Stroke

ORIGINAL CONTRIBUTION

Aging and Gender Modify the Risk of Carotid Plaque Thrombosis Related to Dyslipidemic Profile

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BACKGROUND: Dyslipidemia plays a critical role in carotid plaque instability and related cerebrovascular events. Reduction of low-density lipoprotein cholesterol (LDL-C) levels decreases ischemic stroke risk; however, a residual cardiovascular risk persists. Starting from this evidence, this study evaluated the impact of dyslipidemia on carotid plaque instability while also considering age and gender.

METHODS: In this observational study, a total of 354 carotid plaques from symptomatic and asymptomatic patients undergoing endarterectomy were analyzed histologically. Dyslipidemic profiles, including high LDL-C, remnant cholesterol, triglycerides, and low high-density lipoprotein cholesterol, were assessed alongside other risk factors. Logistic regression identified independent predictors of unstable plaques, and subgroup analyses evaluated the influence of age (<70, ≥70 years) and gender.

RESULTS: Unstable plaques were observed in 45.2% of cases. High LDL-C emerged as the strongest independent risk factor for plaque instability. The combination of high LDL-C with elevated remnant cholesterol or triglycerides significantly increased the risk of plaque destabilization. Age and gender influenced the risk associated with dyslipidemic profiles, with women who had elevated LDL-C combined with high-remnant cholesterol or triglycerides showing a substantially higher risk of carotid plaque instability compared with men. Furthermore, individuals <70 years of age exhibited a greater risk of plaque instability compared with older patients, highlighting the critical role of these nonmodifiable factors.

CONCLUSIONS: The data reported here highlight the importance of a personalized medicine approach to lipid management, addressing not only LDL-C but also remnant cholesterol and triglycerides. Tailored interventions targeting specific dyslipidemic profiles could more effectively reduce the risk of carotid plaque rupture and cerebrovascular events, particularly in women and patients aged <70 years.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atherosclerosis ■ cholesterol ■ dyslipidemia ■ ischemic stroke ■ triglycerides.

Several clinical and pathological studies clearly demonstrate that dyslipidemia, an abnormal amount of lipids in the blood, plays a pivotal role in the progression of carotid artery stenosis and the development of cerebrovascular symptoms.[1–6] In fact, elevated serum levels of low-density lipoprotein cholesterol

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Nonstandard Abbreviations and Acronyms

ANGPTL3	angiopoietin-like 3
APOC3	apolipoprotein CIII
CEA	carotid endarterectomy
HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin/kexin type 9
RC	remnant cholesterol
TRL	triglyceride-rich lipoproteins

(LDL-C), triglycerides, and reduced levels of high-density lipoprotein cholesterol (HDL-C) represent a major modifiable risk factor for atherosclerotic cardiovascular and cerebrovascular disease.

In particular, a significant increase in the risk of cerebrovascular events has been observed in patients with high levels of LDL-C.[7] Although no primary prevention trials for lipid management have specifically targeted stroke as the primary end point, lowering LDL-C levels with statins and in combination with ezetimibe or PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors is effective in secondary prevention of ischemic stroke.[8,9] Noteworthy, meta-analyses strongly suggest that lipid-lowering therapies can also effectively reduce the occurrence of a first stroke in at-risk populations.[10,11]

Even after lowering LDL-C levels below current guideline targets, clinical trials revealed a substantial residual cardiovascular risk, likely attributed to other lipid components beyond LDL-C, such as remnant cholesterol (RC) and TRL (triglyceride-rich lipoproteins).[7,12,13] The effect of TRLs in conferring residual risk is particularly evident in subjects with obesity, metabolic syndrome, and diabetes.[14,15]

It is now well-established that the onset of cerebrovascular events is frequently related to the rupture of carotid plaques and the consequent acute thrombosis.[16] Two types of atherosclerotic lesions are described: stable plaques, characterized by slow and constant growth and low embolic potential and unstable plaques, which show high inflammation, fibrous cap rupture, and acute thrombosis, leading to the detachment and intracerebral release of embolic fragments, ultimately responsible for the onset of acute ischemic symptoms.[17]

The histological composition of the plaque is influenced by various extraparietal risk factors, which can play a crucial role in the process of destabilization of the carotid atheromatous lesions.[4,5,18,19] In this context, it is possible to hypothesize that different dyslipidemic profiles may play a significant role in the mechanisms leading to the rupture and thrombosis of carotid plaques, in synergy with other nonmodifiable risk factors.

