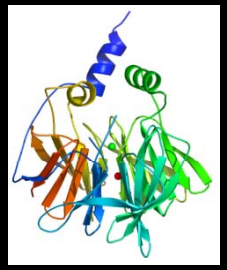
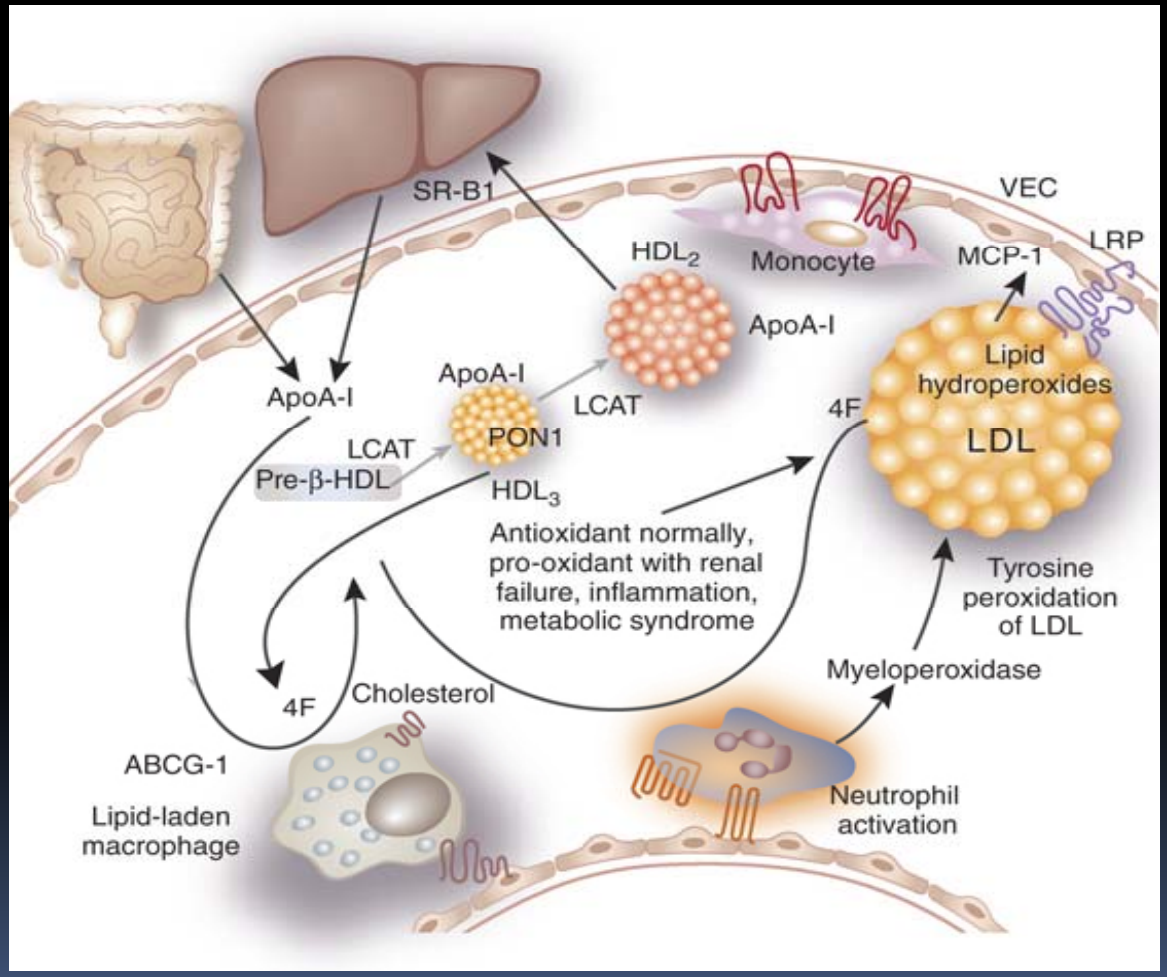
Both CYP2C19 and PON1 Genotypes are Associated with Clinical Outcome of Post-PCI Clopidogrel Therapy in AMI

Ki-Bae Seung, M.D., Ph.D., FACC
Cardiovascular Center and Cardiology Division,
Seoul St. Mary's Hospital and College of Medicine,
The Catholic University of Korea, Seoul, Republic of Korea

No conflicts/disclosure

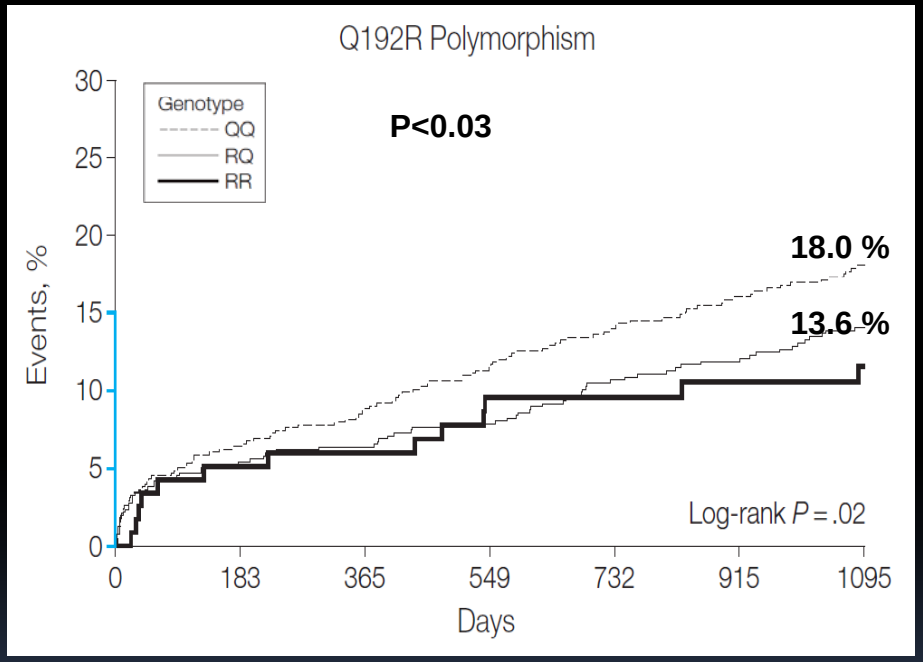
Paraoxonase-1 (PON-1) in Atherosclerosis

