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ORIGINAL PAPER

Morphological characteristics of lesions with thin cap fibroatheroma—a substudy from the COMBINE (OCT-FFR) trial

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Aims

To study if any qualitative or quantitative optical coherence tomography (OCT) variables in combination with thin cap fibroatheroma (TCFA) patients could improve the identification of lesions at risk for future major adverse cardiac events (MACEs).

Methods and results

From the 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: COMBINE (OCT-FFR) trial database (NCT02989740), we performed a detailed assessment OCT qualitative and quantitative variables in TCFA carrying diabetes mellitus (DM) patients with vs. without MACE during follow-up. MACEs were defined as a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization, and hospitalization for unstable angina. From the 390 fractional flow reserve (FFR)-negative DM patients, 98 (25.2%) had ≥1 OCT-detected TCFA, of which 13 (13.3%) had MACE and 85 (86.7%) were event-free (non-MACE). The baseline characteristics were similar between both groups; however, a smaller minimal lumen area (MLA) and lower mean FFR value were observed in MACE group (1.80 *vs.* 2.50 mm^2, $P = 0.01$, and 0.85 *vs.* 0.89, $P = 0.02$, respectively). Prevalence of healed plaque (HP) was higher in the MACE group (53.85 *vs.* 21.18%, $P = 0.01$). TCFA were predominantly located proximal to the MLA. TCFA area was smaller in the MACE group, while no difference was observed regarding the lesion area.

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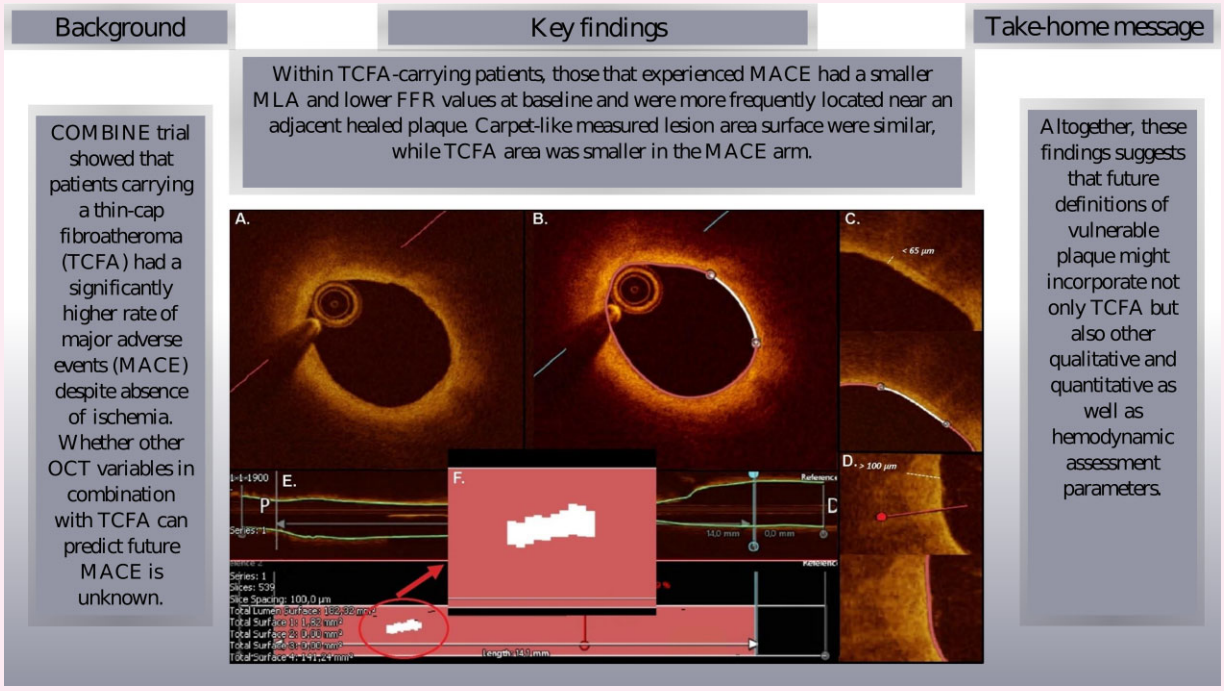
Conclusion Within TCFA carrying patients, a smaller MLA, lower FFR values, and TCFA location adjacent to a HP were associated with future MACE. Carpet-like measured lesion area surface was similar, while the TCFA area was smaller in the MACE arm, and predominantly located proximal to the MLA.

