Prognostic value of intravascular ultrasound in patients with coronary artery disease.

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ABSTRACT

Background: Intravascular ultrasound (IVUS) and radiofrequency (RF-)IVUS have shown to be able to detect high-risk coronary plaque characteristics.

Objectives: We studied the long-term prognostic value of (RF-)IVUS-derived plaque characteristics in patients with coronary artery disease (CAD) undergoing coronary angiography.

Methods: During 2008-2011, (RF-)IVUS was performed in one non-stenotic segment of a non-culprit coronary artery in 581 patients undergoing coronary angiography for acute coronary syndrome (ACS) or stable angina. The predefined primary endpoint was MACE, defined as the composite of all-cause death, non-fatal ACS or unplanned revascularization. Hazard ratios (HR) were adjusted for age, sex and clinical risk factors.

Results: During a median follow-up of 4.7 years, 152 patients (26.2%) had MACE. The presence of a lesion with a minimal luminal area ≤4.0mm^2 was independently associated with MACE (HR:1.49, 95%CI:1.07-2.08, p=0.020), whereas the presence of a thin-cap fibroatheroma lesion or a lesion with a plaque burden ≥70% on their own were not. Results were comparable when the composite endpoint included cardiac death instead of all-cause death. The presence of a lesion with a plaque burden of ≥70% was independently associated with the composite endpoint of cardiac death, nonfatal ACS or unplanned revascularization after exclusion of culprit-lesion related events (HR:1.66, 95%CI:1.06-2.58, p=0.026). Likewise, each 10 units increase in segmental plaque burden was independently associated with a 26% increase in risk of this composite endpoint (HR:1.26 per 10 units increase, 95%CI:1.03-1.52, p=0.022).

Conclusions: IVUS-derived small luminal area and large plaque burden, and not RF-IVUS-derived compositional plaque features on their own, predict adverse cardiovascular outcome during long-term follow-up in patients with CAD.

INTRODUCTION

Patients with coronary artery disease (CAD) are at increased risk of recurrent adverse cardiovascular events, such as acute coronary syndromes (ACS).(1,2) Whereas coronary angiography (CAG) only yields a two-dimensional silhouette of the lumen,(3) greyscale intravascular ultrasound (IVUS) and radiofrequency (RF-)IVUS have shown to be able to identify high-risk coronary plaque characteristics within the coronary artery wall. (4-7) Therefore, (RF-)IVUS may be useful to identify patients at increased risk of future adverse cardiovascular events.(6-8) Autopsy studies suggest that an ACS is often caused by rupture or fissure of a thin-cap fibroatheroma (TCFA), a vulnerable coronary plaque containing a large lipid-rich necrotic core overlaid by a thin inflamed fibrous cap.(9-12) Identification of this vulnerable coronary plaque phenotype by invasive imaging may therefore improve risk stratification and management of CAD patients.

To date, a few studies have investigated the prognostic value of (RF-)IVUS for adverse cardiovascular outcome.(13,14) The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study demonstrated that (RF-)IVUS-derived high-risk plaque characteristics in the three major coronary arteries predict adverse cardiac events in patients admitted with ACS during long-term follow-up.(13) However, patients with stable angina pectoris (SAP) were not included in PROSPECT and the number of endpoint events in that study was primarily driven by rehospitalizations. Our ATHEROREMO-IVUS (European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound) study demonstrated that high-risk plaque characteristics, as derived by (RF-)IVUS in one non-stenotic segment of a non-culprit coronary artery were predictive of adverse cardiovascular events in a broad spectrum of patients with CAD, including SAP, at 1-year follow-up.(15) We now report the long-term (median 4.7 years) follow-up data.

METHODS

Study design and population

The design of the ATHEROREMO-IVUS study has been described in detail elsewhere. (15,16) Briefly, between 2008 and 2011, 581 patients undergoing diagnostic CAG or percutaneous coronary intervention (PCI) for ACS or SAP underwent (RF-)IVUS imaging of a non-culprit coronary artery in the Erasmus MC, Rotterdam, The Netherlands.(15,16) Baseline (RF-)IVUS images were analyzed off-line and were not used for patient care. Thereafter, patients were followed-up on adverse cardiovascular outcome.

The ATHEROREMO-IVUS study was approved by the medical ethics committee of the Erasmus MC and was performed in accordance with the declaration of Helsinki. All

patients provided written informed consent which included approval for long-term follow-up. The ATHEROREMO-IVUS study was registered in ClinicalTrialsgov.org, number NCT01789411.

