Factors related to on-treatment platelet aggregation assessed by multiple electrode aggregometry in percutaneous coronary intervention patients on clopidogrel and aspirin

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Abstract

Introduction: There is ongoing controversy concerning the clinical value of platelet function monitoring in patients undergoing percutaneous coronary interventions (PCI). Patients at risk of high on-treatment platelet aggregation (HPR) may benefit most from such monitoring.

Aim: To define the factors related to HPR on aspirin and clopidogrel, looking at a wider spectrum of variables than those assessed in some previous studies.

Material and methods: We assessed platelet function in 908 patients on clopidogrel and aspirin after PCI using the multielectrode aggregometry system Multiplate to define which clinical, procedural and laboratory factors are related to on-treatment platelet aggregation in response to aspirin and clopidogrel either as linear values or using established cutoff values for HPR.

Results: We found that in PCI patients on clopidogrel and aspirin, age (OR per year 1.06; 95% CI: 1.024–1.097; \( p = 0.001 \)), gender (OR = 0.319; 95% CI: 0.139–0.731; \( p = 0.007 \)), active smoking (OR = 2.57; 95% CI: 1.29–5.15; \( p = 0.008 \)), diabetes (\( \beta = 37.6; 95\% \text{ CI}: 16.5–58.8; p = 0.001 \)) and hypertension (\( \beta = 26.9; 95\% \text{ CI}: 6.73–47.1; p = 0.009 \)) are independently linked to platelet aggregation values treated as linear values and as dichotomous variables at the accepted cutoffs. The same is true for stented segment length (OR per mm 1.033; 95% CI: 1.024–1.047; \( p = 0.001 \)) and stent inflation pressure (OR per atmosphere 0.862; 95% CI: 0.772–0.963; \( p = 0.002 \)).

Conclusions: The study shows that, contrary to some earlier data, in the tested cohort women are better clopidogrel responders, but more often aspirin low-responders. Older age, active smoking, diabetes and hypertension all predispose to HPR. A novel finding is that stented segment length is an independent predictor of lower response both to aspirin and clopidogrel, possibly as a marker of more diffuse atherosclerosis.

Key words: platelet, aggregation, reactivity, coronary intervention, risk factors, Multiplate, clopidogrel.

Introduction

Percutaneous coronary interventions (PCI), either in the setting of stable coronary artery disease (CAD) or in acute coronary syndromes (ACS), have become very common procedures in cardiology [1, 2]. While in patients with ACS the use of newer antiplatelet agents is now advocated, clopidogrel remains the mainstay of dual antiplatelet therapy (DAPT) in elective procedures, and in many countries, also in ACS [3–5]. Despite its efficacy, about 2% to 5% of patients experience stent thrombosis or recurrent ischemic events in the first year following the procedure [6]. On the other hand, the treatment increases the risk of bleeding [7]. Numerous studies have been undertaken attempting to define the safety and efficacy profile of DAPT in different patient populations, and a number of platelet reactivity assessment methods for clinical use are available, but at present none are recommended for routine patient evaluation and treatment.

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[8–10]. Depending on the method of assessment, it is estimated that up to 20–30% of patients on clopidogrel are insufficiently responsive to the drug [11]. A number of factors – clinical, genetic and others – are thought to influence platelet reactivity in patients on DAPT; many have been investigated, but their significance still remains a matter of controversy [12]. While observational studies quite uniformly link clopidogrel underresponse with increased risk of thrombosis or ischemia, the few controlled trials do not support this [13–17]. Overall though, there is accumulating evidence that monitoring platelet aggregation in patients on DAPT may identify those at risk for stent thrombosis and recurrent ischemia as well as those at increased risk for bleeding [18, 19]. Clinical guidelines do not advocate routine platelet aggregation monitoring [1, 20, 21]. Hence, we attempted to define the main factors influencing platelet aggregation in patients undergoing PCI in order to delineate the population of patients at risk – in whom platelet reactivity monitoring could be of most benefit.

Aim

The aim of this study was to ascertain which clinical or laboratory factors significantly correlate with ADP-induced platelet reactivity measured by multiple electrode platelet aggregometry (MEA).

Material and methods

A total of 908 PCI patients (654 men) were enrolled in this study. Patients were recruited in the years 2012–2014. The study protocol was approved by the local Ethical Review Board and the study was conducted in accordance with the Declaration of Helsinki. All patients signed informed consent in order to participate in the study. The study was financed by National Science Centre grants NN 402381438 and NN 403397239.

