**CLINICAL STUDY**

**Increased Circulating Cathepsin L in Patients with Coronary Artery Disease**

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Summary

Cathepsin L (CatL) is a potent collagenase involved in atherosclerotic vascular remodeling and dysfunction in animals and humans. This study investigated the hypothesis that plasma CatL is associated with the prevalence of coronary artery disease (CAD). Between February May 2011 and January 2013, 206 consecutive subjects were enrolled from among patients who underwent coronary angiography and percutaneous coronary intervention treatment. Age-matched subjects (n = 215) served as controls. Plasma CatL and high-sensitive C-reactive protein (hs-CRP) and high-density lipoprotein cholesterol were measured. The patients with CAD had significantly higher plasma CatL levels compared to the controls (1.4 ± 0.4 versus 0.4 ± 0.2 ng/mL, P < 0.001), and the patients with acute coronary syndrome had significantly higher plasma CatL levels compared to those with stable angina pectoris (1.7 ± 0.7 versus 0.8 ± 0.4 ng/mL, P < 0.01). Linear regression analysis showed that overall, the plasma CatL levels were inversely correlated with the high-density lipoprotein levels (r = −0.32, P < 0.01) and positively with hs-CRP levels (r = 0.35, P < 0.01). Multiple logistic regression analyses shows that cathepsin L levels were independent predictors of CAD (add ratio, 1.8; 95% CI, 1.2 to 2.1; P < 0.01). These data demonstrated that increased levels of plasma CatL are closely associated with the presence of CAD and that circulating CatL serves as a useful biomarker for CAD.

**Key words:** Ischemic heart disease, Cysteine protease, Biomarker, High-sensitive C-reactive protein

Cathepsins, which are members of the cysteine protease family, are primary intracellular proteases that act in terminal protein recycling in lysosomes and protein processing in other intracellular organelles, such as hormone secretory granules. Cathepsins were also recently reported to play a critical role in the remodeling of cardiovascular wall extracellular matrix components (e.g., collagens, proteoglycans, and elastin). Emerging evidence has suggested that inflammatory and oxidative stresses resulted in increases in the expression of several proteases including some cysteinyl cathepsins (CatS and CatK), which then modulate vascular endothelial cells and smooth muscle cell events (migration, invasion, apoptosis, and proliferation) in vascular metabolic and inflammatory disorders. The levels of CatS, CatK, and CatB genes and proteins were increased in atherosclerotic lesions in humans and animals. Thus, cathepsins represent a viable target to ameliorate vascular negative remodeling and dysfunction in response to multiple pathogenic stressors.

Among the cathepsin family members, CatL has been shown to be one of the most potent mammalian elastase and collagenases in vivo and in vitro. Accumulating clinical and experimental evidence has led to a number of important findings that contribute to our understanding of a pivotal role of CatL in tissue regeneration and atherosclerotic coronary artery disease (CAD) initiation and progression. For example, endostatin-derived peptides represent novel molecular links between CatL and aminopeptidase N/CD13 in the regulation of angiogenesis in tumor growth. Urbich and colleagues demonstrated that CathL has an important role in the integration of blood endothelial cell progenitor (EPC) into ischemic tissue and is required for EPC-mediated vascularization. The high expression levels of CathL in EPC equip these cells for 'drilling for oxygen' to promote blood supply to ischemic tissues. It was reported that CatL inhibition confers resistance to carotid artery injury by decreasing toll-like receptor-4-mediated inflammation. A clinical study reported a cross-link between serum CatL and mortality in...
older adults.\textsuperscript{21} Given that pharmacological and genetic interventions targeted toward CatL ameliorated cardiovascular atherosclerotic plaque growth and remodeling in several animal models,\textsuperscript{22,23} we hypothesized that increased plasma CatL levels are associated with the presence of CVD. We tested this hypothesis in the present study in patients with CAD in order to explore the relationship between circulating CatL and clinical presentations, and we attempted to identify useful noninvasive blood biomarkers that are suggestive of patients with CAD.

