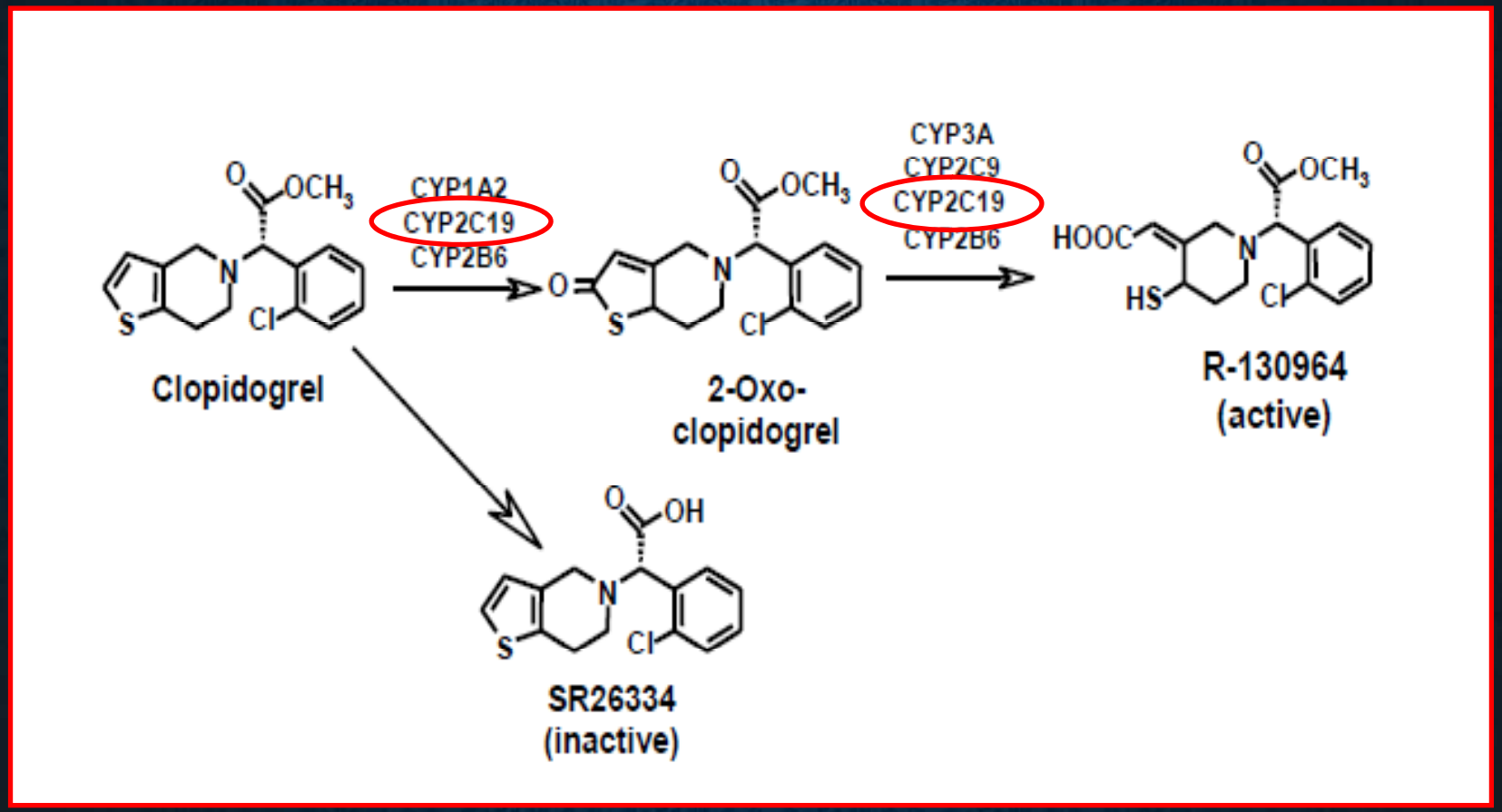
Clinical Impact of the CYP2C19 Genotype on Clopidogrel Response in Coronary Artery Disease

Ki-Bae Seung, M.D., Ph.D., FACC

The Catholic Medical University of Korea
Seoul St. Mary's Hospital Cardiovascular Center

Background

Clopidogrel metabolism



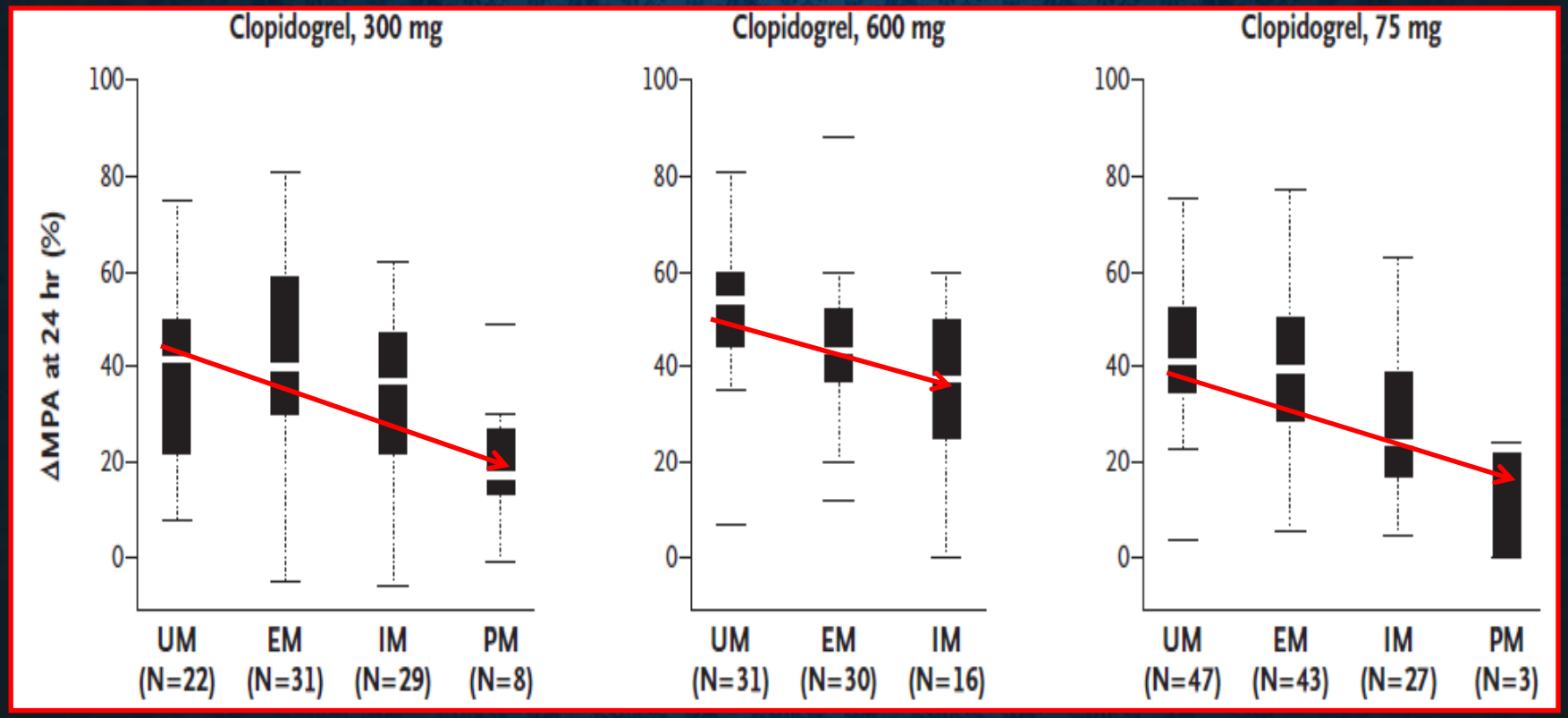
Mega JL, et al. *Circulation* 2009;119:2553

