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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The effect of doubling the dose of acetylsalicylic acid (ASA) on platelet function parameters in patients with type 2 diabetes and platelet hyperreactivity during treatment with 75 mg of ASA: a subanalysis of the AVOCADO study

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Abstract

Background: Individuals with diabetes are at 2- to 4-fold higher risk of cardiovascular disease than those without diabetes. High platelet reactivity (HPR) plays a pivotal role in atherothrombotic complications of diabetes. Polish and American diabetes associations recommend treating high-risk diabetic patients with low doses of acetylsalicylic acid (ASA) in primary and secondary prevention of cardiovascular events. Unfortunately, some patients show HPR despite treatment with ASA.

Aim: To determine the effect of doubling the dose of ASA on platelet reactivity in patients with type 2 diabetes and HPR despite treatment of with 75 mg of ASA.

Methods: 304 type 2 diabetes patients treated with 75 mg of ASA were enrolled into the prospective, randomised, open-label Aspirin Versus/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes (AVOCADO) study. Platelet reactivity was assessed by Platelet Function Analyser (PFA)-100®, VerifyNow® Aspirin Assay, and serum thromboxane B_2 ($sTXB_2$) and urinary 11-dehydrothromboxane B_2 ($u11dhTXB_2$) level measurements. Patients with HPR determined by collagen/epinephrine-induced closure time (CEPI-CT) measured by PFA-100® were randomised in a 2:3 ratio to receive 150 mg of ASA (Group 1) or 75 mg of clopidogrel (Group 2), respectively. Platelet reactivity was assessed at baseline and after 8 weeks of treatment.

Results: Complete clinical data and blood samples were ultimately available for 260 of 304 patients initially enrolled to the study. Subsequently, six patients were excluded from the analysis based on suspected ASA non-compliance ($sTXB_2$ level > 7200 pg/mL). Among 254 patients finally included into analysis, HPR was found in 90 (35.4%) patients of whom 38 patients were randomised to Group 1 and 52 patients to Group 2. Doubling the dose of ASA resulted in a significant CEPI-CT prolongation (Δ 111 s, $p < 0.001$) and reduction of $sTXB_2$ level (Δ –101.3 pg/mL, $p = 0.001$) but did not significantly affect results of other platelet function tests.

Conclusions: Doubling the dose of ASA improved platelet reactivity in patients with type 2 diabetes and HPR.

Key words: platelet activation, aspirin resistance, antiplatelet drugs

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INTRODUCTION

Type 2 diabetes is associated with a 2- to 4-fold higher risk of cardiovascular (CV) disease which results, among others, from increased coagulation related to impaired fibrinolysis, endothelial dysfunction, and high platelet reactivity (HPR) with their increased adhesion, activation, and aggregation [1]. According to the American Diabetes Association and Polish Diabetes Association guidelines, patients with type 2 diabetes should be treated with a low dose of acetylsalicylic acid (ASA; 75–162 mg/day) for primary prevention in patients at high CV risk, and for secondary prevention of CV disease in all patients [2, 3]. In some patients, HPR continues to be seen despite regular administration of ASA. Prevalence of HPR depends on its definition, studied population, drug dose, and the test used to evaluate platelet function. In clinical practice, patient non-compliance is the most common cause of HPR during treatment with ASA, as assessed using cyclooxygenase (COX)-1-dependent tests [4, 5]. Results of previous studies comparing the effect of various ASA doses on platelet reactivity are inconsistent. Such studies were rarely performed in patients with type 2 diabetes, and in most of them patient compliance was self-reported. The purpose of this study was to evaluate the effect of doubling ASA dose on platelet reactivity in clinically stable patients with type 2 diabetes who showed HPR during chronic treatment with 75 mg of ASA, with evaluation of patient compliance based on serum thromboxane B_2 ($sTXB_2$) level measurements.

