CLINICAL STUDY

Association of contrast-induced nephropathy with bare metal stent restenosis in STEMI patients treated with primary PCI

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ABSTRACT

Background: Contrast induced nephropathy (CIN) has been proven as a clinical condition related to adverse cardiovascular outcomes. However, relationship between CIN and stent restenosis (SR) remains unclear. In this study, we aimed to investigate the association of CIN with SR rates after primary percutaneous coronary intervention (PCI) and bare metal stent (BMS) implantation.

Methods: A total number of 3225 patients who had undergone primary PCI for STEMI were retrospectively recruited. The medical reports of subjects were searched to find whether the patients had a control coronary angiogram (CAG) and 587 patients with control CAG were included in the study. The laboratory parameters of 587 patients were recorded and patients who developed CIN after primary PCI were defined. Contrast induced nephropathy was defined as either a 25% increase in serum creatinine from baseline or 0.5 mg/dL increase in absolute value, within 72 h of intravenous contrast administration.

Results: The duration between primary PCI and control CAG was median 12 months [8–24 months]. The rate of SR was significantly higher in CIN (+) group compared to CIN (−) group (64% vs. 46%, \(p<0.01\)). In multivariate Cox regression analysis, male gender, stent length, admission WBC levels and presence of CIN (HR 1.39, 95% CI 1.06–1.82, \(p<0.01\)) remained as the independent predictors of SR in the study population.

Conclusion: Male gender, stent length, higher serum WBC levels and presence of CIN are independently correlated with SR in STEMI patients treated with BMS implantation.

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Introduction

Percutaneous coronary intervention (PCI) is an effective treatment in ST elevation myocardial infarction (STEMI).1 Stent thrombosis and stent restenosis (SR) are two major causes of mortality and morbidity after stent implantation. The rate SR after primary PCI is 12.7% in patients treated with drug eluting stents (DES) and is 20.1% in patients treated with bare metal stents (BMS), but the rate of mortality is similar between the two groups.2 Oxidative stress, inflammation and neointimal tissue proliferation constitute the main pathophysiological mechanisms of SR and markers of inflammation have been shown to predict risk for SR.3–6

Impaired renal function is a risk factor for cardiovascular diseases and in patients with AMI, admission renal function or worsening during the hospitalization has been shown to indicate higher risk for adverse events.7–9 The impact of renal function on development of SR has not been well established in literature.10–12 Contrast induced nephropathy (CIN) is an important complication associated with contrast media (CM) exposure after primary PCI causing higher mortality rates.13,14 However, the correlation of CIN with risk of SR in patients with STEMI treated with stent implantation has not been evaluated before.

Methods

Study population

Medical records of consecutive patients, who were admitted to the emergency department of Dr. Siyami Ersek Research and Training Hospital, with the diagnosis of STEMI and who underwent primary PCI and stent implantation between January 2008 and January 2014...
were retrospectively collected. Patients were enrolled in the study if they fulfilled the following criteria: (1) presented within 12 h of the onset of symptoms (typical chest pain lasting for >30 min), (2) ST segment elevation of greater than or equal to 1 mm in at least two consecutive leads, and (3) treatment with BMS deployment. Patients who did not have stent deployment or had undergone surgical revascularization procedures or had undergone drug eluting stent (DES) implantation were excluded from the study. In addition, patients who had serum creatinine higher than 2.0 mg/dL and who had post-procedural TIMI flow grade 0 were excluded from the study. A total number of 3225 patients who had undergone primary PCI for STEMI were retrospectively recruited. The medical reports of subjects were searched for whether the patients had a control coronary angiogram (CAG) and 587 patients with control CAG were included in the study. The laboratory parameters of 587 patients were recorded and patients who developed CIN after primary PCI were defined. When CAGs were evaluated 292 patients were found to have SR. The predictors of CIN and also SR were investigated in the study population.

Definitions

Data regarding clinical and demographic properties and laboratory parameters were collected from medical records. In addition, total volume of contrast which was used during primary PCI was recorded from angiography database. Hypertension (HT) was defined as a systolic pressure >140 mmHg and/or a diastolic pressure >90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus (DM) was defined as a fasting glucose level >126 mg/dL and/or if the patient was taking anti-diabetic medication. Individuals who reported smoking of at least one cigarette per day during the year before examination were classified as smokers. Contrast induced nephropathy was defined as either a 25% increase in serum creatinine from baseline or a 0.5 mg/dL increase in absolute value, within 72 h of intravenous contrast administration. The study protocol was approved by the local ethics committee.

