ADAPT-DES One-Year Results

Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents

A Large-Scale, Multicenter, Prospective, Observational Study of the Impact of Clopidogrel and Aspirin Hyporesponsiveness on Patient Outcomes

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Disclosures

- Gregg W. Stone
  - Consultant to Eli Lilly, Daiichi Sankyo, AstraZeneca, Medtronic, Boston Scientific, Abbott Vascular, Volcano, The Medicines Company

ADAPT-DES: Background

- From the large-scale prospective, multicenter ADAPT-DES registry, we previously demonstrated a strong relationship between platelet hyporesponsiveness to clopidogrel, but not to aspirin, and subsequent stent thrombosis to 30 days
- With follow-up to 1-year, we now report the overall treatment implications of aspirin and clopidogrel hyporesponsiveness on patient outcomes

ADAPT-DES

Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents

11,000 DES pts prospectively enrolled

No clinical or anatomic exclusion criteria

11 sites in US and Germany

↓

PCI with ≥1 non-investigational DES

Successful and uncomplicated

(IVUS/VH substudy; Up to 3000 pts enrolled)

↓

Assess platelet function after adequate DAPT loading and GPI washout: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded)

↓

Clinical FU at 30 days, 1 year and 2 years

Angio core lab assessment all STs w/1:2 matching controls

ADAPT-DES: Study organization

Principal investigator:	Gregg W. Stone (& Chuck Simonton prior to joining AVD)
Co-principal investigators:	Thomas Stuckey, Bruce Brodie, Mike Rinaldi
Pharmacology committee:	Paul Gurbel and Steve Steinhubl
Sponsor (IDE):	Cardiovascular Research Foundation
Site management & monitoring:	R. Stuart Dickson Institute For Health Studies Michael Dulin, director, Sherry Laurent, consultant
Data management:	R. Stuart Dickson Institute For Health Studies Susan Christopher, project lead
Event adjudication:	Cardiovascular Research Foundation Roxana Mehran and Ecaterina Cristea, directors
Angio and IVUS core labs:	Cardiovascular Research Foundation Ecaterina Cristea and Akiko Maehara, directors
Biostatistics:	Cardiovascular Research Foundation Helen Parise, director
Financial support:	Boston Scientific, Abbott Vascular, Medtronic, Cordis, Biosensors, The Medicines Company, Daiichi-Sankyo, Eli Lilly, Volcano, Accumetrics

ADAPT-DES: Sites and enrollment

8,583 pts were enrolled at 11 sites between 1/7/2008 and 9/16/2010; **2,143 pts** were enrolled in the IVUS substudy

Site	Principal investigator(s)	N enrolled
Charité Benjamin Franklin	Bernhard Witzenbichler	1,435
Columbia University Medical Center	Giora Weisz	1,365
Herz-Zentrum Bad Krozingen	Franz-Josef Neumann	1,035
Carolinas Medical Center	Mike Rinaldi	1,113
Wellmont Holstein Valley	Chris Metzger	790
Minneapolis Heart Institute	Tim Henry and Ivan Chavez	788
Lehigh Valley Hospital	David Cox	673
Firsthealth Moore Regional	Peter Duffy	544
LeBauer CV Research	Bruce Brodie, Tom Stuckey	534
Ohio State University	Ernest Mazzaferri	304
Indiana Heart Institute	Jim Hermiller	2

ADAPT-DES: Baseline features (n=8,583)

Age (years)	63.6 ± 10.9
Female	25.9%
Caucasian	88.6%
Diabetes mellitus	32.4%
- Insulin-treated	11.6%
Hypertension	79.6%
Hyperlipidemia	74.4%
Cigarette smoking, current	22.6%
Prior MI	25.2%
Prior PCI	42.8%
Prior CABG	17.1%
Prior CHF	8.1%
Prior PAD	10.2%
History of renal insufficiency	7.7%
- Dialysis	1.6%
BMI	29.5 ± 5.7

ADAPT-DES: Baseline features (n=8,583)

Presentation during PCI	
- Stable CAD	48.3%
- ACS	51.7%
- UA, biomarker negative	27.7%
- NSTEMI	14.5%
- STEMI	9.5%
Extent of CAD	
- 1 vessel disease	38.3%
- 2 vessel disease	33.0%
- 3 vessel disease	28.7%
- Left main disease	3.0%
LVEF (%)	55.0 ± 14.1
LVEDP (mmHg)	16.7 ± 9.3

ADAPT-DES: PCI procedure (n=8,583)

N = 10,106 vessels, 12,940 lesions

N vessels treated per pt	1.2 ± 0.4
- LM	3.1%
- LAD	39.1%
- LCX	26.2%
- RCA	31.5%
- Bypass graft	4.5%
N lesions treated per pt	1.8 ± 1.1
N stents per pt	1.7 ± 1.0
Total stent length (mm)	32.4 ± 22.3
DES type used per pt / lesion	
- Xience V / Promus	64.5% / 58.5%
- Taxus (Express, Liberté)	16.5% / 14.4%
- Cypher	13.5% / 13.0%
- Endeavor	6.2% / 5.2%
- Resolute	2.2% / 2.1%
- Other	0.2% / 0.2%

