CYP2C19-Clopidogrel

Development of these slides was supported by funding from the IGNITE Network.
When using or adapting any of these slides as part of a presentation, please include the acknowledgement statement provided on the next slide.

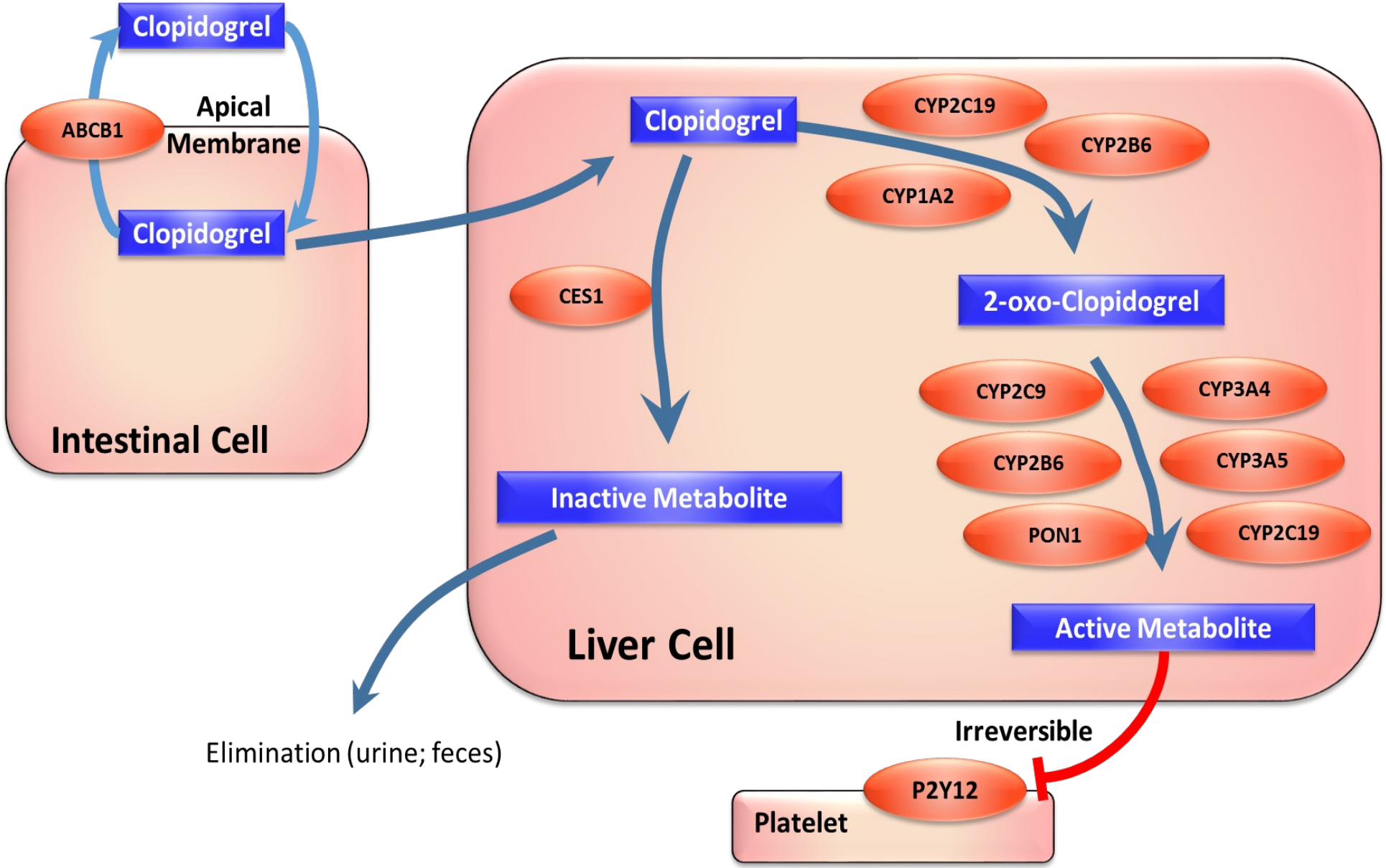
These slides have been adapted from a presentation originally prepared by
Larisa H. Cavallari, PharmD
University of Florida Health Personalized Medicine Program

Acknowledgements

This work was supported by grants from the National Institutes of Health (U01 HG007269, U01 HG007253, U01 HG007762, U01 HG007282, U01 HG007775, U01 HG007278, and by the NIH IGNITE Network (https://ignite-genomics.org/))

Clopidogrel use after Percutaneous Coronary Intervention (PCI)

- Clopidogrel plus aspirin
  - Shown to reduce morbidity and mortality in patients with an ACS who undergo coronary revascularization
  - Reduce the risk for stent thrombosis after PCI
- Significant inter-patient variability in response to clopidogrel



Clopidogrel Metabolism

Sangkuhl K et al. "Clopidogrel pathway" *Pharmacogenet Genomics* (2010). Copyright to PharmGKB.

CYP2C19 Alleles

Allele	SNP	CYP2C19 Function
**1*	N/A	Normal function
**2*	681G>A	No function
**3*	636G>A	No function
**17*	-808C>T	Increased function

CYP2C19 Phenotypes Prevalence

Genotype	Phenotype
*1/*1	Normal Metabolizer (NM)
*1/*2, *1/*3	Intermediate Metabolizer (IM)
*2/*2, *2/*3	Poor Metabolizer (PM)
*1/*17	Rapid Metabolizer (RM)
*17/*17	Ultra-rapid Metabolizer (UM)

Race	PMs	IMs	RM/UM
Whites	2%	25%	40%
Blacks	4%	30%	45%
Asian	14%	50%	<5%

CYP2C19 and Clopidogrel Response

- Loss of function genotype associated with:
  - Less active metabolite
  - Decreased antiplatelet effects
- Meta-analysis (9 trials, 9685 clopidogrel-treated patients) showed increased risk or MACE and stent thrombosis with PM and IM phenotypes

Outcome	Risk Ratio (95% CI)	
	IM vs NM	PM vs NM
MACE*	1.5 (1.1-2.1)	1.8 (1.2-2.5)
Stent thrombosis	2.7 (1.7-4.2)	4.0 (1.8-9.0)

*MACE = Major adverse CV events (CV death, MI, or stroke), NM = Normal metabolizer, IM = Intermediate metabolizer, PM = Poor metabolizer

Mega et al. *N Engl Med* 2009;360:354-62
Mega et al. *JAMA* 2010;304:1821-30.

Other Meta-Analyses

	No. studies	No. patients	HR or RR (95% CI) for LOF carriers vs NMs/RMs/UMs	
			CV events	Stent thrombosis
Jang et al.	16	20,785	1.5 (1.1-2.1)	1.8 (1.2-2.5)
Zabalza et al.	11	16,360	1.2 (1.0-1.6)	2.2 (1.5-3.3)
Holmes et al.	22	26,251	1.2 (1.1-1.3)	1.8 (1.5-2.0)
Sorich et al.	17	26,059	No PCI: 1.0 (0.8-1.2) PCI: 1.2 (1.1-1.3)	1.7 (1.5-2.1)

UM = Ultrarapid metabolizer, NM = Normal metabolizer, IM = Intermediate metabolizer, PM = Poor metabolizer, LOF = loss-of-function

Jang JS, et al. *Am J Cardiol* 2012;110:502-8; Zabalza M, et al. *Heart* 2012;98:100-8;
Holmes MV, et al. *JAMA* 2011;306:2704-14; Sorich MJ, et al. *Circ Cardiovasc Genet* 2014;7:895-903.

