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ST-elevation myocardial infarction risk in the very elderly

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ABSTRACT

Background: Despite the high incidence and mortality of ST-segment elevation myocardial infarction (STEMI) among the very elderly, risk markers for this condition remain poorly defined. This study was designed to identify independent markers of STEMI among individuals carefully selected for being healthy or manifesting STEMI in <24 h.

Methods: We enrolled participants aged 80 years or older of whom 50 were STEMI patients and 207 had never manifested cardiovascular diseases. Blood tests, medical and psychological evaluations were obtained at study admission. Odds Ratio (OR) and attributed risk (AR) were obtained by multivariate regression models using STEMI as dependent variable.

Results: Low glomerular filtration rate (GFR) [OR:4.41 (1.78–10.95); $p = 0.001$], reduced levels of HDL-C [OR:10.70 (3.88–29.46); $p = 0.001$], male gender [OR:12.08 (5.82–25.08); $p = 0.001$], moderate to severe depressive symptoms [OR:10.00 (2.82–35.50); $p = 0.001$], prior smoking [OR:2.00 (1.05–3.80); $p = 0.034$] and current smoking [OR:6.58 (1.99–21.70); $p = 0.002$] were significantly associated with STEMI. No association was found between STEMI and age, diabetes, hypertension, mild depressive symptoms, triglyceride or LDL-C.

Conclusions: This is the first case–control study carried out with very elderlies to assess STEMI risk. Our findings indicate that reduced HDL-C, GFR, male gender, smoking habits and moderate to severe depressive symptoms are markers of STEMI in this age group.

General Significance: In Individuals aged 80 or more years, a greater attention must be paid to low HDL-C and GFR at the expense of conventional STEMI risk factors for younger adults such as diabetes mellitus, hypertension and high LDL-C or triglyceride.

1. Introduction

The 20th century was marked by a 300% increase in the elder population in developed countries [1]. Impressively, another similar increase is expected to take place in half of that time in the present century [2]. In developing countries such as China, Brazil, and Colombia, the growth of the aged population is occurring 3-times faster as compared with developed countries [3]. As one might expect, such rapid growth in longevity has generated a new demographic profile in which there is a larger proportion of individuals 80 years or more.

It is well known that both the incidence and mortality from cardiovascular disease (CVD) in the elderly rises with age [4]. Indeed, the mortality rate after ST-segment elevation myocardial infarction (STEMI) in these individuals is 10-fold higher than in those with 65 years or less [5]. These figures are probably underestimated, considering the difficulty of access to emergency units due to walking difficulties or cognitive dysfunction commonly found among these individuals.

Although primary prevention would certainly be the best strategy for reducing morbidity and mortality related to STEMI, there is currently insufficient data to identify risk predictors in this specific population of patients. In addition, the combined effect of the enhanced incidence and

Abbreviations: CVD, cardiovascular disease; STEMI, ST-segment elevation myocardial infarction; BHS, Brasília Heart Study; MI, myocardial infarction; CK-MB, MB fraction of creatine kinase; BSHA, Brasília Study on Healthy Aging; BDI-II, Beck Depression Inventory version II; GDS, Geriatric Depression Scale; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDTA, ethylenediamine tetraacetic acid; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; SD, standard deviation; IQR, interquartile range; ANCOVA, analysis of covariance; OR, odds ratio; AR, attributable risk.

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mortality from STEMI may favor a selection bias that can distort the association with traditional risk factors and potentially hinder the identification of new ones. In this context, we compared two cohorts of very elderly individuals (≥80 years) who are healthy or in the first hours after STEMI in order to identify independent risk markers.