Seoul St.Mary's Hospital
Cardiovascular Center

Genotype and phenotype of CYP2C19

- UM (ultra-rapid metabolizer) : *1/*17
- EM (extensive metabolizer) : *1/*1
- IM (intermediate metabolizer): *1/*2, *1/*3
- PM (poor metabolizer) : *2/*2, *2/*3, *3/*3

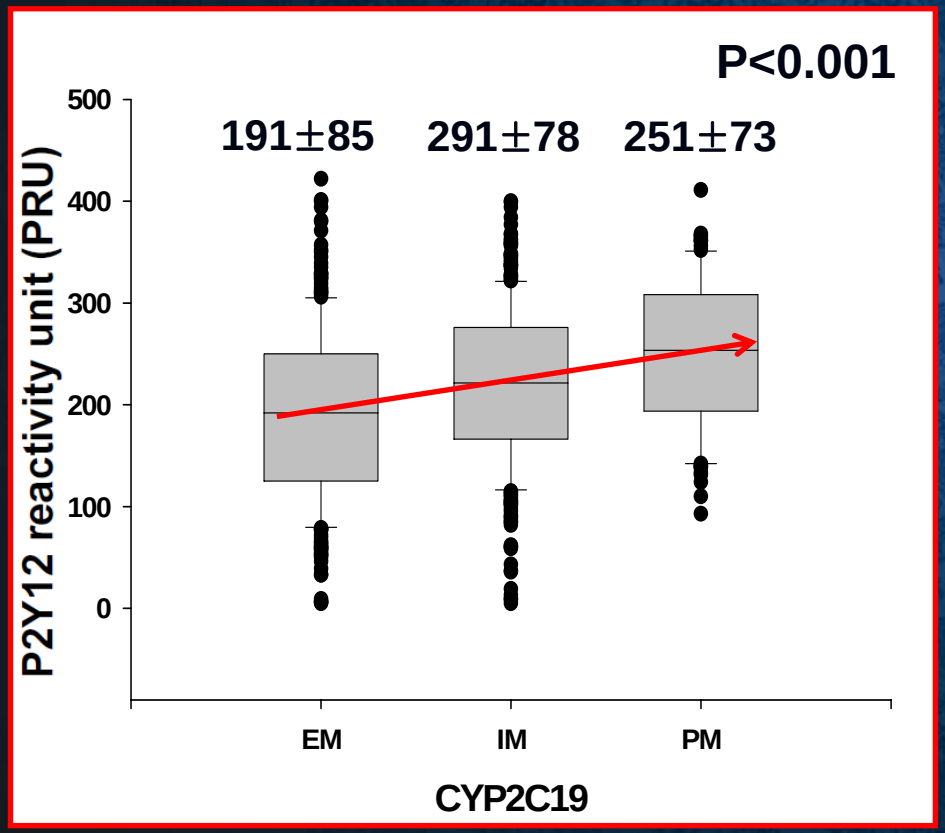
Platelet inhibition on treatment of clopidogrel according to CYP2C19 phenotype

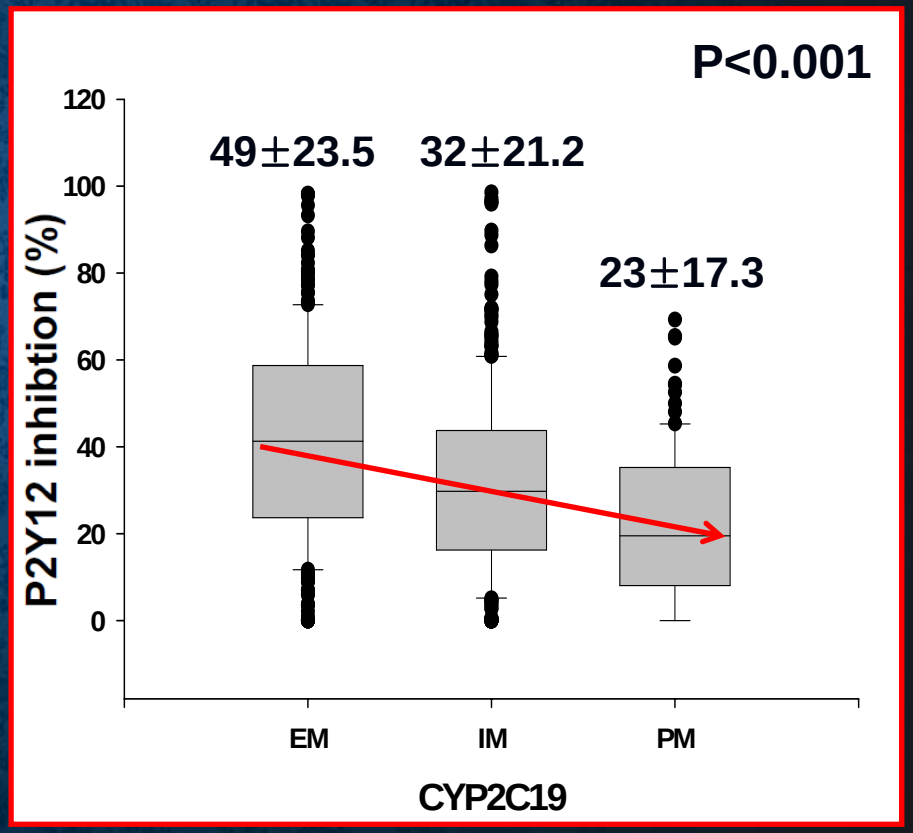


Mega JL, et al. *N Engl J Med* 2009;360:354

Seoul St.Mary's Hospital
Cardiovascular Center

Platelet reactivity & inhibition on treatment of clopidogrel according to CYP2C19 phenotype in coronary artery disease