Therefore, the aim of the present study was to evaluate the impact of dyslipidemic factors on carotid plaque instability, also considering the influence of age and gender.

METHODS

Data Availability

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

All the procedures performed in the research with the participation of humans were in compliance with the ethical standards of the institutional and national ethics committee and with the Helsinki Declaration of 1964 and its subsequent changes, or with comparable ethics standards. The retrospective study protocol was approved by the Ethical Committee of the Policlinico Tor Vergata: approval reference number 120-23.

Patient Selection

A total of 354 carotid plaques were selected from the carotid tissue bank at the University of Tor Vergata (Rome, Italy).[17] These plaques were collected from symptomatic (major stroke or TIA) and asymptomatic patients submitted to surgical carotid endarterectomy (CEA). Only cases with complete clinical and laboratory assessment of the specific component of lipid profile and the other major cardiovascular risk factors were included in the study. All asymptomatic patients showed carotid stenosis >60%, assessed by carotid ultrasonography or, in rare cases, by bilateral CT angiography. The 60% cutoff was selected based on 2021 European Stroke Organisation guidelines, which recommend CEA for asymptomatic individuals with significant (>60%) stenosis to prevent future ischemic events.[20] The surgical endarterectomies were performed by patch reconstruction with use of shunt in case of electroencephalogram monitoring indication.

All patients included in our study received at least antiplatelet monotherapy before undergoing CEA, in accordance with European Society for Vascular Surgery clinical guidelines.[21]

The study protocol adheres to the ethical guidelines of the last Declaration of Helsinki and was approved by the institutional review board of our institution (reference number: 120-23). All patients signed the informed consent document before undergoing CEA.

Histology and Plaque Classification

Only intact plaques, free of artifacts, were included in the histological analysis. The sampling collection has been previously reported.[17,19,22] Briefly, samples were formalin fixed, transversely cut at 5 mm intervals, and stained with both hematoxylin-eosin and Movat stains.

Carotid plaques were classified as stable and unstable.[19] Unstable plaques were further categorized as thrombotic or vulnerable. Thrombotic plaques included those with cap rupture or erosion and healed plaques with an acute thrombus in organization. Vulnerable plaques, or thin-cap fibroatheromas, were

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defined by a fibrous cap thickness of <165 µm and were heavily infiltrated by CD68-positive macrophages (>25 per high magnification field).[16]

In stable plaques, fibroatheroma, fibrous, and fibrocalcific ones were included. Fibroatheroma consisted of a necrotic core covered by a thick fibrous cap (>165 µm) with few inflammatory cells. Fibrocalcific plaques were characterized by fibrous tissue associated with a large noneruptive calcification. Fibrous plaque mainly consisted of fibrous tissue without inflammation.

Two different pathologists (A.M. and F.S.) who were blinded to the clinical data performed the histopathologic examination. The interobserver reliability was >98%.

Risk Factors Definition

According to the 2018 American Heart Association guidelines, dyslipidemia refers to an abnormal amount of lipids in the blood. This includes elevated total cholesterol, LDL-C, triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C).[1] Therefore, in this study, the dyslipidemic profile of each patient included the evaluation of (1) high LDL-C. LDL-C was calculated by the Friedewald equation: LDL-C=cholesterol—(HDL-C+triglycerides/5), except for participants with triglyceride levels >300 mg/dL (3.4 mmol/L), in which case it was measured directly. A cutoff value of LDL-C>100 mg/dL (2.6 mmol/L) was used to differentiate between high and low LDL-C levels; (2) low HDL-C: <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.3 mmol/L) in women; (3) high-RC, calculated as total cholesterol–LDL-C–HDL-C; patients were further divided into 2 subgroups based on the 50th percentile value of RC (28.4 mg/dL; 0.73 mmol/L); and (4) high-triglycerides: serum triglyceride levels >150 mg/dL (>1.70 mmol/L).[2]

The following cardiovascular risk factors were also evaluated. Hypertension was identified in patients with systolic blood pressure >130 mm Hg and diastolic blood pressure >80 mm Hg (in at least 2 different measures), whether or not they were undergoing antihypertensive treatment at the time of CEA.[23] Diabetes was diagnosed in patients with fasting blood glucose levels exceeding 126 mg/dL or those receiving oral medications or insulin therapy. Smoking status was categorized as current or former smokers, with former smokers who had quit <5 years ago classified as smokers, and those who had not smoked for >5 years considered nonsmokers. Lastly, abdominal obesity was defined by a waist circumference of 102 cm or more in men and 88 cm or more in women.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (SPSS Inc, Chicago, IL) software. Continuous variables were expressed as the mean±SD. The Shapiro-Wilk test was used to statistically assess the normal distribution of the data. Comparisons between continuous variables were performed using the independent Student *t* test and the Mann-Whitney *U* test. Categorical data were analyzed using the χ^2 test or the Fisher exact test. A 2-tailed $P<0.05$ was considered statistically significant.

