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ORIGINAL ARTICLE
Epidemiology

Tissue Inhibitor of Matrix Metalloproteinase 1 Increases With Ageing and Can Be Associated With Stroke

— Nested Case-Control Study —

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Background: Increase of collagen in the extracellular matrix occurs with ageing. We investigated whether a collagen marker, tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), was associated with risk of stroke.

Methods and Results: In a nested case-control study of 953 subjects from the general population, we evaluated determinants of TIMP-1 level and stroke risk. Mean subject age was 65.7±8.6 years (53.0% men); TIMP-1 was 72.4±28.2 pg/mL in the control group and 75.3±30.9 pg/mL in the stroke group. The relationship between TIMP-1 quartile and stroke was J-curved. Subjects in the highest TIMP-1 quartile (≥89 ng/mL) had a significantly higher OR of stroke (59–72 ng/mL; OR, 1.90; 95% CI: 1.09–3.31, P=0.023) than those in the second TIMP-1 quartile, and this tended toward significance even after adjusting for confounding factors (P=0.059). Elevation of serum TIMP-1 became more marked after age 65 years. On multiple linear regression analysis, significant determinants of TIMP-1 were older age (B=0.21 per 1 year; 95% CI: 0.52–1.07, P<0.001) and higher systolic blood pressure (SBP; B=0.19 per 1 mmHg, 95% CI: 0.08–0.42, P=0.004).

Conclusions: TIMP-1 increased with ageing and with SBP, and can be associated with stroke.

Key Words: Ageing; Stroke event; Systolic blood pressure; TIMP-1; Tissue inhibitor of matrix metalloproteinase-1

Ageing is associated with increased tissue fibrosis. Collagen metabolism in tissues can be evaluated by measuring matrix metalloproteinases. Tissue inhibitor of matrix mettaloproteinase-1 (TIMP-1) is a marker of extracellular matrix remodeling in the cardiovascular system, and is reported to be associated with hypertension and left ventricular diastolic dysfunction.[1] In the Framingham Heart Study, elevation of TIMP-1 was associated with cardiovascular risk assessed by the Framingham risk score,[2] echocardiographic measures of left ventricular hypertrophy,[2] and carotid artery athoerosclerosis.[3] Increase in TIMP-1 was a predictor of progressive blood pressure (BP) elevation and hypertension in the Framingham Offspring study.[4] Furthermore, increased TIMP-1 was associated with abnormal diurnal variation in BP (non-dipper pattern) in normotensive subjects undergoing ambulatory BP monitoring.[5] This suggested that TIMP-1 could be a marker of cardiovascular stiffening.

An increase in TIMP-1 was reported to be a predictor of future cardiovascular events in patients with coronary artery disease (CAD),[6,7] but there have been few reports on TIMP-1 and the risk of stroke in Western countries,[8] and there have been no reports on the relationship between TIMP-1 and stroke in Japanese population.

The purpose of the present study was therefore to determine whether TIMP-1 was associated with an increased risk of stroke in the general Japanese population, in which the incidence of stroke is higher than that of myocardial infarction.[9]

Methods

Subjects

The Jichi Medical School (JMS) Cohort Study was begun in 1992, with the primary aim of clarifying the risk factors for cardiovascular and cerebrovascular disease in the general Japanese population. The details of the JMS Cohort Study protocol have been reported previously.[10] Baseline data were collected between April 1992 and July 1995 in 12 rural districts using a government-sponsored mass screening system. In each community, a local government office sent invitations by mail to all of the subjects in accordance with the health and medical service law for the aged. The target for mass screening was residents aged 40–69 years in 8 areas of Japan (Iwaizumi, Tako, Kuze, Sakuma, Sakugi, Okawa, Ainoshima, and Akaike). In addition, persons

