A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion

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Background: Lymphovascular space invasion (LVSI) is one of the most important predictors of nodal involvement and recurrence in early stage endometrial cancer (EC). Despite its demonstrated prognostic value, LVSI has not been incorporated into the European Society of Medical Oncology (ESMO) classification. The aim of this prospective multicentre database study is to investigate whether it may improve the accuracy of the ESMO classification in predicting the recurrence risk.

Methods: Data of 496 patients with apparent early-stage EC who received primary surgical treatment between January 2001 and December 2012 were abstracted from prospective multicentre database. A modified ESMO classification including six risk groups was created after inclusion of the LVSI status in the ESMO classification. The primary end point was the recurrence accuracy comparison between the ESMO and the modified ESMO classifications with respect to the area under the receiver operating characteristic curve (AUC).

Results: The recurrence rate in the whole population was 16.1%. The median follow-up and recurrence time were 31 (range: 1–152) and 27 (range: 1–134) months, respectively. Considering the ESMO modified classification, the recurrence rates were 8.2% (8 out of 98), 23.1% (15 out of 65), 25.9% (15 out of 58), and 45.1% (28 out of 62) for intermediate risk/LVSI−, intermediate risk/LVSI+, high risk/LVSI−, and high risk/LVSI+, respectively (P<0.001). In the low risk group, LVSI status was not discriminant as only 7.0% (14 out of 213) had LVSI+. The staging accuracy according to AUC criteria for ESMO and ESMO modified classifications were of 0.71 (95% CI: 0.68–0.74) and 0.74 (95% CI: 0.71–0.77), respectively.

Conclusions: The current modified classification could be helpful to better define indications for nodal staging and adjuvant therapy, especially for patients with intermediate risk EC.

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Endometrial cancer (EC) is a major cause of morbidity and mortality for patients worldwide. Although its incidence differs throughout the world, it is the most common cancer of the female genital tract and the fourth most common cancer in North America and Europe (Jemal et al., 2010; Colombo et al., 2013). Early-stage EC restricted to the uterus represents nearly 80% of all cases (Creasman et al., 1987, 2006). The primary surgical treatment involves removal of the uterus, tubes, and ovaries, with or without nodal pelvic or para-aortic staging (Creasman et al., 1987; Keys et al., 2004). The estimated 5-year overall survival (OS) for early-stage EC is 95% but decreases substantially to 67.0% and 15.9% for local and distant disease, respectively (Creutzberg et al., 2000; Randall et al., 2006; Benedetti Panici et al., 2008; ASTEC study group, 2009).

Recurrence has been reported to occur in 15–20% of early-stage EC (Mariani et al., 2002; Nout et al., 2010). Several epidemiological and histological prognostic markers for poor outcomes have been reported and used in treatment planning (Creutzberg et al., 2000; Keys et al., 2004; Benedetti Panici et al., 2008; ASTEC study group, 2009). Among these is the presence of lymphovascular space invasion (LVSI), which is one of the most important predictors of nodal involvement, recurrence risk, and OS (Morrow et al., 1991; Briët et al., 2005; Gunputalli et al., 2012). The increased demand for clinicians to help patients make informed decisions about treatment options, benefits and risks involves careful consideration of risk factors into the overall treatment recommendations (Creutzberg et al., 2000; Pecorelli, 2009; Colombo et al., 2013). To improve patient risk stratification, the presence of LVSI has been incorporated into international classifications in combination with other clinicopathological factors, such as age, International Federation of Gynecology and Obstetrics (FIGO) stage, pathogenetic types (Bokhman, 1983), histological grade, and depth of myometrial invasion (Keys et al., 2004; Querleu et al., 2011). In contrast, in the European Society of Medical Oncology (ESMO) recurrence risk classification, LVSI is not used to classify patients as being at low, intermediate, or high risk despite its demonstrated prognostic value (Colombo et al., 2013). Furthermore, a considerable heterogeneity of early EC tumour biology and of patient’s characteristics within each risk subgroup has been observed (Creutzberg et al., 2000; Keys et al., 2004; Ballester et al., 2011; Nugent et al., 2012).

