Thin-Cap Fibroatheroma Rather Than Any Lipid Plaques Increases the Risk of Cardiovascular Events in Diabetic Patients: Insights From the COMBINE OCT–FFR Trial

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BACKGROUND: Autopsy studies have established that thin-cap fibroatheromas (TCFAs) are the most frequent cause of fatal coronary events. In living patients, optical coherence tomography (OCT) has sufficient resolution to accurately differentiate TCFA from thick-cap fibroatheroma (ThCFA) and not lipid rich plaque (non-LRP). However, the impact of OCT-detected plaque phenotype of nonischemic lesions on future adverse events remains unknown. Therefore, we studied the natural history of OCT-detected TCFA, ThCFA, and non-LRP in patients enrolled in the prospective multicenter COMBINE FFR-OCT trial (Combined Optical Coherence Tomography Morphologic and Fractional Flow Reserve Hemodynamic Assessment of Non-Culprit Lesions to Better Predict Adverse Event Outcomes in Diabetes Mellitus Patients).

METHODS: In the COMBINE FFR-OCT trial, patients with diabetes and ≥1 lesion with a fractional flow reserve >0.80 underwent OCT evaluation and were clinically followed for 18 months. A composite primary end point of cardiac death, target vessel-related myocardial infarction, target-lesion revascularization, and hospitalization for unstable angina was evaluated in relation to OCT-based plaque morphology.

RESULTS: A total of 390 patients (age 67.5±9 years; 63% male) with ≥1 nonischemic lesions underwent OCT evaluation: 284 (73%) had ≥1 LRP and 106 (27%) non-LRP lesions. Among LRP patients, 98 (34.5%) had ≥1 TCFA. The primary end point occurred in 7% of LRP patients compared with 1.9% of non-LRP patients (7.0% versus 1.9%; hazard ratio [HR], 3.9 [95% CI, 0.9–16.5]; *P*=0.068; log rank-*P*=0.049). However, within LRP patients, TCFA patients had a much higher risk for primary end point compared with ThCFA (13.3% versus 3.8%; HR, 3.8 [95% CI, 1.5–9.5]; *P*<0.01), and to non-LRP patients (13.3% versus 1.9%; HR, 7.7 [95% CI, 1.7–33.9]; *P*<0.01), whereas ThCFA patients had risk similar to non-LRP patients (3.8% versus 1.9%; HR, 2.0 [95% CI, 0.42–9.7]; *P*=0.38). Multivariable analyses identified TCFA as the strongest independent predictor of primary end point (HR, 6.79 [95% CI, 1.50–30.72]; *P*=0.013).

CONCLUSIONS: Among diabetes patients with fractional flow reserve-negative lesions, patients carrying TCFA lesions represent only one-third of LRP patients and are associated with a high risk of future events while patients carrying LRP-ThCFA and non-LRP lesions portend benign outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02989740.

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Key Words: coronary artery disease ■ coronary stenosis ■ diabetes ■ fractional flow reserve, myocardial ■ myocardial infarction ■ plaque, atherosclerotic ■ tomography, optical coherence

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WHAT IS KNOWN

- Optical coherence tomography has sufficient resolution to differentiate thin-cap fibroatheroma from thick-cap fibroatheroma and non lipid rich plaque (LRP); however, the impact of optical coherence tomography-detected plaque phenotype of non-ischemic lesions on future adverse events remains unknown.

WHAT THE STUDY ADDS

- Thin-cap fibroatheroma lesions are associated with a much higher risk of future cardiovascular events compared with patients with thick-cap fibroatheroma (13.3% versus 3.8%, $P<0.01$) and non-LRP (13.3% versus 1.9%, $P<0.01$) which portend similar and benign outcomes (3.8% versus 1.9%, $P=0.38$).
- Not all LRP, but only LRP-thin-cap fibroatheroma patients, which represent only 1/3 of LRP patients, are at high risk of future adverse clinical events.
- This study identifies within the LRP patients a new group of patients (thin-cap fibroatheroma patients) that despite having only angiographically intermediate and nonischemic lesions are at high risk for future adverse clinical events and therefore might benefit from novel and more aggressive treatment strategies.
- The use of this optical coherence tomography criteria allows to narrow down substantially the number of patients who might benefit from novel approaches and pave the way to assess the value of tailored therapeutic strategies in these high-risk patients.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
FFR	fractional flow reserve
HR	hazard ratio
IVUS	intravascular ultrasound
LRP	lipid-rich plaque
MACE	major cardiovascular events
OCT	optical coherence tomography
TCFA	thin-cap fibroatheroma
ThCFA	thick-cap fibroatheroma

