sciendo

JIM Journal of Interdisciplinary Medicine

STUDY DESIGN

CARDIOLOGY // IMAGING

Impact of Coronary Plaque Vulnerability on Acute Cardiovascular Events – Design of a CT-based 2-year Follow-up Study

Noémi Mitra[1], Roxana Hodas[2,3], Evelin Szabó[1], Zsolt Parajkó[1], Theodora Benedek[2,3], Imre Benedek[2,3]

[1] Center of Advanced Research in Multimodality Cardiac Imaging, Cardio Med Medical Center, Târgu Mureș, Romania
[2] University of Medicine, Pharmacy, Science and Technology, Târgu Mureș, Romania
[3] Clinic of Cardiology, Emergency Clinical County Hospital, Târgu Mures, Romania

CORRESPONDENCE

Roxana Hodas
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
E-mail: roxana.hodas@yahoo.ro

ARTICLE HISTORY

Received: April 30, 2019
Accepted: June 1, 2019

Noémi Mitra • Str. 22 Decembrie 1989 nr. 76, 540124 Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail: mitranoemi@gmail.com

Evelin Szabó • Str. 22 Decembrie 1989 nr. 76, 540124 Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail: szaboevelin22@yahoo.com

Zsolt Parajkó • Str. 22 Decembrie 1989 nr. 76, 540124 Târgu Mureș, Romania. Tel: +40 265 217 333, E-mail: parajko.zsolt@gmail.com

Theodora Benedek • Str Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: theodora.benedek@gmail.com

Imre Benedek • Str Gheorghe Marinescu nr. 38, 540139 Târgu Mureș, Romania. Tel: +40 265 215 551, E-mail: imrebenedek@yahoo.com

ABSTRACT

With coronary artery disease (CAD) projected to remain the leading cause of global mortality, prevention strategies seem to be the only effective approach able to reduce the burden and improve mortality and morbidity. At this moment, diagnostic strategies focus mainly on symptomatic patients, ignoring the occurrence of major cardiovascular events as the only manifestation of CAD. As two thirds of fatal myocardial infarction are resulting from plaque rupture, an approach based on the "vulnerable plaque" concept is mandatory in order to improve patient diagnosis, treatment, and, by default, prognosis. Given that the main studies focus on a plaque-centered approach, this is a prospective observational study that will perform a complex assessment of the features that characterize unstable coronary lesions, in terms of both local assessment via specific coronary computed tomography angiography markers of coronary plaque vulnerability and systemic approach based on serological markers of systemic inflammation in patients proved to be "vulnerable" by developing acute cardiovascular events.

Keywords: vulnerable plaque, acute cardiovascular event, systemic inflammation, vulnerability markers

INTRODUCTION

Coronary artery disease (CAD), the most common cause of myocardial ischemia, represents a modern "epidemic" health problem worldwide, with severe implications in terms of mortality, morbidity, and socioeconomic aspects.[1–3] Given that CAD is projected to remain the leading cause of global mortality, prevention strategies seems to be the only effective approach able to reduce the burden and improve mortality and morbidity rates.[4] At this moment, diagnostic strategies focus mainly on symptomatic patients, totally ignoring the occurrence of major cardiovascular events as the only manifestation of CAD.[5] Coronary atheroma has shown a great diversity in terms of development and progress, demonstrating great variety in growth rate and plaque morphology.[6,7]

In previous studies, coronary plaques prone to rupture proved to have individual morphology features compared to stable atheromas. In clinical practice, this provides the opportunity of early noninvasive imaging identification of high-risk patients, even before devastating adverse clinical events occur.[8,9] As two thirds of fatal myocardial infarctions (MI) and sudden cardiac deaths result from sudden luminal thrombosis due to plaque rupture or erosion, defined as transmural fibrous cap rupture, causing lipid-rich core exposal to blood stream,[5,10–12] the concept of "vulnerable plaque" has emerged, involving massive efforts assigned for its recognition. From this point, substantial results of large studies and trials sustain the mandatory need of an approach based on the "vulnerable" plaque concept, in order to improve patient diagnosis, treatment, and, by default, prognosis. From a histopathological point of view, culprit lesions present large plaque volumes and necrotic cores, covered by a thin fibrous cap infiltrated with macrophages,[13] small calcifications in the fibrous cap having a significant role in plaque instability.[14,15] Moreover, vessels tend to be positively remodeled at the site of atheroma disruption.[16,17] As the histopathological characteristics of culprit lesions are well established, it has been proposed that vulnerable lesions exhibit the same features.[18]

