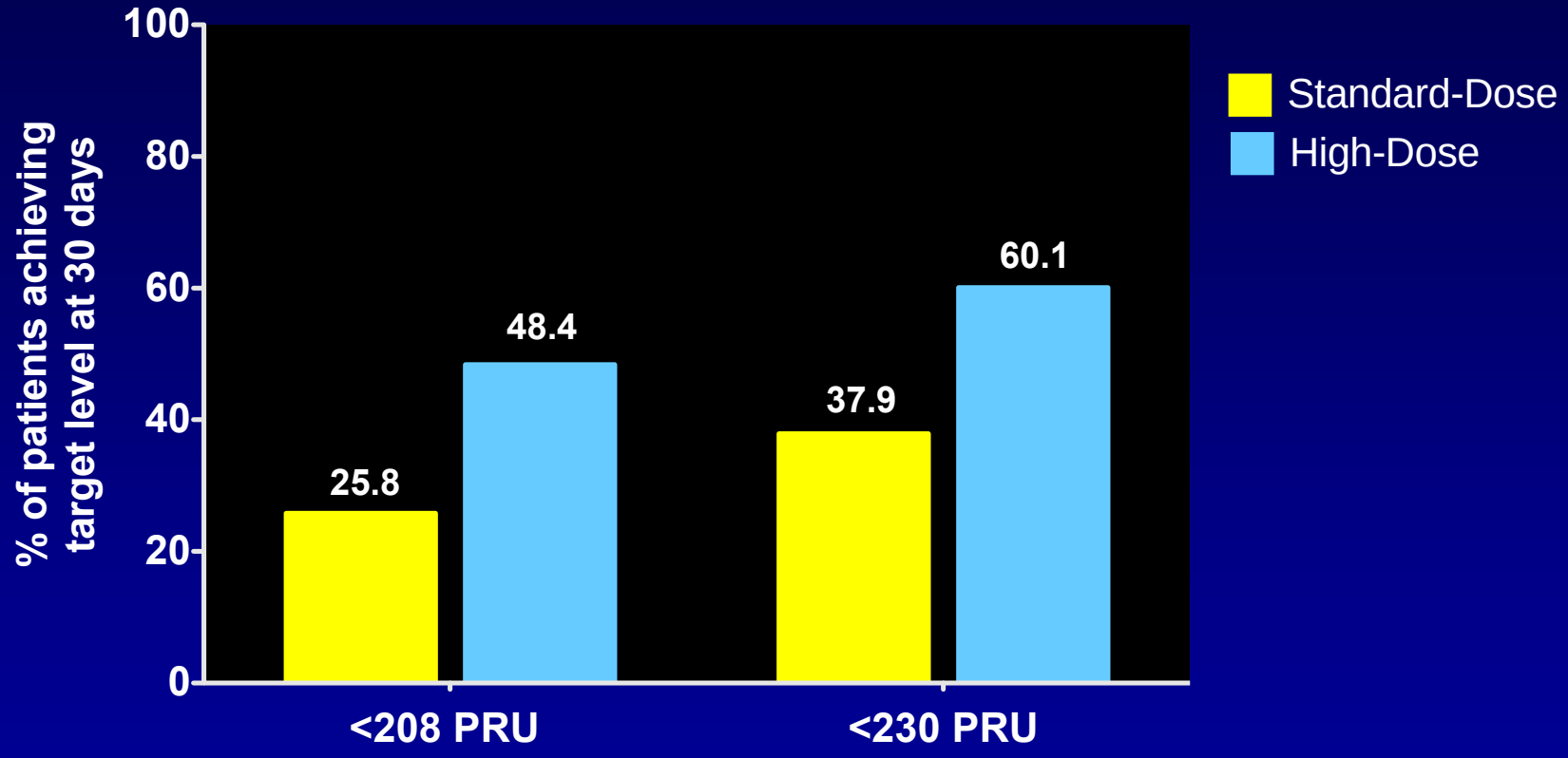


*On-treatment reactivity treated as a time-varying covariate
CrCl = creatinine clearance, ACS = acute coronary syndrome, MI = myocardial infarction

