

Dosing Clopidogrel Using CYP2C19 Genotypes: The ELEVATE-TIMI 56 Trial

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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.**

Study Design



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

2 Not Genotyped

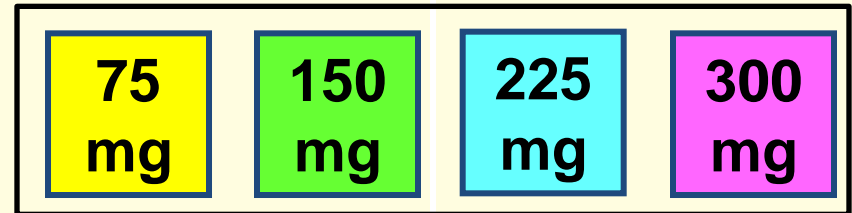
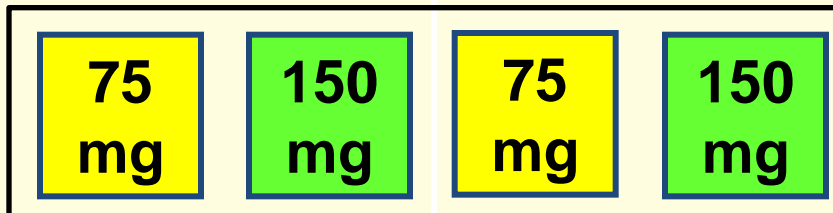
333 Blinded Genotyping

247 *CYP2C192 Non-Carriers**

86 *CYP2C192 Carriers**
(80 Heterozygotes; 6 Homozygotes)

Randomized to various blinded sequences
of daily doses of clopidogrel

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of daily doses of clopidogrel