Graphical Abstract



Keywords optical coherence tomography • fractional flow reserve • thin cap fibroatheroma lesion • major adverse cardiac events

Introduction

Ischaemia-guided revascularization is at the present considered as the gold standard strategy in the catheterization laboratory. However, recent large randomized trials have shown that ischaemia-guided revascularization might not be sufficient to reduce future adverse events.[1,2,3]

Conversely, different prospective studies have emphasized the impact of optical coherence tomography (OCT) thin cap fibroatheroma (TCFA) on the major adverse cardiac events (MACEs) outcomes.[4,5] Another large prospective natural history study, the COMBINE (OCT-FFR) trial, showed that TCFA lesions are drivers of future MACE even among fractional flow reserve (FFR) negative lesions.[6] Therefore, for the first time, this study showed that plaque morphology is also an important predictor of MACE independently from ischaemia. Whether other plaque characteristics evaluated by OCT in combination with TCFA detection could improve the prediction of future MACE remains not adequately studied.

Therefore, in the current study, we performed a detailed analysis of OCT and assessed qualitative and quantitative morphological characteristics of TCFA lesions among patients with vs. without MACE during the follow-up from the COMBINE (OCT-FFR) trial.

Methods

Study design and study population

The rationale and design of the COMBINE (OCT-FFR) trial have been published previously.[7] This study was approved by the Ethics Committee. In brief, diabetes mellitus (DM) patients with any clinical presentation with an intermediate or severe angiographic stenosis underwent FFR assessment. Revascularization was performed in all FFR-positive lesions (FFR <0.80), while in patients with FFR-negative lesions (FFR > 0.80), additional OCT imaging was performed. Based on OCT findings, the FFR-negative patients were further divided into patients with or without TCFA. All FFR-negative patients were treated medically and were clinically followed for 18 months. The primary endpoint was target lesion-related composite of MACE defined as cardiac death, target vessel myocardial infarction (TV-MI), clinically driven target lesion revascularization (CD-TLR), or hospitalization due to unstable or progressive angina.

Target lesion was defined as lesions with intermediate stenosis where FFR and OCT assessment was performed. For the current analysis, only FFR-negative patients with ≥ 1 TCFA lesions were studied and further divided into two groups based on the presence or absence of MACE during the follow-up. The impact of the FFR value, as well as qualitative and quantitative OCT baseline characteristics on future MACE were studied.

OCT—quantitative and qualitative analysis

The OCT analysis methods have been previously extensively described.[6] The OCT analysis was based on a consensus document on the acquisition, measurement, and reporting of OCT studies, reported by Tearney *et al.*[8]

In brief, the proximal and distal reference lumen area was calculated as the maximal area 5 mm proximal and distal to the analyzed lesion. Minimal lumen area (MLA) percentage stenosis was estimated based on the proximal and distal references. TCFA was defined as any lesion with a predominantly lipid-rich plaque with a lipid arc of more than 90°, which in the thinnest part of the atheroma cap measures ≤ 65 μm on OCT