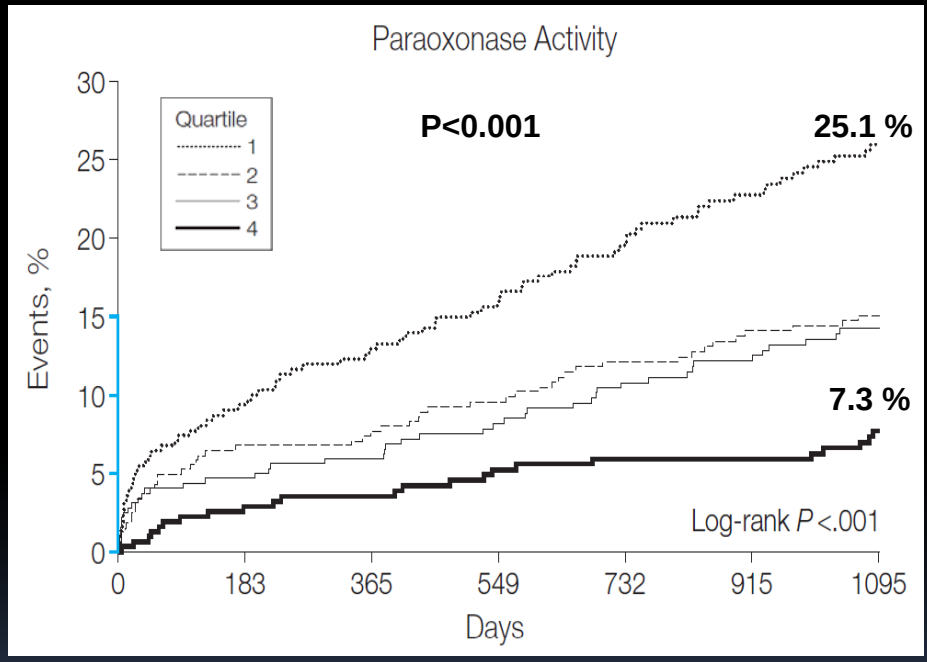




Seoul St.Mary's Hospital
Cardiovascular Center

Relationship between genetic polymorphism of PON1 and cardiovascular risk

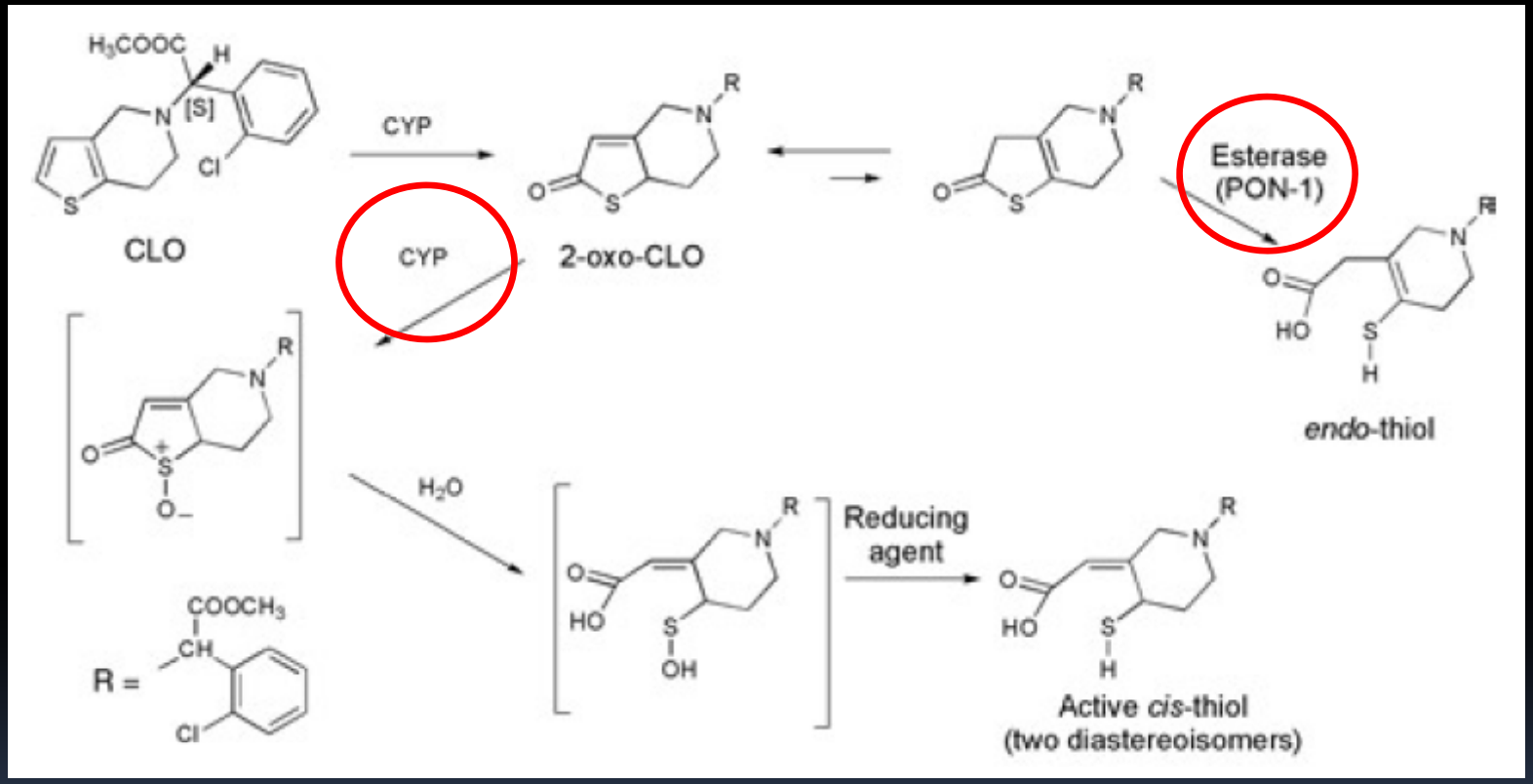




Bhattacharyya T et al, *JAMA* 2008;299:1265-1276

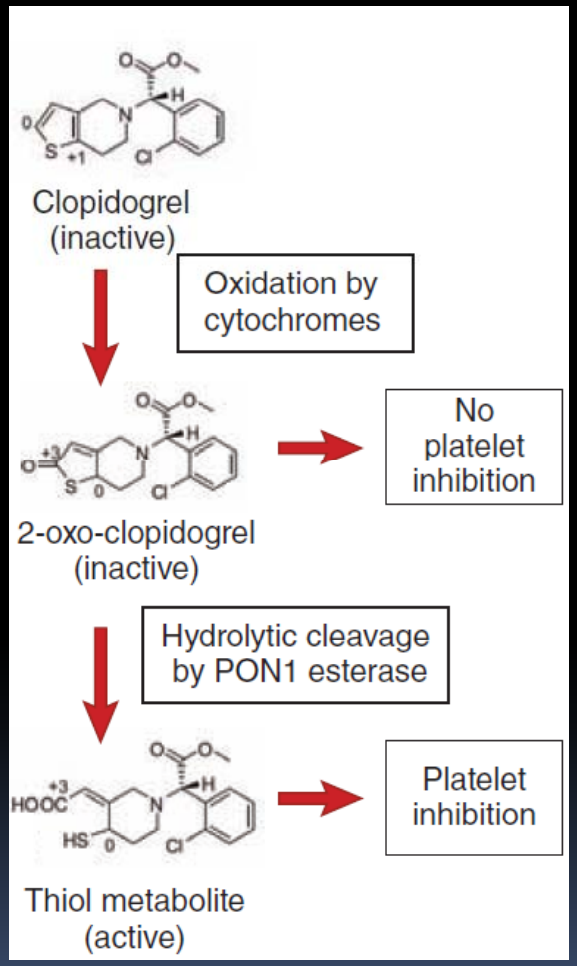
Seoul St.Mary's Hospital
Cardiovascular Center

