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Intraplaque neovascularization attenuated statin benefit on atherosclerotic plaque in CAD patients: A follow-up study with combined imaging modalities

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HIGHLIGHTS

- Plaques with neovascularization exhibited more vulnerable characteristics.
- Neovascularization attenuated the benefit of statins on plaque progression.
- Neovascularization had a stronger influence on fibroatheroma than fibrous plaque.

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ABSTRACT

Background and aims: Plaque progression increases the risk of a cardiovascular event. This study aims to determine whether intraplaque neovascularization (NV) associates with a greater risk of plaque progression.
Methods: Baseline and 12-month follow-up IVUS was used in combination with baseline OCT to assess 164 non-culprit plaques in 118 CAD patients. A generalized estimating equation approach with exchangeable correlation structure was used to correct for the dependency of repeated measurements.
Results: Patients were divided into two groups according to NV (52 patients with 62 NV plaques, 66 patients with 102 non-NV plaques). Non-culprit plaques in the NV group exhibited a more frequent occurrence of TCFA ($p = 0.004$), macrophage ($p = 0.005$), cholesterol crystal ($p = 0.012$), calcification ($p = 0.030$), thinner fibrous cap thickness (FCT) [(86.8 ± 55.1) *vs.* (127.4 ± 70.1) μm, $p = 0.015$], larger lipid arc [(219.5 ± 66.9) *vs.* (179.8 ± 61.4), $p = 0.002$] compared to the non-NV group. A large change in percent atheroma volume (PAV), plaque plus media cross-sectional area (P&M CSA), plaque volume, and plaque burden was observed from baseline to follow-up in the NV group. Changes in P&M CSA, plaque volume, and plaque burden showed significant differences in fibroatheroma with NV. Intraplaque NV could predict a high risk of plaque progression despite statin therapy [OR 6.521 (95% CI 2.457–17.308), $p < 0.001$].
Conclusions: NV might attenuate the benefits of statin therapy in plaque progression. This study may provide a new basis for anti-angiogenic strategies to prevent atherosclerotic plaque progression.

1. Introduction

In intravascular imaging studies, accumulating evidence has demonstrated the benefit of statins in slowing plaque progression and modulating instability of atherosclerotic plaques [1,2]. However, despite high-intensity statin therapy, atherosclerosis will continue to progress in up to one-third of patients [3]. Atherosclerotic plaque progression is associated with an increased risk of clinical events [4]. Retrospective studies have shown that most atherosclerotic plaques responsible for future acute coronary syndromes are angiographically mild [5,6], and plaque related risk factors for clinical cardiovascular events are poorly understood. Only two retrospective optical coherence

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tomography (OCT) studies have related lesion morphology to progression [7,8]. Intraplaque neovascularization (NV), as one of the OCT detectable microstructures, could play a key role in atherosclerotic plaque progression [9].

Intravascular ultrasound (IVUS) can determine atherosclerotic plaque burden, vascular remodeling, and has been widely used to investigate plaque progression [10]. However, IVUS has limited ability to estimate detailed plaque morphologies, such as microchannels, macrophage, and thin-cap fibroatheroma (TCFA). OCT has a resolution of ≈10 μm, ten times greater than IVUS, and is sharp enough to detect the above-mentioned plaque morphologies [11]. Recent studies have suggested that intraplaque NV could be detected as microchannels in an OCT image [12,13]. Given this, the combination of OCT and IVUS in clinical practice can complement one another, providing new insights into plaque progression. Therefore, the aim of this study was to investigate plaque progression from baseline to a 12-month follow-up utilizing IVUS examinations, and to correlate baseline plaque characteristics (especially microchannels), obtained via OCT, with plaque progression in patients with coronary artery disease (CAD).

2. Materials and methods

2.1. Subjects and study design

This was a retrospective, single-center, observational study to determine the morphological changes, especially microchannels, associated with untreated, non-culprit/non-target lesion progression using co-registered OCT and IVUS in patients with CAD who underwent percutaneous coronary intervention. The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University (Harbin, China). All patients provided written informed consent.

