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Do statins influence platelet reactivity on acetylsalicylic acid therapy in patients with type 2 diabetes?

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Abstract

Background: *Type 2 diabetes (T2DM) patients are at increased risk of cardiovascular events despite long-term acetylsalicylic acid (ASA) therapy. This study was performed to establish the prevalence of high platelet reactivity (HPR) on ASA in T2DM and to identify its predictors.*

Methods: *The study included 185 T2DM on chronic ASA therapy and to assess platelet reactivity during long-term ASA therapy, we applied the point-of-care method VerifyNow® aspirin test (Accumetrics, San Diego, CA, USA).*

Results: *Compared with the low platelet reactivity (LPR) group, patients with HPR had higher triglyceride levels (145 vs. 118 mg/dL, p = 0.041), were less frequently treated with statins (57.1% vs. 75.3%; p = 0.038) and tumor necrosis factor-alpha (TNF-α) concentrations were higher (2.15 vs. 1.74 pg/mL; p = 0.052). In a multivariate analysis only statin therapy (OR 0.375; 95% CI 0.15–0.91; p = 0.030) and lower concentrations of TNF-α (for each 1.0 pg/mL: OR 1.3; 95% CI 1.00–1.72; p = 0.046) were predictive of LPR.*

Conclusions: *Our study provides indirect evidence that the beneficial effect of statins on platelet activity may be related to their non-lipid-mediated, pleiotropic mechanisms of action. This might have been partly related to decreased platelet reactivity in patients receiving statin therapy. In our study in patients with T2DM, platelet reactivity on ASA therapy measured with VerifyNow® was associated with TNF-α concentrations and statin therapy. These results may imply a role for subclinical systemic inflammation and a beneficial effect of statins in the development of HPR in T2DM.* (Cardiol J 2012; 19, 5: 494–500)

Key words: acetylsalicylic acid, platelet reactivity, statins, tumor necrosis factor-alpha, coronary artery disease

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Introduction

Type 2 diabetes (T2DM) is associated with progressive atherosclerosis and represents a major cause of cardiovascular morbidity and mortality in developed countries [1]. Despite well-documented benefits, acetylsalicylic acid (ASA) treatment does not provide complete protection against cardiovascular (CV) events. Decreased response to antiplatelet agents, defined as an inadequate inhibition of platelet activation and aggregation when assessed *in vitro*, constitutes an emerging problem in CV pharmacotherapy. Thus, in view of the possible clinical consequences of high platelet reactivity in patients on ASA therapy, a better understanding of its etiology and accurate identification of its risk factors seems of particular importance for optimizing treatment in patients at high CV risk. Increased platelet activity has been also reported in insulin-resistant patients on ASA therapy. In the diabetic population, factors related to ASA low-responsiveness have been reported to include prior CV disease, obesity, poor glycemic control, insulin resistance, total, LDL- and HDL-cholesterol concentrations, triglyceride concentrations, and microalbuminuria [2–7]. In order to assess platelet reactivity in patients with T2DM on long-term ASA therapy, we applied the point-of-care method approved by US Food and Drug Administration VerifyNow® aspirin test (Accumetrics, San Diego, CA, USA) to quantify platelet reactivity. Recent data showed that VerifyNow® assay measurements demonstrate the lowest day-to-day variation and the highest repeatability during ASA therapy among other platelet function tests [8].

The objective of this study was, therefore, to evaluate the prevalence of high platelet reactivity (HPR) on ASA therapy in patients with T2DM and to identify clinical and biochemical variables that may be predisposed to a decreased response to low-dose ASA.

Methods

The study consists of preliminary, exploratory analysis of the AVOCADO trial (Aspirin Vs/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes Study) results, a multi-center, prospective, randomized, open-label study. The study subjects were recruited consecutively from patients with T2DM presenting to the outpatient clinic of the Central Teaching Hospital of the Medical University of Warsaw. The local ethics committee of the Medical University of Warsaw approved both the study protocol and the informed consent form. The study was conducted in accordance with the current version of the Declaration of Helsinki at the time when the study was designed.