FDA-Approved Clopidogrel Labeling

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE *CYP2C19* GENE

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

Plavix package insert, revised September 2016

ACCF/AHA/SCAI Guidelines for PCI

6.1.2. Clopidogrel Genetic Testing: Recommendations

Class IIb: Usefulness/efficacy is less well established

1. Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with Clopidogrel. (Level of Evidence: C)
2. When a patient predisposed to inadequate platelet inhibition with Clopidogrel is identified by genetic testing, treatment with an alternate $P2Y_{12}$ inhibitor (e.g. prasugrel or ticagrelor) might be considered. (Level of Evidence: C)

Class III: NO BENEFIT

1. The routine clinical use of genetic testing to screen patients treated with Clopidogrel who are undergoing PCI is not recommended. (Level of Evidence: C)

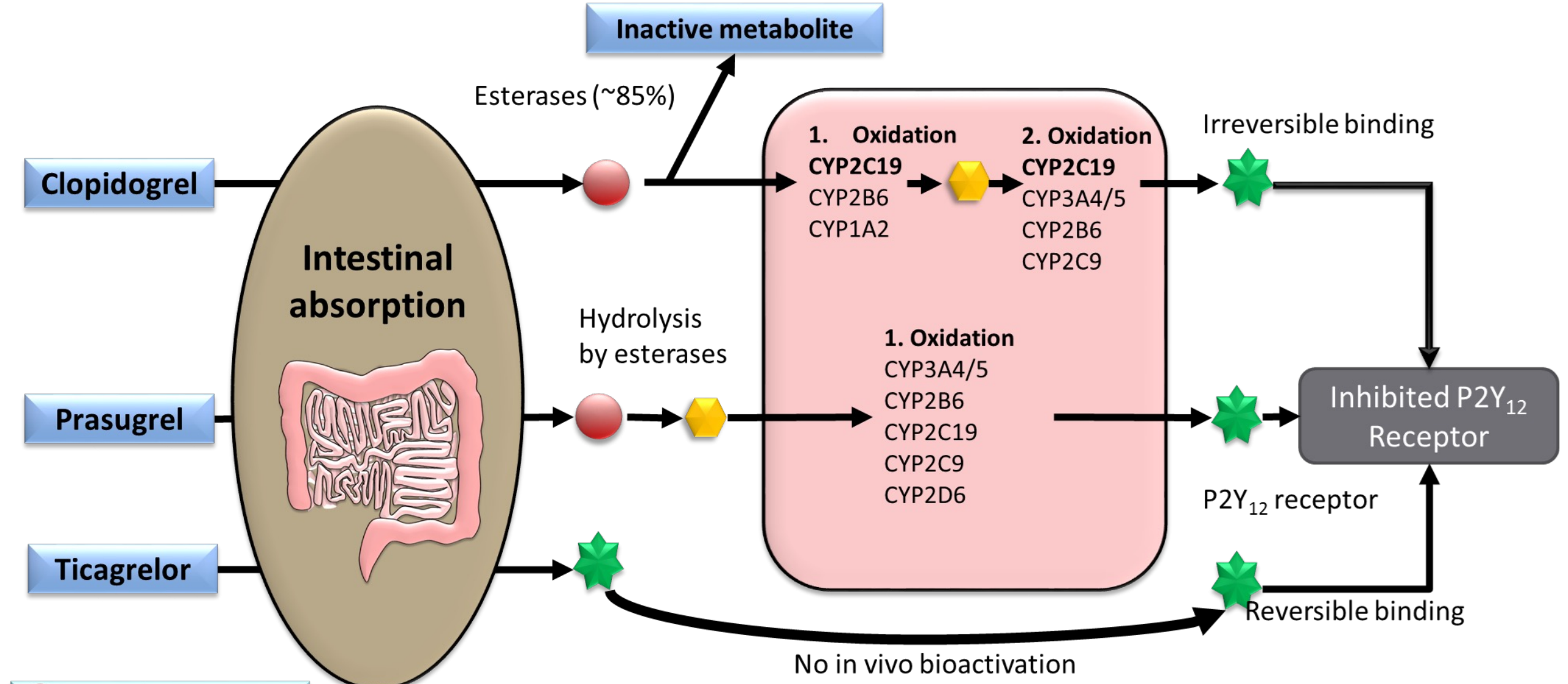
Levine GN, *et al. Circulation* 2011;124:e574-651.

TAILOR-PCI Trial

TAILOR-PCI: Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention

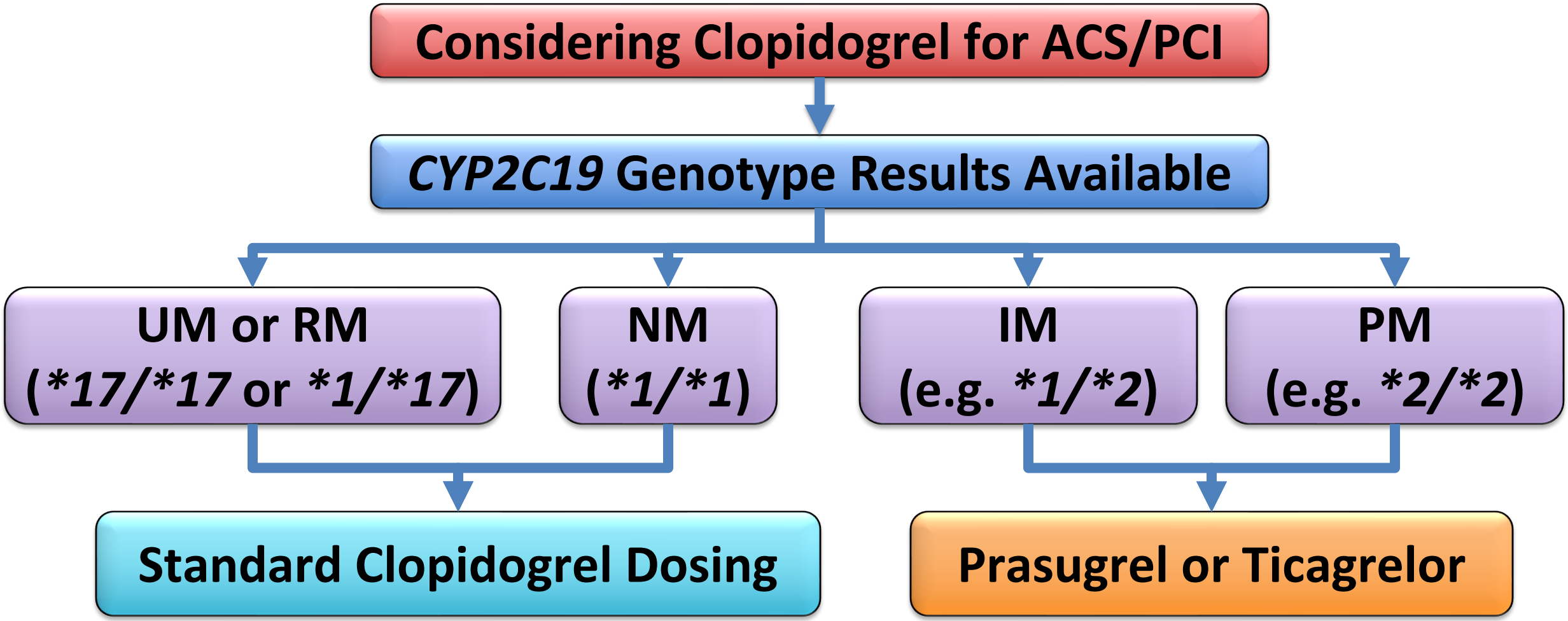
Est. Enrollment	5,270
Inclusion Criteria	PCI
Arms	Genotype-guided strategy (Ticagrelor for PMs and IMs) versus clopidogrel
Outcomes	MACE at 1 year
Est. Completion	3/2020
ClinicalTrials.gov ID	NCT01742117

Alternatives to Clopidogrel



Cavallari LH, et al. *Pharmacogenomics Pers Med* 2011;4:123-36

CPIC Guidelines



CPIC, Clinical Pharmacogenetics Implementation Consortium
Scott SA et al. *Clin Pharmacol Ther* 2013;94:317-23.