A total of 150 patients with CAD undergoing statin treatment were enrolled between May 2010 and May 2013. All the patients were treated with 20 mg atorvastatin once a day from enrollment until 12-month follow up. IVUS and OCT imaging of the three epicardial coronary vessels were performed at baseline after target lesion stent implantation. IVUS was also performed at 12-month follow-up. All angiogram, OCT, and IVUS images were analyzed independently at the Second Affiliated Hospital of Harbin Medical University. Since this was a retrospective study, the patients who had done angiogram, OCT and IVUS examinations, fulfilling the following criteria, were chosen. Image inclusion criteria were as follows: (a) angiogram showing at least one *de-novo* lesion with diameter stenosis between 30 and 70%, (b) lesion located in one of the major epicardial coronary arteries, and (c) proximal and distal identifiable anatomical landmarks. Exclusion criteria were as follows: (a) poor OCT/IVUS image quality, (b) severe calcification, and (c) mismatched images between the two imaging modalities.

2.2. Quantitative coronary angiography

Angiographic images were analyzed at MGH-CLIPI using off-line software (CAAS 5.10.1; Pie Medical Imaging BV, Maastricht, the Netherlands). Minimum lumen diameter (MLD), reference diameter (RD), and diameter stenosis (DS) were measured after calibrating with the catheter tip.

2.3. OCT analysis

OCT image acquisition was performed using time domain (M2/M3 Imaging System; LightLab Imaging, Westford, Massachusetts, USA) or frequency-domain OCT systems (C7-XR OCT Intravascular Imaging System; St Jude Medical, St Paul, Minnesota, USA). All procedures were performed after an intracoronary administration of 100–200 μg of nitroglycerin. OCT image analysis was performed by two experienced investigators who were blinded to clinical information using proprietary software (Light Lab Imaging Inc., Westford, Massachusetts). Corresponding IVUS and OCT images were identified by distances from landmarks such as side branches and stent edges. If there was discordance between the investigators, a consensus was reached by a third investigator. Qualitative and quantitative analyses were performed at 1-mm interval.

All OCT images were analyzed using the previously established criteria for plaque characterization [14,15]. The OCT detected plaque characteristics and representative OCT images (Supplementary Fig.1) of each plaque characteristics are showed in Supplementary Materials.

2.4. IVUS analysis

IVUS images were obtained using a commercially available system (iLab1. 3; Boston Scientific, Fremont, California) and a 40 MHz, 2.6Fr catheter. After intracoronary administration of nitroglycerin 100–200 μg, automatic pullback was performed at 0.5 mm/s from at least 10 mm distal to the target plaque. Offline analysis was performed using a software program (Echo Plaque; Indec Systems, Mountain View, California). All qualitative and quantitative analyses were performed in accordance with the standards of the American College of Cardiology and the European Society of Cardiology [16]. IVUS images were analyzed via side-by-side comparison of baseline and follow-up studies, selection of landmarks, and frame-by-frame viewing for matching segments. Two experienced IVUS reviewers were blinded to the time points (baseline and 12-month follow-up), as well as the results of OCT. The proximal and distal frame numbers of analyzed segments were recorded and the cross-sectional and longitudinal IVUS images were marked with EchoPlaque software. After matching the segment successfully, both quantitative and qualitative IVUS analyses were further blindly analyzed at each time point. When there was a discordance, a third reviewer was involved. The calculation of some IVUS parameters were in Supplementary Materials.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (V.22, IBM Corp, Armonk, New York, USA). A generalized estimating equation (GEE) approach with exchangeable correlation structure was used to correct for the dependency of repeated measurements [17]. Normal distribution of data was assessed with the Shapiro–Wilk test. If the data were normally distributed, statistical significance was evaluated with Student *t*-test (data presented as mean ± standard deviation). If the data failed normality tests, groups were compared using Wilcoxon rank-sum test for 2 groups (data presented as median with 25th and 75th percentiles). Categorical variables are expressed as a number (percent). As for the numerical missing data, mean value imputation was used. A multivariable GEE log-binomial regression model was used to identify factors independently associated with plaque progression. A two-sided p value of < 0.05 was deemed statistically significant.

