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CLINICAL RESEARCH
Interventional cardiology

Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT–FFR trial

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Aims The aim of this study was to understand the impact of optical coherence tomography (OCT)-detected thin-cap fibroatheroma (TCFA) on clinical outcomes of diabetes mellitus (DM) patients with fractional flow reserve (FFR)-negative lesions.

Methods and results COMBINE OCT-FFR study was a prospective, double-blind, international, natural history study. After FFR assessment, and revascularization of FFR-positive lesions, patients with ≥1 FFR-negative lesions (target lesions) were classified in two groups based on the presence or absence of ≥1 TCFA lesion. The primary endpoint compared FFR-negative TCFA-positive patients with FFR-negative TCFA-negative patients for a composite of cardiac mortality, target vessel myocardial infarction, clinically driven target lesion revascularization or unstable angina requiring hospitalization at 18 months. Among 550 patients enrolled, 390 (81%) patients had ≥1 FFR-negative lesions. Among FFR-negative patients, 98 (25%) were TCFA positive and 292 (75%) were TCFA negative. The incidence of the primary endpoint was 13.3% and 3.1% in TCFA-positive vs. TCFA-negative groups, respectively (hazard ratio 4.65; 95% confidence interval, 1.99–10.89; $P < 0.001$). The Cox regression multivariable analysis identified TCFA as the strongest predictor of major adverse clinical events (MACE) (hazard ratio 5.12; 95% confidence interval 2.12–12.34; $P < 0.001$).

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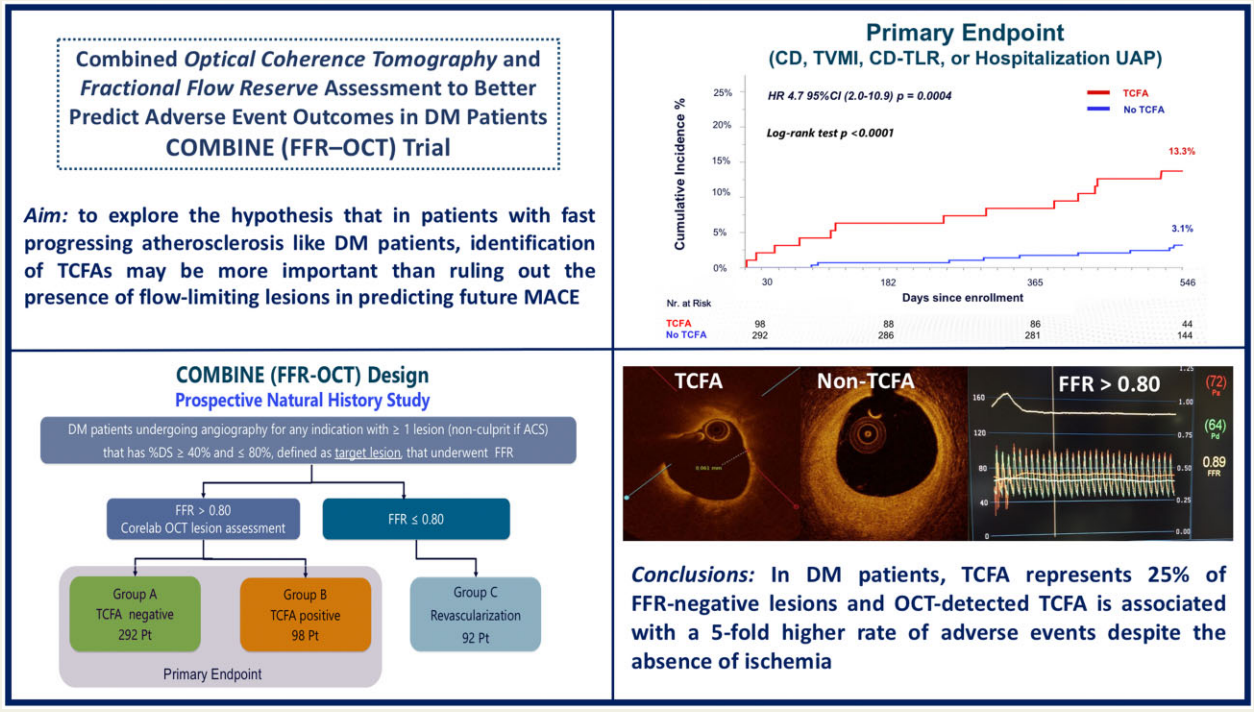
Conclusions Among DM patients with ≥1 FFR-negative lesions, TCFA-positive patients represented 25% of this population and were associated with a five-fold higher rate of MACE despite the absence of ischaemia. This discrepancy between the impact of vulnerable plaque and ischaemia on future adverse events may represent a paradigm shift for coronary artery disease risk stratification in DM patients.

Graphical Abstract



Study design and main results.