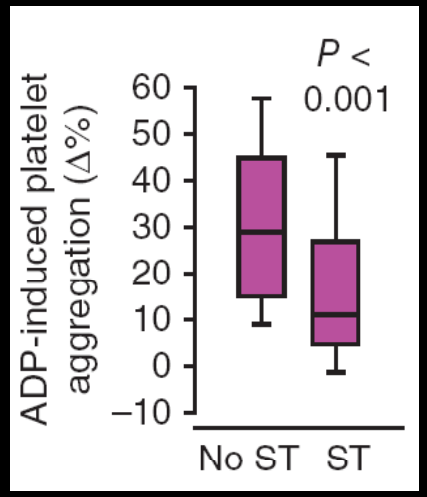
Clopidogrel metabolism

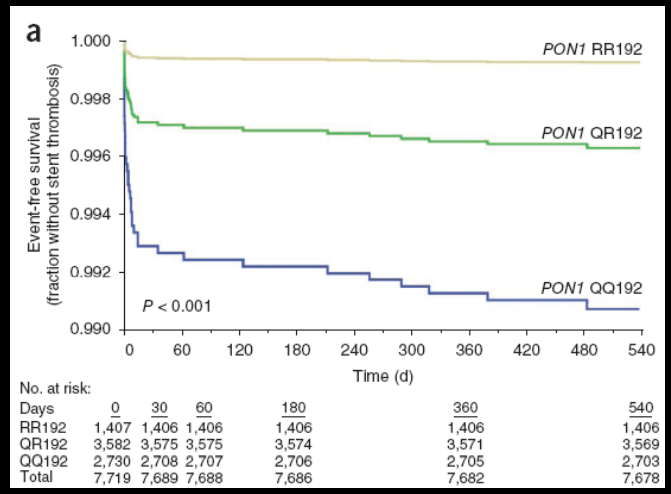


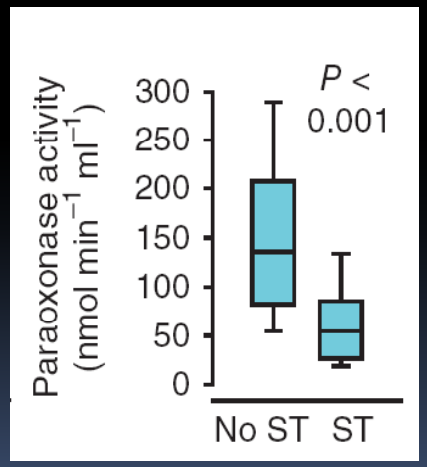
Dansette PM et al. *Nat Med* 2011;17:1040-41

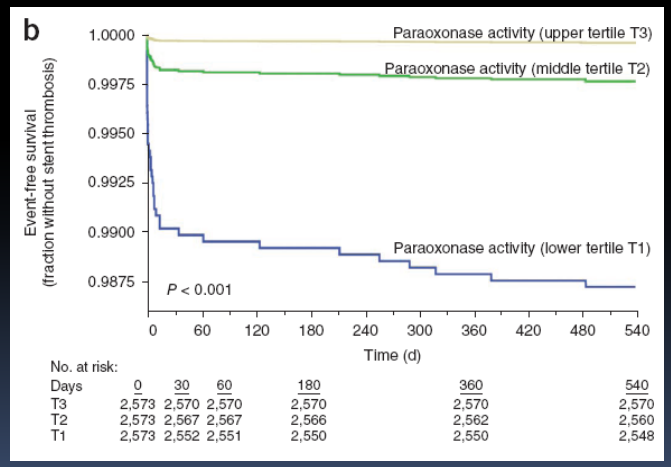
Effect of PON1 on clopidogrel metabolism (1)







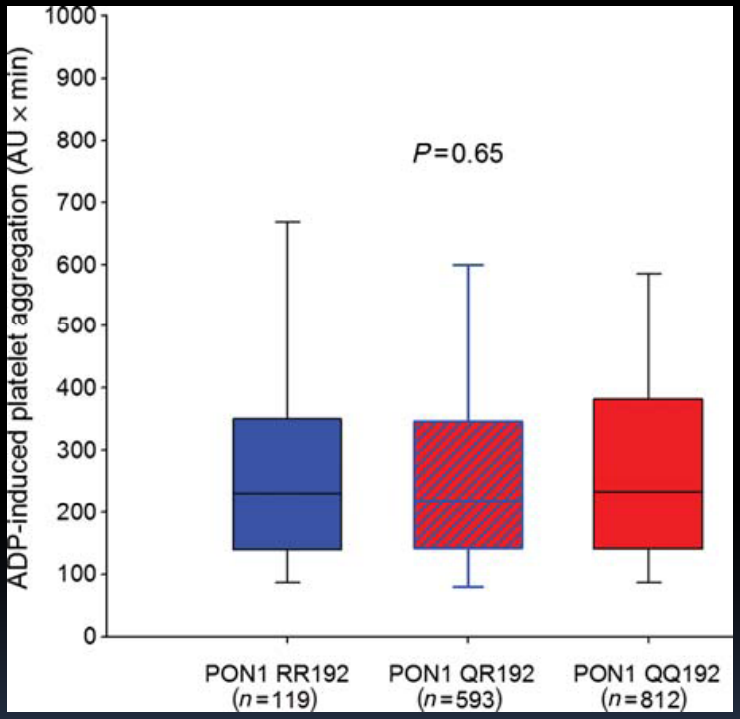


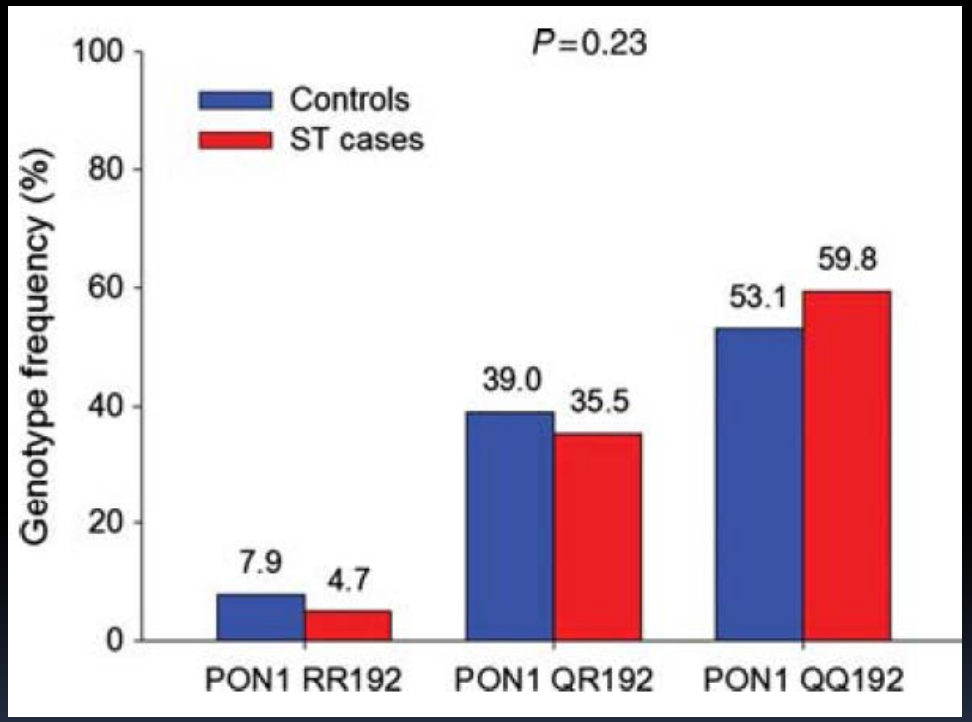


Bouman HJ, et al. *Nat Med* 2011;17:110-6

Seoul St.Mary's Hospital
Cardiovascular Center

Effect of PON1 on clopidogrel metabolism (2)