Despite the considerable ongoing efforts of predicting acute coronary events on individual coronary plaque level, the identification of high-risk patients remains a challenging task for cardiovascular imaging technologies.[4,19,20]

Coronary computed tomography angiography (CCTA) has emerged as the best noninvasive imaging modality, allowing, besides coronary lumen and calcium content evaluation, the noninvasive quantitative analysis of coronary atherosclerotic plaques size and composition,[21,22] information with greater potential in predicting further acute coronary events.[23–25] Multiple previous studies proved all CCTA-derived parameters of plaque characterization as significant and independent predictors of future cardiovascular events.[26] In these terms, a recent CCTA study of non-obstructive CAD, with a follow-up of 100 months, confirmed positive remodeling, napkin-ring sign, increased plaque burden, and the presence of low attenuation as being associated with acute coronary syndromes (ACS).[27] As reported in large studies, the presence of multiple high-risk features proved to involve a greater-than-additive risk, as the presence of remodeling index (RI) and low-attenuation plaques (LAP) involved a 22% probability of ACS development over a 27-month follow-up, and the presence of three high-risk features led to a 60% probability of ACS development in the same follow-up time frame.[28,29]

Besides noninvasive imaging, diagnostic techniques for vulnerable plaque detection include serologic markers, as atherosclerosis is known as a chronic immunoinflammatory disease.[30] From this point of view, inflammation has an important impact on the evolution of the atherosclerotic process and the progression of coronary lesions, commonly related to plaque destabilization, as the involvement of inflammatory mechanisms in weakening the collagen structure of the "thin-capped fibroatheroma" is a widely accepted concept at this moment.[22] Of all systemic inflammatory biomarkers, C-reactive protein (CRP) proved to be the most frequently used, due to its predictive value for acute cardiovascular events in various subgroups of patients, as a series of studies suggested that CRP may be considered a culprit in vascular inflammation and plaque instability.[31] In a meta-analysis, involving 52 studies and 246,669 patients, the assessment of CRP level in patients with intermediate cardiovascular risk was able to prevent additional events over a time frame of 10 years.[32] With regard to IL-6, prospective studies proved the association between elevated serum levels in asymptomatic patients and an increased risk of acute cardiovascular events, but IL-6 assessment does not seem to offer any additional value to CRP measurement. Matrix metalloproteinases (MMPs) proved to be involved in vascular remodeling and fibrous cap thinning or rupture, elevated levels being associated with future acute cardiovascular events.[33]

Therefore, focusing only on plaque characteristics will ignore the effects that systemic inflammation processes exert on plaque stability, as plaque destabilization is a complex process which involves structural features and biological processes.[10,11]

We present the study design of a prospective, single-center trial developed with the main purpose of assessing the role of CCTA-derived markers of plaque vulnerability in the development of acute cardiovascular events during a 2-year follow-up, compared to stable atherosclerotic lesions. Furthermore, the trial aims to investigate the involvement of serological markers of systemic inflammation on the rate of major cardiac events in the same time frame.

METHODS

Study objectives

The primary objective of the study is to evaluate the feasibility of CCTA-derived vulnerability markers as prognostic features for the development of acute cardiovascular events in a follow-up period of 2 years. In this regard,

coronary plaques with CCTA vulnerability features will be compared to stable atheromas in terms of major adverse cardiovascular events (MACE) rates. The secondary aim consists in assessing of impact of systemic inflammation on the rate of acute cardiovascular events, based on the evaluation of serological markers.

Study population

This trial will be a single-center, prospective study, which will include 200 patients referred for CCTA examination for chest pain of varying degrees and a probability of CAD ranging between 15–85%, in accordance with the recommendations of the current guidelines of the European Society of Cardiology (ESC).[34]

Inclusion criteria:

- patients with suspected CAD, pre-test probability of CAD between 15–85%, in whom CCTA identified >1 significant coronary lesion;
- age >18 years;
- willingness to participate in the study.