GRAVITAS

Price MJ et al, *Circulation* 2011;124:1132-1137

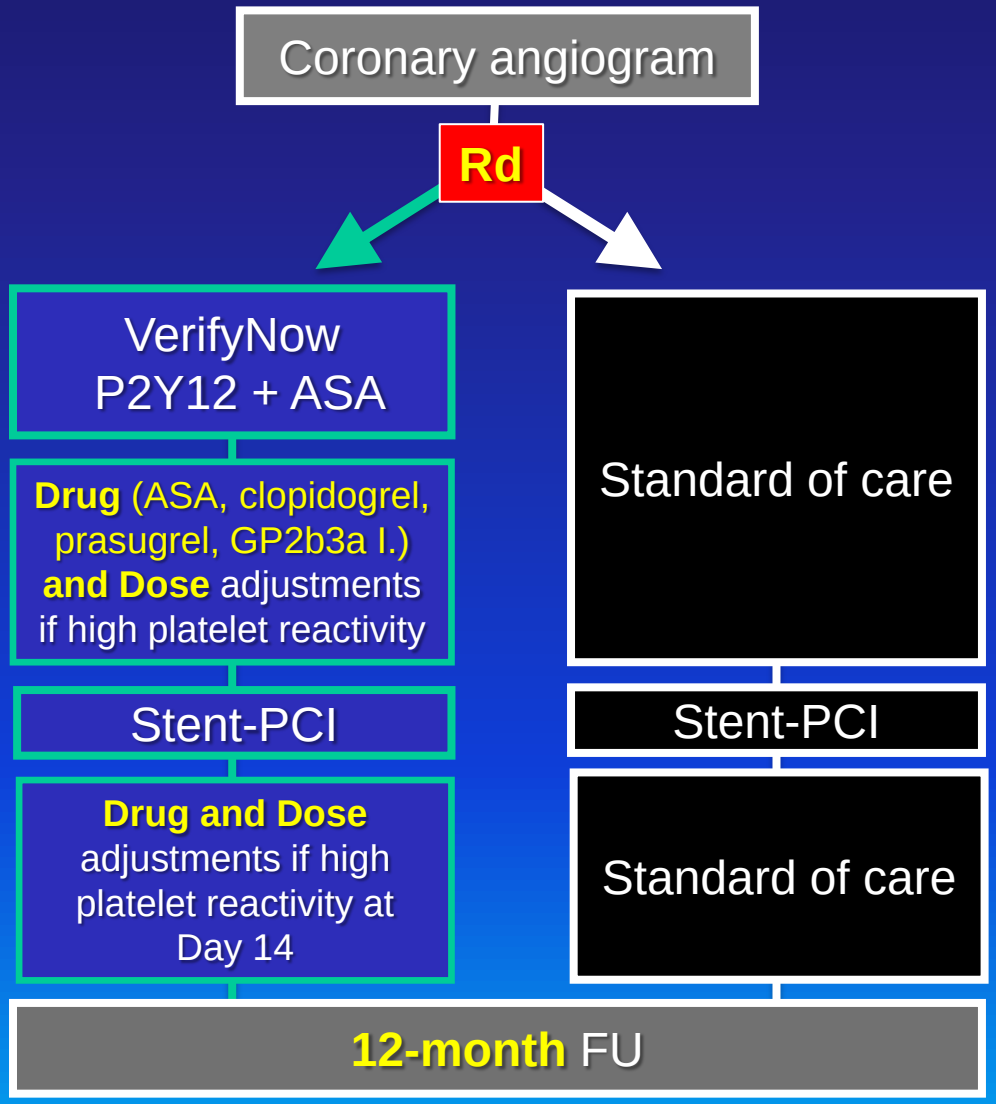
Achieved Levels of On-Treatment Reactivity at 30-Days
Stratified By Randomized Treatment Arm



HD group, CV events according to PRU <208: HR 0.48 [95%CI, 0.18 to 1.25], P=0.14

→ *Less than half of patients with high-dose clopidgrel achieved "therapeutic" PRU*

ARCTIC trial design



Primary endpoint at 12 months:

- Death, MI, stroke, stent thrombosis, urgent revascularization

Statistical considerations:

- Assuming an annual risk of 9% and a 33% relative risk reduction (α risk at 5% and error β of 20%, bilateral test), 2,466 patients were necessary to demonstrate the superiority of the strategy of monitoring and adjustment