Keywords Optical coherence tomography • Thin-cap fibroatheroma • Diabetes mellitus • Fractional flow reserve • Vulnerable plaque • Coronary artery disease

Introduction

Fractional flow reserve (FFR) is the most widely used intracoronary physiology index to guide coronary revascularization strategy in the catheterization laboratory. The safety of FFR as a decision-making tool is based upon multiple large randomized trials showing that coronary revascularization can be safely deferred in lesions with non-ischaemic FFR values (i.e. >0.80), while it is indicated in those with ischaemic FFR values (i.e. ≤0.80).[1,2] Notwithstanding the documented safety of FFR in those trials, evidence suggests that in some patient categories, such as those with diabetes mellitus (DM) and/or acute coronary syndromes (ACS), decision-making on revascularization based on FFR is associated with an excess of cardiovascular events, compared to patients without such clinical features.[3,4] It has been proposed that atherosclerosis progression and destabilization of angiographically intermediate medically treated lesions is considerable in DM patients and responsible for the majority of the adverse events during the follow-up.[5] Particularly, lesions where a thin-cap fibroatheroma (TCFA) morphology on intravascular ultrasound (IVUS) assessment was suspected were related to an excess of cardiovascular events.[6] Therefore, a tentative hypothesis is that in DM patients, identification of TCFAs may be more important than ruling out the presence of flow-limiting lesions in predicting future cardiovascular events. Understanding the impact of TCFAs on the clinical outcomes of non-flow-limiting lesions finds new opportunities in the use of optical coherence tomography (OCT), an imaging modality which, differently from IVUS, has an extremely high-resolution (i.e. 10–20 μm) capable of providing very accurate qualitative information on plaque composition.[7,8] To date, the natural history of OCT-detected TCFA lesions in patients with fast progressing atherosclerosis has not been studied in a prospective and properly powered fashion. To distinguish between the impact of plaque vulnerability and ischaemia, we performed a natural history study, focusing on the impact of OCT-detected TCFA on clinical outcome of DM patients with medically treated, angiographically intermediate but otherwise non-ischaemic (i.e. FFR-negative) lesions.

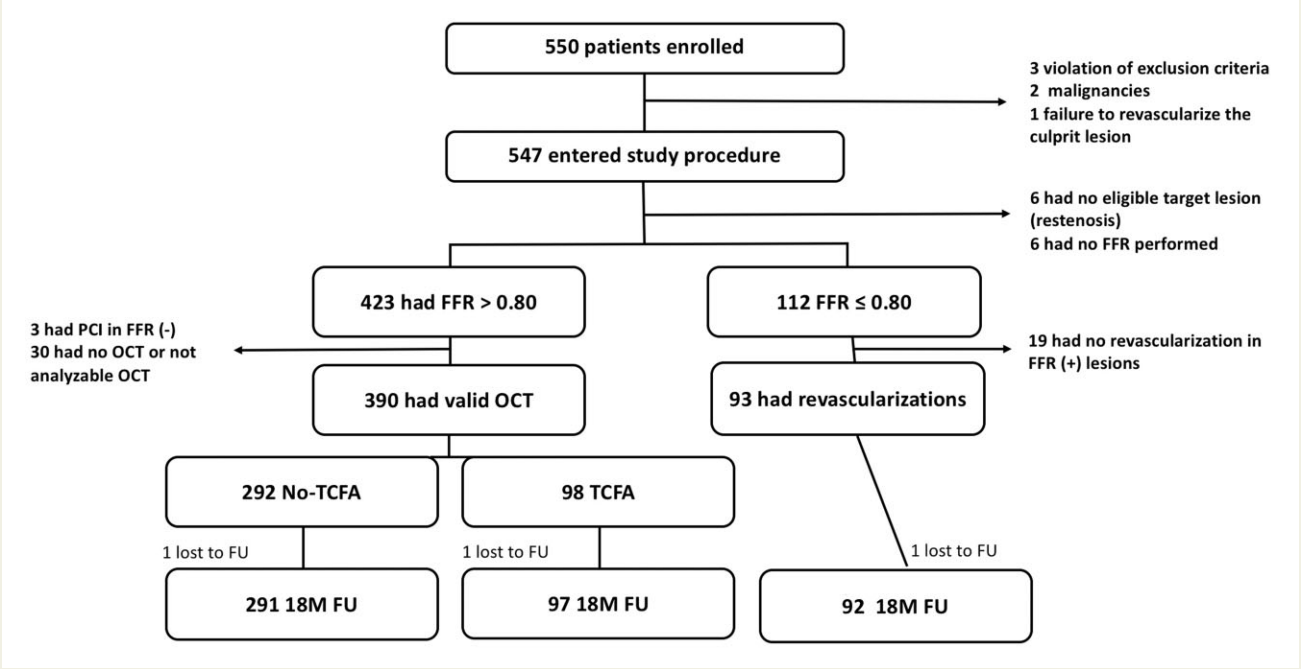


Figure 1 Flowchart of subjects included in the study. FFR, fractional flow reserve; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma. (-) denotes negative and (+) denotes positive.

