Obilježja vulnerabilnog plaka na višeslojnoj kompjutoriziranoj tomografiji koronarnih arterija

Vulnerable Plaque Characteristics at Coronary Computed Tomography Angiography

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RECEIVED:
February 5, 2023
UPDATED:
February 26, 2023
ACCEPTED:
February 28, 2023

SAŽETAK: Kardiovaskularne su bolesti, prema pokazateljima morbiditeta i mortaliteta, vodeći javnozdravstveni problem u Republici Hrvatskoj i Europskoj uniji. Premda stope smrtnosti od ishemijske bolesti srca padaju, Hrvatska se još uvijek ubraja u države visokog kardiovaskularnog rizika. Smjernice Europskoga kardiološkog društva iz 2020. godine za akutni koronarni sindrom (AKS) u bolesnika s niskim do srednjim rizikom od koronarne aterosklerotske bolesti srca (KBS) preporučuju MSCT koronarografiju kao alternativu invazivnoj koronarografiji. U većine bolesnika sa sumnjom na KBS nakon MSCT koronarografije postavi se dijagnoza neopstruktivne bolesti koja uzrokuje većinu slučajeva AKS-a. MSCT uređaji najnovije generacije uz nisku dozu zračenja i mali volumen kontrasta pouzdano prikazuju obilježja vulnerabilnog plaka: (i) pozitivno remodeliranje, (ii) plak niske atenuacije, (iii) točkastu kalcifikaciju i (iv) znak prstena za salvete. Ti su plakovi zbog pozitivnog remodeliranja često neopstruktivni, a prema smjernicama CAD-RADS 2.0 iz 2022. godine, sva njihova obilježja potrebno je na MSCT nalazima posebno naglasiti. Pri procjeni prognostičke vrijednosti obilježja vulnerabilnog plaka za neželjene kardijalne događaje MSCT se pokazao podjednako valjan kao i druge invazivne dijagnostičke metode. Isto tako, kod vulnerabilnih plakova pokazao se korisnim pri indiciranju optimalne medikamentne terapije kao i u praćenju njezina učinka. Rezultati velikih međunarodnih randomiziranih istraživanja upućuju na smjer terapijskog pristupa vulnerabilnom plaku.

SUMMARY: 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 coronarography. 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.

KLJUČNE RIJEČI: vulnerabilni plak, koronarna bolest srca, višeslojna kompjutorizirana tomografija koronarnih arterija, akutni koronarni sindrom.

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

CITATION: Cardiol Croat. 2023;18(1-2):7-21. | https://doi.org/10.15836/ccar2023.7

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TO CITE THIS ARTICLE: Medaković P, Jukić M, Biloglav Z. Vulnerable Plaque Characteristics at Coronary Computed Tomography Angiography. Cardiol Croat. 2023;18(1-2):7-21. | https://doi.org/10.15836/ccar2023.7

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Kardiovaskularne su bolesti, prema pokazateljima morbiditeta i mortaliteta, vodeći javnozdravstveni problem u Republici Hrvatskoj i Europskoj uniji (EU). Prema najnovijim podatcima Hrvatskog zavoda za javno zdravstvo za 2021. godinu, ishemijska bolest srca (IBS) s proporcionalnim mortalitetom od 12,4 % bila je drugi uzrok smrti u muškaraca, dok je u žena s 12,6 % bila vodeći uzrok smrti.[1] Usprkos stalnom smanjenju stopa smrtnosti od IBS-a u posljednjem desetljeću, one su u usporedbi sa stopama u zemljama članicama EU-a još uvijek visoke. Zbog toga su Europsko kardiološko društvo (ESC) i Svjetska zdravstvena organizacija (SZO) uvrstile Hrvatsku među države visokoga KV rizika.[2,3] Visoke stope djelomično su pripisive lošem pokazatelju kvalitete bolničkog liječenja iskazanom na temelju stope mortaliteta bolesnika do 30 dana nakon akutnog infarkta miokarda, prema kojoj je Hrvatska s 11,6 na 100 bolesnika na visokom drugom mjestu među članicama EU-a.[4] Osim toga, sve razine prevencije općenito su nedostatne, za razliku od intervencijske kardiologije koja je dobro razvijena, ali se ishodi liječenja sustavno ne mjere. Razvojem mreže primarnih perkutanih koronarnih intervencija (PCI) stvoreni su preduvjeti za primjenu smjernica u kliničkoj praksi. Naime, Smjernice ESC-a iz 2020. godine za postupak s bolesnicima pri akutnome koronarnom sindromu (AKS) bez elevacije ST-segmenta (NSTEMI) navode da je PCI dijagnostička i terapijska metoda izbora (klasa I.).[5] U tim se smjernicama prvi put MSCT koronarografija preporučuje kao alternativa invazivnoj koronarografiji za isključenje AKS-a u bolesnika s niskim do srednjim rizikom od koronarne aterosklerotske bolesti srca (KBS) i u slučajevima kada su troponini i/ili EKG uredni ili neuvjerljivi (klasa I.). Za razliku od Smjernica za AKS, ESC je još 2019. godine izdao Smjernice za dijagnostiku i liječenje kroničnoga koronarnog sindroma i preporučio MSCT koronarografiju kao početnu pretragu za dijagnosticiranje u simptomatskih bolesnika u kojih opstruktivnu KBS nije moguće isključiti na temelju kliničke procjene.[6] Sama primjena MSCT koronarografije zahtijeva poznavanje tehnike snimanja i može biti praćena određenim teškoćama pri snimanju koje djelomično ovise o obilježjima bolesnika i već su prije opisane.[7]