73% elective, 27% stabilized NSTE-ACS (?USA), no STEMI

al. Am Heart J 2011;161:5-12

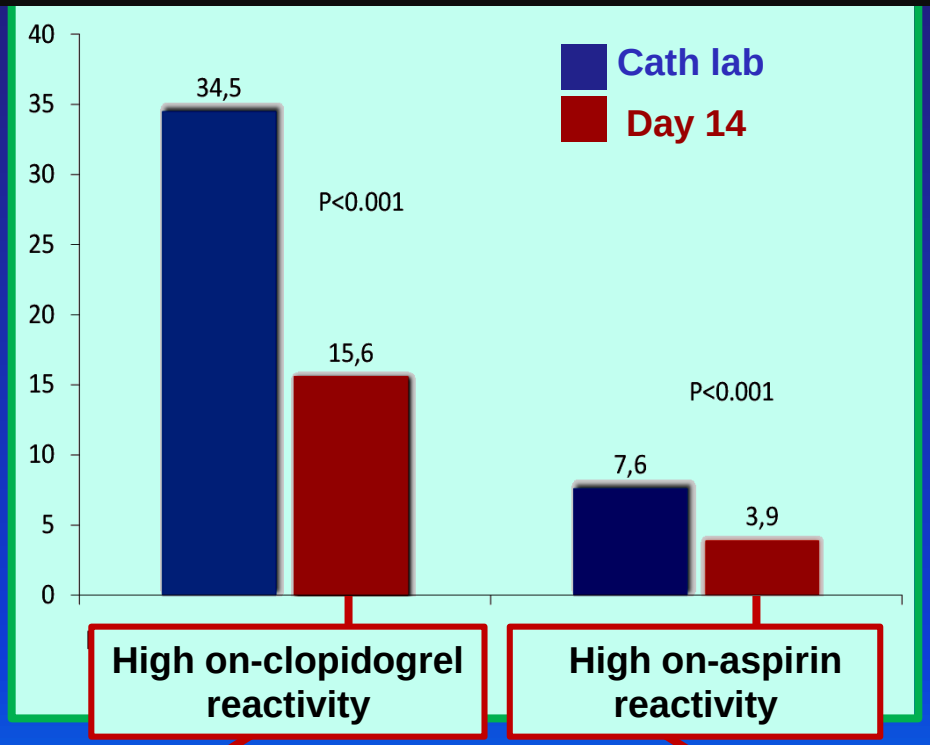
In-Lab monitoring and adjustment

	Conventional (n=1227)	Monitoring (n=1213)
Aspirin poor responders - %	NA	**7.6**
→On-table aspirin loading in poor responders - %	NA	→ 85
Thienopyridine poor responders - %	NA	**35**
→ On-table clopi. loading in poor responders - %	NA	→ 80
→ On-table prasu. loading in poor responders - %	NA	→ 3.3
→ On-table GP IIbIIIa↓ loading in poor responders - %	NA	→ 80

Predominant intervention after procedure: double-dose clopidogrel!