Methods

Study design and oversight

The COMBINE FFR-OCT (NCT02989740) is a prospective, double-blind, international, natural history study that was conducted in 14 sites across 7 countries. The rationale and design of the COMBINE study has been published previously.[9] This investigator-initiated study was sponsored by Isala Hartcentrum, Zwolle, the Netherlands, and supported from an unrestricted institutional grant from St Jude Medical/Abbott Vascular. The principal investigator in collaboration with the steering and executive committees (see Supplementary material online, *Appendix*) was responsible for study design, conduction, and data integrity and reporting. The study protocol (see the Supplementary material online) was approved from the national regulatory agencies and the institutional review boards of all the participating centres.

The first three authors vouched for the accuracy of the reported data. The trial was conducted from the Diagram BV, an ISO-9-certified CRO Zwolle, the Netherlands, while the statistical analysis was performed by the KCRI, Krakow, Poland. St Jude Medical/Abbott Vascular had no role in the study design, conduction, or reporting of the study results.

Study population

Diabetic mellitus patients undergoing coronary angiography for either stable coronary disease or ACS were eligible for enrollment if they had at least one de novo native coronary lesion with a diameter of stenosis between 40% and 80% by visual assessment. In patients who presented with ACS the culprit-lesion was revascularized first. Lesions that were deemed by the operator to be clearly severe (>80% diameter stenosis) and/or had a thrombolysis in myocardial infarction (MI) flow <3 were also eligible for revascularization without physiological assessment. All remaining intermediate lesions underwent FFR assessment in accordance with guideline-adherent best practice and represent the target lesions for this study. Patients who had a least one target lesion represent the population of this study.

Revascularization of the target lesions was guided by the FFR findings. Patients with exclusively FFR-positive lesions (i.e. FFR ≤0.80) underwent mandatory revascularization. Patients with at least one FFR-negative target lesion (i.e. FFR >0.80) underwent OCT assessment and were further treated by guideline-recommended optimal medical therapy. Following core lab analysis of the OCT findings, patients with FFR-negative lesions were further classified as 'TCFA-positive' or 'TCFA-negative' depending on presence or absence of at least one TCFA lesion. The final trial population was composed of three groups: group A, patients with at least one FFR-negative/TCFA-negative lesion; group B, patients with at least one FFR-negative/TCFA-positive lesion; and group C, patients with exclusively FFR-positive lesions, who underwent revascularization (Supplementary material online, *Figure S1*). The full inclusion and exclusion criteria are presented in the Supplementary Appendix. Patients who after enrollment did not undergo the treatment mandated by the protocol and therefore could not be assigned to one of the three groups were excluded from the study (*Figure 1*). To assure for blinding, the operators were not required to perform any OCT analysis during the procedure. In the procedure report only, the results of the FFR but not of the OCT were shared with the treating physicians. The assignment into TCFA-negative or TCFA-positive groups was performed in the core lab and OCT findings were blinded to patients, operators as well as the team that performed the clinical follow-up. The current manuscript reports the outcomes of the FFR-negative patients, based on the presence or absence of TCFA.

Endpoints and definitions

The primary endpoint was the incidence of the target lesion-related composite major adverse clinical event (MACE) which was defined as: cardiac death, target vessel MI, clinically driven target lesion revascularization or

hospitalization due to unstable or progressive angina at 18 months in the FFR-negative and TCFA-positive patients (group B) as compared to the FFR-negative and TCFA-negative patients (group A). Cardiac death and unstable angina events that could not clearly be related to events originating from non-target lesions were considered as target lesion-related. A complete list of definitions can be found in the Supplementary material online, *Appendix*. All adverse events were adjudicated by an independent clinical event committee, with members who were unaware of the patient group allocation.

Patients were considered as suffering from DM if they required medical treatment with insulin or an oral hypoglycaemic agent.

OCT analysis

A detailed summary of OCT definitions and analysis methodology is shown in the Supplementary material online. The OCT analysis was based on the 'Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies' document from Tearney *et al.*[10] OCT image analysis scrutinized serial cross-sectional images of the vessel in every frame of OCT pullback starting 5 mm distal to 5 mm proximal of the OCT-defined lesion border. Signal-rich homogeneous plaques were classified as fibrous, signal-poor regions with diffuse borders were classified as lipidic plaques, and signal-poor regions with well-defined borders were classified as calcified plaques. TCFA was defined as any lesion with predominantly lipid-rich plaque which in the thinnest part of the atheroma cap measures ≤65 µm and lipid arc of >90° on OCT assessment. The OCT analysis was performed from two investigators (BB and TR), and a third investigator (EK) supervised the analysis. The inter-rater agreement analysis for OCT-defined TCFA identification revealed kappa = 0.81 (95% confidence interval 0.70–0.97) and the intra-rater agreement revealed kappa = 0.78 (95% confidence interval 0.61–0.92). The analysis was performed using the CAAS Intravascular 2.0 software (Pie Medical BV, the Netherlands).

