The Role of Combined ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT in the Management of Patients with Pancreatic Neuroendocrine Tumors

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Key Words

Neuroendocrine neoplasm · Pancreatic neuroendocrine tumor · Positron emission tomography · ^{68}Ga · ^{18}F FDG

Abstract

Purpose: The aim of this study was to evaluate the effect of combined ^{68}Ga and ^{18}F -FDG PET/CT on treatment management for patients with pancreatic neuroendocrine tumor (PNET). **Methods:** Between January 2012 and April 2014, 49 consecutive patients with a cytologically and/or histologically proven diagnosis of PNET underwent combined ^{68}Ga and ^{18}F FDG PET/CT on the same day. **Results:** The study group consisted of 21 males and 28 females with a median age of 59 years. Disease detection was achieved in 48 out of the 49 cases with ^{68}Ga imaging, and in 36 of the 49 cases with ^{18}F FDG PET/CT. These results corresponded to sensitivities of 98% for ^{68}Ga versus 73% for ^{18}F FDG PET/CT. Patients with NET-G1/NET-G2 had a positive ^{68}Ga and negative ^{18}F FDG PET/CT in 13 cases, whereas both ^{68}Ga and ^{18}F FDG PET/CT were positive in 27 cases. Patients with NEC-G3 were positive by both ^{68}Ga and ^{18}F FDG PET/CT in 7 cases and positive only by ^{18}F FDG in 1 case. Another NEC-G3 patient was only positive by ^{68}Ga PET/CT. The median Ki67 was 7% for ^{68}Ga PET/CT-positive tumors and 10% for tumors with both ^{68}Ga and ^{18}F FDG PET/CT positivity ($p = 0.130$). Half of the patients with a prevalent uptake of ^{18}F FDG ($n = 7$) had an NEC-G3 compared with 12% of pa-

tients with a prevalent uptake of ^{68}Ga ($p = 0.012$). There were no significant differences between patients with positive ^{68}Ga and those with positive ^{18}F FDG with regards to treatment choice. **Conclusions:** The association of ^{18}F FDG slightly increases sensitivity of ^{68}Ga PET/CT alone in the diagnosis of PNET. A combined dual tracer PET/CT does not influence the choice of treatment strategy.

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Introduction

Pancreatic neuroendocrine tumors (PNETs) comprise a wide and heterogeneous group of neoplasms. Diagnosis can often be challenging due to their rarity. The treatment strategy should be adapted to each single patient according to the tumor characteristics and patient comorbidities [1]. ^{68}Ga PET/CT is becoming the new gold standard for somatostatin receptor imaging of PNET. The sensitivity of this technique varies between 91 and 95% with a specificity of 82–97% [2]. ^{68}Ga -labeled octreotide has several advantages. Firstly, ^{68}Ga is a generator product instead of a cyclotron-produced product and a relatively simple labeling can be performed on an everyday basis [3]. Secondly, ^{68}Ga octreotide is similar to its counterparts that are used for peptide receptor radionuclide therapy (PRRT). Lastly, PET imaging has an accuracy of 2–3 mm

with a consequent high sensitivity [4]. On the other hand, ^{18}F FDG PET is the most widely used functional imaging for cancer in general. It has been demonstrated in patients affected by NET that ^{18}F FDG PET has a high accuracy for poorly differentiated forms despite a relatively low overall sensitivity for these tumors [5, 6]. Dual tracer PET/CT can be performed on a single day owing to the short half-life of ^{68}Ga and can be superior to histopathology by demonstrating tumor heterogeneity, especially for patients with multiple metastases [7]. Only a handful of studies have explored the value of combined ^{68}Ga and ^{18}F FDG PET/CT for PNET [7, 8]. Theoretically, a more accurate functional mapping of these lesions with demonstration of different areas of uptake could select tumors to proper therapeutic groups. Although it has been demonstrated that routine execution of ^{68}Ga PET/CT in patients with PNET causes a therapy modification in almost 50% of cases [9], the clinical impact of combined ^{68}Ga and ^{18}F FDG PET/CT and its role in the treatment strategy is scarcely known. The aims of the current study were: (1) to evaluate the influence of combined ^{68}Ga and ^{18}F FDG PET/CT on treatment management for patients with cytologically or histologically proven PNET, and (2) to analyze the correlation between uptake of dual tracers and tumor grade.

