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Clinical Investigation

Increased Plasma Non–High-Density Lipoprotein Levels and Poor Coronary Collateral Circulation in Patients With Stable Coronary Artery Disease

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Abstract

Background: This study investigated the relationship between coronary collateral circulation (CCC) and non–high-density lipoprotein cholesterol (non–HDL-C) in patients with stable coronary artery disease (CAD). Coronary collateral circulation plays a critical role in supporting blood flow, particularly in the ischemic myocardium. Previous studies show that non–HDL-C plays a more important role in the formation and progression of atherosclerosis than do standard lipid parameters.

Methods: A total of 226 patients with stable CAD and stenosis of more than 95% in at least 1 epicardial coronary artery were included in the study. Rentrop classification was used to assign patients into group 1 (n = 85; poor collateral) or 2 (n = 141; good collateral). To adjust for the observed imbalance in baseline covariates between study groups, propensity-score matching was used. Covariates were diabetes, Gensini score, and angiotensin-converting enzyme inhibitor use.

Results: In the propensity-matched population, the plasma non–HDL-C level (mean [SD], 177.86 [44.0] mg/dL vs 155.6 [46.21] mg/dL; *P* = .001) was statistically higher in the poor-collateral group. LDL-C (odds ratio [OR], 1.23; 95% CI, 1.11-1.30; *P* = .01), non–HDL-C (OR, 1.34; 95% CI, 1.20-1.51; *P* = .01), C-reactive protein (OR, 1.21; 95% CI, 1.11-1.32; *P* = .03), systemic immune-inflammation index (OR, 1.14; 95% CI, 1.05-1.21; *P* = .01), and C-reactive protein to albumin ratio (OR, 1.11; 95% CI, 1.06-1.17; *P* = .01) remained independent predictors of CCC in multivariate logistic regression analysis.

Conclusion: Non–HDL-C was an independent risk factor for developing poor CCC in stable CAD.

Keywords: Coronary artery disease; collateral blood circulation; hypercholesterolemia; inflammation

Introduction

Coronary collateral circulation (CCC) is an adaptive mechanism that occurs in the presence of chronic myocardial ischemia and stress after severe stenosis or obstruction.[1] Previous studies have shown that a well-developed collateral circulation reduces the infarct area, protects cardiac functions, reduces the development of cardiogenic shock, decreases the development of aneurysm of the left ventricle, and plays a very important role in short- and long-term prognoses for coronary artery disease (CAD).[2]

Despite many studies, the factors affecting coronary collateral development cannot be fully explained; however, the normal vascular endothelial layer and its functions are accepted as the basis for collateral development.[3,4] Previous studies on dyslipidemia, metabolic syndrome, diabetes mellitus (DM), and aging have shown the adverse effects of vascular endothelial dysfunction that result from decreasing collateral development.[5-7]

Non–high-density lipoprotein cholesterol (non–HDL-C) contains multiple atherogenic cholesterols, including low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein, intermediate-density lipoprotein cholesterol,

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and lipoprotein a [Lp(a)] cholesterol.[8] It shows the total atherogenic burden better than does LDL-C, which is the primary cholesterol target.[9,10] In addition to providing short- and long-term information for many diseases, such as CAD, various studies have shown that it is an early indicator of vascular endothelial dysfunction and is correlated with various inflammatory markers.[11,12]

This study aimed to investigate the relationship between CCC and non–HDL-C levels in patients with stable CAD.