Multivariate analysis using stepwise logistic regression (using the enter method for variable selection) was used to identify independent risk factors that significantly correlate with the unstable plaque. To include only nonassociated variables in the multivariate analysis, a multicollinearity test was performed on all independent variables. Variables with a variance inflation factor >5 were considered to exhibit high multicollinearity. The possible association between variables with high multicollinearity was assessed using Pearson correlation analysis. A Pearson correlation coefficient >0.7 indicated a strong association between variables. In our data set, high-triglyceride levels and high-RC exhibited high collinearity with a Pearson correlation coefficient of 0.9. Based on this, the multivariate analyses were conducted in 2 steps. In the first analysis, high-RC was included instead of high triglycerides. Conversely, in the second analysis, high triglycerides was included instead of RC. Similarly, due to the significant association between statin treatment and the level of LDL-C ($P<0.001$) in the multivariate analysis, only LDL-C was included.

The odds ratio of an unstable plaque for the different risk factors was calculated by the value of exp (B), where B represents the logistic coefficient. The odds ratio was also specifically evaluated in subgroups of patients divided by age (±70 years) and gender (male or female).

RESULTS

Clinical Data

The most relevant clinical data of patients are reported in Table 1. The mean age of the patients at the time of surgical CEA was 70.9±8.4 years; 159 patients (44.9%) were aged <70 years whereas 195 (55.1%) were aged >70 years. Moreover, 242 patients (68.4%) were male, and the remaining 112 (31.6%) were female.

Regarding levels of atherogenic cholesterol, 213 patients (60.2%) had high LDL-C and 179 (50.6%) were characterized by an increase of RC >50th percentile (ie, 28.4 mg/dL). High triglycerides were found in 158 patients (44.6%), whereas in 183 cases (51.7%), a reduction of HDL-C was observed. Regarding the other risk factors, the hypertension was the most frequently observed (230 out of 354 cases [65.0%]). At the time of CEA, 131 patients were taking statins, 38 of whom still showed elevated LDL-C levels.

Histopathologic Findings

In 194 patients, stable plaques were found; specifically, 162 were classified as fibrocalcific (Figure 1A; 45.8%), with a variable fibrous cap overlying extensive accumulations of calcium in the intima, associated with a small lipid-laden necrotic core. The remaining 32 stable plaques consisted of fibroatheroma (Figure 1B; 9.0%), characterized by the presence of a large atheroma containing extracellular lipid, cholesterol crystals, and necrotic debris. A thick fibrous cap with few inflammatory cells (Table 1) covered these plaques.

Unstable plaques were found in 160 patients (45.2%); among them, 98 showed plaques characterized by cap rupture (Figure 1C) or erosion (Figure 1D) associated to an acute thrombus (27.7%) and 33 had healed plaques with an acute organizing thrombus (9.3%), in which fibrin and a variable number of macrophagic cells with hemosiderin

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Table 1. Baseline Characteristics of Patients

	N (%)
Total cases	n=354
Age, y	
<70	159 (44.9%)
≥70	195 (55.1%)
Gender	
Male	242 (68.4%)
Female	112 (31.6%)
Risk factors	
Dyslipidemic factors	322 (91.0%)*
High LDL-C (>100 mg/dL)	213 (60.2%)
Low HDL-C (<40 mg/dL in men or <50 mg/dL in women)	183 (51.7%)
High cholesterol remnant (>50th percentile, >28.4 mg/dL)	179 (50.6%)
High triglyceride levels (>150 mg/dL)	158 (44.6%)
Other risk factors	
Hypertension	230 (65.0%)
Diabetes	143 (40.4%)
Smoking habit	82 (48.8%)
Obesity	64 (18.1%)
Drugs	
Statins	131 (37.0)
Associated vascular disease	
Previous cardiovascular diseases	124 (36.6)
Peripheral arterial disease	129 (38.5)
Aortic aneurysm	11 (5.8)
Histological type of carotid plaque	
Stable plaques	194 (54.8%)*
Fibroatheroma	32 (9.0%)
Fibrous or fibrocalcific	162 (45.8%)
Unstable plaques	160 (45.2%)*
Thrombotic plaque	98 (27.7)
TCFA	29 (8.2%)
Healed with an acute thrombus in organization	33 (9.3%)

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TCFA, thin-cap fibroatheromas.

were present, along with a network of large, thin-walled vascular channels. The remaining 29 unstable plaques were constituted by thin-cap fibroatheromas (8.2%) characterized by a thin and inflamed fibrous cap (Table 1).