Statistical analysis

The study was powered for superiority for the primary endpoint at 18 months. Assuming a primary endpoint rate in groups A and B of 5% and 20%, respectively, taking into account a patient distribution between groups A and B from 70%/30% to 30%/70%, and assuming the number of patients in group C not to exceed one-third of the entire study population, a total of 500 patients, of whom 334 in groups A and B, was projected to provide a 80% power to reject the null hypothesis with a type I error rate of 0.05. This sample size calculation took into account a loss to follow-up up to 7%.

The cumulative incidence of the primary and secondary endpoints was estimated by using the Kaplan–Meier method and log-rank test. Patients were censured at 546 days or their last known contact. Cox proportional-hazards models were used to calculate the hazard ratios and respective 95% confidence intervals. The primary analysis for the primary endpoint was the per-protocol analysis, which was dictated from the non-randomized nature of this study where the division in FFR-negative, TCFA-positive, or TCFA-negative groups was dependent on the availability of FFR and OCT data. Enrolled patients who could not be allocated in any of these groups were excluded from the analysis. A Cox multivariable regression analysis was performed for the primary endpoint. P-values < 0.05 were considered statistically significant. Statistical analysis was performed using JMP 15.1 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

From March 2015 to December 2018, a total of 550 patients in 14 study centres across 7 European countries and the United Arab Emirates were enrolled in the COMBINE FFR-OCT study of which 483/550 (88%) patients could be classified into groups A, B, or C. The patient flow chart and the reasons for patient exclusion from the analysis are described in *Figure 1*. Patient follow-up was completed in 99% of patients. *Table 1* shows patient demographic and procedural characteristics. The majority of patients (>70%) were treated for stable coronary disease. There were no significant differences among groups A and B (*Table 1*).

Supplementary material online, *Table S1* shows the medication at discharge. Statin usage at discharge was higher in the TCFA-negative group while the use of $P2Y_{12}$ inhibitors was higher in the TCFA-positive group. The rest of the cardiac or DM medications was similarly distributed between groups.

Per definition, all patients with at least one TCFA lesion were classified in the TCFA-positive group (B); therefore, from the 123 target lesions in this group 104 were TCFA and 19 were non-TCFA while all 341 target lesions in the TCFA-negative group were all non-TCFA lesions.

Lesion level quantitative and qualitative OCT data for TCFA-positive (group B) as compared to TCFA-negative (group A) lesions are presented in *Table 2*. Quantitative and qualitative OCT data of non-TCFA lesions from group B are shown in Supplementary material online, *Table S2*. The quantitative analysis showed similar proximal and distal reference lumen diameters between TCFA-positive and TCFA-negative lesions.

Both the baseline transstenotic pressure index and the FFR were similar in both arms (resting distal coronary pressure to aortic pressure ratio 0.95 ± 0.04 vs. 0.95 ± 0.04, $P = 0.74$, FFR 0.88 ± 0.05 vs. 0.88 ± 0.05, $P = 0.66$, in group B vs. A); however, TCFA-positive lesions tended to be somewhat longer and have a slightly smaller minimum lumen area (MLA) as compared to TCFA-negative lesions. The qualitative analysis showed that both groups had a similar prevalence of lesion calcification; however, the overall span of the calcium arc was larger and the presence of protruding calcification more frequent in TCFA-negative lesions. As may be expected from the TCFA definition, a predominantly lipidic plaque was present in all patients of TCFA-positive lesions. Notably, a lipidic plaque also was the most frequent plaque type in TCFA-negative lesions; however, TCFA lesions were characterized by wider lipid arc and significantly higher prevalence of cholesterol clefts, neovascularization, and macrophage infiltration.

Clinical outcomes

The primary endpoint outcomes and its components are shown in *Table 3*. Kaplan–Meier cumulative incidence time-to-event curves for the FFR-negative/TCFA-positive patients (group B) as compared to the FFR-negative/TCFA-negative patients (group A) are shown in *Figure 2*. The primary endpoint occurred in 13.3% of the patients with FFR-negative/TCFA-positive (group B) as compared to 3.1% of the patients with FFR-negative/TCFA-negative (group A) (hazard

