

# Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated with Clopidogrel Predominantly for PCI: Meta-Analysis

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## ***Disclosure Statement***

**AstraZeneca: research grant support through BWH**

**Bristol-Myers Squibb / sanofi-aventis Joint Venture: research grant support through BWH; scientific advisory boards**

**Daiichi-Sankyo: research grant support through BWH**

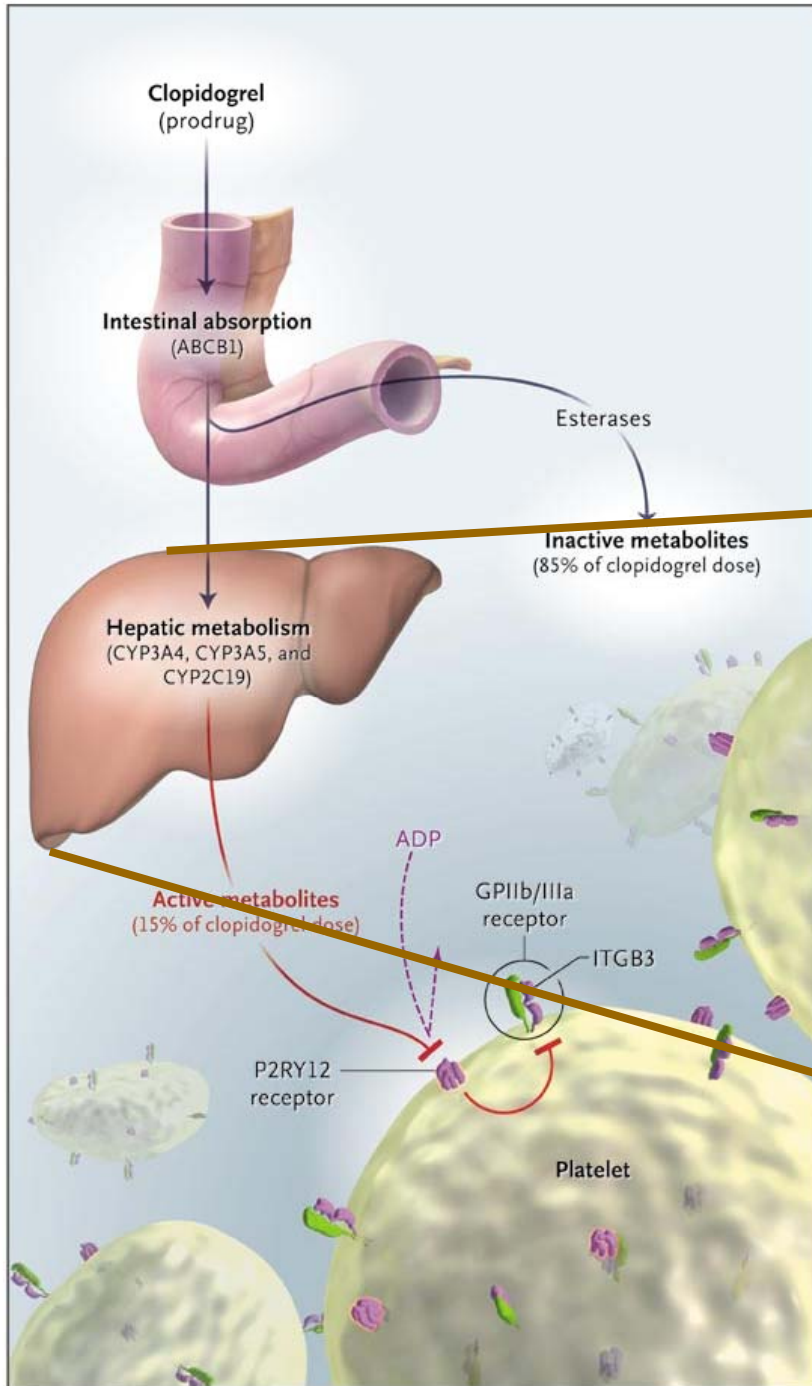
**Daiichi-Sankyo / Lilly Partnership: scientific advisory boards**

**Eli Lilly: honoraria for education presentations**

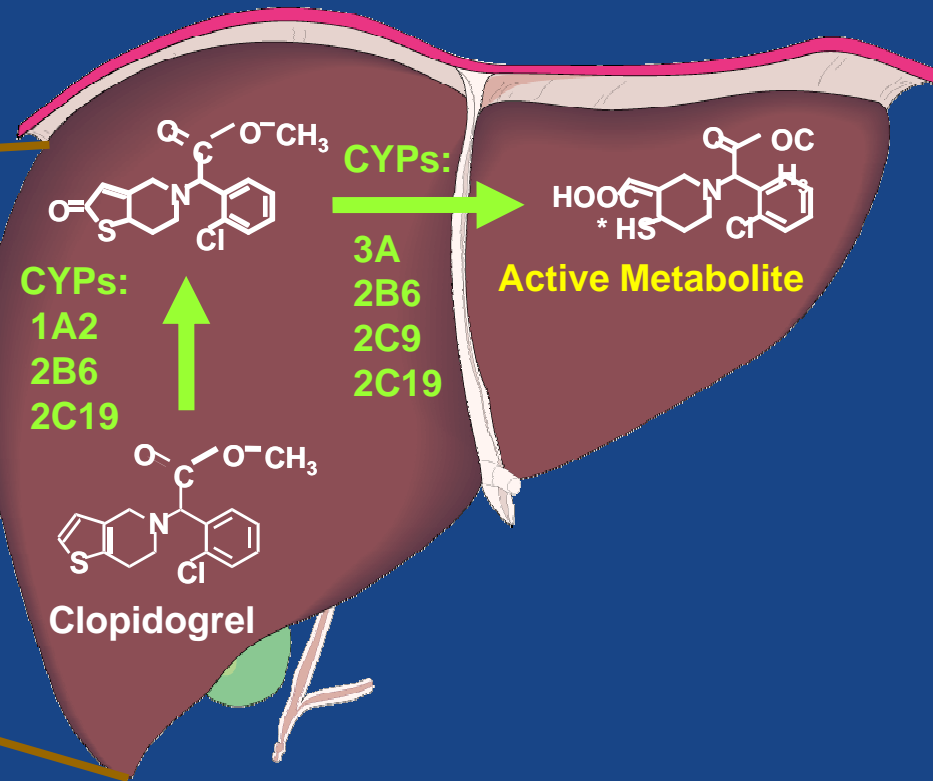
**Nanosphere: research reagents through BWH**

