

# INFLUENCE OF CYTOCHROME P450 2C19 ALLELIC VARIANTS ON CLOPIDOGREL-MEDIATED PLATELET INHIBITION EVALUATED BY FIVE DIFFERENT PLATELET TESTS

Thomas Gremmel<sup>1</sup>, Christoph W. Kopp<sup>1</sup>, Deddo Moertl<sup>2</sup>, Daniela Seidinger<sup>1</sup>, Renate Koppensteiner<sup>1</sup>, Simon Panzer<sup>3</sup>, Christine Mannhalter<sup>4</sup>, and Sabine Steiner<sup>1</sup>

<sup>1</sup> Division of Vascular Medicine and <sup>2</sup> Division of Cardiology, Department of Internal Medicine II, <sup>3</sup> Clinical Department of Blood Group Serology and Transfusion Medicine, <sup>4</sup> Department of Laboratory Medicine, Medical University Vienna, Vienna, Austria

## Introduction

The antiplatelet effect of clopidogrel has been linked to cytochrome P450 (CYP) 2C19 carrier status.

The \*2 allelic variant has been associated with diminished inhibitory effects and an increased risk of ischemic events despite clopidogrel treatment. However, genotyping is only one aspect of predicting response to clopidogrel and several platelet function tests are available to measure platelet response.

## Objective

We studied the relevance of CYP2C19 allelic variants on clopidogrel-mediated platelet inhibition as assessed by 5 different platelet function tests

## Methods

Platelet reactivity was studied in 156 patients taking clopidogrel and aspirin one day after angioplasty and stenting for cardiovascular disease by:

- Light transmission aggregometry (LTA, %)
- VerifyNow P2Y12 assay (P2Y12 Reaction Units/PRU)
- Vasodilator-stimulated phosphoprotein phosphorylation assay (VASP, platelet reactivity index/PRI)
- Multiple electrode aggregometry (MEA, aggregation units/AU)
- Impact-R (surface coverage/SC %)

Further CYP2C19 genotyping was performed by the **Infiniti® CYP450 2C19+ assay**.

**Statistical analysis:** Patients were grouped into CYP2C19 \*2 carriers and non- CYP2C19 \*2 carriers. Multivariable logistic regression was used to identify independent predictive status of CYP2C19 \*2 allele carriage for high on treatment platelet reactivity. Adjustments were made for smoking, sex, age, medication (use of statins, PPI, calcium channel blockers, clopidogrel loading dose) and diabetes using stepwise selection method with a P-value of 0.2 for model entry. Genotype was forced into the models.

## Patient characteristics

**Table 1**

Variable	N=156
Age (years), mean SD	66 11
Male sex, n (%)	94 (60.3)
BMI (kg/m <sup>2</sup> ), mean SD	27.0 4.0
<b>Medical history, n (%)</b>	
Previous MI	37 (23.7)
Previous TIA/stroke	22 (14.1)
Hypertension	147 (94.2)
Hypercholesterolemia	146 (93.6)
Diabetes mellitus	55 (35.3)
Active smoking	62 (39.7)
<b>Procedure, n (%)</b>	
Stent implantation	156 (100)
- peripheral	120 (76.9)
- coronary	9 (5.8)
- carotid	27 (17.3)
<b>Medication pre-intervention, n (%)</b>	
Statins	148 (94.9)
ACE inhibitors	98 (62.8)
Angiotensin receptor blockers	43 (27.6)
Beta blockers	95 (60.9)
Proton pump inhibitors	86 (55.1)
Calcium-channel blockers	59 (37.8)

## Results I

CYP2C19 \*2 carriers (wt/\*2, \*2/\*17, \*2/\*2) showed significantly higher platelet reactivity compared to a combined low-risk genotype of wildtype and \*17 carriers (wt/wt, wt/\*17, \*17/\*17) by the VASP assay and the Impact-R as shown in table 2. High on-treatment residual platelet reactivity (HRPR, n=39) identified by the VASP assay was associated with CYP2C19 \*2 genotype (n=19, P=0.03, table 3). In multiple logistic regression, carriers were 2.3 times more likely to be exhibit HRPR in the VASP assay than non-carriers. No significant associations were found for CYP2C19 \*2 carrier status and the other tests. Platelet reactivity values of patients with CYP2C19 \*17 were comparable to wildtype.

## Results II

**Table 2 Platelet reactivity test results according to CYP2C19 \*2 carrier status**

Platelet Test	*2 carriers N=53		non-carriers N=103		P*
LTA, %	50.7	21.6	46.7	19.5	.24
VerifyNow, PRU	226.8	92.2	201.1	92.3	.10
VASP assay, PRI	54.5	20.8	43.8	23.0	<.01
MEA, AU	45.6	18.7	45.6	21.4	.99
Impact-R, SC%	3.5	2.5	4.5	2.6	.02

\* Results from unpaired student t-test

**Table 3 High on-treatment residual platelet reactivity (HRPR) status for each platelet test for all patients and stratified for CYP2C19 \*2 carriers and non-carriers.**

Test	all pts N=156	*2 carriers N=53	non-carriers N=103	adj. OR (95%CI)**
LTA	39 (25)	17 (32.1)	22 (21.4)	1.47 (0.64, 3.37)
VerifyNow P2Y12	39 (25)	14 (26.4)	25 (24.3)	1.00 (0.5, 2.2)
VASP	39 (25)	19 (35.8)*	20 (19.4)	2.29 (1.03, 5.11)
MEA	41 (26)	17 (32.1)	24 (23.3)	1.33 (0.62, 2.86)
Impact-R	39 (25)	17 (32.1)	22 (21.4)	1.65 (0.79, 3.49)

Data are shown as number (%); \*P=0.03 compared to non-carriers.  
\*\* Adjusted odds ratio for CYP2C19 \*2 carrier status as a predictor in multiple logistic regression with HRPR as dependent variable.

## Conclusion

The prediction of platelet activation by CYP2C19 \*2 carrier status varies between different platelet function tests, being most pronounced when assessed by the VASP test. It remains to be elucidated, which platelet function test is the best predictor of clinical outcome and which combination between a platelet function test and genotyping might improve prognostic value.

**Disclosures to report: None.**