The impact of plaque morphology on future adverse events, particularly in lesions with baseline intermediate stenosis, has been a matter of debate during the last decades. Intravascular ultrasound (IVUS), IVUS virtual histology as well as IVUS near-infrared spectroscopy studies[1–4] have consistently shown that lipid-rich plaques (LRP) have worse clinical outcomes than non-LRP lesions. Interestingly, within LRP, IVUS virtual histology studies showed that thin-cap fibroatheromas (TCFAs) have worse outcomes than thick-cap fibroatheromas (ThCFA).[1,2] However, as IVUS virtual histology lacks sufficient resolution to truly detect TCFA, it could not accurately distinguish between TCFA and ThCFA. Another limitation of these studies was that ischemia detection was not always performed, and therefore, it was difficult to conclude whether the observed events during follow-up were a consequence of myocardial ischemia or related to high-risk lesion morphology.

Conversely, optical coherence tomography (OCT), another intracoronary imaging modality that has become widely available in the last decade, has a resolution of ≈15 µm.[5] Consequently, OCT can clearly differentiate between the 2 distinct LRP morphologies of TCFA and ThCFA. The COMBINE OCT-FFR trial (Combined Optical Coherence Tomography Morphologic and Fractional Flow Reserve Hemodynamic Assessment of Non-Culprit Lesions to Better Predict Adverse Event Outcomes in Diabetes Mellitus Patients)[6] was one of the first natural history study in diabetes patients that reported the impact of OCT-assessed plaque morphology on future adverse clinical events. Importantly, this trial is the only study to date to assess adverse events that derived from lesions that were nonischemic, that is, with negative fractional flow reserve (FFR) at baseline. As a consequence, the impact of plaque morphology on future adverse events could be clearly isolated from that of ischemia. Therefore, in this analysis, we studied the impact of different plaque types (ie, TCFA, ThCFA, and non-LRP) on the risk of experiencing future adverse events in the pool of diabetes patients of the COMBINE OCT-FFR trial.

METHODS

The COMBINE OCT-FFR (NCT02989740) trial is a prospective, double-blind, international, natural history study that was conducted in 14 sites across 7 countries. The design of the COMBINE OCT-FFR trial[7] and the main results have been published previously.[6] In brief, the trial is a multi-center, prospective, natural history study which combined hemodynamic (by FFR) and morphological (by OCT) assessment of nonischemic lesions to better predict adverse events in patients with diabetes. The study population consisted of all patients with diabetes who underwent angiography for any indication and had at least one de-novo native coronary lesion with a diameter stenosis of 40% to 80% by visual assessment (other than the culprit lesion, if patients presented with myocardial infarction).

The full inclusion and exclusion criteria are presented in the Supplemental Material. In patients who presented with acute coronary syndrome (ACS), the culprit lesion was revascularized first. Then all remaining intermediate lesions underwent FFR assessment. Patients with exclusively FFR-positive lesions (ie, FFR ≤0.80) underwent revascularization of these lesions. Yet patients with at least one FFR-negative target lesion (ie, FFR >0.80) underwent OCT assessment and represent the study population of this analysis.

For the present analysis, patients with FFR-negative lesions were classified according to the OCT core-lab analysis into patients with (at least one) LRP or non-LRP. Moreover, LRP

patients where further classified as patients having TCFA or ThCFA. OCT core-lab findings were blinded to patients, operators, and the team that performed the clinical follow-up.

The study was approved from the national regulatory agencies and the institutional review boards of all the participating centers. All patients gave informed consent to participate. Requests for data collected for the study can be made to the corresponding author and will be considered by the steering group on an individual basis.

OCT Analysis

A summary of OCT definitions and analysis methodology has been reported previously.[6,7] The OCT analysis was based on a consensus document about acquisition, measurement, and reporting of OCT studies, reported by Tearney et al.[8] OCT image analysis scrutinized serial cross-sectional images of the vessel in every frame of OCT pullback, starting 5 mm distal to and ending 5 mm proximal of the OCT-defined lesion border. Signal-rich homogeneous plaques were classified as fibrous, signal-poor regions with diffuse borders as LRP, and signal-poor regions with well-defined borders as calcified plaques. TCFA was defined as any lesion with predominantly LRP, the thinnest part of the atheroma cap ≤65 µm, and a lipid arc of >90°. ThCFA was defined as a LRP plaque with the thinnest part of the atheroma cap >65 µm. Calcific nodule was defined as a single or multiple regions of calcium that protrude into the lumen.

The inter-rater agreement analysis for OCT-defined TCFA identification was κ=0.81 (95% CI, 0.70–0.97), and the intra-rater agreement was κ=0.78 (95% CI, 0.61–0.92). The analysis was performed using the CAAS Intravascular 2.0 software, (Pie Medical BV, the Netherlands).

