



Vulnerable Plaque Characteristics at Coronary Computed Tomography Angiography

Petar Medaković^{1*}, Mladen Jukić¹, Zrinka Biloglav²

¹Special Hospital “Agram“, Zagreb, Croatia

²School of Public Health Andrija Štampar, University of Zagreb School of Medicine, Zagreb, Croatia

*Address for correspondence:

Petar Medaković, Specijalna bolnica Agram, Trnjanska cesta 108, HR-10000 Zagreb, Croatia. E-mail: eranio@gmx.at

According to morbidity and mortality indicators, cardiovascular diseases are the leading public health issue in the Republic of Croatia and the European Union. Although mortality rates from ischemic disease have been reduced, Croatia is still categorized among countries with high cardiovascular risk. The guidelines of the European Society of Cardiology from 2020 for acute coronary syndrome (ACS) in patients with low to intermediate risk of coronary atherosclerotic heart disease (CHD) recommend coronary computed tomography angiography (CCTA) as an alternative to invasive coronary angiography. In most patients with suspicion of CHD, CCTA leads to the diagnosis of non-obstructive diseases, which causes the majority of ACS cases. Multi-slice Computed Tomography scanners of the newest generation employ low doses of radiation and low contrast volume to reliably show the characteristics of vulnerable plaque: (i) positive remodeling, (ii) low attenuation plaque, (iii) spotty calcification, and the (iv) napkin-ring sign. Due to positive remodeling, these plaques are often non-obstructive, and according to the CAD-RADS 2.0 guidelines from 2022 all their characteristics should be specifically emphasized in CCTA findings. Based on the assessment of the prognostic value of vulnerable plaque characteristics for adverse cardiac events, CCTA has been shown to be equally valid as other invasive diagnostic methods. Additionally, it was shown to be useful in indicating the optimal medication therapy and monitoring its effects. The results of large international randomized trials indicate the direction of the treatment approach for vulnerable plaque.

Keywords: vulnerable plaque, coronary artery disease, coronary computed tomography angiography, acute coronary syndrome.

According to morbidity and mortality indicators, cardiovascular (CV) diseases are the leading public health issue in the Republic of Croatia and the European Union (EU). According to most recent data from the Croatian Institute of Public Health for 2021, ischemic heart disease (IHD) had a proportional mortality of 12.4% and was the second most common cause of death in men, and was the leading cause of death in women with a proportional mortality of 12.6% (1). Despite a continuous reduction in mortality rates for IHD over the last decade, mortality rates in Croatia are still high in comparison with other EU member states. The European

Society of Cardiology (ESC) and the World Health Organization (WHO) have therefore included Croatia among countries with high CV risk (2, 3). The high mortality rates can be partially attributable to poor indicators of hospital treatment quality, based on mortality rates within 30 days for patients with acute myocardial infarction, according to which Croatia, with a rate of 11.6 per 100 patients, is in second place among EU member countries (4). Additionally, all levels of prevention in Croatia are insufficient in general, as opposed to interventional cardiology which is well-developed, but without systematic measurement of clinical outcomes.

The development of a network for primary percutaneous coronary interventions (PCI) has created the preconditions for the application of guidelines in clinical practice. Namely, the ESC Guidelines from 2020 for patients with acute coronary syndrome (ACS) without ST-segment elevation (NSTEMI) state that PCI is the diagnostic and treatment method of choice (class I) (5). These are the first guidelines to recommend coronary computed tomography angiography (CCTA) as an alternative to invasive coronarography for the exclusion of ACS in patients with low to intermediate risk of coronary atherosclerotic heart disease (CHD) and in cases in which troponins and/or ECG are normal or unconvincing (class I). As opposed to these Guidelines for ACS, the ESC published the guidelines for the diagnosis and treatment of chronic coronary syndrome in 2019 and recommended CCTA as the initial diagnostic test in symptomatic patients in whom obstructive CHD could not be excluded based on clinical assessment (6). The application of CCTA requires familiarity with imaging techniques and may be associated with certain difficulties during imaging that partially depend on patient characteristics and which have been previously described (7).

Coronary heart disease, both acute and chronic, has very heterogeneous morphological characteristics, such as for the extent of the disease, the stage of the narrowing of the coronary arteries, and the type of atherosclerotic plaque. During the decades in which invasive coronarography was applied based on the stenosis significance threshold of 50%, the bivariate categorization of CHD into obstructive and non-obstructive became commonplace. Since this perception completely diminishes the clinical significance of the CV continuum, non-obstructive disease has therefore been diagnostically, therapeutically, and prognostically neglected, and its contribution to the risk of adverse CV events has been neglected as well. It should be emphasized that the group of patients with non-obstructive CHD does not have the same risk distribution for adverse cardiac events, but instead has clearly delineated subgroups with different risk that are meaningful both scientifically and clinically. In addition to severity of stenosis, significant prognostic value can also be ascribed to the extent of the disease, with patients who have triple-vessel disease having poorer prognosis in comparison with patients with single-vessel disease. Additionally, patients with two-vessel stenosis had a 2.6 times higher hazard ratio for adverse cardiac events than patients with single-vessel non-obstructive disease (8, 9).

After CCTA or invasive coronarography, most patients with suspicion of CHD are diagnosed with non-obstructive disease (10, 11). Previous pathological and diagnostic studies that applied both diagnostic methods indicated that most cases of ACS are in fact caused by non-obstructive atherosclerotic plaque (12–15). The improved diagnostic performance of CCTA, which

includes three-dimensional imaging and good contrast and spatial resolution, enables the detection of twice as many atherosclerotic plaques on the coronary tree in comparison with invasive coronarography (16, 17). These advantages of CCTA are especially important since it is known that the development of ACS is ascribable both to the quantitative characteristics of plaque, e.g. the extent of its spread, and its qualitative characteristics – type and morphology. As opposed to the application of invasive and expensive methods such as intravascular ultrasound (IVUS), CCTA provides non-invasive and precise imaging of the type and morphology of atherosclerotic plaque. Acute coronary syndrome is associated with the presence of vulnerable plaque in all of its clinical subcategories (18, 19). Histological studies of vulnerable plaques performed on post mortem samples indicate characteristics that are highly specific to vulnerable plaque, such as positive remodeling, a necrotic core with a thin fibrous cap (<65 µm), macrophage infiltration in the cap, and adventitial neovascularization – vasa vasorum, microcalcifications, and spotty calcification (20, 21). The fact that CCTA can precisely visualize and quantify these characteristics enables risk stratification within the clinical continuum of ACS and optimal choice of treatment modality (22).

Given the burden of IHD, improved availability of advanced MSCT scanners, and lack of human resources, there is a clear need for additional education in coronary CT imaging. Therefore, the goal of this review article is to describe and depict the main diagnostic characteristics of vulnerable plaques, describe their prognostic value for adverse cardiac events, and describe how they are to present at CCTA findings.