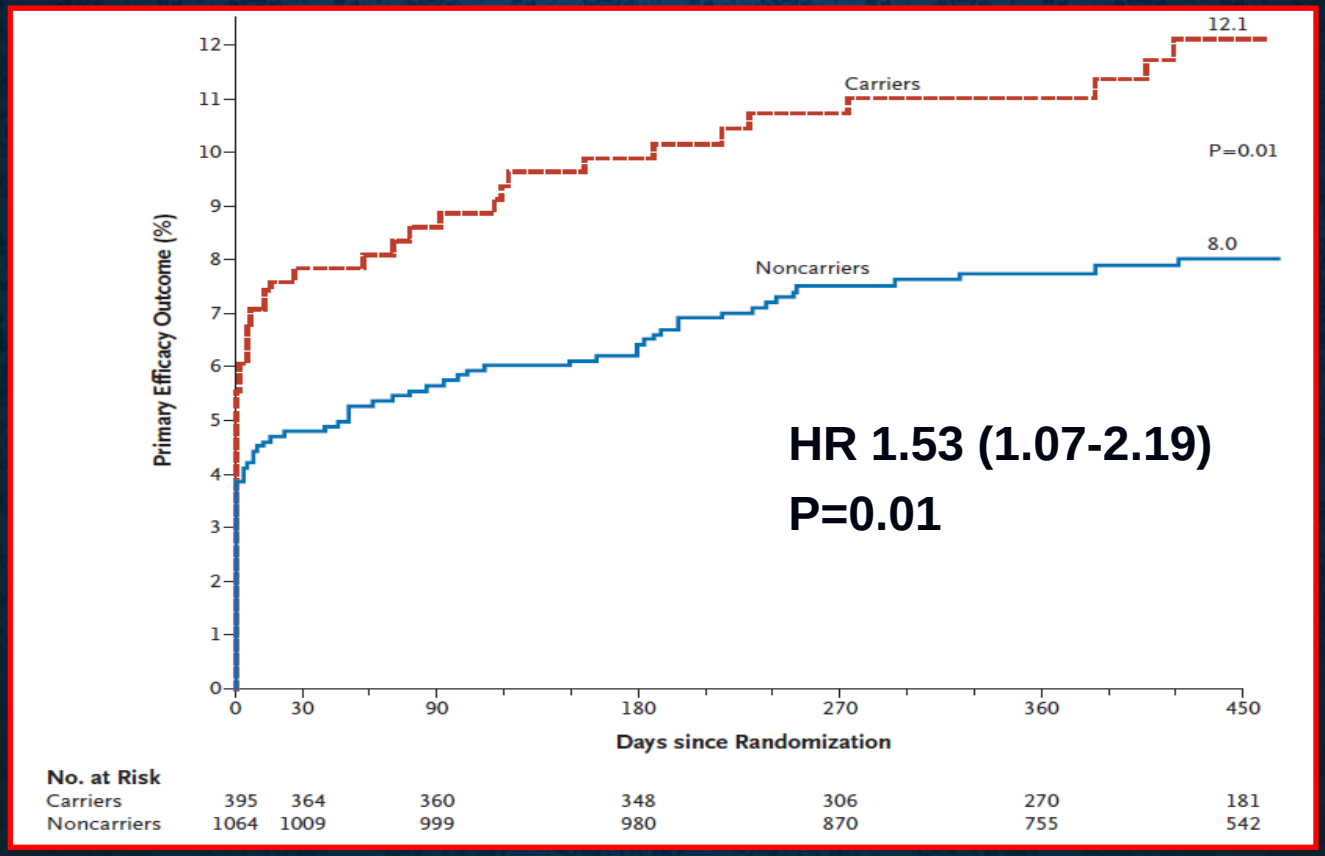




EM (n=271), IM (n=316), PM (n=102) *COACT-gene registry data*

Seoul St.Mary's Hospital Cardiovascular Center

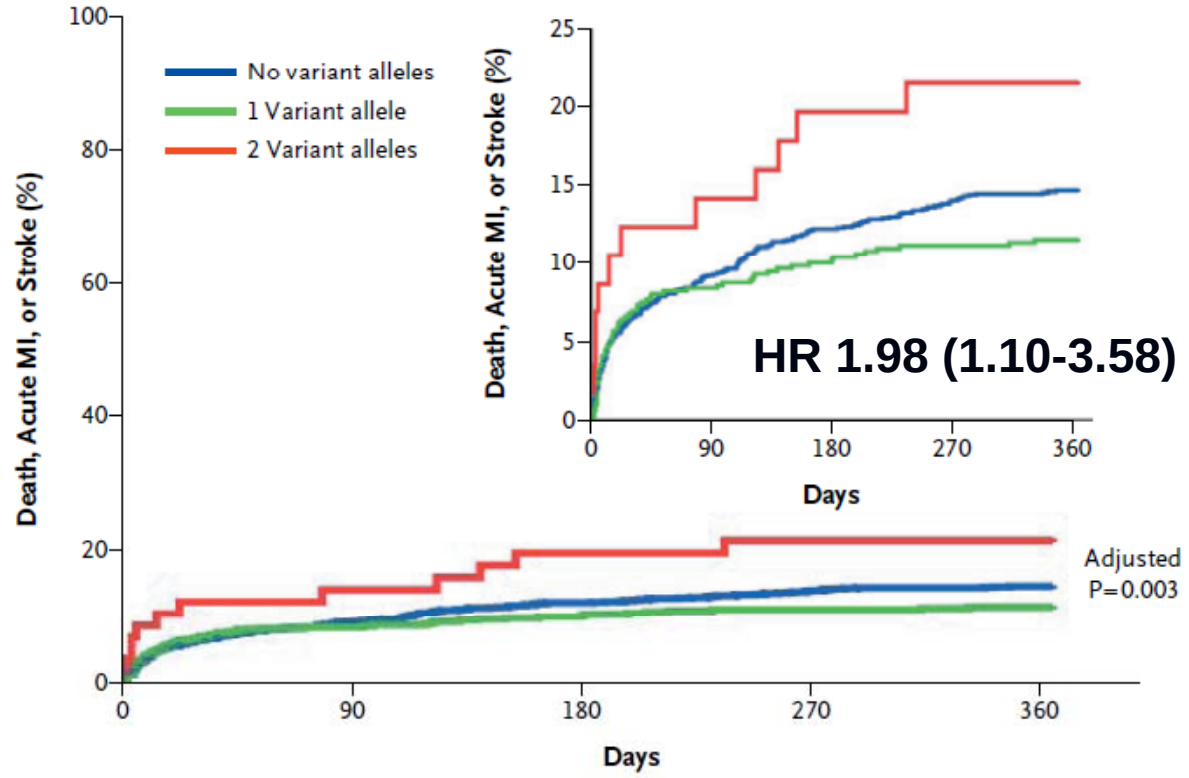
Clinical outcomes in patients with ACS according to reduced-function allele of CYP2C19 (high risk and PCI)