Monitoring and adjustment at Day 14

Effect of HD clopidogrel similar to that seen in GRAVITAS

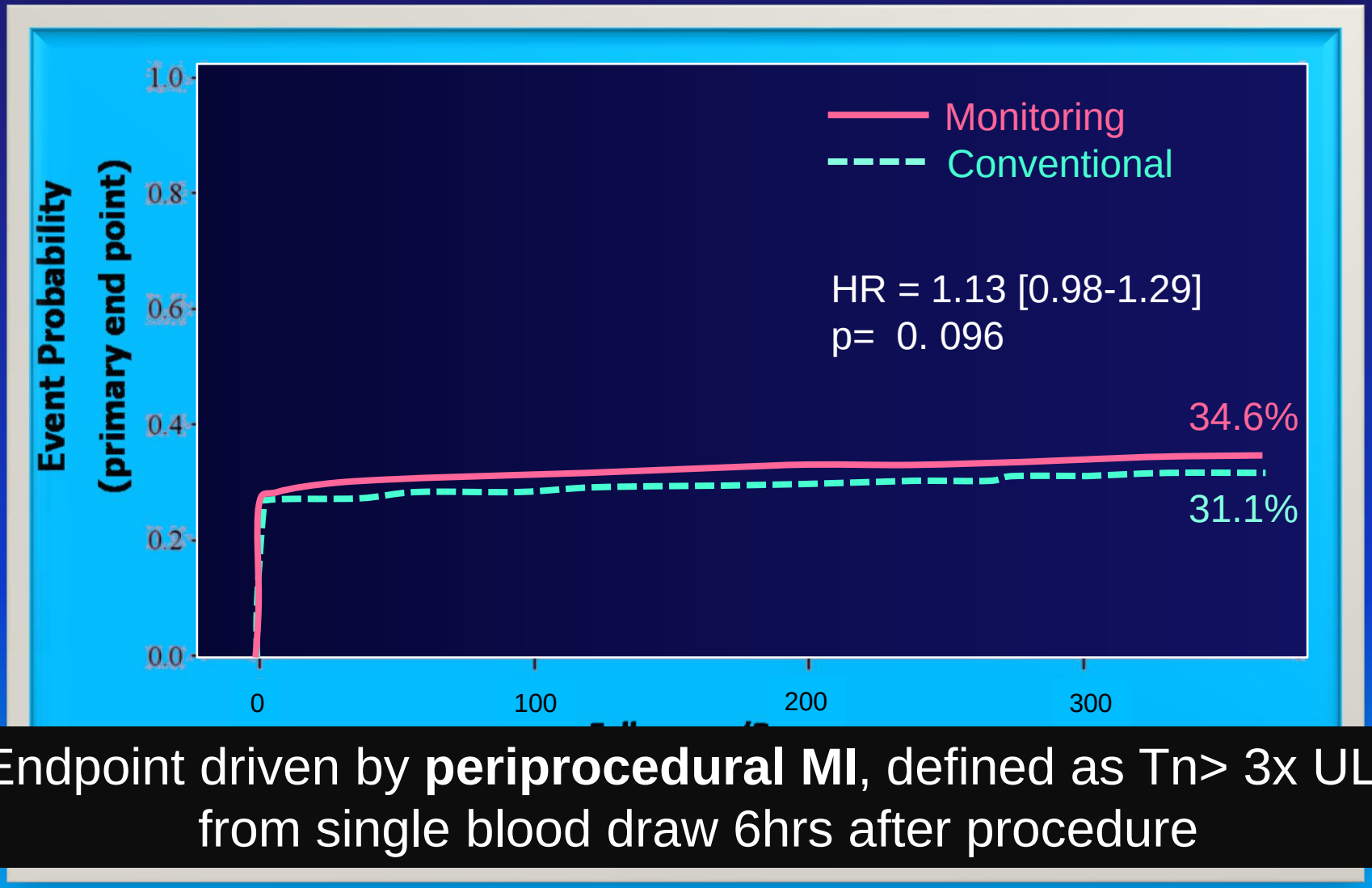


43% had their clopidogrel MD increased
17% were put on prasugrel MD

46% had their aspirin MD increased

Primary Endpoint to 1 year