ADAPT-DES: Anti-platelet agents (n=8,583)

	Aspirin	Thienopyridine
Pre-admission	82.0%	42.9%
Loading dose pre-PCI	88.7%	86.4%
Discharge	99.2%	>99.9%
- clopidogrel	-	99.7%
- ticlopidine	-	0.03%
- prasugrel	-	0.3%
Days taken through 1 year	345 ± 120	334 ± 120
Daily through 1 yr w/o any d/c	87.2%	79.6%
Taking at 1 year	95.4%	83.9%

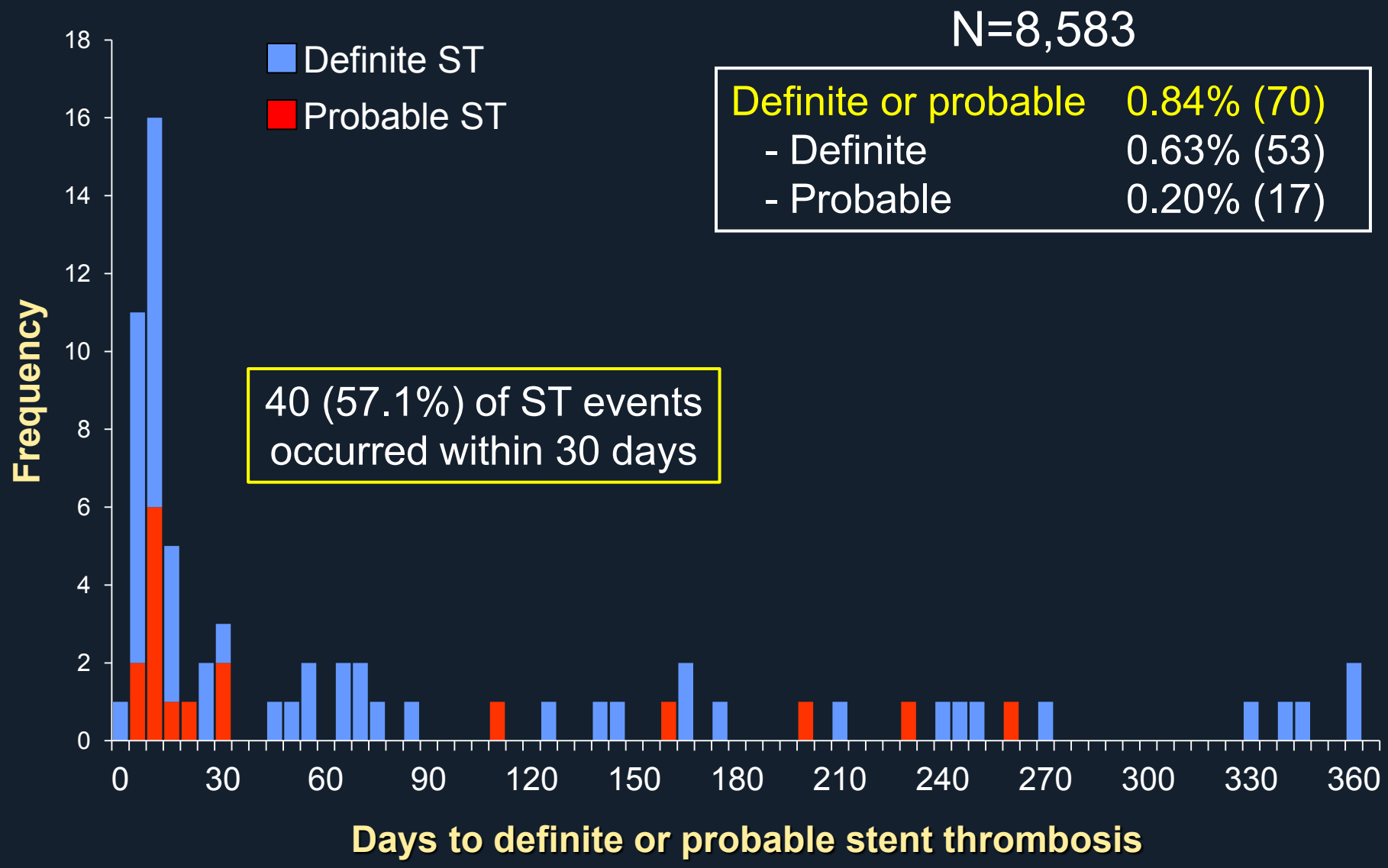
ADAPT-DES: Platelet function test results
(n=8,583; 8,527 with ARU, 8,449 with PRU)