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Table 1. Subject Characteristics According to Stroke History (n=953)				
	Total n=953	Stroke case n=178	Control n=765	P-value†
Age (years)	65.7±8.6	65.9±9.1	65.8±8.5	0.854
Male, %	53.0	46.1	54.5	0.042
BMI (kg/m²)	22.6±3.0	22.6±3.0	22.6±3.4	0.974
Smoking status				0.254
Past smoker, %	20.4	15.8	21.5	
Current smoker, %	28.4	29.7	28.1	
Alcohol intake (g/day)	19.3±33.5	18.5±32.0	18.9±31.4	0.866
Alcohol intake >20 g/day, %	35.2	33.5	35.3	0.672
SBP (mmHg)	134.5±22.7	140.3±23.6	133.1±22.4	<0.001
DBP (mmHg)	79.5±13.2	81.9±12.8	78.8±13.3	0.008
Antihypertensive medication, %	20.6	25.5	19.6	0.093
Hyperlipidemia, %	32.8	36.5	32.0	0.265
Total cholesterol (mg/dL)	191.3±33.4	192.1±34.4	191.2±33.3	0.751
Tryglyceride (mg/dL)	110.2±65.1	106.7±46.2	111.2±69.1	0.406
Diabetes, %	6.3	10.2	5.5	0.024
Glucose (mg/dL)	100.8±25.1	108.1±36.2	99.3±21.5	0.002
TIMP-1 (ng/mL)	73.1±28.7	75.3±30.9	72.4±28.2	0.219
TIMP-1 quartiles (ng/mL)				0.221
Q1, ≤58	25.0	26.4	26.0	
Q2, 59–72	25.0	19.1	26.0	
Q3, 73–88	25.0	25.8	24.3	
Q4, ≥79	25.0	28.7	23.7	

Data given as mean ± SD or %. †Non-paired t-test or chi-squared test. BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIMP-1, tissue inhibitor of matrix metalloproteinase 1.

aged ≥30 years were included in 1 area (Wara), and other age groups were also included in 3 areas (Hokudan, Yamato, and Takasu). The total number of subjects in the JMS Cohort Study at baseline was 12,490 (4,911 men and 7,579 women). The participation rate varied among communities (26–90%), and the overall participation rate in the mass screening program was 65.4%.[9]

Questionnaire and Other Measurements

Information about the baseline medical history and lifestyle was obtained via questionnaire. Reported age was the baseline value. Smoking status was classified as current smoker, ex-smoker, or never smoked. Drinking alcohol was defined as consuming ≥20 g/day. Body mass index (BMI) was calculated as weight (kg)/height (m²). Baseline systolic BP (SBP) and diastolic BP (DBP) were measured using a fully automated and validated upper arm cuff-oscillometric device (BP203RV-II; Nippon Colin, Komaki, Japan).[11] BP was measured once while seated after resting for ≥5 min. Hypertension was defined as either SBP/DBP ≥140/90 mmHg or use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L (126 mg/dL), casual glucose >11.1 mmol/L (200 mg/dL), or use of oral hypoglycemic agents or insulin. Hyperlipidemia was defined as total cholesterol ≥5.7 mmol/L (220 mg/dL) or use of lipid-lowering agents, according to the Japanese Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases. We stratified the subjects into 3 age groups (<65 years old, 65–74 years old, and ≥75 years old) according to the proposal of the Joint Committee of the Japan Gerontological Society and the Japan Geriatric Society.[12]

Baseline Plasma TIMP-1

Blood samples were obtained from participants at the time of the mass screening health check and serum samples were frozen at −80°C until assay. Measurement of serum TIMP-1 was conducted at a single laboratory (SRL, Tokyo, Japan) using an enzyme-linked immunosorbent assay (Fuji Chemical Industries, Toyama, Japan) between 2003 and 2007. The coefficient of variation of the assay was 11.3%. In 125 serum samples, TIMP-1 level was lower than the detection limit (50 ng/mL), and the level in these samples was defined as 25 ng/mL.

Follow-up and BP Data

The mass screening examination system was used to review the subjects every year for 10 years and the details of follow-up have been reported previously.[13] Information on stroke events was obtained at the time of annual mass screening, or telephone interview. In the stroke cases, medical record, brain magnetic resonance imaging and computed tomography were collected from the hospitals at which the subject was diagnosed. Members of independent diagnostic committee confirmed the case.

Informed Consent

The internal review board of the Jichi Medical University School of Medicine approved this study. Written informed consent to participate was obtained individually from all subjects during the mass screening health check.