Methods

This was a retrospective, bi-institutional observational study carried out at the University of Marche, Ancona, and University 'La Sapienza', Rome, Italy. Between March 2012 and April 2014, all consecutive patients with cytologically or histologically proven PNET underwent combined ^{68}Ga and ^{18}F FDG PET/CT. The inclusion criteria were the presence of a cytologically or histologically proven PNET and age >18 years. The only exclusion criterion was the inability to provide written informed consent. The routine use of combined ^{68}Ga and ^{18}F FDG PET/CT was introduced in order to demonstrate tumor heterogeneity and to possibly change the management strategy according to the available evidence [7]. Ethical committee approval was waived because of the retrospective nature of the study according to the regulations of the involved institutions. Demographics, presenting symptoms and radiological findings were prospectively collected. All patients underwent at least one high-resolution imaging technique (CT or MR). A suspected diagnosis of PNET was made in the presence of a hypervascularized mass of the pancreas. Patients underwent PET/CT imaging after a cytological/histological diagnosis was obtained. A routine evaluation of chromogranin A and/or other tumor markers was not considered.

Pathological Evaluation

All patients with a localized pancreatic mass underwent endoscopic ultrasound with fine-needle aspiration. Patients with a pancreatic mass and liver metastases underwent ultrasound-guided liver biopsy. For patients who underwent surgery, a final patho-

logical examination on a surgical specimen was carried out. The diagnosis of PNET was based on cytological or histological findings and immunochemistry, which was performed for all tumors for chromogranin A, synaptophysin and CD56. All cases were classified according to criteria proposed by the World Health Organization [10] and were assigned to a TNM (tumor-node-metastasis)-based staging system according to Rindi et al. [11]. The Ki67 proliferative index was expressed as a percentage based on the count of Ki67-positive cells in tumor cells in the areas of highest immunostaining using the MIB1 antibody (DBA, Milan, Italy). Tumors were then classified into three categories: PNET-G1 (Ki67 $\leq 2\%$), PNET-G2 (Ki67 between 2 and 20%) and PNET-G3 (Ki67 >20%).

Treatment

After diagnostic work-up was concluded, all cases were discussed during a multidisciplinary team meeting held at the two involved institutions. A specific treatment protocol based on dual ^{68}Ga and ^{18}F FDG PET/CT findings was not included. Generally, the treatment strategy was chosen according to the latest European Neuroendocrine Tumor Society (ENETS) guidelines [12]. Briefly, surgical exploration was always indicated in the presence of localized PNET >2 cm or in the presence of symptoms. For PNET with liver metastases, a possible surgical approach was evaluated for each individual patient. Surgery was always contraindicated in the presence of: (i) severe patient comorbidities, (ii) extra-abdominal disease and (iii) diffuse peritoneal carcinomatosis. Somatostatin receptor-targeted therapies were offered only to those patients with a positive ^{68}Ga -DOTANOC ([DOTA, 1-Nal3]-octreotide) PET/CT.

^{68}Ga -DOTANOC Syntheses

The peptide-chelator conjugate DOTANOC was synthesized by standard Fmoc solid-phase synthesis on 2-chlorotriylchloride resin on a peptide synthesizer (Switch 24; Rink CombiChem Technologies[®]). ^{68}Ga -DOTANOC was labelled under sterile conditions in an isolator using a modification of the method described by Zhernosekov et al. [13]. The final product was diluted with 7 ml of saline and then subjected to sterile filtration using a Millex 0.22- μm filter (Millipore[®]). The labelling yield was analyzed by silica gel instant thin-layer chromatography (Pall Inc.[®]) and by high-performance liquid chromatography using a Luna 5- μm , C18(2) 50 $\times$ 3-mm column (Phenomenex[®]) and an acetonitrile-water gradient. The labelling yield and radiochemical purity of ^{68}Ga -DOTANOC were greater than 98% at a specific activity of 14.5–34 GBq/ μmol .

