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ORIGINAL RESEARCH

Evidence of Carotid Atherosclerosis Vulnerability Regression in Real Life From Magnetic Resonance Imaging: Results of the MAGNETIC Prospective Study

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BACKGROUND: Atherosclerosis vulnerability regression has been evidenced mostly in randomized clinical trials with intensive lipid-lowering therapy. We aimed to demonstrate vulnerability regression in real life, with a comprehensive quantitative method, in patients with asymptomatic mild to moderate carotid atherosclerosis on a secondary prevention program.

METHODS AND RESULTS: We conducted a single-center prospective observational study (MAGNETIC [Magnetic Resonance Imaging as a Gold Standard for Noninvasive Evaluation of Atherosclerotic Involvement of Carotid Arteries]): 260 patients enrolled at a cardiac rehabilitation center were followed for 3 years with serial magnetic resonance imaging. Per section cutoffs (95th/5th percentiles) were derived from a sample of 20 consecutive magnetic resonance imaging scans: (1) lipid-rich necrotic core: 26% of vessel wall area; (2) intraplaque hemorrhage: 12% of vessel wall area; and (3) fibrous cap: (a) minimum thickness: 0.06 mm, (b) mean thickness: 0.4 mm, (c) projection length: 11 mm. Patients with baseline magnetic resonance imaging of adequate quality (n=247) were classified as high (n=63, 26%), intermediate (n=65, 26%), or low risk (n=119, 48%), if vulnerability criteria were fulfilled in ≥2 contiguous sections, in 1 or multiple noncontiguous sections, or in any section, respectively. Among high-risk patients, a conversion to any lower-risk status was found in 11 (17%; *P*=0.614) at 6 months, in 16 (25%; *P*=0.197) at 1 year, and in 19 (30%; *P*=0.009) at 3 years. Among patients showing any degree of carotid plaque vulnerability, 21 (16%; *P*=0.014) were diagnosed at low risk at 3 years.

CONCLUSIONS: This study demonstrates with a quantitative approach that vulnerability regression is common in real life. A secondary prevention program can promote vulnerability regression in asymptomatic patients in the mid to long term.

Key Words: cardiac rehabilitation ■ carotid atherosclerosis ■ magnetic resonance imaging ■ modifiable risk factors ■ secondary prevention ■ vulnerability regression

It has been recognized that clinical manifestations of atherosclerotic disease such as myocardial infarction and ischemic stroke are caused by acute thrombosis, which is mostly triggered by atherosclerotic plaque instability rather than by gradual progressive luminal narrowing. Pathology studies have revealed that atherosclerotic plaque destabilization is related to specific "vulnerable" plaque characteristics, such as large lipid-rich necrotic core (LRNC), thin/interrupted fibrous cap (FC), intraplaque hemorrhage (IPH), ulceration, and marked inflammation.

Ischemic stroke is one of the leading causes of death and long-term disability throughout the world. Approximately 15% to 20% of ischemic strokes are secondary to symptomatic carotid stenosis, and randomized

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CLINICAL PERSPECTIVE

What Is New?

- To date, comprehensive quantitative methods to define atherosclerosis vulnerability are lacking, and data showing the regression of plaque vulnerability mostly come from randomized clinical trials with intensive lipid-lowering therapy.
- In this study, we developed a comprehensive quantitative method to assess the vulnerability of carotid atherosclerosis, with simultaneous evaluation of all components associated with instability (lipid-rich necrotic core, intraplate hemorrhage, and fibrous cap), and were able to demonstrate regression of atherosclerosis vulnerability with serial magnetic resonance imaging scans in a real-life cohort undergoing secondary prevention (260 patients, 3 years of follow-up).

What Are the Clinical Implications?

- The clinical implication of this finding is that a secondary prevention program can promote regression of carotid vulnerability in asymptomatic patients in the mid to long term.

Nonstandard Abbreviations and Acronyms

FC	fibrous cap
IPH	intraplaque hemorrhage
LRNC	lipid-rich necrotic core
MAGNETIC	Magnetic Resonance Imaging as a Gold Standard for Noninvasive Evaluation of Atherosclerotic Involvement of Carotid Arteries
RF	risk factor

prospective studies have associated carotid stenosis with symptomatic neurological events.[1–4] However, about 19% to 43% of patients with symptomatic carotid atherosclerosis have stenosis of <30%, and patients with subcritical symptomatic plaques show a high rate of stroke recurrence, suggesting that other atherosclerosis features besides the degree of stenosis are also relevant.[5,6]

Magnetic resonance imaging (MRI) provides a means to noninvasively assess luminal narrowing as well as composition of atherosclerotic carotid plaques.[7–15] Observational studies have shown an association between phenotypes of carotid plaques at risk, as defined by MRI, and cerebral ischemic events.[16–20] However, features of plaque vulnerability are highly frequent even in patients with asymptomatic carotid plaques. For example, in asymptomatic patients with carotid atherosclerosis, 25% of lesions show an IPH or LRNC, and 75% of patients have at least 1 lesion with these characteristics. Despite this, stroke rates are low, averaging around 2% to 5% per year.[21] Preliminary MRI evidence of vulnerability regression exists, specifically of LRNC reduction with aggressive lipid-lowering therapy.[22]

However, it is not known how large the LRNC and IPH should be or how thin the FC should be to significantly increase the risk of plaque instability. It is also unknown if medical therapy can induce the regression of plaque vulnerability features other than LRNC. In general, plaque vulnerability regression has never been demonstrated with a quantitative approach considering all components associated with plaque vulnerability in a real-world setting.

We hypothesized that plaque characteristics and, accordingly, the risk of stroke may change over time, and that quantitative expression of vulnerable features might be relevant in determining the risk of plaque instability.