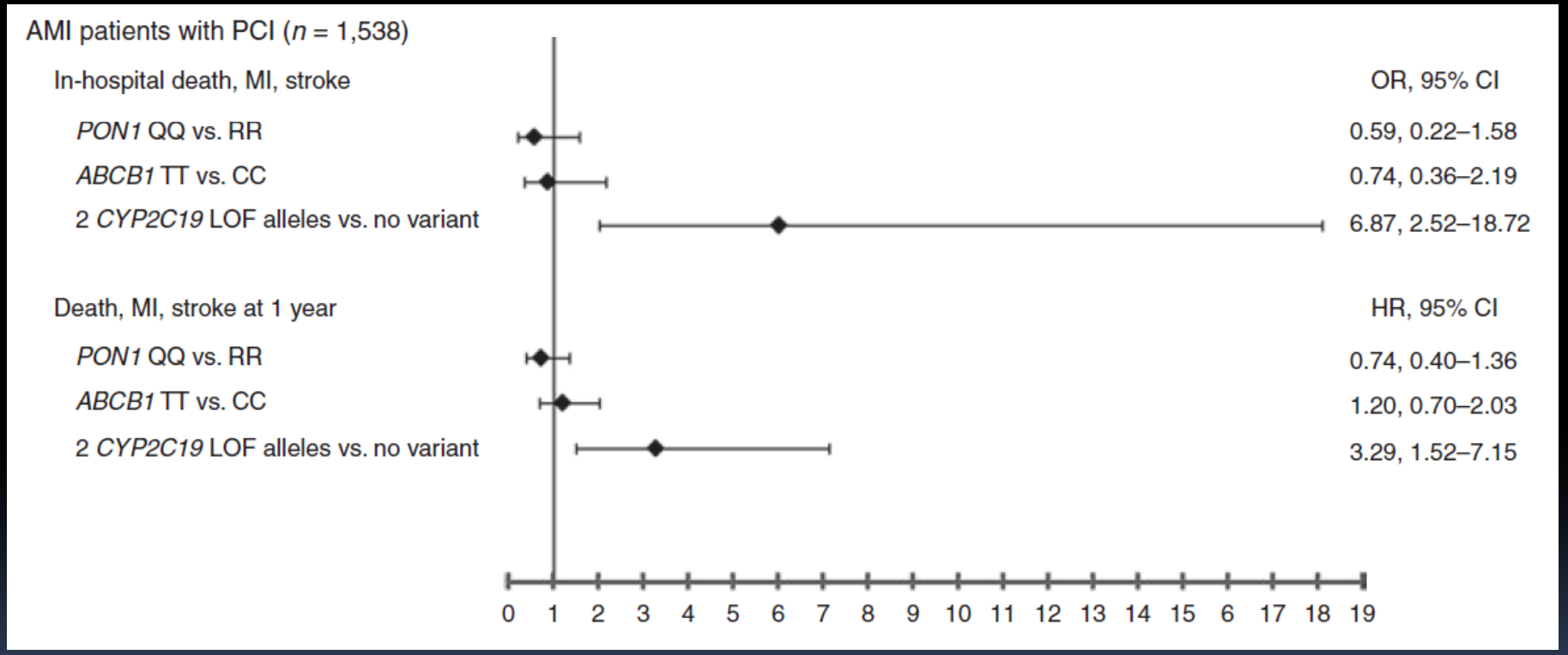




Sibbing D, et al. *Eur Heart J* 2011;32:1605-13

Seoul St.Mary's Hospital Cardiovascular Center

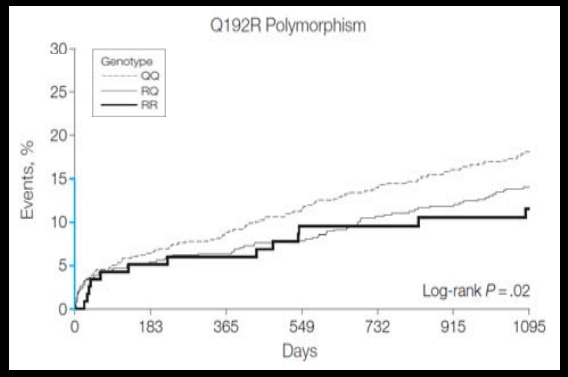
Effect of PON1 polymorphism on clinical outcomes after AMI



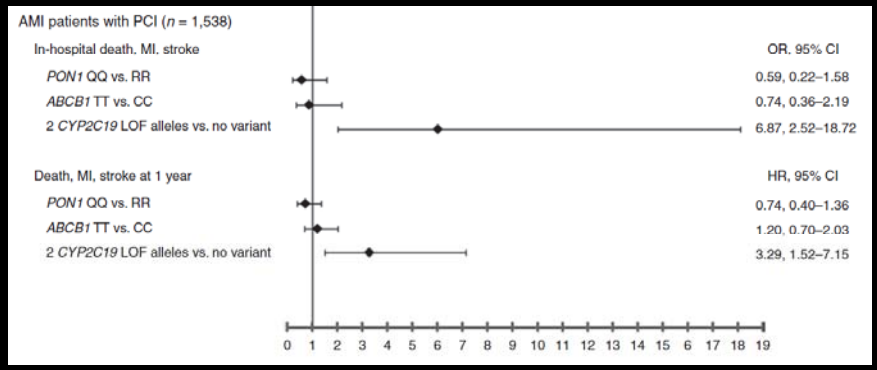
Simon T et al, *Clin Pharmacol Ther* 2011;91:561-567

Seoul St.Mary's Hospital Cardiovascular Center

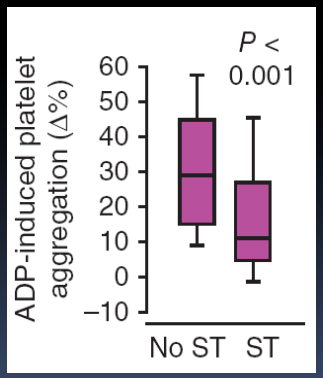
Pros and Cons

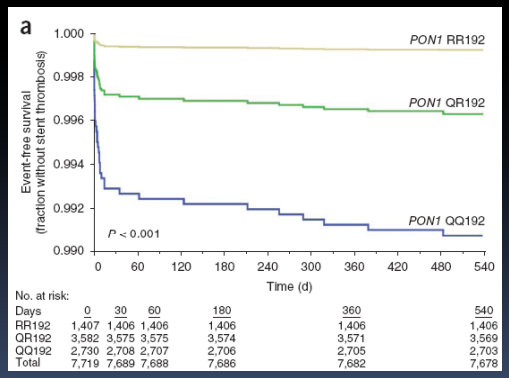


Clopidogrel metabolism (?), MACE (+)
Elective PCI cohort

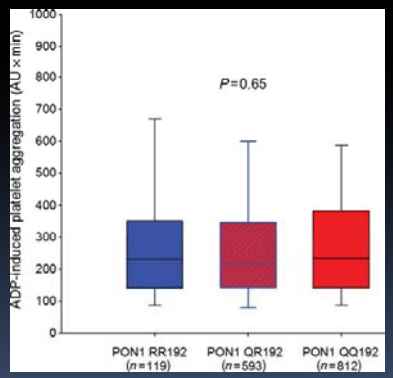


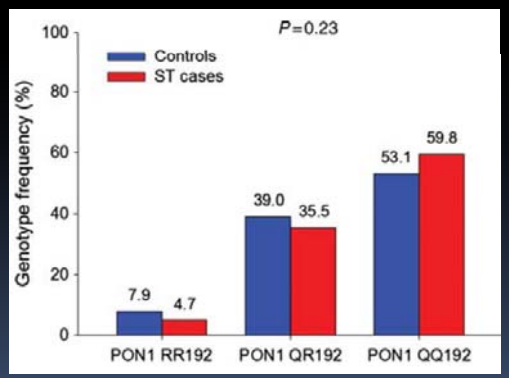
Clopidogrel metabolism (?), MACE (-)
AMI





