Increasing Clopidogrel Based on *CYP2C19* Genotype in Patients with Cardiovascular Disease

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Trial Organization

TIMI Study Group **Brigham and Women's Hospital** **Harvard Medical School**	M Sabatine, MD, MPH (Chairman) J Mega, MD, MPH (PI) W Hochholzer, MD & C Ruff, MD, MPH (Co-Inv) L Grip, BA (Project Director) R Mesa, BS & J Mattimore, BA (Research Monitors) J Cyr, PA & D Berg, MD (Medical Monitors) C Contant, PhD (Director of Biostats) S Mohanavelu, MS & K Crowley, MS (Stats)
Clinical Events Adjudicator	B Scirica, MD, MPH
Independent Data Monitor **UT Southwestern**	J de Lemos, MD
Platelet Function Laboratory **Children's Hospital**	A Michelson, MD A Frelinger, PhD
Genotyping Laboratory **Brigham and Women's Hospital**	J Longtine, MD, PhD M Kluk, MD, PhD
Independent Biostatistics **Harvard Clinical Research Institute**	M Pencina, PhD L Lei & G Doros, PhD

Supported by an Investigator-Initiated Grant from Bristol-Myers Squibb & Sanofi-Aventis.
Research Supplies from Accumetrics and Nanosphere.

