High-density lipoprotein cholesterol, triglycerides, and characteristics of coronary atherosclerosis in patients with significant coronary artery disease newly diagnosed by computed tomography coronary angiography

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ABSTRACT

Background: The Current European Society of Cardiology guidelines indicate specific target low-density lipoprotein cholesterol (LDL-C) levels for different cardiovascular risk categories in terms of prevention. However, the target for high-density lipoprotein cholesterol (HDL-C) and triglycerides has not been established.

Aim: The study aims to investigate the associations between HDL-C, triglycerides, and coronary plaque characteristics.

Methods: This was a prospective single-center study with enrolled consecutive patients with newly diagnosed significant (≥1 stenosis ≥50%) CAD on computed tomography coronary angiography (CTCA). Patients had lipids and CTCA analysis, including high-risk plaque (HRP) features: low-attenuation plaque (LAP), napkin-ring sign (NRS), positive remodeling (PR), and spotty calcium (SC), type of the plaque (calcified, noncalcified, mixed), and their composition (calcified, fibrous, fibro-fatty, necrotic core).

Results: The study included 300 patients (191 men, 66 [8] years). Sixty-six percent of them had lipid-lowering therapy. HRP was found in 208 patients. There was no association between LDL-C, plaque composition, and HRP presence. There was a negative correlation between HDL-C, fibro-fatty and necrotic core plaque components ($P = 0.0002$, $P = 0.0009$). There was a positive correlation between triglycerides and necrotic core ($P = 0.038$). There were differences in HDL-C and triglycerides in patients with and without NRS (47 vs. 53 mg/dl, $P = 0.0002$ and 128 vs. 109 mg/dl, $P = 0.02$). In logistic regression, HDL-C (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.93–0.98; $P < 0.001$), triglycerides (OR, 1.00; 95% CI, 1.00–1.01; $P = 0.02$), and male sex (OR, 3.04; 95% CI, 1.41–6.52; $P = 0.004$) were NRS predictors. In multivariable regression, only HDL-C (OR, 0.96; 95% CI, 0.93–0.99; $P = 0.02$) was an independent predictor of NRS.

Conclusion: Lower HDL-C and higher triglycerides were associated with NRS presence and more necrotic core plaque components in coronary plaques in patients with newly diagnosed CAD.

Key words: cardiovascular prevention, coronary artery disease, HDL cholesterol, high-risk plaque, triglycerides

INTRODUCTION

The current European Society of Cardiology (ESC) guidelines indicate specific target low-density lipoprotein cholesterol (LDL-C) levels appropriate for very high, high, moderate, and low cardiovascular risk in terms of cardiovascular prevention [1, 2]. There are no established treatment goals for triglycerides; however, <150 mg/dl is considered to indicate lower risk [1, 2]. To date, also no specific goals for high-density lipoprotein cholesterol (HDL-C) levels have been determined in clinical

WHAT'S NEW?

The Current European Society of Cardiology guidelines indicate specific target low-density lipoprotein cholesterol (LDL-C) levels for different risk categories in terms of cardiovascular prevention because the role of high-density lipoprotein cholesterol (HDL-C) and triglycerides in the development of coronary atherosclerosis is not well established. The current study showed that patients with napkin-ring sign (NRS) versus patients without NRS had lower HDL-C and higher triglycerides, but they did not present differences in LDL-C. HDL-C was an independent predictor of NRS, independently of the statin therapy. Larger studies are needed to specify cut-off values for HDL-C and triglycerides in the context of high-risk plaque development. The prevention measures introduced in the investigated population did not prevent sufficiently high-risk coronary plaque development. The prevention guidelines focus on lowering LDL-C, while HDL-C and triglycerides may play an important complementary role in the development of vulnerable coronary plaques.

trials although low HDL-C is associated with (residual) risk in patients with atherosclerotic cardiovascular disease [1, 2].

Recent evidence has confirmed that the key initiating event in atherogenesis is the retention of LDL-C and other cholesterol-rich lipoproteins within the arterial wall [1]. While the role of LDL-C appears to be crucial in atherogenesis, the role of HDL-C and triglycerides in the development of coronary atherosclerosis is not well established.

