

Comparison of 3 Different Assays for Measuring Platelet Function and Monitoring Residual Platelet Activity after Clopidogrel Medication in Patient with Coronary Stent Implantation

동아대학교병원 순환기내과¹ , 임상시험센터²

장홍철^{1 2} , 김무현^{1 2} , 곽용철² , 조용락¹ , 백희경¹ , 박경일¹ , 박종성¹ , 박태호¹ , 김영대¹



Introduction

- **Dual pathway inhibition with aspirin and clopidogrel has become standard care of treatment in high-risk patients**
- **Clopidogrel low-responsiveness or high on treatment platelet reactivity (HPR) has emerged to an own clinical entity.**
- **HPR currently has been accepted as a major cardiovascular risk factor.**
- **Used variety platelet function monitoring assay are useful tools to identify patients with or without response.**

Introduction

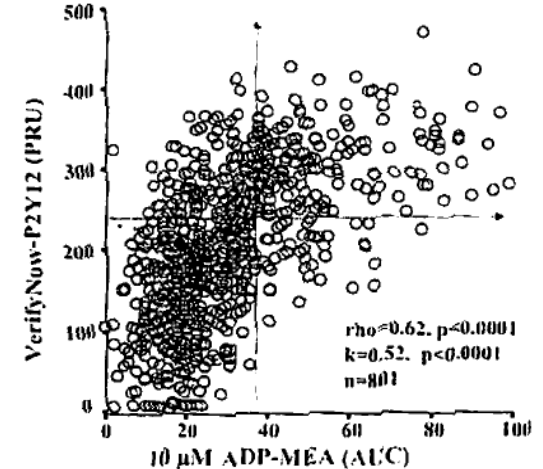
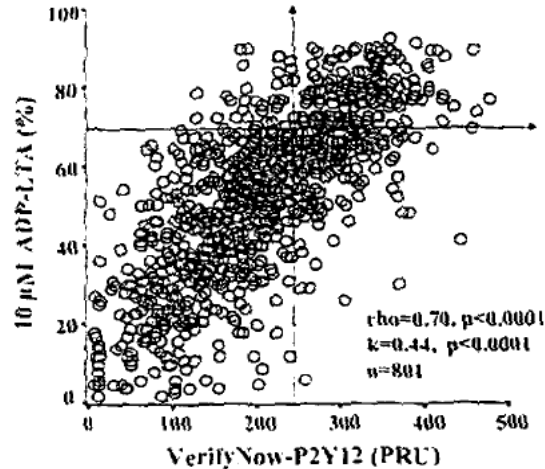
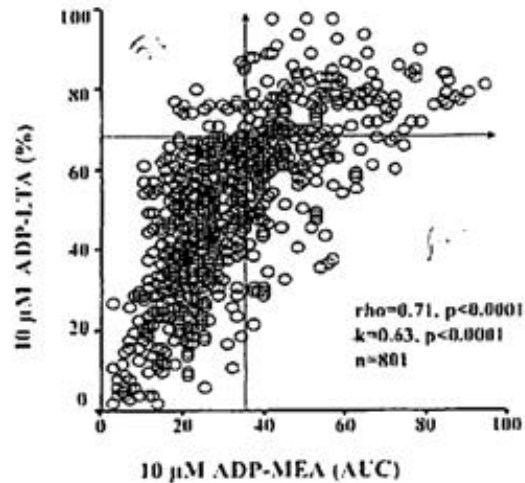
- **Light transmission aggregometry (LTA) is gold standard method.**
considerable time, dedicated laboratories and technicians
- **VerifyNow assay is a fast, standardized point of care test .**
- **Multiple electrode platelet aggregometry (MEA) is based on principle of impedance aggregometry.**

Study	Patients No	Methods	definition	Clinical relevance
Parodi G, et al. JAMA 2011;306:1215-1223	n= 1789, PCI	10µM ADP, LTA	>70%	2 years , MACE
Patti G, et al. JACC 2008;52:1128-1133	n= 160, ASC	VerifyNow	>240 PRU	30d MACE
Sibbing D, et al. Thromb Haemost 2010;103(1): 151-9	n= 1605,	MEA	> 41.6 AUC	6 month stent thrombosis

Comparison of methods for monitoring residual platelet reactivity after clopidogrel by point-of-care tests on whole blood in high-risk patients.