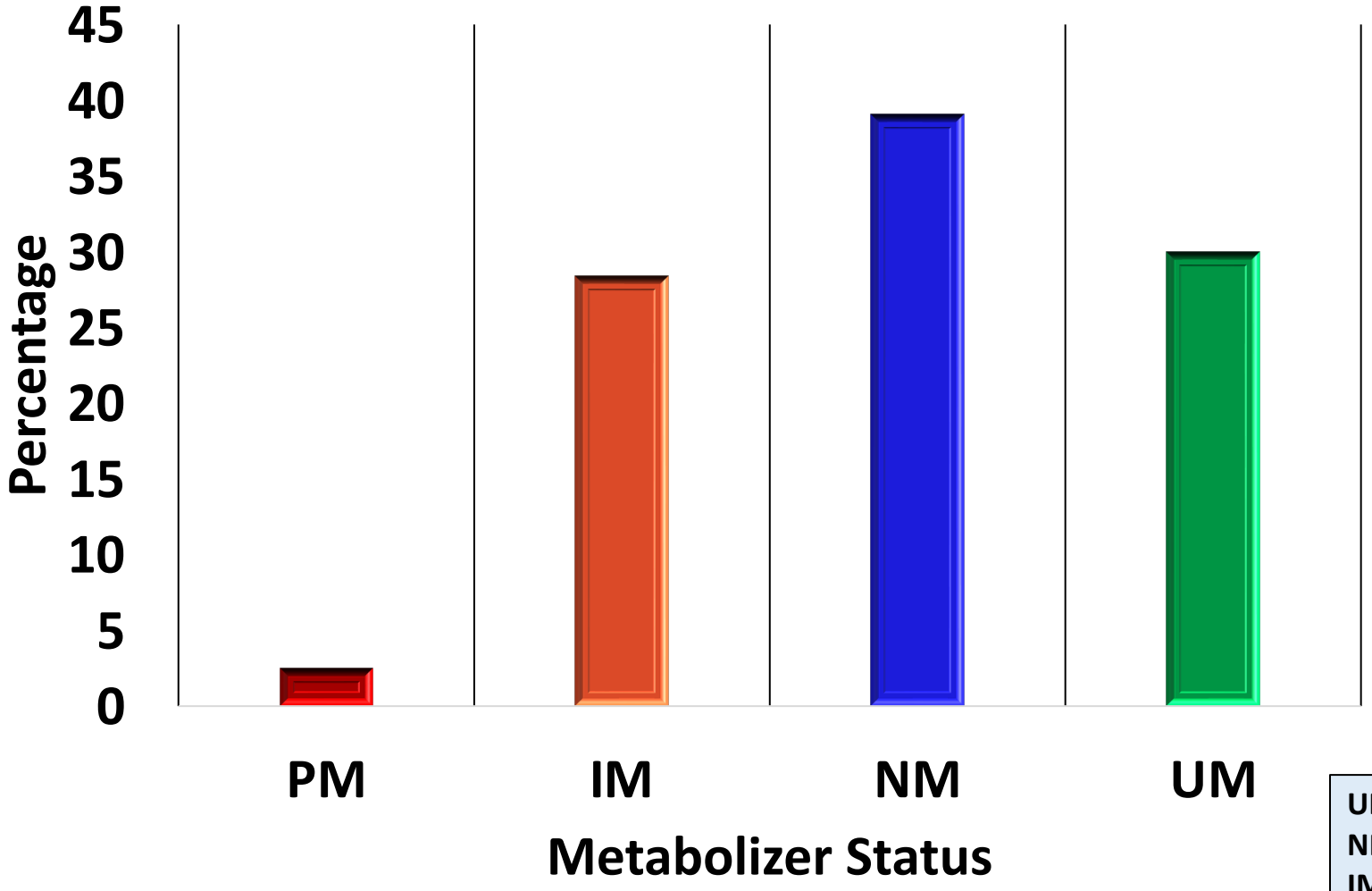
UF Cohort: *CYP2C19*-Clopidogrel Outcomes

- Reviewed EHR for patients who underwent PCI and genotyping
  - June 2012 – June 2014
  - Collected data through 6 months post PCI
- Compared major adverse cardiovascular events (MACE, composite of CV death, myocardial infarction, stroke, or stent thrombosis) between:
  - LOF allele carriers treated with alternative APT vs. Clopidogrel
  - LOF allele carriers treated with alternative APT vs. non-LOF carriers
- Hazard rates compared using Cox regression analysis with propensity score adjustment based on clinical variables

APT = antiplatelet therapy, EHR = Electronic health records, LOF = loss-of-function, PCI = Percutaneous coronary intervention

Cavallari LH, et al. *Circulation* 2015;132:Suppl 3 A11802.

UF Cohort: Phenotype Distribution



N= 408 patients

Actionable genotypes:

PM: 10 (2.5%)

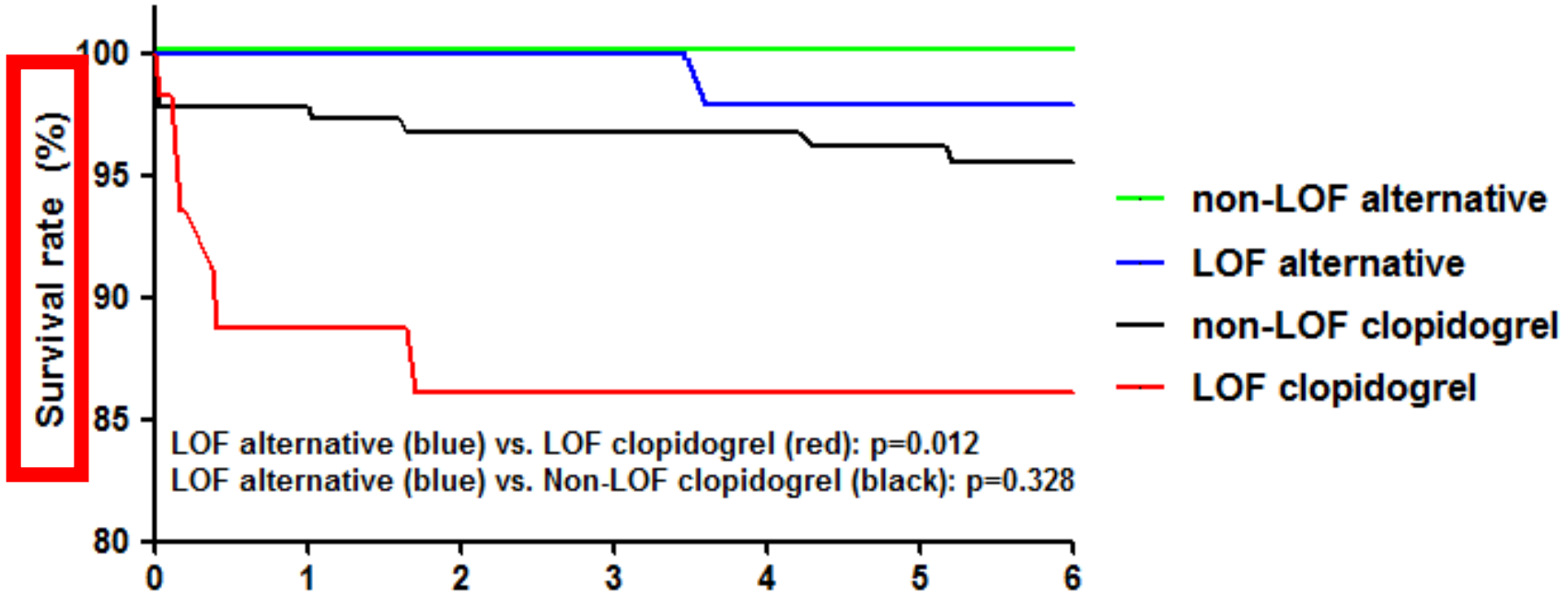
IM: 116 (28.4%)

