Heart Surgery Forum 2024; 27(6): E582–E588
doi: 10.59958/hsf.7385
https://journal.hsforum.com/

Article

Influence of Serum Apelin and CD40L Expression Levels on Adverse Cardiovascular Events after PCI

Jie Zhang[1,†], Yanjun Liu[2,†], Ning Liu[2,*]

[1]Department of Cardiology, Jingzhou First People's Hospital, The First Affiliated Hospital of Yangtze University, 434000 Jingzhou, Hubei, China
[2]Department of Cardiovascular Ward III, Xiantao First People's Hospital, 433000 Xiantao, Hubei, China
*Correspondence: wendaobaoding@163.com (Ning Liu)
[†]These authors contributed equally.

Submitted: 26 February 2024 Revised: 22 March 2024 Accepted: 10 April 2024 Published: 13 June 2024

Abstract

Objective: This study aimed to investigate the effects of serum levels of apelin and CD40L on major adverse cardiovascular events (MACEs) after percutaneous coronary intervention (PCI). **Methods**: A case–control study was conducted to select patients undergoing PCI in our hospital from June 2020 to June 2022. Patients were divided into the occurrence group and the non-occurrence group according to whether MACEs occurred during the 12-month follow-up after surgery. Enzyme-linked immunosorbent assay was used to detect the expression levels of serum apelin and CD40L in the two groups, and the correlation between the expression of apelin and CD40L and prognosis was analyzed. Logistic regression analysis was performed on the indicators with differences to analyze the influencing factors of the prognosis of PCI. **Results**: Compared with the non-occurrence group, the occurrence group had a significantly lower level of apelin and a significantly higher level of CD40L ($p < 0.001$). Apelin was negatively correlated with the occurrence of MACEs after PCI ($r = –0.583$, $p < 0.001$), and CD40L was positively correlated with the occurrence of MACEs after PCI ($r = 0.569$, $p < 0.001$). Logistic regression analysis showed that apelin was a protective factor for MACEs after PCI (odds ratio (OR) = 0.248, $p < 0.001$); CD40L, age, hypertension, and the number of diseased vessels were risk factors for MACEs after PCI (OR = 8.684, 0.018, 0.003, 0.020, $p < 0.05$). The area under curve (AUC) of apelin combined with CD40L was large, and the predictive value was higher than that of apelin and CD40L alone (AUC values were 0.956, 0.857, 0.905, $p < 0.001$; $p < 0.001$; $p < 0.001$). **Conclusions**: This study showed that the levels of apelin and CD40L were correlated with MACEs after PCI. Clinicians should pay close attention to the levels of apelin and CD40L in patients after PCI and be alert to the occurrence of MACEs.

Keywords

percutaneous coronary intervention; adipokines; type II transmembrane glycoprotein; adverse cardiovascular event; influencing factors

Introduction

Coronary heart disease is one of the diseases with the highest mortality worldwide, and it is mainly caused by coronary artery stenosis or occlusion [1–4]. At present, percutaneous coronary intervention (PCI) is one of the main methods for the treatment of this disease; PCI can promote the blood flow of patients to return to normal and ensure that patients have sufficient blood oxygen supply to the myocardium [5–8]. Although PCI treatment has achieved a certain degree of clinical efficacy, some patients still undergo major adverse cardiovascular events (MACEs) after the operation. MACEs mainly include heart failure, myocardial infarction, angina recurrence, and arrhythmia [9–11]. The occurrence of such events brings heavy psychological burden and economic pressure to the patient's family and society, which have a serious impact on the patient.