2. Material and methods

2.1. Study design and participants

For the present study, cases and controls were selected in a one-to-four ratio matching for age based on two studies databases. Only patients 80 years or older from the Brasília Heart Study (BHS) database were selected for analysis ($n = 50$). BHS is a prospective ongoing observational cohort enrolling STEMI patients admitted at the Hospital de Base do Distrito Federal (Brasília, Brazil) since 2006. BHS inclusion criteria was: (i) <24 h after onset of MI symptoms, (ii) ST-segment elevation of at least 1 mm (frontal plane) or 2 mm (horizontal plane) in 2 contiguous leads and (iii) increased myocardial necrosis markers above reference limit of CK-MB (25 U/L) and troponin (0.04 ng/mL) followed by a decline of both markers. Exclusion criteria were (i) cognitive impairment, (ii) inability to attend follow-up and (iii) other comorbidities that lead to significantly shorter life expectancy. BHS is registered at ClinicalTrials.org (NCT02062554) [6].

The control group was composed of individuals consecutively enrolled in the Brasília Study on Healthy Aging (BSHA) ($n = 207$). BSHA is a prospective cohort of healthy very elderly individuals (80 to 102 years) who voluntarily accepted to participate and were followed at the outpatient clinic of the Biocardios Institute of Cardiology (Brasília, Brazil) since 2008. Exclusion criteria were (i) manifested atherosclerotic disease (MI, stroke, or peripheral arterial disease) as indicated by a medical evaluation, electrocardiogram or echocardiogram, (ii) functional dependence or institutionalization, (iii) cognitive impairment assessed by mini-mental state examination (<13 points), (iv) use of any anti-inflammatory drugs in the last 30 days, (v) current or previous diagnosis of neoplastic or immune inflammatory disease, (vi) chronic obstructive pulmonary disease, (vii) glomerular filtration rate < 25 mL/min/1.73 m^2, (viii) hepatic disease (aspartate or alanine transaminases ≥1.5 upper reference limit), (ix) chronic infectious disease (≥3 months), (x) left ventricle ejection fraction <50% on echocardiography and (xi) neoplastic disease at admission or until the first year after enrollment. Neoplastic disease was investigated through evaluation of fecal occult blood, mammography and clinical breast exam, prostate-specific antigen plasma assay, digital rectal examination and Papanicolaou smear analysis according to current guidelines [7]. BSHA is registered at ClinicalTrials.gov (NCT02366104) [8].

Both studies were carried out in accordance with The Declaration of Helsinki [9], and were approved by the local Ethics Committee (BHS: 083/06 and BSHA: 213/08). Informed consent was obtained from all individual participants included in the study.

2.2. Clinical and psychological evaluation

All participants underwent a structured detailed clinical questionnaire, anthropometric measurements, blood collection and psychological tests. Depressive symptoms manifested in the last weeks before STEMI (BHS study) or before the admission into the BSHA study were evaluated by the use of Beck Depression Inventory version II (BDI-II) or Geriatric Depression Scale (GDS), respectively. These two self-reported inventories were validated in this age group and have shown to be highly correlated [10]. Ex smoking status was defined as smoking cessation for at least 6 months. Diabetes was defined as the use of anti-diabetic medications, fasting glycaemia ≥126 mg/dL or glycated hemoglobin (HbA1c) ≥6.5%. Hypertension was defined by the use of antihypertensive drugs or by the systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg.

2.3. Biochemical analysis

Among STEMI patients, blood samples were obtained in the first 24 h from MI symptoms in order to avoid the reported lipid profile changes that occur after this time window [11]. Among controls, blood samples were obtained at admission. Blood samples with EDTA were centrifuged after collection at 5 °C and at 4500 rpm for 15 min to separate plasma and cells. Biochemical analyses were performed in duplicates. An automatic chemical analyzer was used to do the following analysis: C-reactive protein (CRP; high-sensitivity assay, Cardiophase, Dade Behring, Marburg, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, USA), high-density lipoprotein cholesterol (HDL-C, Roche Diagnostics, Mannheim, USA), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, USA), urea and creatinine (GLDH, Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Glomerular filtration rate (GFR) was estimated by abbreviated MDRD equation: Estimated GFR (mL/min/1.73 m^2) = 186 × (creati-(creatinine/88.4)$^{-1.154}$ × (age) $^{-0.203}$ × (0.742, if female) × (1.210, if black) [12].