Coronary angiography data

Angiographic data regarding primary PCI was obtained from the cardiac catheterization laboratory records and was examined by two independent observers. All patients received chewable aspirin (300 mg, unless contraindicated) and clopidogrel (600 mg, loading dose) before a primary PCI. An emergency coronary angiography was performed by a percutaneous femoral approach. In all cases, nonionic, low-osmolality CM was used. The contralateral artery was first injected. The infarct-related artery was graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Heparin (10,000 U) was administered after coronary anatomy was defined. Coronary artery stenosis of more than 50% was considered clinically significant. Primary coronary interventions, including balloon angioplasty and/or stent implantation, were performed only for infarct related artery (IRA) according to lesion anatomy. For each procedure, interventional success at the acute phase was defined as an obstruction and stenosis of the IRA having been reduced to less than 50% stenosis with TIMI 3 flow after primary PCI. After stent placement, clopidogrel was used for more than 1 year and aspirin was used indefinitely.

Second coronary angiographies were performed because of clinical indications, including symptoms of angina (stable or unstable) and abnormal noninvasive test results (treadmill exercise tests or myocardial perfusion scintigraphy). The duration between primary PCI and control CAG was median 12 months [8–24 months]. Data of control coronary angiograms were interpreted by an independent interventional cardiologist who was blinded to patients’ characteristics. Stent restenosis was defined as in-segment restenosis which is greater than 50% stenosis within or immediately adjacent (within 5 mm) to the implanted stent(s) according to the control angiographic data. Patients who had definite or probable stent thrombosis according to the Academic Research Consortium definitions were also excluded from the study.10

Laboratory analysis

The results of laboratory parameters were collected by using electronic database of the hospital. For creatinine measurements, reports of biochemical laboratory analyses belonging to admission blood sample and blood samples of first 72-h of hospitalization were recruited. The highest creatinine measurement and admission creatinine levels were used to define CIN in each patient. For other parameters except for lipid profile and glucose levels, reports of admission blood samples were used. For lipid profile, the results of fasting blood samples collected within the 24-h of hospitalization were used. Total cholesterol, HDL-C and triglyceride levels were measured enzymatically (Architect c-Systems, Abbott, IL) and LDL-C levels were measured from these lipid parameters with Friedewald formula. Complete blood count (CBC) testing utilized clinical laboratory methods (Coulter LH 780 Hematology Analyzer, Beckman Coulter Ireland Inc., Mervue, Galway, Ireland) for hemoglobin,
white blood cell count (WBC) and platelets. Hs-CRP measurements were conducted on Cobas Integra Analyzer (Roche Diagnostics, Istanbul, Turkey) using turbidimetric method.

**Statistical analysis**

All data are presented as a mean ± SD or a median [25th and 75th percentile] for parametric variables and as percentages for categorical variables. Continuous variables were checked for the normal distribution assumption using Kolmogorov–Smirnov statistics. Categorical variables were tested by Pearson’s χ² test and Fisher’s exact test. Differences between the groups were evaluated using Student’s t-test or Mann–Whitney U test as appropriate. Binary logistic regression analysis was used and forward stepwise multivariable regression models were created to identify the independent predictors of CIN. Variables with p < 0.10 in univariable analysis were included in the multivariable model. In addition, Cox regression analyses were used to investigate the univariable and multivariable predictors of SR during the follow-up and Hazard Ratios (HR) with 95% confidence intervals (CI) were reported for every 1 unit increase of continuous variables. Kaplan–Meier estimates and curves were generated, and comparisons were made using log-rank tests. A p value <0.05 was considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, IL).