Computed tomography coronary angiography (CTCA) is a widely used and safe tool to assess the severity of coronary atherosclerosis and allows for reproducible assessment of plaque structures; thus, it allows for the exclusion or diagnosis of coronary artery disease (CAD) and better risk stratification [3]. Moreover, CTCA allows for high-risk plaque (HRP) features detection, including positive remodeling (PR), low attenuation plaque (LAP), napkin-ring sign (NRS), and spotty calcifications (SC) [3]. The lipid profile of patients with newly diagnosed significant CAD (thus at very high risk in terms of cardiovascular prevention) and its association with their profile of coronary atherosclerosis (including plaque type, plaque composition, and the presence of high-risk plaque features) is not well known.

Therefore, this study aimed to assess the association between LDL-C, HDL-C, and triglycerides levels and the type of coronary plaques, their composition, and the presence of high-risk coronary plaque features in patients with newly diagnosed significant CAD on CTCA.

METHODS

Study population

This was a prospective single-center study including 300 consecutive patients with newly diagnosed significant (with at least one ≥50% stenosis) coronary artery disease on CTCA performed due to clinical indications (patients referred by their cardiologists) between 2016 and 2019 (study flowchart presented in [4]). The inclusion criteria were signed informed consent, age over 18 years, and ≥1 plaque with ≥50% narrowing of the coronary artery lumen with a reference diameter >2.0 mm on CTCA. The exclusion criteria were poor quality of CTCA, the presence of artificial heart valves or pacemakers, previous coronary revascularization, and previous myocardial infarction. Atrial fibrillation was not an exclusion criterion in this study because we recruited patients after CTCA. CTCA quality was checked before inclusion in the study. All patients provided informed consent, and the study received the Ethics Committee's approval. The study was funded by the National Science Center (grant no 2016/21/N/NZ5/01450 to AO).

All patients underwent laboratory tests directly after CTCA including complete lipids profile and high-sensitivity C-reactive protein (hsCRP) in the central laboratory of the National Institute of Cardiology. The reference value for hsCRP was <0.5 mg/l. Hypertension, diabetes, and dyslipidemia were defined according to the universal definitions in the ESC guidelines in force at the time of recruitment to the study.

CTCA performance

Coronary computed tomography angiography was performed with a dedicated computed tomography scanner (Somatom Force, Siemens, Germany). Sublingual nitrates (0.8 mg) were administered. If the heart rate was ≥70 beats/min, an intravenous bolus of metoprolol (increasing doses at 2.5 mg intervals, up to a maximum dose of 20 mg) was given if necessary. From 60 to 70 ml of contrast agent (iohexol) were injected intravenously at 6 ml/s. An electrocardiogram-gated retrospective or prospective acquisition protocol was used in all patients when possible. Scan data were reconstructed routinely in mid- to end-diastole (60%–70% of R–R interval).

CTCA analysis

Data sets that contained motion artifacts were individually optimized by changing the reconstruction window. CTCA analyses were performed in our core lab by an experienced reader (at least 10 years with CTCA) blinded to clinical and laboratory data, who evaluated all arteries with a reference diameter of above 2 mm for the presence of coronary stenoses. QAngioCT analysis was performed by a blinded reader professionally trained in QAngioCT analysis.

All coronary stenoses were categorized as minimal <25%, mild 25%–49%, moderate 50%–69%, and severe 70%–100%.