Paniccia R, Antonucci E, Maggini N, Miranda M, Gori AM, Marcucci R, Giusti B, Balzi D, Prisco D, Abbate R.

Department of Medical and Surgical Critical Care, Thrombosis Center, University of Florence, Florence, Italy. rita.paniccia@unifi.it

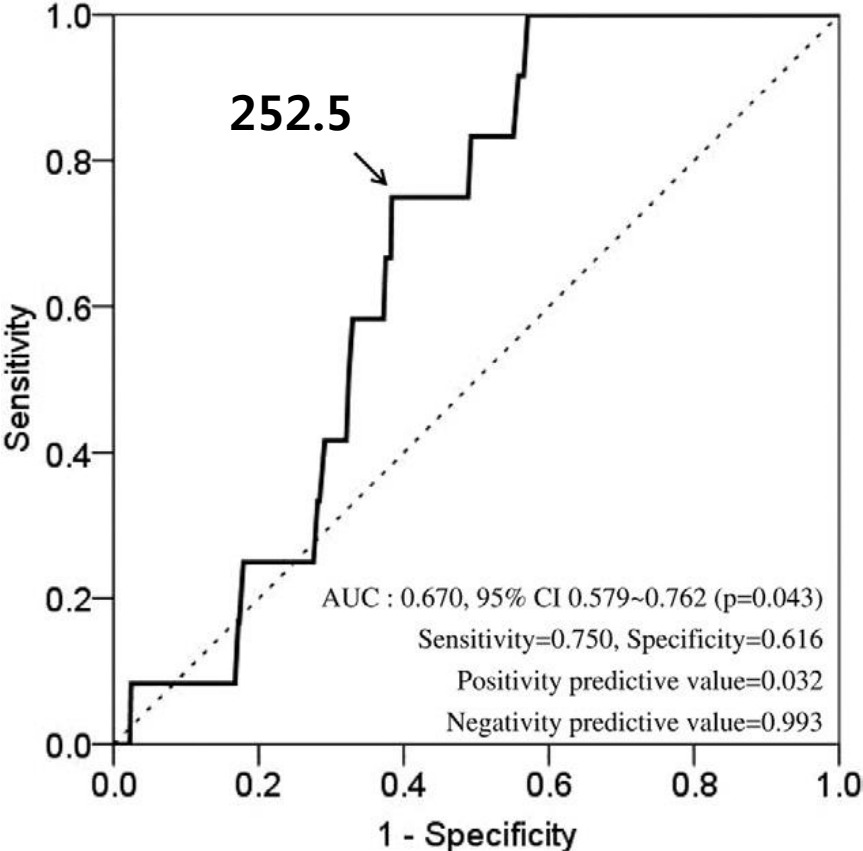


Definition of HPR:

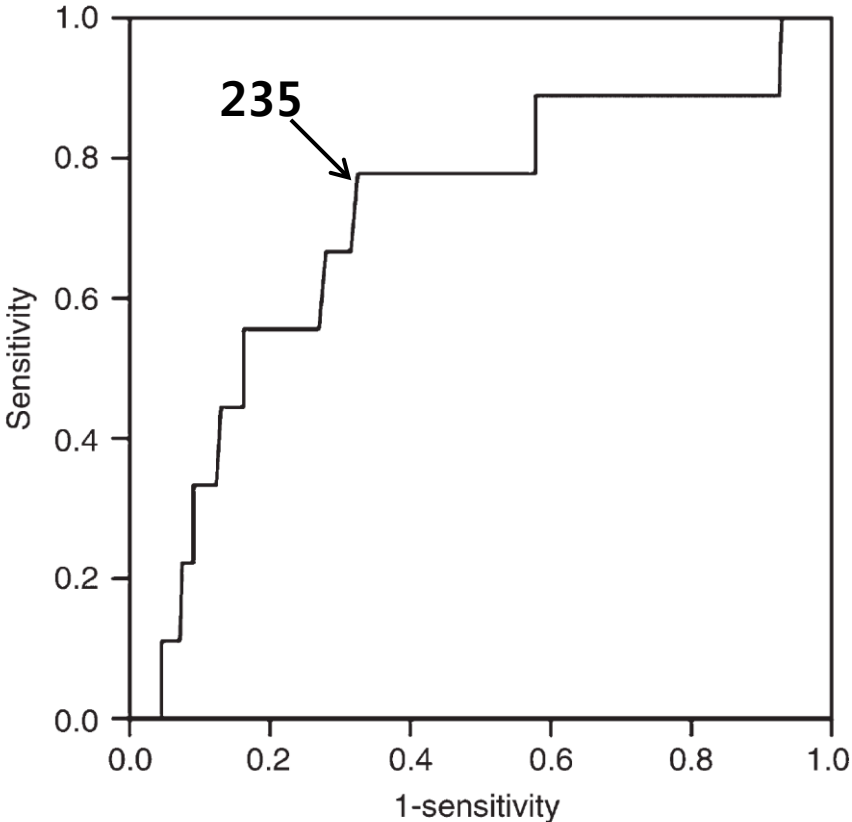
MEA \geq 37 AUC, VerifyNow \geq 240 PRU, LTA \geq 70%