Combined ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT Acquisition

PET/CT images were acquired with an mCT 64-slice scanner (Siemens[®]). Patients fasted from at least 6 h before imaging and blood glucose levels were checked. Those with a blood glucose level above 150 mg/dl did not undergo scanning. Images from the vertex to the proximal femur were obtained while the patients were in the supine position. The ^{68}Ga -DOTANOC PET/CT was performed at 8.00 a.m. and the ^{18}F FDG PET/CT was always subsequently performed at 2.00 p.m. on the same day regardless of the findings of the ^{68}Ga -DOTANOC PET/CT. Both the whole-body ^{68}Ga -DOTANOC (1.5 MBq/kg) PET/CT and whole-body ^{18}F FDG PET/CT (2.96 MBq/kg) imaging were performed approximately 1 h after an intravenous injection. During the waiting period, patients rested in a quiet room without taking any muscle relaxants. PET images were acquired for 2 min per bed position. CT images were also obtained from the patient's integrated ^{68}Ga -DOTANOC

PET/CT and ^{18}F FDG PET/CT with the use of a standardized protocol of 120 kV, care dose of 100 mAs, tube rotation time of 0.5 s per rotation, a pitch of 1.4 and a slice thickness of 5 mm. Patients were allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal and sagittal) with True-D software (Siemens).

Statistical Analysis

The results are presented as frequencies and percentages for categorical variables and as median with interquartile range (IQR) for continuous variables. Patients were divided in two groups according to the PET/CT findings. The first group included those patients who had only a positive ^{68}Ga -DOTANOC PET/CT. The second group included those with tumors that were positive for both ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT, or only positive for the latter. When comparing these two groups, normally distributed continuous variables were analyzed using a two-sample Student t test, while the Mann-Whitney U test was used for nonnormally distributed variables. Categorical variables were compared using the χ^2 test and Fisher's exact test as appropriate. A Wilcoxon matched-pairs signed-rank test was used to compare uptake of ^{68}Ga -DOTANOC and ^{18}F FDG according to tumor grades. All p values were two sided and considered significant when <0.05 . Statistical analyses were performed using IBM SPSS 20.0 for Mac software (SPSS Inc., Chicago, Ill., USA).

Results

The demographics and clinical characteristics of the entire cohort are summarized in table 1. All patients had nonfunctioning PNET except for 1 who had a metastatic insulinoma. Of the 49 patients, ^{68}Ga -DOTANOC PET/CT was true positive in 48 and false negative in 1. The overall sensitivity for ^{68}Ga -DOTANOC PET/CT was 98%. ^{18}F FDG PET/CT was true positive in 36 and false negative in 14 of the patients. The overall sensitivity for ^{18}F FDG PET/CT was therefore 73%. The combined ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT sensitivity was 100%. Overall, 14 patients (28.5%) had only a positive ^{68}Ga -DOTANOC PET/CT, whereas 34 patients (69%) were positive for both ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT. Only 1 patient was only positive by ^{18}F FDG PET/CT. Overall, 8 patients (16%) had a prevalent ^{18}F FDG uptake. In the majority of patients (35/49) a PNET was diagnosed for the first time, whereas 14 patients had a previous diagnosis of PNET. These 14 patients were then restaged after the failure of previous treatment and all but 5 of them were positive on ^{18}F FDG PET/CT.

Pathological Characteristics according to ^{68}Ga -DOTANOC and ^{18}F FDG PET/CT Findings

A comparison of pathological characteristics is illustrated in table 2. Only 3 patients had a tumor diameter

Table 1. Clinical characteristics of 49 patients who underwent combined ^{68}Ga -DOTANOC and ^{18}F -FDG PET/CT

Gender	
Male	21 (43)
Female	28 (57)
Age, years	59 (49–71)
Diagnosis	
Incidental	21 (43)
Not incidental	28 (57)
First diagnosis	
No	14 (29)
Yes	35 (71)
^{68}Ga -DOTANOC PET/CT	
Negative	1 (2)
Positive	48 (98)
^{18}F -FDG PET/CT	
Negative	13 (26.5)
Positive	36 (73.5)

Values are n with percentage in parentheses, or median with IQR in parentheses.

