

# A single-centre, randomised study on platelet reactivity after abrupt or gradual discontinuation of long-term clopidogrel therapy in patients after percutaneous coronary intervention

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## Abstract

**Background:** Clinical studies have suggested increased risk of thrombotic events after planned cessation of clopidogrel therapy, due to increased platelet reactivity (platelet rebound); however, in many studies platelet function was not assessed before introducing clopidogrel. Patients who are scheduled to stop clopidogrel therapy, do it abruptly, so a gradual drug cessation might provide a beneficial treatment strategy.

**Aim:** To determine whether a clopidogrel discontinuation results in platelet rebound hyperaggregability with increased activity compared to pre-treatment values and to assess whether abrupt or tapering clopidogrel cessation may affect platelet reactivity.

**Methods:** Patients with stable coronary artery disease ( $n = 49$ ), on chronic acetylsalicylic acid treatment, who underwent coronary angiography, and were scheduled for elective percutaneous coronary intervention with stent implantation were enrolled. Patients were randomised to either a tapering clopidogrel discontinuation during a two-week period (tapering group,  $n = 25$ ) or abrupt drug cessation (abrupt group,  $n = 24$ ). After 12 months of dual antiplatelet therapy with clopidogrel and acetylsalicylic acid, we performed three follow-up visits with blood sampling. Platelet aggregation was assessed using a multiple electrode aggregometer at inclusion, at cessation day, and seven and 14 days after complete clopidogrel discontinuation. The primary endpoint was the level of adenosine-diphosphate (ADP)-induced platelet aggregation. We also analysed platelet function in the ASPI test and platelet count as secondary endpoints.

**Results:** In 36 patients included in the main analysis, we found significant differences between the two study groups in the levels of ADP-induced platelet aggregation at days seven and 14 after cessation of clopidogrel ( $p = 0.004$  and  $p = 0.04$ , respectively). In the abrupt group, platelet aggregation returned to the values similar to baseline at day seven. There were no significant differences between baseline, seven, and 14 days after drug cessation ( $p = 0.92$  and  $p = 0.37$ , respectively). However, in the tapering group, ADP values at seven and 14 days after drug cessation were significantly decreased, comparing to baseline ( $p < 0.0001$  and  $p = 0.009$ , respectively). For the ASPI test and platelet count we did not find significant differences between the groups. All values returned to levels similar to the baseline. During the follow-up there were no serious cardiovascular events or bleedings.

**Conclusions:** Tapering vs. abrupt discontinuation of clopidogrel treatment results in significantly lower platelet aggregation values after 14 days from complete drug cessation. We found no evidence of a platelet rebound effect.

**Key words:** clopidogrel cessation, platelet reactivity, platelet rebound

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## INTRODUCTION

Clopidogrel is an effective inhibitor of platelet activation and aggregation as a result of selective and irreversible blockade of the P2Y<sub>12</sub> receptor [1]. Depending on the type of stent and the circumstances of stent implantation (elective vs. urgent), current guidelines recommend clopidogrel for one month after elective percutaneous coronary intervention (PCI) with bare metal stent (BMS), at least six months for patients receiving drug-eluting stents (DES) in stable coronary artery disease (CAD), and 12 months in patients with acute coronary syndromes (ACS) [2, 3]. In daily clinical practice, patients who are scheduled to stop clopidogrel therapy do it abruptly [4]. Recently, some studies have suggested increased risk of recurrent cardiovascular events after planned cessation of clopidogrel therapy. It has been postulated that it could be due to increased platelet reactivity compared with pre-treatment values (platelet rebound) [1, 5–9]. However, in many previous studies [3, 4, 10], platelet reactivity before introducing clopidogrel was not assessed, and therefore it is unclear whether platelet reactivity after withdrawal was any higher than pre-treatment levels [1]. Furthermore, in most of the previous studies, the clopidogrel cessation was abrupt. A tapered discontinuation of clopidogrel treatment might provide a beneficial treatment strategy to attenuate this supposed rebound phenomenon of platelets [4]. In our study we aimed to determine whether a clopidogrel discontinuation results in platelet hyperaggregability with increased activity compared to pre-treatment values (platelet rebound). Also, we assessed whether abrupt or tapering clopidogrel cessation may affect platelet reactivity in a different manner.

