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ORIGINAL ARTICLE

Venous thromboembolism treatment outcomes in cancer patients and effect of third-party payers on anticoagulant choice

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Abstract
Purpose The purpose of this study is to compare the rates of recurrent VTE among cancer patients treated with parenteral agents to the oral anticoagulants.
Methods This single-center study was a retrospective chart review of cancer patients with recurrent VTE between January 1, 2009 and December 31, 2014. The primary outcome of the study is the rate of recurrent VTE in patients who received a parenteral anticoagulant (enoxaparin, dalteparin, fondaparinux) versus those who received oral anticoagulants (warfarin and rivaroxaban). Other outcomes investigated include risk factors associated with recurrent VTE events and influence of third-party payer on anticoagulant selection.
Results Four hundred fifty-seven patients met inclusion criteria (178 in the oral anticoagulant group and 279 in the parenteral anticoagulant group). Patients with Medicare were more likely to have received an oral anticoagulant ($P = 0.003$) and patients with private insurance were more likely to have received a parenteral anticoagulant ($P = 0.004$). There were 23 recurrent VTE events, 12 events (6.7 %) in the oral anticoagulant group and 11 events (3.94 %) in the parenteral group ($P = 0.182$). The only significant risk factor noted to increase risk of recurrent VTE was the presence of an IVC filter (adjusted OR 4.38, 95 % CI 1.67–11.53, $P = 0.003$).
Conclusions While there is no statistical difference in VTE events between groups, the oral anticoagulant group numerically had a higher rate. Important associations were found to have an influence on anticoagulant selection and risk of recurrent VTE. These factors must be incorporated into decision making when treating cancer patients with VTE.

Keywords Cancer-associated venous thromboembolism · Anticoagulation management · Warfarin · Low molecular weight heparin · Third-party payer

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Introduction

Cancer is a prothrombotic state resulting in both venous and arterial vascular events. The incidence of venous thromboembolism (VTE) is greater in cancer patients compared to those without cancer with the estimated risk ranging from 13 per 1000 person-years to 68 per 1000 person-years depending on disease- and patient-specific risk factors [1]. Venous thrombosis is the second leading cause of death in patients receiving outpatient chemotherapy and is associated with a twofold increased risk of mortality compared to cancer patients without VTE [2, 3].

Cancer-related factors, treatment-related factors, and patient-related factors all contribute to VTE risk. Specific cancer types, higher-grade tumors, and metastatic disease

increase the risk of clotting events [4]. Treatment-related risk factors include surgery, hospitalizations, chemotherapy, anti-angiogenic therapy, and immunomodulatory agents (thalidomide/lenalidomide), hormonal agents, erythropoiesis-stimulating agents, and central venous devices [4]. Age, comorbidities, obesity, decreased performance status, and other prothrombotic states are patient-related factors that also increase thrombosis [4].

Prophylaxis is the major mechanism of preventing cancer-associated VTE. The American Society of Clinical Oncology Practice (ASCO) guidelines recommend thromboprophylaxis in hospitalized cancer patients, patients receiving certain chemotherapy agents, and patients undergoing major surgery. However, routine prophylaxis is not recommended for ambulatory cancer patients [5]. When thrombosis occurs, anticoagulation is usually indicated. Cancer patients have an increased risk of recurrent thrombosis and anticoagulation-related bleeding compared to patients without cancer [6]. The ASCO guidelines recommend treatment with low molecular weight heparin (LMWH) instead of unfractionated heparin and vitamin K antagonists for at least 6 months [5]. After 6 months, long-term anticoagulation may be considered in patients with active cancer, metastatic disease, or patients receiving chemotherapy [5]. A Cochrane review comparing patients receiving chronic thromboembolism treatment with LMWH versus oral anticoagulants found that there were no major differences in bleeding, thrombocytopenia, or survival outcomes between the two therapy options [7]. However, VTE recurrence was significantly lower with patients receiving LMWH [7]. The analysis concluded that patient preference and value should also be included when evaluating anticoagulation options [7]. Interestingly, Noble and colleagues evaluated the role patient preference in the management of VTE in cancer patients. They found that patients were more concerned with anticoagulant interference with their cancer treatment, efficacy of the VTE treatment, and the risk of bleeding than they were with administration, frequency, or monitoring of the VTE treatment. This demonstrates a general preference towards the safest and efficacious treatment, regardless of the route of administration is more important to patients [8].

