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Report

Reporting Profile of Linezolid-Associated Hyponatremia: An Analysis Using the Japanese Adverse Drug Event Report (JADER) Database

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Distinguishing between disease-induced and drug-associated hyponatremia is important in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This study aimed to characterize the specific reporting profile of linezolid (LZD)-associated hyponatremia using the Japanese Adverse Drug Event Report (JADER) database. Data from the JADER database (April 2004–May 2025) were analyzed. Crude reporting odds ratios (cRORs) for hyponatremia were calculated to confirm the safety signal for LZD. Subsequently, multivariate logistic regression and Weibull distribution analyses were performed for LZD-associated cases to explore demographic factors associated with the reporting and temporal reporting profiles, respectively. Among 4,480 reports of hyponatremia, 117 were associated with anti-MRSA agents (LZD, tedizolid, vancomycin, teicoplanin, daptomycin, and arbekacin). LZD demonstrated a significant reporting signal for hyponatremia (cROR, 10.04; 95% confidence interval [CI], 8.19–12.31). This signal persisted even in the oral administration subgroup (cROR, 3.41; 95% CI, 1.83–6.38). The multivariate logistic regression analysis restricted to LZD-associated cases identified age ≥ 70 years (adjusted reporting odds ratio [aROR], 1.73; $p < 0.001$) and female sex (aROR, 1.52; $p < 0.05$) as demographic factors associated with the reporting. The median time to onset was 5.5 days. The Weibull shape parameter (β) was 1.34, indicating an increasing reporting hazard profile over time during the acute treatment period. These hypothesis-generating findings suggest that cumulative exposure to LZD may lead to hyponatremia, supporting the need for careful serum sodium monitoring, particularly in elderly and female patients.

Key words hyponatremia, linezolid, pharmacovigilance, Japanese Adverse Drug Event Report Database

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections often present with severe systemic complications. Among these, electrolyte abnormalities, particularly hyponatremia, are clinically relevant.[1-2] Hyponatremia is a common yet serious disorder, and even mild cases are associated with increased hospital length of stay, greater resource utilization, and higher mortality rates.[3-4] The etiology of hyponatremia in patients with MRSA is often complex and multifactorial. It can arise from the underlying disease itself, such as the syndrome of inappropriate antidiuretic hormone secretion (SIADH) triggered by systemic inflammation and the infection itself, or as an adverse event of therapy.

Therefore, careful distinction between disease-induced and drug-associated electrolyte imbalances is important for appropriate clinical management of MRSA infections. Among anti-MRSA agents, linezolid (LZD), a widely used oxazolidinone class antimicrobial agent,[5-7] has been implicated in drug-associated hyponatremia in previous small-scale observational studies and case reports.[8-10]

However, distinguishing between true drug-induced hyponatremia and disease-induced hyponatremia, such as SIADH triggered by severe infection, remains a clinical challenge. Because LZD is available in both intravenous (IV) and oral (PO) formulations, the administration route can serve as a surrogate marker for clinical severity; IV therapy is typically required for severe infections, whereas PO therapy is often used for less severe cases or as step-down therapy.[11] Furthermore, a recent clinical study highlighted that the incidence of LZD-associated hyponatremia differs between administration routes, identifying IV administration as an independent risk factor compared to PO administration.[12] Therefore, evaluating the safety signal stratified by administration route is crucial to isolate the intrinsic pharmacological risk of LZD from confounding by indication. While the risk factors for LZD-associated hyponatremia have been investigated in previous clinical studies, comprehensive evaluations of its real-world reporting

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profile—including the impact of clinical severity and temporal onset patterns—remain limited.[13]

Accordingly, the objective of this study was to characterize the specific reporting profile of LZD-associated hyponatremia using the Japanese Adverse Drug Event Report (JADER) database. Specifically, this analysis was designed to: (1) confirm the reporting signal for hyponatremia associated with LZD; and (2) explore demographic factors associated with the reporting and characterize the temporal reporting profile of hyponatremia for the agent demonstrating a safety signal. These analyses aim to provide hypothesis-generating data for future clinical studies.