Statistical Analysis

Of the 12,490 subjects initially enrolled in the JMS cohort study, we selected subjects with a stroke event during the

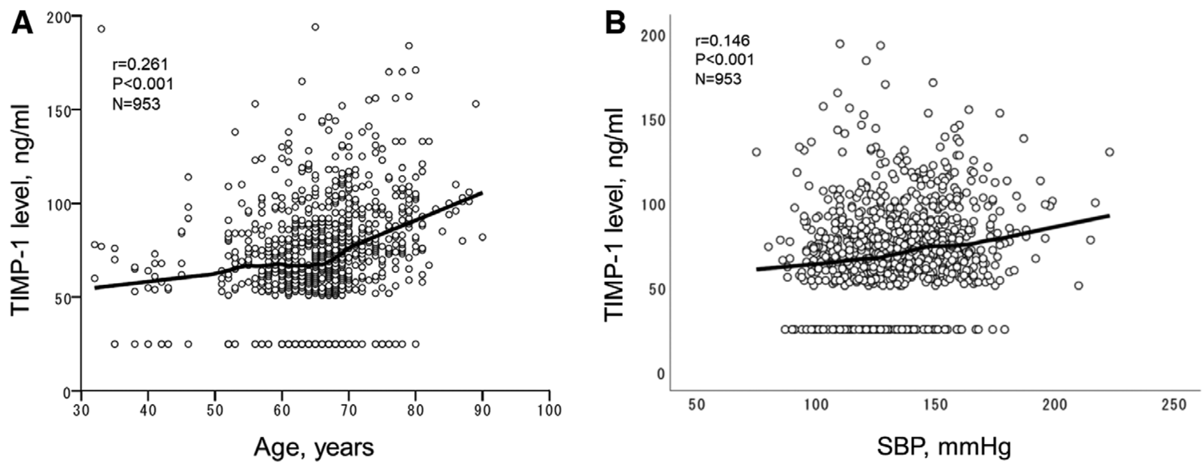

Figure 1. Tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) vs. (**A**) age and (**B**) systolic blood pressure (SBP), on locally weighted scatterplot smoothing estimation. Correlation coefficient (r) was calculated using Pearson's test.

follow-up period and subjects without such an event (at a 1:3 ratio) to evaluate the risk of stroke in the present nested case-control study. Frozen serum samples for measurement of TIMP-1 were available from 953 patients.

Data are reported as mean±SD for continuous variables, and as percentage for dichotomous variables. Locally weighted scatterplot smoothing (LOESS) with iterative reweighting was used to display the relationships between age, SBP, and serum TIMP-1. Determinants of TIMP-1 were evaluated on forced regression analysis that included the following conventional cardiovascular risk factors: age, sex, BMI, smoking status, alcohol intake >20 g/day, SBP, DBP, antihypertensive medication use, hyperlipidemia, and diabetes. Differences in baseline characteristics and TIMP-1 levels between age and SBP subgroups were assessed on analysis of variance (ANOVA) or chi-squared test, while intergroup difference were calculated using Tukey's test. Differences in TIMP-1 levels after adjustment for confounders (sex, BMI, smoking status, alcohol intake >20 g/day, antihypertensive medication use, hyperlipidemia, and diabetes) were evaluated on analysis of covariance (ANCOVA) test, and intergroup differences were calculated using Bonferroni's test. The OR of stroke in each TIMP-1 quartile was evaluated on logistic regression analysis using an unadjusted model and a multivariate adjusted model (adjusted for sex, BMI, SBP, smoking status, alcohol intake >20 g/day, hyperlipidemia, diabetes, and antihypertensive medication use). Analysis was done with IBM-SPSS version 25.0 (IBM, Chicago, IL, USA), and P<0.05 was considered statistically significant.

Results

Subjects

Mean subject age was 65.7±8.6 years (53% men; n=953), and 20.6% were taking antihypertensive drugs. Subject characteristics are listed in **Table 1**. Compared with the total subject population, the SBP, DBP, and use of antihypertensive medications were higher in the present study.[10] Subjects with and without stroke events had significant differences in sex, SBP, DBP, and diabetes, even though the control group was age matched.

