

Effects of teneligliptin on PDMPs and PAI-1 in patients with diabetes on hemodialysis

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Background: Cardiovascular disease (CVD) is the main cause of death among hemodialysis (HD) patients. The effects of the dipeptidyl peptidase-4 inhibitor teneligliptin on CVD-related biomarkers in patients with type 2 diabetes mellitus (T2DM) receiving HD treatment are poorly understood. To determine whether teneligliptin has anti-CVD properties, we assessed its effects on soluble P-selectin (sP-selectin), platelet-derived microparticles (PDMPs), plasminogen activator inhibitor 1 (PAI-1), soluble E-selectin (sE-selectin), soluble vascular adhesion molecule 1 (sVCAM-1), and adiponectin plasma levels in HD and non-HD patients with T2DM.

Methods: Patients with T2DM eligible for teneligliptin monotherapy or combination therapy (eg, teneligliptin plus a sulfonylurea) were administered teneligliptin (20 mg/d) once daily for 6 months. Plasma levels of sP-selectin, PDMPs, PAI-1, sE-selectin, sVCAM-1, and adiponectin were measured by enzyme-linked immunosorbent assay at baseline and after 3 months and 6 months of treatment.

Results: Teneligliptin therapy significantly reduced plasma levels of sP-selectin, PDMPs, and PAI-1 compared with baseline levels, while significantly increasing adiponectin levels. sE-selectin and sVCAM-1 levels were significantly decreased only at 6 months. The reduction in sP-selectin, PDMPs, and PAI-1 was more significant in HD patients than in non-HD patients. However, the improvement in adiponectin levels was unchanged with HD treatment.

Conclusion: By modulating PDMPs or PAI-1, teneligliptin shows an antiatherothrombotic effect that may be beneficial in the primary prevention of CVD in patients with T2DM on HD.

Keywords: type 2 diabetes mellitus, teneligliptin, hemodialysis, PDMP, PAI-1

Introduction

Historically, older patients have often been excluded from hemodialysis (HD) treatment. However, this changed dramatically in the last decade as a result of increased patient longevity and technical advances in HD therapies.¹ Diabetes is the biggest cause of chronic kidney disease in HD patients, and diabetes treatment is a key factor in the overall survival of these patients.²⁻⁵ In addition, cardiovascular disease (CVD) is the main cause of death in HD patients because several factors increase the risk of developing CVD in this patient population.^{6,7}

Patients with type 2 diabetes mellitus (T2DM) typically display hypercoagulability and platelet hyperaggregability, along with increased levels of platelet activation markers.^{8,9} These changes are associated with an increased risk of cardiovascular events.^{10,11} Platelet-derived microparticles (PDMPs) are generated by platelet activation and play roles in normal hemostatic responses to vascular injury.¹²⁻¹⁴ It is thought that PDMPs

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contribute to thrombin generation and thrombus formation by generating tissue factor.^{15,16} Therefore, PDMPs may ultimately cause vascular complications in T2DM with the participation of the blood coagulation system.

Diabetes is also characterized by increased expression of cell adhesion molecules and elevation of plasminogen activator inhibitor 1 (PAI-1).^{17,18} These molecules are associated with vascular complications, along with increased serum levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), and soluble vascular adhesion molecule 1 (sVCAM-1) in patients with T2DM.^{19,20} High levels of PAI-1 have been demonstrated in atherothrombosis as PAI-1 contributes to thrombin generation and thrombus formation by generating tissue factor.^{21–23} The postprandial increase in blood glucose itself is also now considered a risk factor for the progression of atherosclerosis.²⁴

Adiponectin, the most abundant adipose tissue-specific protein, is exclusively expressed in and secreted by adipose tissue.²⁵ Plasma adiponectin concentrations, which are normally high, have been shown to be reduced in obese individuals^{25,26} and those with T2DM²⁷ and to be closely related to insulin sensitivity.²⁸ Adiponectin has been shown to stimulate nitric oxide (NO) production in vascular endothelial cells, ameliorating endothelial function.^{29,30} These observations suggest that the antiatherogenic properties of adiponectin may involve its NO-dependent antiplatelet effects.