Clopidogrel metabolism (+), ST (+)
PCI cohort





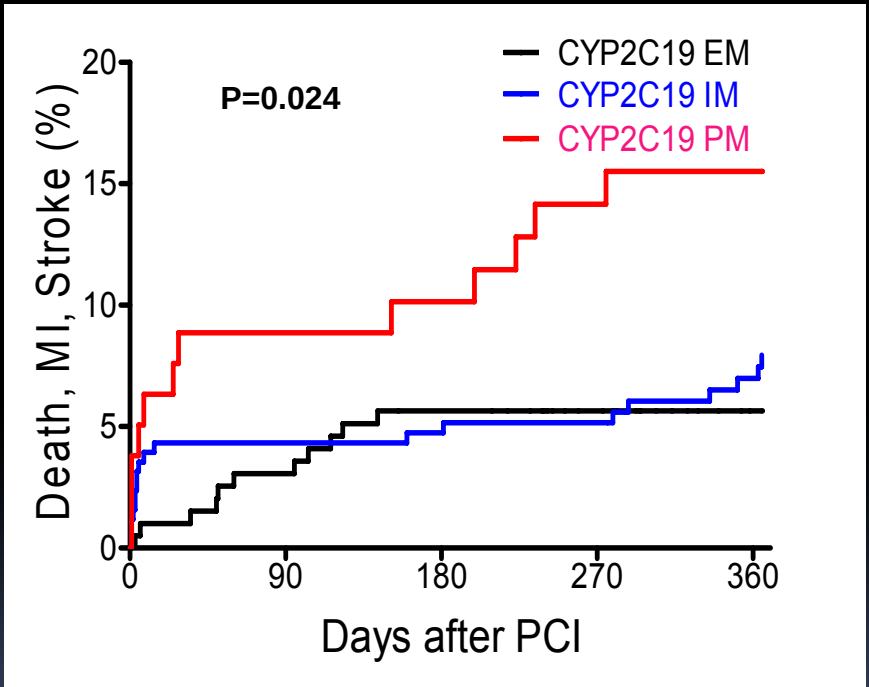
Clopidogrel metabolism (-), ST (-)
PCI cohort

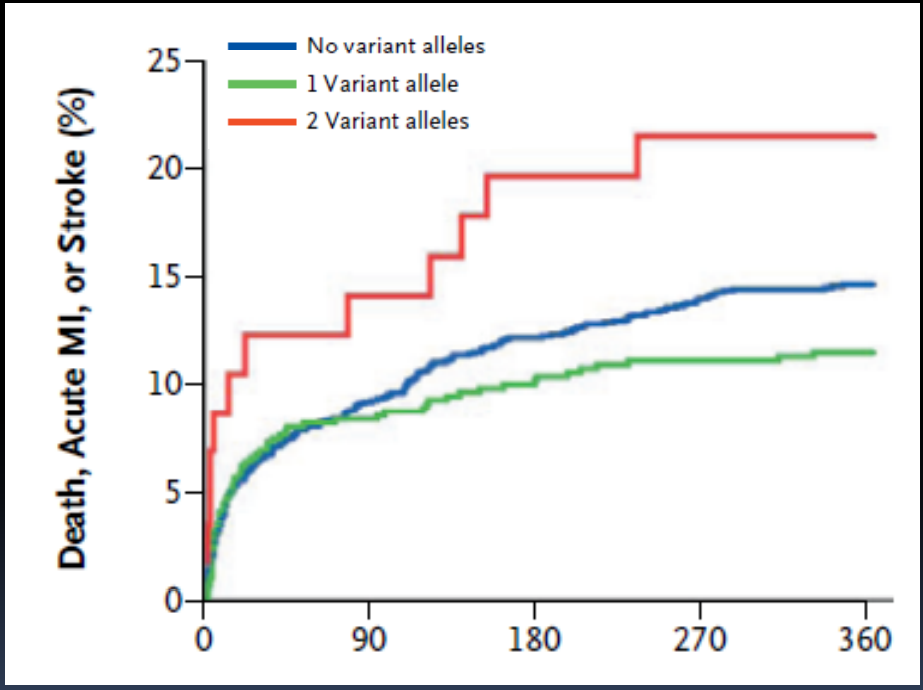
Seoul St.Mary's Hospital
Cardiovascular Center

Unresolved Issues (1)

Whether PON1 Q192R polymorphism may affect on-clopidogrel platelet reactivity by modulating CLOPD metabolism, which will be translated into worse clinical outcome in patients who received DES and clopidogrel?

Clinical outcomes according to reduced-function allele of CYP2C19 in AMI



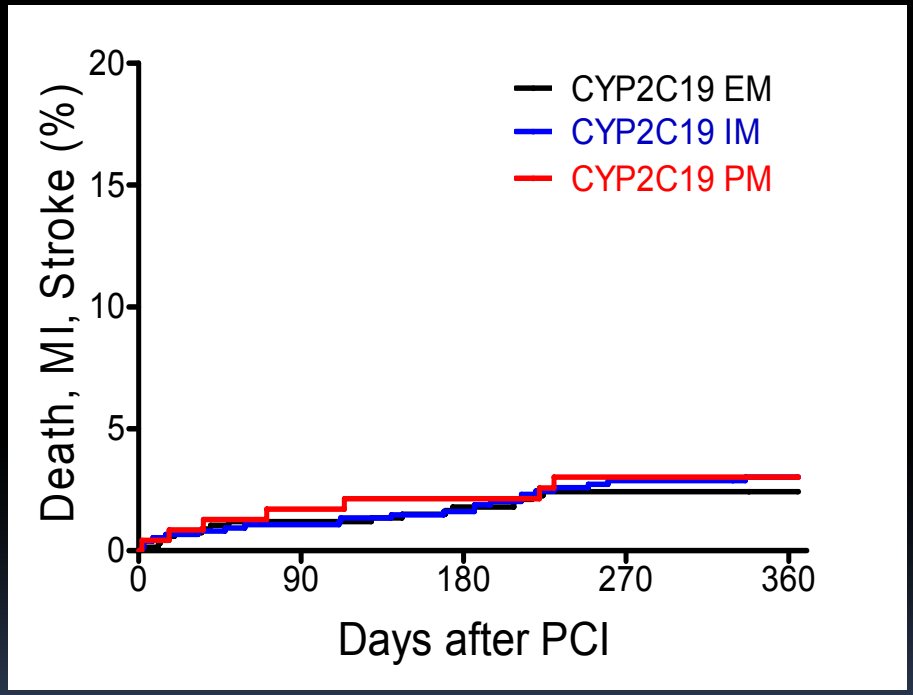


COACT-gene registry data-submission to EHJ

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

Seoul St.Mary's Hospital Cardiovascular Center

Clinical outcomes according to reduced-function allele of CYP2C19 in stable angina



COACT-gene registry data-submission to EHJ

Seoul St.Mary's Hospital
Cardiovascular Center

Racial difference in distribution of CYP2C19 genotype and phenotype

- In TRITON study population (mainly 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 (CMC 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)

Racial difference in PON1 phenotype

	PON1Q192R genotype frequencies (%)		
	QQ	QR	RR
USA - Caucasians	49.7	41.6	8.7
USA – Blacks	15.6	42.6	41.8
Finnish	52	44	4
Indian	47	40	13
Chinese	17	50	33
Malay	24	43	33
Thai	50	42	7.9
Japanese	23	35	42

Mohamed Ali S, Chia SE. *Ind Health* 2008;46:309-17

Unresolved issue (2)

Similar ischemic event rates even though higher CYP2C19 LOF allele may be associated with lower prevalence of PON1 QQ192 phenotype in Asian?