Intravascular ultrasound

Subsequent to the standard index CAG, (RF-)IVUS imaging was performed in a non-stenotic segment of a non-culprit coronary artery. The target segment in this non-culprit coronary artery was required to be at least 40 mm in length and without significant luminal narrowing (<50% stenosis) as assessed by on-line angiography. The order of preference for selection of the non-culprit vessel was; (i) left anterior descending artery, (ii) right coronary artery, (iii) left circumflex artery.(15,16) IVUS images were acquired by the Volcano s5/s5i Imaging system, including a Volcano Eagle Eye Gold IVUS catheter (20 MHz) that was automatically pulled back at a standard speed of 0.5 mm/s (Volcano Corp., San Diego, CA, USA). Greyscale- and RF-IVUS data were analyzed off-line by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) using the pcVH 2.1 and qVH software (Volcano Corp., San Diego, CA, USA). The core laboratory was blinded to all other patient characteristics and outcome data.

Greyscale IVUS measurements included segmental plaque volume and plaque burden. The external elastic membrane and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). Segmental plaque burden was defined as the plaque and media cross-sectional area divided by the external elastic membrane cross-sectional area. A coronary lesion was defined as a segment with a plaque burden of more than 40% in at least 3 consecutive frames. Using RF-IVUS analyses, compositional features of coronary lesions were classified as fibrous, fibro-fatty, necrotic core or dense calcium.(5,15,16) Confluent necrotic core or dense calcium, or the contact of necrotic core with the lumen, were assessed by visual examination performed independently by three investigators blinded to outcome data. Coronary lesions were further classified into 8 different lesion types.(7,15,16) The mentioned criteria should be present in three consecutive frames for a lesion to be considered of a particular category. Three lesions, as identified by (RF-)IVUS, were considered as lesions associated with a high risk for subsequent adverse cardiac events; 1) TCFA lesion, defined as a lesion with the presence of >10% confluent necrotic core in direct contact with the lumen; 2) lesion with a plaque burden ≥70%; 3) lesion with a minimal luminal area ≤4.0mm^2.(15)

Follow-up

Follow-up was reported by January 2015. Vital status of the patients was obtained from municipal civil registries. Subsequently, as a first screening method, follow-up questionnaires were sent to all living patients for identifying possible adverse events. Thereafter, hospital discharge letters were obtained if any hospitalization or possible event was re-

ported. In patients who did not return the questionnaire, the local hospital records were investigated for possible events. Cause of death was obtained from hospital records, autopsy reports or general practitioner notes.

Study endpoints

The predefined primary endpoint consisted of major adverse cardiovascular events (MACE), defined as the composite of all-cause death, non-fatal ACS, or unplanned revascularization during long-term follow-up. In accordance with our previous studies on the prognostic value of (RF-)IVUS and near-infrared spectroscopy (NIRS) in this study population, we also performed a predefined analysis on the composite endpoint of *cardiac* death, non-fatal ACS, or unplanned revascularization. This analysis was performed based on the pathophysiological concept that (RF-)IVUS-derived plaque characteristics would hypothetically be more likely associated with (atherosclerotic-driven) cardiovascular events and not with definite non-cardiac events (such as death because of malignancy). Similarly, an additional analysis was performed on this endpoint after exclusion of *definite* culprit lesion-related events. This exploratory analysis aimed to assess the question as to whether the atherosclerotic burden, as assessed in a single, non-culprit coronary artery segment, would reflect vulnerability of the entire coronary tree.

In accordance with the guidelines of the European Society of Cardiology, non-fatal ACS was defined as the clinical diagnosis of ST-segment Elevation Myocardial Infarction (STEMI), non-STEMI, or unstable angina.(17,18) Unplanned coronary revascularization was defined as urgent revascularization for ACS or unplanned (i.e. not part of pre-planned multi-stage PCI) elective revascularization for progressive angina pectoris. Cardiac death was defined as any death due to proximate cardiac cause, unwitnessed death or death of unknown cause.

Based on original source data of available coronary angiography and hospital records at the time of the event, the clinical event committee adjudicated (blinded to IVUS data) whether the event was related to the coronary site that had been treated during the index procedure (culprit lesion-related event) or as related to a coronary site that had not been treated during the index procedure (non-culprit lesion-related event). Events that were related to both the culprit lesion and a non-culprit site (e.g. revascularization of multiple vessels with CABG) were classified into both categories. When information was not sufficient to classify an event as either culprit lesion related or non-culprit lesion related, the event was classified as indeterminate.(15)

Statistical analysis

Normally-distributed continuous variables were reported as means and standard deviations. Non-normally-distributed variables were reported as medians and interquartile ranges (IQR). Categorical variables were reported as numbers and percentages.

