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ORIGINAL ARTICLE

Long-term effects of L- and N-type calcium channel blocker on uric acid levels and left atrial volume in hypertensive patients

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Abstract Left ventricular (LV) diastolic dysfunction is associated with hypertension and hyperuricemia. However, it is not clear whether the L- and N-type calcium channel blocker will improve LV diastolic dysfunction through the reduction of uric acid. The aim of this study was to investigate the effects of anti-hypertensive therapy, the L- and N-type calcium channel blocker, cilnidipine or the L-type calcium channel blocker, amlodipine, on left atrial reverse remodeling and uric acid in hypertensive patients. We studied 62 patients with untreated hypertension, randomly assigned to cilnidipine or amlodipine for 48 weeks. LV diastolic function was assessed with the left atrial volume index (LAVI), mitral early diastolic wave (E), tissue Doppler early diastolic velocity (E') and the ratio (E/E'). Serum uric acid levels were measured before and after treatment. After treatment, systolic and diastolic blood pressures equally dropped in both groups. LAVI, E/E', heart rate and uric acid levels decreased at 48 weeks in the cilnidipine group but not in the amlodipine group. The % change from baseline to 48 weeks in LAVI, E wave, E/E' and uric acid levels were significantly lower in the cilnidipine group than in the amlodipine group. Larger %-drop in uric acid levels were associated with larger %-reduction of LAVI ($p < 0.01$). L- and N-type calcium channel blocker but not L-type calcium channel blocker may improve LV diastolic function in hypertensive patients, at least partially through the decrease in uric acid levels.

Keywords Hypertension · Uric acid · L- and N-type calcium channel blocking drugs · Diastolic dysfunction

Abbreviations

CCB	Calcium channel blocker
UA	Uric acid
LAV	Left atrial volume
LV	Left ventricular
RAS	Renin–angiotensin system
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LAVI	Left atrial volume index
LVMI	Left ventricular mass index
RWT	Relative wall thickness
E	Peak velocities of early diastolic phase
A	Late diastolic phase of mitral inflow
E'	Mitral annulus velocities
HR	Heart rate
LAD	Left atrial diameter
LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
DT	Deceleration time

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Introduction

Hypertension leads to diastolic dysfunction with left atrial (LA) enlargement and left ventricular hypertrophy [1, 2]. Diastolic dysfunction is associated with increased morbidity and mortality [3] due to enhanced activity of the sympathetic nervous system and the oxidative stress [4–6]. Recent animal studies have shown that L- and N-type calcium channel blocker compared with L-type calcium channel blocker improved the left ventricular diastolic dysfunction and cardiac oxidative stress in Dahl salt-sensitive rats [7]. Moreover, L- and N-type calcium channel blocker has greater inhibition of sympathetic nervous system in hypertensive patients [8–10].

Hyperuricemia play an important role in development of hypertension, cardiovascular disease, chronic kidney disease and metabolic syndrome [11, 12]. L- and N-type calcium channel blocker, cilnidipine decreased serum uric acid levels by increasing the nitrogen monoxide excretion [13].

However, it is unclear whether the L- and N-type calcium channel blocker, cilnidipine or the L-type calcium channel blocker, amlodipine could decrease serum uric acid level and LA volume in patients with untreated hypertension. Thus, the aim of this study was to investigate the impact of decrease in uric acid as a contributor to regression of LA volume index in hypertensive patients following long-term treatment with cilnidipine or amlodipine.

Materials and methods

Subjects

We enrolled 62 patients with untreated hypertension who presented to outpatient clinic of Hyogo College of Medicine between January 2010 and November 2015. Patients were included in the study if they met the following criteria: 20 years of age or older, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 140 and 90 mmHg or over. Patients were excluded if they had secondary hypertension of any cause, angina pectoris or acute coronary artery disease, current or recent history of congestive heart failure, valvular heart diseases, cardiac arrhythmias, renal dysfunction (serum creatinine level over 2.0 mg/dL). Informed consent was obtained from all patients, and the study was designed to comply with the ethical principles of our institution. Eligible patients were randomly assigned in a 1:1 ratio to receive either amlodipine 2.5 mg daily (amlodipine group) or cilnidipine 10 mg daily (cilnidipine group). Target SBP and DBP were below 140 and 90 mmHg, respectively. If blood pressure reduction did not achieve the target level after 4 weeks, the daily dose was increased to 10 mg amlodipine or 20 mg cilnidipine. The third and fourth steps of treatment included the addition of a thiazide and/or alpha-blocker.

