

Blood and urine levels of heavy metal pollutants in female and male patients with coronary artery disease

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Background: Heavy metal pollutants such as cadmium (Cd), lead (Pb), and mercury (Hg) are rarely the subjects of cardiovascular research although they have been suspected for decades to negatively impact the circulatory system.

Methods: Apart from detailed anamnestic data, urinary levels of Cd and full blood levels of Pb and Hg were measured in 53 female (mean age: 68.04±7.03 years) and 111 male (mean age: 60.68±11.43 years) nonsmoking or never-smoking patients with angiographically verified and precisely quantified coronary artery disease (CAD).

Results: Although Cd was quantifiable in 68.3% of subjects, only 34.1% of these patients exceeded the critical 1 µg/L Human Biomonitoring (HBM)-I level. Median Pb (20 µg/L) and Hg (0.55 µg/L) levels were lower than the HBM-I, as well as reference levels of Pb. Wine consumption was the main source for Pb, fish and wine consumption for Hg, and previous nicotine abuse for Cd. There was no correlation between Cd, Pb, or Hg and severity of CAD although severity correlated positively with atherosclerosis parameters (uric acid, creatinine, triglycerides, blood urea nitrogen, C-reactive protein) and negatively with high density lipoprotein cholesterol.

Conclusion: Cd levels detected in CAD patients were high compared to German and European reference levels but it could not be proven that urine levels of Cd and blood levels of Hg or Pb played a major role in the genesis of CAD, particularly when compared to well-known biomarkers such as blood pressure, glucose, and lipids.

Keywords: cadmium, plumbum, mercury, coronary artery disease, pollutants

Introduction

According to the European Cardiovascular Disease Statistics 2012¹ cardiovascular disease (CVD) is responsible for 47% of all deaths in Europe and 40% of deaths in the European Union. The most common coronary manifestations of atherosclerosis are acute coronary syndromes such as myocardial infarction or sudden cardiac death and stable angina pectoris. Of course the mortality rate for CVD strongly depends on several risk factors but in general, men are more likely to die of CVD at a rate of 2.5–4.5:1.² Independent of sex-specific differences in risk factors, the absolute level of coronary artery disease (CAD) in men is higher than in women, although the dose response of most risk factors is the same in women and men, even after menopause, a fact that has been known for a long time.^{3,4} Traditional risk factors causing or promoting CAD are nicotine abuse, diabetes mellitus, arterial hypertension, dyslipidemia, physical inactivity, and overweight/obesity.⁵ However, heavy metal pollutants such as cadmium (Cd), lead (Pb), and mercury (Hg) may also contribute to the genesis of coronary atherosclerosis but they are far less commonly subjected to cardiovascular research

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although the first hints for this assumption were found nearly a century ago.⁶ Cd was associated with an increased risk for suffering hypertension, cardiac arrest, and stroke.^{7–9} Messner et al¹⁰ found a significant association between Cd levels in serum and intima media thickness in female individuals aged 18–22 years. Prozialeck¹¹ suggested E-cadherin, a C^{++} -binding protein localized at the junctions between vascular endothelial cells, as a target for Cd toxicity. Cd is also able to induce the expression of intercellular adhesion molecule 1, an adhesion molecule playing an important role in inflammation.¹² Furthermore, Cd was shown to indirectly generate superoxide and hydroxyl radicals.¹³ Similar to Cd, increased Hg exposure was also suspected to lead to hypertension and cerebral artery occlusion.^{14–16} Wojciechowski and Kowalski,¹⁷ working on rabbits, showed that inhaling Hg vapor over 3 months caused electrocardiogram (ECG) abnormalities, thrombotic lesions in small and medium caliber blood vessels, and necrotic foci. Guallar et al¹⁸ performed a case-controlled study in eight European countries and Israel and found that amounts of Hg in toenails were 15% higher in a group of patients with myocardial infarction compared to controls. Again, similar to Cd, Salonen et al¹⁹ found a correlation between Hg amounts in hair and intima media thickness in men from eastern Finland. Like Cd and Hg, Pb measured in blood and bone (tibia and patella) was associated with hypertension, probably by affecting the renin–angiotensin system, increasing angiotensin converting enzyme levels^{20,21} or by influencing the beta-adrenergic system as suggested by Tsao et al.²² Another explanation may be an impairment of the balance between vasoconstrictive and vasodilative factors to the benefit of vasoconstriction.²³ Furthermore, a damaging effect of Pb on the endothelium may be due to its potential to increase reactive oxygen species. Reactive oxygen species may also be involved in blood pressure increase by increasing Ca^{++} concentration in endothelial cells or by the inactivation of nitrogen oxide.²⁴ The results of the mentioned studies indicate that Cd, Hg, and Pb may increase cardiovascular risk by promoting atherosclerosis per se or by ameliorating the circumstances for atherosclerotic processes.