**Methods**

**Study population:** A total of 206 consecutive patients with CAD who underwent percutaneous coronary intervention (PCI) with drug-eluting stent implantation between February 2011 and January 2013 at Yanbian University Hospital, Jilin, China, were considered for inclusion in the present study. The patients with CAD were subgrouped into those with stable angina pectoris (SAP; \( n = 56 \)), and those with unstable angina pectoris (UAP) and acute myocardial infarction (AMI) (called acute coronary syndrome, ACS, \( n = 150 \)) by symptoms and laboratory examinations. AMI patients included 72 ST elevation myocardial infarction (STEMI) patients and 19 non-ST elevation myocardial infarction (NSTEMI) patients. A total of 215 subjects showed no evidence of CAD, including no typical chest pain on exertion, no myocardial infarction by history or electrocardiogram, negative exercise test result, and < 50% luminal narrowing of the coronary arteries, and they were selected as the controls. The study protocol was approved by the ethics committee of Yanbian University Hospital, and written informed consent was obtained from all patients and control subjects.

**Clinical definition:** Hypertension was defined as a systolic blood pressure > 140 mmHg, a diastolic blood pressure > 90 mmHg, and/or having received treatment for hypertension. Diabetes mellitus (DM) was confirmed if patients had hemoglobin A1c levels \( \geq 6.5\% \), a fasting plasma glucose concentration > 126 mg/dL, and/or a history of any anti-hyperglycemic medication or previous diagnosis of diabetes.

The diagnosis of AMI was based on the elevation of cardiac biomarkers (at least one positive biomarker: creatine kinase-MB or troponin T) and an electrocardiogram indicative of new ischemia (new ST-T change or new left bundle branch block) and a history of prolonged chest pain. SAP was diagnosed as an invariable character of exertional chest pain for 3 months before the subject went to the hospital (with “invariable” meaning the same degree of exertion and excitation provocation and the same location, quality, and 3- to 5-minute duration), which was relieved by rest or nitroglycerin. Unstable angina pectoris was diagnosed by typical chest pain at rest in the 24 hours before going to hospital, depressed ST \( \geq 0.1 \) mV, and/or T-wave inversion on electrocardiogram but normal creatine kinase-MB level. Patients were excluded if they had prior evidence of cardiomyopathy, primary valvular disease, congenital heart disease, cancer, arthritis, autoimmune disease, end-stage renal disease with maintenance hemodialysis, and secondary cardiac muscle disease caused by any known systemic condition. The age, body mass index (BMI), gender, systolic and diastolic blood pressures, smoking history, and medication history were obtained for each subject.

**Laboratory examination:** A blood sample was taken prior to PCI. Plasma CatL levels were evaluated in CAD patients and control subjects by using ELISA kits (Bender MedSystems, Burlingame, CA, USA) in duplicate. Plasma levels of creatinine, high-density lipoprotein (HDL), low-density lipoprotein (LDL), hs-CRP, and hemoglobin A1c (HbA1c) were measured at the clinical laboratory of Yanbian University Hospital (Clinical Laboratory, Yanji, Jilin, China). Plasma CatL values are expressed as ng/mL, and the inter-assay and intra-assay coefficients of variation were < 8%.

**Quantitative coronary angiogram:** Coronary angiography was conducted prior to PCI treatment. Angiography exhibiting the maximal degree of stenosis was adapted for the quantitative coronary angiogram (QCA). The QCA analysis was performed using a contour detection minimum cost algorithm (DSA Artis Zee Biplane; Siemens, Erlangen, Germany). All CAD were found to have \( \geq 50\% \) stenosis in \( \geq 1 \) main coronary artery. The reference segment diameter was averaged from 5-mm-long angiographically normal segments proximal to the lesion; if a normal proximal segment could not be identified, a distal angiographically normal segment was analyzed as described.

**Statistical analysis:** Data are presented as the mean \( \pm \) standard deviation (SD). Comparisons of categorical baseline characteristics were made using the chi-square test. The hs-CRP concentrations were logarithmically transformed because the data showed a skewed distribution. Comparisons of the continuous baseline characteristics were conducted using the unpaired Student-\( t \)-test. If the homogeneity of variance assumption was violated, the nonparametric Kruskal-Wallis test was used instead. The factors that related at the \( P < 0.1 \) level were selected as independent variable candidates for a multiple logistic regression analysis, which was used to evaluate the independent contributions of clinical parameters to CAD. Correlation coefficients were calculated using a linear regression analysis. \( P \) values of less than 0.05 were considered significant. StatFlex (version 7.0; Artech, Osaka, Japan) was used for all statistical analyses.