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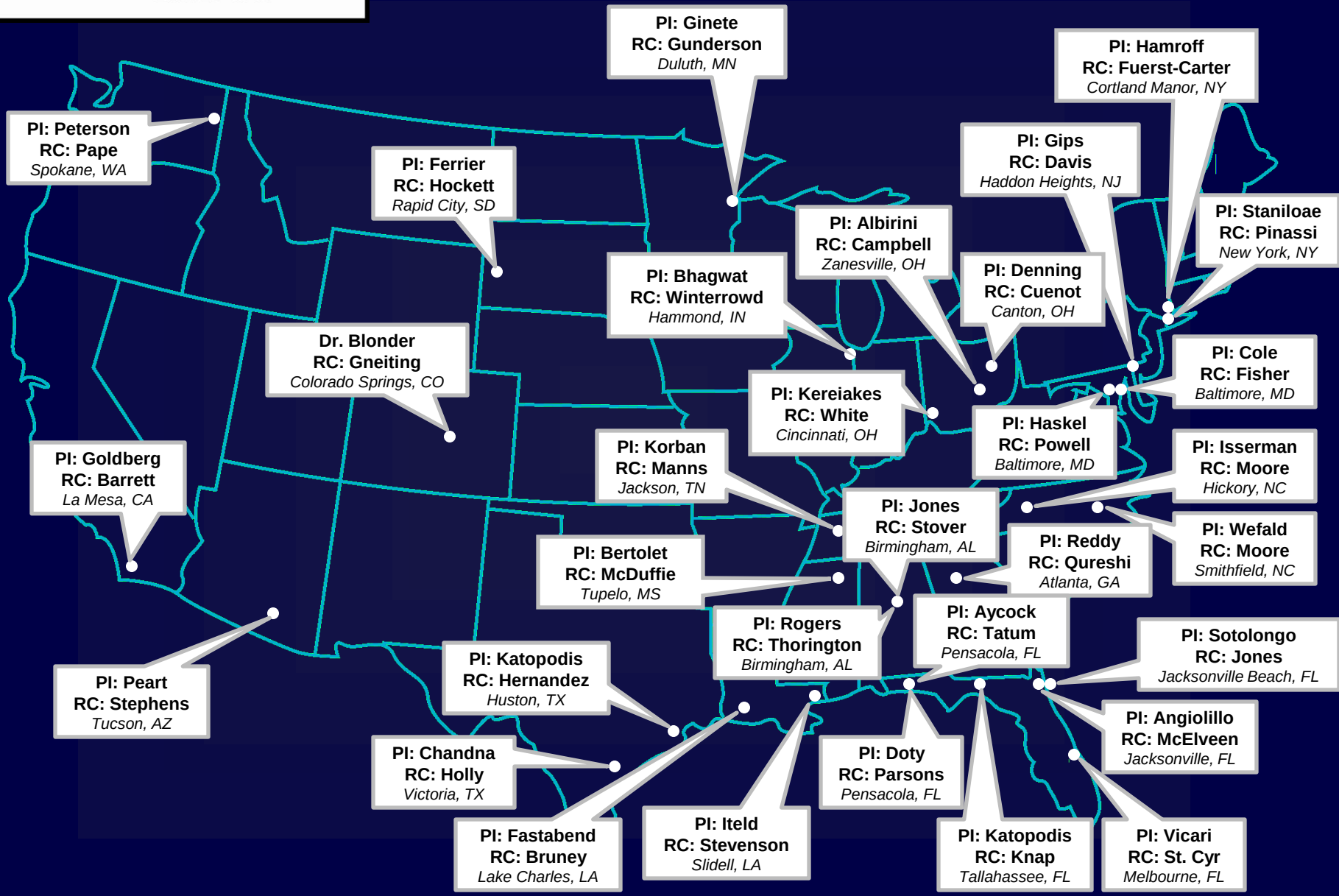
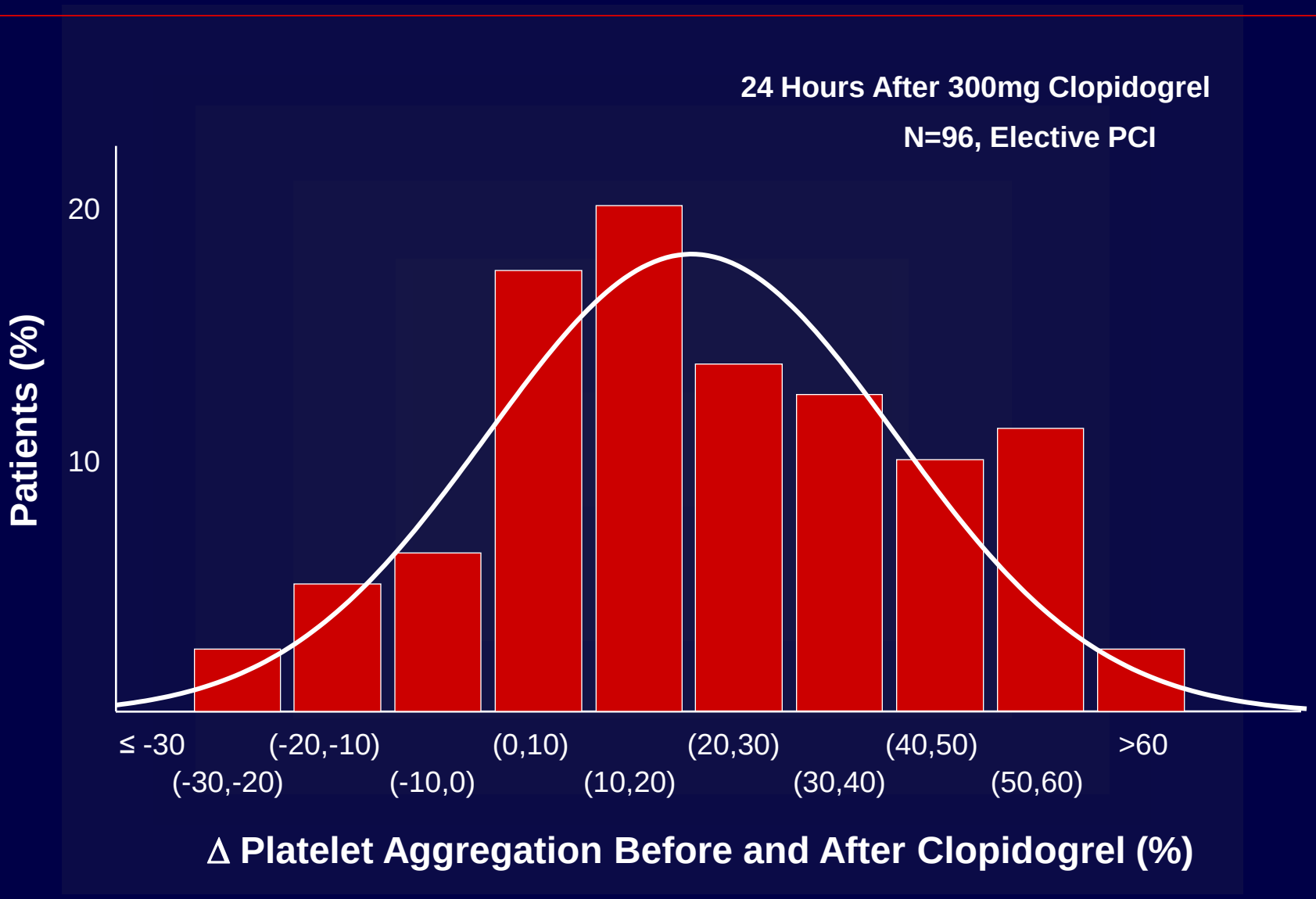
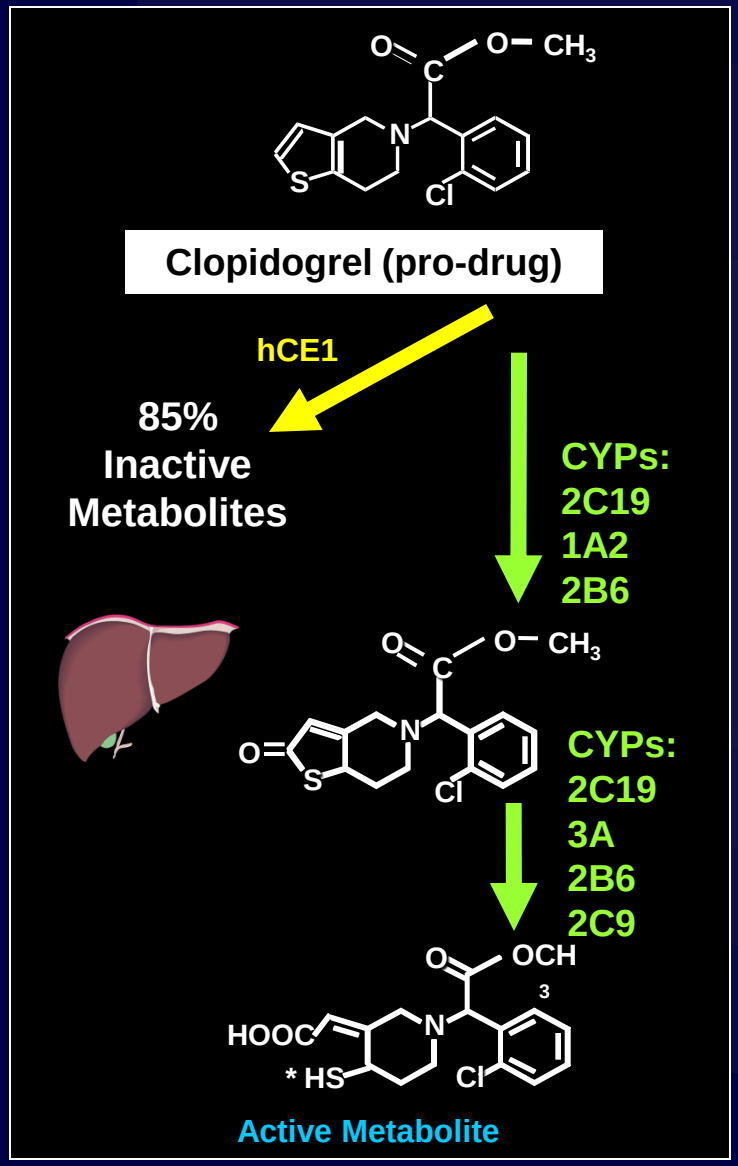