Table 2. Comparison of pathological and stage PET/CT findings between patients only ^{68}Ga -DOTANOC positive and those both ^{68}Ga -DOTANOC and ^{18}F -FDG positive

Characteristic	Only ^{68}Ga -DOTANOC positive (n = 14)	^{68}Ga -DOTANOC and ^{18}F -FDG ¹ positive (n = 35)	p
Tumor status ²			
T1	1 (17)	2 (20)	0.830
T2	4 (66)	6 (60)	
T3	1 (17)	1 (10)	
T4	0 (0)	1 (10)	
Lymph node status ²			
N0	2 (33)	6 (60)	0.205
N+	4 (67)	4 (40)	
Number of liver metastases			
≤5	9 (64)	19 (54)	0.471
>5	5 (36)	16 (48)	
Tumor grade			
NET-G1	3 (22)	8 (23)	0.514
NET-G2	10 (71)	20 (54)	
NEC-G3	1 (7)	8 (23)	

Values are n with percentage in parentheses. Tumor grade is according to the 2010 WHO classification [10].

¹ All patients except 1 were also ^{68}Ga -DOTANOC PET/CT positive.

² Only for patients who underwent surgery.

Table 3. SUV_{max} of PET/CT according to tumor grade

	⁶⁸ Ga-DOTANOC SUV _{max}	¹⁸ F-FDG SUV _{max}
NET-G1	31.5 (8.5–64)	23 (4–26)
NET-G2	53.5 (33–68)	8 (5–9)
NET-G3	16.5 (6–34)	10 (7–14)

Median values are presented, with IQR in parentheses. Tumor grade is according to the 2010 WHO classification [10].

Table 4. Type of treatment administered after combined double ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT

Treatment	⁶⁸ Ga-DOTANOC positive	¹⁸ F-FDG positive ¹
None	1 (7)	1 (3)
Surgery	6 (43)	10 (27)
SSA	3 (21)	4 (12)
PRRT	2 (14)	4 (12)
Chemotherapy	0 (0)	8 (24)
Everolimus	2 (14)	7 (21)

Values are n with percentage in parentheses.

¹ All patients except 1 also had a positive ⁶⁸Ga-DOTANOC PET/CT.

Table 5. Type of treatment administered according to different tumor grading

Treatment	NET-G1	NET-G2	NET-G3
None	1 (10)	1 (3)	0 (0)
Surgery	6 (60)	8 (28)	2 (22)
SSA	1 (10)	6 (21)	0 (0)
PRRT	1 (10)	4 (14)	1 (11)
Chemotherapy	0 (0)	3 (10)	5 (56)
Everolimus	1 (10)	7 (24)	1 (11)

Values are n with percentage in parentheses. Tumor grading is according to the 2010 WHO classification [10].

<2 cm (6%). A cytological diagnosis was made in only 8 patients (16%), whereas the remaining 41 (84%) had a histological diagnosis. The radiological tumor stage was concordant with the PET/CT tumor stage in all cases. ⁶⁸Ga-DOTANOC failed to detect the primary tumor in 1 case, whereas ¹⁸F-FDG PET/CT failed to detect a pancre-

atic lesion in 2 cases. The radiological number of liver metastases was concordant with the PET/CT number of liver metastases in all cases except 2. In 1 of these cases ⁶⁸Ga-DOTANOC PET/CT detected 6 liver metastases compared with 2 metastases detected by CT alone. In the other case, both ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT detected only two liver metastases compared with multiple lesions observed on the CT scan. A total of 30 metastatic sites were defined in 24 patients. The most frequent site was the liver (n = 24) followed by bone (n = 4), lung (n = 1) and spleen (n = 1). ¹⁸F-FDG was false negative for skeletal metastases in 1 case and liver metastases in another. The pathological data of patients with positive ⁶⁸Ga-DOTANOC PET/CT were comparable with those who were both ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT positive, or only ¹⁸F-FDG positive. The two groups were also similar regarding tumor grading, although all but 1 of the patients with NET-G3 had a positive ¹⁸F-FDG PET/CT. The median Ki67 was 7% for ⁶⁸Ga PET/CT-positive tumors and 10% for tumors that were both ⁶⁸Ga and ¹⁸F-FDG PET/CT positive (p = 0.130). Half of the patients with a prevalent uptake of ¹⁸F-FDG (n = 7) had an NET-G3 compared with 12% of patients with a prevalent uptake of ⁶⁸Ga (p = 0.012). The median SUV_{max} for ⁶⁸Ga-DOTANOC PET/CT was 43.5 (IQR 18–107) and 8.5 (IQR 5–23) for ¹⁸F-FDG PET/CT. The tracer uptake according to tumor grade is depicted in table 3.