**Results**

**Baseline clinical characteristics:** The baseline characteristics of the control subjects and CAD patients are presented in Table I. There were no significant differences in gender, BMI, or age, \( (P > 0.05 \) for each comparison). The CAD patients showed a significantly higher prevalence of DM and hypertension \( (P < 0.01) \); these patients were also more likely to have had myocardial infarction or cerebrovascular disease or to have undergone an angioplasty or coronary bypass graft. The frequencies of patients with CAD under treatment with antihypertensive, antilipid, antidiabetic, or antiplatelet medications were higher than those of the control subjects (Table I and Figure).

Table II presents the clinical characteristics of the
The control subjects, stable angina pectoris (SAP), and acute coronary syndrome (ACS) patients. *P < 0.001 versus control subjects by one-way ANOVA followed by Tukey’s post-hoc test.

In the UAP + AMI and SAP groups (P > 0.05 for each comparison), there were also no significant differences in gender, age, or BMI (P > 0.05 for each comparison). With the exception of the prevalence of hypertension and DM, there were no significant differences in medications or clinical histories between the 2 groups (P > 0.05 for each comparison).

Atherosclerotic lesion location and characteristics: With the exception of the diameter stenosis, lesion length, and Syntax score, there were no significant differences in the target lesion location or QCA results of the target lesions in the UAP + AMI and SAP groups (P > 0.05 for each comparison; Table II).

Circulating biomarkers: As compared to the control subjects, the CAD patients showed significantly higher levels of plasma CatL (1.4 ± 0.4 versus 0.4 ± 0.2 ng/mL, P < 0.001; Table II). The levels of hs-CRP (14.1 ± 32.1 versus 19.8 ± 27.3 mg/dL, P < 0.001) and HbA1c (6.9 ± 0.9 versus 4.9 ± 0.9%, P < 0.001) were also significantly higher and the LDL (111.6 ± 30.3 versus 129.2 ± 52.2 mg/mL, P = 0.01) and HDL cholesterol (40.1 ± 11.1 versus 49.2 ± 13.2 mg/mL, P < 0.01) levels were significantly lower in the CAD patients than those of the control subjects, but there was no significant difference in the creatinine levels (Table II).

In the sub-analysis, the patients with ACS had significantly higher CatL (1.7 ± 0.7 versus 0.8 ± 0.4 ng/mL, P < 0.001) and hs-CRP (19.8 ± 27.3 versus 5.1 ± 6.8 mg/mL, P < 0.01) levels than the SAP patients (Table II). However, there were no significant differences in the HbA1c, HDL, LDL, or creatinine levels between both subgroups. We found that the cut-off value of plasma CatL for identifying APS and ACS was 1.2 ng/mL.

The linear regression analysis exhibited that overall, the CatL levels were positively correlated with hs-CRP levels (r = 0.35, P < 0.01) and inversely correlated with the high-density lipoprotein levels (r = −0.32, P < 0.01).

Independence of predictors of CAD: Table III shows our observations of the logistic regression analysis for CAD. In the single logistic regression analysis, hyperten-

| Table I. Demographic and Clinical Variables of Control and CAD Patients |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                        | CAD (n = 206) | Control (n = 215) | P value |
| Demographic characteristics |                           |                           |         |
| Age, years                      | 59.1 ± 12.9    | 56.2 ± 14.2          | 0.091   |
| Female, % of patients           | 42.1           | 39.3                | 0.904   |
| Body mass index, kg/m²          | 27.1 ± 4.2     | 25.2 ± 3.1          | 0.067   |
| Cardiac or coexisting conditions |               |                           |         |
| Hypertension, % of patients     | 72.3           | 22.6                | < 0.001 |
| Diabetes mellitus, % of patients| 44.6           | 13.9                | < 0.001 |
| Current smokers, % of patients  | 60.6           | 52.2                | 0.061   |
| Previous myocardial infarction, % of patients | 16.5 | 0 | 0.001 |
| Previous angioplasty, % of patients | 22.3 | 0 | 0.001 |
| Previous bypass surgery, % of patients | 2.4 | 0 | 0.001 |
| Previous cerebrovascular disease, % of patients | 8.7 | 2.6 | 0.108 |
| Biological parameters           |               |                           |         |
| Low density lipoprotein, mg/dL   | 111.6 ± 30.3   | 129.2 ± 52.1         | 0.009   |
| High density lipoprotein, mg/dL  | 40.1 ± 11.1    | 49.2 ± 13.2          | < 0.01  |
| Hemoglobin A1c, %                | 6.9 ± 0.9      | 4.9 ± 0.9            | < 0.001 |
| Creatinine, mg/dL                | 0.9 ± 0.2      | 0.6 ± 1.3            | 0.113   |
| hs-CRP, mg/dL                    | 14.1 ± 32.1    | 1.9 ± 2.2            | < 0.001 |
| Cathepsin L, ng/mL               | 1.4 ± 0.4      | 0.4 ± 0.2            | < 0.001 |