**Results**

A total number of 587 patients were included in the study. Patients were categorized in two groups: as patients who developed CIN (n = 128) and patients who did not develop CIN (n = 459) during the first 72-h of hospitalization. The demographic, clinical properties and angiographic data of the CIN (+) and CIN (−) groups are summarized in Table 1. The groups were comparable regarding age, gender, HT, DM, dyslipidemia, smoking status, history of MI and PCI, rate of TIMI 3 flow restoration and left ventricular ejection fraction. Admission SBP values were lower in CIN (+) group compared to CIN (−) group (124 ± 14 vs. 130 ± 17 mmHg, p < 0.01). The distribution of culprit arteries, the frequency of the patients treated with direct stenting. Gp2b3a antagonist infusion were similar between two groups. The mean diameter and length of implanted stents were not different between the groups (p = 0.26 and p = 0.56, respectively). The frequency of patients with severe thrombus and mean total contrast volume were higher in CIN (+) group compared to CIN (−) group (28% vs. 19%, p = 0.03 and 189 ± 23 vs. 156 ± 24 mL, p < 0.01).

The duration of follow-up was median 12 months [8–24 months] and was not different between the groups (p = 0.41). Stent restenosis was observed in 292 patients corresponding to 50% of the study population. Stent restenosis was observed in 82 (64%) cases in CIN (+), in 210 (46%) cases in CIN (−) group which was significantly higher (p < 0.01).

Comparison of the laboratory parameters between groups is shown in Table 2. Maximal creatinine and admission CRP levels were significantly higher in CIN (+) group compared to CIN (−) group (1.29 ± 0.56 vs. 0.99 ± 0.19 mg/dL, 8 [4.6–11] vs. 5.0 [3.1–9.1] mg/L, p < 0.01 and p < 0.01). Other laboratory parameters did not differ significantly between two groups.

In univariable logistic regression model, total volume of CM, systolic blood pressure on admission, WBC counts, CRP levels were significantly correlated with CIN (p < 0.05 for each variable). Whereas, age, DM, HT, admission creatinine levels, fasting glucose levels, left ventricular EF were not correlated with CIN in univariable model. In multivariable logistic regression model only total volume of CM used (OR 1.07, 95% CI: 1.05–1.09; p < 0.01) and systolic blood pressure on admission (OR 0.97, 95% CI: 0.95–0.99, p = 0.04)

### Table 1. Comparison of the demographic, clinical, and angiographic properties between CIN (+) group and CIN (−) group.

| Characteristics | CIN (+)     | CIN (−)     | p Values |
|-----------------|-------------|-------------|----------|
| Age             | 56.9 ± 10.3 | 55.7 ± 9.7  | 0.25     |
| Male, n (%)     | 85 (66)     | 303 (65)    | 0.93     |
| Hypertension, n (%) | 63 (49)     | 180 (39)    | 0.16     |
| DM, n (%)       | 34 (26)     | 125 (27)    | 0.88     |
| Dyslipidemia, n (%) | 41 (32)     | 160 (33)    | 0.65     |
| Smoking, n (%)  | 61 (47)     | 194 (42)    | 0.49     |
| Systolic BP, mmHg | 124 ± 14    | 130 ± 17    | <0.01    |
| LV EF, %        | 46 ± 10     | 47 ± 9      | 0.26     |
| Previous PCI, n (%) | 11 (8)      | 35 (7)      | 0.90     |
| Previous MI, n (%) | 10 (7)      | 24 (5)      | 0.43     |
| Culprit artery  |             |             |          |
| CAD, n (%)      | 75 (58)     | 225 (49.0)  | 0.25     |
| Cx, n (%)       | 18 (14)     | 82 (17)     | –        |
| RCA, n (%)      | 35 (27)     | 140 (30)    | –        |
| Severe thrombus, n (%) | 36 (28)     | 87 (19)     | 0.03     |
| Pre-PIC TIMI >0, n (%) | 37 (29)     | 141 (31)    | 0.68     |
| Post-PIC TIMI 3 flow, n (%) | 123 (96)    | 448 (97)    | 0.36     |
| Direct stenting, n (%) | 83 (65)     | 312 (68)    | 0.51     |
| Stent diameter, mm | 2.95 ±0.57  | 3.0 ±0.54   | 0.26     |
| Stent length, mm | 19.4 ±0.9   | 19.1 ±0.61  | 0.56     |
| Gp IIb/IIIa, n (%) | 45 (35)     | 167 (36)    | 0.71     |
| Total contrast volume, mL | 189 ±23     | 156 ±24     | <0.01    |
| Control CAG, months | 12.5 [7.5–25.5] | 13 [9–27]  | 0.41     |
| Stent restenosis, n (%) | 82 (64)     | 210 (46)    | <0.01    |