Blood chemistry

Among 62 enrolled subjects, we could collect blood samples for uric acid measurement from 32 patients in cilnidipine and 27 patients in amlodipine groups. 3 subjects could not be measured because of missing blood samples. Blood samples ($n = 59$) were taken between 0900 and 1100 hours and were immediately placed on ice and centrifuged within 1 h. The specimens were stored at −80 °C until analysis. Uric acid was measured by an automatic biochemical analysis systems Hitachi LABOSPECT.

Echocardiographic studies

Transthoracic echocardiography was performed at baseline and 48 weeks after treatment in all patients. Echocardiography was recorded with iE33 (Philips Medical Systems, Bothell, Washington). A standard, comprehensive, M-mode, 2-dimensional echocardiography and Doppler study were conducted according to the guideline of the American Society of Echocardiography [14]. LA volume was calculated with a formula using an ellipsoid model and was indexed to the body surface area, i.e., LA volume index (LAVI) [15]. LV mass index (LVMI) and relative wall thickness (RWT) were measured by the method described previously [16]. Peak velocities of early diastolic phase (*E*) and late diastolic phase (*A*) of mitral inflow, and the *E*/*A* ratio were measured by pulsed-wave Doppler echocardiography with the sample volume between mitral leaflet tips. Mitral annulus velocities (E') and E/E' ratio were measured at the septal annulus by tissue Doppler imaging.

Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki after receiving approval from the institutional review board of Hyogo College of Medicine. All subjects provided written informed consent prior to participation.

Statistical analysis

The primary outcomes included changes in uric acid and LA volume in hypertensive patients following long-term treatment with amlodipine or cilnidipine. Continuous data were presented as mean and standard error of the mean (±SEM). We compared values at baseline and after treatment using the Wilcoxon signed ranks test. Spearman's rank correlation coefficient was used to examine

the correlations between the change in serum uric acid and LAVI, SBP, heart rate and *E*/*E*′. *p* values <0.05 were considered significant. Statistical computations were performed with JMP version 10.0.1 (SAS Institute, Inc, Cary, North Carolina).

Results

Patient characteristics

We analyzed the data of 35 men and 27 women with mean age of 61 years. The final dose of amlodipine was 5.8 ± 0.4 mg/day and that of cilnidipine was 10.0 ± 0.9 mg/day. Thiazide indapamide 1 mg was added to the basal medications in four patients of amlodipine group and three patients of cilnidipine group and, whereas alpha blocker doxazosin 1 mg was added in three patients of amlodipine group and in no patients of cilnidipine group. Baseline characteristics were similar in both groups of patients (Table 1).

Changes in blood pressure and echocardiographic parameters and serum uric acid

SBP, DBP and LVMI decreased similarly in the cilnidipine and amlodipine groups after 48 weeks of treatment. The serum uric acid, LAVI, *E*/*E*′ and heart rate significantly decreased in the cilnidipine group but not in the amlodipine group. *E* wave significantly increased in the amlodipine group but not in the cilnidipine group (Table 1).

Table 1 Changes in hemodynamic and echocardiographic parameters, and uric acid levels in amlodipine and cilnidipine groups