Studies have shown that the expression of serum apelin and type II transmembrane glycoprotein (CD40L) is closely related to the development of cardiovascular diseases; these compounds have attracted wide research attention [12–14]. Apelin is an endogenous ligand of angiotensin domain type 1 receptor-related protein. As an endogenous natriuretic inhibitory peptide, apelin has been found to have various physiological functions in the cardiovascular system. It is widely distributed in the body and has high expression levels in many vascular systems, such as cardiovascular system and pulmonary vascular system. Expression levels are closely related to various diseases such as heart failure, atrial fibrillation, and myocardial infarction [14,15]. CD40L is a molecule on the surface of T lymphocytes, which is related to inflammation and platelet activation. It has been found to play a key role in atherosclerosis. It has high homology in amino acid level and is an important pathway for regulating various immune and inflammatory processes. It can activate the secretion of macrophages, endothelial cells, and T lymphocytes in plaque to produce components that play an important role in the stability of the plaque in patients [16–19].

Although studies have focused on the expression of apelin and CD40L in cardiovascular diseases, relatively limited research has been conducted on their role in MACE

after PCI. Therefore, to further understand the risk factors of MACE after PCI and determine the correlation between the expression levels of apelin and CD40L in serum, we conducted this case–control study to analyze and evaluate patients undergoing PCI in our hospital from June 2020 to June 2022.

Objects and Methods

Research Object

The clinical data of patients who underwent PCI in our hospital from June 2020 to June 2022 were retrospectively analyzed. The patients were divided into the occurrence group and the non-occurrence group according to whether MACEs occurred during the 12-month follow-up.

Inclusion criteria: (1) All patients met the diagnostic criteria in the "Guidelines for the diagnosis and management of chronic coronary syndrome" [20], and their diagnosis was confirmed by coronary angiography; (2) all patients underwent PCI for the first time and met the indications of PCI in the Chinese guidelines for percutaneous coronary intervention; (3) complete clinical data; (4) implantation of drug-coated stents during operation; (5) age >18 years old; and (6) anticoagulation and antiplatelet drugs were used in both groups before and after the operation.

Exclusion criteria: (1) patients with previous major bleeding events (major bleeding met the bleeding academic research society criteria); (2) death or interruption during follow-up; (3) combined with hematological and infectious diseases; (4) complicated with severe liver, kidney, and other organ dysfunction; (5) combined with malignant tumors; (6) failure of PCI; and (7) previous history of heart failure, myocardial infarction, arrhythmia, and angina.

This study was reported to and approved by the ethics committee of our hospital. Given that this case–control study involved anonymized patient data, informed consent was not required from the patients or their families.

Methods

(1) The baseline data of patients undergoing PCI in our hospital were collected and recorded through the medical record system, including ① general data: gender, age, body mass index, diabetes, hypertension, smoking history, drinking history, family history of heart disease, cardiac function classification, and lesion location; ② biochemical indicators: triglyceride and total cholesterol; and ③ coronary angiography results: the number of diseased vessels, the number of stents implanted, and the degree of coronary artery stenosis. About 5 mL of venous blood was collected from the patients before the operation, and the serum was separated by centrifugation. The supernatant was stored at –70 °C and detected. The levels of serum apelin and CD40L were detected by enzyme-linked immunosorbent assay.

(2) The adverse cardiovascular events of patients after PCI in our hospital were collected by laboratory examination and imaging examination: heart failure (shortness of breath, dyspnea, other symptoms after exercise, left ventricular enlargement, and cardiac ejection fraction function decreased by echocardiography; Killip class III and above), recurrent myocardial infarction (occurrence of symptoms of myocardial infarction and myocardial infarction with significantly increased levels of myocardial infarction markers on electrocardiogram), arrhythmia (sustained ventricular tachycardia or ventricular fibrillation on electrocardiogram), and angina recurrence (angina symptoms and ischemic ST-T segment on electrocardiogram). The patients who underwent PCI were followed up for 1 year, and they were divided into the occurrence group and the non-occurrence group according to whether they had MACEs.

