The International Journal of Cardiovascular Imaging (2019) 35:1785–1790
https://doi.org/10.1007/s10554-019-01639-0

ORIGINAL PAPER

Imaging assessment and accuracy in coronary artery autopsy: comparison of frequency-domain optical coherence tomography with intravascular ultrasound and histology

Aiko Shimokado[1] · Takashi Kubo[1] · Yoshiki Matsuo[1] · Yasushi Ino[1] · Yasutsugu Shiono[1] · Kunihiro Shimamura[1] · Yosuke Katayama[1] · Akira Taruya[1] · Tsuyoshi Nishiguchi[1] · Manabu Kashiwagi[1] · Hironori Kitabata[1] · Atsushi Tanaka[1] · Takeshi Hozumi[1] · Takashi Akasaka[1]

Received: 24 January 2019 / Accepted: 27 May 2019 / Published online: 7 June 2019

Abstract

Optical coherence tomography (OCT) is a coronary artery imaging technique with high resolution. Second-generation frequency-domain OCT (FD-OCT) technology allows safer and faster clinical application compared with first-generation time-domain OCT (TD-OCT). Only limited validation studies compare FD-OCT with other modes of analysis: histology, which is the current gold standard, and intravascular ultrasound (IVUS). This study therefore aims to demonstrate the accuracy of FD-OCT images compared with IVUS and histology. FD-OCT and IVUS images were acquired from 203 segments from 31 coronary arteries obtained at autopsy from 20 cadavers. Of these, 30 randomly-selected pairs were used to create three classifications of plaque type based on morphological features in FD-OCT and IVUS compared with corresponding histopathology. The remaining 173 pairs were used to demonstrate the diagnostic accuracy for classification of coronary plaques by FD-OCT. Plaque type distributions were 27% fibroatheroma, 22% fibrocalcific plaque and 51% fibrous plaque. The diagnostic accuracies of FD-OCT for fibroatheroma, fibrocalcific plaque and fibrous plaque were 90, 95 and 93%, respectively. Those of IVUS were 81, 89 and 84%, respectively. FD-OCT achieved high diagnostic accuracy for the classification of coronary plaques comparable to TD-OCT. Physicians should consider the differences in the ability to classify plaque morphology of OCT of imaging devices when applying their use.

Keywords Optical coherence tomography · Frequency-domain OCT · Intravascular ultrasound · Plaque classification

Introduction

Optical coherence tomography (OCT) generates unprecedented intracoronary images with high resolution [1]. Time-domain OCT (TD-OCT) was the first-generation implementation of the modality developed for intravascular imaging, and, compared to other conventional devices, it provided extremely high resolution, in vivo images of superficial histological findings [2]. However, the probe was not a monorail-type rapid exchange catheter, but a low-profile Imagewire that was advanced through an over-the-wire occlusion balloon catheter after exchanging it with the guidewire. To perform imaging, blood clearance was achieved with proximal balloon occlusion and distal low-volume Ringer's lactate solution injection, and a 0.5–1.5 mm/s pullback was performed over 30 s, resulting in transient ischemia that could cause complications. A non-occlusive method of continuous low-molecular weight dextran infusion was later developed to simplify the imaging procedure, but acquisition remained slow and limited [3]. Second generation frequency-domain OCT (FD-OCT) technology allows safer and faster clinical application than first-generation TD-OCT [4]. There are also structural improvements in FD-OCT over TD-OCT, such as use of a tunable light source and the fixation of mechanically rotated mirrors. These changes in technology result in a better signal-to-noise ratio and faster sweeps, allowing a dramatically faster image acquisition and pullback speed than TD-OCT [5]. Much research has been performed to validate the accuracy of TD-OCT compared

✉ Takashi Kubo
takakubo@wakayama-med.ac.jp

[1] Department of Cardiovascular Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8510, Japan

with histology, which is the gold standard, and compared with intravascular ultrasound (IVUS). Meanwhile, only limited validation studies which compare FD-OCT to TD-OCT and to histology are available [5, 6]. A lack of correlation between FD-OCT images of neointima after stenting and corresponding histological tissue characteristics was suggested in a previous study [6]. FD-OCT images generated by newer technology therefore require reevaluation. This study aims to demonstrate the accuracy of FD-OCT images compared with IVUS and histology.