	Amlodipine		Cilnidipine	
	Before treatment	48 weeks	Before treatment	48 weeks
Age (years)	60 ± 2		62 ± 2	
Sex (female/male)	11/19, 30		16/16, 32	
Hight (cm)	161 ± 2		160 ± 2	
Body weight (kg)	65 ± 2	65 ± 2	61 ± 2	61 ± 2
SBP (mmHg)	165 ± 3	132 ± 3***	162 ± 3	132 ± 2***
DBP (mmHg)	94 ± 2	81 ± 2***	93 ± 2	77 ± 2***
HR (bpm)	74 ± 2	74 ± 2	71 ± 2	65 ± 2*
LAD (mm)	37 ± 1	37 ± 1	38 ± 1	37 ± 1
LAVI (ml/m^2)	21 ± 1	24 ± 1*	24 ± 1	22 ± 1**
LVEDD (mm)	48 ± 1	48 ± 1	48 ± 1	48 ± 1
LVESD (mm)	29 ± 1	30 ± 1	31 ± 1	30 ± 1
RWT	0.42 ± 0.06	0.38 ± 0.01**	0.41 ± 0.02	0.36 ± 0.01*
LVEF (%)	67 ± 1	67 ± 1	66 ± 2	69 ± 1
LVMI (g/m^2)	104 ± 3	93 ± 3***	100 ± 6	86 ± 4***
E (m/s)	58 ± 3	68 ± 3**	62 ± 2	63 ± 2
A (m/s)	72 ± 3	78 ± 3	73 ± 3	78 ± 3
E/*A*	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
DT (ms)	202 ± 8	202 ± 9	206 ± 8	215 ± 10
E′ (cm/s)	5.7 ± 0.3	6.1 ± 0.3**	5.2 ± 0.2	6.1 ± 0.3***
E/*E*′	11 ± 1	12 ± 1	12 ± 1	11 ± 1**
Serum uric acid (mg/dl)	5.2 ± 0.2	5.5 ± 1.3	5.6 ± 0.2	5.4 ± 0.2*
Comorbidity				
Dyslipidemia (%)	4 (13)		7 (22)	
Diabetes mellitus (%)	3 (10)		4 (13)	
Smoking (%)	2 (6)		3 (9)	
Baseline Medication				
Statin *n* (%)	4 (13)		4 (13)	
Sulfonylurea *n* (%)	3 (10)		4 (13)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *LAD* left atrial diameter, *LAVI* left atrial volume index, *LVEDD* left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *RWT* relative wall thickness, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *DT* deceleration time

* $p < 0.05$ versus baseline; ** $p < 0.01$ versus baseline; *** $p < 0.001$ versus baseline