*hs-CRP indicates high-sensitive c-reactive protein; ARBs, angiotensin II receptor blockers; ACEI, angiotensin converting enzyme inhibitor. Values are expressed as mean ± SD or number (%).
Table II. Demographic and Clinical Variables of SAP and UAP-AMI

| Variable                                      | SAP (n = 56) | ACS (n = 150) | P value |
|-----------------------------------------------|-------------|--------------|---------|
| **Demographic characteristics**               |             |              |         |
| Age, years                                    | 58.2 ± 11.4 | 56.9 ± 18.1  | 0.232   |
| Female sex, % of patients                     | 36.0        | 39.3         | 0.835   |
| Body mass index, kg/m²                        | 27.1 ± 5.1  | 26.9 ± 4.2   | 0.364   |
| **Cardiac or coexisting conditions**          |             |              |         |
| Hypertension, % of patients                   | 58.7        | 77.3         | 0.120   |
| Diabetes mellitus, % of patients              | 12.5        | 56.7         | < 0.01  |
| Current smokers, % of patients                | 44.6        | 66.7         | 0.188   |
| Previous myocardial infarction, % of patients | 5.4         | 20.6         | 0.093   |
| Previous angioplasty, % of patients           | 12.5        | 26.0         | 0.084   |
| Previous bypass surgery, % of patients        | 3.6         | 2.0          | 0.519   |
| Previous cerebrovascular disease, % of patients | 3.6       | 10.6         | 0.102   |
| **Biological parameters**                     |             |              |         |
| Low density lipoprotein, mg/dL                | 116.9 ± 22.8| 111.8 ± 19.3 | 0.870   |
| High density lipoprotein, mg/dL               | 47.1 ± 6.9  | 40.9 ± 19.1  | 0.091   |
| Hemoglobin A1c, %                            | 6.0 ± 1.8   | 6.9 ± 1.9    | 0.128   |
| Creatinine, mg/dL                             | 0.7 ± 0.4   | 0.8 ± 0.5    | 0.232   |
| hs-CRP, mg/dL                                 | 5.1 ± 6.8   | 19.8 ± 27.5  | < 0.008 |
| Cathepsin L, ng/mL                            | 0.8 ± 0.4   | 1.7 ± 0.7    | < 0.001 |
| **Medications**                               |             |              |         |
| ARBs or ACEIs, % of patients                  | 42.9        | 36.7         | 0.432   |
| CCBs, % of patients                           | 50.0        | 42.6         | 0.309   |
| Beta-blockers, % of patients                  | 8.9         | 13.3         | 0.213   |
| Anti-lipids, % of patients                    | 92.9        | 89.3         | 0.451   |
| Aspirin, % of patients                        | 100.0       | 100.0        |         |
| Insulin, % of patients                        | 7.1         | 24.6         | 0.058   |
| **Target lesion location**                    |             |              |         |
| Left main artery                              | 1           | 6            | 0.843   |
| Left anterior descending artery               | 34          | 125          | 0.062   |
| Left circumflex artery                        | 12          | 83           | 0.176   |
| Right coronary artery                         | 36          | 89           | 0.128   |
| **QCA of target lesions**                     |             |              |         |
| Minimal lumen diameter, mm                    | 9.7 ± 0.2   | 8.9 ± 0.5    | 0.483   |
| Reference vessel diameter, mm                 | 2.9 ± 0.5   | 2.7 ± 0.5    | 0.201   |
| Diameter stenosis, %                          | 83.1 ± 5.1  | 90.1 ± 8.9   | 0.022   |
| Lesion length, mm                             | 14.5 ± 3.9  | 19.1 ± 4.5   | < 0.001 |
| **Stent types**                               |             |              |         |
| Firebird                                      | 41.3        | 58.7         | 0.229   |
| Partner                                       | 46.6        | 53.4         | 0.193   |
| **Syntax score**                              | 10.1 ± 7.1  | 18.1 ± 11.0  | < 0.010 |

QCA indicates quantitative coronary angiography; SAP, stable angina pectoris; ACS, acute coronary syndrome; Other abbreviations as in Table I. Values are expressed as mean ± SD or number (%).