Between January 2007 and October 2008, 642 patients were screened for eligibility. The full characterization of the study inclusion and exclusion criteria were published previously [9]. Briefly, 185 patients with T2DM were recruited who, at the time of enrollment, had been taking ASA tablets at the dose of 75 mg per day for at least 3 months for primary or secondary prevention of myocardial infarction. No clopidogrel or antiplatelet drugs other than ASA were used in any of the investigated patients. All patients had been taking oral antidiabetic agents and/or insulin for at least 6 months; diet-controlled diabetic patients were not included. Compliance to ASA therapy was determined at the study entry based upon the patient's own statements and serum thromboxane B2 (S-TxB2) level measurement.

Blood sample and assay procedures

Blood samples were taken in the morning 2–3 h after the last ASA dose. Whole blood for S-TxB2 was allowed to clot at 37°C for 1 h before separating serum by centrifugation. Regular laboratory testing was performed using standard techniques and included complete blood cell and platelet counts, fasting glycemia, glycosylated hemoglobin, lipid profile, C-reactive protein (CRP) and serum creatinine concentrations. Serum tumor necrosis factor-alpha (TNF-α) concentration was quantified using a commercially available enzyme immunoassay: hsTNF-α human (R & D Systems, Abingdon, UK) according to the manufacturer's instructions. Assays were performed in duplicate in batches. S-TxB2 was measured also with an enzyme immunoassay kit according to the manufacturer's instructions (Cayman Chemicals, Ann Arbor, MI, USA). Samples with results outside the standard curve were re-assayed with appropriate dilutions. An optimal compliance was confirmed by S-TxB2 levels below 7.2 ng/mL in all patients as described previously in a diabetic population [6, 9]. Of 185 patients with T2DM, a subgroups of subjects with high platelet reactivity (HPR) and low platelet reactivity (LPR) were selected on the basis of the results of the VerifyNow® Aspirin Assay system (Accumetrics Inc, San Diego, CA).

Platelet function analysis

VerifyNow. VerifyNow® Aspirin Assay (Accumetrics, San Diego, CA, USA) is a point-of-care

Table 1. Important variables impacting on acetylsalicylic acid resistance in a simple logistic regression model.

Variable	OR	95% CI	P
Gender	1.14	0.54–2.38	0.729
Age [years]	0.82	0.54–1.26	0.374
Total cholesterol	1.54	0.85–1.57	0.359
LDL-cholesterol	1.17	0.92–1.47	0.191
HDL-cholesterol	1.41	0.57–3.50	0.453
Triglycerides	1.13	0.98–1.29	0.093
TNF-α	1.31	1.01–1.70	**0.040**
hsCRP	0.89	0.71–1.11	0.303
Body mass index	0.86	0.59–1.26	0.446
Waist to hip ratio	0.90	0.60–1.35	0.602
Systolic blood pressure	0.90	0.74–1.10	0.305
Diastolic blood pressure	0.88	0.64–1.20	0.408
Heart rate	0.75	0.51–1.11	0.150
Current smoking	1.20	0.37–3.87	0.760
Fasting glucose	1.05	0.92–1.20	0.440
HbA_{1c}	1.05	0.80–1.41	0.717
Hemoglobin	1.21	0.92–1.60	0.170
Red blood cells	1.13	0.75–1.70	0.563
White blood cells	1.00	0.83–1.21	0.984
Platelet count	0.98	0.72–1.34	0.919
Mean platelet volume	1.02	0.74–1.40	0.923
Fibrinogen	0.89	0.63–1.25	0.495
Serum creatinine	1.02	0.91–1.14	0.702
eGFR	0.83	0.57–1.21	0.328
Statins	0.44	0.20–0.94	**0.034**
Fibrates	0.79	0.25–2.48	0.689
Metformin	1.53	0.69–3.42	0.298
Sulphonylurea derivatives	0.64	0.30–1.36	0.248
Insulin	1.11	0.51–2.41	0.795
ACE-inhibitors	0.61	0.29–1.29	0.196
Beta-blockers	1.30	0.55–2.94	0.564
Calcium channel blockers	1.73	0.82–3.66	0.148
Nitrates	0.41	0.05–3.33	0.405
Proton pump inhibitors	0.98	0.95–1.11	0.696

OR — odds ratio; CI — confidence interval; LDL — low density lipoprotein; HDL — high density lipoprotein; TNF-α — tumor necrosis factor-alpha; hsCRP — high-sensitivity C-reactive protein; HbA_{1c} — glycosylated hemoglobin; eGFR — estimated glomerular filtration rate; ACE — angiotensin-converting enzyme

system that uses cartridges containing a lyophilized preparation of human fibrinogen-coated beads, arachidonic acid, preservative and buffer. When aggregation occurs, the system converts luminosity transmittance units into ASA reaction units (ARU) for VerifyNow®. According to the manufacturer, ARU ≥ 550 indicates no effect of ASA on platelet aggregation, whereas ARU < 550 indicates platelet dysfunction due to ASA [8, 9].