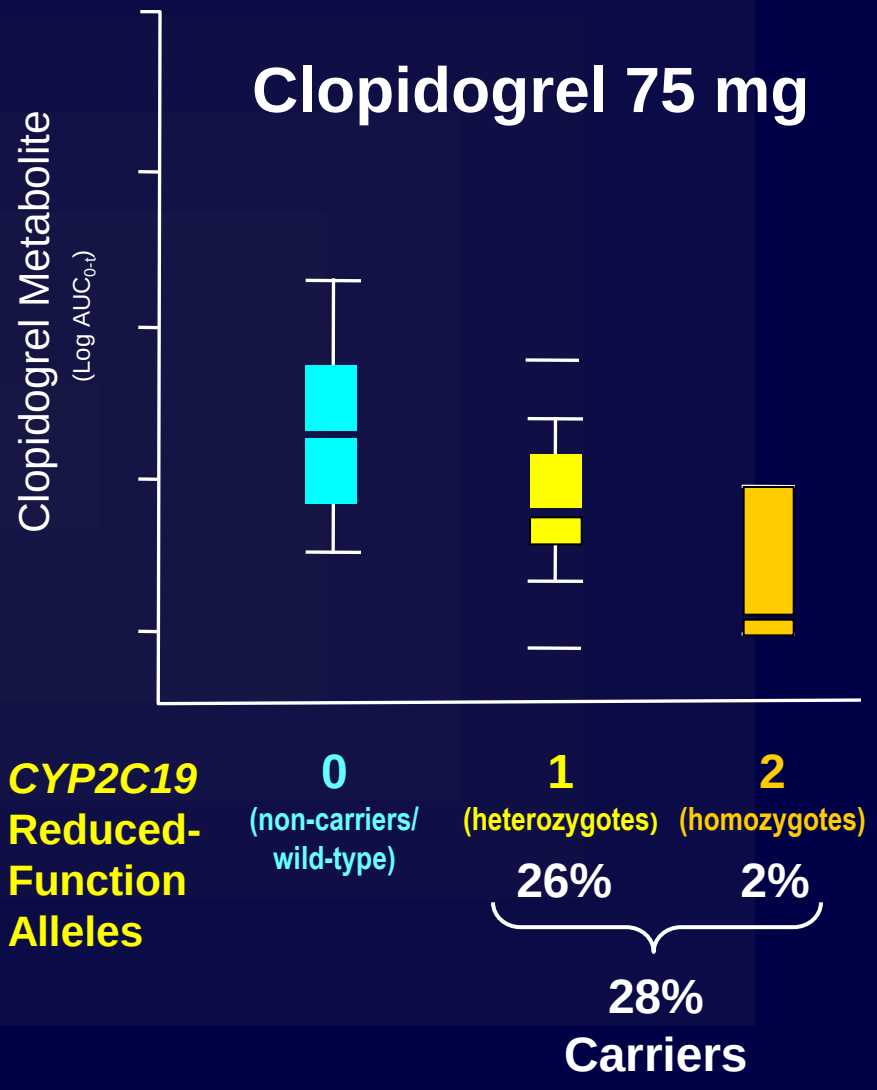
Variable Response to Clopidogrel



Gurbel PA et al. *Circulation* 2003;107:2908-13.

