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Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction ☆

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ABSTRACT

Substantial variability of antiplatelet action is an important limitation of clopidogrel. The aim of this study was to evaluate time-related changes in determinants of clopidogrel responsiveness in patients after myocardial infarction.

The study population comprised 191 consecutive patients treated with primary percutaneous coronary intervention for acute myocardial infarction. Follow-up visits were scheduled at 3, 6 and 9 months after discharge. ADP-induced platelet aggregation was tested with Multiplate Analyzer. Patients with ADP-PA > 46.8 U were defined as clopidogrel non-responders.

The prevalence of clopidogrel non-responsiveness was highest during hospitalization and at 9 month follow-up visit, while it was lowest at 3 and 6 months after myocardial infarction ($P=0.004$). According to multivariate analysis, platelet count, mean platelet volume, concentration of hsCRP and leukocyte count influenced ADP-induced platelet aggregation in multiple assessment points. BMI, concentrations of hemoglobin, glycated hemoglobin, and BNP, hematocrit, adherence to medication, and patient's age were found to be independent predictors of high on-treatment ADP-induced platelet aggregation only at a single follow-up visit.

Determinants of clopidogrel responsiveness in patients after myocardial infarction change within the long-term therapy. During hospitalization and early after discharge only biological factors affect ADP-induced platelet aggregation, while non-adherence to antiplatelet therapy may be a significant factor in determining clopidogrel non-responsiveness during late follow-up visits.

1. Introduction

Despite the availability of new oral antiplatelet agents such as prasugrel or ticagrelor, clopidogrel still remains the most widely used $P2Y_{12}$ receptor inhibitor. Substantial variability of antiplatelet action is an important limitation of clopidogrel (Navarese et al., 2011). It has been shown that a significant proportion of patients do not respond to clopidogrel sufficiently, being defined as non-responders ADP-induced platelet aggregation (ADP-PA) > 46.8 U (Tantry et al., 2013; Kubica et al., 2011; Koziński et al., 2011). Several factors of poor response to clopidogrel including the patient's low adherence to medication, drug–drug interactions, diabetes, genetic polymorphism of CYP2C19 enzyme and other temporal biological factors, such as inflammation and platelet activation due to plaque rupture should be taken into account (Kubica et al., 2011a, 2011b; Siller-Matula et al., 2012; da Silva et al., 2012; Karaźniewicz-Łada et al., 2012). Almost all available knowledge regarding factors influencing the antiplatelet effect of clopidogrel is based on acute-phase studies. With long-term

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therapy though, it is likely that importance of at least some of these factors can change. However, according to our best knowledge, no systematic analysis of this issue is yet available.

The aim of this study was to evaluate time-related changes in determinants of clopidogrel responsiveness in patients after myocardial infarction (MI).

2. Material and methods

2.1. Study design and patients characteristics

This was a prospective, observational, single-center study with a 9 month follow-up. The study population comprised 191 consecutive patients treated with primary percutaneous coronary intervention (pPCI) for acute MI, who gave their informed written consent. Exclusion criteria were defined as follows: the need for prolonged use of heparin or fondaparinux, oral anticoagulant therapy, bleeding disorders (including thrombocytopenia $< 100 \times 10^3/\mu l$), anemia with hemoglobin (HGB) < 10.0 g/dl, active inflammation, congestive heart failure (CHF) in NYHA class III and IV and life expectancy < 1 year. In-hospital management and discharge treatment recommendations strictly adhered to the European Society of Cardiology guidelines. Patients received a 600 mg loading dose and 75 mg maintenance dose of clopidogrel in combination with aspirin doses of 300 mg and 75 mg, respectively. To avoid additional confounding factors concomitant therapy was standardized and included bisoprolol, perindopril and simvastatin if no contraindication was present. When therapy with proton pomp inhibitor was indicated, only pantoprazole was allowed. In case of a necessity to use additional medication, drugs with known or potential drug–drug interaction with clopidogrel were avoided. All patients were informed about the need of systematic intake of prescribed drugs and the dangers of their premature termination. Study population characteristics are displayed in Table 1.

Follow-up visits were scheduled at 3, 6 and 9 months after discharge. During every visit ADP-PA was assessed.