End Points

The primary end point, a composite of cardiac death, target vessel related myocardial infarction, target-lesion revascularization, or hospitalization due to unstable angina at 18 months, was assessed in relation to the OCT-detected plaque morphology. Cardiac death and unstable angina events that could not clearly be related to events originating from nontarget lesions were considered as target lesion-related. A complete list of definitions can be found in the Supplemental Material. All adverse events were adjudicated by an independent clinical event committee, with members who were blinded to the results of the OCT analysis.

Statistical Analysis

Categorical variables were expressed as absolute frequencies and percentages, while continuous variables were given as mean±SD or median (interquartile range), as appropriate. The categorical data were compared using Fischer exact test or χ^2 test. Normally distributed data were compared using Student *t* test (or ANOVA for >2 groups with post hoc Tukey HSD method), and non-normally distributed data were compared using Mann-Whitney test (or Kruskal-Wallis test for >2 groups with post hoc Steel Dwass method). Post hoc comparisons for categorical variables were performed using false discovery rate adjustment to account for multiple comparisons.

The cumulative incidence of the primary and secondary end points, in relation to OCT-detected plaque morphology on a patient level, was estimated using the Kaplan–Meier method with at risk table and log-rank test. Cox proportional-hazards models were used to calculate the hazard ratios (HRs) and respective 95% CIs. All variables deemed clinically important or that showed *P* values <0.10 in simple cox regression were included in the multiple cox regression model. The final model was obtained using a stepwise approach with minimization of Bayesian Information Criterion as target and adjusted for statin usage at discharge. Model validation was performed using bootstrap resampling; proportional hazard assumption was tested by examination of Schoenfeld residuals. *P* values <0.05 were considered statistically significant. All statistical analyses were performed in R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria, 2021) with package rms version 6.2-0 and survminer version 0.4.9.

RESULTS

Study Population

From a total of 550 diabetes patients, 390 patients had ≥1 nonischemic (FFR >0.80) lesion and underwent OCT evaluation. Mean age of the population was 67.5±9 years, 63% were male, and the mean FFR value was 0.88±0.05. 284 patients had ≥1 LRP while 106 had only non-LRP (Table S1). Among LRP patients, 98 (34.5%) had ≥1 TCFA. There were no significant differences in baseline clinical characteristics between the 3 groups (TCFA, ThCFA, and non-LRP) with the only exception being statin therapy (Table 1).

OCT Analysis

The quantitative and qualitative OCT findings are showed in Table 2. The quantitative analysis showed between the 3 groups significant differences in minimal lumen area (*P*=0.025), percentage of the stenotic area (*P*=0.032), and lesion length (*P*<0.01). These differences were more pronounced between the non-LRP and TCFA groups, while between the non-LRP and ThCFA no significant difference was found. Notably, lesion length was longer in the TCFA than in ThCFA (Table 2). Conversely, the qualitative OCT findings showed several between-group differences. Interestingly, there were more calcified noduli in the non-LRP plaque, while there were more macrophages and cholesterol clefts in the LRP, particularly LRP-TCFA (Table 2).

Clinical Outcomes

The primary composite end point occurred more frequently in LRP than in non-LRP patients (7.0% versus 1.9%; HR, 3.9 [95% CI, 0.9–16.5]; *P*=0.068; log rank *P*=0.049; Figure 1). Among all LRP patients, the primary end point was predominantly driven by the TCFA group: TCFA versus ThCFA, (13.3% versus 3.8%; HR, 3.8 [95% CI, 1.5–9.5]; *P*<0.01; Figure 2 and Table 3). Similarly, TCFA patients had much higher risk for reaching the primary end point than non-LRP patients (13.3% versus 1.9%; HR, 7.7 [95% CI, 1.7–33.9]; *P*<0.01). Between