Clopidogrel → Active Metabolite





Mega JL, Close SL, Wiviott SD et al. *N Eng J Med.* 2009;360:354-62.

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Hypotheses

- **Increasing** the daily maintenance dose of clopidogrel in patients who carry a *CYP2C19*2* allele will **reduce** platelet reactivity.

- Among carriers of *CYP2C19*2*, a **higher maintenance dose** of clopidogrel will reduce platelet reactivity to the levels achieved in non-carriers treated with the **standard 75 mg daily dose** of clopidogrel.

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Study Design

Investigator-Initiated Study
IND #: 107635

335 Patients Enrolled
Stable CAD Pts on Clopidogrel 75 mg daily
(>4 Weeks and <6 Months Post-MI or PCI)

2 Not Genotyped

333 Blinded Genotyping

247 *CYP2C19*2* Non-Carriers

86 *CYP2C19*2* Carriers
(80 Heterozygotes; 6 Homozygotes)

Randomized to various blinded sequences of daily doses of clopidogrel

247 *CYP2C19*2* Non-Carriers			
75 mg	150 mg	75 mg	150 mg

Randomized to various blinded sequences of daily doses of clopidogrel

86 *CYP2C19*2* Carriers			
75 mg	150 mg	225 mg	300 mg

Each dose given for ~14 days followed by platelet function testing (VASP and VerifyNow $P2Y_{12}$ assays) and assessment for events

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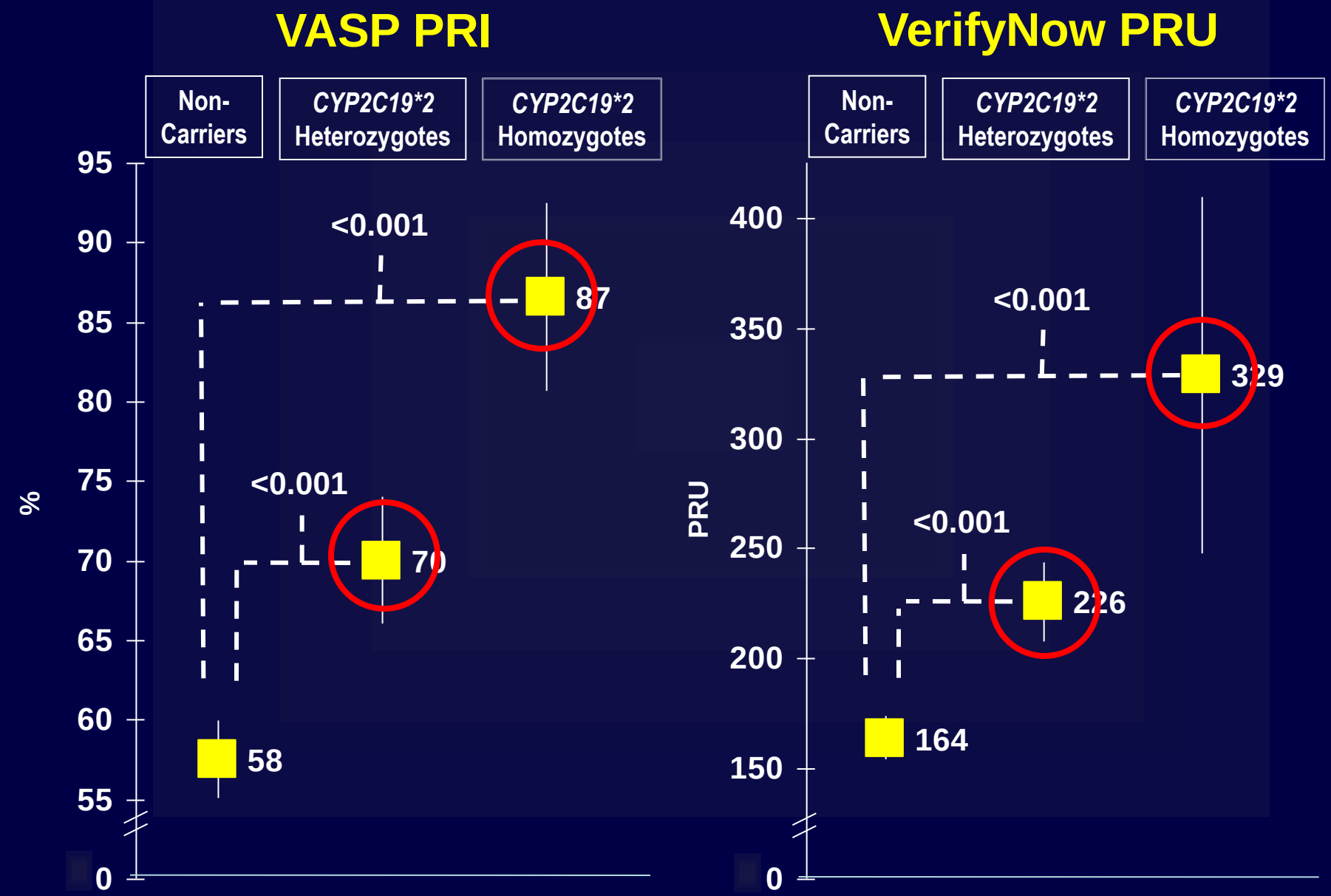
75 mg Clopidogrel Daily