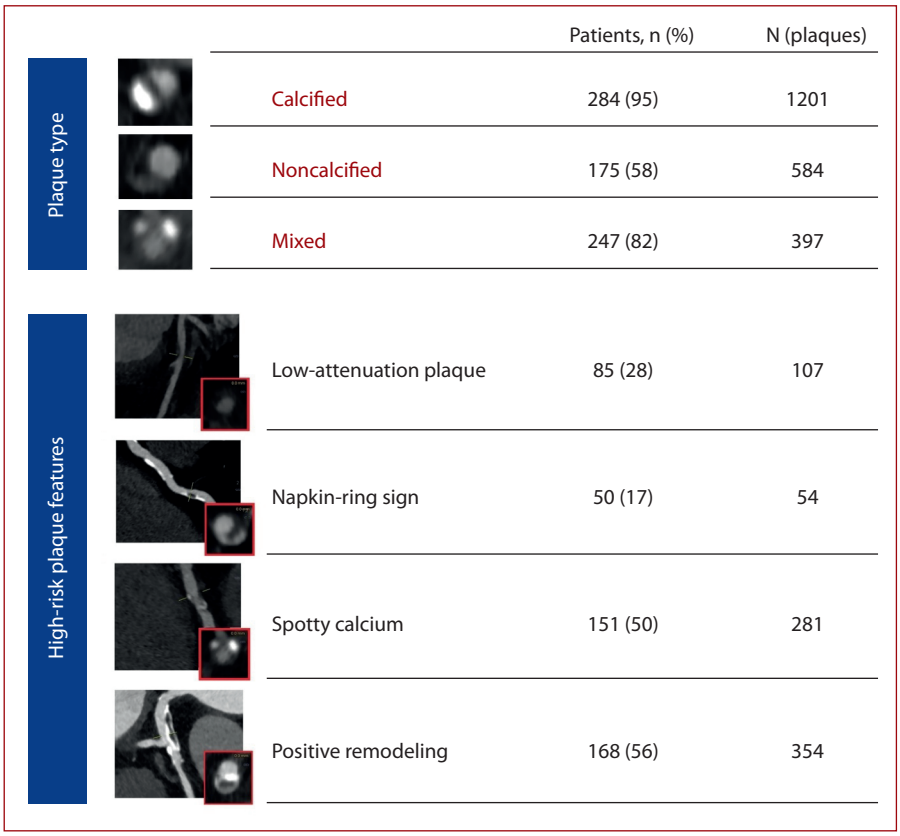

Figure 1. Prevalence of different plaque morphology and high-risk plaque features on computed tomography coronary angiography

In the study population, we assessed the presence of HRP features: low-attenuation plaque (LAP), napkin-ring sign (NRS), positive remodeling (PR) and spotty calcium (SC) (Syngo, Siemens), type of the plaque (calcified, mixed, noncalcified) (Syngo, Siemens), and their composition (calcified, fibrous, fibro-fatty, necrotic core) (QAngioCT, Medis) (Figure 1) [3, 5, 6].

Low-attenuation plaque was defined as any plaque containing a central area with ≤30 Hounsfield units (HU). The napkin-ring sign was defined as a ring-like peripheral higher attenuation of the noncalcified portion of the coronary plaque. Spotty calcification was defined as the presence of calcification <3 mm in any direction within a plaque. The threshold of 1.1 was used to define positive remodeling [7, 8].

The atheroma composition was distinguished based on tissue attenuation ranges in Hounsfield units: dense calcium (>351 HU), fibrous plaque (151 to 350 HU), fibro-fatty plaque (31 to 150 HU), and necrotic core (–30 HU to 30 HU) [7, 9]. The combination of fibro-fatty and necrotic core components was analyzed together as a vulnerable plaque component.

Statistical analysis

The distribution of the variables was tested using the Shapiro-Wilk test. Continuous variables with normal distribution are presented as means with standard deviation (SD). Non-normally distributed variables are presented as medians with interquartile range (IQR). The categorical variables are presented as numbers and percentages. The differences between patients were determined with Student's t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution), as appropriate. The differences between the qualitative variables were determined using the χ^2 test or Fisher's exact test, as appropriate. The correlation analysis was used for determining the association between lipids and plaque components. Finally, logistic regression and multivariable logistic regression were used for analyses of HRPs predictors. Analyses were performed separately for each HRP. Clinical risk factors including age, sex, body mass index (BMI), hypertension, dyslipidemia, diabetes mellitus, and current smoking were also tested. Multivariable analysis was adjusted for factors significantly associated with HRP in univariable analysis or with a trend (P <0.1) and additionally was adjusted for statin therapy. P <0.05 was considered statistically significant. All analyses were performed using MedCalc Software (version 13.2.2, Ostend, Belgium).

RESULTS

Study population

The study included 300 patients (191 men, 66 [8] years). The study group characteristics are provided in Table 1. Male patients had more widespread cardiovascular risk factors: 59 (64% of all smokers) were past or active smokers, they more often had diabetes — 55 (74% of diabetic patients), and BMI was significantly higher in men than women

Table 1. Patient characteristics

Parameter	Value (n = 300)
Clinical characteristics	
Age, years, mean (SD)	66 (8)
Male sex, n (%)	191 (64)
BMI, kg/m^2, median (IQR)	27.5 (24.7–33.2)
CKD G3a, n (%)	6 (2)
CKD G3b, n (%)	40 (13)
Stroke[a], n (%)	16 (5)
CAD risk factors	
Hypertension, n (%)	257 (86)
Dyslipidemia[b], n (%)	203 (68)
Diabetes, n (%)	74 (25)
Family history, n (%)	51 (17)
Smoking — current, n (%)	46 (15)
Smoking — in the past, n (%)	42 (14)
Medications	
β-blocker, n (%)	207 (69)
Statin, n (%)	180 (60)
Other lipid lowering drugs, n (%)	23 (8)
ACEi, n (%)	99 (33)
ARB, n (%)	89 (30)
Calcium antagonist, n (%)	106 (35)
Diuretic — any, n (%)	98 (33)
Oral antidiabetic — any, n (%)	74 (25)
Insulin, n (%)	7 (2)
Acetylsalicylic acid, n (%)	143 (48)

