CYP2C19 genotype profiling for management after primary PCI

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on behalf
of GIANT Study investigators

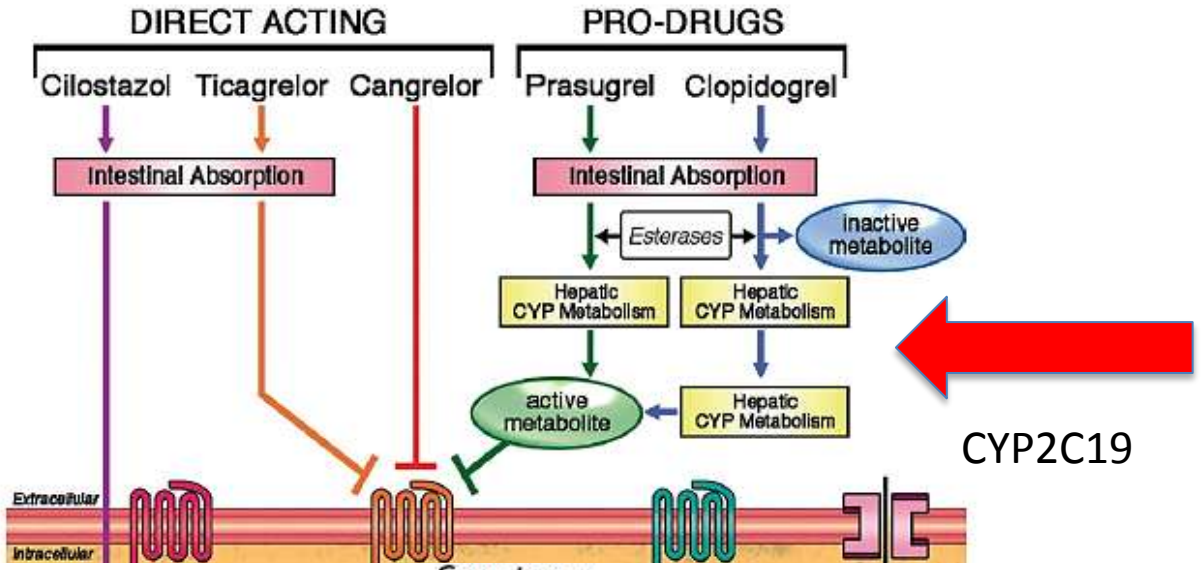
NCT01134380 – Sponsor: Biotronik

Genotyper les patients en phase aigue d'**I**nfarctus pour **A**juster et de **N**ormaliser leur traitement **T**hienopyridine

Disclosure

In the last five years , I received research grants or speaker fees or I am/was consultant for: Abbott Vascular, Asahi, Astra Zeneca, AVI, Boston Scientific, Biotronik, Colibri, Cook, Cordis, Daichi-Sankyo, Eli-Lilly, Iroko, Medtronic, Terumo. I am currently minor shareholder & general director of CERC (CRO)

Background



CYP2C19

Likely phenotype	Genotypes
Ultrarapid metabolizer: normal or increased activity (~5–30% of patients)	An individual carrying two increased-activity alleles (**17*), or one functional allele (**1*) plus one increased-activity allele (**17*)
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (**1*) alleles
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (**1*) plus one loss-of-function allele (**2–*8*)
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (**2–*8*)

CYP2C19 & post ACS events

CYP2C19 But Not *PON1* Genetic Variants Influence Clopidogrel Pharmacokinetics, Pharmacodynamics, and Clinical Efficacy in Post–Myocardial Infarction Patients

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(*Circ Cardiovasc Interv*. 2011;4:422-428.)

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

A Systematic Review and Meta-analysis

Michael V. Holmes, MBBS, MSc

Pablo Perel, PhD

Tina Shah, PhD

Aroon D. Hingorani, PhD

Juan P. Casas, PhD

JAMA. 2011;306(24):2704-2714

Clinical, Angiographic, and Genetic Factors Associated With Early Coronary Stent Thrombosis

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JAMA. 2011;306(16):1765-1774

LOF allele are more frequent in East Asian population

Circ Cardiovasc Interv. 2011 Dec 1;4(6):585-94. doi: 10.1161/CIRCINTERVENTIONS.111.962555. Epub 2011 Nov 1.

Effect of CYP2C19*2 and *3 loss-of-function alleles on platelet reactivity and adverse clinical events in East Asian acute myocardial infarction survivors treated with clopidogrel and aspirin.