The present study measured Cd levels in urine and Hg and Pb levels in blood, and correlated them with the severity of CAD with regard to sex and sex-specific aspects, and compared them with other well established cardiovascular risk factors, eg, blood pressure, blood glucose, and lipids.

Materials and methods

In total, 111 male and 53 female never-smoking or ex-smoking (for at least 7 years) patients with angiographically

verified CAD of differing severity were recruited at the Department of Cardiology, Medical University of Vienna. The study group consisted of 49.4% of patients with chronic CAD, defined as at least one coronary ischemic event in the past documented by coronary angiography, and 50.6% of patients who had never had an ischemic event.

Detailed anamnestic data were collected by means of an interview taking into account exposure to heavy metal sources like housing, nutrition, past smoking behavior, amalgam fillings, and other factors. Alcohol intake was quantified in units (1 unit = 0.02 L of spirits, 0.25 L of wine, or 0.3 L of beer). Meat and fish intake were quantified by times/week. Tap water consumption was measured in L/week. Blood pressure was measured at least three times during the in-patient stay. An ECG was taken, routine laboratory parameters were measured, and all patients had to undergo an angiography for diagnostic and/or therapeutic reasons on the grounds of their underlying disease. The coronary arteries were divided into 17 segments (left main, proximal/medial/distal left anterior descending artery, ramus circumflexus, first and second marginal branch, posterolateral branch, first and second diagonal branch, proximal/medial/distal left circumflex artery, proximal/medial/distal right coronary artery, ramus interventricularis posterior) and stenosis grade for each segment was measured. A simple 3-point grading system (coronary score) was developed considering both frequency and severity of CAD: 0 points for non-stenosed or only calcified segments, 1 point for each stenosis from 30%–<50%, 2 points for each stenosis from 50%–<70%, and 3 points for each stenosis >70%. Hg and Pb levels were measured in full blood, and Cd was measured in urine. The outcrop of full blood samples for the determination of Pb and Hg was done by 2 mL ultrapure water and 2 mL nitric acid (68% subboiled). The sample aliquot was 0.5 mL and the backfilling volume was 20 mL. The determination of Pb and Cd was performed by inductively coupled plasma mass spectrometry according to the ÖNORM EN ISO 17294-2. The determination of Hg was done by atomic fluorescence spectroscopy according to the ÖNORM EN 17852. The outcrop of urine samples for the determination of Cd was done by 2 mL ultrapure water and 2 mL nitric acid (68% subboiled). The sample aliquot was 5 mL and the backfilling volume was 20 mL. The detection/quantification limits were 0.4/2 $\mu\text{g/L}$ for Pb, 0.067/0.13 $\mu\text{g/L}$ for Hg, and 0.12/0.40 $\mu\text{g/L}$ for Cd. In case the quantification limit was undercut, the following expected amounts were used: Cd, 0.3 $\mu\text{g/L}$; Pb, 1 $\mu\text{g/L}$; Hg, 0.1 $\mu\text{g/L}$. Cd and Hg Human Biomonitoring (HBM)-I and -II values and the Pb reference values from the German Environmental Agency^{25,26} were used for comparison.