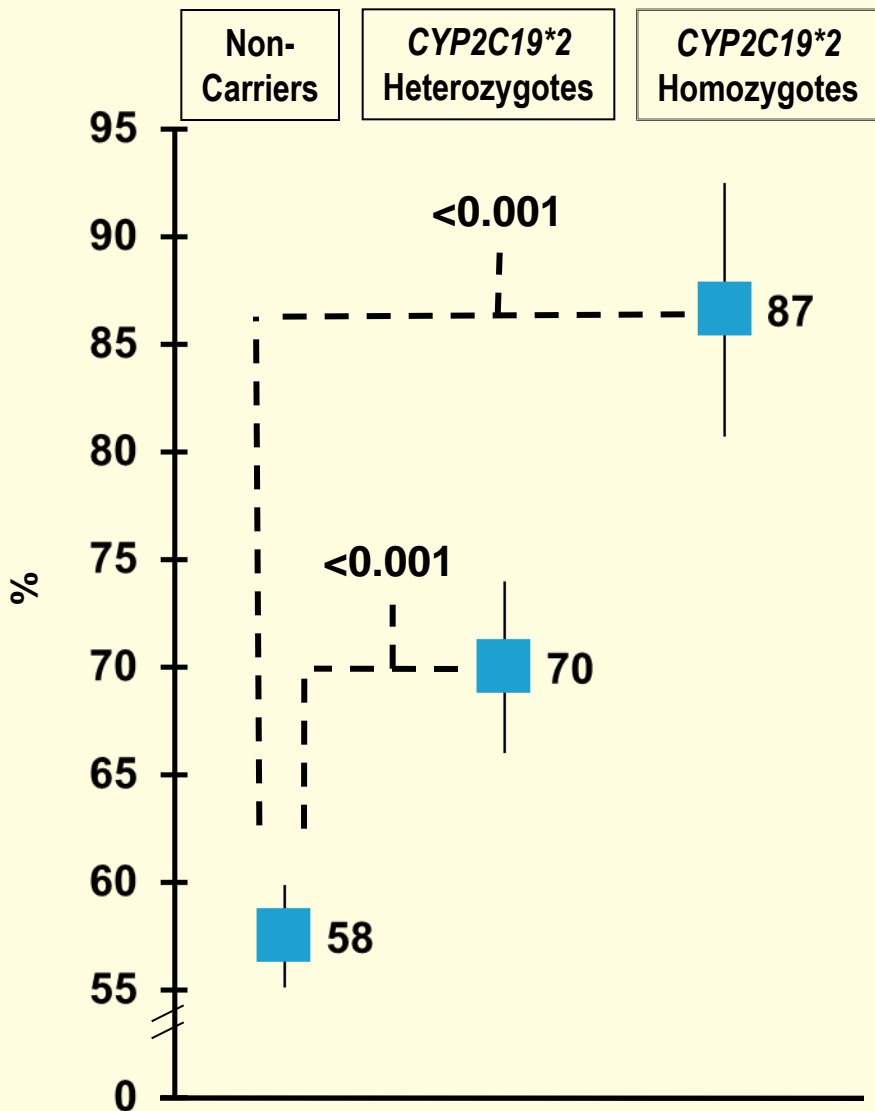


Each dose given for ~14 days followed by platelet function testing
(VASP and VerifyNow P2Y₁₂ assays) and assessment for events