**sanofi-aventis: research grant support through BWH; scientific advisory boards**

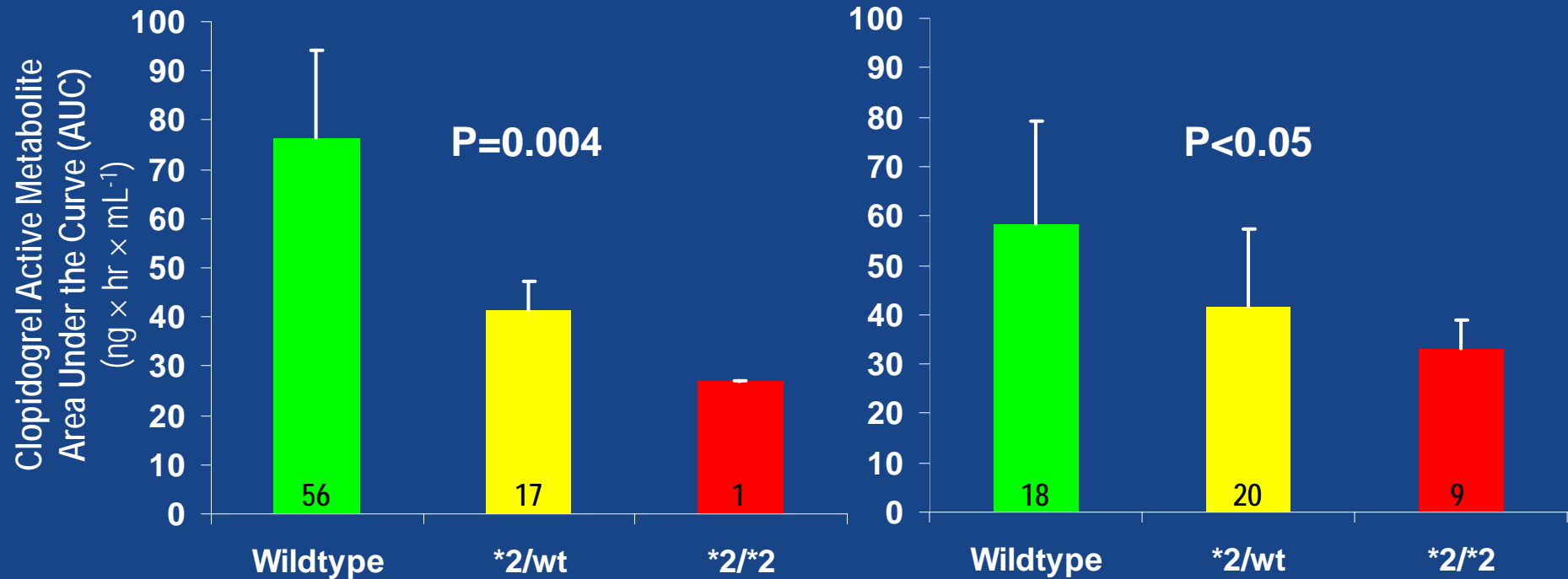
**Schering-Plough: research grant support through BWH**