Methods

Autopsy specimens

This study complies with the Declaration of Helsinki and the protocol was approved by the Wakayama Medical University Institutional Review Board. Written informed consent was obtained from relatives. Thirty-one coronary arteries were obtained between September 2011 and June 2014 from 20 cadavers. The major coronary arteries were examined by both FD-OCT and IVUS imaging immediately after removal of the heart from cadavers, within 72 h after death. Following FD-OCT and IVUS image acquisition as described below, the coronary arteries were pressure-fixed in formalin and decalcified if necessary using ethylenediaminetetraacetic acid to maintain its orientation and size for comparison with FD-OCT and IVUS images, as previously described [7]. The proximal and middle portions of the three coronary arteries were examined, but the left main coronary artery, distal portion, and all branches were not.

Histological processing

The segments were serially sectioned to the longitudinal axis of the vessel at 3-mm intervals. From the distal side of each 3-mm block, 4-μm histopathology slides were prepared and stained with hematoxylin and eosin (HE). Each histopathology slide was digitized using a microscope at low magnification (×1.25). The measurements of external elastic membrane area and luminal area were determined by Image J software (National Institutes of Health, Bethesda, MD).

The histopathological cross sections were reviewed by a histology observer (A.S.) blinded to clinical, FD-OCT and IVUS data.

FD-OCT and IVUS image acquisition

At FD-OCT image acquisition, the Dragonfly OCT imaging catheter (Abbott Vascular, Santa Clara, CA) was introduced into the coronary artery with a guide wire. When possible, the guide wire was removed for image acquisition. Sequential FD-OCT images were obtained at a pullback rate of 20 mm per second during continuous infusion of phosphate-buffered saline perfused at 100 mmHg using a pressure infusor. For offline analysis, FD-OCT images were acquired at 100 frames per second and were digitally archived in the frequency-domain OCT C7XR imaging system (Abbott Vascular). Likewise, IVUS imaging was performed using IVUS system (iLab™ Boston Scientific. Fremont, CA) and a 40-MHz Atlantis SR Pro 2/OptiCross IVUS catheter (Boston Scientific) at 0.5 mm per second pullback. All images were stored digitally for subsequent analysis.

OCT and IVUS image interpretation and analysis

Offline FD-OCT analysis was performed using the proprietary OCT console software (Abbott Vascular) by two experienced independent observers (Y.M. and T.N.) blinded to both histopathology and IVUS. In the case of discordance between the observers, a consensus reading was obtained. FD-OCT images were analyzed using previously validated criteria for plaque characterization and classified into the following three plaque types: fibroatheroma (lipid plaque), fibrocalcific plaque, or fibrous plaque [8]. Briefly, fibroatheroma were defined as signal-poor regions with diffusely delineated borders, calcium was defined as a signal-poor region with sharply delineated border and fibrous plaques were defined as homogenous and signal-rich regions [9]. All IVUS images were analyzed by study-blinded, experienced observers (Y.K. and A.T.) using QIvus (iMAP Basic Viewer version 3.0.12.0; Medis Medical Imaging, Leiden, the Netherlands).

Correlation between histopathology and intracoronary images

Out of 1463 cross sections from 31 arteries (13 left anterior descending, 7 left circumflex and 11 right coronary arteries) in 20 cadavers, 231 cross sections were analyzable by all three modes of analysis. The histopathological cross sections and corresponding FD-OCT and IVUS images were matched using luminal configuration and anatomical landmarks, such as side branches, perivascular structures and distances from side branches or distal end [10]. From the 203 pairs of histopathological cross sections and corresponding images after excluding adaptive intimal thickening (n = 28) to focus on plaque classification, 30 pairs in 16 arteries (6 left anterior descending, 6 left circumflex and 4 right coronary arteries) were randomly selected for a training data set and used to create three plaque type classifications on the basis of morphological features in FD-OCT and IVUS as compared with corresponding histopathology. Subsequently, the remaining 173 pairs in 31 arteries (13 left anterior descending, 7 left circumflex and 11 right coronary arteries) were used as a validation data set. The FD-OCT and IVUS definitions for plaque morphology established from the training data set were prospectively applied for the validation data set.

