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Coronary plaque composition of culprit/target lesions according to the clinical presentation: a virtual histology intravascular ultrasound analysis

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Aims To evaluate the plaque composition obtained by virtual histology (VH) IVUS according to the clinical presentation and to compare those data to previously published histopathology data.
Methods and results VH was performed on 95 *de novo* significant lesions (>75% stenosis) in 85 patients [28 acute coronary syndrome (ACS) patients, 30 lesions; 57 stable angina pectoris (SAP) patients, 65 lesions]. There were a higher prevalence of positive remodelling (47 vs. 22%, $P = 0.013$), thrombus (20 vs. 1.5%, $P = 0.0037$), and echo-lucent area (23.3 vs. 7.7%, $P = 0.047$) in ACS patients. At the minimal lumen site, fibrous plaque area was significantly larger in ACS lesions than in SAP lesions (66.0 ± 10.7 vs. $61.4 \pm 8.9\%$, $P = 0.034$), whereas necrotic core and dense calcium plaque area were smaller in ACS lesions (Necrotic core: 6.8 ± 6.0 vs. $11.0 \pm 8.3\%$, $P = 0.02$; Dense calcium: 2.6 ± 3.0 vs. $4.9 \pm 5.8\%$, $P = 0.03$). No differences in rate of thin cap fibroatheroma, thick fibrotheroma, or for the presence of multiple necrotic core layers were observed between both groups.
Conclusion Plaque composition obtained by VH-IVUS shows less necrotic core and more fibrous tissue in ACS compared to SAP lesions, which is in contradiction with previously published histopathologic data.

Introduction

Despite improvement of medical and interventional therapies, coronary artery disease (CAD) remains a frequent cause of sudden death in developed countries. Sudden changes in coronary plaque luminal surface morphology consisting of plaque rupture or fissure have been recognized as important mechanisms of thrombosis. Plaque disruption is a reflection of enhanced inflammatory activity within the plaque, and the risk of plaque rupture has been shown to be associated to the plaque composition, which includes a large lipid core, a thin fibrous cap, and a high macrophage density.[1–3] Most of our knowledge about the morphological characteristics of plaques that are vulnerable and have a high risk of disruption has been obtained from necropsy studies analysing lesions that have already undergone disruption.[4–8] Observational and prospective studies investigating the annual acute event risk of a mild/moderate coronary lesion for an acute event reported rates of 5–10%.[9–14] The risk of inducing an acute event increases proportionally with the stenosis severity.[15–18] However, most of myocardial infarctions result from thrombosis of a lesion that by itself is not haemodynamically significant, reflecting the fact that mild/moderate lesions by far outnumber significant lesions.[19] *In vivo* detection of mild/moderate vulnerable lesions would potentially allow the initiation of specific therapies before a coronary event occurs. Recently, different approaches have emerged with the goal of identifying plaque at risk of future events. *In vivo* plaque morphology evaluation is limited with the use of grey-scale intravascular ultrasound. However, virtual histology (VH) IVUS using spectral analysis of the radiofrequency ultrasound backscatter signals allows identification of four different components of atherosclerotic plaques: fibrous, fibro-fatty, dense calcium, and necrotic core.[20,21] *Ex vivo* validation studies, analysing selected regions of interest, representing homogeneous plaque components on the histology specimen, have reported high accuracy for the classification of those plaque components. A recent *in vivo* study showed that VH provides information with a high predictive accuracy as compared with atherectomy specimens.[22]

Although identification of mild/moderate vulnerable stenosis has the most relevant clinical implication, clinical validation and confirmation of VH data on culprit lesions, which are the lesion subset best studied, are required.

The purpose of this study was to evaluate the plaque composition obtained by VH IVUS according to the clinical presentation and to compare those data to previously published histopathology data.

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Methods

Study population

In our centre, IVUS is used routinely during percutaneous coronary interventions (PCIs) in all patients. The choice of the IVUS catheter was left to the discretion of the operator. Between October 2004 and July 2005, VH IVUS, using motorized pull-back system, was performed on 121 native *de novo* target lesions (>75% angiographic stenosis by visual estimation) in 110 patients and were included in a database. Twenty-six lesions in 25 patients belonging to a company-conducted registry were excluded. The remaining study population included 95 native *de novo* target lesions in 85 patients. Exclusion criteria were ostial and/or bifurcation lesions. Clinical presentation was classified either as stable angina pectoris (SAP), according to the Canadian Cardiovascular Society classification, or acute coronary syndrome (ACS). ACS includes unstable angina, according to the Braunwald classification, or acute myocardial infarction (with or without ST elevation). Secondary causes for angina (Braunwald classification class IA, IIA, and IIIA) were excluded. The present study was approved by the hospital ethics committee, and written informed consent was obtained from all patients.

