



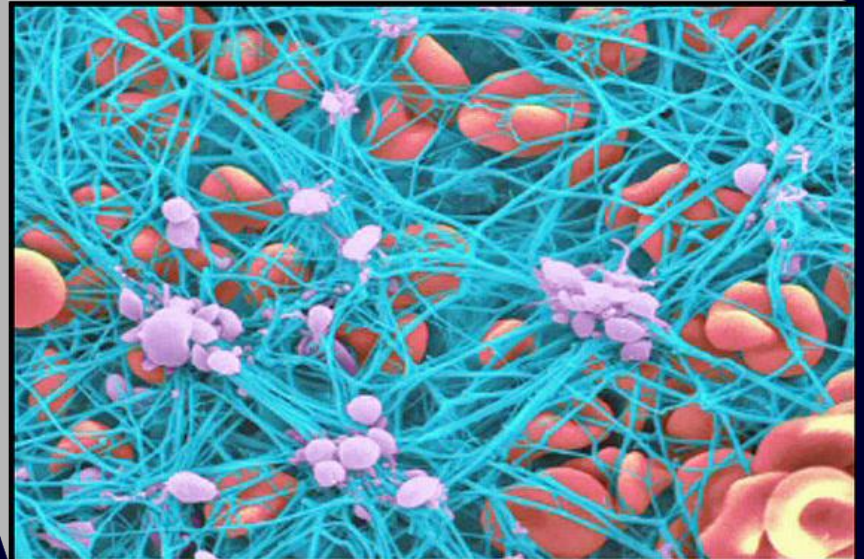
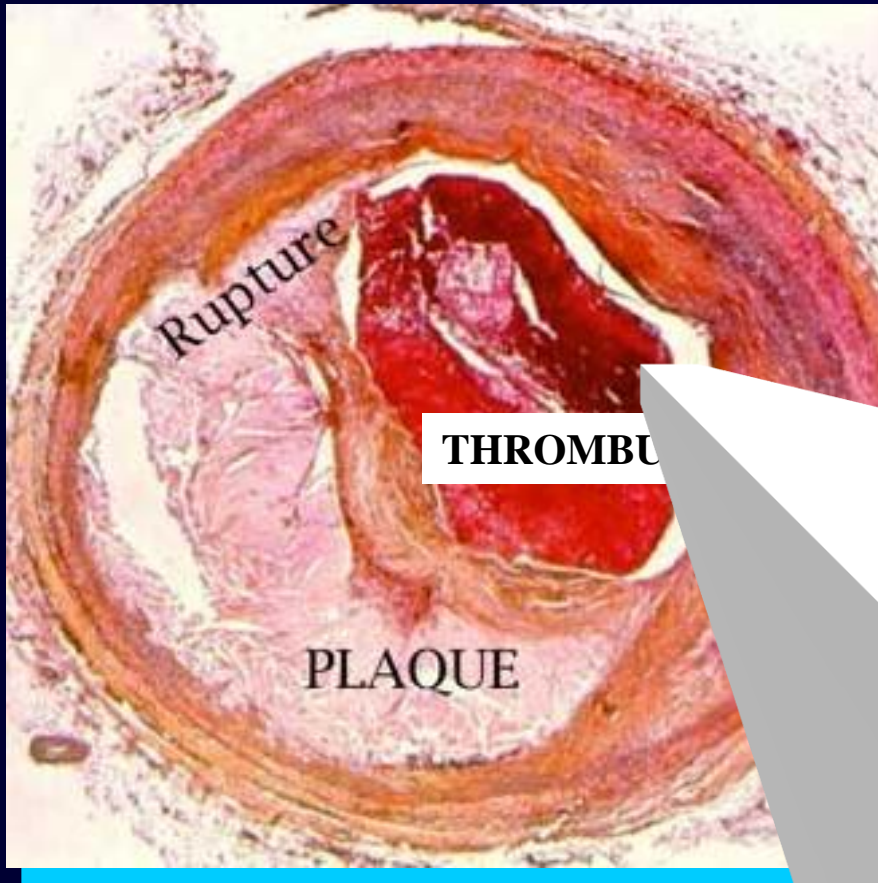
Clopidogrel and Genetic Variance

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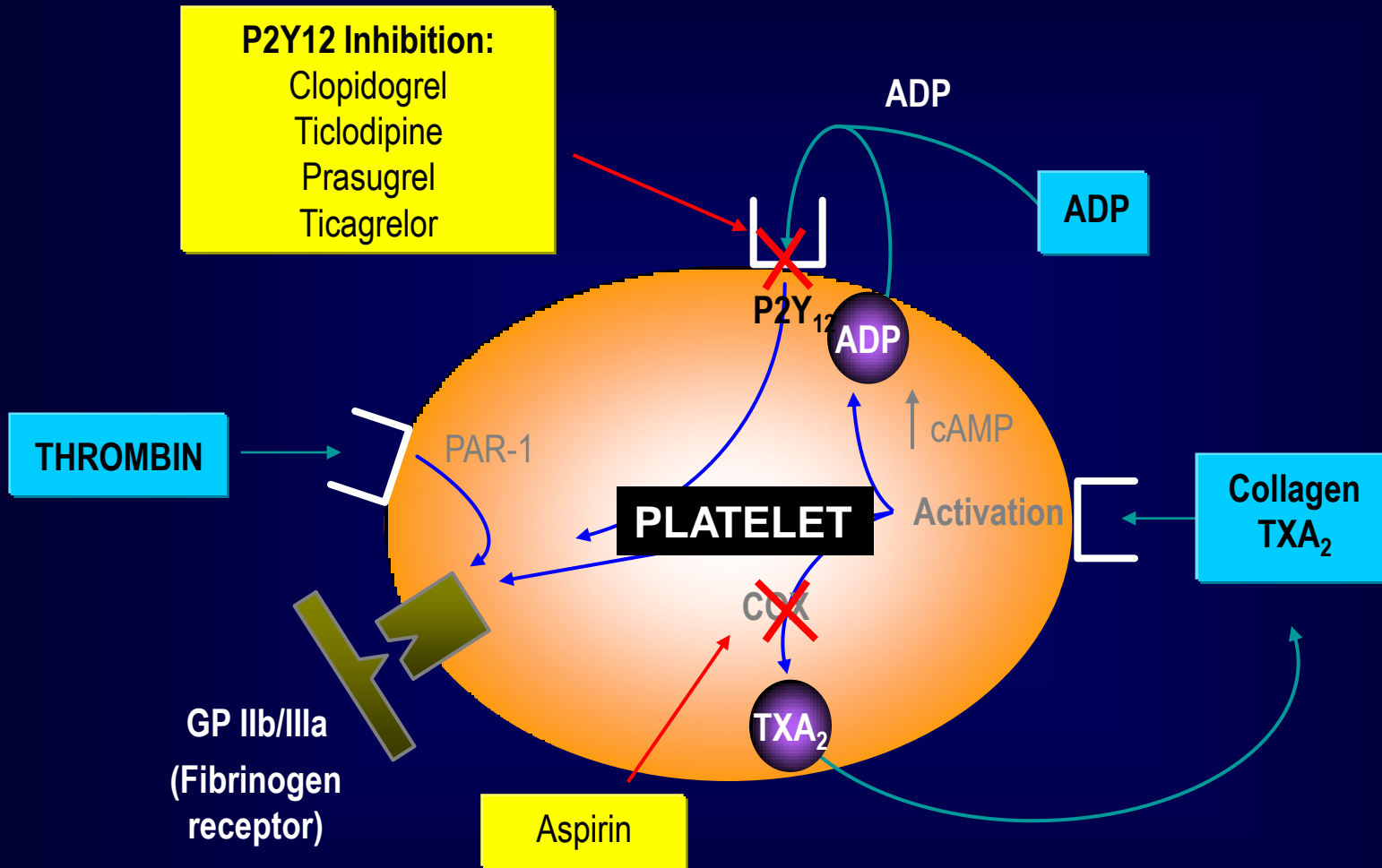
Disclosures

- ❑ Research grants: Johnson & Johnson, Bayer Healthcare, BMS, Eli Lilly, Daiichi Sankyo
- ❑ Consultant: BMS
- ❑ Honoraria: Novartis

