Relative Association of Genetic Variants to Clopidogrel Responsiveness in Patients Undergoing Percutaneous Coronary Intervention

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Background

- Percutaneous coronary intervention (PCI), the implantation of stents using balloon-tipped catheters, is the most common revascularization procedure for coronary artery disease
- Dual anti-platelet therapy with aspirin and clopidogrel (PLAVIX®) is the gold standard treatment after PCI
- However, clinical studies have shown up to 30% of patients exhibit high post-treatment platelet reactivity (HPPR); these patients remain at risk for adverse cardiovascular outcomes (stent thrombosis, myocardial infarction, death)[1,2]
- Clopidogrel, an irreversible inhibitor of ADP $P2Y_{12}$ receptors, is a pro-drug requiring biotransformation into its active metabolite

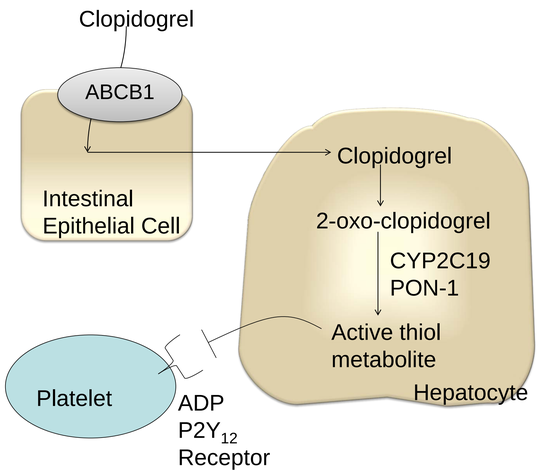

Figure 1. Clopidogrel biotransformation pathway

- In addition to clinical and cellular factors, genetic variants—based on their role in absorption and metabolism of clopidogrel—account for variability in platelet response
- Carriage of cytochrome P450 2C19*2 (CYP2C19*2) loss-of-function (LOF) allele has been associated with diminished efficacy of clopidogrel and increased adverse outcomes[3,4]
- Other CYP2C19 polymorphisms, and variants of ABCB1 and Paraoxonase-1 (PON-1) have been implicated in clopidogrel efficacy (Table 1)[5,6]

Objective

To investigate the relative association of other genetic variants, including CYP2C19*3, *17, PON-1 QQ, and ABCB1 TT to HPPR in patients undergoing PCI who were treated with clopidogrel

Methods

Study Design

- Retrospective cohort study
- Patients (n=183) analyzed from RAPID GENE randomized control trial (clinicaltrials.gov NCT01184300)
- Consent was obtained for genotyping candidate single nucleotide polymorphisms (SNPs)

Inclusion Criteria

- ♂ and ♀ 18-75 years old
- Underwent PCI in context of stable coronary artery disease (CAD) or non-ST-elevation acute coronary syndrome (ACS)
- Able to provide informed consent
- Received 600 mg bolus of clopidogrel at least 24 hours prior to PCI

Exclusion Criteria

- Absence of genotype status and/or platelet reactivity data
- Antiplatelet therapy other than aspirin and clopidogrel prior to PCI
- Anti-coagulation therapy (warfarin, dabigatran)
- History of stroke or transient ischemic attack
- Platelet count < 100,000/μL
- Hematocrit <32% or >52%
- Creatinine clearance < 30 ml/min
- Severe liver dysfunction
- Pregnancy

Methods

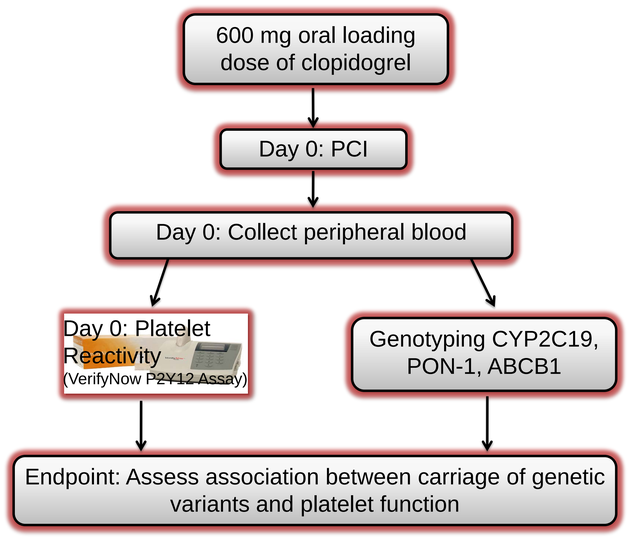

Figure 2. Schematic of retrospective analysis

Definitions

Table 1. Candidate genetic variants for HPPR and definition of carrier status.