The primary study objective was to prove that plaque vulnerability regression is possible in asymptomatic mild to moderate carotid atherosclerosis patients on medical treatment, through the use of a quantitative method considering all major features linked to plaque instability (LRNC, IPH, and FC) and prespecified criteria of plaque vulnerability. Secondary objectives were to assess whether (1) optimal treatment of well-known modifiable atherosclerotic risk factors (RFs) is associated with plaque vulnerability regression; and (2) quantitative assessment of carotid plaque vulnerability may predict patients' carotid ischemic events or all-cause mortality.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The MAGNETIC (Magnetic Resonance Imaging as a Gold Standard for Noninvasive Evaluation of Atherosclerotic Involvement of Carotid Arteries) study is an observational study designed to investigate, with serial multisequence MRI assessments, the natural history of vulnerable carotid plaques, in a cohort of patients with asymptomatic mild to moderate carotid atherosclerosis, medically treated in a tertiary rehabilitation setting. The Ethical Committee of Istituti Clinici Scientifici Maugeri (Pavia, Italy) approved the study, and all patients gave informed consent to participate. All methods were carried out in accordance with relevant guidelines and regulations.

Study Design

This was a single-center prospective observational study. Sizing of the sample calculated that, with α equal

to 5%, power equal to 80%, and an estimated conversion rate of 30% from vulnerability to stability, 60 to 65 subjects at high risk of carotid vulnerability had to be enrolled. Because up to 75% of patients with asymptomatic carotid plaques show evidence of LRNC or IPH, and assuming that only one-third of them have high-risk plaques, we estimated that 260 patients needed to be screened. This number of patients was enrolled for 3 years, starting in 2013, and followed up for 3 years, until the study was completed in 2019. This study was not powered to show clinical outcomes.

Carotid Plaque Vulnerability

Vulnerability definition was considered per carotid section. It was based on the presence of a percent area of LRNC, a percent area of IPH, or a projection length of FC above the normal limit or a minimum/average thickness of FC below the normal limit. Cutoff values were derived from the calculation of the 95th or the 5th percentiles of those metrics, in a sample of 20 unselected consecutive MRI exams (baseline assessment of the first 20 patients enrolled in this study). Derived cutoff values were (1) LRNC: 26% of vessel wall area; (2) IPH: 12% of vessel wall area; and (3) FC: (a) minimum thickness: 0.06 mm, (b) mean thickness: 0.4 mm, (c) projection length: 11 mm. Patients were classified as high or intermediate risk if vulnerability criteria were fulfilled in ≥2 contiguous sections or in ≥1 noncontiguous sections, respectively, or low risk if no vulnerability criteria were found.

More details about the study design and risk classification are available in a previous publication.[23]

Baseline Assessments

At the study entry, patients underwent medical examination, ECG, carotid MRI, and blood chemistry. All examinations were obtained on the same day. Clinical evaluation included a neurologic assessment. Patients were excluded from the study if they had had any type of ischemic stroke at any time in their life. Patients were also excluded if they had a National Institutes of Health Stroke Scale score >2 at the baseline assessment. Anthropometric data, atherosclerotic RF profile (according to current European Society of Cardiology guidelines), documented history of coronary artery disease or peripheral arterial disease, and pharmacologic therapy were also recorded.

Follow-Up

High-risk patients underwent 6-month, 1-year, and 3-year follow-up reevaluations as at baseline (physician visit, ECG, blood chemistry, and carotid MRI). Intermediate-risk patients underwent a 1-year structured telephone interview and a 3-year reassessment at baseline. Low-risk patients underwent a 1-year structured telephone interview and a 3-year reassessment as at baseline without MRI. A telephonic contact, with structured interview and retrieving of events records, was obtained in the case of patients who refused to undergo follow-up visits. At each visit or telephone contact, patients were given advice about lifestyle (diet, smoking, and physical exercise) and pharmacologic counseling to reach targets of secondary prevention according to the current European Society of Cardiology guidelines. Patients who failed to undergo a follow-up MRI scan (about 10% of the tests in total) were still included in the analysis considering their carotid vulnerability unchanged from the previous MRI.

Outcomes

The primary outcome was the rate of conversion from a highly vulnerable condition to any lower-risk status, or from any vulnerability condition to a low-risk status, during the follow-up. Secondary outcomes were (1) atherosclerotic RF-level differences between vulnerable patients improving in the follow-up and patients remaining in a vulnerable status; (2) carotid ischemic events or all-cause mortality differences between vulnerable and stable patients.

MRI Protocol and Image Analyses

MRI protocol and image analyses were performed as previously described.[23] In brief, with a 3.0 T MRI scanner (Discovery MR750, GE Healthcare, Chicago, IL), a multisequence protocol was acquired, including black-blood 2D sequences T1 (without and with gadobutrol 1.0 mmoL/mL, 0.1 mmol/kg—Bayer AG, Leverkusen, Germany), proton density and T2 weighted, as well as bright-blood 3-dimensional time-of-flight angiography (typical acquisition parameters: field of view, 16 cm; matrix size, 256×256; in-plane resolution, 0.62×0.62 mm; 2 signal-intensity averages). Images with a sufficient quality were postprocessed to quantify plaque components with a validated software (MRI-Plaque View, VPDiagnostic, Seattle, WA), through semiautomatic identification of the common and internal carotid artery contours by a trained operator (O.C.). The analysis of the follow-up exams was blinded with respect to the previous ones.