Regarding statin therapy, a significant correlation with plaque stability was observed (P<0.001). Among the 131 patients receiving statins, 89 (67.9%) exhibited stable plaques, whereas 42 (32.1%) presented with unstable ones. In contrast, the 223 patients not treated with statins showed a different distribution: 105 (47.1%) displayed stable plaques, whereas 118 (52.9%) had unstable ones. Interestingly, in line with literature data, we identified a subset of 38 (29.0%) patients who, despite statin therapy, maintained elevated LDL-C levels. Among these individuals, only 11 (28.9%) exhibited unstable plaques.[24]

Plaque Instability and Risk Factors

Among the analyzed modifiable risk factors (Table 2), at univariate analysis, high LDL-C emerged as the most relevant one associated with plaque instability (P=0.001). In fact, an unstable carotid plaque was found in 70.6% (113/160) of patients with high LDL-C. Regarding gender, males showed a higher incidence of unstable plaques than females (P=0.003) because unstable plaques were observed in 121 of the 242 (50.0%) male patients and only in 39 of the 112 (34.8%) female patients.

Multivariate analysis showed that the main risk factor correlated with the presence of an unstable plaque was high LDL-C, with an odds ratio of 2.38 (95% CI, 1.49–3.81). The other factors did not significantly increase the risk, with the exception of RC, which showed an odds ratio of 1.31 (95% CI, 0.82–2.0; Figure 2).

The concurrent high levels of RC or serum triglycerides in patients with high LDL-C significantly increased the risk of plaque instability (Figure 2). Specifically, in individuals with both increased RC and LDL-C, the odds ratio of plaque instability raised to 3.97 (95% CI, 1.9–8.2). Noteworthy, in patients with high LDL-C and low levels of RC, the odds ratio decreased to 1.72 (95% CI, 0.9–3.3).

Data analysis showed similar results considering high-triglycerides instead of RC (Figure 2), as expected given the strict metabolic correlation between these dyslipidemic factors. Indeed, in patients with concomitant high LDL-C and high triglycerides, the odds ratio of plaque instability increased to 4.19 (95% CI, 1.9–9.2), whereas in patients with high LDL-C and lower levels of triglycerides, the odds ratio decreased to 1.77 (95% CI, 0.9–3.3).

Multivariate analyses displayed that age (Table 3) and gender (Table 4) influence the risk of carotid plaque instability related to high LDL-C. In detail, patients aged <70 years showed a significant raise in plaque instability risk, if having both high LDL-C and RC or triglycerides, reaching odds ratio values of 7.92 (95% CI, 2.42–25.92) and 9.91 (95% CI, 2.6–38.4), respectively (Table 3). In patients >70 years, elevated RC or triglyceride levels did not alter the risk of plaque instability related to high LDL-C (Table 3).

Considering gender, a substantially increased risk of plaque instability emerged in women who had concurrently high levels of LDL-C and RC with odds ratio values of 10.18 (95% CI, 1.9–54.7) or concomitant raise of LDL-C and triglycerides with odds ratio of 8.9 (95% CI, 1.6–48.9; Table 4). On the contrary, in male individuals, the same dyslipidemic profiles resulted in a slight raise in the risk of plaque instability, with odds ratios equal to 3.0 (95% CI, 1.3–7.0) if considering high LDL-C and RC or 3.5 (95% CI, 1.4–9.0) when high LDL-C was associated to high triglycerides (Table 4).