Dipeptidyl peptidase-4 (DPP-4) is an enzyme involved in the degradation of the intact (active) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide, to their inactive metabolites. GLP-1 and glucose-dependent insulinotropic peptide are released by the intestine into the circulation in response to a meal, and both hormones increase glucose-dependent insulin secretion by inhibiting the degradation of active incretins. Tenelegliptin is a DPP-4 inhibitor that increases active incretin concentrations, thereby enhancing their glucoregulatory effects.^{31–33} Tenelegliptin exhibits stronger hydrophobic interactions with the active site of DPP-4, mediated by the “anchor lock domain,” which relates to the residence time of the inhibitor in DPP-4 and its long in vivo duration of action.³⁴ In addition, several clinical trials have shown that tenelegliptin improves insulin resistance.^{35–37} However, the effects of tenelegliptin on PDMPs, PAI-1, and adiponectin in patients with T2DM, whether on HD or not, are poorly understood. To determine whether tenelegliptin has anti-CVD properties, we assessed its effects on PDMP, PAI-1, and adiponectin concentrations in HD and non-HD patients with T2DM.

Patients and methods

Patients

The study cohort included 103 patients with T2DM, 47 with and 56 without HD (Table 1), selected from among those admitted to our hospital between May 2012 and March 2015 for the treatment of hypertension, hyperlipidemia, and diabetes. The study protocol was approved by the institutional review board of Kansai Medical University, and written informed consent was obtained from each patient. Individuals were excluded if they had a history (within 3 months prior to enrollment) of inflammatory, coronary artery, or cerebrovascular disease or if they had clinically detectable hepatic dysfunction (elevated transaminases), infection (fever or an elevated white blood cell count), or malignancy (detected on ultrasound or computed tomography). Of the included patients, 13 were taking aspirin because of a previous cerebral infarction or angina pectoris, 28 were taking angiotensin II receptor blockers, 18 were taking Ca-antagonists, and 56 were taking statins (Table 1). The doses of these drugs were not adjusted, and there were no other changes to drug therapy, during this study.

Study design

Patients were eligible for tenelegliptin if their diet/exercise therapy had continued unchanged for 3 months. Patients who had used a biguanide (metformin), a sulfonylurea (glibenclamide or glimepiride), a thiazolidinedione (glitazone), or

Table 1 Demographic and clinical characteristics of the patients with diabetes with and without hemodialysis

	All patients	HD	Non-HD
n	103	47	56
Men/women (n)	61/42	30/17	31/25
Age (years)	68±7	69±6	71±7
BMI (kg/m ²)	26.8±4.6	25.8±4.3	28.7±4.9
FBG (mg/dL)	158±42	131±39	175±56
HbA1c (%)	7.1±1.3	6.6±1.1	7.5±1.8
TC (mg/dL)	224±36	216±34	239±37
HDL-C (mg/dL)	42±16	43±15	39±17
LDL-C (mg/dL)	139±45	133±41	150±51
Complication, n (%)			
Angina pectoris	20 (28.2)	12 (25.5)	9 (16.1)
Heart failure	11 (10.7)	7 (14.9)	4 (7.1)
Cerebral infarction	13 (12.6)	6 (12.8)	7 (12.5)
Medication, n (%)			
Statins	56 (54.4)	30 (63.8)	26 (46.4)
ARBs	28 (27.2)	13 (27.7)	15 (26.8)
Ca-antagonists	18 (17.5)	8 (17.0)	10 (17.9)
Aspirin	13 (12.6)	7 (14.9)	6 (10.7)

Note: Data are shown as mean ± SD.

Abbreviations: HD, hemodialysis; n, number of participants; BMI, body mass index; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ARB, angiotensin II receptor blocker; SD, standard deviation.

insulin for 3 months were eligible for combination therapy with that agent plus teneligliptin. Patients were administered teneligliptin (20 mg/d) once daily for 6 months. Clinical and biochemical data were obtained before and 3 months and 6 months after starting teneligliptin treatment.