3. Results

3.1. Clinical characteristics and laboratory findings

From 150 eligible patients, 32 were excluded due to no analyzable plaque ($n = 8$), no identifiable landmarks ($n = 10$), poor image quality ($n = 9$), and being mismatched ($n = 5$). In total, 118 patients with 164 lesions were included in the analyses. Enrolled patients were divided into patients with NV (52 patients with 62 plaques) and patients without NV (66 patients with 102 plaques). Baseline characteristics and follow-up laboratory findings of the patients are summarized in Supplementary Table1. Following the baseline study, most patients were discharged on dual antiplatelet therapy. No differences were observed between the two groups except the differences in smoking and

Table 1
Plaque characteristics at baseline.

	Lesions with neovascularization (n = 62)	Lesions without neovascularization (n = 102)	*p* value (GEE)
Angiographic findings			
Lesion location (vessel)			0.603
RCA	[a] 33 (53.2%)	40 (39.2%)	
LAD	19 (30.6%)	39 (38.2%)	
LCX	10 (16.1%)	23 (22.5%)	
Lesion location (distance)			0.604
Proximal	26 (41.9%)	51 (50.0%)	
Middle	27 (43.5%)	38 (37.3%)	
Distal	9 (14.5%)	13 (12.7%)	
Lesion length, mm	11.6 ± 4.8	10.3 ± 4.3	0.473
MLD, mm	1.8 ± 0.57	1.9 ± 0.48	0.215
RD, mm	3.1 ± 0.72	3.1 ± 0.62	0.595
DS, %	42.5 ± 11.0	39.9 ± 9.4	0.193
Culprit vessel	23 (37.1%)	28 (27.5%)	0.052
Optical coherence tomographic findings			
Lipidic plaque	48 (77.4%)	73 (71.6%)	0.409
Thinnest cap thickness, μm	86.8 ± 55.1	127.4 ± 70.1	0.015
Lipid arc, deg.	219.5 ± 66.9	179.8 ± 61.4	0.002
Lipid length, mm	13.7 ± 8.4	10.6 ± 6.6	0.028
TCFA	20 (32.3%)	16 (15.7%)	0.004
Macrophage	42 (67.7%)	45 (44.6%)	0.005
Cholesterol crystal	24 (38.7%)	18 (17.6%)	0.012
Calcification	30 (48.4%)	32 (31.4%)	0.030
Spotty calcification	23 (37.1%)	25 (24.5%)	0.068
Large calcification	12 (19.4%)	12 (11.8%)	0.248
Thrombus	4 (6.5%)	4 (3.9%)	0.645
Rupture	8 (12.9%)	6 (5.9%)	0.256
Intravascular ultrasound findings			
Lumen CSA, mm^2	8.0 ± 3.5	7.7 ± 2.9	0.933
EEM CSA, mm^2	15.0 ± 6.5	14.2 ± 5.1	0.773
P&M CSA, mm^2	8.5 ± 3.4	8.8 ± 4.3	0.336
Lumen volume, mm^3	159.1 ± 90.9	147.7 ± 101.7	0.527
Vessel volume, mm^3	339.4 ± 176.1	320.0 ± 212.4	0.665
Plaque volume, mm^3	180.4 ± 96.5	172.4 ± 120.7	0.819
PAV, %	53.3 ± 7.9	52.9 ± 9.9	0.566
Plaque burden, %	63.7 ± 10.0	61.3 ± 11.2	0.540
Remodeling index	0.93 ± 0.15	0.98 ± 0.12	0.019
Attenuated plaque	21 (33.9%)	20 (19.6%)	0.034
Positive remodeling	12 (19.4%)	29 (28.4%)	0.369
Lumen area $< 4\,mm^2$	30 (48.4%)	32 (31.4%)	0.051
Plaque burden $> 70\%$	16 (25.8%)	23 (22.5%)	0.902

RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex; MLD, minimum lumen diameter; RD, reference diameter; DS, diameter stenosis; TCFA, thin-cap fibroatheroma; CSA, cross-sectional area; EEM CSA, external elastic membrane cross-sectional area; P&M CSA, plaque plus media cross-sectional area; PAV, percent atheroma volume; OCT, optical coherence tomography; IVUS, intravascular ultrasound.
[a] Categorical data are presented as *n* (%). Continuous data are presented as the mean ± SD.

patients with history of acute myocardial infarction.

3.2. Plaque characteristics at baseline

QCA findings were compared between the two groups with or without NV. As shown in Table 1, there was no difference in the distribution of plaques between the two groups. Furthermore, no significant differences were found in MLD, RD, or DS between the two groups (all $p > 0.05$).

Table 1 shows the baseline plaque characteristics derived by OCT in the two groups. Plaques with NV presented a more frequent occurrence of TCFA, macrophage, cholesterol crystal, and calcification than those in the group without NV (32.3% *vs.* 15.7%, $p = 0.004$; 67.7% *vs.* 44.6%, $p = 0.005$; 38.7% *vs.* 17.6%, $p = 0.012$; and 48.4% *vs.* 31.4%, $p = 0.030$, respectively). The FCT in the NV group was thinner compared to the group without NV [(86.8 ± 55.1) *vs.* (127.4 ± 70.1) μm, $p = 0.015$]. Moreover, the NV group displayed a larger lipid arc [(219.5 ± 66.9) *vs.* (179.8 ± 61.4), $p = 0.002$] and longer lipid length [(13.7 ± 8.4) *vs.* (10.6 ± 6.6) mm, $p = 0.028$] compared to the group without NV.

Baseline IVUS findings are also showed in Table 1. Plaques with NV presented a smaller remodeling index [NV group (0.93 ± 0.15) *vs.* (0.98 ± 0.12), $p = 0.019$] and more attenuated plaques (33.9% *vs.* 19.6%, $p = 0.034$) compared to those in the group without NV. Apart from this, there were no other differences found in baseline IVUS findings.

3.3. Baseline NV vs. 12-month plaque progression

Changes of the 12-month follow-up minus baseline IVUS parameters are shown in Table 2. Changes in PAV, presented as △PAV%, was calculated as ((PAV at follow-up minus PAV at baseline)/PAV at baseline)*100. There were large changes in PAV [△PAV%: (2.9 ± 4.7) *vs.* (−1.6 ± 5.2)%, $p < 0.001$], P&M CSA [(△P&M CSA, mm^2): (0.88 ± 2.4) *vs.* (−0.71 ± 2.0) mm^2, $p < 0.001$], plaque volume [(△Plaque volume, mm^3): (4.2 ± 22.6) *vs.* (−11.0 ± 25.2) mm^3, $p = 0.003$], and plaque burden [△Plaque burden%: (4.7 ± 6.0) *vs.* (−2.0 ± 7.9)%, $p < 0.001$] in plaques with NV compared to those without from baseline to 12-month follow-up. However, when the groups were divided by plaque categories (fibroatheroma *vs.* fibrous plaque) on the basis of NV, △P&M CSA, mm^2, △Plaque volume, mm^3, and △Plaque burden% ($p = 0.234$, $p = 0.238$, and $p = 0.083$, respectively) showed no obvious difference in fibrous plaques with or without NV.

Table 2
Baseline neovascularization *vs*. 12-month plaque progression.

