A Point-of-Care Platelet Function Assay and C-Reactive Protein for Prediction of Major Cardiovascular Events After Drug-Eluting Stent Implantation

: A prospective, observational, single-center cohort study

Duk-Woo Park, MD, PhD

Professor of Medicine, Interventional Cardiology,
University of Ulsan College of Medicine, Asan Medical Center,
Seoul, Korea

Disclosure Information

Supported by research grants from
the Korea Health 21 R&D Project, Ministry of Health and Welfare, Korea (A090264).

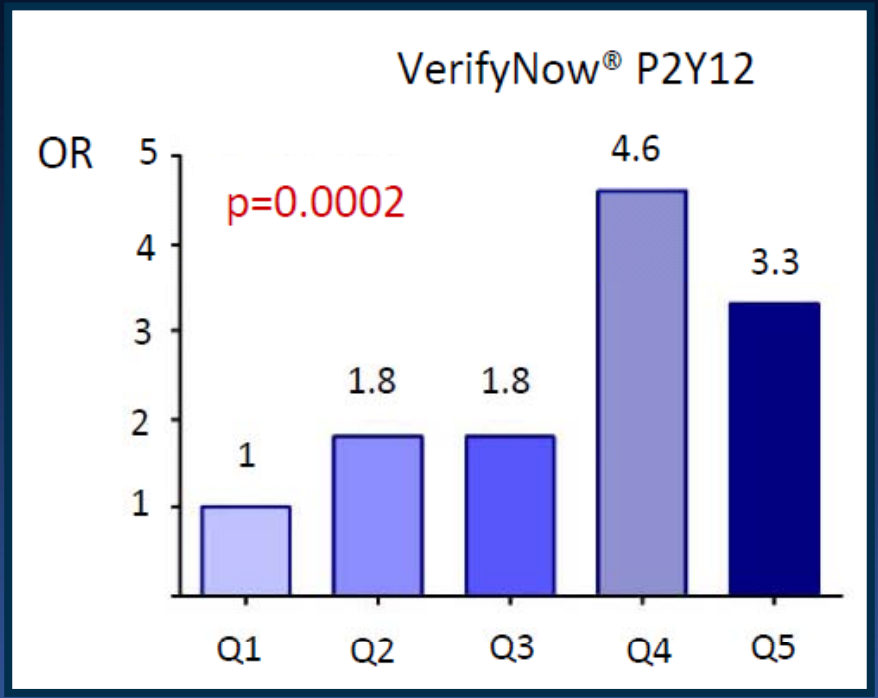
No industry sponsorship relevant to this study

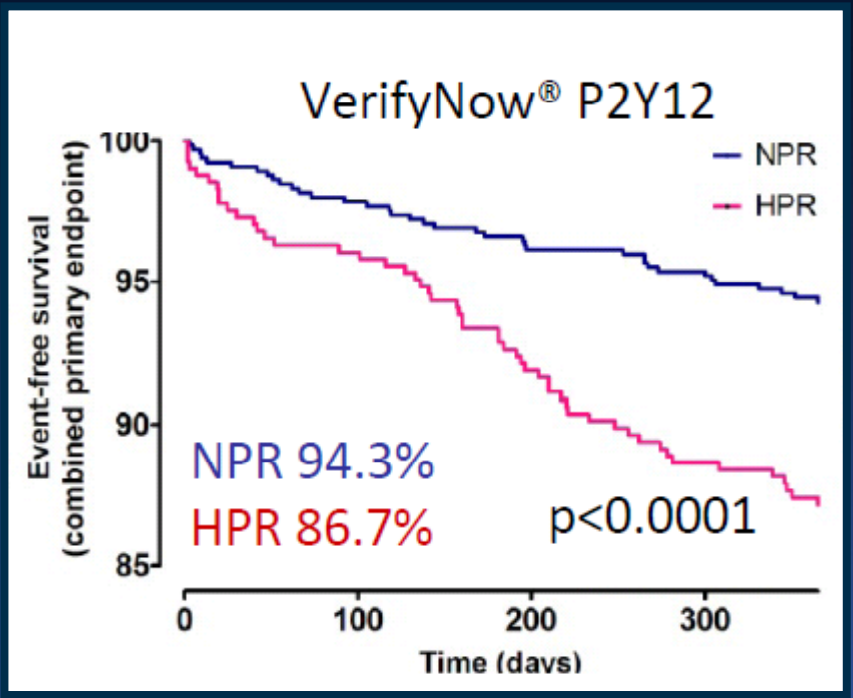
Background

- A wide inter-individual response to clopidogrel has been observed and a lower degree of platelet inhibition (i.e., high on-treatment platelet reactivity; HTPR) after clopidogrel therapy is associated with adverse ischemic events after PCI.
- Multiple studies suggested a relationship between HTPR, as measured by point-of-care assays, and post-PCI ischemic events.
- However, these studies were hampered by small number of events, few patients, or limited duration of follow-up. It is unknown whether HTPR associated with the risks for periprocedural or mid-term events are the same as those associated with long-term risks.