Purpose

Evaluates the effects of
CYP2C19 and PON1 genotypes
on clinical outcome of clopidogrel therapy
in patients with either stable angina or AMI

Methods

COACT-gene registry

- COACT-gene registry : CathOlic medical center percutAneous Coronary inTervention gene registry
- 8 affiliated hospital of Catholic Medical Center

- Data registered from Jan 2005 to Dec 2009
- Prospective multicenter registry dedicated to patients who underwent PCI with DES and sampled for DNA analysis

Study population

Inclusion

1) PCI with DES
2) ≥21 years old
3) Dual antiplatelet therapy with aspirin and clopidogrel continued for more than 12 months
4) Informed consent for genotyping

Exclusion

1) contaminated/insufficient sample
2) unknown phenotype
3) Dual antiplatelet therapy less than 12 months
4) follow up loss

Primary endpoint

Composite of major adverse cardiac and cerebrovascular events (MACCE) during 1 year

1) Death from any cause
2) Nonfatal myocardial infarction
3) Stroke

Platelet function test

- VerifyNow P2Y12® at day 2 to 7 following PCI (Accumetrics, San Diego, California)
- PRU value estimation :
  by the increase of light transmittance from the adenosine diphosphate-induced platelet aggregation
- % inhibition of platelet reactivity :
  ((Baseline PRU − Post-Drug PRU) / Baseline PRU) × 100

Genotyping

- Genotyping were performed by investigators who were blinded to CVD status and other clinical information about patient.
- ABI PRISM® genetic analyzer and its mounted GeneMapper® software.
  : All tested genotypes satisfied Hardy-Weinberg equilibrium and showed no statistical significance for all SNPs tested ($p>0.05$)
- CYP2C19 allele classification

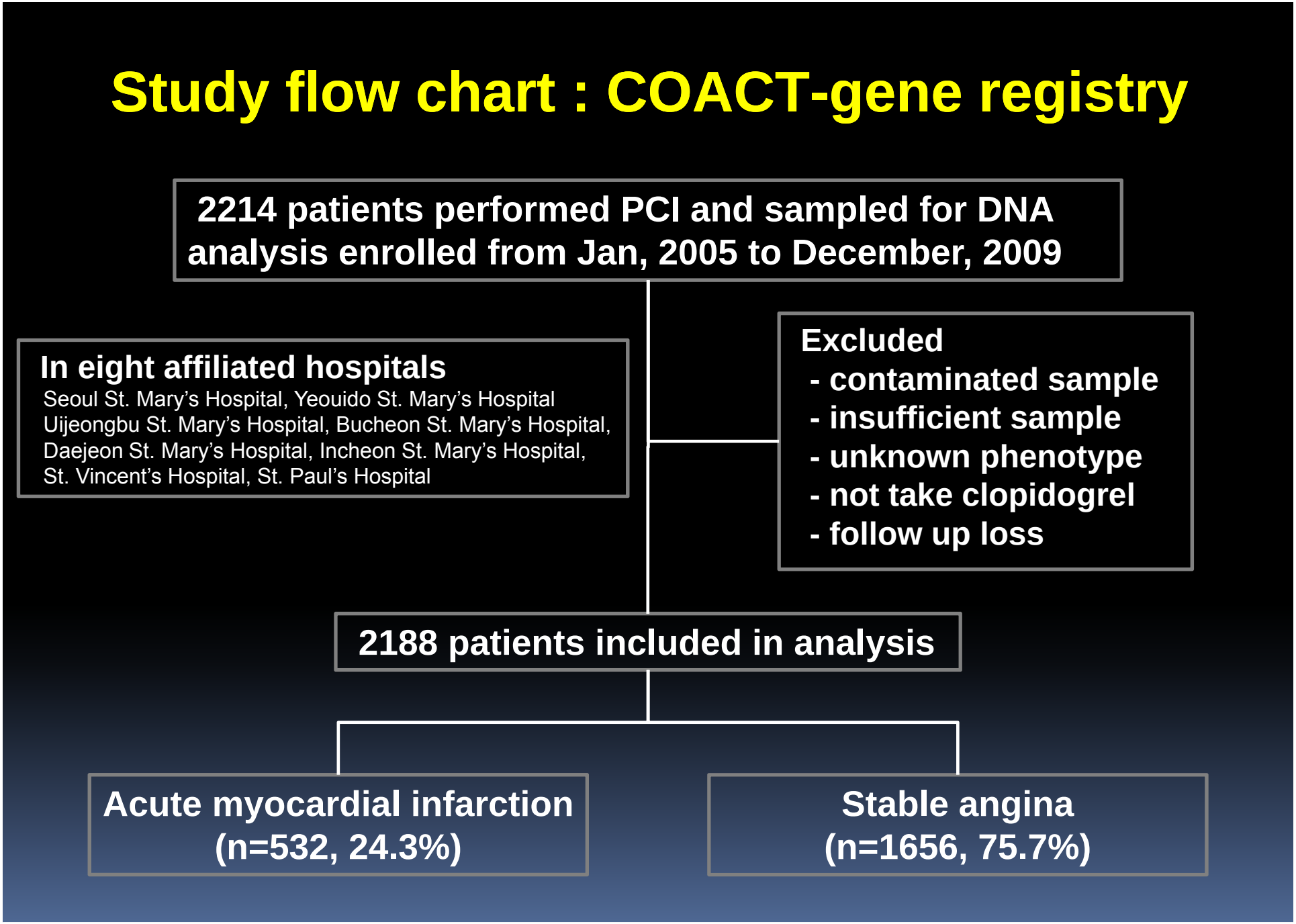
  CYP2C19 EM; CYP2C19*1/*1 and heterozygous for CYP2C19*17 allele
  CYP2C19 IM; CYP2C19*1/*2 and CYP2C19*1/*3)
  CYP2C19 PM; CYP2C19*2/*2, CYP2C19*2/*3 and CYP2C19*3/*3

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

Study flow chart : COACT-gene registry



Seoul St.Mary's Hospital Cardiovascular Center

Baseline characteristics

Variables		AMI (n=532)	Angina (n=1656)	P value
Age (mean ± SD)		62.4 ± 12.4	63.9 ± 9.9	0.02
BMI (mean ± SD)		24.0 ± 3.2	24.9 ± 3.1	<0.001
Sex (male, %)		400 (75.2)	1049 (63.4)	<0.001
Hypertension (%)		257 (48.3)	1043 (63.0)	<0.001
Diabetes (%)		174 (32.7)	651 (39.3)	0.006
Hypercholesterolemia (%)		123 (24.0)	317 (19.7)	0.04
Family history of CAD (%)		34 (6.4)	88 (5.3)	0.34
Current smoker (%)		137 (25.8)	252 (15.2)	<0.001
Previous MI (%)		34 (6.4)	121 (7.3)	0.47
Previous PCI (%)		32 (6.0)	177 (10.7)	0.001
Previous CABG (%)		4 (0.8)	16 (1.0)	0.80
Previous CVA (%)		32 (6.0)	111 (6.7)	0.55
Chronic kidney disease (%)		40 (7.9)	56 (2.3)	<0.001
CLOPD loading dose	600mg	447 (84.0)	1325 (80.0)	0.047
	300mg	85 (16.0)	331 (20.0)	

Seoul St.Mary's Hospital
Cardiovascular Center

Baseline Genotypes

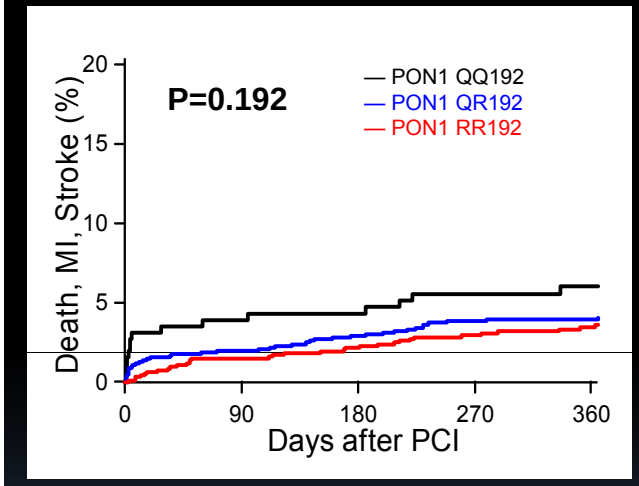
Variables	AMI (n=532)	Angina (n=1656)	P value
CYP2C19 phenotype			0.42
EM	199 (37.4)	673 (40.6)	
IM	254 (47.7)	749 (45.2)	
PM	79 (14.9)	234 (14.1)	
PON1 Q192R (rs662)			
QQ	68 (12.8)	187 (11.3)	0.646
QR	240 (45.11)	763 (46.1)	
RR	224 (42.11)	706 (42.6)	
CYP2B6			0.164
*1/*1	364 (68.4)	1202 (72.6)	
*1/*6, *1/*9	156 (29.3)	417 (25.2)	
*6/*6, *9/*9	12 (2.3)	37 (2.2)	
CYP3A4			0.341
*1/*1	516 (97.0)	1598 (96.5)	
*1/*18	14 (2.6)	56 (3.4)	
*18/*18	2 (0.4)	2 (0.1)	