Statistical Analysis

Categorical variables were expressed as count and percentage, and continuous variables as median and interquartile range. The χ^2 test was used to assess a significant change of vulnerability during the follow-up; a regression from a highly vulnerable condition to any lower-risk status in >20% of subjects and a transition from any vulnerability state to a low-risk condition in >10% of subjects were considered biologically significant. Differences between

risk groups were analyzed using Kruskal–Wallis, Mann–Whitney, or Wilcoxon tests for continuous variables and χ^2 test for binary variables. Kaplan–Meier analysis was used to test carotid ischemic events and all-cause mortality survival differences between groups with different carotid plaque vulnerability. Multivariable Cox regression analysis was used to assess independent associations of conventional variables and carotid plaque vulnerability with prognosis. Proportional hazard assumption was graphically tested using plots of the log estimated cumulative baseline hazard against time. Two-sided tests and a significance level <0.05 were used for hypothesis testing. Statistical analysis was performed using SPSS software (IBM, Armonk, NY).

RESULTS

The cross-sectional part of the study (ie, the focus of this article) enrolled 260 White patients. Because of poor image quality of both carotid axes, 13 patients were excluded from the study. The remaining 247 patients entered this longitudinal observational study. According to the baseline MRI, carotid plaque vulnerability was classified as high risk in 63 (26%) patients, intermediate risk in 65 (26%) patients, and low risk in 119 (48%) patients.

Baseline characteristics of the study population as a whole and for each risk group are summarized in Table 1. As expected according to MRI classification criteria, significant differences between groups were found regarding components associated with plaque vulnerability (P<0.001). Moreover, a progressive increase of the maximum stenosis from the lower- to the higher-risk group was observed (P<0.001). A significant progressive increase in coronary artery disease comorbidity (P<0.01) and a borderline association with coronary artery disease family history and high-sensitivity C-reactive protein was noted. Finally, triglycerides (P<0.05/<0.001) and body mass index (P<0.05) were significantly higher in patients at intermediate risk.

Correction of modifiable RFs was already good at the study entry. During the follow-up, there were favorable changes such as increase of high-density lipoprotein cholesterol, decrease of current tobacco use, and decrease of high-sensitivity C-reactive protein; and unfavorable modifications such as increase of body mass index, blood pressure, and hemoglobin A_{1c} and decrease of estimated glomerular filtration rate (Table 2). Although statistically significant, changes were small and of doubtful biological meaning in some cases (high-density lipoprotein, body mass index, hemoglobin A_{1c}, and estimated glomerular filtration rate).

Among the 63 patients found at high risk of carotid plaque vulnerability at baseline, a conversion to any lower-risk status was found in 11 patients (17%; P=0.614) at 6 months, in 16 (25%; P=0.197) at 1 year, and in 19 (30%; P=0.009) at 3 years (Figure 1A). Patients whose risk status improved did not show any significant difference in modifiable RF variation during the follow-up with respect to patients with persistent high vulnerability (Table 3). There was substantial agreement between the 2 carotid sides. Improvement of 1 carotid artery and deterioration of the other side were very rare and occurred in only 1 patient at 36 months of follow-up.

Among the 128 patients showing any degree of carotid plaque vulnerability at baseline (high or intermediate risk), 21 patients (16%; P=0.014) were diagnosed at low risk at 3-year follow-up (Figure 1B). Patients whose status improved to a low-risk level showed mild but significant regression of maximum stenosis and borderline reduction of low-density lipoprotein cholesterol (LDL-C) with respect to a slight increase in patients at persistent risk (Table 4). Figure 2 shows examples of highly vulnerable plaques at baseline with favorable evolution in the follow-up.All study patients completed the follow-up, during which 13 patients experienced a carotid ischemic event (3 strokes, 3 transient ischemic attacks, 6 endarterectomies, and 1 carotid stent) and 18 patients died. At survival analysis, patients with vulnerable carotid plaque at baseline (high or intermediate risk) did not experience a higher rate of carotid ischemic events with respect to stable patients. However, they showed borderline higher 3-year all-cause mortality (Kaplan–Meier Log-rank test, P=0.070; Figure 3). Multivariable Cox regression analysis, with adjustment for all variables with significant or borderline association (P<0.100) at baseline (Table S1), confirmed a borderline association of plaque vulnerability with prognosis (hazard ratio, 2.5 [95% CI, 0.9–7.1]; P=0.077; Table S2). Age was the only independent predictor of survival at multivariable testing (hazard ratio, 4.2 [95% CI, 1–14]; P=0.022).

DISCUSSION

In recent decades, plaque characterization, particularly the presence of significant LRNC and IPH or thinned FC, has emerged as an indicator of plaque propensity to ulceration/erosion, triggering thrombosis and ischemia. However, to date, cutoffs of the plaque components that determine vulnerability are not available.

MRI can noninvasively assess the composition of carotid plaques. Using MRI, previous studies have shown that LRNC or IPH is frequently found in asymptomatic patients, even with moderate or mild stenosis. However, rates of ischemic stroke in this population are generally low and have shown a declining trend since the mid-1980s, according to the results of randomized clinical trials.[24]

Table 1. Baseline Characteristics of the Study Population (247 Eligible Patients)*