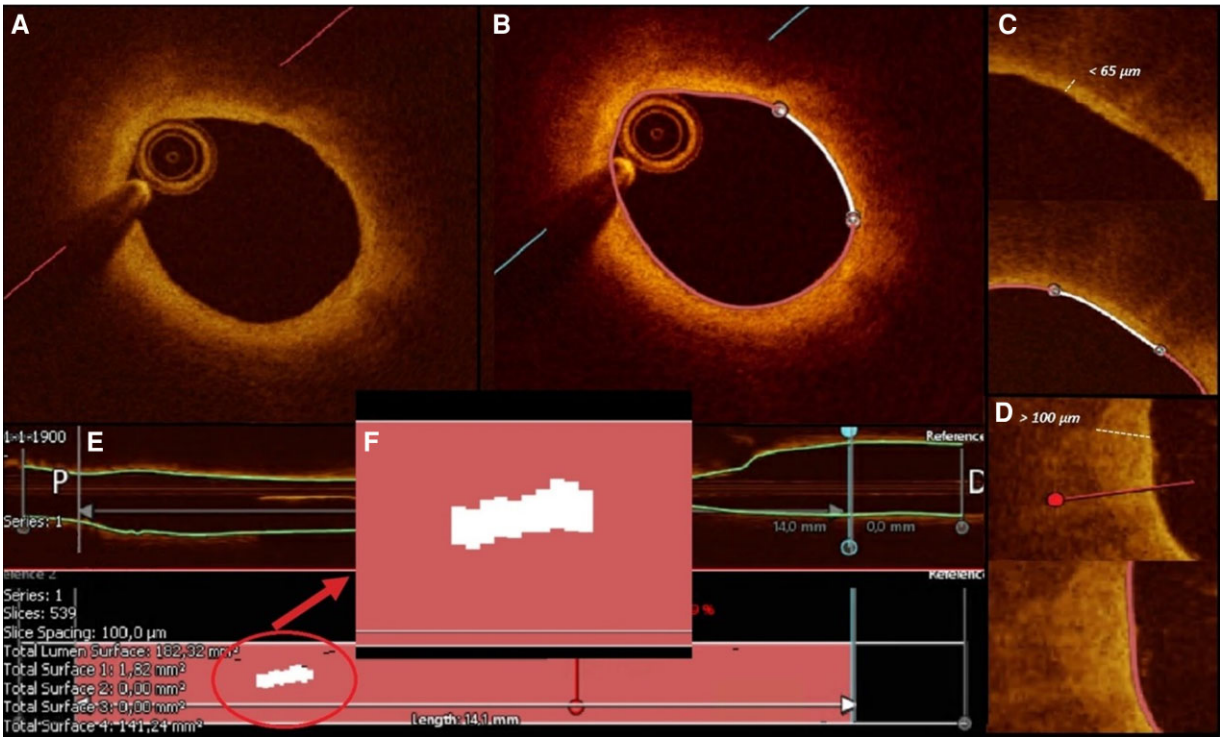


Figure 1 Representative TCFA image. The OCT-assessed cross-section area of TCFA lesion (*A*); same image after applying colour mapping for TCFA (*B*); illustration of white line mapping for—the thin cap fibroatheroma < 65 µm (*C*); pink line representing circumference segments with cap layer > 65 µm (*D*); a carpet-like view of the lesion after analysis was made frame by frame (*E*); zoomed TCFA surface area as analyzed by frame by frame (*F*).

assessment. The calcific nodule was defined as a single or multiple regions of calcium that protrude into the lumen. Plaque rupture (PR) was defined as a discontinuous fibrous cap with a poor signal or a cavity inside the plaque. Plaque erosion (PE) was defined as a thrombotic lesion with an irregular surface without evidence of fibrous cap disruption. Intracoronary thrombus was defined as a mass attached to the luminal surface or floating in the lumen. Healed plaques (HPs) were represented by multiple tissue layers of different optical densities overlying a signal-poor region.[9] Macrophage accumulations were defined as signal-rich, separate, or confluent punctate regions presenting higher intensity of background speckle noise. New microvessels were defined as signal-poor, sharply delineated areas, usually followed in multiple frames and predominantly communicated with the surface of the lumen.[8] Furthermore, we determined the precise localization of TCFA in relation to the lesion frame with the MLA. The OCT analysis was performed using the CAAS software (PIE Medical, Maastricht, The Netherlands).

In addition, in this study, we performed a new OCT analysis method that permits calculating the surface of the TCFA area and the surface of the entire lesion, *Figure 1*. For this purpose, sequential frame-by-frame analysis was performed for each pullback for the entire lesion length. Cross-sectional area, the minimal and maximal diameter of the vessel was measured. Cap thickness was measured manually and then colour-mapped for the entire circumference of the frame. The cap thickness of ≤ 65 µm was coloured white for the entire circumferential length, where the cap thickness remained ≤ 65 µm. The remaining part of the circumference where the cap thickness was more than 65 µm was coloured pink. In this way, using the CAAS intravascular imaging, we were able to create a carpet-like appearance of TCFA. Respectively the lesions and TCFA surface area were calculated. Subsequently, all TCFA surfaces have been individually indexed to the total lesion surface, *Figure 1*.

Statistical analysis

Categorical variables were expressed as number and percentage, while continuous variables were presented as mean ± standard deviation or median with (interquartile range), as appropriate. Differences between the two groups were analyzed using the student's *t*-test adjusted for unequal variances if necessary or the Mann–Whitney *U* test applied for non-normally distributed continuous variables. Categorical variables were compared with Pearson's χ^2 or Fisher's exact test as appropriate. Monte Carlo simulation for Fisher's test using tables of higher dimensions than 2 × 2 was used. *P* values less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed using the R, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria, 2021) and JMP 15.2 (SAS Institute Inc, Cary, NC, USA, 2021).

