

# The Global Immune-Nutrition Inflammation Index for Predicting Coronary Slow Flow Phenomenon in Patients with Angina and No Obstructive Coronary Arteries

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**Background:** Chronic inflammatory responses are involved in the initiation and development of the coronary slow flow phenomenon (CSFP). However, as a newly developed immuno-nutritional inflammation indicator, the global immune-nutrition inflammation index (GINI) has not been well elaborated for predicting CSFP in patients with angina and no obstructive coronary arteries (ANOCA).

**Methods:** A total of 1422 individuals with ANOCA were consecutively included in this study, of whom 93 developed CSFP (CSFP group). We selected 186 (1:2 matched) age- and sex-matched patients with ANOCA and angiographically proven normal coronary blood flow as the controls (the control group). Multivariate logistic regression analysis was used to investigate predictors of CSFP in patients with ANOCA. The optimal cutoff values for GINI were calculated.

**Results:** In total, 93 patients developed CSFP, including 29% (27) in one vessel, 28% (26) in two vessels, and 43% (40) in three vessels. Patients with CSFP had an elevated CRP level, white blood cell (WBC) count, neutrophil count, GINI, fasting blood glucose (FBG) level, and a lower lymphocyte count ( $P < 0.05$ ). Multivariate logistic analysis showed that the GINI and FBG levels were independent predictors of CSFP in patients with ANOCA. Moreover, we found that the more vessels affected by CSFP, the higher the GINI level. The receiver operating characteristic (ROC) showed that GINI had a better predictive value than indicators alone. When the GINI AISI was  $>84.1$ , the sensitivity and specificity were 88.2% and 58.7%, respectively [The Area Under the ROC curve (AUC): 0.774; 95% CI: 0.721–0.827;  $P < 0.001$ ].

**Conclusion:** Elevated GINI is a reliable predictor of CSFP in patients with ANOCA. Moreover, GINI had a superior predictive value compared to the indicators alone. As a newly developed inflammatory indicator, GINI can be used for further risk stratification of patients with ANOCA.

**Keywords:** global immune-nutrition inflammation index, coronary slow flow phenomenon, angina no obstructive coronary arteries, predictors

## Introduction

The coronary slow flow phenomenon (CSFP) was first discovered by Tambe et al in 1972 and is characterized by delayed coronary blood flow in the absence of obstructive coronary artery disease (CAD).<sup>1</sup> With the widespread use of coronary angiography (CAG), CSFP is common in clinical practice. According to literature, the incidence of CSFP varies from 1% to 7%.<sup>2</sup> In fact, CSFP is not the only angiographic finding proven to have clinical significance. The international standardization of diagnostic criteria for microvascular angina suggested CSFP as a subtype of microvascular angina (MVA).<sup>3</sup> It has been suggested that CSFP is associated with recurrent chest pain, arrhythmias, and adverse cardiovascular outcomes.<sup>4,5</sup> Evidences suggested that inflammation, endothelial dysfunction, oxidative stress, or microvascular dysfunction may participate in the initiation and development of CSFP;<sup>6</sup> however, the exact pathogenesis of CSFP remains



undetermined. Nonetheless, it has been suggested that chronic local or systemic inflammatory reactions play a key role in the occurrence and development of CSFP.<sup>7–10</sup>

The global immune-nutrition inflammation index (GINI) is a newly developed indicator that combines blood biochemistry and blood routine components and can comprehensively assess the status of immunity, inflammation, and nutrition.<sup>11</sup> As an easily acquired indicator in routine clinical practice, GINI has been suggested as a prognostic predictor in patients, with stage IIIC non-small cell lung cancer receiving definitive concurrent chemo-RT.<sup>11</sup> Topkan et al also discovered that an elevated GINI value is closely related to a poor prognosis in patients, with glioblastoma multiforme undergoing the standard Stupp protocol.<sup>12</sup> GINI has also been suggested as a valuable predictor of survival outcomes in grade 4 adult-type diffuse gliomas.<sup>13</sup> Since immune-nutrition-inflammation also plays a key role in the initiation and development of CSFP, we speculated that the newly developed indicator may be a reliable tool for predicting the presence of CSFP in ANOCA patients. Hence, the present study aimed to investigate the association between GINI and CSFP in patients with ANOCA, which could be helpful for risk stratification and optimal management of these specific populations.