2.4. Statistical analysis

Normal data are presented as mean ± SD and skewed data as median and interquartile range (IQR). Categorical and continuous baseline data were tested using chi-square and t-Student tests, respectively. Analyses of covariance (ANCOVA) with adjustments for gender and age were performed for comparison of mean change from the baseline. Assumptions of the ANCOVA models (linearity, normality of distribution and equal variance) were checked using histograms, normal probability plots and residual scatter plots. Ordinal logistic regression analyses were used to assess the association between the presence of STEMI and the following continuous variables categorized into tertiles: age, LDL-C, HDL-C, triglyceride levels and GFR. Binary logistic regression was used to assess the association between STEMI and categorical binary data: gender, diabetes mellitus, hypertension, depressive symptoms, and current/ex smoking. Odds ratios (OR) for STEMI are reported across individual risk factors in unadjusted and fully adjusted models. For all multivariable procedures, variables that displayed a p-value <0.05 in univariate analyses were selected as covariable. Attributable Risk (AR) was used to estimate the impact of each risk marker of STEMI in the very elderly. Statistical analysis was performed using SPSS®, version 21 for Mac (IBM) and SAS Analytics®, version U for Mac (SAS Institute Inc.) for AR. Probability value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical and laboratorial characteristics

Clinical and laboratorial baseline characteristics of study participants are in Table 1. Higher frequency of female gender and higher levels of HDL-C and GFR were found in controls. Moderate to severe depressive symptoms, prior and current smoking were more frequently found in cases. Controls had quit smoking for longer than cases (32 ± 17 *vs.* 20 ± 12 years; $p = 0.027$).

3.2. STEMI risk markers

Table 2 shows all individual categorical risk markers in unadjusted analysis (Model 1) and after fully adjustment (Model 2). In order to avoid over-fitting, prior and current smoking status were pooled together as smoking. Based on the univariate analysis, selected covariates for adjustments were: gender, depressive symptoms, smoking, GFR, and HDL-C.

Although the age of participant ranged between >2 decades, it was not related to STEMI occurrence. In contrast, reduced levels of GFR or HDL-C were associated with STEMI in both unadjusted and fully

Table 1
Baseline characteristics of clinical and laboratory data of participants.

Characteristics	Controls $n = 207$	Cases $n = 50$	p-Value	ANCOVA p-value[a]
Age, (years)	83 (6)	84 (8)	0.257	–
Gender: female, % (n)	79 (164)	24 (12)	<0.001	–
Depressive symptoms, % (n)	22 (31)	32 (13)	0.001	0.001
Mild	16 (27)	12 (5)	0.884	0.895
Moderate to severe	2 (4)	20 (8)	<0.001	0.001
Diabetes mellitus, % (n)	23 (48)	16 (8)	0.341	0.449
Hypertension, % (n)	77 (159)	68 (34)	0.205	0.981
Current smoking, % (n)	2 (5)	14 (7)	0.003	0.021
Prior smoking, % (n)	27 (55)	42 (21)	0.039	0.590
Antihypertensive drugs, % (n)	83 (171)	58 (29)	0.004	0.119
Aspirin, % (n)	29 (59)	26 (13)	0.861	0.355
Statin, % (n)	39 (81)	2 (1)	<0.001	0.001
Glomerular filtration rate, (mL/min)	69.8 ± 18.9	54.8 ± 20.8	<0.001	0.003
HDL-C, (mg/dL)	55 ± 14	44 ± 10	<0.001	0.763
LDL-C, (mg/dL)	114 ± 36	110 ± 39	0.495	0.571
Triglycerides, (mg/dL)	115 (65)	105 (55)	0.085	0.616
C-reactive protein, (mg/dL)	1.90 (2.38)	0.52 (1.09)	<0.001	0.001
Systolic blood pressure, (mm Hg)	142 (25)	130 (40)	0.040	0.001
Diastolic blood pressure, (mm Hg)	73 (15)	80 (30)	0.009	0.001
Heart rate, (bpm)	73 (15)	70 (26)	0.436	0.001

[a] Analysis of covariance with adjustment for gender and age. HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol. Normal data are presented as mean ± SD and skewed data as median and interquartile range (IQR).

adjusted models. The association of GFR and STEMI was not disrupted even after exclusion of 4 patients with SBP < 100 mm Hg (Table 5). Indeed, the inverse association between HDL-C levels and STEMI seems to be dose-dependent.