Table 1 Patient characteristics

Variables	FFR(−)/TCFA(+), *n* = 98	FFR(−)/TCFA(−), *n* = 292	*P*-value
Age, years, median (IQR)	70 (59–76)	68 (62–74)	0.87
BMI, kg/m^2, mean (IQR)	29 (27–33)	29 (26–32)	0.99
Male sex, *n* (%)	65 (66.3)	180 (61.6)	0.41
Insulin-dependent DM, *n* (%)	35 (35.7)	100 (34.2)	0.79
Oral antidiabetics, *n* (%)	82 (83.7)	240 (82.2)	0.74
Smoking status, *n* (%)			
Current smoking	22 (22.4)	53 (18.7)	0.42
Previous smoking	23 (34.8)	64 (31.1)	0.57
Hypercholesterolemia, *n* (%)	61 (62.2)	171 (58.8)	0.54
Hypertension, *n* (%)	75 (76.5)	214 (73.8)	0.59
Previous ACS, *n* (%)	42 (42.9)	97 (33.2)	0.08
Previous PCI, *n* (%)	41 (41.8)	103 (35.3)	0.24
Previous CABG, *n* (%)	4 (4.1)	8 (2.7)	0.51
Previous CVA, *n* (%)	12 (12.2)	20 (6.8)	0.09
SCD at presentation, *n* (%)	77 (78.6)	215 (73.6)	0.78
ACS at presentation, *n* (%)	21 (21.4)	77 (26.4)	0.78
MI at presentation, *n* (%)	12 (12.2)	50 (17.1)	0.25
Total no. of lesions, *n* (per patient)	204 (2.08)	493 (1.69)	0.02
1 vessel disease	38 (38.8%)	157 (53.8%)	0.01
2 vessel disease	49 (50.0%)	114 (39.0%)	0.07
3 vessel disease	11 (11.2%)	21 (7.2%)	0.29
Lesions revascularized, *n* (per patient)	81 (0.83)	152 (0.52)	0.003
FFR-negative target lesions, *n* (per patient)	123 (1.26)	341 (1.17)	0.50
Distribution FFR-negative lesions			0.14
Left main	1 (0.8%)	5 (1.5%)	
LAD	45 (36.6%)	156 (45.7%)	
CX	33 (26.8%)	93 (27.3%)	
RCA	44 (35.8%)	87 (25.5%)	
Total cholesterol, mg/dL, median (IQR)	161 (142–189)	154 (135–193)	0.18
LDL-cholesterol, mg/dL, median (IQR)	88 (82–93)	91 (81–99)	0.52
Triglycerides, mg/mL, median (IQR)	168 (120–242)	150 (106–231)	0.25
Hemoglobin A1c, %, median (IQR)	7.3 (6.7–7.9)	7.3 (6.6–8.1)	0.78

(-) denotes negative and (+) denotes positive.
ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; CX, circumflex coronary artery; DM, diabetes mellitus; FFR, fractional flow reserve; IQR, interquartile range; LAD, left anterior descending artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SCD, stable coronary disease; TCFA, thin-cap fibroatheroma.

ratio 4.65; 95% confidence interval, 1.99–10.89, $P < 0.001$). Interestingly, all target vessel MI at follow-up occurred in the TCFA-positive patients (group B) whereas no target vessel MI was observed in the TCFA-negative patients (group A). Similarly, clinically driven target lesion revascularization and unstable angina pectoris incidence was significantly higher in the FFR-negative/TCFA-positive patients (*Table 3*).

Interestingly, a significantly higher incidence of clinically driven target lesion revascularization was observed in the FFR-negative/TCFA-positive group (*Table 3*).

The Cox regression multivariable analysis was performed taking into account the following clinical and procedural variables: age, MI at presentation, previous percutaneous coronary intervention, defined FFR-negative and TCFA-positive group, total cholesterol level, as well as the MLA (decrease of 1 mm^2). Among FFR-negative patients, TCFA positivity (hazard ratio 5.12; 95% confidence interval 2.12–12.34, $P < 0.001$), MI at presentation (hazard ratio 2.77; 95% confidence interval 1.04–7.35, $P = 0.04$) as well as a smaller MLA (decrease of 1 mm^2) (hazard ratio 2.29; 95% confidence interval 1.11–4.69, $P = 0.04$) were positive predictors for the primary endpoint.

Statin at discharge was not entered as a variable in the multivariate analysis as it was not found a predictor of future MACE in univariate analysis (hazard ratio 1.79, 95% confidence interval 0.70–4.56, $P = 0.22$).

Discussion

The major finding of this study is that despite a lack of flow-limiting lesions, the incidence of the composite primary endpoint was high

Table 2 Lesion level quantitative and qualitative optical coherence tomography analysis results in patients with and without thin-cap fibroatheroma