[a]2 hemorrhagic strokes, 1 transient ischemic attack, 13 ischemic strokes; [b]Dyslipidemia diagnosis in the medical records on the day of CTCA
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CASC, coronary artery calcium score; CKD, chronic kidney disease; CTCA, computed tomography coronary angiography; IQR interquartile range; SD, standard deviation

(26.3 [23.2–29.9] kg/m^2 vs. 28.3 [26.0–30.9] kg/m^2; $P = 0.001$). Obesity (BMI ≥30 kg/m^2) and diabetes were associated with lower HDL-C (49.0 [41.8–57.1] mg/dl vs. 53.0 [45.8–63.3] mg/dl; $P = 0.002$, for patients with vs. without obesity, respectively, and 47.0 [40.0–56.0] mg/dl vs. 53.0 [45.0–63.0] mg/dl; $P = 0.002$, for patients with vs. without diabetes, respectively). Obese patients had also higher triglyceride levels (132.0 [95.8–177.5] mg/dl vs. 106.0 [83.0–145.5] mg/dl; $P = 0.001$, for patients with vs. without obesity, respectively).

Lipid-lowering therapy and lipids control

Overall, 185 patients received lipid-lowering therapy including 180 patients who received statins before CTCA (88 rosuvastatin, 71 atorvastatin, 2 pravastatin, and 19 simvastatin), 15 patients who received fibrate, and 7 patients who received ezetimibe (Figure 2). For 18 (6%) patients, detailed data about lipid-lowering treatment (at least drug dose or drug name) were unavailable. Additional 4 patients discontinued statin treatment before CTCA due to symptoms of intolerance, and 5 patients refused statin therapy due to personal decision despite referring physician's recommendations.

In laboratory tests, 10 (3%) patients had LDL-C ≥190 mg/dl, 74 (25%) patients had between 115–189.99 mg/dl, 41 (14%) patients had between 100–114.99 mg/dl, 94 (31%) had between 70–99.99 mg/dl, 55 (18%) had between 55–69.99 mg/dl, and 26 (9%) patients had <55 mg/dl. Triglyceride levels >150 mg/dl were presented in 86 (29%) patients. HDL-C levels <45 mg/dl were in 9 (8%) women, between 40–45 mg/dl in 24 (13%) men, and <40 mg/dl in 40 (21%) men. The lipid profile test results in the study population were presented in Supplementary material, *Table S1* and according to statin use in Supplementary material, *Table S2*.

Coronary plaques characteristics

On CTCA, 2184 coronary plaques were found, from which 1201 (55%) were calcified, 584 (27%) were noncalcified, and 397 (18%) were mixed (Figure 1). From all analyzed plaques, 864 (40%) caused minimal stenosis, 613 (28%) caused mild stenosis, 500 (23%) caused moderate stenosis, and 207 (9%) caused severe stenosis. HRP features were found in 208 (69%) patients, the number of patients and the number of each high-risk plaque feature were presented in Figure 1. In total, 52 (17%) patients had only 1 HRP feature, and 156 (52%) patients had ≥2 HRP features. The median calcium score (CASC) per patient was 565.2 (220.4–988.8). The median dose length product for CTCA was 431.8 (346.6–576.2) mGy × cm.

Associations between lipids and plaque composition

There was no correlation between LDL-C level and fibro-fatty ($P = 0.4$), necrotic core ($P = 0.4$), calcium ($P = 0.9$), and fibrous ($P = 0.4$) plaque components.

There was a negative correlation between HDL-C levels and fibro-fatty ($P = 0.0002$), as well as necrotic core ($P = 0.0009$) plaque component (when analyzed together as vulnerable plaque components [$P = 0.0001$]). There was a positive correlation between HDL-C levels and calcium ($P = 0.005$), but there was no correlation with the fibrous plaque component ($P = 0.4$).