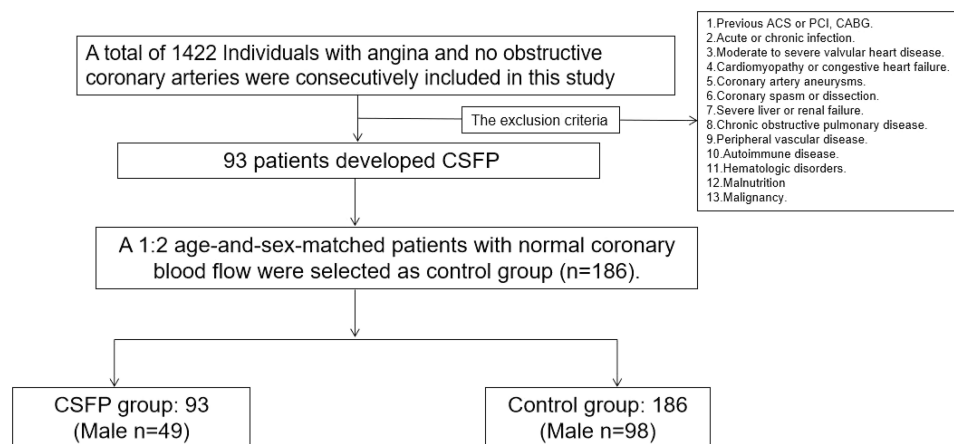
## Methods

### Study Population

This study was conducted between May 2019 and May 2024. The flowchart of the study is shown in Figure 1. The clinical and angiographic characteristics of 1422 individuals with ANOCA were recorded and analyzed. In total, 93 patients were diagnosed with CSFP (CSFP group). We selected two age and sex-matched patients from each of the 93 individuals. If there were more than 2, we used a simple random sampling method to select controls (n=186). The exclusion criteria are shown in Figure 1. This study was approved by the ethics committee of Luohu People's Hospital and consent was obtained from all participants. This study was conducted in compliance with the Declaration of Helsinki. All patients informed consent before participation.

### Coronary Angiography

All the patients received Judkins coronary angiography (CAG), and the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) was used to assess the coronary blood flow.<sup>14</sup> The first frame was determined when the contrast medium filled 70% of the proximal coronary vessel. The last frame was obtained when the contrast reached the mustache area for the left anterior descending artery (LAD), distal bifurcation of the longest bifurcation segment for the left circumflex artery (LCX), and first branch of the posterolateral artery for the right coronary artery (RCA).<sup>14</sup> The TFC of LAD was divided by 1.7 to acquire the corrected TFC (cTFC) for the LAD.<sup>14</sup> The cut-off value of TFC for the diagnosis



**Figure 1** The study flowchart.

of CSFP was  $36.2 \pm 2.6$  for the LAD ( $21.1 \pm 1.5$  cTFC),  $22.2 \pm 4.1$  for the LCX, and  $20.4 \pm 3.1$  for the RCA.<sup>14</sup> The mean TFC (mTFC) was calculated by dividing the sum of the TFC of the three coronary arteries by three.<sup>2,7-10</sup>

## Laboratory Measurements

Blood samples were obtained from the antecubital area after overnight fasting on admission, before CAG. Blood routine, biochemical, and lipid indicators were tested in the central laboratory before CAG. The testing of CRP was carried out using the Abbott Architect c8000 Biochemistry Autoanalyzer, while blood cell counts were determined using the RUBY CELL-DYN Ruby version 2.2. The GINI was calculated as  $[(C\text{-reactive protein} \times \text{Monocytes} \times \text{Platelets} \times \text{Neutrophils}) \div (\text{Albumin} \times \text{Lymphocytes})]$ .<sup>11</sup>

## Statistical Analysis

Categorical variables are presented as percentages and compared using the chi-square or Fisher's exact test. Continuous variables are shown as the mean  $\pm$  standard deviation and were compared using *t*-tests. Multivariate regression analyses were used to explore the independent predictors of CSFP. The baseline indicators ( $p < 0.1$ ) were included in the univariate analysis, and parameters with  $p < 0.05$  were then added to the multivariate logistic regression analysis to determine the independent predictors of CSFP. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of the indicators for CSFP and to determine the cut-off value of GINI for the diagnosis of CSFP. The 2-sided  $P < 0.05$  was considered statistically significant.