	All patients (n=247)	High risk (n=63)	Intermediate risk (n=65)	Low risk (n=119)	*P* value
Sex, m, n (%)	188 (76)	50 (79)	53 (82)	85 (71)	0.240
Age, y (IQR)	71 (64–76)	71 (66–76)	71 (63–77)	71 (64–76)	0.815
Atherosclerosis risk factors					
Family history of premature coronary artery disease, n (%)	48 (19)	16 (25)	16 (25)	16 (13)	0.072
Former or current tobacco use, n (%)	179 (73)	43 (68)	53 (82)	83 (70)	0.159
Current tobacco use, n (%)	62 (25)	19 (30)	16 (25)	27 (23)	0.540
Hypercholesterolemia, n (%)	161 (65)	37 (59)	44 (68)	80 (67)	0.459
Diabetes, n (%)	87 (35)	19 (30)	23 (35)	45 (38)	0.589
Hypertension, n (%)	195 (79)	48 (76)	52 (80)	95 (80)	0.824
Total no. of risk factors, n (IQR)	4 (3–4)	3 (3–4)	4 (3–4)	4 (3–4)	0.164
≥3 RF, n (%)	201 (81)	49 (78)	58 (89)	94 (79)	0.163
Body mass index, kg/m^2 (IQR)	25 (23–28)	25 (24–28)	25 (23–29)	25 (22–28)	0.102
Body mass index ≥30 kg/m^2, n (%)	26 (11)	6 (10)	13 (20)	7 (6)	0.011
Extra carotid atherosclerosis					
Coronary artery disease, n (%)	164 (66)	51 (81)	46 (71)	67 (56)	0.003
Peripheral arterial disease, n (%)	49 (20)	10 (16)	16 (25)	23 (19)	0.455
Blood chemistry					
LDL-C, mg/dL (IQR)	78 (59–105)	76 (60–104)	84 (58–114)	77 (59–105)	0.611
LDL-C ≥70 mg/dL, n (%)	148 (60)	37 (59)	41 (63)	70 (59)	0.833
Triglycerides, mg/dL (IQR)	116 (89–169)	107 (85–144)	139 (92–186)	119 (92–161)	0.044
Triglycerides ≥150 mg/dL, n (%)	73 (30)	11 (18)	30 (46)	32 (27)	0.001
HDL-C, mg/dL (IQR)	43 (33–52)	41 (33–50)	40 (32–51)	45 (34–54)	0.166
HDL-C ≤35 mg/dL, n (%)	76 (31)	19 (30)	24 (37)	33 (28)	0.431
Hemoglobin A_{1c}, mmol/mol (IQR)	43 (39–52)	42 (38–45)	44 (40–53)	43 (39–53)	0.267
Hemoglobin A_{1c} ≥54 mmol/mol, n (%)	47 (19)	8 (13)	14 (22)	25 (21)	0.332
HS CP, mg/L (IQR)	3.6 (1.3–12.8)	4.9 (1.6–12.9)	5 (2–15)	2.8 (1.1–9.3)	0.052
HS-CRP ≥3 mg/dL, n (%)	36 (15)	11 (18)	11 (17)	14 (12)	0.481
eGFR, mL/min/1.73 m^2 (IQR)	69 (55–83)	68 (55–85)	65 (53–80)	72 (57–85)	0.169
eGFR, <60 mL/min/1.73 m^2, n (%)	63 (34)	23	25	35	0.394
Arterial blood pressure					
Systolic BP, mm Hg (IQR)	130 (110–140)	120 (110–130)	130 (115–140)	130 (110–140)	0.190
Systolic BP ≥140, mm Hg, n (%)	66 (27)	11 (18)	20 (31)	35 (29)	0.154
Diastolic BP, mm Hg (IQR)	70 (65–75)	70 (65–75)	70 (65–80)	70 (70–75)	0.455
Diastolic BP, ≥90 mm Hg, n (%)	6 (2)	2 (3)	2 (3)	2 (2)	0.762
Medical therapy					
Aspirin/antiplatelet, n (%)	220 (89)	60 (95)	59 (91)	101 (85)	0.090
ACE-inhibitors/ARB, n (%)	185 (75)	44 (70)	51 (79)	90 (76)	0.514
Statins, n (%)	187 (76)	52 (83)	51 (79%)	84 (71)	0.168
Plaque characteristics					
Vulnerable side (right/left/both), n (%)	…	17 (27)/38 (59)/9 (14)	…	…	…
Maximum stenosis, % (IQR)	65 (57–62)	69 (62–76)	65 (57–71)	62 (56–69)	<0.001
Lipid-rich necrotic core, n (%)	8 (5–11)	12 (10–15)	8 (6–11)	5 (3–8)	<0.001
Fibrous cap, mm (IQR)	0.09 (0.06–0.16)	0.06 (0.04–0.08)	0.07 (0.05–0.11)	0.14 (0.08–0.23)	<0.001
Fibrous cap mean thickness, mm (IQR)	0.45 (0.33–0.57)	0.37 (0.28–0.48)	0.44 (0.29–0.57)	0.50 (0.42–0.63)	<0.001
Fibrous cap maximum projection, mm (IQR)	10 (7–14)	13 (10–16)	11 (8–15)	8 (5–12)	<0.001
Intraplaque hemorrhage, n (%)	2 (1–4)	5 (3–7)	3 (2–4)	1 (0–2)	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C high-density lipoprotein cholesterol; HS-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; and RF, risk factor.

*Patients with baseline cardiac magnetic resonance of adequate quality.

Table 2. Modifiable Risk Factors and Other Significant Biomarkers During the Study Follow-Up (n=247)

	Baseline	End of study	*P* value
LDL-C, mg/dL (IQR)	77 (59–105)	81 (64–97)	0.271
Triglycerides, mg/dL (IQR)	116 (89–169)	112 (89–157)	0.489
HDL-C, mg/dL (IQR)	43 (33–52)	45 (37–54)	<0.001
Hemoglobin A_{1c}, mmol/mol (IQR)	43 (39–52)	44 (40–51)	0.011
Systolic BP, mm Hg (IQR)	130 (110–140)	135 (125–150)	<0.001
Diastolic BP, mm Hg	70 (65–75)	75 (70–80)	<0.001
Current tobacco use, n %	62 (25)	40 (16)	0.001
Body mass index, kg/m^2 (IQR)	25 (23–28)	26 (24–29)	<0.001
eGFR, mL/min/1.73 m^2 (IQR)	69 (55–83)	67 (54–79)	<0.001
High-sensitivity C-reactive protein, mg/L (IQR)	3.6 (1.3–12.8)	1.8 (1.0–4.4)	<0.001

For deceased patients, the last available value was considered as the end of study. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

Our working hypothesis was that plaque vulnerability could be a potentially reversible condition and a threshold phenomenon. We aimed to test this in a real-life sample with asymptomatic carotid atherosclerosis. Consequently, we hypothesized that lowering the plaque components associated with vulnerability below a critical level may be possible in patients on a secondary prevention program, leading to plaque stabilization. To test this hypothesis, a quantitative and comprehensive approach to carotid plaque vulnerability was required. We sought to define quantitative limits for the major plaque components associated with the vulnerability (LRNC, IPH, and FC). Then, based on preestablished criteria, we classified patients as high, intermediate, or low risk at study entry. Patients were periodically reevaluated over a 3-year period.