Different cutoff for Risk Prediction

Korean



Caucasian



Suh JW et al. J Am Coll Cardiol. 2011;57:280-9

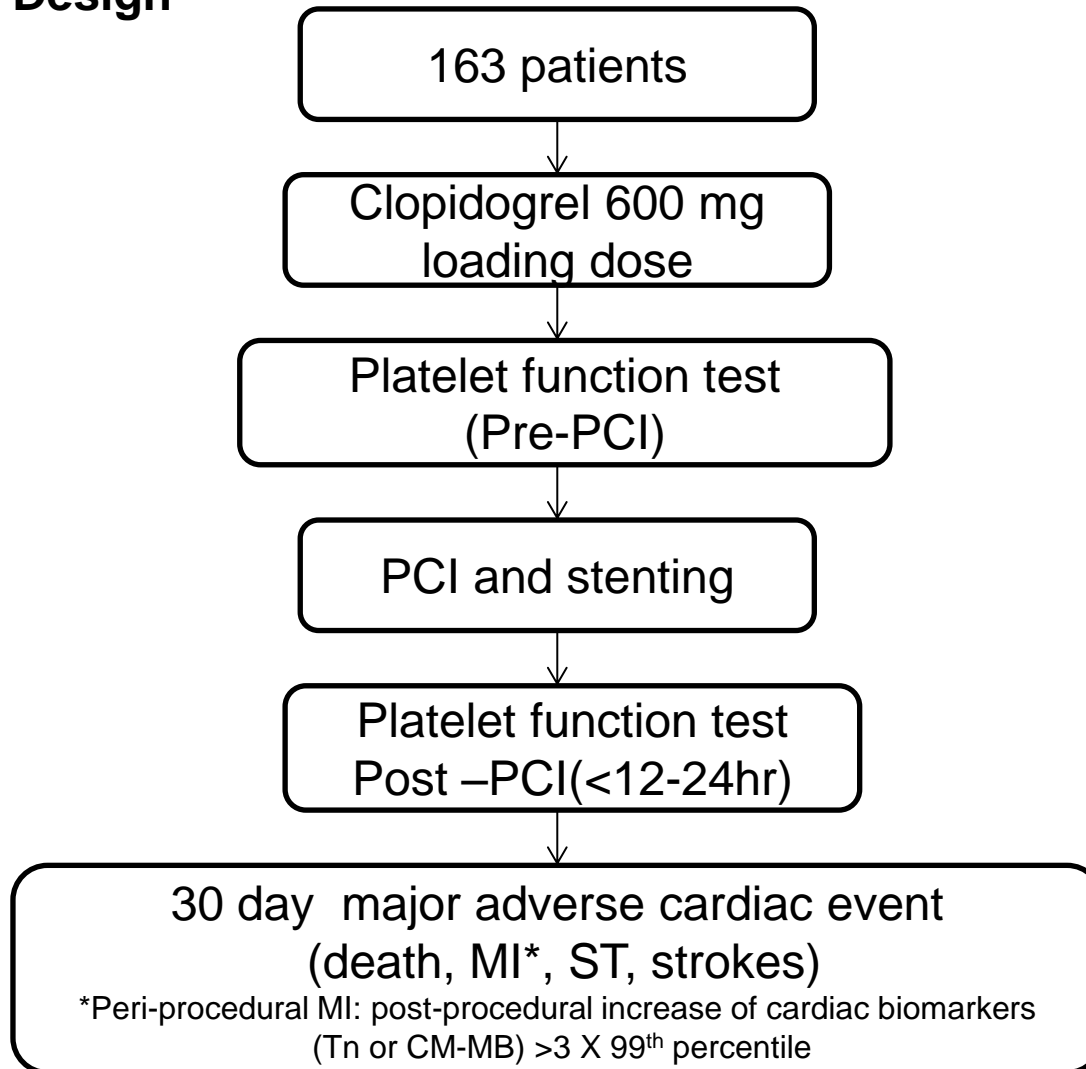
Price et al. Eur Heart J. 2008;29:992-1000