MATERIALS AND METHODS

Study Design The JADER database, which covers records from April 2004 to May 2025, was obtained from the Pharmaceuticals and Medical Devices Agency website (http://www.pmda.go.jp/; accessed October 24, 2025). The database comprises four comma-separated value tables: patient demographic information (e.g., age, sex, and body weight), drug information (e.g., drug name and administration start date), adverse event information (e.g., type of adverse event and onset date), and primary disease information. The data were processed using JMP Student Edition 18 (SAS Institute Inc., Cary, NC, USA).

Data for the analysis were extracted by combining tables containing demographic, drug, and adverse event information after removing duplicates. For the disproportionality analysis, the entire eligible dataset was utilized to minimize selection bias. Cases with missing demographic data (age, sex, or body weight) were excluded only for the subsequent multivariate logistic regression and time-to-onset analyses. For this analysis, reports were exclusively selected if the target drugs were explicitly coded as "suspected drugs" according to the JADER drug classification system, indicating a primary suspected causal relationship by the reporter. Concomitant medications were not included in the primary exposure group. Targeted drugs included anti-MRSA agents (LZD, tedizolid, vancomycin, teicoplanin, daptomycin, and arbekacin). The target adverse event was hyponatremia. Crude reporting odds ratios (cRORs) were first calculated to evaluate the effect of anti-MRSA agents on the onset of drug-associated hyponatremia and detect safety signals. Subsequently, for agents that demonstrated a significant safety signal, additional analyses were conducted to characterize their risk profiles. Specifically, adjusted reporting odds ratios (aRORs) were calculated using a multivariate logistic regression model. For the analysis restricted to LZD-associated reports, the model included age, sex, and body weight as covariates. Then Weibull distribution analysis was used to examine the time to onset profile.

Definitions of Adverse Events Adverse events were defined using the Medical Dictionary for Regulatory Activities, Japanese version (MedDRA) 28.1. Hyponatremia was identified using the standardized MedDRA query 20000141, comprising 32 preferred terms at the time of the study. These terms comprehensively cover specific clinical diagnoses (e.g., "hyponatraemia"), laboratory test abnormalities (e.g., "blood sodium decreased"), and related secondary complications.

Analysis of RORs To calculate the cROR, reports were categorized into four groups based on a case-non-case design: (a) patients who received the target drug and exhibited the target adverse event (hyponatremia); (b) patients who received the target drug and exhibited other adverse events; (c) patients who received other drugs and exhibited the target adverse event; and (d) patients who received other drugs and exhibited other adverse events.

The cROR was calculated as follows:

$$\text{cROR} = (a / b) / (c / d)$$

The 95% confidence interval (CI) was calculated as follows:

$$\exp\left[\log(\text{ROR}) \pm 1.96 \sqrt{(1/a) + (1/b) + (1/c) + (1/d)}\right].$$

A safety signal was detected when the lower limit of the 95% CI of the cROR exceeded 1. RORs were expressed as point estimates with 95% CIs, and data were analyzed using Fisher's exact test to evaluate the statistical significance of the associations in the contingency tables. However, following established pharmacovigilance methodologies, a safety signal was defined based on the disproportionality analysis (lower limit of the 95% CI of the cROR > 1).

Subgroup Analysis by Route of Administration To address potential confounding by indication—specifically the possibility that the severity of the underlying infection (a risk factor for SIADH) might influence the reporting of hyponatremia—a subgroup analysis for LZD was performed. Reports were stratified into three categories based on the route of administration: IV, PO, and unknown/mixed, as recorded in the JADER database. For each subgroup, cRORs and 95% CIs were calculated using the entire dataset, consistent with the primary disproportionality analysis, to evaluate whether the safety signal persisted regardless of the administration route.

Analysis of Demographic Factors and Onset of Adverse Events To identify demographic factors associated with the reporting of hyponatremia associated with the implicated agent, aRORs were calculated using a multivariate logistic regression model, as previously described.[14]

In this model, the following patient characteristics were included as independent variables: sex (female vs. male), age (≥ 70 years vs. 0–69 years), and body weight (< 50 kg vs. ≥ 50 kg). As patient age in the JADER database is recorded in categories by decade (e.g., 20s and 30s) and exact continuous ages are unavailable, patients were dichotomized at 70 years to evaluate the impact of advanced age. Male sex, age 0–69 years, and body weight ≥ 50 kg served as reference categories. Statistical significance was set at $p < 0.05$.