	FFR(−)/TCFA(+), *n* = 104a	FFR(−)/TCFA(−), *n* = 341	*P*-value
Quantitative OCT analysis, median (IQR)			
MLA, mm^2	2.35 (1.70–3.18)	2.60 (1.90–3.50)	0.09
% area stenosis, %	65 (57–73)	62 (53–70)	0.07
Lesion length, mm	27.65 (18.10–36.10)	20.10 (14.10–29.60)	<0.001
Proximal RLD, mm	3.10 (2.70–3.50)	3.00 (2.60–3.50)	0.63
Distal RLD, mm	2.50 (2.30–3.00)	2.60 (2.20–3.00)	0.68
Qualitative OCT analysis			
Fibrous cap thickness, µm, median (IQR)	60 (56–63)	151 (109–218)	–
Calcification present, *n* (%)	91 (87.5)	292 (85.6)	0.99
Calcium arc, °, median (IQR)	112 (80–192)	159 (88–244)	0.02
Protruding calcification, *n* (%)	36 (34.6)	157 (46.0)	0.04
Cholesterol clefts, *n* (%)	75 (72.8)	149 (44.1)	<0.001
Lipidic plaque, *n* (%)	104 (100)	201 (58.9)	<0.001
Lipidic arc, °, median (IQR)	241 (193–287)	169 (126–214)	<0.001
Neovascularization, *n* (%)	88 (84.6)	232 (68.0)	0.002
Macrophage infiltration, *n* (%)	72 (69.9)	157 (46.0)	<0.001

FFR, fractional flow reserve; IQR, interquartile range; MLA, minimum lumen area; OCT, optical coherence tomography; RLD, reference lumen diameter; TCFA, thin-cap fibroatheroma.
[a]Number represent only TCFA hosting lesions.

Table 3 Patients' clinical outcomes at 18-month follow-up

Variable	FFR(−)/TCFA(+) (*n* = 98)	FFR(−)/TCFA(−) (*n* = 292)	Hazard ratio (95% confidence interval)	*P*-value
Primary endpoint,[a] *n* (%)	13 (13.3)	9 (3.1)	4.65 (1.99–10.89)	<0.001
Cardiac death, *n* (%)	0 (0)	1 (0.34)	–	–
Death (any), *n* (%)	0 (0)	3 (1.03)	–	–
TV MI, *n* (%)	4 (4.1)	0 (0)	–	–
Spontaneous MI (any), *n* (%)	8 (8.2)	3 (1.0)	8.26 (2.19–31.14)	0.002
CD-TLR, *n* (%)	11 (11.2)	4 (1.4)	8.72 (2.78–27.39)	<0.001
Revascularization (any), *n* (%)	17 (17.3)	17 (5.8)	3.26 (1.66–6.38)	<0.001
Unstable angina requiring hospitalization, *n* (%)	6 (6.1)	5 (1.7)	3.76 (1.15–12.32)	0.03
Cardiac death and TV MI, *n* (%)	4 (4.1)	1 (0.3)	12.84 (1.44–114.92)	0.02
Death and any MI, *n* (%)	9 (9.2)	6 (2.0)	4.70 (1.68–13.22)	0.003
Cardiac Death, TV MI and CD-TLR, *n* (%)	11 (11.2)	5 (1.7)	7.0 (2.43–20.14)	<0.001
Death, MI and revascularization, *n* (%)	17 (17.3)	20 (6.8)	2.77 (1.45–5.28)	0.002

CD-TLR, clinically driven target lesion revascularization; FFR, fractional flow reserve; MI, myocardial infarction; TCFA, thin-cap fibroatheroma; TV MI, target vessel myocardial infarction.
[a]Primary endpoint defined as: cardiac death, TV MI, CD-TLR, or hospitalization due to unstable or progressive angina at 18 months in the FFR-negative and TCFA-positive patients (group B) as compared to the FFR-negative and TCFA-negative patients (group A).

and predominantly clustered in patients with TCFA-positive lesions (group B) who had a 4.7-fold higher incidence of the primary endpoint vs. TCFA-negative patients (group A) (*Graphical abstract*). These findings raise concerns regarding the safety of revascularization deferral based solely on FFR interrogation and support the use of image-based methods for more accurate risk profiling in patients with DM.

In our population of DM patients, the MACE rate in the TCFA-positive patients was mainly driven by target vessel MI, which occurred only in this group, and target lesion revascularization, which occurred 8 times more often in TCFA-positive patients (as compared to TCFA-negative patients). Interestingly, any-MI rate was also higher in TCFA-positive patients, a finding that may suggest that presence of TCFA might be a sign of a more aggressive atherosclerosis disease in these patients.