The following factors were analyzed as potential determinants of clopidogrel responsiveness: age, sex, risk factors for coronary

Table 1
Characteristics of study population.

Clinical and demographic characteristics of study population				
Feature	Baseline median ($n=191$)	3 month follow-up	6 month follow-up	9 month follow-up
		(Upper quartile – lower quartile) or number (percent)		
Age (years)	60.0 (53.0–67.0)			
Waist (cm)	96.0 (89.0–103.5)	96.0 (89.5–103.0)	96.0 (89.5–104.0)	96.0 (90.0–103.0)
Gender (male/female)	142 (74.3%)/49 (25.7%)			
STEMI	165 (86.4%)			
NSTEMI	26 (13.6%)			
Prior diagnosis of CAD	48 (25.1%)			
Prior MI	19 (9.9%)			
Prior PCI	13 (6.8%)			
Prior CABG	5 (2.6%)			
Prior CHF	13 (6.8%)	27.3 (24.8–30.5)	27.4 (24.9–29.9)	27.7 (25.0–30.5)
BMI (kg/m^2)	27.7 (24.9–30.8)	75 (42.4%) *including 14 newly diagnosed diabetes*	61 (40.7%)	71 (40.6%)
Arterial hypertension	106 (55.5%)			
Diabetes	67 (35.1%)			
Ex-smokers	39 (20.4%)	32 (18.1%)	31 (20.7%)	30 (17.1%)
Current smokers	99 (51.8%)			
Family history of CAD	50 (26.2%)			
Total cholesterol (mg/dl)	213.0 (178.0–240.0)			
Cholesterol LDL (mg/dl)	137 (115.0–170.0)			
LDL $\geq$ 115 mg/dl	143 (74.9%)			
Cholesterol HDL (mg/dl)	40.0 (34.0–47.0)			
Triglycerides (mg/dl)	102.0 (70.0–155.0)	6.1 (5.7–6.5)	6.1 (5.8–6.5)	6.1 (5.7–6.5)
Glycemia at admission (mg/dl)	138.0 (118.0–162.5)			
HbA1 (%)	6.2 (5.8–6.4)	6.76 (5.76–7.96)	6.78 (5.92–8.04)	6.81 (5.73–7.85)
WBC ($10^3/\mu l$)	7.77 (6.47–9.19)			
RBC ($10^6/\mu l$)	4.5 (4.2–4.8)	4.8 (4.5–5.1)	4.8 (4.5–5.9)	4.7 (4.5–5.0)
HGB (g/dl)	13.5 (12.8–14.4)	14.3 (13.6–14.9)	14.2 (13.5–14.9)	14.2 (13.5–14.9)
HCT (%)	39.4 (37.0–42.3)	41.6 (39.5–43.4)	41.3 (39.5–42.6)	41.1 (39.2–42.8)
PLT ($10^3/\mu l$)	208.0 (176.0–242.0)	210.0 (185.0–252.5)	213.0 (187.0–252.0)	209.0 (179.0–248.0)
MPV (fl)	10.9 (10.3–11.4)	10.8 (10.2–11.3)	10.6 (10.2–11.3)	10.7 (10.1–11.3)
BNP (pg/dl)	119.2 (65.4–228.6)	43.4 (27.4–88.2)	42.9 (28.1–82.4)	44.4 (28.5–88.2)
hsCRP (mg/l)	12.1 (4.9–31.8)	1.9 (1.1–4.1)	2.3 (1.2–4.6)	1.4 (0.7–3.1)

Procedure-related characteristics of study population	
Feature	Median (upper quartile – lower quartile) or number (percent) ($n=191$)
Angiographic assessment/ number of stented vessels (sv)	
One-vessel disease/1 sv	80 (41.8%)/80 (100%)
Two-vessel disease/ 1 / 2 sv	48 (25.1%)/21/27
Tree-vessel disease/ 1/2/3 sv	63 (33.0%)/47/8/8
Baseline coronary flow in IRA	
TIMI 0	82 (42.9%)
TIMI 1	18 (9.4%)
TIMI 2	20 (10.5%)
TIMI 3	71 (37.2%)
Post-procedural coronary flow in IRA	