## METHODS

### *Study design and clinical characteristics*

Between July 2012 and February 2013, 49 patients were enrolled in this single-centre, randomised, controlled, open-label, parallel group study at the Third Department of Cardiology, Medical University of Silesia (Katowice, Poland). Patients with stable CAD, already on chronic (> 3 months) treatment with acetylsalicylic acid (ASA) (75 mg/day), but without clopidogrel, who underwent coronary angiography and were scheduled for elective PCI with stent implantation, were enrolled. After informed consent was granted, a baseline blood sample was taken before the 600 mg loading dose of clopidogrel was administered. After the PCI dual antiplatelet therapy (DAPT) with clopidogrel (original, 75 mg daily, 12 months) and ASA (enteric-coated, 75 mg daily, life-time) was recommended for both BMS and DES receivers as we had to standardise the term of clopidogrel therapy. Patients were randomised to either a tapering (tapering group) or abrupt cessation of clopidogrel (abrupt group). We drew envelopes with a cessation group code to randomise each patient. After 12 months, all patients were asked for three

follow-up visits (day of cessation, and seven and 14 days after complete drug cessation) as clopidogrel cessation procedure with blood sampling was started. Clopidogrel cessation was over a pre-defined period of 14 days with complete cessation of clopidogrel after that (tapering group) or abrupt discontinuation of clopidogrel (abrupt group). In the tapered cessation group, patients were scheduled to take clopidogrel every second day for the first week and then every third day during the second week, after which the drug was withdrawn (Fig. 1). Clopidogrel compliance was evaluated during an interview with the patient (Fig. 1).

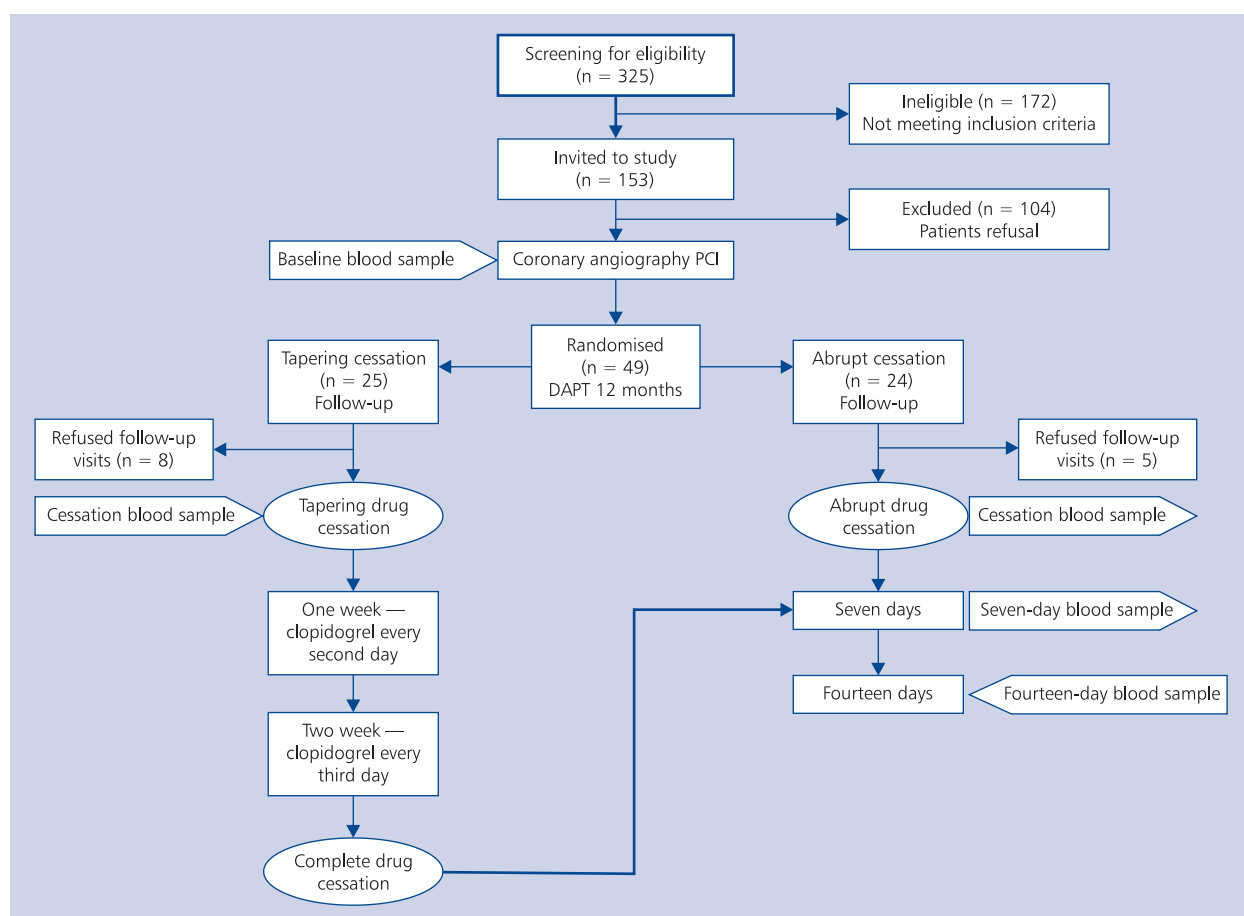
During the whole study period patients were followed for major adverse cardiovascular events defined as a composite of death, myocardial infarction, and stent thrombosis. The bleeding events were registered using Bleeding Academic Research Consortium (BARC) classification. These data were reported via phone contact during clopidogrel therapy and at follow-up visits during cessation period.