# Clopidogrel Metabolism



# CYP2C19 and Clopidogrel Active Metabolite

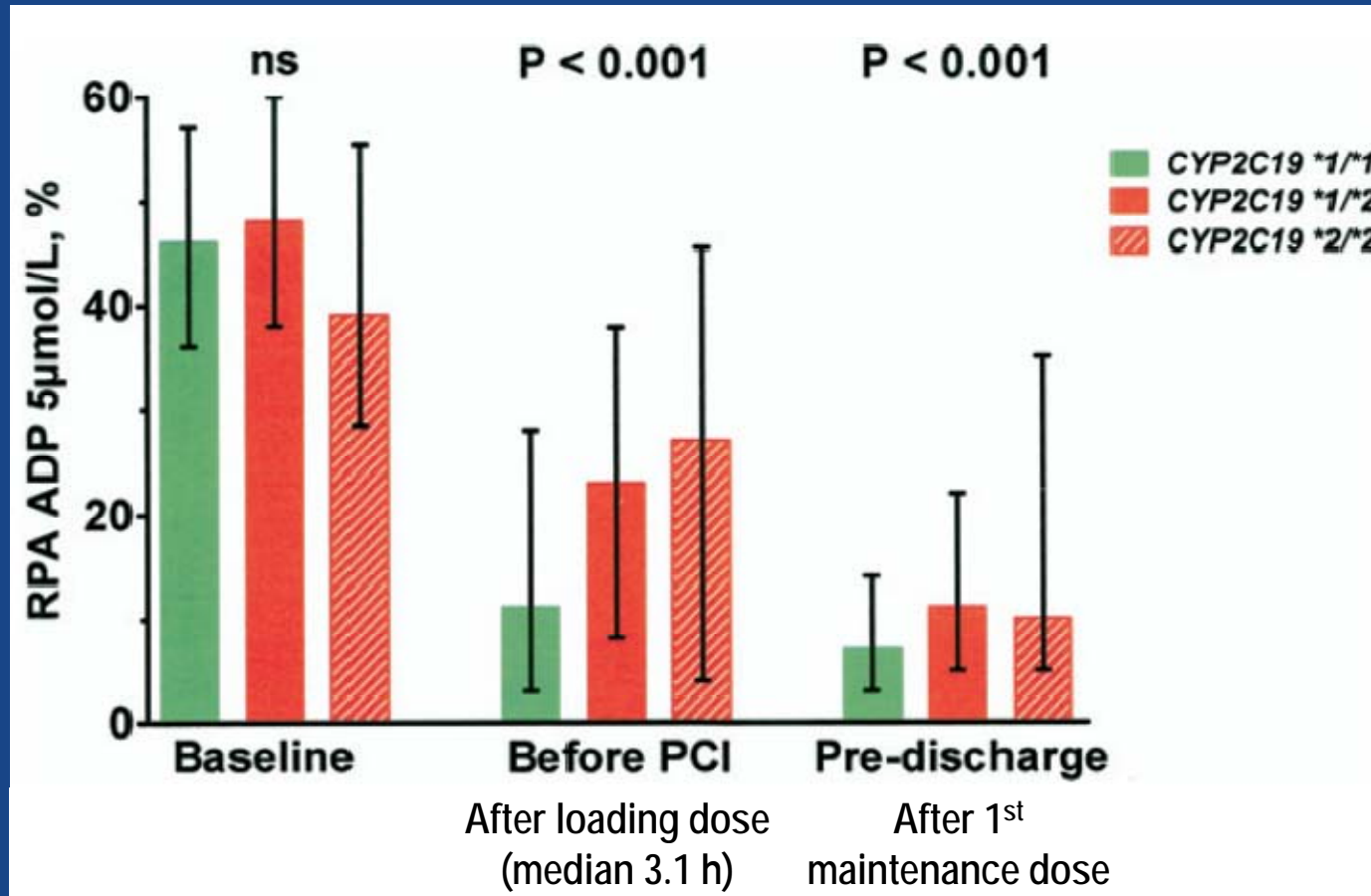


Brandt JT et al. *J Thromb Haemost*  
2007;5:2429-2436

Umemura K et al. *J Thromb Haemost*  
2008; 6:1439-1441

# CYP2C19 and Platelet Inhibition

797 patients treated with clopidogrel 600 mg before PCI

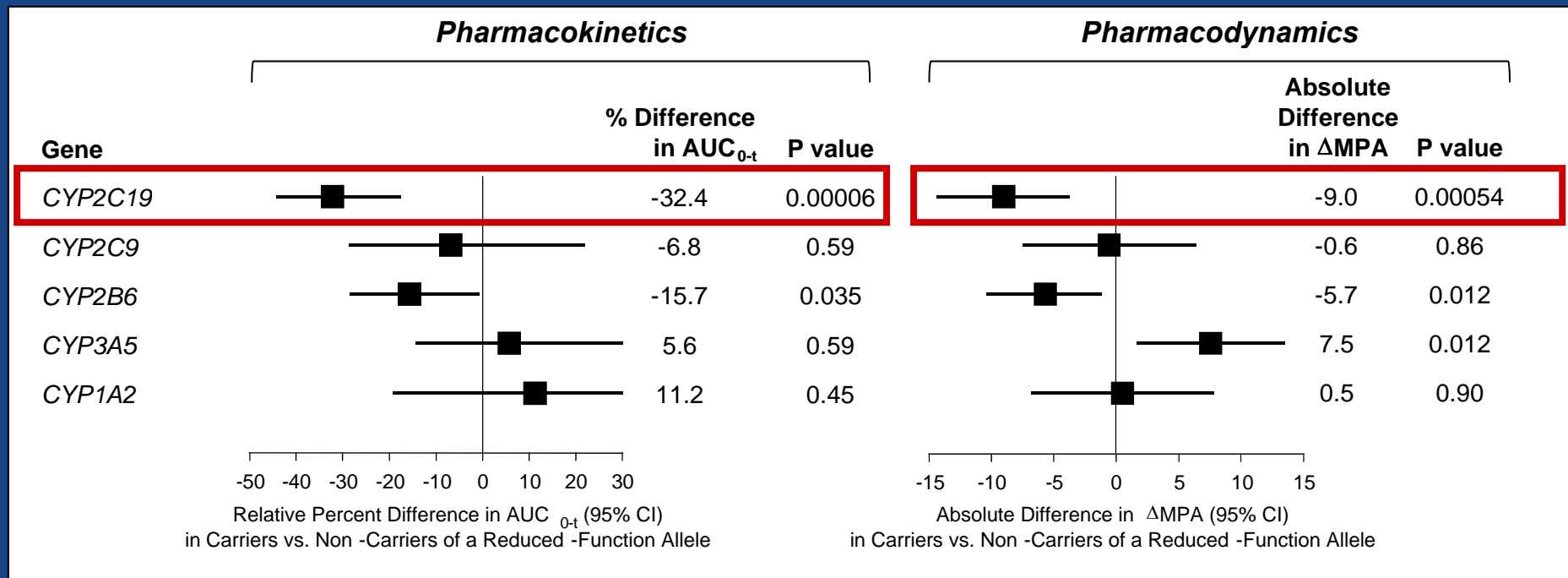


# CYP450 Genetic Variants & PK/PD

162 healthy individuals

PK: active metabolite measured by LC-MS