We hypothesised that in the near future a combination of LVSI status with existing clinico-histopathological features may become an important surrogate risk marker and determinant to better adapt adjuvant therapies in patients with early-stage EC. The aim of this prospective multicentre database study was therefore to investigate whether LVSI may improve the accuracy of the ESMO classification in predicting the recurrence risk in patients with early EC.

**MATERIALS AND METHODS**

**Study population.** Data of all patients with apparent early-stage EC who received primary surgical treatment between January 2001 and December 2012 were abstracted from four institutions with maintained EC databases in France (Tenon University Hospital, Reims University Hospital, Dijon Cancer Center, and Creteil Hospital) and from the Senti-Endo trial (Ballester et al., 2011). All the patients had undergone a preoperative endometrial biopsy. All enrolled patients underwent a preoperative MRI unless contraindicated, in which case a CT scan was performed. Patients with histologically proven EC were staged on the basis of final pathological findings according to the 2009 FIGO classification (Pecorelli, 2009). Clinical and pathological variables included patient age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), surgical procedure, 2009 FIGO stage, and final pathological analysis (histology type and grade, depth of myometrial invasion, and LVSI status). A tumour was considered LVSI-positive when tumour emboli were found within a space clearly lined by endothelial cells (Tsuzuki et al., 1995). The research protocol was approved by the Consultative Committee for Protection of Persons in Biomedical Research of Paris 6 (France).

**Treatment and follow-up.** Patients were included if they had undergone primary surgical treatment, including at least total hysterectomy with bilateral salpingo-oophorectomy, with or without nodal staging (pelvic +/− para-aortic lymphadenectomy) according to the current guidelines and the surgeon’s discretion. If a sentinel lymph node (SLN) biopsy had been undertaken, a dual cervical injection was performed intracervically based on the histological validation of SLN by Delpech et al. (2007). If the pelvic SLN was found to be metastatic on intraoperative histology or after final histology, a para-aortic lymphadenectomy was recommended. Systematic pelvic and para-aortic lymphadenectomy was also recommended for patients with type 2 EC (clear-cell, serous EC and carcinosarcoma) and type 1, grade 3 with myometrial invasion > 50% EC. Adjuvant therapy was administered on an individual basis at the discretion of the pluridisciplinary committee, based on international guidelines and involved vaginal brachytherapy (VBT) and/or external beam radiotherapy (EBRT) and/or chemotherapy (Colombo et al., 2013). Clinical follow-up consisted of physical examinations and the use of imaging techniques according to the findings. Follow-up sessions were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

**Statistical analysis**

ESMO risk groups and LVSI. Based on definitive histology, three risk groups according to the ESMO guidelines for EC were defined as follows (Colombo et al., 2013): low risk (type 1 EC, stage IA grade 1 or 2); intermediate risk (type 1 EC, stage IA grade 3, or stage IB grade 1 or 2); and high risk (type 1 EC, stage IB grade 3, or type 2 EC of any stage and grade). A modified ESMO classification including six risk groups (low risk/LVSI −; low risk/LVSI +; intermediate risk/LVSI −; intermediate risk/LVSI +; high risk/LVSI −; high risk/LVSI +) was created after inclusion of the LVSI status in the current ESMO classification.

Recurrence event and recurrence-free survival (RFS). Disease recurrence was diagnosed by biopsy or imaging studies and defined as a relapse without differentiating between their local or distant nature. Survival estimates were based on Kaplan–Meier calculations and RFS defined as the time from the date of surgery to the date of recurrence. Cox proportional hazard models were fitted to independently evaluate the influence of co-variates (age, adjuvant therapy, ESMO classification, and ESMO modified classification). Effects were expressed as hazard ratios with 95% confidence intervals as appropriate. Log-rank tests were used to examine the individual effects of variables on RFS.

**Staging accuracy.** The recurrence accuracy of the ESMO and modified ESMO classifications were evaluated with respect to discrimination, that is, whether the relative ranking of individual predictions was in the correct order, quantified with the area under the receiver operating characteristic curve (AUC) (Hanley and McNeil, 1982). The AUC index is the probability that given two randomly selected patients the patient with the worse outcome prediction will have the worse outcome. The AUC index ranges from 0 to 1, with 1 indicating perfect concordance and 0.5 indicating no association.
Other statistical analysis. Statistical analysis was based on Student’s t-test and the Mann–Whitney test for parametric and non-parametric continuous variables, respectively, and the Chi-square test or Fisher’s exact test, as appropriate, for categorical variables. Values of $P<0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software, available online.