The studied cohort included patients with stable CAD and ACS patients. Patients on chronic anticoagulants or medications known to influence platelet aggregation (such as IIb/IIIa inhibitors, non-steroid anti-inflammatory agents or steroids) were excluded.

All patients were pretreated with clopidogrel. The ACS patients were loaded with 600 mg of clopidogrel either prior to or immediately after admission and received 300 mg of acetylsalicylic acid (ASA). Stable CAD patients were either pretreated with clopidogrel and ASA for at least three days prior to the procedure or similarly loaded. All patients were subsequently treated with acetylsalicylic acid and clopidogrel at a daily dose of 75 mg each. Angiography and PCI procedures were performed according to the guidelines of the European Society of Cardiology [20], with no restriction as to stent selection, which was left to the discretion of the operator. Post-dilatation with non-compliant balloons for procedure optimization was strongly encouraged.

Platelet function assessment

ADP-induced platelet reactivity assessment was performed directly prior to patient discharge, but no earlier than on day three after admission, meaning at least 3 days after loading. The multiple electrode platelet aggregometry (MEA) analyzer Multiplate (Dynabyte, Munich, Germany) was used. The method has been described several times previously [19, 22, 23]. In short, 3 ml of whole blood is collected into a tube containing a direct thrombin inhibitor. All analyses were performed between 30 min and 3 h after collecting blood. After dilution with saline and agitation while incubating at 37°C for 3 min in test cuvettes, 6.4 µmol of ADP was added. Platelet aggregation was recorded continuously for 6 min and plotted against time in AU × min arbitrary units representing the area under the curve (ADPtest). The test result was the average of two parallel measurements.

The same analyzer was also used to assess platelet response to acetylsalicylic acid (ASA). In this case 0.5 mM solution of arachidonic acid was used as the agonist (ASPtest).

According to the international consensus statement [24], the upper cutoff MEA values for ADP-induced platelet aggregation and arachidonic acid-induced platelet aggregation were 468 AU × min and 203 AU × min, respectively. Higher platelet aggregation values were considered high on-treatment platelet aggregation (HPR). The lower cutoff value of the ADPtest was accepted as 188 AU × min. As there is controversy as to the lower cutoff of the ASPtest, we did not use this value in our analyses. We also analyzed the ADPtest and ASPtest values as linear parameters.

Statistical analysis

Relations between quantitative variables were evaluated using Spearman’s correlation coefficients. Distributions of ADPtest and ASPtest values were compared between subgroups with the Mann-Whitney test (in the case of two subgroups) or Kruskal-Wallis test (in the case of more than two subgroups). Relationships between the analyzed clinical, procedural and laboratory parameters and the results of the ADPtest and ASPtest were estimated using multiple regression models. Two types of models were used. Linear regression models were applied for ADP and ASP variables treated as continuous variables, while logistic regression models were used for dichotomized variables. All calculations were performed using IBM SPSS Statistics version 20.0. P-values smaller than 0.05 where interpreted as statistically significant.

Results

A cohort of 908 patients (654 men) aged 67 ±10.5 years, undergoing PCI, was studied. The main demographic features of the analyzed cohort are shown in Table I.
We assessed the relation of a number of clinical, procedure-related and laboratory factors to ADPtest and ASPItest values, either as dichotomous variables or linear variables.

ADPtest and ASPItest results as numerical variables

The correlation between clinical (gender, age, hypertension, diabetes, active smoking status, STEMI, NSTEMI), procedural (treated vessel, stent type, size, length, deployment pressure), and laboratory (estimated glomerular filtration rate, hemoglobin level, platelet count) parameters and ADPtest as well as ASPItest values treated as linear variables was investigated.

