

# High on-treatment platelet reactivity: risk factors and 5-year outcomes in patients with acute myocardial infarction

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## ABSTRACT

**Objective:** The aim of the present study was to assess long-term prognostic value of high on-treatment platelet reactivity (HTPR) in patients after acute myocardial infarction (MI) and its association with possible risk factors.

**Methods:** This prospective, case-control study was an observation of 198 patients who had acute MI. Response to aspirin and clopidogrel was assessed using impedance aggregometry. Patients were divided into groups of adequate response, dual poor responsiveness (DPR), poor responsiveness to aspirin (PRA), and poor responsiveness to clopidogrel (PRC). Simultaneously, potential risk factors of HTPR development were recorded. After 5 years, MI recurrence and overall mortality were assessed.

**Results:** HTPR was more frequent in New York Heart Association Class III and IV patients, and in patients with left ventricle systolic dysfunction. Five-year mortality rate was higher in all groups of patients with HTPR compared to patients with sufficient response to antiplatelet treatment: in PRA patients, 38.1% vs. 19.2%,  $p < 0.01$ ; in PRC patients, 45.2% vs. 17.3%,  $p < 0.001$ ; and in DPR patients, 50.0% vs. 19.9%,  $p < 0.05$ . Risk of repeat MI also increased (hazard ratio [HR] 4.0,  $p < 0.05$  for DPR group; HR 4.37,  $p < 0.01$  for PRA group; and HR 3.25,  $p < 0.05$  for PRC group).

**Conclusion:** PRA, PRC, and DPR are independent predictors of increased 5-year mortality and risk of repeat non-fatal MI. The study has demonstrated that HTPR is frequently observed in patients with severe heart failure and left ventricle systolic dysfunction.

(*Anatol J Cardiol* 2017; 17: 113-8)

**Keywords:** aspirin, clopidogrel, myocardial infarction, platelet reactivity

## Introduction

Aspirin and clopidogrel-based antiplatelet treatment of coronary artery disease is well established. Its usefulness in the reduction of mortality and repeat ischemic events has been proven in many studies (1, 2).

Despite this dual antiplatelet treatment, platelet reactivity remains high in many patients (3–5). Etiology of high on-treatment platelet reactivity (HTPR) is multifactorial. Clinical causes of poor response to aspirin (PRA) include younger age or heavier weight of patient (6), patient non-compliance, drug malabsorption (7), pharmacological interactions (8), hyperglycemia, hypercholesterolemia, oxidative stress (9), or catecholamine surge (10). Subcellular causes are more controversial. They may include polymorphism of platelet membrane receptors such as P1 (A1/A2) membrane glycoprotein (11), collagen, or adenosine di-

phosphate (ADP) receptor (12, 13).

Etiology of poor response to clopidogrel (PRC) is also complex. Contrary to PRA, PRC is mainly caused by insufficient pro-drug activation by cytochrome P450 2C19 and 3A4 (14, 15) or by P2Y12 receptor polymorphism (16). Other causes of PRC include diabetes mellitus (DM) (17), heart failure (18), patient non-compliance, drug malabsorption (19), and drug-drug interactions (20–22). Many factors mentioned above have only laboratory, not clinical relevance. Most of these factors are only of temporary significance. That correlates with finding of variable response to antiplatelet treatment over time, especially during first month after myocardial infarction (MI) (23).

Clinical impact of HTPR is substantial, as it is associated with two- to fourfold higher risk of MI, stroke, and death (24, 25). Unfortunately, there is no exact recommendation on timing of aggregability testing in patients with known HTPR. For decision-

Parts of this research project were presented at the 20<sup>th</sup> Congress of the European Hematology Association, June 11–14, 2015, Vienna, Austria.

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**Accepted Date:** 18.07.2016 **Available Online Date:** 05.10.2016

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DOI:10.14744/AnatolJCardiol.2016.7042



making related to HTPR patients, knowledge of long-term prognostic value is of substantial importance.