(3) Measurement of apelin and CD40L levels in patients undergoing PCI in our hospital: apelin and CD40L levels were detected in patients 2 days after PCI. In the morning, 2 mL of fasting venous blood was collected from the patients, and the level of apelin was detected by enzyme-linked immunosorbent assay. The kit used was an apelin kit (manufacturer: Shanghai Xitang Biotechnology Co., Ltd., China; Specifications: F00124; Origin: Shanghai, China). The level of CD40L was detected by double-antibody sandwich enzyme-linked immunosorbent assay. The kit was CD40L kit (manufacturer: Guangzhou Weibo Technology Co., Ltd.; Specification: 96T; Origin: Guangzhou, Guangdong, China).

Observation Indicators

(1) The occurrence of MACEs of patients after PCI was counted.

(2) The baseline data and the expression levels of apelin and CD40L were collected and compared between the two groups. Logistic regression analysis was performed to obtain the influencing factors of adverse events after PCI.

Statistical Methods

Statistical analysis was performed using IBM SPSS Statistics for Windows version 27.0 (IBM Corp. Armonk, NY, USA). Measurement data conforming to normal distribution were expressed as ($\bar{x} \pm$ s). Those who did not conform to the normal distribution were transformed into the normal distribution, and statistical analysis was performed by t test. Count data, expressed as [n (%)], were compared using the χ^2 test, and $p < 0.05$ was considered statistically significant. Binary logistic regression analysis was performed to analyze the prognostic factors of PCI. Spearman correlation analysis was used for correlation analysis, and $p < 0.05$ was considered statistically significant.

Results

Occurrence of MACEs after PCI

The 12-month follow-up results after PCI showed that a total of 42 patients with MACEs were included in the occurrence group, accounting for 20.90% (42/201). The remaining patients without MACEs were included in the non-occurrence group, accounting for 79.10% (159/201), as shown in Fig. 1.

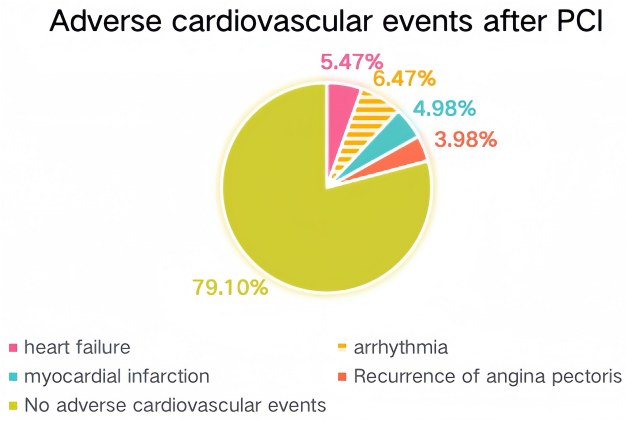

Fig. 1. Occurrence of adverse cardiovascular events after percutaneous coronary intervention (PCI).

Single-Factor Comparison of Adverse Cardiovascular Events after PCI

Statistical analysis revealed significant differences in age, hypertension, number of diseased vessels, smoking history, and serum apelin and CD40L expression levels between the two groups ($p < 0.05$; Table 1).

Apelin and CD40L are Correlated with the Occurrence of MACEs after PCI

As shown in Table 2, apelin was negatively correlated with the occurrence of MACEs after PCI (r = –0.583, $p < 0.05$), and CD40L was positively correlated with the occurrence of MACEs after PCI (r = 0.569, $p < 0.05$).

Independent Variable Assignment

As shown in Table 3, the MACEs after PCI were used as the dependent variable Y. The age, hypertension, number of diseased vessels, smoking history, serum apelin, and serum CD40L were used as the independent variables X1, X2, X3, X4, X5, and X6 for assignment processing, respectively, as shown in Table 3.

Multivariate Analysis of the Prognosis of PCI

Logistic regression equation showed that apelin was a protective factor for MACEs after PCI (odds ratio (OR) <1). Age, hypertension, number of diseased vessels, smoking history, and CD40L were all risk factors for MACEs after PCI, with OR values >1. Details can be found in Table 4.