Background

The POPular Study





VerifyNow® P2Y12 assay is able to identify PCI patients at high risk

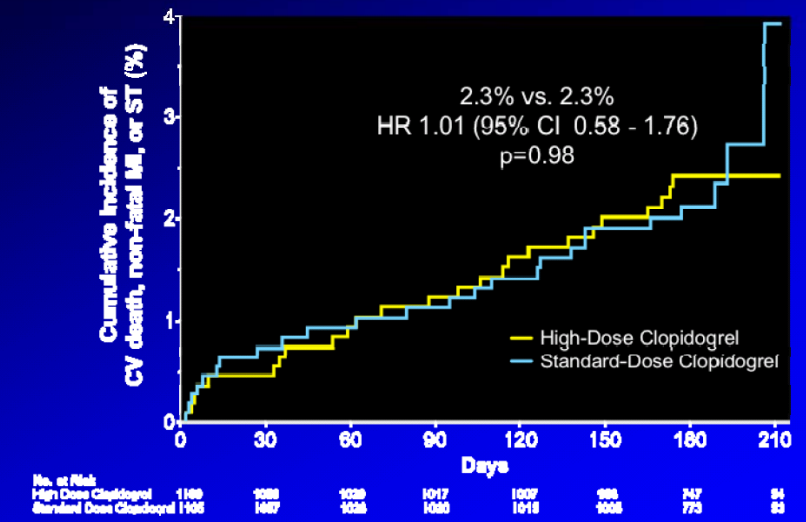
Breet NJ et al. JAMA. 2010;303:754-762

Background

The GRAVITAS Study

High vs. Standard Dose Clopidogrel

Primary Endpoint: CV Death, MI, Stent Thrombosis

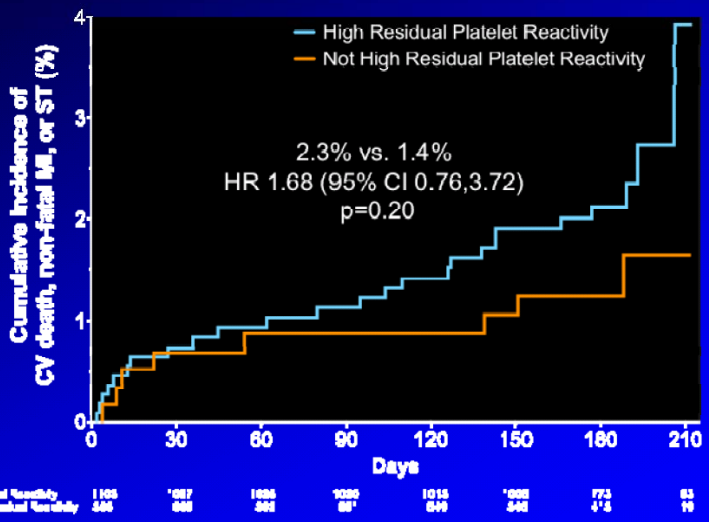


Observed event rates are listed; P value by log rank test.

GRAVITAS

High vs. Normal HTPR

Secondary Comparison: High vs. Not High Reactivity Treated with Clopidogrel 75-mg daily



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

GRAVITAS

- GRAVITAS did not support high-dose clopidogrel tailored therapy based on HTPR measured by VerifyNow® P2Y12 assay.
- There was no statistical significance in the rates of outcomes between high and normal platelet reactivity.

CardioVascular Research Foundation

Price MJ et al. JAMA.2011;305:1097-1105.

UNIVERSITY OF ULSAN COLLEGE MEDICINE

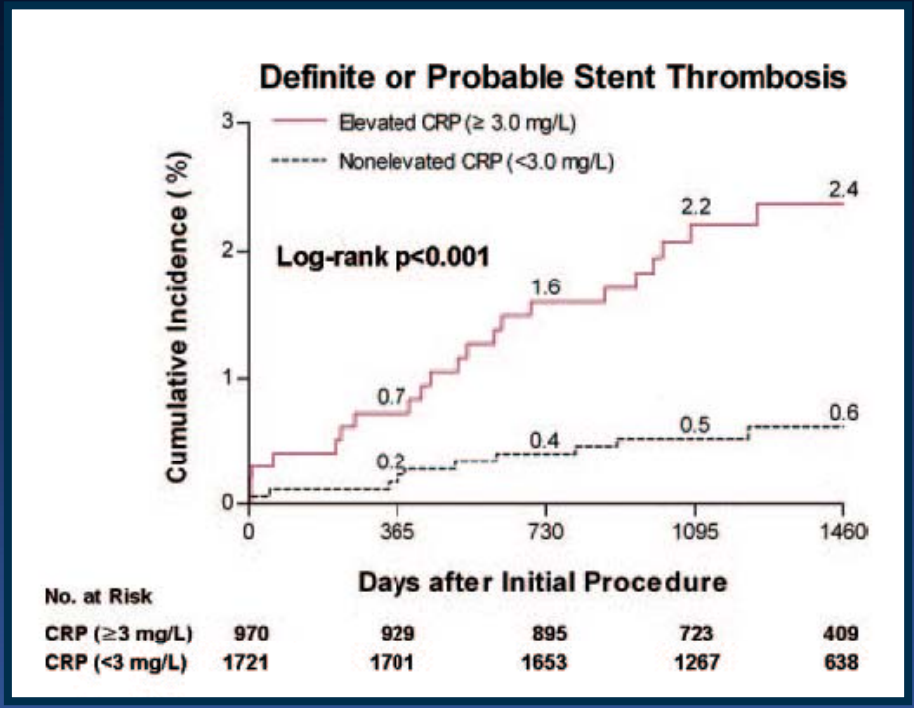
ASAN Medical Center

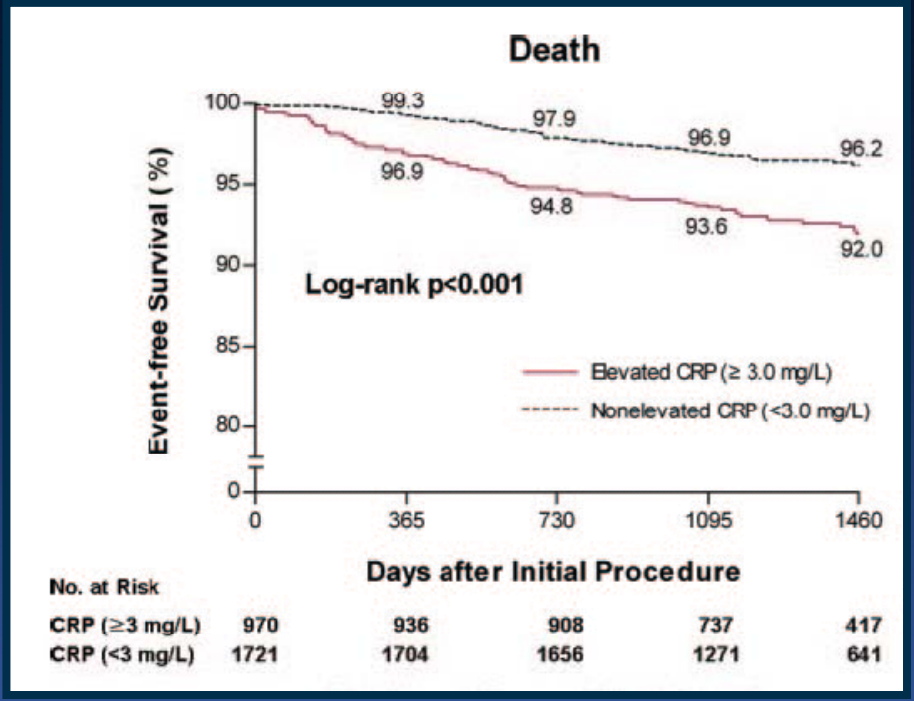
Background

- As a distinct biologic pathway, inflammatory biomarker such as C-reactive protein (CRP) has been postulated to be a hemostatic risk factor predicting atherothrombosis.
- Several studies and our previous observations suggested that high level of CRP was associated with major cardiovascular events or stet thrombosis in patients treated with DES.
- Enhanced risk assessment with the addition of these laboratory assays (on-site platelet function assay or CRP) on conventional clinical and procedural risk factors would be of great clinical value if it could more accurately identify people at high risk after PCI.