## Methods

In the period from April 2007 to July 2008, 198 patients admitted to University Hospital Hradec Kralove, Czech Republic, were enrolled in the study with prospective, observational, case-control design (132 men, 58 women; average age  $67.7 \pm 8.1$  years). All patients with confirmed MI (26) treated with percutaneous coronary intervention and stent implantation were screened for the study. Exclusion criteria included age older than 80 years, cardiogenic shock, proven malignancy, sepsis, or severe renal disease. Patients on long-term anticoagulation treatment or patients treated with glycoprotein IIb/IIIa inhibitor were also excluded from the study. Of 826 patients screened, 265 were not enrolled due to exclusion criteria, 213 were not available for laboratory analysis due to death, discharge from hospital, transfer to another hospital, or unavailability of aggregability analysis. Another 116 patients declined to participate, and 32 patients were excluded as they were not eligible for heart failure symptoms assessment (immobility, extracardial dyspnea etc.). Two patients were excluded due to low platelet reactivity in thrombin receptor agonist peptide (TRAP) test.

All study patients were given aspirin 500 mg intravenous loading dose followed by 100 mg daily during entire period of follow-up. Clopidogrel treatment was initiated with loading dose of 300 to 600 mg followed by 75 mg daily for 6 to 12 months (median 10 months). Every patient was administered single dose of unfractionated heparin approaching 70 to 100 U/kg, controlled using activated clotting time during procedure.

Response to antiplatelet treatment was assessed using Multiplate assay (Dynabyte GmbH, Munich, Germany) between third and fifth day of treatment. Multiplate assay is one of devices recommended for on-clopidogrel reactivity testing (27). Blood samples were collected early in the morning before next dose of anticoagulant drug. Hirudin-anticoagulated whole blood was stored at room temperature before analysis within half an hour to 2 hours of blood sampling. Extent of platelet aggregation is measured by resistance (impedance) changes between 2 electrodes, and then depicted as a graph (28). Area under the curve is used as aggregometry parameter of the Multiplate test.

Response to aspirin was assessed using platelet aggregation in response to arachidonic acid with area under the curve threshold value of 30 U. Response to Clopidogrel was assessed using test of platelet aggregation in response to adenosine-5'-diphosphate with area under the curve threshold value of 46 U (27). According to response to antiplatelet treatment, patients were divided into groups with normal response to antiplatelet treatment, poor responsiveness to aspirin (PRA), poor responsiveness to clopidogrel (PRC), and poor response to both aspirin and clopidogrel (dual poor responsiveness [DPR]). Patients in DPR group were simultaneously included in PRA and PRC

groups. TRAP test was used as positive control, thus patients with insufficient platelet aggregability were excluded from the study. Presence and severity of heart failure was assessed on day of blood sample collection. Diagnostic criteria and functional classification were according to European Society of Cardiology guidelines for diagnosis and treatment of acute and chronic heart failure 2008 (29).

Mean follow-up of patients was 65 months (range: 61–69 months). Data about response to antiplatelet treatment were available for all participants. Mortality data were obtained from the Czech National Population Register, which is assured to be 100% accurate.

This research was approved by the Institutional Ethics Committee and all participants gave written, informed consent.

## Statistical analysis

For sample size calculation, we anticipated high on-treatment platelet reactivity in 20% of patients and twofold higher event rate (25) (10% vs. 20% per year; follow-up 5 years). Choosing a power of 80% and 2-sided p value of 0.05, an overall sample size of at least 154 patients was required (30).

We used Statistica 12 software (StatSoft Inc., Tulsa, OK, USA) for all statistical analysis. Differences in incidence of PRA, PRC, and DPR were assessed using Fisher's exact test. For multivariable analysis of risk factor independence, Cox analysis was used. Mortality in all groups was described using Kaplan-Meier analysis. Differences in mortality were evaluated using Cox's F-test.

## Results

### Baseline characteristics

Baseline characteristics of entire study group are shown in Table 1. Procedure and lesion characteristics are provided in Table 2.

**Table 1. Baseline characteristics of study group (n=198)**

Age, years (median [Q1-Q3])	68 (60.5–76.5)
Male gender, n (%)	132 (66.7)
Diabetes mellitus, n (%)	49 (24.7)
Previous myocardial infarction, n (%)	43 (21.7)
Smokers, including former smokers, n (%)	141 (71.2)
Previous omeprazole treatment, n (%)	47 (23.7)
Newly initiated omeprazole treatment, n (%)	21 (11.1)
Initial diagnosis of STEMI	115 (58.1)
Initial diagnosis of NSTEMI	83 (41.9)
Patients in NYHA Class III-IV, n (%)	29 (14.7)
Average left ventricle ejection fraction, % (mean±SD)	46.8±13.5
Poor responsiveness to aspirin, n (%)	41 (20.7)
Poor responsiveness to clopidogrel, n (%)	42 (21.2)
Dual poor responsiveness, n (%)	22 (11.6)
NSTEMI - non ST-segment elevation myocardial infarction; NYHA - New York Heart Association; STEMI - ST-segment elevation myocardial infarction	