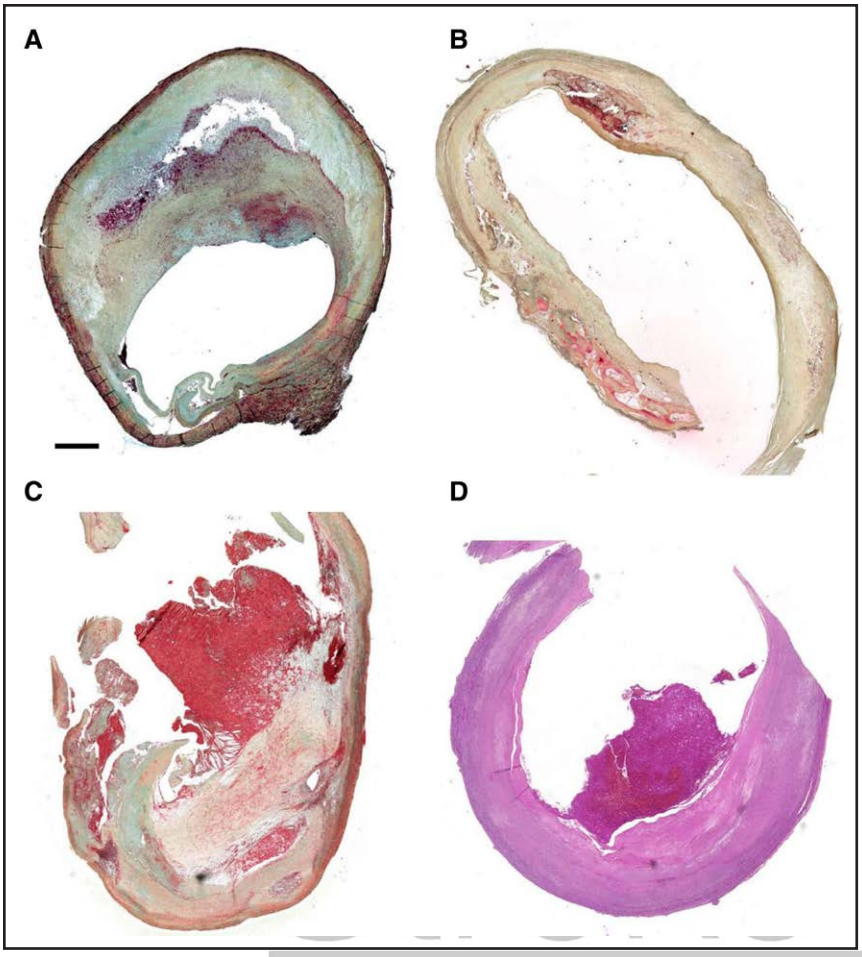

Figure 1. Histological aspects of atherosclerotic carotid plaques. **A**, A fibrocalcific carotid plaque with foci of bone metaplasia. **B**, A stable fibroatheromatic plaque characterized by a thick fibrous cap. **C**, A thrombotic ruptured plaque. **D**, A plaque with erosion associated with an acute thrombus. Scale bar represents 800 µm.

Detailed multivariate analysis data regarding the risk of plaque instability related to different dyslipidemic factors are provided in the Tables S1 through S4.

DISCUSSION

The results of this extensive histological study demonstrated that changes in the dyslipidemic profile significantly influence the destabilization of carotid plaques. The increase in LDL-C levels resulted in the principal risk factor for plaque instability, particularly in association with high-RC or high triglycerides. The effect of these dyslipidemic factors on plaque instability is influenced by age and gender of the patients. Women with elevated LDL-C and high-RC or high triglycerides exhibited the highest risk of plaque instability, as compared with men. A significant increase in the risk of plaque instability was also observed in patients aged <70 years exhibiting elevated LDL-C and high-RC or high triglycerides.

Data reported in our study support the evidence emerging from several meta-analyses regarding the importance of the reduction of lipid levels in the prevention of acute cerebrovascular events. In this regard, it has been demonstrated that statin therapy reduces the risk of first stroke among high-risk individuals, likely due to decreased plaque vulnerability, as demonstrated by our findings.[10,11,25,26] The critical role of statin therapy in enhancing atherosclerotic plaque stability may also be attributed to their well-recognized pleiotropic effects. The observation that only 28.9% of patients (11/38) who maintained elevated LDL-C, despite statin therapy, exhibited stable plaque supports this effect. The anti-inflammatory properties of statins, together with the promotion of collagen synthesis, contribute to the thickening of the fibrous cap and a reduction in lipid content within the plaque core. Collectively, these effects enhance plaque stability, reducing susceptibility to rupture and thrombosis.[27,28]

Data from our study offer a unique opportunity to demonstrate that high LDL-C levels are associated with the presence of histological evidence of carotid plaque vulnerability. Previous investigations assessed the severity of carotid plaques mainly by using imaging techniques. Nevertheless, the identification of unstable carotid plaques using imaging techniques is difficult, due to the impossibility of precisely assessing both the thickness of the fibrous cap and the inflammation of the plaque, fundamental elements for defining a high-risk plaque.[29] The accurate evaluation of these morphological features is currently achievable only through histological analysis.[30,31]