Death, MI, stroke, stent thrombosis, urgent revascularization

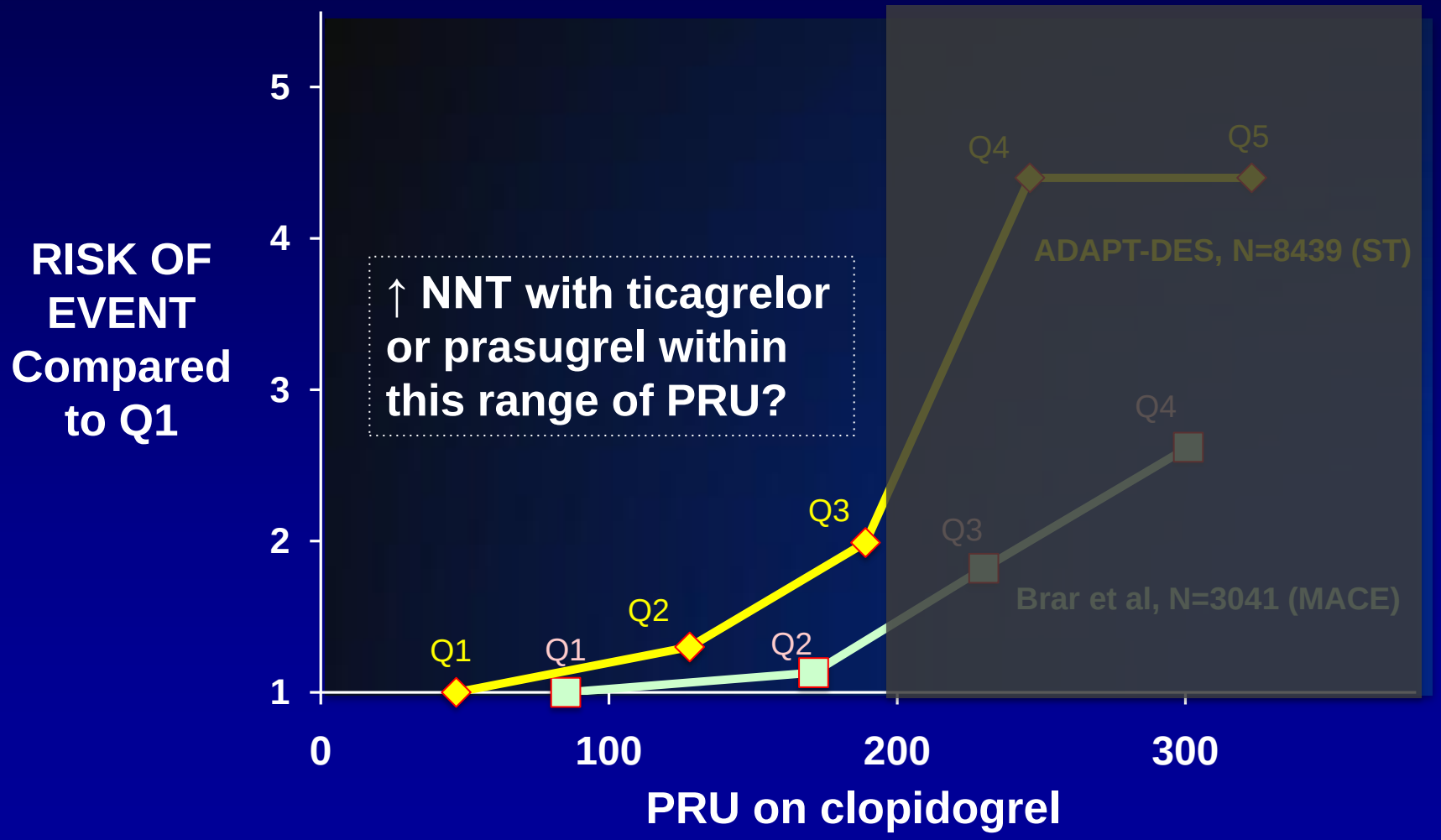


Endpoint driven by **periprocedural MI**, defined as Tn> 3x ULN from single blood draw 6hrs after procedure

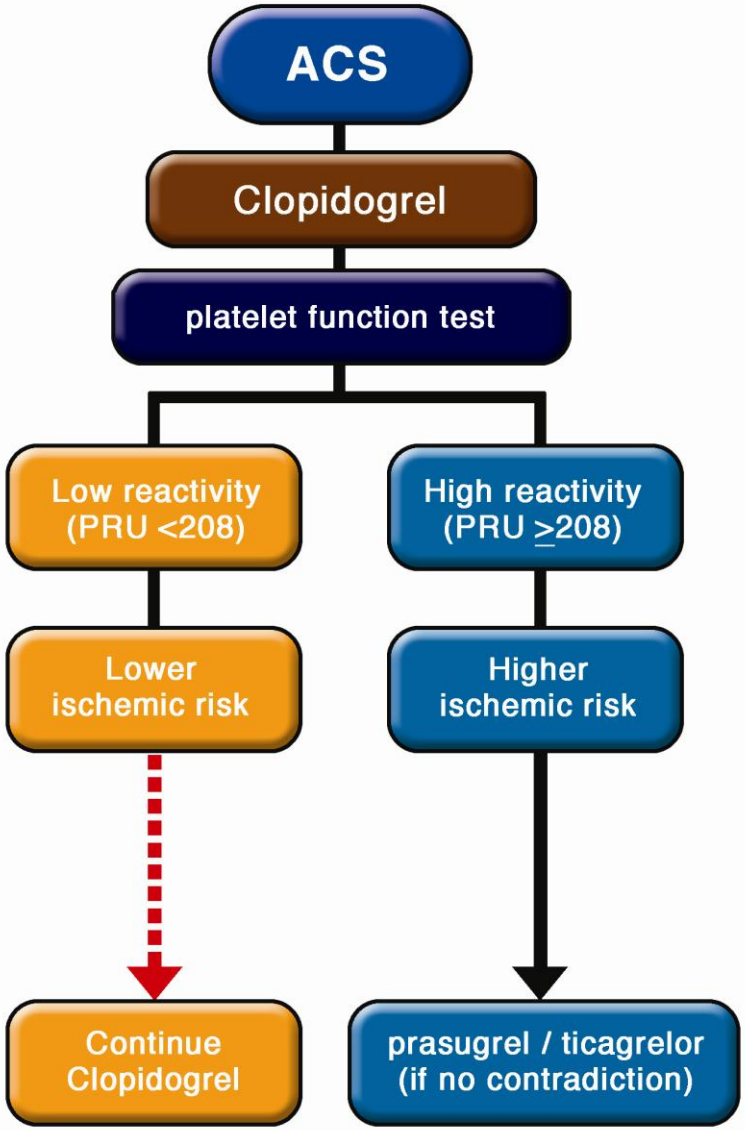
Why Not Prasugrel or Ticagrelor for All ACS Patients?