While LMWHs seem like the ideal agent to prevent recurrence, they are not without complications. Low molecular weight heparin provides quick therapeutic anticoagulation and does not require frequent monitoring. Treatment with LMWH usually involves once or twice daily injections, which can be inconvenient for the patient and cause localized adverse effects like pain, erythema, ecchymosis, and hematoma [9], although there is qualitative evidence that suggests that adverse effects associated with injections are considered acceptable compared to the frequent laboratory monitoring requirements of warfarin and poor quality of life associated with symptomatic VTE [10, 11]. Renal dysfunction and heparin-induced thrombocytopenia can also limit the use of LMWH in some patients. Lastly, it is important to recognize the cost-prohibitive nature of brand and generic LMWH agents, as these agents are not always covered by third-party payers and there are few patient assistance programs available [9].

There are various advantages and disadvantages to the oral anticoagulants. Warfarin is an inexpensive, once daily oral therapy that is complicated by a narrow therapeutic index, frequent monitoring requirements, drug and dietary interactions, and extensive interpatient dosing variability. Rose et al. showed that cancer patients on warfarin spent more time outside of the therapeutic international normalized ratio (INR) range and had more variable INRs than patients without cancer [9, 12]. Many prescribers may continue to choose warfarin over LMWHs despite warfarin's inferiority for patients who cannot afford LMWH or prefer an oral therapy.

The direct-acting oral anticoagulants (DOACs), like dabigatran, rivaroxaban, and apixaban, are relatively new oral agents being used to treat VTE. The DOAC agents lack the frequent monitoring requirements and drug and dietary interactions that are problematic with warfarin. However, unlike warfarin, there are few currently available targeted antidotes for treating bleeding events [13]. Utilizing DOAC agents to treat thromboembolism in cancer patients is limited due to the small populations of cancer patients in the studies [14–17]. These DOAC studies only compared DOACs to warfarin and not to LMWH, which the inferiority of warfarin to LMWH has already been established for cancer patients [14, 17–19]. Based on this issue, ASCO guidelines and the American College of Chest Physicians guidelines for VTE do not support DOACs as a first-line therapy due to the insufficient evidence available for cancer patients [5, 9]. Despite these uncertainties, prescribers may utilize DOACs to treat thrombosis in cancer patients due to the convenience and the availability of patient cost-assistance programs.

At the UT Southwestern Medical Center William P. Clements Jr. University Hospital (UTSW), prescribers have utilized LMWH, warfarin, or DOAC agents (mainly rivaroxaban) for VTE treatment in cancer patients. We conducted a retrospective evaluation of recurrent VTE events in cancer patients utilizing these various anticoagulants over a 6-year period.

Methods

Study design This retrospective study was conducted by chart review at UTSW on patients who met inclusion criteria between January 1, 2009 and December 31, 2014 and was approved by the UTSW Institutional Review Board. This study included patients 18 years and older with active cancer who had a newly diagnosed deep vein thrombosis (DVT), pulmonary embolism (PE), or both confirmed by computerized

tomography (CT), magnetic resonance imaging (MRI), ultrasonography, nuclear imaging, or angiography. Patients anticoagulated with warfarin, rivaroxaban, enoxaparin, dalteparin, or fondaparinux were evaluated for recurrent VTE events. While fondaparinux is a factor Xa inhibitor, it was grouped with LMWH agents due to its use as a parenteral agent. Exclusion criteria included patients without anticoagulation treatment for the thrombotic event, patients without at least one follow-up visit post-initiation of their anticoagulant therapy, patients diagnosed with another hypercoaguable state, multiple myeloma, basal-cell or squamous-cell carcinomas of the skin, and patients who are pregnant or incarcerated.

Data collection For all patients meeting inclusion criteria, data was collected on demographics, type of cancer and site, type of initial VTE and date of occurrence, initial anticoagulant received, type of recurrent VTE and date of occurrence, anticoagulant utilized after recurrence, compliance with anticoagulant at time of recurrent event (defined as a physician-documented compliance issue), and international normalized ratio (INR) or anti-Xa level at time of recurrent event. Additionally, information on smoker status, hormonal therapy utilization (selective estrogen receptor modulators, SERM), presence of an inferior vena cava (IVC) filter, fatal bleeding or fatal thrombotic events, and third-party payer was collected. Fatal bleeding or thrombotic events were defined as contributing to death if listed as a contributing diagnosis on inpatient death discharge summary.

