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Guided antiplatelet therapy in patients undergoing PCI

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Declaration of Conflict Of Interest

I have no potential conflict of interest to report

Antiplatelet drugs targeting P2Y₁₂

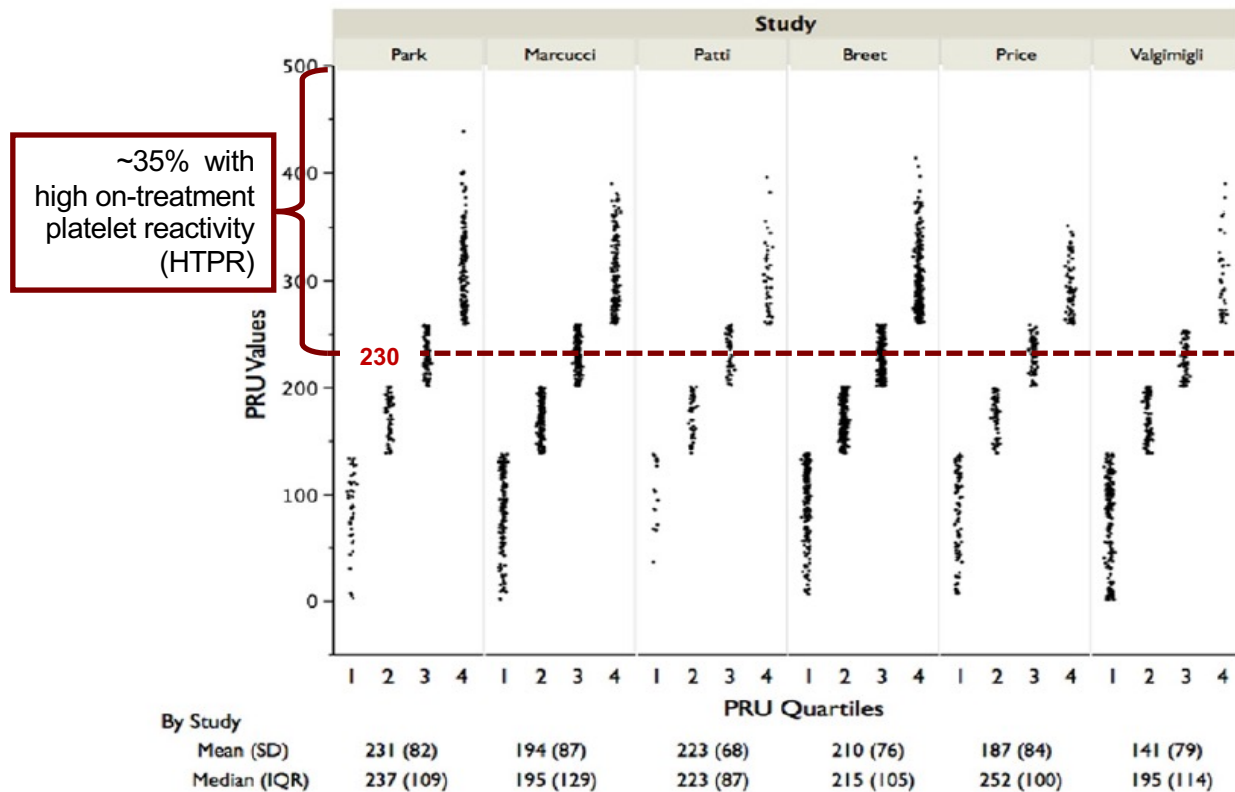
Thienopyridines (pro-drugs whose active metabolites irreversibly inhibit P2Y₁₂)