Data acquisition and medication

All patients, other than the ACS cases, were given aspirin (100 mg/day) and ticlopidine (200 mg/day) for at least 1 week prior to the procedure. During the procedure, heparin was given as a bolus of 150 U/kg with additional boluses to 2000 U/h. All baseline angiography and IVUS imaging were performed after administration of 200 μg of nitroglycerin. Angiography was taken so that each lesion was viewed from over two angles. For the IVUS procedure, a 20 MHz, 3.2 F, phased-array IVUS catheter (Eagle Eye, Volcano therapeutics, Rancho Cordova, CA, USA) was used. After placing the IVUS catheter at a point distal to the lesion, the catheter was pulled back to the aortic ostium using the motorized pull-back system at 0.5 cm/s. During pullback, grey-scale IVUS was recorded and raw RF data was captured at the top of the R wave for reconstruction of the colour-coded map by a VH IVUS data recorder (Volcano therapeutics).

Grey scale and VH IVUS analyses

The smallest lumen at the culprit lesion was identified from axial and longitudinal plaque distribution. At the smallest lumen site of the culprit lesion, vessel cross-sectional area (CSA) and lumen CSA were calculated, and the difference between the two values was defined as plaque plus media CSA. Per cent plaque plus media CSA (=plaque burden) was defined as plaque plus media CSA divided by vessel CSA. Remodelling index (RI) was calculated as the external elastic membrane CSA at the minimal lumen site divided by the proximal reference external elastic membrane CSA. Positive remodelling was defined as a RI $\geq$ 1.05. Atherosclerotic coronary plaques were characterized by classification trees based on mathematical autoregressive spectral analysis of IVUS backscattered data (IVUSLab software, Volcano Therapeutics), as described previously.[21] Fibrous areas were marked in green, fibro-fatty in yellow, dense calcium in white, and necrotic core in red on the reconstructed colour-coded tissue map. The area and per cent area of each plaque component in the tissue map were calculated automatically by IVUSLab software. Measurements were made for the region of interest, which was defined as the segment between distal to proximal reference site that were the most normal looking within 5 mm proximal and distal to the lesion. Volumetric data were generated by the software using Simpson's method.

VH IVUS-derived thin cap fibroatheroma (TCFA) and VH IVUS-derived fibroatheroma (FA) were defined, according to previously published data, as lesions fulfilling the following criteria in at least three consecutive cross-sectional images by two experienced, independent observers.[23,24] TCFA: plaque burden >40%, per cent necrotic core area >20% without evidence of fibrous cap. FA: per cent necrotic core area >20% with presence of a fibrous cap. Grey scale and VH IVUS analysis were performed by an experienced analyst who was blinded to the quantitative analysis and baseline clinical and lesion characteristics.

Statistical analysis

Continuous data is reported throughout this text and in the tables as mean $\pm$ standard deviation. Categorical data were expressed as number or frequencies of occurrence. For the patient-based analysis, comparison of continuous data was performed by two-sided unpaired Student's *t*-test or by one-way analysis of variance (ANOVA). The Pearson χ^2 test, or Fisher's exact test for sparse data, were used for comparing frequency of occurrence. For lesion-based analyses, comparison of continuous data was performed by the two-way ANOVA test, with clinical presentation and the number of lesions per patient as variables. The software JMP 5.1.2 (SAS institute) was used for data analysis. A probability value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline patient and lesion characteristics

Clinical diagnosis was ACS in 28 patients (30 lesions) and SAP in 57 patients (65 lesions). ACS group included 13 patients with acute myocardial infarction. The ACS patients group had a reduced left ventricular (LV) ejection fraction (EF)(46.5 $\pm$ 7.0 vs. 54.3 $\pm$ 8.9%, $P = 0.0005$) compared to SAP patients. There were no other differences in baseline patient and lesion characteristics (*Table 1*).