objectives

- **Asians higher ex vivo platelet reactivity compared with Caucasians. Therefore results from in Caucasians cannot be directly extrapolated to Asians.**
- **The aim of this study was to assess the correlation and agreement in different device the prediction cutoffs of early clinical outcome suggested by MEA, LTA and VerifyNow assay in Korean patients undergoing PCI.**

Methods

Study Design



Methods

Patients

- Ages >18 years
- The indication for the procedure may be stable angina or ischemia, unstable angina without ST changes, or non-ST-elevation ACS (unstable angina with ST depression, or a non-ST-elevation MI).
- The ability to comply with study procedures and protocol.

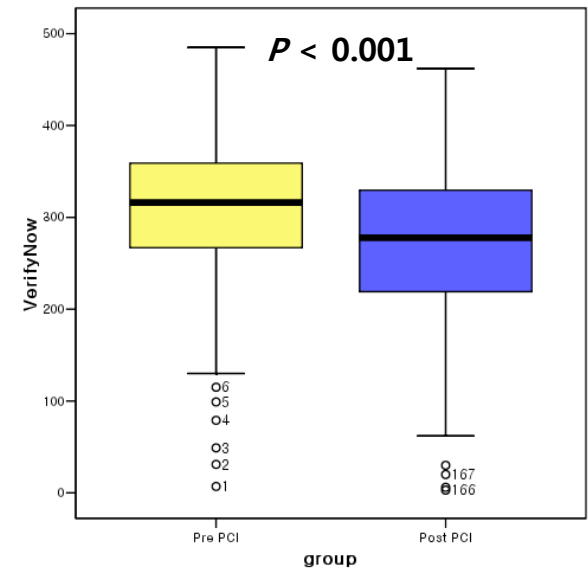
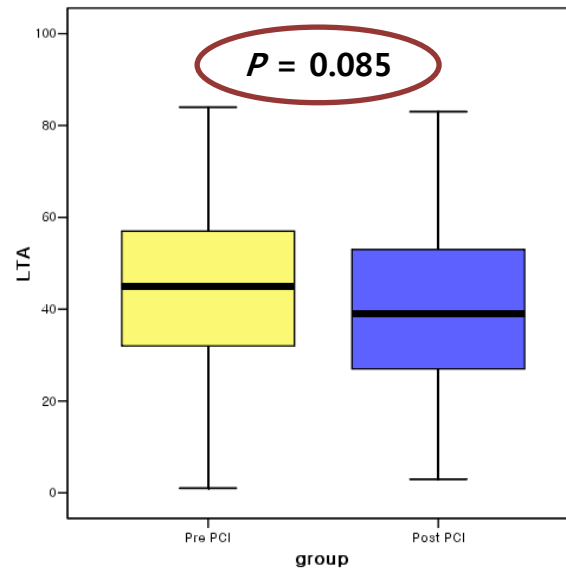
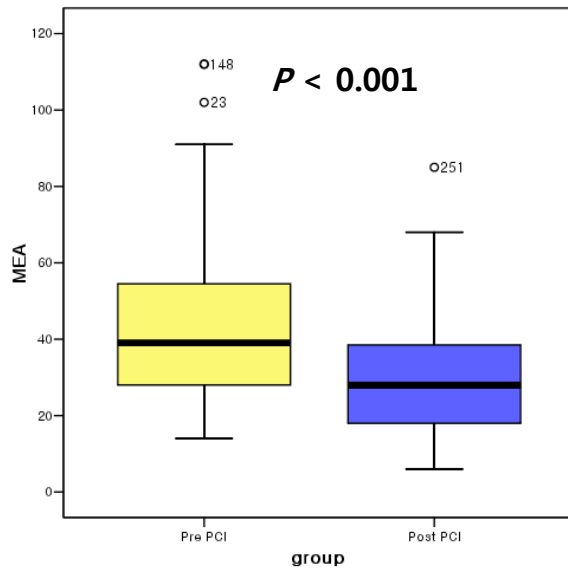
Exclusion Criteria:

- Bleeding diathesis, gastrointestinal bleeding, hemorrhagic stroke, MI <48 h, non-hemorrhagic CVA < 3 mo, major surgery < 6 wk, illicit drug or alcohol abuse, coagulopathy, platelets <100,000/mm³, hematocrit <25%, creatinine >2 mg/dL

Baseline clinical characteristics of the study populations

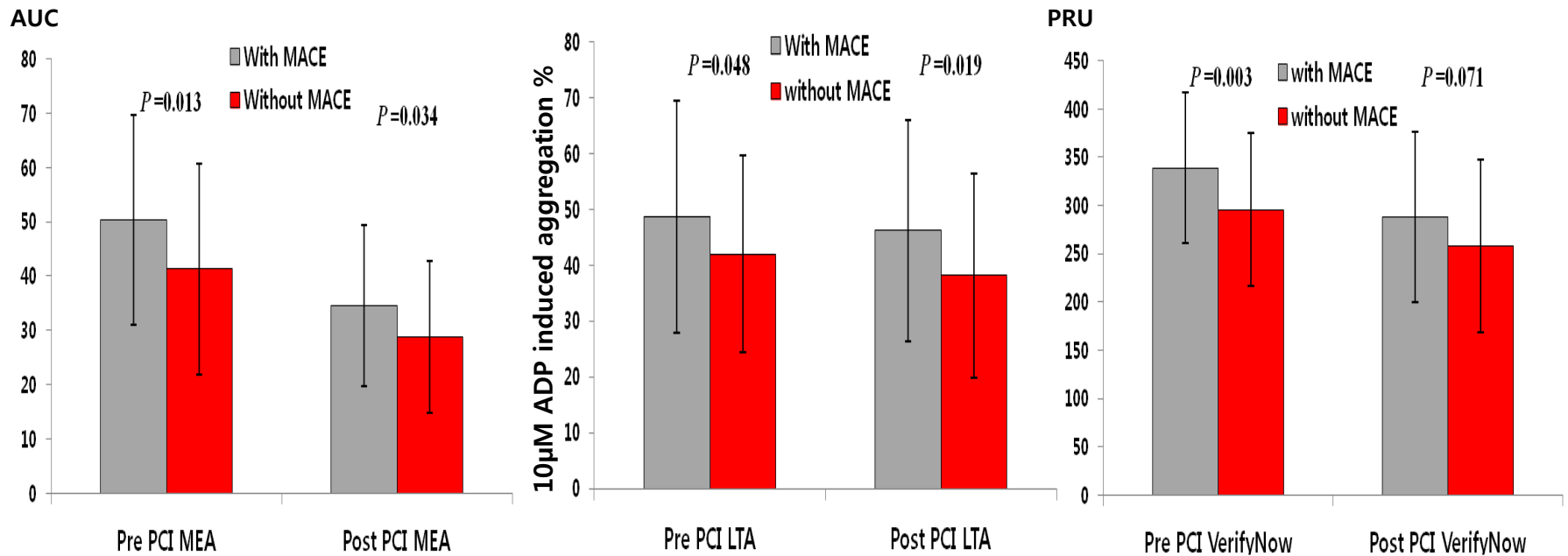
Variables	No. of Patients (%)
Age, years	64.6±10.3
Female, n (%)	45 (27.6)
BMI, kg/m²	24.5±3.2
Diagnosis, n (%)	
Stable angina	17 (10.4)
Unstable angina	97 (59.5)
NSTEMI	45 (27.6)
STEMI	4 (2.5)
Risk factor, n (%)	
Diabetes Mellitus	60 (36.8)
Hypertension	122 (74.8)
Hyperlipidemia	83 (50.9)
Active Smoker	51 (31.3)
Pre-PCI, n (%)	54 (33.1)
Pre-MI, n (%)	35 (21.5)
Pre-stroke, n (%)	19 (11.7)
Hemoglobin, g/dL	13.2±1.8
Platelet count, 10³/μL	207.9±64.7
Peri-procedural MI	39 (23.9)
Discharge medication	No. of Patients (%)
Calcium blocker, n (%)	32 (19.6)
Statins CYP3A4, n (%)	59 (36.2)
Statins nonCYP3A4, n (%)	20 (12.3)
Proton pump inhibitor, n (%)	3 (1.8)
Cilostazol, n (%)	15 (9.2)

