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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Prediction of high risk of non-adherence to antiplatelet treatment

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Abstract

Background: Dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel is the standard of care for secondary prevention. Premature discontinuation of clopidogrel is associated with an increased risk of myocardial infarction (MI) or death, and greater health care expenditure.

Aim: To develop an objective method for identification of patients with high risk of non-adherence to clopidogrel after MI.

Methods: A total of 189 patients were enrolled into a prospective, observational, single-centre study with a nine-month follow-up. Patients received a 600-mg loading dose and 75-mg maintenance dose of clopidogrel in combination with ASA doses of 300 mg and 75 mg, respectively. Adenosine diposphate-induced platelet aggregation (ADP-PA) was assessed during baseline hospitalisation and at three, six, and nine months after discharge. Adherence to medication with clopidogrel was defined as the proportion of drug availability based on data from the National Health Fund regarding prescribed drug purchases. Adherence was arbitrarily judged adequate when the proportion exceeded 80%.

Results: According to our hypothesis, ADP-PA in non-adherent patients should be higher at follow-up visits (at least once) as compared with measurement at hospitalisation. Based on the ROC curve analysis, the optimal cut-off point equal to 4 U was defined ($p < 0.0001$, 95% CI 0.562–0.654; sensitivity: 60.6%, specificity: 57.1%, positive predictive value: 63.3%, negative predictive value: 54.2%). The prevalence of true adherence to medication in groups of high and low probability of adherence defined according to developed criteria amounted 60 (50.8%) and 23 (32.4%) cases, respectively ($p = 0.01$).

Conclusions: The newly developed method of objective identification of patients with high risk of non-adherence to clopidogrel after MI is easily applicable and cheap, and, despite relatively low sensitivity and specificity, it efficiently differentiates patients with regard to clinical end-points during follow-up.

Key words: clopidogrel, ADP-induced platelet aggregation, adherence to medication

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INTRODUCTION

Dual antiplatelet therapy (DAT) with acetylsalicylic acid (ASA) and clopidogrel reduces the risk of thrombotic events and is recommended in the management of patients with acute coronary syndromes (ACS) and in patients after stent implantation [1, 2]. Premature discontinuation of clopidogrel, shown to be associated with an increased risk of myocardial infarction (MI) or death, and greater health care expenditure [3–5], remains one of the concerns regarding this therapy. Patients identified to have a high risk of non-adherence to clopidogrel may benefit from additional educational interventions aimed at improvement of adherence to clopidogrel instead of instan-

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taneous switching to newer P2Y12 inhibitors. Unfortunately, non-adherence to treatment with clopidogrel remains common and difficult to detect due to often misleading patient declarations [6–9].

Despite DAT, platelet activation usually achieves its highest level early after ACS due to inflammation and plaque rupture [10]. Several other biological factors, including diabetes and genetic polymorphism of CYP2C19 enzyme, have a more stable impact on response to clopidogrel during hospitalisation and follow-up [11–13]. Thus, we hypothesised that after exclusion of drug–drug interactions, it is mainly patients' non-adherence to medication that leads to clopidogrel therapy failure resulting in insufficient inhibition of platelet aggregation [13, 14].

The aim of the study was to develop an objective method for identification of patients with high risk of non-adherence to clopidogrel after MI.

METHODS

Study design and patient characteristics

Two hundred consecutive patients treated with primary percutaneous coronary intervention (pPCI) for acute MI, who gave their informed, written consent, were initially enrolled into this prospective, observational, single-centre study with a 12-month clinical follow-up. The study population comprised 189 patients for whom data from at least one follow-up visit were available. Clinical follow-up was carried out on the basis of data derived from the National Health Fund. Patients received a 600-mg loading dose and 75-mg maintenance dose of clopidogrel in combination with ASA doses of 300 mg and 75 mg, respectively. To avoid additional confounding factors, concomitant therapy was standardised and included bisoprolol, perindopril, and simvastatin if no contraindications were present. When therapy with a proton pump inhibitor was indicated, only pantoprazole was allowed because no interaction between this drug and clopidogrel has been revealed [13]. Patients requiring any additional treatment were excluded due to potential drug–drug interactions. All patients were informed regarding the need for 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 three, six, and nine months after discharge.

