CYP2C19 genetic profiling for thienopyridine management after primary percutaneous coronary intervention: Results of the GIANT study

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on behalf

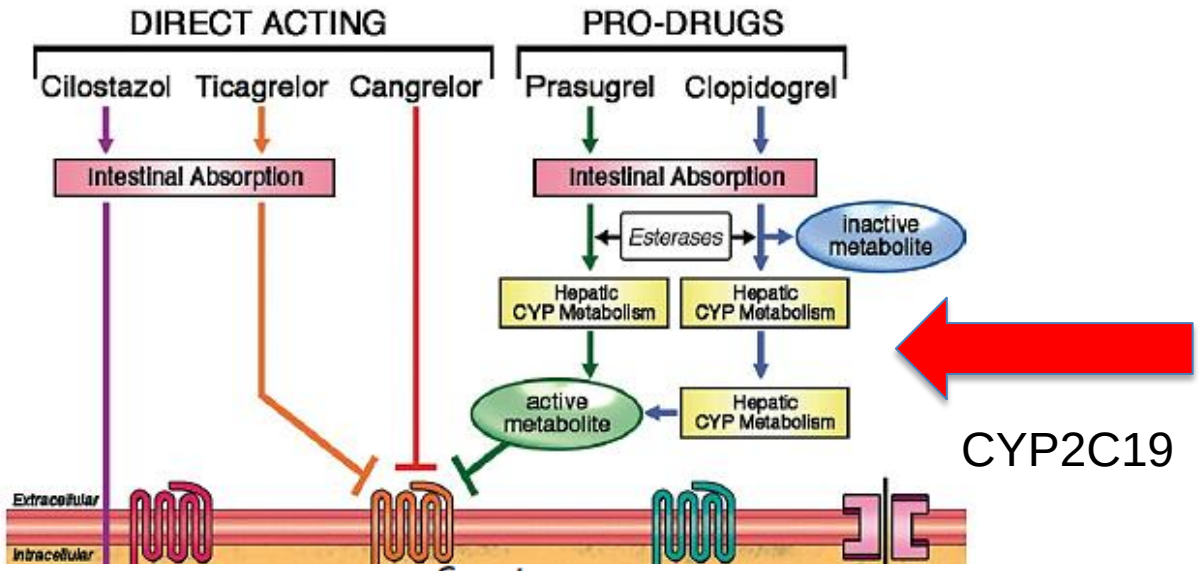
of GIANT Study investigators

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



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)

Platelet activation → Stabilization of Platelet Aggregation

CYP2C19 & post ACS events

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

Jean-Sébastien Hulot, MD, PhD*; Jean-Philippe Collet, MD, PhD*; Guillaume Cayla, MD, PhD; Johanne Silvain, MD, PhD; Frédérick Allanic, BSc; Anne Bellemain-Appaix, MD; Stuart A. Scott, PhD; Gilles Montalescot, MD, PhD

(*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

Guillaume Cayla, MD, PhD
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JAMA. 2011;306(16):1765-1774

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

Dimitrios Alexopoulos, MD,* Gerasimos Dimitropoulos, MD,* Periklis Davlouros, MD,*
Ioanna Xanthopoulou, MD,* George Kassimis, MD,* Eleana F. Stavrou, PHD,†
George Hahalis, MD,* Aglaia Athanassiadou, PHD†