METHODS

Our study was a subanalysis of the prospective, randomised, open-label Aspirin Versus/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes (AVOCADO) study, performed at the First Chair and Department of Cardiology, Warsaw Medical University, supported by a grant from Adamed, Poland, pharmaceutical company. The study was approved by the Bioethics Committee at the Warsaw Medical University which accepted the study protocol and the informed consent form. From January 2008 to August 2010, 304 clinically stable patients aged 30–80 years with at least a 6-month history of type 2 diabetes treated with oral hypoglycaemic drug and/or insulin, taking 75 mg of ASA daily for at least 3 months, were included into the study [6]. Exclusion criteria included diabetes other than type 2; diabetes diagnosed less than 6 months earlier or treated with diet only; ASA intolerance; active peptic ulcer disease; severe hepatic dysfunction; neoplasm (active or within 5 years prior to the study inclusion); systemic connective tissue disease; therapy with other antiplatelet drugs; chronic administration of non-steroidal anti-inflammatory drugs (NSAIDs) other than ASA and/or non-ASA NSAID use within 10 days before blood sampling; use of low-molecular-weight heparin or unfractionated heparin and/or treatment with oral vitamin K antagonists; history of bleeding diathesis; hereditary coagulation disorder; platelet count $< 100 \times 10^3$/mL or $> 450 \times 10^3$/mL; haemoglobin level < 8 g/dL; haematocrit < 30%; white cell count $< 2 \times 10^3$/mL; history of heparin-induced thrombocytopenia; history of a myeloproliferative disorder; end-stage kidney disease requiring dialysis therapy; an acute coronary syndrome, percutaneous coronary intervention or coronary artery bypass surgery within 12 months; surgery within 8 weeks; reproductive age in women not using oral contraceptives; pregnancy or breastfeeding; planned surgery in the study period; and lack of patient consent.

All patients underwent history taking, physical examination, and venous blood sampling, with 25 mL of blood taken from an antecubital vein in a fasting state in morning hours, 2–3 h after the last ASA dose was administered. Blood was transferred to test tubes for platelet function testing (containing 3.8% sodium citrate for testing with the Platelet Function Analyser [PFA]-100®, and 3.2% sodium citrate for the VerifyNow® test) and routine biochemical tests. Serum was obtained by allowing the blood to clot for 30 min, followed by centrifugation at 1000 g for 15 min. Blood samples for $sTXB_2$ measurements were left to clot for an hour at 37°C as per manufacturer instructions. A urine sample was also taken from each patient for urinalysis and urinary 11-dehydrothromboxane-B_2 ($u11dhTXB_2$) measurement.

Within 2 h of blood collection, platelet function was measured using PFA-100® and VerifyNow® tests according to the manufacturers' instructions. Based on the results of testing with PFA-100®, patients were categorised into the HPR group (defined as collagen/epinephrine-induced closure time [CEPI-CT] < 193 s) or the low platelet reactivity group (defined as CEPI-CT ≥ 193 s). Patients with HPR were then randomised in a 2:3 ratio to receive 150 mg of ASA once daily (Group 1) or 75 mg of clopidogrel once daily (Group 2, Areplex®, generic clopidogrel provided by Adamed, Poland). Randomisation was unblinded, and results in the clopidogrel group are the subject of separate papers to be submitted. Systematic ASA use was verified by patient self-reporting and $sTXB_2$ level measurements. Platelet function and routine biochemical parameters were retested during a follow-up visit at 8 months. The presented subanalysis was performed in Group 1 patients.

Platelet function testing

PFA-100®. The PFA-100® analyser (Siemens AG, Germany) is a point-of-care device which simulates in vitro the process of arterial intimal damage. For platelet function testing with PFA-100®, two types of cassettes are used, with collagen-epinephrine (CEPI) and collagen-adenosine diphosphate (CADP) as agonists. The test involves measurement of the time from the beginning of the test to flow cessation due to occlusion of the test cassette aperture by the platelet aggregate (closure time). According to the manufacturer data, treatment with ASA prolongs CEPI-CT but has no effect on collagen/adenosine

diphosphate-induced closure time (CADP-CT) [7, 8]. Different cutoff values of CEPI-CT have been used in the literature to define HPR during treatment with ASA, but the value which has been most commonly used in the recent studies is < 193 s [9].

VerifyNow®. The VerifyNow® system consists of the main analyser device and a VerifyNow® Aspirin Assay cassette containing arachidonic acid and fibrinogen. Arachidonic acid-activated platelets bind fibrinogen which leads to formation of platelet aggregates. The resulting aggregates change light transmittance which is measured by the device and reported in aspirin reaction units (ARU). According to the manufacturer data, a result of ≥ 550 ARU in patients taking ASA indicates no platelet dysfunction induced by ASA, i.e. normal platelet function despite treatment with ASA.

$sTXB_2$ and $u11dhTXB_2$. $u11dhTXB_2$ level was measured by immunoenzymatic method according to the manufacturer instructions (EIA kit, Cayman Chemical) after sample extraction and purification in SPE C18 test tubes (Waters Associates, Milford, MA, USA). $u11dhTXB_2$ level was indexed for urine creatinine level. $sTXB_2$ level was also measured by immunoenzymatic method according to the manufacturer instructions (Cayman Chemicals, Ann Arbor, MI, USA). If results were outside the standard concentration curve, measurements were repeated using appropriate dilutions. $sTXB_2$ level above 7200 pg/mL during treatment with ASA was considered to indicate that the patient did not take the medication or took it irregularly [10].