Box plot analyses of MEA, LTA and VerifyNow

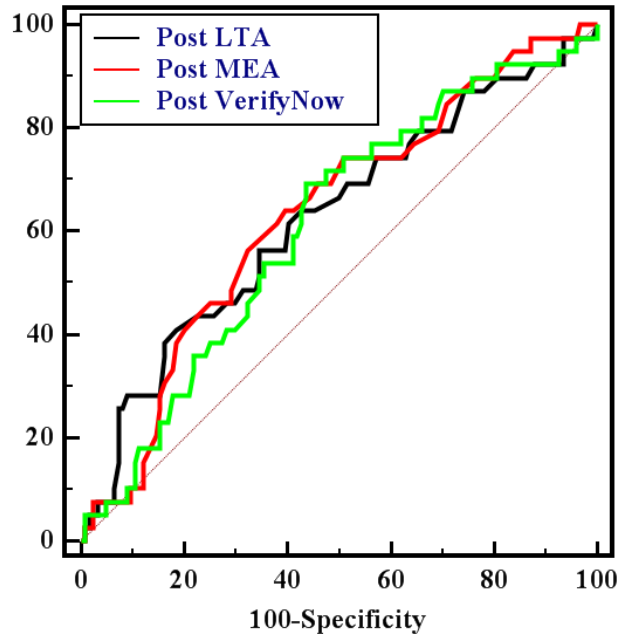


	Group	n	Mean \pm SD	P-value
MEA	Pre PCI	163	43 \pm 20	< 0.001
	Post PCI	163	30 \pm 15	
LTA	Pre PCI	163	44 \pm 19	0.085
	Post PCI	163	40 \pm 19	
VerifyNow	Pre PCI	163	306 \pm 81	<0.001
	Post PCI	163	265 \pm 90	