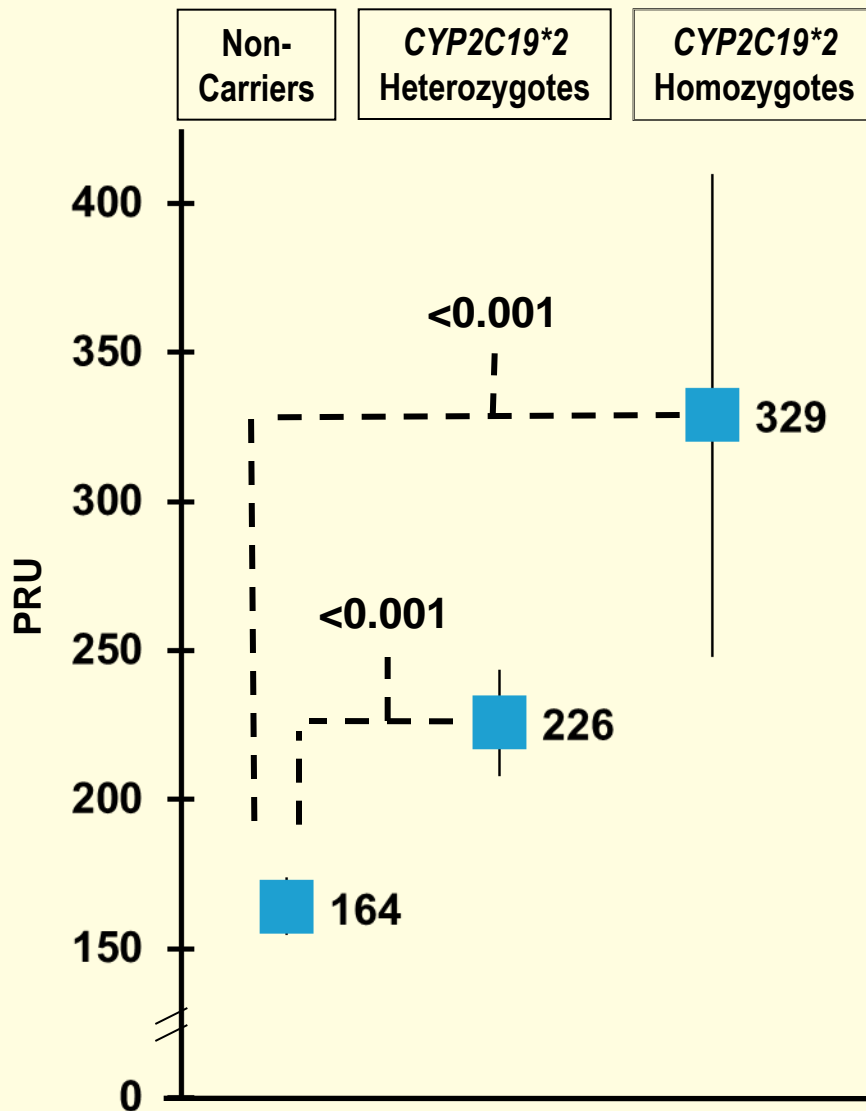
Mean Platelet Reactivity



VASP PRI



VerifyNow PRU

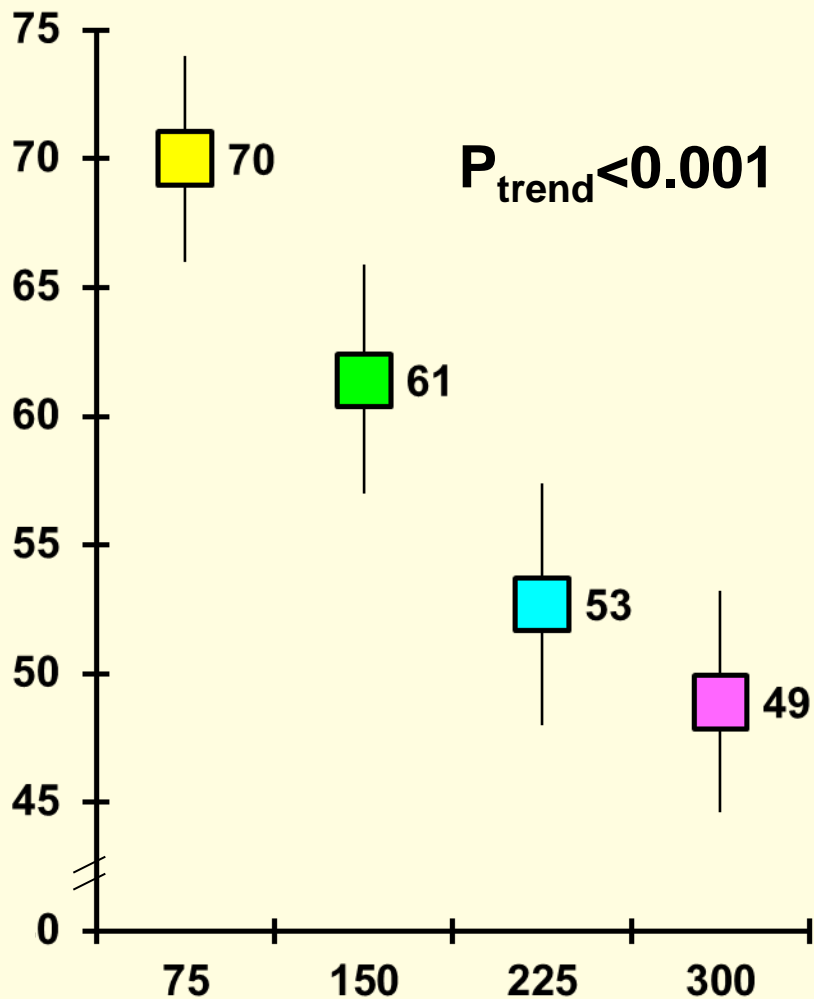


Squares represent the means and vertical lines the 95% confidence intervals.