Statistical analysis

Mean values and standard deviations were given for quantitative variables (or medians and interquartile ranges for asymmetrically distributed variables), and absolute numbers and percentages for quantitative variables. Wilcoxon test was used to evaluate difference between platelet reactivity parameters. Statistical significance was set at $\alpha = 0.05$.

RESULTS

All clinical and biochemical data were available for 260 patients who completed the study. In this population, elevated $sTXB_2$ level (> 7200 pg/mL) suggesting noncompliance was found in 2.3% of patients (n = 6) who were excluded from further analyses. Among 254 patients ultimately included into the analysis, HPR by PFA-100® testing was found in 35.4% of patients (n = 90) of whom 15% (n = 38) patients were randomised to Group 1 and 20.5% (n = 52) patients to Group 2. Detailed characteristics of Group 1 are shown in Table 1. At 8 weeks of treatment with the doubled ASA dose, patients in Group 1 showed significant improvement of platelet reactivity to treatment manifested by a significant increase in CEPI-CT and reduction in $sTXB_2$ level (Table 2). We also found trends for an increase in CADP-CT (p = 0.065) and reduction in ARU (p = 0.053). Doubling the dose of ASA had no significant effect on $u11dhTXB_2$ level (p = 0.148).

Table 1. Characteristics of the study group

	N (%) or mean/median ± SD/(Q1–Q3)
Demographic data	
Male gender	25 (65.8)
Age [years]	66.1 ± 9.7
SBP [mm Hg]	141.9 ± 23.2
DBP [mm Hg]	80.1 ± 12.7
BMI [kg/m^2]	31.0 ± 5.9
WHR	0.99 ± 0.09
Hypertension	34 (89.5)
Ischaemic heart disease	24 (63.2)
Previous MI	14 (36.8)
Dyslipidaemia	29 (76.3)
Chronic heart failure	16 (42.1)
Previous stroke and/or TIA	7 (18.4)
Past smokers	24 (63.2)
Current smokers	3 (7.9)
Duration of diabetes [years]	5 (3–10)
Drug therapy	
Oral hypoglycaemic drugs	32 (84.2)
Insulin	11 (28.9)
Beta-blocker	28 (73.7)
ACE-I	25 (65.8)
ARB	11 (28.9)
Statin	27 (71.1)
Proton pump inhibitor	5 (13.2)
Laboratory parameters	
Leukocyte count [× 10^3/μL]	7.0 ± 1.7
Haemoglobin [g/dL]	14.0 ± 1.4
Haematocrit [%]	42.2 ± 4.1
Platelet count [× 10^3/μL]	229.6 ± 72.2
MPV [fl]	9.7 ± 1.1
eGFR (MDRD formula) [mL/min/1.73 m^2]	71.2 ± 23.1
HbA1c [%]	6.8 ± 1.0
TC [mg/dL]	170.4 ± 39.3
HDL-C [mg/dL]	48.5 ± 14.8
LDL-C [mg/dL]	94.3 ± 31.6
Triglycerides [mg/dL]	139.6 ± 61.5
vWF [%]	159.1 ± 74.6

N — number of patients in each group; SD — standard deviation; Q1–Q3 — interquartile range; SBP — systolic blood pressure; DBP — diastolic blood pressure; BMI — body mass index; WHR — waist-to-hip ratio; MI — myocardial infarction; TIA — transient ischaemic attack; ACE-I — antiogensin-converting enzyme inhibitors; ARB — angiotensin receptor antagonist; MPV — mean platelet volume; eGFR — estimated glomerular filtration rate; MDRD — Modification of Diet in Renal Disease; HbA1c — haemoglobin A1c; TC — total cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; AWF — von Willebrand factor

Table 2. Changes in platelet function parameters in the study group at 8 weeks

	Baseline visit median (Q1–Q3)	Follow-up visit median (Q1–Q3)	Δ median (Q1–Q3)	P
CEPI-CT [s]	155 (114 to 178)	292 (177 to 300)	111 (20 to 148)	< 0.001
CADP-CT [s]	82 (68 to 99)	90 (77 to 107)	10 (–8 to 28)	0.065
VerifyNow® [ARU]	448 (427 to 536)	429 (402 to 501)	–4 (–68 to 0)	0.053
u11dhTXB$_2$ [pg/mmoL creatinine]	39.14 (22.27 to 63.05)	31.64 (20.57 to 43.43)	–1.68 (–29.41 to 9.58)	0.148
sTXB$_2$ [pg/mL]	229.2 (38.7 to 954.1)	33.4 (14.5 to 95.9)	–101.3 (–561.7 to –8.4)	0.001