Mechanisms for the development of acute coronary syndrome and characteristics associated with vulnerable plaque

Intracoronary thrombi at the location of atherosclerotic plaque are the most common cause of ACS, whereas spontaneous dissection of the coronary artery and/or coronary vasospasm are less common causes. The pathophysiological mechanisms for the development of intracoronary thrombi most commonly cited in the scientific literature are theories on plaque rupture, plaque erosion, and nodule calcification (23–25). Plaque rupture denotes the rupture of the thin fibrous cap of the fibroatheroma with leakage of necrotic fatty contents into the arterial lumen, which leads to the formation and accretion of thrombi. Vulnerable plaque was defined differently in the past. It was described by *Muller et al.* in 1989 as coronary plaque highly vulnerable to rupture (19). More recent definitions place more emphasis on its clinical importance, and e.g. *Stone et al.* defined it in 2011 as a characteristic in pa-

tients who have increased risk of future adverse cardiac events (26).

The rupture risk of vulnerable plaque is determined by numerous factors, and pathohistological studies have shown that a fibrous cap thinner than 65 µm plays a significant role (27). The thickness of the fibrous cap is inversely correlated to the size of the central necrosis, and ruptured plaques have larger central necroses in comparison with non-ruptured plaques (20, 28, 29). Macrophage infiltration in the fibrous cap reduces its thickness, increasing rupture risk (29).

Positive remodeling is common in vulnerable plaque (21). This term denotes the outward growth of plaque with sparing of the lumen from narrowing, which is accompanied by neovascularization and formation of the vasa vasorum that destabilizes plaque since it causes bleeding due to the immaturity of the vessel wall (30, 31). In contrast to calcified plaques, which are considered stable, microcalcifications or spotty calcifications, especially in the fibrous cap, are characteristics specific to vulnerable plaque (32, 33). It should be emphasized that positive remodeling, central necrosis, and spotty calcifications in vulnerable plaque were initially demonstrated on pathohistological samples that had been analyzed exclusively post mortem for many years. Only recently has the development of IVUS enabled plaque imaging in patients, but the invasiveness of that procedure and its high price limit its wider availability. Today, technologically advanced and non-invasive MSCT scanners are more widely available and allow the visualization of plaques with a low dose of ionizing radiation and low contrast volume. The application of this diagnostic method is limited by the lack of experts trained in the field of CV imaging, as well as radiology technologists and radiology specialists who know how to apply appropriate imaging techniques.

Vulnerable plaque characteristics at coronary computed tomography angiography

The current Coronary Artery Disease-Reporting and Data System 2.0 (CAD-RADS 2.0) guidelines from 2022 replaced the term “vulnerable plaque” with the term “high-risk plaque” (22). However, since the original term, “vulnerable plaque”, has become commonplace in the medical community, we retained its use in this article. The following characteristics of this type of plaque are clearly visible at CCTA:

- positive remodeling,
- low attenuation plaque,
- spotty calcification, and the
- napkin-ring sign. The prevalence of these characteristics is relatively high and estimated at approximately 30%.

The current guidelines emphasize the importance of standardized notation in patient charts and recommend

describing all of these characteristics of atherosclerotic plaque (22). HRP (high risk plaque) should be added as a modifier to written examination findings when two or more of these characteristics are present.

Positive remodeling

Positive remodeling is most commonly seen in clinical practice. It denotes the outward expansion of the blood vessel wall at the location of the atherosclerotic plaque, leading to partial conservation of the lumen at the narrowing site of the coronary artery (34) (Figure 1, Figure 2). This characteristic can be quantified using the remodeling index initially suggested in studies with IVUS. Using IVUS, the remodeling index is calculated as the ratio of the area of the cross section at the narrowest spot and the area of the cross section of the vessel proximally and distally from the narrowing (35) (Figure 3). CCTA often overestimates these values, and those greater than 1.1 are considered clinically significant (Figure 4). Patients with ACS have higher index values than patients with angina and those with culprit plaques (36, 37). The remodeling index calculation for CCTA represents the ratio of the outer diameter of the vessel at the location of the plaque and the average normal diameter of the vessel proximally and distally from the stenosis. Plaques with positive remodeling at CCTA also have larger necroses and are more often described as thin-cap fibroatheroma (TFCA) on IVUS, whereas the positive remodeling index in TFCA measured by MSCT shows higher values than when using optical coherence tomography (OCT) (38, 39).

Low attenuation plaque

Low attenuation plaque is defined as non-calcified plaque with a core that has an attenuation value lower than 30 Hounsfield units (HU) in any measurement voxel (22). In clinical practice, it is important to differentiate low attenuation plaque from positive remodeling, since the attenuation values in positive remodeling are often higher than 30 HU. It should be emphasized that the 30 HU threshold is generally accepted in clinical practice due to its high sensitivity and specificity in the detection of lipid-rich plaques (40) (Figure 4). Lower attenuation values, as a rule, match the necrotic contents of the core, while higher diameter values of the core increase risk of ACS (Figure 1, Figure 2). Plaques with lipid contents on CCTA in comparison with IVUS readings generally have lower attenuation values (40, 41). However, both in studies and in clinical practice, using CCTA to differentiate between soft plaque with lipid contents and fibrous plaque is more challenging due to the density overlap in these two entities (40, 42) (Figure 2). Additionally, in comparison with OCT, low at-

