Medical Sciences 2020 Vol. 8 (19), p. 151-159

e-ISSN: 2345-0592
Online issue
Indexed in *Index Copernicus*

Medical Sciences

Official website:
www.medicsciences.com

Comparison of coronary plaque components between non-culprit lesions in patients with acute coronary syndrome without ST segment elevation and target lesions in patients with stable angina: virtual histology – intravascular ultrasound analysis.

Norvydas Zapustas[1], Ali Aldujeli[1], Ramūnas Unikas[1]

[1]*Hospital of Lithuanian University of Health Sciences Kauno klinikos. Department of interventional Cardiology, Kaunas, Lithuania.*

ABSTRACT

Objective: Patients with acute coronary syndrome (ACS) are thought to have multiple vulnerable coronary plaques components, comparing with stable angina (SAP) patients. We compared relationship between coronary plaque components of non-culprit lesions in patients with acute coronary syndrome without ST segment elevation and target lesions in patients with stable angina: virtual histology – intravascular ultrasound (VH-IVUS) analysis.

Methods: We compared virtual histology – intravascular ultrasound findings between 25 ACS without ST segment elevation non-culprit lesions and 22 stable angina target lesions. Using virtual histology – intravascular ultrasound classified the color-coded tissue into four major components: green (fibro-elastic); light green (fibro-fatty); white (dense calcium) and red (necrotic). Planar VH-IVUS analysis at the minimum luminal site in stable angina pectoris patients' group and non-culprit lesion at ACS without ST segment elevation and volumetric analysis over a 10-mm-long segment centered at the minimum luminal site was performed.

Results. Patients with ACS without ST elevation the plaque burden was significantly smaller (90,8 ±21 mm^3 vs. 102,6 ± 28 mm^3, p <0,05) compared with SAP patients' group. Volumetric analysis showed, non-culprit lesions in acute coronary syndrome without ST segment elevation patients had a greater necrotic core volume (19.1 vs. 12.4, mm^3, p<0,05) and dense calcium volume (15.6 vs. 9.6 mm3, p<0.05) and fibro-fatty volume (15.8 vs. 15.5, mm3, p>0,05) compared with target lesions in stable angina patients at the minimum lumen site.

Conclusions: In the present study, the VH-IVUS detected necrotic core was significantly larger in atherosclerotic lesions in patients in acute phase of ACS without ST elevation compared to the stable angina subjects and it could be considered a marker of plaque vulnerability.

Keywords: intravascular ultrasound, coronary plaque, plaque components.

Introduction

Plaque disruption, with superimposed thrombosis, is the main cause of acute coronary syndromes (ACS) [1, 2]. Ruptured plaques compose the vast majority of atherosclerotic lesions associated with acute thrombi and mor- phological characteristics and histological composition of these plaques have been reported in previous studies. Thin- cap fibroatheroma (TFCA), the lesions most likely to experience rupture, usually have an extensive necrotic core and a thin fibrous cap [3, 4]. Recognition of these high risk atheroma plaques (the so called ‘‘vulnerable’’ plaques) is a challenge for cardiologists as previous studies have suggested that leaving these lesions untreated may be associated with events at follow up [5, 6]. However, an angiographic study reported that plaque instability is not merely a local vascular accident but presumably reflects more generalized pathophysiologic processes with the potential to destabilize atherosclerotic plaques through out the coronary tree [7]). To assess the relevant detail of clinical syndrome (stable and unstable) and coronary plaque morphology is more important for the prevention of ACS. However, the difference of tissue components of atheromatous plaque in the culprit and non-culprit lesions between ACS without ST segment elevation and stable angina pectoris (SAP) has not been fully clarified by use of Virtual histology-intravascular ultrasound (VH-IVUS). So the aim of our study is to assess the tissue characteristics of coronary plaques between ACS without ST segment elevation of non-culprit lesions and SAP of culprit lesion.

Subjects and Methods

Study population

A total of 47 patients were enrolled who had undergone coronary angiography, grayscale and VH-IVUS in non-culprit lesion in ACS without ST segment elevation and in target lesion in SAP patients between January, 2016 and October, 2017 were identified from the Lithuanian University of Health Sciences VH-IVUS registry database. We compared VH-IVUS findings between 25 ACS without ST segment elevation non-culprit lesions and 22 SAP target lesions. The presence of SAP was determined according to the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [8] and ACS with non-ST segment elevation are considered to be closely related conditions whose pathogenesis and clinical presentations are similar, but of differing severity (i.e., they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I). Once it has been established that no biochemical marker of myocardial necrosis has been released, the patient with an ACS may be considered to have experienced unstable angina, whereas the diagnosis of non-ST segment elevation myocardial infarction is established if a marker of myocardial injury has been released [9].