Mega JL, et al. *N Engl J Med* 2009;360:354

Seoul St.Mary's Hospital Cardiovascular Center

Clinical outcomes in patients with AMI according to CYP2C19 phenotype

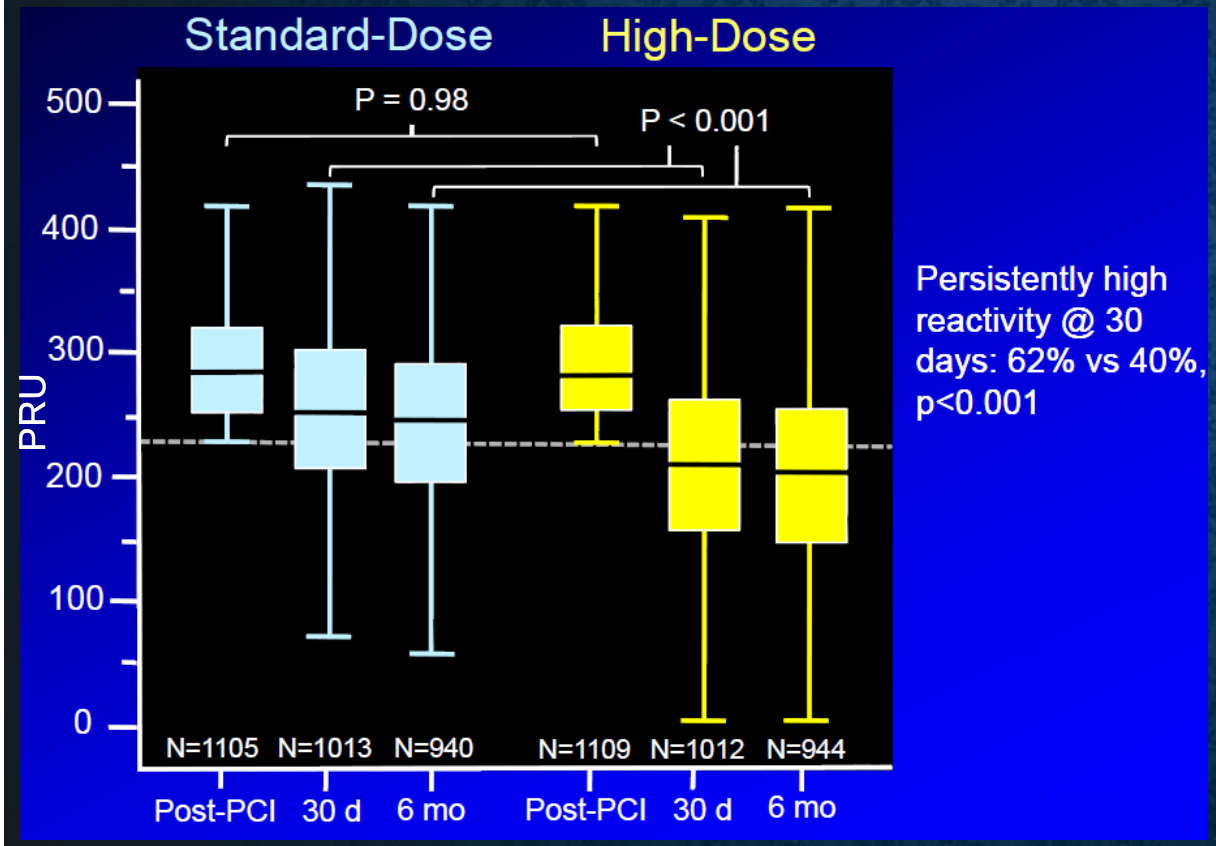


No. at Risk					
No variant alleles	1572	1334	1288	1211	1208
1 Variant allele	576	502	491	468	446
2 Variant alleles	58	47	44	42	40

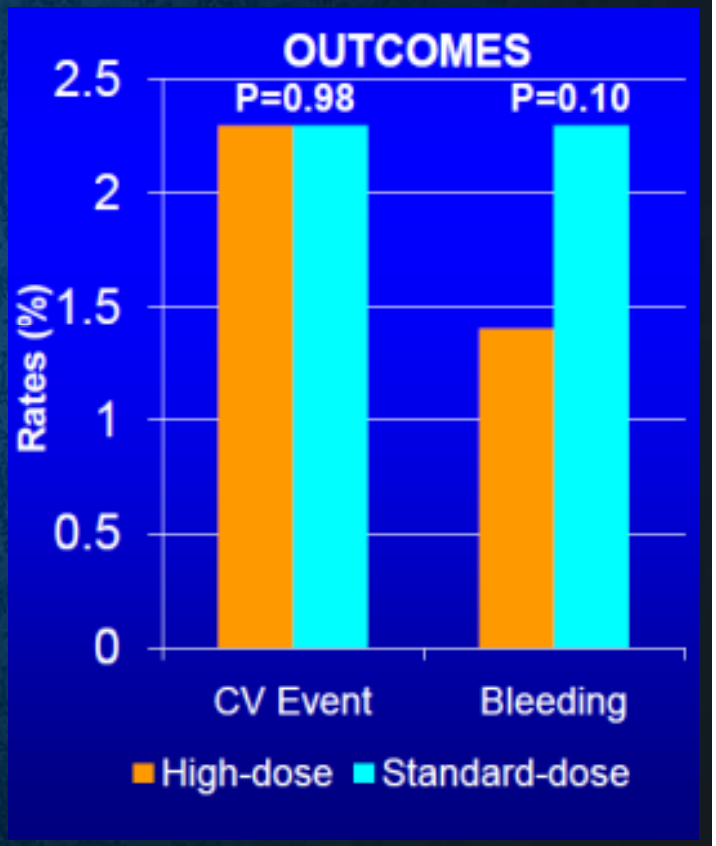
Simon T ,et al. *N Engl J Med* 2009;360:363

Seoul St.Mary's Hospital
Cardiovascular Center

Primary results of the Gauging Responsiveness with A VeryfyNow assay-Impact on Thromobosis And Safety trial



Persistently high reactivity @ 30 days: 62% vs 40%, p<0.001



Price MJ, Berger PB et al. *AHA 2010 Scientific Sessions*

Seoul St.Mary's Hospital Cardiovascular Center

Racial difference in distribution of CYP2C19 genotype and phenotype

- In TRITON study population (manly Caucasians)

Gene	Dichotomous classification	Predicted Phenotype	Observed Genotypes[a]	Number of Subjects (%)	
				PK/PD	TRITON-TIMI 38
CYP2C19	Non-carrier	UM	*17/*17, *1A/*17	44 (30)	1064 (73)[b]
		EM	*1A/*1A	53 (36)	
	Carrier	IM	*1A/*2A, *1A/*3, *1A/*4, *1A/*8	43 (29)	357 (24)
		PM	*2A/*2A, *2A/*3, *2A/*4 *2A/*5A, *2A/*8	8 (5)	38 (3)
	n/a	Unknown[c]	*1A/*9, *1A/*10, *2A/*17, *6/*17	NI[c]	NI[c]

Mega JL, et al. *N Engl J Med* 2009;360:354

- In Korean population (COACT-gene registry data)

Gene	Dichotomous classification	Predicted Phenotype	Observed Genotypes	Number of Subjects (%)
CYP2C19	Non-carrier	EM	*1/*1	872 (40)
	Carrier	IM	*1/*2, *1/*3	1003 (46)
		PM	*2/*2, *2/*3, *3/*3	313 (14)

Seoul St.Mary's Hospital Cardiovascular Center

Hypothesis

- The clinical impact of CYP2C19 genotype in patients with coronary artery disease (CAD) who undergo DES implantation might be different according to the clinical indications of PCI such as AMI or angina

- Korean patients with higher frequency of CYP2C19 poor metabolizer genotype (14%) might provide a more information group to elucidate this uncertainty.

