Paper I

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ORIGINAL ARTICLE

Hyperglycemia, assessed according to HbA_{1c}, and future risk of venous thromboembolism: the Tromsø study

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Summary. *Background:* HbA_{1c}, a marker of average plasma glucose level during the previous 8–12 weeks, is associated with the future risk of cardiovascular disease and all-cause mortality. *Objectives:* To examine the association between hyperglycemia, assessed according to HbA_{1c}, and the future risk of venous thromboembolism (VTE) in a population-based cohort. *Methods:* HbA_{1c} was measured in 16 156 unique subjects (25–87 years) who participated in one or more surveys of the Tromsø study (Tromsø 4, 1994–1995; Tromsø 5, 2001–2002; and Tromsø 6, 2007–2008). All subjects were followed, and incident VTE events were recorded up to 31 December 2010. *Results:* There were 333 validated first VTE events, of which 137 were unprovoked, during a median follow-up of 7.1 years. HbA_{1c} was not associated with the future risk of VTE in analyses treating HbA_{1c} as a continuous variable, or in categorized analyses. The risk of VTE increased by 5% per one standard deviation (0.7%) increase in HbA_{1c} (multivariable-adjusted hazard ratio [HR] 1.05; 95% confidence interval [CI] 0.97–1.14), and subjects with $HbA_{1c} \geq 6.5\%$ had a 27% higher risk than those with $HbA_{1c} < 5.7\%$ (multivariable-adjusted HR 1.27; 95% CI 0.72–2.26). There was no significant linear trend for an increased risk of VTE across categories of HbA_{1c} ($P = 0.27$). *Conclusions:* Serum levels of HbA1c were not associated with the future risk of VTE in multivariable analysis. Our findings suggest that hyperglycemia does not play an important role in the pathogenesis of VTE.

Keywords: cardiovascular diseases; diabetes mellitus; glucose metabolic disorders; Glycated Hemoglobins; pulmonary embolism; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disorder with serious short-term and long-term complications, and a potentially fatal outcome [1,2]. The incidence of VTE is 1–2 per 1000 persons per year in the general population, with a steep increase with age. Even though many environmental and inherited predisposing factors have been associated with VTE [1–5], 30–50% of the events have no obvious provoking factors [6–8]. Thus, it is vital to identify biomarkers and risk behaviors of VTE that could be subject to modification, in order to minimize the disease burden.

The prevalence of hyperglycemia is increasing markedly throughout the world, and hyperglycemia, along with subsequent diabetes mellitus (DM), has become an important public health challenge [9]. HbA_{1c}, which is formed by a simple chemical reaction between hemoglobin and blood glucose, reflects the average plasma glucose level in an individual over the preceding 8–12 weeks [10]. Experimental studies have suggested that hyperglycemia may facilitate thrombosis through activation of the coagulation system [11], as well as by impairing fibrinolysis [12], and a consistent relationship between HbA_{1c} and arterial cardiovascular disease (CVD) [13,14] has been suggested. Furthermore, both hyperglycemia and diabetes are known risk factors for arterial thromboembolic events [15,16].

Previous studies on the relationships between hyperglycemia, DM and the risk of VTE have yielded divergent results. Some studies have found an increased risk [17–19], whereas others have failed to find an association [20–24]. The inconsistency between the studies may, to some extent, be attributable to differences in the definition of diabetes (e.g. non-fasting or fasting glucose levels, self-reported data, or use of antidiabetic drugs), and failure to control for important confounders such as obesity. Alternatively, other measures of hyperglycemia, rather than diabetes itself, may be more important in the risk assessment of VTE [25,26]. It is of note that the risk of arterial cardiovascular disease and all-cause mortality have been shown to increase across levels of HbA_{1c}, independently of the presence of diabetes [14]. Therefore, we set out to examine the association between hyperglycemia, assessed according to HbA_{1c}, and the future risk of VTE in a general adult population.