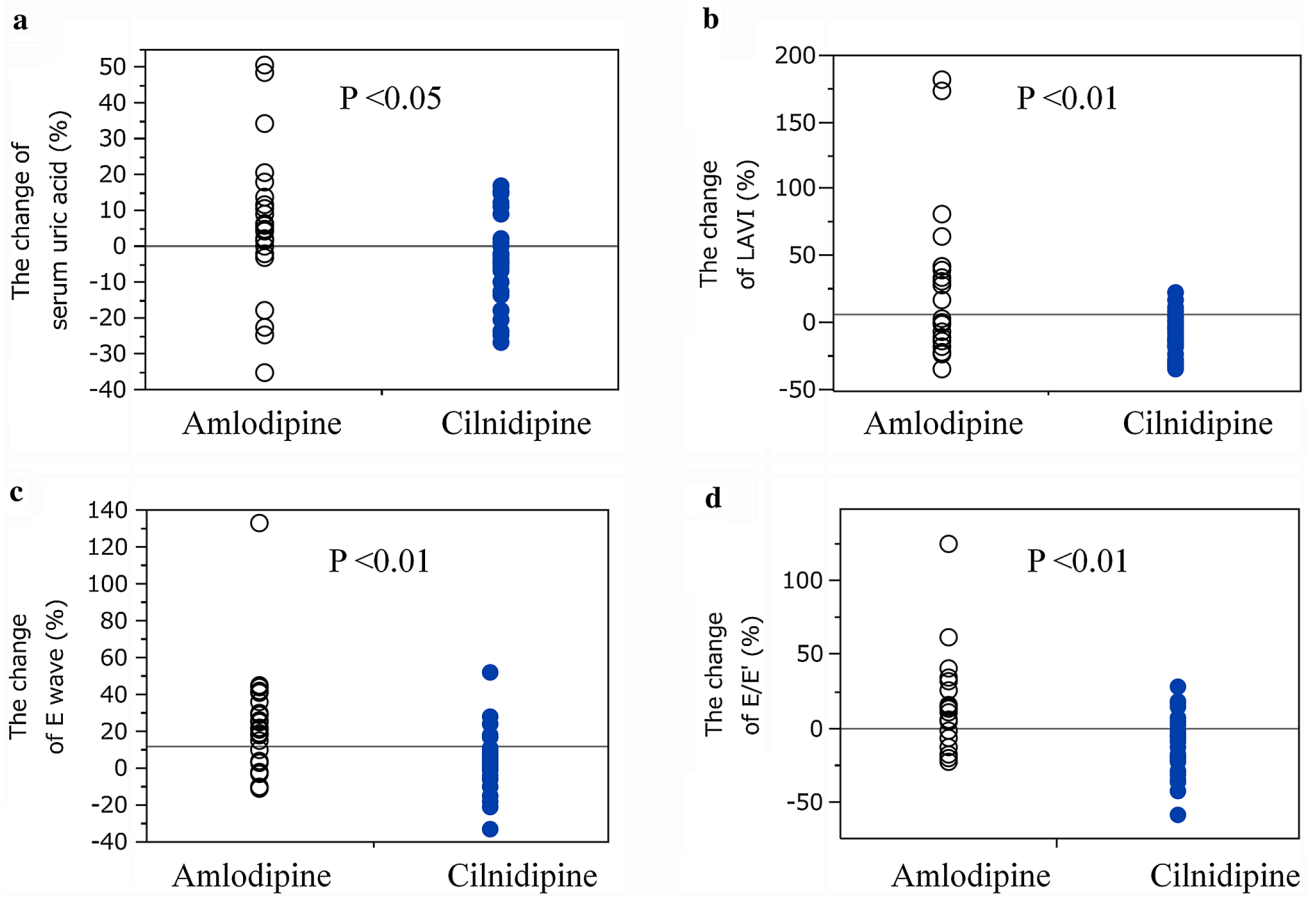

Fig. 1 Percent change in serum uric acid (**a**), LAVI (**b**), trans mitral *E* wave peak velocity (*E*) (**c**), and ratio of *E* to mitral annular *E′* velocity (*E′*) velocity (*E*/*E′*) (**d**)

Effects of cilnidipine and amlodipine on LAVI, *E*/*E′* and serum uric acid

Percent changes from the baseline in LAVI, *E* wave, *E*/*E′* and serum uric acid levels were lower in the cilnidipine group than in the amlodipine group (-9 ± 3 vs. 26 ± 10 %, $p < 0.01$, 3 ± 3 vs. 20 ± 5 %, $p < 0.01$, -12 ± 4 vs. 12 ± 6 %, $p < 0.01$, -3 ± 3 vs. 8 ± 5 %, $p < 0.05$ as percentage reduction from the values before treatment) (Fig. 1a–d).

Correlation between serum uric acid and LAVI

Larger percent-drop in serum uric acid were associated with larger percent-reduction of LAVI in the cilnidipine group ($\rho = 0.49$, $p < 0.01$) but not in the amlodipine group (Fig. 2). No association was showed between the percent changes in serum uric acid and the changes in SBP, heart rate and *E*/*E′* in both groups.

Discussion

Main findings in the present study were: (1) While blood pressure reduction over 48 weeks was similar between cilnidipine and amlodipine groups, serum uric acid, LAVI, *E*/*E′* and heart rate decreased only in cilnidipine group; (2) In cilnidipine group, percent decrease in LAVI was correlated with percent decrease in serum uric acid.

These data suggest that cilnidipine decreased LV filling pressure and LA volume at least partially through the reduction of uric acid levels in hypertensive patients.