Purpose

- To evaluate the association between CYP2C19 genotypes and clinical outcomes in two different subpopulations of our cohort, namely patients with angina and AMI

Study design : COACT-gene registry

2214 patients performed PCI and sampled for DNA analysis enrolled from Jan, 2005 to December, 2009

In eight affiliated hospitals

Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital
Uijeongbu St. Mary's Hospital, Bucheon St. Mary's Hospital,
Daejeon St. Mary's Hospital, Incheon St. Mary's Hospital,
St. Vincent's Hospital, St. Paul's Hospital

Excluded
- **contaminated sample**
- **insufficient sample**
- **unknown phenotype**
- **not take clopidogrel**
- **follow up loss**

2188 patients included in analysis

872 extensive metabolizer

1003 intermediate metabolizer

313 poor metabolizer

Seoul St.Mary's Hospital Cardiovascular Center

Inclusion Criteria

1) Patients are ≥21 years old
2) Dual antiplatelet therapy with aspirin and clopidogrel continued for more than 12 mo nths
3) Informed consent for genotyping

Study objective

- Primary objective
  - Composite of major adverse cardiac and cerebrobascular events (MACCE), defined as
    : death from any cause, nonfatal myocardial infarction, or stroke at 1-year follow-up between angina patients and AMI patients
- Landmark analysis
  - to evaluate the effect of CYP2C19 genotype on the clinical outcome of clopidogrel therapy at different time periods

    : with the expectation to clarify the clinical impact of CYP2C19 genotypes within the first months after an index PCI or thereafter

Genotyping

- Performed with the validated genotyping technology platform established at The PharmacoGenomics Research Center (PGRC), Inje University College of Medicine, Busan, Korea

- All genotypes were determined by the single-base extension method according to the manufacturer's protocol using an ABI PRISM® genetic analyzer and its mounted GeneMapper® software.

  Hardy-Weinberg disequilibrium was not significant for all SNPs tested (P>0.05)

Genotyping

- Tested for the presence of single nucleotide poly-morphisms identifying

  CYP2B6*4 (rs2279343), CYP2B6*6 (rs2279343, rs3745274), and CYP2B6*9 alleles(rs3745274), CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), CYP2C19*17(rs12248560), CYP3A4*18 (rs28371759), CYP3A5*3 (rs776746), and P2Y12 742T>C(rs2046934), ABCB1 2677G>A/T (rs 2032582) and ABCB1 3435C>T (rs1045642)

- All subjects were classified as

(according to the number of functional allele of CYP2C19 genotype)

Extensive metabolizer(EM) : CYP2C19*1/*1 or CYP2C19*17

Intermediate metabolizer (IM) : CYP2C19*1/*2 or *1/*3

Poor metabolizer (PM) : CYP2C19*2/*2, *2/*3 or *3/*3

Statistical analysis

- Most of the data were collected with the use of electronic charts. All outcomes of interest were confirmed by source document and were centrally adjudicated by a local events committee at the Cardiovascular Center of Seoul St. Mary's Hospital.

- For validation of complete follow-up data, information on censored survival data was obtained through September 30, 2010 from the database of the National Health Insurance Corporation with the use of a unique personal identification number.

Statistical analysis

- SAS software version 9.2
- Continuous variables
  : Wilcoxon rank-sum test after testing for normality
- Categorical variables
  : Chi-square test
  Fisher's exact fest
- Cumulative event rate : Kaplan-Meier method
- Univariate and multivariable, Cox proportional hazards model

Results

Baseline characteristics

Variables	Angina (n=1656)	AMI (n=532)	P value
Age (mean ± SD)	63.9 ± 9.9	62.4 ± 12.4	0.02
BMI (mean ± SD)	24.9 ± 3.1	24.0 ± 3.2	<0.001
Sex (male, %)	1049 (63.4)	400 (75.2)	<0.001
Hypertension (%)	1043 (63.0)	257 (48.3)	<0.001
Diabetes (%)	651 (39.3)	174 (32.7)	0.006
Hypercholesterolemia (%)	317 (19.7)	123 (24.0)	0.04
Family history of CAD (%)	88 (5.3)	34 (6.4)	0.34
Current smoker (%)	252 (15.2)	137 (25.8)	<0.001
Previous MI (%)	121 (7.3)	34 (6.4)	0.47
Previous PCI (%)	177 (10.7)	32 (6.0)	0.001
Previous CABG (%)	16 (1.0)	4 (0.8)	0.80
Previous CVA (%)	111 (6.7)	32 (6.0)	0.55
Chronic renal failure (%)	56 (2.3)	40 (7.9)	<0.001

Baseline Genotype Frequency

Variables	Angina (n=1656)	AMI (n=532)	P value
CYP2B6			0.27
*1/*1	1202 (72.6)	364 (68.4)	
*1/*6, *1/*9	417 (25.2)	156 (29.3)	
*6/*6, *9/*9	37 (2.2)	12 (2.3)	
CYP3A4			0.34
*1/*11	1598 (96.5)	516 (97.0)	
*1/*18	56 (3.4)	14 (2.6)	
*18/*18	2 (0.1)	2 (0.4)	
CYP3A5			0.14
*1/*1	105 (6.3)	39 (7.3)	
*1/*3	568 (34.3)	203 (38.2)	
*3/*3	983 (59.4)	290 (54.5)	

Baseline Genotype Frequency

Variables	Angina (n=1656)	AMI (n=532)	P value
ABCB 12677 G>A/T			0.96
GG	337 (20.4)	108 (20.3)	
GA	261 (15.8)	93 (17.5)	
GT	537 (32.4)	169 (31.8)	
AA	45 (2.7)	15 (2.8)	
AT	227 (13.7)	71 (13.4)	
TT	249 (15.0)	76 (14.3)	
ABCB 13435 C>T			0.56
CC	707 (42.7)	218 (41.0)	
CT	719 (43.4)	245 (46.0)	
TT	230 (13.9)	69 (13.0)	
P2Y12 742 T>C			0.39
TT	1145 (69.1)	351 (66.0)	
TC	454 (27.4)	160 (30.0)	
CC	57 (3.4)	21 (4.0)	