Relationship of TIMP-1 to Age and SBP

The LOESS model of the relationship of TIMP-1 to age is shown in **Figure 1A**. The increase of TIMP-1 with age became steeper after 65 years. In contrast, TIMP-1 had a linear relationship with SBP (**Figure 1B**). On multiple linear regression analysis, the determinants of TIMP-1 were older age (unstandardized B=0.21 per 1 year; 95% CI: 0.52–1.07) and higher SBP (B=0.19 per 1 mmHg; 95% CI: 0.08–0.42; **Supplementary Table 1**). In the parallel analysis stratified by age group, the determinants of TIMP-1 were higher SBP in non-elderly subjects (P=0.009), and older age in young elderly subjects (P<0.001); there was no significant determinant of TIMP-1 in old elderly subjects.

TIMP-1 and Baseline Characteristics vs. Elderly Subgroups

Baseline characteristics and TIMP-1 according to age subgroup are listed in **Supplementary Table 2**. The old elderly subjects (≥75 years) had significantly higher SBP and TIMP-1 compared with the non-elderly subjects (<65 years) and the young elderly subjects (65–74 years). Additionally, the old elderly subjects had a significantly lower BMI than the non-elderly subjects.

When we stratified the subjects according to age and SBP (<120 mmHg, 120–139 mmHg, and ≥140 mmHg), TIMP-1 was significantly higher in young elderly subjects with SBP ≥140 mmHg, while it was significantly elevated in old elderly subjects regardless of SBP (**Figure 2A**). After adjustment for conventional cardiovascular risk factors (sex, BMI, alcohol intake ≥20 g/day, smoking, hyperlipidemia, and diabetes), TIMP-1 was significantly higher in subjects with SBP ≥140 mmHg in young elderly subjects, as well as in those with SBP ≥120 mmHg in old elderly subjects (**Figure 2B**).

TIMP-1 and Stroke Risk

Subject Characteristics according to TIMP-1 quartile are listed in **Table 2**. The present subjects (n=953) were followed up for an average of 114.2±40.3 months (9,072 person-years). Of the patients with stroke (n=178), there were 115