RESULTS

Characteristics of the study population. During the study period, 496 patients with EC were documented as having received primary surgical treatment according to the following distribution: Dijon Cancer Center ($n=129$; 26%), Creteil Hospital ($n=97$; 20%), Reims University Hospital ($n=92$; 19%), Tenon University Hospital ($n=59$; 12%), and Senti-Endo trial ($n=119$; 24%). The demographics and clinicopathological characteristics of the whole cohort are reported in Table 1. The median age and BMI of the patients were 67.7 years (range 33–98 years) and 27.7 kg m$^{-2}$ (range 16.8–48.8), respectively. Postoperative pathogenetic types (Bokhman, 1983) was 83% (415) and 16% (77) for type 1 and 2, respectively. Forty-four percent ($n=213$), 32% (156), and 23% (127) of patients were at low, intermediate, and high risk according to the ESMO classification, respectively. Comparatively, 43% (213), 18% (91), 13% (65), 12% (58), and 14% (69) of patients were at low risk, intermediate risk/LVSI $+$, intermediate risk/LVSI $+$, high risk/LVSI $+$, and high risk/LVSI $+$ according to the modified ESMO classification, respectively. Surgical approach consisted of nodal staging for 79.7% (331 out of 415) and SLNB for 53.7% (178 out of 331). One hundred and forty-four patients (29%) were found to have LVSI on final histology. Epidemiological, surgical, histological, and outcome characteristics of patients according to LVSI status are reported in Table 2.

Recurrence and lymph node metastasis rates according to the ESMO and the modified ESMO classifications. The recurrence rate in the whole population was 16.1% (80 out of 496). When comparing patients with and without LVSI, the recurrence rates were 30.6% (44 out of 144) vs 10.2% (36 out of 352), respectively ($P<0.001$). When considering each subgroup of the ESMO classification, the recurrence rates were 6.5% (14 out of 213), 14.1% (23 out of 163), and 35.8% (43 out of 120) for low-, intermediate-, and high-risk patients, respectively ($P<0.001$). When considering each subgroup of the ESMO modified classification, the recurrence rates were 7.0% (14 out of 198), 0% (0 out of 15), 8.2% (8 out of 98), 23.1% (15 out of 65), 25.9% (15 out of 58), and 45.1% (28 out of 62) for low risk/LVSI $-$, low risk/LVSI $+$, intermediate risk/LVSI $-$, intermediate risk/LVSI $+$, high risk/LVSI $-$, and high risk/LVSI $+$, respectively ($P<0.001$). Lymph node metastases were found, respectively in 6.6% (12 out of 181), 20% (25 out of 125), and 33% (34 out of 102) for low-, intermediate-, and high-risk patients of the ESMO classification ($P<0.001$). Using the ESMO modified classification, lymph node metastases were found, respectively in 6.6% (12 out of 181), 10% (7 out of 70), 32.7% (18 out of 55), 17.6% (9 out of 51), and 49% (25 out of 51) for low risk, intermediate risk/LVSI $-$, intermediate risk/LVSI $+$, high risk/LVSI $-$, and high risk/LVSI $+$ ($P<0.001$).

RFS according to the ESMO and the ESMO modified classifications. The median follow-up and initial recurrence time were 31 (range: 1–152) and 27 (range: 1–134) months, respectively. The respective 5-year RFS rates according to the ESMO classification were 91.4% (95% CI, 86.8–96.2), 77.8% (95% CI, 69.7–86.7), and 48.5% (95% CI, 37.2–63.3) ($P<0.0001$) for low-, intermediate-, and high-risk patients (Figure 1). The subset analysis of the ESMO modified classification according to the LVSI status reported 5-year RFS of 87.3% (95% CI, 79.3–96.2) vs 63.2% (95% CI, 48.5–82.3) for intermediate risk/LVSI $-$ and intermediate risk/LVSI $+$ ($P=0.0144$) and 59.5% (95% CI, 42.4–83.6) vs 36.9% (95% CI, 23.6–57.8) for high risk/LVSI $-$, high risk/LVSI $+$ patients, respectively ($P=0.0142$; Figure 2).