Table 2. Important variables impacting on high on acetylsalicylic acid platelet reactivity in a multiple logistic regression model.

Variable	OR	95% CI	P
Total cholesterol	0.847*	0.45–1.60	0.608
Statins	1.248**	0.96–1.63	0.103
Triglycerides	1.147†	1.00–1.31	**0.046**
TNF-α	0.790‡	0.60–1.04	0.088
hsCRP	0.375	0.15–0.91	**0.030**

*Odds ratio (OR) for each 50 mg/dL total cholesterol increment; **OR for each 50 mg/dL triglycerides increment; †OR for each 0.5 pg/mL TNF-α increment; ‡OR for each 2.0 mg/dL hsCRP increment; CI — confidence interval; TNF-α — tumor necrosis factor-alpha; hsCRP — high-sensitivity C-reactive protein

Statistical analysis

Normally distributed continuous variables are presented as means ± standard deviation (SD), whereas variables with a highly skewed distribution are presented as medians (interquartile ranges). Categorical variables are presented as frequencies (percentages). Normality of distribution was assessed using graphical methods. Differences between HPR and LPR group were analyzed using Student's t-test, the Mann-Whitney U-test, the χ^2 or Fisher's exact test, as appropriate.

Selected variables were checked for associations with HPR using a univariate logistic regression model. The final multivariate model was derived using the Akaike information criterion. The results are presented as odds ratios (OR) with their 95% confidence intervals (CI). All statistical tests were performed at significance level $\alpha = 0.05$ (two-sided). Univariate and multivariate analyses of predictors for HPR are shown in Tables 1 and 2. The reported analysis is exploratory and therefore no formal a priori power analysis was performed.

Results

A total of 185 subjects with T2DM were enrolled and their results analyzed. Mean ± SD demographic data, concurrent medications and biochemical and hematological parameters for the study population are presented in Tables 3–5. Inadequate platelet inhibition defined as HPR with 75 mg ASA daily was detected in 35 (18.92%) patients. Patient characteristics were similar among patients with LPR and HPR patients for all pertinent demographic and clinical data (Tables 3–5). Of the biochemical and hematological parameters evaluated, patients with HPR had higher triglyceride levels (145 vs. 118 mg/dL, p = 0.041) and higher

Table 3. Demographics data.

Characteristics	LPR (n = 150)	HPR (n = 35)	P
Age [years]	66.7 ± 8.5	65.2 ± 9.5	0.375
Female	82 (54.7%)	18 (51.4%)	0.851
Body mass index [kg/m^2]	30.7 ± 5.3	29.9 ± 4.6	0.448
Waist to hip ratio	0.97 ± 0.09	0.96 ± 0.09	0.604
Waist circumference [cm]	105.2 ± 13.3	105.4 ± 13.3	0.927
Systolic blood pressure [mm Hg]	143.3 ± 19.6	139.6 ± 17.3	0.306
Diastolic blood pressure [mm Hg]	80.2 ± 11.8	78.3 ± 13.2	0.410
Duration of diabetes [years]	9 (4; 15)	6 (3; 19)	0.607
History of smoking	85 (56.7%)	22 (62.9%)	0.671
Current smoking	15 (10%)	4 (11.8%)	0.757
Dyslipidemia	127 (84.7%)	27 (77.1%)	0.316
Hypertension	134 (89.3%)	32 (91.4%)	1.000
Metabolic syndrome	129 (86%)	30 (85.7%)	1.000
Coronary artery disease	90 (60%)	22 (62.9%)	0.849
Prior myocardial infarction	47 (31.3%)	12 (34.3%)	0.841
Prior stroke	12 (8%)	1 (2.9%)	0.468
Prior TIA	7 (4.7%)	1 (2.9%)	1.000
Heart failure	60 (40.3%)	17 (48.6%)	0.447

LPR — low platelet reactivity; HPR — high platelet reactivity; TIA — transient ischemic attack

Table 4. Concurrent medications.