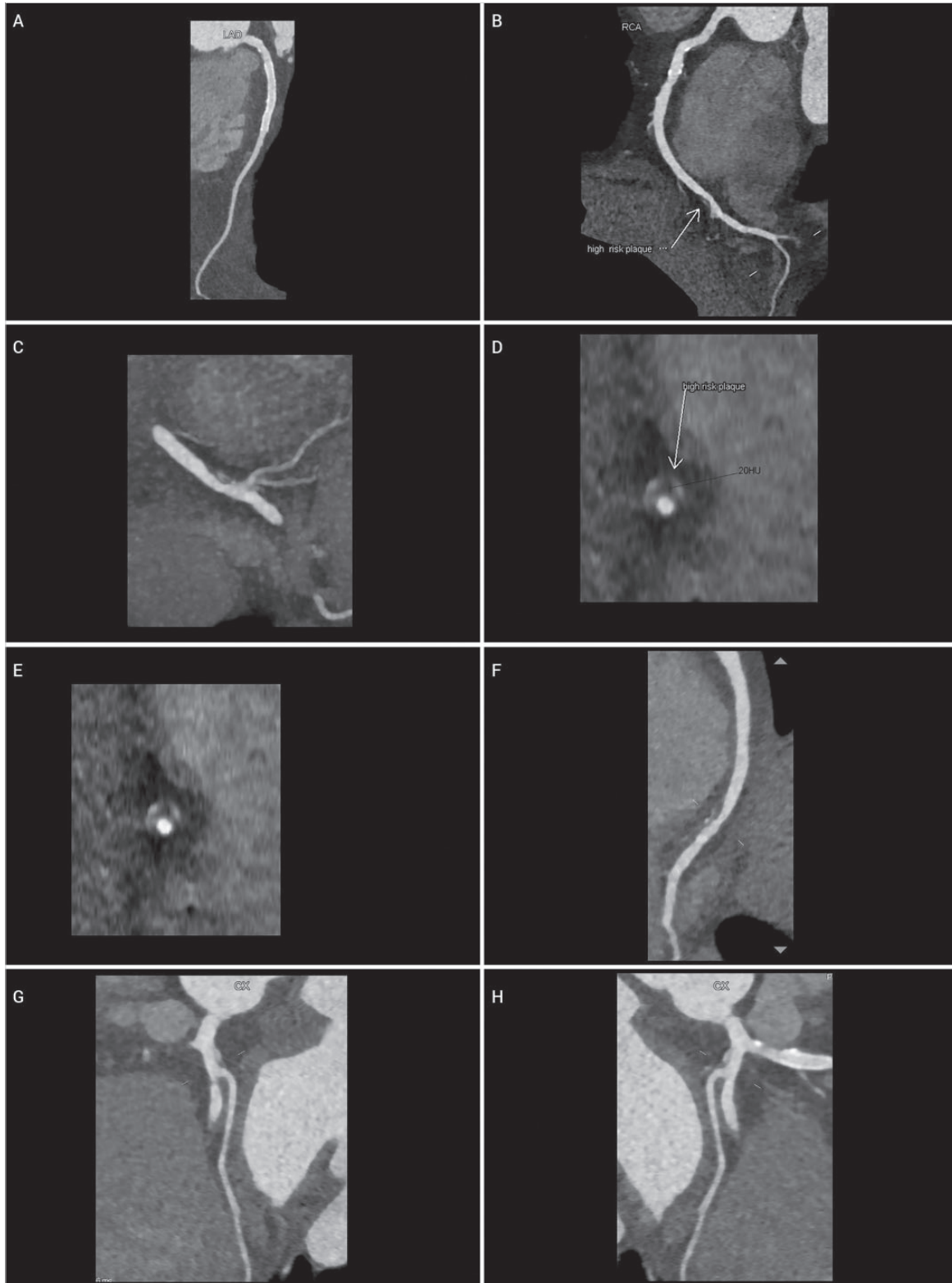


FIGURE 1. Male patient, 58 years old, with previously diagnosed coronary artery disease and a stent in the proximal left anterior descending artery referred to cardiac computed tomography angiography due to atypical chest symptoms and palpitations. Cardiac computed tomography angiography showed a stent in left anterior descending artery and non-obstructive non-calcified plaque in the distal right coronary artery (A, B C). Detailed plaque analysis in the distal right coronary artery revealed high-risk plaque features – positive remodeling (remodeling index >1.1) with low attenuation values (20 Hounsfield units), and napkin-ring sign (D, E, F). Additionally, non-obstructive fibrous plaque with positive remodeling and attenuation values >30 hounsfield units was revealed in the proximal circumflex artery (G, H). LAD = Left Anterior Descending Artery; RCA = Right Coronary Artery; Cx = Circumflex Artery; HU = Hounsfield Units.

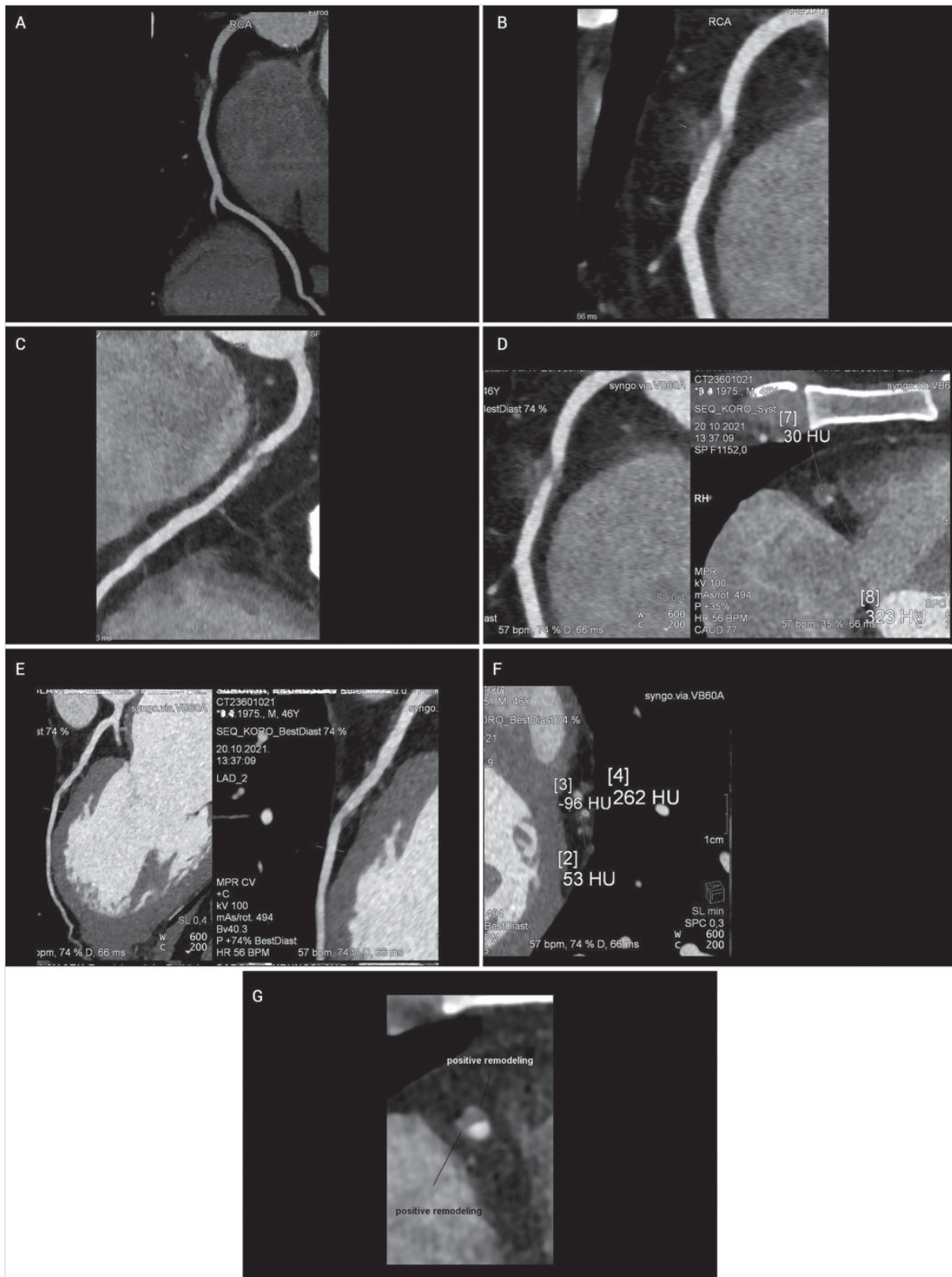


FIGURE 2. Male patient, 46 years old, referred to cardiac computed tomography angiography with typical chest symptoms of angina and shortness of breath. Cardiac computed tomography angiography revealed sub-occlusive non-calcified high-risk plaque with positive (and negative) remodeling (remodeling index >1.1) and low attenuation values (30 Hounsfield units) in the proximal right coronary artery (A, B, C D). Additionally, non-obstructive non-calcified plaque was revealed in the mid left anterior descending artery with positive remodeling and an attenuation value of 53 Hounsfield units (E, F, G). RCA = Right Coronary Artery; HU = Hounsfield Units.

tenuation plaques on CCTA are associated with TFCA findings on OCT (43). Despite differentiation between lipid plaque and fibrous plaque being challenging, as many as 88% of ruptured plaques in ACS have attenuation values lower than 30 HU, compared with only 18% in stable plaques. Automatized software solutions used for interpreting CCTA enable more reliable quantification of low attenuation plaque (44, 45).