We excluded patients with ST-segment elevation myocardial infarction, Thrombolysis in Myocardial Infarction (TIMI) 0-1 flow, coronary artery bypass graft lesion, chronic total occlusion, restenosis after stenting, important systemic disease such as systemic lupus erythematosus, amyloidosis, sarcoidosis, human immunodeficiency virus infection, and malignancies, and so on, or serum creatinine >2.5 mg/dL. Culprit lesion in ACS without ST segment elevation patients was defined as plaques viewed on an angiogram. Target lesion in SAP patients was defined as a coronary lesion whose diameter stenosis by quantitative coronary angiography (QCA) was greatest if the patient had multivessel disease. Plaques with more than a 30% diameter stenosis as compared with the reference diameter by IVUS were included in our study. Each plaque was separated by at least 5 mm from the edge of any other plaque or implanted stent edge. The protocol was approved by the institutional review board. Hospital records of all patients were reviewed to obtain clinical demographics and medical history.

Coronary angiography

Coronary angiogram was analyzed with validated a QCA system. With the outer diameter of the contrast- filled catheter as the calibration standard, the reference diameter and minimal lumen diameter were measured in diastolic frames from orthogonal projections. Perfusion was evaluated according to TIMI criteria.

Intravascular ultrasound imaging and analysis

VH-IVUS examination was performed before any intervention and after the intracoronary administration of nitroglycerin 0.2 mg using a motorized transducer pullback system (0.5 mm/s) at SAP patient group and after the culprit lesion treatment in ACS without ST segment elevation group. A 2.9Fr IVUS imaging catheter (Eagle Eye; Volcano Corporation, Rancho Cordova, California) incorporated a 20-MHz phased-array transducer. Conventional gray-scale quantitative IVUS analyses were performed according to criteria of the clinical expert consensus document on IVUS to include external elastic membrane (EEM), luminal, and plaque and media (P&M; defined as EEM minus luminal) areas [10]. Plaque burden was defined as P&M area divided by EEM area. Planar gray-scale

and VH-IVUS analysis was performed at the site of the minimal luminal area. Volumetric VH-IVUS analysis was performed along a 10-mm segment centered on the minimal luminal area; calculations were made using Simpson's rule. VH-IVUS analysis classified and color-coded tissue as green (fibrotic), yellow-green (fibrofatty), white (dense calcium), and red (necrotic core) [11;12]. VH- IVUS analyses are reported in absolute amounts and as percentages (relative amounts) of plaque area and volume.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 17.0) for Windows,(SPSS Inc., Chicago, IL, USA) was used for all analyses. Continuous variables were presented as the mean value±1SD; comparisons were conducted by a Student's t-test or nonparametric Wilcoxon test if the normality assumption was violated. Discrete variables were presented as percentages and relative frequencies. Comparisons were conducted by chi-square statistics or Fisher's exact test as appropriate. Multivariate analysis was performed to determine the independent predictors of TCFA. All variables with $p<0.1$ in the univariate analysis were entered into the multivariate analysis. A p of <0.05 was considered statistically significant. We also used Spearman rank correlation is a non-parametric test that is used to measure the degree of association between two variables.

Results

A total of 47 patients were enrolled (65.0 ± 11.9 years old), 25 patients with ACS without ST segment elevation and 22 stable angina pectoris patients.

VH-intravascular ultrasound analysis showed that patients' group with ACS without ST segment elevation had statistically significant greater amount necrotic core and dense-calcium volumes in non-culprit lesions, compared with stable angina pectoris patient group by absolute amount and percentage (fig. 1., fig. 2).