Jeong YH[1], Tantry US, Kim IS, Koh JS, Kwon TJ, Park Y, Hwang SJ, Bliden KP, Kwak CH, Hwang JY, Gurbel PA.

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Abstract

BACKGROUND: As compared with whites, East Asians more often carry the cytochrome P450 (CYP) 2C19 loss-of-function (LOF) allele with the CYP2C19*3 variant. The influence of the CYP2C19 LOF alleles (*2 and *3) on clopidogrel response and clinical outcomes in East Asians with acute myocardial infarction (AMI) has not been reported. We sought to evaluate the effect of the CYP2C19 variants on clopidogrel pharmacodynamics and long-term prognosis in these patients.

METHODS AND RESULTS: Patients who survived an AMI (n=266) were enrolled in a single-center registry. Predischarge platelet reactivity was assessed with light transmittance aggregometry and the VerifyNow P2Y12 assay; the CYP2C19*2, *3, *17 and ABCB1 3435C>T variants were determined. The primary clinical end point was the composite of cardiovascular death, nonfatal MI, and ischemic stroke. The median exposure to clopidogrel was 21 months (interquartile range, 13-29). The ABCB1 3435C>T was not related to clopidogrel response or cardiovascular events. Carriage of the CYP2C19 LOF variant allele was relatively high (60.9%, n=162; *2/*17=2, *3/*17=1, *1/*2=96, *1/*3=29, *2/*2=20, and *2/*3=14). Platelet reactivity increased proportionally according to the number of the CYP2C19 LOF alleles. In a multivariate regression analysis, the risk of high on-treatment platelet reactivity (HPR) increased depending on the number of CYP2C19 LOF allele [1 LOF allele; odds ratio (OR), 1.8; 95% confidence interval (CI), 0.8 to 4.2, P=0.152; and 2 LOF alleles; OR, 2.8; 95% CI, 1.2 to 6.5; P=0.016]; platelet reactivity and the rate of HPR did not differ between the CYP2C19*2 versus *3 allele carriage. In addition, cardiovascular event occurrence increased according to the number of the CYP2C19 LOF allele; compared with noncarriers, carriers of 1 [hazard ratio (HR), 3.1; 95% CI, 0.8 to 11.6; P=0.089] and 2 CYP2C19 LOF allele(s) (HR, 10.1; 95% CI, 1.8-58.8; P=0.008) were associated with clinical end point. The clinical impact of the CYP2C19*2 versus *3 allele carriage also did not differ.

CONCLUSIONS: Among East Asian patients who survived an AMI, the CYP2C19 LOF allele carriage appears to affect clopidogrel pharmacodynamics and cardiovascular events according to the number of the CYP2C19 LOF allele; the influence of the CYP2C19*2 and *3 alleles on clopidogrel response and long-term outcomes does not differ.

Strategy for loss of fonction carriers

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Prasugrel Overcomes High On-Clopidogrel Platelet Reactivity Post-Stenting More Effectively Than High-Dose (150-mg) Clopidogrel

The Importance of *CYP2C19*2* Genotyping

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On 03-12-2010
FDA added a warning box to clopidogrel label

FDA Boxed Warning on Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

PLAVIX (clopidogrel bisulfate) tablets PI.

Primary objective of GIANT trial

Evaluation of the clinical impact of CYP2C19 genotype transmission within 48 hours to the cardiology team in charge of acute myocardial infarction patients treated with primary PCI using coronary stents.

GIANT Trial design

Acute MI < 24 hrs

Primary PCI

DNA sampling

CYP2C19 genotype < 48hrs

Adjustement 12 m DAPT

F-up @ 1y

Compliance assessment

Loss of function carrier: prasugrel or clopidogrel double dose if CI to prasugrel

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (*CYP2C19*) Genotype and Clopidogrel Therapy

SA Scott[1], K Sangkuhl[2], EE Gardner[3], CM Stein[4,5], J-S Hulot[6,7], JA Johnson[8,9,10], DM Roden[11,12], TE Klein[2] and AR Shuldiner[13,14]

Inclusion/Exclusion Criteria

- Inclusion
  - Any MI (<24hrs) treated with PPCI using coronary stent
- Exclusion
  - Cardiogenic shock
  - Permanent anticoagulation
  - Contra-indication for PCI
  - Life expectancy < 1 y