- Ticlopidine
- Clopidogrel
- Prasugrel

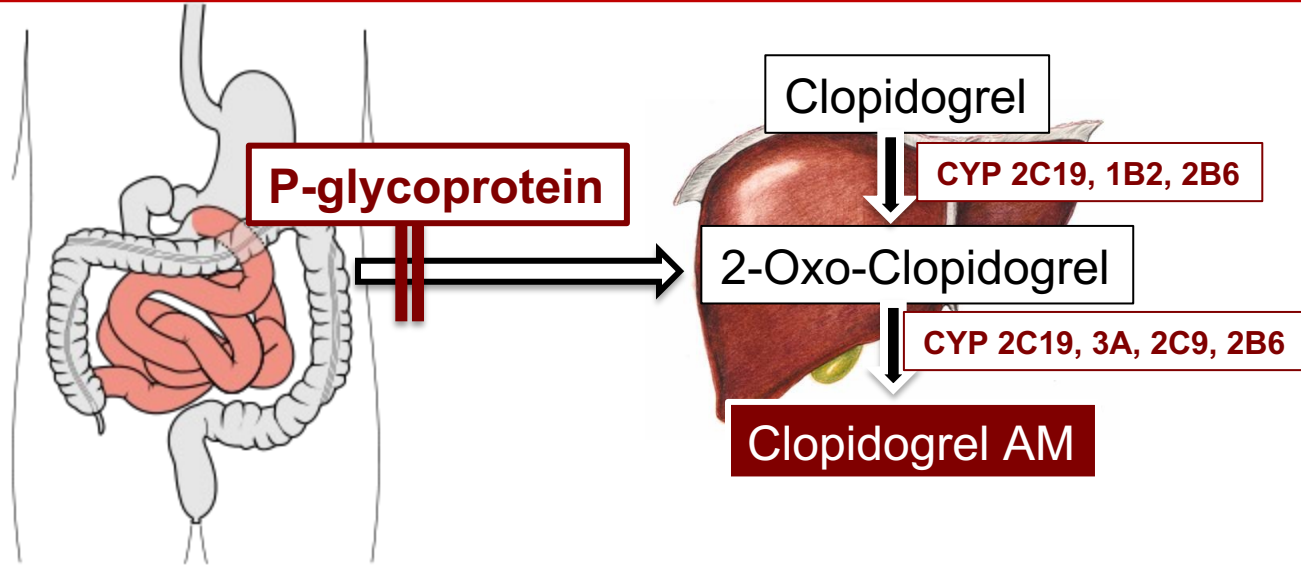
Ticagrelor (direct acting, reversible (T_{1/2}≈8h), oral P2Y₁₂ inhibitor)

Cangrelor (direct acting, reversible (T_{1/2}≈2.5 min), parenteral P2Y₁₂ inhibitor)

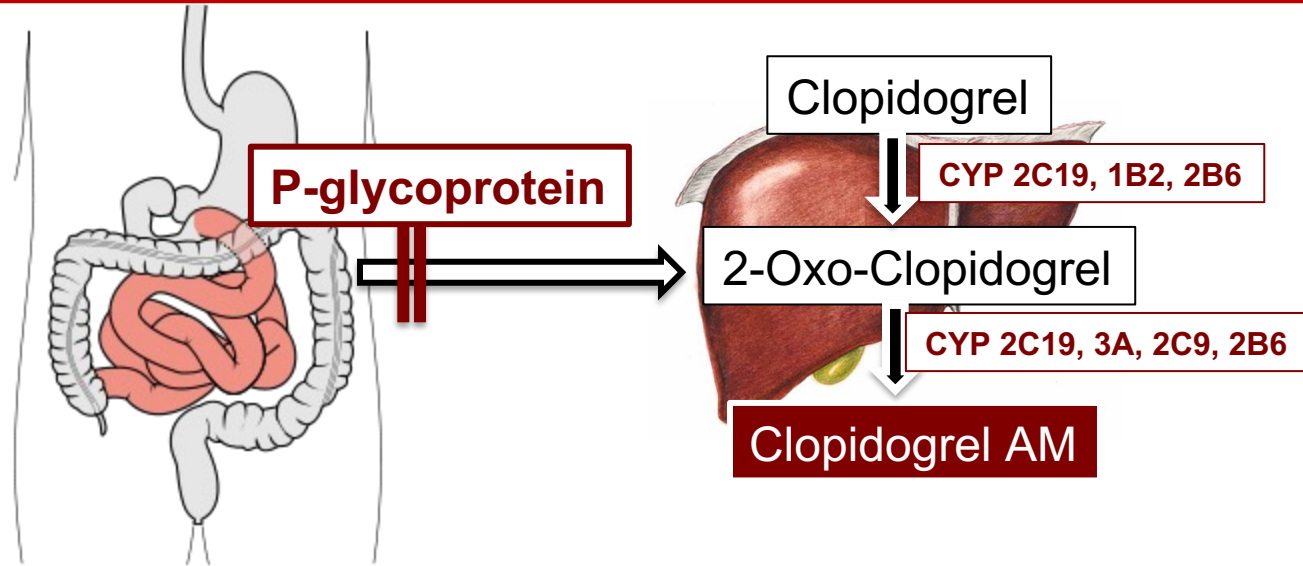
Distribution of Platelet Reactivity Units (PRU), measure with VerifyNow P2Y12 in Clopidogrel-treated Patients, by Study and Quartile