About a quarter (26%) of the study population was classified as high risk at baseline. This group underwent the most intensive follow-up program, which showed a favorable evolution of carotid atherosclerosis vulnerability from the 6-month short-term follow-up visit, with 17% transitioning to a lower risk. This result was confirmed in the medium to long term, with 25% and 30% of patients no longer found to be at high risk at 1 and 3 years, respectively. Results were similar considering high- or intermediate-risk patients at baseline, cumulatively approximately half of the study sample (52%). Of these, 16% of patients regressed to the low-risk group at 3 years of follow-up.

These findings were in line with our working hypothesis on the potential reversibility of the high-risk vulnerability of atherosclerosis in patients undergoing medical treatment. To our knowledge, this is the first study showing the reversibility of plaque vulnerability by a quantitative method, considering LRNC, IPH, and FC simultaneously. Previous studies with different imaging methods have shown that a decrease in the

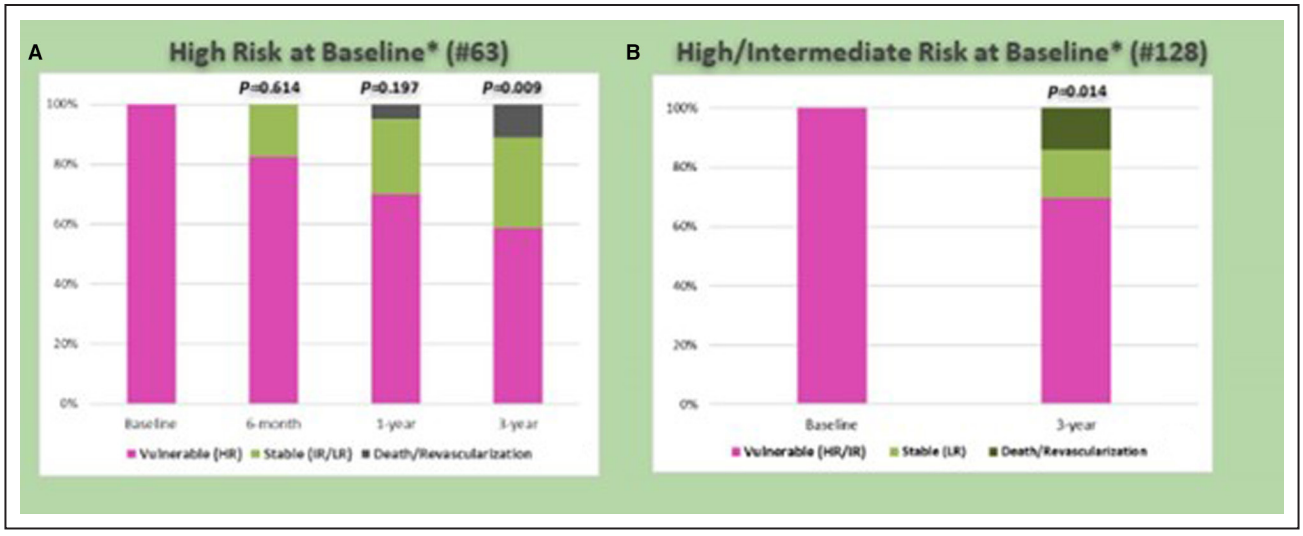

Figure 1. Regression of carotid plaque vulnerability during the study in patients who at baseline were at high risk (A), and at intermediate or high risk (B).

*Vulnerability risk of atherosclerosis defined by the quantitative assessment of the lipid-rich necrotic core, the fibrous cap, and intraplaque hemorrhage. HR indicates high risk; IR, intermediate risk; and LR, low risk.

Table 3. Modifiable Risk Factors Change (Δ=End-of-Study Minus Baseline) in Patients at Risk at Baseline (High Risk) With Plaque Vulnerability Persistence or Reduction (Intermediate or Low Risk) at 36 Months

	All patients* (n=56)	Persistent vulnerability at 3 years (n=37)	Lower vulnerability at 3 years (n=19)	*P* value
Current tobacco use, n (%)	7 (13)	5 (14)	2 (11)	0.722
LDL-C, mg/dL (IQR)	0 (–15 to 14)	2 (–13 to 14)	–13 (–18 to 20)	0.315
Triglycerides, mg/dL (IQR)	0 (–29 to 16)	0 (–27 to 5)	1 (–32 to 51)	0.431
HDL-C, mg/dL (IQR)	8 (–1 to 12)	8 (–1 to 14)	6 (0 to 11)	0.690
Hemoglobin A_{1c}, mmol/mol (IQR)	1 (–2 to 5)	0 (–2 to 4)	2 (–4 to 9)	0.208
High-sensitivity C-reactive protein, mg/L (IQR)	–0.1 (–1 to 0)	0 (–0.7 to 0)	0.3 (–1.5 to 0)	0.305
eGFR, mL/min/1.73 m^2 (IQR)	–1 (–11 to 7)	–2 (–9 to 6)	0 (–15 to 9)	0.723
Systolic BP, mm Hg (IQR)	10 (0 to 26)	10 (–3 to 20)	20 (0 to 30)	0.217
Diastolic BP, mm Hg (IQR)	3 (–5 to 15)	0 (–5 to 10)	5 (–5 to 15)	0.220
Body mass index, kg/m^2 (IQR)	1 (0 to 2)	0 (0 to 2)	1 (0 to 2)	0.399
Maximum stenosis, %	2 (–1 to 10)	1 (–1 to 10)	6 (–2 to 11)	0.664

BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

*Patients who died or experienced ischemic events were excluded.

overall plaque volume of coronary and carotid atherosclerosis can occur in patients undergoing medical treatment.[25,26] More recent research in clinical trials testing aggressive lipid-lowering therapies in acute or chronic coronary syndromes has also demonstrated a positive effect on plaque composition. Using intravascular ultrasound or optical coherence tomography, a substantial reduction in plasma lipids has been shown to cause thickening of the FC and shrinking of the LRNC.[27] Small studies have also shown a reduction in LRNC volume of carotid plaques with statin therapy.[22]

Our research adds to previous knowledge on atherosclerosis reversibility and provides evidence that plaque vulnerability regression is a common occurrence even outside the highly controlled setting of a clinical trial, in which LDL-C decreases to levels hardly seen in clinical practice.[28] Until now, it was believed that a large reduction in plasma concentration of lipoprotein-containing apolipoprotein Bs was required for regression of advanced complex atherosclerotic plaques. An LDL-C threshold of 70 mg/dL has been proposed as a theoretical reversal point from progression to regression of atherosclerosis.[29] However, the level of LDL-C at which plaque vulnerability begins to regress was not known. Our study shows that the vulnerability of atherosclerosis can regress at a similar cholesterol level if a multidimensional effort to control all modifiable RFs is fielded. The patient sample we observed had on average good control of all modifiable RFs, which remained good during the follow-up, without reaching extremely

Table 4. Modifiable Risk Factor Change (Δ=End-of-Study Minus Baseline) in Patients at Risk at Baseline (High or Intermediate) With Plaque Vulnerability Persistence or Reduction (Low Risk) at 36 Months

	All patients* (n=109)	Persistent vulnerability at 3 years (n=88)	Reduced vulnerability at 3 years (n=21)	*P* value
Current tobacco use, n (%)	24 (22)	18 (21)	6 (29)	0.234
LDL-C, mg/dL (IQR)	0 (–18 to -18)	1 (–15 to 19)	–14 (–29 to 12)	0.098
Triglycerides, mg/dL (IQR)	0 (–35 to 19)	0 (–42 to 16)	–11 (–31 to 83)	0.827
HDL-C, mg/dL (IQR)	4 (–4 to 11)	5 (–3 to 11)	1 (–6 to 15)	0.509
Hemoglobin A_{1c}, mmol/mol (IQR)	0 (–2 to 5)	0 (–1 to 5)	1 (–6 to 5)	0.752
High-sensitivity C-reactive protein, mg/L (IQR)	–0,1 (–1.1 to 0)	–0.1 (–1.0 to 0.0)	–0.3 (–1.4 to 0.0)	0.616
eGFR mL/min/1.73 m^2 (IQR)	–2 (–12 to 6)	0 (–12 to 7)	–4 (–16 to 2)	0.104
Systolic BP, mm Hg (IQR)	10 (0 to 29)	8 (0 to 30)	10 (–3 to 23)	0.646
Diastolic BP, mm Hg (IQR)	5 (–3 to 15)	5 (0 to 15)	5 (–5 to 18)	0.932
Body mass index, kg/m^2 (IQR)	1 (0 to 2)	1 (0 to 2)	0 (–2 to 2)	0.376
Maximum stenosis, % (IQR)	2 (–1 to 9)	2 (0 to 10)	–1 (–8 to 5)	0.017

Patients who died or experienced ischemic events were excluded. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

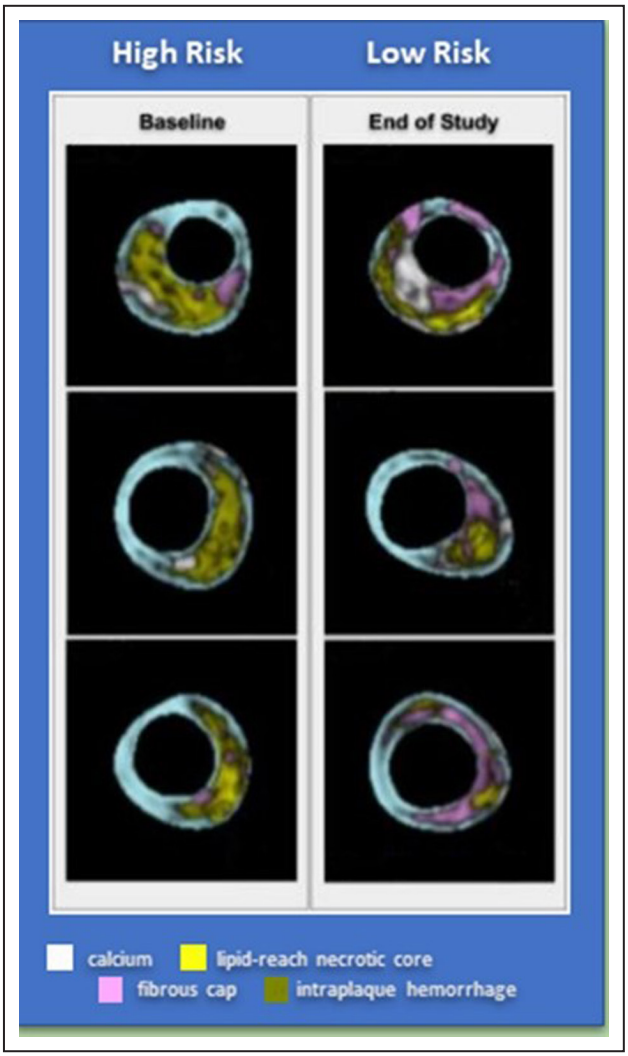

Figure 2. Examples of highly vulnerable plaques at baseline with favorable evolution at end of study.