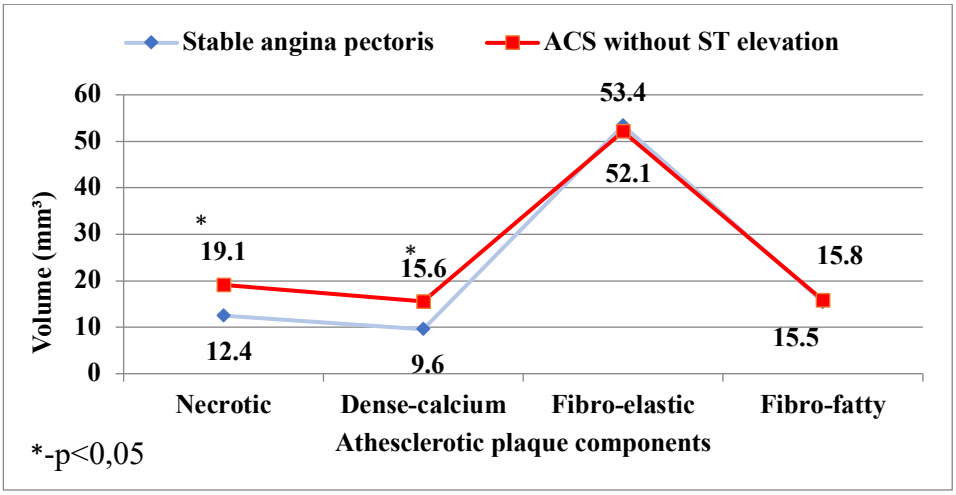

Fig. 1. Athesclerotic plaque components volume.

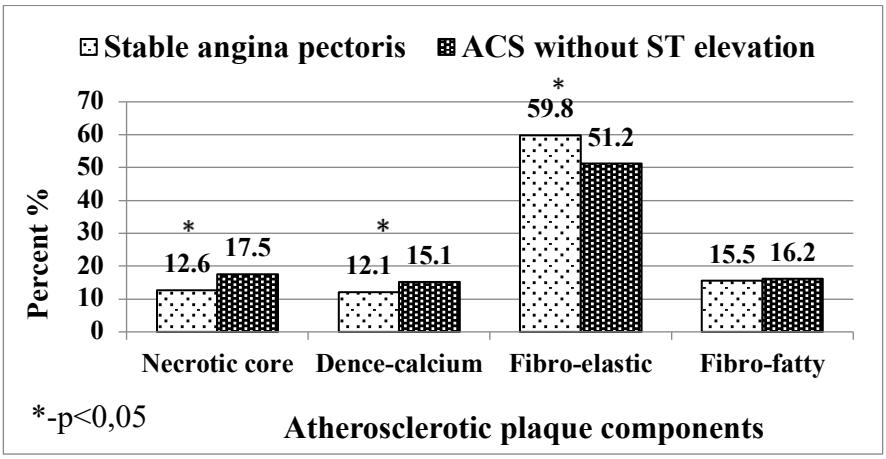

Fig. 2. Athesclerotic plaque components percentage.

In the conventional IVUS analysis the total plaque volume was significantly greater in SAP patients group compared with patients ACS without ST segment elevation group (fig. 3).

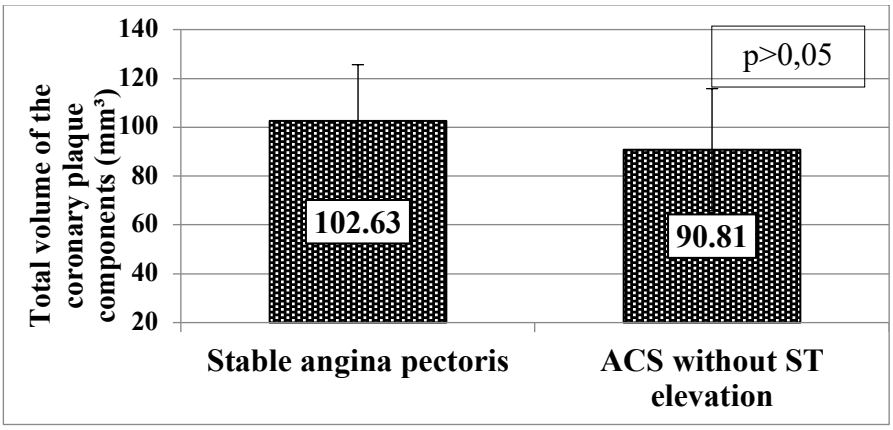

Fig. 3 Total volume of coronary plaque components.

Analyzing the plaque component dependence to the plaque volume, our results are that non-culprit lesion of ACS without ST segment elevation group and in SAP target lesion group necrotic volumes in atherosclerotic plaque statistically significant depends to the plaque volume, but it has stronger relationship in ACS without ST segment elevation group comparing to the SAP target lesion group (fig. 4.).