Absorption and metabolism of clopidogrel



Absorption and metabolism of clopidogrel



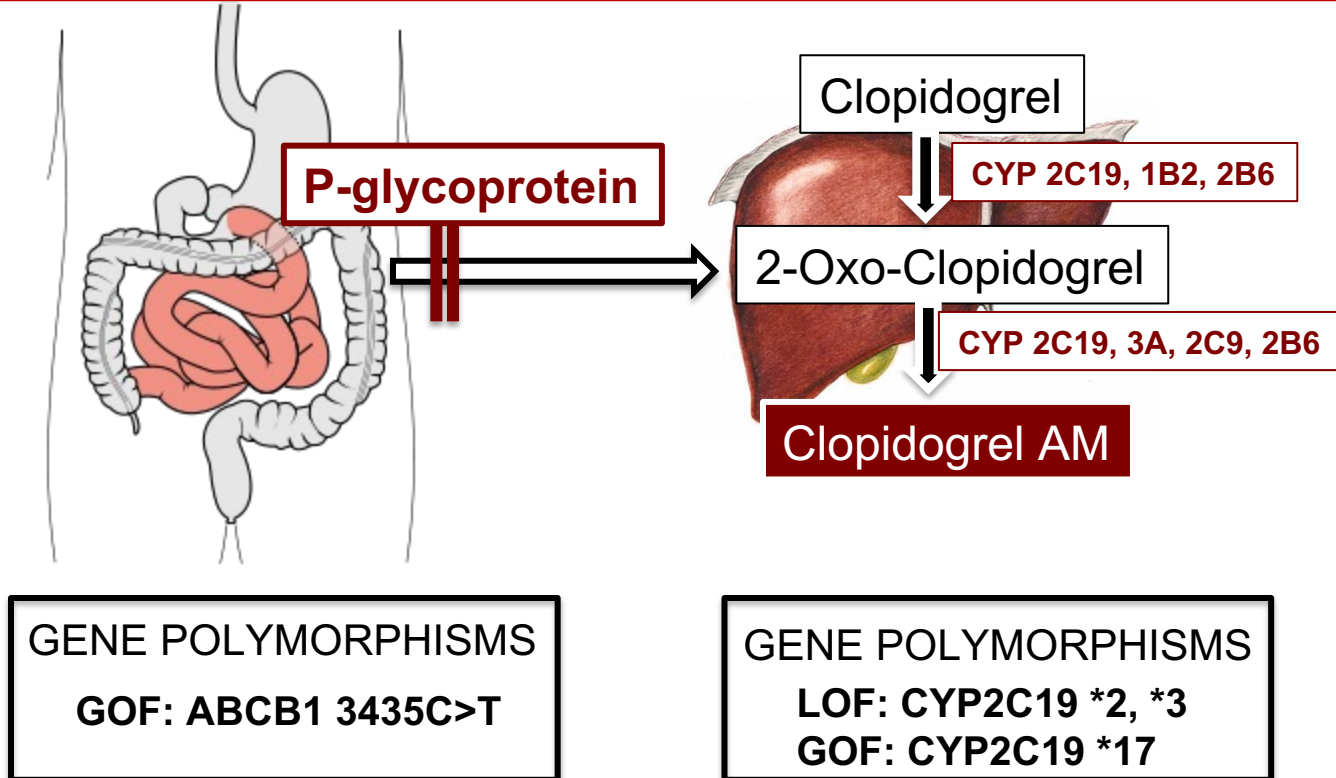
GENE POLYMORPHISMS

GOF: ABCB1 3435C>T

ABCB1 affects clopidogrel absorption - Influence of C3435T polymorphism

Plasma level (ng/mL)	3435T/T	3435C/T and 3435C/C
Clopidogrel	13.3 +/- 5.2	49.7 +/- 41.6**
Clopidogrel active metabolite	2.5 +/- 1.2	6.6 +/- 3.6*