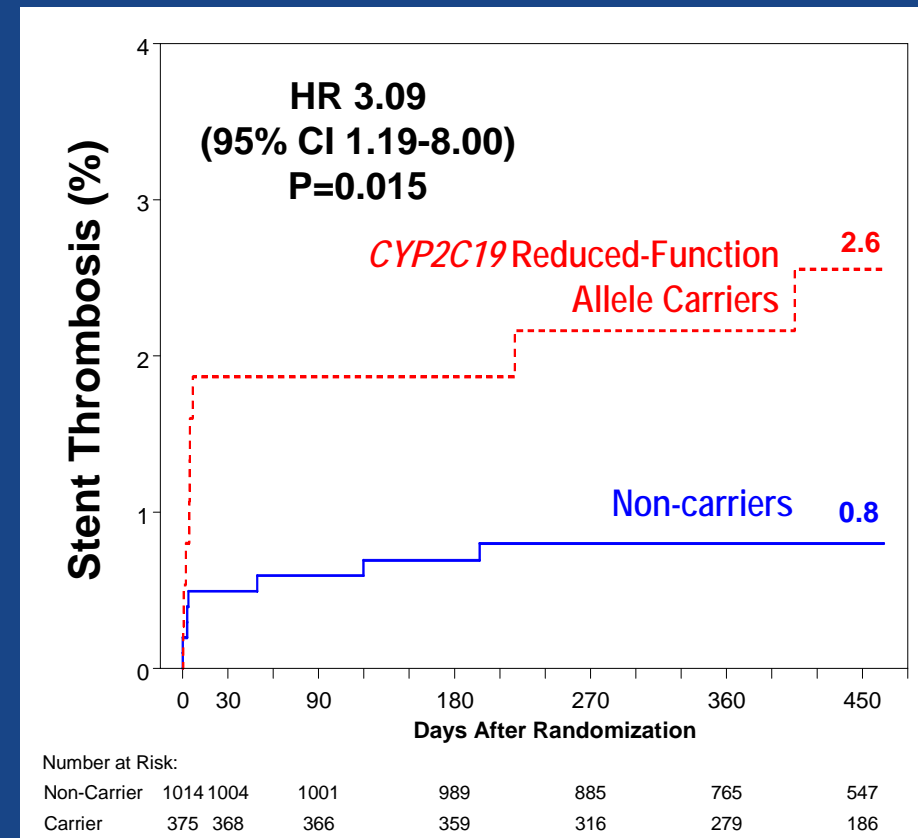
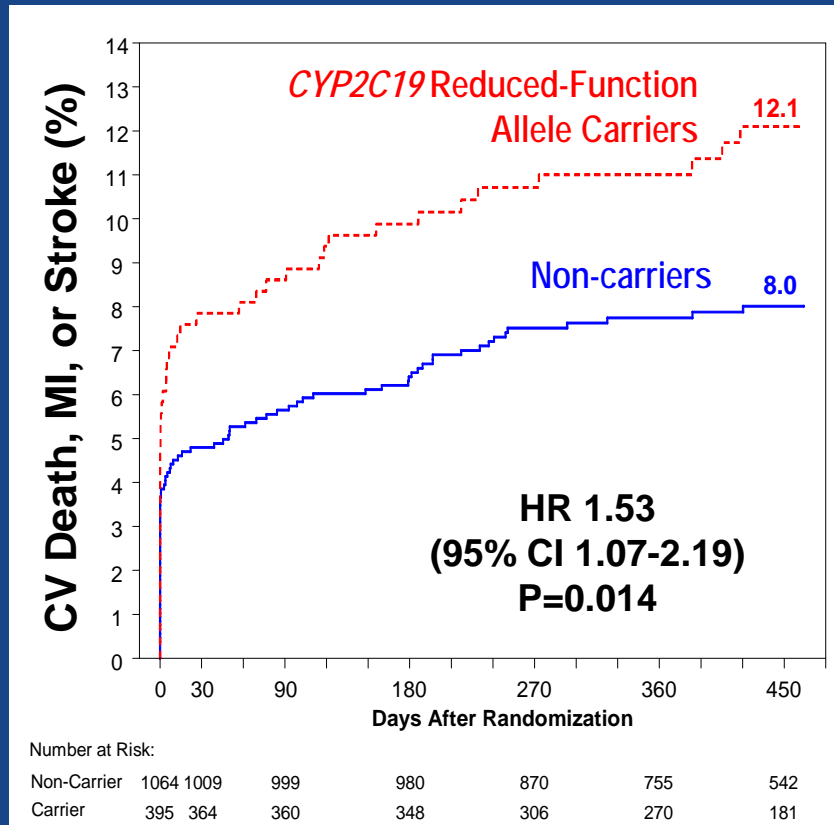
PD: LTA w/ 20  $\mu$ M ADP;  $\Delta$ MPA = abs  $\downarrow$  max plt agg from BL (overall  $36.0 \pm 20.5\%$ )



Mega JL et al. & Sabatine MS. *N Engl J Med* 2009;360:354-62.

# CYP2C19 & Clinical Outcomes

1477 Patients w/ ACS and planned PCI Rx'd w/ clopidogrel



Carriers ~30% of the population

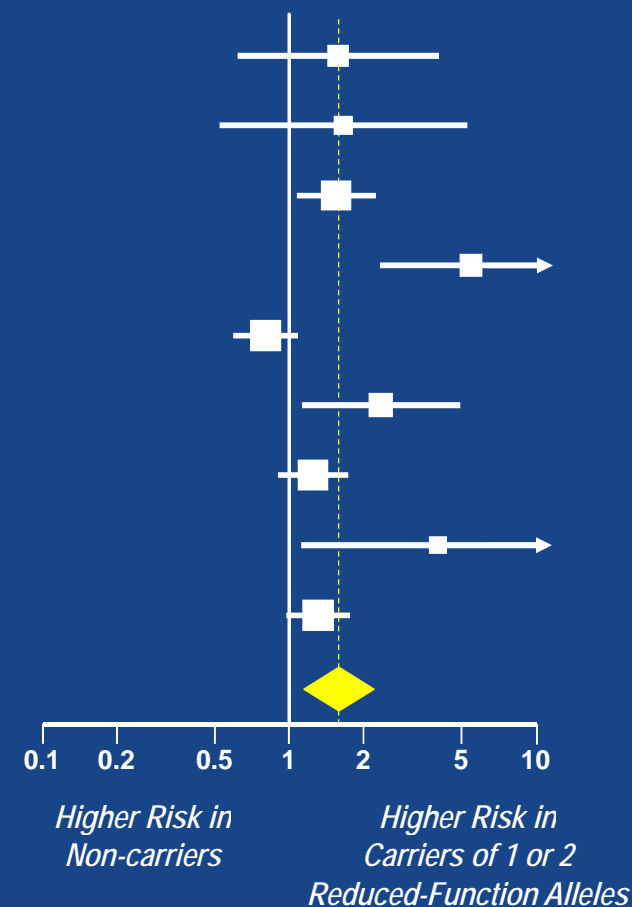
Mega JL et al. & Sabatine MS. *N Engl J Med* 2009;360:354-62.