Total: 126 (30.9%)

UM = Ultrarapid metabolizer
NM = Normal metabolizer
IM = Intermediate metabolizer
PM = Poor metabolizer

Cavallari LH, et al. *Circulation* 2015;132:Suppl 3 A11802.

UF Cohort: Kaplan-Meier Survival Curve



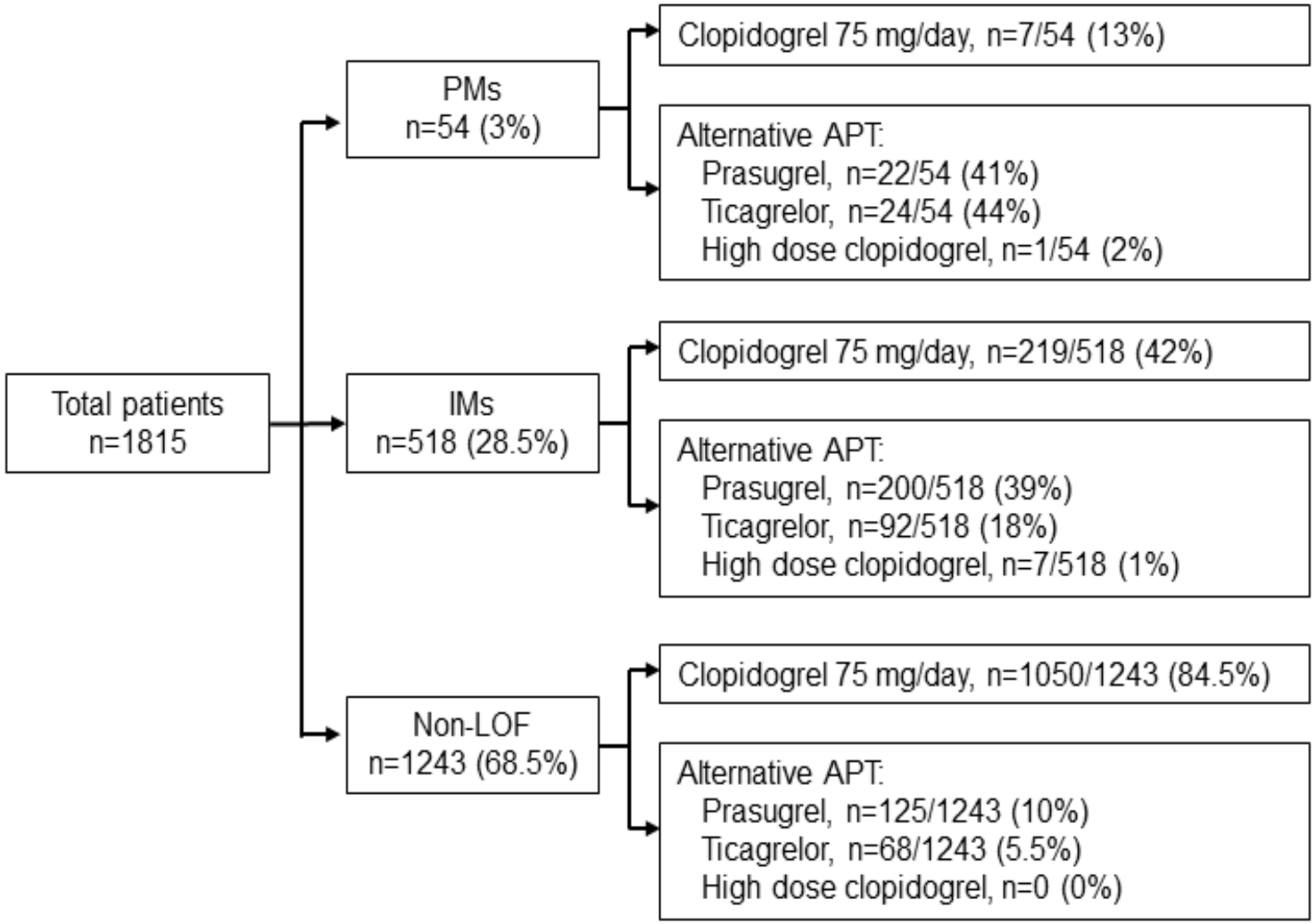
Number at risk							
LOF clopidogrel	58	37	32	29	26	24	22
Non-LOF clopidogrel	272	205	185	175	162	148	139
LOF alternative	68	59	54	51	47	45	40
Non-LOF alternative	10	8	6	6	5	5	5
Total	408	309	277	261	240	222	206

Log-rank (Mantel-Cox) p-values shown

Survival rate = event free survival with events defined as cardiovascular death, myocardial infarction, stroke, or stent thrombosis
LOF = Loss-of-function (intermediate or poor metabolizers)

Cavallari LH, et al. *Circulation* 2015;132:Suppl 3 A11802.

IGNITE: Multisite investigation of outcomes with implementation of *CYP2C19* genotype-guided antiplatelet therapy after PCI