To identify the time of onset of hyponatremia, data with missing administration start dates or adverse event onset dates were excluded. Onset time was calculated as follows:

Time to onset (days) = (date of onset of adverse event) − (date of start of treatment) + 0.5

In cases with multiple dosing start dates, the first date prior to the onset of the adverse event was used. For this analysis, all reported cases with a documented time-to-onset were included without applying an arbitrary cutoff period.

The time to onset was fitted to a Weibull distribution on a cumulative incidence graph by plotting the hazard instead of the survival rate. The Weibull distribution is represented by a scale parameter (α) and a shape parameter (β). The shape parameter β characterizes the onset profile: β = 1 indicates a constant hazard over time; β > 1 indicates an increasing hazard over time; and β < 1 indicates a decreasing hazard over time.[15] Furthermore, to investigate whether the temporal profile differs according to the clinical phase of treatment, descriptive

statistics (median and range) for the time-to-onset were calculated separately for the IV and PO subgroups. Statistical analyses were performed using the JMP Student Edition 18 (SAS Institute Inc., Cary, NC, USA).

Ethics Approval This study was an observational study based on the anonymous open dataset JADER. Therefore, the requirement for ethical approval was waived by the institutional review board.

RESULTS

A total of 992,073 reports from April 2004 to May 2025 were retrieved from the JADER database. In this disproportionality analysis, all eligible reports, including those with missing demographic data, were included to minimize selection bias. Table 1 summarizes the number of hyponatremia cases, other adverse events, and cRORs for anti-MRSA agents (LZD, tedizolid, vancomycin, teicoplanin, daptomycin, and arbekacin). Among these agents, 99 cases of hyponatremia were associated with LZD, while cases associated with other agents were distributed as follows: vancomycin (n = 8), teicoplanin (n = 5), daptomycin (n = 3), arbekacin (n = 2), and tedizolid (n = 0). LZD demonstrated a significant safety signal for hyponatremia (cROR = 10.04; 95% CI, 8.19–12.31).

To evaluate the potential impact of clinical severity, a subgroup analysis for LZD was conducted based on the route of administration using the 99 reported cases (Table 2). Among these, 83 cases were associated with IV administration, 10 cases with PO administration, and 6 cases with unknown or mixed routes. Safety signals were detected in both the IV group (cROR = 15.61; 95% CI, 12.47–19.54) and the PO group (cROR = 3.41; 95% CI, 1.83–6.38). This persistent signal in the PO group suggests an intrinsic risk of LZD-associated hyponatremia, independent of the severe clinical conditions typically requiring IV administration.

Following the detection of these signals, subsequent analyses focused on exploring demographic factors related to LZD-associated hyponatremia. Of the 99 reports, 40 included complete patient background information (age, sex, weight), the date of treatment initiation, and the date of onset of the adverse event. Multivariate logistic regression analysis was performed using a complete case dataset comprising a total of 770 LZD-associated reports, consisting of 40 cases of hyponatremia and 730 non-cases.

Table 3 summarizes the results of the multivariate logistic regression analysis performed with a case-non-case approach. The analysis identified age ≥ 70 years (aROR = 1.73; 95% CI, 1.21–2.47) and female sex (aROR = 1.52; 95% CI, 1.08–2.13)

Table 1. Number of Reported Cases and Crude ROR (95%CI) of Hyponatremia on Linezolid, Tedizolid, Vancomycin, Teicoplanin, Daptomycin, and Arbekacin

	Hyponatremia			
	Cases	Non-cases	Crude ROR	95% CI
Linezolid	99	2218	10.04	8.19-12.31
Tedizolid	0	51	N/A	N/A
Vancomycin	8	3171	1.80	0.90-3.61
Teicoplanin	5	990	0.90	0.37-2.16
Daptomycin	3	673	0.98	0.32-3.06
Arbekacin	2	263	1.68	0.42-6.74
Total (anti-MRSA agents)	117	7366	–	

*Using all cases (992,073 cases) from the JADER dataset from April 2004 to May 2025. Among 4,480 reports of hyponatremia, 117 were associated with anti-MRSA agents. The reporting odds ratio (ROR) and 95% confidence intervals (95% CI) of hyponatremia were calculated for linezolid, tedizolid, vancomycin, teicoplanin, daptomycin, and arbekacin. N/A: not available.