Abbreviations and Acronyms

CAD	coronary artery disease
CAR	CRP to serum albumin ratio
CCC	coronary collateral circulation
CRP	C-reactive protein
DM	diabetes mellitus
HDL-C	high-density lipoprotein cholesterol
Lp(a)	lipoprotein a
LDL-C	low-density lipoprotein cholesterol
NO	nitric oxide
PS	propensity score
TC	total cholesterol
SII index	systemic immune-inflammatory index

Patients and Methods

This retrospective cross-sectional study was conducted in patients who underwent coronary angiography between December 2016 and December 2020 at a single center after ethics committee approval (Adnan Menderes University Non-Interventional Clinical Research Ethics Committee permission dated December 10, 2021, and numbered 2021/65). Patients who were diagnosed with stable CAD according to the criteria recommended by the European Society of Cardiology and who underwent coronary angiography and were determined to have coronary stenosis of 95% or more in at least 1 major coronary vessel were included in the study. All patients included in the study had angina or angina-equivalent symptoms, and coronary angiography indications were established with positive noninvasive tests (exercise stress test, stress echocardiography, and myocardial perfusion scintigraphy). The study was conducted in accordance with the Declaration of Helsinki.

Exclusion criteria for the study were as follows: anemia, kidney failure or kidney disease affecting kidney clearance, history of coronary bypass surgery, malignant disease, collagenous connective tissue disease, congestive heart failure, acute cerebrovascular disease, percutaneous coronary intervention after previous acute coronary syndrome, fever, active infection, and the use of statins or other antihyperlipidemic drugs. After applying the exclusion criteria, 226 patients were enrolled in the study.

The demographic, clinical, and angiographic characteristics of all patients included in the study were recorded. All patients were interviewed in detail about hypertension, DM, smoking, history of myocardial infarction, family health history, and medication use. Chronic kidney failure was defined as a glomerular filtration rate of less than 60 mL/min for over 3 months. A diagnosis of hypertension was accepted if antihypertensive treatment was given or if there were at least 3 measurements of higher than 140 mm Hg systolic and 90 mm Hg diastolic. A diagnosis of DM was made if patients were taking antidiabetic medication or had at least 2 fasting blood glucose measurements above 126 mg/dL.

Echocardiographic Evaluation

Echocardiographic examination of all patients included in the study was performed using an iE33 cardiac ultrasound system (Phillips Healthcare) and a 2.5- to 5-MHz probe system. Ejection fraction was measured using the modified Simpson method.

Evaluation of Coronary Angiography

Coronary angiography was performed using the Allura Xper FD 10 (Phillips Healthcare). Angiography was performed by puncture of the femoral artery with 6F Judkins standard right and left catheters. Iodixanol was used as the radiological contrast agent. At least 4 projections for the left coronary system and at least 2 projections for the right coronary system were recorded in digital and analog formats. Two independent cardiologists examined the coronary angiography results without knowing patient characteristics. The culprit vessel (stenosis of ≥95%) areas were divided and recorded according to 3 groups: right coronary artery, left coronary artery, and circumflex coronary artery. Rentrop classification was used as a basis for the evaluation of CCC. Rentrop grade 0 is accepted as the absence of collateral flow, grade 1 is defined as the presence of side branches without an occluded main coronary artery, grade 2 is defined as partial visibility of an occluded main coronary artery, and grade 3 is defined as complete visibility of an occluded main coronary artery. Consistent with previous studies, Rentrop grades 0 and 1 were accepted

as poor collateral flow, whereas Rentrop grades 2 and 3 were accepted as good collateral flow.[13]

Evaluation of CAD Severity

Gensini scoring was used to grade the extent and severity of atherosclerosis in the coronary arteries for all patients. According to the degree of angiographic stenosis, 1 point was given for 1% to 25% stenosis, 2 points for 26% to 50% stenosis, 4 points for 51% to 75% stenosis, 8 points for 76% to 90% stenosis, 16 points for 91% to 99% stenosis, and 32 points for 100% total lesions. The Gensini score was calculated by multiplying these scores with the coefficient defined for each segment of the coronary arteries and summing the results. The segments and their coefficients were multiplied by 5 for the left main coronary artery, 2.5 for the proximal segment of the left coronary artery, 1.5 for the middle, 1 for the apical, 1 for diagonal 1 and 0.5 for diagonal 2, 2.5 for the proximal segment of the circumflex coronary artery, 1 for the distal, 1 for the obtuse marginal, 1 for the posterior descending artery if left dominant, 0.5 for the posterolateral artery, 1 for the right coronary artery proximal, 1 for the middle, 1 for the distal, and 1 for the posterior descending artery.[14]

Analysis of Lipid Profile and Other Biochemical Values

Blood samples from all patients who participated in the study were collected after overnight fasting. The LDL-C, HDL-C, non–HDL-C, and total cholesterol (TC) levels of the patients were measured. The non–HDL-C level was measured by subtracting the HDL-C level from the TC level. In addition, the patients' other hematological and biochemical values were measured and recorded.