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

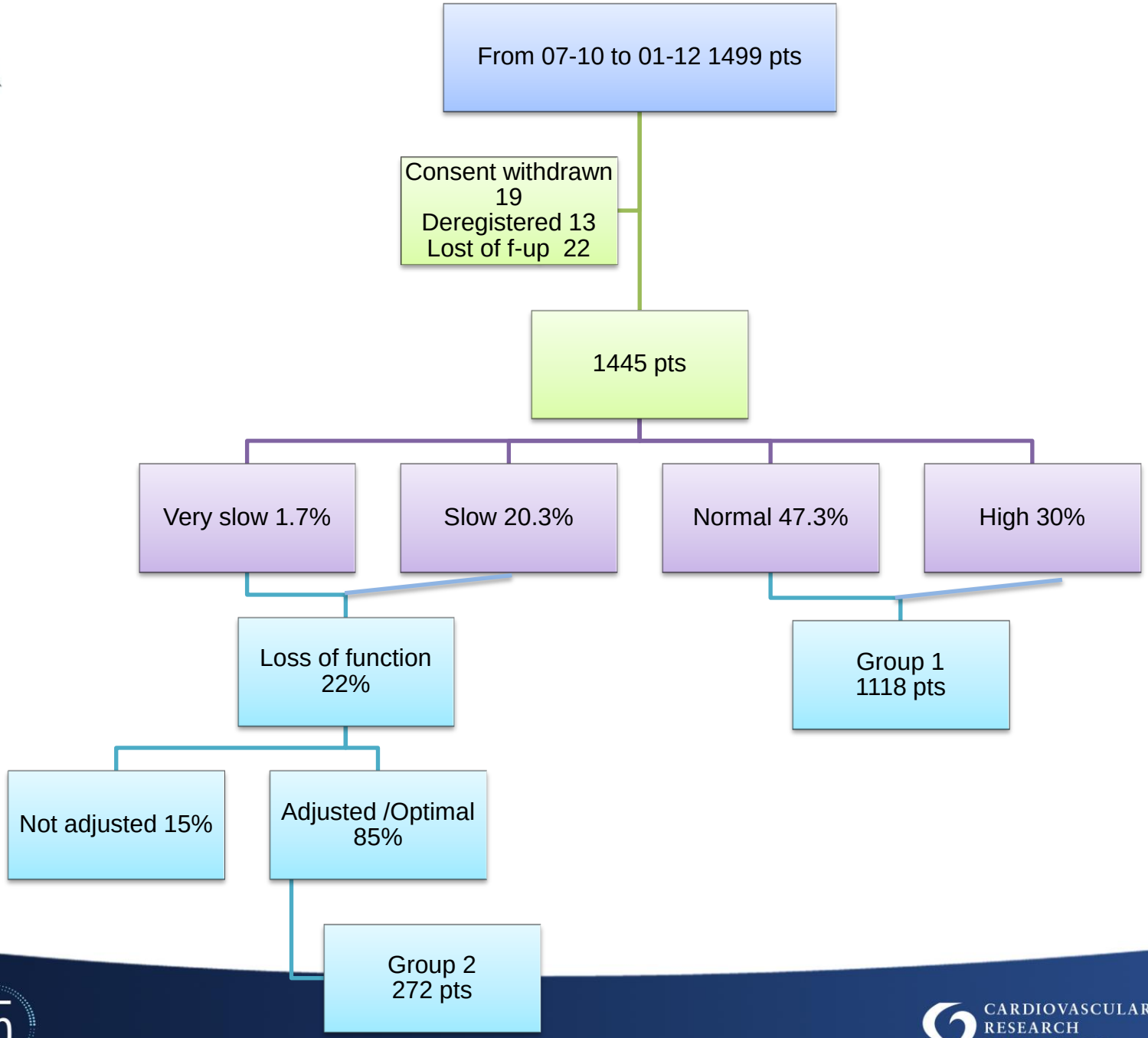
- Stent choice at the discretion of the operator