Comparison of Platelet function data obtained with or without MACE

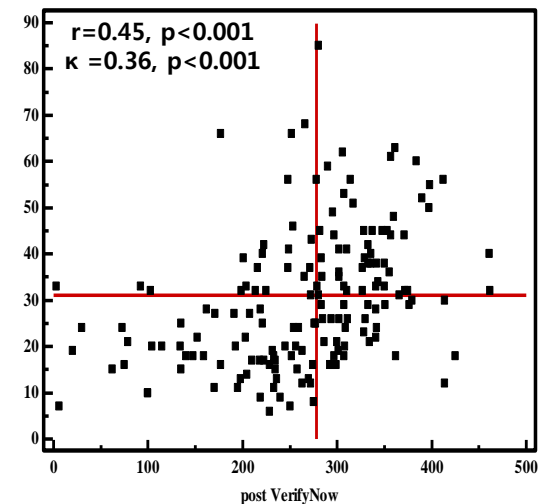
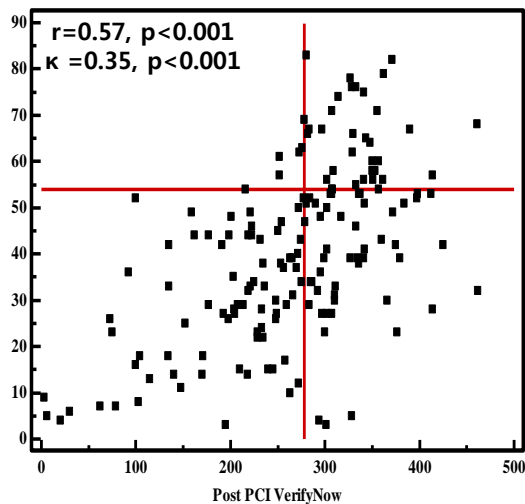
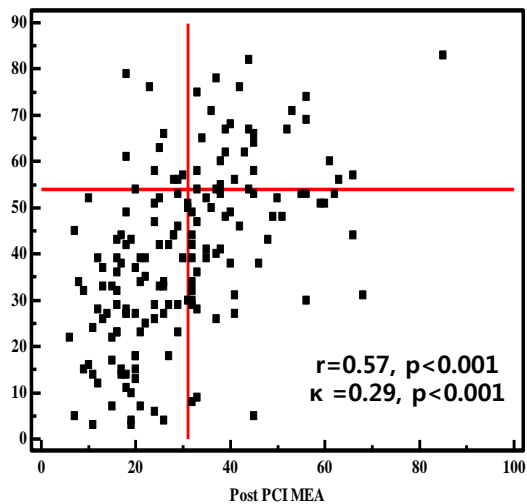
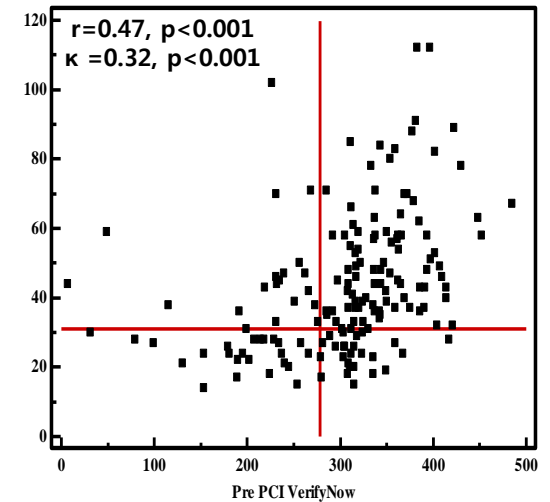
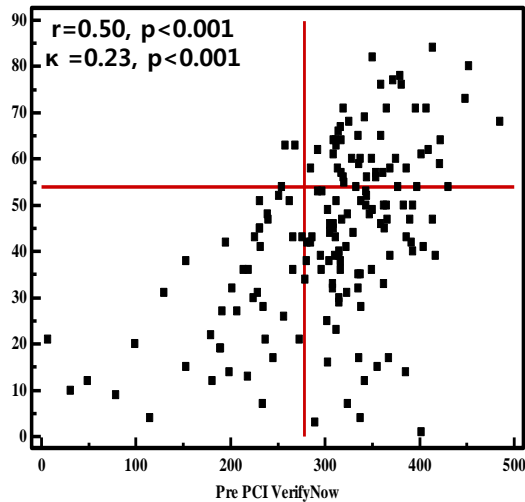
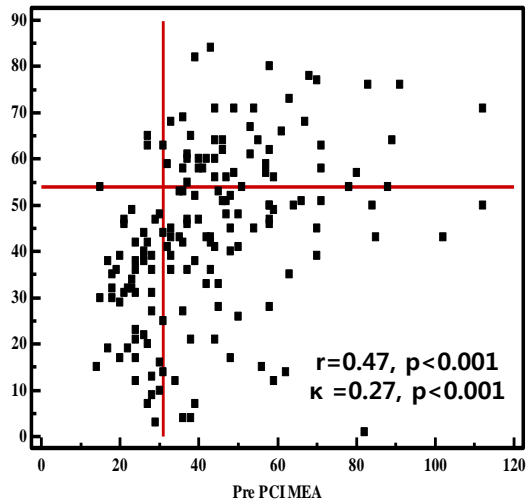


ROC curve analysis for MACE 30 days (LTA, MEA and VerifyNow)



	MEA (95% CI)	LTA (95% CI)	VerifyNow (95% CI)
ACU	0.63 (0.56-0.71)	0.63 (0.55-0.7)	0.61 (0.53-0.69)
Sensitivity (%)	64.1	41	69.2
Specificity (%)	60.5	81.5	56.5
Positive likelihood ratio	1.6 (1.2-2.1)	2.2 (1.5-3.3)	1.6 (1.2-2.1)
Negative likelihood ratio	0.6 (0.4-1.0)	0.7 (0.5-1.1)	0.6 (0.3-0.9)
Cutoff value	>31	≥54	≥278
p-value	0.008	0.018	0.028