Outcome measures The primary outcomes evaluated the rate of recurrent VTE events with oral anticoagulants versus parenteral agents. Observational analyses evaluated the relationships of third-party payer relationship to anticoagulant choice and risk factors for recurrent events. Examination of the physician-documented compliance issues, INR and anti-Xa levels at the time of recurrence, time to recurrent event, fatal bleeding and thrombotic events, and rates of recurrence with rivaroxaban alone were also included.

Statistical analysis Based on the results of the CLOT trial, we anticipated needing 552 patients (276 in each group) to achieve a power of 0.80 and a two-sided alpha of 0.5. Sample demographics were summarized as mean (standard deviation) or frequency (percentage) and compared between anticoagulant groups: oral anticoagulant versus parenteral anticoagulant. A *T* test was utilized for continuous variables and chi-squared test for categorical variables. Risk factors for recurrent VTE were analyzed by unadjusted odds ratios (OR) and adjusted odds ratios using logistic regression. Categories not showing any recurrent VTE were removed from the logistic regression: patients <30 or >90 years old, patients with cancer of the brain, skin, or "other" sites, and patients with no insurance information available. All statistical analyses were performed with Stata 13.1 (StataCorp, College Station, TX).

Results

Enrollment & baseline characteristics Nine hundred forty patient charts were reviewed with 457 patients meeting inclusion criteria (178 in the oral anticoagulant group and 279 in the parenteral anticoagulant group) as shown in Fig. 1. The included population had an average age of 63 years, 50 % were male, 13 % were smokers, and 94 % had medical insurance. Forty-eight percent of the study group had a DVT, 40 % had a PE, and 12 % had both a PE and a DVT. Two hundred seventy-five patients received enoxaparin, 170 patients utilized warfarin, 8 patients received rivaroxaban, and 2 patients each received dalteparin and fondaparinux as their anticoagulation therapy. Baseline characteristics were mostly similar between groups (Table 1). The distributions of cancer sites among patients and the insurance type were significantly different between oral and parenteral groups. Patients with gastrointestinal (GI) or lung cancers were significantly more likely to receive a parenteral agent than an oral anticoagulant. These differences are likely to reflect avoidance of absorption or metabolism issues in patients with GI/hepatic cancers and also may reflect specific provider influence. When examining insurance type, Medicare patients were significantly more likely to utilize an oral anticoagulant (60.7 versus 46.2 %, $P = 0.003$) and patients with private insurance were more likely to utilize a parenteral agent (45.5 versus 32 %, $P = 0.004$). Selective estrogen receptor modulator utilization was also significantly higher for oral anticoagulant patients (9.8 versus 3.4 %, $P = 0.045$), although this was a small proportion of patients overall.