Exclusion criteria:

- documented CAD, ACS, percutaneous coronary intervention (PCI) or bypass grafting;
- moderate or severe valvular heart disease;
- unstable hemodynamic condition;
- cardiac arrhythmia;
- Agatston coronary artery calcium score (CAC) >2,000;
- non-diagnostic CCTA image quality;
- known allergy to contrast agents;
- life expectancy under 2 years;
- chronic kidney disease.

Study groups

Two hundred patients, eligible according to the selection criteria, will be included in two study groups based on the CCTA analysis: group 1 – patients with plaques presenting CCTA-derived markers of vulnerability; group 2 – patients without any marker of vulnerability. In patients with myocardial infarction developed during the follow-up time, a second CCTA evaluation will be performed at 2 years from the baseline assessment. These patients will be divided into two subgroups based on the number of CCTA-derived markers of vulnerability, as follows: group 1A – patients with 1–2 markers of vulnerability; group 1B – patients presenting >2 markers of vulnerability.

Study procedures

CCTA scan protocol

CCTA will be performed using a CT-scanner with 128-multislice dual source (Somaton definition, Siemens Healthcare, Germany), with the following scan parameters: 120 kV tube voltage, gantry rotation time of 0.33 s, 128 × 0.6 collimation, with patients in inspiratory breath-hold position, following the same protocol. All examinations will be performed at a stable heart rate below 60 beats/minute after the administration of an oral beta-blocker. CAC will be assessed during the pre-contrast scan, and a CAC >2,000 will be considered exclusion criteria, as intense calcifications will alter CCTA acquisitions. During an inspiratory breath-hold, 80–100 mL of iodinated contrast agent (Ultravist 370 mgI/mL, Bayer Healthcare, Germany) will be administered according to the patient's body weight, with a flow rate of 5.5 mL/s, followed by 50 mL of 0.9% saline solution at the same flow rate.

Analysis of CCTA

All CCTA acquisitions will be transferred to a Siemens (Siemens AG, Erlangen, Germany) workstation for data processing, measurements, and interpretation, using the QAngioCT RE (Medis, Leiden. Netherlands) dedicated software. Based on current recommendations, coronary arteries with at least 2 mm in lumen will be assessed by a 17-segment model. The quantitative assessment of atherosclerotic lesions will contain atheroma length, atheroma, vessel, and lumen volume, and minimal luminal area. Plaque composition assessment will involve the determination of calcified and non-calcified (lipid-rich and fibrotic) components. Qualitative plaque analysis will include spotty calcifications, positive remodeling, low attenuation core, and napkin-ring sign.

Study definitions

In terms of stenosis severity, plaques will be divided in obstructive (stenosis >50%) and non-obstructive (stenosis <50%). Based on CT density, plaques will be classified in non-calcified (density <30 HU, lipid cores), calcified (density >220 HU), mixed (non-calcified plaques presenting small amounts of calcified elements), and fibrous plaques (density 30–150 HU). Lesions with a low-density core (at-