Analysis of the Predictive Value of Different Indicators

The area under the curve (AUC) of apelin combined with CD40L was large, and the predictive value was higher than that of apelin or CD40L alone ($p < 0.001$). Details can be found in Table 5.

Discussion

PCI is one of the most commonly used procedures for coronary heart disease in cardiology, which has good diagnosis and treatment effects. However, some patients will have MACEs after PCI, bringing a heavy blow to the quality of life and economy of patients. Studies have shown that apelin is an adipokine, which has an important effect on the stability of carotid plaque in the body. It has low levels in patients with myocardial ischemia and other diseases and is closely related to vascular diseases [21–23]. CD40L is involved in the adhesion of activated platelets to vascular endothelium to form thrombosis, and it can stabilize coronary plaque [17,24]. Therefore, the clinical diagnosis and treatment of patients should be promoted to determine the influencing factors leading to MACE after surgery and explore its correlation with the expression levels of apelin and CD40L.

The 12-month follow-up results showed that a total of 42 patients (20.90%) had MACEs. We found significant differences in age, hypertension, number of diseased vessels, smoking history, and serum apelin and CD40L expression levels between the two groups ($p < 0.05$). Correlation analysis revealed that apelin was negatively correlated with the occurrence of MACEs after PCI (r = –0.583, $p < 0.05$), whereas CD40L was positively correlated with the occurrence of MACEs after PCI (r = 0.569, $p < 0.05$). Exploring its effect on patients after PCI is of great significance to reduce the occurrence of MACEs. Logistic regression equation was used to calculate the difference between the two groups. The results indicated that apelin was a protective factor for MACEs after PCI (OR = 0.248, $p < 0.001$), whereas CD40L was a risk factor for MACEs after PCI (OR = 8.684, $p < 0.001$). We conducted predictive value analysis and found that the AUC of apelin combined with CD40L was large, and the predictive value was higher than that of apelin and CD40L alone ($p < 0.001$). Mughal *et al.* [25] concluded that the apelin receptor signal transduction axis has a protective effect in the cardiovascular system. Previous studies have found that apelin can regulate the body's

Table 1. Comparison of general data.

The project		Occurrence group (n = 42)	Non-occurrence group (159)	χ^2/z	p
Gender (n, %)	Male	24 (57.14)	96 (60.38)	0.144	0.704
	Female	18 (42.86)	63 (39.63)		
Body mass index (kg/m^2)		22.20 (20.68, 23.30)	21.60 (20.30, 22.90)	−1.150	0.250
Smoking history (n, %)	Yes	27 (64.29)	57 (35.95)	11.044	0.001
	None	15 (35.71)	102 (64.05)		
Drinking history (n, %)	Yes	10 (23.81)	52 (32.70)	1.232	0.267
	None	32 (76.19)	107 (67.30)		
Family history of heart disease (n, %)	Yes	4 (9.52)	15 (9.43)	0.001	0.986
	None	38 (90.48)	144 (90.57)		
Cardiac function classification (n, %)	Level III	17 (40.48)	64 (40.25)	0.001	0.979
	Level IV	25 (59.52)	95 (59.75)		
Lesion location (n, %)	Left main coronary artery	15 (35.71)	52 (32.70)	0.141	0.932
	Right main coronary artery	20 (47.62)	80 (50.31)		
	Three coronary artery lesions	7 (16.67)	27 (16.98)		
Age (n, %)	<60 years old	12 (28.57)	98 (61.64)	14.659	<0.001
	≥60 years old	30 (71.43)	61 (38.36)		
Hypertension (n, %)	Yes	27 (64.29)	50 (31.45)	15.161	<0.001
	None	15 (35.71)	109 (68.55)		
Number of diseased vessels (n, %)	1–2	18 (42.86)	115 (72.33)	12.890	<0.001
	≥3	24 (57.14)	44 (27.67)		
Number of stents (n, %)	1–2	18 (42.86)	71 (44.65)	0.043	0.835
	≥3	24 (57.14)	88 (55.35)		
Degree of coronary artery stenosis (%)		86.00 (83.00, 90.25)	87.00 (83.00, 91.00)	−0.632	0.527
Triglyceride (mmol/L)		1.99 (1.82, 2.21)	1.93 (1.78, 2.13)	−1.278	0.201
Total cholesterol (mmol/L)		4.94 (4.72, 5.13)	4.92 (4.68, 5.07)	−1.137	0.256
CD40L (μg/L)		7.18 (6.71, 7.98)	8.59 (8.17, 9.00)	−8.255	<0.001
Apelin (ng/L)		27.61 (26.53, 28.55)	25.60 (24.82, 26.88)	−7.111	<0.001
Perioperative medication					
Antiplatelet agents		24 (57.14)	92 (57.86)	0.007	0.933
Statins		13 (30.95)	50 (31.45)	0.004	0.951
Nitrates		8 (19.05)	33 (20.75)	0.060	0.807
Beta-blockers		9 (21.43)	35 (22.01)	0.007	0.935