Results

Patients' population and baseline clinical characteristics

From a total of 390 with a ≥ 1 FFR-negative lesions, 98 patients had ≥ 1 TCFA lesion of which 13 (13.27%) had events during follow-up and were assigned to the MACE group while 85 (86.73%) were event-free and served as control (non-MACE) group. MACEs were composed from 4 TV-MI, 11 CD-TLR, and 6 unstable angina pectoris requiring hospitalization (UAP). From the 11 CD-TLR, 8 (72.3%) were associated with acute coronary syndromes [4 myocardial infarction (MI) and 4 UAP]. In both groups approximately two-thirds of patients were men, and the median age was ∼70 years. No significant differences were observed regarding total cholesterol, triglycerides, and glycosylated hemoglobin between arms. Similarly, the number of insulin

Table 1 Patient's demographic and clinical characteristics

Parameter	MACE n = 13	Non-MACE n = 85	P value
Male—no. (%)	9 (69.2)	56 (65.9)	0.81
Age (IQR)—yr	69.0 (62.0–76.5)	70.00 (57.5–77.0)	0.88
Present smoking—no. (%)	5 (38)	18 (21)	0.17
UA at admission—no. (%)	1 (7.7)	1 (1.2)	0.12
STEMI at admission—no. (%)	5 (38.5)	22 (25.9)	0.34
NSTEMI at admission—no. (%)	1 (7.7)	13 (15.3)	0.47
Total cholesterol > 190 mg/dl—no. (%)	1 (7.7)	9 (10.6)	0.75
Triglycerides > 150 mg/dl—no. (%)	3 (23.1)	29 (34.1)	0.43
HbA1c > 6.0%—no. (%)	5 (38.5)	31 (36.5)	0.89
Hyperlipidaemia[a]—no. (%)	8 (61.5)	55 (64.7)	0.82
Hypertension—no. (%)	9 (69.2)	66 (77.6)	0.51
Previous ACS—no. (%)	7 (53.9)	35 (41.2)	0.39
Previous PCI—no. (%)	9 (69.2)	31 (36.5)	0.03
Previous CABG—no. (%)	0 (0)	4 (4.7)	0.42
Aspirin—no. (%)	12 (92.3)	62 (72.9)	0.13
Insulin dependent—no. (%)	3 (23.1)	32 (37.6)	0.69
Oral anti-diabetic—no. (%)	10 (76.9)	71 (83.5)	0.56
Statin at discharge—no. (%)	9 (69.2)	65 (76.5)	0.57

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; IQR, interquartile range; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention, STEMI, ST-elevation myocardial infarction; UA, unstable angina.
[a]Represents patients known with or receiving treatment for hyperlipidaemia at baseline.

dependent DM patients was not different between arms. Previous percutaneous coronary intervention (PCI) was more frequent in the MACE group (69.2 *vs.* 36.5%, $P = 0.02$). Clinical syndrome at presentation was similar between the two arms. Detailed baseline characteristics of patients are presented in *Table 1*.

FFR findings

On a lesion level analysis FFR values were significantly lower in the MACE group (0.85 ± 0.04 *vs.* 0.89 ± 0.05, $P = 0.02$).

OCT analysis

The results of the quantitative and qualitative OCT analysis are presented in *Tables 2* and *3*. The TCFA's surface was smaller in the MACE group than in the non-MACE group [respectively: 0.19 (0.07–0.33) mm^2 vs. 0.37 (0.18–0.76) mm^2, $P = 0.03$]. Our analysis shows that in both groups, TCFA's were predominantly located proximal to the lesion frame with the MLA, *Table 2*.

The quantitative analysis presented in *Table 3*, showed a similar lesion length between the two arms but a significantly lower MLA and minimal lumen diameter (MLD) value in the MACE arm [respectively: 1.80 (1.30–2.30) mm^2vs. 2.40 (1.80–3.20) mm^2, $P = 0.02$; 1.20 (1.05–1.55) mm vs. 1.50 (1.23–1.70) mm, $P = 0.04$]. Interestingly the presence of HP adjacent to TCFA was statistically higher in the MACE group (53.85 vs. 21.18%, $P = 0.01$), while calcified nodule, cholesterol clefts, macrophages, new microvessels and PE were similarly distributed between arms. All the lesions were by definition lipidic, and the lipid arc angle was not statistically different between arms.