HBM values are derived on the basis of toxicological and epidemiological studies and are a tool to quickly assess whether exposure related health effects can be expected. However, they do not reflect the total body burden of heavy metal pollutants. At a concentration level higher than the HBM-I it is suggested that analytic results be verified to identify specific sources of exposure and to reduce the exposure in an adequate way. At levels higher than HBM-II values immediate action to reduce exposure is required. The reference values permit the assessment of exposure of individuals or population groups compared to ubiquitous background exposure. In the case of Pb, the German Commission has suspended the HBM values for Pb in blood due to the fact that no threshold can be derived for the persisting adverse effects on brain development and also due to the carcinogenicity of Pb compounds.^{27,28}

Statistical analysis was done with SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Continuous and normally distributed data are described by mean \pm standard deviation, group differences are tested by independent sample *t*-test, and correlation is calculated using Pearson's correlation coefficient. Continuous data with skew distribution or outliers are described by median, first and third quartile, and minimum and maximum values. Group differences are tested by Mann–Whitney *U* test and correlations were calculated using Spearman's correlation. For data with values below the quantification limit a value below quantification limit was imputed (the same value for all observations) and the nonparametric Mann–Whitney *U* test was used. All tests were performed two-sided and $P \leq 0.05$ were considered significant. The protocol was approved by the Ethical Commission of the Medical University of Vienna and informed consent was obtained from patients.

Results

Data concerning age, body mass index (BMI), heart rate, blood pressure, and ECG are shown in Table 1. Male patients were significantly younger compared to female patients ($P < 0.01$). There was no significant difference between BMI ($P = 0.22$), systolic blood pressure ($P = 0.88$), heart rate ($P = 0.99$), and ECG data. However, men showed a significantly higher diastolic blood pressure compared to women ($P < 0.01$). Atrial fibrillation was observed in 13 male and three female patients, PQ in patients without atrial fibrillation was 169.07 \pm 28.98 ms in male and 155.14 \pm 29.22 ms in female patients ($P < 0.01$). The prevalence of traditional cardiovascular risk factors is shown in Table 2. The prevalence of hypertension and previous nicotine abuse was higher in

Table 1 Anthropometric data, blood pressure, and electrocardiogram data

	Female	Male	Total	P-value
Age (years)	68.04 \pm 7.03	60.68 \pm 11.43	63.05 \pm 10.96	<0.01
BMI (kg/m ²)	27.28 \pm 5.35	28.40 \pm 5.50	28.04 \pm 5.46	0.22
SBP (mmHg)	131.26 \pm 16.08	130.86 \pm 15.36	130.99 \pm 15.55	0.88
DBP (mmHg)	72.15 \pm 8.28	78.41 \pm 11.35	76.39 \pm 10.84	<0.01
Heart rate (bpm)	70.57 \pm 14.01	70.53 \pm 12.85	70.54 \pm 13.19	0.99
PQ (ms)	155.14 \pm 29.22	169.07 \pm 28.96	164.36 \pm 29.70	<0.01
QTc (ms)	453.08 \pm 41.57	440.33 \pm 43.22	444.45 \pm 42.98	0.08
QRS (ms)	104.74 \pm 28.59	106.01 \pm 44.62	105.60 \pm 40.06	0.85

Notes: Anthropometric data, systolic and diastolic blood pressure, heart rate, and electrocardiogram data of the coronary artery disease patients. Data is presented as mean \pm standard deviation. *P*-values show the sex-specific statistical difference.

Abbreviations: BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

male patients whereas female patients had a higher prevalence of diabetes mellitus and physical inactivity, defined as less than 3 hours of walking per week.

Parameters of special interest from routine laboratory analyses are shown in Table 3. Severity of CAD is described in detail in the Materials and methods. Female patients had a mean coronary score of 6.43 \pm 5.87 points with a maximum of 24 points. Male patients had a mean coronary score of 8.46 \pm 5.29 with a maximum of 29 points.

The levels of Cd, Pb, and Hg among the CAD patients were compared to levels within the German population as well as with HBM-I/II and reference levels.^{25,26} Mean Cd, Pb, and Hg levels in the German population were 0.335 μ g/L, 35.6 μ g/L, and 0.86 μ g/L, respectively. The HBM-I level for Cd is 1 μ g/L and 5 μ g/L for Hg. The HBM-II levels are 4 μ g/L and 15 μ g/L for Cd and Hg, respectively. There are no HBM levels for Pb. Reference levels are 0.8 μ g/L for Cd, 2.0 μ g/L for Hg, and 70 and 90 μ g/L for Pb in women and men, respectively. The heavy metal levels in the CAD patients are