Coronary artery branches containing microvessels were measured in histology stained by HE, FD-OCT and IVUS images, and categorized into three ranges: medium to large branch (> 300 µm), microvessel (50 to 300 µm) and small microvessel (< 50 µm). Vessel was defined as a no-signal tubuloluminal structure and recognized on at least three consecutive cross-sectional FD-OCT or IVUS images.

Statistical analysis

Data analyses were performed using JMP pro 13.0 (SAS Institute, Cary, NC, USA). Continuous values were expressed as mean ± standard deviation and compared by Student's *t* test. Categorical data were reported as absolute values and percentages and analyzed by Pearson's Chi square test, or Fisher's exact test if an expected cell count was < 5. $P < 0.05$ was considered to be statistically significant.

Results

Clinical demographics

Mean age at death of the 20 autopsied subjects was 69 ± 14 years and 17 (85%) were men. The cause of death was ischemic heart disease in two cases (10%), six (30%) had a prior history of coronary artery disease. Hypertension, type 2 diabetes mellitus and smoking were documented in seven (35%), six (30%) and three (15%) patients, respectively (Table 1).

Table 1 Clinical characteristics of donors for autopsy studies

Patients, n	20
Age, years (SD)	69 (14)
Male, n (%)	17 (85)
Cardiac death, n (%)	2 (10)
Prior PCI, n (%)	5 (25)
Prior CABG, n (%)	1 (5)
Coronary risk factor	
Hypertension, n (%)	7 (35)
Diabetes mellitus, n (%)	6 (30)
Dyslipidemia, n (%)	4 (20)
Smoking, n (%)	3 (15)

PCI percutaneous cardiovascular intervention, *CABG* coronary artery bypass graft surgery

Plaque classification

A total of 203 sections were analyzed. Adaptive intimal thickening (n = 28) was excluded from plaque classification. The histological lesion characteristics and the representative images are shown in Table 2 and Fig. 1, respectively. Of these, thirty sections were classified into three types as the training set. Plaque type distributions were 13% fibroatheroma, 27% fibrocalcific plaque and 60% fibrous plaque. In the validation data set, plaque type distributions were 27% fibroatheroma, 22% fibrocalcific plaque and 51% fibrous plaque and the diagnostic accuracies of FD-OCT for fibroatheroma, fibrocalcific plaque and fibrous were 90, 95 and 93%. Those of IVUS were 81, 89 and 84% (Table 3).

Detection of branches or microvessels by intracoronary imaging devices

Histology detected 25 vessels. Both FD-OCT and IVUS identified most of the medium in large vessels (16/17, 15/17, respectively). FD-OCT identified 67% of microvessels, but IVUS could not detect any. Small microvessels were undetected by both FD-OCT and IVUS (Table 4).

Discussion

We demonstrated that FD-OCT was superior to IVUS in terms of accuracy for assessment of plaque type and detection of microvessels. Moreover, we demonstrated that FD-OCT achieved high diagnostic accuracy for the classification of coronary plaques, similar to that of TD-OCT.

In the current study, the sensitivity and specificity of FD-OCT for plaque classification were similar or better to those of TD-OCT. Ranges of sensitivity and specificity of TD-OCT compared with histology have been reported as 69 to 94% and 88 to 94% for lipid-rich plaque, 67 to 95% and 92 to 97% for fibrocalcific plaque, and 64 to 88% and 88 to 98% for fibrous plaque [1, 11, 12]. In the current

Table 2 Histological lesion characteristics

n	173
RCA/LAD/LCx, n	59/74/40
Proximal/mid/distal, n	82/81/10
Vessel area, mm^2 (SD)	9.1 (3.7)
%stenosis, % (SD)	64.1 (9.6)
Plaque classification	
Fibroatheroma, n (%)	47 (27)
Fibrocalcium, n (%)	38 (22)
Fibrous, n (%)	88 (51)

LAD left anterior descending artery, *LCx* left circumflex artery, *RCA* right coronary artery