Also, our results show that calce-densium component dependence to the plaque volume in non-culprit lesion of ACS without ST segment elevation group are statistically significant comparing with SAP target lesion group (fig.5.). That shows the non-culprit lesion of ACS without ST segment elevation had more vulnerable plaque components comparing wit SAP patient group.

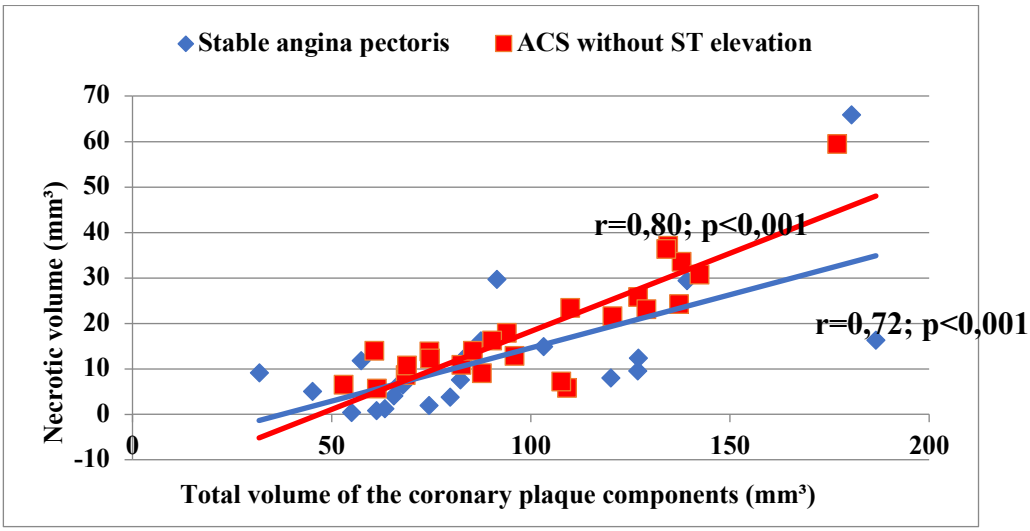

Fig. 4. Necrotic component volume dependence to the plaque volume

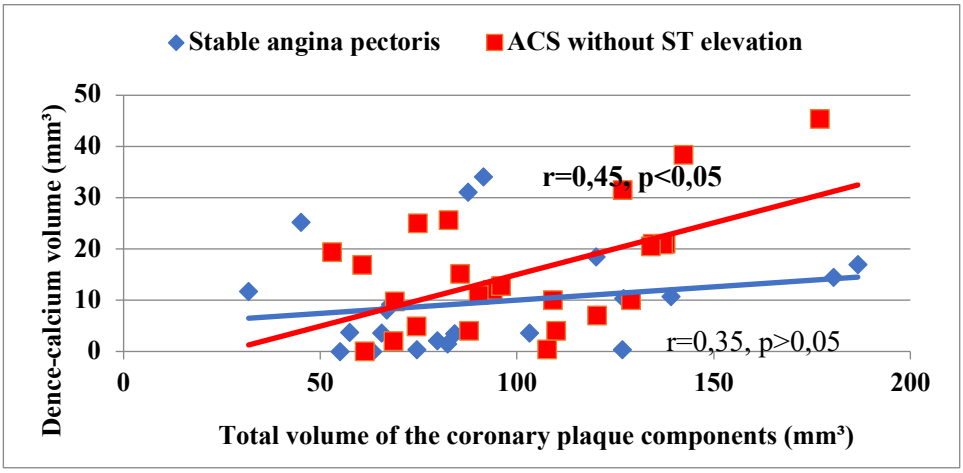

Fig.5. Dence-calcium component volume dependence to the plaque volume

Also, we find that non-culprit lesion of ACS without ST segment elevation group and target lesion of SAP patient group fibro-elastic component volume in atherosclerotic plaque strongly, statistically significant depends to the plaque volume (fig. 6.).