Spotty calcification

In most cases of sudden cardiac death, histopathological plaque samples contain microcalcifications that are not visible at CCTA, as opposed to reliable imaging of spotty calcification (34). Spotty calcifications are small calcifications within soft non-calcified plaque. Their attenuation is higher than 130 HU, and they are classified into the following categories: small (<1 mm), medium (1-3 mm), and massive (>3 mm) (46–48) (Figure 4). Spotty calcifications are associated with plaques that cause ACS, and studies performed with CCTA demonstrated that this characteristic of vulnerable plaque is comparable with findings obtained by IVUS (37, 48, 49) (Figure 3).

Napkin-ring sign

The napkin-ring sign is a unique CCTA characteristic of vulnerable plaque that can be seen on cross sections of non-calcified plaque. It comprises a necrotic core zone with low attenuation that borders the lumen and is surrounded by a ring-shaped zone of higher attenuation that matches the fibrous tissue (50, 51) (Figure 1). This is a reliable marker for the detection of TFCA and matches pathohistological and OCT findings (39, 51, 52). The technological development of MSCT scan-

ners at the start of the past decade has enabled us to conduct studies in which the napkin-ring sign was compared with other characteristics present in invasive cardiologic diagnostic methods and pathohistological findings. Diagnostic studies preceded studies focused on the assessment of the prognostic value of vulnerable plaque characteristics for adverse cardiac events.

Prognostic value of vulnerable plaque characteristics at coronary computed tomography angiography

The results of studies based on invasive and non-invasive imaging methods of the coronary arteries indicate that ACS was associated with non-obstructive plaque (<50%) in the majority of patients, moreover those with non-obstructive CHD (in comparison with patients without CHD) had significantly higher risk of cardiac death and ACS (9, 53, 54). Previous studies on pathohistological samples demonstrated an association between vulnerable plaque characteristics and the clinical entity of ACS. Cardiologic and radiologic diagnostic methods for coronary imaging also allow us to quantify the risk of adverse cardiac events. Most studies focused on the prognostic values of vulnerable plaque characteristics, in addition to differences in study design and study populations, are also marked by different CV outcomes and follow-up times. Despite these differences, almost all studies found increased risk of adverse events to be associated with an increased number of vulnerable plaque characteristics. Additionally, some studies did not take into account the undoubtedly positive effect of optimal medication therapy (OMT), which certainly impacted the outcomes. Follow-up time is extremely important, since reliable assessment of the prognostic value of individual characteristics of vulnerable plaque requires long follow-up periods due to

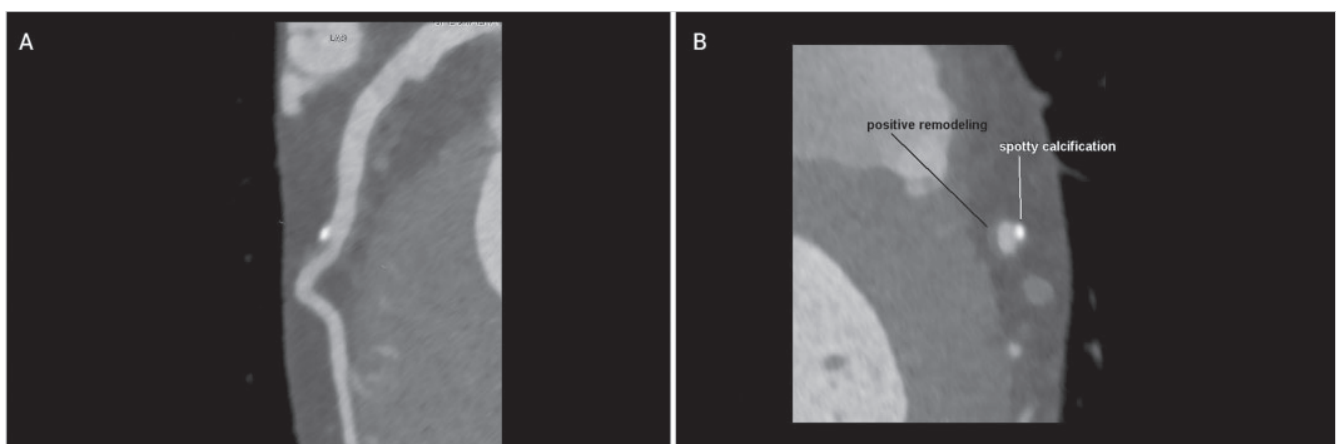


FIGURE 3. Female patient, 64 years old, referred to cardiac computed tomography angiography due to long-standing insufficiently regulated diabetes and multiple cardiovascular disease risk factors. Cardiac computed tomography angiography revealed diffuse non-obstructive coronary artery disease. Curved multiplanar reconstruction and cross-section analysis of the proximal left anterior descending artery showed non-obstructive non-calcified plaque with positive remodeling (remodeling index <1.1) and spotty calcification (A, B)