Squares represent the means and vertical lines the 95% confidence intervals.

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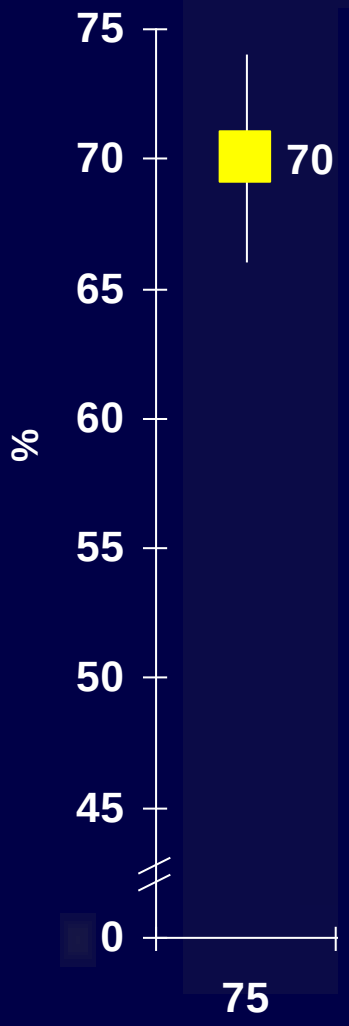
*CYP2C19*2* Heterozygotes

VASP PRI



Clopidogrel Daily Dose (mg)

Squares represent the means and vertical lines the 95% confidence intervals.

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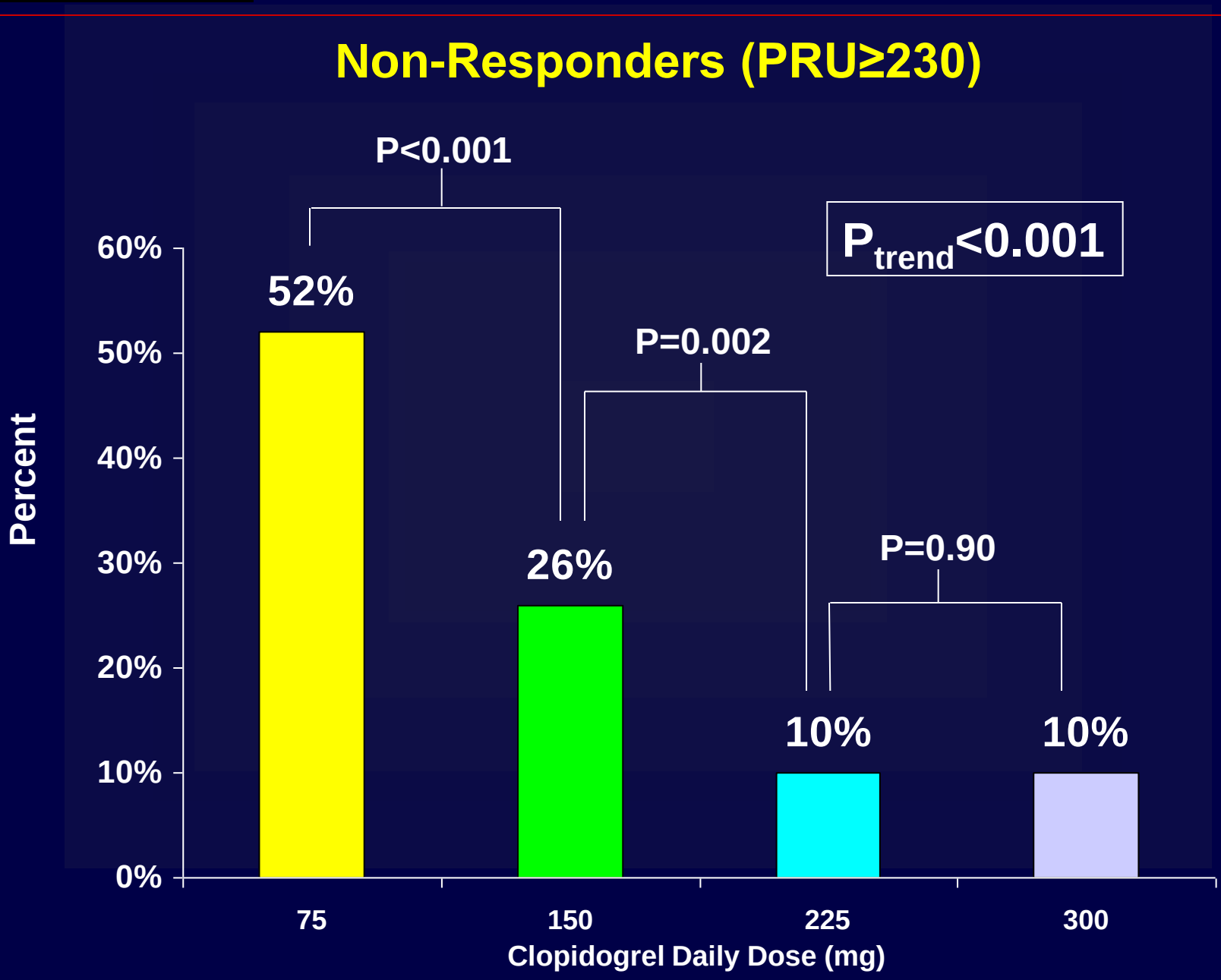
*CYP2C19*2* Heterozygotes