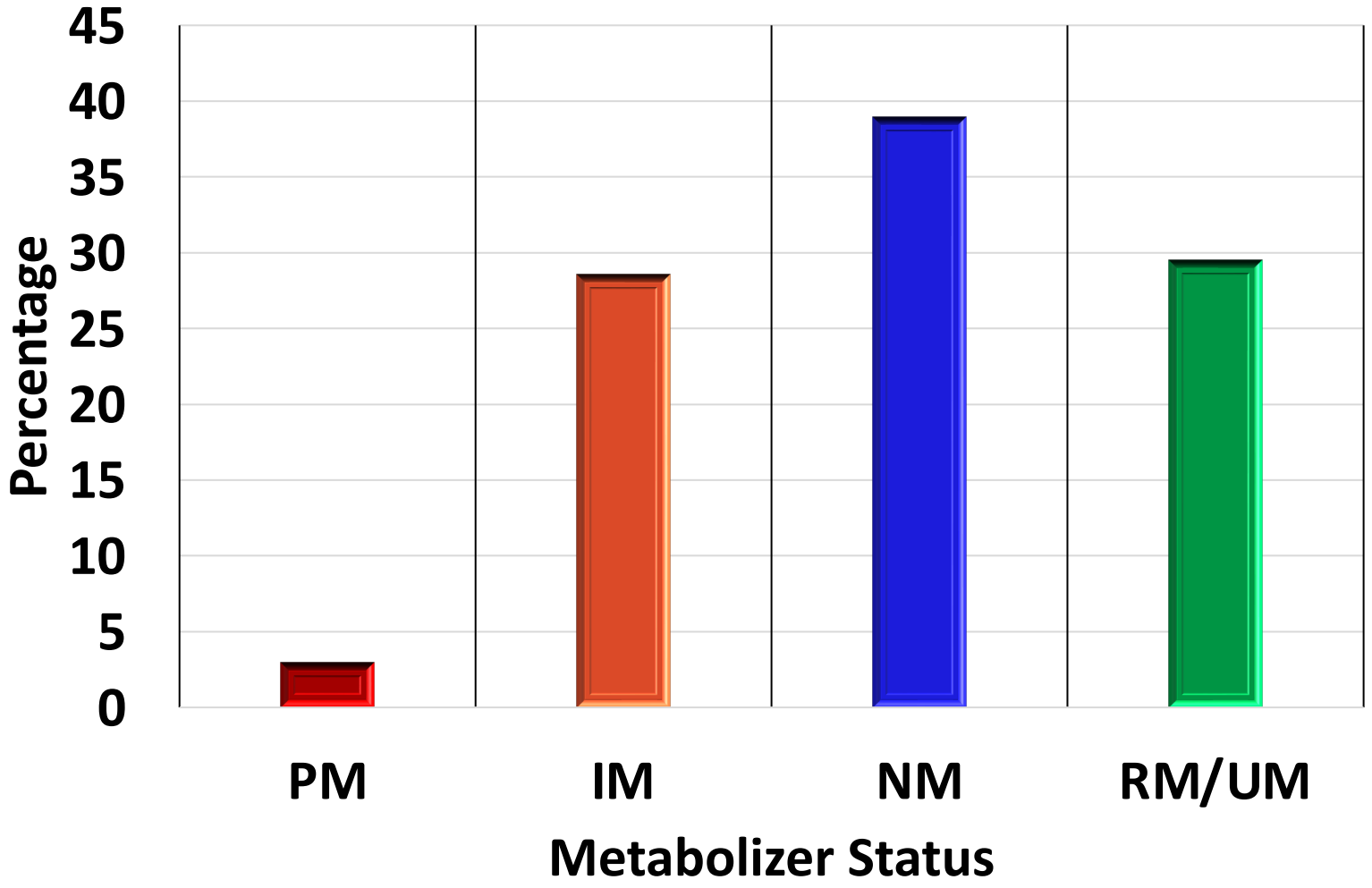


- 7 institutions
- **Of the 54 PMs, only 7 (13%) were treated with clopidogrel**
- Alternative therapy:
  - prasugrel (65%)
  - ticagrelor (34%)
  - high-dose clopidogrel (1%)

APT = antiplatelet therapy
IM = intermediate metabolizer
LOF = loss-of-function
PM = poor metabolizer

Cavallari LH, et al. *J Am Coll Cardiol Intv.* 2018;11:181-81.

IGNITE: Phenotype Distribution



N= 1,815 patients

Actionable genotypes:

PM: 54 (3.0%)

IM: 518(28.6%)

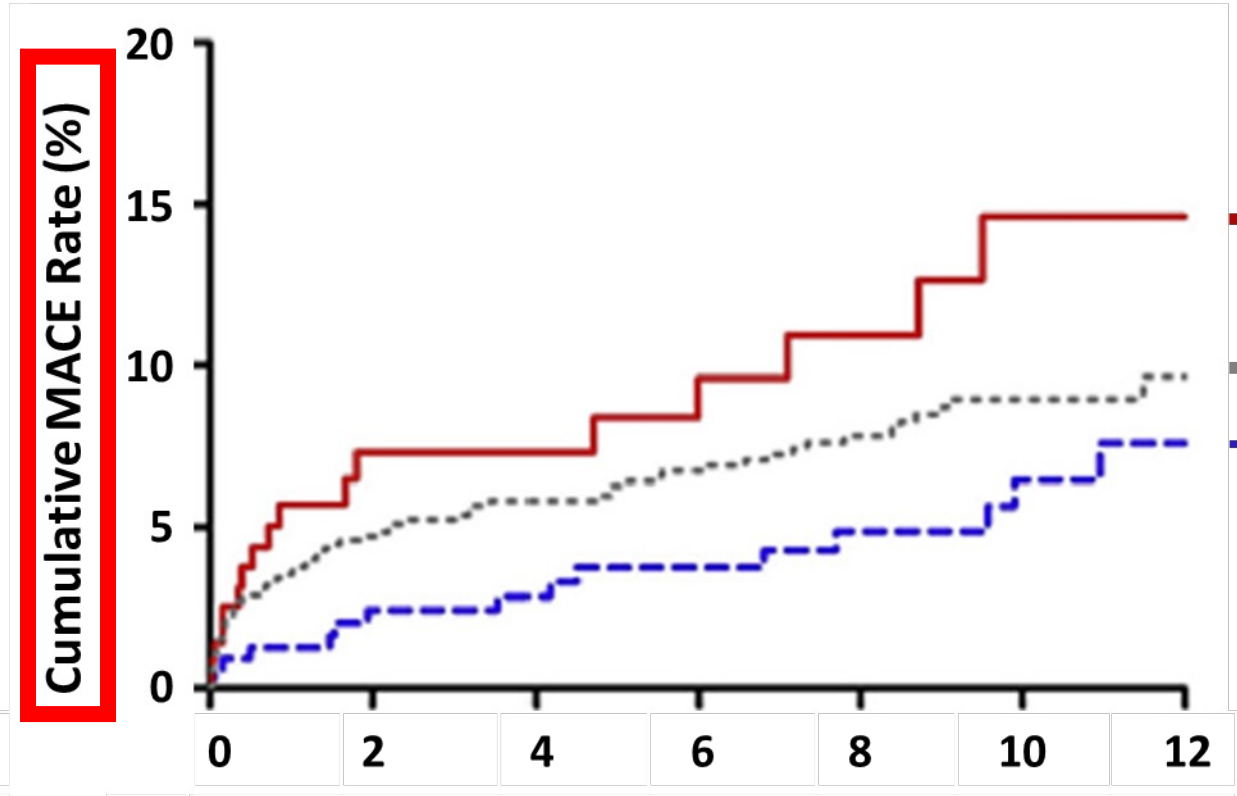
Total: 572 (31.6%)

UM = Ultrarapid metabolizer
RM = Rapid metabolizer
NM = Normal metabolizer
IM = Intermediate metabolizer
PM = Poor metabolizer

Cavallari LH, et al. *J Am Coll Cardiol Intv.* 2018;11:181-81.