Post-PCI to VerifyNow (hrs)	20.3 ± 8.3
VerifyNow Aspirin (ARU)	419 ± 55
- >550 ARU*	5.6%
VerifyNow P2Y12 (BASE)	310 ± 58
VerifyNow P2Y12 (PRU)	188 ± 97
- >208 PRU*	42.7%
- ≥230 PRU*	35.0%
VerifyNow P2Y12 Inhibition (%)	40.0 ± 28.3
VerifyNow IIb/IIIa PAU	193 ± 53

*Pre-specified cut-off values

ADAPT-DES: Time to First Stent Thrombosis

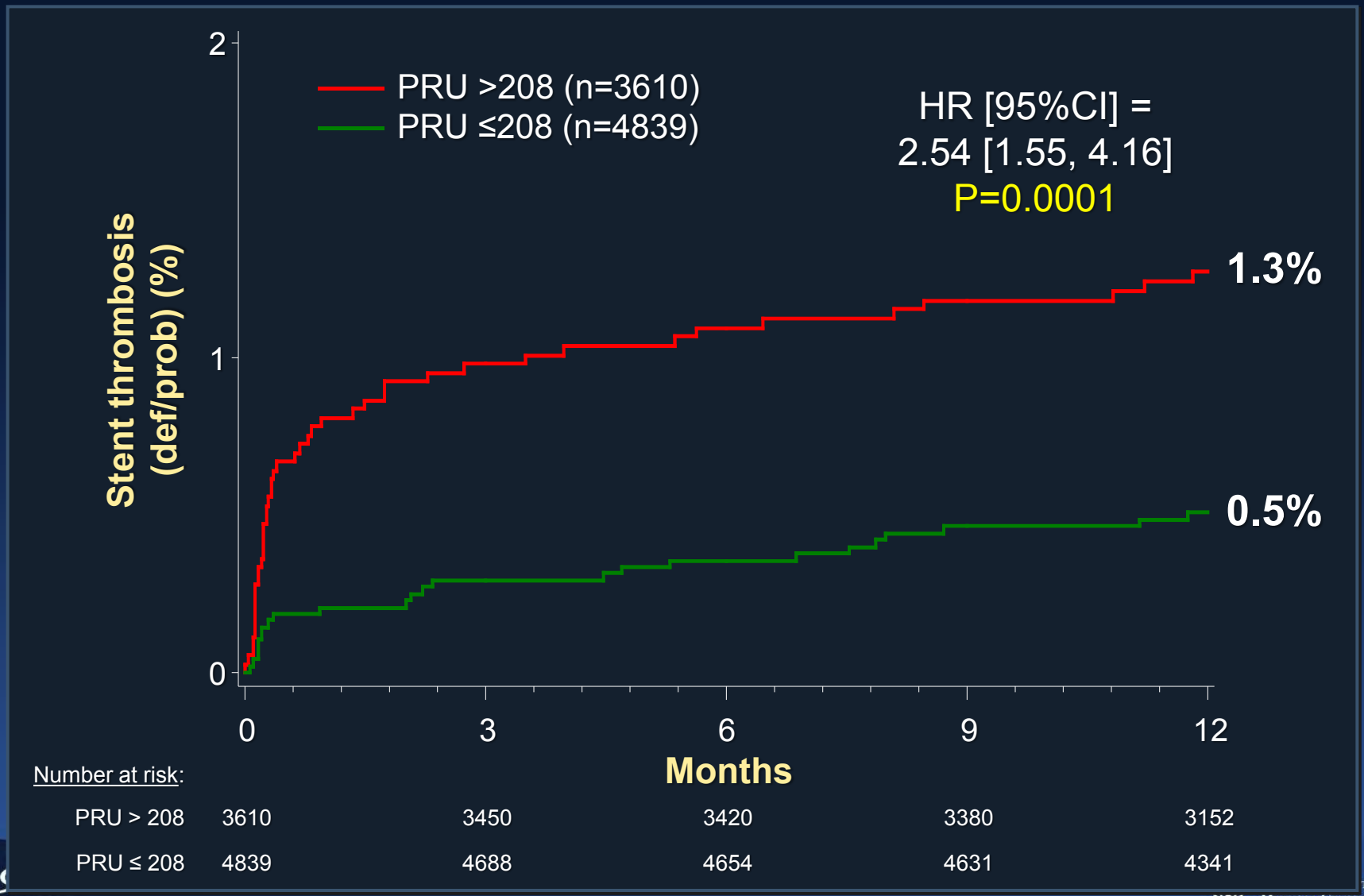
70 patients (0.84%) developed 74 ST events (ARC def/prob)