Note: The reference range of triglyceride (mmol/L) was <1.7 mmol/L as appropriate level, 1.70–2.25 mmol/L as borderline elevated, and ≥2.26 mmol/L as elevated. The reference range of total cholesterol (mmol/L) was <5.18 mmol/L, which was the ideal range, 5.18–6.19 mmol/L was borderline elevated, and ≥6.22 mmol/L was elevated.

Table 2. Correlation of apelin and CD40L with the occurrence of adverse cardiovascular events after PCI.

Indicators	Cardiovascular adverse events occurred after PCI	
	r	p
Apelin	–0.583	<0.001
CD40L	0.569	<0.001

Table 3. Independent variable assignment table.

Variate	Variable name	Assignment method
Y	Adverse cardiovascular events after PCI	0 = no occurrence, 1 = occurrence
X1	Age	0 = < 60 years old, 1 = ≥60 years old
X2	Hypertension.	0 = no, 1 = yes
X3	Number of diseased vessels	0 = 1–2, 1 = ≥3
X4	Smoking history	0 = no, 1 = yes
X5	Serum apelin	Measured value
X6	Serum CD40L	Measured value

Table 4. Multivariate analysis of factors affecting the outcome of PCI procedures.

The project	β	SE	Waldχ^2	p value	OR value	OR value 95% CI
Apelin	−1.395	0.393	12.601	<0.001	0.248	0.115–0.535
CD40L	4.230	1.122	14.216	<0.001	8.684	7.621–19.001
Age	1.890	0.800	5.575	0.018	6.619	1.379–31.776
Hypertension.	2.484	0.822	9.124	0.003	11.991	2.392–60.099
Number of diseased vessels	1.939	0.836	5.375	0.020	6.952	1.350–35.815
Smoking history	1.089	0.745	2.135	0.144	2.971	0.690–12.799

OR, odds ratio; CI, confidence interval.

Table 5. Analysis of the predictive value of different indicators.

The project	AUC	Standard error	Confidence interval	Sensitivity	Specificity	p value
Apelin	0.857	0.030	0.798–0.916	0.541	0.976	<0.001
CD40L	0.905	0.024	0.858–0.951	0.690	0.931	<0.001
The two combined	0.956	0.014	0.929–0.983	0.952	0.830	<0.001

AUC, area under the curve.

blood vessels, improve cardiac systolic function, and has the effect of protective vasodilatation, which plays a crucial role in the cardiovascular system and heart development of patients and is an important predictor of adverse cardiovascular events after PCI [26]. CD40L is a strong activator of nuclear factors in platelets, which can initiate and enhance platelet activation in response to thrombus stimulation, promote inflammatory response, and cause plaque rupture, leading to adverse cardiovascular events [27]. In addition, Kłósek *et al*. [28] found that CD40L plays an important role in systemic immune function and is a risk indicator for a variety of cardiovascular diseases. These studies showed the effect of apelin and CD40L on the prognosis of patients undergoing PCI, and the data of this study revealed that the two were significantly correlated with the prognosis. At the same time, the combination of apelin and CD40L had a high diagnostic value in predicting adverse events after PCI.