Table 2 Prevalence of traditional risk factors

	Female	Male	Total	P-value
Hypertension	94.3 (50)	99.3 (98)	90.2 (148)	0.22
Pos Fam history	54.7 (29)	55.0 (61)	54.9 (90)	0.98
Diabetes mellitus	37.8 (20)	22.5 (25)	45.0 (17)	0.04
Diabetes (no insulin)	20.8 (11)	12.6 (14)	15.2 (25)	
Diabetes (insulin)	17.0 (9)	9.9 (11)	12.2 (20)	
Hyperlipidemia	88.7 (47)	89.2 (99)	89.0 (146)	0.92
Previous MI/stroke	41.5 (22)	40.5 (35)	40.9 (67)	0.97
Ex-smoking	39.6 (21)	65.8 (73)	57.3 (94)	<0.01
Physical inactivity	30.2 (16)	27.9 (31)	28.7 (47)	0.77

Notes: Prevalence in percent (n) of traditional cardiovascular risk factors for female and male coronary artery disease patients. Physical inactivity was defined as <3 hours of walking per week. *P*-values show the sex-specific statistical difference.

Abbreviations: Pos Fam, positive family; MI, myocardial infarction.

Table 3 Important routine laboratory parameters

	Female	Male	Total	P-value
Uric acid (mg/dL)	5.85±1.89	6.64±2.03	6.39±2.01	0.02
Triglycerides (mg/dL)	131 (97–169)	130 (94–183)	130 (95–176)	0.60
Cholesterol (mg/dL)	19.222±48.37	168.45±48.63	175.98±49.66	<0.01
HDL (mg/dL)	54.83±15.58	41.36±10.21	45.92±13.81	<0.01
LDL (mg/dL)	111.98±41.73	100.91±38.14	104.65±39.59	0.12
LDL/HDL (mg/dL)	2.14±0.88	2.56±1.09	2.42±1.04	0.02
HbA _{1c} (rel %)	6.1 (5.7–7.0)	5.9 (5.4–6.4)	6.0 (5.5–6.9)	0.10
CRP (mg/dL)	0.50 (0.17–1.60)	0.62 (0.22–2.84)	0.59 (0.20–2.42)	0.36

Notes: Extract of routine laboratory parameters of special interest. Data are presented as mean ± standard deviation or median (first to third quartile). P-values show the sex-specific statistical difference.

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein; HbA_{1c}, glycated hemoglobin; LDL, low density lipoprotein.

shown in Table 4. Cd was quantifiable in 68.3% of patients, Pb in 100% of patients, and Hg in 83.5% of patients, and the remaining patients were below the quantification limit. Concerning Cd, female patients had higher levels compared to men but men showed higher levels of Pb and Hg for which the difference was significant ($P=0.02$). The P -values (and correlation coefficients) for the correlations of the coronary score with Cd, Pb, and Hg in female patients was 0.64 (0.07), 0.06 (–0.26), and 0.51 (0.09); for male patients it was 0.65 (–0.05), 0.79 (0.03), and 0.06 (–0.18), respectively. Analyzing the whole population, the P -values were 0.82 (–0.02), 0.50 (–0.05), and 0.60 (–0.04) for Cd, Pb, and Hg, respectively. After splitting the population into patients with chronic CAD (stents, bypasses) and patients who suffered their first event, again there was no significant correlation observable for Cd,

Pb, or Hg. Performing multivariate analyses (with regard to the cardiovascular risk factors) did not show a significant correlation between the severity of CAD and the heavy metal levels. On the contrary, the coronary score correlated positively with laboratory markers that are associated with CAD, eg, uric acid ($P=0.03$), creatinine ($P=0.01$), blood urea nitrogen (BUN) ($P=0.03$), triglycerides ($P=0.03$), C-reactive protein (CRP) ($P<0.01$), pro brain natriuretic peptide (proBNP) ($P<0.01$), and fibrinogen Clauss ($P<0.01$), and negatively with high density lipoprotein (HDL) ($P=0.02$). Furthermore, it correlated positively with BMI ($P=0.02$).