53 centers enrolled 1499 pts

Dr Khalifé	Hôpital Bon Secours / Metz	120
Dr Schmutz	CHU Caremeau / Nîmes	111
Dr Funck	CH René Dubos / Pontoise	97
Dr Berthier	CH Sud Francilien / Corbeil-Essonnes	75
Pr Piot	CH Arnaud de Villeneuve / Montpellier	69
Dr Hannebicque	CH Schaffner / Lens	57
Pr Montalescot	APHP La Pitié Salpetrière / Paris	56
Dr Lognone	CHU Côte de Nacre / Caen	52
Dr De Poli	CH Haguenau	50
Dr Chevalier	ICPS / Massy	47
Dr Schneeberger	Hôpital Albert Schweitzer / Colmar	47
Dr Delarche	CH Mitterrand / Pau	47
Dr Faure	CH Bastia	46
Dr Aelion	APHP Cochin / Paris	41
Dr Godin	CH Charles Nicolle / Rouen	38
Pr Gilard	CHU La Cavale Blanche / Brest	34
Dr Ritz	St Joseph St Luc / Lyon	32
Dr Barraud	Clinique des Dômes / Clermont-Ferrand	31
Dr Barnay	CH Duffaut / Avignon	30
Dr Nait Saidi	Hôpital Front Pré / Toulon	29
Dr Le Dref	Centre Cardiologique / Evecquemont	26
Dr Garot	Claude Gallien / Quincy	25
Dr Rangé	Hôpital Louis Pasteur / Chartres	23
Dr Georges	Hôpital André Mignot / Le Chesnay	23
Dr Robin	Convert / Bourg en Bresse	22

53 centers enrolled 1499 pts

Pr Cottin	CHU Dijon	21
Dr Loic Belle	CH Annecy	20
Dr Souteyrand	CH Gabriel Montpied / Clermont Ferrand	20
Dr Lafont	HEGP Georges Pompidou / Paris	20
Pr Leborgne	CHU Amiens	19
Dr Dupouy	Hôpital Privé Antony	19
Dr Dupouy	Clinique les Fontaines / Melun	17
Dr Shayne	Clinique du Diaconat / Mulhouse	15
Dr Chapon	CH Valence	13
Dr Boureux	CH Saint-Jean / Perpignan	12
Dr Faure	CH Brive la Gaillarde	11
Dr Benamer	Hôpital Européen La Roseraie / Aubervilliers	10
Pr Furber	CHU Angers	9
Dr Ormezzano	CHU Grenoble	9
Dr Bayet	Clinique Rhône Durance / Avignon	8
Dr Karrillon	CH Simone Veil / Eaubonne	8
Dr Luc Maillard	Clinique Axium / Aix en Provence	6
Dr Grentzinger	CH Belfort	6
Dr Avran	Clinique Générale Marignane	6
Dr Koning	Clinique St Hilaire / Rouen	5
Dr Dumant	CHI / Villeneuve St Georges	4
Dr Lamit	CH Fréjus	3
Dr Dauphin	CH Croix Rousse / Lyon	3
Dr Drogoul	Institut Arnault Tzanck / St Laurent du Var	2
Dr Cuisset	La Timone / Marseille	2
Dr Wittenberg	Hôpital Privé Beauregard / Marseille	1
Dr Laury	CH Rodez	1
Dr Robert	Clairval / Marseille	1