The systemic immune-inflammatory index (SII index), platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, and C-reactive protein (CRP) to serum albumin ratio (CAR) were determined from patients' blood counts and biochemical values. The SII index was calculated according to the formula platelet count × neutrophil count / lymphocyte count.

Statistical Analysis

SPSS Statistics for Windows (version 25.0; IBM) and Amos (version 24.0; IBM) statistical packages were used to analyze the data. Descriptive statistics (mean [SD], median [IQR], No. [%]) for categorical and continuous variables were reported. Homogeneity of variances, one of the assumptions of parametric tests, was tested using the Levene test. The normality assumption was tested using the Shapiro–Wilk test. To assess differences between the 2 groups, the independent *t* test was used when the assumptions of the parametric tests were met, whereas the Mann-Whitney U test was used when they were not. The relationship between the 2 continuous variables was assessed using the Pearson correlation coefficient, and when the conditions for the parametric test were not met, the Spearman correlation coefficient was calculated. $P < .05$ was considered statistically significant. Univariate analysis was used to calculate the association of different variables with CCC. Variables for which the unadjusted *P* value in the logistic regression model was <.05 were identified as potential risk markers and included in the full multivariate model.

Propensity-Score Matching

To attenuate the observed imbalance in baseline covariates between the study groups, a propensity-score (PS) matching technique was used. A 1-to-1 pair-matching method with a specified tolerance distance was used to identify matched cohorts. This method resulted in a PS-matched population with 84 patients in the poor-collateral group and 84 patients in the good-collateral group.

Results

A total of 226 patients were included in this study. According to Rentrop classification, groups were divided into those that had good (Rentrop grades 2-3) or poor (Rentrop grades 0-1) collateral. In the original study population, the median age of the 85 patients (68 males, 17 females) in the poor-collateral-circulation group was 67 (65.1-74.50) years. The mean age of the 141 patients (101 males, 40 females) in the good-collateral-circulation group was 69 (63.50-78) years.

Baseline clinical, demographic, and angiographic features are compared in Table I. Diabetes status, Gensini score, and use of angiotensin-converting enzyme inhibitors differed substantially between the 2 groups. Because of the differences in key baseline characteristics, the PS-matching method was used. In the 1-to-1 PS-matched data set, 84 patients remained in the good-collateral group and 84 patients remained in the poor-collateral group. All the variables were well balanced between the groups after the PS match (Table I).

TABLE I. Baseline Characteristics, Preoperative Medications, and Angiographic Findings