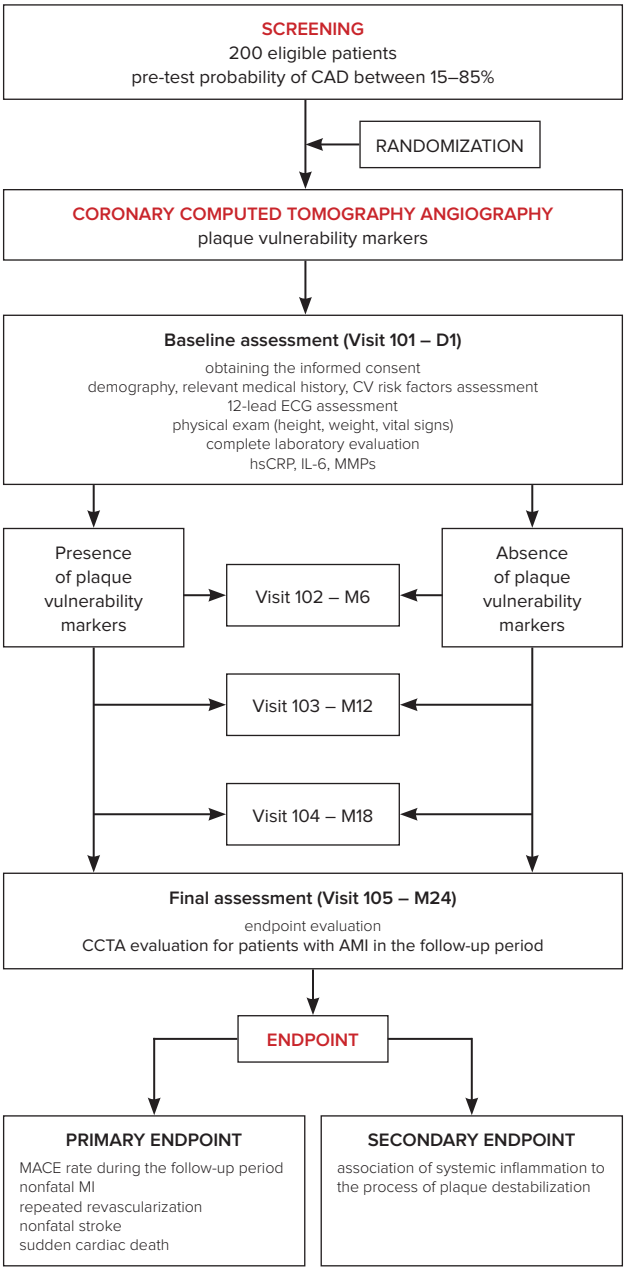

FIGURE 1. Study protocol. CAD – coronary artery disease; CCTA – coronary computed tomography angiography; MACE – major adverse cardiovascular events; AMI – acute myocardial infarction; MMPs – matrix metalloproteinases; hs-CRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6

tenuation <30 HU) and volume larger than 6 mm^3 will be considered LAP. The RI will be defined as the ratio between vessel diameter at the plaque site and a reference diameter. Positive remodeling will be considered in the presence of a RI >1.1. The napkin-ring sign will be considered in the presence of a lesion core presenting low attenuation, surrounded by a rim-like area of high attenuation. Spotty calcification will be considered at a size <3 mm (with density >130 HU).

Study timeline

This clinical study will be conducted between October 2019 and May 2020, with a further 2-year follow-up period, as shown in the study protocol (Figure 1).

Screen – Visit 1

- checking for inclusion/exclusion criteria;

Visit 101 – D1

- obtaining the informed consent;
- CCTA scanning and post-processing;
- demography, relevant medical history, CV risk factors assessment;
- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- complete laboratory evaluation;
- hsCRP, IL-6, MMPs.

Visit 102 – M6

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 103 – M12

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 104 – M18

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- relevant medical history;
- MACE.

Visit 105 – M24

- 12-lead ECG assessment;
- physical exam (height, weight, vital signs);
- CCTA for AMI patients;
- endpoint assessment.

Data analysis

The analyses will be performed with GraphPad Prism 8 (GraphPad Software, San Diego, CA) at a level of significance of 5%. Normality tests will be applied for all study data. Continuous variables will be summarized as mean ± SD and categorical variables as percentages/frequencies. The Chi-square test will be performed in order to compare categorical variables. The Mann-Whitney U test or independent-samples t test will be used for group comparisons. All statistical tests will be two-tailed, and a p value <0.05 will be assigned to determine statistical significance.

Ethics

This study will be carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the local institutional Ethics Committee. Individual informed consent will be signed by each study participant.

Outcome assessment

The primary outcome of the study will be represented by MACE rates during the follow-up time. MACE will be defined as: nonfatal myocardial infarction, repeated revascularization, nonfatal stroke, and sudden cardiac death. Secondary outcome refers to the association of systemic inflammation to the process of plaque destabilization, leading to acute cardiovascular events.

DISCUSSIONS

This study design describes the protocol for a prospective, single-center trial developed with the main purpose of assessing the feasibility of CCTA-derived markers of plaque vulnerability as prognostic features in the development of acute cardiovascular events during a 2-year follow-up, compared to stable atherosclerotic lesions, in patients referred to CCTA evaluation. In this regard, coronary plaques with CCTA vulnerability features will be compared to stable atheromas in terms of MACE rate.