ACS and Thrombus Formation



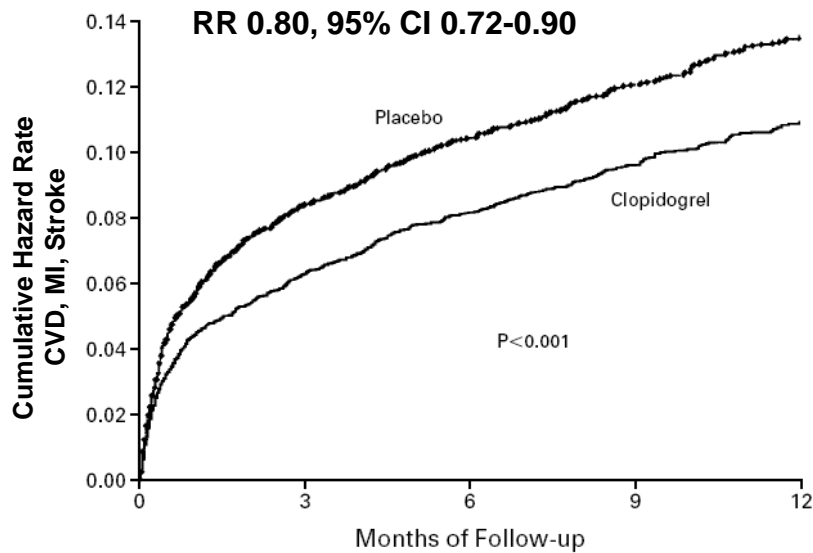
Dual Anti-Platelet Therapy



Outcomes with Clopidogrel

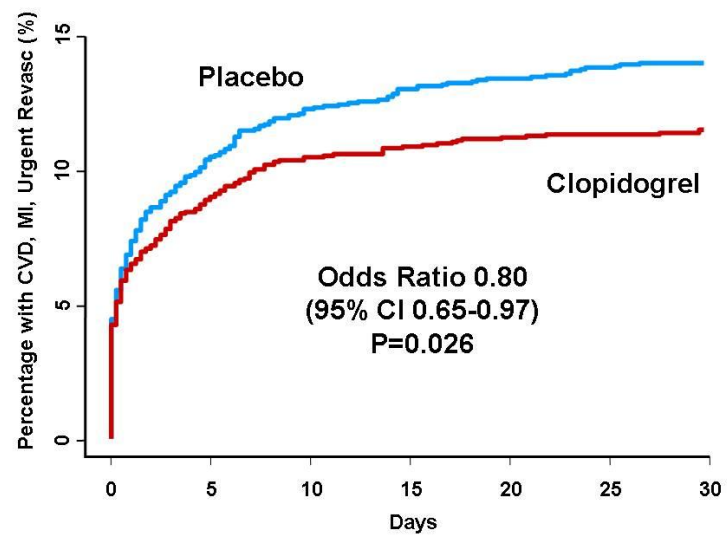
CURE

12,562 Patients with NSTEMI ACS

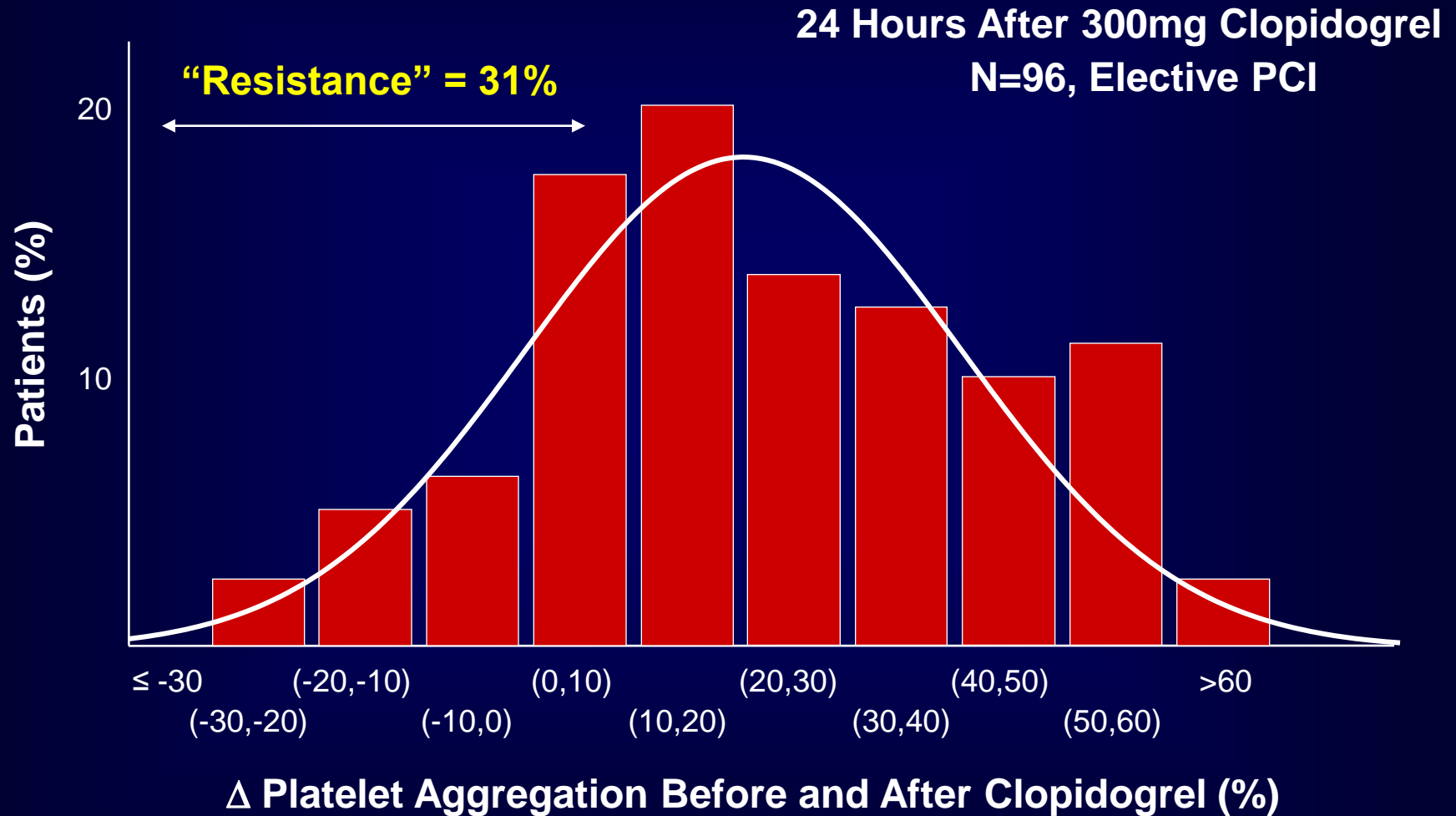


CLARITY-TIMI 28

3,491 Patients with STEMI



Variable Response to Clopidogrel

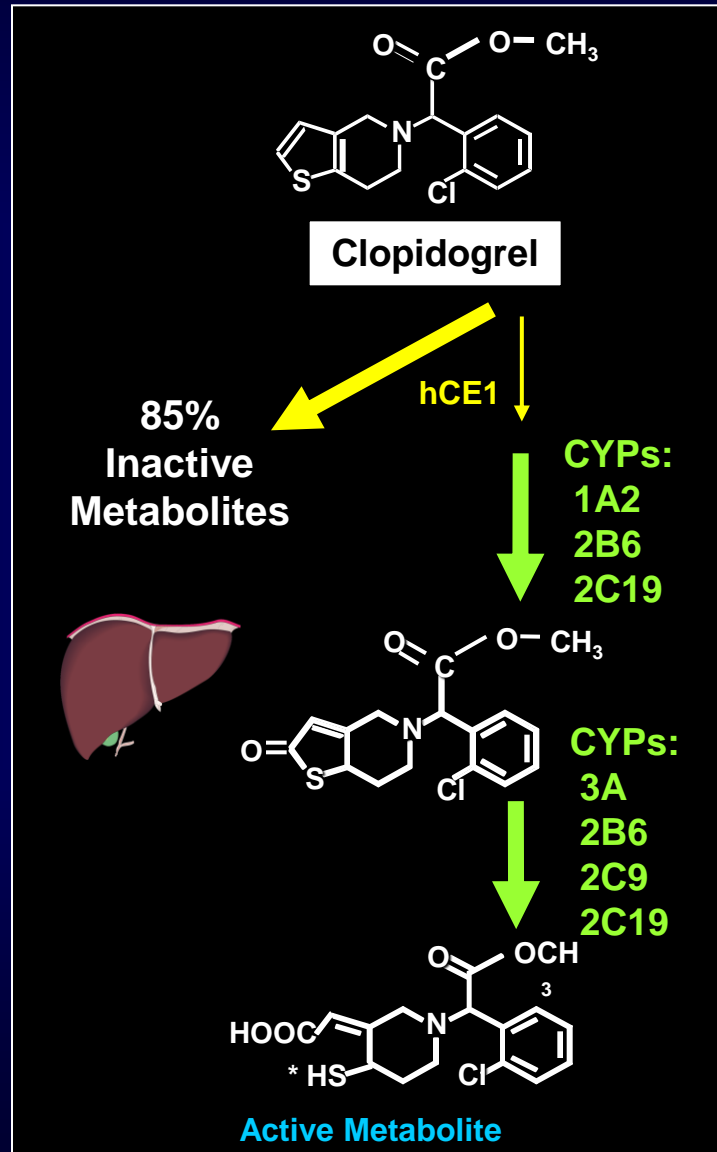


“Resistance” = $\leq 10\%$ Δ platelet aggregation

Clopidogrel → Active Metabolite

Compliance

Environmental
Drug-Drug
Genetics



Pro-drug

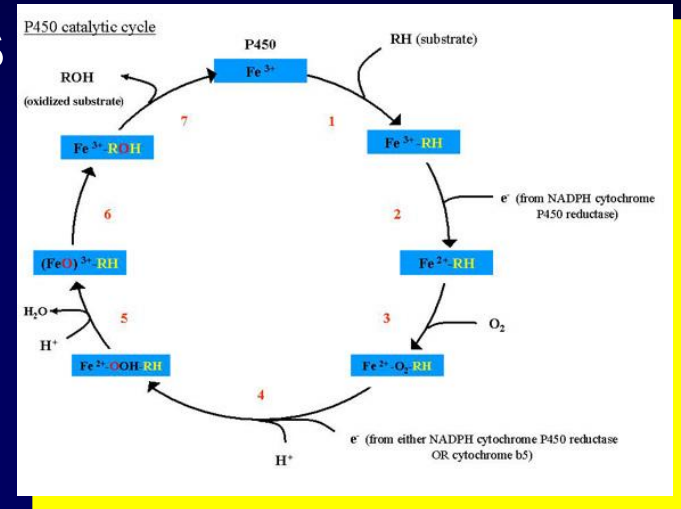
Hydrolysis
(Esterases)

Oxidation
(Cytochrome P450)

CYP450 Enzymes & Genes

- **Enzymes:**

- 57 human CYPs (in 18 families and 42 subfamilies)
- Account for > 90% of drug transformations