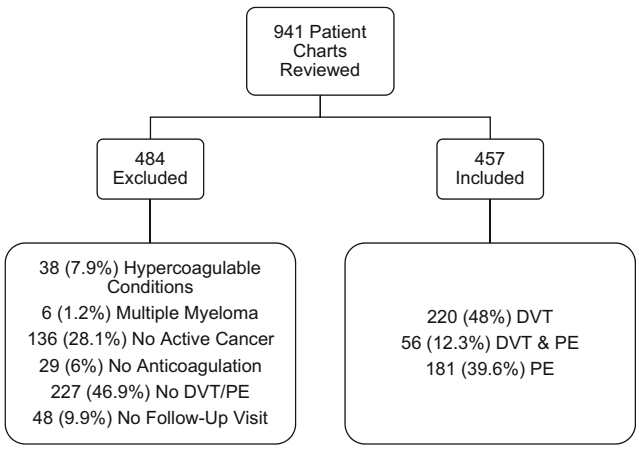

Fig. 1 Inclusion & exclusion summary

Table 1 Baseline characteristics

Characteristic	Oral anticoagulant (n = 178)	Parenteral agent (n = 279)	P value
Age (years), mean (SD)	64.1 (14.9)	61.6 (12.6)	0.063
Gender, n (%)			0.146
Female	82 (46.1)	148 (53.1)	
Male	96 (53.9)	131 (47)	
Cancer site, n (%)			0.027
Brain	9 (5.1)	9 (3.2)	0.327
Breast	25 (14)	29 (10.4)	0.238
GI	28 (15.7)	69 (24.7)	0.022
GU	50 (28.1)	74 (26.5)	0.713
H&N	17 (9.6)	25 (9)	0.831
Lung	19 (10.7)	50 (17.9)	0.035
Hematologic	16 (9)	13 (4.7)	0.064
Skin	6 (3.4)	5 (1.8)	0.090
Other	8 (4.5)	5 (1.8)	0.283
SERM use, n (%)	8 (9.8)	5 (3.4)	0.045
IVC filter present, n (%)	27 (15.2)	38 (13.6)	0.644
Smoker, n (%)	22 (12.4)	39 (14)	0.620
Insurance type, n (%)			0.019
Not available/none	8 (4.5)	17 (6.1)	0.464
Private insurance	57 (32)	127 (45.5)	0.004
Medicare	108 (60.7)	129 (46.2)	0.003
Medicaid	5 (2.8)	6 (2.2)	0.654

T test utilized for continuous variables, chi-squared test for categorical variables

GI gastrointestinal, *GU* genitourinary, *SERM* selective estrogen receptor modulator, *IVC* inferior vena cava

Efficacy outcomes & risk factor analysis There were 23 (5 %) recurrent VTE events in the study group. The percentage of recurrent VTE was not statistically different between oral (6.7 %) and parenteral (3.9 %) anticoagulants (Table 2, adjusted OR 0.54, 95 % CI 0.22–1.33, P = 0.181). A logistic regression was conducted to evaluate risk factors that may influence thrombotic recurrence. As seen in Table 3, of these risk factors, only the presence of an IVC filter significantly increased the risk of a recurrent event, (adjusted OR 4.38, 95 % CI 1.67–11.53, P = 0.003). No statistical difference was found for the other risk factors evaluated: selective estrogen receptor modulator use (adjusted OR 2.23, 95 % CI 0.18–28.44, P = 0.536), smoking status (adjusted OR 0.48, 95 % CI 0.1–2.26, P = 0.354), and insurance category (adjusted OR 0.81, 95 % CI 0.28–2.38, P = 0.706). Interestingly, the median time to second event suggests patients in the parenteral group fail treatment sooner than oral group (median of 72 versus 106.5 days), although this difference was not statistically significant.

Anticoagulation treatment & compliance There were no recurrent events with rivaroxaban-treated patients. In the warfarin-treated patients with recurrent events, there were four patients with subtherapeutic INRs, four with supratherapeutic INRs, and three therapeutic INRs, and one unknown INR at the time of the event (median INR 2.6, range 1.2–5.9). In the parenteral group, two patients were subtherapeutic, two were supratherapeutic, and two were therapeutic for the anti-Xa level at the time of the event (median anti-Xa 0.7, range 0.39–1.32). Five patients did not have an anti-Xa level drawn upon admission.

Of the patients with recurrent events, compliance was noted by the inpatient physician to be an issue in five of the parenteral group compared to none in the oral group

Table 2 Recurrent event analysis

Outcome	Oral anticoagulant	Parenteral anticoagulant	P value
Recurrent VTE, n (%)	12 (6.7)	11 (3.9)	0.181
Time to recurrent event, median days (IQR)	106.5 (41–332)	72 (33–164)	0.220