IGNITE

IGNITE: Risk of Major Adverse Cardiovascular Events



LOF-Clopidogrel

Non-LOF

LOF-Alternative

Log-rank p=0.016

Log-rank p=0.15

No. at risk							
LOF-Clopidogrel	226	112	89	76	63	39	3
Non-LOF	1243	759	636	577	451	293	28
LOF-Alternative	346	245	221	195	161	112	9

LOF-Clop vs. LOF-Alt

Adjusted HR 2.26 (1.18-4.32), P=0.013

Non-LOF vs. LOF-Alt

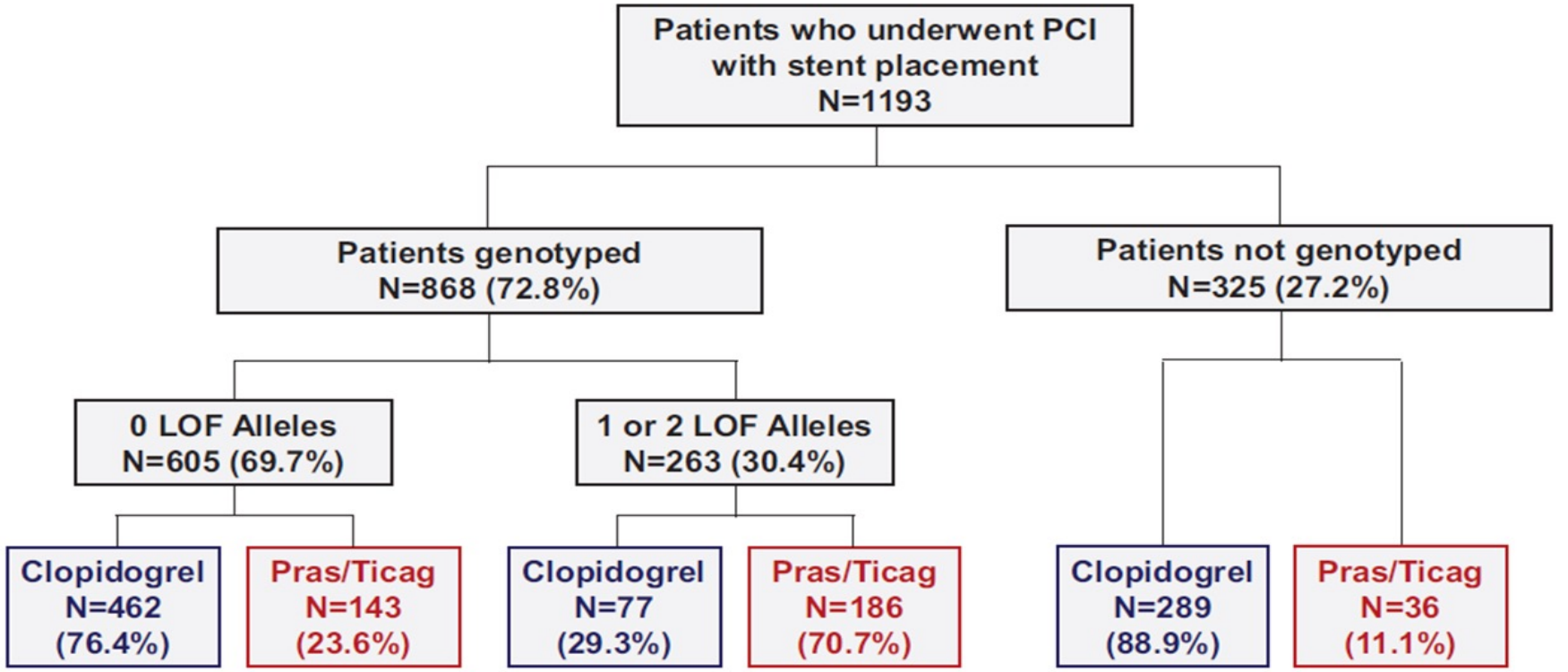
Adjusted HR 1.14 (0.69-1.88), P=0.600

LOF = Loss of function (intermediate or poor metabolizers)
Clop = Clopidogrel
Alt = Alternative antiplatelet (prasugrel or ticagrelor)
MACE = Major Adverse Cardiovascular Events (Death, MI, or ischemic stroke)

Cavallari LH, et al. *J Am Coll Cardiol Intv.* 2018;11:181-81.

IGNITE

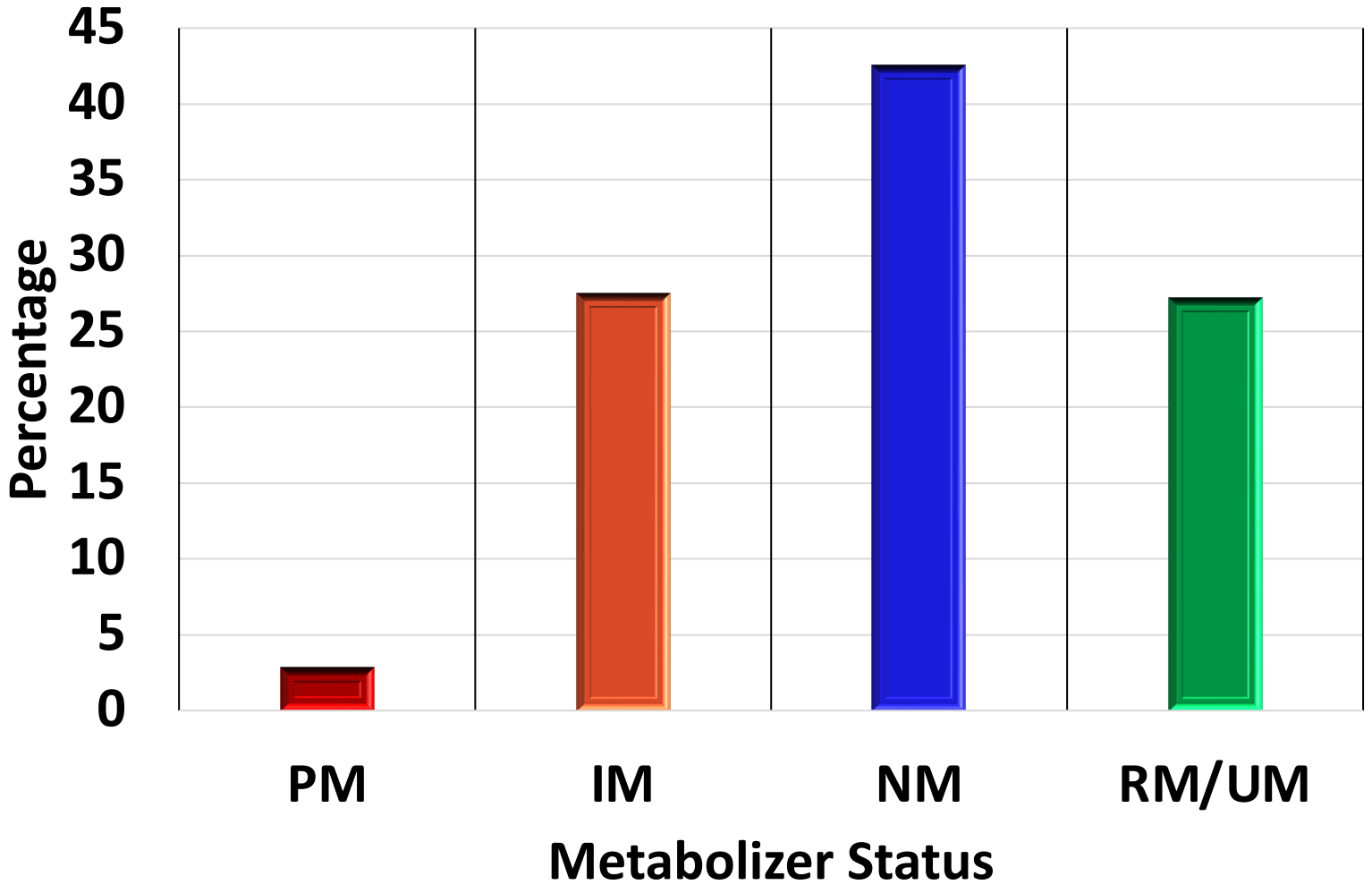
UNC Cohort: *CYP2C19*-Guided Antiplatelet Therapy after PCI



- **Single-center observational cohort study**
- Primary outcome: major adverse cardiovascular and cerebrovascular events (MACCE)
  - Death, myocardial infarction, stent thrombosis, acute coronary syndrome/unstable angina admission, ischemic cerebrovascular accident, transient ischemic attack

Lee CR, et al. *Circ Genom Precis Med.* 2018;11:e002069.