Table 2. Correlation Between Risk Factors and Plaque Instability

	Stable plaque, n=194	Unstable plaques, n=160	Multivariate analysis (*P* value)
Age, y			
<70	89 (45.9%)	70 (43.8%)	0.61
≥70	105 (54.1%)	90 (56.2%)	
Gender			
Male	121 (62.4%)	121 (75.6%)	0.003
Female	73 (37.6%)	39 (24.4%)	
Hypertension			
N	66 (34.0%)	58 (36.3%)	0.51
Y	128 (66.0%)	102 (63.8%)	
Diabetes			
N	108 (55.7%)	103 (74.4%)	0.42
Y	66 (44.3%)	57 (35.6%)	
Smoking habit			
N	153 (78.9%)	121 (75.6%)	0.96
Y	41 (21.1%)	39 (24.4%)	
High LDL-C			
N	94 (48.5%)	47 (29.4%)	0.001
Y	100 (51.5%)	113 (70.6%)	
Low HDL-C			
N	90 (46.4%)	81 (50.6%)	0.24
Y	104 (53.6%)	79 (49.4%)	
High cholesterol remnant (>50th percentile)			
N	103 (53.1%)	91 (45.0%)	0.58
Y	91 (46.9%)	88 (55.0%)	
High-triglyceride levels			
N	114 (58.8%)	82 (51.3%)	0.96
Y	80 (41.2%)	78 (48.7%)	
Obesity			
N	157 (80.9%)	133 (83.1%)	0.85
Y	37 (19.1%)	27 (16.9%)	

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Although it is widely recognized that lowering LDL-C is effective in reducing cardiovascular risk, it has also emerged that lowering LDL-C levels alone has not abolished atherosclerotic cardiovascular risk.[32] Indeed, it has been demonstrated a significant residual cardiovascular risk in patients treated with statins, likely due to the role of other lipid fractions, such as RC and high triglycerides.[33] Indeed, results of the PROVE IT (TIMI 22) trial showed that in statin-treated patients with postacute coronary syndrome, the presence of elevated triglycerides was associated with higher cardiovascular risk, as compared with patients with normal triglyceride levels.[32]

According to this evidence, more recent approaches tend to consider high-triglyceride levels just as a marker for elevated RC. In fact, partially hydrolyzed TRL carry not only triglycerides but also significant quantities of cholesterol coming from VLDL and chylomicrons in their lipoprotein particles. These particles correspond to the so-called RC. Thus, increased triglyceride levels may be considered a risk marker for cardiovascular disease, but RC is likely to be the true culprit particles driving the progression of the atherosclerotic plaques.[33]

In this evolving scenario, our histology-based study may help shed light on the contribution of triglycerides and RC in the process of carotid plaque instability. Results from this study showed that patients with elevated levels of both LDL-C and either high-RC or high triglycerides had a significantly higher risk of plaque instability. In line with recent insights from clinical trials, we hypothesize that among individuals with elevated LDL-C, the additional risk of plaque instability observed in patients with concomitantly high-triglyceride levels serves as a surrogate marker of the true underlying risk factor driving plaque vulnerability, namely, elevated RC levels.

The mechanisms through which RC contributes to plaque instability are multifaceted and complex.[34,35] One of the primary pathways involves the infiltration and retention of these lipoproteins within the arterial wall. Unlike triglycerides, which has not been found in atherosclerotic plaques,[26] RC particles can penetrate through the endothelium into the arterial intima, accumulating in the subendothelial space.[36,37] This deposition triggers a series of inflammatory responses, attracting immune cells, such as macrophages, to the site.[38] Macrophages phagocytize RC particles, transforming into foam cells, which are hallmark components of atherosclerotic plaques. Furthermore, the retained RC induces the expression of proinflammatory cytokines and adhesion molecules, perpetuating a chronic inflammatory state within the arterial wall.[39,40] Inflammation not only promotes further lipid deposition but also destabilizes existing plaques making them more prone to rupture. Besides inflammatory mechanisms, RC particles can exacerbate oxidative stress within the arterial wall, causing additional endothelial damage and promoting a proatherogenic environment.[41]