Multivariate analysis. In a multivariate analysis including the ESMO classification risk groups, adjuvant therapies (VBT, EBRT, EBRT, and/or hysterectomy), LVSI status, and LVSI status according to the ESMO modified classification, the recurrence rates were 44% (213), 32% (156), and 24% (127) for low risk/LVSI $-$, low risk/LVSI $+$, and high risk/LVSI $+$, respectively ($P<0.001$). Using the ESMO modified classification, the recurrence rates were 40% (198), 3% (15), 18% (91), 13% (65), 12% (58), and 14% (69) for low risk/LVSI $-$, low risk/LVSI $+$, intermediate risk/LVSI $-$, intermediate risk/LVSI $+$, high risk/LVSI $-$, and high risk/LVSI $+$, respectively ($P<0.001$).
and chemotherapy), and nodal staging, we found that adjuvant chemotherapy (HR = 2.47 (95% CI, 1.48–4.11)) and nodal staging (HR = 0.43 (95% CI, 0.22–0.84)) were independently correlated to 5-year RFS. In a multivariate analysis including the modified ESMO classification risk groups, adjuvant therapies (VBRT, EBRT, and chemotherapy), and nodal staging, we found that intermediate risk/LVSI+ (HR = 2.64 (95% CI, 1.18–5.89), P = 0.0171), high risk/LVSI+ (HR = 2.69 (95% CI, 1.18–6.14), P = 0.0180), high risk/LVSI+ (HR = 4.92 (95% CI, 2.34–10.33), P < 0.001), and adjuvant chemotherapy (HR = 2.36 (95% CI, 1.42–3.93), P < 0.001) were independently correlated to 5-year RFS (Table 3).

**DISCUSSION**

Our results demonstrate that the recurrence risk stratification in patients with early-stage EC can be improved by the inclusion of the LVSI status in the current ESMO classification, especially for patients with intermediate risk EC.

In the past decade, LVSI status has progressively gained importance as an independent intrauterine risk factor for patients with early-stage EC (Morrow et al, 1991; Briet et al, 2005; Guntupalli et al, 2012). It is currently considered to be one of the first steps in the metastatic spread even for patients with tumours that seem to be confined to the uterus. In previous studies, the presence of LVSI has been reported as a strong independent prognostic marker with respect to disease recurrence, nodal metastasis, and survival (Morrow et al, 1991; Table 2. Comparison of epidemiological, surgical, and histological characteristics of patients with and without LVSI at final histology

|                      | No LVSI n = 352 (%) | LVSI n = 144 (%) | P-value |
|----------------------|---------------------|-----------------|---------|
| Age (years), mean (range) | 65.9 (33–92)       | 67.4 (40–98)    | 0.17    |
| BMI (kg m⁻²), mean (range) | 29.1 (16.9–40.2)   | 28.7 (16.9–40.3) | 0.65    |
| Follow-up mean (range), months | 35.9 (1–134)      | 30.4 (0–152)   | 0.017   |
| **Histological type** |                     |                 |         |
| Type 1               | 87.7% (309)         | 73.6% (106)     | 0.0003  |
| Type 2               | 12.3% (43)          | 26.4% (38)      |         |
| **ESMO risk classification** |                   |                 |         |
| Low risk             | 54.2% (198)         | 10.4% (15)      | < 0.0001|
| Intermediate risk    | 25.9% (91)          | 45.1% (65)      |         |
| High risk            | 17.9% (63)          | 44.4% (64)      | < 0.0001|
| Nodal staging        | 77.8% (228/293)     | 84.4% (103/122) | 0.12    |
| Nodal metastasis     | 8.5% (25/293)       | 38.5% (47/122)  | < 0.0001|
| Vaginal brachytherapy | 53.1% (187)         | 50.7% (73)      | 0.4366  |
| EBRT                 | 28.4% (100)         | 63.9% (92)      | < 0.0001|
| Chemotherapy         | 9.9% (35)           | 31.2% (45)      | < 0.0001|
| Recurrence rates     | 10.8 (36)           | 30.6 (44)       | < 0.0001|

Abbreviations: BMI = body mass index; EBRT = external beam radiotherapy; ESMO = European Society of Medical Oncology; LVSI = lymphovascular space invasion.