Effect of cilnidipine on hemodynamics and left atrial volume

Enlargement of LA has adverse cardiovascular outcomes, including heart failure [17–19], atrial fibrillation [20], stroke [21], and mortality [2]. LA dilatation has been

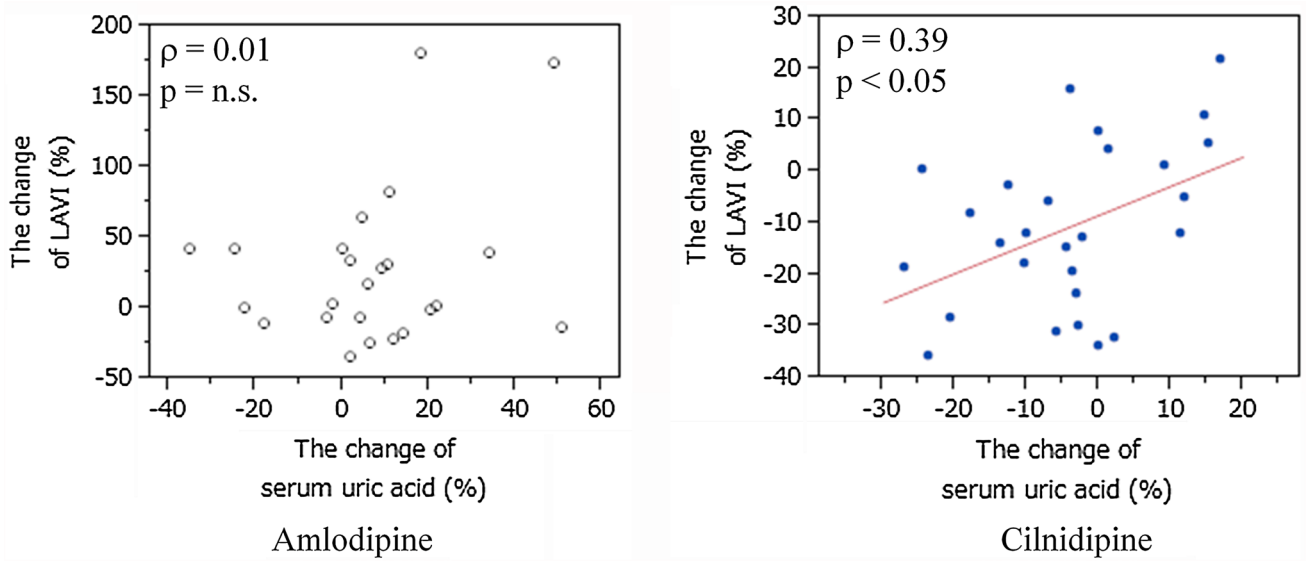

Fig. 2 Correlation between percent change in serum uric acid and percent change in LAVI. *Left* amlodipine, *right* cilnidipine

associated with LV diastolic dysfunction, independent of age, gender and LV ejection fraction [1, 22]. Since LA dilatation can be attributed to a sustained elevation of LV filling pressure and an atrial volume overload due to diastolic dysfunction in hypertensive patients [23, 24], the reduction of LA volume might be associated with improvement in cardiovascular events. In this study, LAVI, E/E' and heart rate decreased only in cilnidipine group, not in amlodipine group. L- and N-type calcium channel blocker, cilnidipine has improved diastolic dysfunction or cardiac fibrosis in hypertensive patients and hypertensive rats [7, 25, 26]. Moreover, cilnidipine has anti-sympathetic nerve activity, anti-inflammation effect, anti-oxidation effect, anti-renin–angiotensin–aldosterone system, in addition to its antihypertensive effect [10, 27–31].

Takatsu et al. [7] described that cilnidipine reduced left ventricular diastolic dysfunction compared with amlodipine in Dahl salt-sensitive rats. Soeki et al. [10] reported that cilnidipine inhibited the oxidative stress in hypertensive patients. Konda et al. [27] found that cilnidipine, compared with amlodipine, inhibited renin angiotensin system due to the anti-sympathetic nerve activity in hypertensive model rats. Aritomi et al. [52] demonstrated that cilnidipine suppressed the aldosterone synthase (CYP11B2) expression in human adrenocortical cells. The improvement in diastolic function with cilnidipine might be at least partially attributed to the inhibition of cardiac oxidative stress, inflammation and renin–angiotensin–aldosterone gene expression.