Background

The ASAN-Biomarker Study





Inflammatory risk assessment with CRP are predictive for stent thrombosis, death, and MI in patients receiving DES.

Park et al. Circulation. 2009;120:1987-1995

Objective

- As a primary study objective, we test the hypothesis that HTPR measured by VerifyNow P2Y12 assay is associated with long-term atherothrombotic risks in patients undergoing DES implantation.
- Secondarily, on an a priori basis, we compared the incremental usefulness of on-site platelet function assay (VerifyNow P2Y12 assay) and inflammatory biomarker (CRP) from different disease pathways to predict clinical outcome in such patients.

Study Population

Inclusion Criteria

- The study population included 2,849 consecutive patients with

  (1) stable angina or non–ST-elevation ACS with significant CAD treated with 1 or more DES.

  (2) had VerifyNow P2Y12 assays measured at 24 to 48 hours post-PCI between March 2006 and December 2009.

- Baseline CRP was also measured in 2,546 (90%) of these patients.

Exclusion Criteria

- STEMI or cardiogenic shock
- Periprocedural use of glycoprotein IIb-IIIa inhibitor
- Known platelet function disorder or thrombocytopenia <80,000
- Concomitant inflammatory conditions (i.e., active infection or connective tissue disorder) or malignancy.
- Contraindication to aspirin or clopidogrel

Procedures and Laboratory Measurements

PCI Procedures

- The choice of DES types was left to the operator's discretion.
- All patients received optimal clopidogrel treatment (defined as a maintenance of 75 mg/d therapy for >5 days or a loading dose of 300 mg or 600 mg ≥12 hours before PCI) and aspirin (loading dose, 200 mg).
- After PCI, patients were prescribed aspirin (100-200 mg) indefinitely and clopidogrel (75 mg once daily) for at least 12 months, regardless of DES type.

VerifyNow® P2Y12 assay and CRP measurements

- VerifyNow® P2Y12 assay was performed at 24-48hrs post PCI.
- For CRP measurement, fasting blood samples were obtained in the morning before the procedure and was assayed with a latex-enhanced high-sensitivity CRP immunoassay.

Study Endpoints

Primary end point

- The first occurrence of major cardiovascular events defined as a composite of all-cause death, nonfatal myocardial infarction (MI), stent thrombosis (definite or probable), and stroke.

Secondary end points

- Death
- MI
- Stent thrombosis
- Stroke
- Target-vessel revascularization (TVR).
- Cardiac death, MI, stent thrombosis, and stroke
- TIMI-bleeding, major or all type

Definitions (1)

- All deaths were considered to be from cardiovascular causes unless an unequivocal noncardiac cause could be established.
- The diagnosis of acute MI was based on the universal definition of MI; periprocedural or postprocedural elevations of cardiac enzymes were disregarded if ischemic signs or symptoms were absent.
- Stent thrombosis was assessed by the ARC criteria.
- Stroke, as detected by the occurrence of a new neurologic deficit, was confirmed by a neurologist and on imaging.
- TVR was defined as any percutaneous or surgical revascularization of the target vessel.
- Major and all type of bleedings were assessed in accordance with TIMI criteria.

Definitions (2)

- Based on a prior observation* of a same ethnic population that used ROC analysis to define the optimal cutoff of VerifyNow P2Y12 assay for prediction high reactivity on standard LTA, HTPR was defined by a PRU value >235 and/or a % inhibition <15%.
- Based on the cutoff point that has been suggested in the literature and in the our previous report, a CRP levels ≥3 mg/L were considered elevated.
- In our practice, alteration of antiplatelet therapy was not done according to the results of VerifyNow P2Y12 assay or CRP measurements.