Baseline Genotypes

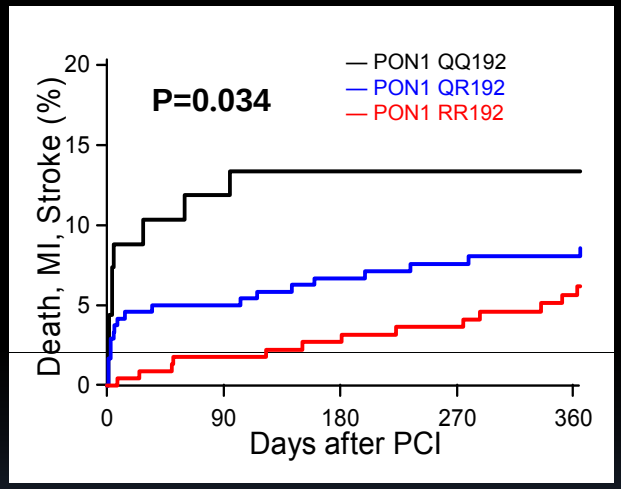
Variables	AMI (n=532)	Angina (n=1656)	P value
CYP3A5			0.140
*1/*1	39 (7.3)	105 (6.3)	
*1/*3	203 (38.2)	568 (34.3)	
*3/*3	290 (54.5)	983 (59.4)	
ABCB1 2677 G>A/T (rs2032582)			0.963
GG	108 (20.3)	337 (20.4)	
GA	93 (17.5)	261 (15.8)	
GT	169 (31.8)	537 (32.4)	
AA	15 (2.8)	45 (2.7)	
AT	71 (13.4)	227 (13.7)	
TT	76 (14.3)	249 (15.0)	
ABCB1 3435 C>T (rs1045642)			0.559
CC	218 (41.0)	707 (42.7)	
CT	245 (46.0)	719 (43.4)	
TT	69 (13.0)	230 (13.9)	
P2RY12 742 T>C (rs2046934)			0.388
TT	351 (66.0)	1145 (69.1)	
TC	160 (30.0)	454 (27.4)	
CC	21 (4.0)	57 (3.4)	

Kaplan-Meier curves of MACCE according to PON1 genotypes

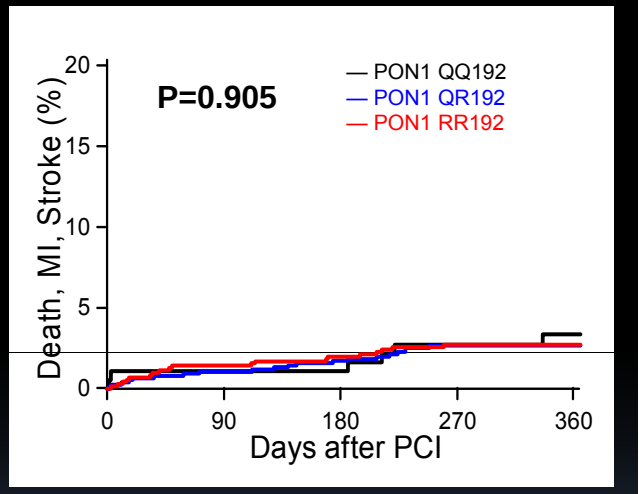
Overall



AMI



Stable angina



No. at risk															
QQ	255	243	234	220	195	68	58	55	53	50	187	185	179	167	145
QR	1003	975	948	886	766	240	225	216	200	181	763	750	732	686	585
RR	930	908	884	820	731	224	218	209	199	177	706	690	675	621	554

Seoul St.Mary's Hospital
Cardiovascular Center

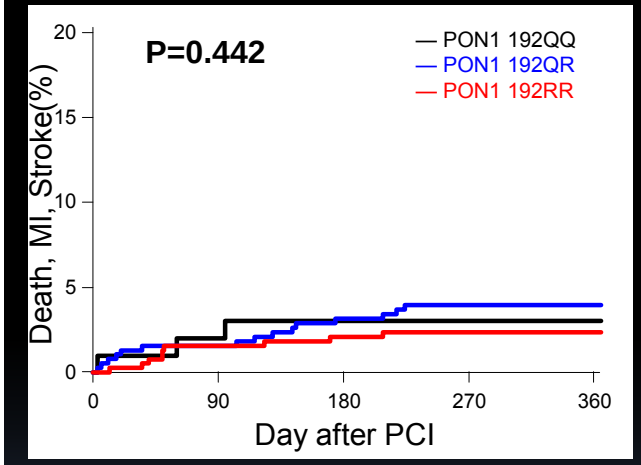
Primary outcomes in AMI and angina patients at 12 months according to functional allelic variants

	Acute MI				Stable angina			
	Without MACCE (n=490)*	With MACCE (n=42)*	HR (95% CI)	P *	Without MACCE (n=1611)*	With MACCE (n=45)*	HR (95% CI)	P *
CYP2C19								
EM	188(38.4)	11 (26.2)	1.00	-	657 (40.8)	16(35.6)	1.00	-
IM	235(48.0)	19 (45.2)	1.37 (0.65-2.88)	0.404	727 (45.1)	22(48.9)	1.24 (0.65-2.36)	0.517
PM	67(13.7)	12 (28.6)	2.88 (1.27-6.53)	0.011	227 (14.9)	7(15.6)	1.26 (0.52-3.06)	0.612
PON1 Q192R								
QQ	59 (12.0)	9 (21.4)	1.00	-	181 (11.2)	6(13.3)	1.00	-
QR	220 (44.9)	20 (47.6)	0.60 (0.27-1.31)	0.196	743 (46.1)	20(44.4)	0.81 (0.33-2.02)	0.656
RR	211 (43.1)	13 (31.0)	0.40 (0.17-0.94)	0.035	687 (42.6)	19(42.2)	0.84 (0.34-2.11)	0.712

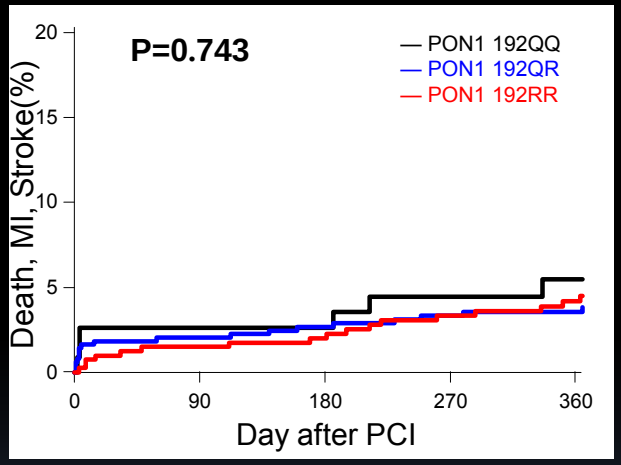
* Hazard ratios and P values were calculated using the univariate Cox proportional-hazards model