Characteristics	LPR (n = 150)	HPR (n = 35)	P
Beta-blockers	104 (69.3%)	26 (74.3%)	0.683
ACE inhibitors	99 (66%)	19 (54.3%)	0.241
Angiotensin receptor blocker	25 (16.7%)	9 (25.7%)	0.229
Aldosterone antagonists	11 (7.3%)	2 (5.7%)	1.000
Loop diuretics	25 (16.7%)	4 (11.4%)	0.607
Thiazide diuretics	50 (33.3%)	13 (37.1%)	0.695
Statins	113 (75.3%)	20 (57.1%)	**0.038**
Fibrates	21 (14%)	4 (11.4%)	0.791
Calcium channel blockers	49 (32.7%)	16 (45.7%)	0.170
Nitrates	10 (6.7%)	1 (2.9%)	0.693
Proton pump inhibitor	37 (24.6%)	9 (25.7%)	0.897
Metformin	93 (62%)	25 (71.4%)	0.334
Sulphonylurea derivatives	72 (48%)	13 (37.1%)	0.265
Alpha-glucosidase inhibitors	11 (7.3%)	1 (2.9%)	0.468
Insulin	48 (32%)	12 (34.3%)	0.842

LPR — low platelet reactivity; HPR — high platelet reactivity; ACE — angiotensin-converting enzyme

TNF-α concentrations, at marginal significance level (2.15 vs. 1.74 pg/mL, p = 0.052). HPR group in comparison to LPR group had significantly higher level of S-TxB2 (median 0.16 ng/mL [25; 75 percentiles — 0.07; 0.47] vs. 1.62 ng/mL [25; 75 percentiles — 0.37; 4.28], p < 0.001). Concomitant medications were comparable in both groups, with the exception of statin usage. Patients with adequate platelet response to ASA were taking statins more frequently than HPR patients — 113 (75.3%) vs. 20 (57.1%); p = 0.038. No other significant differences were observed between two investigated groups. In the simple logistic regression model, only two parameters were found to be predictive of HPR:

Table 5. Baseline biochemistry and hematology.

Characteristics	LPR (n = 150)	HPR (n=35)	P
Hemoglobin [g/dL]	13.8 ± 1.2	14.1 ± 1.9	0.296
Hematocrit [%]	41.1 ± 3.3	41.9 ± 5.1	0.435
Leukocytes [10^3/mm^3]	7.0 ± 2.1	7.1 ± 1.6	0.984
Platelet count [10^3/mm^3]	230.9 ± 59.6	229.8 ± 60.5	0.919
Mean platelet volume [fL]	9.8 ± 1.2	9.8 ± 1.2	0.923
Fasting glucose [mg/dL]	127 (110; 151)	133 (113; 156)	0.318
Urea [mg/dL]	42.8 ± 15.1	41.9 ± 16.9	0.756
Creatinine [mg/dL]	1.01 ± 0.32	1.03 ± 0.30	0.703
eGFR [mL/min/1.73]	71.8 ± 21.5	67.9 ± 18.5	0.329
Uric acid [mg/dL]	5.7 ± 1.4	5.7 ± 1.5	0.759
Total cholesterol [mg/dL]	163.7 ± 34.5	169.8 ± 40.2	0.361
Triglycerides [mg/dL]	118 (87; 160)	145 (105; 180)	**0.041**
HDL-cholesterol [mg/dL]	49.3 ± 14	46.3 ± 14.1	0.259
LDL-cholesterol [mg/dL]	86 ± 29.6	93.6 ± 35.6	0.191
HbA_{1c} [%]	7.1 ± 1.2	7.2 ± 1.2	0.718
VerifyNow [ARU]	452 ± 45	597 ± 39	**< 0.001**
Serum TxB2 [ng/mL]	0.16 (0.12; 0.47)	1.62 (0.37; 4.28)	**< 0.001**
TNF-α [pg/mL]	1.744 (1.217; 2.423)	2.148 (1.521; 2.696)	0.052
hsCRP [mg/L]	2.8 (1.5; 5.4)	2.3 (1.3; 4.0)	0.405