Endpoints

- Primary
  - Death, MI & Stent thombosis @ 1y in slow responders with appropriate therapy after genotyping vs non slow responders
    - Hypothesis 7% in normal function and 14% in loss of function pts
    - Loss of fonction 28% of global cohort and 20% lost of f-up → 1500 pts
    - Non-inferiority as secondary analysis (1% absolute margin)
- Secondary
  - Compliance @ 1 y
- Tertiary
  - Major bleeding @ 1 y (Steeple definitions) according to genotype

Genotyping Methods

- Saliva DNA collectors (Oragene DNA, dnagenotek) shipped to La Pitié-Salpêtrière Hospital for DNA extraction and genetic analyses
- Screen for CYP2C19 reduced function (*2, *3, *4, *5, *6) and enhanced function (*17) alleles using specific Taqman allelic discrimination assays
- Quick notification of results to investigators
- Results reported as CYP2C19 metabolizer phenotype:

Observed Genotype	***17/*17 *1/*17**	***1/*1 *2/17, *3/*17, *4/*17**	***1/*2 *1/*3, *1/*4, *1/*6**	***2/*2**
Predicted phenotype	Rapid	Normal	Slow	Very Slow

Study organization

Coordinating Committee

- B.Chevalier G. Montalescot JS. Hulot L. Belle G. Cayla

Study Organisation

- CERC, Massy, France

Clinical Event Committee

- G. Dambrin, H. Lebreton, E. Teiger

Monitoring (CERC)

- AE (653) + 15% random

Sponsor Biotronik

- Stent choice at the discretion of the operator

BIOTRONIK
excellence for life

From 07-10 to 01-12 1499 pts

Consent withdrawn 19 Deregistered 13 Lost of f-up 22

1445 pts

Very slow 1.7%

Slow 20.3%

Normal 47.3%

High 30%

Loss of function 22%

Group 1 1118 pts

Not adjusted 15%

Adjusted /Optimal 85%

Group 2 272 pts

Study patients

	Group 1	Group 2	p
Male gender	82.1%	77.7%	0.01
Age	58	57	0.24
Smoker	67%	71.5%	0.14
Dyslipidemia	42.7%	44.5%	0.58
HTN	38%	43.8%	0.08
Diabetes	13.6%	15.7%	0.37
Family story	18%	20%	0.42
Prior MI	4.4%	6.9%	0.08
Prior PCI	6.3%	6.9%	0.68
Prior CABG	0.6%	1.5%	0.24
Prior Stroke	1.9%	3.6%	0.07

Study patients

	Group 1	Group 2	p
Treated vessel			
LAD	47,8%	41%	0.045
RCA	42%	41,8%	0,91
LCX	20,6%	27;5%	0,02
LM	0,8%	1,1%	0,7
SVG	0%	0,4%	0,2
Radial	69.8%	67.2%	NS
6F	93.7%	97.1%	NS