# CYP2C19 Meta-Analysis

9 Studies, 9685 Patients, 91.5% Underwent PCI

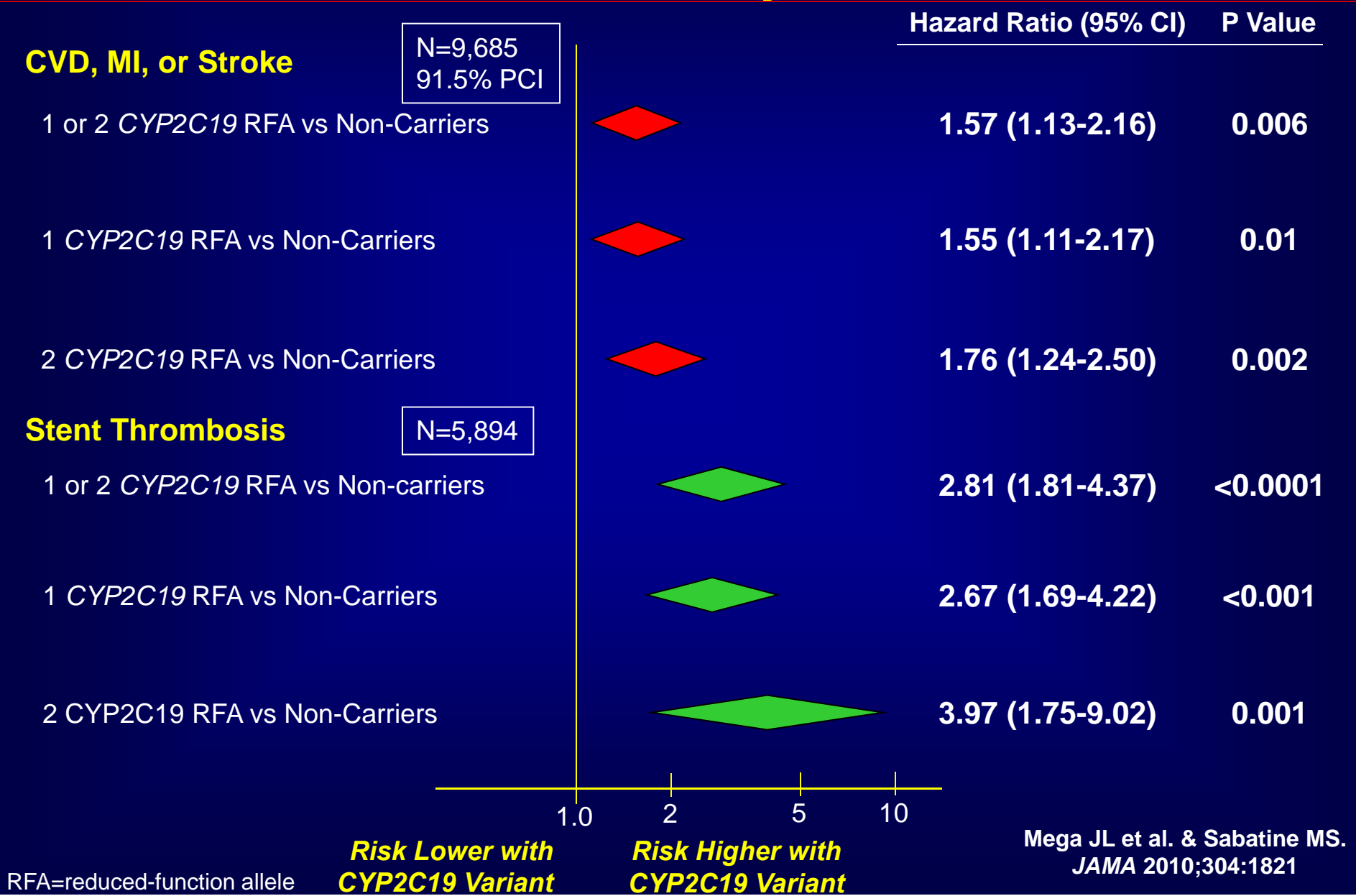
CYP2C19 Reduced-Function Alleles

	One or Two	None	HR (95% CI)
CLARITY-TIMI 28	8/77	10/150	1.56 (0.61-3.94)
EXCELSIOR	5/243	7/554	1.63 (0.52-5.14)
TRITON-TIMI 38	46/395	83/1064	1.53 (1.07-2.19)
AFIJI	15/73	11/186	5.38 (2.32-12.47)
FAST-MI	63/635	193/1573	0.79 (0.59-1.06)
RECLOSE	15/247	14/525	2.32 (1.12-4.81)
ISAR	55/680	119/1805	1.23 (0.89-1.70)
CLEAR-PLATELETS	6/68	4/160	3.95 (1.11-14.02)
INTERMOUNTAIN	68/344	141/906	1.29 (0.97-1.72)
<b>OVERALL</b>	<b>281/2762</b>	<b>582/6923</b>	<b>1.57 (1.13-2.16)</b> <b>P=0.006</b>