Table 1. Patient Characteristics

Variables	Non-LRP, n=106	LRP-ThCFA, n=186	LRP-TCFA, n=98	*P* value
Median age (IQR), y	69 (63–74)	67 (62–74)	70 (59–76)	0.424
Median BMI (IQR)*	29 (26–32)	29 (27–32)	29 (26–33)	0.999
Male sex, n (%)	62 (58.5)	118 (63.4)	65 (66.3)	0.499
Insulin dependent diabetes, n (%)	34 (32.1)	66 (35.5)	35 (35.7)	0.811
Oral antidiabetics, n (%)	82 (77.4)	158 (85.0)	82 (83.7)	0.258
Current smoking, n (%)	21 (19.8)	32 (18.1)	22 (22.4)	0.686
Previous smoking, n (%)	23 (30.3)	41 (31.5)	23 (34.8)	0.835
Hypercholesterolemia, n (%)	62 (58.5)	109 (58.9)	61 (62.2)	0.829
Hypertension, n (%)	81 (77.1)	133 (71.9)	75 (76.5)	0.533
Previous ACS, n (%)	36 (34.0)	61 (32.8)	42 (42.9)	0.227
Previous PCI, n (%)	38 (35.9)	65 (35.0)	41 (41.8)	0.505
Previous CABG, n (%)	1 (0.9)	7 (3.8)	4 (4.1)	0.249
Previous CVA, n (%)	10 (9.4)	10 (5.4)	12 (12.2)	0.117
SCD at presentation, n (%)	77 (72.6)	138 (74.2)	77 (78.6)	0.783
ACS at presentation, n (%)	29 (27.4)	48 (25.8)	21 (21.4)	0.783
Median total cholesterol (IQR), mg/mL	154 (135–193)	154 (135–193)	161 (142–189)	0.325
Median LDL cholesterol (IQR)	78 (62–100)	84 (61–116)	88 (69–123)	0.381
Median triglycerides (IQR), mg/mL	155 (113–210)	142 (100–252)	168 (120–242)	0.485
Median hemoglobin A1c (IQR), %	7.0 (6.6–7.9)	7.3 (6.7–7.9)	7.3 (6.7–7.9)	0.378
Aspirin	77 (72.64%)	144 (77.42%)	74 (75.51%)	0.658
P2Y12 antagonist	26 (24.53%)	57 (30.65%)	36 (36.73%)	0.167
Oral anticoagulation	15 (14.15%)	31 (16.67%)	12 (12.24%)	0.591
Beta-blocker	69 (65.09%)	126 (67.74%)	67 (68.37%)	0.862
ACE inhibitor	41 (38.68%)	81 (43.55%)	35 (35.71%)	0.408
ARB	34 (32.08%)	49 (26.34%)	19 (19.39%)	0.115
Statins†	92 (86.79%)	148 (79.57%)	67 (68.37%)	0.006
Oral antidiabetics	82 (77.36%)	158 (84.95%)	82 (83.67%)	0.258
Insulin treatment	34 (32.08%)	66 (35.48%)	35 (35.71%)	0.811

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker, BMI, body mass index; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; IQR, interquartile range; LDL, low-density lipoprotein; LRP, lipid rich plaque; PCI, percutaneous coronary interventions; SCD, stable coronary disease; TCFA, thin-cap fibroatheroma; and ThCFA thick-cap fibroatheroma.

*BMI is the weight in kilograms divided by the square of the height in meters.

†LRP-TCFA versus non-LRP *P*=0.008.

ThCFA and non-LRP patients, there was no significant difference in the rate of the primary end point (3.8% versus 1.9%; HR, 2.0 [95% CI, 0.42–9.7]; *P*=0.38; Table 3).

Furthermore, a (secondary) composite end point of cardiac death, target vessel related myocardial infarction, or target-lesion revascularization occurred more frequently in LRP as compared with non-LRP patients (5.6% versus 0%, *P*<0.01), and its rate was higher in TCFA than in ThCFA (11.2% versus 2.7%, *P*<0.01). Again, patients with TCFA had much higher adverse event risk than those with ThCFA (HR, 4.4 [95% CI, 1.5–12.8]; *P*<0.01; Table 3).

Multivariable analysis identified TCFA (HR, 6.79 [95% CI, 1.50–30.72]; *P*=0.013), ACS at presentation (HR, 3.00 [95% CI, 1.29–6.97]; *P*=0.011), and % area stenosis at the minimal lumen area (HR, 1.55 [95% CI, 1.01–2.38]; *P*=0.047) to be independent predictors of the primary clinical end point (Table 4).

Lipid arc was not a predictor of MACE in LRP patients (HR per 10° increase 1.04; [95% CI, 0.98–1.1]; *P*=0.17). As a sensitivity analysis in LRP patients, final multivariable model was adjusted for lipid arc and revealed that TCFA compared with ThCFA (HR, 3.8 [95% CI, 1.4–10.3]; *P*<0.01,), and % area stenosis at the minimal lumen area (HR, 1.7 [95% CI, 1.1–2.8]; *P*=0.02) were still independent predictors of the primary clinical end point, ACS presentation showed a trend to be a predictor (HR, 2.4 [95% CI, 0.99–5.99]; *P*=0.053), while lipid arc was not (HR per 10° increase 0.99 [95% CI, 0.9–1.1]; *P*=0.8).