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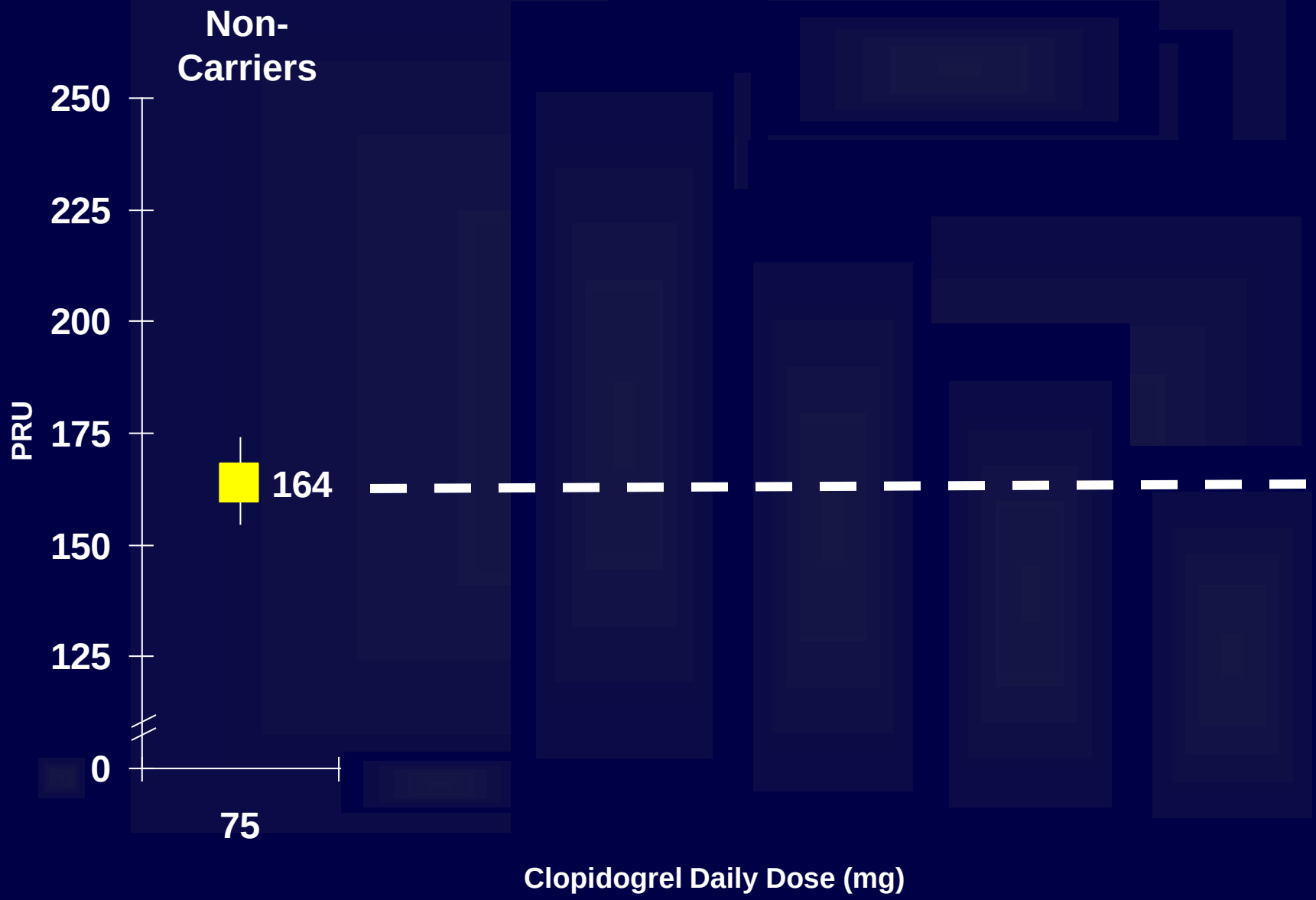
↑ Clopidogrel in *CYP2C19**2* Heterozygotes vs. 75 mg in Non-Carriers