*Jeong YH et al. Eur Heart J. 2008;**29**:2186-7

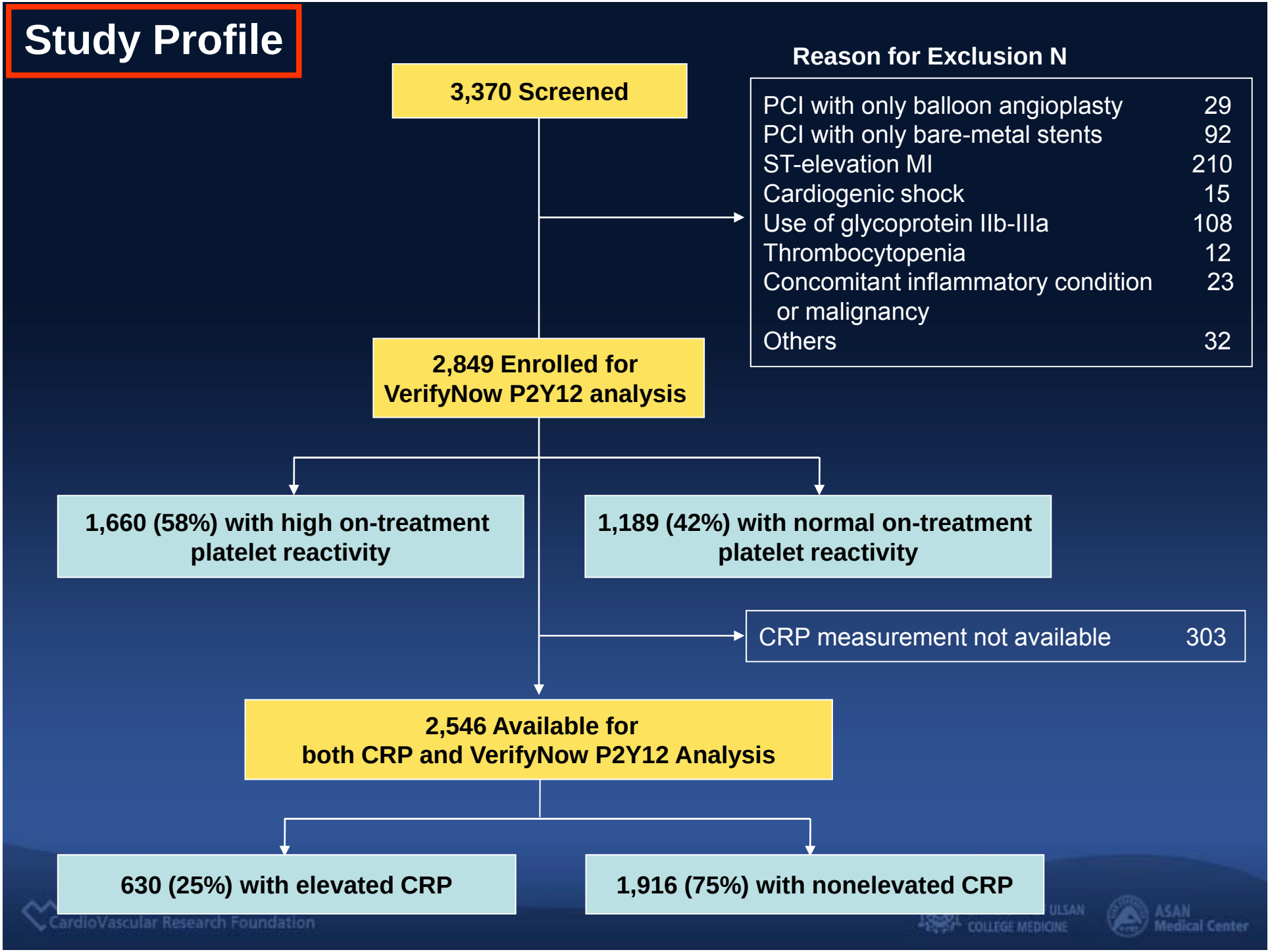
Data Collection and Follow-up

- Clinical follow-up was recommended at 1 month, 6 months, and 1 year, and then every 6 months thereafter.
- Clinical status, interim occurrence of adverse events, and anti-platelet drug therapy (use of aspirin and clopidogrel) were checked at each follow-up.
- Information about vital status was obtained from the *Korea National Statistical Office* using a unique personal ID.

Statistical Analysis

- Cumulative probability and survival curves were constructed from Kaplan–Meier estimates and compared by use of the log-rank test.
- The relations of HTPR and CRP to clinical outcomes were investigated using Cox proportional-hazards models.
- The incremental value of adding HTPR and/or CRP into the conventional clinical and procedural risk factors for predicting clinical events were examined using C statistics.

Study Profile



Baseline Clinical Characteristics

Variable	On-Treatment Platelet Reactivity		P Value
	High (n=1660)	Normal (n=1189)	
Age — yr	62.6±9.5	60.4±9.9	<0.001
Male gender — no. (%)	1121 (67.5)	906 (76.2)	<0.001
Body-mass index	25.1±2.9	24.9±2.9	0.02
Diabetes — no. (%)	482 (29.0)	329 (27.7)	0.43
Hypertension — no. (%)	1013 (61.0)	664 (55.8)	0.006
Current smoking — no. (%)	400 (24.1)	312 (26.2)	0.19
Hypercholesterolemia — no. (%)	1028 (61.9)	711 (59.8)	0.25

*Mean ± SD or N (%)

Baseline Clinical Characteristics

Variable	On-Treatment Platelet Reactivity		P Value
	High (n=1660)	Normal (n=1189)	
Previous MI — no. (%)	90 (5.4)	77 (6.5)	0.24
Previous PCI — no. (%)	281 (16.9)	233 (19.6)	0.07
Previous bypass surgery — no. (%)	50 (3.0)	30 (2.5)	0.44
Previous stroke — no. (%)	90 (5.4)	51 (4.3)	0.17
Renal insufficiency — no. (%)	32 (1.9)	18 (1.5)	0.41
Clinical indication — no. (%)			0.85
Stable angina	921 (55.5)	664 (55.8)	
Acute coronary syndrome	739 (44.5)	525 (44.2)	
Ejection fraction — %	59.2±6.7	59.5±7.0	0.24

***Mean** ± SD or N (%)

Baseline Procedural Characteristics

Variable	On-Treatment Platelet Reactivity		P Value
	High (n=1660)	Normal (n=1189)	
Multivessel disease — no. (%)	845 (50.9)	624 (52.5)	0.41
LAD disease — no. (%)	1204 (72.5)	891 (74.9)	0.15
Left main disease — no. (%)	159 (9.6)	148 (12.4)	0.02
ACC/AHA B2 or C type — no. (%)	1332 (80.2)	963 (81.0)	0.62
Bifurcation lesion — no. (%)	601 (36.2)	408 (34.3)	0.30
No. of stents implanted	2.0±1.1	2.1±1.2	0.32
Total stent length — mm	50.0±31.4	50.8±31.7	0.52
Minimal stent diameter — mm	3.1±0.4	3.1±0.4	0.14

***Mean** ± SD or N (%)

Discharge Medications

Characteristic	On-Treatment Platelet Reactivity		P Value
	High (n=1660)	Normal (n=1189)	
Cardiac-Related Medications — no. (%)			
ACE inhibitor	472 (28.4)	295 (24.8)	0.03
ß-blockers	1149 (69.2)	806 (67.8)	0.42
Calcium channel blocker	1458 (87.8)	1048 (88.1)	0.80
Statin	1325 (79.8)	936 (78.7)	0.48
Warfarins	12 (0.7)	6 (0.5)	0.47
Proton pump inhibitor	47 (2.8)	26 (2.2)	0.28