## Results

### Baseline and Clinical Characteristics

Among 1381 individuals (excluding 41 patients), the incidence of CSFP was 6.73%. The demographic and clinical characteristics of patients are shown in Table 1. Although patients in the CSFP group had a higher prevalence of current smoking, hypertension, and diabetes mellitus, no significant difference was found between the two groups ( $p > 0.05$ ) (Table 1). Other demographic characteristics, including age, sex, and BMI, were also comparable between the two groups ( $p > 0.05$ ) (Table 1). The medication history before admission was also similar between the two groups ( $p > 0.05$ ) (Table 1).

### Laboratory Parameters of the Two Groups

The comparison of laboratory parameters is displayed in Table 2. Patients with CSFP had an elevated CRP level, white blood cell (WBC) count, neutrophil count, GINI, fasting blood glucose (FBG) level, and a lower lymphocyte count ( $P < 0.05$ ). Other indicators including monocyte count, platelets count, Cr, uric acid, ALB, total cholesterol (TC),

**Table 1** Baseline Characteristics and Medication of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
Age, years	56.8 $\pm$ 9.3	56.8 $\pm$ 9.3	1
Male sex, n (%)	49(52.7)	98(52.7)	1
BMI, Kg/m <sup>2</sup>	25.3 $\pm$ 3.4	25.6 $\pm$ 3.6	0.471
Current smoking, n (%)	31(33.3)	42(22.6)	0.061
Hypertension, n (%)	38(40.9)	62(33.3)	0.235
Diabetes mellitus, n (%)	29(31.2)	38(20.4)	0.054
ACEI/ARB/ARNI, n (%)	25(26.9)	46(24.7)	0.771
Beta-blocker, n (%)	22(23.7)	40(21.5)	0.760
Calcium canal blocker, n (%)	20(21.5)	42(22.6)	0.880
Antiplatelet, n (%)	26(28.0)	57(30.6)	0.679
Statin, n (%)	28(30.1)	55(29.6)	1
Nitrates, n (%)	32(34.4)	52(28.0)	0.272

**Abbreviations:** BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor enkephalinase inhibitor.

**Table 2** Laboratory Parameters of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
CRP, mg/dL	2.6±2.1	1.5±1.8	<0.001
WBC count, 10 <sup>9</sup> /L	7.9±3.0	6.8±1.9	<0.001
Neutrophils count, 10 <sup>9</sup> /L	5.6±2.5	4.4±1.9	<0.001
Lymphocytes count, 10 <sup>9</sup> /L	1.6±0.5	1.7±0.6	0.046
Monocytes count, 10 <sup>9</sup> /L	0.6±0.2	0.6±0.2	0.228
Platelets count, 10 <sup>9</sup> /L	216.7±53.9	206.5±54.5	0.139
GINI	343.2±269.2	165.9±198.9	<0.001
FBG, mmol/l	5.7±0.4	5.6±0.6	0.015
Cr, mmol/l	74.2±28.3	70.9±18.6	0.248
Uric acid, umol/L	359.6±112.1	353.3±98.3	0.632
ALB, g/L	39.5±3.1	40.2±2.9	0.057
TC, mmol/l	4.3±0.8	4.4±0.9	0.406
TG, mmol/l	1.6±1.0	1.7±1.3	0.298
HDL-C, mmol/l	1.0±0.3	1.0±0.3	0.979
LDL-C, mmol/l	2.7±0.6	2.7±0.7	0.540

**Abbreviations:** CRP, C-reactive protein; WBC, white blood cell; GINI, global immune-nutrition inflammation index; FBG, fasting blood glucose; Cr, creatinine; ALB, albumin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) showed no statistically significant differences ( $p>0.05$ ) (Table 2).