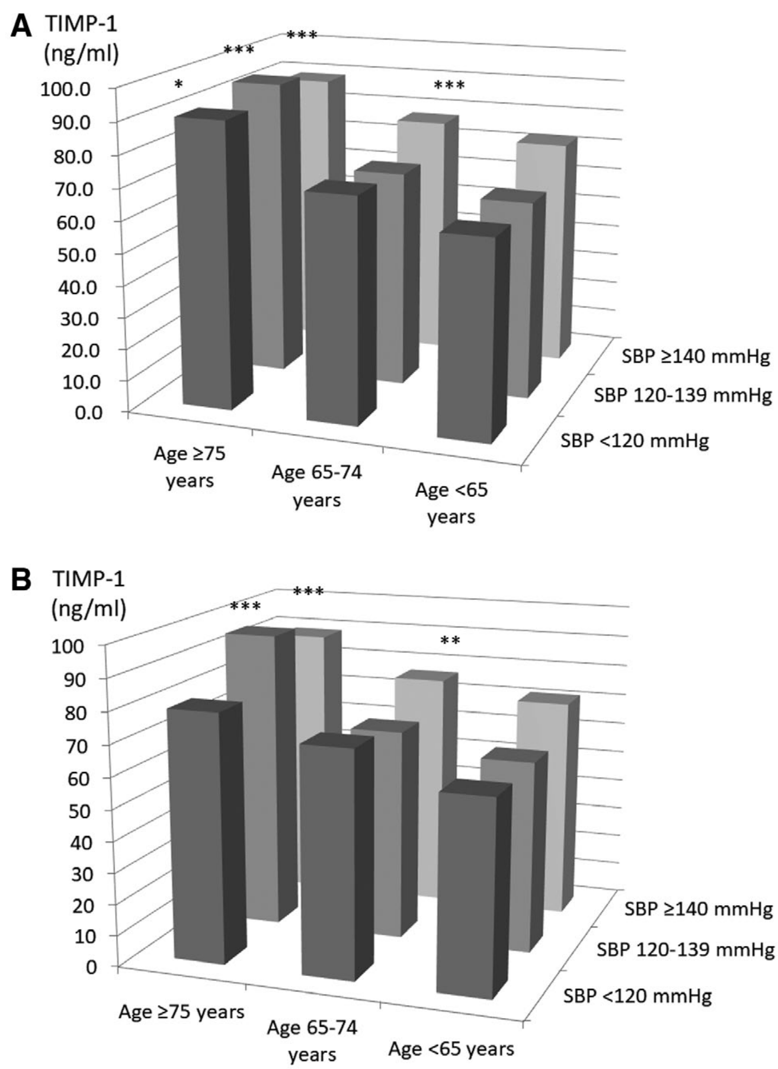

Figure 2. Tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) vs. age and systolic blood pressure (SBP) category in the (**A**) unadjusted model and (**B**) multivariate adjusted model. Sex, body mass index, current smoking, alcohol intake >20 g/day, diabetes, dyslipidemia, and antihypertensive drug use were included in the multivariate adjusted model. *P<0.05; **P<0.01; ***P<0.001 vs. Age <65 years and SBP <120 mmHg.

Table 2. Subject Characteristics vs. Serum TIMP-1 Quartile

	Q1 (≤58 ng/mL) n=242	Q2 (59–72 ng/mL) n=230	Q3 (73–88 ng/mL) n=233	Q4 (≥89 ng/mL) n=231	P-value†
Age (years)	62.9±8.2	63.6±7.8	66.7±8.4	69.4±8.5	<0.001
Male, %	47.1	58.7	51.5	52.8	0.091
BMI (kg/m²)	22.6±2.9	22.4±2.8	22.7±3.1	22.6±3.4	0.837
Smoking status					0.039
Past smoker, %	17.1	25.1	22.5	16.3	
Current smoker, %	24.8	30.2	25.5	33.2	
Alcohol intake (g/day)	20.1±26.0	17.2±28.7	18.2±37.0	22.1±41.4	0.486
Alcohol intake >20 g/day	41.6	33.7	32.0	33.7	0.152
SBP (mmHg)	130.8±21.6	132.8±21.9	135.8±22.4	139.5±24.5	<0.001
DBP (mmHg)	78.5±12.5	79.5±13.5	78.8±12.3	81.5±14.5	0.089
Antihypertensive medication, %	19.7	15.9	24.0	22.9	0.162
Hyperlipidemia, %	33.5	33.0	34.8	30.7	0.828
Total cholesterol (mg/dL)	193.6±33.3	187.4±33.5	194.4±31.2	189.8±35.1	0.076
Triglyceride (mg/dL)	112.4±57.0	110.8±65.5	110.2±65.4	107.4±72.3	0.861
Diabetes, %	4.7	6.1	8.2	6.5	0.515
Glucose (mg/dL)	104.7±25.0	100.6±21.0	101.1±31.6	96.8±20.7	0.007

Data given as mean ± SD or %. †ANOVA or chi-squared test. Abbreviations as in Table 1.

Table 3. OR for Stroke Events According to TIMP-1 Quartile

Stroke event	Event/n	Unadjusted			Model adjusted for significant covariates			Model adjusted for conventional risk factors		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (≤58 ng/mL)	47/246	1.62	0.95–2.78	0.077	1.59	0.92–2.74	0.098	1.65	0.95–2.86	0.077
Q2 (59–72 ng/mL)	34/233	1.00			1.00			1.00		
Q3 (73–88 ng/mL)	46/232	1.56	0.88–2.76	0.125	1.45	0.81–2.58	0.207	1.47	0.82–2.64	0.199
Q4 (≥89 ng/mL)	51/232	1.90	1.09–3.31	0.023	1.72	0.98–3.02	0.059	1.76	0.98–3.16	0.059

Data were calculated using logistic regression modeling. Significant covariates included sex, SBP and diabetes. Conventional risk factors included age, sex, BMI, smoking status, alcohol consumption >20 g/day, SBP, antihypertensive medication use, presence of hyperlipidemia, and diabetes. Abbreviations as in Table 1.

cases of ischemic stroke, 38 cases of cerebral hemorrhage, and 25 cases of subarachnoid hemorrhage. Subjects in the top TIMP-1 quartile had a significantly higher OR of stroke (OR, 1.90; 95% CI: 1.00–3.31, P=0.023) than those in the second TIMP-1 quartile, and the relationship tended toward significance even after adjustment for confounding factors (P=0.059; **Table 3**).