**Table 2. Procedure and lesion characteristics**

	DPR	PRA	PRC	Sufficient response	P
Indication, n (%)					
STEMI	14 (63.6%)	21 (48.8%)	25 (59.5%)	55 (59.1%)	NS
NSTEMI	8 (36.3%)	20 (51.2%)	17 (40.5%)	38 (40.9%)	NS
Infarct related artery, n (%)					
Left main	0 (0%)	2 (4.8%)	0 (0%)	2 (2.2%)	NS
LAD	10 (45.5%)	15 (36.6%)	19 (45.2%)	39 (41.9%)	NS
RCX	4 (18.2%)	9 (21.9%)	7 (16.6%)	18 (19.3%)	NS
RCA	8 (36.3%)	15 (36.6%)	16 (38.1%)	34 (36.6%)	NS
Peak creatine kinase level, $\mu$ kat/L	22.3 $\pm$ 16.7	18.5 $\pm$ 13.9	21.2 $\pm$ 17.1	17.4 $\pm$ 12.8	NS
DPR - dual poor responsiveness; LAD - left anterior descending artery; NSTEMI - non ST-segment elevation myocardial infarction; PRA - poor responsiveness to aspirin; PRC - poor responsiveness to clopidogrel; RCA - right coronary artery; RCX - ramus circumflexus; STEMI - ST-segment elevation myocardial infarction					

**Table 3. Risk of high on-treatment platelet reactivity**

Risk factor	Relative risk of HTPR, RR (95% CI); P*		
	DPR (n=22)	PRA (n=41)	PRC (n=42)
Heart failure, NYHA class III-IV	8.35 (3.7–18.8); P<0.0001	3.47 (1.95–5.57); P<0.0001	4.34 (2.58–6.51); P<0.0001
Left ventricle ejection fraction <40%	2.08 (0.85–4.96); P=NS	1.86 (1.34–3.29); P<0.05	1.59 (0.86–2.84); P=NS
Age >70 years	1.35 (0.90–2.05); P=NS	0.82 (0.47–1.42); P=NS	1.38 (1.1–2.12); P<0.05
Male gender	1.16 (0.45–3.32); P=NS	0.94 (0.35–2.71); P=NS	0.71 (0.29–1.8); P=NS
Previous myocardial infarction	0.76 (0.24–2.39); P=NS	0.76 (0.32–1.62); P=NS	2.04 (0.68–2.56); P=NS
Diabetes mellitus	1.18 (0.42–3.04); P=NS	1.34 (0.45–3.62); P=NS	1.59 (0.60–4.01); P=NS
Smoking habit	1.57 (0.65–3.54); P=NS	1.32 (0.51–3.32); P=NS	0.92 (0.35–2.3); P=NS
Concomitant omeprazole medication	2.56 (1.02–6.37); P<0.05	1.09 (0.34–2.83); P=NS	1.24 (0.48–3.11); P=NS
*P value according to Fisher's exact test. CI - confidence interval; DPR - dual poor responsiveness; HTPR - high on-treatment platelet reactivity; NYHA - New York Heart Association; PRA - poor responsiveness to aspirin; PRC - poor responsiveness to clopidogrel; RR - relative risk			

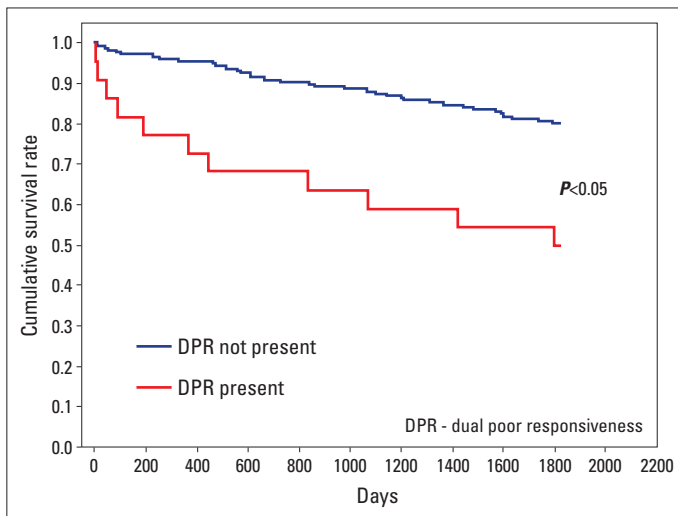
**Risk factors of HTPR**

Patients in New York Heart Association Class III or IV heart failure were at high risk of all types of HTPR (e.g., DPR, PRA or PRC) and patients with left ventricle systolic dysfunction were at increased risk of PRA. We documented increased risk of DPR in patients under treatment with omeprazole, and risk of PRC in patients older than 70 years (Table 3).