Patients' adherence to the medication regimen was assessed based on data from the National Health Fund regarding the purchase of prescribed drugs. Adherence was defined as the proportion of drug availability (the number of purchased clopidogrel tablets) to drug requirement (the number of clopidogrel tablets needed to complete the treatment = number of follow-up days). Following previously published studies [15–18], adherence was arbitrarily judged adequate when the proportion exceeded 80%.

Table 1. Study population characteristics (n = 189)

Feature	Median (upper quartile–lower quartile) or no. (%)
Male	141 (74.6%)
Age [years]	60.0 (53.0–67.0)
Height [cm]	169.9 (164.0–176.0)
Body mass [kg]	80.0 (70.0–90.0)
Waist [cm]	96.0 (89.0–103.5)
BMI > 25 kg/m^2	140 (74.1%)
Hypertension	104 (55.0%)
Diabetes	61 (32.3%)
Smokers	98 (51.9%)
LDL ≥ 115 mg/dL	141 (74.6%)
Extent of CAD:	
1-vessel disease	80 (42.3%)
2-vessel disease	48 (25.4%)
3-vessel disease	61 (32.3%)
Baseline coronary flow:	
TIMI 0	82 (43.4%)
TIMI 1	18 (9.5%)
TIMI 2	20 (10.6%)
TIMI 3	69 (36.5%)
Post-PCI coronary flow:	
TIMI 0	0 (0%)
TIMI 1	1 (0.5%)
TIMI 2	4 (2.1%)
TIMI 3	184 (97.4%)
Number of stents:	
1	133 (70.4%)
2	38 (20.1%)
≥ 3	18 (9.5%)
Total length of stents [mm]	24.0 (15.0–32.0)

CAD — coronary artery disease; BMI — body mass index; LDL — low density lipoprotein; PCI — percutaneous coronary intervention

The study protocol was approved by the Ethical Committee of Nicolaus Copernicus University.

Platelet function assessment

Adenosine diphosphate induced platelet aggregation (ADP-PA) was assessed during baseline hospitalisation and at every follow-up visit. Blood samples were collected at 10:00 a.m. for impedance aggregometry. Whole blood was tested with impedance aggregometry using a Multiplate Analyser (Medical Cyclotron, Munich, Germany). The analyser detects the impedance change related to platelet adherence onto the sensor wires, and transforms it into arbitrary aggregation units (AU) that are plotted against time. The area under the aggregation curve (AUC) is an estimator of platelet aggregation displayed in

Table 2. Adherence to medication with clopidogrel with regard to results of adenosine diphosphate induced platelet aggregation (ADP-PA) measurements at follow-up visits

	Quartiles				P
	I (n = 120) ADP-PA < 11	II (n = 128) 11 ≤ ADP-PA < 19	III (n = 120) 19 ≤ ADP-PA ≥ 29	IV (n = 134) ADP-PA ≥ 29	
Adherence [%]*	84.4 (47.5–92.1)	88.2 (53.7–99.7)	84.4 (35.7–99.7)	76.7 (32.4–99.7)	0.15

*Range of patients' adherence to the medication regimen defined as the proportion of drug availability (the number of purchased clopidogrel tablets) to drug requirement (the number of clopidogrel tablets needed to complete the treatment = number of follow-up days)

arbitrary units (10 AU × min = 1 U). Examination of ADP-PA was used to reflect the effect of P2Y12 receptor inhibition by clopidogrel active metabolite.

According to our hypothesis, patients non-adherent to clopidogrel have higher ADP-PA at follow-up visit (at least once) as compared with ADP-PA assessed during hospitalisation [18]. Receiver operating characteristics (ROC) curve analysis was used to determine cut-off points defining patients with high risk of non-adherence. The DeLong method was applied for evaluation of the significance of the area under the ROC curves. We compared the prevalence of adverse clinical events in patients divided into groups according to the risk of non-adherence to clopidogrel during follow-up visits. ADP-PA ≤ 45 U at follow-up visit was arbitrarily defined as a borderline value of adequate response to clopidogrel according to previously performed research [19].

Statistical analysis

According to the Shapiro-Wilk test, the investigated continuous variables were non-normally distributed; therefore, they were reported as medians and interquartile ranges (IQR). For comparisons between two and three groups, the Mann-Whitney unpaired rank sum test and the Kruskal-Wallis one-way analysis of variance were used, respectively. Categorical variables were expressed as the number of patients presenting the given feature and the percentage of patients in the analysed group. Categorical variables were compared using the χ^2 test with the Yates' correction if required. The Cochran-Armitage test was used to assess the presence of linear trends among categorical variables. Differences were considered significant at $p < 0.05$. The statistical analysis was carried out using the Statistica 10.0 package (StatSoft, Tulsa, USA).