Q1–Q3 — interquartile range; Δ — difference between the value at the follow-up visit and the value at baseline; CEPI-CT — collagen/epinephrine-induced closure time; CADP-CT — collagen/adenosine diphosphate-induced closure time; ARU — aspirin reaction unit; u11dhTXB$_2$ — urinary 11-dehydrothromboxane B$_2$; sTXB$_2$ — serum thromboxane B$_2$

DISCUSSION

In our study, doubling the dose of ASA was associated with a significant improvement of platelet reactivity to treatment manifested by a significant increase in CEPI-CT and reduction in sTXB$_2$ level, and trends toward modest changes in the other parameters.

Our findings are consistent with the results by Capodanno et al. [11] who showed that increasing the daily dose of ASA from 81 to 162 mg in a population of patients with type 2 diabetes was associated with a significant reduction in sTXB$_2$ level, and a borderline reduction in ARU by VerifyNow® testing ($p = 0.083$). Similarly, doubling the daily dose of ASA from 81 to 162 mg in patients with type 2 diabetes in the ASPECT study resulted in a significant increase in CEPI-CT (208 ± 69 vs. 251 ± 67 s, respectively, $p = 0.02$) and reduction of u11dhTXB$_2$ level (413 ± 110 vs. 332 ± 106 pg/mmoL creatinine, respectively; $p = 0.01$) but had no effect on the results of testing using the VerifyNow® device [12]. Only increasing the daily ASA dose from 81 to 325 mg resulted in a significant reduction of ARU in this patient group. In view of a beneficial trend observed when the effect of doubling ASA dose was measured using the VerifyNow® device, we can suspect that the lack of statistical significance in our study and other reported studies may have resulted from too small samples in these studies (38 patients in our study, 20 patients in the study by Capodanno et al. [11], and 30 patients in the ASPECT study).

A significant reduction in sTXB$_2$ level suggests that increasing the dose of ASA results in more suppression of thromboxane A$_2$ synthesis, i.e. inhibition of COX-1. At the same time, increase in CEPT suggests that improved response to ASA is associated with a decrease in platelet reactivity.

In a metaanalysis published in 2008, Reny et al. [13] showed that reduction of CEPI-CT in patients with coronary artery disease is associated with more than twofold increase in the risk of recurrent ischaemic events (odds ratio 2.1, 95% confidence interval 1.4–3.4, $p < 0.001$). Our findings may suggest that prolongation of CEPI-CT associated with increasing the dose of ASA may be associated with a reduction in the risk of CV events. Although such an association was not found in the metaanalysis by Simpson et al. [14], comparing the effect of various ASA doses on the risk of CV events, this metaanalysis included only 2 randomised studies in patients receiving a moderate (101–325 mg) daily dose of ASA, with only 2% of patients with diabetes in both study populations, which largely reduces the ability to extrapolate those findings to our study population.

In summary, doubling the dose of ASA in patients showing HPR despite treatment with 75 mg of ASA was associated with a significant improvement in platelet reactivity, but only a study with clinical endpoints may answer the question whether this effects lead to a meaningful improvement of outcomes.

Limitations of the study

The main limitation of our study was to use PFA-100® to evaluate HPR instead of the gold standard of light transmission aggregometry (LTA) with arachidonic acid as the agonist. However, LTA is a complicated method characterised by a relatively flat learning curve and long measurement times [15]. Both PFA-100® and VerifyNow® are technically easy bedside methods which give a test result within 10–15 min [16]. In addition, LTA using arachidonic acid as the agonist evaluates only one pathway of platelet activation. In our study, we used several methods evaluating various pathways which allowed more comprehensive evaluation of platelet reactivity. Our findings indicate that increasing the dose of ASA affects both the thromboxane A2-related pathway (as manifested by a decrease in sTXB$_2$ level) and general platelet reactivity to other agonists such as collagen and epinephrine (as manifested by a large prolongation of CEPI-CT).

CONCLUSIONS

Doubling the dose of ASA in patients with type 2 diabetes and HPR during treatment with 75 mg of ASA was associated with improved platelet reactivity.