Figure 1. Recurrence-free survival according to ESMO risk classification.

Figure 2. Recurrence-free survival according to modified ESMO risk classification.

**Staging accuracy.** The staging accuracy according to AUC criteria for ESMO and ESMO modified classifications were 0.71 (95% CI: 0.68–0.74) and 0.74 (95% CI: 0.71–0.77), respectively (Figure 3).
et al (2013) demonstrate that LVSI is highly associated with LN metastasis and is a strong marker of local and distant disease recurrence. Our results are thus in complete accordance with these previous results, showing that LVSI status is an independent prognostic marker for recurrence and decreased RFS.

There are several unresolved issues with regards to accurately classifying the risk of recurrence of early-stage EC and the impact on indications for adjuvant therapies. Previous efforts of risk grouping have led to the development of recommendations in which several reliable factors were combined (Creutzberg et al, 2000; Keys et al, 2004; Colombo et al, 2013). The main interest of such an approach is to stratify patients not only to plan surgical or adjuvant treatment but also to provide better information to patients about treatment options. Although these approaches constitute a more reliable estimation of the risk of recurrence than the physician’s judgment, their predictive capability is based on the assumption that all patients within a given risk group are equal. However, in clinical practice, both biological heterogeneity of endometrial tumours and heterogeneity of patients’ characteristics within each subgroup have been observed, especially in early-stage EC (Creutzberg et al, 2000; Keys et al, 2004; Ballester et al, 2011, 2012). The current ESMO classification established three risk groups of recurrence based on depth of myometrial invasion, histological grade, and type, without taking into account the LVSI status (Colombo et al, 2013). In the present study, we hypothesised that LVSI status may improve the ESMO accuracy. Indeed, the introduction of LVSI status within the current ESMO classification resulted in an improvement of its discrimination accuracy with an AUC of 0.74. Moreover, we found that patients with IR/LVSI + EC had similar recurrence rates and RFS to those with HR/LVSI –. This is in accordance with the GOG-99 study that established a high–intermediate risk (HIR) group for recurrence based on the LVSI status, invasion of tumour into the outer one-third of the myometrium, and histological grade 2–3. The authors found that, in the intermediate HIR risk group, 21% of patients with negative LN and 42% of patients with positive LN experienced a recurrence (Keys et al, 2004).

There is a persistent debate about the relevance of lymphadenectomy in standard management of EC despite the publication of two randomised trials showing that there is no advantage in performing systematic lymphadenectomy in this setting (Benedetti Panici et al, 2008; ASTEC study group et al, 2009). Currently, the ESMO group recommends a hysterectomy with bilateral pelvic lymphadenectomy ± bilateral pelvic-para-aortic lymphadenectomy, underlining that indications for nodal staging in this specific subgroup are somewhat blurred (Colombo et al, 2013). In our study, we found that 32.7% of patients with IR/LVSI + had nodal metastases (vs 17.6% in the HR/LVSI –), with a recurrence rate of 27.7%. In contrast, we found that 10% of patients with IR/LVSI – had nodal metastases, with a recurrence rate of 14.2%. These results compare favourably with those of Nugent et al (2012), strongly suggesting that information on nodal status cannot be omitted in this subgroup of patients to better adapt adjuvant therapies. This is in accordance with the results of the Senti-Endo study showing that 15% of patients with intermediate-risk EC have LN metastases that could go undetected if there is no nodal staging (Ballester et al, 2011). Hence, SLN biopsy appears as a relevant alternative for the IR/LVSI + risk group of recurrence. Moreover, because of the high rate of discrepancies between preoperative and postoperative risk groups, comprehensive lymphadenectomy can always be performed later.