RESULTS

Of 189 patients, 177 (93.7%) declared regular intake of clopidogrel during all follow-up visits. According to self-declarations, only 12 (6.3%) patients were non-adherent to antiplatelet treatment at least once, while according to the data from the National Health Fund the number of such patients was 84 (46.7%).

According to ADP-PA assessment, an overall number of 45 cases of insufficient response to clopidogrel (> 45 U) were revealed during follow-up visits in 36 patients, while in the remaining 153 patients (457 measurements) ADP-PA was ≤ 45 U. Adherence to clopidogrel in both groups amounted to 52.8% (30.7–100.0%) and 84.4% (47.5–99.7%), respectively ($p = 0.13$). The prevalence of patients defined as non-adherent to medication with clopidogrel (drug availability ≤ 80%) was not significantly different in both groups (55.6% vs. 41.2%; $p = 0.09$). No significant difference regarding clinical end-points between the groups was found (STEMI 0% vs. 4.6%, $p = 0.41$; ACS 11.1% vs. 7.2%, $p = 0.66$; unscheduled cardiac hospitalisation 27.8% vs. 14.4%, $p = 0.054$). The results of ADP-PA measurements obtained during follow-up visits did not reflect adherence to medication (Table 2). However, the curves reflecting changes of ADP-PA during the study period in patients adherent to clopidogrel (drug availability > 80%) and those who were non-adherent (drug availability ≤ 80%) suggest an increasing rate of non-adherence to clopidogrel at the end of follow-up (Figs. 1, 2).

According to our hypothesis, ADP-PA in non-adherent patients should be higher at follow-up visits (at least once) as compared to measurements taken at hospitalisation [20]. Using the drug availability proportion as the reference, a ROC curve analysis was performed to determine ADP-PA cut-off points defining patients at high risk of non-adherence. The area under the curve was 0.609 ($p < 0.0001$); 95% confidence interval (CI) 0.562–0.654; positive predictive value: 63.3%; negative predictive value: 54.2%; and the optimal cut-off point was identified at 4 U. According to this definition, a difference in ADP-PA between hospitalisation and any of the follow-up visits of more than 4 U is associated with high risk of non-adherence to clopidogrel (≤ 80% drug availability) with a sensitivity of 60.6% and a specificity of 57.1%, identifying the non-adherence (N-A) group (n = 118). The remaining 71 patients, who were supposed to be adherent to antiplatelet medication, constituted the adherence (A) group (Table 3). Drug availability in group A was higher ($p = 0.04$) as compared with group N-A, 92.1% (53.7–99.7%) vs. 76.7% (32.4–96.1%), respectively. As a consequence, the prevalence of patients defined as adherent to medication with clopidogrel was 60 (50.8%) in group A and 23 (32.4%) in group N-A ($p = 0.01$). The developed definition was tested as a clinical differentiation tool, with the following clinical end-points being evaluated: cardiovascular death, acute MI, any ACS, and unscheduled cardiac hospitalisation (Table 3).

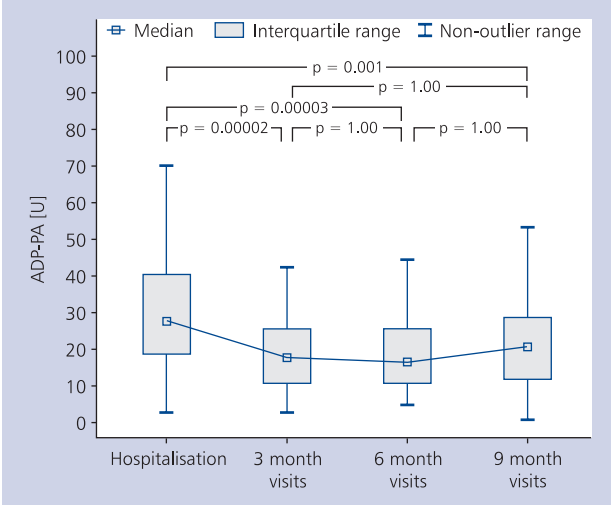

Figure 1. Results of adenosine diphosphate-induced platelet aggregation (ADP-PA) evaluation in adherence group