Discussion

The present study has shown that serum TIMP-1, a marker of fibrosis due to collagen in the extracellular matrix, increased steeply after the age of 65 years and was influenced by older age and higher SBP. The risk of stroke was increased in subjects from the highest TIMP-1 quartiles compared with those in the second TIMP-1 quartile. This is the first study to demonstrate, in a general Japanese population in which TIMP was lower than in a Western population, that the association between TIMP-1 and stroke risk was J-shaped, and that subjects with the highest TIMP-1 quartile could have a higher OR of stroke compared with those in the second TIMP-1 quartile.

In this case-control study of age-matched groups with relatively low serum TIMP-1, subjects in the highest TIMP-1 quartile had an increased risk of stroke. This supports the results of a longitudinal study in the general Swedish population, in which an increase of TIMP-1 by 1 SD was associated with a 1.18-fold higher risk of stroke.[8] In addition, the novel finding of the present study was that TIMP-1 quartile and an increased risk of stroke tended to have a J-curve relationship. Matrix metalloproteinases (MMP) degrade collagen in the extracellular matrix and TIMP are reported to regulate MMP activity,[14] with the balance between MMP and TIMP influencing arterial stiffness.[15] Extremely low TIMP-1 could be a marker of the risk of future stroke events, but further investigation is required to confirm this result.

Serum TIMP-1 (63 ng/mL for female subjects and 69 ng/mL for male subjects in the control group) in the Japanese general population was much lower than in subjects with suspected CAD (697 ng/mL),[6] hypertension (400 ng/dL),[16] the general population (781 ng/mL),[2] and normotensive subjects (776 ng/mL for male and 734 for female subjects)[17] in Western studies, although the average age of the present subjects (66.3 years for women and 65.2 years for men) was older than the average age of the normotensive subjects in the Framingham Heart Study (55 and 54 years, respectively).[17] The reasons why Japanese subjects had lower TIMP-1 than Western subjects were unclear. The JMS cohort study was conducted in relatively rural area in Japan, and the level of C-reactive protein, a marker of inflammation, was also lower than in a Western population.[18,19]

In the present study, TIMP-1 may have been a surrogate marker of ageing, because the age at which it began to increase sharply was close to the chronological age defining elderly subjects (65 years old). In particular, TIMP-1 level was significantly associated with ageing in young elderly subjects (65–74 years), but was not in old elderly subjects (>75 years). Given that the present baseline data were collected between 1992 and 1995, the definition of elderly might be appropriate for assessing the relationship of age to this marker of extracellular matrix collagen at that time. Recently, the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society has proposed redefining elderly persons as those aged ≥75 years, because a "rejuvenation" phenomenon has been noted with regard to physical function among the older population, including improvement of gait speed and grip strength.[12] Therefore, we also need to evaluate the age at which TIMP-1 increases in the current population.

Compared with non-elderly subjects, lower SBP (<120 mmHg) was associated with less collagen fibrosis in old elderly subjects (**Figure 2B**), because of the age-associated increase in TIMP-1. Therefore, intensive BP lowering to office SBP 130 mmHg was found to reduce cardiovascular events, even in very elderly subjects with frailty.[20] Elevation of TIMP-1, however, produced an increase in SBP in non-elderly subjects, and hence management of SBP could be important to suppress TIMP-1 increase in non-elderly subjects.

There were some limitations of the present study. It was a case-control study, therefore the TIMP-1 levels in the present study might not represent those in the total population.

Conclusions

Elevation of TIMP-1 was related to older age and higher SBP, and serum TIMP-1 level may be associated with the risk of stroke in the general Japanese population, in whom serum TIMP-1 is lower than in Western countries.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circrep.CR-19-0084