# CYP2C19 and Treatment with Clopidogrel Predominantly for PCI



## Clopidogrel Boxed Warning

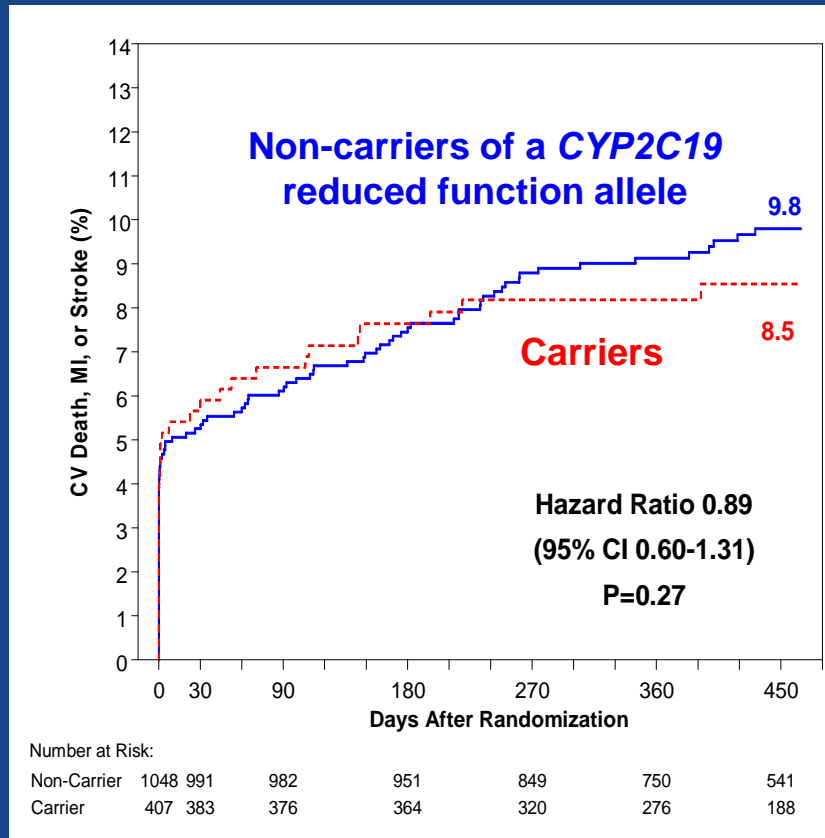
### WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

*See full prescribing information for complete boxed warning.*

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

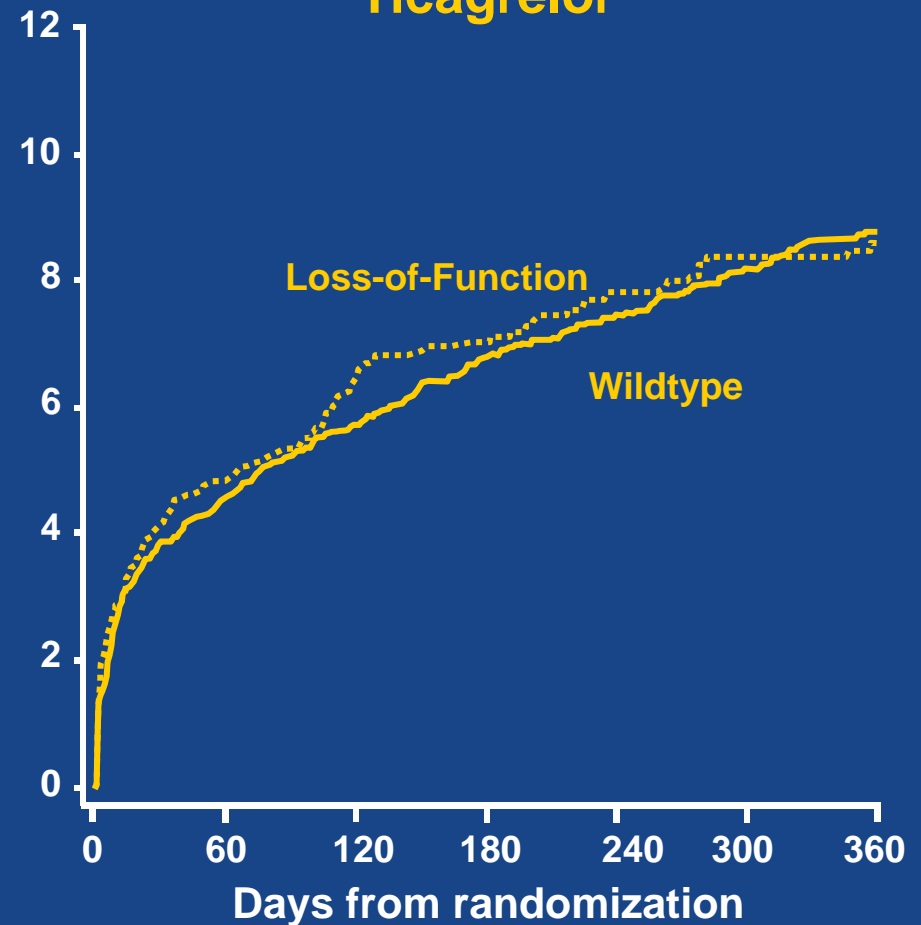
# CYP2C19 Genotype Does Not Affect Prasugrel or Ticagrelor

## Prasugrel



Mega JL et al. & Sabatine MS.  
*Circulation* 2009;119:2553-60.