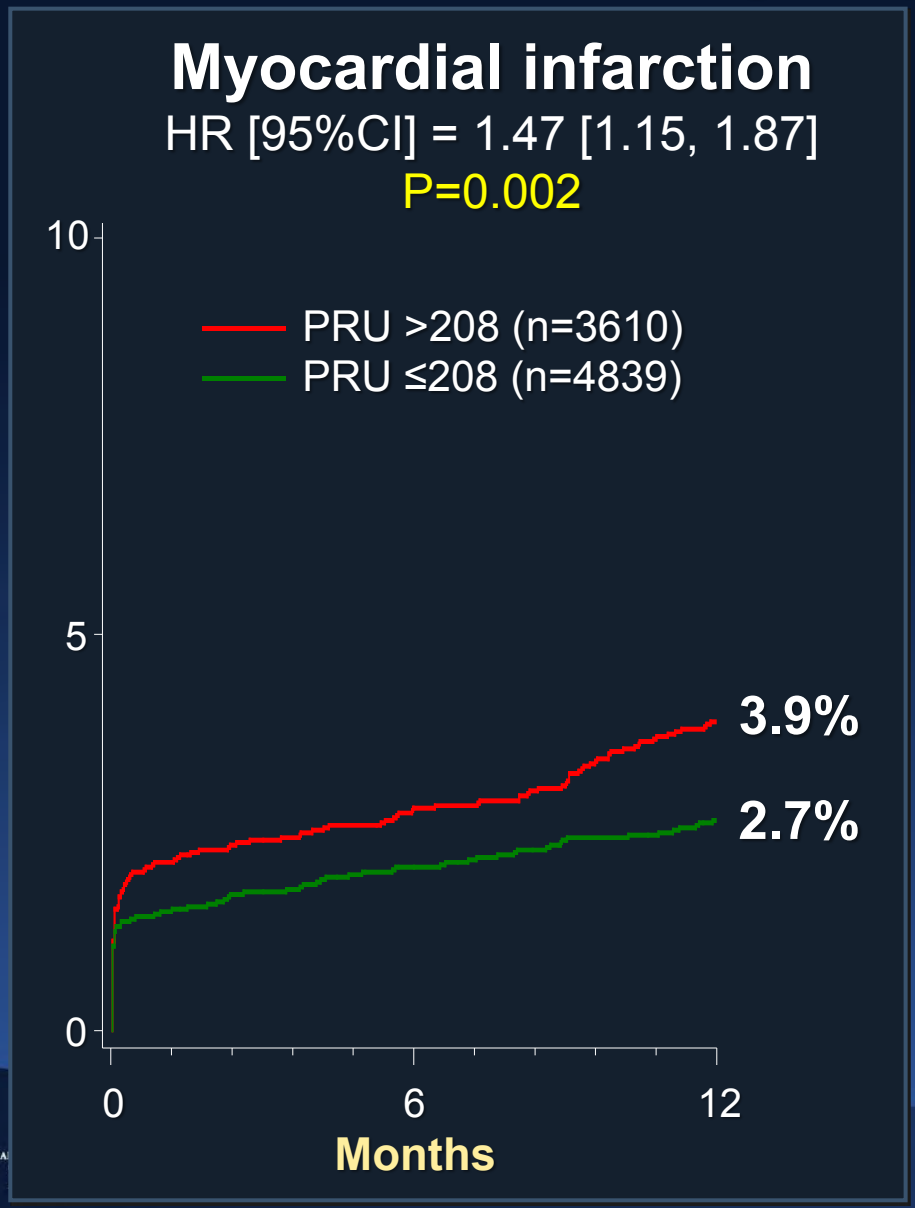
ADAPT-DES: Relationship between VerifyNow platelet response to DAPT and subsequent 1-year def/prob stent thrombosis (n=8,583)