Discussion

The current analysis is the first to date that studied in detail the impact of haemodynamic and morphological baseline characteristics of non-ischaemic but otherwise highly vulnerable lesions on future MACE during an intermediate duration follow-up.

The main finding of this analysis is that TCFA lesions that progressed to future MACE had lower MLA and FFR values at baseline. Interestingly, TCFA lesions that progressed to MACE had a 2.5-fold higher prevalence of a HP located adjacent to TCFA. Finally, the TCFA surface in lesions that progressed to MACE was smaller as compared to non-MACE related lesions.

A previous virtual histology intravascular ultrasound (IVUS) study had already pointed at the impact of TCFA in future adverse events by showing that TCFA presence in DM patients was associated with a > 3- fold higher MACE rate than DM patients without a TCFA, and > five-fold higher MACE compared with patients without DM or TCFA, despite the known resolution limitations of this imaging technique.[10] OCT, having a much higher resolution allows for a more accurate distinction between TCFA and lipid-rich but non-TCFA lesions. Indeed, in another subanalysis from the COMBINE (OCT-FFR) trial, we have already shown that OCT-assessed TCFAs are associated with a 4-fold risk for future events compared to lipid-rich thick cap fibroatheromas and almost 8-fold compared to non-fibroatheroma lesions.[11]

A similar impact of TCFA on future adverse events has been shown also in the CLIMA trial.[4] Interestingly, the CLIMA trial also stressed the clinical role of OCT detected macrophages in adjunct to other variables. While in the main COMBINE (OCT-FFR) trial similarly to CLIMA trial, TCFA lesions had indeed a higher macrophage concentration compared to non-TCFA lesions, in the actual analysis which focusses only on TCFA lesions that have already a high percentage of macrophages at baseline, no difference could be observed.

Furthermore, the role of TCFA on future adverse events was also described from Kubo *et al.*[5] Indeed, in this study, similarly, to COMBINE (OCT-FFR) trial, TCFA and in particular, a combination of TCFA with a large lipid pool, were associated with a high rate of future

Table 2 Quantitative and qualitative intravascular imaging analysis of TCFA among the MACE and the non-MACE lesions

Parameter	MACE (n = 13)	Non-MACE(n = 85)	P value
TCFA area surface (IQR)—mm^2	0.19 (0.07–0.33)	0.37 (0.18–0.76)	0.03
Total lesion surface (IQR)—mm^2	190(86–249.5)	221.5(145–271.5)	0.09
TCFA length (IQR)—mm	0.20 (0.15–0.35)	0.30 (0.20–0.58)	0.06
TCFA to MLA distal localization—no. (%)	2 (15.4)	22 (25.9)	0.58
TCFA to MLA proximal localization—no. (%)	11 (84.6)	52 (61.2)	0.13
TCFA arc (IQR)—°	33.00 (24.0–43.5)	49.00 (36.0–63.0)	0.02

IQR, interquartile range; MLA, minimal lumen area.

Table 3 Lesion level quantitative and qualitative OCT analysis results in MACE and non-MACE group

Parameter	MACE n = 13	Non-MACE n = 85	P value
Localization of the TCFA—no. (%)			
LAD	7 (53.9)	27 (31.8)	0.15
CX	4 (30.8)	22 (25.9)	0.15
RCA	2 (15.4)	35 (42.4)	0.15
FFR value	0.85 ± 0.04	0.89 ± 0.05	0.02
Lesion length (IQR)—mm	22.10 (11.1–35.1)	27.20 (18.6–36.1)	0.31
Proximal lumen diameter (IQR)—mm	3.45 (3.0–3.8)	3.40 (3.1–3.8)	0.94
Distal lumen diameter (IQR)—mm	2.50 (2.5–2.9)	2.70 (2.5–3.2)	0.13
Min. lumen diameter (IQR)—mm	1.20 (1.1–1.6)	1.50 (1.2–1.7)	0.04
MLA (IQR)—mm^2	1.80 (1.3–2.3)	2.40 (1.8–3.2)	0.02
Stenosis reference (IQR)—%	67.00 (55.5–76.5)	64.00 (57.5–72.0)	0.24
Lumen volume (IQR)—mm	118.40 (50.1–141.6)	138.10 (85.6–185.9)	0.14
Calcific plaque—no. (%)	10 (76.9)	75 (88.2)	0.26
Calcium arc (IQR)—o	150.00 (94.0–210.0)	116.00 (76.0–200.0)	0.59
Protruding calcification—no. (%)	5 (38.5)	30 (35.3)	0.82
Cholesterol Cleft—no. (%)	10 (76.9)	60 (70.6)	0.64
Lipid plaque—no. (%)	13 (100)	85 (100)	
Lipid arc (IQR)—o	206.00 (193.0–299.0)	240.00 (191.5–285.5)	0.88
Plaque rupture—no. (%)	3 (23.1)	28 (32.9)	0.47
Plaque erosion—no. (%)	2 (15.4)	9 (10.6)	0.61
Healed plaque—no. (%)	7 (53.9)	18 (21.2)	0.01
New micro vessels—no (%)	10 (76.9)	72 (84.7)	0.48
Macrophages—no (%)	7 (53.8)	62 (72.9)	0.16