***Mean** ± SD or N (%)

Status of dual antiplatelet therapy

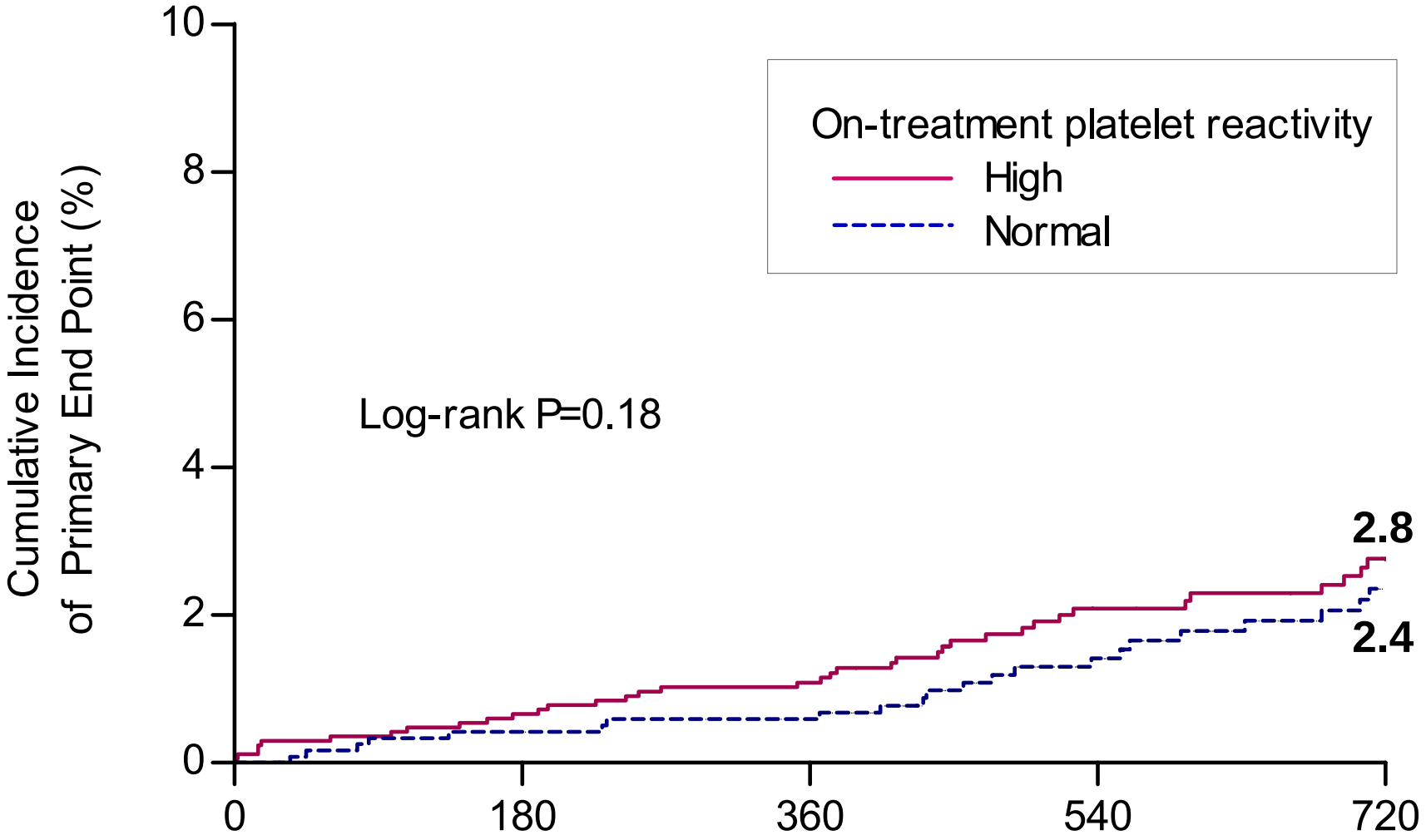
Characteristic	On-Treatment Platelet Reactivity		P Value
	High (n=1660)	Normal (n=1189)	
Clopidogrel loading at pre-procedure — no. (%)			0.28
75 mg/d for more than 5 days	507 (30.5)	396 (33.3)	
300 mg ≥12 hours before PCI	1107 (66.7)	759 (63.8)	
600 mg ≥12 hours before PCI	46 (2.8)	34 (2.9)	
Clopidogrel maintenance — no./total no. (%)			
At discharge	1658/1660 (99.9)	1188/1189 (99.9)	>0.99
6 Mo after procedure	1605/1644 (97.6)	1146/1182 (97.0)	0.27
12 Mo after procedure	1472/1578 (93.3)	1041/1135 (91.7)	0.12
18 Mo after procedure	834/1018 (81.9)	638/794 (80.3)	0.40
24 Mo after procedure	539/752 (71.7)	426/609 (70.0)	0.49
Aspirin maintenance — no./total no. (%)			
At discharge	1657/1660 (99.8)	1186/1189 (99.7)	0.70
6 Mo after procedure	1620/1644 (98.5)	1169/1182 (98.9)	0.41
12 Mo after procedure	1542/1578 (97.7)	1101/1135 (97.0)	0.25
18 Mo after procedure	973/1018 (95.6)	761/794 (95.8)	0.78
24 Mo after procedure	703/752 (93.5)	577/609 (94.7)	0.33

*Mean ± SD or N (%)

Outcomes According to Status of HTPR

- The median follow-up was 2.2 years (IQR, 1.3 to 3.4).
- Complete follow-up data for major clinical events were obtained in 99.1% of the overall cohort.

Primary end point according to HTPR



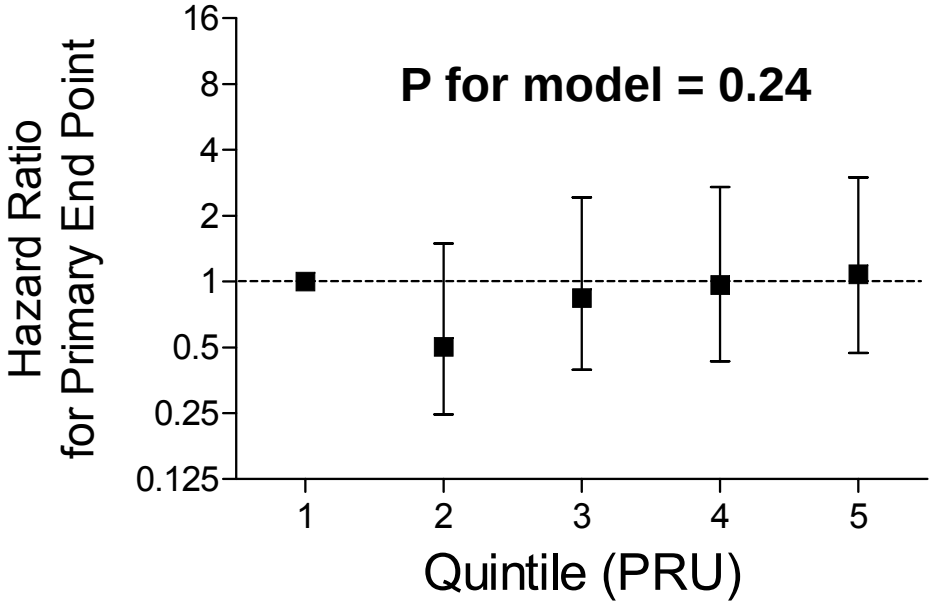
No. at Risk					
High reactivity	1660	1643	1602	1060	801
Normal reactivity	1189	1178	1154	831	662