There was a positive correlation between triglyceride levels and necrotic core ($P = 0.038$). There was no correlation between triglyceride levels and fibro-fatty ($P = 0.1$), calcium ($P = 0.3$), and fibrous ($P = 0.2$) plaque components.

Associations between lipids and high-risk coronary plaque features

There were no significant differences between LDL-C levels in patients with and without LAP (94 [73–124] mg/dl vs. 87 [67–117] mg/dl; $P = 0.2$), NRS (96 [71–120] vs. 88 [68–119] mg/dl; $P = 0.8$), PR (93 [71–120] mg/dl vs. 88 [66–118] mg/dl; $P = 0.3$), and SC (96 [74–123] mg/dl vs. 84 [66–117] mg/dl; $P = 0.1$).

We observed differences in HDL-C levels in patients with and without NRS (47 [38–56] mg/dl vs. 53 [46–63] mg/dl; $P = 0.0002$), but no differences were detected for LAP (52 [41–63] mg/dl vs. 51 [45–61] mg/dl; $P = 0.8$), PR (52 [43–61] mg/dl vs. 51 [45–63] mg/dl; $P = 0.6$), and SC (50 [43–60] mg/dl vs. 53 [46–65] mg/dl; $P = 0.07$).

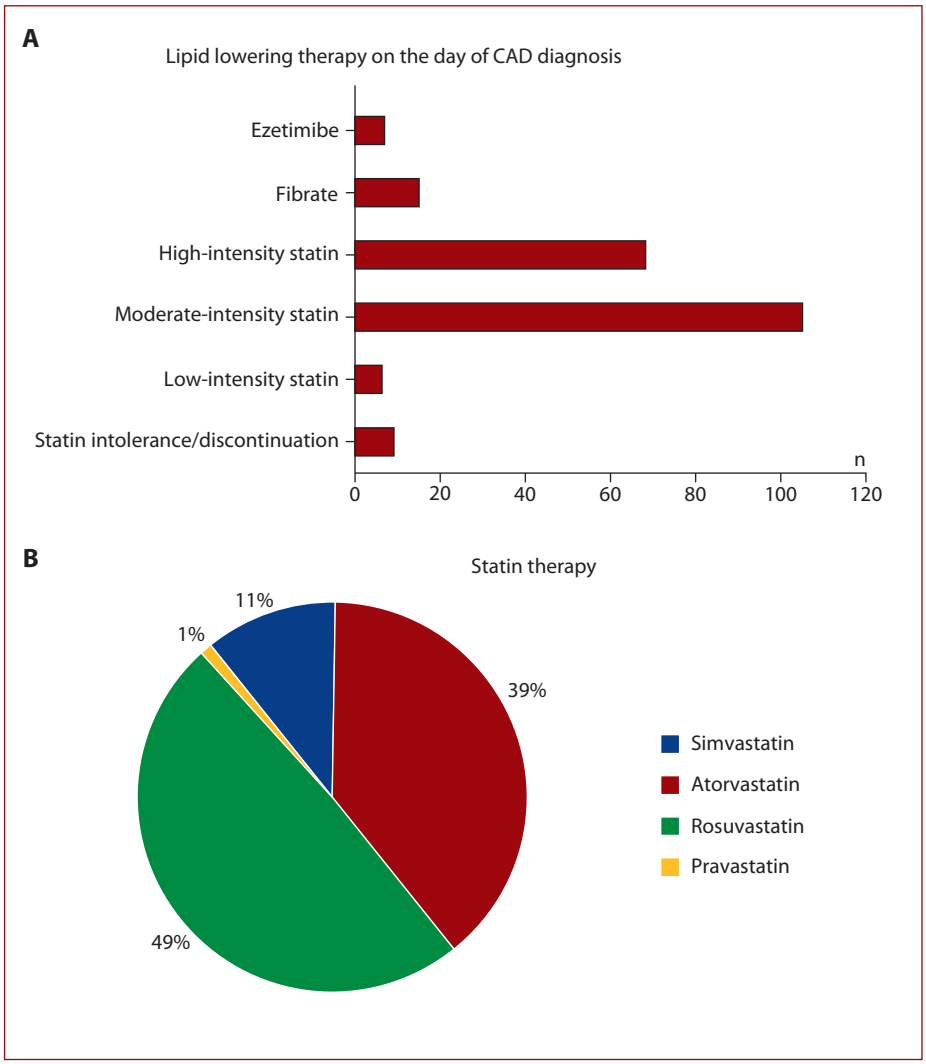

Figure 2. Lipid-lowering therapy in the study population at the time of computed tomography coronary angiography