Absorption and metabolism of clopidogrel



Contribution of CYP 2C19 genotypes to HTPR during clopidogrel therapy

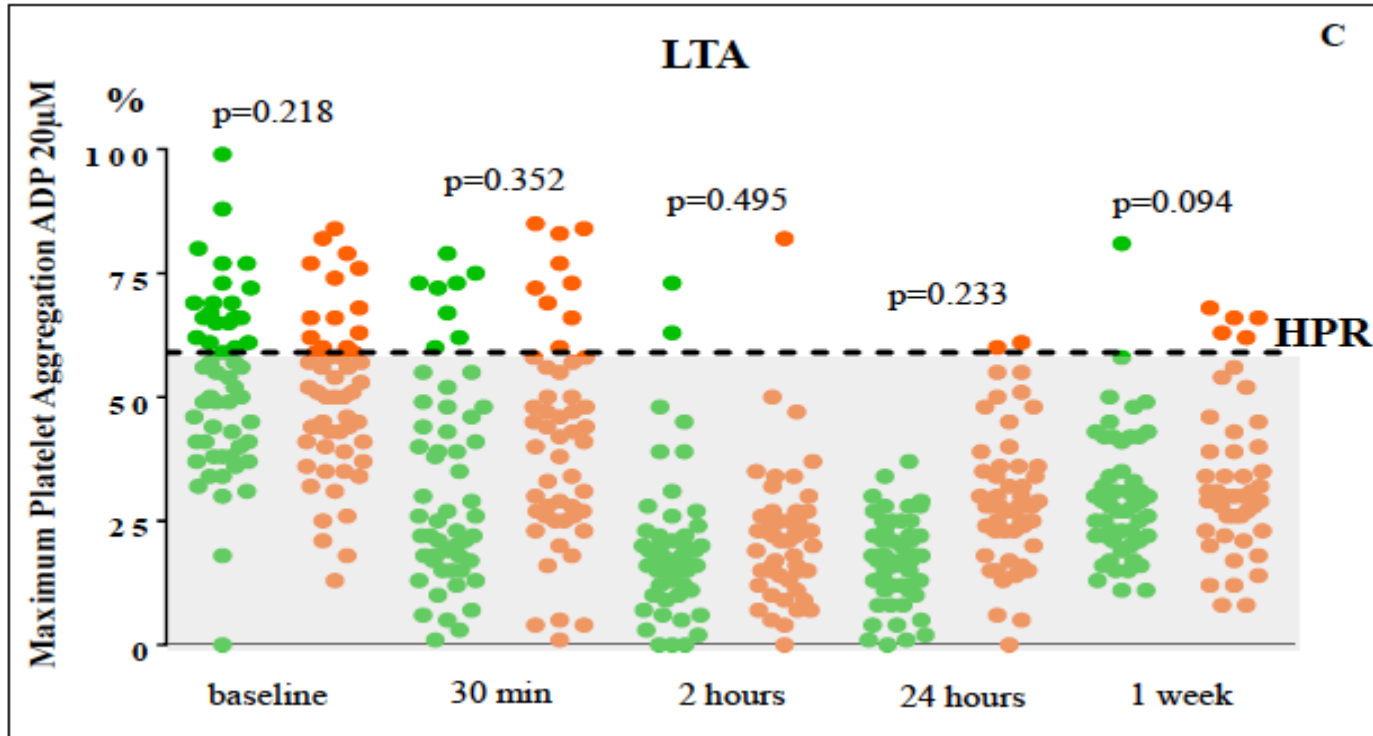
Study	Genotype	% attributable risk of HTPR
Shuldiner et al, <i>JAMA 2009</i>	CYP 2C19*2	12.0%
Hochholzer et al, <i>JACC 2010</i>	CYP 2C19*2	5.2%
Price et al, <i>JACC 2012</i>	CYP 2C19 LOF	5.2%

Meta-analyses of **observational studies** evaluating the relation of HTPR* on clopidogrel and clinical outcomes in PCI

Study	No. of patients	Assays	Composite MACE
Snoepp et al, Am Heart J 2007	3688 ACS = <u>28.4%</u>	LTA; VASP; platelet bound fibrinogen (flow cyt)	OR=8.00 95% CI=3.36-19.05
Sofi et al, Thromb Haemost 2010	4564 ACS = <u>47.6%</u>	LTA; VASP, VerifyNow P2Y12	OR=5.67 95%CI=2.97-10.84
Aradi et al, Am Heart J 2010	9187 ACS = <u>43.1%</u>	LTA; VASP, VerifyNow P2Y12 MEA (Multiplate®)	OR=4.95 95%CI=3.34-7.34
Brar et al, JACC 2011	3059 ACS = <u>35.3%</u>	VerifyNow P2Y12	OR=2.10 95%CI=1.62-2.73
Yamaguchi et al, Platelets 2013	4817 ACS = <u>39.7%</u>	VerifyNow P2Y12	OR=3.05 95%CI=2.33-3.98