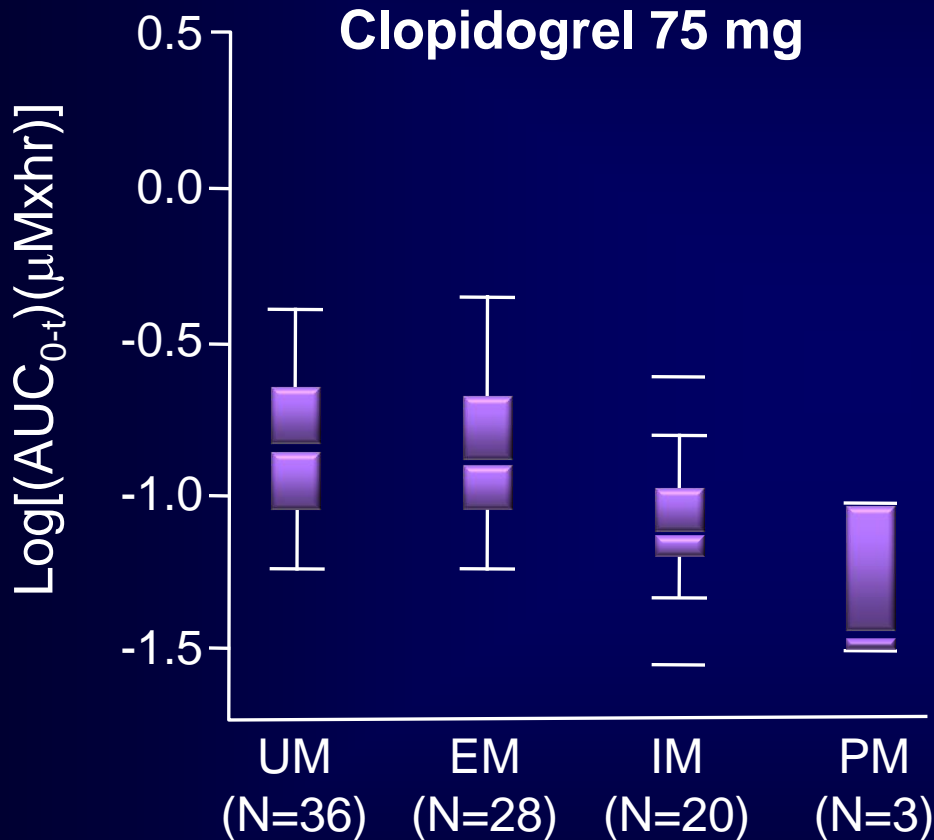


- **Genes:**

- Highly polymorphic
- Common-consensus star allele nomenclature (e.g., *CYP2C19**2 refers to haplotype containing 681G>A)
- Certain alleles confer reduced enzymatic function (e.g., splicing defect)

CYP2C19 & Clopidogrel Metabolite

N=162 Healthy Volunteers

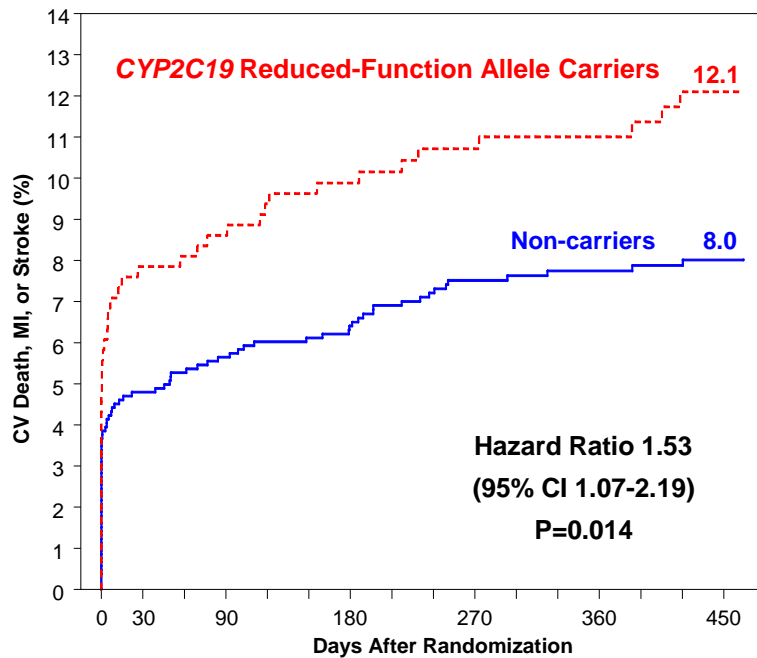


Carriers of a reduced-function *CYP2C19* allele (IMs and PMs) experienced ~32% reduction in exposure to the active clopidogrel metabolite as compared with non-carriers (P<0.001).

EM=extensive metabolizer
IM=intermediate metabolizer
PM=poor metabolizer
UM=ultrarapid metabolizer.

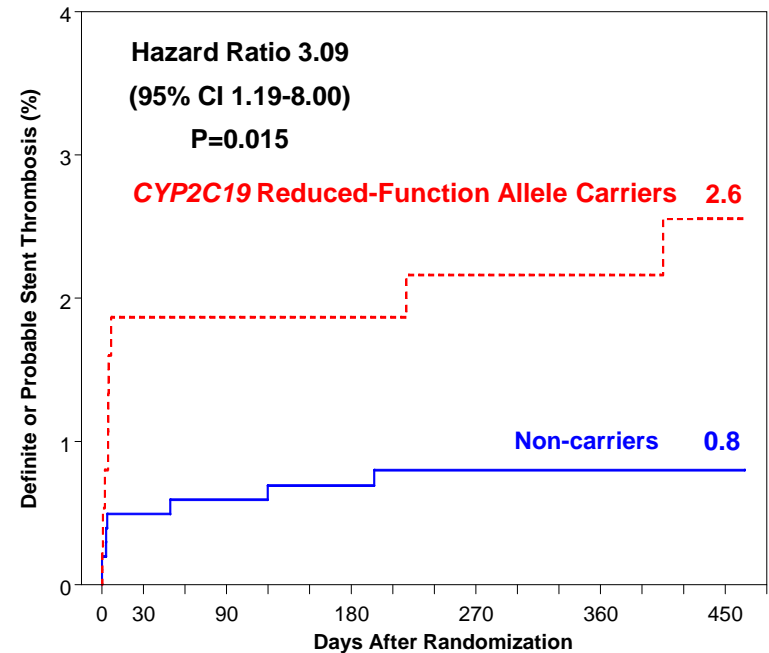
CYP2C19 and CVD, MI, or Stroke

N=1477 ACS Subjects Treated with Clopidogrel



Number at Risk:

Non-Carrier	1064	1009	999	980	870	755	542
Carrier	395	364	360	348	306	270	181

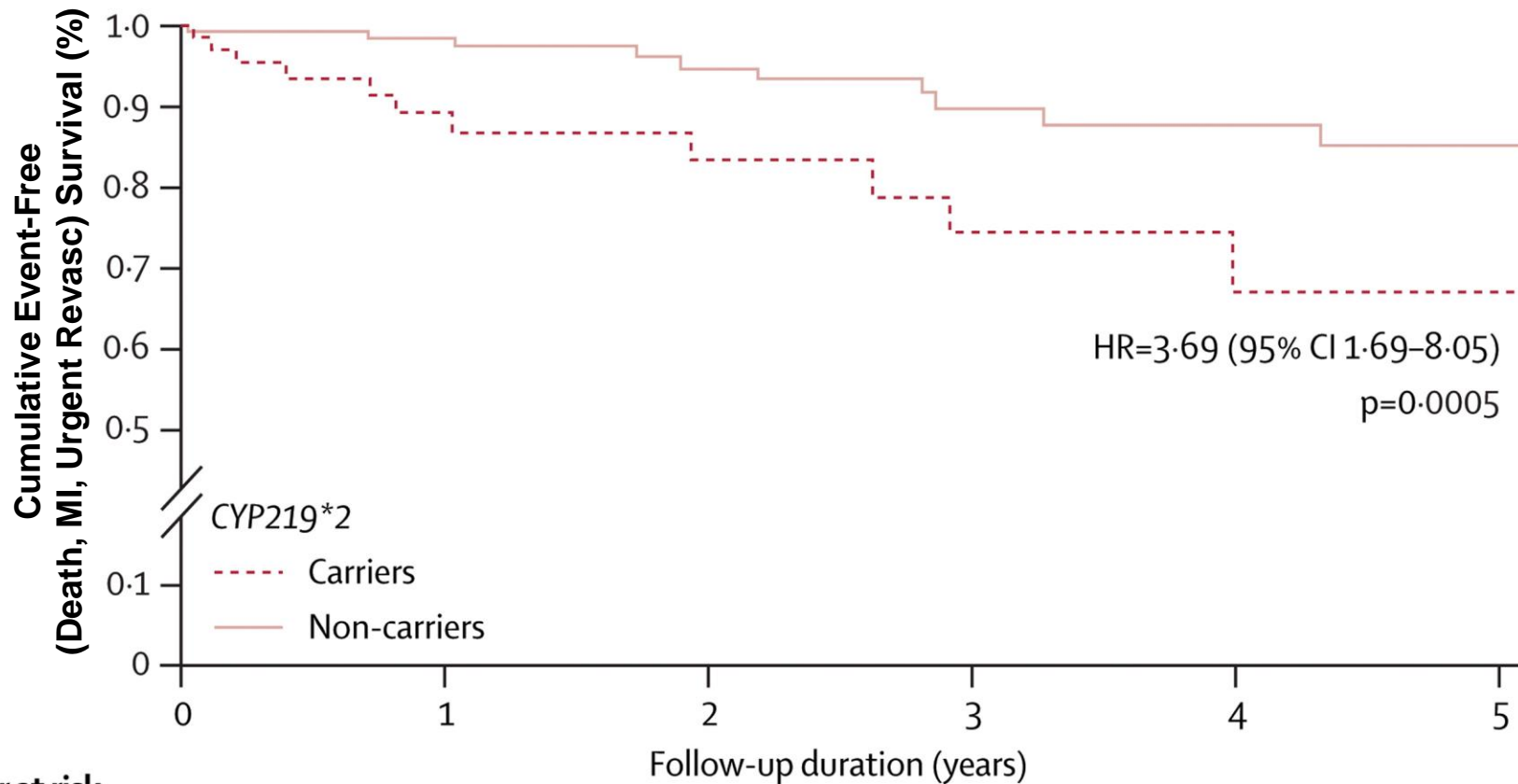


Number at Risk:

Non-Carrier	1014	1004	1001	989	885	765	547
Carrier	375	368	366	359	316	279	186

* Carriers ~30% of the population

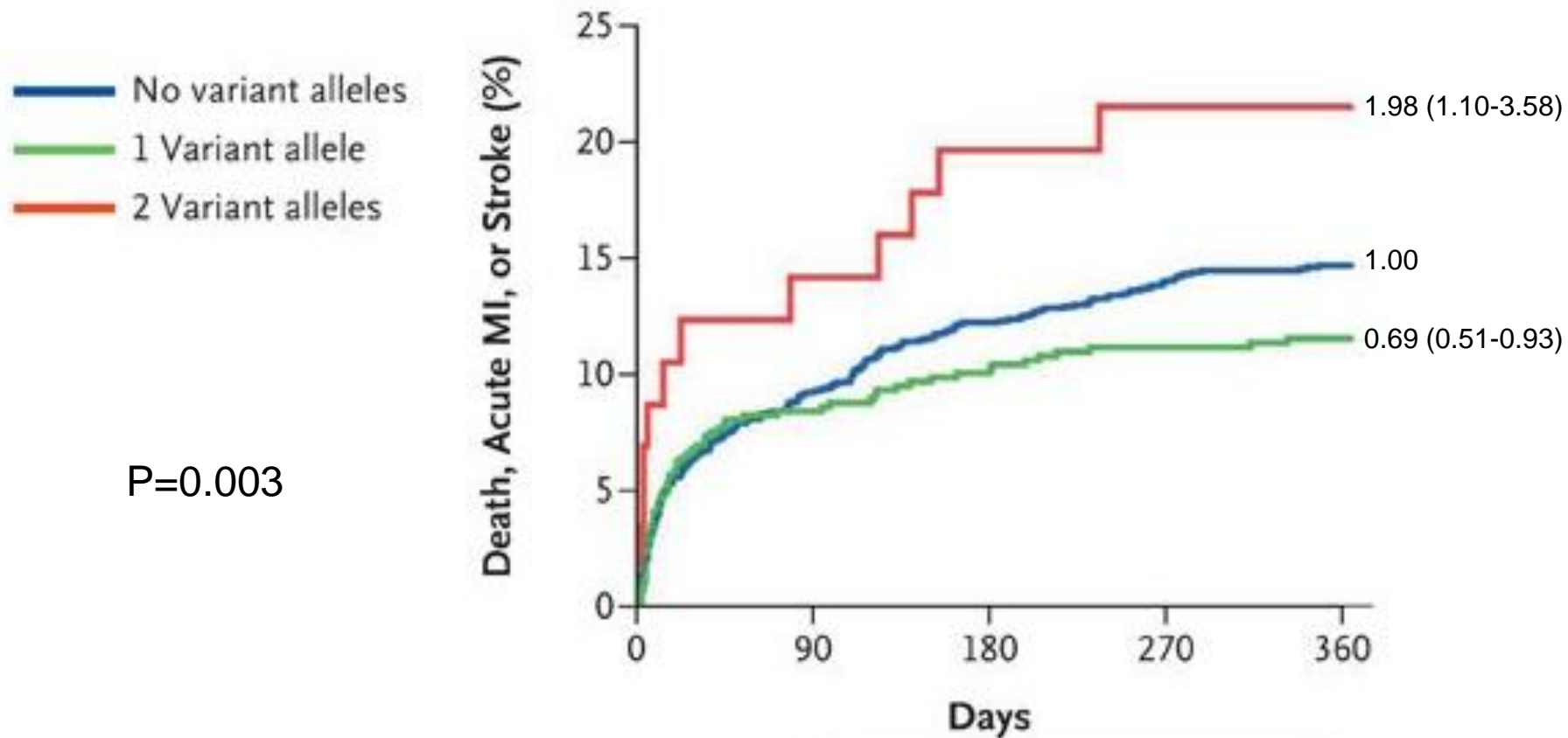
CYP2C19*2 and Outcomes with Clopidogrel



Number at risk

	0	1	2	3	4	5
Non-carriers	186	100	68	50	35	23
*2 carriers	73	35	23	15	8	5

CYP2C19*2 and Outcomes with Clopidogrel

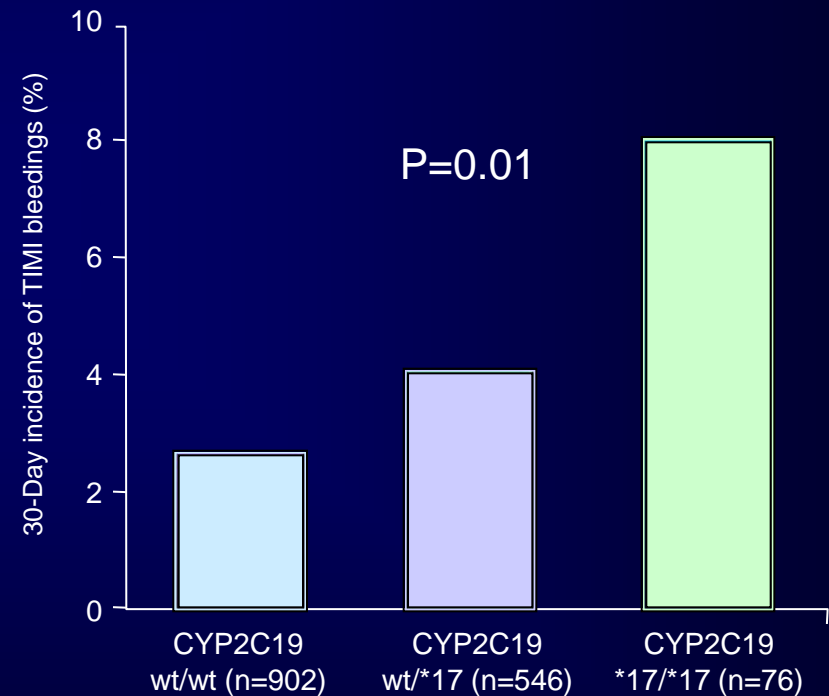


CYP2C19*17 and Bleeding with Clopidogrel

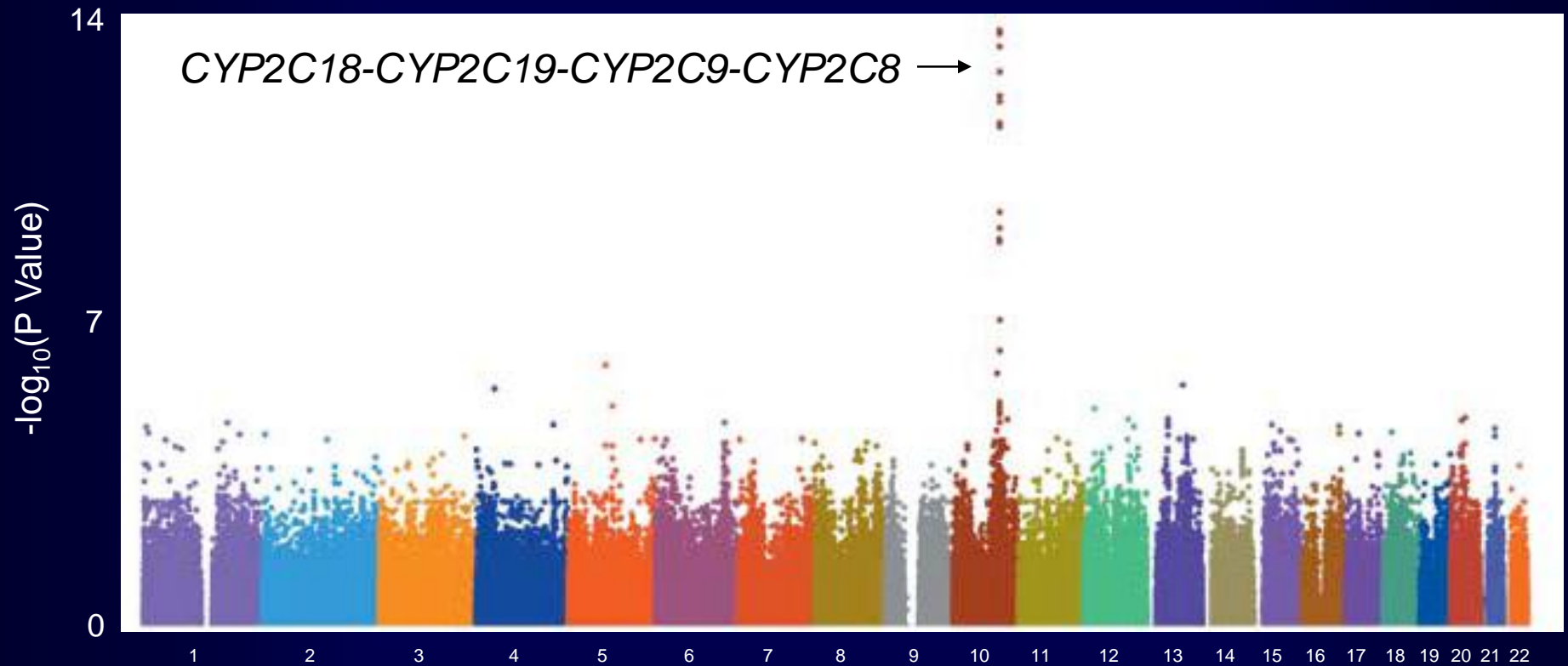
Platelet Function Testing

	ADP-Ag mean (sd) (%)	PRI-VASP mean (sd) (%)
CYP2C19*17		
CC	57.03 (18.5)	55.9 (22.8)
CT	55.5 (19)	50.11 (24.3)
TT	50.8 (27.3)	45.79 (17.71)
P Value	0.2813	0.0206

Major or Minor TIMI Bleeding



GWAS of Platelet Aggregation in Response to Clopidogrel



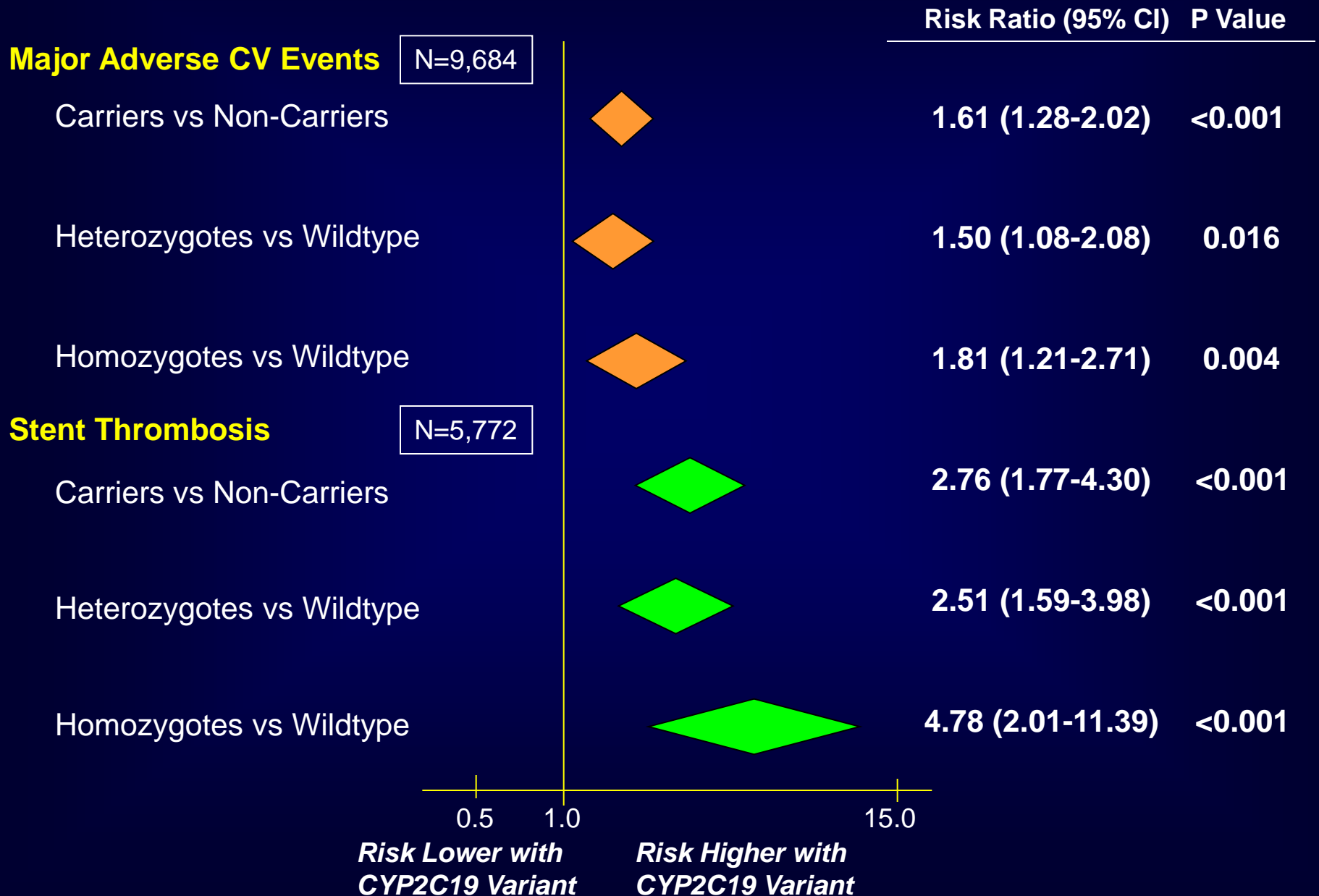
Remaining Questions

1. Is this relationship between *CYP2C19* limited to ***2 homozygotes** (~2% of the population) or does it involve ***2 carriers** (~30% of the population)? What is the role of ***17** and other genes?
2. Are *CYP2C19* variants associated with an **increase in adverse cardiovascular events** in patients following an ACS, regardless of thienopyridine therapy?
3. Do variants in *CYP2C19* alter the pharmacologic response to other thienopyridines such as **prasugrel**?