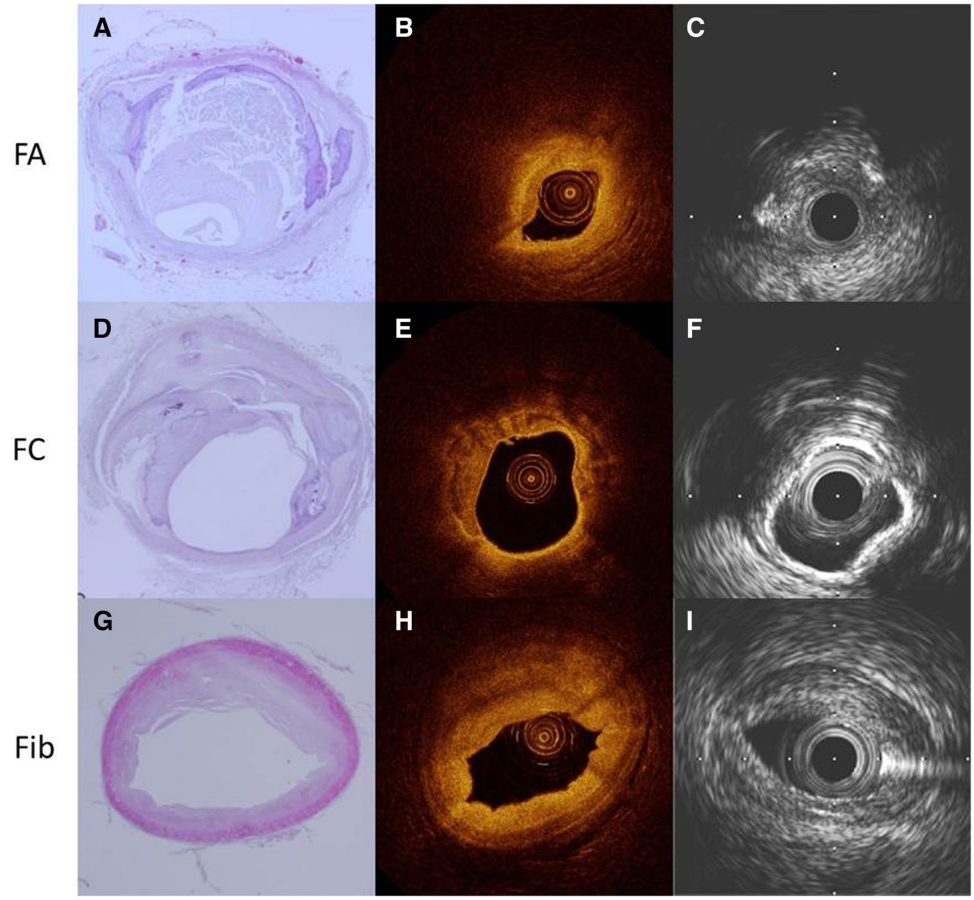

Fig. 1 Representative histology, OCT and IVUS images for each plaque classification. **a** Histological image of fibroatheroma. **b** and **c** Corresponding FD-OCT and IVUS images in A. **d** Histological image of fibrocalcific plaque. **e** and **f** Corresponding FD-OCT and IVUS images in **d**. **g** Histological image of fibrous plaque. **h** and **i** Corresponding FD-OCT and IVUS images in G. *FA* fibroatheroma, *FC* fibrocalcific plaque, *Fib* fibrous plaque, *IVUS* intravascular ultrasound, *FD-OCT* frequency-domain optical coherence tomography

Table 3 (A) Assessment of FD-OCT criteria for characterization. (B) Assessment of IVUS criteria for characterization

	Histology			Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	FA	FC	Fib						
(A)									
FD-OCT									
FA	39	6	6	51	89	91	77	96	90
FC	0	33	1	34	83	99	97	95	95
Fib	5	1	82	88	92	94	93	93	93
Total	44	40	89	173					
(B)									
IVUS									
FA	14	2	1	17	32	98	82	81	81
FC	10	35	4	49	88	90	71	96	89
Fib	20	3	84	107	94	77	79	97	84
Total	44	40	89	173					

FA fibroatheroma, *FC* fibrocalcific plaque, *FD-OCT* frequency-domain optical coherence tomography, *Fib* fibrous plaque, *IVUS* intravascular ultrasound, *NPV* negative predictive value, *PPV* positive predictive value

study, FD-OCT had a sensitivity and specificity of 89 and 91% for lipid plaque, 83 and 99% for fibrocalcific plaque, and 92 and 94% for fibrous plaque.