*HTPR (High on Treatment Platelet Reactivity) varied between 21% and 46.4%

Changes in the prevalence of “high on-treatment platelet reactivity”
after switching clopidogrel-treated patients to treatment
with **prasugrel** or **ticagrelor**

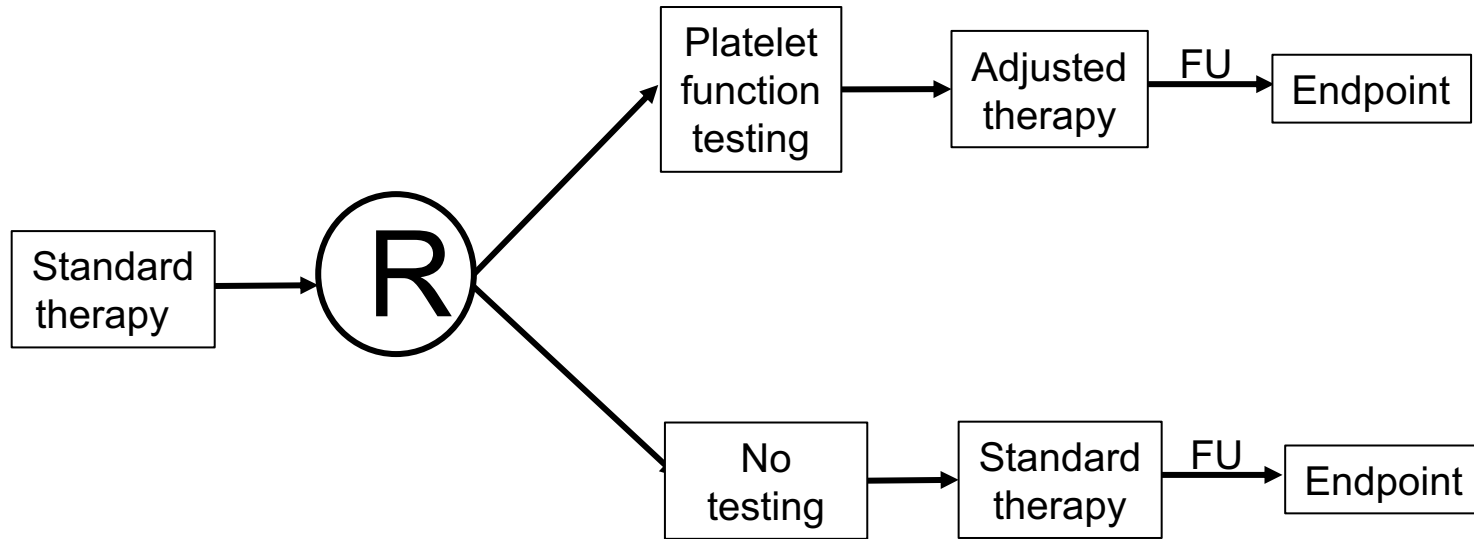


Response variability to Clopidogrel

The solution?

“Laboratory monitoring of antiplatelet treatment”:
increase the dose of Clopidogrel (use another drug)
in patients with HTPR
(based on the results of platelet function tests)

RCTs evaluating safety/efficacy of **PFT-guided** anti-P2Y12 therapy - **Design**