Measurement of PDMP

PDMP levels were measured twice and mean values were recorded. Furthermore, some basic studies were carried out prior to this assessment using clinical specimens. An enzyme-linked immunosorbent assay (ELISA) kit (Otsuka Pharmaceutical, Tokyo, Japan) was used for PDMP measurements.³⁸

Measurement of soluble molecules and adiponectin

Blood samples from patients and controls under fasting conditions were collected into tubes with or without sodium citrate and allowed to clot at room temperature for a minimum of 1 hour. Citrated plasma or serum, respectively, was isolated by centrifugation at $1,000 \times g$ for 20 minutes at 4°C and stored at -30°C until analyzed. Plasma concentrations of sP-selectin, sE-selectin, sVCAM-1, and PAI-1 were measured using monoclonal antibody-based ELISA kits (Thermo Fisher Scientific, Waltham, MA, USA), and plasma adiponectin was measured with adiponectin ELISA kits (Otsuka Pharmaceuticals Co. Ltd, Tokyo, Japan). The recombinant products and standard solutions provided with each kit were used as positive controls in each assay, and all procedures were performed according to the manufacturers' instructions.

Statistics

Data were expressed as mean \pm standard deviation. Between-group comparisons were analyzed using the Newman-Keuls test and Scheffe's test. The significance of differences among variables was determined by analysis of variance. *P*-values <0.05 were considered statistically significant. All analyses were performed using the StatFlex program (version 6; Artech Co., Ltd., Osaka, Japan).

Results

Patients' demographic and clinical characteristics are shown in Table 1. Sex and age were similar in the HD and non-HD groups, except for concentrations (Table 1). The levels of body mass index, fasting blood glucose, hemoglobin (Hb) A1c, total cholesterol, and low-density cholesterol were higher in non-HD than in HD patients (Table 1). However, high-density cholesterol was lower in non-HD than in HD patients (Table 1).

Administration of teneligliptin to 103 patients for 3 months significantly reduced fasting blood glucose and HbA1c levels (data not shown). In addition, both 3-month and 6-month administration significantly reduced plasma concentrations of sP-selectin, PDMPs, and PAI-1, relative to baseline (3 months, $P<0.05$; 6 months, $P<0.01$ each; Figure 1A–C). Furthermore, teneligliptin treatment significantly increased adiponectin concentrations after 3 months ($P<0.05$) and 6 months ($P<0.01$), relative to baseline (Figure 1D). Teneligliptin also decreased sE-selectin and sVCAM-1 concentrations after 6 months, relative to baseline, although the differences were not significant after 3 months (Figure 1E and F).

We divided patients with diabetes into two subgroups according to whether they were receiving HD treatment or not. HD patients showed significant reductions in plasma concentrations of sP-selectin, PDMPs, and PAI-1 relative to baseline ($P<0.01$ for each; Figure 2A–C), and all three concentrations were significantly lower in HD than in non-HD after 3 months and 6 months of teneligliptin treatment (two-factor analysis of variance; $P<0.05$ each). However, there were no significant differences in HbA1c and adiponectin levels between HD and non-HD patients (Figure 2D and E).

Discussion

Postprandial hyperglycemia is an early manifestation of T2DM and is caused by the loss of early-phase insulin response.³⁹ Postprandial hyperglycemia in patients with diabetes may also be associated with the activation of platelets. In this study, PDMPs, sP-selectin, sE-selectin, sVCAM-1, and PAI-1 were increased in patients with T2DM. These markers decreased significantly with teneligliptin treatment; in particular, PDMPs and PAI-1, which are risk factors for CVD, were significantly decreased in HD patients with T2DM. Treatment with teneligliptin was shown to significantly reduce body mass index and waist circumference,^{40,41} as well as prevent nephropathic complications in patients with T2DM.⁴² Thus, our results suggest that teneligliptin may lead to the improvement of atherosclerosis in patients with T2DM with HD by modulating PDMPs and/or PAI-1. Several factors are associated with the development of atherosclerosis in T2DM, one of which is oxidative stress.⁴³ Recently, Kimura et al⁴⁴ reported that the structure of teneligliptin has a scavenging activity on hydroxyl radical that may contribute to the prevention of diabetic complications, a finding that supports our results.