On the other hand, the sensitivity and specificity ranges of IVUS compared with histology have been reported as 10 to 70% and 81 to 96% for lipid-rich plaque, 37 to 98% and 94

Table 4 Microstructure identification

	Histology	FD-OCT	IVUS
Macrophage, n	24	19	–
Branch			
Medium to large > 300 µm, n	17	16	15
Microvessel (50–300 µm), n	3	2	0
Small microvessel < 50 µm, n	5	0	0

FD-OCT frequency-domain optical coherence tomography, *IVUS* intravascular ultrasound

to 98% for fibrocalcific plaque, and 63 to 89% and 59 to 90% for fibrous plaque [11–15]. In our study, sensitivity and specificity of IVUS compared with histology were 32 and 98% for lipid plaque, 88 and 90% for fibrocalcific plaque and 94 and 77% for fibrous plaque. Aside from the inferior specificity for fibrocalcific plaque, this is accuracy concordant with that of previous reports. We attributed the low sensitivity for lipid plaque to the difficulty in distinguishing it from fibrous plaque. One reason for this is that extracellular lipid deposit plaque that did not have lipid core was common. Other reasons are the imaging problems of non-uniform rotational distortion (NURD) and comparatively low resolution. For this study, we utilized 40 MHz IVUS. If recently developed 60 MHz IVUS was utilized instead, the accuracy of IVUS plaque identification may have improved [16]. Finally, there were also misclassified calcific plaques. Calcium closer to the lumen than target plaque influences the diagnosis. FD-OCT was also shown to be superior to IVUS for the identification of both vessels and macrophages.

Our present study has some limitations including the small sample size and it being a single-center study. In performing intracoronary imaging and histology validation, there might be a fundamental difficulty in aligning OCT and IVUS images with their histologic counterparts, leading to the potential error despite meticulous attention. We did not perform comparisons between TD-OCT and FD-OCT. Further work is needed to overcome these limitations, but we believe the results of this study, using autopsy hearts and over a relatively long period of time, are important to fundamental understanding of the potential of FD-OCT. In the current study, we focused on assessment of autopsy tissue. Based on the ideas raised by Bezerra et al., future study will focus on application of FD-OCT for detection of native coronary disease compared with detection by IVUS and histology. FD-OCT reportedly depicts severe native coronary artery disease better than IVUS owing to clearer depiction of vessel lumen.

FD-OCT has high diagnostic ability in classification of coronary plaques comparable to TD-OCT. Physicians should consider the potential of modality-based measurement differences of imaging devices when applying their use.

Acknowledgements The authors would like to thank Mayumi Akira for technical assistance and Yasuteru Muragaki, Department of Pathology and Shin-ichi Murata, Department of Human Pathology, Wakayama Medical University, Wakayama, Japan, for their valuable advice regarding the pathological aspects of this work. We acknowledge proofreading by Benjamin Phillis, Clinical Study Support Center, Wakayama Medical University.

Compliance with ethical standards

Conflict of interest Takashi Kubo has received lecture fees from Abbott Vascular. Yasutsugu Shiono received lecture fees from Abbott Vascular. T. Akasaka has received lecture fees from Abbott Vascular and Boston Scientific, and research grants from Abbott Vascular. No other authors have relationships to disclose relevant to the contents of this paper.