Grey-scale IVUS data of ACS vs. SAP patient lesions

Lesions in ACS patients differed from SAP patients with an increased RI (1.06 $\pm$ 0.23 vs. 0.96 $\pm$ 0.20, $P = 0.011$), a higher prevalence of lesions with positive remodelling (47 vs. 22%, $P = 0.013$), thrombus (20 vs. 1.5%, $P = 0.0037$), and echo-lucent area (23.3 vs. 7.7%, $P = 0.047$). At the minimum lumen diameter (MLD) site of ACS patient lesions, there was a trend for increased vessel area and plaque burden, although not reaching statistical significance (*Table 2*).

VH data of ACS vs. SAP patient lesions

Plaque components are given in square millimetres and as per cent plaque area at the MLD, and as volume and per cent volume for the entire lesion length (*Table 2*). At the MLD, fibrous plaque CSA was significantly larger in ACS patient lesions than in SAP patient lesions when expressed in relative value (66.0 $\pm$ 10.7 vs. 61.4 $\pm$ 8.9%, $P = 0.034$), but not when expressed in absolute value. On the other hand, necrotic core and dense calcium plaque CSA were smaller in ACS patient lesions when expressed in relative value (Necrotic core: 6.8 $\pm$ 6.0 vs. 11.0 $\pm$ 8.3%, $P = 0.02$; Dense calcium: 2.6 $\pm$ 3.0 vs. 4.9 $\pm$ 5.8%, $P = 0.03$), but not when expressed in absolute value. For the volumetric analysis of the entire lesion length, fibrous plaque volume was significantly larger in ACS patient lesions when expressed either as absolute or relative values (128.0 $\pm$ 89.9 vs. 85.4 $\pm$ 56.6 mm^3, $P = 0.0077$; 67.9 $\pm$ 7.3 vs. 63.9 $\pm$ 8.4%, $P = 0.044$). Fibro-fatty volume was also larger in ACS patients, but only when expressed as absolute

Table 1 Baseline patient and lesion characteristics

	ACS (patients = 28; lesions = 30)	SAP (patients = 57; lesions = 65)	*P*-value
Age (years)	63.5 ± 17.1	65.4 ± 9.2	0.50
Male sex	25 (89.3)	46 (80.7)	0.37[a]
Diabetes mellitus	7 (25)	22 (38.6)	0.21
Current smoker	10 (35.7)	20 (35.1)	0.95
Hypertension	17 (60.7)	36 (63.2)	0.83
Hypercholesterolemia	13 (46.4)	36 (63.2)	0.14
Multivessel disease	9 (32.1)	16 (28.1)	0.70
LV EF (%)	46.5 ± 7.0	54.3 ± 8.9	0.0005
Target coronary artery			0.16
LM	0	9 (14.1)	
LAD	10 (33.3)	19 (29.7)	
LCX	5 (16.7)	12 (18.7)	
RCA	15 (50)	24 (37.5)	

Data are expressed as number with frequency (%) in parentheses or as mean ± standard deviation. LM, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right cornoary artery.
[a]Fisher's exact test.

values (43.4 ± 34.6 vs. 30.1 ± 25.5 mm^3, $P = 0.035$). Regarding the VH qualitative assessment, no differences in rate of TCFA, thick FA, or for the presence of multiple necrotic core layers were observed between both groups (*Table 2*).

Discussion

Data of our study can be summarized as follows: (i) clinical characteristic and grey-scale data are in line with previously published data, with an increased frequency of positive remodelling, echo-lucent zone, and presence of thrombus in ACS lesions compared to SAP lesions. (ii) Plaque composition obtained by VH IVUS is in contradiction with the histopathology data, with less necrotic core and more fibrous tissue in ACS lesions.

Epidemiology of vulnerable plaques

In vivo detection of vulnerable plaque would allow initiating specific therapies before a coronary event occurs. About 80% of all infarctions result from thrombosis of a lesion, which by itself is not haemodynamically significant. This does not mean that a mild/moderate stenosis has an increased risk of inducing an acute event compared to a severe stenosis, but reflects the fact that mild/moderate lesions by far outnumber flow-limiting lesions by a factor of about 10. It is, therefore, the cumulative risk of all the non-significant stenosis that prevails.[15–19] The interest in clinical practice is, however, to detect mild/moderate vulnerable lesions, as the significant ones will anyway receive the appropriate treatment.