LPR — low platelet reactivity; HPR — high platelet reactivity; HbA_{1c} — glycosylated hemoglobin; HDL — high density lipoprotein; LDL — low density lipoprotein; eGFR — estimated glomerular filtration rate; TNF-α — tumor necrosis factor-alpha, hsCRP — high-sensitivity C-reactive protein

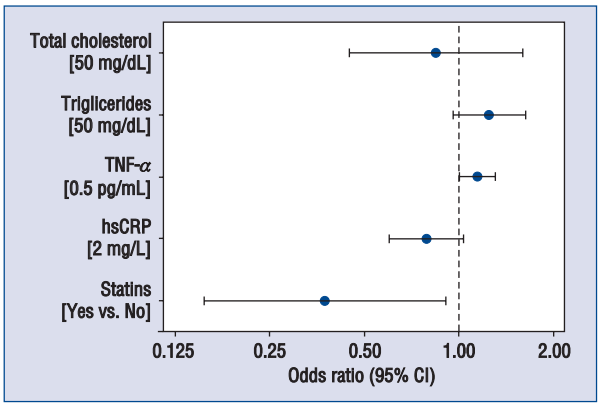

Figure 1. Results of the multivariate logistic regression model; TNF-α — tumor necrosis factor-alpha; hsCRP — high-sensitivity C-reactive protein; CI — confidence interval.

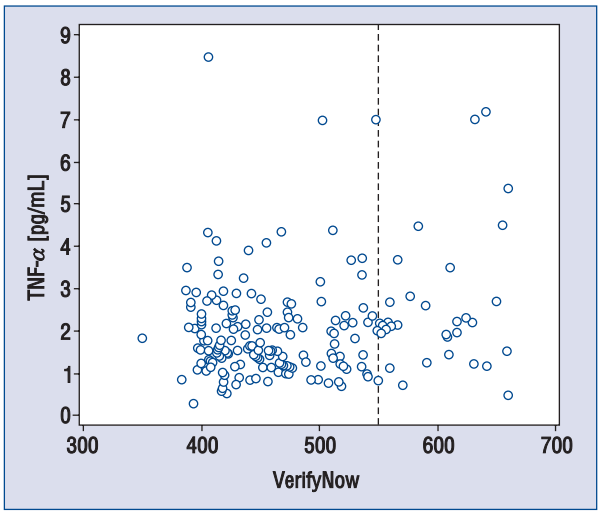

Figure 2. Scatterplot of tumor necrosis factor-alpha (TNF-α) concentrations vs. ASA reaction units values by VerifyNow® Aspirin Assay.

current statin therapy (p = 0.034) and TNF-α concentration (p = 0.040). Variables with p < 0.10 together with parameters affected by statin therapy were entered into the multivariate analysis to determine their independent association with ASA low-responsiveness. Variables associated with HPR in the multivariate analysis were: TNF-α concentrations (for each 1.0 pg/mL: OR 1.3; 95% CI 1.00–1.72; p = 0.046; for each 0.5 pg/mL: OR 1.147; 95% CI 1.00–1.31; p = 0.046) and statin therapy (OR 0.375; 95% CI 0.15–0.91; p = 0.030) (Fig. 1). The distribution of TNF-α concentrations in relation to ARU values is shown in Figure 2. In additional analysis

neither the type of statin used, nor the dose of statin were found to be predictive of HPR in diabetic population (OR 1.007; 95% CI 0.280–3.63; p = 0.992).

Discussion

There are relatively few publications, which focus on identifying risk factors of HPR in patients with T2DM on ASA therapy. In patients with diabetes, the prevalence of residual platelet reactivity despite ASA therapy has been estimated by others to be as low as 2.8% up to 22%, which corresponds to the prevalence of increased platelet reactivity on ASA therapy observed in this study population [4, 6, 7, 10]. In comparison to most previous studies, all of the patients included in our study were taking an uniform ASA dose of 75 mg as in study presented by Mortensen et al. [6]. VerifyNow® Aspirin Assay is considered to be an optimal method to detect ASA effect on platelets as it demonstrates a very high sensitivity to ASA effect [11]. Thus, it is not surprising that in our study we observed statistically higher levels of S-TxB2 in the group with HPR in comparison to the LPR group (Table 5), which is in accordance to that previously reported [12].