	Lesions with neovascularization (n = 62)	Lesions without neovascularization (n = 102)	*p* value (GEE)
△ Lumen CSA, mm²	[a] **-0.48 ± 1.9**	**−0.14 ± 1.9**	**0.193**
FA	−0.38 ± 1.3	−0.26 ± 1.5	0.701
FP	−0.81 ± 3.2	0.15 ± 2.6	0.227
△ EEM CSA, mm²	**−0.11 ± 5.1**	**−0.11 ± 1.9**	**0.956**
FA	−0.09 ± 5.7	−0.02 ± 1.7	0.996
FP	−0.18 ± 2.6	−0.32 ± 2.5	0.847
△ P&M CSA, mm²	**0.88 ± 2.4**	**−0.71 ± 2.0**	**< 0.001**
FA	1.0 ± 2.6	−0.83 ± 1.8	0.001
FP	0.37 ± 1.7	−0.41 ± 2.3	0.234
△ Lumen volume, mm³	**−10.8 ± 25.0**	**−1.90 ± 32.7**	**0.089**
FA	−12.2 ± 22.4	−3.3 ± 25.6	0.081
FP	−6.2 ± 32.8	1.8 ± 46.3	0.524
△ Vessel volume, mm³	**−6.5 ± 38.1**	**−13.0 ± 46.4**	**0.417**
FA	−7.4 ± 33.0	−13.7 ± 38.8	0.359
FP	−3.4 ± 53.4	−11.2 ± 62.5	0.686
△ Plaque volume, mm³	**4.2 ± 22.6**	**−11.0 ± 25.2**	**0.003**
FA	4.8 ± 22.3	−10.2 ± 24.6	0.005
FP	2.0 ± 24.5	−12.9 ± 27.2	0.238
[b] **△ PAV, %**	**2.9 ± 4.7**	**−1.6 ± 5.2**	**< 0.001**
FA	3.1 ± 4.7	−1.3 ± 4.3	< 0.001
FP	2.1 ± 4.6	−2.5 ± 6.9	0.008
△ Plaque burden, %	**4.7 ± 6.0**	**−2.0 ± 7.9**	**< 0.001**
FA	4.8 ± 6.5	−2.5 ± 6.9	< 0.001
FP	4.4 ± 4.3	−0.55 ± 9.8	0.083

CSA, cross-sectional area; EEM CSA, external elastic membrane cross-sectional area; P&M CSA, plaque plus media cross-sectional area; PAV, percent atheroma volume.
[a] Continuous data are presented as the mean ± SD.
[b] △PAV = Follow up PAV - Baseline PAV.

3.4. Analysis of plaque progression from multivariable GEE log-binomial regression

Table 3 shows the analytical results of plaque progression from multivariable GEE log-binomial regression. Model 1 is the full model with all covariates, and model 2 is the final model excluding variables based on collinearity and reverse causality. The microchannels [OR 6.521 (95% CI 2.457–17.308), $p < 0.001$], the presence of TCFA [OR 8.667 (95% CI 2.571–29.221), $p < 0.001$], LDL-C higher than median value [OR 3.833 (95% CI 1.212–12.125), $p = 0.022$] and being male [OR 6.285 (95% CI 1.852–21.325), $p = 0.003$] could predict a high risk of plaque progression despite statin therapy. Whereas, the presence of large calcium [OR 0.070 (95% CI 0.009–0.530), $p = 0.010$] showed negative correlation with the risk of plaque progression.

4. Discussion

In this study, the delay of plaque progression after standardized statin treatment was investigated from baseline through 12-month follow-up via IVUS examinations, and the correlations of baseline plaque characteristics, especially microchannels, with plaque progression in patients with coronary artery disease were established.

Table 3
Analysis of plaque progression from multivariable GEE log-binomial regression.