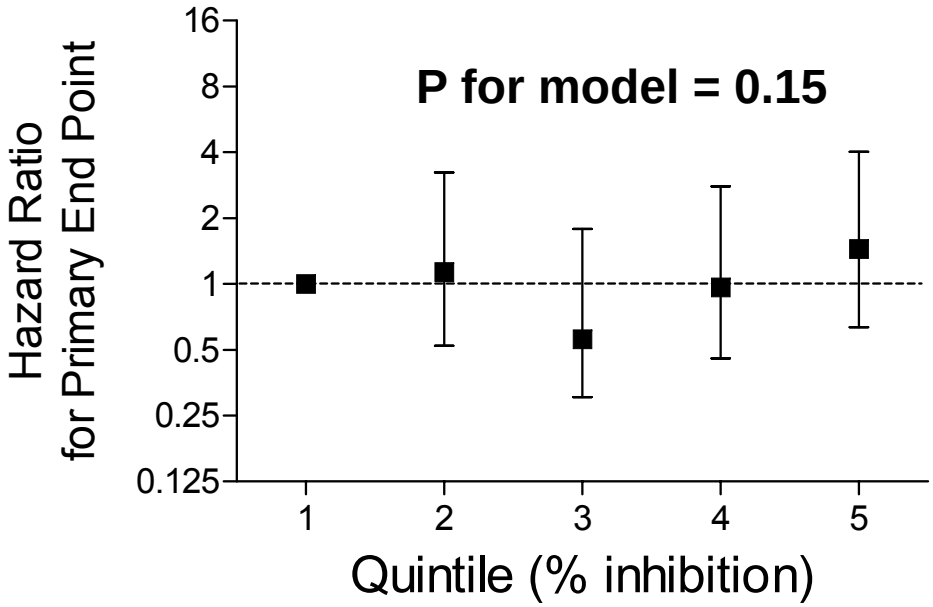
*Primary end points: composite of death, MI, stent thrombosis, stroke

Clinical outcomes According to On-Treatment Platelet Reactivity

Outcomes	Cumulative Event Rate At 24 Months		Hazard Ratio† (95% CI)	P Value
	Platelet Reactivity			
	High (n=1660)	Normal (n=1189)		
Death, MI, Stent thrombosis, or stroke	**2.8**	**2.4**	**1.33 (0.88-2.01)**	**0.18**
Death	2.0	2.0	1.10 (0.69-1.75)	0.71
MI	0.3	0.3	1.34 (0.37-4.83)	0.66
Stent thrombosis	0.2	0.2	1.45 (0.27-7.92)	0.67
Stroke	0.9	0.7	1.54 (0.68-3.47)	0.30
TVR	4.3	5.1	0.94 (0.67-1.31)	0.71
Cardiac death, MI, stent thrombosis or stroke	2.2	1.3	1.46 (0.88-2.43)	0.15
TIMI bleeding				
All	3.3	2.6	1.31 (0.87-1.98)	0.20
Major	0.9	0.6	1.29 (0.59-2.83)	0.52

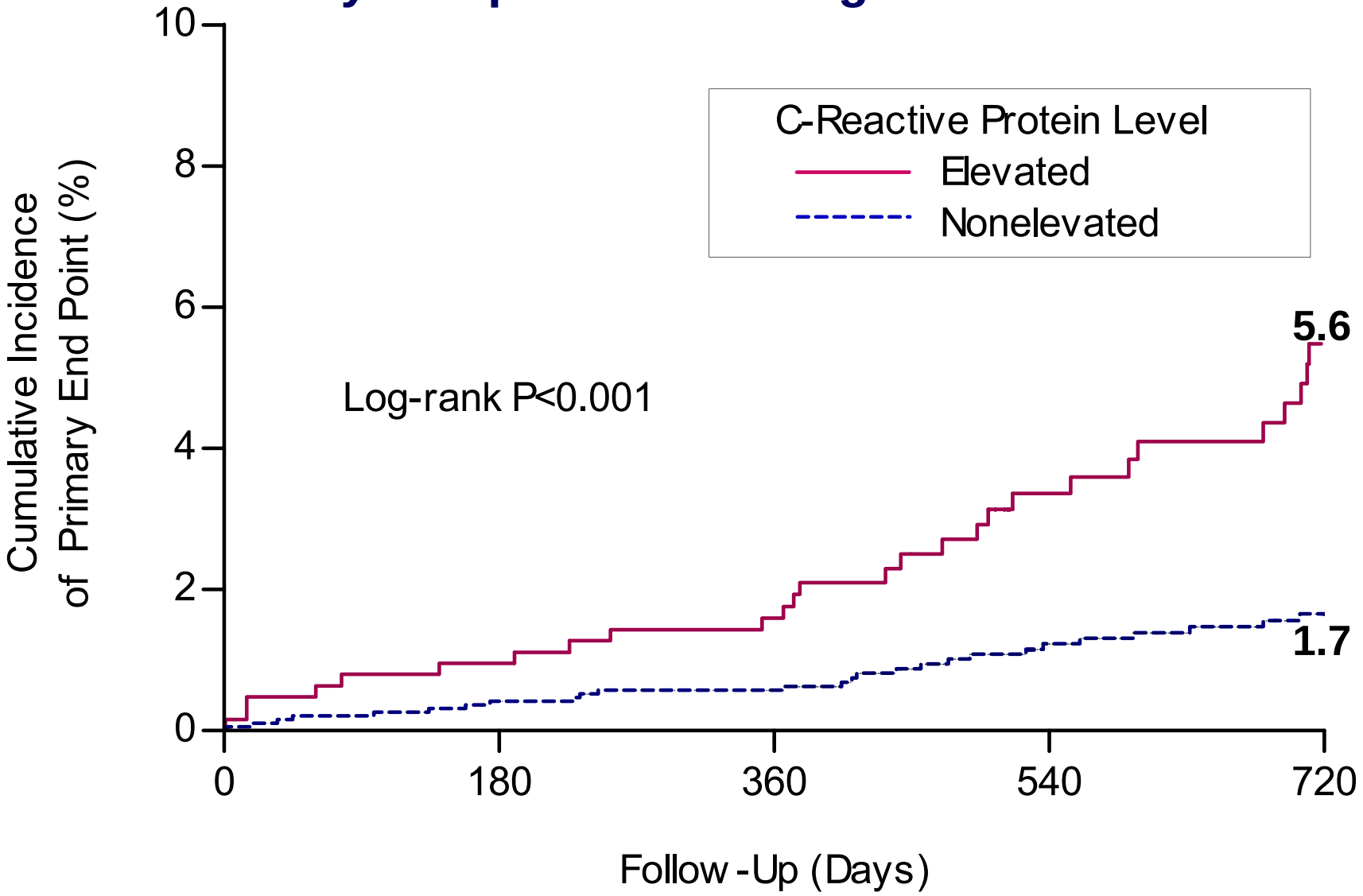
Primary end point according to PRU or % inhibition quintiles