In the case of the ADPtest we found that patients’ age (per each year; \( \beta = 1.5; 95\% \text{ CI}: 0.54–2.39; p = 0.002 \)), hypertension (\( \beta = 26.9; 95\% \text{ CI}: 6.73–47.1; p = 0.009 \)), diabetes (\( \beta = 37.6; 95\% \text{ CI}: 16.4–58.8; p = 0.001 \)), and smoking status (\( \beta = 46.1; 95\% \text{ CI}: 24.2–67.8; p < 0.0001 \)) were independently correlated with ADPtest results. Out of procedural parameters we found stented segment length (per each mm; \( \beta = 0.84; 95\% \text{ CI}: 0.23–1.65; p = 0.042 \)) and inflation pressure (per each atmosphere; \( \beta = –3.62; 95\% \text{ CI}: \text{from } –6.49 \text{ to } –0.74; p = 0.014 \)) to be independently correlated with ADPtest result. Out of laboratory findings only platelet count was correlated with ADPtest as a linear variable (per each G/l; \( \beta = 0.28; 95\% \text{ CI}: 0.12–0.43; p = 0.001 \); Table II).

The ASPI test values treated linearly were independently correlated with age (per each year; \( \beta = 0.65; 95\% \text{ CI}: 0.004–1.29; p = 0.049 \)), smoking status (\( \beta = 31.74; 95\% \text{ CI}: 16.67–46.81; p < 0.0001 \)) and stented segment length (per each mm; \( \beta = 0.94; 95\% \text{ CI}: 0.38–1.50; p = 0.001 \)) only.

**Table I. Basic demographic data of the studied cohort**

| Clinical features             | Number of patients (%) |
|------------------------------|------------------------|
| Gender (male)                | 654 (72)               |
| DM type 2                    | 429 (47)               |
| STEMI                        | 94 (10)                |
| NSTEMI                       | 105 (12)               |
| eGFR < 30 ml/min/1.73 m²     | 19 (2)                 |
| Smoking                      | 198 (22)               |
| Hypertension                 | 664 (73)               |
| HPR                          | 55 (6)                 |
| HPR                          | 94 (10)                |
| Stent type (DES vs. BMS)     | 770 (85)               |

**Table II. Statistically significant correlations of study variables with ADPtest and ASPItest results analyzed as numerical values**

| Variable                     | \( \beta \) coefficient | 95% confidence interval | \( P \)-value |
|------------------------------|--------------------------|-------------------------|--------------|
| ADPtest values:              |                          |                         |              |
| Age [years]                  | 1.5                      | 0.54                    | 2.39         | 0.002        |
| Hypertension                 | 26.9                     | 6.73                    | 47.1         | 0.009        |
| Diabetes type 2              | 37.6                     | 16.4                    | 58.8         | 0.001        |
| Smoking                      | 46.1                     | 24.2                    | 67.8         | < 0.0001     |
| Stented segment length [mm]  | 0.84                     | 0.23                    | 1.65         | 0.042        |
| Inflation pressure [atm]     | –3.62                    | –6.49                   | –0.74        | 0.014        |
| Platelet count [G/l]         | 0.28                     | 0.12                    | 0.43         | 0.001        |

| ASPItest values:             |                          |                         |              |
| Age [years]                  | 0.65                     | 0.004                   | 1.29         | 0.049        |
| Smoking                      | 31.74                    | 16.67                   | 46.81        | < 0.0001     |
| Stented segment length [mm]  | 0.94                     | 0.38                    | 1.5          | 0.001        |
defined as the ADPtest result at the higher cutoff, above 468 AU × min.

We found that women had a smaller chance of HPR than men (OR = 0.319; 95% CI: 0.139–0.731; p = 0.007). On the other hand, age (OR per each year 1.06; 95% CI: 1.024–1.1; p = 0.001), positive smoking status (OR = 2.573; 95% CI: 1.29–5.15; p = 0.008), and platelet count (OR per each G/l 1.007; 95% CI: 1.002–1.012; p = 0.008) were all associated with ADPtest result above 468 AU × min (HPR). Of interest, HPR was also more frequent in patients in whom the PCI procedure was performed on the circumflex branch as compared to the left anterior descending branch (OR = 3.28; 95% CI: 1.54–6.96; p = 0.002). Out of procedural variables we found that stented segment length (OR per each mm 1.033; 95% CI: 1.01–1.057; p = 0.004) and stent inflation pressure (OR per each atmosphere 0.862; 95% CI: 0.772–0.963; p = 0.009) were independently related to HPR.

The relation of the same variables to the lower cutoff of the ADPtest – below 188 AU × min – was assessed as well. Patients with an MEA result below this value are often termed “enhanced responders” and are thought to be prone to bleeding complications. We found that hypertension, diabetes, smoking and higher platelet count significantly reduced the odds of platelet reactivity being below 188 AU × min (details see Table III).