Baseline Genotype Frequency

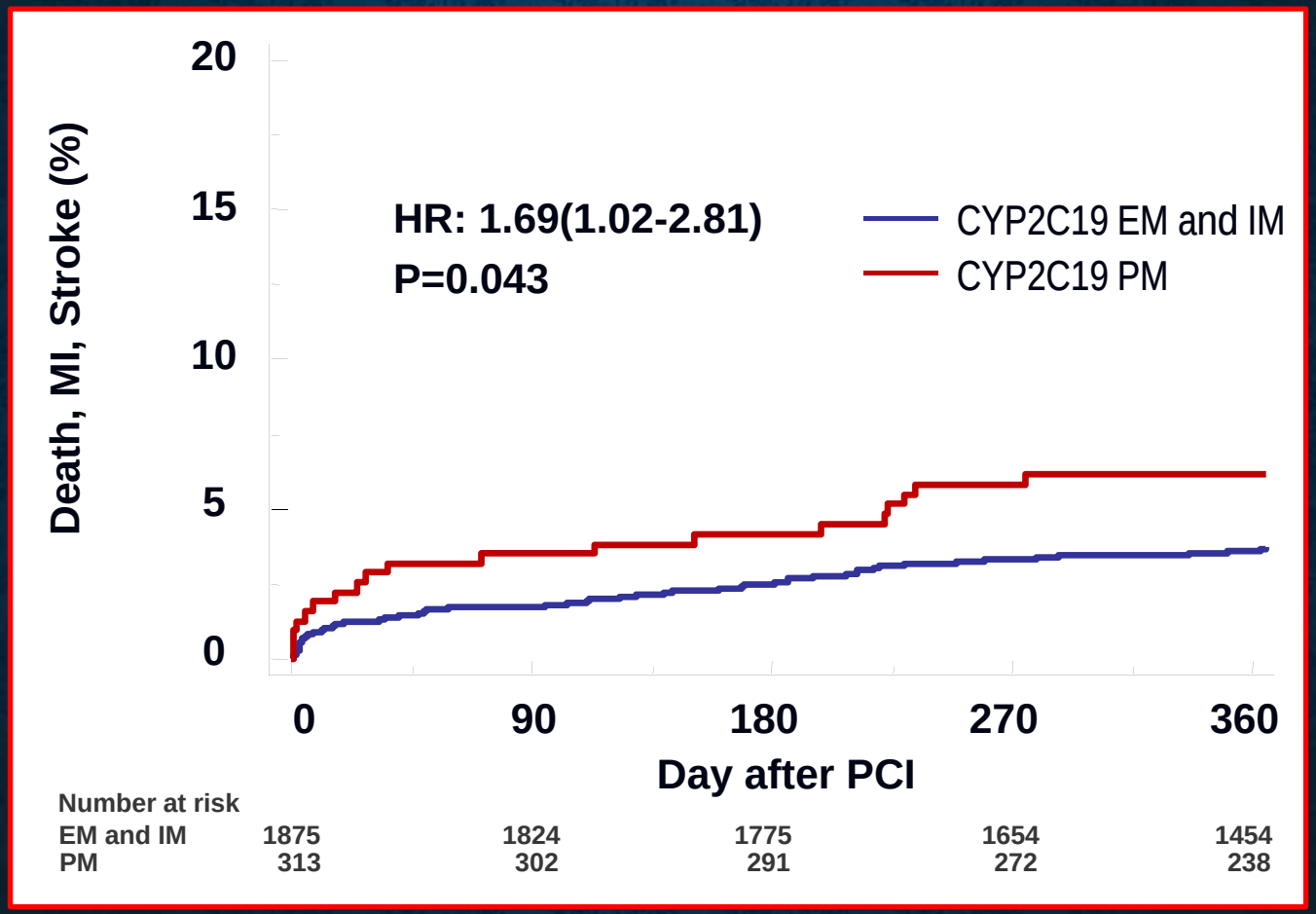
Variables	Angina (n=1656)	AMI (n=532)	P value
CYP2C19			0.93
*1/*1	632 (38.2)	187 (35.2)	
*1/*17	25 (1.5)	8 (1.5)	
*1/*2	570 (34.4)	195 (36.7)	
*1/*3	179 (10.8)	59 (11.1)	
*2/*17	12 (0.7)	2 (0.4)	
*2/*2	135 (8.2)	43 (8.1)	
*2/*3	82 (5.0)	30 (5.6)	
*3/*17	4 (0.2)	2 (0.4)	
*3/*3	17 (1.0)	6 (1.1)	
CYP2C19 phenotype			0.42
EM	673 (40.6)	199 (37.4)	
IM	749 (45.2)	254 (47.7)	
PM	234 (14.1)	79 (14.9)	

Predictors of MACCE in all PCI patients

Predictors	MACCE at 1 month		MACCE at 12 months	
	Adjusted HazardRatio (95% CI)	P value	Adjusted HazardRatio (95% CI)	P value
Age > 65	2.76 (1.16-6.55)	0.022	3.51 (2.08-5.94)	<0.001
MI (diagnosis at PCI)	4.61 (2.14-9.93)	<0.001	2.72 (1.75-4.23)	<0.001
Chronic renal failure	6.32 (2.79-14.32)	<0.001	6.32 (3.80-10.51)	<0.001
PM of CYP2C19	2.47 (1.13-5.39	0.024	1.87 (1.12-3.12)	0.016
PPI co-administration	2.86 (1.06-7.74)	0.039	2.18 (1.12-4.17)	0.023

COACT-gene registry data

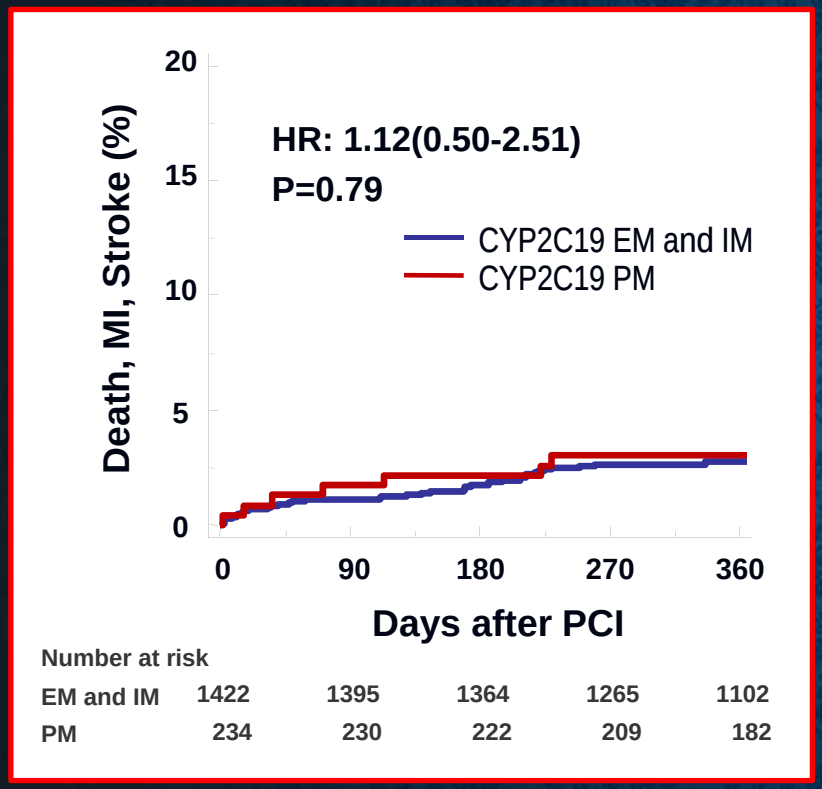
Clinical outcomes in all PCI patients according to CYP2C19 phenotype