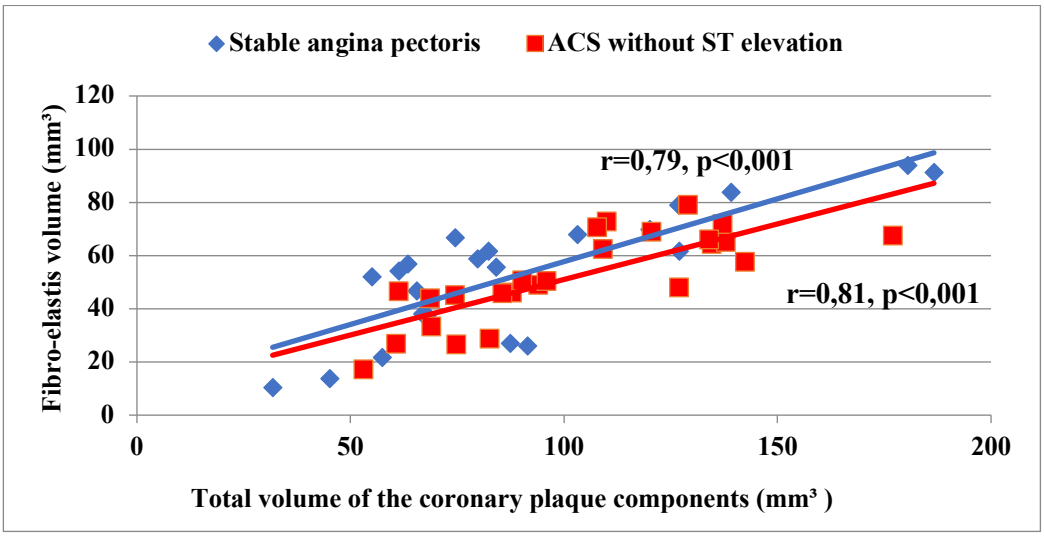

Fig. 6. Fibro-elastic component volume dependence to the plaque volume

Comparing the fibro-fatty plaque component dependence to plaque volume we find that target lesion of SAP patient group fibro-fatty component volume in atherosclerotic plaque strongly, statistically significant depends to the plaque volume and there is no correlation between the fibro-fatty component volume in atherosclerotic plaque in ACS without ST segment elevation group (fig. 7.).

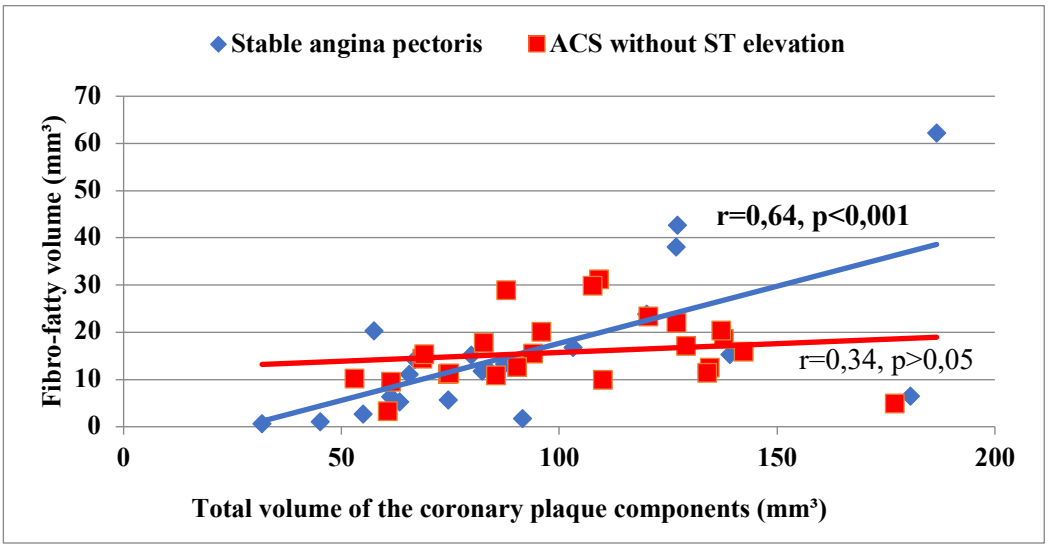

Fig. 7. Fibro-elastic component volume dependence to the plaque volume

Discussion

The main result of this study is that there is a significant difference in the structure of the atherosclerotic plaque in patients with an acute phase of ACS, without the elevation of ST segments, compared to the patients with a stable angina. The first exhibits a significantly higher portion of the necrotic core, which correlates to the subsequent research [13,14]. A significantly higher portion of the necrotic core in the lesions not directly accountable for the occurrence of ACS supports the fact that ACS is a multifocal process [13].