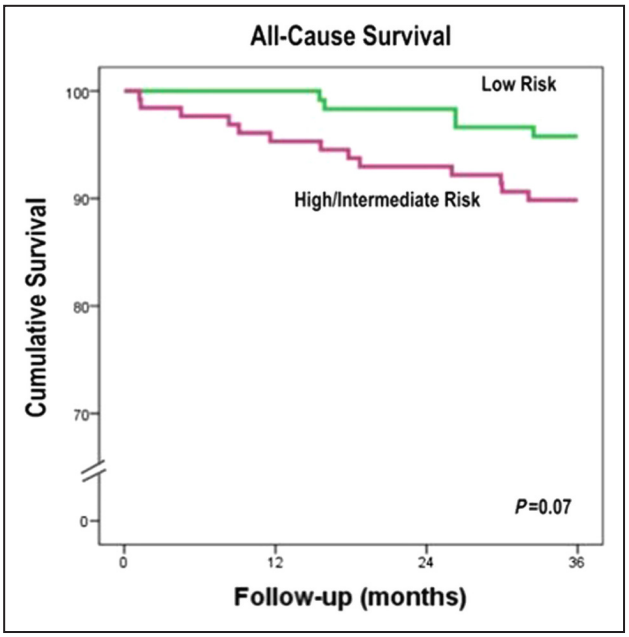

Figure 3. Kaplan–Meier survival curves (all-cause death) of patients with vulnerable carotid plaques (high or intermediate risk) and patients with stable atherosclerosis at baseline.

low levels for any of them. For example, the median LDL-C value was 77 mg/dL at baseline and 88 mg/dL at the study end. Although each RF was not aggressively reduced, we observed a significant rate of regression from a vulnerable atherosclerosis condition. Accordingly, this study seems to prove that an enduring RF control has a continuous positive effect on plaque characteristics over time and that plaque vulnerability is a highly dynamic process that can be positively influenced by a moderate comprehensive lowering of as many RFs as possible. Nevertheless, we observed that patients who regressed to the lowest vulnerability risk level had a borderline reduction in LDL-C during the study, while LDL-C levels were unchanged in patients with a persistent risk of vulnerability. Overall, the results of this study confirm the importance of achieving and maintaining the therapeutic goal for as many modifiable RFs as possible, as outlined in the guidelines, with a focus on LDL-C.

This study also provided some clues as to the timing of plaque vulnerability regression and its relationship with the degree of stenosis. We observed that, with a comprehensive approach to RF control, changes in plaque composition can occur in the short term (6 months), although the prespecified biological significance in this study was achieved in the medium to long term (3 years). It is known from randomized clinical trials that the faster and more intense the reduction of lipids, the greater and earlier the regression of the plaque. Likewise, the strength of the modifiable RF correction could potentially affect the timing and extent of atherosclerosis vulnerability regression.

Through prospective observation of our cohort, we found that favorable changes in atherosclerotic plaque composition are accompanied by a small but significant decrease in maximal stenosis, while a slight increase was noted in patients with persistent vulnerability. The link between progressive growth (or regression) and vulnerability of atherosclerotic plaque is complex and not entirely clear. Atherosclerosis is known to progress both by a slow, gradual growth and through rapid periodic changes in the geometry, size, and morphology of the plaque. The sudden increase in plaque size is often a sign of plaque instability, usually attributable to IPH causing inflammatory cell infiltration and expansion of the necrotic nucleus. In contrast, with intensive lipid-lowering therapy, decreased LRNC and increased fibrosis appear to precede any reduction in plaque volume.

Consequently, both the size of the plaque and its composition are important in predicting the vulnerability of atherosclerotic lesions and their evolution over time.

The prognostic value of atherosclerotic plaque vulnerability has a sound basis, which is particularly solid for coronary artery disease. Meta-analytical studies have shown a direct relationship between the progression of coronary atherosclerosis and cardiovascular adverse events.[30] Furthermore, observational studies have found that at-risk carotid atherosclerosis phenotypes, as defined by MRI, are associated with cerebral ischemic events. The present study was not powered to evaluate differences in prognosis. However, it is interesting to note that survival analysis showed a trend toward higher all-cause mortality in patients with vulnerable plaque, as if the vulnerability of carotid atherosclerosis could be a worse prognosis indicator beyond ischemic risk. Although medical treatment of atherosclerosis risk factors, particularly LDL-C reduction, has been shown in separate studies to reduce coronary and cerebral ischemic events as well as to promote the regression of plaque vulnerability, it is still unknown whether a causal relationship exists between the 2 observations. Therefore, further outcome studies are needed to conclusively demonstrate that regression of vulnerable plaque characteristics results in a more favorable prognosis. This will have practical implications for the individual patient, by better defining the risk–benefit ratio of revascularization procedures, and at group level, by more accurately assessing the effectiveness of preventive and therapeutic interventions.

CONCLUSIONS

This study confirms with a quantitative approach that carotid plaque vulnerability is a potentially reversible condition that commonly occurs in real-life patients undergoing a secondary prevention program. Optimal medical therapy has a favorable effect, promoting the regression of carotid plaque vulnerability in a significant proportion of cases in the mid to long term. Further outcome studies are warranted to definitively confirm an improvement of prognosis with regression of atherosclerosis vulnerability.