Logistic regression equation showed that age, hypertension, and the number of diseased vessels were independent risk factors for MACEs after PCI. The reasons were as follows: (1) the increase in age will lead to the deterioration of the function of tissues and organs in the body, and the thickness of blood vessel wall will increase, resulting in the increase in blood flow resistance and the decrease in blood flow velocity, which will affect the blood circulation of patients. In addition, the older the patient is, the body's immunity, metabolism, and other functions are reduced, and the postoperative recovery becomes slow. Many factors cause poor surgical healing. Liu *et al*. [29] found that the patient's age is a risk factor for poor prognosis of PCI. (2) d'Entremont *et al*. [30] believed that hypertension is an important risk factor for coronary artery disease and an important predictor of the prognosis of PCI. Hypertension can cause relevant target organ damage in patients after PCI, including increased sympathetic nerve activity, enhanced inflammatory response and oxidative stress, and inhibited cardiac function, resulting in continuous hypotension, heart failure, and other adverse conditions. (3) Previous studies have shown that the incidence of MACEs increases with the increase in the number of involved vessels, and the number of diseased vessels is an important influencing factor [31]. As the number of diseased vessels increases, the complexity and risk of the operation and operation time increase as well. The large number of diseased vessels, stenosis, and obstruction of multiple vessels increase the risk of myocardial insufficiency, and the patient's myocardium cannot receive sufficient oxygen and nutrients for oxygen supply, resulting in an increased risk of MACEs.

The selection of patients who underwent PCI at our hospital within a specific time frame may have resulted in limitations of the sample. This study adopted a case–control study design, which could not completely exclude potential confounding factors and information bias. However, we attempted to collect other information of the two groups, which showed that the two groups were comparable. This study was conducted only in a specific medical setting, and the particular characteristics of that setting may limit the generalizability of the findings to other medical settings with different backgrounds and nursing practices. These limitations should be considered when interpreting the findings and incorporated into a comprehensive assessment of the study's conclusions. Future studies can compensate for these limitations through elaborate designs and large sample size multicenter studies. Despite these limitations, this study provides substantial support for the analysis of influencing factors of cardiovascular adverse events during PCI and a theoretical basis for clinical physicians to intervene.

Conclusions

In conclusion, many influencing factors are responsible for the occurrence of MACEs after PCI. Age, hypertension, number of diseased vessels, CD40L, and serum apelin are all independent influencing factors. Moreover, apelin

is negatively correlated with the occurrence of MACEs, and CD40L is positively correlated with the occurrence of MACEs. Therefore, timely and effective intervention of the above factors can improve the prognosis of PCI and enhance the reference basis for clinicians' diagnosis and treatment.

Availability of Data and Materials

Data to support the findings of this study are available on reasonable request from the corresponding author.

Author Contributions

NL: Conceptualization, Methodology, Software, Investigation, Formal Analysis, Funding Acquisition, and Writing - Original Draft. YL: Data Curation, Writing - Original Draft, Software, and Validation. JZ: Visualization, Investigation, Resources, Supervision, and Writing - Review and Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study has been approved by the Committee of Xiantao First People's Hospital, approval no.: 2024-03-001. This case–control study involved anonymized patient data, so informed consent was not required from the patients or their families.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Sethi NJ, Safi S, Korang SK, Hróbjartsson A, Skoog M, Gluud C, *et al*. Antibiotics for secondary prevention of coronary heart disease. The Cochrane Database of Systematic Reviews. 2021; 2: CD003610.