References

1. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, Kauffman CR, Shishkov M, Kang DH, Halpern EF, Tearney GJ (2002) Characterization of human atherosclerosis by optical coherence tomography. Circulation 106(13):1640–1645
2. Jang IK, Tearney GJ, MacNeill B, Takano M, Moselewski F, Iftima N, Shishkov M, Houser S, Aretz HT, Halpern EF, Bouma BE (2005) In vivo characterization of coronary atherosclerotic plaque by use of optical coherence tomography. Circulation 111(12):1551–1555. https://doi.org/10.1161/01.CIR.0000159354.43778.69
3. Kataiwa H, Tanaka A, Kitabata H, Imanishi T, Akasaka T (2008) Safety and usefulness of non-occlusion image acquisition technique for optical coherence tomography. Circ J 72(9):1536–1537
4. Bezerra HG, Attizzani GF, Sirbu V, Musumeci G, Lortkipanidze N, Fujino Y, Wang W, Nakamura S, Erglis A, Guagliumi G, Costa MA (2013) Optical coherence tomography versus intravascular ultrasound to evaluate coronary artery disease and percutaneous coronary intervention. JACC Cardiovasc Interv 6(3):228–236. https://doi.org/10.1016/j.jcin.2012.09.017
5. Hamdan R, Gonzalez RG, Ghostine S, Caussin C (2012) Optical coherence tomography: from physical principles to clinical applications. Arch Cardiovasc Dis 105(10):529–534. https://doi.org/10.1016/j.acvd.2012.02.012
6. Lutter C, Mori H, Yahagi K, Ladich E, Joner M, Kutys R, Fowler D, Romero M, Narula J, Virmani R, Finn AV (2016) Histopathological differential diagnosis of optical coherence tomographic image interpretation after stenting. JACC Cardiovasc Interv 9(24):2511–2523. https://doi.org/10.1016/j.jcin.2016.09.016
7. Asakura T, Karino T (1990) Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circ Res 66(4):1045–1066
8. Tian J, Ren X, Vergallo R, Xing L, Yu H, Jia H, Soeda T, McNulty I, Hu S, Lee H, Yu B, Jang IK (2014) Distinct morphological features of ruptured culprit plaque for acute coronary events compared to those with silent rupture and thin-cap fibroatheroma: a combined optical coherence tomography and intravascular ultrasound study. J Am Coll Cardiol 63(21):2209–2216. https://doi.org/10.1016/j.jacc.2014.01.061
9. Kitabata H, Tanaka A, Kubo T, Takarada S, Kashiwagi M, Tsujioka H, Ikejima H, Kuroi A, Kataiwa H, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Hirata K, Nakamura N, Mizukoshi M, Imanishi T, Akasaka T (2010) Relation of microchannel structure identified by optical coherence tomography to plaque vulnerability in patients with coronary artery disease. Am J

Cardiol 105(12):1673–1678. https://doi.org/10.1016/j.amjcard.2010.01.346
10. Lee JB, Mintz GS, Lisauskas JB, Biro SG, Pu J, Sum ST, Madden SP, Burke AP, Goldstein J, Stone GW, Virmani R, Muller JE, Maehara A (2011) Histopathologic validation of the intravascular ultrasound diagnosis of calcified coronary artery nodules. Am J Cardiol 108(11):1547–1551. https://doi.org/10.1016/j.amjcard.2011.07.014
11. Rieber J, Meissner O, Babaryka G, Reim S, Oswald M, Koenig A, Schiele TM, Shapiro M, Theisen K, Reiser MF, Klauss V, Hoffmann U (2006) Diagnostic accuracy of optical coherence tomography and intravascular ultrasound for the detection and characterization of atherosclerotic plaque composition in ex vivo coronary specimens: a comparison with histology. Coron Artery Dis 17(5):425–430
12. Guo J, Sun L, Chen YD, Tian F, Liu HB, Chen L, Sun ZJ, Ren YH, Jin QH, Liu CF, Han BS, Gai LY, Yang TS (2012) Ex vivo assessment of coronary lesions by optical coherence tomography and intravascular ultrasound in comparison with histology results. Zhonghua Xin Xue Guan Bing Za Zhi 40(4):302–306
13. Farb A, Burke AP, Tang AL, Liang Y, Mannan P, Smialek J, Virmani R (1996) Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. Circulation 93(7):1354–1363. https://doi.org/10.1161/01.cir.93.7.1354
14. Kume T, Akasaka T, Kawamoto T, Watanabe N, Toyota E, Neishi Y, Sukmawan R, Sadahira Y, Yoshida K (2006) Assessment of coronary arterial plaque by optical coherence tomography. Am J Cardiol 97(8):1172–1175. https://doi.org/10.1016/j.amjcard.2005.11.035
15. Brown AJ, Obaid DR, Costopoulos C, Parker RA, Calvert PA, Teng Z, Hoole SP, West NE, Goddard M, Bennett MR (2015) Direct comparison of virtual-histology intravascular ultrasound and optical coherence tomography imaging for identification of thin-cap fibroatheroma. Circ Cardiovasc Imaging 8(10):e003487. https://doi.org/10.1161/CIRCIMAGING.115.003487
16. Katagiri Y, Tenekecioglu E, Serruys PW, Collet C, Katsikis A, Asano T, Miyazaki Y, Piek JJ, Wykrzykowska JJ, Bourantas C, Onuma Y (2017) What does the future hold for novel intravascular imaging devices: a focus on morphological and physiological assessment of plaque. Expert Rev Med Devices 14(12):985–999. https://doi.org/10.1080/17434440.2017.1407646