Table 2. Subgroup Analysis of Linezolid-Associated Hyponatremia Based on the Route of Administration

Subgroup	Cases	Non-cases	Crude ROR	95% CI
Overall (linezolid)*	99	2218	10.04	8.19-12.31
Intravenous	83	1193	15.61	12.47-19.54
Oral	10	647	3.41	1.83-6.38
Unknown/Mixed	6	378	–	

* Includes reports with missing demographic data.
The reporting odds ratio (ROR) and 95% confidence intervals (95% CI) of hyponatremia were calculated for linezolid.

Table 3. Multivariate Logistic Regression Analysis of Demographic Factors Associated with the Reporting of Linezolid-Associated Hyponatremia

Demographic factor		aROR (95% CI)*	*P* value
Age (years)			
	< 70	Reference	–
	≥ 70	1.73 (1.21-2.47)	**< 0.001**
Sex			
	Male	Reference	–
	Female	1.52 (1.08-2.13)	**< 0.05**
Body weight (kg)			
	≥ 50	Reference	
	< 50	1.19 (0.85-1.68)	0.31

CI: Confidence interval; aROR: Adjusted reporting odds ratio.
*The analysis was conducted using a complete-case dataset of 770 linezolid-associated reports (comprising 40 cases of hyponatremia and 730 non-cases) that provided complete data for age, sex, and body weight. Statistically significant P values are shown in bold.

as significant demographic factors associated with the reporting of LZD-associated hyponatremia. In contrast, no significant association was observed for body weight < 50 kg (aROR = 1.19; 95% CI, 0.85-1.68).

Furthermore, an analysis of the time to onset was conducted using the foregoing 40 cases of hyponatremia. A Weibull analysis of 40 cases of LZD-associated hyponatremia revealed a shape parameter β of 1.34 (95% CI, 1.09–1.76) and a scale parameter α of 8.12 days (95% CI, 6.35–10.39). A β value > 1 suggests an increasing hazard profile, indicating that the tendency of this adverse event to be reported increases over time with continued administration. The median time to onset was 5.5 days (interquartile range: 4.5–9.5 days) (Fig. 1). When exploring the time-to-onset stratified by administration route, the median time-to-onset for the IV group (n = 36) was 5.5 days (range: 0.5-28.5 days). For the PO group (n = 4), the median time-to-onset was 9.0 days (range: 1.5-11.5 days). Because of the limited number of PO cases with complete temporal data, a robust Weibull distribution analysis to estimate shape parameters for each route independently was not feasible.

DISCUSSION

In the present analysis using the JADER database, a significant safety signal for hyponatremia was observed for LZD, with a cROR of 10.04 (95% CI, 8.19-12.31). In contrast, no significant safety signals were detected for tedizolid, vancomycin, teicoplanin, daptomycin, and arbekacin (non-LZD agents). The clinical importance of these results is supported by the significant reporting signal for hyponatremia associated with LZD therapy, suggesting a pharmacological reporting profile associated with LZD.[13] This reporting profile suggests the need for careful electrolyte monitoring during LZD administration.