Table 3 Unadjusted and adjusted risk factors for recurrent events analysis

			Unadjusted		Adjusted		
Risk factor Analyzed	*N*	Events, *n* (%)	OR	95 % CI	OR	95 % CI	*P* value
Age category (years)							
30–49	64	4 (6.3)	–		–		
50–69	233	12 (5.2)	0.81	0.25–2.61	0.60	0.16–2.22	0.442
70–89	147	7 (4.8)	0.75	0.21–2.66	0.47	0.1–2.25	0.341
Sex							
Female	230	12 (5.2)	–		–		
Male	227	11 (4.9)	0.92	0.40–2.14	0.88	0.34–2.3	0.800
SERM use							
No	444	22 (5)	–		–		
Yes	13	1 (7.7)	1.60	0.04–11.70	2.23	0.18–28.44	0.536
IVC filter present							
No	392	14 (3.6)	–		–		
Yes	65	9 (13.9)	4.34	1.57–11.31	4.38	1.67–11.53	0.003
Smoker							
No	396	21 (5.3)	–		–		
Yes	61	2 (3.3)	0.60	0.07–2.59	0.48	0.1–2.26	0.354
Insurance							
Private insurance	184	10 (5.4)	–		–		
Medicare	237	12 (5.1)	0.93	0.39–2.20	0.81	0.28–2.38	0.706
Medicaid	11	1 (9.1)	1.74	0.20–14.90	2.80	0.26–29.84	0.394

Adjusted OR were calculated using multivariate logistic regression analysis; patients <30 or >90 years old and patients with no insurance information were not included in the analysis since they did not present recurrent events

OR odds ratio, *95 % CI* 95 % confidence interval for each odds ratio, *P* chi-squared test of significance for each factor

(P = 0.008). Of the five non-compliant patients, two were reported to have had issues affording the parenteral agent, one patient had switched to once daily dosing due to issues with the injection, and two reported having missed or delayed doses. One of the patients that was unable to afford the parenteral anticoagulant died during their admission for the second event. Only two out of the five patients that were non-compliant had anti-Xa levels available (one therapeutic level and one subtherapeutic).

Fatal adverse events There were four thrombotic events and one bleeding event that were listed as contributory diagnoses on the inpatient death summary. Two of these fatal events occurred in the oral anticoagulant group (one bleeding, one thrombotic), whereas three fatal thrombotic events occurred in the parenteral group. Of the thrombotic events, two patients were supposed to be receiving anticoagulation, whereas the other two thrombotic events had already completed a specific duration of therapy and had been off anticoagulation therapy. One patient with a thrombotic event was supposed to be taking enoxaparin but could not afford the agent and had stopped therapy and no anti-Xa level was available for this patient. The second patient was utilizing enoxaparin and the anti-Xa level was subtherapeutic at 0.04. For the one fatal bleeding event, the patient had a supratherapeutic INR at 4.1 and died from a large hemothorax.

Discussion

A 2013 National Health Interview Survey found that to save money, 8 % of adults did not take their medication as prescribed and 15 % asked their doctor for a lower-cost medication [20]. Those over 65 years of age were twice as likely to not take a medication as prescribed to save money [20]. Our study results indicate that Medicare patients are significantly more likely to utilize an oral anticoagulant than a parenteral anticoagulant, despite the clinical trial and guideline recommendations that support utilization of LMWHs for cancer-associated VTE. Medicare patients are typically patients with fixed incomes that are unable to afford the high out-of-pocket costs of parenteral agents. Patients with private insurance were more likely to utilize a parenteral agent. This reflects an association between insurance type and anticoagulant choice. With the increased risk of recurrent events in cancer patients, it is imperative that they are

able to afford their anticoagulant. Additionally, it is important that the most affordable anticoagulant for the patient is also effective in treating and preventing recurrent events.

Our study showed that parenteral agents have reduced rates of recurrent events compared to oral anticoagulants. However, these results were not statistically significant due to lack of power. These results are similar to the large, prospective CATCH trial conducted by Lee et al. comparing tinzaparin versus warfarin for the treatment of VTE in cancer patients [21]. Lee et al. demonstrated that recurrent events were lower with tinzaparin compared with warfarin; however, these results were not statistically significant (HR 0.65, 95 % CI 0.41–1.03, $P = 0.07$), likely due to a lower than expected recurrence rate that reduced the trial's power [21]. Tinzaparin was also associated with significantly reduced non-major bleeding events compared to warfarin [21]. In contrast, the CLOT trial comparing dalteparin with warfarin for secondary prophylaxis of VTE showed recurrent VTE was reduced by 52 % in the dalteparin group (HR 0.48, $P = 0.002$) [18]. The CLOT trial also demonstrated no significant differences in bleeding rates between dalteparin and warfarin [18]. The differences in outcomes between the CATCH and CLOT trials are likely due to differences in thrombotic risks between the patient populations, in administration of the anticoagulants, and in design of the trials. The rate of recurrent events in our study was lower than both the CATCH and CLOT trials. This is likely due to the retrospective, single-center nature of the study, as patients could have had recurrent events not documented in the UTSW medical record. The previously mentioned Cochrane analysis shows results consistent with that of CLOT trial, although the CLOT trial was the largest study included in this analysis [7]. It is also important to note that none of these trials have shown a beneficial effect on mortality with utilizing LMWH over the oral anticoagulants [7, 18, 21]. Overall, our trial and the CATCH trial showed numerically lower recurrent events with LMWH which provides further evidence for its use as a preferred treatment. This, again, is problematic as Medicare patients were less likely to receive LMWH treatment.