Variables	Model 1 (full)		Model 2 (final)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Microvessels	7.684 (2.734-21.595)	< 0.001	6.521 (2.457-17.308)	< 0.001
Macrophage	1.501 (0.487-4.630)	0.480		
Cholesterol crystal	2.740 (0.669-11.227)	0.161		
Large calcium	0.060 (0.007-0.510)	0.010	0.070 (0.009-0.530)	0.010
Thrombus	2.520 (0.190-33.509)	0.484		
Rupture	0.426 (0.044-4.126)	0.462		
TCFA	22.727 (4.669-110.638)	< 0.001	8.667 (2.571-29.221)	< 0.001
Attenuated	0.293 (0.084-1.023)	0.054		
Lumen area < 4 mm²	0.371 (0.087-1.572)	0.178		
Plaque burden > 70%	1.240 (0.309-4.982)	0.761		
Age (> median)	2.621 (0.693-9.919)	0.156		
Gender (male)	9.011 (1.842-44.083)	0.007	6.285 (1.852-21.325)	0.003
Diabetes mellitus	1.016 (0.204-5.046)	0.985		
Hypertension	1.226 (0.428-3.514)	0.704	1.424 (0.502-4.041)	0.507
Current smoking	0.557 (0.127-2.455)	0.440	0.595 (0.169-2.097)	0.419
Prior MI	2.727 (0.605-12.295)	0.192	2.048 (0.520-8.060)	0.305
LDL-C (> median)	4.884 (1.101-21.670)	0.037	3.833 (1.212-12.125)	0.022
hs CRP (> median)	1.214 (0.344-4.285)	0.763	1.009 (0.376-2.708)	0.986
HbA1c (> median)	1.261 (0.205-7.774)	0.802		
ACS	1.662 (0.202-13.648)	0.636	3.111 (0.693-13.975)	0.139

TCFA, thin-cap fibroatheroma; MI, myocardial infarction; LDL-C, low density lipoprotein cholesterol; hs-CRP, hypersensitive C-reactive protein; HbA1c, hemoglobin A1c; ACS, acute coronary syndrome.

Despite reducing progression and promoting regression of coronary atherosclerosis, statin therapy does not fully address residual cardiovascular risk. Baseline OCT results showed that non-culprit plaques in CAD patients with NV exhibited more vulnerability characteristics. These results may be consistent with previous animal experiments and pathological studies of NV. For instance, NV within atherosclerotic plaques act as a double-edged sword [18]. At the early stage, NV functions as a conduit for the supply of nutrients and oxygen. However, with the imbalance between antiangiogenic and proangiogenic factors, the NV become more immature and leaky, promoting the conversion of a stable plaque to an unstable phenotype.

The NV of the atherosclerotic areas supplies not only O_2, but also lipoproteins and other nutrients, which allow lipid core expansion [19]. Intraplaque NV provides an advantage for lipid entry into the plaque, especially in the areas where the neovessels permeate to the necrotic core [20]. This may have caused the larger lipid arc and increased lipid length found in this study in patients with NV. The irregular NV from atherosclerotic plaques was highly immature, leaky, and similar to those found in cancers [21], thus, allowing the influx of leukocytes in the plaque, as well as increasing the likelihood of intraplaque hemorrhage. Among the leukocytes, macrophages, for instance, can accumulate lipids and become static foam cells, which produce cytokines in favor of the local inflammatory burden [22]. A high density of neovessels is often accompanied by intraplaque hemorrhages within the atherosclerotic plaque. Intraplaque hemorrhages elicit local cholesterol crystal formation, as well as protease activation [23]. While the activation of various proteases may degrade the fibrous cap, thus promoting plaque instability, erosion or rupture [24], cholesterol crystals can disrupt cell membranes and erode the intraplaque neovessels, thus inducing cell damage, vascular leakage, and expansion of a lipid core [25].