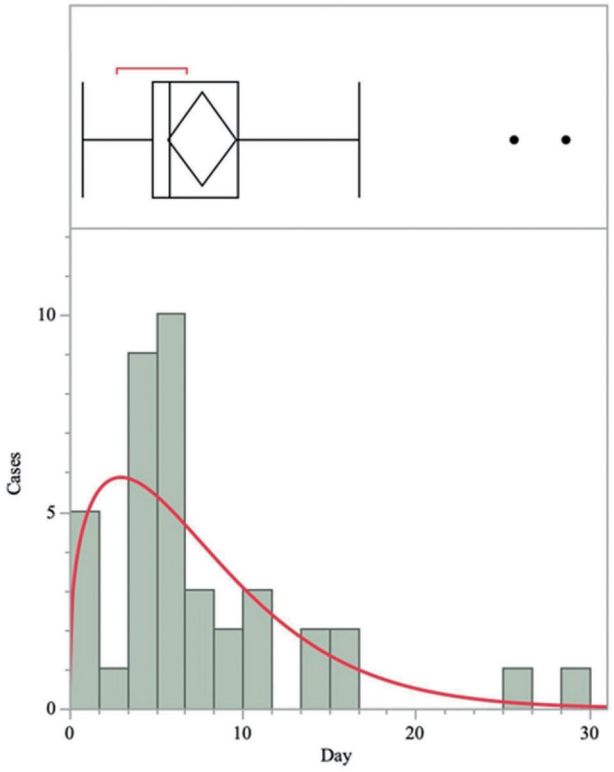

Fig. 1. Weibull Analysis of Hyponatremia by Linezolid (n = 40).

(Top) Box plot including outliers. The median time to onset was 5.5 days (IQR: 4.5–9.5) (Bottom) Histogram and Weibull density curve. α = 8.12 (95% CI: 6.35–10.39), β = 1.34 (95% CI: 1.09–1.76).

The subgroup analysis stratified by administration route provides insights into the relationship between infection severity and the safety signal for LZD-associated hyponatremia. The route of administration can serve as a surrogate marker for clinical severity; intravenous therapy is typically prioritized for critically ill patients with severe infections. In such patients, physiological stress and severe systemic inflammation are known risk factors for the development of SIADH. Therefore, the cROR (15.61) observed in the IV group likely reflects "confounding by indication," where the underlying disease severity contributes significantly to the reporting of hyponatremia. Previous studies have identified several clinical risk factors for LZD-associated hyponatremia;[16,17] however, distinguishing true drug-associated adverse events from SIADH caused by severe underlying infections remains clinically challenging. In this context, a significant safety signal was also observed in the PO group (cROR = 3.41; 95% CI, 1.83–6.38). PO LZD is generally used for patients with less severe infections or as step-down therapy for those in a stable clinical condition. The persistence of the signal in this relatively stable population suggests that LZD-associated hyponatremia may be partially attributable to its pharmacological properties, independent of infection severity. These findings suggest the importance of monitoring serum sodium levels regardless of the administration route or the patient's clinical severity.

Although the exact pharmacological mechanisms underlying LZD-associated hyponatremia remain to be fully elucidated, accumulated evidence suggests the involvement of SIADH.[8] Previous reports have documented cases of severe electrolyte disturbances attributable to LZD-associated SIADH, occasionally presenting as a rare triad with hypoglycemia and bone marrow suppression in older patients.[8,9] It has been hypothesized that LZD or its active metabolites may stimulate the secretion of antidiuretic hormones or enhance the sensitivity of the renal collecting ducts to antidiuretic hormone, thereby promoting excessive water reabsorption and leading to dilutional hyponatremia.

Regarding the temporal profile, the median time to onset was 5.5 days. In the time-to-onset analysis, the Weibull shape parameter (β) for LZD-associated hyponatremia was 1.34 (95% CI: 1.09–1.76). Since the lower limit of the 95% CI is greater than 1, this indicates an increasing hazard profile over time,[15] suggesting that the hazard of developing hyponatremia increases during continuous LZD administration. In the clinical context of LZD therapy, this increasing hazard reflects a cumulative exposure risk within the typical 10-to-14-day acute treatment window, where the hazard increases rapidly following continuous administration. Similar to LZD-associated thrombocytopenia, which typically manifests after 7–10 days of continuous therapy,[10,18] progressive accumulation of LZD may exacerbate SIADH, culminating in clinical hyponatremia. Therefore, these findings suggest the importance of careful serum sodium monitoring from the first week of LZD therapy, particularly between days 4 and 10. Furthermore, the descriptive analysis stratified by route showed a median time-to-onset of 5.5 days for the IV group and 9.0 days for the PO group. Clinically, PO LZD is often utilized as step-down therapy

after initial IV treatment. If hyponatremia is primarily driven by cumulative LZD exposure, patients switched to PO therapy might present with delayed adverse events during the outpatient phase. While these limited observations raise the hypothesis that extended monitoring might be beneficial after transitioning to PO therapy, the extremely small sample size (n = 4) precludes any definitive clinical recommendations. Further longitudinal studies are needed to elucidate these temporal differences.