Outcomes According to Baseline CRP Levels

Primary end point according to CRP levels



No. at Risk

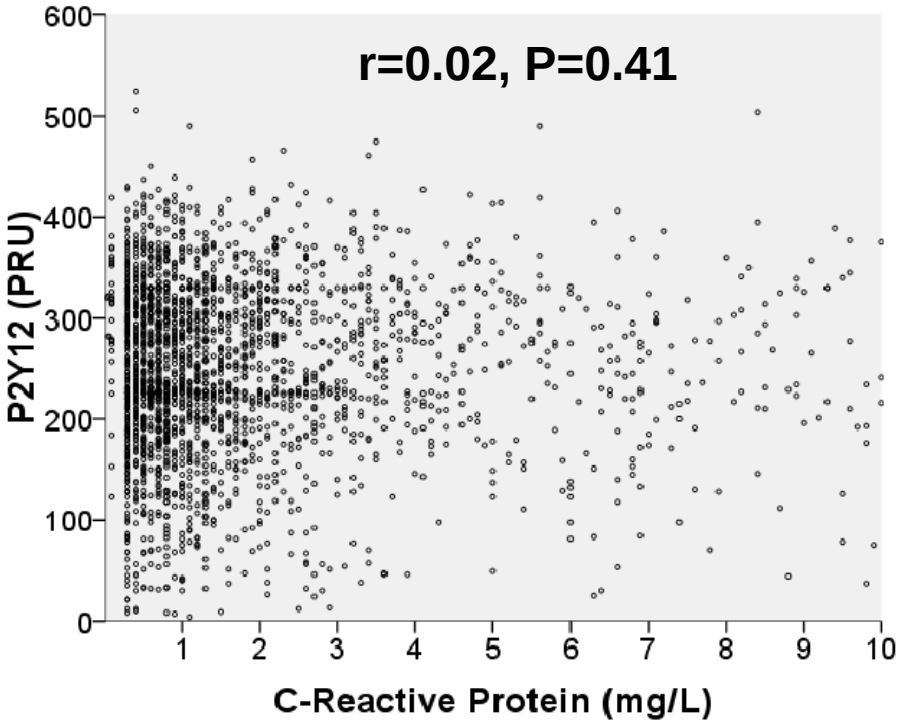
Elevated CRP	630	620	605	421	334
Nonelevated CRP	1916	1900	1858	1326	1039

Clinical outcomes According to CRP Level

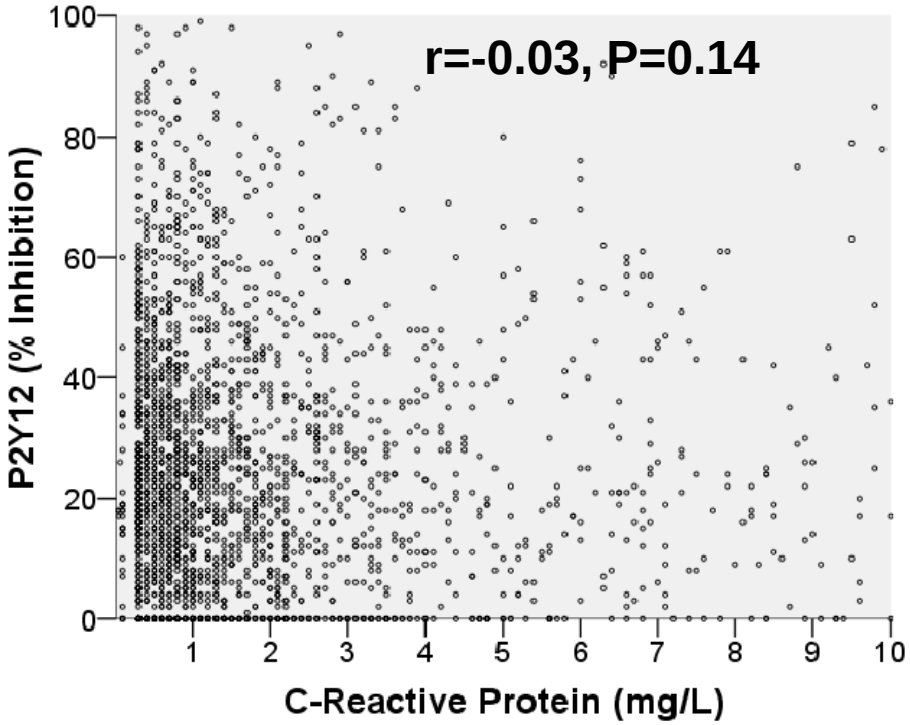
Outcome	Cumulative Event Rate At 24 Months		Hazard Ratio† (95% CI)	P Value
	C-Reactive Protein Level			
	Elevated (n=630)	Non-elevated (n=1916)		
Death, MI, Stent thrombosis, or stroke	**5.6**	**1.7**	**2.81 (1.83-4.31)**	**<0.001**
Death	4.6	1.3	2.94 (1.81-4.79)	<0.001
MI	0.8	0.2	2.17 (0.61-7.71)	0.23
Stent thrombosis	0.5	0.2	3.06 (0.62-15.14)	0.17
Stroke	1.2	0.4	2.88 (1.17-7.10)	0.02
TVR	3.7	5.0	0.75 (0.48-1.16)	0.20
Cardiac death, MI, stent thrombosis or stroke	4.2	0.9	3.01 (1.78-5.08)	<0.001
TIMI bleeding				
All	3.0	2.7	1.29 (0.81-2.06)	0.28
Major	0.8	0.6	1.16 (0.46-2.97)	0.75