By comparing stable and vulnerable plaques, Sano et al. [15] have established a greater percentage of the lipid- necrotic component in vulnerable plaques. Previous pathological studies of vulnerable plaques after ACS showed that the share of the necrotic core represents a marker of plaque vulnerability [15].

Kubo et al. [16] used serial IVUS-RF imaging to investigate the natural evolution of non-obstructive plaques and showed that in contrast to fibrous and calcified plaques, which remained unchanged, the intimal thickening and thick cap fibroatheromas may evolve to thin cap fibroath- eromas at 12 months follow-up.

Furthermore, in tumors researches, it is well-known that subpopulations of macrophages present in atherosclerotic plaques promote angiogenesis [17]. However, these newly formed blood vessels frequently lack the appropriate structural integrity and may cause bleeding inside the plaque, which leads to lesion growth and jeopardizes the stability of the plaque [18].

Of all parameters pertaining to the vulnerability of the atherosclerotic plaque, the most significant are the presence of the necrotic core and a thin fibrous cap which sep arates it from the lumen (14, 15). Plaque ruptures are most frequently formed from the previously angiographically insignificant lesions (19). Out of all of examined lesions, in our study only four were angiographically diagnosed as significant (>70% stenosis). Therefore, an VH-IVUS analysis may be used for the purpose of revealing vulner- able lesions (13, 20). The fact that IVUS-VH has a reduced axial resolution (range: 100-200μm) limits its ability to identify some of these characteristics (e.g. plaque disrup- tion, macrophage infiltration) and measure the thickness of the fibrous cap [21].

These limitations of VH-IVUS may be overcome by the use of optical coherence tomography (OCT). The high resolution of OCT enables the identification of lipid pools and, unlike IVUS-VH, detection of the internal and exter- nal elastic lamina [22, 23]. OCT further enables a precise quantification (measurement) of fibrous cap thickness, enables a reliable evaluation of the cap disruption and erosion and can clearly visualize the presence and type of the thrombus [21, 24]. The limitation of this model is the reduced axial penetration which may aggravate the estimate of lipid pool dimensions and the identification of positive remodeling. For overcoming these limitations, it has been suggested that a combined use of VH-IVUS and OCT be used [25].

Finally, an aggressive lipid defense therapy should also be administered for the purpose of stabilizing other plaques, independent of angiographically significant sten-oses. Possible new episodes of ACS may be prevented in this manner [26].

Study limitation

This study was a single-center study with a small number of patients, thus possibly posing a risk of patient selection bias. Our results of plaque components were not evaluated by histology or other diagnostic modalities such as optical coherence tomography. VH- IVUS cannot determine the presence of thrombus. Total occlusions, bifurcation lesions, lesions with severe angulations, and heavily calcified lesions were excluded from this study. Therefore, this study might not represent the whole spectrum of patients with ACS and patients with SAP.

Conclusion

In the present study, the VH-IVUS detected necrotic core was significantly larger in atherosclerotic lesions in patients in acute phase of ACS without ST elevation compared to the stable angina subjects and it could be consid- ered a marker of plaque vulnerability.

References

1. Jacob Fog Bentzon, Fumiyuki Otsuka, Renu Virmani, Erling Falk. Mechanisms of Plaque Formation and Rupture. *Circ Res*. 2014;114:1852-1866.
2. Gimbrone MA Jr, Garcia-Cardena G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. Cardiovasc Pathol. 2013 Jan;22(1):9-15. Epub 2012 Jul 18.
3. Miyamoto Y, Okura H, Kume T, Kawamoto T, Neishi Y, Hayashida A et al. Plaque characteristics of thin-cap