Our study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Silesia. All patients gave written informed consent before entering the study. Inclusion and exclusion criteria are shown in Table 1.

### *Blood sampling*

Peripheral venous blood samples were collected in a fasting state. Platelet function was measured in whole blood with a multiple electrode platelet aggregometer (MEA). Blood was placed in 3-mL plastic tubes containing anticoagulant (Hirudin Blood tube, Verum Diagnostica GmbH, Munich, Germany). For platelet count measurement we used a BD Vacutainer System (2 mL plastic tubes). Blood samples were kept at room temperature for at least 30 min before testing. As blood samples were blinded, the laboratory technician was not aware of the patient allocation.

Blood for platelet function testing was taken at pre-specified time points during the study. The baseline sample (ASPI B, ADP B, PLT B) was taken in the hospital directly after study inclusion but before pre-angioplasty loading with 600 mg of clopidogrel. Further samples were taken during follow-up visits after 12 months of clopidogrel treatment and were scheduled as follows: first on the last day of clopidogrel therapy (ASPI C, ADP C, PLT C samples) and then at seven days (ADP 7) and 14 days (ASPI 14, ADP 14, PLT 14) after its discontinuation. The time interval between ASA and/or clopidogrel ingestion and blood sampling was at least 1–2 h and maximum up to 6 h. Aggregation in whole blood was assessed using an impedance aggregometer with MEA on the Multiplate analyser (Dynabyte GmbH, Munich, Germany). After dilution (1:2 with 0.9% sodium chloride) of hirudin-anticoagulated whole blood and stirring for 3 min in the test cuvettes at 37°C, the agonist was added. Aggregation was recorded continuously



**Figure 1.** Diagram of flow of participants and study design; DAPT — dual antiplatelet therapy; PCI — percutaneous coronary intervention

**Table 1.** Inclusion and exclusion criteria

Inclusion criteria
Age 18–80 years
Stable coronary artery disease
Elective PCI with stent implantation
12-months of DAPT (ASA + clopidogrel) recommendation
Receiving 75 mg ASA for at least 3 months
Exclusion criteria
Unable/unwilling to give informed consent
Acute coronary syndrome < 3 months
Platelet count < $50 \times 10^3/\mu\text{L}$
Currently taking antiplatelet or anticoagulant drugs other than ASA (clopidogrel, prasugrel, ticagrelor, warfarin, acenocoumarol, rivaroxaban, dabigatran, apixaban)
Prior treatment with glycoprotein IIb/IIIa inhibitors < 3 months pregnancy

PCI — percutaneous coronary intervention; DAPT — dual antiplatelet therapy, ASA — acetylsalicylic acid

for 6 min. Platelet aggregation was measured by MEA in response to 6.4 mol/L adenosine-diphosphate (ADP) in the presence of 9.4 nmol/L prostaglandin E1 (ADP high sensitivity test [ADP-HS]). To investigate ASA effect on aggregation and the potential synergistic effect of clopidogrel and ASA, we also performed ASPI test, where platelets are activated by arachidonic acid. Aggregation measured with MEA is quantified as aggregation units (AU) and area under the curve of AU [AU × min]. All material used, including the different agonists, was obtained from the manufacturer (Dynabyte). Platelet count was assessed using an impedance method on an ABX Pentra 120 analyser (Horiba Ltd, Kyoto, Japan).

### Endpoints

The primary endpoint of the study was the level of ADP-induced platelet aggregation measured in the pre-specified time points after discontinuation of clopidogrel. Also, we analysed platelet function in the ASPI test and platelet count, to examine other potential platelet reactivity confounding factors as secondary endpoints.

### Statistical analysis

Qualitative data was summarised by absolute frequencies and percentages of its values. Categorical variables were compared using exact Fisher's test. Quantitative data were presented as mean with standard deviation ( $\pm$  SD) and median with interquartile range (for normal and non-normal distributed data, accordingly). The normality assumption was tested using Shapiro-Wilk's test. The significance of between-group differences was assessed using unpaired t-test or Wilcoxon-Mann-Whitney test, whereas within-group differences were analysed using Wilcoxon signed-rang test.

The interpretation of statistical significance was based on a value of  $\alpha = 0.05$ . Comparisons at different time points and different therapy cessation were regarded as exploratory. Therefore, no corrections in  $\alpha$  for multiple comparisons were applied. All statistical analyses were performed using the SAS statistical software package, version 9.4 (SAS Institute Inc., Gary, NC).