## Angiographic Findings of the Two Groups

The comparison of angiographic findings is presented in Table 3. In total, 93 patients developed CSFP: 29% (27) in one vessel, 28% (26) in two vessels, and 43% (40) in three vessels (Table 2). From the aspect of arteries affected, the most frequently affected was the RCA (Table 3). The TFCs in the CSFP group were significantly higher than those in the controls ( $p < 0.05$ ) (Table 3).

**Table 3** Angiographic Findings of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
TIMI frame count			<0.001
LAD	34.8±5.0	26.1±1.5	
LCX	23.1±4.2	19.5±2.8	
RCA	25.5±3.1	18.9±1.9	
Mean TFC	27.8±2.8	21.5±1.4	
Distribution of SCFP			
LAD, n (%)	69 (74.2)		
LCX, n (%)	58 (62.4)		
RCA, n (%)	72 (77.4)		
Numbers of vessels involved in SCFP			
1, n (%)	27 (29.0)		
2, n (%)	26 (28.0)		
3, n (%)	40 (43.0)		

**Abbreviations:** TIMI, thrombolysis in myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TFC, TIMI frame count; CSFP, coronary slow flow phenomenon.

**Table 4** Univariate and Multivariate Logistic Regression Analysis for Presence of SCFP

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Diabetes mellitus	1.174	0.887–1.521	0.541			
Current smoking	0.583	0.336–1.012	0.055			
FBG	1.771	1.113–2.817	0.016	1.955	1.168–3.271	0.001
GINI	1.003	1.002–1.004	<0.001	1.003	1.002–1.004	<0.001

**Abbreviations:** FBG, fasting blood glucose; GINI, global immune-nutrition inflammation index.

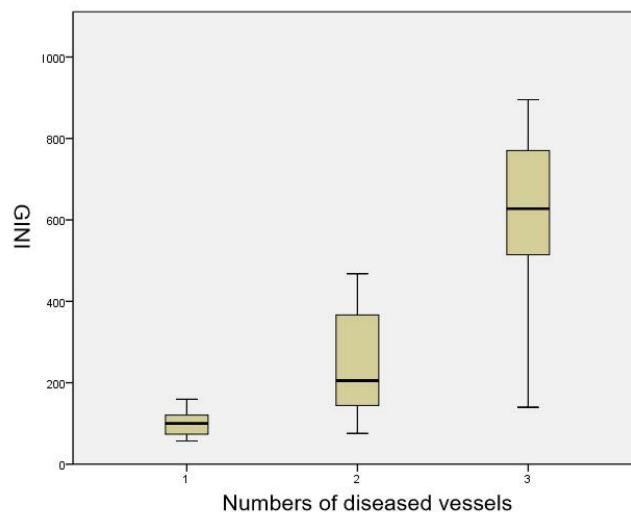
## Predictors of CSFP

Univariate logistic regression analysis showed that GINI and FBG levels were associated with CSFP and were added to the multivariate logistic analysis to investigate the independent predictors for the occurrence of CSFP. We discovered that the GINI and FBG levels were independent predictors of CSFP in patients with ANOCA (Table 4). Moreover, we found that the more vessels affected by CSFP, the higher the GINI level (Figure 2). The ROC curve showed that GINI had a better predictive value than indicators alone (Table 5). When the GINI was >84.1, the sensitivity and specificity were 88.2% and 58.7%, respectively ( $P < 0.001$ ) (Figure 3).

## Discussion

Our study revealed that the GINI and FBG levels were independent predictors of CSFP in patients with ANOCA. In addition, we found that GINI had a higher predictive value than the indicators alone. Moreover, the GINI increased as the number of arteries involved in CSFP increased. The GINI is a reliable indicator of risk assessment and a potential intervention target for CSFP in ANOCA.