As shown in Table 3, gender, moderate to severe depressive symptoms, prior and current smoking was associated with STEMI in unadjusted models. After fully adjustments, all risk factors remained significantly related to STEMI, except for prior and current smoking.

Table 2
Multivariable ordinal regression models to assess the association between categorical variables split in tertiles and STEMI in elderly participants.

Age		OR(95% CI); p-value	
	1st tertile	2nd tertile	3rd tertile
	≤82 years $n = 107$	82–86 years $n = 70$	≥86 years $n = 80$
Model 1	Ref group	1.70(0.80–1.61); 0.168	1.32(0.62–2.81); 0.466
Model 2	Ref group	2.87(0.82–10.07); 0.100	1.81(0.54–6.15); 0.335
LDL-C	1st Tertile	2nd Tertile	3rd Tertile
	≤96.92 mg/dL	96.92–127.83 mg/dL	≥127.83 mg/dL
	$n = 84$	$n = 85$	$n = 85$
Model 1	Ref group	0.62(0.28–1.35); 0.227	0.86(0.41–1.79); 0.678
Model 2	Ref group	1.42(0.42–4.76); 0.568	1.25(0.40–3.96); 0.703
Triglycerides	1st Tertile	2nd Tertile	3rd Tertile
	≤95.92 mg/dL	137–95.92 mg/dL	≥137 mg/dL
	$n = 84$	$n = 84$	$n = 86$
Model 1	Ref group	0.81(0.39–1.69); 0.577	0.52(0.24–1.14); 0.104
Model 2	Ref group	0.55(0.14–2.07); 0.375	0.31(0.09–1.08); 0.066
HDL-C	3rd Tertile	2nd Tertile	1st Tertile
	≥58 mg/dL	58-45 mg/dL	≤45 mg/dL
	$n = 87$	$n = 91$	$n = 76$
Model 1	Ref group	2.98(1.02–8.67); 0.045	10.70(3.88–29.46); 0.001
Model 2	Ref group	5.83(1.16–29.16); 0.032	7.00(1.53–32.04); 0.012
Model 3	Ref group	3.14(10.7–9.22); 0.037	13.67(4.84–38.59); 0.001
	3rd Tertile	2nd Tertile	1st Tertile
GFR	≥74.40 mL/min	58.42–74.40 mL/min	≤58.42 mL/min
	$n = 83$	$n = 83$	$n = 83$
Model 1	Ref group	2.39(0.92–6.22); 0.073	4.41(1.78–10.95); 0.001
Model 2	Ref group	1.72(0.50–5.82); 0.386	4.37(1.30–14.69); 0.017
Model 3	Ref group	2.74(1.04–7.20); 0.041	4.90(1.95–12.33); 0.001

Model 1: Unadjusted; Model 2: Fully adjusted; Model 3: Fully adjusted, including CRP. OR: Odds ratio; CI: Confidence interval; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; GFR: Glomerular filtration rate.

3.3. Attributable risk

Table 4 shows AR for each significant STEMI risk factors. According to AR values, male gender, low HDL-C level and low HDL-C associated with low GFR were the three strongest risk factors, followed by moderate to severe depressive symptoms, current smoking, low GFR and prior smoking.

Since both low HDL-C and low GFR were the main determinants of the AR, we hypothesized that increased systemic inflammatory activity would potentially mediate the association between these two factors and STEMI. Plasma CRP was therefore included in the modeling in order to verify its potential mediating effect between HDL-C or GFR and STEMI risk (Table 2, model 3). HDL-C and GFR associations to STEMI remained unchanged after adjustment for CRP.

4. Discussion

To the best of our knowledge, this is the first case-control study designed to investigate independent risk markers for STEMI among very elderly individuals. Our findings indicate that, in this population, STEMI is associated with: (i) male gender, (ii) low HDL-C levels, (iii) moderate to severe depressive symptoms, (iv) low GFR, and (v) smoking status. Of note, low GFR and/or low HDL-C underlies >50% of the AR for these individuals.