Materials and methods

Study population

Participants were recruited from the fourth, fifth and sixth surveys of the Tromsø study (conducted in 1994–1995, 2001–2002, and 2007–2008, respectively) [27]. Members of the population aged ≥ 25 years living in the municipality of Tromsø, Norway, were invited to participate in these surveys. The overall participation rate was high, ranging from 78% in Tromsø 4 to 66% in Tromsø 6. A total of 18 080 individuals aged 25–87 years participated in at least one survey, and, of these, 6140 participated in two or more surveys. A detailed description of study participation has been published elsewhere [27]. Subjects who did not consent to taking part in medical research (n = 225), subjects who were not officially registered as inhabitants of the municipality of Tromsø at baseline (n = 18) and subjects with a known pre-baseline history of VTE (n = 121) were excluded from the study. Furthermore, subjects were excluded if they had missing HbA_{1c} values at all visits (n = 1560). In total, 16 156 subjects were included in the study (Fig. 1), and followed from the date of enrollment to the end of the study period, 31 December 2010. The study was approved by the regional committee of medical and health research ethics, and all participants gave their informed written consent to participate.

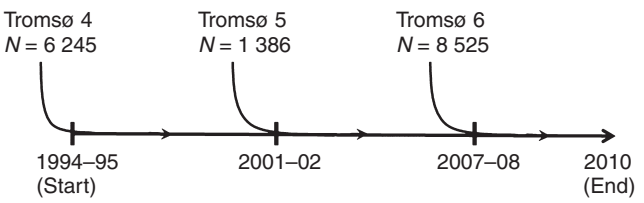

Fig. 1. Presentation of the follow-up of subjects included from the different Tromsø visits (1994–1995, 2001–2002, and 2007–2008); 5647 subjects participated in two or more surveys.

Measurements

Baseline information was collected by physical examinations, from blood samples, and from self-administered questionnaires [21]. Information on self-reported diabetes, CVD (angina pectoris, myocardial infarction [MI], and stroke), current daily smoking and physical activity (≥ 1 h per week) during leisure time was collected from the questionnaires. The self-reported diabetes data were supplemented with data on confirmed diagnoses of diabetes mellitus from the MI registry of the Tromsø study. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg m^{-2}). Non-fasting blood samples were collected from an antecubital vein, and serum was prepared by centrifugation at 3000 × g for 10 min after 1 h at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. The Cobas Mira instrument was used to quantify HbA_{1c} with an immunoturbidimetric method (Unimate 5 HbA_{1c}; Hoffmann-La Roche, Basel, Switzerland). The normal reference range was 4.0–6.5%.

VTE ascertainment

All first events of VTE among the participants during follow-up were recorded from the date of enrollment to the end of the study period, as previously described in detail [28]. On the basis of the presence of provoking factors at the time of diagnosis, the VTE event was classified as unprovoked (no provoking factors) or provoked (one or more provoking factors). Major surgery, trauma or an acute medical condition (acute MI, ischemic stroke, or major infectious disease) [29,30] within 8 weeks prior to the event, active cancer at the time of the event and marked immobilization (e.g. bed rest for ≥ 3 days, use of a wheelchair [31,32], or long-distance travel for ≥ 4 h within 14 days prior to the event) were considered to be provoking factors.

Statistical analysis

Statistical analysis was carried out with SPSS version 19.0 (SPSS, Chicago, IL, USA) and STATA version 12 (Stata Corporation, College Station, TX, USA). The significance level was 0.05. PASS (Number Cruncher Statistical Systems, Kaysville, UT, USA) was used to estimate the lowest detectable effect size in our study population with a power of 0.80. The date of study enrollment for each individual was determined as the date of attendance in the first survey in which HbA_{1c} measurements were available (Fig. 1). Person-years were accrued from enrollment to the date when a VTE event was first diagnosed. Subjects who did not experience an event during follow-up

were censored from the date of migration or death or at the end of the study period (31 December 2010).