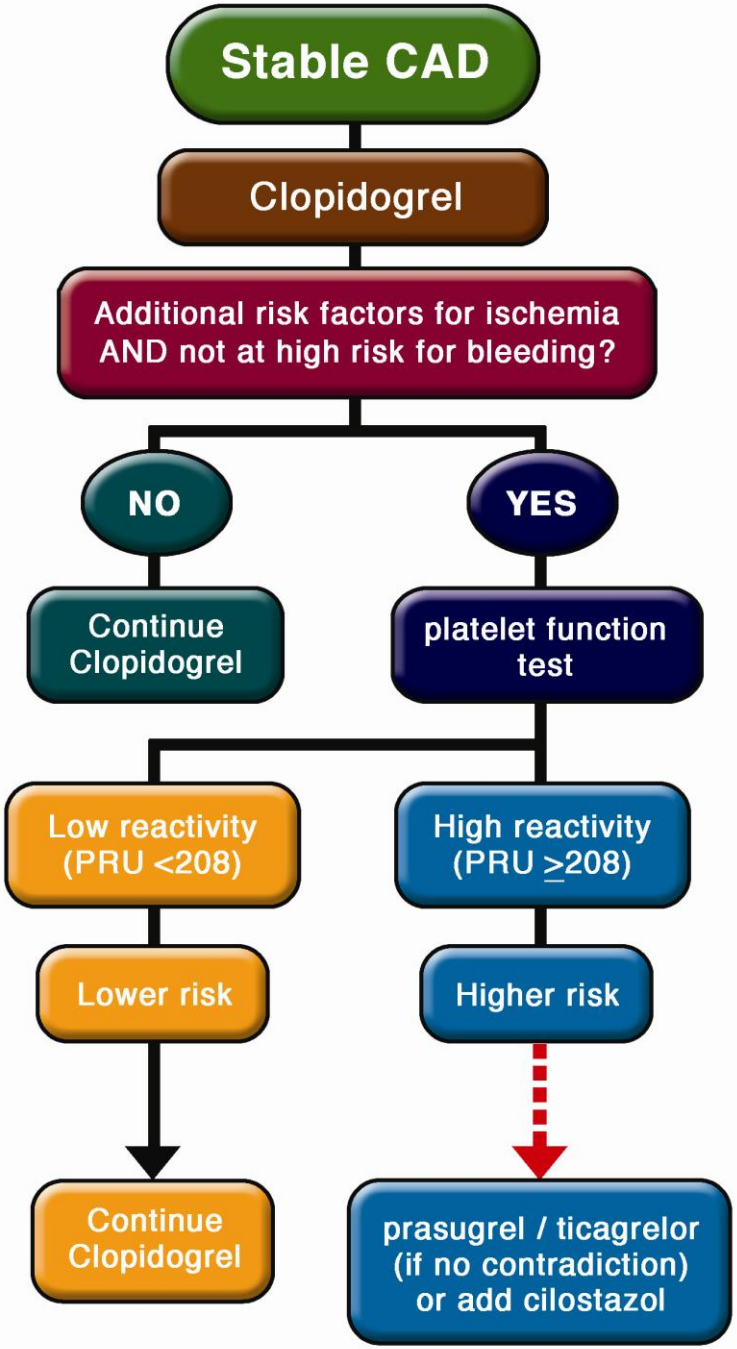
- EXPENSIVE
- BLEEDING RISK
- AHA/ACC guidelines do not recommend one over the other
- → Only fraction of ACS patients are being treated with these agents despite being available for several years
- Can PFT help us *select the most appropriate patient for clopidogrel or a newer oral P2Y12 inhibitor?*

Events in >11,000 PCI Patients According to PFT: By Necessity, Less Benefit With More Expensive and Potent Agents In Patients with Good Clopidogrel Effect