Plasma concentrations of adiponectin are lower in obese than in nonobese individuals²⁵ and are closely related to

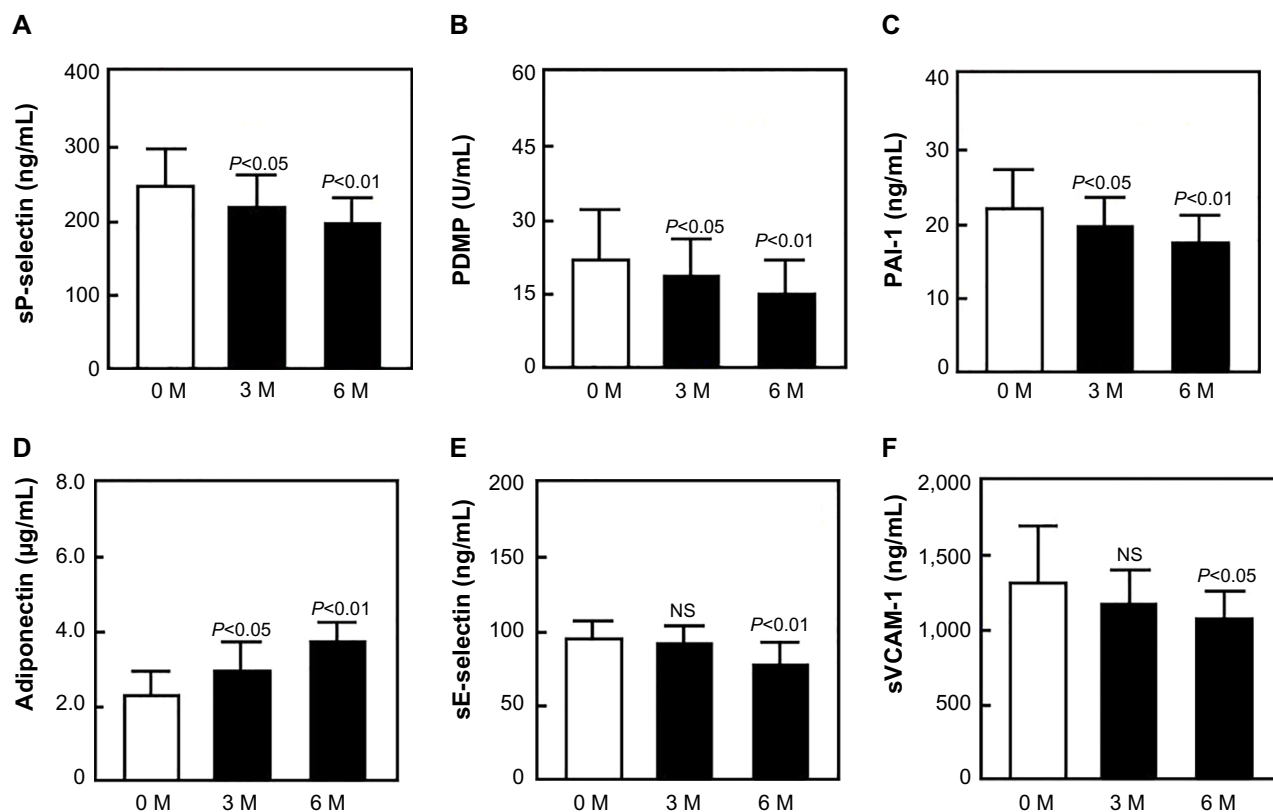


Figure 1 Plasma concentrations of sP-selectin (A), PDMP (B), PAI-1 (C), adiponectin (D), sE-selectin (E), and sVCAM-1 (F) before and after teneligliptin treatment of patients with diabetes.

Notes: Data are shown as mean \pm SD. P-values shown for 0 M vs 3 M and 0 M vs 6 M.