Cumulative events rates were estimated by the Kaplan-Meier method and differences between groups were evaluated by the Log-rank test. Patients that were lost to follow-up were censored at the date of last contact. In case a patient had multiple events, the first event was counted for the composite endpoint.

The associations between (RF-)IVUS characteristics and study endpoints were further analyzed by Cox proportional hazard regression analysis. We applied multivariable Cox regression, with adjustment for age, sex, diabetes mellitus, hypertension, dyslipidemia, indication for CAG (ACS or SAP), history of myocardial infarction, history of PCI, history of CABG, history of peripheral artery disease and PCI performed at index procedure. These potential confounders were chosen based on clinical relevance or their significant association with MACE in univariable Cox regression analysis. Hazard ratios (HRs) were reported with 95% confidence intervals (95% CIs).

In case the composite endpoint was defined with exclusion of culprit lesion-related events, the occurrence of a culprit lesion-related event as a first event during follow-up was not counted and the patient was not censored as this patient is considered to be still at risk of a non-culprit lesion-related or indeterminate event during further follow-up. When the composite endpoint was based on non-culprit lesion-related or indeterminate events, patients were only censored in case a non-culprit lesion-related or indeterminate event occurred, if they were lost-to-follow-up or if they died.

All statistical tests were two-tailed and p-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS statistics version 21.0 (IBM Corp., Armonk, New York).

RESULTS

Baseline characteristics

Mean age of the patients was 61.6 ± 11.3 years, 75.6% were men and 54.7% presented with an ACS (Table 1). Median segmental plaque burden was 39.1 (IQR: 30.0-46.4)%, and plaque volume was 222.7 (IQR: 136.1-326.6)mm^3. On the basis of (RF-)IVUS, 724 lesions were identified in 508 (87.4%) patients that had at least one lesion in the imaged segment, including 127 (17.5%) lesions with a plaque burden ≥70% in 124 (21.3%) patients, 206 (28.5%) lesions with a minimal luminal area ≤4.0 mm^2 in 182 (31.3%) patients and 74 (10.2%) lesions with both plaque characteristics in 74 (12.7%) patients. On the basis of RF-IVUS, 271 (37.4%) TCFA lesions were identified in 242 (41.7%) patients, including 71 (9.8%) TCFA lesions with a plaque burden ≥70% in 69 patients (11.9%), 61 (8.4%) TCFA lesions with a minimal luminal area ≤4.0 mm^2 in 61 (10.5%) patients and 35 (4.8%) TCFA lesions with both plaque characteristics in 35 (6.0%) patients.

Table 1. Baseline characteristics	
	N = 581 patients
Clinical characteristics	
Age, years	61.6 ± 11.3
Men, n (%)	439 (75.6)
Diabetes Mellitus, n (%)	99 (17.0)
Hypertension, n (%)	300 (51.6)
Dyslipidemia, n (%)	321 (55.2)
Current smoking, n (%)	169 (29.1)
Positive family history, n (%)	301 (51.8)
Previous MI, n (%)	184 (31.7)
Previous PCI, n (%)	186 (32.0)
Previous CABG, n (%)	18 (3.1)
Previous CVA, n (%)	26 (4.5)
History of peripheral artery disease, n (%)	36 (6.2)
History of renal impairment, n (%)	32 (5.5)
History of heart failure, n (%)	19 (3.3)
Median C-reactive protein, mg/L	2.1 [0.9-5.4]
Procedural characteristics	
Indication for coronary angiography	
Acute MI, n (%)	167 (28.7)
Unstable angina, n (%)	151 (26.0)
Stable angina, n (%)	254 (43.7)
Other, n (%)	9 (1.5)
PCI performed, n (%)	511 (88.0)
Coronary artery disease	
No significant stenosis, n (%)	43 (7.4)
1-vessel disease, n (%)	308 (53.0)
2-vessel disease, n (%)	168 (28.9)
3-vessel disease, n (%)	62 (10.7)
IVUS characteristics	
Imaged coronary artery	
Left anterior descending, n (%)	210 (36.1)
Left circumflex, n (%)	195 (33.6)
Right coronary artery, n (%)	176 (30.3)
Median imaged segment length, mm	44.3 [33.8-55.4]
Median segmental plaque burden, %	39.1 [30.0-46.4]
Median segmental plaque volume, mm^3	222.7 [136.1-326.6]