## RESULTS

### Clinical characteristics

A total of 49 patients were enrolled in this study, of whom 25 were randomised into the tapering cessation group and 24 into the abrupt discontinuation group. Thirty-six participants completed all scheduled visits and were included in the main analysis, and 13 patients withdrew consent (Fig. 1). Baseline characteristics of the patients according to the cessation group are presented in Table 2, and both groups showed comparable baseline characteristics in terms of demographic and clinical data. During cessation and follow-up visits, patients did not report any significant changes in pharmacotherapy.

Based on test characteristics provided by the producer, we defined cut-off values indicating platelet inhibition  $< 425$  AU  $\times$  min and  $> 998$  AU  $\times$  min for increased platelet reactivity in ADP-HS test and 706–1148 AU  $\times$  min for ASPI test, respectively. According to this level, when we analysed the test results, we found that 11 (27%) patients for the ADP test and two (5.5%) patients for ASPI showed decreased platelet inhibition despite DAPT at cessation day. Seven days after cessation we found that six (31%) patients in the abrupt group and one (5.8%) patient in tapering group showed increased platelet reactivity in the ADP test. After 14 days, we found nine (47%) patients in the abrupt group and four (23%) patients in the tapering group presenting increased platelet reactivity in the ADP test. Accordingly, one (5.2%) patient in the abrupt group and no patients in the tapering group showed increased platelet reactivity in ASPI test (Tables 2, 3).

### Primary endpoint

The baseline values of the ADP and ASPI, as well as platelet counts, were comparable between groups (Table 3). For both groups the level of platelet aggregation was significantly lower

at cessation in comparison to baseline values ( $p < 0.002$  and  $p < 0.001$ ). No significant differences were observed between groups at baseline and cessation ( $p = 0.25$  and  $p = 0.73$ , respectively) indicating that clopidogrel therapy was equally effective in both groups (Table 4). For the primary endpoint of the study we found significant differences between the two study groups in the levels of ADP-induced platelet aggregation at days seven and 14 after cessation of clopidogrel ( $p = 0.004$  and  $p = 0.04$ , respectively; Fig. 2). In the abrupt cessation group, platelet aggregation returned to values similar to baseline at day seven, and there were no significant differences between baseline, and seven and 14 days after drug cessation ( $p = 0.92$  and  $p = 0.37$ , respectively). However, in the tapering group, ADP values at seven and 14 days after drug cessation were significantly decreased, compared to baseline ( $p < 0.0001$  and  $p = 0.009$ , respectively) (Table 4, Fig. 2).

### Secondary endpoints

The platelet function using ASPI test was carried out to examine other potential platelet reactivity confounding factors and to investigate the potential synergistic effect of clopidogrel and ASA. For the AA-induced platelet aggregation (ASPI test), we did not find significant differences between investigated groups (Table 4). Figure 3 shows the distribution of platelet aggregation values in the ASPI test. For both groups (abrupt and tapering) differences between baseline and cessation aggregation values were significant (Table 4), indicating that dual antiplatelet therapy was effective. In the abrupt cessation group, after 14 days, platelet aggregation returned to the level similar to baseline values ( $p = 0.07$ ). In the tapering group, aggregation values at 14 days after drug cessation did not show a significant difference ( $p = 0.12$ ) (Table 4, Fig. 3).

For the platelet count, we also did not find significant differences between the study groups, except for a comparison between baseline versus cessation level in the abrupt group ( $p = 0.01$ ). Figure 4 shows a comparison of platelet counts between groups. For both groups (abrupt and tapering), after 14 days, platelet count had a comparable level of baseline values (Table 4).

### Clinical follow-up

During the follow-up there were no serious cardiovascular events or bleedings (Fig. 4).

## DISCUSSION

The leading result of our study is that a tapering discontinuation of clopidogrel treatment as compared with abrupt cessation results in significantly lower platelet aggregation values after complete drug discontinuation. Previously published studies did not report such findings. Sibbing et al. [4], in a similar study, compared tapering and abrupt clopidogrel cessation in 69 patients and did not find significant differences in platelet aggregation between the groups. One of the pos-