Impact of ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT on Treatment Choice

Table 4 illustrates a comparison of treatment choice between patients who were positive by ⁶⁸Ga-DOTANOC and those positive by both ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT, or only ¹⁸F-FDG. Overall, 16 patients underwent surgery (5 pancreaticoduodenectomies, 6 distal pancreatectomy, 3 atypical pancreatic resections and 2 pancreatic resection with associated liver resection). Only 8 patients (16%) underwent chemotherapy. All these 8 patients were positive on both ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT. Of these, 5 had a PNET-G3 tumor whereas 3 had a PNET-G2 tumor (table 5). Two patients with a PNET-G2 tumor underwent chemotherapy because of the failure of previous treatment with somatostatin analogue (SSA) and PRRT. One patient with PNET-G2 (Ki67 = 12%) with high uptake for ⁶⁸Ga-DOTANOC and moderate uptake for ¹⁸F-FDG PET/CT (fig. 1) underwent SSA and chemotherapy with oxaliplatin and capecitabine during hospitalization for severe diarrhea with hepatorenal syndrome. Of 8 patients with a prevalent uptake of ¹⁸F-FDG, 3 underwent surgery for a

Fig. 1. A 38-year-old woman with a clinical diagnosis of metastatic PNET. The patient presented with severe diarrhea and abdominal pain. ^{68}Ga -DOTANOC PET/CT (indicated by A) revealed multiple areas of tracer uptake (SUV_{max} 69) and a weak area of ^{18}F -FDG uptake (SUV_{max} 8; indicated by B).

Fig. 2. A 75-year-old man presented with a hypervascularized mass of the pancreatic head on CT scan. ^{68}Ga -DOTANOC PET/CT imaging did not show any tracer uptake (indicated by A). ^{18}F -FDG PET/CT showed tracer uptake (SUV_{max} 7) in the head of the pancreas (indicated by B).

localized tumor and 4 underwent chemotherapy. The remaining patient was not treated due to chronic leukemia. Only 1 patient was negative by ^{68}Ga -DOTANOC PET/CT and positive only by ^{18}F -FDG PET/CT (fig. 2). This patient had a localized PNEC-G3 and underwent radical surgery. He then developed multiple liver metastases (positive on ^{18}F -FDG PET/CT) only 8 months after surgery. Another patient with PNEC-3 underwent PRRT as the high uptake for ^{68}Ga -DOTANOC (SUV_{max} 44) whereas the remaining patient with PNEC-G3 was administered everolimus.

Discussion

The current study demonstrates that a routine use of combined ^{68}Ga -DOTANOC and ^{18}F -FDG PET/CT does not significantly influence the treatment strategy in patients affected by PNET despite dual tracer functional imaging often revealing tumor heterogeneity. Prior studies have focused mainly on the accuracy of dual tracer PET/CT imaging in the diagnosis and staging of this disease [7, 8]. The sensitivity of ^{68}Ga PET/CT was reported