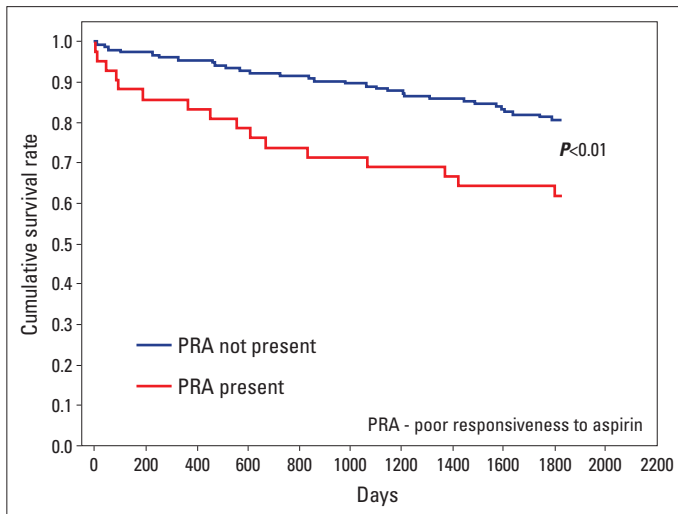
**HTPR as predictor of worse outcomes**

During the 5-year follow-up, 46 (23.2%) patients died. Eleven (23.9%) of these patients were in DPR group, 19 (41.3%) were in

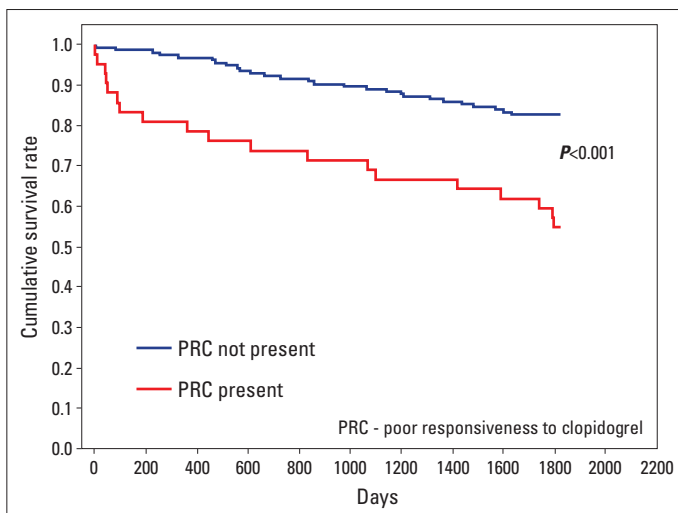
PRA group, 16 (34.8%) were in PRC group, and 9 (4.5%) patients were in group of sufficient response to antiplatelet treatment. Mortality was significantly higher in all groups of patients with HTPR compared with patients with sufficient response to antiplatelet treatment: in DPR patients 50.0% vs. 19.9% in patients without DPR,  $p<0.05$ ; in PRA patients 38.1% vs. 19.2% in patients without PRA,  $p<0.01$ ; and in PRC patients 45.2% vs. 17.3% in patients without PRC,  $p<0.001$  (Fig. 1–3). Risk of repeat non-fatal MI was increased in all groups of HTPR patients as well (Table 4). In PRC group, 7 of 16 (43.8%) deaths and 4 of 12 non-fatal (33.3%) MI occurred prior to clopidogrel cessation.