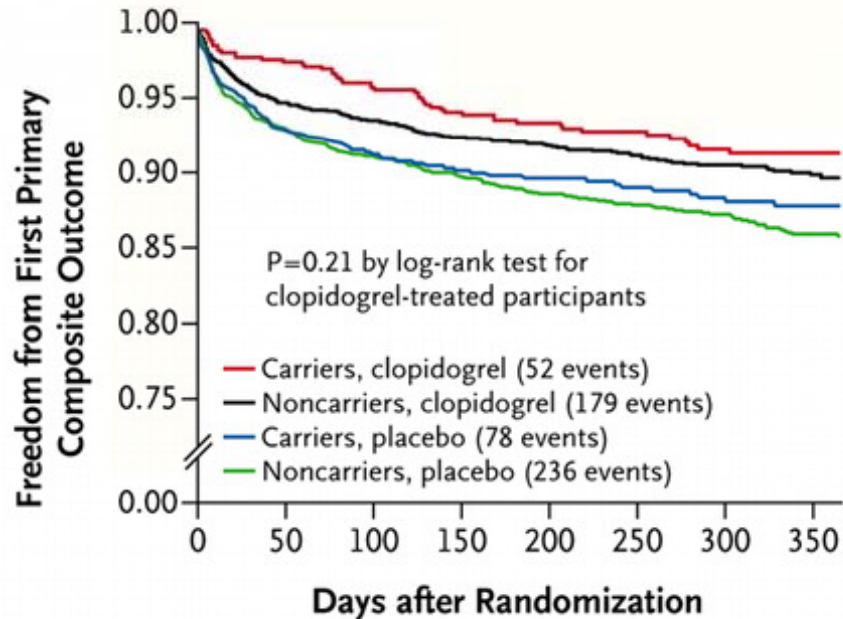
## Ticagrelor



Wallentin L et al  
*Lancet* 2010; 376:1320

# CURE Genetics Substudy

A First Primary Composite Outcome According to Loss-of-Function Allele Carrier Status

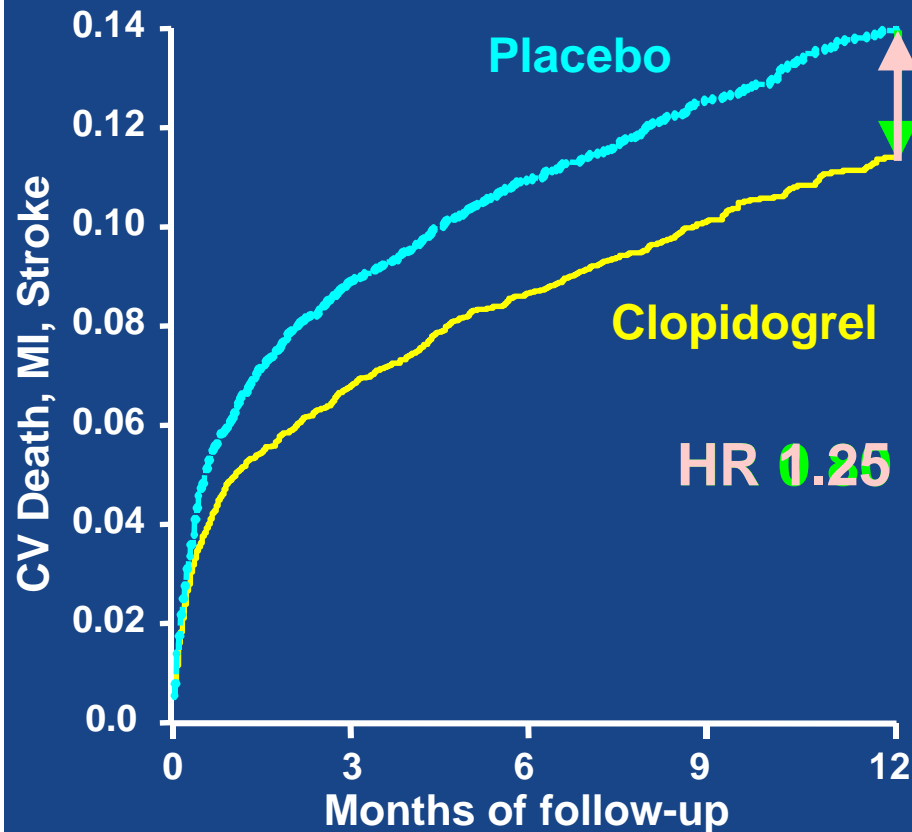


No association seen between *CYP2C19* and outcomes in clopidogrel arm.

**BUT**, patients treated conservatively (only ~15% rate of PCI).

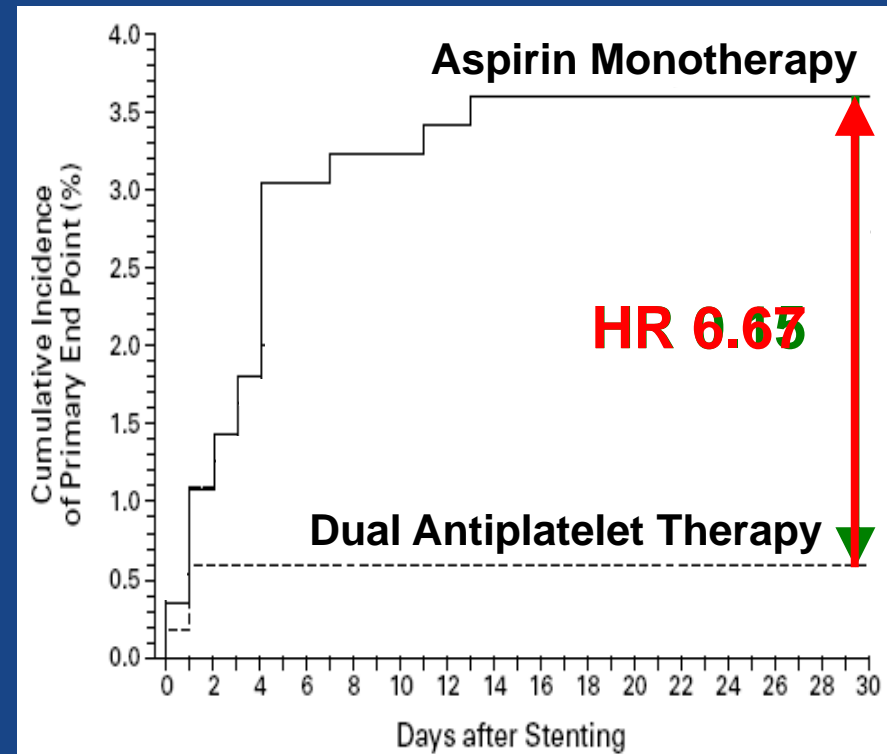
# Magnitude of PGx Interaction Will Depend on Relative Benefit of Clopidogrel