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Conflict of interests: *The study was supported by a grant from the Adamed company. Marek Rosiak, Marek Postuła, and Agnieszka Kapłon-Cieślicka received remuneration for their participation in this research project.*

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Wpływ podwojenia dawki kwasu acetylosalicylowego (ASA) na parametry funkcji płytek krwi u pacjentów z cukrzycą typu 2 i nadreaktywnością płytek w trakcie terapii 75 mg ASA: subanaliza badania AVOCADO

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Streszczenie

Wstęp: Cukrzyca wiąże się z 2- do 4-krotnie wyższym ryzykiem chorób sercowo-naczyniowych. Jednym z kluczowych zaburzeń, które jest odpowiedzialne za zwiększone ryzyko sercowo-naczyniowe u chorych na cukrzycę, stanowi stan nadkrzepliwości wynikający m.in. z nadreaktywności płytek krwi (HPR). Polskie i amerykańskie towarzystwa diabetologiczne zalecają chorym na cukrzycę przyjmowanie małych dawek kwasu acetylosalicylowego (ASA) w ramach prewencji pierwotnej i wtórnej incydentów sercowo-naczyniowych. Część pacjentów mimo leczenia za pomocą ASA charakteryzuje się HPR.

Cel: Celem pracy było określenie wpływu podwojenia dawki ASA na reaktywność płytek krwi u stabilnych klinicznie pacjentów z cukrzycą typu 2 z HPR w trakcie przewlekłej terapii 75 mg ASA, z uwzględnieniem obiektywnej oceny przestrzegania zaleceń dotyczących przyjmowania leku.

Metody: Badanie jest subanalizą prospektywnego, randomizowanego badania AVOCADO (*Aspirin Versus/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes study*) z otwartą próbą, przeprowadzonego w I Katedrze i Klinice Kardiologii Warszawskiego Uniwersytetu Medycznego. W okresie od stycznia 2008 do sierpnia 2010 r. do badania włączono 304 stabilnych klinicznie pacjentów w wieku 30–80 lat z rozpoznaną przed co najmniej 6 miesiącami cukrzycą typu 2 leczoną doustnymi lekami hipoglikemizującymi i/lub insuliną, przyjmujących od co najmniej 3 miesięcy ASA w jednorazowej dawce 75 mg/d. Reaktywność płytek krwi oceniano przy użyciu 4 różnych metod: aparatu Platelet Function Analyzer (PFA)-100®, urządzenia VerifyNow®, stężenia tromboksanu-B_2 w surowicy ($sTXB_2$) oraz stężenia 11-dehydrotromboksanu-B_2 w moczu ($u11dhTXB_2$). Na podstawie wyniku badania aparatem PFA-100® kwalifikowano pacjentów do grupy z HPR (CEPI-CT < 193 s) lub grupy z niską reaktywnością płytek (LPR; CEPI-CT ≥ 193 s). Pacjentów z HPR losowo włączano, w stosunku ilościowym 2:3, do przyjmowania 150 mg ASA (grupa 1) lub klopidogrelu w dawce 75 mg/d. (grupa 2). Stosowanie się do zaleceń regularnego przyjmowania ASA przeprowadzano na podstawie deklaracji pacjentów i oceny stężenia $sTXB_2$. Po 8 tygodniach podczas wizyty kontrolnej ponownie oceniano funkcję płytek krwi i podstawowych parametrów biochemicznych. Opisywaną subanalizę przeprowadzano wśród pacjentów z grupy 1.

Wyniki: Wszystkie kliniczne i biochemiczne dane były dostępne w przypadku 260 pacjentów, którzy ukończyli badanie. Spośród badanej grupy u 2,3% (n = 6) osób zaobserwowano podwyższone (> 7200 pg/ml) stężenie $sTXB_2$, sugerujące niestosowanie się do zaleceń przyjmowania ASA, w związku z czym osoby te wyłączono z dalszych analiz. Spośród 254 pacjentów ostatecznie włączonych do analizy 35,4% (n = 90) stanowili chorzy z HPR, z czego 15% (n = 38) należało do grupy 1, a 20,5% (n = 52) do grupy 2. Po 8 tygodniach obserwacji w grupie 1 nastąpiła poprawa parametrów funkcji płytek krwi wyrażająca się istotnym wydłużeniem CEPI-CT [155 *vs.* 292 s; Δ (Q1–Q3): 111 (20–148) s; p < 0,001] oraz istotną redukcją stężenia $sTXB_2$ [229,2 *vs.* 33,4 pg/ml; Δ (Q1–Q3): –101,3 (od –561,7 do –8,4) pg/ml; p = 0,001].

Wnioski: Podwojenie dawki ASA u pacjentów z cukrzycą typu 2 i HPR w trakcie leczenia ASA w dawce 75 mg wiązało się z poprawą w zakresie reaktywności płytek krwi.

Słowa kluczowe: aktywacja płytek, aspirynooporność, leki przeciwpłytkowe

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