Squares represent the means and vertical lines the 95% confidence intervals. Differences are reported as least squares differences.

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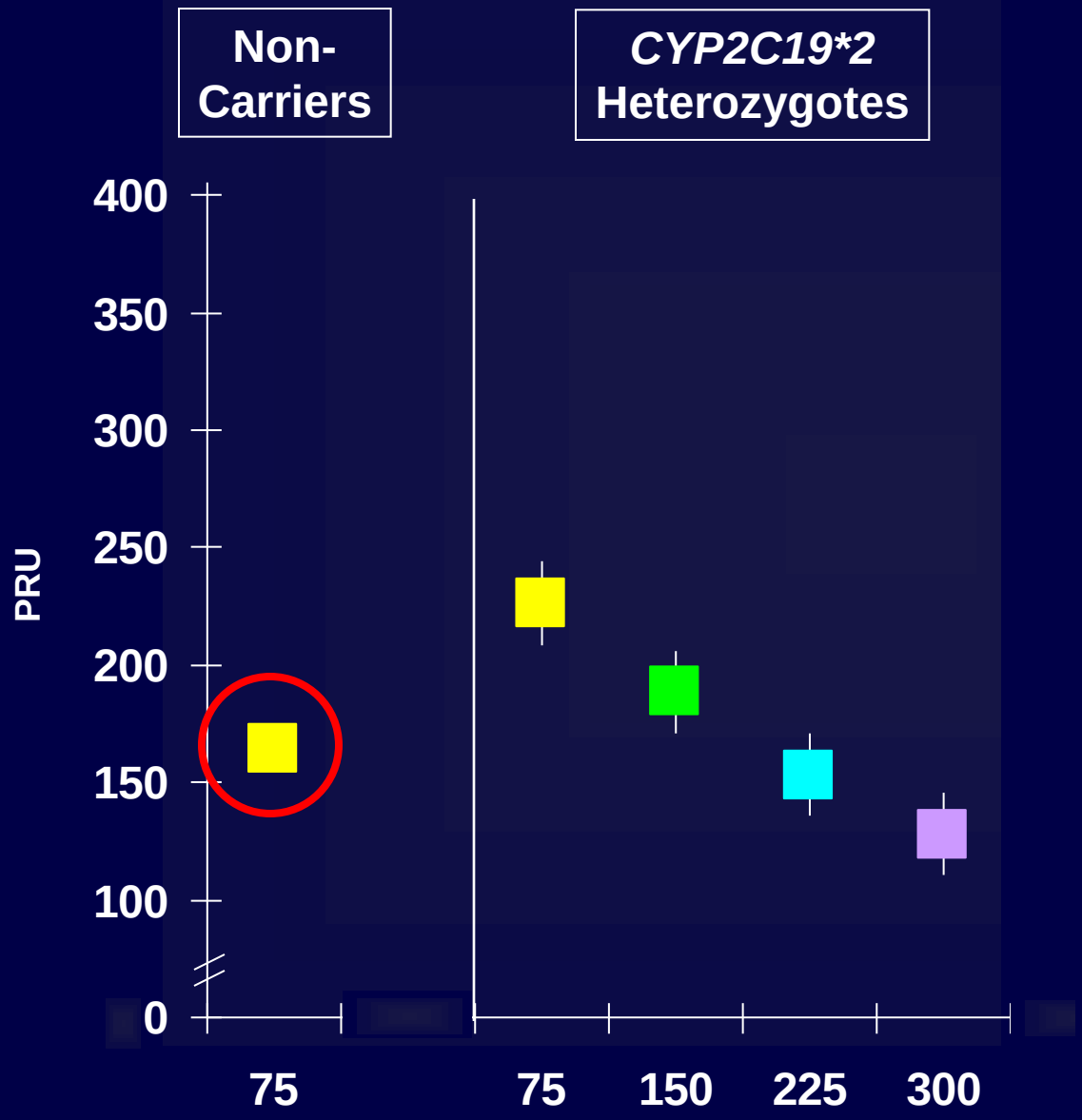
Platelet Reactivity with ↑ Clopidogrel



Squares represent the means and vertical lines the 95% confidence intervals.