UNC Cohort: Phenotype Distribution



N= 868 patients

Actionable genotypes:

PM: 24 (2.8%)

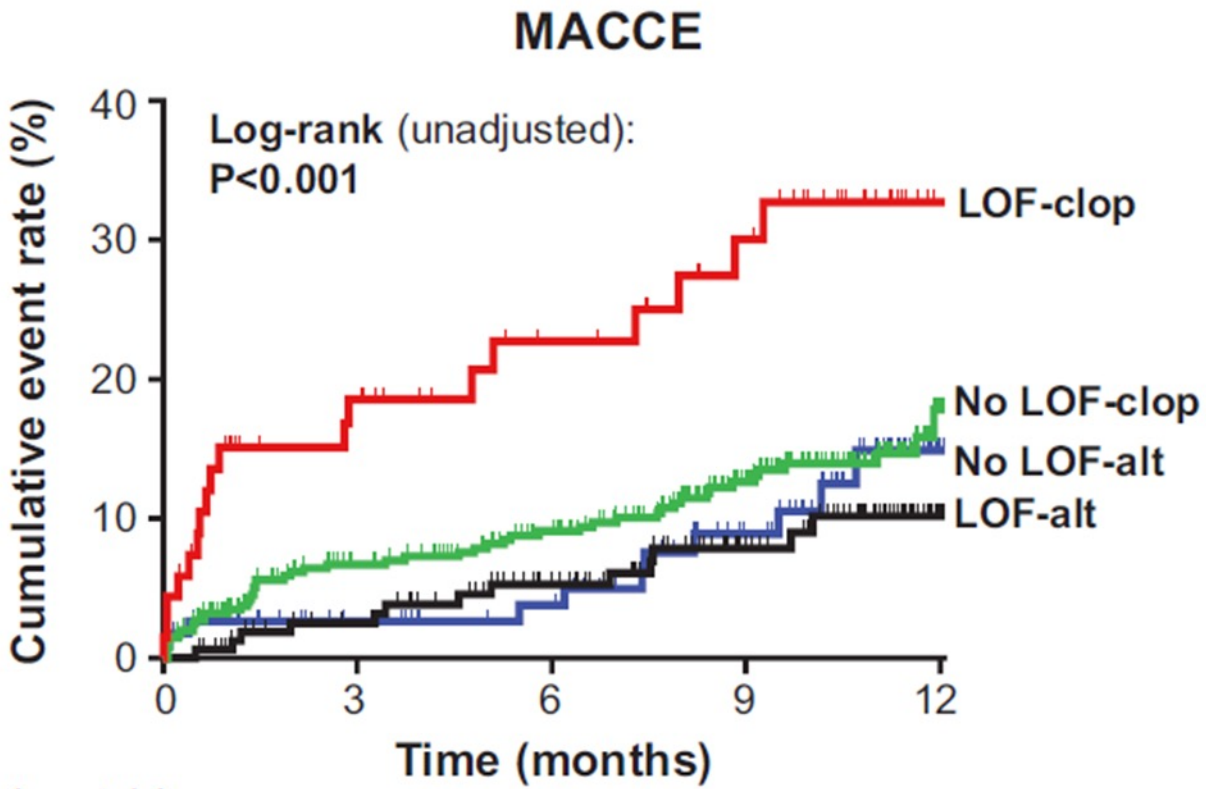
IM: 239(27.5%)

Total: 263 (30.3%)

UM = Ultrarapid metabolizer
RM = Rapid metabolizer
NM = Normal metabolizer
IM = Intermediate metabolizer
PM = Poor metabolizer

Lee CR, et al. *Circ Genom Precis Med.* 2018;11:e002069.

UNC Cohort: Risk of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)



Number at risk

LOF-clop	68	48	36	28	2
No LOF-clop	405	329	295	208	20
No LOF-alt	113	93	85	61	4
LOF-alt	165	147	123	86	10
Total	751	617	539	383	36

Group	Reference	Adjusted HR (95% CI)	P-value
LOF-clop	vs. LOF-alt	**4.65** (2.22-10.0)	**<0.001**
No LOF-clop	vs. No LOF-alt	**1.37** (0.72-2.85)	**0.347**
LOF-clop	vs. No LOF-clop	**2.71** (1.52-4.66)	**0.001**
LOF-alt	vs. No LOF-alt	**0.80** (0.35-1.86)	**0.601**

LOF = Loss of function (intermediate or poor metabolizers)
Clop = Clopidogrel
Alt = Alternative antiplatelet (prasugrel or ticagrelor)
MACCE = Major Adverse Cardiovascular and Cerebrovascular Events D(eath, MI, stent thrombosis, ACS/UA admission, ischemic cerebrovascular accident, TIA)

Lee CR, et al. *Circ Genom Precis Med.* 2018;11:e002069.

What is the role of *CYP2C19* genotyping with ticagrelor?

- PLATO Study

Design	Subjects	Intervention	Outcome	Results
• Multicenter • RCT • Double blind	18,624 Patients with ACS (61% underwent PCI)	Ticagrelor: 180mg LD followed by 90mg BID. Clopidogrel: 300-600mg LD followed by 75mg daily.	Primary: Composite death from vascular causes, MI & stroke at 12 months	Primary: 9.8% Ticagrelor 11.7% Clopidogrel patients
Ticagrelor associated with higher rate of non-CABG-related major bleeding (4.5% vs. 3.8%) and more intracranial bleeding including fatalities. (0.3%, n=26 vs. 0.2%, n=14)				

Wallentin L, et al. *Lancet* 2010;376:1320-8.

PLATO Genetic Substudy

	TICAG	CLOP	HR (95% CI)	p value
CV death, MI, or CVA event rate				
Any LOF allele	8.6%	11.2%	0.77 (0.60-0.99)	0.04
No LOF allele	8.8%	10.0%	0.86 (0.74-1.01)	0.06
Stent thrombosis event rate				
Any LOF allele	1.6%	2.3%	0.71 (0.36-1.37)	0.30
No LOF allele	1.0%	1.5%	0.62 (0.36-1.05)	0.08

CLOP = clopidogrel, CV = cardiovascular, CVA = cerebrovascular accident, LOF = Loss-of-function, MI = myocardial infarction, TICAG = ticagrelor

Wallentin L, et al. *Lancet* 2010;376:1320-8.

PLATO Genetic Substudy

	TICAG	CLOP	HR (95% CI)	p value
CV death, MI, or CVA event rate				
Any LOF allele	8.6%	11.2%	0.77 (0.60-0.99)	0.04
No LOF allele	8.8%	10.0%	0.86 (0.74-1.01)	0.06
Stent thrombosis event rate				
Any LOF allele	1.6%	2.3%	0.71 (0.36-1.37)	0.30
No LOF allele	1.0%	1.5%	0.62 (0.36-1.05)	0.08

CLOP = clopidogrel, CV = cardiovascular, CVA = cerebrovascular accident, LOF = Loss-of-function, MI = myocardial infarction, TICAG = ticagrelor

In the clopidogrel group, higher rate of events with LOF allele at 30 days (HR 1.37, 95% CI 1.04-1.82)

Wallentin L, et al. *Lancet* 2010;376:1320-8.