Cox proportional hazards regression models were used to estimate age-adjusted, sex-adjusted and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for all VTE events, as well as for provoked and unprovoked VTE events, by increasing levels of HbA_{1c}. HbA_{1c} was analyzed in predefined categories (< 5.7%, normal; 5.7–6.5%, pre-diabetes; and ≥ 6.5%, DM) according to the American Diabetes Association [33] and the World Health Organization reports [34]. The lowest category of HbA_{1c} was used as the reference group in each model. In the multivariate model, we adjusted for age, sex, BMI, smoking, physical activity, and history of CVD. The potential confounders were chosen because of their known association with HbA_{1c}/diabetes [35–37] and possible association with VTE [38–40]. Potential interactions were tested by using cross-product terms in the proportional hazards models for HbA_{1c} with age and sex. The proportional hazards assumption was verified by evaluating the parallelism between the curves of the log–log survivor function for different categories of HbA_{1c}.

Multivariable-adjusted associations between HbA_{1c} (as a continuous variable) and risk of VTE were visualized by use of a generalized additive regression plot. In this plot, HbA_{1c} (log transformed) values were modeled with a four degree of freedom smoothing spline fit in Cox proportional hazards models, including the same covariates as described above.

Additionally, a Cox regression model with HbA_{1c} entered as a time-varying covariate with multiple records per individual was used to minimize the regression dilution effect. These analyses included individuals who had attended the second visit of Tromsø 4 and one or more of the following surveys (unless they had migrated or died before Tromsø 5), in which HbA_{1c} and potential confounders were remeasured (n = 5647). If a subject had only two repeated measures (that is, a recording of HbA_{1c} from either Tromsø 5 or Tromsø 6 was missing), the last HbA_{1c} value was carried forward until a new value was obtained. Age was used as the time scale in the time-dependent model.

Results

The baseline characteristics of participants across the predefined categories of HbA_{1c} are shown in Table 1. Subjects with HbA_{1c} values in the upper category (≥ 6.5%) were older, and more frequently women, than those with values in the lower categories. Furthermore, they had higher BMI, systolic blood pressure, and triglyceride levels, had lower HDL-cholesterol levels, and were less physically active. As expected, subjects within the upper categories of HbA_{1c} had a higher proportion of concomitant diseases (diabetes and prior CVD).

There were 333 validated incident VTE events during a median of 7.1 years of follow-up. The overall crude incidence rate of VTE was 2.9 per 1000 person-years (95% CI 2.61–3.24), reflecting the relatively high mean age of the study population. The characteristics of VTE patients at the time of the event are shown in Table 2. Among the subjects with VTE, 56.8% had DVT and 43.2% had PE, and 137 (41.1%) of the events were classified as unprovoked. Cancer was the most common provoking factor (24.3% of the VTE patients had a cancer-related VTE event), followed by immobilization (20.1%) (Table 2).

Table 1 Baseline characteristics of subjects enrolled in the Tromsø study (1994–1995, 2001–2002, and 2007–2008)

	HbA_{1c} (%)		
	< 5.70	5.70–6.50	≥ 6.50
Age (years)	54 ± 11	59 ± 9	61 ± 10
Sex (% women)	45 (5152)	51.2 (2099)	54.8 (339)
Body mass index (kg m^{-2})	26.0 ± 3.9	27.4 ± 4.4	29.8 ± 5.1
Systolic blood pressure (mmHg)	135 ± 22	140 ± 23	145 ± 23
Diastolic blood pressure (mmHg)	80 ± 12	81 ± 12	81 ± 12
Triglycerides (mM)	1.50 ± 0.90	1.78 ± 1.05	2.31 ± 2.16
Total cholesterol (mM)	6.04 ± 1.29	6.23 ± 1.27	5.83 ± 1.48
HDL-cholesterol (mM)	1.53 ± 0.43	1.45 ± 0.42	1.28 ± 0.38
Smoking (%)	25.6 (2909)	30.3 (1243)	21.8 (135)
Physical activity (%) *	51.4 (4377)	50.8 (1312)	42.0 (148)
Diabetes (%)	0.6 (63)	3.4 (138)	100 (619)
Cardiovascular disease (%)	7.2 (813)	13.1 (529)	26.3 (156)

Values are percentages with numbers in parentheses, or means ± 1 SD. *Sweat production and breathlessness for ≥ 1 h per week during leisure time.

When HbA_{1c} was analyzed as a continuous variable, no association was found between HbA_{1c} levels and VTE after adjustments for potential confounders (Fig. 2).