	Original study population			PS-matched population		
	Poor (n = 85)	Good (n = 141)	*P* value[a]	Poor (n = 84)	Good (n = 84)	*P* value[a]
Demographic features						
Age, median (IQR), y	67.0 (65.1-74.5)	69.0 (63.5-78.0)	.36	66.5 (65.1-74.50)	69.0 (60.50-79.0)	.62
Male, No. (%)	68 (80)	101 (71.6)	.16[b]	67 (79.7)	58 (69.0)	.43
Comorbidities, No. (%)						
Hypertension	45 (52.9)	71 (50.3)		44 (52.3)	52 (61.9)	.13[b]
Diabetes	57 (67.0)	62 (43.9)	.001	28 (33.3)	29 (34.5)	.50[b]
Smoking	30 (35.2)	46 (32.6)	.68[b]	30 (35.7)	28 (33.3)	.43[b]
PAD	1 (1.1)	0 (0)	.20[b]	0 (0)	1 (0.1)	.45[b]
COPD	17 (20.0)	21 (14.8)	.32[b]	17 (20.2)	15 (17.8)	.42[b]
Present preoperative medications, No. (%)						
ACEI	42 (49.4)	48 (34.0)	.022[b]	42 (50)	39 (46.4)	.37[b]
ARB	4 (4.7)	14 (9.9)	.16[b]	3 (0.3)	8 (0.9)	.11[b]
β-Blocker	21 (24.7)	26 (18.4)	.26[b]	21 (25.0)	20 (23.8)	.55[b]
CCB	7 (8.2)	11 (7.8)	.91[b]	7 (0.8)	5 (0.5)	.38[b]
ASA	7 (8.2)	7 (4.9)	.32[b]	7 (0.8)	6 (0.7)	.51[b]
Angiographic features						
Gensini score, mean (SD)	59.7 (27.6)	109.5 (39.1)	.001	88.3 (29.6)	90.1 (32.1)	.55
Culprit vessel, No. (%)						
LAD	15 (17.6)	13 (9.2)		11 (13.1)	12 (14.2)	
LCx	10 (11.7)	16 (11.3)		14 (16.6)	13 (15.4)	
RCA	60 (70.5)	112 (79.4)	.06	59 (70.3)	59 (70.2)	.11

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; LCx, left circumflex artery; LAD, left anterior descending artery; PAD, peripheral artery disease; PS, propensity score; RCA, right coronary artery.

[a] $P < .05$ was considered statistically significant.
[b] Pearson χ^2 test.

In the PS-matched population, there was no difference between groups in terms of hematological and kidney function values. The CRP levels, SII index, and CAR were increased in the poor-collateral group (Table II). In a comparison of the two groups in terms of lipid parameters, there were no differences in the triglyceride and HDL-C levels. Low-density lipoprotein cholesterol, TC, and non–HDL-C levels were increased in the poor-collateral group in the PS-matched population (Table III).

Multivariate logistic regression analysis showed that LDL-C, non–HDL-C, CRP, SII index, and CAR remained independent predictors of poor-collateral development (Table IV).

Discussion

This study is the first to examine the relationship between CCC and non–HDL-C in patients with stable CAD. In this study, high non–HDL-C was an independent risk factor for developing poor collaterals in patients with stable CAD.

Similar to previous studies, this study also supports the findings that LDL-C, CRP, SII index, and CAR are independent risk factors for poor-collateral development. A high LDL-C level, which is one of the most critical risk factors for developing endothelial dysfunction and atherosclerosis, is a risk factor for the development of poor collateral in many clinical and demographic stud-

TABLE II. Basic Laboratory Parameters of the Patients

	Poor CCC (n = 84)	Good CCC (n = 84)	*P* value[a]
Hemoglobin, mean (SD), g/dL	12.73 (2.22)	12.45 (2.10)	.21
Hematocrit, mean (SD), %	37.38 (6.0)	38.36 (6.01)	.29
Leukocyte count, mean (SD), $\times 10^9$/L	9.05 (2.3)	9.12 (2.6)	.97
Lymphocyte count, mean (SD), $\times 10^9$/L	2.1 (0.8)	21.9 (0.7)	.31
Platelet count, mean (SD), $\times 10^9$/L	250 (86)	250 (77)	.44
Urea, mean (SD), mg/dL	41.0 (11.2)	44.4 (10)	.77
Creatinine level, mean (SD), mg/dL	1.0 (0.23)	1.0 (0.20)	.65
Sodium level, mean (SD), mmol/L	139.4 (3.4)	139.3 (3.4)	.56
Potassium level, mean (SD), mmol/L	4.4 (0.4)	4.3 (0.43)	.25
Calcium level, median (IQR), mmol/L	9.0 (8.9-9.32)	9.1 (8.91-9.40)	.57
PLR, mean (SD)	149 (110.15)	141.4 (76.2)	.45
NLR, mean (SD)	4.16 (3.4)	3.7 (2.9)	.61
C-reactive protein, mean (SD), mg/L	9.5 (4.1)	4.1 (2.4)	.001
SII index, mean (SD)	1,328.4 (832.5)	1,040.5 (611.1)	.045
CAR, mean (SD)	2.8 (1.1)	1.10 (1.12)	.001
Ejection fraction, median (IQR), %	55(40-65)	55 (45-65)	.74