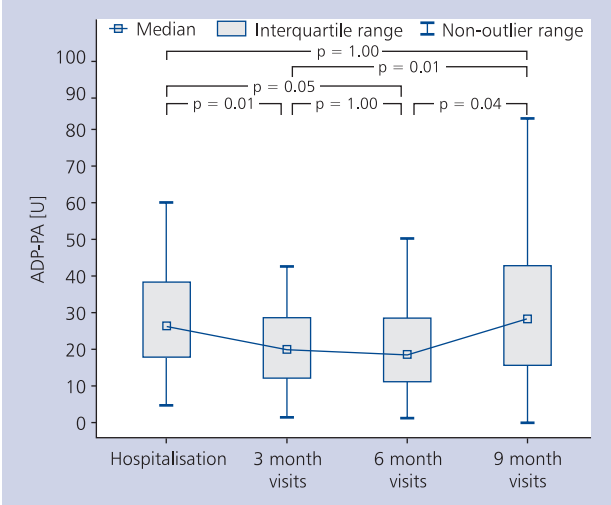

Figure 2. Results of adenosine diphosphate-induced platelet aggregation (ADP-PA) evaluation in not-adherence group

Table 3. Prevalence of clinical end-points in patients with high risk of non-adherence to medication with clopidogrel (N-A group) as compared with low risk of non-adherence patients (A group)

Clinical end-points	N-A group (n = 118)	A-group (n = 71)	P
Cardiovascular death	0 (0%	0 (0%)	–
Acute myocardial infarction	5 (4.2%)	2 (2.8%)	0.91
Acute coronary syndrome	13 (11.0%)	2 (2.8%)	**0.044**
Unscheduled cardiac hospitalisation	25 (21.2%)	7 (9.9%)	**0.04**

DISCUSSION

Antiplatelet therapy is the cornerstone of treatment for patients with ACS and/or those undergoing PCI. The pharmacodynamic response to clopidogrel shows substantial inter-patient variability, and patients with coronary disease and lesser platelet inhibition in response to clopidogrel appear to be at increased risk of cardiovascular events [3, 11]. Genetic factors, accelerated platelet turnover, up-regulation of the P2Y12 pathways, high baseline platelet reactivity, poor adherence to medication, under-dosing, and drug–drug interactions play important roles in the antiplatelet effect of clopidogrel [12, 21, 22]. All mechanisms of ineffective platelet inhibition, except for non-adherence to medication, can be overcome by replacing clopidogrel with newer P2Y12 inhibitors [23]. Thus, identification of patients who do not follow doctors' recommendations is pivotal [24]. Poor adherence to medication is probably the major cause of clopidogrel "resistance" [25]. Despite the importance of secondary prevention, non-adherence rates for patients with MI range from 13% to 60% for prescribed, evidence-based medicines [4, 7, 8, 26, 27]. However, it is difficult to prove without additional confirmatory measures that the drug has not been administered. Kronish et al. [28] used an electronic chip stored in the pill bottle cap for this purpose. Detection of plasma levels of unchanged clopidogrel, an active thiol metabolite, and inactive carboxyl metabolite was tested by Serebruany et al. [6] as an objective method of patient-adherence assessment. They revealed that plasma inactive carboxyl metabolite, but not unchanged clopidogrel, or active thiol metabolite are useful markers to monitor compliance to clopidogrel. However, these methods cannot be used in everyday practice [6, 28]. Other simple methods based on patients' declarations or monitoring of drug prescription purchases are ineffective due to low credibility or the need for long observation periods. Single measurements of P2Y12 receptor inhibition may also not reflect adherence due to the multifactorial mechanism of the patient's responsiveness to clopidogrel [29]. However, we hypothesised that patient non-adherence to DAT is the strongest factor that may increase platelet activity during the follow-up period above the level observed during the acute phase. Based on this hypothesis, we tried to develop an objective identification method for patients with high risk of non-adherence to clopidogrel after MI. According to the ROC curve analysis, ADP-PA during any follow-up visit > 4 U, as compared with the initial in-hospital assessment, is associated with high risk of non-adherence to clopidogrel. The relatively low sensitivity and specificity indicates that this is not the best tool to differentiate patients with regard to adherence to medication. Nevertheless, we

have proven the clinical usefulness of the developed definition with regard to study population differentiation according to clinical end-points. The prevalence of ACSs was almost four-fold higher, and unscheduled cardiac hospitalisation was more than two-fold more frequent in patients at high risk of non-adherence to clopidogrel.