Compared to mean Cd levels that were found in the German population (0.335 µg/L urine), the CAD patients showed much higher median levels (0.67 µg/L) and 34.1% of the CAD patients exceeded the HBM-I level of 1 µg/L and 8.5% of CAD patients exceeded the HBM-II level of 4 µg/L. Concerning mean Pb and Hg levels in the German population (35.6 and 0.86 µg/L full blood, respectively), CAD patients showed much lower median levels (20 and 0.42 µg/L, respectively) and HBM-I/II levels were exceeded only by single cases.

Concerning nutrition, significant positive correlations were found for Pb and the number of consumed units of red wine ($P=0.001$) and white wine ($P<0.01$) per week and for Hg with white wine ($P<0.01$) and fish consumption ($P<0.01$). Ex-smoking patients had significantly higher amounts of Cd in urine compared to patients who never smoked (0.84 versus 0.58 µg/L, respectively; $P=0.03$). Also Pb was higher in full blood in ex-smokers compared to never-smokers but without statistical significance (21.5 versus 19.5 µg/L, respectively; $P=0.15$). Patients with amalgam fillings showed significantly higher levels of Hg compared to patients without amalgam fillings (0.51 versus 0.27 µg/L, respectively; $P<0.01$). Patients living in a big city (>100,000 citizens) had median Cd levels of 0.62 µg/L, Pb levels of 20.0 µg/L, and Hg levels of 0.43 µg/L. Patients living in a small town had median Cd

Table 4 Heavy metals in coronary artery disease patients

	Female	Male	P-value	Total
Cd				
n (%)	67.9	68.5		68.3
Median (first/ third quartile)	0.72 (<0.40/1.45)	0.65 (<0.40/1.50)	0.84	0.67 (0.30/1.50)
Minimum/ maximum	<0.40/16.00	<0.40/27.00		<0.40/27.00
Pb				
n (%)	100	100		100
Median (first/ third quartile)	19.0 (12.0/28.5)	21 (15.0/31.0)	0.26	20.0 (14.0/30.8)
Minimum/ maximum	4.9/65.0	6.6/240.0		4.9/240.0
Hg				
n (%)	81.1	84.7		83.5
Median (first/ third quartile)	0.34 (0.17/0.34)	0.53 (0.22/0.92)	0.02	0.42 (0.20/0.82)
Minimum/ maximum	<0.13/2.10	<0.13/11.00		<0.13/11.00

Notes: Heavy metal analysis in coronary artery disease patients including number of patients (%) in whom each metal could be quantified. Data is presented as median (first to third quartile), minimum and maximum values, and P-value of sex-specific differences. For cadmium the first quartile is below the detection limit of 0.40 µg/L.

Abbreviations: Cd, cadmium; Hg, mercury; Pb, lead.

levels of 0.82 µg/L, Pb levels of 21.5 µg/L, and Hg levels of 0.47 µg/L, and patients who lived in rural areas had median Cd levels of 0.87 µg/L, Pb levels of 22.5 µg/L, and Hg levels of 0.33 µg/L.

Discussion

Although heavy metal exposure by ubiquitous pollutants has frequently been associated with atherosclerosis, Cd, Hg, and Pb also play a tangential role in cardiovascular research and have been overshadowed by heavy weights such as hypertension, diabetes mellitus, and physical inactivity. This study is the first to correlate urine levels of Cd and blood levels of Hg and Pb with the extent of severity of CAD in 164 CAD patients.

The main sources of contamination (dependent on the metal) are industry, traffic, tobacco consumption, and agriculture/nutrition. Heavy metals are long lasting substances which persist for decades, are transported within environmental media, and are partly accumulated in individuals after incorporation.²⁹ Within CAD patients, Pb levels and the number of consumed units of red and white wine per week, and Hg levels and white wine and fish consumption correlated positively. Concerning red wine consumption and Pb, this correlation has been shown before,^{30–32} even within the female Austrian population.³³ However, a connection between blood Hg levels and white wine consumption is hard to find in literature. On the contrary, much research has been done investigating the influence of fish consumption and Hg levels, especially methyl-mercury. The correlation between Hg amounts in blood and fish consumption has been described in large studies (eg, in the Canadian population³⁴ and US children and women³⁵). However, although Hg intake by fish consumption seems unequivocal the cardioprotective effects of a fish-rich diet seem to predominate. The Diet and Reinfarction Trial³⁶ studied the influence of fish oil intake on total mortality and myocardial infarction (MI) in more than 2,000 men who had already suffered an MI with a follow-up period of 2 years. Patients who were asked to consume fish 2 times/week showed a 29% reduction in total mortality which was mostly driven by a 32% reduction in fatal MI. Other studies showed similar results^{18,37–39} and considering these results it seems that the positive effect of fish consumption on the cardiovascular system predominates but might be diminished by Hg content.