PLATO Genetic Substudy

	TICAG	CLOP	HR (95% CI)	p value
CV death, MI, or CVA event rate				
Any LOF allele	8.6%	11.2%	0.77 (0.60-0.99)	0.04
No LOF allele	8.8%	10.0%	0.86 (0.74-1.01)	0.06
Stent thrombosis event rate				
Any LOF allele	1.6%	2.3%	0.71 (0.36-1.37)	0.30
No LOF allele	1.0%	1.5%	0.62 (0.36-1.05)	0.08

CLOP = clopidogrel, CV = cardiovascular, CVA = cerebrovascular accident, LOF = Loss-of-function, MI = myocardial infarction, TICAG = ticagrelor

In the clopidogrel group, higher rate of events with LOF allele at 30 days versus the ticagrelor group (HR 0.77, 95% CI 0.60-0.99)

Wallentin L, et al. *Lancet* 2010;376:1320-8.

PLATO Genetic Substudy

	TICAG	CLOP	HR (95% CI)	p value
CV death, MI, or CVA event rate				
Any LOF allele	8.6%	11.2%	0.77 (0.60-0.99)	0.04
No LOF allele	8.8%	10.0%	0.86 (0.74-1.01)	0.06
Stent thrombosis event rate				
Any LOF allele	1.6%	2.3%	0.71 (0.36-1.37)	0.30
No LOF allele	1.0%	1.5%	0.62 (0.36-1.05)	0.08

CLOP = clopidogrel, CV = cardiovascular, CVA = cerebrovascular accident, LOF = Loss-of-function, MI = myocardial infarction, TICAG = ticagrelor

The event rates were not significantly different between ticagrelor and clopidogrel group in the absence of the LOF allele

Wallentin L, et al. *Lancet* 2010;376:1320-8.

Prasugrel vs Clopidogrel by Genotype: Genetic Substudy of TRITON TIMI-38

Event (and group)	Prasugrel [% (95% CI)]	Clopidogrel [% (95% CI)]	Relative risk* (95% CI)
CV death, non-fatal MI, or non-fatal stroke			
CYP2C19 NM	9.6 (8.3 – 10.8)	9.8 (8.3 – 11.3)	0.98 (0.80 – 1.20)
CYP2C19 RM	8.5 (6.2 – 11.4)	15.0 (11.6 – 18.8)	0.57 (0.39 – 0.83)
CV death			
CYP2C19 NM	1.9 (1.2 – 2.5)	0.9 (0.3 – 1.7)	2.07 (0.96 – 5.66)
CYP2C19 RM	1.6 (0.6 – 3.2)	4.2 (2.2 – 6.1)	0.36 (0.13 – 0.96)
Non-fatal MI			
CYP2C19 NM	7.4 (6.4 – 8.5)	8.3 (7.0 – 9.6)	0.89 (0.72 – 1.11)
CYP2C19 RM	6.2 (4.2 – 8.5)	11.6 (8.7 – 14.8)	0.53 (0.34 – 0.81)
Major or Minor Bleeding			
CYP2C19 NM	4.7 (3.7 – 5.7)	3.4 (2.6 – 4.2)	1.38 (1.00 – 1.93)
CYP2C19 RM	5.5 (3.6 – 8.1)	3.5 (2.0 – 5.5)	1.60 (0.8 – 3.1)

Estimates in outcome risks for CYP2C19 **normal metabolizers (NM)** and **CYP2C19 reduced metabolizer (RM)** outcome risks over 15 months for individuals with unstable angina or non-ST segment elevation myocardial infarction scheduled for percutaneous coronary intervention and treated with either prasugrel or clopidogrel.

CI: Confidence interval, CV: Cardiovascular, MI: Myocardial infarction. *Risk with prasugrel as a fraction of the risk with Clopidogrel.

Sorich et al. *J Thromb Haemost* 2010;8:1678-84.

Prasugrel vs Clopidogrel by Genotype: Genetic Substudy of TRITON TIMI-38

Event (and group)	Prasugrel [% (95% CI)]	Clopidogrel [% (95% CI)]	Relative risk* (95% CI)
CV death, non-fatal MI, or non-fatal stroke			
CYP2C19 NM	9.6 (8.3 – 10.8)	9.8 (8.3 – 11.3)	0.98 (0.80 – 1.20)
CYP2C19 RM	8.5 (6.2 – 11.4)	15.0 (11.6 – 18.8)	0.57 (0.39 – 0.83)
CV death			
CYP2C19 NM	1.9 (1.2 – 2.5)	0.9 (0.3 – 1.7)	2.07 (0.96 – 5.66)
CYP2C19 RM	1.6 (0.6 – 3.2)	4.2 (2.2 – 6.1)	0.36 (0.13 – 0.96)
Non-fatal MI			
CYP2C19 NM	7.4 (6.4 – 8.5)	8.3 (7.0 – 9.6)	0.89 (0.72 – 1.11)
CYP2C19 RM	6.2 (4.2 – 8.5)	11.6 (8.7 – 14.8)	0.53 (0.34 – 0.81)
Major or Minor Bleeding			
CYP2C19 NM	4.7 (3.7 – 5.7)	3.4 (2.6 – 4.2)	1.38 (1.00 – 1.93)
CYP2C19 RM	5.5 (3.6 – 8.1)	3.5 (2.0 – 5.5)	1.60 (0.8 – 3.1)

The composite outcome was significantly higher in CYP2C19 reduced metabolizers (RM) versus CYP2C19 normal metabolizers (NM).

CI: Confidence interval, CV: Cardiovascular, MI: Myocardial infarction. *Risk with prasugrel as a fraction of the risk with Clopidogrel.

Sorich et al. *J Thromb Haemost* 2010;8:1678-84.

Prasugrel vs Clopidogrel by Genotype: Genetic Substudy of TRITON TIMI-38

Event (and group)	Prasugrel [% (95% CI)]	Clopidogrel [% (95% CI)]	Relative risk* (95% CI)
CV death, non-fatal MI, or non-fatal stroke			
CYP2C19 NM	9.6 (8.3 – 10.8)	9.8 (8.3 – 11.3)	0.98 (0.80 – 1.20)
CYP2C19 RM	8.5 (6.2 – 11.4)	15.0 (11.6 – 18.8)	0.57 (0.39 – 0.83)
CV death			
CYP2C19 NM	1.9 (1.2 – 2.5)	0.9 (0.3 – 1.7)	2.07 (0.96 – 5.66)
CYP2C19 RM	1.6 (0.6 – 3.2)	4.2 (2.2 – 6.1)	0.36 (0.13 – 0.96)
Non-fatal MI			
CYP2C19 NM	7.4 (6.4 – 8.5)	8.3 (7.0 – 9.6)	0.89 (0.72 – 1.11)
CYP2C19 RM	6.2 (4.2 – 8.5)	11.6 (8.7 – 14.8)	0.53 (0.34 – 0.81)
Major or Minor Bleeding			
CYP2C19 NM	4.7 (3.7 – 5.7)	3.4 (2.6 – 4.2)	1.38 (1.00 – 1.93)
CYP2C19 RM	5.5 (3.6 – 8.1)	3.5 (2.0 – 5.5)	1.60 (0.8 – 3.1)

Prasugrel is significantly safer than clopidogrel in CYP2C19 reduced metabolizer (RM) however this is not significantly different in normal metabolizers

CI: Confidence interval, CV: Cardiovascular, MI: Myocardial infarction. *Risk with prasugrel as a fraction of the risk with Clopidogrel.

Sorich et al. *J Thromb Haemost* 2010;8:1678-84.