As large studies reported plaque rupture as the substrate for ACS development in at least two thirds of patients,[35–37] the "vulnerable plaque" concept has emerged straight away, with massive efforts assigned for its recognition. From this point, substantial results of studies and trials sustain the mandatory need of an approach based on the "vulnerable" plaque concept in order to improve patient diagnosis, treatment, and, by default, prognosis. Based on previous work, a series of vulnerability features were established on the basis of autopsy findings in culprit lesions, criteria considered to be sufficient and unambiguous for the definition of high-risk plaque. These features are represented by the presence of active inflammation, thin cap fibroatheroma, fissured plaque, calcified nodule, intraplaque hemorrhage, and positive remodeling process. As the histopathological characteristics of culprit lesions are well established, it was presumed that vulnerable lesions exhibit the same features.[18]

Despite the considerable ongoing efforts to predict acute coronary events on individual coronary plaque level, the identification of high-risk patients remains a challenging task for cardiovascular imaging technologies.[4,19,20] Of these, CCTA has emerged as the best noninvasive imaging technique in plaque vulnerability assessment, multiple previous studies proving all CCTA-derived parameters of plaque characterization as significant and independent predictors of future cardiovascular events.[26] From CCTA assessment, at this moment, coronary lesions are most commonly characterized as prone to rupture when possessing large lipid cores with low attenuation and thin adluminal fibrous caps.

In a prospective trial conducted by Motoyama *et al*. in 1,059 subjects, followed over a period of 2 years after CCTA assessment, positive remodeling and low attenuation proved to be specific plaque parameters associated with increased risk of plaque rupture and development of ACS.[28] Another retrospective study identified a significantly higher incidence of positive remodeling, low density plaque components, and spotty calcifications in culprit lesions, all of these features being significant predictors for ACS.[38] In a study conducted by Yamagishi *et al*. although at the time of initial evaluation the lumen area was preserved, coronary culprit plaques exhibited larger plaque volume, with eccentric plaque distribution and echolucent zones in the proximity of luminal surface,[39] this marker proving to be the lipid-rich core, in which metalloproteinases were associated with fibrous cap erosion.[40] These results prove that eccentric plaque distribution involves a higher degree of vulnerability than concentric lesions.[41–43] Another aspect of the presence of rich lipid-core was confirmed by necropsy studies, in which the size of plaque area proved to be less significant than the presence of lipid-rich core.[44] While a series of studies have demonstrated the presence of lipid-rich atheroma with very low CT densities (<30 HU) in culprit lesions as a marker of vulnerability, there is an almost total lack of quantitative assessment of this component.[45,46] A previous study reported larger volumes of low-density lipid-rich cores in unstable plaques, with a critical plaque volume of 6.0 mm^3 and CT density <30 HU as a cut-off value for differentiation between culprit and non-culprit lesions. Besides atheroma composition, a series of morphological characteristics provide prognostic information about plaque vulnerability. The napkin-ring sign, characterized by a plaque core with low attenuation surrounded by a rim-like area of higher attenuation, proved to be a surrogate CT-derived marker of precursor lesions for rupture, independent of other CCTA features.[29] Surprisingly, in a prediction CCTA study, Otsuka *et al*. identified the napkin-ring sign in 41% of ACS events, an even higher incidence compared with intravascular ultrasound investigations.[29]

In this context, the present study will evaluate the feasibility of CCTA-derived markers of vulnerability and structural component parameters as predictive features for further acute cardiovascular events. As the ability to identify "vulnerable" plaques involves major clinical implications, these results may allow the selection of high-risk patients for aggressive risk factor interventions in order to reduce morbidity and mortality.[47]

With the widespread adoption in the literature of the notion that structural plaque features alone can define plaque vulnerability, most efforts have been directed toward correlating imaging features with specific morphologies, leaving aside systemic inflammation and its impact on plaque vulnerability.

As a secondary objective, the trial aims to investigate the impact of serological markers of systemic inflammation on the rate of major cardiac events in the same time frame. A series of studies have suggested the involvement of systemic inflammation, as assessed by C-reactive protein, in the development of ACS.[48] The main concept relies on inflammatory mechanisms as regulators of defective structural stability, combined with the thrombogenic potential of the lipid core. As this concept is widely accepted, however, inflammation may not be responsible for all acute thrombotic events, as one large study has shown that almost half of ACS developed in the absence of high levels of CRP.[49] Moreover, a recent OCT study demonstrated that in one-third of patients with ACS and plaque rupture, there was a lack of inflammatory cell infiltration, with normal levels of CRP.[50]

Despite the recent considerable improvement of imaging techniques' ability to visualize and assess coronary plaques, we are still facing a plaque-centered approach, mainly focused on the precise description of a still frame of the atheroma configuration, not the continuous and variable interaction with its surroundings. Therefore, this study's main contribution is to incorporate both CCTA-derived vulnerability markers and serum biomarkers of systemic inflammation in a complex and complete local and systemic assessment of the patient proved to be "vulnerable" by developing acute cardiovascular events.