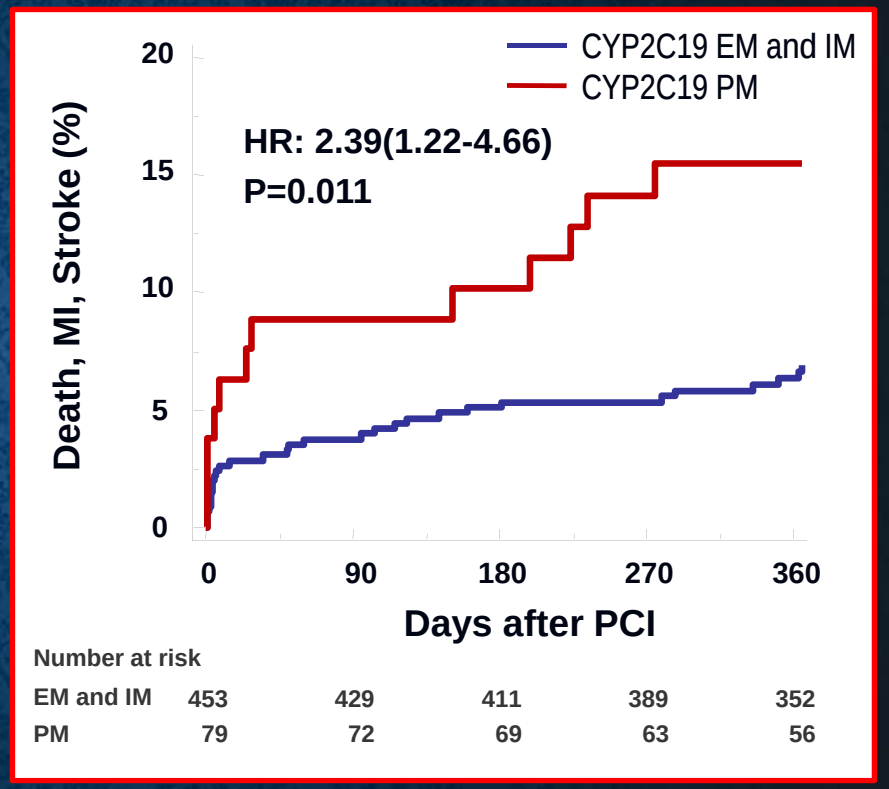


COACT-gene registry data

Seoul St.Mary's Hospital
Cardiovascular Center

Clinical outcomes according to CYP2C19 phenotype and disease subset



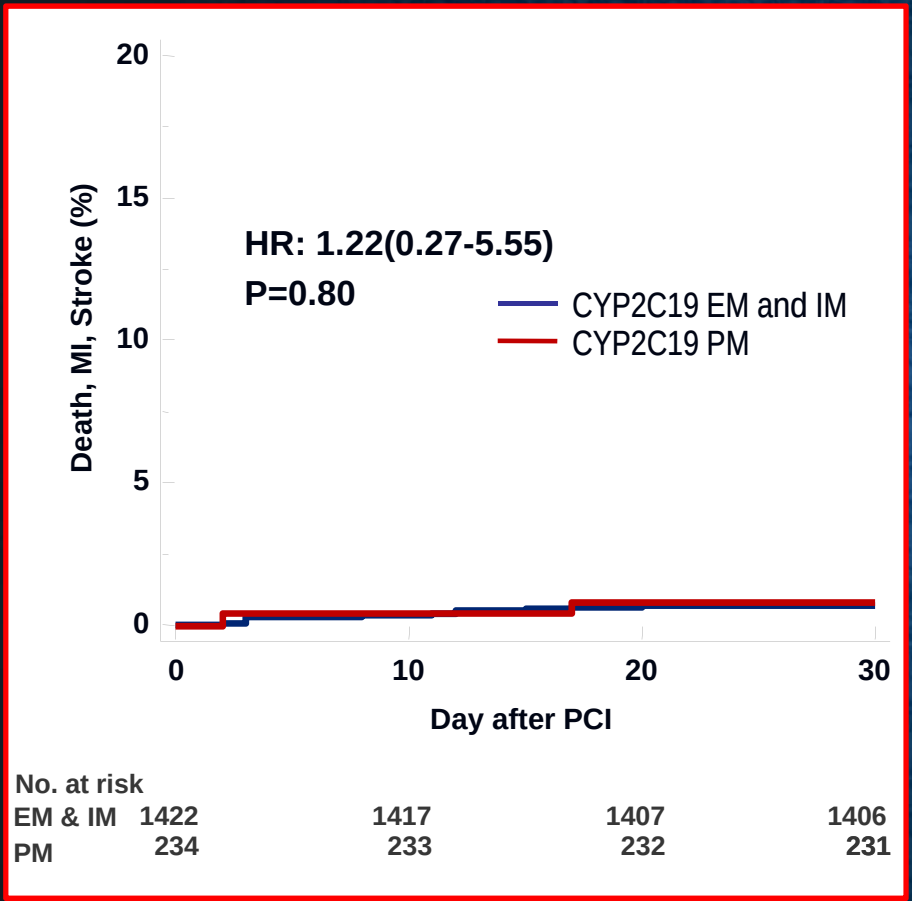


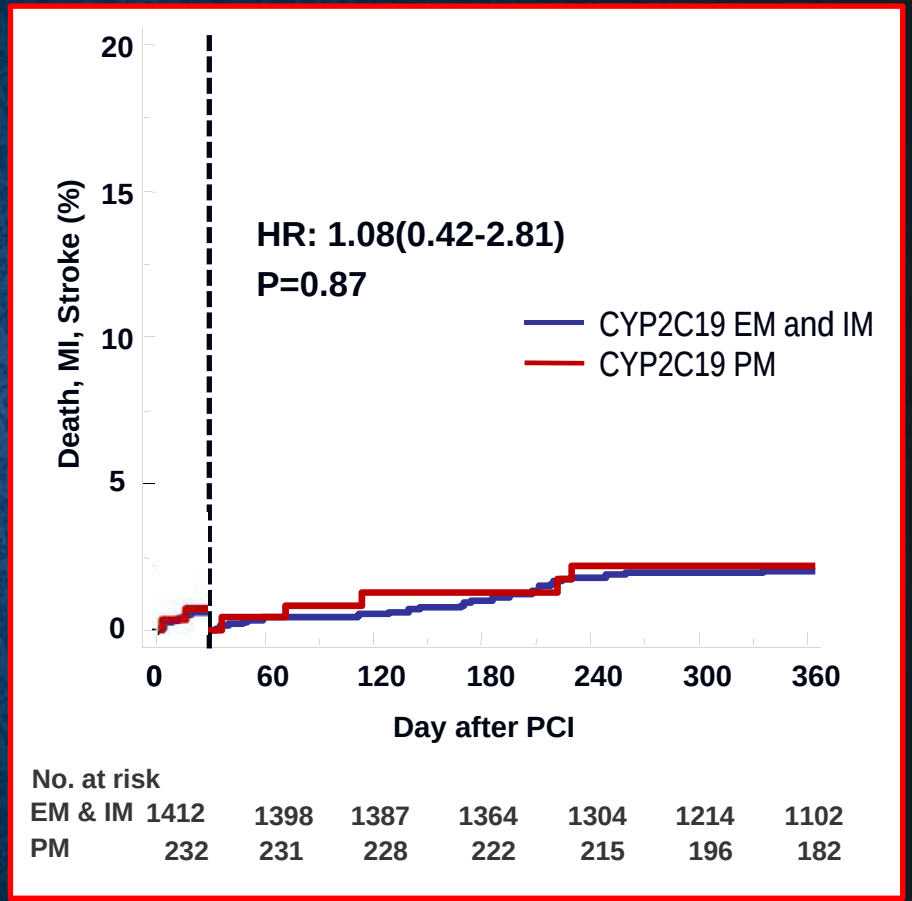
Angina patients Interaction P<0.001 **AMI patients**