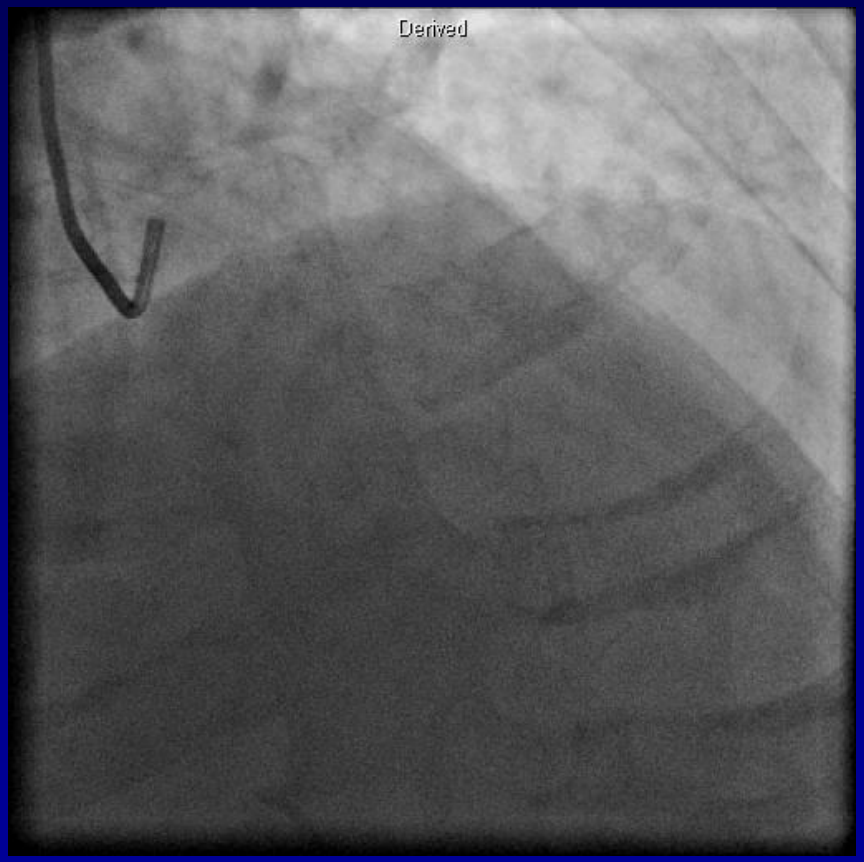
Brar S, ten Berg J, Marcucci R, Price MJ et al, J Am Coll Cardiol 2011; 58:1945-1954
Stone G, TCT 2011