CONCLUSIONS

In conclusion, this will be the first study that will perform a complex assessment of features that characterize unstable coronary lesions, in terms of both local assessment via spe-

cific CCTA markers of coronary plaque vulnerability and a systemic approach based on serological markers of systemic inflammation.

CONFLICT OF INTEREST

Nothing to declare.

ACKNOWLEDGEMENT

This research was supported via the research grant no. 103544/2016 - PLaqueIMAGE, contract number 26/01.09.2016, financed by the Romanian Ministry of European Funds, the Romanian Government and the European Union.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics—2011 Update: A Report From the American Heart Association. *Circulation*. 2011;123:e18-e209.
2. Park K. Park's Textbook of Preventive and Social Medicine. Jabalpur: M/S Banarsidas Bhanot; 2011.
3. Barton GR, Irvine L, Flather M, McCann GP, Curzen N, Gershlick AH. Economic Evaluation of Complete Revascularization for Patients with Multivessel Disease Undergoing Primary Percutaneous Coronary Intervention. *Value Health*. 2017;20:745-751.
4. Braunwald E. Epilogue: What Do Clinicians Expect From Imagers? *J Am Coll Cardiol*. 2006;47:C101-C103.
5. Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. Comprehensive plaque assessment by coronary CT angiography. *Nat Rev Cardiol*. 2014;11:390-402.
6. Mohler ER, Sarov-Blat L, Shi Y, et al. Site-Specific Atherogenic Gene Expression Correlates With Subsequent Variable Lesion Development in Coronary and Peripheral Vasculature. *Arterioscler Thromb Vasc Biol*. 2008;28:850-855.
7. Box LC, Angiolillo DJ, Suzuki N, et al. Heterogeneity of atherosclerotic plaque characteristics in human coronary artery disease: A three-dimensional intravascular ultrasound study. *Catheter Cardiovasc Interv*. 2007;70:349-356.
8. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. *Nat Clin Pract Cardiovasc Med*. 2008;5:S2-S10.
9. Finn AV, Nakano M, Narula J, Kolodgie FD, Virmani R. Concept of Vulnerable/Unstable Plaque. *Arterioscler Thromb Vasc Biol*. 2010;30:1282-1292.
10. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262-1275.
11. Huang X, Yang C, Zheng J, et al. 3D MRI-based multicomponent thin layer structure only plaque models for atherosclerotic plaques. *J Biomech*. 2016;49:2726-2733.
12. Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. *Circulation*. 1990;82:II38-46.
13. Narula J, Finn AV, DeMaria AN. Picking Plaques That Pop. *J Am Coll Cardiol*. 2005;45:1970-1973.
14. Naghavi M, Libby P, Falk E, et al. From Vulnerable Plaque to Vulnerable Patient: A Call for New Definitions and Risk Assessment Strategies: Part I. *Circulation*. 2003;108:1664-1672.
15. Schaar J. Terminology for high-risk and vulnerable coronary artery plaques. *Eur Heart J*. 2004;25:1077-1082.
16. Schoenhagen P, Ziada KM, Kapadia SR, Crowe TD, Nissen SE, Tuzcu EM. Extent and Direction of Arterial Remodeling in Stable Versus Unstable Coronary Syndromes: An Intravascular Ultrasound Study. *Circulation*. 2000;101:598-603.
17. Hassani S-E, Mintz GS, Fong HS, et al. Negative Remodeling and Calcified Plaque in Octogenarians With Acute Myocardial Infarction. *J Am Coll Cardiol*. 2006;47:2413-2419.
18. Kolodgie FD. Pathologic assessment of the vulnerable human coronary plaque. *Heart*. 2004;90:1385-1391.
19. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the Future of Cardiovascular Disease in the United States: A Policy Statement From the American Heart Association. *Circulation*. 2011;123:933-944.
20. Waxman S, Ishibashi F, Muller JE. Detection and Treatment of Vulnerable Plaques and Vulnerable Patients: Novel Approaches to Prevention of Coronary Events. *Circulation*. 2006;114:2390-2411.
21. Achenbach S, Friedrich MG, Nagel E, et al. CV Imaging: What Was New in 2012? *JACC Cardiovasc Imaging*. 2013;6:714-734.
22. Achenbach S, Raggi P. Imaging of coronary atherosclerosis by computed tomography. *Eur Heart J*. 2010;31:1442-1448.
23. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34:719-728.
24. Narula J, Nakano M, Virmani R, et al. Histopathologic Characteristics of Atherosclerotic Coronary Disease and Implications of the Findings for the Invasive and Noninvasive Detection of Vulnerable Plaques. *J Am Coll Cardiol*. 2013;61:1041-1051.
25. Ferencik M, Schlett CL, Ghoshhajra BB, et al. A Computed Tomography-Based Coronary Lesion Score to Predict Acute Coronary Syndrome Among Patients With Acute Chest Pain and Significant Coronary Stenosis on Coronary Computed Tomographic Angiogram. *Am J Cardiol*. 2012;110:183-189.
26. Stefanadis C, Antoniou C, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *J Am Heart Assoc*. 2017;6:e005543.
27. Conte E, Annoni A, Pontone G, et al. Evaluation of coronary plaque characteristics with coronary computed tomography angiography in patients with non-obstructive coronary artery disease: a long-term follow-up study. *Eur Heart J Cardiovasc Imaging*. 2017;18:1170-1178.
28. Motoyama S, Sarai M, Harigaya H, et al. Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome. *J Am Coll Cardiol*. 2009;54:49-57.
29. Otsuka K, Fukuda S, Tanaka A, et al. Napkin-Ring Sign on Coronary CT Angiography for the Prediction of Acute Coronary Syndrome. *JACC Cardiovasc Imaging*. 2013;6:448-457.
30. Achenbach S, Ropers D, Hoffmann U, et al. assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol*. 2004;43:842-847.
31. Koenig W, Khuseyinova N. Biomarkers of Atherosclerotic Plaque Instability and Rupture. *Arterioscler Thromb Vasc Biol*. 2007;27:15-26.
32. The Emerging Risk Factors Collaboration. C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. *N Engl J Med*. 2012;367:1310-1320.
33. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. *Circ Res*. 2002;90:251-262.
34. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949-3003.
35. Davies MJ. The Composition of Coronary-Artery Plaques. *N Engl J Med*. 1997;336:1312-1314.
36. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276-1282.
37. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-C18.
38. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:319-326.
39. 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 acute coronary syndrome. *J Am Coll Cardiol*. 2000;35:106-111.
40. Grønholdt ML, Nordestgaard BG, Wiebe BM, Wilhjelm JE, Sillesen H. Echolucency of computerized ultrasound images of carotid atherosclerotic plaques are associated with increased levels of triglyceride-rich lipoproteins as well as increased plaque lipid content. *Circulation*. 1998;97:34-40.
41. Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J*. 1985;53:363-373.

42. Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. *Am J Cardiol*. 1989;63:114E-120E.
43. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation*. 1996;93:1354-1363.
44. Fernández-Ortiz A, Badimon JJ, Falk E, et al. Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J Am Coll Cardiol*. 1994;23:1562-1569.
45. Kitagawa T, Yamamoto H, Horiguchi J, et al. Characterization of noncalcified coronary plaques and identification of culprit lesions in patients with acute coronary syndrome by 64-slice computed tomography. *JACC Cardiovasc Imaging*. 2009;2:153-160.
46. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol*. 2006;47:1655-1662.
47. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet Lond Engl*. 1994;344:1383-1389.
48. Liuzzo G, Biasucci LM, Gallimore JR, et al. The Prognostic Value of C-Reactive Protein and Serum Amyloid A Protein in Severe Unstable Angina. *N Engl J Med*. 1994;331:417-424.
49. Cristell N, Cianflone D, Durante A, et al. High-Sensitivity C-Reactive Protein Is Within Normal Levels at the Very Onset of First ST-Segment Elevation Acute Myocardial Infarction in 41% of Cases. *J Am Coll Cardiol*. 2011;58:2654-2661.
50. Scalone G, Niccoli G, Refaat H, et al. Not all plaque ruptures are born equal: an optical coherence tomography study. *Eur Heart J – Cardiovasc Imaging*. 2017;18:1271-1277.