The strengths of the present study are inclusion of a study population of only diabetic patients with established coronary artery disease (CAD) or with multiple CAD risk factors and assessment of compliance. Of the ASA low-responsiveness risk factors that had been reported previously, only triglyceride concentration differed significantly between the HPR and LPR groups when investigated in our study population. However, in the multivariate analysis, triglyceride concentration was not predictive of HPR. No significant differences between the HPR and LPR groups were found with respect to glycemic control or cholesterol concentration.

In the current study, only two variables (i.e., TNF-α concentration and statin therapy) were found to be independent predictors of HPR by the multivariate analysis. To our knowledge, this is the first study to demonstrate a correlation between TNF-α concentrations and increased platelet reactivity on ASA therapy in an exclusively diabetic population. Although the association between inflammation and enhanced platelet reactivity has long been recognized, there are only a few reports of increased CRP and interleukin-6 concentrations in patients with high platelet reactivity on ASA therapy [13]. Possible mechanisms linking inflammation with increased platelet reactivity on antiplatelet therapy include: increased platelet turnover, endothelial dysfunction, enhanced expression of cyclooxygenase isoenzyme 2, non-platelet sites of thromboxane A_2 synthesis, and increased levels of various prothrombotic clotting factors with platelet-activating properties [3, 14]. However, only a few studies that examined the effects of statins on TNF-α demonstrate that statins either have no effect on or reduce circulating TNF-α concentrations [15–17]. We assume that the ambiguous effect of statins on TNF-α concentration could in part explain the observed association with TNF-α, but not with CRP level. Thus, subclinical systemic inflammation might, therefore, be the key link between T2DM and high platelet reactivity on ASA therapy.

Our study is also the first one to demonstrate a possible beneficial influence of statin therapy on platelet reactivity in a diabetic population on long-term ASA treatment. To date, only a few studies have shown a positive effect of statins on platelet responsiveness to ASA [18–20]. In the study by Tirnaksiz et al. [18], high-dose atorvastatin therapy resulted in improvement of ASA responsiveness in 13 of 20 patients with stable CAD, as assessed with a Platelet Function Analyzer (PFA-100®). In another study, a combination of atorvastatin and ASA in patients with myocardial infarction reduced thromboxane A_2 synthesis and platelet aggregation measured by light transmission aggregometry (LTA) when compared to patients receiving ASA [18]. In our study, concomitant statin therapy was predictive of low platelet reactivity measured with VerifyNow®, irrespective of type and dose of statin, or cholesterol and triglyceride levels.

Our study provides indirect evidence that the beneficial effect of statins on platelet activity may be related to their non-lipid-mediated, pleiotropic mechanisms of action. This might have been partly related to decreased platelet reactivity in patients receiving statin therapy.

In our study in patients with T2DM, platelet reactivity on ASA therapy measured with VerifyNow® was associated with TNF-α concentrations and statin therapy. This implies inflammation having a role in the development of ASA resistance in T2DM, as well as a protective effect of statins related to their lipid-independent mechanisms of action.

Limitations of the study

Our study has two important limitations. First, we assessed platelet reactivity on ASA therapy with use of a point-of-care test — VerifyNow® Aspirin Assay — instead of the "gold standard" LTA [11]. However, the mode of action of the VerifyNow® Aspirin Assay is similar to LTA, and the VerifyNow® system is one of the most widely used methods for assessing platelet function. In addition, according

to previous reports, the VerifyNow® method demonstrates the highest correlation with arachidonic acid-induced LTA in comparison to other platelet function tests [11]. Secondly, a prospective, randomized experimental study would be more beneficial for directly demonstrating any beneficial influence of statin therapy on platelet reactivity. However, the aim of our current study was to identify potential independent risk factors of increased platelet reactivity in a population of T2DM patients for future investigation. Pretreatment measurements could not be conducted because all patients included in this study had diagnosed CAD or multiple risk factors for CAD and therefore were on ASA therapy at the time of enrollment.

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Conflict of interest: none declared

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