We observed differences in triglyceride levels in patients with and without NRS (128 [98–177] mg/dl vs. 109 [83–155] mg/dl, $P = 0.02$), but no differences were detected for LAP (115 [91–177] mg/dl vs. 111 [84–159] mg/dl; $P = 0.3$), PR (115 [90–170] mg/dl vs. 108 [83–157] mg/dl; $P = 0.09$), and SC (115 [89–170] mg/dl vs. 109 [83–154] mg/dl; $P = 0.2$).

High-risk plaque features predictors

We performed regression analysis to find high-risk plaque features predictors (Table 2). In multivariable regression, only HDL-C was an independent predictor of NRS despite statin therapy. The hsCRP was not found to be an HRP predictor (NRS [odds ratio, OR, 0.99; 95% confidence interval, CI, 0.90–1.09; $P = 0.8$], LAP [OR, 0.84; 95% CI, 0.55–1.28; $P = 0.4$], PR [OR, 0.99; 95% CI, 0.96–1.02; $P = 0.5$], and SC [OR, 1.19; 95% CI, 0.87–1.62; $P = 0.3$]).

DISCUSSION

The most important finding of our study is that patients with napkin-ring sign had lower HDL-C levels and higher triglycerides despite statin therapy. In multivariable regression analysis, only HDL-C level was an independent predictor of NRS.

The NRS is a qualitative plaque feature and can be defined in a noncalcified plaque cross-section by the presence of two features: a central area of low CT attenuation that is apparently in contact with the lumen; and ring-like higher attenuation plaque tissue surrounding this central area [3]. In clinical investigations, the NRS had 96%–100% specificity for the identification of thin-cap fibroatheroma (TCFA) or culprit acute coronary syndrome lesions [10, 11]. The NRS was more frequent in TCFA compared with non-TCFA plaques defined by optical coherence tomography (OCT) in two different studies (TCFA 44%–65% versus non-TCFA 4%–16%; $P < 0.0001$) [11,12]. The NRS also predicted future acute coronary syndromes (ACS) events (independently of positive remodeling and low attenuation plaque) in a prospective study of 895 patients with a mean follow-up of 2.3 years (HR, 5.6; $P < 0.001$) [13]. Among various HRP features, the necrotic core seems to have special importance. An increase in the amount of necrotic core contributes to fibrous cap attenuation [14] and positive remodeling, there-

Table 2. Analysis of the predictors of high-risk coronary plaque features

	Univariable[a]		Multivariable	
Parameter	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Low attenuation plaque				
Male sex	2.50 (1.40–4.46)	0.002	2.32 (1.28–4.20)	0.006
Statin treatment[b]	1.13 (0.66–1.94)	0.65	1.12 (0.65–1.94)	0.68
Napkin-ring sign				
HDL-C	0.95 (0.93–0.98)	0.0002	0.96 (0.94–0.99)	0.02
Triglycerides	1.00 (1.00–1.01)	0.02	1.00 (1.00–1.01)	0.53
Male sex	3.04 (1.41–6.52)	0.004	2.13 (0.91–4.96)	0.08
Statin treatment[b]	0.93 (0.49–1.77)	0.83	0.83 (0.43–1.62)	0.59
Positive remodeling				
HDL-C	0.98 (0.93–0.99)	0.05	1.01 (0.99–1.02)	0.44
Triglycerides	1.00 (1.00–1.01)	0.04	1.00 (1.00–1.01)	0.07
Statin treatment[b]	1.14 (0.70–1.86)	0.59	1.11 (0.68–1.81)	0.69
Spotty calcium				
HDL-C	0.98 (0.97–1.00)	0.05	1.00 (0.98–1.01)	0.60
Male sex	2.54 (1.57–4.14)	0.0002	2.25 (1.31–3.87)	0.003
Statin treatment[b]	1.07 (0.66–1.74)	0.79	1.05 (0.64–1.73)	0.84

[a]Apart from statin treatment, the only parameters significantly related to HRP features or with a trend in univariable analysis were presented among all analyzed parameters; [b]Statin treatment was included additionally in multivariable models prepared for each HRP feature separately, independently of the lack of its statistical significance in univariable analysis