Limitations of the study

The current analysis has several potential limitations. First, our study was a single-centre and relatively small research project. Therefore, the generalisability of our findings is uncertain. Second, drug availability does not necessarily reflect its actual intake. This methodological limitation, however, should be initially taken into account at choice-making regarding approaches to be used for evaluation of adherence to medication. Third, despite relatively high reproducibility and precision of the multiplate analyser [30], the difference of 4 U between assessment during hospitalisation and follow-up visit is low. Thus, any result of ADP-PA evaluation during any follow-up visit higher than at baseline suggests a possibility of non-adherence to medication with clopidogrel. Our study also has several strengths, including the high follow-up attendance with clinical and platelet aggregation assessment.

CONCLUSIONS

In conclusion, this study demonstrated a newly developed method of objective identification of patients at high risk of non-adherence to clopidogrel after MI. The method is easily applicable and cheap, and, despite its relatively low sensitivity and specificity, it efficiently differentiates patients with regard to clinical end-points during follow-up.

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Conflict of interest: *none declared*

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Identyfikacja zwiększonego ryzyka nieprzestrzegania zaleceń lekarskich dotyczących stosowania leków antyagregacyjnych

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Streszczenie

Wstęp: Podwójna terapia przeciwpłytkowa złożona z kwasu acetylosalicylowego (ASA) i klopidogrelu stanowi standard leczenia w prewencji wtórnej. Przedwczesne zaprzestanie stosowania klopidogrelu wiąże się z większym ryzykiem zawału serca (MI) lub zgonu, a także większymi wydatkami na służbę zdrowia.

Cel: Celem pracy było stworzenie obiektywnej metody identyfikacji pacjentów cechujących się zwiększonym ryzykiem nieprzestrzegania zaleceń lekarskich dotyczących stosowania klopidogrelu po MI.

Metody: Do prospektywnego, obserwacyjnego, jednoośrodkowego badania włączono 189 pacjentów, których obserwowano przez 9 miesięcy. Pacjenci otrzymali klopidogrel w dawce nasycającej (600 mg), a następnie w dawce podtrzymującej (75 mg) w połączeniu z ASA w dawkach, odpowiednio, 300 mg i 75 mg. Agregację płytek krwi indukowaną ADP (ADP-PA) oznaczano w trakcie hospitalizacji oraz 3, 6 i 9 miesięcy po wypisaniu ze szpitala. Stosowanie się do zaleceń lekarskich dotyczących przyjmowania klopidogrelu oparto na danych uzyskanych z Narodowego Funduszu Zdrowia, a zdefiniowane było ono przez stosunek ilości leku wykupionego do ilości leku niezbędnej do kontynuacji terapii. Arbitralnie przyjęto, że stosowanie się do zaleceń lekarskich jest zadowalające, jeśli stosunek ten przekracza 80%.

Wyniki: Nawiązując do naszej hipotezy, ADP-PA u pacjentów nieprzestrzegających zaleceń lekarskich powinno być wyższe w czasie wizyt kontrolnych (przynajmniej podczas jednej wizyty) w porównaniu z danymi reaktywności płytek krwi uzyskanymi w trakcie hospitalizacji. Na podstawie analizy krzywych ROC za optymalny punkt odcięcia uznano wartość 4 U ($p < 0,0001$; 95% CI 0,562–0,654; czułość: 60,6%, swoistość: 57,1%, pozytywna wartość predykcyjna: 63,3%, negatywna wartość predykcyjna: 54,2%). W zdefiniowanych na podstawie tych kryteriów grupach — o wysokim i niskim prawdopodobieństwie stosowania się do zaleceń lekarskich — rzeczywista liczba stosujących się do zaleceń wynosiła odpowiednio 60 (50,8%) oraz 23 pacjentów (32,4%); $p = 0,01$.

Wnioski: Nasza nowo opracowana metoda pozwala obiektywnie zidentyfikować pacjentów cechujących się podwyższonym ryzykiem nieprzestrzegania zaleceń lekarskich w zakresie stosowania klopidogrelu po MI. Łatwa w zastosowaniu, tania, pomimo stosunkowo niskiej czułości i swoistości, skutecznie różnicuje pacjentów w odniesieniu do klinicznych punktów końcowych.

Słowa kluczowe: klopidogrel, agregacja płytek krwi indukowana ADP, stosowanie się do zaleceń lekarskich

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