Furthermore, the higher rate of clinically driven non-MI-related target lesion revascularizations might point that TCFA is not only a

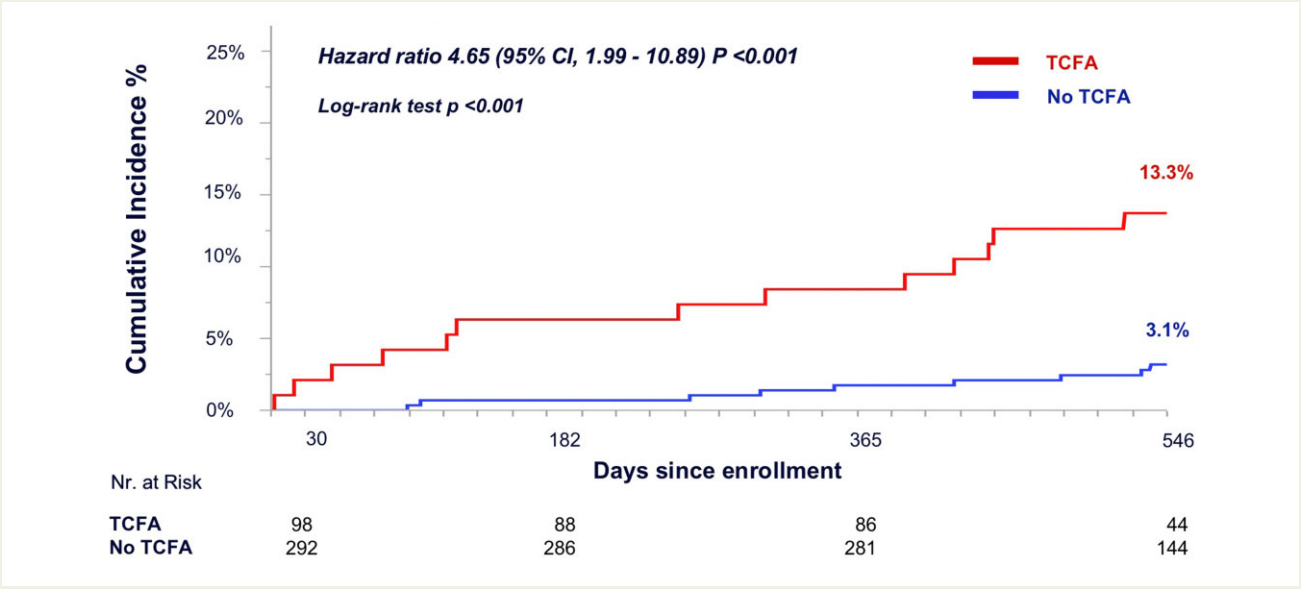


Figure 2 Incidence of the primary endpoint, a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization or hospitalization due to unstable or progressive angina at 18 months. A hazard ratio above 1.00 denotes a higher incidence of the primary endpoint in the fractional flow reserve-negative and thin-cap fibroatheroma-positive patients as compared to the fractional flow reserve-negative and thin-cap fibroatheroma-negative patients. FFR, fractional flow reserve; TCFA, thin-cap fibroatheroma.

predictor of MI but also plaque progression and MLA reduction leading to angina. In fact, a clear trend for a smaller MLA, MLA stenosis percentage, and longer lesion length was present already at baseline in TCFA-positive lesions, a finding that is in line with the results from the COMPLETE-OCT sub study,[11] where angiographically obstructive lesions had a higher prevalence of TCFA. Altogether these findings suggest that a similar prevalence of TCFA in patients with or without ACS at presentation, as was the case in our study, might not be surprising considering that these syndromes may be different presentations of the same underlying disease, at least in the early phase of atherosclerosis progression.

Moreover, the incidence of unstable angina was significantly higher in the TCFA-positive group, although this did not contribute substantially to the primary endpoint outcome as patients who developed unstable angina generally also underwent a target vessel revascularization. Nevertheless, this finding further supports that the vast majority of repeat revascularizations were truly clinically driven.

Vulnerable plaque, OCT-detected TCFA, and risk of future adverse events

Thin-cap fibroatheromas originally described as lipid-rich plaques covered by a fibrous cap of <65 μm, frequently infiltrated by macrophages,[12] have been identified from histopathological studies as a substrate for ACS including MI and sudden cardiac death.[13] Due to their frequent association with compensatory vessel remodelling, 90% of TCFAs are located in large plaques with intermediate or severe cross-sectional stenosis area of >50%.[14] Therefore, future adverse events are likely to originate from TCFA lesions with at least intermediate degree of stenosis as is the case in our study. As predicted from aforementioned histopathology work, our study demonstrated that the adverse clinical events were clearly clustered in the TCFA-positive patients.

The prevalence of TCFA in our study was very similar to that reported in previous studies.[15,16] Furthermore, CLIMA, a large prospective study by Prati *et al.*,[17] identified TCFA as the strongest predictor of adverse cardiovascular events in a patient with angiographically non-obstructive lesions. The current study confirms those findings and even expands that message by confirming the impact of TCFA in future MACE in FFR- negative lesions.