ANOCA has been suggested as a common clinical entity. Nearly half of patients suspected of having coronary artery disease (CAD) undergoing CAG were found to have normal coronary arteries,<sup>15</sup> which presents great challenges for the clinical management of these patients. They have unique and diverse pathogenesis. Moreover, ANOCA is quite different from the traditional atherosclerotic disease, which requires a new diagnostic method and new treatment strategies. Nonetheless, coronary microvascular disorders are the primary pathogenesis of ANOCA.<sup>15</sup> Therefore, coronary function testing (CFT) is important for diagnosis and subtype determination.<sup>15</sup> However, in clinical practice, CFT is difficult to perform in all ANOCA patients. Therefore, exploring alternative indicators for assessing ANOCA is of clinical



**Figure 2** Correlation between the number of vessels affected by CSFP and GINI.

**Table 5** ROC Analysis of the Elevated Parameters

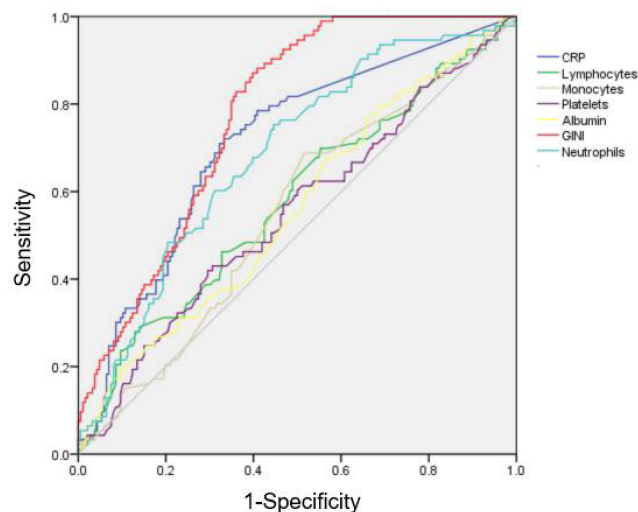
	AUC	95% CI	P value
CRP	0.710	0.646–0.775	<0.001
Neutrophils	0.684	0.619–0.749	<0.001
Lymphocytes	0.577	0.505–0.649	0.036
Monocytes	0.551	0.480–0.621	0.168
Platelets	0.550	0.477–0.622	0.175
ALB	0.559	0.488–0.631	0.106
GINI	0.774	0.721–0.827	<0.001

**Abbreviations:** CRP, C-reactive protein; ALB, albumin; GINI, global immune-nutrition inflammation index.

significance. The international standardization of diagnostic criteria for microvascular angina suggested CSFP as a subtype of microvascular angina (MVA).<sup>3</sup> Therefore, the coronary blood flow can be used to assess microvascular function in clinical practice. Investigating the predictors of CSFP could help us to understand the possible pathogenesis of ANOCA.

As early as 1972, angiographic findings of CSFP have been reported by Tambe et al.<sup>1</sup> However, in the academic background of that time, CSFP was only recognized as an angiographic finding, and its clinical significance was not determined. However, with the rapid development of interventional cardiology, especially intracoronary function testing, the importance of CSFP has gradually been recognized. Reportedly, 20% of patients with CSFP experience recurrent chest pain resembling acute coronary syndrome.<sup>8–10</sup> Moreover, in some cases, CSFP is associated with sudden cardiac death<sup>4</sup> or the presence of ST-segment elevation myocardial infarction (STEMI).<sup>5</sup> Therefore, investigation of potential risk factors is essential for the management of these patients.

Although the pathogenesis of CSFP remains unclear, chronic inflammatory reactions play a fundamental role in the initiation and development of CSFP. As a well-established parameter for assessing inflammation, C-reactive protein (CRP) level has been suggested as a reliable risk factor for CSFP.<sup>16</sup> Moreover, in recent years, combined indicators from routine blood tests to assess the degree of inflammatory reaction, such as the neutrophil-to-lymphocyte ratio (NLR),<sup>7</sup> systemic immune-inflammation index (SII) (NLR×total preoperative peripheral platelet count),<sup>7</sup> systemic inflammation response index (SIRI) (neutrophil count×monocyte count/lymphocyte count),<sup>9</sup> platelet-to-lymphocyte ratio,<sup>17</sup> and Pan-Immune-Inflammation Value (neutrophil count×platelet count×monocyte count/lymphocyte count)<sup>18</sup> have also been