Prospective angiographic studies investigating the annual acute event risk of a mild/moderate coronary lesion for an acute event reported rates varying from 2 to 12%.[9–11] Only a few studies looked at the features of coronary plaques before an event occurred, and they showed an increased rate of IVUS echo-lucent zones, higher RI, and a marked eccentric pattern.[14] In another prospective study using integrated backscatter IVUS, increased lipid area (72 ± 10% vs. 50 ± 16%, $P < 0.0001$) and decreased fibrous area (23 ± 6% vs. 47 ± 14%, $P < 0.0001$) were observed in patients who subsequently suffered ischaemic events.[12]

Most of our knowledge about the morphological characteristics of plaques that are vulnerable and have a high risk of disruption has been obtained from necropsy studies analysing lesions that have already undergone disruption. In our study, we consequently chose to investigate culprit significant lesions, to allow an adequate comparison with autopsy studies. Indeed, before trying to detect mild/moderate vulnerable plaques, clinical validation/confirmation of VH on the subset of lesions that have been studied (autopsy) is necessary.

Characteristics of vulnerable plaques

Studies of the pathology of plaques in the human aorta and coronary arteries that have undergone disruption have been used to determine the characteristics of intact plaques that have a risk of disruption. Autopsy studies and study of material retrieved at atherectomy in stable and unstable angina show that currently stable plaques whose structure and composition makes them likely to undergo an episode of thrombosis in the future include a large lipid core, a thin fibrous cap, and a high macrophage density.[4–8,25–28]

There is, however, only scarce data giving the amount of the different plaque components as absolute or relative numbers. Besides, different terminology and slightly different definitions have been used to describe the presence of extracellular lipid and necrotic materials (necrotic core, lipid pool, pultaceous debris, etc.). In a necropsy study of subjects dying of SCD secondary to IHD, looking at aortic plaque with or without ulcerations, the amount of lipid pool was significantly higher in ulcerated plaques compared to intact plaque (56.7% vs. 12.7%, $P =$ significant) with a cutoff value of more than a 40% lipid pool area between both groups.[5] In another SCD necropsy study comparing coronary plaque morphology between subjects who died of acute MI with SCD subjects who had significant CAD but no signs of myocardial necrosis, more necrotic core was observed in the former group in lesions with >75% stenosis (16% vs. 7%, $P = 0.01$) but no differences in mild or

Table 2 Grey scale and VH data

	ACS (lesions = 30)	SAP (lesions = 65)	*P*-value
Grey-scale IVUS data			
MLD LA mm^2	4.28 ± 1.16	4.22 ± 0.92	0.78
MLD VA mm^2	18.47 ± 4.81	17.05 ± 5.2	0.18
MLD PA mm^2	14.4 ± 4.95	12.98 ± 4.87	0.16
MLD PA (%)	75.6 ± 8.4	74.3 ± 6.3	0.31
RI	1.06 ± 0.23	0.96 ± 0.20	0.011
Pos RI >1.05	14 (47%)	14 (22%)	0.013
Echo-lucent area	7 (23.3%)	5 (7.7%)	0.047
Thrombus	6 (20%)	1 (1.5%)	0.0037
Plaque composition at MLD			
F MLD mm^2	7.01 ± 3.12	5.81 ± 2.78	0.06
FF MLD mm^2	2.78 ± 1.61	2.34 ± 2.06	0.25
NC MLD mm^2	0.70 ± 0.66	0.95 ± 0.70	0.16
DC MLD mm^2	0.27 ± 0.32	0.39 ± 0.46	0.19
F MLD (%)	66.0 ± 10.7	61.4 ± 8.9	0.034
FF MLD (%)	25.6 ± 9.8	22.1 ± 12.4	0.16
NC MLD (%)	6.8 ± 6.0	11.0 ± 8.3	0.02
DC MLD (%)	2.6 ± 3.0	4.9 ± 5.8	0.03
Plaque composition over entire lesion length			
F ROI mm^3	128.0 ± 89.9	85.4 ± 56.6	0.0077
FF ROI mm^3	43.4 ± 34.6	30.1 ± 25.5	0.035
NC ROI mm^3	11.9 ± 12.4	12.6 ± 11.0	0.82
DC ROI mm^3	6.7 ± 9.9	6.3 ± 7.7	0.82
F ROI (%)	67.9 ± 7.3	63.9 ± 8.4	0.044
FF ROI (%)	23.8 ± 9.7	21.4 ± 9.8	0.18
NC ROI (%)	7.5 ± 5.9	10.1 ± 6.1	0.071
DC ROI (%)	3.0 ± 2.8	5.3 ± 7.8	0.11
Qualitative data			
TCFA	2 (7%)	11 (17%)	0.22[a]
Thick FA	4 (13.3%)	4 (6.1%)	0.26[a]
Multiple NC layer	4 (13.3%)	17 (26.2%)	0.16