A further source of pollution, this time for Cd, seems to be nicotine consumption and second hand smoking, as shown in several studies,^{40–42} and this was also observed in our CAD patients. Although we recruited only patients who never smoked or stopped smoking at least 7 years ago, ex-smokers

had about 76% higher levels, probably due to bioaccumulation of Cd. Furthermore, we found significantly higher levels of Hg in patients with amalgam fillings compared to patients without amalgam fillings, although this topic cannot escape controversy. However, concerning the place of residence (urban, suburban, rural) we found no connection to Cd, Hg, or Pb.

As mentioned before, the core of this study was the investigation of heavy metal levels in blood and urine in patients with CAD of different, but exactly quantified severity, by means of angiography. Firstly, it has to be said that the CAD patients showed much higher median urinary Cd levels compared to levels that were found in the German population.²⁵ Furthermore, it was striking that although Cd was only quantifiable in 68.3% of patients, nearly 34.1% of all patients exceeded the HBM-I level of 1 µg/L in urine. Within the European HBM study Demo-COPHES (consortium to perform human biomonitoring on a European scale), mean levels in women (age <45 years) were 0.22 µg/L and the 90% percentile was 0.62.⁴³ Concerning Pb and Hg, we found levels which were much lower in nearly all patients compared to both the German population²⁵ and reference levels,²⁶ respectively. Messner et al¹⁰ found a significant association of Cd levels in serum and intima media thickness in young healthy female individuals as a sign for early atherosclerosis.⁴⁴ We analyzed urinary Cd and blood Hg and Pb amounts and quantified the severity of CAD but found no correlations. To this extent, this appears as rather surprising as the system of CAD quantification (described in the Materials and Methods section) seems to be appropriate because the score correlated positively with several (established) parameters of atherosclerosis (uric acid, creatinine, triglycerides, BUN, CRP, BMI, proBNP) and negatively with HDL cholesterol, even when these patients were under medication. One point of criticism may be that patients with long-term CAD and previous stent implants were also recruited. However, within the study group 50.6% had never had a cardiovascular event and there was again no observable correlation between heavy metals and severity of CAD. Unfortunately, although literature delivers interesting findings, the comparison of data is often difficult because heavy metal amounts are measured in various media (full blood, urine, hair, toenails, liver/kidney tissue). It is well recognized that once individuals are exposed to Cd, Pb, or Hg the metals can be detected in blood and urine but are quickly sequestered into tissue.⁴⁵ It is therefore difficult to reveal the total burden of Cd, Hg, and Pb on the body. However, as the vascular system was in the foreground of this study the measurement of Hg and Pb in blood and Cd in urine was obvious despite the fact that several circumstances⁴⁶ may affect the levels in these media.

Furthermore, analysis is partly made in animals or humans which/who were confronted with enormous and (for “normal” populations) unrealistic heavy metal exposure, eg, rabbits which were fed with 8 mg Cd/kg/day over 8 months⁴⁷ or Hg determination in workers of a chlorine producing factory.⁴⁸

The present study is the first that assesses Cd, Pb, and Hg levels in CAD patients with precisely quantified CAD. Considering the results of this study, it seems very probable that nutrition (above all, fish and alcohol consumption) and smoking are the main sources of heavy metal incorporation but it seems unlikely that Cd, Hg, or Pb, in quite low amounts, play a major role in the genesis of CAD, particularly when compared to the influence of blood pressure, blood glucose, and lipid profile in Austria.

Limitations

Circulating heavy metal levels are influenced by numerous circumstances making it hard to control. Due to the dynamics of heavy metal pollutants, a single blood/urine sample does not reflect the total body burden but as the vasculature damage was in the foreground of this study it seemed the most appropriate.

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Disclosure

The authors have no disclosure to make.

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