CCC, coronary collateral circulation; CAR, C-reactive protein/serum albumin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation.

[a] $P < .05$ was considered statistically significant.

TABLE III. Lipid Parameters of the Patients

	Poor CCC (n = 84), mean (SD), mg/dL	Good CCC (n = 84), mean (SD), mg/dL	*P* value[a]
Triglycerides	199.6 (103.6)	189.6 (106.6)	.51
HDL-C	39.7 (10.07)	39.9 (15.05)	.93
LDL-C	138.33 (39.2)	121.50 (41.2)	.03
TC	214.25 (45.4)	195.2 (49.7)	.001
Non–HDL-C	177.86 (44.0)	155.6 (46.21)	.001

CCC, coronary collateral circulation; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; non–HDL, non–high-density lipoprotein cholesterol; TC, total cholesterol.

[a] $P < .05$ was considered statistically significant.

TABLE IV. Multivariate Logistic Regression Analysis of the Risk Factors for Poor Collateral Circulation

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value[a]	Odds ratio	95% CI	*P* value[a]
LDL-C	1.11	1.05-1.16	.01	1.23	1.11-1.30	.01
TC	1.42	0.81-1.69	.38			
Non–HDL-C	1.14	1.05-1.21	.01	1.34	1.20-1.51	.01
CRP	1.31	1.21-1.40	.01	1.21	1.11-1.32	.03
SII index	1.11	1.01-1.22	.03	1.14	1.05-1.21	.01
CAR	1.06	1.02-1.10	.01	1.11	1.06-1.17	.01

CAR, CRP to serum albumin ratio; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol; SII index, systemic immune-inflammatory index; TC, total cholesterol.

[a] $P < .05$ was considered statistically significant.

ies. You et al[15] showed that high LDL-C levels are an independent risk factor for developing poor collateral. In in vitro studies, CRP, one of the most noteworthy markers of inflammation, has been shown to reduce nitric oxide (NO) levels, which is a very important element of collateral development and angiogenesis inhibition. Gulec et al[16] showed that high CRP levels are an independent risk factor for poor-collateral development. According to Fan et al[17] in their study of 1,158 patients, high CRP levels were associated with poor-collateral development in patients with stable CAD. The SII index and CAR are inflammatory markers that have emerged in recent years, and various studies[18,19] have shown them to be more predictive markers for inflammation than the platelet to lymphocyte ratio, the neutrophil to lymphocyte ratio, and CRP. According to Keleşoğlu et al,[20,21] high SII index and CAR levels in patients with stable CAD are risk factors for developing poor collateral.

Although most studies do not fully explain the mechanism of collateral development, most agree that it is a complex process of cell organization.[1,2] In previous studies, angiogenesis and arteriogenesis have been shown to be the 2 primary mechanisms for collateral development. Angiogenesis involves the coordinated migration, proliferation, and differentiation of endothelial cells and pericytes from existing vascular beds. On the other hand, arteriogenesis is the growth of muscular arteries requiring similar events regulated by endothelial cells and smooth muscle cells from preexisting arteries.[22] A solid and functional vascular endothelial layer is essential for the healthy continuation of angiogenesis and arteriogenesis processes.[23] The presence of vascular endothelial dysfunction is accepted as one of the main reasons for poor-collateral development. Numerous studies have shown that hyperlipidemia causes vascular endothelial dysfunction and adversely affects collateral development.[24,25] Aras et al[26] showed that at high Lp(a) levels, vascular endothelial growth factor secretion is negatively affected by Lp(a) and collateral development is poor as a result of endothelial dysfunction. Morishita et al[27] showed that transforming growth factor-β release is decreased because of endothelial dysfunction resulting from high Lp(a), and collateral development is adversely affected. Duan et al[28] demonstrated that collateral vessel formation and angiogenesis in response to hindlimb ischemia were significantly attenuated in rats with dietary hypercholesterolemia, which is related to endothelial cell dysfunction and decreased endothelium-derived NO.[28] Shen et al[29] found that in patients with DM, it was observed that Lp(a) levels were correlated with LDL-C and non–HDL-C; in addition, poor-collateral development was 4 times higher with high Lp(a) levels.