Another topic of controversy is related to indications for adjuvant therapies in patients with early-stage EC. For intermediate-risk EC, the current ESMO guidelines recommend observation or VBT (Colombo et al, 2013). In the case of negative prognostic factors, pelvic EBRT and/or adjunctive chemotherapy could be considered. In HR patients with early-stage EC, Guntupalli et al, 2012). Indeed, Briët et al (2005) reported that LVSI status is related to an increased risk of pelvic lymph node metastasis and higher rates of recurrence. In this specific setting, Laufer et al (2013) showed that LVSI emerged as the strongest independent variable associated with pelvic lymph node metastasis compared with histological grade and depth of myometrial invasion. Similarly, both Guntupally et al (2012) and Simpkins et al (2013) showed that LVSI status may improve the ESMO accuracy. Indeed, the introduction of LVSI status within the current ESMO classification resulted in an improvement of its discrimination accuracy with an AUC of 0.74. Moreover, we found that patients with IR/LVSI + EC had similar recurrence rates and RFS to those with HR/LVSI –. This is in accordance with the GOG-99 study that established a high–intermediate risk (HIR) group for recurrence based on the LVSI status, invasion of tumour into the outer one-third of the myometrium, and histological grade 2–3. The authors found that, in the intermediate HIR risk group, 21% of patients with negative LN and 42% of patients with positive LN experienced a recurrence (Keys et al, 2004).

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the PORTEC-1 trial found that EBRT decreased local recurrence rates from 14% to 4% \( (P = 0.001) \), with no difference in OS (81% 5-year survival in the radiotherapy group vs 85%, \( P = 0.31 \)) or in the development of distant metastatic disease (Creutzberg et al., 2000). These results were confirmed by the GOGG 99 trial in patients who had undergone systematic lymphadenectomy (Keys et al., 2004). These findings, coupled with our results, suggest that among patients with intermediate risk a subset of patients with negative prognostic factors, such as our subgroup of patients with IR/LVSI + without LN metastases, could benefit from EBRT.

Intraoperative assessment of the LVSI status may allow a more precise stratification of these tumours and therefore remains a very important clinical challenge. However, its role in decision making for surgical staging of EC remains controversial (Guntupalli et al., 2012; Laufer et al., 2013; Simpkins et al., 2013). Indeed, as previously reported, the intraoperative assessment is based on a limited sample and may not be in agreement with the final pathology (Guntupalli et al., 2012; Laufer et al., 2013; Simpkins et al., 2013). Hence, further studies are needed to confirm its clinical value.

The strengths of our study reside in its multicentre design and the large number of patients as we were able to demonstrate the prognostic weight of the LVSI and the accuracy of the ESMO modified by the incorporation of LVSI. However, some weaknesses deserve to be mentioned. First, there is the inherent selection bias found at large multicentre tertiary referral centres. Second, during the data collection period, modifications occurred in staging modalities (FIGO classification; Pecorelli, 2009) and surgical techniques (LN staging; Benedetti Panici et al., 2008; ASTEC study group et al., 2009; Ballester et al., 2011). Third, our analysis does not take into account some histological characteristics, such as the tumour size. Because of the low number of event recurrence, we were unable to perform an analysis according to locoregional and distant recurrence. Fourth, to avoid any interpretation bias, we did not assess the significance of isolated tumour cells and the prognostic value of the number of LVSI. Finally, we could not demonstrate a statistical difference in low-risk patients according to the LVSI status, probably due to the low incidence of LVSI in this subgroup of patients (type I/low grade tumours). However, O’Brien et al. (2009) reported that in patients with early-stage well-differentiated adenocarcinoma of the endometrium, the presence of LVSI is associated with a high risk of death. In addition, the latest recommendations on EC elaborated in France have used a modified classification that takes into account the presence of LVSI to define LVSI + as high-risk EC (Quereleu et al., 2011).

In conclusion, our results confirm that LVSI appears to be highly predictive of disease recurrence and decreased RFS in early stage EC. Furthermore, the inclusion of the LVSI status into the current ESMO classification improves its accuracy, especially in patients with intermediate-risk early-stage EC. This criterion should be taken into consideration to better adapt indications for nodal staging and adjuvant therapies. In the future, improving health-care management could be achieved by combining the molecular (Dai et al., 2014) and immunohistochemical biomarkers (Ballester et al., 2013) with current risk factors to provide more precise information that will allow for more individualised treatments.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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