CABG, coronary artery bypass graft; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Incidence of study endpoints

Median follow-up time was 4.7 (IQR: 4.2-5.6) years. Follow-up questionnaires were sent to all 528 (90.9%) living patients and were completed by 86%. The predefined composite endpoint of all-cause death, non-fatal ACS or unplanned revascularization occurred in 152 patients (26.2%) (Table 2). A total of 27 events were classified as definite culprit lesion-related, 72 as non-culprit lesion-related and 53 as indeterminate event (Table 2). The composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization occurred in 125 patients (21.5%) (Table 2). The composite endpoint of cardiac death, non-fatal ACS or unplanned revascularization after exclusion of definite culprit lesion-related events occurred in 98 patients (16.9%) (Table 2).

Table 2. Incidence of composite endpoints.

	Definite CLR events	Definite non-CLR events	Indeterminate events	Non-CLR and indeterminate events combined	All events
Composite of MACE, n	27	72	53	125	152[a]
Death from any cause, n	1	11	38	49	50
Cardiac death, n	1	4	20	24	25
Nonfatal ACS, n	13	24	10	34	47
Unplanned revascularization, n	13	37	5	42	55
Composite of cardiac death, nonfatal ACS or unplanned revascularization, n	27	63	35	98[c]	125[b]

a. Composite of MACE; all-cause death, nonfatal ACS or unplanned revascularization.
b. Composite of cardiac death, nonfatal ACS or unplanned revascularization.
c. Non-culprit lesion-related and indeterminate cardiac death, nonfatal ACS or unplanned revascularization.
ACS, acute coronary syndrome; CLR, culprit lesion-related; MACE, major adverse cardiovasulcar events.
Numbers refer to the first event counted for the composite endpoint.

Association between (RF-)IVUS and MACE

The presence of a lesion with a minimal luminal area ≤4.0 mm^2 was significantly and independently associated with MACE (cumulative MACE incidence when present: 33.9% vs. 22.2% when absent; adjusted HR: 1.49, 95% CI: 1.07-2.08, p=0.020) (Table 3). Furthermore, the presence of a TCFA lesion with a plaque burden ≥70% was significantly associated with MACE (cumulative MACE incidence when present: 37.7% vs. 24.6% when absent; adjusted HR: 1.73, 95% CI: 1.12-2.66, p=0.013), while the presence of a TCFA lesion or a lesion with a plaque burden ≥70% itself was not independently associated with MACE (Table 3). After multivariable adjustment, segmental plaque burden and plaque volume remained no longer independently associated with MACE (Table 3). Re-

sults were essentially similar when definite culprit lesion-related events were excluded. Cox regression analysis with follow-up duration as time-dependent variable showed that both the presence of a TCFA lesion and a lesion with a plaque burden ≥70% were strong predictors of MACE for the first year of follow-up, but not beyond 1-year follow-up. On the contrary, a lesion with a minimal luminal area ≤4.0 mm^2 itself was not an independent predictor in the first year of follow-up (adjusted HR: 1.40, 95% CI: 0.83-2.34, p=0.21), but did predict MACE beyond 1-year of follow-up (1-year to 5-year follow-up adjusted HR: 1.58, 95% CI: 1.04-2.40, p=0.032). Results remained essentially similar when we performed an exploratory multivariable analysis applying the model used for the 1-year follow-up data (which comprised 6 variables instead of the 11 variables used in the model for the current analyses) (Supplemental table 1).

Table 3. Associations of (RF-)IVUS and risk of adverse cardiac events at 4.7-years follow-up