**Figure 3** ROC curve showing the predicting value of risk factors for the presence of CSFP.

demonstrated to be associated with the presence of CSFP. Moreover, the most abundant protein in human plasma, albumin, together with its derivative parameters, such as the plasma fibrinogen-to-albumin ratio,<sup>10</sup> plasma uric acid-to-albumin ratio,<sup>2</sup> and neutrophil percentage-to-albumin ratio,<sup>8</sup> have also been demonstrated as independent predictors of CSFP. The GINI combined indicators associated with CSFP, such as CRP, neutrophil count, platelet count, monocyte count, lymphocyte count, and albumin, so we suggest that the GINI may provide a better predictive value than the indicators alone. Therefore, we aimed to explore the association between GINI and CSFP in ANOCA patients.

As a newly developed indicator, GINI combines blood routine, CRP, and albumin, which can comprehensively reflect the immunological, inflammatory, and nutritional status of patients. However, the pathogenesis of CSFP and the close relationship between GINI and CSFP in patients still remain undetermined. GINI participated in initiation and development in various ways. We suggest that it is more reasonable and logical to interpret these results based on biochemical or cellular parameters separately. GINI can be presented as the CRP-to-albumin ratio (CAR)×PIV, CAR×SIRI×total preoperative peripheral platelet count, or CAR×SII×monocyte count. Recently, an association between the SII, SIRI, PIV, and CSFP has been reported. These indicators are calculated using three or more markers, and have been suggested as valuable predictors of CSFP. In a study performed by Wang et al that included 89 patients with CSFP and 167 normal controls with chest pain and normal coronaries, it was suggested that SII was an independent predictor of CSFP occurrence.<sup>7</sup> Subsequently, Kaplangoray et al suggested in a retrospective study that PIV showed a superior predictive value for CSFP than NLR, PLR, and SII and could serve as a valuable and independent predictor of CSFP.<sup>18</sup> A more recent study by Prof Wang included 1422 patients with ischemia and no obstructive coronary arteries (INOCA), of whom 89 were diagnosed with CSFP. They discovered that patients with CSFP had an elevated SIRI, which could improve the predictive value of CSFP compared with neutrophils, monocytes, and lymphocytes alone.<sup>9</sup> These newly developed indices showed a better predictive value than the binary indices, which may be attributed to the more integrated parameters developed and less individualized differences.

As reported in previous studies, nutrition has been suggested as an important parameter in assessing the occurrence, development, and prognosis of various cardiovascular disease. Plasma albumin is the most widely used indicator for assessing the status of human nutrition. Numerous studies have demonstrated the predictive value of albumin level in the presence of CSFP.<sup>2,8,10</sup> As a comprehensive indicator, GINI was first developed by Topkan et al,<sup>12</sup> and has been demonstrated to be a prognostic indicator of tumor-related diseases.<sup>12,13</sup> This study is the first to demonstrate an association between GINI and CSFP, which may provide a valuable and helpful parameter for the identification and management of patients with CSFP. We discovered that a higher GINI was a risk factor and independent predictor of CSFP in patients with ANOCA.

## Limitations

This study had some limitations. First, it was a single-center study with a limited sample size. Second, due to the complex pathogenesis and varied indicators for predicting CSFP in the literature, although multivariate analysis was performed, residual confounding remains possible (medication adherence, socioeconomic factors, et al), which may introduce bias. Third, due to the inherent limitations of the retrospective design, there may bring in a bias in the present study. Moreover, the study establishes associations, not causality, due to its observational design. Fourth, other important parameters for assessing inflammatory status, including IL-6, were not tested in our study. Moreover, whether anti-inflammatory treatment is useful in the management of CSFP remains unclear.

## Conclusion

We suggested that higher GINI was a reliable indicator for the prediction of the presence of CSFP in ANOCA patients. GINI is significantly associated with CSFP, and further prospective studies are needed to confirm causality. The GINI is a promising parameter for the identification and management of patients with CSFP.

## Data Sharing Statement

The datasets are available from the corresponding author upon reasonable request.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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