We found a significantly higher prevalence of macrophage infiltration and neovascularization in the TCFA-positive lesions as compared to TCFA-negative lesions, suggesting a higher inflammation level that might eventually lead to fibrous cap destabilization and plaque rupture.[13,18,19]

Interestingly, while a lipid-rich plaque was also the predominant plaque phenotype (about 60%) in the TCFA-negative group, the primary endpoint event rate in this group was very low, suggesting that presence of lipid-rich plaque alone, in the absence of TCFA features like thin fibrous cap, macrophage infiltration, and neovascularization, is associated with a low rate of future adverse events and as such a safer substrate. To date OCT represents the only imaging modality that has sufficient resolution capable of identifying these plaque vulnerability features.[8,10,20,21]

Interplay between plaque phenotype and intracoronary physiology indices

Our study provides new, prospectively gathered information on the relationship between plaque composition and FFR values. 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.[22–24] Based on that observation, it was proposed that the safety of deferring revascularization in FFR-negative lesions stems from the two-fold benefit of identifying lesions that are non-flow limiting and with a low risk of triggering acute ischaemic events. Our prospective study demonstrates that such hypothesis is not correct, at least in patients with DM and that the presence of TCFAs hosted in non-ischaemic lesions constitutes 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[1,25] and subsequently addressed by revascularization. Our findings may explain why an ischaemia-guided revascularization approach can significantly reduce angina but fails to reduce future adverse events, as was recently shown by the ISCHEMIA trial.[26] Similarly our findings may also explain why surgical revascularization, which by-passes the proximal epicardial segments where vulnerable lesions are frequently hosted, has a superior outcome compared to percutaneous coronary intervention in DM patients, as has been shown by the FREEDOM trial.[27]

Clinical relevance of our findings

The main important lesson derived from this study is that at the lesion level the absence of myocardial ischaemia does not predict a low risk of future events in diabetic patients. The present study shows for the first time that these OCT-detected vulnerable plaques represent up to 25% of these angiographically intermediate FFR-negative lesions but are responsible for >80% of future adverse events despite optimal medical treatment, alternatively the remaining 75% of FFR-negative lesions which do not show vulnerability features are truly at low risk of future adverse events. Therefore, for the treatment of isolated non-ischaemic but vulnerable coronary lesions, alternative future treatment options need to be explored. Whether plaque passivation, and/or more potent lipid-lowering drugs provides the future, requires further investigation. Current revascularization guidelines[28,29] focus exclusively on the importance of ischaemia and do not mention once the term 'vulnerable plaque'. Our study and other recently published studies[11,17] have provided important insights by showing that ischaemia is not the only predictor of future adverse events, and therefore, intravascular imaging and vulnerable plaque detection merits further attention in future guideline drafting.

Our study has limitations. The results of this study cannot be generalized to all patients with FFR-negative lesions; however, DM patients represent more than one-third of all patients undergoing coronary angiography. Baseline differences, arising from the non-randomized nature of this study, may partly persist despite statistical adjustment. The statin usage at discharge was higher in the TCFA negative group; however, it did not significantly impact future MACE. Conversely, a higher rate of events was observed in the TCFA group despite a higher use of $P2Y_{12}$ inhibitors in this group. MI at presentation was found a predictor of future MACE; therefore, whether these results apply also to stable angina patients requires further investigation. The follow-up window for the primary endpoint had a margin of ±3 weeks; therefore in some patients the follow-up might have taken place 1–3 weeks before the 18-month timeframe. The impact of a stricter glycaemic or lipidic control on future adverse events is not deductible from our study and whether an improvement could be achieved, especially with newer lipid and glycaemic lowering drugs, needs to be studied in dedicated trials. The study was underpowered for the detection of differences in low incidence endpoints (e.g. cardiac mortality). Plaque burden, a strong predictor of future adverse events, cannot be well evaluated by OCT; however, a diameter stenosis ≥40–80%, and a MLA of <3 mm^2 as was the case in our study may suggest that these patients have also a high plaque burden. Plaque assessment by OCT may result in overestimation of the TCFA prevalence; however, OCT remains the most sensitive tool to detect TCFA to date.[30]

Conclusions

In conclusion, in DM patients, OCT-detected TCFA is associated with a five-fold higher rate of adverse events despite the absence of ischaemia. The clinical demonstration of such discrepancy between the impact of vulnerable plaque and ischaemia on future adverse events may represent a paradigm shift for coronary artery disease risk stratification and paves the way for novel therapeutic strategies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data collected for the study will not be made available to others.

Conflict of interest: E.K. reports personal fees from Abbott and Medtronic outside the submitted work. H.G.G. reports other from Medtronic, Boston Scientific, Abbott, Biotronik, Neovasc, Corflow, Shockwave, and Chiesi, outside the submitted work. C.v.B. reports institutional research grants (to the research department of Thoraxcentrum Twente) from Abbott Vascular, Biotonik, Boston Scientific, and Medtronic, outside the submitted work. B.P. reports grants from Diagram B.V., during the conduct of the study. H.N. reports personal fees from Abbott Vascular, grants from Abbott Vascular, and grants and personal fees from SMT Medical, outside the submitted work. W.W. reports personal fees from Abbott Vascular, outside the submitted work. All other authors have nothing to disclose.

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