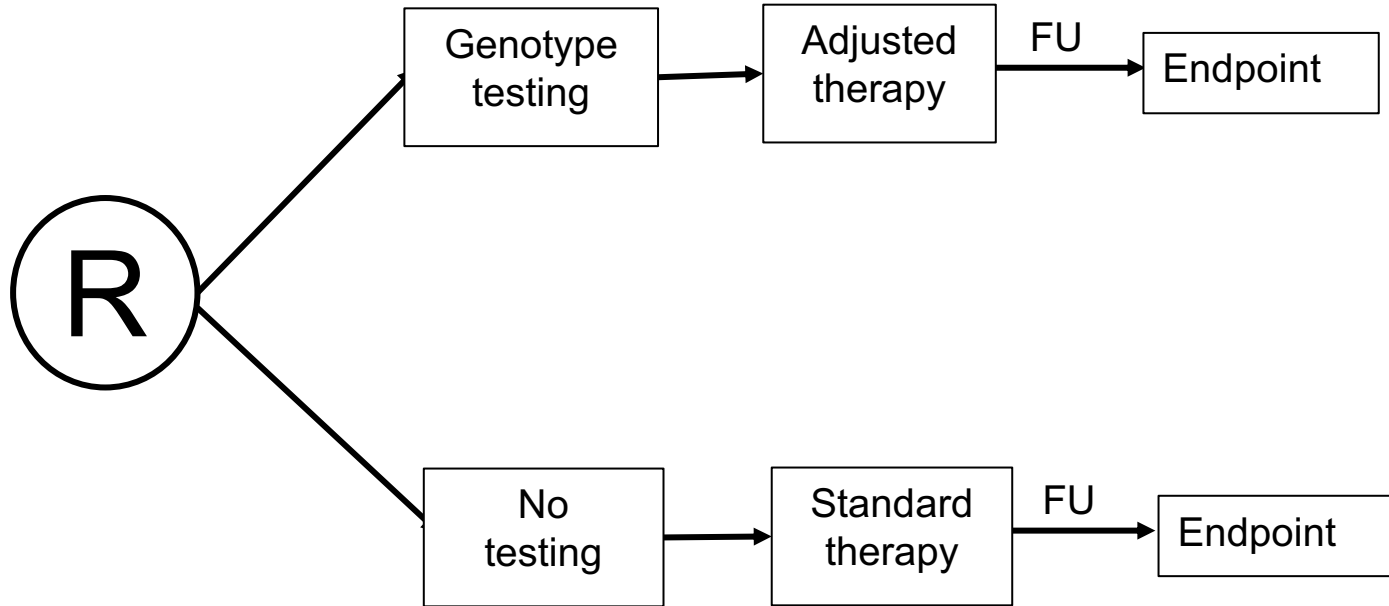


Response variability to Clopidogrel

Another solution?

Identify “a priori” potential poor responders
based on their genotype
(personalized antiplatelet therapy)

RCTs evaluating safety/efficacy of **genotype-guided** anti-P2Y12 therapy - **Design**



Pooled estimates of Guided vs Standard anti-P2Y12 therapy
for MACE and Major Bleeding
in 5 systematic reviews with meta-analyses

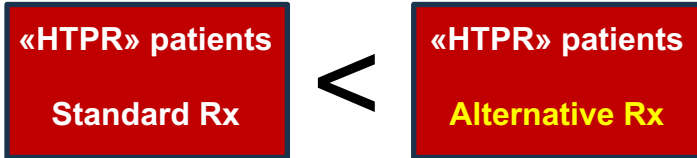
Study	Design	MACE RR (95% C.I.)	Major bleeding RR (95% C.I.)
Aluvilu et al, 2022	PFT-GT + HTPR-Therapy*	0.95 (0.83-1.08)	1.03 (0.63-1.70)
Yamani et al, 2022	Genotype-GT + PFT-GT + HTPR-Therapy*	0.78 (0.62-0.99)	0.78 (0.66-0.91)
Galli et al, 2021	Genotype-GT + PFT-GT	0.78 (0.63-0.95)	0.88 (0.77-1.01)
Tang et al, 2022	Genotype-GT	0.60 (0.44-0.82)	1.03 (0.75-1.41)
Wang et al, 2020	Genotype-GT	0.64 (0.52-0.79)	0,79 (0.57-1.11)

* = RCTs of HTPR-Therapy did not evaluate safety and efficacy of Guided vs Standard Therapy