Table III. Independent Predictors of CAD According to Multivariable Logistic Regression Analysis

| Variable                                      | Single Odds Ratio Estimate | 95% CI | P value | Multiple Odds Ratio Estimate | 95% CI | P value |
|-----------------------------------------------|---------------------------|--------|---------|-------------------------------|--------|---------|
| Age, years                                    | 1.3                       | 0.6-1.1| 0.577   | 1.11                          | 0.7-1.1| 0.234   |
| Gender                                        | 0.8                       | 0.3-1.9| 0.482   |                               |        |         |
| BMI, kg/m²                                     | 0.8                       | 0.7-0.8| < 0.013 | 0.81                          | 0.8-0.9| 0.431   |
| Diabetes mellitus, %                          | 8.2                       | 3.1-45.2| 0.009   | 8.12                          | 2.2-39.1| 0.010   |
| Hypertension, %                               | 10.9                      | 2.9-60.0| 0.045   | 11.0                          | 2.81-57.1| 0.011   |
| LDL cholesterol, mg/dL                        | 0.8                       | 0.7-1.2| 0.114   |                               |        |         |
| HDL cholesterol, mg/dL                        | 0.9                       | 0.6-1.0| < 0.050 | 1.1                           | 0.7-1.3| < 0.013 |
| hs-CRP                                        | 2.9                       | 2.0-7.1| < 0.050 | 3.3                           | 2.1-6.5| < 0.008 |
| Cathepsin L                                   | 1.3                       | 1.4-4.1| < 0.001 | 1.9                           | 1.2-2.1| < 0.010 |

Multiple regression model includes all variables at baseline with P < 0.05 by univariable analysis. CI indicates confidence interval; other abbreviations as in Table I.
sion, DM, hs-CRP, LDL, HDL, and CatL, were significantly associated with CAD (Table III). The multiple logistic regression analysis with age, BMI, hypertension, DM, LDL, HDL, and CatL demonstrated that the DM (odds ratio [OR], 8.1; 95% CI, 2.2 to 39.1; \( P < 0.01 \)), hypertension (OR, 11.0; 95% CI, 2.81 to 57.1; \( P < 0.01 \)), hs-CRP (OR, 3.3; 95% CI, 2.1 to 6.5; \( P < 0.01 \)), HDL (OR, 1.1; 95% CI, 0.7 to 1.3; \( P < 0.01 \)) and CatL (OR, 1.9; 95% CI, 1.2 to 2.1; \( P < 0.01 \)) levels were significantly correlated with CAD (Table III).

**Discussion**

This study provides evidence that increased levels of plasma CatL are independently associated with the prevalence of CAD after adjustment for conventional CAD risk factors (i.e., blood pressure, dyslipidemia and BMI). Excess inflammation is closely associated with an increased risk of metabolic cardiovascular disease. CAT gene and protein are overexpressed in animal and human atherosclerotic lesions as well as injury-induced neointimal lesions, and the expression of its endogenous inhibitor, cystatin C in the arterial tissues is decreased in atherosclerosis-based arterial and vein disorders such as aneurysms and varicose veins. Thus, these results indicate that elevated circulating CatL levels could be a useful marker of CAD associated with inflammation.

Recent studies highlighted that CatL is the most abundant and important protease synthesized by cardiovascular cells and inflammatory cells, and that it is relevant to atherosclerosis-related cardiovascular disease and its implications. However, limited studies have examined circulating CatL levels in cardiovascular disease in humans. Our present data show that the levels of blood CatL were higher in the CAD patients than those of the control subjects. Our multivariable logistic regression analysis revealed that elevated plasma CatL levels were independent predictors of CAD. Together with the finding that circulating CatK was elevated in patients with coronary artery atherosclerotic stenosis and ectasia, these findings indicated that these cathepsins may be involved in coronary artery aneurysm and restenosis.