An interesting aspect found in this study was that IVC filter placement was significantly associated with VTE recurrence. Imberti et al. showed cancer patients are about two times more likely to have an IVC filter placed than those without malignancy (7.3 % with cancer versus 4.1 % without cancer, OR 1.83, 95 % CI 1.15–2.90, $P = 0.005$) [6]. Prior studies have found that while IVC filters may decrease rates of PE, DVT rates increase, and there is no benefit on overall survival [22]. Multiple studies have found that there may be limited benefit in patients with advanced stage malignancies due to the limited impact of IVC filters on mortality, and IVC filters may negatively impact quality of life [23–25]. Therefore, it is important for providers to account for expected life-span and quality of life of cancer patients before placing an IVC filter.

Another unusual observation was that recurrence rates were not always accompanied by subtherapeutic levels. Recurrent events occurred in relatively similar frequency in subtherapeutic, supratherapeutic, and therapeutic patients. Therefore, other confounding factors are likely to be contributing to recurrent events. While it is unlikely that all the oral anticoagulant patients were compliant, physician-documented non-compliance was only noted to be problematic in the parenteral therapy group and may have contributed to recurrent events in this group. Physicians documented issues with affordability, dosing, and injections to be the main causes of patient non-compliance in the parenteral group. These observations further support the need for affordable anticoagulation for the treatment of VTE in cancer patients.

Only eight patients in the study utilized rivaroxaban. The low utilization of rivaroxaban was likely due to the time frame that the study included (rivaroxaban was not approved for treatment of VTE until 2012) and that guidelines do not yet recommend these agents for cancer patients. None of the rivaroxaban patients had recurrent events during the study period. While this is a small population overall, the information is important as many patients request an oral therapy that requires little monitoring. Further research needs to be conducted on patients utilizing these agents and their rates of recurrent events.

The results of our study must be interpreted carefully due to the inherent limitations of a retrospective chart review. With the smaller than expected rates of recurrence and the small population size, the study did not meet statistical power. While we collected multiple confounding variables such as age, compliance, treatment with hormonal therapy, tobacco use, and site of cancer, there are multiple potential confounding factors not evaluated in this study. Additionally, our study included varying rates of follow-up time. Included patients were only required to have one follow-up visit after their initial VTE event. The varied follow-up rate contributed to the unexpectedly low recurrence rates as patients may have had recurrent events outside the UTSW system or patients died fairly soon after their initial event. Lastly, our study only examined fatal bleeding and thrombotic events, whereas CATCH and CLOT trials looked at major and minor bleeding risks. Since tinzaparin showed reduced non-major bleeding rates in CATCH trial, it is possible that LMWH may be a safer agent.

Conclusions

Patients with cancer are at a significantly increased rate of morbidity and mortality when VTE events occur. Effective

anticoagulation will help reduce rates of recurrent VTE in this high-risk population. While no statistically significant differences in recurrence rates were found between oral and parenteral agents utilized in cancer-associated VTE, patients utilizing oral anticoagulants had a numerically higher recurrence rate. Ideally, insurance providers should provide coverage for the most efficacious agent for the treatment of cancer-associated VTE. However, this study showed Medicare patients were significantly more likely to receive an oral anticoagulant rather than a LMWH. Other risk factors for thrombosis, concerns about compliance, and bleeding risks should be weighed when deciding on an appropriate anticoagulant choice for a cancer patient. With the higher cost of LMWH therapy, it is imperative to ensure the patient is able to afford the therapy long term and can maintain compliance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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