Relationship of On-Treatment Platelet Reactivity and C-Reactive Protein

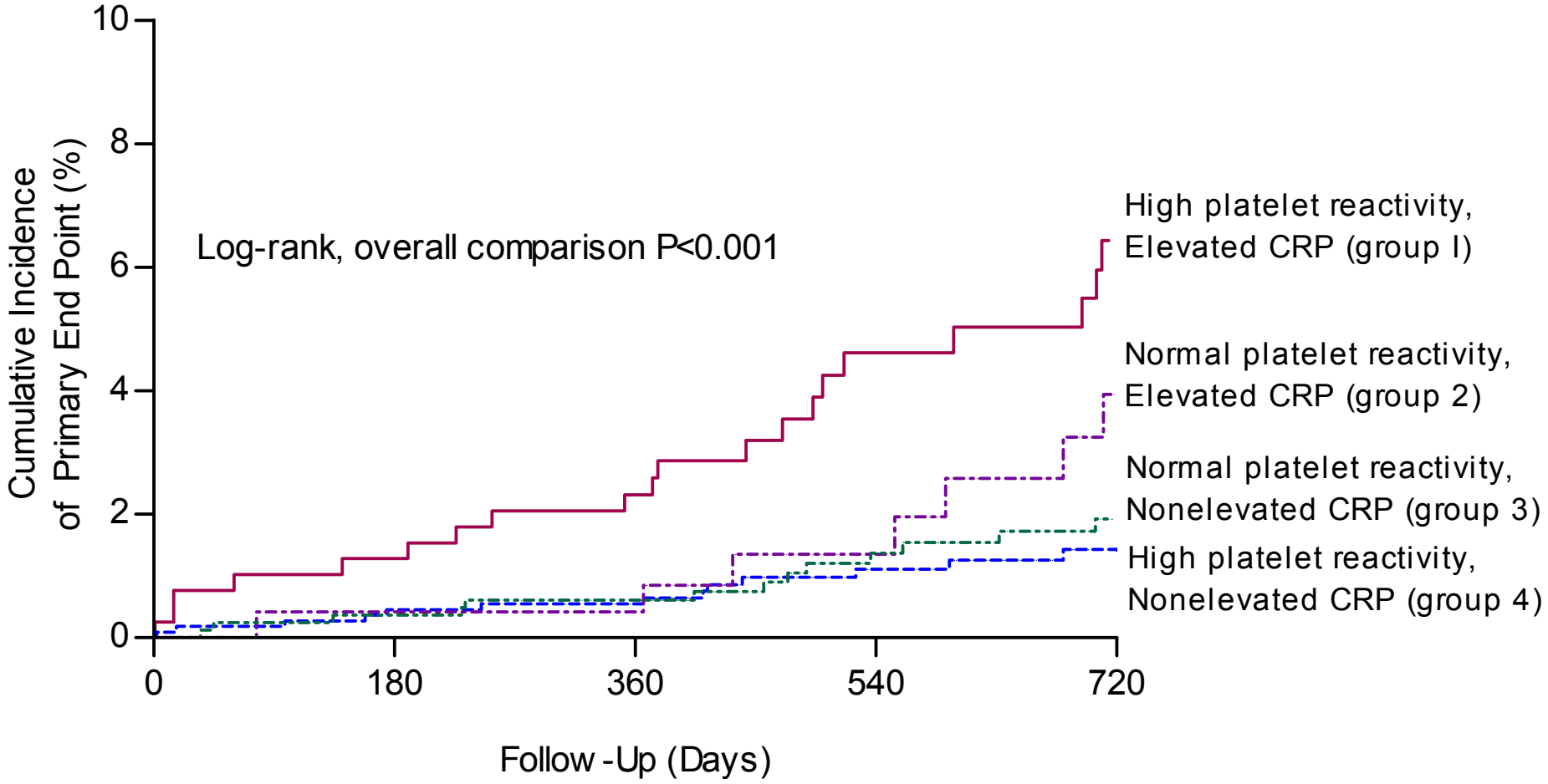
A



B



Outcomes According to the Status of Both On-Treatment Platelet Reactivity and C-Reactive Protein



No. at Risk

Group I	392	384	371	253	198
Group 2	238	236	234	168	136
Group 3	822	814	794	595	484
Group 4	1094	1086	1064	730	555

C Statistic for Cox Regression Models for Prediction of Primary End Point

Model	C Statistic	Estimated difference (95% CI)	P value
Risk Factors and Laboratory Assay			
Conventional clinical and procedural risk factors*	0.729	Referent	Referent
Conventional clinical and procedural risk factors **plus HTPR**	0.733	0.003 (-0.007 to 0.013)	0.54
Conventional clinical and procedural risk factors **plus elevated CRP levels**	0.759	0.031 (0.002 to 0.058)	0.03
Conventional clinical and procedural risk factors **plus HTPR and elevated CRP levels**	0.762	0.032 (0.003 to 0.062)	0.03

*Conventional clinical risk factors were age, sex, BMI, diabetes, hypertension, hypercholesterolemia, previous MI, previous stroke, renal insufficiency, EF, and ACS;
*Conventional procedural risk factors were multivessel disease, B2 or C type lesions, bifurcation lesions, total number of stent, total stent length, and minimal stent diameter.

Conclusion

- In a large cohort of consecutive patients who received DES implantation, we observed that high-on treatment reactivity measured by VerifyNow P2Y12 assay failed to predict long-term risk of atherothrombotic events.

- In contrast, elevated CRP levels were significantly associated with atherothrombotic events and also had incremental predictive values beyond on conventional clinical and procedural risk factors.

Clinical Implications

- Tailored therapy based on on-site platelet function test should be confirmed from ongoing large clinical trials (ARCTIC, TARGET-PCI, TRIOLOGY-ACS…).

- Inflammatory risk stratification with CRP as an adjunct to conventional risk factors may be useful and could be accomplished quickly, since this biomarker is already well established for diagnostic use.

- Interestingly, the observed differences of outcomes based on HTPR in patients with elevated CRP levels might pose the hypothesis that elevated CRP could represent a ***"higher-risk population"*** who might benefit from a selective platelet function test or tailored antiplatelet therapy.