	Unadjusted model HR (95% CI)	P-value	Full model HR (95% CI)	P-value
MACE				
TCFA	1.20 (0.87-1.65)	0.27	1.27 (0.91-1.77)	0.16
PB ≥70%	1.50 (1.05-2.16)	0.028	1.33 (0.92-1.93)	0.13
MLA ≤4.0 mm^2	1.57 (1.13-2.17)	0.007	1.49 (1.07-2.08)	0.020
TCFA + PB ≥70%	1.90 (1.25-2.90)	0.003	1.73 (1.12-2.66)	0.013
TCFA + MLA ≤4.0 mm^2	1.47 (0.93-2.33)	0.10	1.50 (0.93-2.44)	0.10
TCFA + PB ≥70% + MLA ≤4.0 mm^2	1.64 (0.93-2.89)	0.089	1.74 (0.97-3.13)	0.066
PB≥70% + MLA ≤4.0 mm^2	1.29 (0.83-2.01)	0.26	1.30 (0.82-2.04)	0.26
Segmental plaque burden, %	1.24 (1.07-1.44)	0.004	1.15 (0.98-1.34)	0.079
Segmental plaque volume, mm^3	1.07 (0.96-1.20)	0.23	1.02 (0.90-1.14)	0.79
Composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization				
TCFA	1.04 (0.73-1.49)	0.83	1.12 (0.77-1.61)	0.56
PB ≥70%	1.63 (1.10-2.42)	0.014	1.43 (0.96-2.15)	0.083
MLA ≤4.0 mm^2	1.85 (1.30-2.64)	0.001	1.82 (1.26-2.64)	0.001
TCFA + PB ≥70%	1.95 (1.23-3.09)	0.005	1.78 (1.11-2.85)	0.017
TCFA + MLA ≤4.0 mm^2	1.74 (1.08-2.81)	0.023	1.86 (1.11-3.10)	0.018
TCFA + PB ≥70% + MLA ≤4.0 mm^2	1.84 (1.02-3.34)	0.044	2.09 (1.12-3.89)	0.020
PB≥70% + MLA ≤4.0 mm^2	1.45 (0.91-2.32)	0.12	1.51 (0.93-2.45)	0.093
Segmental plaque burden, %	1.28 (1.09-1.50)	0.003	1.17 (0.99-1.39)	0.070
Segmental plaque volume, mm^3	1.06 (0.93-1.20)	0.40	0.98 (0.86-1.12)	0.80

Table 3 (*continued*)

	Unadjusted model HR (95% CI)	P-value	Full model HR (95% CI)	P-value
Composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization exclusive of culprit lesion-related events				
TCFA	0.99 (0.66-1.48)	0.95	1.07 (0.70-1.62)	0.76
PB ≥70%	2.08 (1.36-3.18)	0.001	1.66 (1.06-2.58)	0.026
MLA ≤4.0 mm^2	2.03 (1.37-3.03)	<0.001	1.88 (1.24-2.83)	0.003
TCFA + PB ≥70%	2.17 (1.32-3.59)	0.002	1.84 (1.10-3.07)	0.021
TCFA + MLA ≤4.0 mm^2	1.64 (0.95-2.84)	0.078	1.75 (0.98-3.13)	0.059
TCFA + PB ≥70% + MLA ≤4.0 mm^2	1.97 (1.02-3.79)	0.042	2.03 (1.03-4.02)	0.041
PB≥70% + MLA ≤4.0 mm^2	1.77 (1.07-2.92)	0.026	1.73 (1.04-2.90)	0.035
Segmental plaque burden, %	1.41 (1.18-1.69)	<0.001	1.26 (1.03-1.52)	0.022
Segmental plaque volume, mm^3	1.13 (0.99-1.30)	0.080	1.03 (0.89-1.20)	0.68

Hazard ratios per 10 and 100 units increase in segmental plaque burden and plaque volume, respectively. CI, confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MLA, minimal luminal area; PB, plaque burden; RF, radiofrequency; TCFA, thin-cap fibroatheroma.

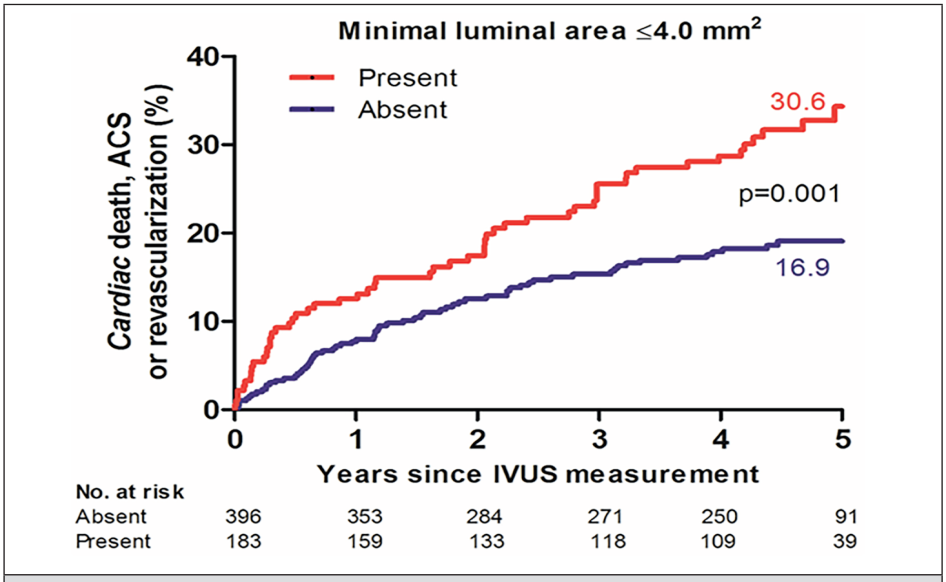

Figure 1. Association between the absence or presence of a lesion with a minimal luminal area ≤4.0 mm^2 and the composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization. P-value obtained by the Log-rank test.
ACS, acute coronary syndrome; IVUS, intravascular ultrasound