Overall, owing to the interactions with inflammation, intraplaque hemorrhages, protease activation, cholesterol crystal, and many other factors, plaque NV is strongly correlated with atherosclerotic plaque progression, instability, and rupture. Unlike previous animal or pathological studies, in this study, we detected the presence of NV in vivo using OCT and serial IVUS examination. Consequently, we uncovered that NV significantly correlated with the benefit attenuation of statins on plaque burden and other IVUS parameters (e.g., PAV, P&M CSA, and plaque volume) related to plaque burden from baseline to 12-month follow-up. This suggests that the presence of NV has a larger influence on fibroatheroma than fibrous plaque. It was reported that neovessel density is higher in lipid-rich inflammatory lesions than in fibrocalcific plaques [26,27], which might partly explain why NV has a stronger influence on fibroatheroma. Moreover, apart from hypoxia, inflammation is no doubt a strong initial trigger for NV [28]. Furthermore, it is obvious that the lipid and lipoproteins in fibroatheroma act as critical initiating event in sparking an inflammatory response [29]. Inflammation and NV tend to feed each other in a vicious cycle. Specifically, in that inflammatory cells in the plaque increase oxygen demand, thereby triggering further NV. In turn, the highly permeable microchannels recruit more inflammatory cells into the plaque [30]. Taking the abovementioned into account, the NV in fibroatheroma may be more irregular and immature. Ultimately, there appears to be an inflammation-driven pathological angiogenesis in fibroatheroma. In other words, intra-plaque NV accelerates plaque expansion. This supports the notion that intraplaque NV demonstrates a stronger influence on fibroatheroma.

OCT detected microchannels were reported as possible predictors of plaque progression in our previous study [8]. However, no study to date has applied serial IVUS imaging of 12-month follow-up in combination with baseline OCT findings to discuss the relationship between NV and plaque progression. Additionally, the current study found that the NV in fibroatheroma contributes more to attenuate the benefit of statin therapy than in fibrous plaques. Growing evidence [31] suggests that NV may be suggesting it as an outstanding target for anti-atherosclerotic therapy. However, some agents against NV including bevacizumab, an anti-VEGF monoclonal antibody, as well as thalidomide have been shown to be unsuccessful as treatment options owing to serious side effects [32,33]. New atherosclerosis agents that effectively and safely target NV are desperately needed. Considering the different effect of intra-plaque NV on fibroatheroma and fibrous plaque, a more targeted strategy focused on inflammation-driven pathological angiogenesis, while preserving physiological angiogenesis, may be effective. C-C motif chemokines (CC-chemokines) play a critical role in inflammation-driven angiogenesis, meanwhile, they have little involvement in ischemia-mediated angiogenesis [34]. Therefore, CC-chemokines may be ideal candidates to break inflammation-driven pathological angiogenesis in fibroatheroma. Strategies targeting miRNA also have therapeutic potential to tackle NV dysfunction and promote maturation, including miR-126, miR-221, miR-222, and miR-92a [30].

There are several limitations in this study. First, this was a single-center study with a modest number of patients with CAD. Second, we did not study left main lesions, side branches, or distal segments. Third, culprit plaques were not assessed in the current study. Forth, 32 out of 150 patients (21%) were excluded from the analysis. Finally, there was no 12-month follow-up OCT data corresponding to baseline OCT findings.

4.1. Conclusions

In conclusion, this OCT and serial IVUS study demonstrated that non-culprit plaques in CAD patients with NV exhibited more vulnerable OCT characteristics and might significantly correlated with the benefit attenuation of statins on plaque burden and other IVUS parameters related to plaque burden. Additionally, intraplaque NV could predict a high risk of plaque progression, despite statin therapy. Originally, we found that NV in fibroatheroma might contribute more to attenuate the benefit of statins than in fibrous plaques. This study may provide a new basis for the development of anti-angiogenic strategies to prevent atherosclerotic plaque progression and instability.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Conceptualization, J.W.T. and B.Y.; methodology, X.G.; software, X.D.W.; formal analysis, Z.L.X.; investigation, X.Y.W.; data curation, X.L.L.; writing—original draft preparation, X.X.L.; writing—review and editing, X.X.L. and C.B.S.; visualization, X.X.L., C.B.S. and J.W.T.; supervision, J.W.T. and B.Y.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.912.

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