fibroatheroma evaluated by OCT and IVUS. JACC Cardiovasc Imag 2014; 4: 638–646.
4. Jason M. Tarkin, Marc R. Dweck, Nicholas R. Evans, Richard A.P. Takx, Adam J. Brown,
5. Ahmed Tawakol et al. Imaging Atherosclerosis. *Circ Res*. 2016;118:750-769.
6. Yamagishi M, Terashima M, Awano K et al. Morphology of vulnerable coronary plaque: Insights from follow-up of patients examined by intravascular ultrasound before an acutecoronary syndrome. J Am Coll Cardiol 35:106–111, 2015.
7. Jinwei Tian, Xuefeng Ren, Rocco Vergallo, Lei Xing, Huai Yu, Haibo Jia et al. Distinct Morphological Features of Ruptured Culprit Plaque for Acute Coronary Events Compared to Those With Silent Rupture and Thin-Cap Fibroatheroma. J Am Coll Cardiol. Vol. 63, No. 21, 2016
8. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000; **343:** 915 – 922.
9. J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano et. al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC), *European Heart Journal*, Volume 41, Issue 3, 14 January 2020, Pages 407 477, https://doi.org/10.1093/eurheartj/ehz425
10. K.Thygesen, J. S Alpert, A. S Jaffe, B. R Chaitman, J. J Bax, D. A Morrow et al. ESC Scientific Document Group, Fourth universal definition of myocardial infarction (2018), *European Heart Journal*, Volume 40, Issue 3, 14 January 2019, Pages 237–269, https://doi.org/10.1093/eurheartj/ehy462
11. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM, Yock PG. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001;37:1478 –1492.
12. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince G. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation* 2002;106:2200 – 2206.
13. Rodriguez-Granillo GA, García-García HM, Mc Fadden EP, Valgimigli M, Aoki J, de Feyter P, Serruys PW . In vivo intravascular ultrasound- derived thin-cap fibroatheroma detection using ultrasound radiofrequency data analysis. *J Am Coll Cardiol* 2005;46:2038 –2042
14. Rodriguez-Granillo GA, McFadden EP, Valgimigli M, Van Mieghem CAG, Regar E, De Feyter PJ, et al. Coronary plaque composition of nonculprit lesions, assessed by in vivo intracoronary ultrasound radio frequency data analysis, is related to clinical presentation. Am Heart J. 2006; 151(5):1020-4.
15. Rodriguez-Granillo GA, García-García HM, Wentzel J, Valgimigli M, Tsuchida K, Van der Giessen W, et al. Plaque composition and its relationship with acknowledged shear stress patterns in coronary arteries. J Am Coll Cardiol. 2006; 47(4):884-5.
16. Sano K, Kawasaki M, Ishihara Y, Okubo M, Tsuchiya K, Nishigaki K, et al. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. J Am Coll Cardiol. 2006; 47(4):734-41.
17. Kubo T, Maehara A, Mintz GS, Doi H, Tsujita K, Choi SY, et al. The dynamic nature of coronary artery lesion morphology assessed by serial virtual histology intravascular ultrasound tissue characterization. J Am Coll Cardiol. 2010; 55(15):1590-7.
18. Sica A, Larghi P, Mancino A, Rubino L, Porta C, Totaro MG, et al. Macrophage polarization in tumour progression. SeminCancer Biol. 2008; 18:349-55.
19. Sluimer JC, Daemen MJ. Novel concepts in atherogenesis: angiogenesis and hypoxia in atherosclerosis. J Pathol. 2009; 218:7-29
20. Ohlmann P, Kim SW, Mintz GS, Pregowsky J, Tyczynski P, Maehara A, et al. Cardiovascular events in patients with coronary plaque rupture and nonsignificant stenosis. Am J Cardiol. 2005; 96:1631-5.
21. Valgimigli M, Rodriguez-Granillo GA, Garcia-Garcia HM, Malagutti P, Regar E, de Jaegere P, et al. Distance from the ostium as an independent determinant of coronary plaque composition in vivo: an intravascular ultrasound study based

radiofrequency data analysis in humans. Eur Heart J. 2009; 27(6):655-63.
22. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol. 2012; 50(10):933-9.
23. Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, Seung KB, et al. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. J Am Coll Cardiol. 2002; 39(4):604-9.
24. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. Circulation. 2002; 106(13):1640-5.
25. Kume T, Akasaka T, Kawamoto T, Ogasawara Y, Watanabe N, Toyota E, et al. Assessment of coronary arterial thrombus by optical coherence tomography. Am J Cardiol. 2006; 97(12):1713-7.
26. Sawada T, Shite J, Garcia-Garcia HM, Shinke T, Watanabe S, Otake H, et al. Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma. Eur Heart J. 2008; 29(9):1136-46.
27. Hong MK, Park DW, Lee CW, Lee SW, Kim YH, Kang DH, et al. Effects of statin treatments on coronary plaques assessed by volumetric virtual histology intravascular ultrasound analysis. JACC Cardiovasc Interv. 2009; 2(7):679- 88.