Correlation and agreement of results obtained by MEA, LTA and VerifyNow



High On-Treatment Platelet Reactivity to ADP and Clopidogrel No responsiveness to Post-PCI Adverse Clinical Event Occurrence

Study	Patients, No.	Methods	Definition	Clinical Relevance
Gurbel et al. Circulation 2005;111:1153–9.	Elective PCI (120)	5- μ M ADP-LTA	Mean periprocedural platelet aggregation 50%	Periprocedural myonecrosis
Gurbel et al. Platelets 2008;19:595– 604.	Elective PCI (297)	5- and 20- μ M ADP-LTA	HPR post-procedural (ROC) 46% 5- μ M ADP 59% 20- μ M ADP	2-yr ischemic events 5- μ M ADP OR: 3.9 20- μ MADP OR: 3.8
Marcucci R et al. Thromb Haemost 2010;104:279-286.	Elective PCI (1108)	10 μ M ADP-LTA	HPR (ROC) LTA\geq55%	1-yr cardiovascular death, non-fatal MI
Patti et al. J Am Coll Cardiol 2008;30:1128-1133.	PCI (160)	VerifyNow P2Y12 assay	HPR 240 PRU (Pre-PCI)	1-month major cardiovascular event occurrence
Gremmel T et al. Thromb haemost 2009;101:333-339	Elective PCI (80)	10 μ M ADP-LTA, VerifyNow	Upper quintile LTA \geq 62%, PRU \geq 273	
Ko YG et al. Am Heart J 2011;161:383-390	Elective PCI (222)	VerifyNow	PRU\geq274	1-month major cardiovascular event occurrence
Sibbing et al. J Am Coll Cardiol 2009;53:849-856.	PCI/DES (1,608)	6.4-mol/l ADP Multiplate analyzer	Upper quintile (416 AU/min) (ROC)	1-month definite ST (OR: 9.4)

Correlation between platelet function measurement

Study	No.	Methods	Correlation
Paniccia R et al. Thromb Haemost 2010;104:287-292.	801	LTA and VerifyNow, MEA and LTA, MEA and VerifyNow,	$r=0.7$, $r=0.71$, $r=0.62$; all $p < 0.001$
Gremmel T et al. Thromb haemost 2009;101:333-339	80	VerifyNow and LTA, MEA and LTA	$r=0.62$, $p < 0.001$; $r=0.35$, $p=0.001$
Kim IS et al. J Thromb Thrombolysis 2010;30:486-495	1058	5 μ M, 20 μ M ADP LTA and VerifyNow	$r=0.65$, $p < 0.001$; $r=0.68$, $p < 0.001$
Park YW et al. Platelets	246	5 μ M, 20 μ M ADP LTA and MEA	$r=0.68$, $P < 0.001$; $r=0.66$, $P < 0.001$
Ko YG et al. Am Heart J 2011;161:383-390	222	MEA and VerifyNow	$r=0.39$, $p < 0.001$
Sibbing D et al. Thromb Haemost 2008;99:121-126.	149	5 μ M, 20 μ M ADP LTA and MEA	$r=0.71$, $p < 0.001$; $r=0.71$, $p < 0.001$
Our study	163	Pre , post PCI LTA and VerifyNow, MEA and LTA, MEA and VerifyNow	$r=0.50$, $r=0.47$, $r=0.47$; $r=0.57$, $r=0.57$, $r=0.45$; All $p < 0.001$

Limitations

- I. This is an observational study, the sample size was not predetermined.**
- II. Our study use 10 μ M ADP induced LTA assays, we could not assess the correlation use 5 and 20 μ M ADP induced LTA assays.**
- III. Our study only comprised Korean, so mean value of PR and HPR somewhat high in Caucasians.**
- IV. Investigation the platelet function not use similar anticoagulant (MEA assay use hirudin; LTA and VerifyNow assay use citrate anticoagulant).**

Conclusion

- I. This study indicates that cutoff value might predict 30-day events.**
- II. Use three differed device for monitoring residual platelet reactivity after clopidogrel administration might help identify patients in whom individualized antiplatelet strategies might be indicated with coronary intervention.**
- III. Compared three differed device used in Korean patients observed low correlation and agreement than in Caucasians study.**