Kaplan-Meier curves of MACCE according to PON1 genotypes stratified by CYP2C19 genotype in all patient cohort

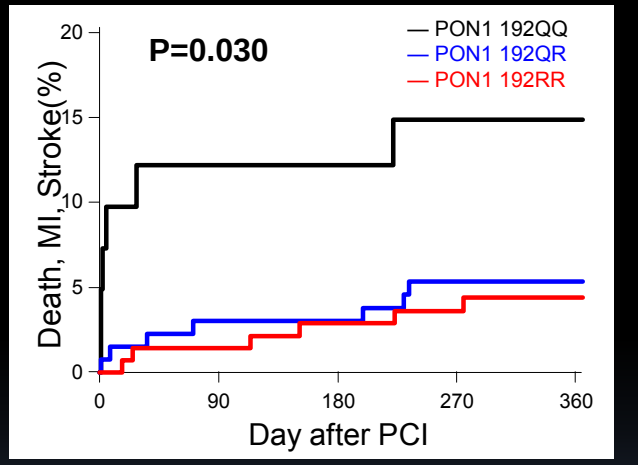
CYP2C19 EM



CYP2C19 IM



CYP2C19 PM



No. at risk

QQ	100	97	93	89	80	114	110	108	99	88	41	36	33	32	27
QR	382	373	361	341	295	489	474	461	429	373	132	128	126	116	98
RR	390	390	371	341	302	400	390	381	355	316	140	138	132	124	113

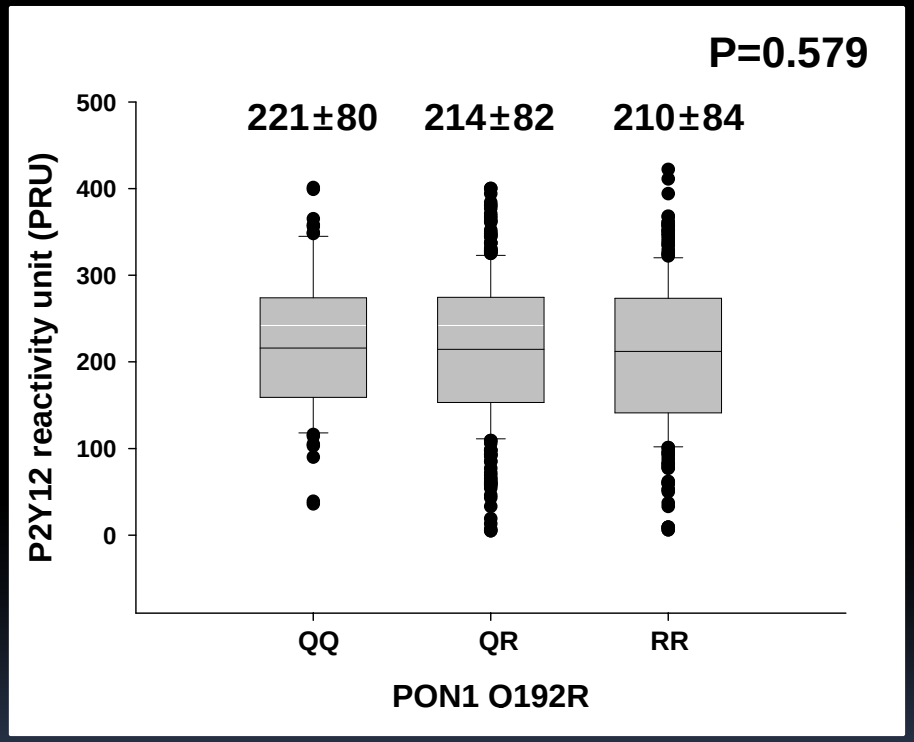
Seoul St.Mary's Hospital Cardiovascular Center

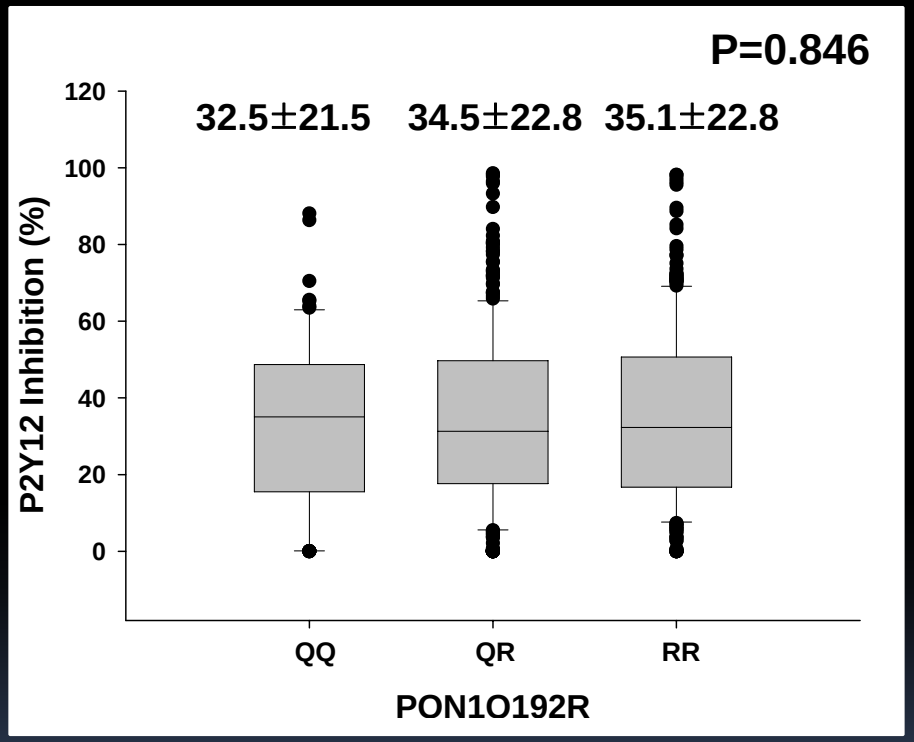
Effect of combined CYP2C19/PON1 genotype on MACCE

Covariates	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Angina patients				
CYP2C19 EM/IM and PON1 QR/RR	1.00 (reference)		1.00 (reference)	
CYP2C19 PM and PON1 QQ	2.72 (0.66-11.23)	0.167	2.83 (0.38-21.23)	0.311
AMI patients				
CYP2C19 EM/IM and PON1 QR/RR	1.00 (reference)		1.00 (reference)	
CYP2C19 PM and PON1 QQ	5.97 (2.13-16.76)	<0.001	10.16 (2.84-36.40)	<0.001

Unadjusted and adjusted interaction P<0.001 (adjusted for age, sex, BMI, diabetes, hypercholesterolemia, current smoking, chronic renal failure, family history of coronary artery disease, and history of myocardial infarction, cerebrovascular accident, and coronary artery bypass graft)

Platelet reactivity & inhibition on treatment of clopidogrel according to PON1 phenotype





QQ (n=73), QR (n=336), RR (n=282)

Seoul St.Mary's Hospital Cardiovascular Center

Summary

- CYP2C19 PM and PON1 192QQ genotypes
  - significantly associated with higher risk of MACCE
  - particularly in AMI patients, not in stable angina

- PON1 genotype
  - Positive association of QQ genotype with higher risk of MACCE
  - However, no association with clopidogrel metabolism
  - maybe, due to anti-atherogenic effect and etc(?)

Conclusion

1. Combined CYP2C19 PM/PON1 QQ genotype is a poor prognostic biomarker and may be used as an indicator of personalized pharmacotheraphy in patients with AMI
2. Further studies are required to elucidate the role of the PON genetic polymorphism in CAD