COACT-gene registry data

Seoul St.Mary's Hospital Cardiovascular Center

Landmark analysis in COACT-gene registry



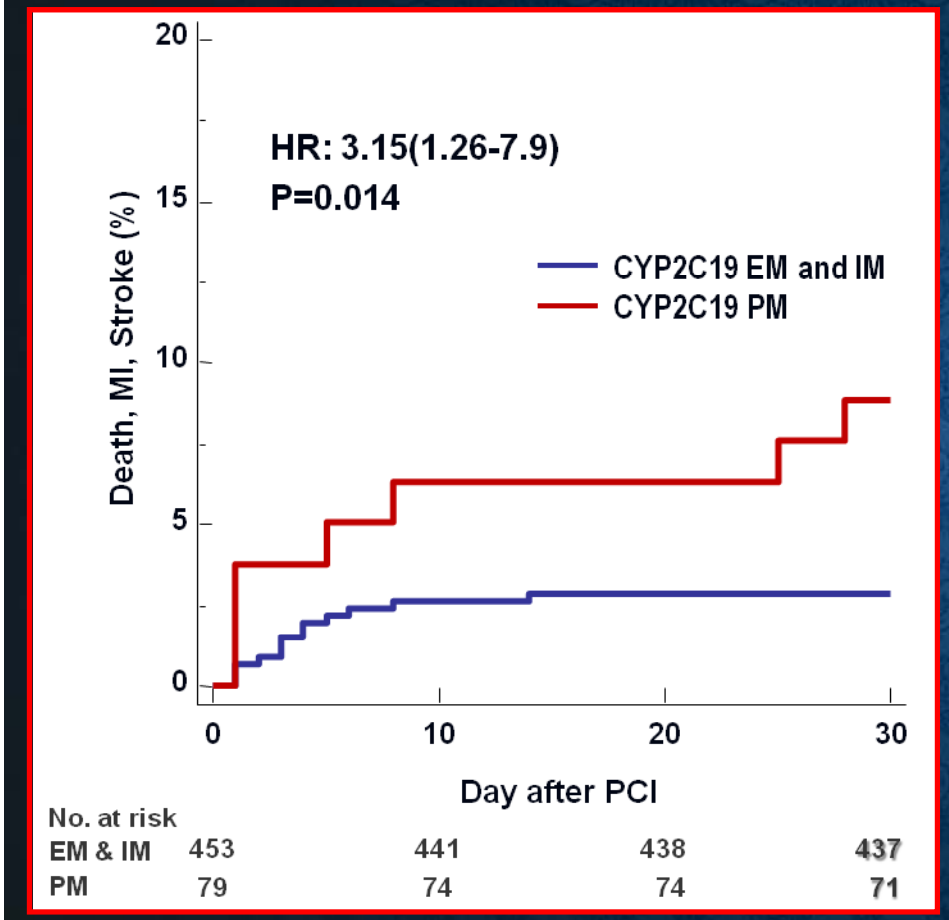


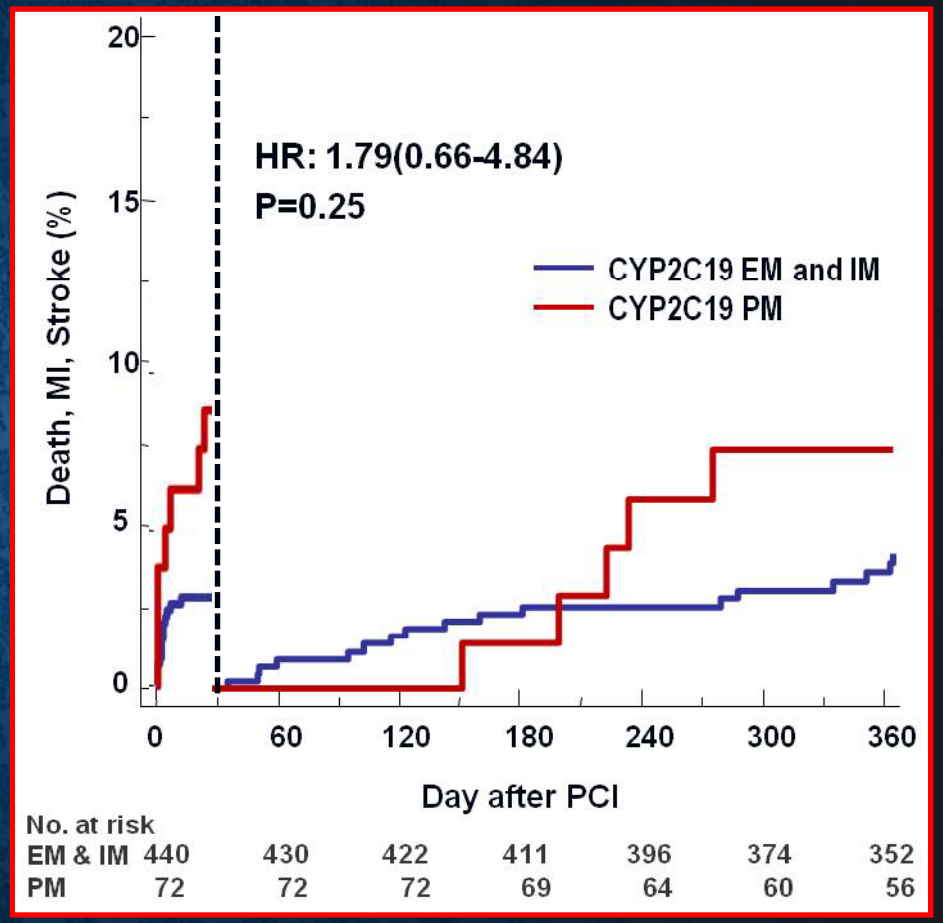
Angina patients

COACT-gene registry data

Seoul St.Mary's Hospital Cardiovascular Center

Landmark analysis in COACT-gene registry





AMI patients

COACT-gene registry data

Seoul St.Mary's Hospital Cardiovascular Center

Conclusion

- The incidence of LOF CYP2C19 allele was higher(60%, PM;14%) in Korean compared to Caucasian.
- Poor metabolizers of CYP2C19 gene had a higher event rate in patients with acute myocardial infarction within the first 30days of the therapy but not beyond up to 1 year.
- In angina PCI patients, poor metabolizers were not associated with subsequent clinical events.