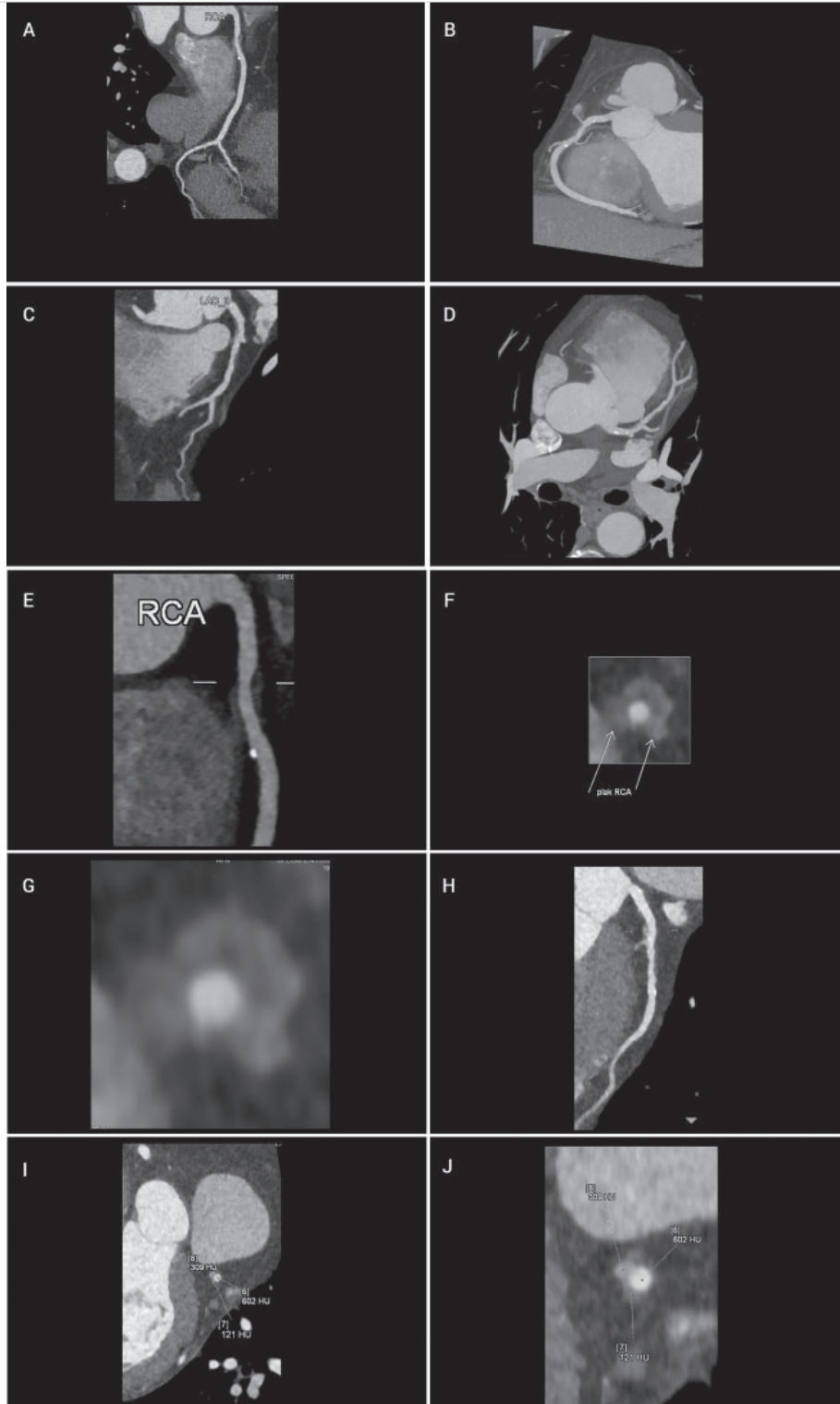


FIGURE 4. Male patient, 64 years old, with previously diagnosed non-obstructive coronary artery disease and low adherence to optimal medical therapy. Cardiac computed tomography angiography revealed non-obstructive non-calcified plaque in the proximal right coronary artery and proximal and mid left anterior descending artery (A, B, C, D). Detailed plaque analysis in the proximal RCA revealed considerable positive remodeling (remodeling index >1.1) with different attenuation values from 20 to 80 hounsfield units that was consistent with lipid rich and fibrous components (E, F, G). Proximal left anterior descending cross-section plaque analysis revealed non-calcified fibrous plaque with positive remodeling and an attenuation value of 120 hounsfield units, and spotty calcification (>300 Hounsfield units) (H, I). In comparison, attenuation values of 600 Hounsfield units are consistent with the contrast agent within the lumen (J). LAD = Left Anterior Descending Artery; RCA = Right Coronary Artery; HU = Hounsfield Units

potential plaque stabilization. In that sense, CCTA has shown itself to be a reliable tracking method for monitoring the natural course of CHD, and additionally improved prognostic values regarding plaque level are also partially ascribable to more recent software solutions that allow more precise quantification (40, 55, 56). One of the first prospective studies on the prognostic values of low attenuation plaque, positive remodeling, and spotty calcification for predicting adverse cardiac events after more than two years of follow-up identified low attenuation plaque and positive remodeling as predictors (57). Along with positive remodeling and low attenuation plaque, the napkin-ring sign was also shown to be a predictor for ACS and cardiac death after 2.3 years of follow-up (58). A meta-analysis demonstrated a significant 12.1 times higher hazard ratio in patients with vulnerable plaque characteristics in comparison with those who had stable plaque, as well as a significantly higher number of low attenuation plaques (<30 HU) in ACS patients compared with the number of plaques detected in patients with stable angina (37). Given the nature of positive remodeling from the lumen outwards, vulnerable plaque often causes non-obstructive stenosis, and the benefits of OMT are therefore to be expected. The diagnosis of non-obstructive disease is established in a large proportion of patients referred to CCTA for suspicion of CHD, which is associated with most ACS cases. According to the results of the PARADIGM study, the characteristics of vulnerable plaque did not influence the dynamic of the progression of non-obstructive plaque to obstructive plaque after two years of follow-up, whereas this role was instead demonstrated for initial percentage volume of the atheroma and the stenosis diameter percentage, which were the only significant predictors of the development of obstructive lesions (59, 60). This study also found differences with regard to sex, namely a significantly lower prevalence and slower plaque progression in women (61). These results are in contrast with the results of the PROSPECT study, where IVUS was used for the detection of vulnerable plaque in patients with ACS, who were then followed-up for 3.4 years (62). In this study, 596 cases of TFCA were found in a sample of 700 patients, and of a total of 74 adverse cardiac events, only six could be ascribed to cardiac death and non-fatal myocardial infarction after somewhat more than three years of follow-up. Other studies, such as for example VIVA, used IVUS and reported similar results (63, 64). These results obtained by imaging of the coronary arteries and plaques partially correspond to the results of pathohistological studies, according to which plaque rupture in 10-20% of non-significant plaques was not accompanied by clinical symptoms (65). It is likely that most plaques rupture and heal without causing ACS. Such results bring into question the very concept of risk assessment by detecting vulnerable plaque, as well as the concepts of “vulnerable” and “high-risk” plaque. These results are con-

trary to the results of MSCT studies where the volume of non-calcified plaque in patients with non-obstructive lesions and NSTEMI was shown to be a significant predictor of adverse cardiac events after 16 months of follow-up (66). In patients with acute chest pain, vulnerable plaque characteristics after CCTA were shown to be a significant predictor of ACS, regardless of stenosis stage (49). These studies formed a basis for the implementation of CCTA in the clinical practice of emergency services which would be in line with the recommendations from the ESC Guidelines for ACS (5). Reliable assessment of the prognostic value of vulnerable plaque for adverse cardiac events regardless of the imaging methods assumes adjustment for other risk factors for ACS. In addition to vulnerable plaque characteristics, simultaneous or asynchronous presence of systemic factors such as prothrombotic milieu, localized or systemic inflammatory state, and environmental proinflammatory factors influences the risk of ACS development. The effect of OMT using statins, aspirin, and anti-inflammatory medications further modifies the risk assessment for vulnerable plaque rupture, which should also be considered in the clinical risk assessment.

The effect of treatment on vulnerable plaque

The protective effect of OMT for adverse cardiac events has been confirmed by large international studies. Additionally, the application of CCTA increases OMT prescription, especially in patients with non-obstructive CHD (67). After CCTA, medication therapy was changed in more than half of patients, while the indication for invasive coronarography was eliminated in as many as three fourths of patients (68). An early study using invasive coronarography demonstrated the positive effects of statins, such as for example moderate regression and stabilization of plaques based on the reduction of the necrotic plaque core and the inflammatory component, with reduced macrophage infiltration and thickening of the fibrous cap (69). Stabilization of vulnerable plaques and their characteristics improved treatment outcomes in patients with ACS, which encouraged the introduction of atorvastatin into the therapy (70). Similar results were obtained in the PARADIGM study, which aimed to quantify the influence of statin therapy on plaques (71). Namely, statins slow down the progression of total atherosclerosis volume, increase plaque calcification, and reduce the development of new vulnerable plaques by up to 35% on follow-up CCTAs in a period longer than two years. However, the proportion of patients with stenosis progressing from non-obstructive to obstructive over two years did not differ significantly. In patients with unstable angina pectoris, high statin doses led to thickening of the fibrous cap in the fibroatheroma, and in combination with ezetimibe