to be between 91 and 95% [2], which is much higher compared with that reported for ^{18}F -FDG PET/CT [7, 8, 14]. In the present study we found similar results, as the sensitivity of ^{68}Ga PET/CT was 98%. This sensitivity was higher than that reported by Kayani et al. [7], possibly related to the profile of tracer DOTANOC which has affinity for SSTR2, SSTR3 and SSTR5 compared with that of DOTATATE [15]. The accuracy could also have been biased by the inclusion of only histologically proven PNET in the study and, similarly, the fact that high pre-test probability usually affects the accuracy of functional imaging for PNET. For these reasons, specificity is generally not considered for this imaging and specificity of ^{18}F -FDG is inevitably low as this represents the most accurate functional imaging for cancer [14]. If we exclude the value of PET/CT in the diagnostic accuracy of PNET, the real significance of this procedure remains mostly related to its potential influence on treatment strategy. The clinical impact of ^{68}Ga -DOTANOC has been previously proven [9]. Ambrosini et al. [9] demonstrated that ^{68}Ga -DOTANOC PET/CT influenced the management of patients in more than half of the studied population. In particular, the effect of PET on therapy was to initiate or

continue PRRT or SSA medical therapy on the basis of the demonstration of somatostatin receptor expression. Data on the clinical impact of combined dual tracer PET/CT imaging are limited to those described by Kayani et al. [7]. In their study they reported that for 4 patients (3 high-grade NET and 1 intermediate-grade NET), ^{18}F FDG showed more intense and more widespread uptake than ^{68}Ga PET/CT. In view of this pattern, the patients were assigned to receive chemotherapy instead of PRRT. They concluded that the use of ^{18}F FDG led to a change in clinical management from PRRT to chemotherapy in 25% of intermediate- and high-grade NET. In the present study, therapy was not influenced by the routine use of dual tracer PET/CT imaging. In particular, the use of ^{18}F FDG did not influence the clinician's choice regarding chemotherapy. Moreover, 1 patient with localized pancreatic NET underwent surgery despite the high uptake of ^{18}F FDG. The treatment strategy in the present study was mainly influenced by tumor grade, symptoms and previous clinical history. Two patients with moderately differentiated tumors underwent chemotherapy, in 1 case due to the presence of a severe clinical syndrome and in the other because of the failure of previous receptor-based treatment. Nevertheless, the majority of patients had a higher uptake of ^{68}Ga -DOTANOC, except for 8 patients with a localized tumor. Evaluations on treatment strategy were then more influenced by the expression of somatostatin receptors than by the increased glycolytic activity of tumor cells. The real value of combined ^{68}Ga and ^{18}F FDG PET CT consists mainly in the possibility to demonstrate areas of different tumor grading among the same lesions. This was clearly demonstrated by the Kayani et al. [7] study, in which patients with high-grade tumors had a significantly higher median SUV_{max} of ^{18}F FDG, whereas patients with well-differentiated tumors had a higher uptake for ^{68}Ga -DOTATATE. In the present study, patients who also had positive ^{18}F FDG PET/CT imaging had tumors with a trend toward a higher median Ki67, although this was not statistically significant. Moreover, we observed a significantly higher incidence of NEC-G3 lesions among those patients with a prevalent uptake of ^{18}F FDG. This result confirms the presence of tumor heterogeneity that seems to be a specific trait of neuroendocrine neoplasms [16]. Tumor heterogeneity cannot be assessed by tumor biopsy and this can represent a distinctive advantage of combined dual tracer PET/CT imaging. On the other hand, in this preliminary experience, it seems that physicians still place greater trust in histology, or even cytology, rather than functional imaging. Long-term survival data will be of

paramount importance to definitely assess the value of dual tracer PET/CT and the role of tumor heterogeneity on outcomes.

This study has some limitations. Firstly, it was a retrospective study although a prospective evaluation could potentially bias the physicians' choices on treatment strategy. Secondly, a relatively small sample size could have influenced some results, especially after patients were classified into subgroups. In particular, the relatively small sample size, as well as the wide range of therapeutic options, did not allow a statistical analysis between the different groups to be performed. As a consequence, these results should be taken cautiously and corroborated by larger series.

Conclusion

A routine use of combined ^{68}Ga and ^{18}F FDG PET/CT in patients with PNET seems not to be justified in clinical practice and still represents an area of research. In routine use the association of these two tracers could be reasonable in selected patients affected by PNET with a Ki67 >10%. The association of long-term outcomes and findings obtained by dual tracer PET/CT imaging has to be evaluated.

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Disclosure Statement

The authors have no conflict of interest to declare.

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