***CYP2C19* Collaborative Meta-Analysis**

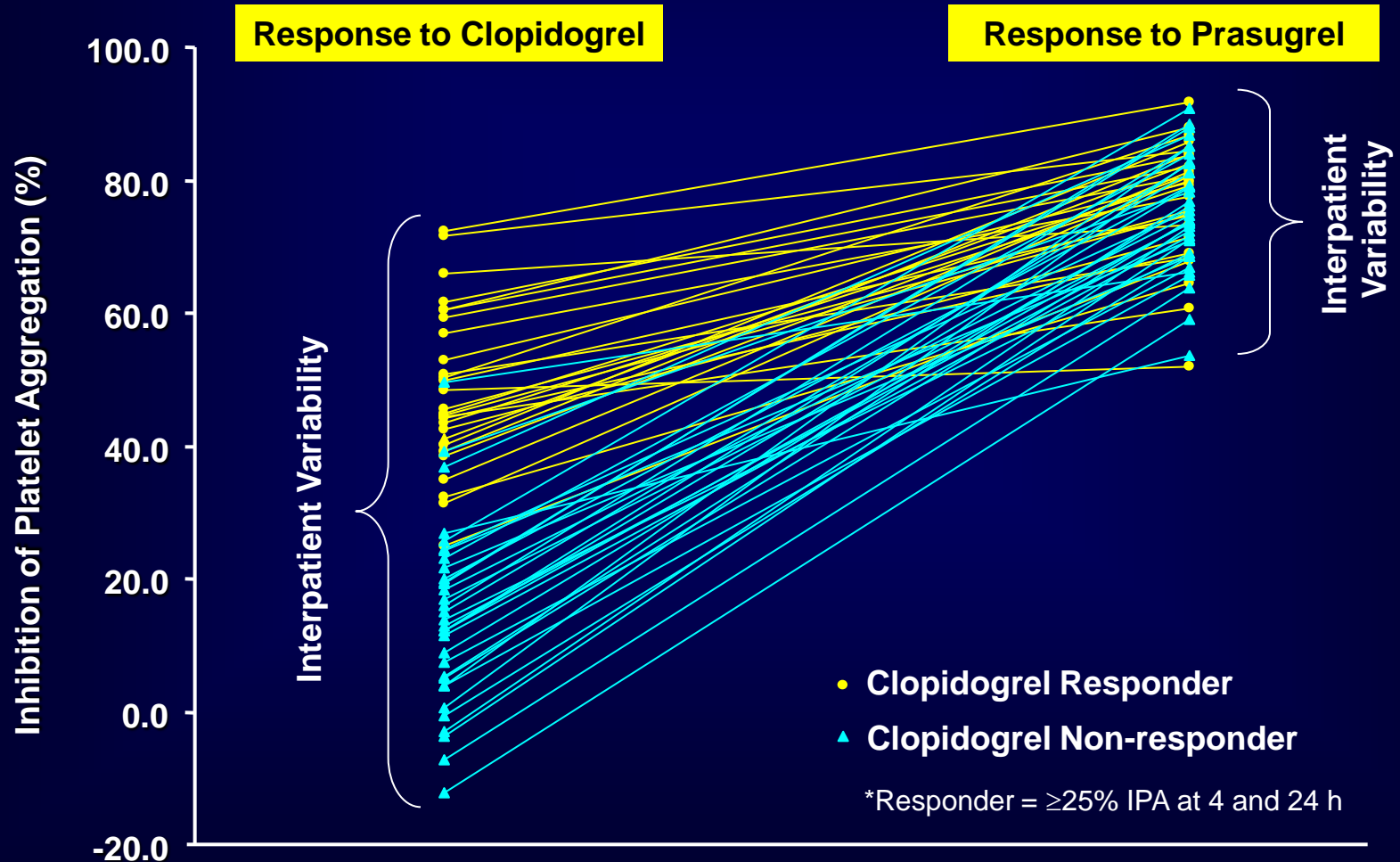
- **9 studies of *CYP2C19* alleles (mostly *2) and outcomes in patients treated with clopidogrel**
- **Subjects**
 - 9684 MACE
 - 5772 Stent Thrombosis
- **Genotypes**
 - Wildtype 71.5%
 - Carriers 28.5% (Heterozygotes 26.3%, Homozygotes 2.2%)
- **Meta-analysis performed using a random-effects model with weighting based on inverse variance.**