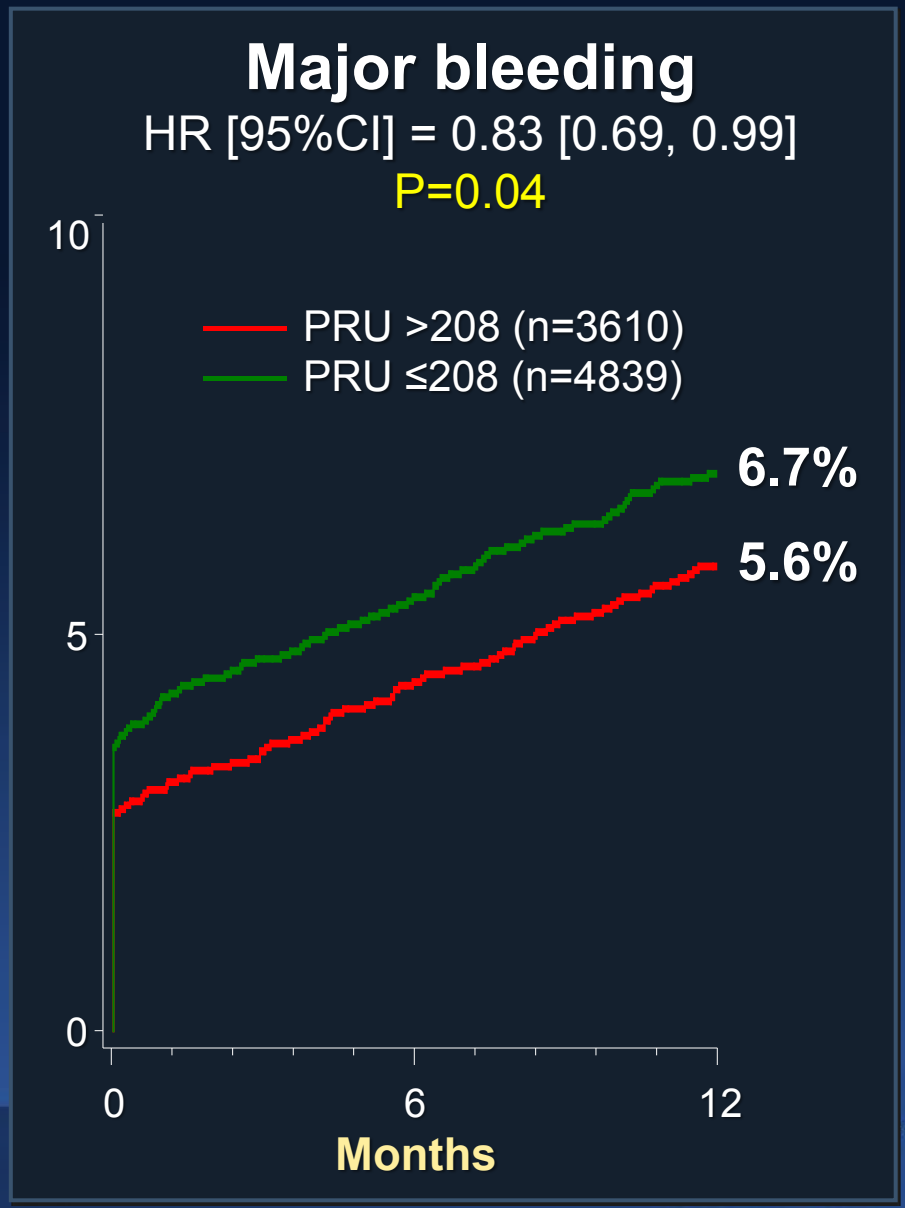
VerifyNow test	Def/prob ST (n=70)	No def/prob ST (n=8,513)	P
Aspirin ARU	426 ± 58	419 ± 55	0.30
- ARU ≥550	7.2%	5.6%	0.54
P2Y12 Base	305 ± 60	310 ± 58	0.56
P2Y12 PRU	234 ± 97	188 ± 97	<0.0001
- PRU >208	65.2%	42.5%	0.0002
- PRU ≥230	53.6%	34.9%	0.001
P2Y12 % Inhibition	24.8 ± 27.0	40.1 ± 28.2	<0.0001
- Inhibition ≤11%	44.9%	19.9%	<0.0001
IIb/IIIa PAU	194 ± 56	193 ± 54	0.92