Plasma LDL-C is among the main risk factors for atherosclerotic disease in adults and young elders [13–15]. In contrast, this association seems to become weaker or non-significant among older patients [16,17]. With regards to HDL-C, the strength of the association tends to increase with aging [18,19]. Our present findings corroborate these reports. We found that low HDL-C levels are singularly associated with a 7-fold increase in STEMI risk while LDL-C and triglycerides levels posed no impact. Interestingly, 73% of population-attributed risk may be related to low HDL-C levels, deeming it the most impactful risk factor of STEMI in the very elderly.

A broad spectrum of mechanisms paves the existence of a mutual association between cardiovascular and renal diseases. In fact, renal dysfunction is both cause and consequence of atherosclerosis [20]. As one may expect, at 80 years or older, the residual GFR is decreased due to its inherent lifetime decline [21]. Nevertheless, we found that 54% of the cases and 31% of the controls had GFR bellow the expected value for age and gender [22], thus indicating that the accelerated decline in renal function may have contributed to STEMI. In general,

Table 3
Multivariable binary logistic regression models to assess the association between binary variables and STEMI in elderly participants.

Diabetes mellitus	OR(95% CI); p-value
Model 1	0.631(0.277–1.436); 0.272
Model 2	0.302(0.081–1.131); 0.075
Hypertension	OR(95% CI); p-value
Model 1	0.642 (0.326–1.261); 0.198
Model 2	0.601(0.182–1.990); 0.405
Gender: male	OR(95% CI); p-value
Model 1	12.08(5.82–25.08); 0.001
Model 2	12.08(3.75–38.97); 0.001
Mild depressive symptoms	OR (95% CI); p-value
Model 1	0.93(0.33–2.61); 0.884
Model 2	1.43(0.35–5.83); 0.615
Moderate to severe depressive symptoms	OR(95% CI); p-value
Model 1	10.00(2.82–35.50); 0.001
Model 2	38.20(4.81–303.48); 0.001
Current smoking	OR(95% CI); p-value
Model 1	6.58(1.99–21.70); 0.002
Model 2	1.52(0.17–13.33); 0.706
Ex smoking	OR(95% CI); p-value
Model 1	2.00(1.05–3.80); 0.034
Model 2	1.36(0.47–3.87); 0.570

Model 1: Unadjusted; Model 2: Fully adjusted. OR: Odds ratio; CI: Confidence interval.

Table 4
Attributable risk of independent risk markers.

Characteristics	Attributable Risk (95% CI)	Pr > |Z|
Gender: Male	85.47% (81.08–88.20)	<0.001
Depressive symptoms: moderate to severe	75.00% (58.33–82.14)	<0.001
Current smoking	69.91% (42.34–79.65)	0.004
Prior smoking	42.02% (8.85–57.48)	0.023
Low GFR	68.18% (50.42–76.57)	<0.001
Low HDL-C	85.44% (79.82–88-61)	<0.001
Low HDL-C and low GFR	83.83% (74.75–87.89)	<0.001
Low HDL-C or low GFR	72.34% (61.59–78.38)	<0.001

Low GFR: ≤58.42 mL/min; Low HDL-C: ≤45 mg/dL. 3rd versus 1st tertiles were tested. HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; GFR: Glomerular filtration rate.

prior investigations have demonstrated that low GFR is a risk factor for short-term mortality after MI [23,24]. Our findings corroborate this by showing that even a mild to moderate reduction of GFR may increase STEMI risk in >4-fold among very old individuals. Such degree of renal dysfunction may explain up to 52% of the STEMI risk of this aged population. Surprisingly, low GFR and low HDL-C were not additive in their impact on STEMI risk, suggesting a common mechanism of interaction. Although plausible, increased systemic inflammatory activity does not seem to be one of the mediators for these interactions since the inclusion of plasma CRP in the models did not change the associations between GFR or HDL-C and STEMI.