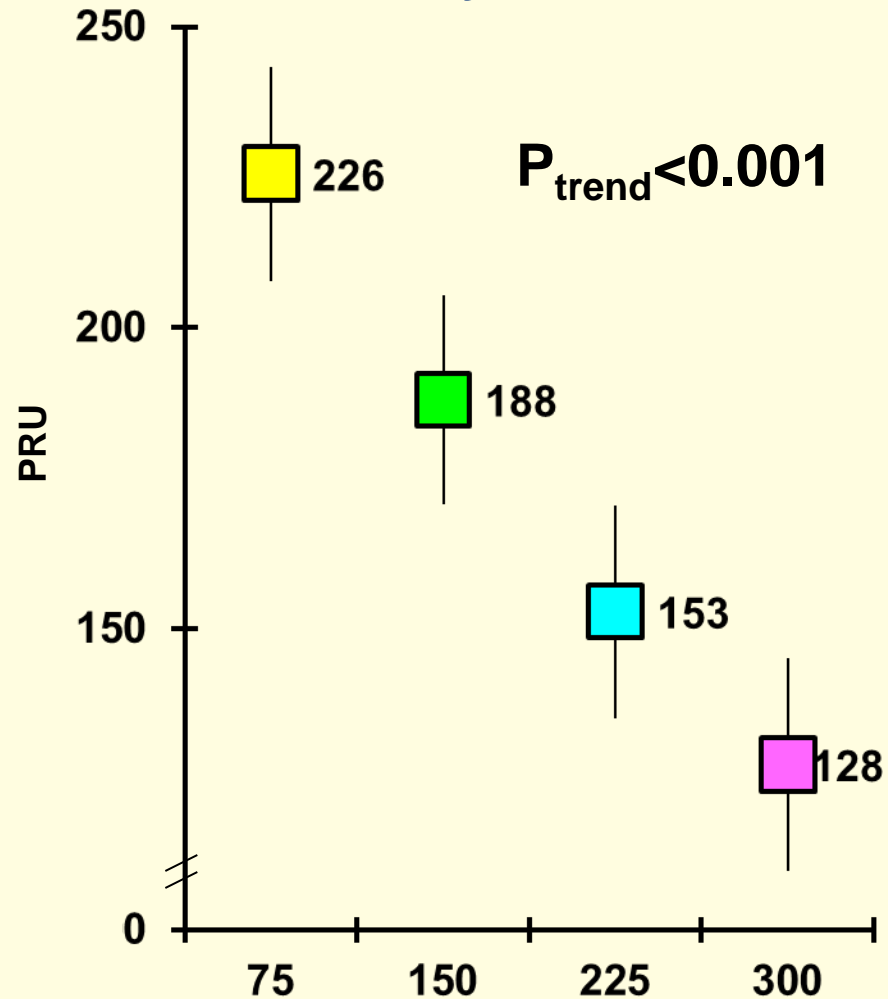
CYP2C19*2 Heterozygotes



VASP PRI



VerifyNow PRU



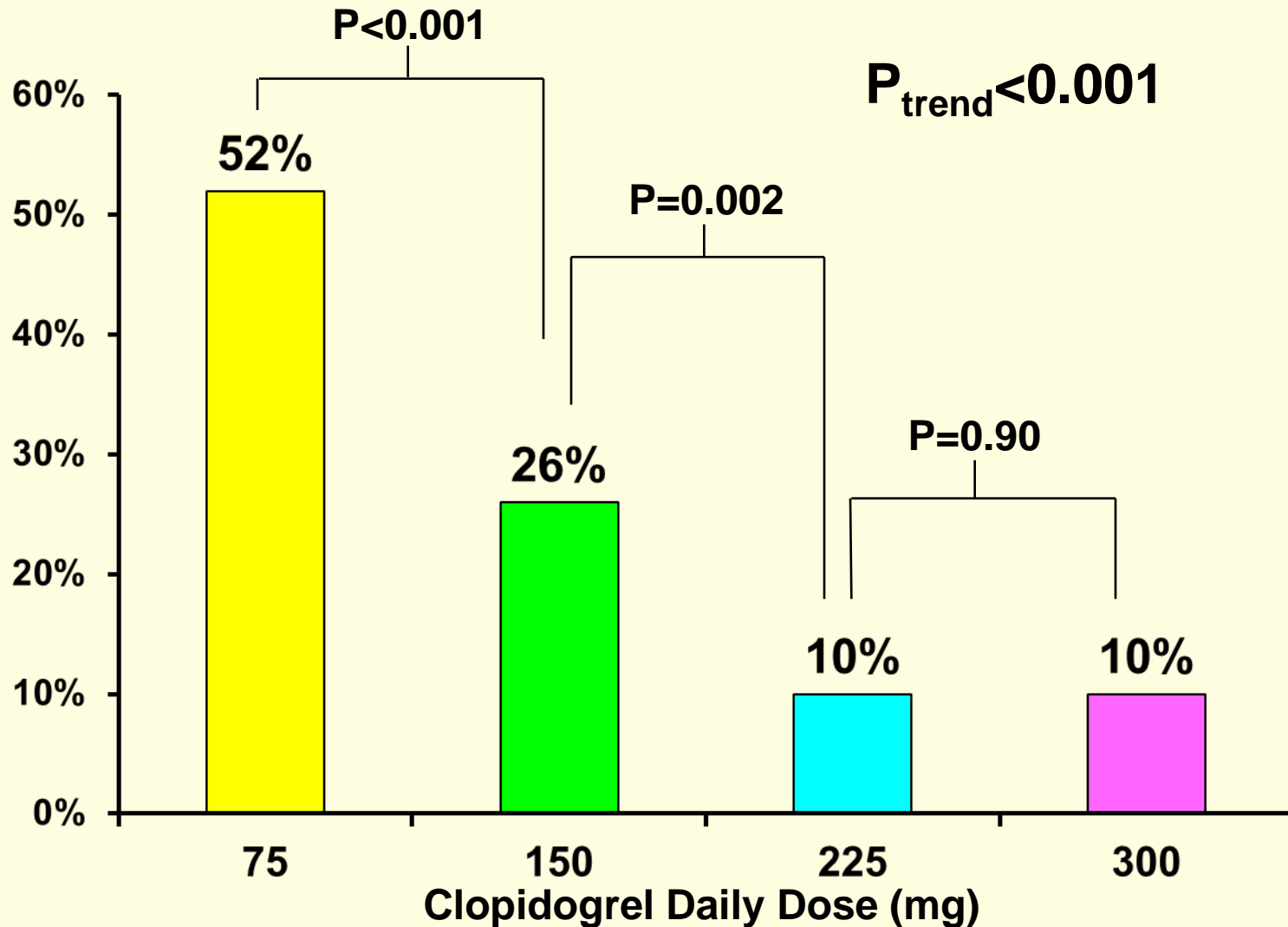
Clopidogrel Daily Dose (mg)