DISCUSSION

The current analysis is the largest prospective study with OCT-assessment of plaque phenotype that investigated the potential incremental value of an

Table 2. Lesion Level Quantitative and Qualitative OCT Analyses

Variables	Group 1 Non-LRP, n=140	Group 2 LRP-ThCFA, n=201	Group 3 LRP-TCFA, n=104	*P* value	*P* value, 1 vs 2	*P* value, 1 vs 3	*P* value, 2 vs 3
Quantitative OCT analysis							
MLA (IQR), mm^2	1.9 (1.6–2.3)	1.8 (1.6–2.1)	1.8 (1.5–2)	0.025	0.058	0.042	0.86
% area stenosis (IQR), %	60 (52–70)	63 (55–71)	65 (57–73)	0.032	0.153	0.031	0.542
Lesion length (IQR), mm	19.1 (12.43–28.1)	21.1 (14.1–30.1)	27.65 (18.1–36.1)	<0.001	0.563	<0.001	0.002
Proximal RLD (IQR), mm	3.3 (2.9–3.88)	3.3 (2.9–3.7)	3.4 (3.1–3.8)	0.209	0.358	0.992	0.252
Distal RLD (IQR), mm	2.8 (2.4–3.4)	2.8 (2.5–3.2)	2.7 (2.5–3.2)	0.905	0.999	0.942	0.892
Qualitative OCT analysis							
Fibrous cap thickness (IQR), µm	…	150 (110–220)	60 (60–60)	…	…	…	…
Lipid arc (IQR), °	…	170 (127–215)	241 (193–288)	<0.001	…	…	…
Calcification present, n (%)	131 (93.57%)	161 (80.10%)	91 (87.50%)	0.001	0.003	0.474	0.435
Calcium arc (IQR), °	204 (108–290)	124 (76–209.5)	112 (80–192)	<0.001	<0.001	<0.001	0.939
Calcific nodule, n (%)	89 (63.57%)	68 (33.83%)	36 (34.62%)	<0.001	<0.001	<0.001	0.999
Cholesterol clefts, n (%)	25 (17.86%)	124 (62.63%)	75 (72.82%)	<0.001	<0.001	<0.001	0.3
Neovascularization, n (%)	85 (60.71%)	147 (73.13%)	88 (84.62%)	<0.001	0.064	<0.001	0.103
Macrophage infiltration, n (%)	42 (30.00%)	115 (57.21%)	72 (69.90%)	<0.001	<0.001	<0.001	0.128

IQR indicates interquartile range; LRP, lipid rich plaque; MLA, minimal lumen area; OCT, optical coherence tomography; RLD, reference lumen diameter; TCFA, thin-cap fibroatheroma; and ThCFA, thick-cap fibroatheroma.

OCT evaluation of plaque morphology in patients with intermediate but otherwise nonischemic lesions. The identification of coronary plaques at risk of future cardiovascular events remains a major challenge in cardiovascular research, and this analysis addressed the important question whether LRP-TCFA rather than any LRP increases the risk of major cardiovascular events (MACE).