**Table 2.** Baseline patient characteristics (n = 36)

	Tapering (n = 17; 47%)	Abrupt (n = 19; 53%)	P
Gender: male	10 (58.8%)	12 (63.2%)	1.00
Age [years] (mean ± SD)	64.1 ± 6.8	62.4 ± 8.3	0.50
Hypertension	16 (94.1%)	16 (84.2%)	0.61
Diabetes	4 (23.5%)	4 (21.1%)	1.00
Dyslipidaemia	15 (88.2%)	16 (84.2%)	1.00
Smoking status:			1.00
Never	9 (52.9%)	9 (47.4%)	
Former	6 (35.3%)	7 (36.8%)	
Current	2 (11.8%)	3 (15.8%)	
Body mass index (mean ± SD)	29.2 ± 3.0	26.9 ± 3.9	0.09
Overweight	7 (41.2%)	9 (47.4%)	0.72
Obesity	5 (29.4%)	2 (10.5%)	0.21
CAD in family history	8 (47.1%)	6 (31.5%)	0.73
Previous PCI	7 (41.2%)	10 (52.6%)	0.53
DES implantation	12 (70.6%)	16 (84.2%)	0.43
BMS implantation	5 (29.4%)	3 (15.8%)	
Previous myocardial infarction	5 (29.4%)	3 (15.8%)	0.43
Heart failure	4 (23.5%)	2 (10.5%)	0.66
Arrhythmias	3 (17.7%)	1 (5.3%)	0.33
Glucose concentration (mean ± SD)	91.1 ± 27.4	87.3 ± 11.7	0.24*
T-C concentration (mean ± SD)	182.0 ± 36.3	161.4 ± 38.2	0.11
HDL-C concentration (mean ± SD)	46.4 ± 13.7	42.2 ± 8.6	0.28
LDL-C concentration (mean ± SD)	106.0 ± 24.8	89.8 ± 27.7	0.10*
Triglycerides concentration (mean ± SD)	146.1 ± 65.9	136.6 ± 89.5	0.34*
Drugs:			
Beta-blockers	17 (100%)	18 (94.7%)	1.00
ACE-I/ARB	14 (82.3%)	17 (89.4%)	0.65
Diuretics	7 (41.2%)	8 (42.1%)	1.00
Calcium channel blockers	4 (23.5%)	5 (26.3%)	1.00
Statins	16 (94.1%)	17 (89.4%)	1.00
Proton pump inhibitors	5 (29.4%)	8 (42.1%)	0.32
Omeprazole	1 (5.8%)	3 (15.8%)	0.61
Pantoprazole	4 (23.5%)	5 (26.3%)	0.72
Other (CYP inducers or inhibitors)	1 (5.8%)	2 (10.5%)	1.00

SD — standard deviation; CAD — coronary artery disease; PCI — percutaneous coronary intervention; DES — drug-eluting stent; BMS — bare metal stent; T-C — total cholesterol; LDL-C — low-density lipoprotein cholesterol; HDL — high-density lipoprotein cholesterol; ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; CYP — cytochrome P450

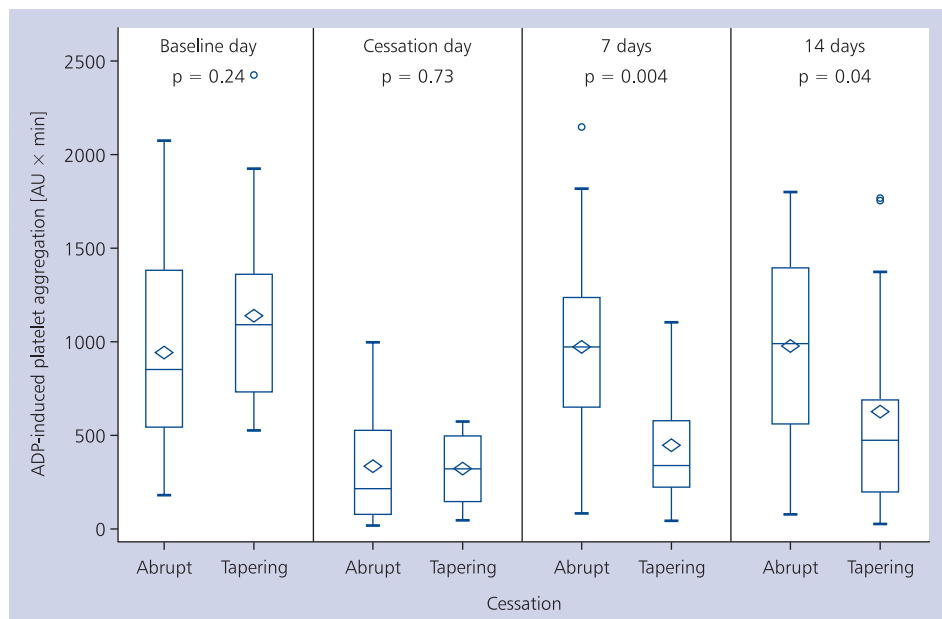
**Table 3.** Laboratory parameter characteristics at baseline and cessation time-points (median)

Laboratory parameters	Baseline			Cessation day		
	Tapering group	Abrupt group	P	Tapering group	Abrupt group	P
ASPI-test [AU × min]	432	446	0.85	233	113	0.51
ADP-test [AU × min]	1095	853	0.25	325	224	0.73
Platelet count [ $\times 10^3/\mu\text{L}$ ]	204	206	0.74	204	244	0.34