DM: diabetes mellitus; LV EF: left ventricular ejection fraction; CAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery; GpIIb/IIa: glycoprotein IIb/IIIa receptor antagonist; CAG: coronary angiography; PCI: percutaneous coronary intervention; MI: myocardial infarction. Continuous variables are presented as mean ± SD or median [25th and 75th percentile].
Table 2. Comparison of the laboratory parameters between CIN (+) group and CIN (−) group.

| Characteristics          | CIN (+) | CIN (−) | p Values |
|--------------------------|---------|---------|----------|
| Hemoglobin, g/dL         | 143 ± 2.2 | 143 ± 1.4 | 0.36     |
| WBC, 10⁹/μL              | 12.4 ± 3.7 | 11.6 ± 4.0 | 0.06     |
| Platelet, 10⁹/μL         | 241 ± 59  | 242 ± 62  | 0.86     |
| Glucose, mg/dL           | 107 [92–129] | 103 [94–130] | 0.08     |
| Total cholesterol, mg/dL | 184 ± 44  | 185 ± 47  | 0.92     |
| LDL-cholesterol, mg/dL   | 115 ± 37  | 111 ± 38  | 0.25     |
| HDL-cholesterol, mg/dL   | 37 ± 10   | 39 ± 10   | 0.14     |
| Triglycerides, mg/dL     | 145 [101–193] | 146 [100–199] | 0.76     |
| CK-MB, IU/L              | 129 [49–247] | 120 [60–210] | 0.86     |
| Na, mg/dL                | 137 ± 4.1 | 138 ± 3.8 | 0.12     |
| K, mg/dL                 | 4.3 ± 0.6 | 4.3 ± 0.6 | 0.27     |
| CRP, mg/L                | 8 [4.6–11] | 5.0 [3.1–9.1] | < 0.01  |
| Admission creatinine, mg/dL | 0.86 ± 0.28 | 0.88 ± 0.21 | 0.18    |
| Maximal creatinine, mg/dL | 1.29 ± 0.56 | 0.99 ± 0.19 | < 0.01  |

WBC: white blood cell; LDL: low density lipoprotein; HDL: high density lipoprotein; CK-MB: creatine kinase-muscle brain isoenzyme; Na: sodium; K: potassium; CRP: C-reactive protein.

Continuous variables are presented as mean ± SD or median [25th and 75th percentile].

Table 3. Univariate and multivariate Cox regression analysis for the possible predictors of stent restenosis in the study population.

| Variables                          | Unadjusted HR (95% CI)a | p     | Adjusted HR (95% CI)b | p     |
|------------------------------------|-------------------------|-------|------------------------|-------|
| Age                                | 0.99 (0.98–1.001)       | 0.42  | 0.99 (0.98–1.001)      | 0.42  |
| Male gender                        | 1.48 (1.14–1.91)        | < 0.01| 1.52 (1.16–2.1)        | < 0.01|
| Hypertension                       | 0.81 (0.63–1.01)        | 0.06  | 0.86 (0.67–1.01)       | 0.23  |
| Smoking                            | 1.05 (0.84–1.32)        | 0.65  | 0.65                   | 0.65  |
| DM                                 | 0.88 (0.67–1.15)        | 0.35  | 0.35                   | 0.35  |
| Presence of pre-PCI                | 1.57 (0.22–11.2)        | 0.65  | 0.65                   | 0.65  |
| TIMI 0 flow                        | 1.44 (1.11–1.86)        | < 0.01| 1.28 (0.86–1.91)       | 0.23  |
| Direct stenting                     | 0.89 (0.70–1.12)        | 0.31  | 0.31                   | 0.31  |
| Stent diameter                     | 1.16 (0.91–1.45)        | 0.2   | 0.2                    | 0.2   |
| Stent length                       | 1.04 (1.02–1.06)        | < 0.01| 1.03 (1.02–1.05)       | < 0.01|
| Gp2b3a therapy                     | 1.31 (1.03–1.67)        | 0.03  | 1.02 (0.71–1.49)       | 0.89  |
| Hemoglobin                         | 1.07 (0.98–1.17)        | 0.13  | 0.13                   | 0.13  |
| WBC                                | 1.04 (1.01–1.07)        | 0.02  | 1.04 (1.01–1.08)       | < 0.01|
| CRP                                | 1.02 (0.99–1.04)        | 0.29  | 0.29                   | 0.29  |
| Admission creatinine               | 0.73 (0.44–1.22)        | 0.23  | 0.23                   | 0.23  |
| Maximal creatinine                 | 1.11 (0.85–1.44)        | 0.46  | 0.46                   | 0.46  |
| CIN (+) vs. CIN (−)                | 1.44 (1.12–1.87)        | < 0.01| 1.39 (1.06–1.82)       | < 0.01|