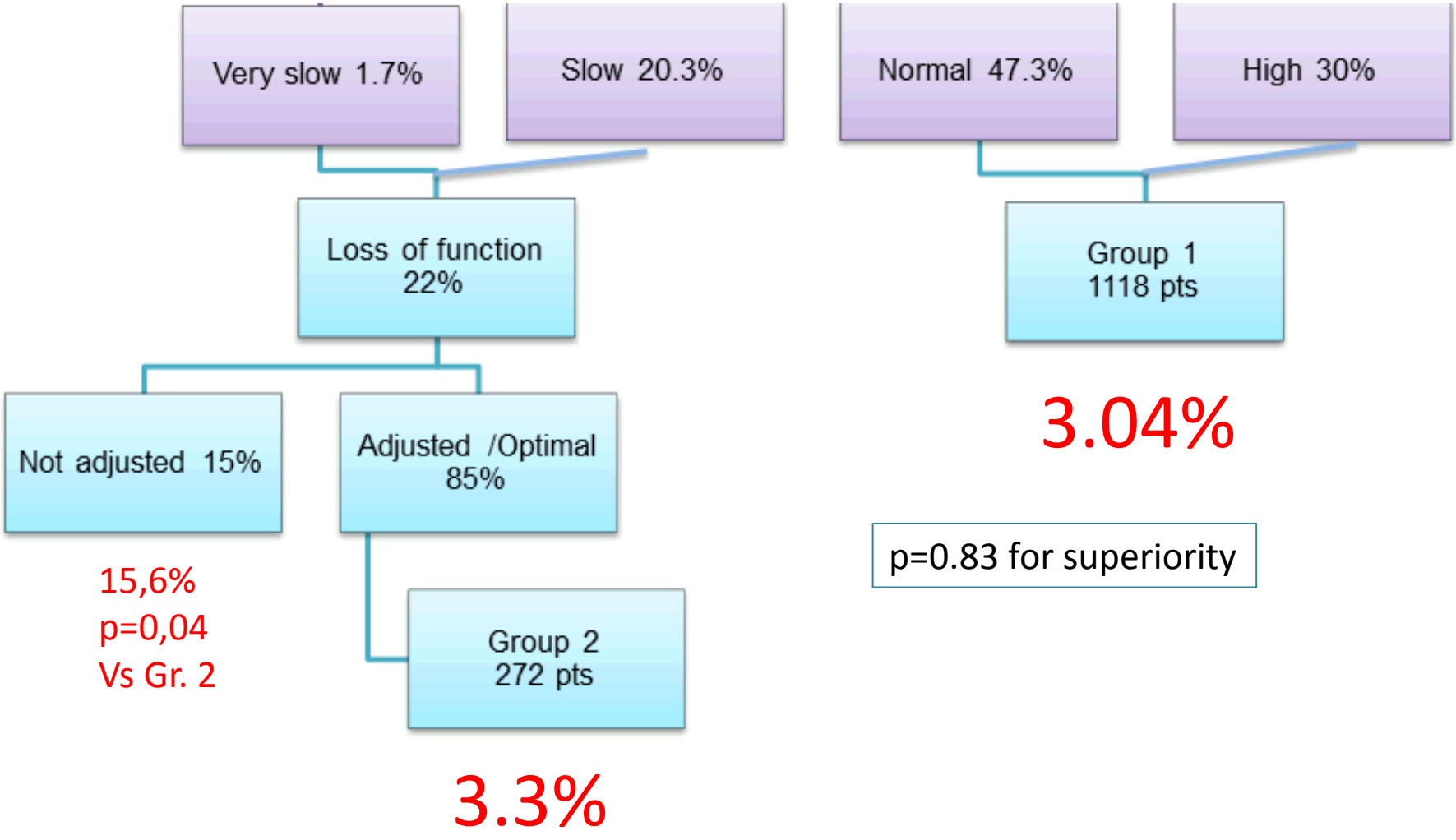
Study patients

	Group 1	Group 2	p
HNF	36,8%	43,8%	NS
LMWH	70,5%	66,4%	NS
Aspirin	94,9%	95,3%	NS
IIb / IIIa inhib.	52.6%	56.2%	NS
Bivalirudine	2.8%	4%	NS
N lesions	1.31	1.33	NS
N stents	1.44	1.49	NS
DES	29.3%	33.9%	NS
BMS	75%	71.2%	NS
Thienopyridine adjustment	11.4%	39.4%	<0.0001