On the other hand, L-type calcium channel blocker, amlodipine, might activate renin–angiotensin–aldosterone system due to increase in sympathetic tone via a rapid and large reduction in blood pressure [28, 32, 33]. Nishimura et al. [34] showed increment in LV end-diastolic pressure as well as prolongation of the time constant of relaxation by calcium channel blocker. In this study, LAVI and E were increased in the amlodipine group. These data suggested that L-type calcium channel blocker, amlodipine may not improve LV preload through activated sympathetic nerve as compared to L- and N-type calcium channel blocker, cilnidipine. These data suggest cilnidipine may have a beneficial effect on anti-sympathetic nerve activity, LV filling pressure and LA volume as well.

However, it has not been fully clarified whether the LA volume reduction directly results in the improvement in cardiovascular outcomes. Further research intervention studies are required to establish whether the LA volume reduction directly results in the improvement in cardiovascular mortality.

Effect of cilnidipine on serum uric acid and left atrial reverse remodeling

There are several possible mechanisms that might explain how cilnidipine could decrease serum uric acid level. Hamada et al. reported that cilnidipine significantly decreased the serum uric acid level and increased uric nitrogen monoxide synthesis in hypertensive patients. Similarly, Uchida et al. observed that cilnidipine improved uric acid metabolism in hypertensive patients with chronic kidney disease. This mechanism of the serum uric acid reduction by cilnidipine inhibited the production of uric acid precursor, hypoxanthine, in the skeletal muscle [13, 51].

The present study, the larger decrease in serum uric acid was associated with the larger reduction of LAVI in

cilnidipine group. Previous studies demonstrated that hyperuricemia was associated with the dilatation of left atrial size or elevated left atrial pressures [35, 36]. In addition, hyperuricemia promote hypertension, metabolic syndrome, cardiac fibrosis, cardiac oxidative stress, LV hypertrophy, LV diastolic dysfunction and endothelial dysfunction [6, 11, 12, 38–42]. The pro-oxidant activity of serum uric acid increased the inflammatory cytokines such as monocyte chemo attractant protein-1 (MCP-1) and cyclooxygenase (COX-2), and the oxidant species such as peroxynitrite [43–45]. Randomized trial showed that allopurinol, a xanthine oxidase inhibitors, decreased plasma renin activity and blood pressure in patients with hypertension [37]. This study suggested that decreasing serum uric acid may be associated with afterload reduction and improving renin–angiotensin–aldosterone system. Therefore, it is speculated that the lowering of uric acid would be accompanied by the left atrial size reduction.

However, serum uric acid is not only pro-oxidant effects [43–45] but also anti-oxidant effects [48, 49]. Administration of uric acid has been reported to improve endothelial function [49, 50]. Sugihara et al. [47] found that very low serum uric acid (below 0.8 mg/dL) was associated with endothelial dysfunction by increasing oxidative stress. The correlation between serum uric acid levels and cardiovascular events were J-shaped in PIUMA study [46]. Although raising serum uric acid levels protected against oxidative stress, these studies investigate the effect of acute uric acid administration, younger population and very low serum uric acid concentrations. Middle aged hypertensive patients were included in the present study. Moreover, there were no patients with very low serum uric acid levels in the present study. Therefore, serum uric acid in this study may be recognized as a marker of pro-oxidant rather than an anti-oxidant.

Limitations

There are several limitations in this study. First, the small number of patients is enrolled in this study. Therefore, a large number of patients is needed to confirm our results. Second, neither invasive hemodynamic evaluation nor the activation of oxidative stress, renin–angiotensin–aldosterone and hypoxanthine were available in the present study. In future, we need to elaborate the detailed relations between invasive hemodynamic monitoring and cardiac structure. Third, we used only one calcium channel blocker for each hypertensive patient group (cilnidipine and amlodipine). Therefore the evaluation of other calcium channel blockers may be necessary in the future study.

Perspectives

The cilnidipine seems to decrease serum uric acid and LAVI, differently from amlodipine. There were significant correlations between percent decrease in serum uric acid and percent decreases in LAVI. These data suggest that suppression of serum uric acid by the L- and N-type calcium channel blocker contributed to reverse remodeling of LA in hypertensive patients. The L- and N-type calcium channel blocker, which improve LV diastolic dysfunction, may be useful in heart failure with preserved ejection fraction.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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