In the categorized analysis adjusted for age and sex, subjects with HbA1c ≥ 6.5% had a 67% higher risk of VTE than those with HbA1c < 5.7% (HR 1.67; 95% CI 1.01–2.74), and there was a significant linear trend for an increased risk of VTE across categories of HbA_{1c} (P-value for trend of 0.04) (Table 3). However, after further adjustments, in which BMI was the covariate with the largest influence, the risk estimates were attenuated and no longer statistically significant; multivariable HR 1.27 (95% CI 0.72–2.26), P-value for trend of 0.27. In a separate analysis of unprovoked and provoked VTE, subjects with HbA1c ≥ 6.5% appeared to have a 1.6-fold higher risk of provoked VTE (multivariable HR 1.56; 95% CI 0.78–3.13) than those with HbA1c < 5.7%, and the P-value for trend across categories was 0.09. No consistency was found in analyses of unprovoked VTE (multivariable HR for upper vs. lower category of HbA1c of 0.89; 95% CI 0.32–2.49, P-value for trend of 0.69). However, in these subgroup analyses, the number of events in

Table 2 Characteristics of venous thromboembolism (VTE) events (n = 333); the Tromsø study (1994–1995, 2001–2002, and 2007–2008)

	% (n)
Deep vein thrombosis	56.8 (189)
Pulmonary embolism	43.2 (144)
Unprovoked*	41.1 (137)
Clinical risk factors	
Estrogens (HRT, oral contraceptives)	5.7 (19)
Heredity†	2.7 (9)
Pregnancy	0 (0)
Other medical conditions‡	24.3 (81)
Provoking factors	
Surgery	18.3 (61)
Trauma	6.9 (23)
Acute medical conditions	14.4 (48)
Cancer	24.3 (81)
Immobilization (bed rest for > 3 days, wheelchair)	20.1 (67)
Other§	4.5 (15)

HRT, hormone replacement therapy. *No provoking factors at the time of diagnosis. †Heredity: family history of VTE in a first-degree relative before the age of 60 years. ‡Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders). §Other factor specifically described as provoking in the medical record (e.g. intravascular catheter).

the upper category was low, and the results should therefore be interpreted with caution.

Repeated measures of HbA_{1c} were carried out in 5647 participants (contributing to 13 576 exposure periods), and there were 240 VTE events among these subjects during follow-up. In analyses with HbA_{1c} level as a time-dependent exposure, all risk estimates remained essentially unchanged (multivariable HR for upper category vs. lower category of HbA_{1c} of 1.18; 95% CI 0.73–1.90, P = 0.8) (Table 4).

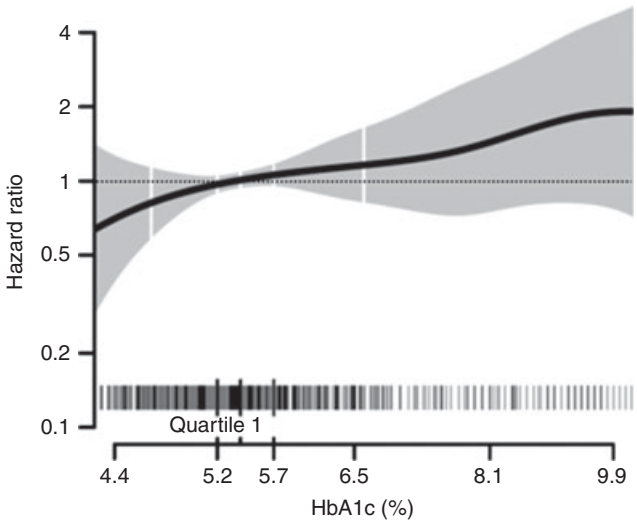

Fig. 2. Dose–response relationship between HbA_{1c} and risk of venous thromboembolism obtained by generalized linear regression. The regression model is adjusted for age, sex, body mass index, smoking, physical activity, and self-reported cardiovascular disease. The solid line shows hazard ratios, and the shaded area shows 95% confidence intervals. Density plots show the distribution of HbA_{1c}, and white vertical lines indicate the 2.5th, 25th, 50th, 75th and 97.5th percentiles.