CYP2C19 and Treatment with Clopidogrel

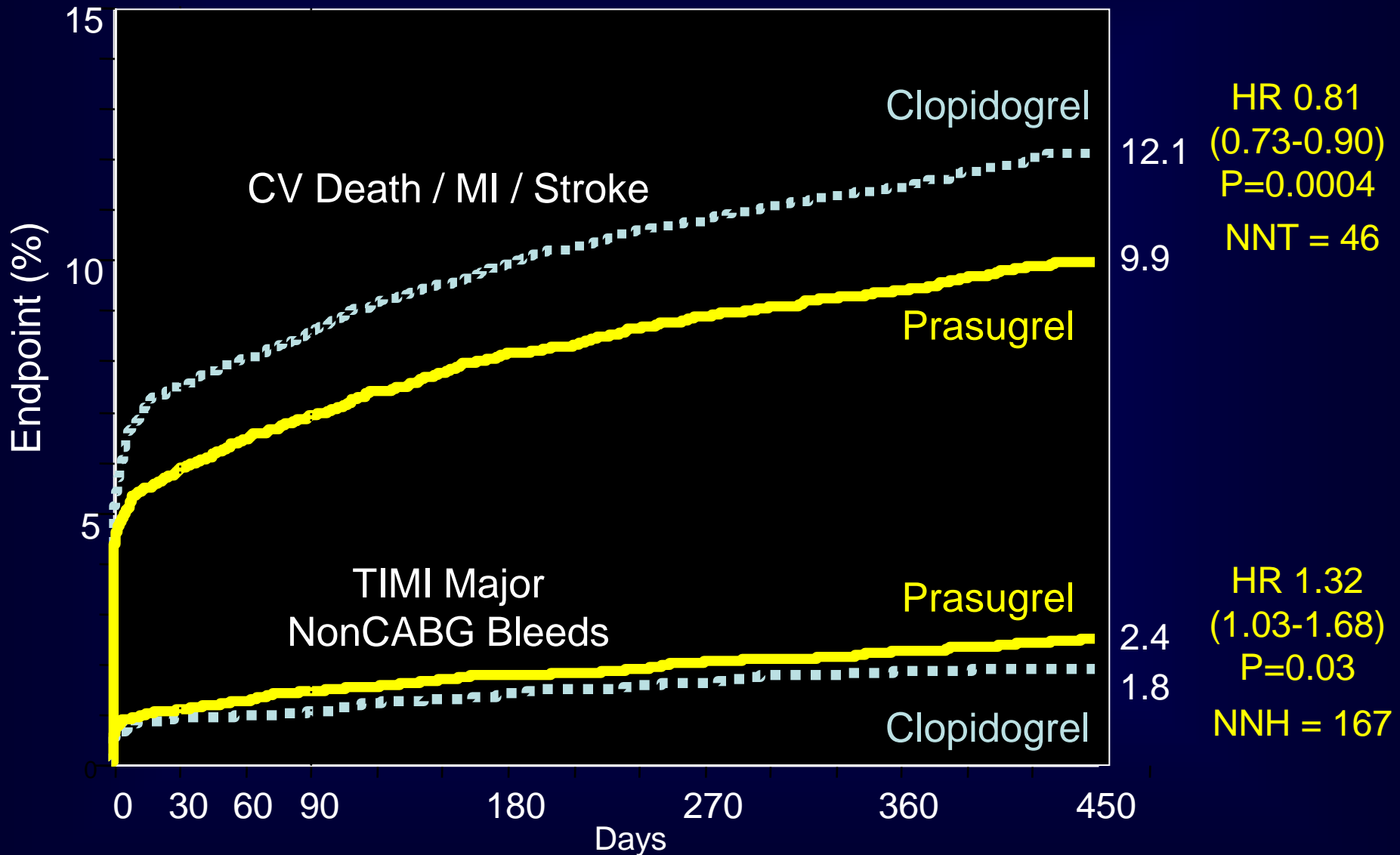


Inhibition of Platelet Aggregation: Clopidogrel and Prasugrel

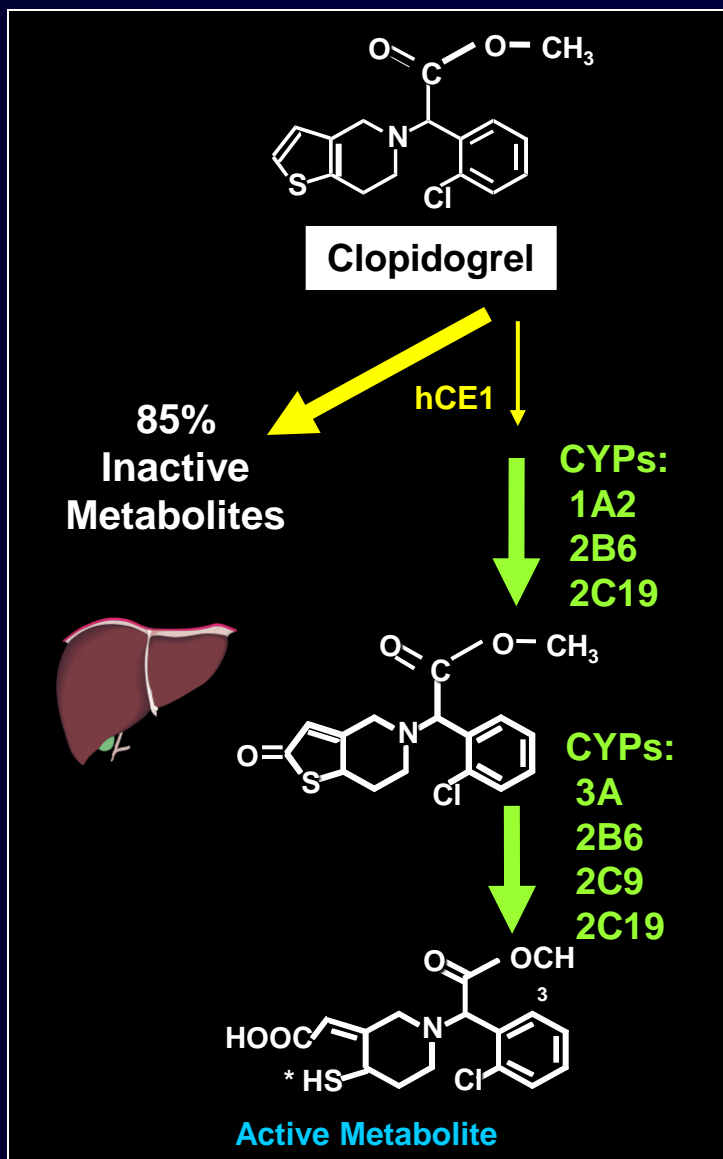
Healthy Volunteers at 24 Hours, N=68



Efficacy and Safety



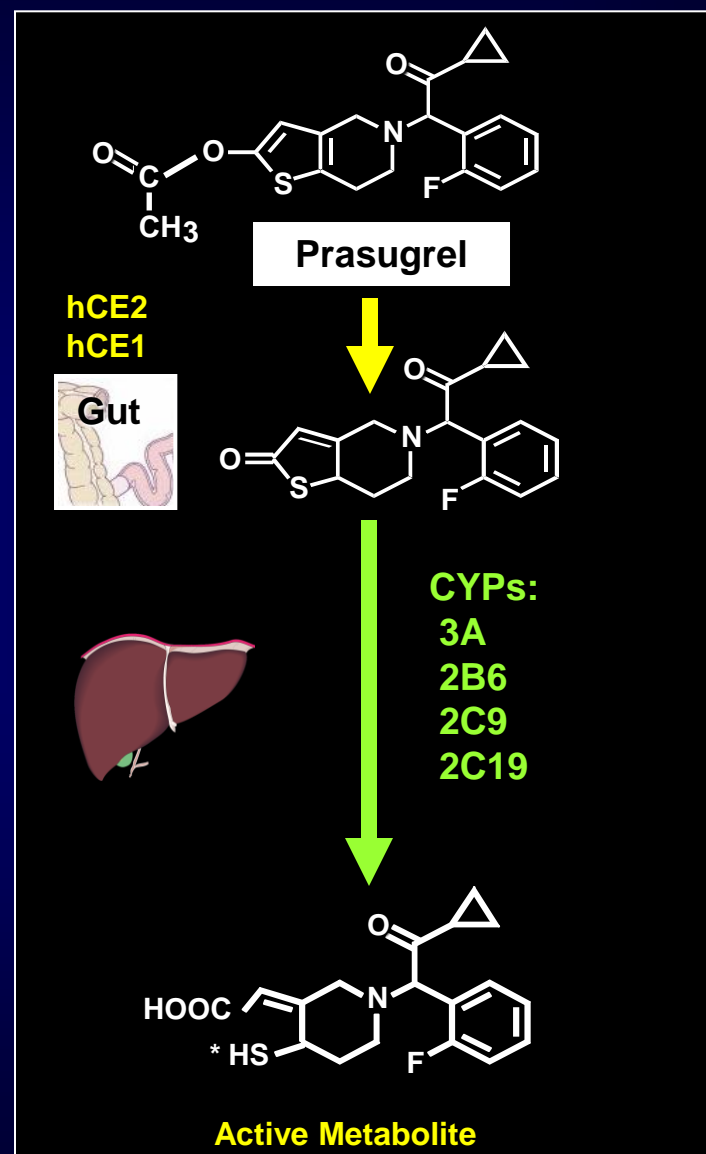
Thienopyridines: Formation of Active Metabolite



Pro-drug

Hydrolysis
(Esterases)

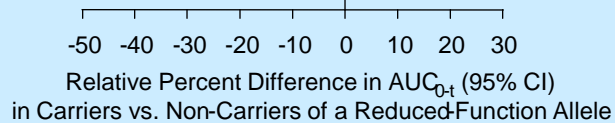
Oxidation
(Cytochrome P450)



Genetic Effects on PK/PD

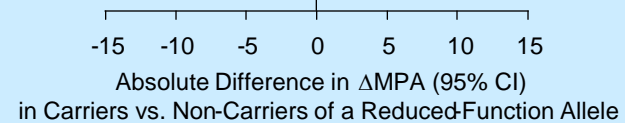
Pharmacokinetics

Gene	% Difference in AUC_{0-t}	P value
<i>CYP2C19</i>	-6.1	0.061
<i>CYP2C9</i>	-5.3	0.27
<i>CYP2B6</i>	-0.4	0.90
<i>CYP3A5</i>	-0.8	0.82
<i>CYP1A2</i>	-3.5	0.47



Pharmacodynamics

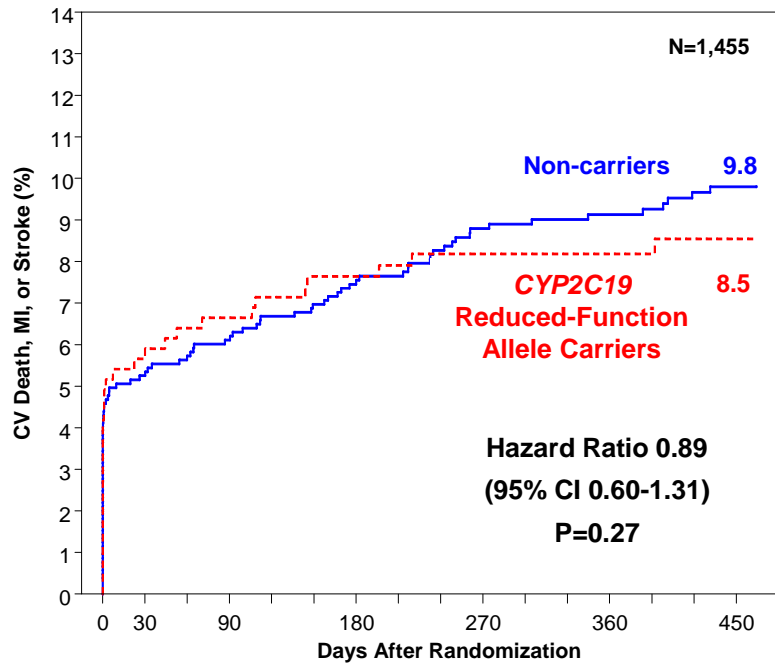
Gene	Absolute Difference in ΔMP_A	P value
<i>CYP2C19</i>	-1.3	0.63
<i>CYP2C9</i>	-1.7	0.42
<i>CYP2B6</i>	-0.6	0.65
<i>CYP3A5</i>	1.3	0.38
<i>CYP1A2</i>	-1.6	0.37