DM: diabetes mellitus; Gp2b3a: glycoprotein IIb/IIIa receptor antagonist; WBC: white blood cell; CRP-reactive protein.

Univariate Cox regression analysis was performed to investigate the possible predictors of SR in the study population (Table 3). In univariate regression analysis, male gender, stent length, presence of severe thrombus, Gp2b3a therapy, WBC levels and development of CIN were correlated with SR. In multivariate Cox regression analysis, using model adjusted for parameters with p values < 0.10 in univariate analysis, presence of CIN (HR 1.39, 95% CI: 1.06–1.82, p = 0.01), increased WBC levels (HR 1.04, 95% CI: 1.01–1.08, p < 0.01), stent length and male gender independently predicted SR. The Kaplan–Meier curve showed a significant difference in SR rates between CIN (+) and CIN (−) groups (Figure 1).

Discussion

The main findings of the present study are: male gender, stent length, elevated levels of WBC and developing of CIN after primary PCI were independent predictors of SR in STEMI patients treated with primary PCI and BMS implantation. In addition, in STEMI patients treated with primary PCI, we have found that only systolic blood pressure on admission and total volume of CM used were independently correlated with CIN.

Primary percutaneous coronary intervention is the gold standard treatment modality of patients with STEMI. Coronary stents have become the prominent revascularization method as the rates of recoiling, re-occlusion and target vessel revascularization (TVR) is high after balloon angioplasty without stent implantation. Stent thrombosis and SR are the major problems after stent implantation.15 Various factors related with the patients (smoking status, DM), the anatomical properties of the coronary arteries (small vessel diameter, long lesions) and the type of the stents have been defined as predictors of SR.3 Drug eluting stents which inhibit the inflammatory response and neo-intimal proliferation within the vessel wall dramatically decreases the rates of SR after PCI.

Prognostic importance of renal failure has been shown in patients with coronary artery disease, acute coronary syndrome (ACS) and STEMI.7,16,17 Similar with admission renal failure, in-hospital worsening of renal function is also correlated with short-term mortality in ACS patients and long-term mortality after MI.7,8 In literature, the effect of renal failure on SR has not been clarified yet. Renal insufficiency was not found to be related with SR of DES and BMS.18–21 However, Sukhija et al. indicated that creatinine levels higher than 1.5 mg/dL predicted SR in diabetic patients with ACS.22 In another study conducted in STEMI patients, increased admission creatinine levels were found to be associated with restenosis of BMS.23 Similarly, urinary albumin-to-creatinine ratio which is a marker of renal insufficiency was reported as an independent predictor of restenosis of DES and BMS after elective PCI.24 Upon these conflicting results, a meta-analysis was performed and it was reported that 1 year-TV rates were similar between patients with mild and moderate renal failure.25 In our study, admission creatinine level was not an

remained as the independent correlates of CIN in the study population.

Univariate and multivariate Cox regression analyses were performed to investigate the possible predictors of SR in the study population (Table 3). In univariate regression analysis, male gender, stent length, presence of severe thrombus, Gp2b3a therapy, WBC levels and development of CIN were correlated with SR. In multivariate Cox regression analysis, using model adjusted for parameters with p values < 0.10 in univariate analysis, presence of CIN (HR 1.39, 95% CI: 1.06–1.82, p = 0.01), increased WBC levels (HR 1.04, 95% CI: 1.01–1.08, p < 0.01), stent length and male gender independently predicted SR. The Kaplan–Meier curve showed a significant difference in SR rates between CIN (+) and CIN (−) groups (Figure 1).
independent predictor of SR in STEMI patients treated with BMS implantation.