Discussion

In the present study, HbA_{1c} was not associated with the future risk of overall VTE in multivariable analyses, with either a continuous or a categorical approach. Furthermore, HbA_{1c} showed no significant association with either unprovoked or provoked VTE in subgroup analyses. However, a tendency for increased risk of provoked VTE was observed in subjects with HbA_{1c} levels of $\geq$ 6.5%, suggesting that hyperglycemia may predispose to VTE through associated hospitalization or comorbidities. Nevertheless, the number of events in the upper category was low, and the results of these subgroup analyses should be interpreted with caution.

In contrast to our findings, a case–control study [25] suggested that hyperglycemia was related to an increased risk of VTE, independently of known diabetes. However, in this study, non-fasting glucose levels were measured on admission for a suspected DVT [25], and the elevated glucose levels in VTE patients could potentially be attributable to the inflammatory and counter-regulatory hormone action initiated by the VTE event itself [26].

The impact of hyperglycemia and diabetes on the risk of VTE is controversial [17–25,41]. In a pilot study by Petrauskiene *et al*. [19], diabetes was a risk factor for VTE. However, the risk estimates were not adjusted for BMI. Abdominal obesity has previously been shown to be the main contributory risk factor for VTE among persons with metabolic syndrome [21]. Thus, high BMI in patients with diabetes may have confounded the observed association between diabetes and VTE. This notion was supported in our study, where adjustment for BMI in the multivariable analyses highly attenuated the association between HbA_{1c} and the risk of VTE. The prevalence of insulin resistance is increased in obese individuals [42], and improves with weight loss [43–45]. Schouwenburg *et al*. [46] showed that insulin resistance was not associated with the risk of VTE after adjustment for BMI in a population-based cohort. In contrast, a recent report from the Iowa Women's Health Study [18] showed an association between diabetes and VTE in women, even after adjustment for BMI. However, the use of self-reported data on weight and height in this study may have led to an underestimation of BMI, and thereby attenuated the true confounding effect of BMI. Furthermore, the Longitudinal Investigation of Thromboembolism Etiology (LITE) study [17], which combined information from two prospective cohorts (the Atherosclerotic Risk in Community [ARIC] study and the Cardiovascular Health Study), showed that diabetes was

Table 3 Associations between categories of HbA_{1c} and risk of total venous theomboembolism (VTE), provoked VTE, and unprovoked VTE

	HbA_{1c} (%)			
	< 5.70	5.70–6.50	≥ 6.50	*P* for trend
Total VTE				
Person-years	85 108	26 009	3504	
Events	226	90	17	
IR*	2.66 (2.33–3.03)	3.46 (2.81–4.25)	4.85 (3.01–7.80)	
HR†	1.00 (reference)	1.17 (0.92–1.50)	1.67 (1.01–2.74)	0.04
HR‡	1.00 (reference)	1.12 (0.86–1.46)	1.27 (0.72–2.26)	0.27
Provoked VTE				
Person-years	84 282	25 794	3477	
Events	129	57	10	
IR*	1.53 (1.29–1.82)	2.21 (1.70–2.87)	2.88 (1.55–5.35)	
HR†	1.00 (reference)	1.31 (0.96–1.80)	1.74 (0.91–3.33)	0.03
HR‡	1.00 (reference)	1.27 (0.91–1.76)	1.56 (0.78–3.13)	0.09
Unprovoked VTE				
Person-years	84 025	25 591	3437	
Events	97	33	7	
IR*	1.15 (0.94–1.40)	1.29 (0.92–1.81)	2.04 (0.9–4.28)	
HR†	1.00 (reference)	0.99 (0.66–1.47)	1.56 (0.72–3.39)	0.53
HR‡	1.00 (reference)	0.92 (0.60–1.41)	0.89 (0.32–2.49)	0.69

HR, hazard ratio; IR incidence rate. *IR per 1000 person-years. †Adjusted for age and sex. ‡Adjusted for age, sex, body mass index, smoking, physical activity (hard), and self-reported cardiovascular disease.