ADAPT-DES: Stent thrombosis (definite or probable) according to post-PCI PRU

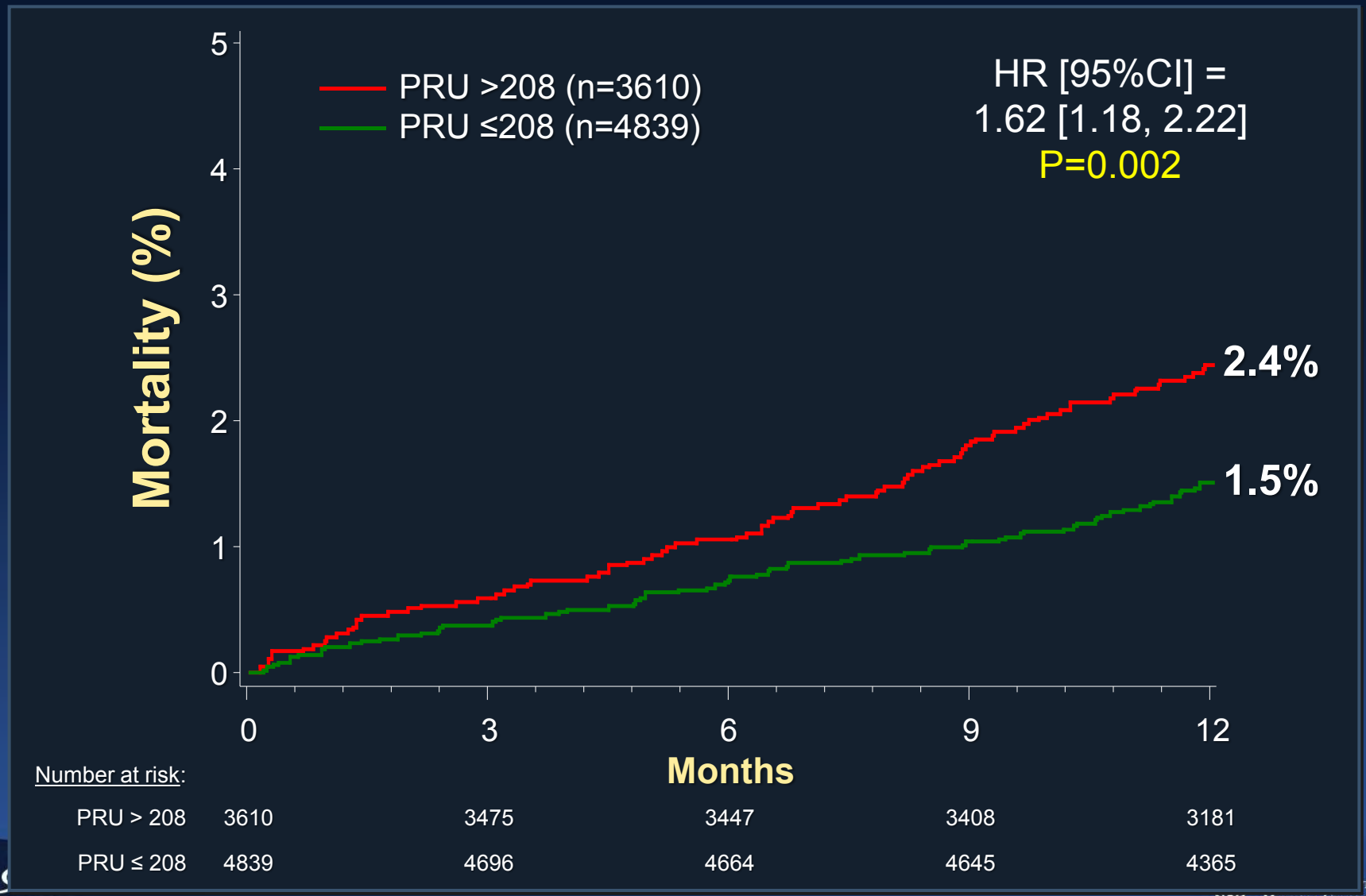


ADAPT-DES: MI and major bleeding according to post-PCI PRU

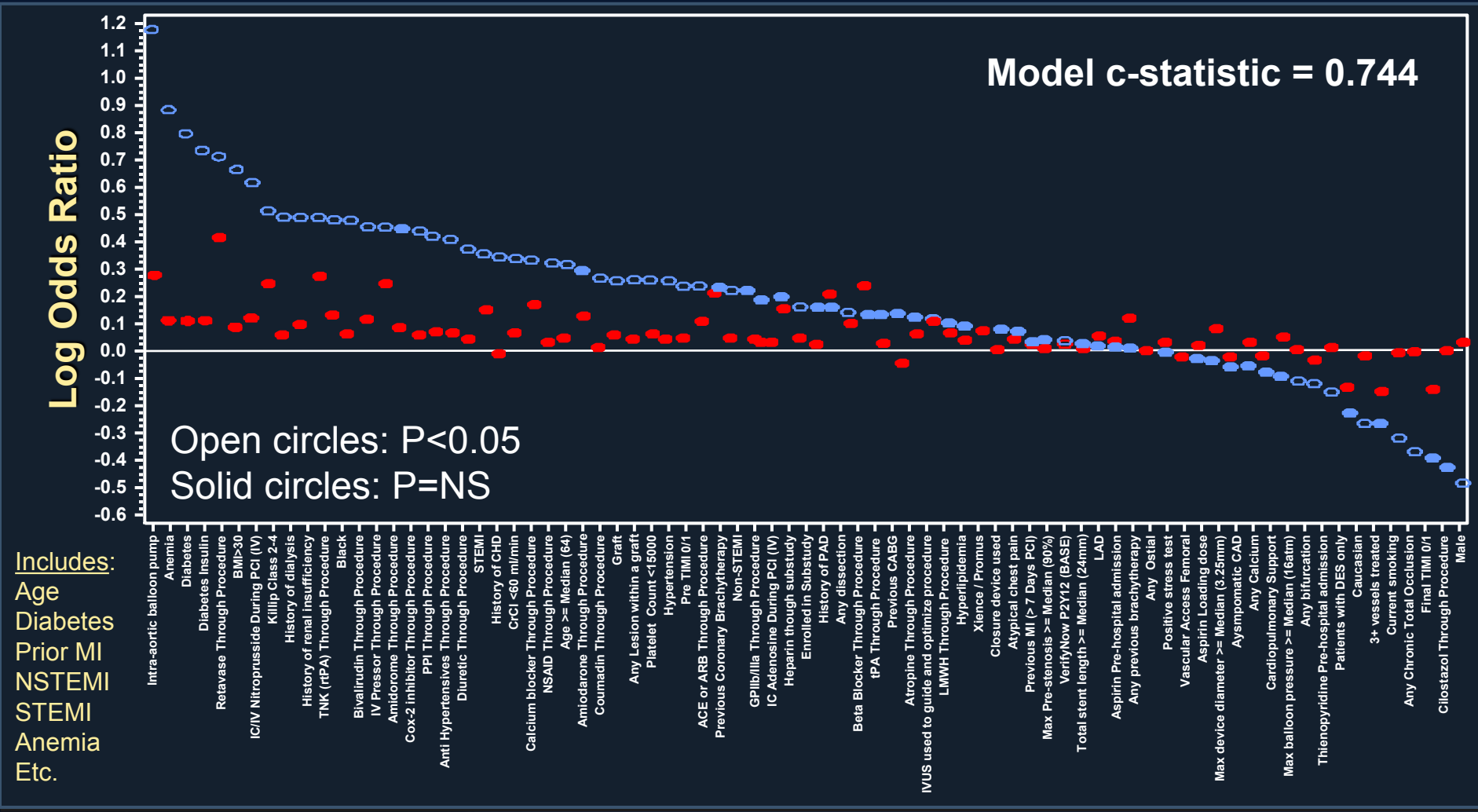




ADAPT-DES: Mortality according to post-PCI PRU



ADAPT-DES: Assessment of Propensity Score Model to Adjust for 87 Baseline Predictors of VerifyNow P2Y12 >208 PRU



Includes:
Age
Diabetes
Prior MI
NSTEMI
STEMI
Anemia
Etc.

No variables remain significant in the adjusted model

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ADAPT-DES: Multivariable propensity score adjusted risk of VerifyNow PRU >208 for subsequent 1-year adverse events (n=8,583)

Event	Adj HR [95%CI]	P value
ST, def/prob	2.49 [1.43, 4.31]	0.001
- Definite	3.05 [1.62, 5.75]	0.0006
MI	1.42 [1.09, 1.86]	0.01
Major bleeding	0.73 [0.61, 0.89]	0.002
Death, all-cause	1.20 [0.85, 1.70]	0.30