Abbreviations: sP-selectin, soluble P-selectin; PDMP, platelet-derived microparticle; PAI-1, plasminogen activator inhibitor; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhesion molecule; 0 M, 0 months (baseline); 3 M, 3 months after treatment; 6 M, 6 months after treatment; NS, not significant; SD, standard deviation.

whole-body insulin sensitivity.²⁷ Adiponectin levels are also reduced in patients with T2DM.²⁷ Adiponectin has been reported to suppress the attachment of monocytes to endothelial cells⁴⁵ and to play a role in protection against vascular injury, suggesting that hypoadiponectinemia is associated with endothelial dysfunction.⁴⁶ In this study, sE-selectin and sVCAM-1 increased in patients with T2DM, particularly those receiving HD treatment. Furthermore, these biomarkers decreased significantly after teneligliptin treatment. Hypoadiponectinemia has also been associated with platelet activation. Nitric oxide (NO) levels, which regulate platelet activation, are reduced in hypoadiponectinemia because adiponectin stimulates NO production by vascular endothelial cells.^{29,30,47} Thus, platelet activation due to low NO concentrations occurs in hypoadiponectemic individuals. Therefore, the teneligliptin-induced increase in adiponectin may have an antiplatelet effect by enhancing NO production,⁴⁸ as demonstrated by the significant reduction in PDMPs and sP-selectin in patients with diabetes treated with teneligliptin.

Various posttranslational modifications, including the glycosylation of lysine residues, have been shown to be necessary for the multimerization of adiponectin.⁴⁹ These intracellular posttranslational processes may be affected by hyperglycemia, leading to functional impairment at the organ level in patients with diabetes.^{50–52} Therefore, the teneligliptin-induced improvement in postprandial hyperglycemia may alter the posttranslational modification of adiponectin. Patients in our study received teneligliptin monotherapy or teneligliptin in combination with other antidiabetic drugs. Therefore, it is unknown whether the therapeutic effects of teneligliptin observed in this study were related to monotherapy or not. However, Ito et al³⁶ reported that teneligliptin monotherapy improved homeostasis model assessment of insulin resistance.

The exact mechanism by which teneligliptin treatment increases circulating adiponectin concentrations remains unclear, although the gut-derived incretin hormone GLP-1 is likely involved. GLP-1 is rapidly degraded by DPP-4; therefore, teneligliptin treatment increases plasma concentrations