Association between (RF-)IVUS and the composite endpoint of cardiac death, non-fatal ACS or unplanned revascularization

The presence of a lesion with a minimal luminal area ≤4.0 mm^2 was also significantly and independently associated with a higher rate of the composite endpoint of cardiac death, non-fatal ACS or unplanned revascularization (cumulative incidence of composite endpoint when present: 30.6% vs. 16.9% when absent; adjusted HR: 1.82, 95% CI:1.26-2.64, p=0.001) (Figure 1 and Table 3). The same was true for TCFA lesions with a plaque burden ≥70% or a minimal luminal area ≤4.0 mm^2 (Table 3). The highest risk, in terms of adjusted HRs, was among patients who had a TCFA lesion with both a plaque burden ≥70% and a minimal luminal area ≤4.0 mm^2 (cumulative incidence of composite endpoint when present: 34.3% vs. 20.7% when absent; adjusted HR: 2.09, 95% CI: 1.12-3.89, p=0.020) (Table 3).

These associations remained essentially unchanged after *exclusion* of culprit lesion-related events (Figure 2 and Table 3). In addition, a significant association was observed

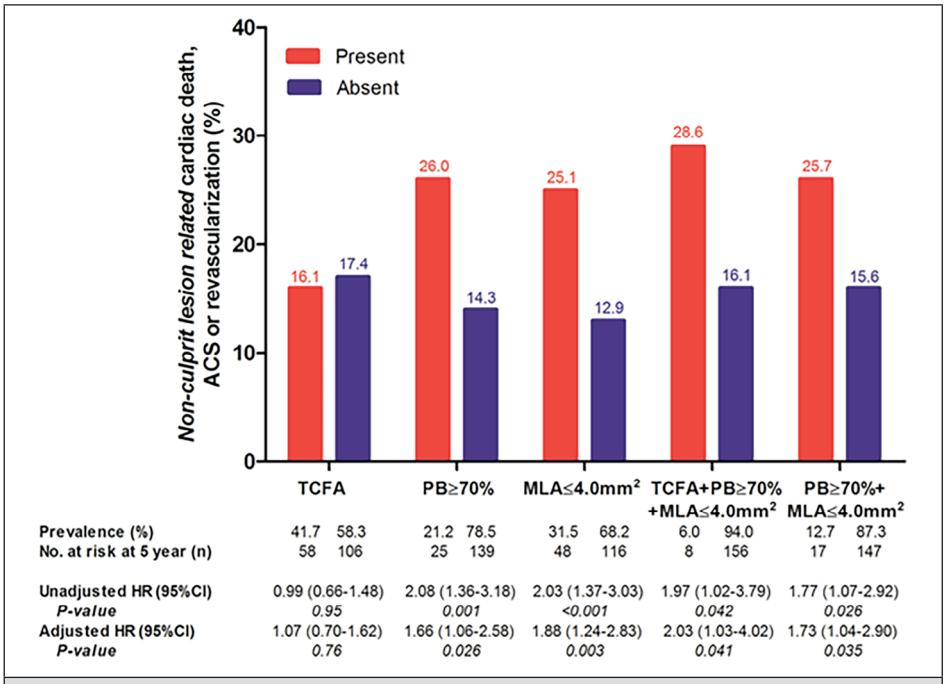

Figure 2. Association between (RF-)IVUS derived lesion characteristics and the composite endpoint of *cardiac* death, non-fatal ACS or unplanned revascularization, after exclusion of culprit lesion-related events. Percentages are cumulative events rates estimated by the Kaplan-Meier method. Prevalence (%) in the footer refers to the prevalence of the specific (RF-)IVUS characteristic. P-values are obtained by the Log-rank test. Hazard ratios are estimated by univariate Cox regression analyses.