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

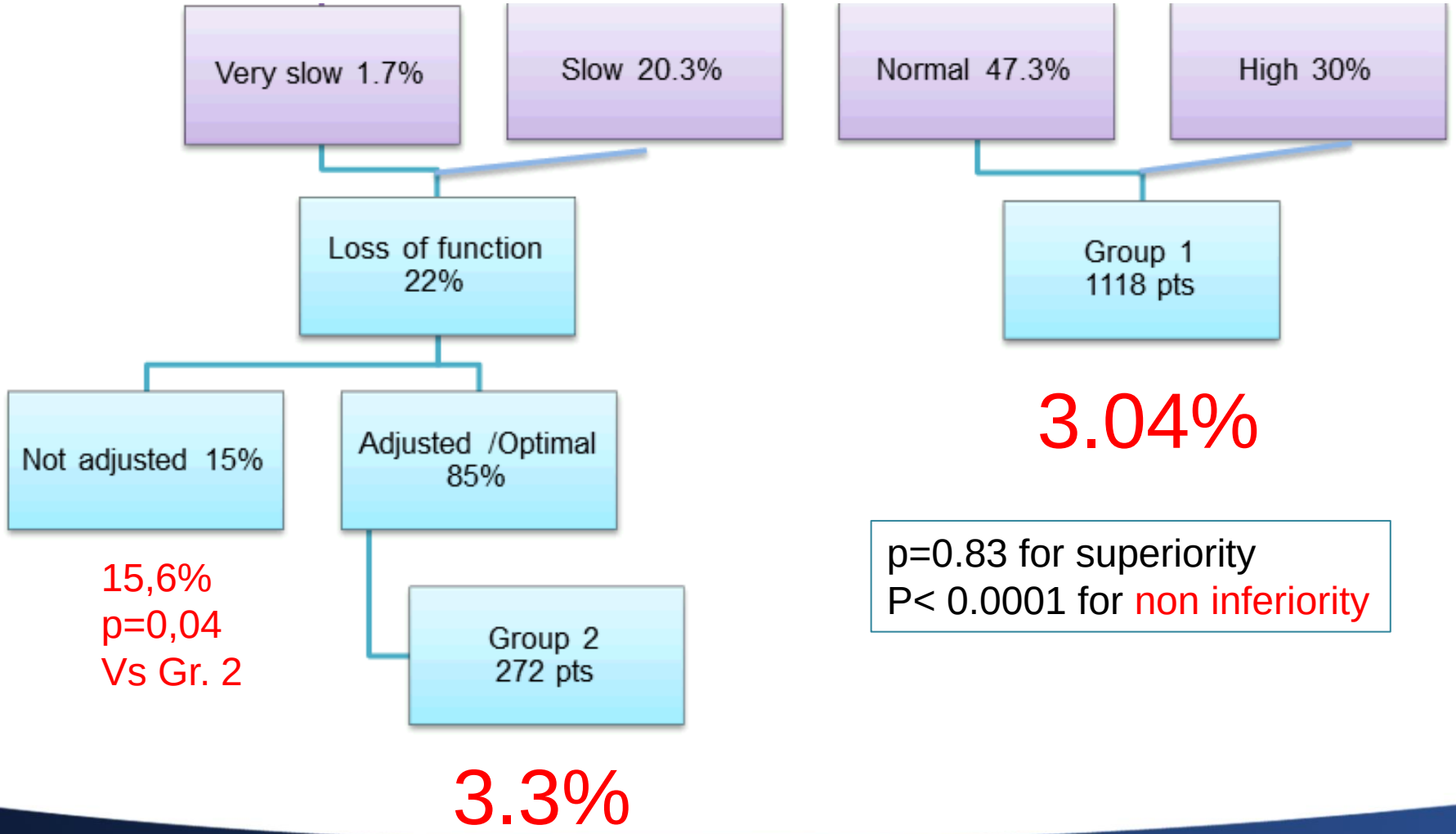
Study patients

	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

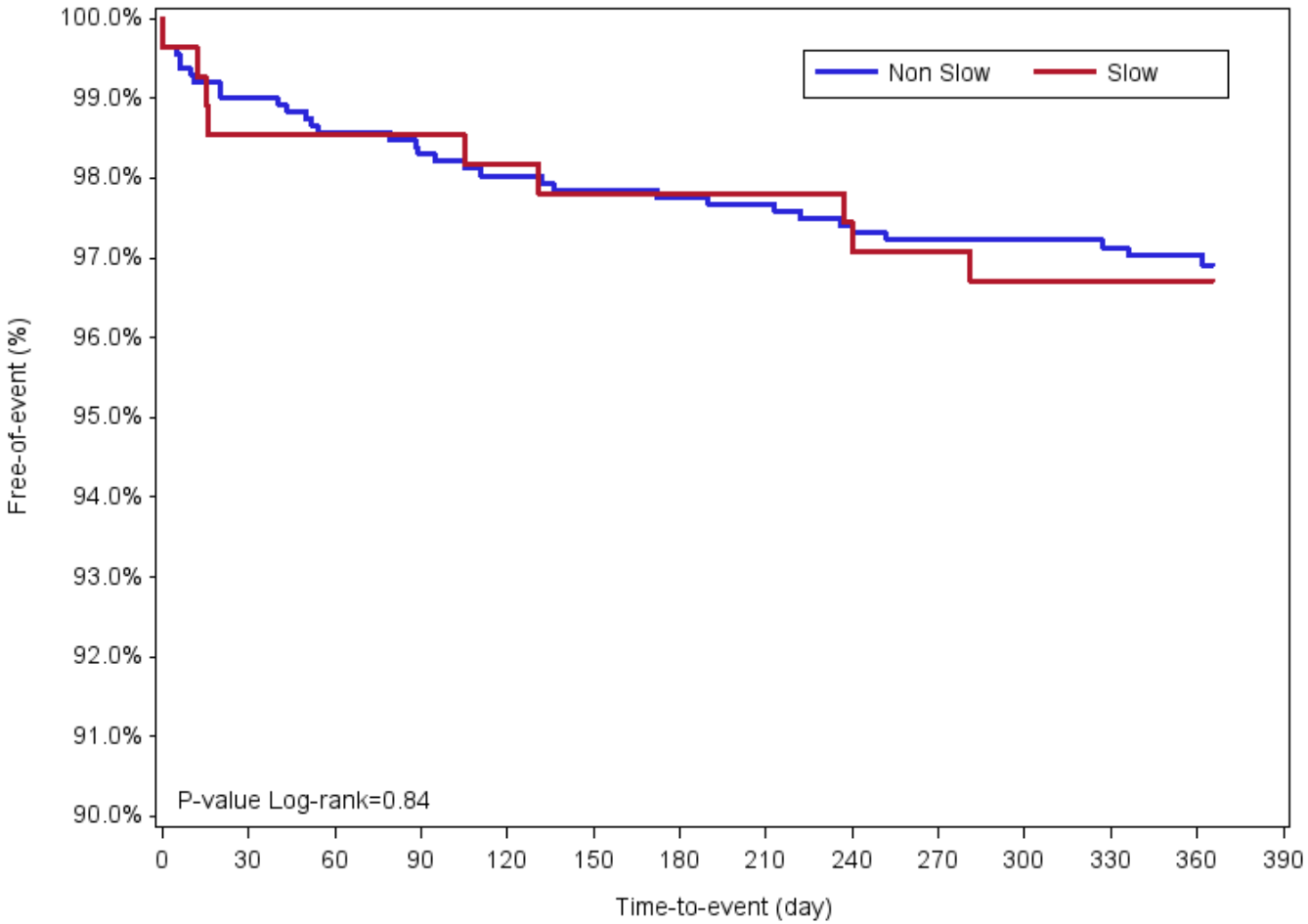
	Group 1	Group 2	p
Before Genotyping			
Clopidogrel 75 mg	35,6%	34,7%	NS
Clopidogrel 150 mg	10%	9,1%	NS
Prasugrel 10 mg	53,3%	55,5%	NS
After Genotyping			
Clopidogrel 75 mg	44,5%	0%	<0,001
Clopidogrel 150 mg	8,9%	16,8%	<0,05
Prasugrel 10 mg	46,1%	83,1%	<0,001