Thus, evidences from clinical studies have clearly demonstrated that the residual cardiovascular risk associated with elevated TRL cannot be reduced by a simple triglyceride-lowering pharmacological approach, reflecting the complexity of the metabolism of TRL.[42] Recent research has identified promising approaches to reduce RC levels through inhibition of APOC3 (apolipoprotein CIII) or ANGPTL-3 (angiopoietin-like 3).[32]

Regarding the role of age, there is a gradual shift in older individuals from inflammatory plaques to more calcified and fibrotic stable ones, which are less prone to rupture but may still cause only luminal narrowing.[43] This evidence is consistent with the results of the present study, showing that the dyslipidemic profile seems to play a less significant role in plaque destabilization in older individuals, as compared with those <70 years. Moreover, this finding is also supported by the study of Nanna et al,[44] which demonstrated that LDL-C was not

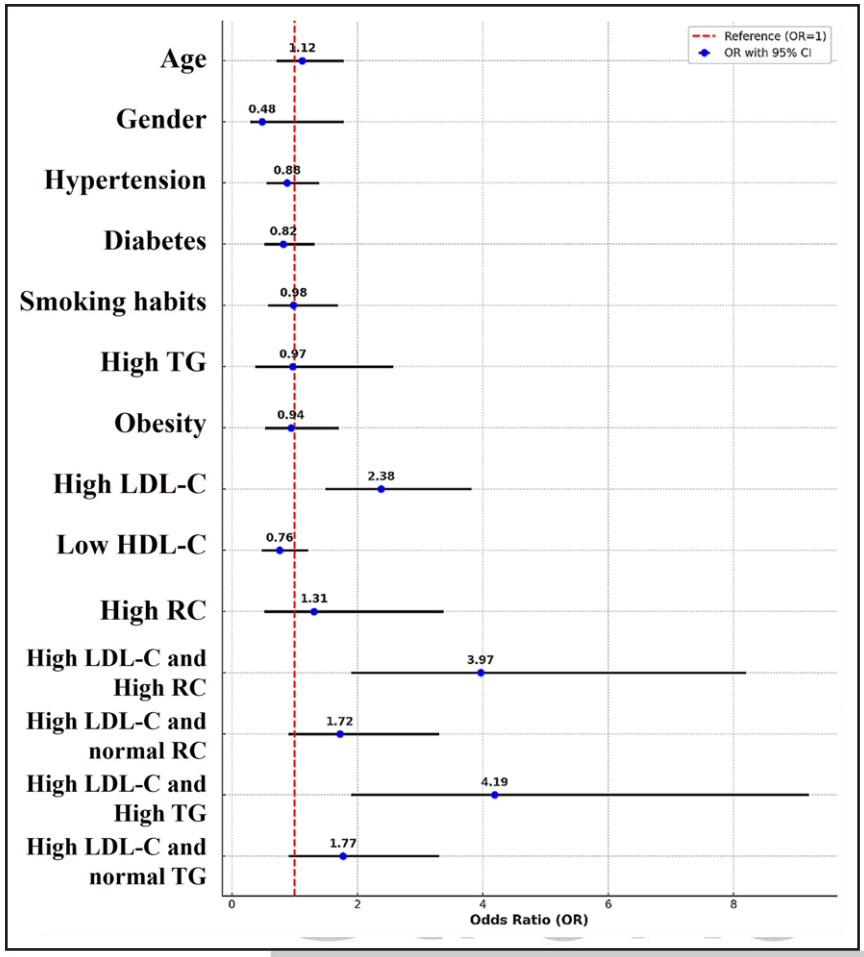

Figure 2. Multivariate analysis. Graph presents the odds ratios (ORs) of plaque instability with 95% CIs for examined variables including high low-density lipoprotein cholesterol (LDL-C) alone and in combination with remnant cholesterol (RC) and triglycerides (TG). Each point represents the estimated OR for the corresponding condition, with the horizontal bars illustrating the range of the 95% CI. The red dashed line at OR=1 serves as the reference point, indicating no effect or association. HDL-C indicates high-density lipoprotein cholesterol.

associated with CVD risk among 2667 adults aged 75 years or older, even in the presence of other risk factors.

The increased risk of carotid plaque instability observed in women with elevated LDL-C and high-RC or high-triglycerides, as compared with men, appears surprising and in contrast with the scientific literature, which typically reports a higher cardiovascular risk in men. This result could reflect the generally more favorable lipid profiles in women during their reproductive years.[45] However, menopause reverses the protective effect of estrogen on atheromatous plaque development, leading to higher LDL-C levels and increased cardiovascular risk.[46] Remarkably, the female population in this study included only subjects over the age of 55 who were already postmenopausal, which may at least partially explain these findings.