Variables in model: age, gender, diabetes, hypertension, hyperlipidemia, current smoking, prior MI, CKD, stable vs NSTEMI vs STEMI, hemoglobin, WBC, platelet count, creatinine clearance, MVD, premature DAPT discontinuation within 6 months, PRU >208 (forced in), ARU >550 (forced in)

ADAPT-DES: Relationship between adverse events and death at 1 year

- 161/8583 pts (1.9%) died within 1 year -

Event type	Event	No event	HR [95%CI]	P value
	Definite ST	No definite ST		
N	53	8530		
Deaths	5 (9.6%)	156 (1.9%)	5.47 [2.25, 13.31]	<0.0001
	MI w/o ST	No MI w/o ST		
N	224	8359		
Deaths	21 (9.7%)	140 (1.7%)	5.78 [3.65, 9.14]	<0.0001
	Major bleeding	No major bleeding		
N	531	8052		
Deaths	45 (8.6%)	116 (1.5%)	5.97 [4.23, 8.42]	<0.0001

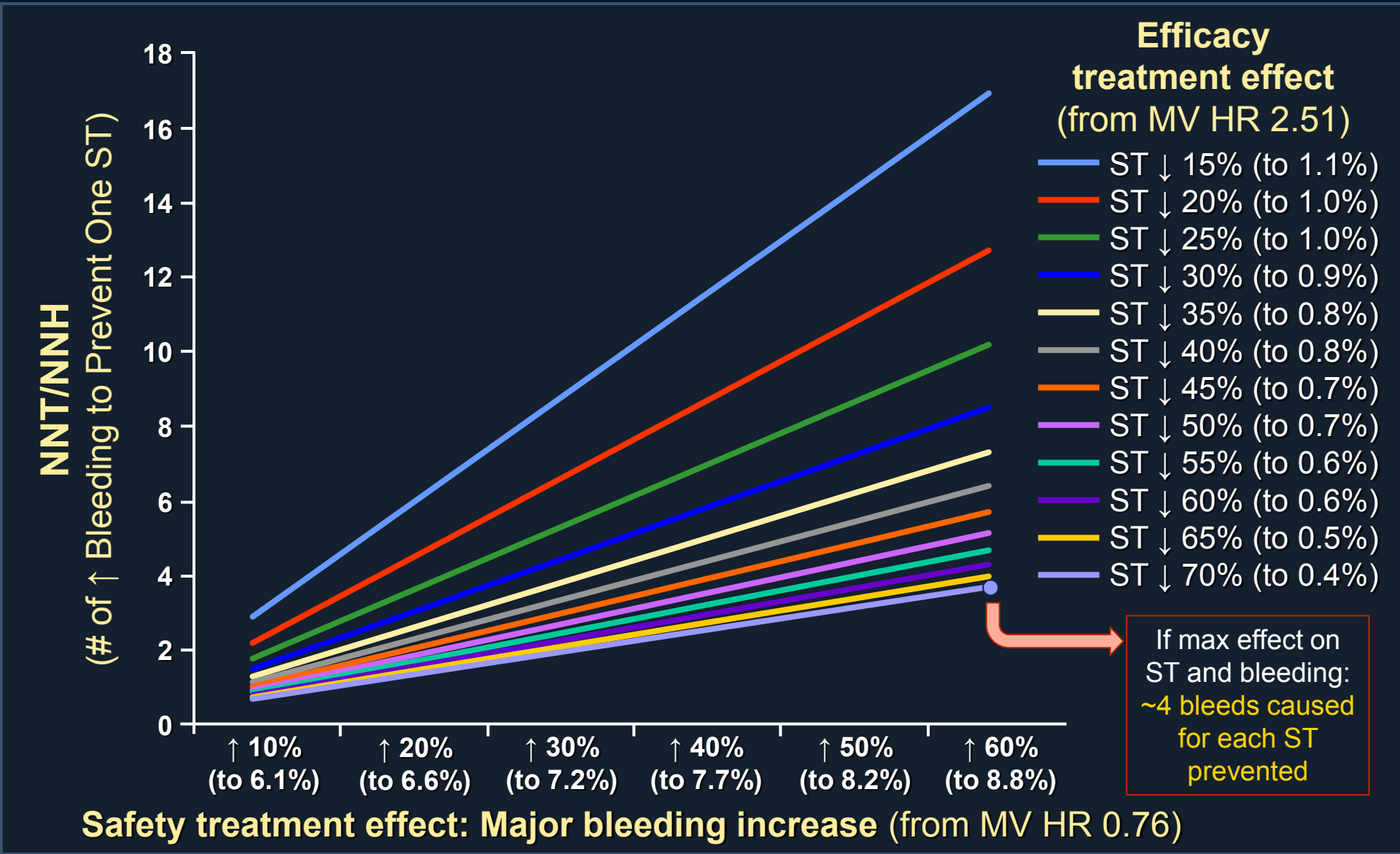
1 year event rates (n=8,583)
Definite ST: 53 (0.6%); MI w/o def :ST 224 (2.6%);
Major bleeding: 531 (6.2%)