**Figure 1.** Cumulative survival rate according to dual poor responsiveness



**Figure 2.** Cumulative survival rate according to poor responsiveness to aspirin



**Figure 3.** Cumulative survival rate according to poor responsiveness to clopidogrel

**Table 4. Relative risk of repeated non-fatal myocardial infarction according to response to antiplatelet treatment**

	Relative risk	<i>P</i> *
Dual poor responsiveness, RR (95% CI)	4.0 (1.25–11.5)	<0.05
Poor responsiveness to aspirin, RR (95% CI)	4.37 (1.51–12.77)	<0.01
Poor responsiveness to clopidogrel, RR (95% CI)	3.25 (1.11–9.36)	<0.05

\**P* value according to Fisher's exact test. CI - confidence interval; RR - relative risk

As mentioned above, all types of HTPR are associated with severe symptoms of heart failure and PRA is associated with systolic dysfunction. Such association might contribute to increased mortality mentioned above. To avoid misinterpretation, multivariable analysis was performed. In this analysis, influence of age, HTPR, heart failure, systolic dysfunction, DM, and smoking habit on patient survival were assessed. Only HTPR and left ventricle systolic dysfunction were proven to be independent predictors of increased mortality (hazard ratio [HR] 1.54, 95% confidence interval [CI] 1.17–2.02,  $p < 0.01$  for HTPR; HR 2.07, 95% CI 1.02–4.22,  $p < 0.05$  for systolic dysfunction).

### Discussion

In the present study, HTPR risk factors and prognostic impact were analyzed. In recent years, many concerns have been raised regarding clinical impact of HTPR. Presented results bring insight to long-term influence of this phenomenon.

This study assessed aggregability within first days of MI. Thus far, no exact recommendation for timing of aggregability measurement has been provided. Generally, platelet function testing in early days after MI enables early therapeutic intervention to cover the period of highest likelihood of adverse events. On the other hand, early monitoring is substantially influenced by acute coronary syndrome itself, and does not correlate with delayed findings, so some concerns have been raised about early timing of platelet function testing (23). Our data suggest that early timing of analysis provides valuable long-term prognostic data and supports recent recommendations for timing of HTPR assessment (27).

### Risk factors

We documented heart failure as a factor strongly associated with HTPR. Until now, only a few studies have analyzed this association. In concordance with our results, risk of HTPR was approximately fourfold higher in patients with heart failure and stable coronary disease or stroke (18, 31). To our knowledge, none of the studies analyzed effect of heart failure in patients in early phase of MI. The pro-aggregatory effect of heart failure has been repeatedly described (32), so it is reasonable to include heart failure monitoring in design of further studies. Of note, in our study, HTPR incidence was more affected by severity of symptoms than by sole left ventricular systolic dysfunction.

### Mortality findings

Finding of increased mortality in HTPR patients is also in agreement with previous studies. Unfortunately, most studies have reported only short- or mid-term results with 1–12 months follow-up (25, 33–34). Studies with follow-up longer than 1 year are rare (24). We do not know of any other study with comparable follow-up.

According to previous studies, HTPR might be associated with multiple factors related to poor prognosis of patients such as heart failure and DM (17). However, according to our results, HTPR itself seems to be an independent predictor of worse outcomes, which enables it to be used as a laboratory marker for long-term risk stratification.

### Study limitations

Main limitation of this study is relatively small number of patients enrolled. For this reason, in multivariable analysis only general HTPR was analyzed. We were also unable to perform reliable multivariable analysis of all anticipated risk factors associated with HTPR. However, according to previous studies, we suspect that omeprazole treatment and higher age are not independently associated with HTPR.

Additionally, design of the study does not warrant assessing if HTPR is cause or consequence of heart failure and increased mortality.

### Conclusion

HTPR is strong independent predictor of increased 5-year mortality and risk of repeat non-fatal MI. The study has shown that HTPR is frequently observed in patients with heart failure and left ventricle systolic dysfunction.

**Acknowledgements:** The authors are grateful to Daniel I. Simon (director, University Hospitals Harrington Heart and Vascular Institute, Case Western Reserve University, Cleveland, OH, USA) for valuable comments and help with results interpretation, Eva Cermakova for statistical analysis and Lucie Pravdova for help with data collecting.

**Institutional and financial support:** The work was supported by a long-term organization development plan 1011 (FMHS) and by program PRVOUK P 37/03.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – M.J.; Design – M.J., R.P., Supervision – R.P.; Funding – J.M.H.; Materials – I.F.; Data collection &/or processing – M.J., R.S.; Analysis and/or interpretation – J.M.H., M.J., I.F.; Literature review – M.J., R.S.; Writing – M.J.; Critical review – All authors.

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