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

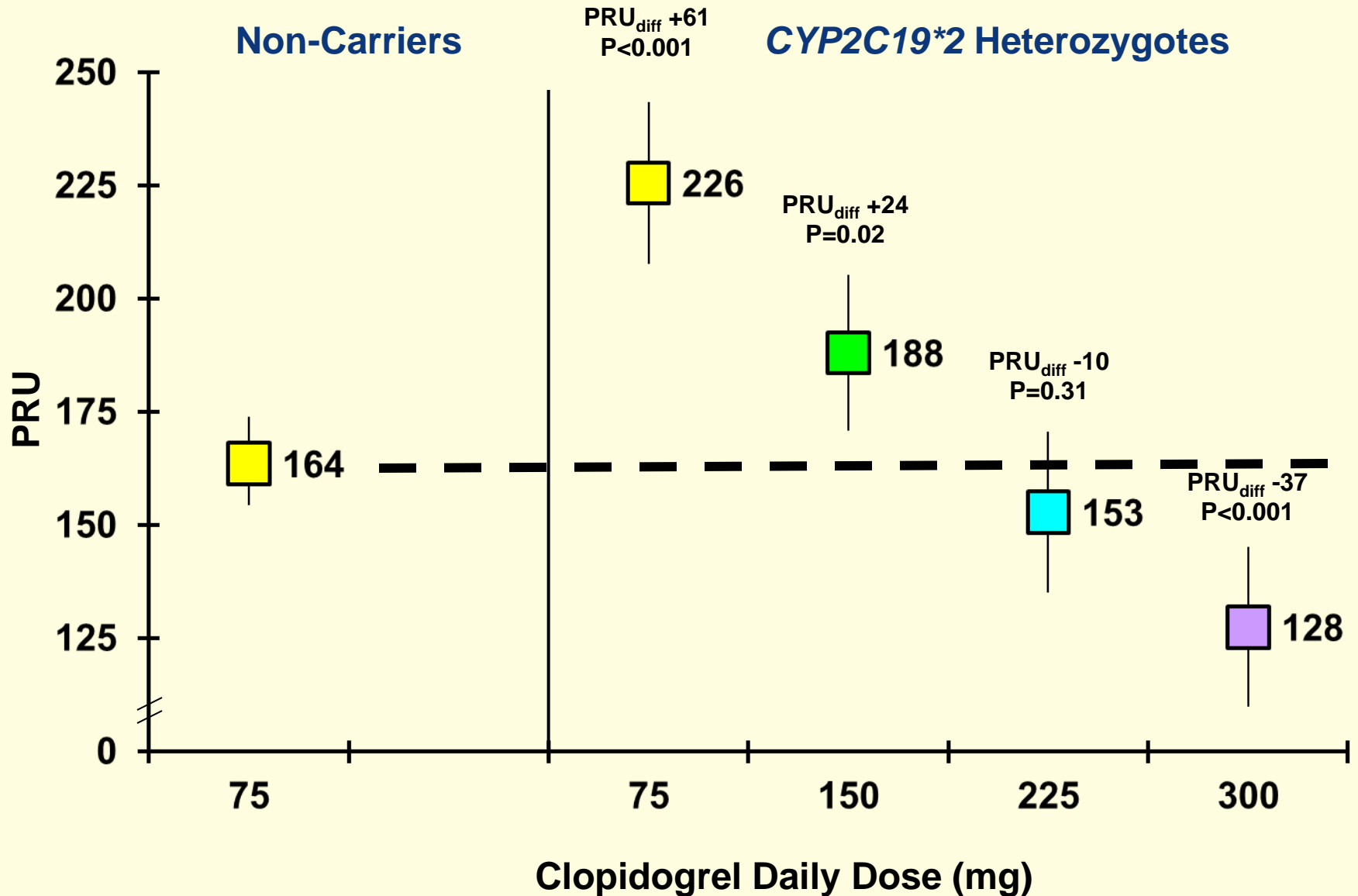
CYP2C19*2 Heterozygotes



Non-Responders (PRU \geq 230)