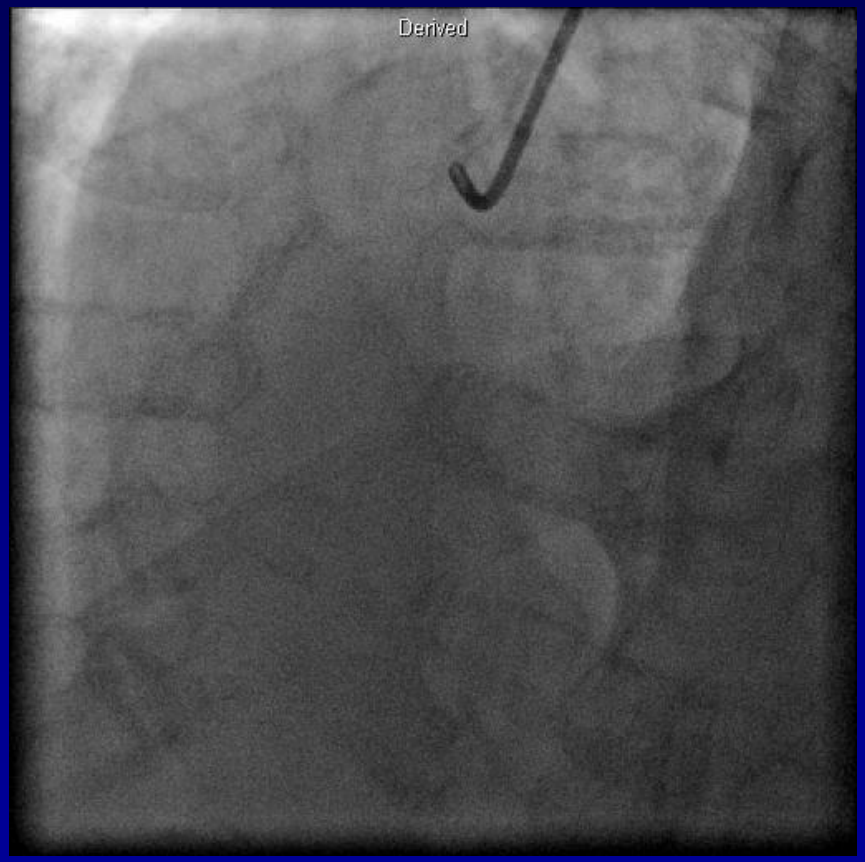




Price MJ, JACC 2013 in press

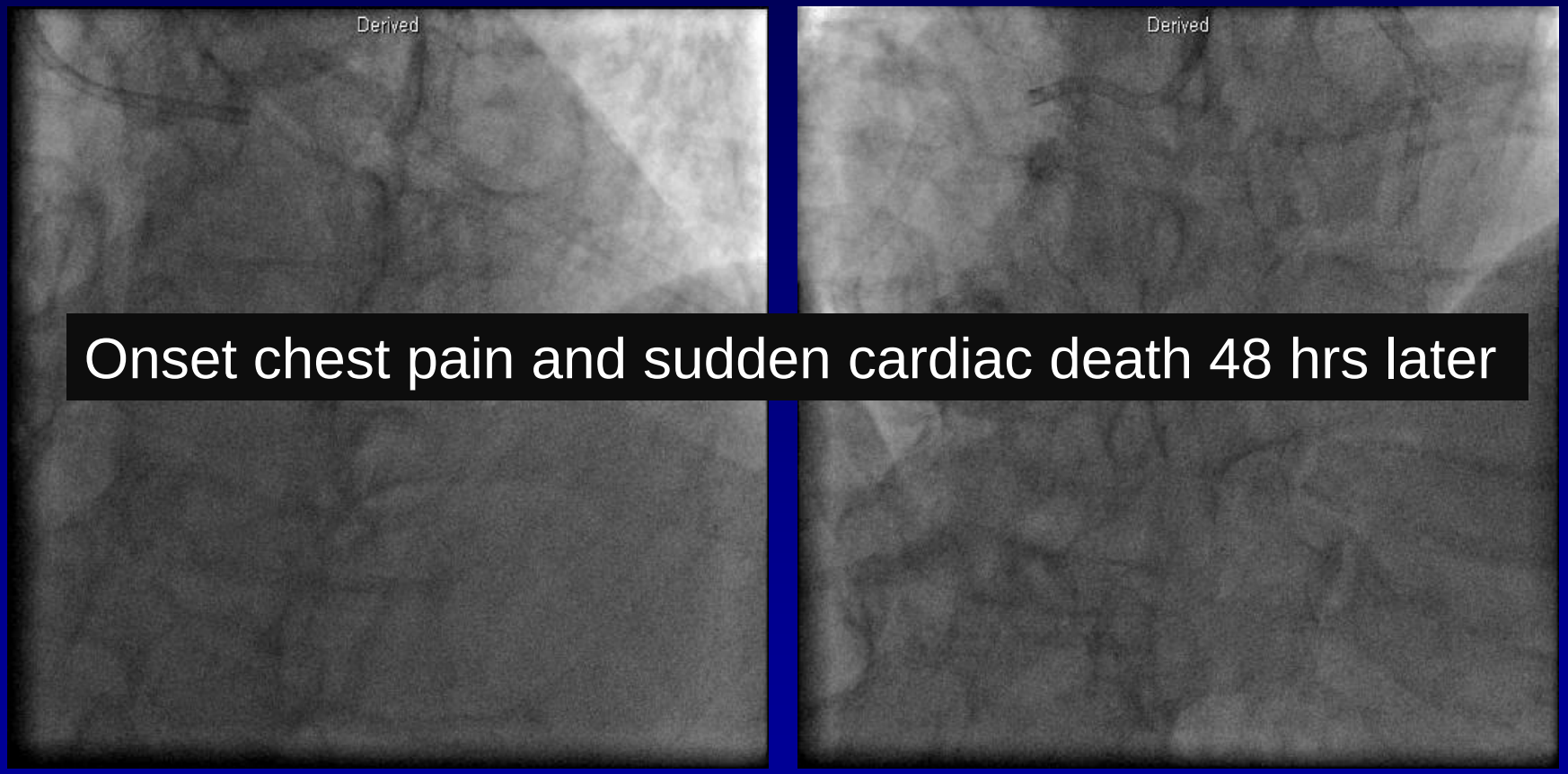
61 year-old male, HTN, dyslipidemia, angina, USA (nl troponin and ECG)





SYNTAX score 24; Adamantly refused CABG after family discussion

2 DES in LAD, 3 DES in RCA



Already on clopidogrel; was discharged home on clopidogrel 75mg daily: No PFT

Conclusions

- Large, observational studies and post-hoc analysis of GRAVITAS support the contention that platelet reactivity is a strong prognostic marker for events post-PCI
- No randomized trial data to support adjustment of DAPT after PCI by PFT (limitations: elective pts, high-dose clopidogrel, underpowered for post-disharge events)
- PFT could be incorporated into a treatment strategy for ACS-PCI to identify the patients who would get the most benefit from costly newer agents.
- Models for elective or “low-risk” USA patients to identify those most at-risk for ST who may benefit from PFT are needed.