Many recent studies have shown that non–HDL-C is a good indicator for cardiovascular diseases compared with LDL-C, which is the primary target.[8-10] It is also the primary indicator for endothelial dysfunction and is associated with various inflammatory markers. The mechanism of poor-collateral development with high non–HDL-C is thought to occur from more than 1 factor. Hyperlipidemia, especially with high non–HDL-C, may adversely affect collateral development by causing vascular endothelial dysfunction. Wang and Chang[12] stated that non–HDL-C was an early marker of vascular endothelial dysfunction in patients with type 2 diabetes and was correlated with CRP. In a study that investigated serum lipid levels and the risk of microangiopathy in patients with type 2 diabetes, Toth et al[30]

showed that each 1-mg/dl increase in non–HDL-C increased the risk of microangiopathy by 0.3%. In addition, the risk level was observed to be 17.3% in patients who were above the non–HDL-C target. Karasek et al[31] found a positive correlation between non–HDL-C and high-sensitivity CRP, which is an inflammatory marker; C-peptide and homeostatic model assessment for insulin resistance, which is a marker of insulin resistance; and plasminogen activation inhibitor. In addition, many studies have shown that the presence of high non–HDL-C is an independent risk factor for increased arterial stiffness.[32] de Oliveira Alvim et al[33] showed that high non–HDL-C is associated with increased arterial stiffness; as a result of this increased stiffness, high systolic blood pressure, low diastolic blood pressure, and increased pulse pressure develop. Baykan et al[34] showed that coronary perfusion and shear stress decrease as a result of increased arterial stiffness and adversely affect coronary collateral arteriogenesis.

Limitations

This study has some limitations. The study's main limitations are that it is based on a single center with a small sample and it is a retrospective study. Apolipoprotein B levels are a better indicator than non–HDL-C of atherogenic burden, but were not measured in this study. Vascular endothelial growth factor, fibroblast growth factor, NO, and interleukin levels, which are very important in pathophysiology, are also not measured. Another limitation is the lack of short- and long-term follow-up of the patients.

Conclusion

This study demonstrates that high non–HDL-C levels negatively affect the development of stable CAD collateral. With this result, one can understand the pathophysiology of collateral development and new treatment strategies can be developed. Large and long-term prospective studies may help us better understand the diagnostic and therapeutic value of non–HDL-C in collateral development.