Non-carriers vs. Heterozygotes



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

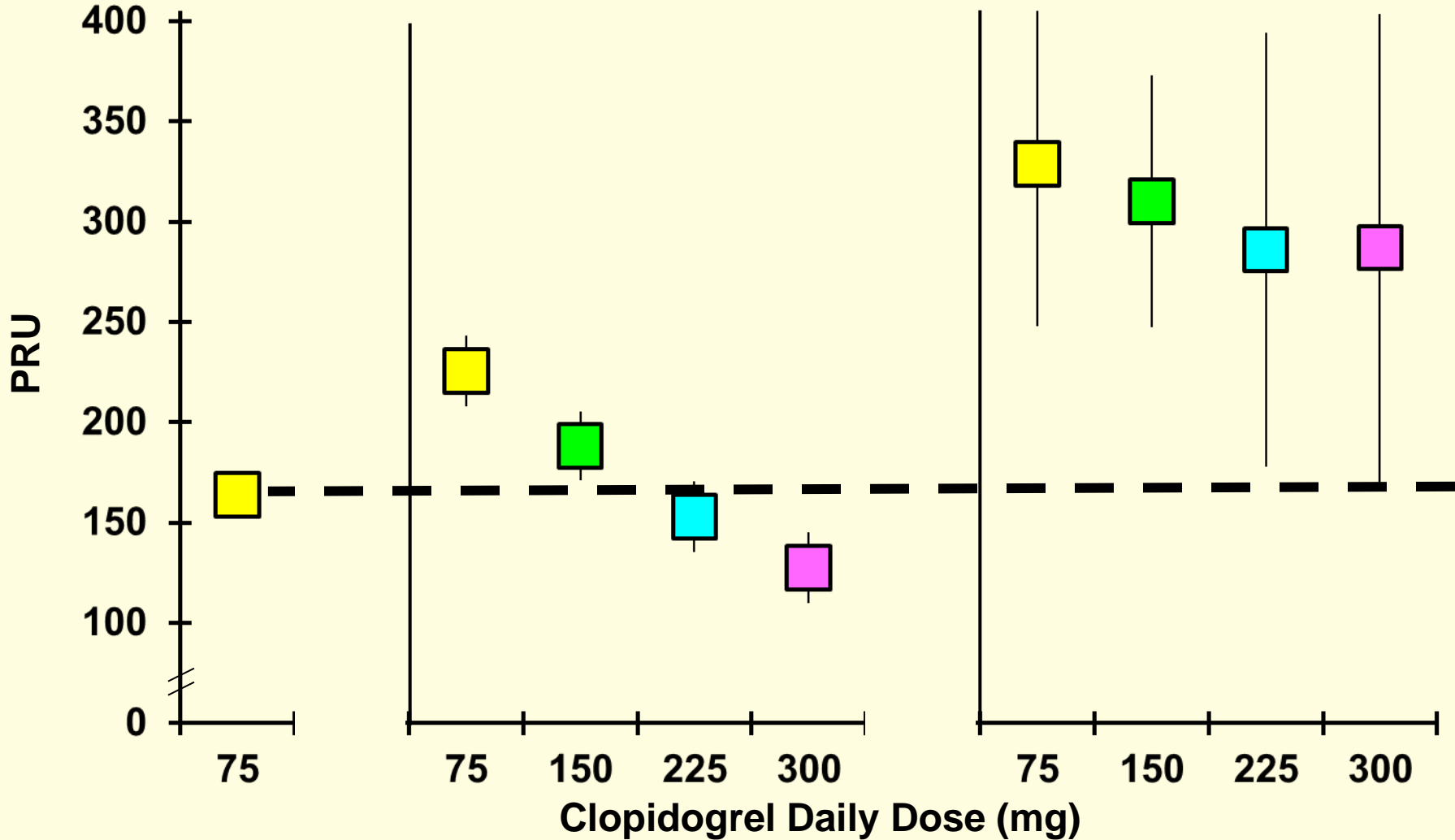
Homozygotes vs. Heterozygotes



Non-Carriers

*CYP2C19*2*
Heterozygotes

*CYP2C19*2*
Homozygotes



Compliance and Events (*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.



Conclusions



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.