**Table 4.** General comparisons of main effects between time-points and group differences

Main effects differences (p value):	Median of ADP-test [AU × min]	Median of ASPI-test [AU × min]	Median of PLT [×10 <sup>3</sup> /μL]
Measurement: B vs. C (abrupt)	853 vs. 224 (p = 0.002)	446 vs. 113 (p = 0.02)	206 vs. 244 (p = 0.01)
Measurement: B vs. 7 days (abrupt)	853 vs. 975 (p = 0.92)	–	–
Measurement: B vs. 14 days (abrupt)	853 vs. 997 (p = 0.37)	446 vs. 296 (p = 0.07)	206 vs. 235 (p = 0.10)
Measurement: B vs. C (tapering)	1095 vs. 325 (p < 0.0001)	432 vs. 233 (p = 0.0006)	204 vs. 204 (p = 0.05)
Measurement: B vs. 7 days (tapering)	1095 vs. 344 (p < 0.0001)	–	–
Measurement: B vs. 14 days (tapering)	1095 vs. 475 (p = 0.009)	432 vs. 195 (p = 0.12)	204 vs. 197 (p = 0.72)
Abrupt vs. tapering — Baseline	853 vs. 1095 (p = 0.24)	446 vs. 432 (p = 0.85)	206 vs. 204 (p = 0.74)
Abrupt vs. tapering — Cessation	224 vs. 325 (p = 0.73)	113 vs. 233 (p = 0.51)	244 vs. 204 (p = 0.34)
Abrupt vs. tapering — 7 days	975 vs. 344 (p = 0.004)	–	–
Abrupt vs. tapering — 14 days	997 vs. 475 (p = 0.04)	296 vs. 195 (p = 0.62)	235 vs. 197 (p = 0.19)

B — baseline; C — cessation day; PLT — platelet count



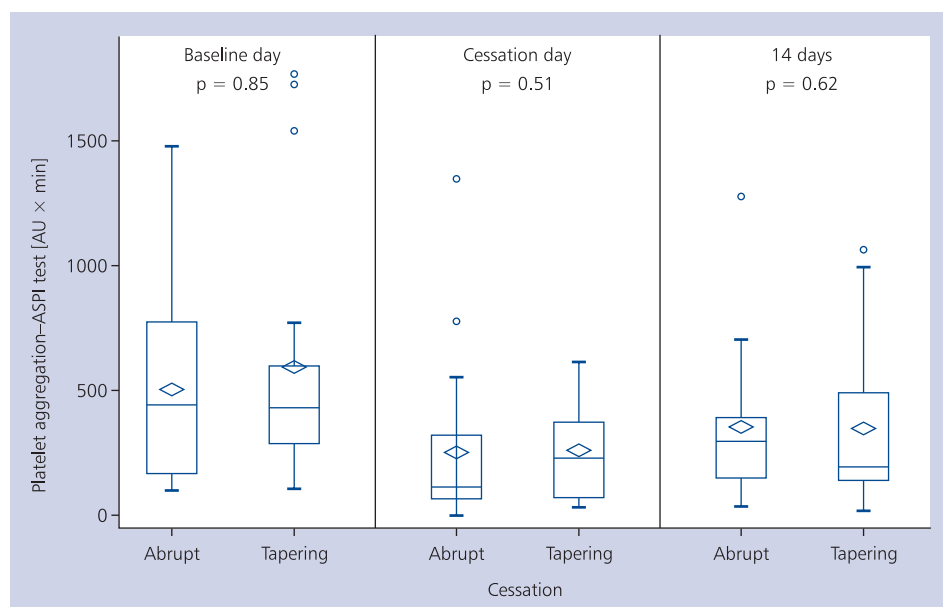
**Figure 2.** Adenosine-diphosphate (ADP)-induced platelet aggregation. Boxplots with bars indicate median, boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles (interquartile range [IQR]), and whiskers indicate upper and lower limits, with outliers beyond 1.5 × IQR from the 25<sup>th</sup> to 75<sup>th</sup> percentiles

sible explanations of the presented results is that we measured platelet baseline aggregation before clopidogrel loading (which remarkably affects study results) as a baseline and after cessation aggregation were compared. In many previous studies, platelet reactivity before introducing clopidogrel was not assessed, and therefore it is unclear whether platelet reactivity after drug withdrawal was higher than pre-treatment levels.