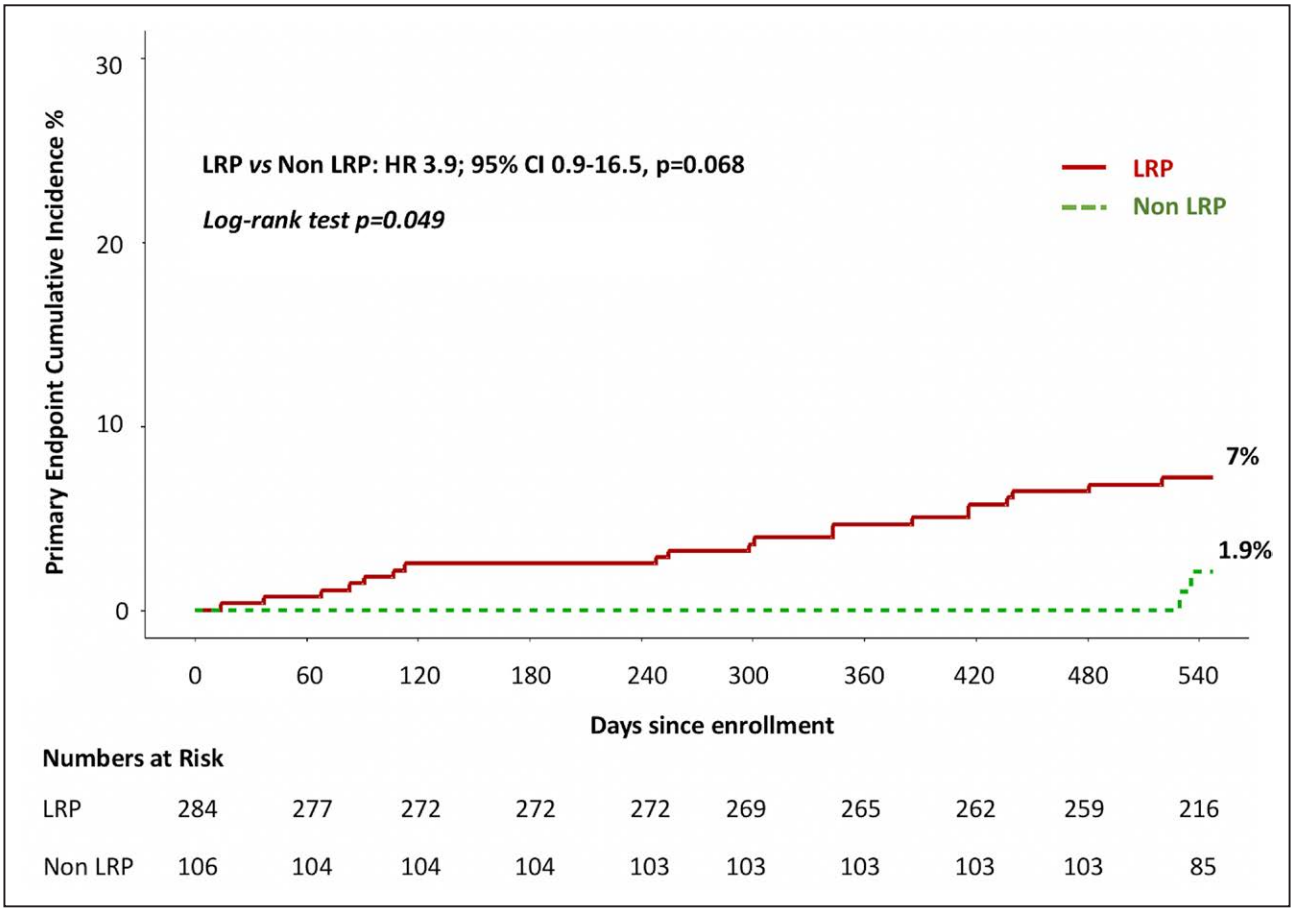

Figure 1. Kaplan Meier curves for primary end point in lipid-rich vs non-lipid-rich plaque (LRP) groups.

HR indicates hazard ratio.