LIMITS OF THE STUDY

Low-risk patients at baseline did not undergo MRI follow-up because it was judged unethical by the ethics committee. Therefore, it was not possible to assess the proportion of patients in the low-risk group who switched to a higher-risk group. This information would have made the study more comprehensive, although our goal was primarily to quantitatively demonstrate that plaque vulnerability regression is possible in a real-life scenario.

The lack of a control group is another limitation of this study. However, it cannot be considered acceptable to deny established treatments (all measures aimed at containing RFs for atherosclerosis) to patients with known, albeit asymptomatic, atherosclerosis. Male predominance and racial homogeneity may also limit the generalization of the study results.

Finally, the risk classification we used might be considered arbitrary, being based on a statistical approach. Interestingly, minimum FC thickness (60 μ, calculated as the 5th percentile in the reference sample), one of the criteria used to define thin-cap atheroma, is the same cutoff as that usually used in optical coherence tomography studies.

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Disclosures

None.

Supplemental Material

Table S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics and end-of-study modifiable risk factors of all eligible patients and for all-cause death.

BASELINE	All patients* (n=247)	Survivors (n=229)	All-cause deaths (n=18)	p
Sex (m)	188 (76%)	175 (76%)	13 (72%)	0.688
Age (≥ 70 years)	137 (56%)	122 (53%)	15 (83%)	0.013
Atherosclerosis risk factors				
Family history of premature CAD	48 (19%)	46 (20%)	2 (11%)	0.354
former or current tobacco use	179 (73%)	166 (73%)	13 (72%)	0.981
Current tobacco use	62 (25%)	59 (26%)	3 (17%)	0.391
Hypercholesterolemia	161 (65%)	154 (67%)	7 (39%)	0.015
Diabetes	87 (35%)	83 (36%)	4 (22%)	0.230
Hypertension	195 (79%)	182 (80%)	13 (72%)	0.467
≥3 RF	201 (81%)	189 (83%)	12 (67%)	0.096
BMI ≥30 kg/m^2	26 (11%)	24 (11%)	2 (11%)	0.933
Extra carotid atherosclerosis				
Coronary artery disease	164 (66%)	148 (65%)	16 (89%)	0.036
Peripheral arterial disease	49 (20%)	45 (20%)	4 (22%)	0.792
Blood Chemistry				

LDL Cholesterol ≥ 70 mg/dl	148 (60%)	141 (62%)	7 (39%)	0.059
Triglycerides ≥ 150 mg/dl	73 (30%)	67 (29%)	6 (33%)	0.715
HDL ≤ 35 mg/dl	76 (31%)	70 (31%)	6 (33%)	0.807
HbA1c ≥ 54 mmol/mol	47 (19%)	45 (20%)	2 (11%)	0.374
HS-CRP ≥ 3 mg/dl	36 (15%)	33 (14%)	3 (17%)	
EGFR, < 60	63 (34%)	(%)	(%)	
Arterial blood pressure				
SBP ≥ 140 mmHg	66 (27%)	62 (27%)	4 (22%)	0.654
DBP ≥ 90 mmHg	6 (2%)	6 (3%)	0 (0%)	0.487
Medical Therapy				
aspirin/antiplatelet	220 (89%)	204 (89%)	16 (89%)	0.980
ACE-inhibitors/ARBs	185 (75%)	174 (76%)	11 (61%)	0.161
Statins	187 (76%)	173 (76%)	14 (78%)	0.832
Carotid plaque vulnerability high/intermediate risk	128 (52%)	115 (50%)	13 (72%)	0.072
END-OF-STUDY §				
LDL Cholesterol. ≥ 70 mg/dl	161 (65%)	154 (67%)	7 (39%)	0.015
Triglycerides ≥ 150 mg/dl	69 (28%)	65 (28%)	4 (22%)	0.575

HDL ≤ 35 mg/dl	(%)	(%)	(%)	
HbA1c ≥ 54 mmol/mol	54 (22%)	51 (22%)	3 (17%)	0.580
SBP ≥ 140 mmHg	121 (49%)	116 (51%)	5 (28%)	0.062
DBP ≥ 90 mmHg	23 (9%)	23 (10%)	0 (0%)	0.158
Current tobacco use	40 (16%)	38 (17%)	2 (11%)	0.543
BMI ≥30 kg/m^2	27 (12%)	27 (12%)	0 (0%)	0.362
EGFR < 60 ml/min/1,73 m^2	89 (36%)	79 (35%)	10 (55%)	0.073
HS-CRP ≥ 3 mg/dl	13 (5%)	11 (5%)	2 (11%)	0.249

* patients with baseline CMR of adequate quality; § for deceased patients the last available datum was considered CAD=coronary artery disease; BMI=body mass index; LDL=low density lipoprotein; HDL high density lipoprotein; HbA1c=glycosylated hemoglobin; HS-CRP=high sensitivity C reactive protein; EGFR=estimated glomerular filtration rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; ACE=angiotensin converting enzyme; ARB= angiotensin receptor blocker

Table S2. Results of multivariable Cox regression model.

Covariates	Coefficient	Standard error	P value	HR	95% CI	
					Lower	Upper
Age (≥ 70 years)	1.445	0.633	0.022	4.243	1.228	14.659
Carotid plaque vulnerability (high/intermediate risk)	0.932	0.526	0.077	2.540	0.905	7.126
Hypercholesterolemia	-0.770	0.549	0.161	0.463	0.158	1.358
Coronary artery disease	1.003	0.772	0.193	2.728	0.601	12.374
LDL Cholesterol (≥ 70 mg/dl)	-0.499	0.499	0.318	0.607	0.228	1.615
≥3 Risk factors	-0.315	0.562	0.575	0.730	0.243	2.195