Cx, circumflex artery; IQR, interquartile range; LAD, left anterior descending; MLA, minimal lumen area; RCA, right coronary artery.

adverse events. Indeed, a large lipid pool, which in turn correlates with MLA, needs to be stressed, as another study from Xing at al. showed that lipid rich plaque with a smaller MLA were associated with a higher event rate.[12] However in this study, differently from the COMBINE (OCT-FFR) trial, where lesions per definition have a diameter of stenosis > 40%, the degree of the stenosis of the lesions studied was very low. This could also be the reason why this study failed in detecting TCFA as a predictor of future events.

From the above, it appears that presence of TCFA in lipid rich lesions with lower MLA is an important predictor of future events and therefore, identifying this type of vulnerable plaques and applying individualized treatment strategies, might have a potential role in improving patients' outcomes independently from the presence or absence of ischaemia.

Furthermore, the recently published PROSPECT II study demonstrated that combined near-infrared spectroscopy and IVUS could detect angiographically non-obstructive lesions with a high lipid

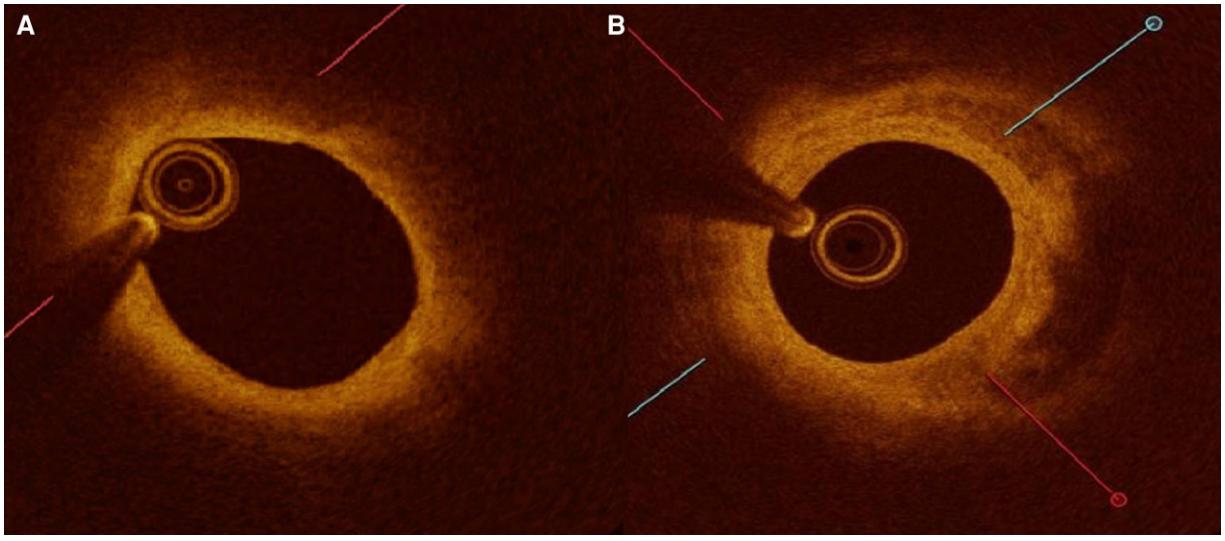


Figure 2 Comparison of healed plaque and TCFA imaging by OCT. OCT shows healed plaque. (*A*); OCT cross-section area shows TCFA lesion. (*B*).