Death + MI + Stent thrombosis @ 1 year



p=0.83 for superiority
P< 0.0001 for non inferiority

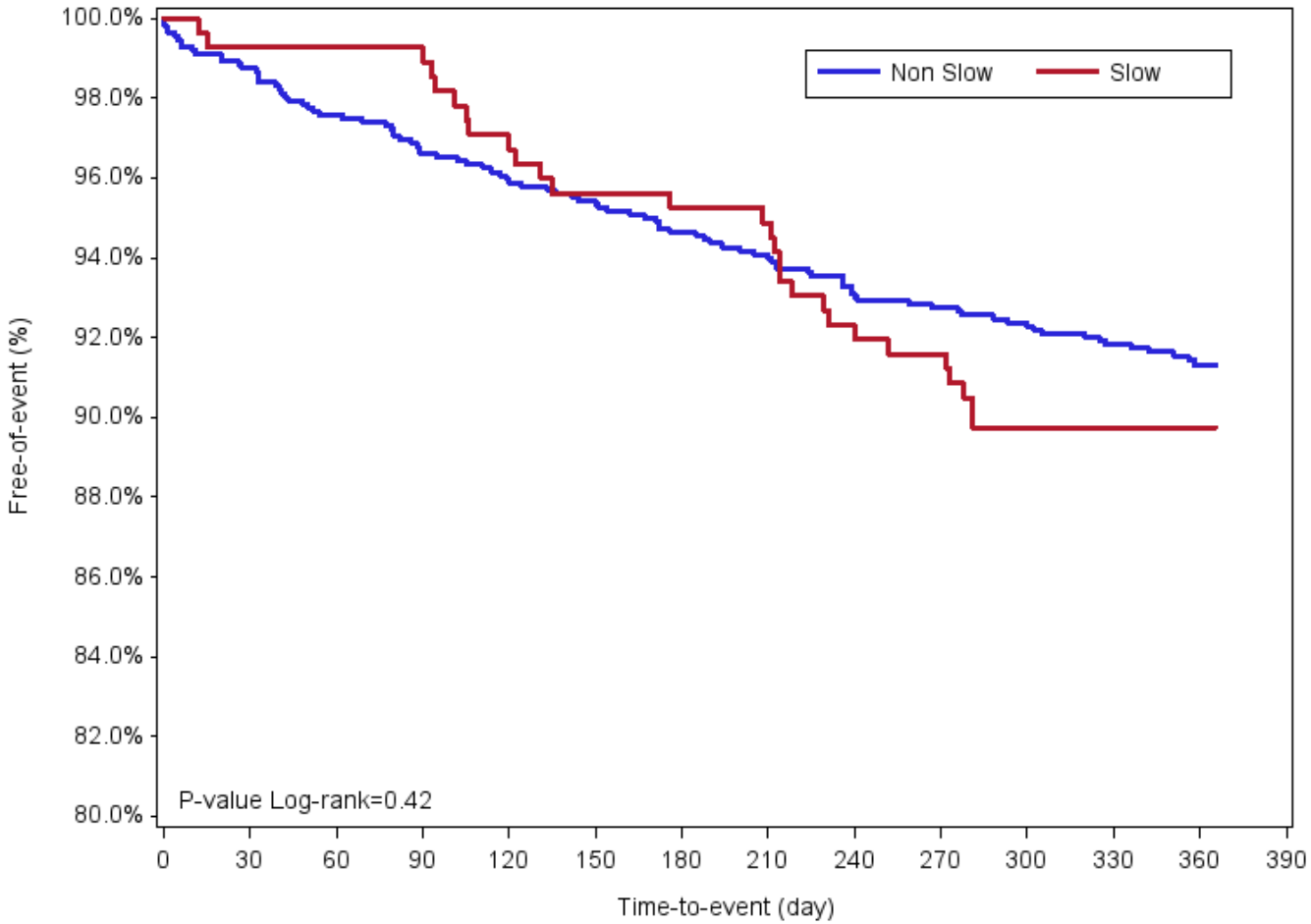
Death + Myocardial infarction + Stent thrombosis



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

MACCE


Non Slow
Slow
100.0%
98.0%
96.0%
94.0%
92.0%
90.0%
88.0%
86.0%
84.0%
82.0%
80.0%
Free-of-event (%)
P-value Log-rank=0.42
0
30
60
90
120
150
180
210
240
270
300
330
360
390
Time-to-event (day)

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.