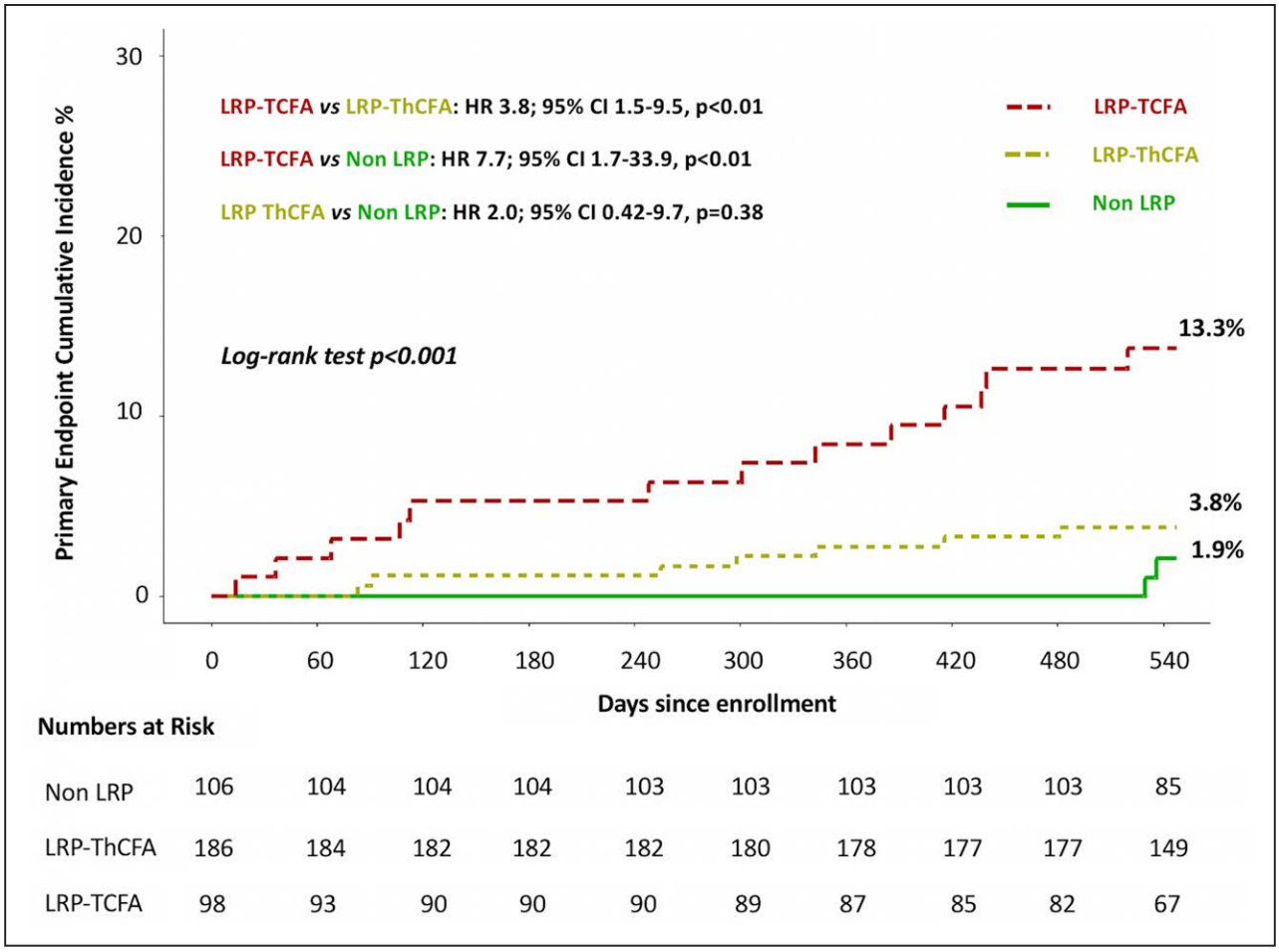

Figure 2. Kaplan Meier curves for primary end point in thin-cap fibroatheroma (TCFA) vs thick-cap fibroatheroma (ThCFA) vs non-lipid-rich plaque (LRP) groups.
HR indicates hazard ratio.

The main findings of the present study are the following: (1) Patients with LRP have a higher MACE rate than patients without LRP lesions. (2) However, among all LRP patients, adverse events were clustered in the subpopulation of patients with LRP-TCFA, which represent only 1/3 of all LRP patients. (3) Patients with LRP-TCFA showed a 4-fold higher MACE rate as compared with the remaining 2/3 of LRP patients (who had LRP-ThCFA plaques). (4) The LRP subpopulation of patients with LRP-ThCFA had a risk of MACE that was similar to patients without LRP.

LRP Versus Non-LRP Comparison

Our results further corroborate the findings of 3 previous studies with IVUS near-infrared spectroscopy.[3,4,9] Similarly to our findings, the LRP trial found a 4-fold increase in event risk in lesions with high versus low lipid content.[3] Furthermore, another prospective study with IVUS near-infrared spectroscopy by Oemrawsingh et al[9] also showed a 4-fold higher MACE rate in patients with high versus low lipid plaque content. Finally, in the PROSPECT 2 trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II),[4] the nonculprit lesion event rates for patients with high versus low lipid plaque content lesions in combination with a plaque burden >70% were 7.0% versus 2.2%, which is quite similar to that observed in the present trial.

LRP-TCFA Versus LRP-ThCFA Comparison

Our findings regarding the impact of LRP-TCFA on clinical outcome are also in line with the recent CLIMA study,[10] which reported a HR of 7.5 associated with TCFA lesions. Similarly, another study from Kubo at al[11] identified patients with LRP-TCFA as those with the highest risk for future ACS. Interestingly, in that study LRP-TCFA had also had an incidence of future ACS that was 3-fold higher than in patients with LRP, which is similar to the findings of our current study.

Relevance of the Study Findings

The novelty of our study is based on the fact that (1) we succeeded in confining the actual group at risk of future

Table 3. Major Cardiovascular Events According to Plaque Morphology

Outcomes	Total	Non-LRP	ThCFA	TCFA	*P* value	TCFA vs ThCFA		TCFA vs non-LRP		ThCFA vs non-LRP	
						HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary end point CD, TVR-MI, TLR, UA, n (%)	22 (5.64%)	2 (1.89%)	7 (3.76%)	13 (13.27%)	<0.01	3.8 (1.5–9.5)	<0.01	7.7 (1.7–33.9)	<0.01	2.0 (0.42–9.7)	0.38
CD, TVR-MI, TLR, n (%)	16 (4.10%)	0	5 (2.69%)	11 (11.22%)	<0.01	4.4 (1.5–12.8)	<0.01	…	…	…	…
CD, TVR-MI, UA, n (%)	16 (4.10%)	2 (1.89%)	4 (2.15%)	10 (10.20%)	<0.01	5.1 (1.6–16.1)	<0.01	5.8 (1.3–26.4)	0.02	1.1 (0.2–6.2)	0.88
CD, n (%)	1 (0.26%)	0	1 (0.54%)	0	…	…	…	…	…	…	…
TVR-MI, n (%)	4 (1.03%)	0	0	4 (4.08%)	…	…	…	…	…	…	…
TLR, n (%)	15 (3.85%)	0	4 (2.15%)	11 (11.22%)	<0.01	5.5 (1.77–17.4)	<0.01	…	…	…	…
UA, n (%)	11 (2.82%)	2 (1.89%)	3 (1.61%)	6 (6.12%)	0.11	4.0 (0.997–15.9)	0.051	3.4 (0.7–17.0)	0.13	0.9 (0.1–5.1)	0.87

CD indicates cardiac death; HR, hazard ratio; LRP, lipid rich plaque; TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma; TLR, target-lesion revascularization; TVR-MI, target vessel related myocardial infarction; and UA, hospitalization due to unstable angina.