The multivariate logistic regression analysis identified advanced age (≥ 70 years; aROR, 1.73) and female sex (aROR, 1.52) as demographic factors associated with the reporting. However, it should be noted that due to the inherent limitations of spontaneous reporting databases like JADER, full adjustment for critical confounding factors such as concurrent use of high-risk medications (e.g., diuretics), daily fluid intake, or the severity of the underlying disease was not possible. These demographic vulnerabilities can be explained by physiological changes in body fluid homeostasis. Aging is associated with a progressive decline in renal function and a reduction in skeletal muscle mass, which serves as the primary reservoir of total body water. Likewise, females typically possess a lower proportion of body water than males.[19] Thus, both advanced age and female sex inherently reduce endogenous water storage capacity, rendering these populations more susceptible to fluid shifts. Furthermore, although low body weight (< 50 kg) did not reach statistical significance, it showed a trend toward an association with reporting. Because LZD is typically administered at a fixed standard dose (1200 mg/day), individuals with low body weight may be more susceptible to relative drug overexposure, potentially exacerbating dose-dependent toxicity.[20]

Regarding other anti-MRSA agents, vancomycin exhibited a lower cROR for hyponatremia (0.39). This inverse signal does not necessarily imply a protective biological effect; rather, it may be primarily attributable to the "masking effect," a well-known reporting bias inherent to spontaneous reporting systems, where reports of severe adverse events frequently associated with vancomycin (e.g., acute kidney injury) mathematically suppress the relative reporting proportion of other events like hyponatremia.[21] Therefore, hyponatremia reported in cases involving non-LZD agents may reflect the clinical background of MRSA infections, such as infection-induced SIADH, rather than a direct drug-induced effect.

Although tedizolid belongs to the same oxazolidinone class, no safety signals for hyponatremia were detected. This discrepancy was likely attributable to the limited number of adverse event reports for tedizolid in our dataset (n = 51), rendering the analysis underpowered to detect true safety signals. Furthermore, while LZD is often administered for 10 to 14 days or longer, tedizolid is typically prescribed for a shorter duration of 6 days.[22] Given that hyponatremia in this study exhibited a cumulative reporting profile, the relatively short administration period of tedizolid may be insufficient for this adverse event to manifest clinically. Furthermore, pharmacodynamic and pharmacokinetic differences between these two oxazolidinones may biologically contribute to the differential risk of hyponatremia. LZD acts as a weak, reversible monoamine oxidase (MAO) inhibitor, potentially enhancing serotonergic activity in the central nervous system.[23] Because serotonin is a known secretagogue for antidiuretic hormone, LZD-induced MAO inhibition may mechanistically promote SIADH.[8,24] Conversely, tedizolid exhibits negligible MAO inhibition at standard clinical doses.[25] Additionally, LZD has relatively lower plasma protein binding (approximately 31%) compared to tedizolid (70–90%), yielding a higher unbound fraction that readily crosses the blood-brain barrier.[26] This high central nervous system exposure could facilitate direct interactions with the hypothalamic-pituitary axis. These pharmacological distinctions, combined with the shorter treatment duration, might explain the absence of a safety signal for tedizolid.

This study has several limitations. First, because the JADER database relies on spontaneous reporting, it is susceptible to biases, including underreporting and the Weber effect, precluding calculation of true incidence rates.[21] Second, the case-non-case design estimates disproportionality rather than true epidemiological risk or causal associations.[27] Third, residual confounding from factors such as concurrent use of high-risk medications or daily fluid intake could not be fully addressed.[28] Finally, owing to database privacy specifications, demographic variables such as body weight are categorized (e.g., in 10-kg increments), which may introduce data uncertainty.[14,29] Therefore, our findings should be considered hypothesis-generating, and further prospective clinical studies are warranted to validate these results.

In conclusion, this pharmacovigilance analysis using the JADER database characterized the specific reporting profile of LZD-associated hyponatremia. Advanced age (≥ 70 years) and female sex were identified as demographic factors associated with the reporting. Temporal analysis revealed an increasing hazard profile, with a median time to onset of 5.5 days. Taken together, these hypothesis-generating findings may support careful serum sodium monitoring from the first week of LZD therapy, particularly in older and female populations.

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Conflict of interest The authors declare no conflict of interest.

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