Contrast induced nephropathy is an important clinical problem after exposure to CM such as coronary angiography and interventional procedures. While incidence of CIN varies widely among the existing literature, it is thought to be about 19% in the setting of primary PCI. Several predictors of CIN have been defined and in our study, we have found that systolic blood pressure and total volume of CM used are correlated with risk of CIN. In STEMI, early coronary intervention is important for myocardial salvage and in most of the cases admission laboratory parameters including creatinine levels could not be evaluated before CAG. As restoration of the coronary flow is vital, higher volumes of CM are usually needed compared to diagnostic and elective interventional procedures. Some patients may have depressed cardiac functions and lower blood pressure which deteriorated perfusion of renal cells. In addition, acute MI provokes a systemic reaction causing inflammation and oxidative stress which increases the susceptibility of renal cells to toxic effects of CM.

Studies about the relationship between CIN and rates of SR are limited. In a recent study Giacoppo et al. reported that CIN is associated with higher rates of TVR in ACS patients during a follow-up period of 1-year. However, their study is heterogeneous regarding the type of the implanted stents (65% DES) and the treatment regimens. In our study, for the first time in literature, we have found that in-hospital worsening of renal function after primary PCI may predict SR of BMS. Patients with CIN had 1.39 times higher risk for development of SR. Even if, our study was retrospective, we used angiographically diagnosed SR as the outcome rather than reinfarction and TVR. In addition, we excluded cases with DES implantation and stent thrombosis in order to delineate the correlation of CIN with SR developing secondary to inflammatory reactions and neo-intimal hyperplasia.

Oxidative stress, inflammation, neo-intimal hyperplasia and vascular remodeling are thought to be involved in pathophysiology of SR. Angioplasty and stent deployment cause dissection of both the intima of the plaque and vessel media. The healing process provokes neointimal hyperplasia which is closely related to the inflammatory milieu in the subendothelial area. Secretion of many cytokines, proliferation of smooth muscle cells and collection of extracellular matrix cause neointimal hyperplasia that leads to SR. Accordingly, increased level of inflammatory markers such as CRP, fibrinogen, interleukin-1beta, interleukin-6, interleukin-10, and the complement components were found to predict SR. In our study, we have found that higher WBC counts were correlated with SR. Higher CRP levels and WBC counts were correlated with CIN in univariable logistic regression analysis, and higher WBC counts were independently correlated with CIN in multivariable model. Our findings support that inflammatory markers

![Figure 1. Kaplan–Meier event-free survival curve for stent restenosis in CIN (+) and CIN (−) groups.](image-url)
are correlated with risk of CIN and SR after BMS implantation in patients with STEMI.

Oxidative stress and inflammation are the major contributors of development of CIN. Oxidative stress markers and paraoxonase-1 activity were found to be independent predictors of CIN in STEMI patients undergoing primary PCI. In another study, CRP levels were found to be correlated with creatinine clearance in patients with acute coronary syndrome. These findings indicate a common systemic pathophysiological pathway which involves inflammatory reactions that cause damage to renal cells and hyper-activation of vascular cells resulting in higher risk for CIN and SR.

**Limitations**

Our study has several limitations. This study was conducted on a retrospective basis and represented a single center experience. Definition of SR was based on visual inspections, not on quantitative measurements. The frequency of patients treated with DESs were low in the STEMI patients during the study period, thus we decided to exclude patients with DES implantation. So, our findings may not be generalized to STEMI patients treated with DES implantation. Despite we have found some relations, we could not draw a causal relationship between CIN and development of SR. The severity of inflammation during the acute phase of STEMI may be a common mechanism for development of CIN and SR. But, as we have collected laboratory data of the first 72 h, we could not show the persistence of elevation of inflammatory markers, especially, hs-CRP levels in the study population.

**Conclusion**

Development of CIN is an important predictor of SR in patients treated with BMS implantation after STEMI. Further studies are needed to confirm and to reveal clinical implications of our findings.

**Disclosure statement**

The authors report no conflicts of interest.

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