ADAPT-DES: Multivariable propensity score adjusted Cox model for all-cause mortality (n=8,583), including events during FU as time-adjusted covariates

Baseline features	**Adj HR [95%CI]**	**P value**
Age (years)	1.03 [1.01, 1.05]	0.001
Male gender	1.95 [1.32, 2.87]	0.0008
Diabetes mellitus	1.84 [1.30, 2.62]	0.0007
Current smoking	1.48 [0.96, 2.29]	0.08
Hyperlipidemia	0.59 [0.41, 0.85]	0.005
Creatinine clearance	0.99 [0.98, 1.00]	0.004
Hemoglobin (g/dL)	0.74 [0.66, 0.83]	<0.0001
WBC (x10^3/mL)	1.03 [1.01, 1.05]	0.003
STEMI/NSTEMI (vs stable CAD)	1.38 [0.96, 2.00]	0.08
Premature DAPT D/C w/i 6 months	4.30 [2.96, 6.26]	<0.0001
Adverse events (time-adjusted)		
Definite stent thrombosis	3.43 [1.48, 7.98]	0.004
MI (w/o definite ST)	4.52 [2.84, 7.17]	<0.0001
Major bleeding	4.17 [2.84, 6.13]	<0.0001

Other variables in model: prior MI, NSTEMI/STEMI, hypertension, platelet count, creatinine clearance, MVD, VerifyNow P2Y12 > 208 PRU and VerifyNow Aspirin > 550 ARU

Hypothetically Increasing Clopidogrel Response in Pts with >208 PRU → Incremental Decrease in Stent Thrombosis (from 1.3%) vs. Increase in Bleeding (from 5.5%)



ADAPT-DES: Multivariable propensity score adjusted risk of VerifyNow ARU >550 for subsequent 1-year adverse events (n=8,583)

Event	Adj HR[95%CI]	P value
ST, def/prob	1.46 [0.58, 3.64]	0.42
- Definite	1.60 [0.57, 4.48]	0.37
MI	0.81 [0.46, 1.42]	0.46
Major bleeding	0.65 [0.43, 0.99]	0.04
Death, all-cause	1.42 [0.83, 2.43]	0.20

Variables in model: age, gender, diabetes, hypertension, hyperlipidemia, current smoking, prior MI, CKD, stable vs NSTEMI vs STEMI, hemoglobin, WBC, platelet count, creatinine clearance, MVD, premature DAPT discontinuation within 6 months, PRU >208 (forced in), ARU >550 (forced in)

ADAPT-DES: Conclusions and Implications I

- In the large-scale, prospective ADAPT-DES study, on-treatment hyporesponsiveness to clopidogrel after DES was an independent predictor of 1-year ST and MI, but was also protective against major bleeding, both of which were strongly related to mortality
- As a result, on-treatment clopidogrel hyporesponsiveness was not independently predictive of 1-year mortality

ADAPT-DES: Conclusions and Implications II

- Overcoming clopidogrel hyporesponsiveness with more potent antiplatelet agents is therefore unlikely to improve survival unless the beneficial effects of reducing ST and MI can be uncoupled from the likely increase in bleeding with greater platelet inhibition
- Hyporesponsiveness to aspirin was unrelated to ST, MI or death, but may be related to bleeding, questioning the utility of aspirin in pts treated with DES