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio

fore, supporting formation of vulnerable plaques prone to rupture [15]. In our study, higher necrotic core plaque components were associated with lower HDL-C levels. In a study by Weber et al., investigating 350 patients, male sex and typical angina were identified as risk factors for fast total plaque volume progression while HDL-C had a protective effect (odds ratio per 10 mg/dl increase of HDL-C was 0.72; P <0.01) [16]. However, the authors investigated a quite healthy population, whereas obstructive CAD (defined as any coronary stenosis >50%) was found in only 13 (3.7%) patients at baseline and 35 (10%) patients on follow-up CTCA scans [16]. The finding that patients with fast progression of total plaque volume had lower HDL-C is in line with the results that HDL-C levels are negatively associated with coronary artery disease burden and progression when assessed with intravascular ultrasound (IVUS) [17, 18]. Also, a higher triglyceride level has been demonstrated to be a risk factor for the development of cardiovascular disease and a higher incidence of recurrent events in CAD patients [16–25]. Coronary endothelial dysfunction and the progression of vulnerable coronary plaque have been suggested as pathogenetic mechanisms. In a study by Asakura et al. investigating patients who underwent optical coherence tomography imaging, the prevalence of lipid-rich plaques (thin-cap fibroatheromas) was significantly higher in the higher triglycerides group as compared to those in the lower triglycerides group, particularly in patients with higher LDL-C levels [26]. In a study by Bayturan et al. [27], patients with coronary atherosclerosis progression assessed by serial IVUS examination demonstrated higher baseline levels of triglycerides (158 mg/dl vs. 133 mg/dl; P = 0.004). Our study, by showing that patients with higher triglyceride levels have more necrotic core, we reinforce the results of the previous studies.

An integrated analysis of various invasive coronary angiography and IVUS studies has demonstrated that only intensive lipid-lowering therapy can halt plaque progression. There is evidence that plaque progression can be prevented when LDL-C levels have been lowered to about 70 mg/dl, but regression in plaque volume requires that LDL-C levels be even lower [28–30]. In a study by Seo et al., using IVUS imaging, follow-up LDL-C levels <70 mg/dL with any types of statins and an increase of HDL-C were associated with regression of noncalcified plaque volume ≥10% in patients with coronary artery disease [31]. Patients with high LDL-C levels are more likely to be prescribed statins, especially high-dose statins. Therefore, our results showing no correlation between LDL-C level and HRP presence may be seen as evidence for the effectiveness of the statins in the investigated population. What is interesting, in our analysis, females had higher LDL-C levels than men. Women less often receive moderate or high-dose statins (52% vs. 58%). HDL-C was significantly higher in women and may play an additional protective role against HRP development. Male patients had more widespread other risk factors: 59 (64% of all active smokers) were past or active smokers, they had more often diabetes, and their BMI was significantly higher.

However, there is limited data on the role of other lipids, including HDL-C and triglycerides, in coronary atherogenesis and the development of high-risk plaque, prone to rupture. Wang et al. showed that the triglyceride/HDL-C ratio predicted TCFA on OCT [32]. However, statin treatment has lower ability to improve HDL-C levels and triglycerides

in comparison to its impact on LDL-C levels. More effective therapies and more emphasis on lifestyle modification and diet are needed.

Our study results suggest that optimal control of LDL-C represents only one component of a successful prevention strategy in patients with established coronary artery disease. The guidelines focus on lowering LDL-C levels as a target for prevention while HDL-C and triglycerides may also play an important role in the development of some types of vulnerable plaque, i.e., the napkin-ring sign. Further studies on larger populations are needed to investigate this issue.

LIMITATIONS

The limitations of our study include its single-center design. However, the National Institute of Cardiology is one of the leading cardiac centers in Poland. We did not have specific data on how long patients took lipid-lowering therapy before CTCA and what cardiovascular risk category they had before introducing lipid-lowering therapy.

CONCLUSIONS

Higher necrotic core plaque components were associated with lower HDL-C levels and higher triglycerides. Patients with napkin-ring sign (NRS) had lower HDL-C levels and higher triglycerides, but they did not present differences in LDL-C levels. HDL-C was an independent predictor of NRS, independently of the LDL-C level and statin therapy.

The introduced prevention measures in the investigated population did not prevent sufficiently high-risk coronary plaque development. The guidelines focus on lowering LDL-C levels as a target for cardiovascular prevention; however, HDL-C and triglycerides may play an important complementary role in the development of vulnerable coronary plaques.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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