ACS, acute coronary syndrome; MLA, minimal luminal area; PB, plaque burden; TCFA, thin-cap fibroatheroma

for the presence of a lesion with a plaque burden ≥70%, or its combination with a minimal luminal area ≤4.0 mm^2, as well as for segmental plaque burden with each 10 units increase in segmental plaque burden resulting in a 26% increase in risk for occurrence of the composite endpoint of cardiac death, non-fatal ACS or unplanned revascularization after exclusion of culprit lesion-related events (adjusted HR: 1.26 per 10 units increase, 95% CI: 1.03-1.52, p=0.022) (Figure 2 and Table 3).

DISCUSSION

This 4.7-year follow-up of the ATHEROREMO-IVUS study demonstrated that a small luminal area and a large plaque burden, but not RF-IVUS-derived compositional plaque features on their own, are independent determinants of (non-culprit lesion-related) adverse cardiac events in patients with CAD. The increased risk associated with a minimal luminal area ≤4.0 mm^2 was not observed at 1-year follow-up,(15) whereas the prognostic value of plaque burden ≥70% was confirmed although statistical significance was not consistently present for all different composite endpoints. In contrast, the independent association between a TCFA lesion as an isolated characteristic and adverse outcome at 1-year did not persist during long-term follow-up. Still, patients with a TCFA lesion with a large plaque burden and/or a small luminal area were at increased risk.

In line with the PROSPECT study, we found that a lesion with a large plaque burden, small luminal area, or their combination with a TCFA lesion, predicted adverse cardiovascular events in patients with CAD during long-term follow-up. In contrast to the PROSPECT and Virtual histology Intravascular ultrasound in Vulnerable Atherosclerosis (VIVA) study, we did not find such an independent association for a TCFA lesion on its own.(13,14) However, the results of our study and the PROSPECT study cannot be directly compared since different definitions of study endpoints were used. In addition, PROSPECT only included patients admitted with ACS and the study endpoint was primarily driven by rehospitalizations.(13) Furthermore, in the VIVA study only univariable regression analysis was performed due to the small number of endpoints.(14) Importantly, in both the PROSPECT and VIVA study, (RF-)IVUS was applied in all three major coronary arteries, whereas in our study only one single non-stenotic non-culprit coronary artery segment was investigated.(13,14)

We consider several possible explanations for the inconsistent association between the presence of a TCFA lesion as an isolated characteristic and the risk of adverse cardiac events during short-term versus long-term follow-up. First, controversy exists about the ability of RF-IVUS to correctly discern and identify the thin-cap and necrotic core as individual components of a TCFA lesion, due to the limitations with respect to spatial resolution.(4,19) Second, the dynamic nature of TCFA lesions over time should be

appreciated, since it has been described that particularly (proximal) TCFA lesions with a large plaque burden heal less often and might have a greater tendency to rupture.(20) This may explain our finding that the presence of a TCFA lesion with a large plaque burden was associated with an increased risk for adverse cardiac events over 4.7-years of follow-up, whereas a TCFA lesion in itself was not. Third, previous studies have demonstrated that a lesion with a large plaque burden is a consistent and prevalent predictor for adverse cardiac outcome. However, whereas the atherosclerotic disease burden has been shown as a consistent and strong predictor of adverse cardiovascular events, no study has yet demonstrated that a TCFA lesion by itself independently predicts adverse cardiovascular outcome after adjustment for plaque burden and other potential confounders.(13,14,21,22)

Our current study suggests that a RF-IVUS-derived TFCA lesion only has long-term prognostic value if accompanied with other high-risk plaque features. Therefore, this study further adds to the discussion as to whether RF-IVUS offers incremental prognostic value to greyscale IVUS in terms of identification of high-risk coronary plaque phenotypes based on compositional features. In addition, our current study demonstrates for the first time that (RF-)IVUS plaque characteristics, as assessed in one non-stenotic segment of a non-culprit coronary artery, predicts adverse cardiovascular events in patients with CAD during long-term follow-up. A post-hoc analysis did not show heterogeneity in the HR estimates in patients with ACS versus SAP. Moreover, the large number of endpoints allowed for a separate analysis with exclusion of culprit-lesion related endpoint events, with results that remained essentially unchanged. This indicates that (RF-)IVUS-derived plaque characteristics, as identified in one non-culprit coronary artery segment, may reflect atherosclerotic vulnerability of the entire coronary tree.