[2] Ingebrigtsen TS, Marott JL, Vestbo J, Nordestgaard BG, Lange P. Coronary heart disease and heart failure in asthma, COPD and asthma-COPD overlap. BMJ Open Respiratory Research. 2020; 7: e000470.

[3] Chen X, Wang R, Chen W, Lai L, Li Z. Decoy receptor-3 regulates inflammation and apoptosis via PI3K/AKT signaling pathway in coronary heart disease. Experimental and Therapeutic Medicine. 2019; 17: 2614–2622.

[4] Enas EA, Varkey B, Dharmarajan TS, Pare G, Bahl VK. Lipoprotein(a): An underrecognized genetic risk factor for malignant coronary artery disease in young Indians. Indian Heart Journal. 2019; 71: 184–198.

[5] Reynolds HR, Bairey Merz CN, Berry C, Samuel R, Saw J, Smilowitz NR, *et al*. Coronary Arterial Function and Disease in Women with No Obstructive Coronary Arteries. Circulation Research. 2022; 130: 529–551.

[6] Ozaki Y, Hara H, Onuma Y, Katagiri Y, Amano T, Kobayashi Y, *et al*. CVIT expert consensus document on primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) update 2022. Cardiovascular Intervention and Therapeutics. 2022; 37: 1–34.

[7] Tabrizi AT, Moghaddasi H, Rabiei R, Sharif-Kashani B, Nazemi AE. Development of a Catheterization and Percutaneous Coronary Intervention Registry with a Data Management Approach: A Systematic Review. Perspectives in Health Information Management. 2019; 16: 1b.

[8] Kassimis G, Karamasis GV, Katsikis A, Abramik J, Kontogiannis N, Didagelos M, *et al*. Should Percutaneous Coronary Intervention be the Standard Treatment Strategy for Significant Coronary Artery Disease in all Octogenarians? Current Cardiology Reviews. 2021; 17: 244–259.

[9] Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, *et al*. Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. European Heart Journal. 2019; 40: 2632–2653.

[10] Park S, Park SJ, Park DW. Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Revascularization of Left Main Coronary Artery Disease. Korean Circulation Journal. 2023; 53: 113–133.

[11] Park S, Park SJ, Park DW. Percutaneous Coronary Intervention for Left Main Coronary Artery Disease: Present Status and Future Perspectives. JACC Asia. 2022; 2: 119–138.

[12] Rozwadowski J, Borodzicz-Jażdżyk S, Czarzasta K, Cudnoch-Jędrzejewska A. A Review of the Roles of Apelin and ELABELA Peptide Ligands in Cardiovascular Disease, Including Heart Failure and Hypertension. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2022; 28: e938112.

[13] Bosmans LA, Bosch L, Kusters PJH, Lutgens E, Seijkens TTP. The CD40-CD40L Dyad as Immunotherapeutic Target in Cardiovascular Disease. Journal of Cardiovascular Translational Research. 2021; 14: 13–22.

[14] Askin L, Askin HS, Tanrıverdi O, Ozyildiz AG, Duman H. Serum apelin levels and cardiovascular diseases. Northern Clinics of Istanbul. 2022; 9: 290–294.

[15] Chapman FA, Maguire JJ, Newby DE, Davenport AP, Dhaun N. Targeting the apelin system for the treatment of cardiovascular diseases. Cardiovascular Research. 2023; 119: 2683–2696.

[16] Daub S, Lutgens E, Münzel T, Daiber A. CD40/CD40L and Related Signaling Pathways in Cardiovascular Health and Disease-The Pros and Cons for Cardioprotection. International Journal of Molecular Sciences. 2020; 21: 8533.

[17] Shami A, Edsfeldt A, Bengtsson E, Nilsson J, Shore AC, Natali A, *et al*. Soluble CD40 Levels in Plasma Are Associated with

Cardiovascular Disease and in Carotid Plaques with a Vulnerable Phenotype. Journal of Stroke. 2021; 23: 367–376.