Study Limitations

Although the morphological assessment of carotid plaques represents the gold standard for defining plaque

Table 3. Multivariate Analysis Showing the Effect of Aging on the Risk of Plaque Instability Related to Modifiable Risk Factors

	Patients with high remnant cholesterol				Patients with high triglycerides			
	<70 y		≥70 y		<70 y		≥70 y	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Gender	0.37 (0.14–1.03)	0.6	0.42 (0.14–1.27)	0.12	0.39 (0.13–1.15)	0.09	0.49 (0.15–1.60)	0.24
Diabetes	2.61 (0.92–7.3)	0.7	1.21 (0.42–3.50)	0.72	2.51 (0.84–7.51)	0.1	1.01 (0.33–3.12)	0.98
Hypertension	0.99 (0.34–2.8)	0.98	0.50 (0.18–1.39)	0.19	1.05 (0.34–3.27)	0.93	0.42 (0.14–1.28)	0.13
Smoking habit	0.70 (0.24–2.0)	0.52	0.98 (0.29–3.3)	0.97	0.60 (0.19–1.86)	0.38	0.83 (0.21–3.23)	0.79
High LDL-C	7.92 (2.4–25.92)	0.001	2.23 (0.82–6.05)	0.12	9.91 (2.56–38.37)	0.001	2.02 (0.67–6.15)	0.21
Low HDL-C	0.60 (0.23–1.57)	0.30	1.05 (0.41–2.69)	0.93	0.63 (0.22–1.79)	0.39	1.48 (0.52–4.25)	0.47
Obesity	0.91 (0.3–2.8)	0.87	1.6 (0.39–5.58)	0.52	1.08 (0.34–3.47)	0.89	1.85 (0.38–8.91)	0.44

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Table 4. Multivariate Analysis Showing the Effect of Gender on the Risk of Plaque Instability Related to Modifiable Risk Factors

	Patients with high remnant cholesterol				Patients with high triglycerides			
	Women		Men		Women		Men	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age, y	0.85 (0.20–3.54)	0.82	1.33 (0.61–2.90)	0.48	0.85 (0.21–3.52)	0.83	1.63 (0.67–3.93)	0.28
Diabetes	10.86 (2.19–53.93)	0.004	0.88 (0.38–2.08)	0.78	8.51 (1.60–45.20)	0.01	0.82 (0.33–2.04)	0.67
Hypertension	1.21 (0.32–4.62)	0.79	0.62 (0.26–1.52)	0.30	1.22 (0.32–4.70)	0.77	0.55 (0.20–1.50)	0.24
Smoking habit	1.57 (0.18–14.10)	0.69	1.02 (0.43–2.45)	0.96	1.05 (0.10–10.93)	0.97	0.94 (0.37–2.44)	0.90
High LDL-C	10.18 (1.89–54.69)	0.007	3.03 (1.32–7.00)	0.009	8.92 (1.63–48.87)	0.01	3.54 (1.39–9.02)	0.008
Low HDL-C	0.55 (0.10–2.95)	0.49	0.91 (0.43–1.95)	0.81	0.66 (0.11–4.13)	0.66	1.16 (0.50–2.68)	0.73
Obesity	0.63 (0.11–3.52)	0.59	1.78 (0.62–5.12)	0.29	0.58 (0.10–3.31)	0.54	2.35 (0.73–7.57)	0.15

HDL-C indicates high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

vulnerability, it may also represent a limitation of the study, as it restricts the study population to patients undergoing CEA.

Conclusions

This histological study underscores the significant contribution of dyslipidemia to carotid plaque instability. Given this evidence, lipid management strategies that focus solely on lowering LDL-C might be insufficient to reduce the risk of plaque destabilization and, consequently, stroke occurrence.

The risk of plaque instability in patients with dyslipidemia is notably influenced by age and gender, with women and individuals aged <70 years exhibiting increased susceptibility.

The identification of lipid profiles, in combination with the control of the other well-known cardiovascular risk factors, such as lipoprotein(a), paves the way for the development of personalized medicine approaches in atherosclerosis.[47]

In particular, a comprehensive, patient-tailored approach to lipid management that addresses both LDL-C and other atherogenic lipid fractions, such as RC, may be more effective in reducing acute cerebrovascular events, especially in women and patients aged <70 years.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

STROBE Checklist
Tables S1–S4

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