Table 4. Multivariable Analysis for Primary End Point

Variables	HR	95% CI	*P* value
ThCFA	1.78	0.37–8.62	0.47
TCFA	6.79	1.50–30.72	0.013
ACS presentation	3.00	1.29–6.97	0.011
Statin at discharge	0.69	0.27–1.80	0.452
% area stenosis at minimal lumen area	1.55	1.01–2.38	0.047

ACS indicates acute coronary syndrome, HR, hazard ratio; TCFA, thin-cap fibroatheroma; and ThCFA, thick-cap fibroatheroma.

adverse events (LRP-TCFA patients) to only a third of all patients with LRP and (2) we excluded a potential role of ischemia on future adverse events by studying lesions that were nonischemic, that is, FFR-negative at baseline.

The general clinical relevance of this approach and our study findings is that it brings in evidence of a newly identified group of patients that, despite optimal medical treatment, are at high risk for future adverse clinical events. Typically, these nonischemic LRP-TCFA lesions do not undergo coronary revascularization according to current clinical practice (as they are not ischemic). Nevertheless, as shown in the present and previous studies[2,10] contemporary medical therapies actually fail to prevent future adverse events in a considerable number of these patients. Considering the high risk this population carries, novel therapeutic strategies should, therefore, be contemplated. While currently aggressive systemic medical treatment with novel more potent cholesterol-lowering drugs is the most appropriate approach in these patients, yet, as of now, large-scale OCT studies about the effectivity of these drugs in stabilizing plaques and improving lesion composition are scarce.[12,13]

Theoretically, considering the low MACE rate of OCT-guided focal stenting as compared with the high MACE rate under medical treatment, future clinical trials might assess even the usefulness of plaque sealing by focal percutaneous coronary treatment. A similar strategy was already tested in the PROSPECT-ABSORB trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II Combined With a Randomized, Controlled, Intervention),[14] using guidance by intracoronary imaging with IVUS near-infrared spectroscopy. Our present OCT-based approach, confines the vulnerable plaque subgroup of patients to a quarter of the ischemia-free patients with angiographically intermediate lesions and to about one third of all patients with LRP.

As mentioned, OCT can be used to identify patients who might benefit from a novel treatment, and the use of stringent OCT-based criteria to guide potential treatment will reduce the number needed to treat by identifying and excluding patients in whom treatment benefit is unlikely. Furthermore, the fact that OCT guidance during percutaneous treatment is believed to improve clinical outcome makes the suggested approach even more appealing.[15] While sealing nonischemic LRP-TCFA lesions with current generation drug-eluting

stents is not recommended in current international guidelines, novel stents, scaffolds, or other therapeutic options may emerge for this indication. Then, the percutaneous OCT-guided approach for treating nonischemic LRP-TCFA lesions may represent an appealing novel strategy for assessing the safety and clinical efficacy of such therapeutic options in the clinical setting.

Limitations

This study is based on a sub-group analysis of the COMBINE OCT-FFR trial, and findings should be considered hypothesis generating. Nevertheless, the present analysis with OCT is the largest to date in a diabetic patient cohort. Yet, absolute numbers remain limited. These findings could not be extrapolated to nondiabetes patients, however, previous studies have shown that TCFA is a driver of events even in nondiabetes patients.[16] Further studies should evaluate the impact of OCT detected TCFA in nonischemic lesions of nondiabetes patients.

The COMBINE OCT-FFR trial reflects a real-world clinical scenario, and the identification of intermediate angiographic lesions was based on visual assessment; nevertheless, OCT analysis confirmed that the percent area stenosis of these lesions was intermediate. While multivariable analysis did not show an impact of statin prescription at discharge on clinical outcome, the potential role of a stricter lipid or glycemic control on future adverse events is not deductible from our study.

Conclusions

Among diabetes patients with nonischemic lesions, LRP-TCFA lesions are associated with a much higher risk of future events as compared with patients with either LRP-ThCFA or non-LRP lesions who portend more benign outcomes. OCT assessment shows that the LRP-TCFA patients represent only one third of the total LRP patients and, therefore, allows to narrow down substantially the number of patients who might benefit from a more aggressive novel treatment. Future studies should assess the value of a tailored therapeutic approach of combined OCT-guided focal percutaneous treatment and optimal medical therapy, as appropriate.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Table S1

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