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References

1. Seiler C, Stoller M, Pitt B, Meier P. The human coronary collateral circulation: development and clinical importance. *Eur Heart J.* 2013;34(34):2674-2682. doi:10.1093/eurheartj/eht195
2. Seiler C. The human coronary collateral circulation. *Eur J Clin Invest.* 2010;40(5):465-476. doi:10.1111/j.1365-2362.2010.02282.x
3. Zimarino M, D'Andreamatteo M, Waksman R, Epstein SE, De Caterina R. The dynamics of the coronary collateral circulation. *Nat Rev Cardiol.* 2014;11(4):191-197. doi:10.1038/nrcardio.2013.207
4. Allahwala UK, Khachigian LM, Nour D, et al. Recruitment and maturation of the coronary collateral circulation: current understanding and perspectives in arteriogenesis. *Microvasc Res.* 2020;132:104058. doi:10.1016/j.mvr.2020.104058
5. Dodd T, Wiggins L, Hutcheson R, et al. Impaired coronary collateral growth in the metabolic syndrome is in part mediated by matrix metalloproteinase 12-dependent production of endostatin and angiostatin. *Arterioscler Thromb Vasc Biol.* 2013;33(6):1339-1349. doi:10.1161/ATVBAHA.113.301533
6. Shen Y, Ding FH, Dai Y, et al. Reduced coronary collateralization in type 2 diabetic patients with chronic total occlusion. *Cardiovasc Diabetol.* 2018;17:26. doi:10.1186/s12933-018-0671-6
7. Chen J, Liu X, Qin X, et al. Coronary collateral microcirculation reserve becomes vestigial with aging. *Cardiology.* 2021;146(1):11-18. doi:10.1159/000509915
8. Enkhmaa B, Prakash N, Berglund L. Non-HDL-C levels and residual cardiovascular risk: do population-specific precision approaches offer any advantages? *Atherosclerosis.* 2018;274:230-231. doi:10.1016/j.atherosclerosis.2018.05.010
9. Kathariya G, Aggarwal J, Garg P, Singh S, Manzoor S. Is evaluation of non-HDL-C better than calculated LDL-C in CAD patients? MMIMSR experiences. *Indian Heart J.* 2020;72(3):189-191. doi:10.1016/j.ihj.2020.05.008
10. Catapano AL, Graham I, De Backer G, et al; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J.* 2016;14;37(39):2999-3058. doi:10.1093/eurheartj/ehw272
11. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA.* 2005;294(3):326-333. doi:10.1001/jama.294.3.326
12. Wang CY, Chang CT. Non-HDL cholesterol level is reliable to be an early predictor for vascular inflammation in type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2004;89(9):4762-4767. doi:10.1210/jc.2004-0820
13. Cohen M, Rentrop KP. Limitation of myocardial ischemia by collateral circulation during sudden controlled coronary artery occlusion in human subjects: a prospective study. *Circulation.* 1986;74(3):469-476. doi:10.1161/01.cir.74.3.469
14. Rampidis GP, Benetos G, Benz DC, Giannopoulos AA, Buechel RR. A guide for Gensini Score calculation. *Atherosclerosis.* 2019;287:181-183. doi:10.1016/j.atherosclerosis.2019.05.012
15. You XD, Jin JL, Zhang H, et al. Lipoprotein(a) as a marker for predicting coronary collateral circulation in patients with acute myocardial infarction. *Per Med.* 2020;17(1):67-78. doi:10.2217/pme-2018-0127