Gene	Variants of Interest	Carrier
CYP2C19	CYP2C19*2 (LOF)	≥ 1 copy of *2
	CYP2C19*3 (LOF)	≥ 1 copy of *3
	CYP2C19*17 (GOF)	≥ 1 copy of *17
PON-1	PON-1 Q192R (LOF)	2 copies (QQ)
ABCB1	ABCB1 3435 C>T (LOF)	2 copies (TT)

Gain-of-function, GOF, Loss-of-function, LOF

Table 2. Platelet reactivity threshold for responsiveness

Clopidogrel Response	$P2Y_{12}$ Reactivity Unit (PRU)
Responder	≤208 or ≤234
Non-responder (HPPR)	>208 or >234

Note: HPPR thresholds were selected based on evidence of association with major adverse cardiovascular outcomes.[7,8,9]

Statistical Analysis

Proportions of clopidogrel non-responders among carriers and non-carriers were compared using Fisher's Exact test for each genetic variant. Probability values <0.05 were considered statistically significant.

Results

Table 3. Prevalence of carrier status for genetic variants among subset of patients included in retrospective analysis

Genetic Variant	No. of Carriers (%) (n=183)	No. of Non-carriers (%) (n=183)
CYP2C19*2	45 (24.6)	138 (75.4)
CYP2C19*3	0 (0)	183 (100)
CYP2C19*17	73 (39.9)	110 (60.1)
PON-1 QQ	97 (53.0)	86 (47.0)
ABCB1 TT	52 (28.4)	131(71.6)

Results

Genetic Variant	HPPR Threshold	Proportion of Carriers	Proportion of Non-carriers	P-value
CYP2C19*2	>208	23/45 (51.1%)	34/138 (24.6%)	<0.0005
	>234	18/45 (40.0%)	26/138 (18.8%)	<0.05
CYP2C19*17	>208	22/73 (30.1%)	35/110 (31.8%)	0.871
	>234	17/73 (23.3%)	27/110 (24.5%)	1.000
PON-1 QQ	>208	35/97 (36.1%)	22/86 (25.6%)	0.151
	>234	25/97 (25.8%)	19/86 (22.1%)	0.605
ABCB1 TT	>208	16/52 (30.1%)	41/131 (31.3%)	1.000
	>234	13/52 (25.0%)	31/131 (23.7%)	0.850

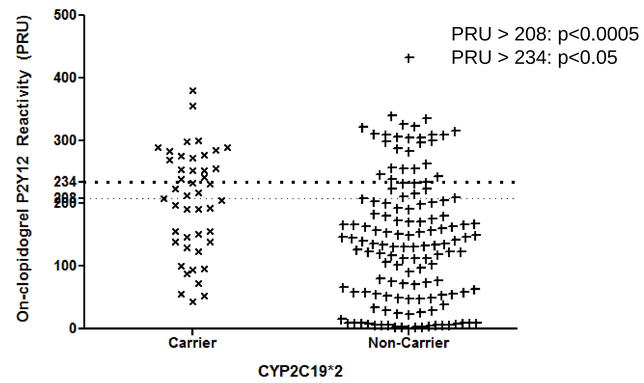

Figure 3. Individual on-clopidogrel P2Y12 reactivity among carriers and non-carriers of CYP2C19*2; PRU, P2Y12 reactivity unit

Conclusions

- CYP2C19*2 shows the strongest association to HPPR in response to clopidogrel
- The low prevalence of CYP2C19*3 is consistent with other studies[10,11]
- There were no significant associations found between CYP2C19*3, CYP2C19*17, PON-1 Q192R, or ABCB1 3435 C>T and HPPR

Future Directions

- Multivariate analysis combining genetic factors and clinical risk factors (body mass index, smoking, ACS, glucose intolerance, and proton pump inhibitors)
- Developing an algorithm that takes into account genetic and clinical risk factors to prospectively predict clopidogrel non-responsiveness
- Pharmacogenetic-based personalized anti-platelet therapy

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