Increased circulating CatL in patients with obvious coronary artery stenosis is consistent with the concept that coronary stenosis is a proteolytic process involving proteases such as CatS and CatK, which is shear-sensitive and upregulated during atherosclerotic lesion and neointimal formation. Due to the coronary artery anatomic characteristics, i.e., the multiple branches, narrowings, and inflections, oscillatory flows during cardiac systole and diastole changes, and collateral circulation counterflow during coronary artery obstruction, it is plausible that the vascular wall may secrete CatL into the circulating blood under the influence of inflammation and result in higher blood CatL. Elevated expressions of CatL mRNA and/or protein in *in vivo* and *in vitro* cultured vascular endothelium and smooth muscles in response to inflammatory cytokines were reported, suggesting that these vascular cell types may also influence circulating CatL levels in patients with CAD.

It is well-known that atherosclerotic plaque instability and rupture induced by inflammation are the critical mechanisms of acute coronary syndrome or an acute clinical event. Accumulating evidence indicates that increased levels of CRP, an acute-phase protein widely used as a marker of inflammation, are predictive of the risk of acute coronary syndrome and acute myocardial infarction. The severity of the superficial inflammation seen in atherosclerotic plaques has been implicated as being significantly associated with atherosclerotic plaque instability and rupture. Here, we observed higher CatL levels in the patients with ACS compared to those with SAP. Likewise, we also observed that the patients with AMI or UAP had higher levels of hs-CRP compared to the control subjects. Moreover, our data revealed a significant positive correlation between CatL and hs-CRP in all subjects. Although there is no advantage to assessing plasma CatL levels in potential CAD patients compared with plasma hs-CRP, the linear regression analysis exhibited that overall, the CatL levels were positively correlated with hs-CRP levels (\( r = 0.35, P < 0.01 \)). A comprehensive review article highlighted the cathepsin-mediated metabolism of the major components of the vascular extracellular matrix, including the fibrous cap of atherosclerotic plaques.

The activation of CatL and CatS/K by monocytes/macrophages has been shown to promote plaque instability. Animal studies revealed that the pharmacological or genetic inhibition of CatL mitigates the atherosclerotic plaques’ extracellular matrix metabolism and prevents its disruption. Thus, CatL production by activated inflammatory cells and its release into the circulation appear to be strongly linked to the plaque instability and plaque rupture associated with local inflammatory processes within the vascular wall. On the other hand, the most extensively studied molecular candidates for rupture-producing proteases are the matrix metalloproteinases. It was shown that the presence of atherosclerotic plaque rupture in the culprit lesion was closely related to the high levels of metalloproteinase-9 in patients with UAP or AMI. Thus, elevated CatL levels together with the enhancement of the matrix metalloproteinase levels may provide a noninvasive method of monitoring and documenting coronary inflammatory atherosclerotic lesion vulnerability during acute coronary syndrome.

The involvement of CatK in ApoB-100 modification is likely to contribute to the extracellular lipid droplet formation, LDL particle aggregation, and LDL retention of arterial proteoglycans. CatL deficiency resulted in an increase in cholesterol ester storage in bone marrow macrophages of ApoE−/− mice, which was kept in large lysosomal compartments. Both CatS and CatK have been shown to control cholesterol efflux by the degradation of preβ-HDL and apoA-1. Our present data revealed a negative correlation between CatL and HDL in all subjects. Thus, similar to other cathepsins, CatL appears to modulate macrophage-derived foam cell formation and atherosclerotic plaque growth via the modulation of cholesterol uptake and/or efflux.

**Study limitations:** Several limitations of the present study should be considered. 1) The small sample size of CAD patients and non-CAD subjects limited the power to prove differences and associations and to conduct the subgroup analysis.
analysis of SAP and ACS patients; 2) this study was not planned to evaluate the association of blood CatL to coronary plaque characteristics (including plaque volumes and fibrous volumes) by intravascular ultrasound; 3) it is well-known that circulating markers of collagen turnover and CatL are not coronary-specific. It is almost impossible to separate collagen metabolites and CatL markers from different vessels (coronary artery, peripheral artery, carotid artery, or cerebral artery, etc.) and tissues (bone, adipose, myocardium, etc.). On the other hand, comprehensive review articles have highlighted that long-term treatment with blood pressure-lowering, glucose-lowering, and lipid-lowering drugs not only suppressed plasma cathpesins such as CatS, CatK, and CatL, but also protected cardiovascular remodeling and renal injury in various animal models.1,11 Moreover, the frequencies of CAD patients received drug therapies with lipid-lowering (statins) and the manuscript. No conflicts of interest to disclose with respect to this manuscript.

Conflicts of interest: The authors declare that they have no conflicts of interest to disclose with respect to this manuscript.

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