it reduced adverse cardiac events in comparison with statin therapy alone (72, 73). These studies confirmed the greater influence of statins on the soft components of the plaque and the reduction of total plaque volume in comparison with coronary artery narrowing, as well as a positive effect on survival due to the reduction of the frequency of adverse cardiac events. In addition to statins, effective reduction of the inflammatory component was also observed with other medications, such as for example lipoprotein-associated phospholipase A2 inhibitors, colchicine, methotrexate, and interleukin-1 antagonists. Lipoprotein-associated phospholipase A2 inhibitors were effective in slowing down the development of the necrotic core in vulnerable plaque, but large randomized trials did not demonstrate benefit in clinical outcomes (74, 75). Compared with placebo, the use of colchicine in small doses (0.5 mg) in patients with recent myocardial infarction significantly reduced future adverse cardiac events, including spontaneous myocardial infarction, after 2.5 years of follow-up (76). In contrast to these results, methotrexate at low doses of 15-20 mg per week in comparison with placebo did not show reduction of inflammatory parameters or a reduction in the rate of adverse cardiac events after 2.3 years of follow-up (77). Canakinumab, a monoclonal antibody, significantly reduced CV events in comparison with placebo after 3.7 years of follow-up in patients with previous myocardial infarction (78). The significant role of inflammatory parameters in the etiology of ACS has been demonstrated in numerous studies, and the negative results of individual medications where the goal was to demonstrate benefits of OMT are ascribable primarily to the inadequately identified biochemical and pathohistological mechanisms of action of these medications in CHD rather than to the questionability of the concept of reducing local and systemic inflammation parameters. As opposed to studies on vulnerable plaque that aimed to demonstrate the benefit of OMT, primarily statins, other studies attempted to identify the benefit of applying percutaneous coronary interventions. Due to their still-superior resolution in comparison with CCTA, many studies used IVUS and OCT for the quantification of individual parameters of the characteristics of vulnerable plaque, but the availability of these invasive imaging methods is relatively poor, requiring more resources and operator experience. We already noted that vulnerable plaques often cause non-obstructive narrowing (<50%) due to positive remodeling, but they are considered high-risk nevertheless. The recent PROSPECT-ABSORB study did not show a significant reduction of adverse cardiac events in patients with vulnerable plaques treated with bioresorbable stents in comparison with OMT after four years of clinical follow-up (79). The results of the PECTUS study were similar, in which OCT was used for the detection of non-obstructive vulnerable plaque, but the study was discontinued due the withdrawal of bioresorbable

stents from the market (80). The low number of patients in that study reduces its scientific usefulness. The current studies, such as PREVENT (NCT02316886) and VULNERABLE (NCT0559906), aim to demonstrate the benefits of PCI for non-obstructive vulnerable plaque, and will surely elucidate the benefits of this approach in patients with ACS. The results of studies performed so far do not indicate a significant benefit from PCI in comparison with OMT with regard to the reduction of adverse cardiac events in patients with vulnerable plaque diagnosed by invasive or non-invasive methods.

Conclusion

Coronary heart disease represents the leading public health issue in the Republic of Croatia, and its diagnosis includes the application of both invasive coronarography and CCTA. Due to its non-invasiveness, CCTA has numerous advantages, especially with regard to its diagnostic performance, which allows clear visualization of qualitative and quantitative characteristics of atherosclerotic plaque. Identification of these characteristics has risen in clinical importance, as the rupture of most stable and vulnerable plaques is not accompanied by clinical symptoms. Thus, current guidelines emphasize that vulnerable plaque characteristics, such as for example positive remodeling, low attenuation plaque, spotty calcification, and the napkin-ring sign should be noted in the examination findings in order to allow risk assessment for rupture and ACS. In the assessment of prognostic value for adverse cardiac events, vulnerable plaque characteristics on CCTA had positive results, but a higher level of scientific evidence is needed to confirm this examination as the sole method of choice for risk assessment. The results of randomized clinical studies without doubt show the positive effect of statins on the stabilization of vulnerable plaque, but also on the reduction of systemic and local inflammation parameters. Optimal medication therapy showed similar therapeutic effectiveness with regard to the reduction of adverse cardiac events at vulnerable plaque, as did the methodologically safe invasive percutaneous approach. However, it should be emphasized that there is currently no unambiguous answer to this therapeutic challenge that is increasingly common in everyday clinical practice.

Declaration of interest

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

References

1. Hrvatski zdravstveno-statistički ljetopis za 2021. godinu [Internet]. Hrvatski zavod za javno zdravstvo; 2022. Dostupno na: <https://www.hzjz.hr/hrvatski-zdravstveno-statisticki-ljetopis/hrvatski-zdravstveno-statisticki-ljetopis-za-2021-tablicni-podaci/> (January 21, 2023).