N=238

CYP2C19 and Outcomes: Prasugrel

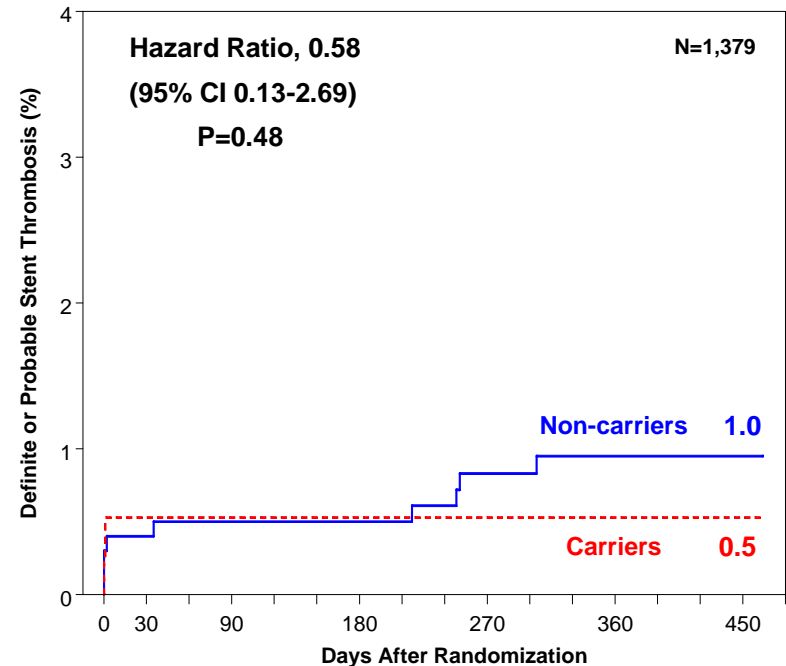
CV Death, MI, Stroke



Number at Risk:

Non-Carrier	1048	991	982	951	849	750	541
Carrier	407	383	376	364	320	276	188

Stent Thrombosis



Number at Risk:

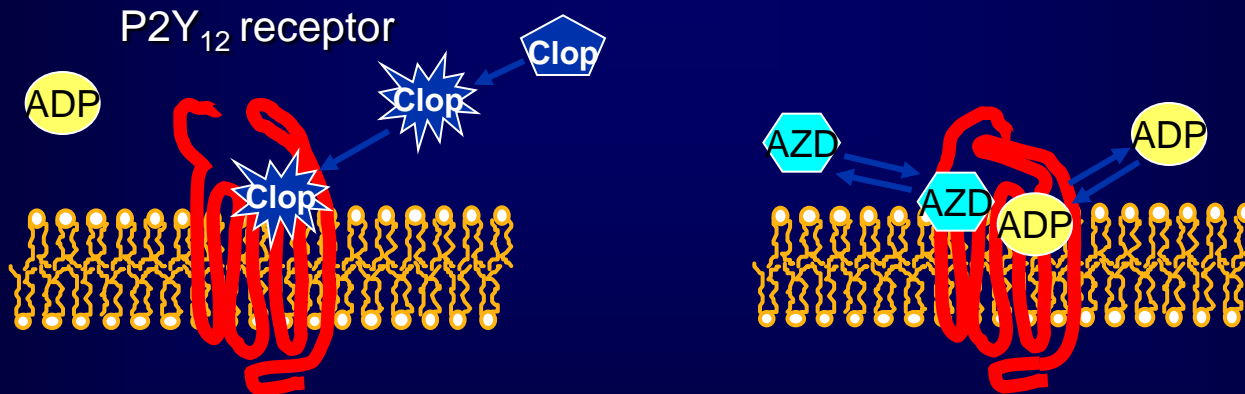
Non-Carrier	1000	992	990	969	870	764	550
Carrier	379	374	371	363	323	276	189

Ticagrelor

Ticagrelor is not a prodrug

Exhibits a more rapid onset of action and less interpatient variability than some thienopyridines

Acts via an allosteric modulation site



Clopidogrel prevents ADP binding and causes extra cellular structural change

Ticagrelor (AZD) binds independently from ADP but inhibits conformational change

CYP Genes and P2Y12 Inhibition

- Data suggest that the *CYP2C19* variants do not significantly impact the pharmacologic or clinical outcomes in patients treated with prasugrel. Ticagrelor is not a pro-drug.
- The impact of reduced-function *CYP2C19* alleles appears to be confined to patients taking clopidogrel.

Future Clinical Directions: Pharmacogenetic Testing

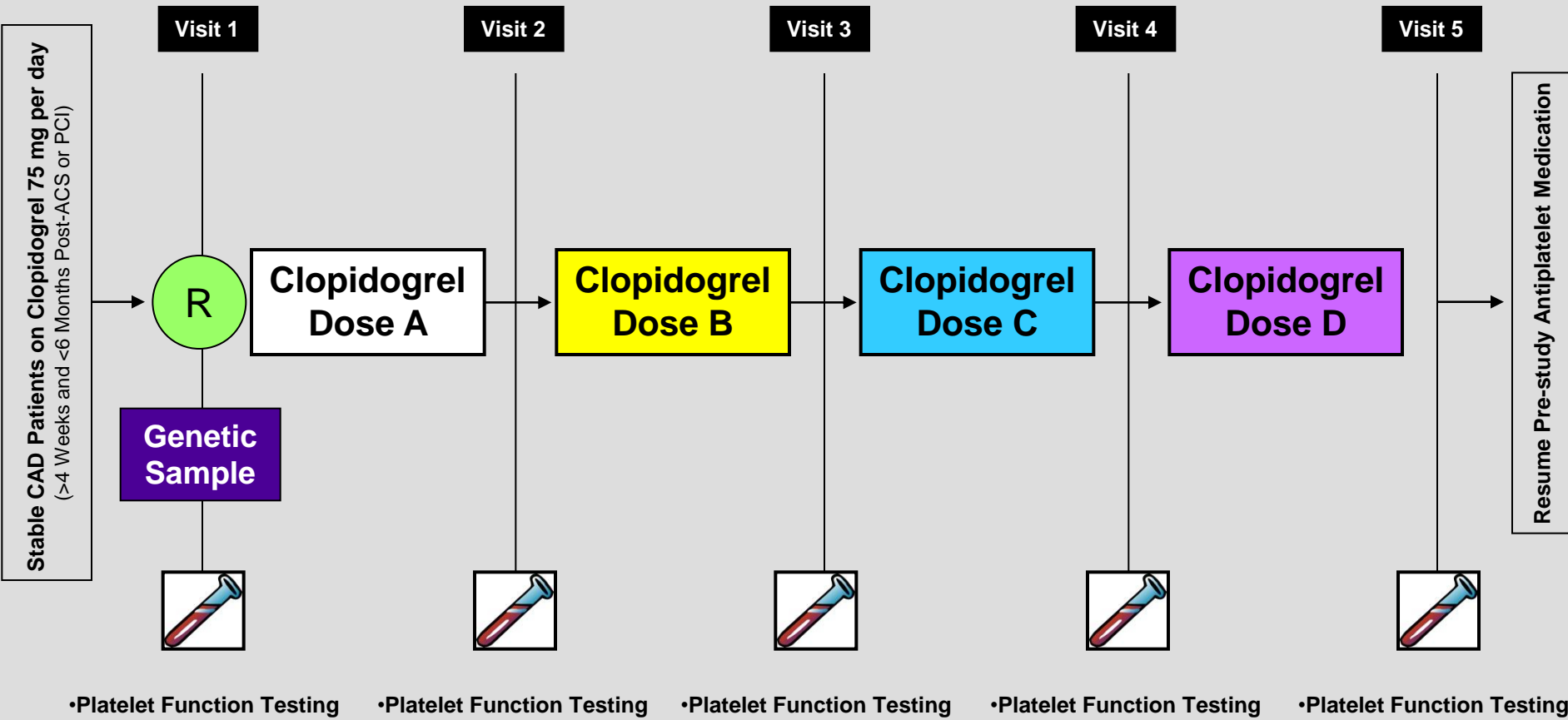


- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.



STUDY DESIGN

Schedule 0 weeks 2 weeks 4 weeks 6 weeks 8 weeks



•Platelet Function Testing •Platelet Function Testing •Platelet Function Testing •Platelet Function Testing •Platelet Function Testing