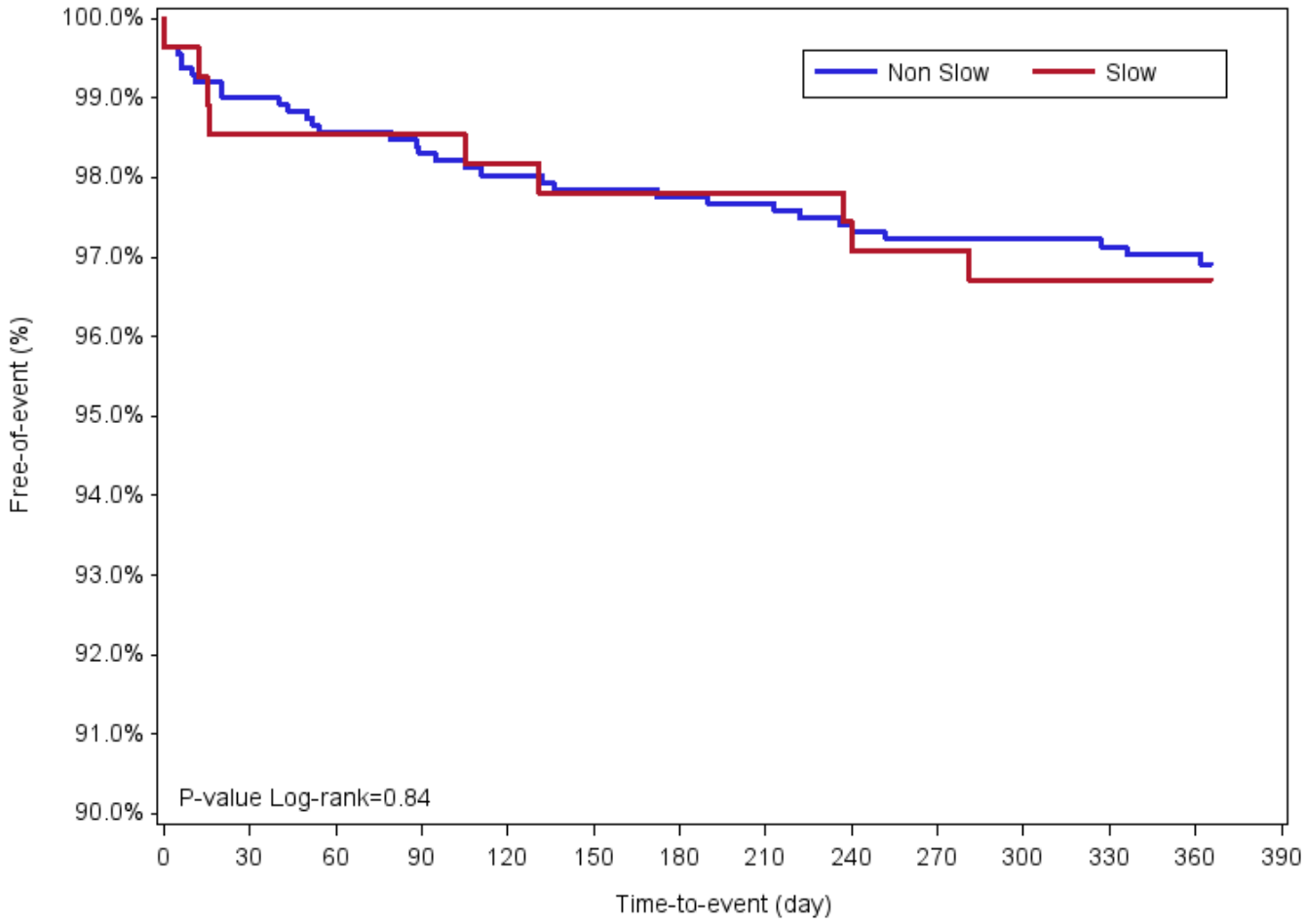
Study patients: Thienopyridine adjustment

	Group 1	Group 2	p
Before Genotyping			
Clopidogrel 75 mg	35,6%	34,7%	NS
Clopidogrel 150 mg	10%	9,1%	NS
Prasugrel 10 mg	53,3%	55,5%	NS
After Genotyping			
Clopidogrel 75 mg	44,5%	0%	<0,001
Clopidogrel 150 mg	8,9%	16,8%	<0,05
Prasugrel 10 mg	46,1%	83,1%	<0,001

Death + MI + Stent thrombosis @ 1 year



Death + Myocardial infarction + Stent thrombosis



MACCE

	Group 1	Group 2	p
Cardiac Death	0.4%	0.7%	NS
MI	2%	1.5%	NS
Urgent TVR	3.6%	5.8%	NS
Stent thrombosis	1.15%	0.73%	NS
Stroke	0.3%	0%	NS
MACCE	8.6%	10.2%	NS

Compliance @ 1 y

At one year follow-up, 917 patients were tested using Verify Now
In case of high platelet reactivity a loading dose was given
A new test was performed 4 hrs later
Pts with normal response at 2nd test were considered as non-compliant

Prevalence of non-complicance =4.9%

	Compliant	Non-compliant	p
N	857	45	
MACCE	8.6%	13.3%	0.21

N lesions

Major bleeding @ 1 y

	Loss of function Group 2	Normal function Group 1	Gain of function Group 1	p
N pts	274	684	434	
M Bleeding	2.2%	1.9%	1.6%	NS

N lesions

Conclusion

- In this cohort of AMI patients treated with PPCI, 22% of patients had loss of function allele
- This genotype information obtained before discharge allowed treatment optimization in 86% of them
- Consequently, ischemic outcomes of this optimized group do not differ from that of patients with a good response genotype and is better than LOF patients with 75 mg clopidogrel treatment
- This strategy is not associated with higher major bleeding risk even in case of gain of function allele genotype
- Poor complicance to treatment was objectively identified in 4.9% of patients at one year, with numerically more ischemic events.