Data are expressed as mean ± standard deviation or as number with frequency (%) in parentheses. F, fibrous; FF, fibro-fatty; NC, necrotic core; DC, dense calcium; ROI, region of interest.
[a]Fisher's exact test.

moderate lesions (6% vs. 4%, P = ns).[7] Mauriello *et al.*[8] showed that necrotic core of the culprit lesions in SCD subjects due to AMI was 58.5 ± 4.9%, with the minimum value being 30%. In the SCD series of Virmani *et al.*,[29] ruptured culprit coronary lesions had 34 ± 17% necrotic core. Atherectomy data looking at plaque composition differences between ACS and stable angina patients also showed an increased incidence and percentage of lipid pool in ACS culprit lesions compared to target SA lesions.[26,27,30] *In vivo* data obtained by grey-scale IVUS and angioscopy show similar trends between lesions in ACS compared to stable angina patients.[31–34]

In our study, clinical characteristic and grey-scale data are in line with previously published data. Lesions in ACS patients have been described to be associated with an increased frequency of positive remodelling, echo-lucent zone, and the presence of thrombus, which is similar in our data.[31,33–35] This confirms that our ACS lesions population is indeed a high-risk population. Our *in vivo* VH IVUS data are, however, in contradiction with the pathological data. Pathological data show that high-risk plaques have more necrotic core (lipid pool) and less fibrous tissue than stable plaques. Besides, the percentage occupied by the lipid pool area is reported to be high, with values far greater than those obtained by VH IVUS. A recently published study comparing the coronary plaque composition of non-culprit lesions, obtained by VH IVUS in ACS and SAP patients, also shows results contradicting ours.[36] In this study, data are reported only at the MLD site as relative values. The plaque composition values obtained for the overall study population are very similar between both studies (Rodriguez *et al.*: NC = 9.43 ± 6.6%, DC = 0.99 ± 0.9%, F = 68.04 ± 9.8%, FF = 19.31 ± 7.3; Our data: NC = 9.7 ± 7.8%, DC = 4.11 ± 5.2%, F = 62.9 ± 9.7%, FF = 23.2 ± 11.7%). However, comparison between groups has the opposite significance or trend. Some of the differences might result from differences in patient/lesion population, as they investigated non-culprit