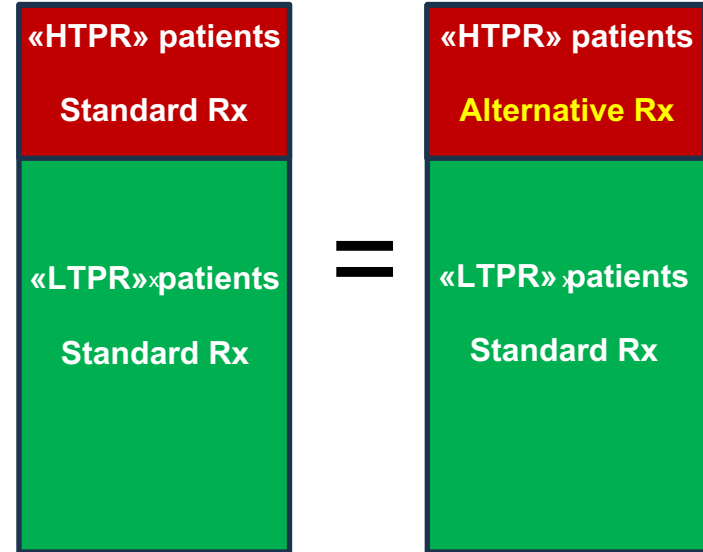
HTPR-Therapy vs PFT-Guided Therapy

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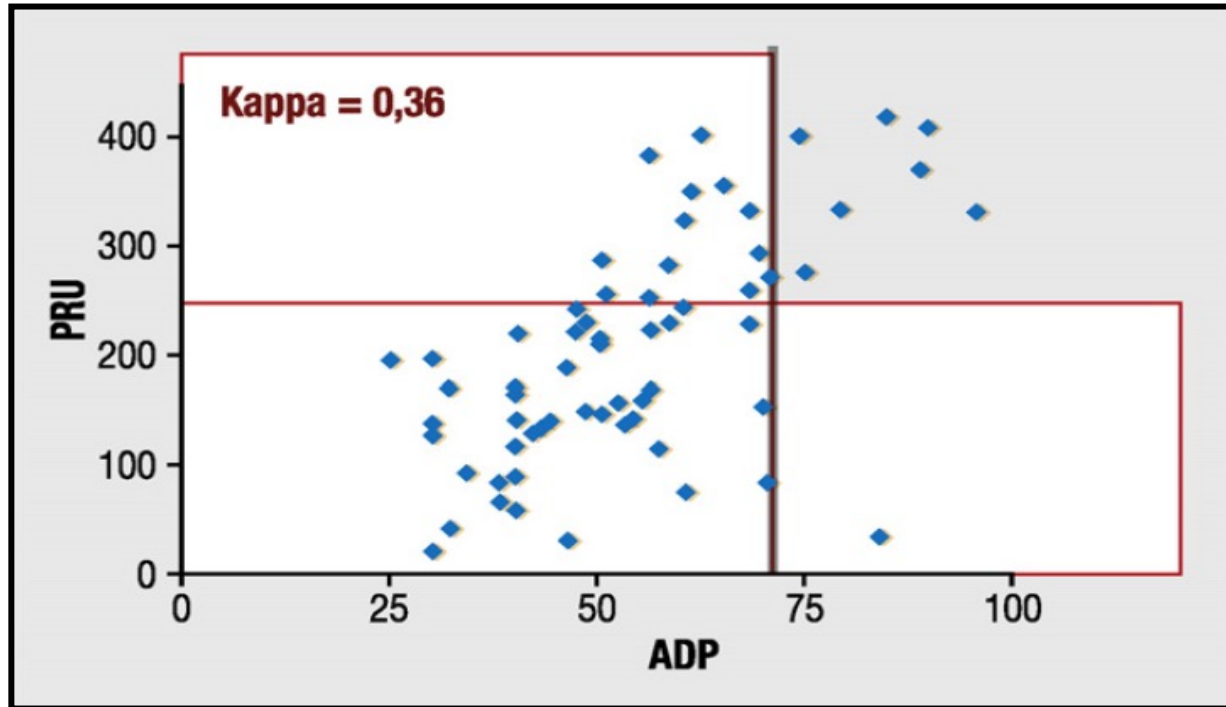
HTPR-Therapy