2. Visseren FLJ, Mach F, Smulders YM, et al.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021 Sep 7; 42(34): 3227–3337. <https://doi.org/10.1093/eurheartj/ehab484>
3. World Health Organization. Disease burden and mortality estimates. www.who.int/healthinfo/global_burden_disease/estimates/en
4. Džakula A, Vočanec D, Banadinović M, et al. Croatia: Health system review. *Health Systems in Transition* 2021; 23(2): 1–146. Available at: <https://apps.who.int/iris/handle/10665/348070>
5. Collet JP, Thiele H, Barbato E, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021 Apr 7; 42(14): 1289–1367. <https://doi.org/10.1093/eurheartj/ehaa575>
6. Knuuti J, Wijns W, Saraste A, et al.; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020 Jan 14; 41(3): 407–477. <https://doi.org/10.1093/eurheartj/ehz425>
7. Medaković P, Biloglav Z. New-generation Computed Tomography Scanners for Coronary Artery Disease Imaging – Implications for Future Service Provision. *Cardiol Croat* 2021; 16(5–6): 208–14. <https://doi.org/10.15836/ccar2021.208>
8. Emond M, Mock MB, Davis KB, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994 Dec; 90(6): 2645–57. <https://doi.org/10.1161/01.CIR.90.6.2645>
9. Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA* 2014 Nov 5; 312(17): 1754–63. <https://doi.org/10.1001/jama.2014.14681>
10. Medaković P, Biloglav Z, Padjen I, et al. Quantification of coronary atherosclerotic burden with coronary computed tomography angiography: adapted Leaman score in Croatian patients. *Int J Cardiovasc Imaging* 2018 Oct; 34(10): 1647–1655. <https://doi.org/10.1007/s10554-018-1376-3>
11. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010 Mar 11; 362(10): 886–95. <https://doi.org/10.1056/NEJMoa0907272>
12. Mann JM, Davies MJ. Assessment of the severity of coronary artery disease at postmortem examination. Are the measurements clinically valid? *Br Heart J* 1995 Nov; 74(5): 528–30. <https://doi.org/10.1136/hrt.74.5.528>
13. Bittencourt MS, Hulthen E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. *Circ Cardiovasc Imaging* 2014 Mar; 7(2): 282–91. <https://doi.org/10.1161/CIRCIMAGING.113.001047>
14. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988 Nov; 78(5 Pt 1): 1157–66. <https://doi.org/10.1161/01.CIR.78.5.1157>
15. Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? *Circulation* 1996 Nov 15; 94(10): 2662–6. <https://doi.org/10.1161/01.CIR.94.10.2662>
16. Butler J, Shapiro M, Reiber J, et al. Extent and distribution of coronary artery disease: A comparative study of invasive versus noninvasive angiography with computed angiography. *Am Heart J* 2007 Mar; 153(3): 378–84. <https://doi.org/10.1016/j.ahj.2006.11.022>
17. Kolossváry M, Szilveszter B, Édes IF, et al. Comparison of Quantity of Coronary Atherosclerotic Plaques Detected by Computed Tomography Versus Angiography. *Am J Cardiol* 2016 Jun 15; 117(12): 1863–7. <https://doi.org/10.1016/j.amjcard.2016.03.031>
18. Lloyd-Jones D, Adams RJ, Brown TM, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010 Feb 23; 121(7): e46–e215. <https://doi.org/10.1161/CIRCULATIONAHA.109.192667>
19. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989 Apr; 79(4): 733–43. <https://doi.org/10.1161/01.CIR.79.4.733>
20. 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 Mar 12; 61(10): 1041–51. <https://doi.org/10.1016/j.jacc.2012.10.054>
21. Varnava AM, Mills PG, Davies MJ. Relationship between coronary artery remodeling and plaque vulnerability. *Circulation* 2002 Feb 26; 105(8): 939–43. <https://doi.org/10.1161/hc0802.104327>
22. Cury RC, Leipsic J, Abbara S, et al. CAD-RADS™ 2.0 – 2022 Coronary Artery Disease-Reporting and Data System: An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the North America Society of Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2022 Nov-Dec; 16(6): 536–557. <https://doi.org/10.1016/j.jcct.2022.07.002>
23. Schaar JA, Muller JE, Falk E, et al. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J* 2004 Jun; 25(12): 1077–82. <https://doi.org/10.1016/j.ehj.2004.01.002>
24. 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 May; 20(5): 1262–75. <https://doi.org/10.1161/01.ATV.20.5.1262>
25. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J* 2013 Mar; 34(10): 719–28. <https://doi.org/10.1093/eurheartj/ehs411>
26. Stone GW, Maehara A, Mintz GS. The reality of vulnerable plaque detection. *JACC Cardiovasc Imaging* 2011 Aug; 4(8): 902–4. <https://doi.org/10.1016/j.jcmg.2011.06.006>
27. 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 May 1; 336(18): 1276–82. <https://doi.org/10.1056/NEJM199705013361802>
28. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014 Jun 6; 114(12): 1852–66. <https://doi.org/10.1161/CIRCRESAHA.114.302721>
29. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006 Apr 18; 47(8 Suppl): C13–8. <https://doi.org/10.1016/j.jacc.2005.10.065>
30. Narula J, Strauss HW. The popcorn plaques. *Nat Med* 2007 May; 13(5): 532–4. <https://doi.org/10.1038/nm0507-532>
31. Sluimer JC, Kolodgie FD, Bijnens AP, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. *J Am Coll Cardiol* 2009 Apr 28; 53(17): 1517–27. <https://doi.org/10.1016/j.jacc.2008.12.056>
32. Vengrenyuk Y, Carrier S, Xanthos S, et al. A hypothesis for vulnerable plaque rupture due to stress-induced debonding around cellular microcalcifications in thin fibrous caps. *Proc Natl Acad Sci U S A* 2006 Oct 3; 103(40): 14678–83. <https://doi.org/10.1073/pnas.0606310103>
33. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004 Nov 30; 110(22): 3424–9. <https://doi.org/10.1161/01.CIR.0000148131.41425.E9>
34. Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. Comprehensive plaque assessment by coronary CT angiography. *Nat Rev Cardiol* 2014 Jul; 11(7): 390–402. <https://doi.org/10.1038/nrcardio.2014.60>
35. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, et al. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol* 2004 Mar 3; 43(5): 842–7. <https://doi.org/10.1016/j.jacc.2003.09.053>
36. Gauss S, Achenbach S, Pflederer T, et al. Assessment of coronary artery remodelling by dual-source CT: a head-to-head comparison with intravascular ultrasound. *Heart* 2011 Jun; 97(12): 991–7. <https://doi.org/10.1136/hrt.2011.223024>
37. Thomsen C, Abdulla J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 2016 Feb; 17(2): 120–9. <https://doi.org/10.1093/ehjci/jev325>
38. Kröner ES, van Velzen JE, Boogers MJ, et al. Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. *Am J Cardiol* 2011 Jun 15; 107(12): 1725–9. <https://doi.org/10.1016/j.amjcard.2011.02.337>
39. Ito T, Terashima M, Kaneda H, et al. Comparison of in vivo assessment of vulnerable plaque by 64-slice multislice computed tomography versus optical coherence tomography. *Am J Cardiol* 2011 May 1; 107(9): 1270–7. <https://doi.org/10.1016/j.amjcard.2010.12.036>
40. Marwan M, Taher MA, El Meniawy K, et al. In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. *Atherosclerosis* 2011 Mar; 215(1): 110–5. <https://doi.org/10.1016/j.atherosclerosis.2010.12.006>
41. Pohle K, Achenbach S, MacNeill B, et al. Characterization of non-calcified coronary atherosclerotic plaque by multi-detector row CT: comparison to IVUS. *Atherosclerosis* 2007 Jan; 190(1): 174–80. <https://doi.org/10.1016/j.atherosclerosis.2006.01.013>
42. Benedek T, Jako B, Benedek I. Plaque quantification by coronary CT and intravascular ultrasound identifies a low CT density core as a marker of plaque instability in acute coronary syndromes. *Int Heart J* 2014; 55(1): 22–8. <https://doi.org/10.1536/ihj.13-213>
43. Sato A, Hoshi T, Kakefuda Y, et al. In vivo evaluation of fibrous cap thickness by optical coherence tomography for positive remodeling and low-attenuation plaques assessed by computed tomography angiography.