**ASPItest results**

We tested the relation of the same set of variables to the higher cutoff of the ASPItest – above 203 AU × min (high on-aspirin platelet reactivity – HAR). We found that, conversely to ADPtest values, women had higher odds of inadequate response to aspirin (ASPItest > 203 AU × min) than men (OR = 2.07; 95% CI: 1.22–3.5; p = 0.007). Also, smoking increased the probability of HAR (OR = 2.5; 95% CI: 1.58–4.23; p < 0.001). Stented segment length was the only procedural parameter related to ASPItest > 203 AU × min (OR = 1.024; 95% CI: 1.005–1.042; p = 0.011).

Platelet aggregation values of patients with acute coronary syndromes did not differ from those of elective PCI patients. No other tested laboratory parameters were correlated with MEA platelet aggregation values.

The main findings of the study are summarized in Tables II and III.

**Discussion**

The study is an analysis of possible risk factors related to HPR in an unselected group of PCI patients, where HPR is defined according to the international consensus statement based on data derived from comparable cohorts [24].

| Parameter | Odds ratio | 95% confidence interval | P-value |
|-----------|------------|-------------------------|--------|
| **ADPtest > 468 AU × min (HPR):** | | | |
| Gender (female vs. male) | 0.319 | 0.139 | 0.731 | 0.007 |
| Age [years] | 1.06 | 1.024 | 1.097 | 0.001 |
| Smoking | 2.57 | 1.29 | 5.15 | 0.008 |
| Platelet count [G/l] | 1.007 | 1.002 | 1.012 | 0.008 |
| Stented segment length [mm] | 1.033 | 1.010 | 1.057 | 0.005 |
| Inflation pressure [atm] | 0.862 | 0.772 | 0.963 | 0.009 |
| Stented vessel (Cx vs. LAD) | 3.28 | 1.54 | 6.96 | 0.002 |
| **ADPtest < 188 AU × min:** | | | |
| Hypertension | 0.52 | 0.37 | 0.71 | < 0.0001 |
| Diabetes type 2 | 0.52 | 0.36 | 0.73 | < 0.0001 |
| Smoking | 0.47 | 0.32 | 0.68 | < 0.0001 |
| Platelet count [G/l] | 0.99 | 0.994 | 0.999 | 0.028 |
| **ASPItest > 203 AU × min (HAR):** | | | |
| Gender (women vs. men) | 2.07 | 1.22 | 3.5 | 0.007 |
| Smoking | 2.58 | 1.58 | 4.23 | < 0.0001 |
| Stented segment length [mm] | 1.024 | 1.005 | 1.042 | 0.011 |

Cx – circumflex branch, LAD – left anterior descending branch.
There is conflicting evidence as to the clinical risk factors related to poorer patient response to clopidogrel and aspirin. This study confirms predominant data indicating that higher age and type 2 diabetes are independent predictors of HPR. Other main findings are as follows: the diagnosis of hypertension is correlated with poorer response to clopidogrel; stented segment length is a predictor of HPR, while stent inflation pressure is actually a predictor of better clopidogrel response. Unexpectedly, we found that women in the studied cohort had a better response to clopidogrel than men and that active smoking is also linked to HPR.

Contrary to clopidogrel response, women were more likely to exhibit an inadequate response to aspirin. Other predictors of inadequate response to aspirin were smoking and stented segment length.

We found no new specific factors predisposing to enhanced clopidogrel response.

It is interesting how variably the risk factors of HPR have been described in the literature. The least controversy is associated with age [25–27], diabetes mellitus [28–31] and smoking. Active smoking has been found to be an independent predictor of better clopidogrel response, explained by the drug’s pharmacodynamics [32–36], the so-called “smoker’s paradox”. However, we found a poorer smokers’ clopidogrel response in our cohort, both for clopidogrel and aspirin, as have others [22, 33]. Smoking was also found to have no influence on clopidogrel response in some studies [25, 37]. However, as available data quite convincingly and predominantly confirm that smoking enhances platelet response to clopidogrel, how can we explain our results? We measured clopidogrel response in hospitalized patients, several days after admission. They had therefore not been smoking for at least three to 5 days preceding platelet reactivity testing. Hence, the metabolic influence of cigarette smoke on cytochrome P450 isoenzyme CYP1A2 may have ceased [38]. Alternatively, albeit unlikely, our results may reflect genetic differences of the studied cohort compared to other patient groups.