Table 4 Incidence rates (IRs) and hazard ratios (HRs) of venous thromboembolism (VTE) across categories of HbA_{1c}; time-dependent analysis of 5647 subjects with repeated measures (surveys 4, 5, and/or 6) in the Tromsø study 1994–2010

	HbA_{1c} (%)			
	< 5.70	5.70–6.50	≥ 6.50	*P* for trend
Person-years	55 795	15 053	3565	
Events	164	55	21	
IR*	2.9 (2.5–3.4)	3.6 (2.8–4.8)	5.9 (3.8–9.0)	
HR†	1.00 (reference)	0.99 (0.73–1.35)	1.43 (0.90–2.27)	0.3
HR‡	1.00 (reference)	0.93 (0.68–1.27)	1.18 (0.73–1.90)	0.8

Repeated measurements with age as time scale: 5647 subjects contributed to 13 576 exposure periods, and there were 240 VTE events during follow-up. *Incidence rate per 1000 person-years. †Adjusted for sex. ‡Adjusted for sex, smoking, body mass index, physical activity (hard), and self-reported cardiovascular disease.

a modest risk factor for VTE, whereas impaired fasting glucose was not related to VTE. However, in a later reanalysis of the ARIC data [23], no relationship was found between diabetes mellitus and VTE. The inconsistency between these two studies may be explained by the different study groups, and the fact that Wattanakit *et al.* [23] performed time-dependent analysis. Furthermore, the LITE study only observed a significant association between diabetes and provoked VTE events. Thus, their finding that diabetes, but not impaired fasting glucose, was associated with VTE may be explained by other provoking factors rather than diabetes itself. Several other studies support our findings of no association between hyperglycemia and the risk of VTE [20,22,24]. In a report by Heit *et al.* [20], the observed link between diabetes and VTE was explained by more frequent hospitalization of persons with diabetes. As diabetes and HbA_{1c} are interlinked, this may explain the increased risk estimate for provoked events in subjects with $HbA_{1c} \geq 6.5\%$. Hence, the apparent relationship between HbA1c and total VTE in our study may partly be mediated through provoking factors, such as arterial cardiovascular events or immobilization.

The main strengths of our study are the large number of participants and validated VTE events, the prospective design, and the long-term follow-up. To address the potential problem of regression dilution effects (i.e. the fact that intraindividual changes in HbA_{1c} during long-term follow-up could bias the risk estimates towards the null), we additionally performed a time-dependent analysis, which allowed for changes in HbA_{1c} and important covariates such as BMI over time in subjects who attended more than once. Our findings in the time-dependent analysis were similar to those obtained from baseline measures only, supporting the robustness of our findings. However, the study has some potential limitations. As

some of the variables were self-reported measurements, misclassification may have occurred. Fasting glucose levels were not measured, and we therefore used HbA_{1c} to assess hyperglycemia. In a systematic review of primary cross-sectional studies, no evidence was found for fasting plasma glucose being superior to HbA_{1c} in screening for diabetes or impaired glucose tolerance [47]. The study provided sufficient statistical power for assessment of an HR of 1.16 for VTE with the continuous HbA_{1c} variable. However, in the categorical analyses, the number of events in the upper HbA_{1c} category was low, and the study only provided sufficient statistical power (80%) for assessment of an HR of 1.97 for total VTE in the upper vs. lower category. Thus, as our non-significant finding may be attributable to a type II error, we cannot rule out the possibility that subjects within the upper category may be at increased risk of VTE. Moreover, subgroup analyses had limited power, and firm conclusions regarding the association with provoked and unprovoked VTE could not be made. Information on concomitant treatment was not available in our study, and could therefore not be taken into consideration.

In our prospective population-based study, HbA_{1c} levels were not significantly associated with future risk of VTE after adjustment for BMI. Our findings suggest that hyperglycemia does not play an important role in the pathogenesis of VTE, and that obesity is a more important contributor to VTE in subjects with hyperglycemia.

Addendum

G. Lerstad and K. F. Enga carried out statistical analysis. G. Lerstad and E. Brodin interpreted the results and drafted the manuscript. S. K. Brækkan and J. B. Hansen designed the study, collected data, and critically revised the manuscript. G. Lerstad and S. K. Brækkan had full access to the data, and take full responsibility for its integrity and the accuracy of data analysis.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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