Recently, we have demonstrated that the lipid core burden index, as assessed by NIRS in a single non-culprit coronary artery segment, predicts adverse cardiovascular outcome, independent of clinical characteristics and IVUS-derived segmental plaque burden, over 4 years in CAD patients referred for CAG.(23) In this context, a combined NIRS-IVUS catheter may improve the (long-term) prognostic value of intravascular imaging in patients with CAD.(24)

Limitations

Several study limitations warrant consideration. First, the number of TCFA lesions might be overestimated by RF-IVUS because of the limited spatial resolution with respect to the identification of the thin-cap of a TCFA lesion. Second, IVUS imaging was not repeated during follow-up. Therefore, we could not account for the potential dynamic nature of coronary lesions. It should also be noted that this study does not provide insight in how the individual lesion correlates to the adverse event. Third, the follow-up questionnaire was completed by 86% of the patients. Although for the majority of the remaining

patients follow-up information was retrieved from our local hospital records, we cannot fully exclude the possibility that loss to follow-up was in part selective. However, our study reflects daily clinical practice since patients admitted with both ACS and SAP were included. Besides, the current study represents a long-term study investigating the association between (RF-)IVUS-derived plaque characteristics and adverse cardiovascular outcome during 4.7-years of follow-up in patients with ACS or SAP, which represents the longest follow-up reported so far.

Conclusions

This study demonstrates that a small luminal area and a large plaque burden, and not RF-IVUS-derived compositional plaque features on their own, as assessed by (RF-)IVUS in *one* single non-stenotic segment of a non-culprit coronary artery, predict (non-culprit lesion-related) adverse cardiovascular outcome during long-term follow-up over 4.7-years in patients with CAD. In contrast, this study did not show a single isolated imaging parameter as derived by RF-IVUS to be of long-term independent prognostic value.

PERSPECTIVES

Core Clinical Competencies

Competency in Medical Knowledge

Whereas coronary angiography only yields a two-dimensional silhouette of the lumen, greyscale intravascular ultrasound (IVUS) and radiofrequency (RF-)IVUS have been shown to be able to identify high-risk coronary plaque characteristics within the coronary artery wall. Therefore, (RF-)IVUS may be useful to identify patients at increased risk of future adverse cardiovascular events. Identification of high-risk coronary plaque characteristics by invasive imaging may therefore improve risk stratification and management of patients with coronary artery disease.

Translational Outlook

Future studies should investigate whether a combined NIRS-IVUS catheter as an invasive imaging tool may improve risk prediction, as well as prevention and treatment of patients at increased risk of adverse cardiovascular outcome.

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Supplemental table 1. Associations of (RF-)IVUS characteristics and risk of MACE at 4.7-years of follow-up using two different models for multivariable adjustment.

	1-year follow-up data – adjusted model with 6 covariates HR (95% CI)	P-value	5-year follow-up data – adjusted model with 6 covariates HR (95% CI) †	P-value	5-year follow-up data – adjusted model with 11 covariates HR (95% CI) ‡	P-value
MACE						
TCFA	1.98 (1.09-3.60)	0.026	1.25 (0.90-1.73)	0.18	1.27 (0.91-1.77)	0.16
PB≥70%	2.90 (1.60-5.25)	<0.001	1.42 (0.99-2.05)	0.059	1.33 (0.92-1.93)	0.13
MLA≤4.0mm^2	1.23 (0.67-2.26)	0.50	1.51 (1.09-2.09)	0.014	1.49 (1.07-2.08)	0.020
TCFA+PB≥70%	–	–	1.80 (1.18-2.75)	0.007	1.73 (1.12-2.66)	0.013
TCFA+ MLA≤4.0mm^2	–	–	1.61 (1.01-2.57)	0.046	1.50 (0.93-2.44)	0.10
TCFA+PB≥70%+ MLA≤4.0mm^2	–	–	1.82 (1.02-3.26)	0.043	1.74 (0.97-3.13)	0.066
Segmental plaque burden (per 10 units increase)	–	–	1.17 (1.01-1.36)	0.040	1.15 (0.98-1.34)	0.079
Segmental plaque volume (per 100 units increase)	–	–	1.03 (0.92-1.16)	0.63	1.02 (0.90-1.14)	0.79

CI, confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MLA, minimal luminal area; PB, plaque burden; RF, radiofrequency; TCFA, thin-cap fibroatheroma.

† Variables entered in the 6-covariate model were age, gender, diabetes mellitus, hypertension, history of percutaneous coronary intervention and indication for coronary angiography.

‡ Variables entered in the 11-covariate model were age, gender, diabetes mellitus, hypertension, history of percutaneous coronary intervention, indication for coronary angiography, dyslipidemia, history of myocardial infarction, history of coronary artery bypass grafting, history of peripheral artery disease and percutaneous coronary intervention performed at index.