content and large plaque burden that are at increased risk for future adverse cardiac outcomes.[13] Retrospective studies, based on mixed populations of patients with and without DM, suggested the existence of a positive relationship between the presence of TCFAs and ischaemic FFR values (<0.80).[14] Therefore, it was proposed that the safety of deferring revascularization in FFR negative lesions stem from the twofold benefit of identifying lesions that are non-flow limiting and with a low risk of triggering acute ischaemic events. However, the COMBINE (OCT-FFR) trial demonstrated that such a hypothesis is not correct, at least in patients with DM, where presence of TCFAs hosted in lesions with a diameter stenosis > 40%, but other ways non-ischaemic constitute an important predictor of future vessel-related cardiovascular events in these patients. Interestingly, only one-third of these high or intermediate stenotic lesions that are at high risk of future adverse events can be detected by FFR and subsequently treated by revascularization.[15] In the present analysis, despite the fact that we included only patients with negative hyperaemic pressure ratios, the FFR values in lesions from the MACE group were significantly lower than in the non-MACE group. FFR is often interpreted in a dichotomous manner ($\leq$ 0.80/ > 0.80), but studies have demonstrated a linear correlation where lower FFR values are associated with a higher rate of clinical events and greater benefit from revascularization.[16,17]

In the present sub-analysis of the COMBINE (OCT-FFR) trial, we performed a detailed comparison of morphological differences in OCT detected TCFA patients with vs. without MACE during follow-up. The TCFA surface was significantly smaller in the MACE group when compared to the non-MACE, with over a two-fold difference. Moreover, lesions from the MACE group had significantly smaller MLA when compared with the non-MACE group. This finding is in line with previous studies, where smaller MLA was associated with increased MACE rates.[18] The presence of TCFA in lesions with a smaller MLA than the TCFA surface itself, seems to be a more important parameter influencing the frequency of MACE.

Another interesting finding of our study is that in the MACE group HP adjacent to TCFA were two times more frequent than in the non-MACE. Recent studies have stressed the relationship between HP and future adverse events, questioning the previous concept that HP represents a quiescent lesion.[19,20] In line with this analysis results, another recently published study demonstrated that the presence of HP in the non-culprit lesions with OCT demonstrated that TCFA and MLA < 3.5 mm^2 were independently associated with increased MACE rates.[18] Furthermore another study from Yin *et al.*[21] showed that HP were a predictor of rapid plaque progression. Indeed, the coexistence of a HP and TCFA might represent a sign of ongoing inflammation and atherosclerosis progression, despite medical treatment and warrants further research, *Figure 2*.

Additionally, in the current study, TCFAs in both arms, but even more in the MACE group, were predominantly located proximally to the lesion frame with MLA. Interestingly, recent studies demonstrated that both wall shear stress (WSS) and detection of vulnerable plaque are associated with plaque rupture.[22,23] Whether the interplay between TCFA location and lesion shear stress could further bring to light new TCFA destabilization mechanisms remains unknown but may warrant further research.

Our observations add to the currently understood need for multimodality imaging and/or hybrid approaches for coronary lesions evaluation. With the granularity of information provided by OCT imaging, the development of further software that would integrate OCT imaging with functional lesion assessment could lead to a new and more accurate diagnosis of high-risk lesions.

Conclusions

Among TCFA carrying lesions, those that progressed to MACE were more frequently located adjacent to a HP, had a smaller MLA, and had lower FFR values at baseline. Altogether, this finding suggests that future definitions of vulnerable plaque might incorporate not only TCFA but also other qualitative and quantitative as well as hemodynamic assessment parameters.

Study limitations

The results of this study cannot be generalized to all patients. However, DM patients represent more than one third of all patients undergoing coronary angiography. Our study population included only non-culprit lesions. Despite this subanalysis derives from a large set of data, the absolute number of events in TCFA lesions was small, and larger studies are required to corroborate the prognostic value of our findings. Previous PCI were more frequent in the MACE arm, however

considering that per protocol we studied *de novo* lesions located in native arteries and MACE were per definition a target lesion derived event, in absence of death or MI derived from previous stented segments in the same vessel, the impact of such finding in the actual results is unlikely. Finally baseline differences, arising from the non-randomized nature of this study may partly bias our findings; therefore, the findings of this study should be considered as hypothesis generating.

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None.

Conflict of interest: Nothing to Disclose.

Data availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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