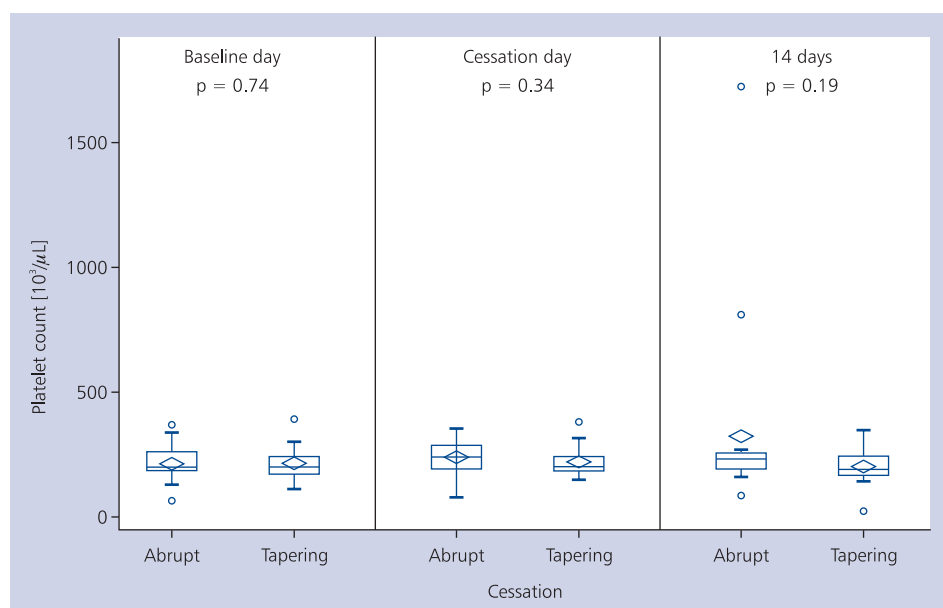
Also, in our study we measured platelet aggregation using a high-sensitivity method, which might enhance the precision of the results. As we also examined platelet reactivity using ASPI test and platelet count and did not find significant differences between the examined groups, we assumed that

platelet aggregation differences are specifically due to the strategy of clopidogrel cessation. However, previous data suggested that there is an interaction between clopidogrel and the arachidonic acid-induced pathway of platelet reactivity [11–14]. Sambu et al. [14] reported finding that when clopidogrel is withdrawn one year after DES implantation, there is a significant increase in AA-induced platelet reactivity in addition to an increase in ADP-induced platelet reactivity. Similarly, Djukanovic et al. [15] found that stopping one year of clopidogrel therapy led patients to show an increase in AA-induced platelet aggregation, which is an attenuation of the response to ASA.





**Figure 3.** Platelet aggregation in ASPI test. Boxplots with bars indicate median, boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles (interquartile range [IQR]), and whiskers indicate upper and lower limits, with outliers beyond  $1.5 \times$  IQR from the 25<sup>th</sup> to 75<sup>th</sup> percentiles



**Figure 4.** Platelet count. Boxplots with bars indicate median, boxes represent 25<sup>th</sup> to 75<sup>th</sup> percentiles (interquartile range [IQR]), and whiskers indicate upper and lower limits, with outliers beyond  $1.5 \times$  IQR from the 25<sup>th</sup> to 75<sup>th</sup> percentiles

Another important result of our study is that we did not find evidence for the presence of platelet rebound phenomenon after clopidogrel cessation. All platelet outcomes returned to approximate baseline levels or were lower by two weeks after drug cessation; none of them exceeded the baseline level. We investigated platelet reactivity until 14 days after the drug was stopped, but we do not think that the rebound phenomenon will occur after that time point because a full re-

covery of platelet function after discontinuation of clopidogrel is observed within five to seven days after complete withdrawal of the drug [4]. A few small studies showed an increase in platelet reactivity after planned cessation of clopidogrel in patients with diabetes mellitus [1, 8] and/or stable CAD [1, 10, 13]. Among patients stopping clopidogrel 12 months after stent insertion, Mylotte et al. [10] found a peak in light transmission platelet aggregation at one month after cessation

of treatment compared with three months, whereas a study by Diehl et al. [3] found increased whole blood aggregation at two and six weeks compared with 17 weeks. However, none of these studies included a pre-treatment baseline. Similarly to our findings, in a recently published study by Ford et al. [1], where pre- and post-treatment platelet aggregation was assessed, no evidence for rebound of platelet reactivity to above baseline level was found in 171 patients. In other crossover studies of P2Y12 inhibitors for stable CAD patients [1, 16] or stable CAD with diabetes [1, 17], where also pre- and post-treatment platelet aggregation were assessed, there were no significant differences compared to baseline seven to ten days after withdrawal.

Available clinical studies provided conflicting results when we consider the occurrence of clinical thrombotic events after stopping clopidogrel. Because of small patient numbers we were not able to demonstrate a potential protective effect of tapering strategy of clopidogrel cessation on lowering clinical thrombotic events, although our findings suggest such a possibility. In a recently published study, Fiedler et al. [18] found that tapered discontinuation of chronic clopidogrel therapy is not superior to abrupt discontinuation, regarding the primary clinical endpoint; however, this result must be interpreted in view of the premature termination of the trial and low event rates. In a retrospective cohort study of 3137 ACS patients carried out by Ho et al. [5], a large number of deaths or myocardial infarctions were observed in the first weeks after stopping clopidogrel in both medically-treated and PCI-treated patients [4]. Results of other studies do not confirm these findings. In an observational study including 10,778 patients with sirolimus-eluting stent implantation, discontinuation of thienopyridine treatment alone was not associated with an excess of ischaemic events in any of the time intervals studied [4, 19].