16. Gulec S, Ozdemir AO, Maradit-Kremers H, Dincer I, Atmaca Y, Erol C. Elevated levels of C-reactive protein are associated with impaired coronary collateral development. *Eur J Clin Invest.* 2006;36(6):369-375. doi:10.1111/j.1365-2362.2006.01641.x
17. Fan Y, Li S, Li XL, et al. C-reactive protein as predictor for poor collateral circulation in patients with chronic stable coronary heart disease. *Ann Med.* 2016;48(1-2):83-88. doi:10.3109/07853890.2015.1136429
18. Erdoğan M, Erdöl MA, Öztürk S, Durmaz T. Systemic immune-inflammation index is a novel marker to predict functionally significant coronary artery stenosis. *Biomark Med.* 2020;14(16):1553-1561. doi:10.2217/bmm-2020-0274
19. Kalyoncuoglu M, Durmus G. Relationship between C-reactive protein-to-albumin ratio and the extent of coronary artery disease in patients with non-ST-elevated myocardial infarction. *Coron Artery Dis.* 2020;31(2):130-136. doi:10.1097/MCA.0000000000000768
20. Keleşoğlu S, Yilmaz Y, Elcık D, Kalay N. Systemic immune inflammation index: a novel predictor for coronary collateral circulation. *Perfusion.* 2022;37(6):605-612. doi:10.1177/02676591211014822
21. Keleşoğlu S, Yilmaz Y, Elcık D. Relationship between C-reactive protein to albumin ratio and coronary collateral circulation in patients with stable coronary artery disease. *Angiology.* 2021;72(9):829-835. doi:10.1177/00033197211004392
22. Meier P, Schirmer SH, Lansky AJ, Timmis A, Pitt B, Seiler C. The collateral circulation of the heart. *BMC Med.* 2013;11:143. doi:10.1186/1741-7015-11-143
23. Schaper W. Collateral circulation: past and present. *Basic Res Cardiol.* 2009;104(1):5-21. doi:10.1007/s00395-008-0760-x
24. Joseph G, Soler A, Hutcheson R, et al. Elevated 20-HETE impairs coronary collateral growth in metabolic syndrome via endothelial dysfunction. *Am J Physiol Heart Circ Physiol.* 2017;312(3):H528-H540. doi:10.1152/ajpheart.00561.2016
25. Epstein SE, Lassance-Soares RM, Faber JE, Burnett MS. Effects of aging on the collateral circulation, and therapeutic implications. *Circulation.* 2012;125(25):3211-3219. doi:10.1161/CIRCULATIONAHA.111.079038
26. Aras D, Geyik B, Topaloglu S, et al. Serum level of lipoprotein (a) is inversely associated with the development of coronary collateral circulation. *Coron Artery Dis.* 2006;17(2):159-163. doi:10.1097/00019501-200603000-00010
27. Morishita R, Sakaki M, Yamamoto K, et al. Impairment of collateral formation in lipoprotein(a) transgenic mice: therapeutic angiogenesis induced by human hepatocyte growth factor gene. *Circulation.* 2002;105(12):1491-1496. doi:10.1161/01.cir.0000012146.07240.fd
28. Duan J, Murohara T, Ikeda H, et al. Hypercholesterolemia inhibits angiogenesis in response to hindlimb ischemia: nitric oxide-dependent mechanism. *Circulation.* 2000;102(19 suppl 3):III370-III376. doi:10.1161/01.cir.102.suppl_3.iii-370
29. Shen Y, Chen S, Dai Y, et al. Lipoprotein (a) interactions with cholesterol-containing lipids on angiographic coronary collateralization in type 2 diabetic patients with chronic total occlusion. *Cardiovasc Diabetol.* 2019;18(1):82. doi:10.1186/s12933-019-0888-z
30. Toth PP, Simko RJ, Palli SR, Koselleck D, Quimbo RA, Cziraky MJ. The impact of serum lipids on risk for microangiopathy in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol.* 2012;11:109. doi:10.1186/1475-2840-11-109
31. Karasek D, Vaverkova H, Cibickova L, Gajdova J, Kubickova V. Apolipoprotein B vs non-high-density lipoprotein cholesterol: association with endothelial hemostatic markers and carotid intima-media thickness. *J Clin Lipidol.* 2017;11(2):442-449. doi:10.1016/j.jacl.2017.01.020
32. Wen J, Huang Y, Lu Y, Yuan H. Associations of non-high-density lipoprotein cholesterol, triglycerides and the total cholesterol/HDL-c ratio with arterial stiffness independent of low-density lipoprotein cholesterol in a Chinese population. *Hypertens Res.* 2019,42(8):1223-1230. doi:10.1038/s41440-019-0251-5
33. de Oliveira Alvim R, Mourao-Junior CA, Magalhães GL, et al. Non-HDL cholesterol is a good predictor of the risk of increased arterial stiffness in postmenopausal women in an urban Brazilian population. *Clinics (Sao Paulo).* 2017;72(2):106-110. doi:10.6061/clinics/2017(02)07
34. Baykan AO, Gür M, Acele A, et al. Coronary collateral development and arterial stiffness in patients with chronic coronary total occlusion. *Scand Cardiovasc J.* 2015;49(4):228-234. doi:10.3109/14017431.2015.1062130