- raphy. *Int J Cardiol* 2015 Mar 1; 182: 419–25. <https://doi.org/10.1016/j.ijcard.2015.01.021>
44. Ozaki Y, Okumura M, Ismail TF, et al. Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angiography. *Eur Heart J* 2011 Nov; 32(22): 2814–23. <https://doi.org/10.1093/eurheartj/ehr189>
45. Dey D, Cheng VY, Slomka PJ, et al. Automated 3-dimensional quantification of noncalcified and calcified coronary plaque from coronary CT angiography. *J Cardiovasc Comput Tomogr* 2009 Nov-Dec; 3(6): 372–82. <https://doi.org/10.1016/j.jcct.2009.09.004>
46. Motoyama S, Kondo T, Sarai M, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007 Jul 24; 50(4): 319–26. <https://doi.org/10.1016/j.jacc.2007.03.044>
47. 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 Jul 15; 110(2): 183–9. <https://doi.org/10.1016/j.amjcard.2012.02.066>
48. van Velzen JE, de Graaf FR, de Graaf MA, et al. Comprehensive assessment of spotty calcifications on computed tomography angiography: comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis. *J Nucl Cardiol* 2011 Oct; 18(5): 893–903. <https://doi.org/10.1007/s12350-011-9428-2>
49. Puchner SB, Liu T, Mayrhofer T, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMI-CAT-II trial. *J Am Coll Cardiol*. 2014 Aug 19; 64(7): 684–92. <https://doi.org/10.1016/j.jacc.2014.05.039>
50. Maurovich-Horvat P, Hoffmann U, Vorpahl M, et al. The napkin-ring sign: CT signature of high-risk coronary plaques? *JACC Cardiovasc Imaging* 2010 Apr; 3(4): 440–4. <https://doi.org/10.1016/j.jcmg.2010.02.003>
51. Maurovich-Horvat P, Schlett CL, Alkadhi H, et al. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. *JACC Cardiovasc Imaging* 2012 Dec; 5(12): 1243–52. <https://doi.org/10.1016/j.jcmg.2012.03.019>
52. Seifarth H, Schlett CL, Nakano M, et al. Histopathological correlates of the napkin-ring sign plaque in coronary CT angiography. *Atherosclerosis* 2012 Sep; 224(1): 90–6. <https://doi.org/10.1016/j.atherosclerosis.2012.06.021>
53. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012 Mar; 33(6): 734–44. <https://doi.org/10.1093/eurheartj/ehr331>
54. Chow BJ, Small G, Yam Y, et al.; CONFIRM Investigators. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: An International Multicenter registry) registry. *Arterioscler Thromb Vasc Biol* 2015 Apr; 35(4): 981–9. <https://doi.org/10.1161/ATVBAHA.114.304351>
55. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, et al. Natural history of coronary atherosclerosis by multislice computed tomography. *JACC Cardiovasc Imaging* 2012 Mar; 5(3 Suppl): S28–37. <https://doi.org/10.1016/j.jcmg.2012.01.009>
56. Versteilen MO, Kietselaer BL, Dagnelie PC, et al. Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. *J Am Coll Cardiol* 2013 Jun 4; 61(22): 2296–305. <https://doi.org/10.1016/j.jacc.2013.02.065>
57. 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 Jun 30; 54(1): 49–57. <https://doi.org/10.1016/j.jacc.2009.02.068>
58. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging* 2013 Apr; 6(4): 448–57. <https://doi.org/10.1016/j.jcmg.2012.09.016>
59. Lee SE, Sung JM, Andreini D, et al. Differences in Progression to Obstructive Lesions per High-Risk Plaque Features and Plaque Volume With CCTA. *JACC Cardiovasc Imaging* 2020 Jun; 13(6): 1409–1417. <https://doi.org/10.1016/j.jcmg.2019.09.011>
60. Lee SE, Chang HJ, Rizvi A, et al. Rationale and design of the Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography IMaging (PARADIGM) registry: A comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J* 2016 Dec; 182: 72–79. <https://doi.org/10.1016/j.ahj.2016.09.003>
61. Lee SE, Sung JM, Andreini D, et al. Sex Differences in Compositional Plaque Volume Progression in Patients With Coronary Artery Disease. *JACC Cardiovasc Imaging* 2020 Nov; 13(11): 2386–2396. <https://doi.org/10.1016/j.jcmg.2020.06.034>
62. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al.; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011 Jan 20; 364(3): 226–35. <https://doi.org/10.1056/NEJMoa1002358>
63. Calvert PA, Obaid DR, O’Sullivan M, Shapiro LM, McNab D, Densem CG, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. *JACC Cardiovasc Imaging* 2011 Aug; 4(8): 894–901. <https://doi.org/10.1016/j.jcmg.2011.05.005>
64. Barlis P, Serruys PW, Gonzalo N, et al. Assessment of culprit and remote coronary narrowings using optical coherence tomography with long-term outcomes. *Am J Cardiol* 2008 Aug 15; 102(4): 391–5. <https://doi.org/10.1016/j.amjcard.2008.03.071>
65. Arbab-Zadeh A, Fuster V. The myth of the “vulnerable plaque”: transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol* 2015 Mar 3; 65(8): 846–855. <https://doi.org/10.1016/j.jacc.2014.11.041>
66. Kristensen TS, Kofoed KF, Kühl JT, et al. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. *J Am Coll Cardiol* 2011 Jul 26; 58(5): 502–9. <https://doi.org/10.1016/j.jacc.2011.01.058>
67. Hulten E, Bittencourt MS, Singh A, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy and lower low-density lipoprotein cholesterol. *Circ Cardiovasc Imaging* 2014 Jul; 7(4): 629–38. <https://doi.org/10.1161/CIRCIMAGING.113.001564>
68. Jukić M, Pavić L, Cerkez Habek J, et al. Influence of coronary computed tomography-angiography on patient management. *Croat Med J* 2012 Feb 15; 53(1): 4–10. <https://doi.org/10.3325/cmj.2012.53.4>
69. Vaughan CJ, Gotto AM Jr, Basson CT. The evolving role of statins in the management of atherosclerosis. *J Am Coll Cardiol*. 2000 Jan; 35(1): 1–10. [https://doi.org/10.1016/S0735-1097\(99\)00525-2](https://doi.org/10.1016/S0735-1097(99)00525-2)
70. Schwartz GG, Olsson AG, Ezekowitz MD, et al.; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001 Apr 4; 285(13): 1711–8. <https://doi.org/10.1001/jama.285.13.1711>
71. Lee SE, Chang HJ, Sung JM, A, et al. Effects of Statins on Coronary Atherosclerotic Plaques: The PARADIGM Study. *JACC Cardiovasc Imaging* 2018 Oct; 11(10): 1475–1484. <https://doi.org/10.1016/j.jcmg.2018.04.015>
72. Komukai K, Kubo T, Kitabata H, et al. Effect of atorvastatin therapy on fibrous cap thickness in coronary atherosclerotic plaque as assessed by optical coherence tomography: the EASY-FIT study. *J Am Coll Cardiol* 2014 Dec 2; 64(21): 2207–17. <https://doi.org/10.1016/j.jacc.2014.08.045>
73. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015 Jun 18; 372(25): 2387–97. <https://doi.org/10.1056/NEJMoa1410489>
74. Serruys PW, Garcia-Garcia HM, Buszman P, et al.; Integrated Biomarker and Imaging Study-2 Investigators. Effects of the direct lipoprotein-associated phospholipase A(2) inhibitor darapladib on human coronary atherosclerotic plaque. *Circulation* 2008 Sep 9; 118(11): 1172–82. <https://doi.org/10.1161/CIRCULATIONAHA.108.771899>
75. O’Donoghue ML, Braunwald E, White HD, et al.; SOLID-TIMI 52 Investigators; Steen DL. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA* 2014 Sep 10; 312(10): 1006–15. <https://doi.org/10.1001/jama.2014.11061>
76. Nidorf SM, Fiolet ATL, Mosterd A, et al.; LoDoCo2 Trial Investigators. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med* 2020 Nov 5; 383(19): 1838–1847. <https://doi.org/10.1056/NEJMoa2021372>
77. Ridker PM, Everett BM, Pradhan A, et al.; CIRT Investigators. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N Engl J Med* 2019 Feb 21; 380(8): 752–762. <https://doi.org/10.1056/NEJMoa1809798>
78. Everett BM, MacFadyen JG, Thuren T, et al. Inhibition of Interleukin-1β and Reduction in Atherothrombotic Cardiovascular Events in the CANTOS Trial. *J Am Coll Cardiol* 2020 Oct 6; 76(14): 1660–1670. <https://doi.org/10.1016/j.jacc.2020.08.011>
79. Stone GW, Maehara A, Ali ZA, et al.; PROSPECT ABSORB Investigators. Percutaneous Coronary Intervention for Vulnerable Coronary Atherosclerotic Plaque. *J Am Coll Cardiol* 2020 Nov 17; 76(20): 2289–2301. <https://doi.org/10.1016/j.jacc.2020.09.547>
80. Mol JQ, Bom MJ, Damman P, et al. Pre-Emptive OCT-Guided Angioplasty of Vulnerable Intermediate Coronary Lesions: Results from the Prematurely Halted PECTUS-Trial. *J Interv Cardiol* 2020 Dec 3; 2020: 8821525. <https://doi.org/10.1155/2020/8821525>