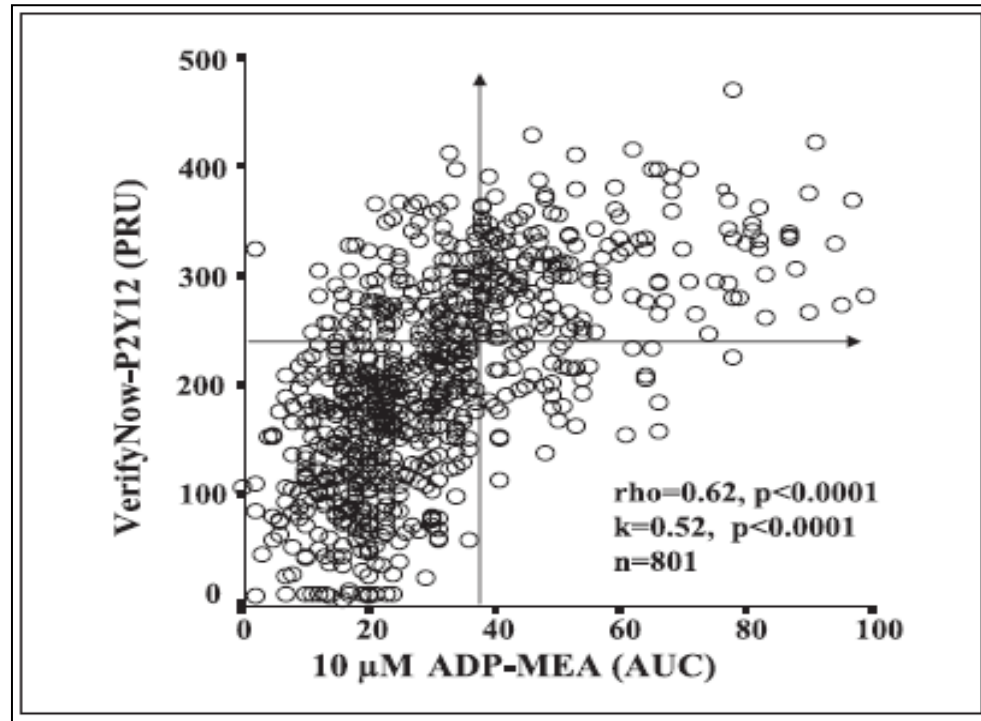
PFT-Guided Therapy



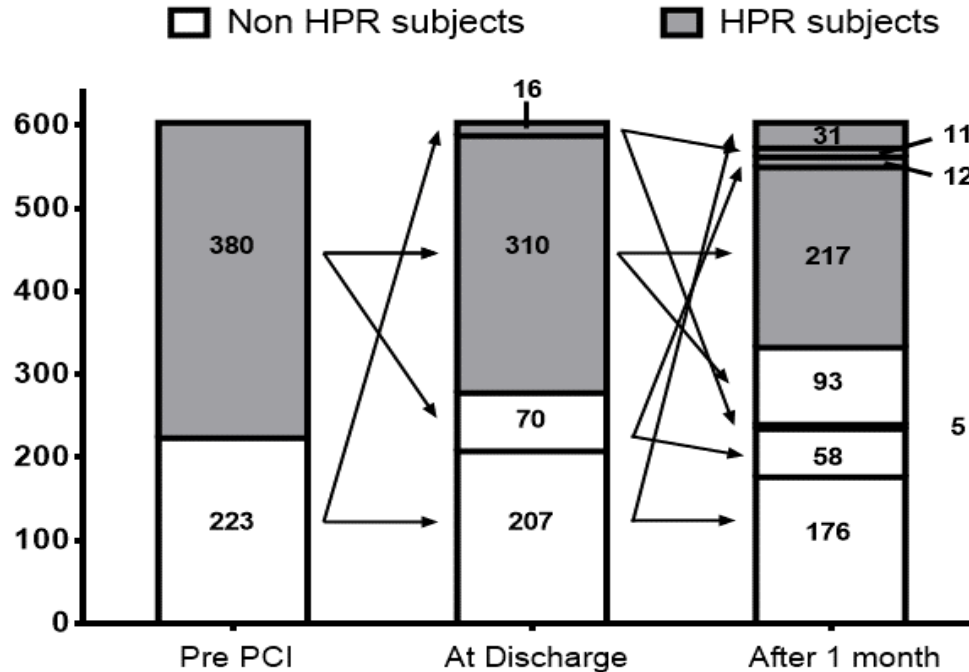
Agreement between LTA and Verify-Now in detecting patients who are resistant to clopidogrel



Correlation and agreement of results obtained by Multiplate (MEA) and VerifyNow P2Y12 Assay in 801 CAD patients



Variations in the platelet reactivity status across the three determinations of PRI (VASP phosphorylation assay) made in the **GEPRESS Study**



Conclusions

- Genotype-Guided and Platelet Function Tests-Guided anti-P2Y12 Therapy in patients undergoing PCI do not affect the risk of Major Bleeding or MACE

Conclusions -1

- Genotype-Guided and Platelet Function Tests-Guided anti-P2Y12 Therapy in patients undergoing PCI do not affect the risk of Major Bleeding or MACE
- Genotype-Guided and Platelet Function Tests-Guided anti-P2Y12 Therapy reduced the risk of MACE in RCTs performed in China, but not in patients enrolled elsewhere

Conclusions -2

- Genotype-Guided Therapy was superior to Platelet Function Tests-Guided Therapy both in RCTs performed in China and in RCTs performed elsewhere

Conclusions -2

- Genotype-Guided Therapy was superior to Platelet Function Tests-Guided Therapy both in RCTs performed in China and in RCTs performed elsewhere
- The parallel analysis of RCTs on Platelet Function Tests-Guided Therapy and of RCTs on HTPR-Therapy suggest that inaccuracy of platelet function tests to diagnose HTPR is responsible for the lack of efficacy of Platelet Function Tests-Guided Therapy