[18] Gergei I, Kälsch T, Scharnagl H, Kleber ME, Zirlik A, März W, *et al*. Association of soluble CD40L with short-term and long-term cardiovascular and all-cause mortality: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Atherosclerosis. 2019; 291: 127–131.

[19] França TT, Al-Sbiei A, Bashir G, Mohamed YA, Salgado RC, Barreiros LA, *et al*. CD40L modulates transcriptional signatures of neutrophils in the bone marrow associated with development and trafficking. JCI Insight. 2021; 6: e148652.

[20] Yongguang G, Yibing S, Ping X, Jinyao Z, Yufei F, Yayong H, *et al*. Diagnostic efficacy of CCTA and CT-FFR based on risk factors for myocardial ischemia. Journal of Cardiothoracic Surgery. 2022; 17: 39.

[21] Akbari H, Hosseini-Bensenjan M, Salahi S, Moazzen F, Aria H, Manafi A, *et al*. Apelin and its ratio to lipid factors are associated with cardiovascular diseases: A systematic review and meta-analysis. PLoS ONE. 2022; 17: e0271899.

[22] Kucukosmanoglu M, Sahin S, Urgun OD, Yildirim A, Kilic S, Sen O, *et al*. The Impact of Transcatheter Aortic Valve Implantation (TAVI) on Serum Apelin Levels in Patients with Aortic Valvular Stenosis. Brazilian Journal of Cardiovascular Surgery. 2021; 36: 372–378.

[23] Guo S, Luo X, Huang L, Wang C, Yang Y, Yang L. Hot spots and trends in PCI prognostic research: A bibliometric analysis with CiteSpace. Medicine. 2023; 102: e35599.

[24] Kojok K, Akoum SE, Mohsen M, Mourad W, Merhi Y. CD40L Priming of Platelets via NF-κB Activation is CD40- and TAK1-Dependent. Journal of the American Heart Association. 2018; 7: e03677.

[25] Mughal A, Sun C, O'Rourke ST. Apelin Reduces Nitric Oxide-Induced Relaxation of Cerebral Arteries by Inhibiting Activation of Large-Conductance, Calcium-Activated K Channels. Journal of Cardiovascular Pharmacology. 2018; 71: 223–232.

[26] Zhao E, Xie H, Zhang Y. A Nomogram Based on Apelin-12 for the Prediction of Major Adverse Cardiovascular Events after Percutaneous Coronary Intervention among Patients with ST-Segment Elevation Myocardial Infarction. Cardiovascular Therapeutics. 2020; 2020: 9416803.

[27] Bosmans LA, van Tiel CM, Aarts SABM, Willemsen L, Baardman J, van Os BW, *et al*. Myeloid CD40 deficiency reduces atherosclerosis by impairing macrophages' transition into a pro-inflammatory state. Cardiovascular Research. 2023; 119: 1146–1160.

[28] Kłósek M, Sędek Ł, Lewandowska H, Czuba ZP. The effect of ethanolic extract of Brazilian green propolis and artepillin C on aFGF-1, Eselectin, and CD40L secreted by human gingival fibroblasts. Central-European Journal of Immunology. 2021; 46: 438–445.

[29] Liu Z, Xiang Q, Mu G, Xie Q, Zhou S, Wang Z, *et al*. Effectiveness and Safety of Platelet ADP -P2Y12 Receptor Inhibitors Influenced by Smoking Status: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2019; 8: e010889.

[30] d'Entremont MA, Yagi R, Salia SJS, Zhang S, Shaban L, Bene-Alhasan Y, *et al*. The effect of diabetes on surgical versus percutaneous left main revascularization outcomes: a systematic review and meta-analysis. Journal of Cardiothoracic Surgery. 2022; 17: 61.

[31] Poredos P, Blinc A, Novo S, Antignani PL. How to manage patients with polyvascular atherosclerotic disease. Position paper of the International Union of Angiology. International Angiology. 2021; 40: 29–41.