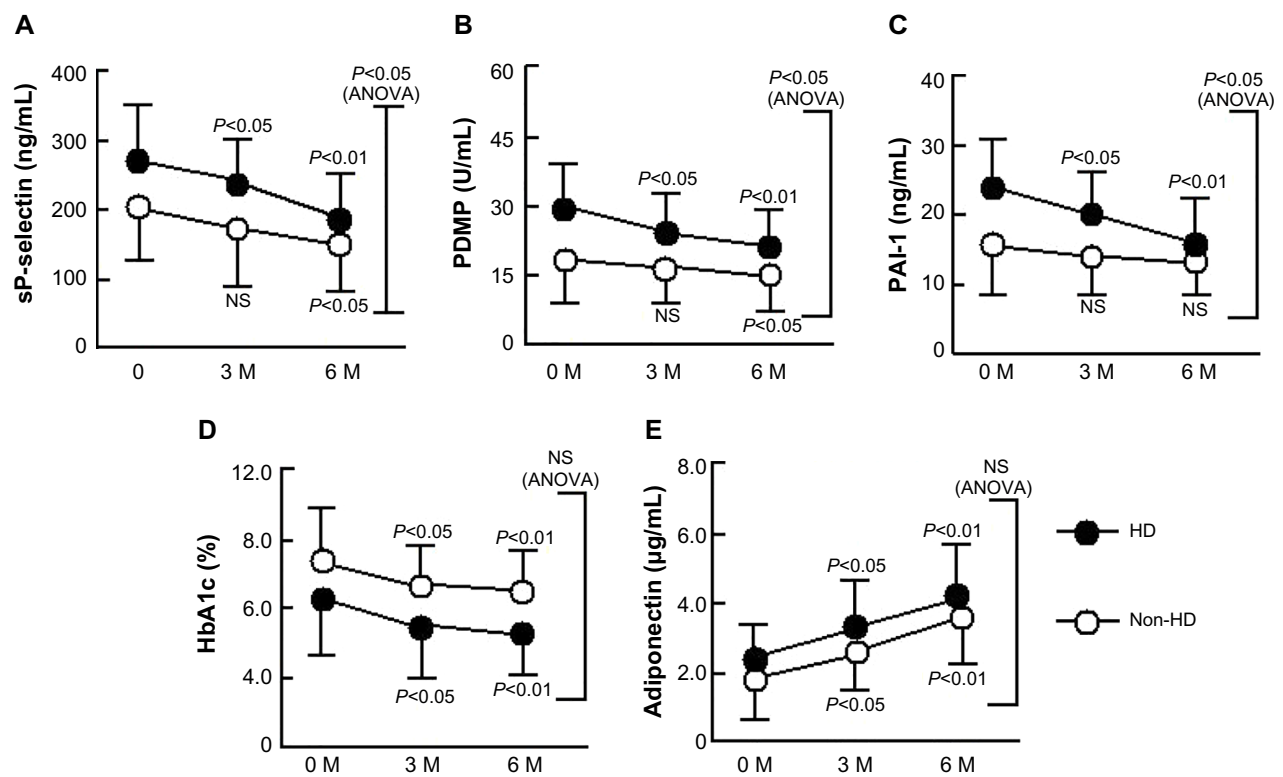


Figure 2 Changes in sP-selectin (A), PDMP (B), PAI-1 (C), HbA1c (D), and adiponectin (E) in response to treatment with teneligliptin of patients with diabetes with and without hemodialysis.

Notes: Bars show the mean \pm SD. *P*-values are for comparison with each baseline parameter (0 M vs 3 M and 0 M vs 6 M). ANOVA was used to analyze differences between HD and non-HD patients.

Abbreviations: HbA1c, hemoglobin A1c; sP-selectin, soluble P-selectin; PDMP, platelet-derived microparticle; PAI-1, plasminogen activator inhibitor; HD, hemodialysis; 0 M, 0 months (baseline); 3 M, 3 months after treatment; 6 M, 6 months after treatment; NS, not significant; ANOVA, analysis of variance; SD, standard deviation.

of active GLP-1.³¹ GLP-1-based therapies have been shown to reduce glucose concentrations and exert antiobesity effects in patients with T2DM.⁵³ Teneligliptin was found to enhance the secretion of active GLP-1, suggesting that the antidiabetic properties of teneligliptin depend, in part, on GLP-1.⁵⁴ In addition, GLP-1 was shown to promote adiponectin secretion,^{55,56} resulting in enhanced NO production.⁴⁸ Therefore, teneligliptin may inhibit the progression of atherothrombosis by promoting adiponectin- and NO-dependent reductions in plasma PDMPs, sP-selectin, sE-selectin, sVCAM-1, and PAI-1. However, further studies are necessary to elucidate the effects of teneligliptin itself on adiponectin production.

Strengths and limitations

This study has two potential strengths. First, despite the treatment of many patients with T2DM with teneligliptin, no previous study had assessed the effects of teneligliptin on serum markers of disease such as PDMP and PAI-1. Second, it showed that investigation of appropriate serum markers can be used to address atherosclerosis in T2DM with HD. However, this study also had several limitations. First, changes in clinical

parameters of atherothrombosis such as ankle brachial index were not routinely recorded. Second, we could not identify the causative differences in groups of HD and non-HD. HD patients had poorer serum values at the onset of teneligliptin treatment, suggesting a uremic factor associated with these differences. Third, we could not clarify the significance of PAI-1 and endothelial cell markers relative to atherosclerosis after teneligliptin treatment. Confirmation of these findings in larger and more particular studies would be useful. Finally, we were unable to evaluate the therapeutic effects of teneligliptin using glycated albumin (GA), a parameter used to assess glycemic control in HD patients with T2DM, given that HbA1c underestimates glycemic control in this patient population.⁵⁷ Recently, Wada et al⁵⁸ reported that teneligliptin improved GA and HbA1c in patients with T2DM undergoing HD. Therefore, the assessment of GA in teneligliptin-treated patients with T2DM would be beneficial.

Conclusion

Teneligliptin significantly reduced plasma levels of PDMPs and PAI-1 and increased circulating adiponectin

concentrations in patients with T2DM, particularly those receiving HD treatment. In addition, teneligliptin treatment reduced sP-selectin, sE-selectin, and sVCAM-1 levels. Teneligliptin may be beneficial in the primary prevention of atherothrombosis in patients with T2DM.^{59,60} However, larger clinical trials are required to test this hypothesis.

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Disclosure

The authors report no conflicts of interest in this work.

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