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Compliance and Events

*CYP2C19*2* Carriers

Clopidogrel Doses (mg)	75	150	225	300
Compliance (%)	97.3%	98.1%	98.6%	98.3%
Adverse Events (n)	12	10	2	6
Serious Adverse Events (n)	2	0	0	1
TIMI Bleeding Requiring Medical Attention (n)	1	0	1	1
Cardiac Ischemic Events (n)	1	0	0	0

There were no deaths, cerebrovascular events, or TIMI major or minor bleeding events.

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Conclusion

Among patients with stable CV disease:

- ***CYP2C19*2* heterozygotes**: tripling the maintenance dose of clopidogrel to 225 mg daily achieved levels of platelet reactivity similar to the standard 75 mg dose in non-carriers.

- ***CYP2C19*2* homozygotes**: even 300 mg of clopidogrel daily, is unlikely to result in optimal degrees of platelet inhibition.

ORIGINAL CONTRIBUTION

ONLINE FIRST

Dosing Clopidogrel Based on *CYP2C19* Genotype and the Effect on Platelet Reactivity in Patients With Stable Cardiovascular Disease

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Context Variants in the *CYP2C19* gene influence the pharmacologic and clinical response to the standard 75-mg daily maintenance dose of the antiplatelet drug clopidogrel.

Objective To test whether higher doses (up to 300 mg daily) improve the response to clopidogrel in the setting of loss-of-function *CYP2C19* genotypes.

Design, Setting, and Patients ELEVATE-TIMI 56 was a multicenter, randomized, double-blind trial that enrolled and genotyped 333 patients with cardiovascular disease across 32 sites from October 2010 until September 2011.

Interventions Maintenance doses of clopidogrel for 4 treatment periods, each lasting approximately 14 days, based on genotype. In total, 247 noncarriers of a *CYP2C19**2 loss-of-function allele were to receive 75 and 150 mg daily of clopidogrel (2 periods each), whereas 86 carriers (80 heterozygotes, 6 homozygotes) were to receive 75, 150, 225, and 300 mg daily.

Main Outcome Measures Platelet function test results (vasodilator-stimulated phosphoprotein [VASP] phosphorylation and VerifyNow $P2Y_{12}$ assays) and adverse events.

Results With 75 mg daily, *CYP2C19**2 heterozygotes had significantly higher on-treatment platelet reactivity than did noncarriers (VASP platelet reactivity index [PRI]: mean, 70.0%; 95% CI, 66.0%-74.0%, vs 57.5%; 95% CI, 55.1%-59.9%, and VerifyNow $P2Y_{12}$ reaction units [PRU]: mean, 225.6; 95% CI, 207.7-243.4, vs 163.6; 95% CI, 154.4-173.9; $P<.001$ for both comparisons). Among *CYP2C19**2 heterozygotes, doses up to 300 mg daily significantly reduced platelet reactivity, with VASP PRI decreasing to 48.9% (95% CI, 44.6%-53.2%) and PRU to 127.5 (95% CI, 109.9-145.2) ($P<.001$ for trend across doses for both). Whereas 52% of *CYP2C19**2 heterozygotes were nonresponders (≥230 PRU) with 75 mg of clopidogrel, only 10% were nonresponders with 225 or 300 mg ($P<.001$ for both). Clopidogrel, 225 mg daily, reduced platelet reactivity in *CYP2C19**2 heterozygotes to levels achieved with standard clopidogrel, 75 mg, in noncarriers (mean ratios of platelet reactivity, VASP PRI, 0.92; 90% CI, 0.85-0.99, and PRU, 0.94; 90% CI, 0.84-1.04). In *CYP2C19**2 homozygotes, even with 300 mg daily of clopidogrel, mean VASP PRI was 68.3% (95% CI, 44.9%-91.6%) and mean PRU, 287.0 (95% CI, 170.2-403.8).

Conclusion Among patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in *CYP2C19**2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in noncarriers; in contrast, for *CYP2C19**2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition.

Trial Registration clinicaltrials.gov Identifier: NCT01235351

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CLOPIDOGREL BLOCKS THE platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor, inhibition of which has been shown to reduce cardiovascular events in patients with an acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI).[1-4] Although the standard 75-mg daily maintenance dose of clopidogrel has proven to be clinically efficacious in these settings, variability in the pharmacodynamic response to clopidogrel is well recognized, and patients with higher platelet reactivity while receiving clopidogrel are at increased risk of adverse cardiovascular events.[5] Clopidogrel, a prodrug, needs to undergo biotransformation to form an active metabolite, and interindividual differences in clopidogrel metabolism are a

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