Throughout life, the impact of hypertension and diabetes on MI risk appears to wean and eventually ceases to exist at 85 years of age [25]. Consistently, our findings support the weakening of the impact of diabetes and hypertension on STEMI risk. This lack of association in the very elderly may be explained by differences in the pathogenesis of atherosclerosis between the young and the very old. For example, in contrast to younger individuals, the onset of diabetes in the elderly is more likely to result from the failure of beta cells because of cellular senescence of pancreatic islets rather than from increased resistance to insulin [26]. Likewise, in contrast to the young, the increase of blood pressure is frequently related to the development of vascular stiffening in the elderly [27].

Despite the reduction in smoking prevalence with aging [13,15], our results demonstrate its persistent relevance on the risk of MI among the very elderly. In opposition to prior reports of risk cessation around 6 years after smoke interruption [28], the present study indicates that the impact of smoking habit on atherogenesis may persist for a longer period of time after its cessation. According to our data, the smoking-related risk was persistent around 20 years after interruption and former smoking was responsible for AR of 69.91%. As the smoking abstention time was higher in controls than in cases, one may infer that the risk attenuation is a continuous and slow process.

The presence and magnitude of depressive symptoms has long been associated with the risk of MI [29]. From a pathophysiological point of view, this association may be due to direct effects, *i.e.*, increased inflammatory activity and thrombogenesis, and indirect, such as physical inactivity, smoking and poor adherence to the control of risk factors [30]. Some differences between young adults and the very elderly, however, have prevented the extrapolation of this concept. For example, in the very elderly, age-related biological and behavioral changes such as immunosenescence, increased thrombogenesis and inability to change habits would potentially undermine this association. In addition, although the prevalence of depressive symptoms increases with age, the psychobiological constructs that favor such manifestation is progressively changed with aging [31]. Our study demonstrates that despite the above-mentioned changes, moderate to severe depressive symptoms may account for 75% of STEMI AR.

In all ranges of age, gender has been consistently proven to play a marked role in atherosclerotic burden and cardiovascular risk. Undeniably, men are more prone to manifest ischemic heart disease than women, at any given age, lagging forward by approximately 10 years [32]. In our study, although aging over 80 years did not significantly influenced STEMI risk, male gender favors a 12-fold increase in risk.

Our study has some limitations that must be discussed. Mainly, the enrollment and, by this way, the sample size was limited by the inclusion criteria of the cases, *e.g.* admission in the first 24 h from the onset of STEMI symptoms. This criterion was decided based on these three aspects: (i) to select individuals at undeniable high risk, (ii) to have plasma lipid profile obtained before the metabolic change induced by MI, and (iii) to avoid selection bias due to the high mortality of STEMI in this age group. This limitation may favor an over- or underestimation of the magnitude of the associations and may also influence the lack of statistical significance in some of the analyses. Nevertheless, the uniqueness of the data and its consistency with age-related biological processes involved in atherosclerotic disease make it relevant and plausible.

4.1. Conclusions

In conclusion, this is the first case–control study carried out with very elderly participants that aimed to identify independent risk markers for STEMI. Our findings indicate that reduced levels of HDL-C and GFR are the most frequent and strongest risk markers in this age group.

Table 5
Multivariable ordinal logistic regression models to assess the association between GFR split in tertiles and STEMI in elderly, excluding participants with SBP < 100 mm Hg.

		OR (95% CI); p-value	
	3rd tertile	2nd tertile	1st tertile
GFR	≥74.83 mL/min $n = 82$	58.59–74.83 mL/min $n = 82$	≤58.59 mL/min $n = 81$
Model 1	Ref group	2.83 (1.04–7.72); 0.041	4.43 (1.68–11.68); 0.003
Model 2	Ref group	2.65 (0.74–9,54); 0.135	5.20 (1.43–18.90); 0.012
Model 3	Ref group	3.21 (1.17–8.85); 0.024	4.89 (1.83–13.03); 0.002

Model 1: Unadjusted; Model 2: Fully adjusted; Model 3: Fully adjusted, including CRP. OR: Odds ratio; CI: Confidence interval; GFR: Glomerular filtration rate.

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Disclosures

The authors declare that there is no conflict of interest, no plagiarism, fraud and ethical conflicts in this paper.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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