### Limitations of the study

The main limitation of the present study is the small number of patients we enrolled, and 13 of them refused follow-up visits. Hence, the study was not powered to assess clinical endpoints. We included in our study only patients with stable CAD. Additionally, there may be differences in platelet reactivity and response to clopidogrel between DES and BMS receivers [20]; in our study the majority of patients received DES. Another limitation is related to the relatively short monitoring period; however, considering the short half-life of platelets and the irreversible inhibition by clopidogrel, we think it is unlikely that we could have missed an earlier, or a later platelet rebound phenomenon. Additionally, we assessed platelet reactivity using only MEA method. Also, we did not implement any objective method to evaluate clopidogrel adherence. Using enteric coated ASA could also have an impact on the observed results because the enteric coating can reduce the antiplatelet effect of ASA compared to plain ASA [21].

### CONCLUSIONS

Our study demonstrated that a tapering versus abrupt discontinuation of long-term clopidogrel treatment in patients with stable CAD, who underwent PCI with stent implantation, results in significantly lower platelet aggregation values 14 days after complete drug cessation. Additionally, the findings of this study reassure us that there is no evidence of a platelet rebound effect after clopidogrel cessation in patients with stable CAD. Adequately powered, randomised trials are necessary to assess the clinical benefits of clopidogrel tapering versus abrupt cessation in patients undergoing PCI, particularly in those with a high risk of thrombotic complications.

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**Conflict of interest:** none declared

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# Randomizowane badanie aktywności płytek krwi po jednorazowym lub stopniowym zaprzestaniu podawania kłopidogrelu u pacjentów po zabiegach angioplastyki tętnic wieńcowych

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## Streszczenie

**Wstęp:** Wyniki badań klinicznych pokazały przejściowy wzrost częstości występowania incydentów zakrzepowych po zaprzestaniu długoterminowej terapii kłopidogrelem. Za zjawisko to może odpowiadać zniesienie hamującego wpływu kłopidogrelu na płytki krwi i występowanie mechanizmu z odbicia — wzrost aktywności płytek krwi po odstawieniu kłopidogrelu do poziomów wyższych niż aktywność płytek przed zastosowaniem tego leku.

**Cel:** Celem badania była ocena aktywności płytek krwi po standardowym, nagłym zaprzestaniu stosowania kłopidogrelu i stopniowym odstawianiu tego leku przeciwpłytkowego u pacjentów po zabiegach angioplastyki tętnic wieńcowych.

**Metody:** Do badania włączono 49 pacjentów z chorobą wieńcową, długotrwałe leczonych kwasem acetylosalicylowym (ASA), którzy po koronarografii zostali zakwalifikowani do angioplastyki tętnic wieńcowych z implantacją stentu. Pacjenci zostali losowo przydzieleni do grupy stopniowego wyłączenia kłopidogrelu przez okres 14 dni lub do grupy standardowego zakończenia terapii przeciwpłytkowej. Aktywność płytek krwi oceniano na podstawie agregacji płytek wywołanej przez adenylozynylofosforan (test ADP) w chwili włączenia pacjenta do badania i podczas trzech wizyt po zaprzestaniu podawania kłopidogrelu. Drugorzędowy punkt końcowy obejmował aktywność płytek krwi w odpowiedzi na kwas arachidonowy (test ASPI).

**Wyniki:** Wykazano istotne różnice w aktywności płytek krwi w teście ADP między obiema badanymi grupami w 7. i 14. dniu po zaprzestaniu podawania kłopidogrelu (odpowiednio,  $p = 0,004$  i  $p = 0,04$ ). W grupie jednorazowego odstawienia leku zaobserwowano powrót aktywności płytek krwi do wartości wyjściowych już w 7. dniu po odstawieniu kłopidogrelu. Aktywność płytek nie różniła się statystycznie w dniu 7. i 14. po zakończeniu leczenia od wartości wyjściowych (odpowiednio  $p = 0,92$  i  $p = 0,37$ ). W grupie stopniowego odstawiania kłopidogrelu wartości aktywności płytek krwi w 7. i 14. dniu po zaprzestaniu przyjmowania leku były istotnie mniejsze od wartości wyjściowych (odpowiednio,  $p < 0,0001$  i  $p = 0,009$ ). W przypadku testu ASPI nie stwierdzono istotnych statystycznie różnic między badanymi grupami. Podczas obserwacji pacjentów nie wystąpiły żadne poważne incydenty sercowo-naczyniowe ani epizody krwawienia.

**Wnioski:** Stopniowe odstawianie kłopidogrelu w porównaniu z odstawieniem nagłym prowadziło do istotnie mniejszej aktywności płytek krwi 14 dni po zaprzestaniu leczenia kłopidogrelem.

**Słowa kluczowe:** odstawienie kłopidogrelu, reaktywność płytek, płytkowy „zespół z odbicia”

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