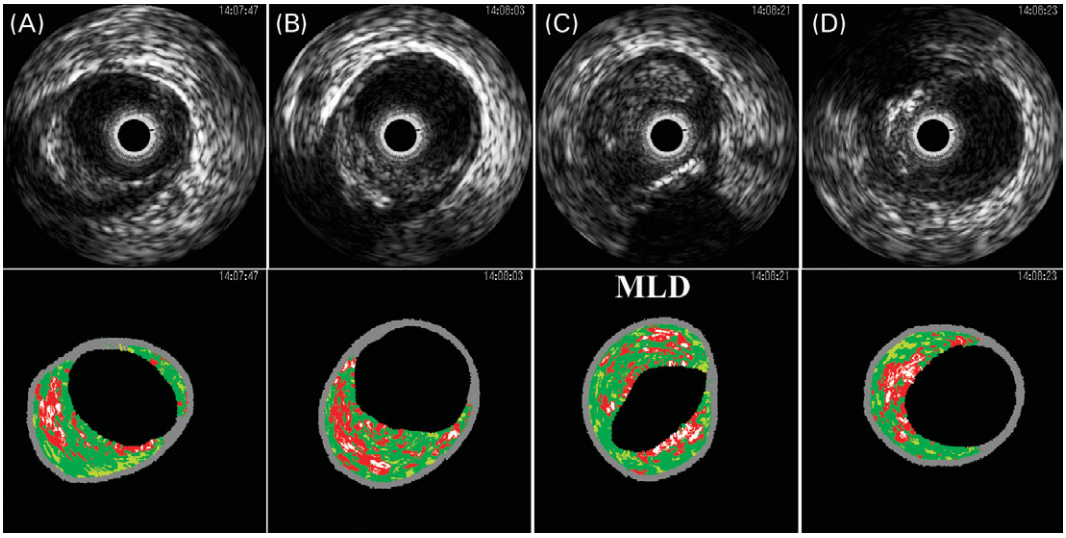

Figure 1 Four cross-sectional images from proximal to distal within a same lesion. Grey-scale IVUS is displayed on the upper panels, and reconstructed IVUS-VH images on the lower panels. A thick fibrous cap overlying a necrotic core can be seen in (*A*). In (*B*), another thick FA can be seen, but the thick overlying fibrous cap contains small spots of necrotic core. In (*D*), a TCFA can be seen. (*C*) shows the MLD site. Fibrous, fibro-fatty, necrotic core, and dense calcium are labelled green, yellow, red, and white, respectively.

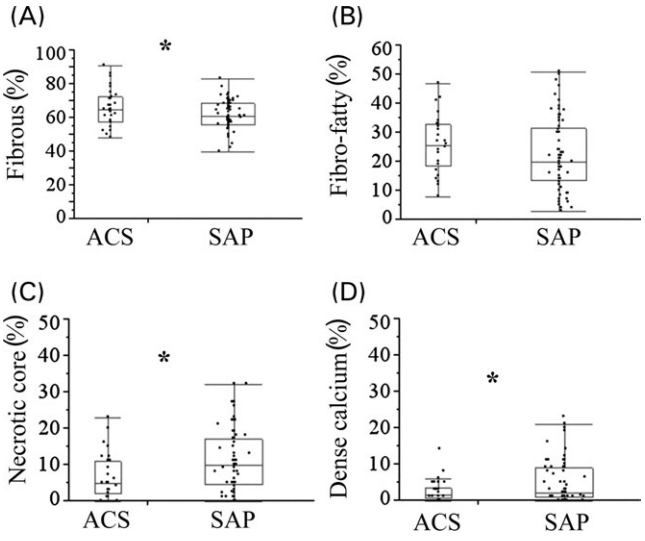

Figure 2 Point representation (jittered display) with superimposed box plot of the four VH components at the MLD site expressed as relative values. Although statistical significance is achieved for three components, a large overlap of the individual values can be observed. *$P < 0.05$.

lesions with less than 50% stenosis and we investigated culprit or target lesions with significant stenosis (>75% stenosis). From a theoretical point of view, these differences in lesion selection should have influenced the results in the opposite direction. As mentioned earlier, significant stenoses have *per se*, a higher risk of inducing acute events. Besides, in the necropsy study from Kragel *et al.*,[7] differences in necrotic core between ACS and SAP lesions were observed only for significant stenosis (>75% stenosis). Also, most of our knowledge of vulnerable plaque comes from plaques that have ruptured, which is in this regard probably similar to culprit lesions in ACS patients. Presence of thrombus in ACS lesions may have influenced the plaque composition, as thrombus is not recognized as a different component, but assigned one of the four available colours (usually green or yellow from our experience). This may have also influenced the results for other plaque components, such as necrotic core or dense calcium, when expressed as relative values but not when expressed in absolute values. Another limitation may lie in the VH validation itself. *Ex vivo* VH validation studies have reported a high accuracy for the classification of plaque components. Those studies analysed selected regions of interest representing homogeneous plaque components on the histology specimen. However, validation studies for VH tissue maps of entire plaque cross sections, in terms of absolute or relative values, have not yet been published. Regarding the definition used for TCFA, we should remember that the resolution of VH IVUS is about 100–200 μm, which is above the histopathological definition of a thin fibrous cap (<65 μm). It is, therefore, not certain that the VH definition used for the detection of TCFA can be applied for this purpose, since it has not been validated in histopathological studies.

Although atherosclerosis is a pan-coronary syndrome, coronary thrombosis occurs at focal sites of increased vulnerability. It is difficult to know which way of reporting the data is clinically the most appropriate (*Figure 1*). We, therefore, reported the data as absolute and as relative values at the MLD site and for the entire lesion length. Another concern is that although statistical significance is achieved for some components, the clinical significance seems, however, small. A clinical cut-off value is difficult to define, due to the important overlap of the individual values in both clinical presentations, as illustrated in *Figure 2*.

Conflict of interest: none declared.

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