## Conservatively managed



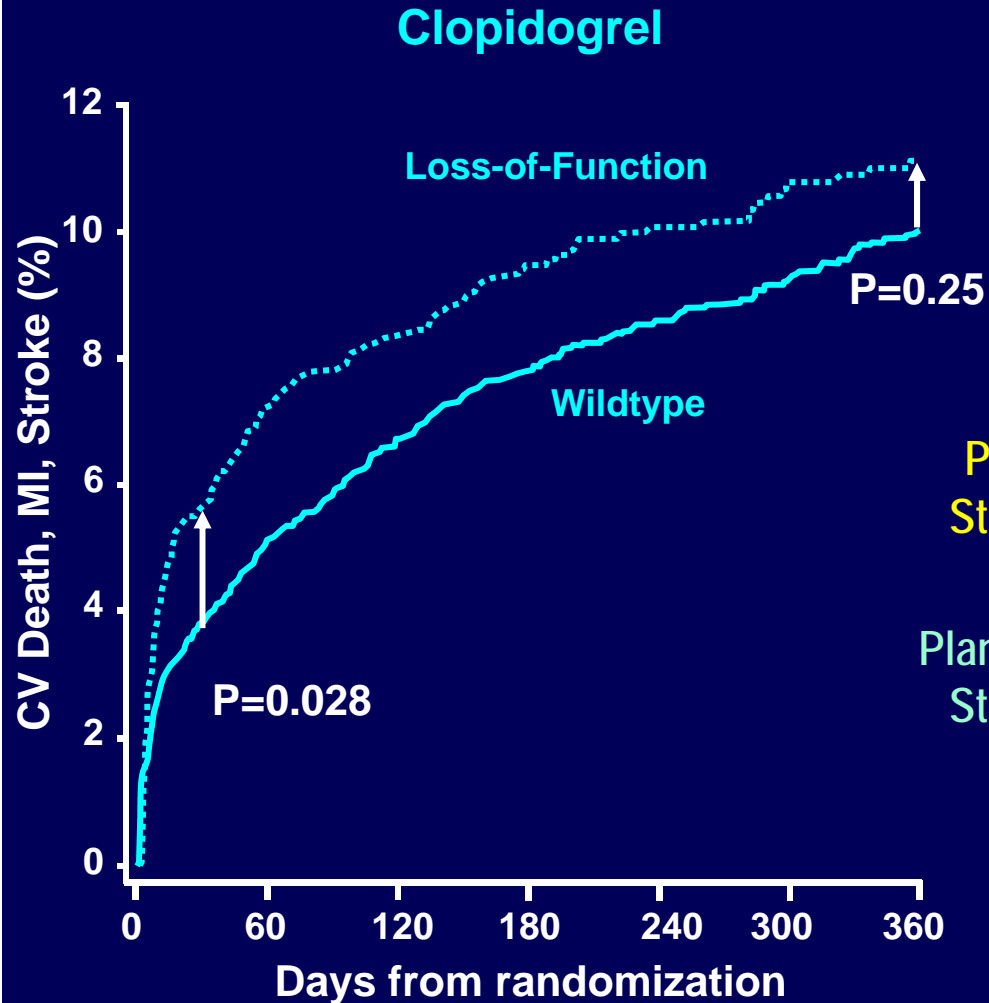
CURE. *NEJM* 2001;345:494-502

## Invasively managed



STARS. *NEJM* 1998; 339: 1665.

# CYP2C19 Genotype and Outcomes



HR for CV Death, MI, or Stroke for carriers vs. non-carriers of *CYP2C19* LOF allele

Planned Invasive Strategy (77% PCI)

**1.29 (1.03-1.63)**

Planned Conservative Strategy (21% PCI)

**0.94 (0.69-1.28)**

# CYP2C19 and Treatment with Clopidogrel

## CVD, MI, or Stroke:

Carriers of 1 or 2 CYP2C19 Variants vs Non-Carriers

Est. Hazard Ratio (95% CI)

Meta-Analysis (91.5% PCI)

1.57 (1.13-2.16)

PLATO Invasive Strategy (77% PCI)

**PREDOMINANTLY INVASIVE**

1.48 (1.14-1.91)

CURE (15.5% PCI)

CHARISMA (stable CAD or risk factors)

**P heterogeneity = 0.013**

PLATO Conservative Strategy (21% PCI)

**PREDOMINANTLY CONSERVATIVE**

0.98 (0.80-1.19)

0.5 1.0 1.5 3.0

Risk Lower with  
CYP2C19 Variant

Risk Higher with  
CYP2C19 Variant

Mega JL et al. & Sabatine MS.  
JAMA 2010;304:1821  
Wallentin. Lancet 2011; 377:637

# Conclusions

- ~30% of whites, 40% of blacks, and 55% of East Asians harbor a reduced-function *CYP2C19* allele
- Almost all of these are the \*2 allele, which is a null, loss-of-function allele
- Among patients treated with clopidogrel for PCI, carriers of a reduced-function *CYP2C19* allele have:
  - ↓ active metabolite
  - ↓ platelet inhibition
  - ↑ rates of ischemic events and stent thrombosis