We found that women were more likely to respond better to clopidogrel than men, but less likely to respond well to aspirin. Some authors have found no association between gender and antiplatelet drug response [39], while others reported greater prevalence of HPR in women [40]. Similarly, our finding that hypertension increased the odds of HPR may be confirmed in the literature [30, 41], but one may also find evidence to testify otherwise [42]. In our study we did not find a relation of renal function to HPR or HAR, similarly to some authors [43], yet unlike other data, including our earlier study in a different cohort [44–47], possibly due to a low percentage of patients with significantly impaired renal function (eGFR below 30 ml/min/1.73 m²). We have also recently documented that diabetic ACS patients have a higher risk of HPR-related stent thrombosis and death [48]. However, in the present study, ACS occurrence was not independently linked to HPR.

We were able to demonstrate in this study that stented segment length is independently related to HPR in the case of both clopidogrel and aspirin. Stented segment length may be considered a marker of increased and more diffuse atherosclerosis. Our data would therefore accord with an earlier study demonstrating that increased plaque burden is associated with high platelet reactivity on clopidogrel treatment [49]. It is more difficult to relate to our finding that stent inflation pressure is inversely related to the incidence of HPR; we are unable at present to provide a plausible cause of this finding. It would seem that greater inflation pressures, if anything, would also be a marker of increased atherosclerosis and calcification, so the association should in theory be similar to that observed for stented segment length. Of course, one may speculate that lower inflation pressures lead to higher incidence of malposition resulting in increased platelet activation and possibly stent thrombosis, a problem now widely discussed in BVS trials [50]. That, however, seems a somewhat far-fetched idea, as local platelet activation would unlikely be detectable by MEA.

An interesting observation is the fact that in a controlled setting of in-hospital clopidogrel administration we found that only 6% of patients exhibited HPR. This is less than the usually described percentage of 10% to over 30%, as observed in other studies [51]. However, in a recently published observation the incidence of HPR on clopidogrel was only 16%, which is also a low value considering the acute coronary syndrome setting in that study [52]. On the other hand, while HPR on prasugrel and ticagrelor is generally 1–5%, there are new observations indicating it may be as high as 13% in some cohorts [53].

Our aim was to attempt to clinically define the population in whom platelet reactivity monitoring and tailored therapy may be of value. We hoped to define risk factors that could possibly be incorporated into a risk score, an idea similar to that of the authors of the PREDICT-STABLE trial [54]. We found that age, hypertension, diabetes and smoking predispose to higher platelet aggregation values, as does longer stented segment length and lower stent inflation pressure. However, due to the variability of HPR risk factors in the literature, developing a risk score seems exceedingly difficult. The variability of factors influencing clopidogrel response across studies over a number of years may be due to different cohort characteristics, different platelet reactivity assessment methods and confounding factors, such as patient compliance [55, 56]. This phenomenon may also explain why platelet function testing has failed to prove efficacious in randomized clinical trials. However, overwhelming observational evidence generally shows that inadequate platelet inhibition by DAPT results in increased risk of stent thrombosis and patient death [55, 57]. That is why we really need to
know how to reliably measure platelet reactivity, which tests are of value and whom to test – namely, what the characteristics of the population at risk are. The present study adds to this. However, data heterogeneity suggests that in order to develop a risk score, pooling of data from numerous studies is required. There have been the first, very interesting attempts at this approach [58], but more large meta-analyses are probably underway.

The study design precludes any causal relationship inferences. The studied group was medium-sized and somewhat heterogeneous – some relevant subgroups were underrepresented or missing, such as renal failure patients or type 1 diabetes patients. Only one method of platelet reactivity assessment was used. The number of variables tested for association with clopidogrel and aspirin response in the study was limited.

Conclusions
We found that in PCI patients on clopidogrel and aspirin, age, hypertension, diabetes and smoking predispose to higher platelet aggregation values, as does longer stented segment length and lower stent inflation pressure. If based on these data one was to suggest a subgroup of patients in whom to monitor platelet aggregation during aspirin and clopidogrel treatment, it would comprise older patients with diabetes and hypertension, actively smoking, with long stent-treated lesions.

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Conflict of interest
The authors declare no conflict of interest.

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