Koronarna bolest srca, kako akutna, tako i kronična, ima izrazito heterogena morfološka obilježja, kao što su primjerice proširenost bolesti, stupanj suženja koronarnih arterija i vrsta aterosklerotskoga plaka. Tijekom desetljeća primjene invazivne koronarografije na temelju praga značajnosti stenoze od 50 % uvriježila se bivarijatna kategorizacija KBS-a na opstruktivnu i neopstruktivnu. Kako takva percepcija u cijelosti zanemaruje kliničko značenje KV kontinuuma, neopstruktivna je bolest, sukladno tomu, dijagnostički, terapijski i prognostički zapostavljana, a njezin rizik za neželjene KV događaje podcjenjivan. Treba naglasiti da skupina bolesnika s neopstruktivnim KBS-om nema jednaku distribuciju rizika za neželjene kardijalne događaje, već se unutar nje jasno razabiru podskupine s različitim rizicima koji, uz znanstvenu, imaju i kliničku važnost. Osim stupnja stenoze, značajna prognostička vrijednost pripisiva je i proširenosti bolesti pa tako bolesnici s trožilnom bolesti imaju lošiju prognozu u usporedbi s onima s jednožilnom. Isto tako, u bolesnika s dvožilnom bolesti zabilježen je 2,6 puta veći omjer rizika od neželjenoga kardijalnog događaja nego u onih s jednožilnom neopstruktivnom bolesti.[8,9]

U većine se bolesnika sa sumnjom na KBS nakon MSCT koronarografije ili invazivne koronarografije postavi dijagnoza

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 counties 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 heterogenous 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 bivariant 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]

neopstruktivne bolesti.[10,11] Prijašnja patološka i dijagnostička istraživanja u kojima su primijenjene obje dijagnostičke metode upućuju na to da je većina AKS-a prouzročena upravo neopstruktivnim aterosklerotskim plakovima.[12-15] Bolje dijagnostičke performanse MSCT koronarografije, što uključuje trodimenzionalni način oslikavanja i dobru kontrastnu i prostornu rezoluciju, omogućuju da u usporedbi s invazivnom koronarografijom detektira dvostruko više aterosklerotskih plakova na koronarnom stablu.[16,17] Te prednosti MSCT koronarografije dobivaju na važnosti jer se zna da je nastanak AKS-a pripisiv kako kvantitativnim obilježjima plaka, npr. proširenosti, tako i njegovim kvalitativnim obilježjima – vrsti i morfologiji. Za razliku od primjerice invazivne i skupe metode poput intravaskularnog ultrazvuka (IVUS), MSCT koronarografija neinvazivno i precizno prikazuje vrstu i morfologiju aterosklerotskog plaka. Akutni koronarni sindrom u svim svojim kliničkim potkategorijama povezuje se s prisutnošću vulnerabilnih plakova.[18,19] Histološka istraživanja vulnerabilnih plakova provedena na *post mortem* uzorcima upućuju na obilježja koja su za njih visokospecifična, poput pozitivnog remodeliranja, nekrotične jezgre s tankom fibroznom kapicom (<65 µm), infiltracije kapice makrofagima te neovaskularizacije iz adventicije – *vasa vasorum*, mikrokalcifikacije i točkaste kalcifikacije.[20,21] Kako se MSCT koronarografijom mogu precizno vizualizirati i kvantificirati prije navedena obilježja, tako je moguće i stratificirati rizik unutar kliničkog kontinuuma AKS-a i odabrati optimalan terapijski modalitet.[22]

S obzirom na opterećenje IBS-om, veću dostupnost tehnološki naprednih MSCT uređaja i nedostatne ljudske resurse, neupitna je potreba za dodatnom edukacijom iz područja koronarnog oslikavanja MSCT-om. Stoga je cilj ovoga preglednog članka opisati i slikovno prikazati glavna dijagnostička obilježja vulnerabilnih plakova, navesti njihovu prognostičku vrijednost za neželjene kardijalne događaje i prikazati način njihova opisivanja na nalazima MSCT koronarografije.

Mehanizam nastanka akutnoga koronarnog sindroma i obilježja povezana s vulnerabilnim plakom

Intrakoronarni ugrušak na mjestu aterosklerotskog plaka najčešći je uzrok AKS-a, dok su spontana disekcija koronarne arterije i/ili koronarni vazospazam rjeđi. Među patofiziološkim mehanizmima nastanka intrakoronarnog ugruška u stručnoj zajednici najčešće se navode teorije o rupturi plaka, eroziji plaka i kalcifikaciji čvora.[23-25] Pod pojmom ruptura plaka razumijevamo pucanje tanke fibrozne kapice fibroateroma s izlijevanjem nekrotičnoga masnog sadržaja u lumen arterije, što dovodi do stvaranja i taloženja ugruška. Vulnerabilni se plak u prošlosti različito definirao. Tako ga Muller *i sur.* 1989. godine opisuju kao koronarni plak visoko osjetljiv za rupturu.[19] Novije definicije više naglašavaju njegovu kliničku važnost, pa tako Stone *i sur.* 2011. godine pod tim pojmom navode obilježje bolesnika koji imaju povećan rizik od budućih neželjenih kardijalnih događaja.[26]

Rizik od rupture kod vulnerabilnog plaka određuju brojni čimbenici, a prema patohistološkim istraživanjima fibrozna kapica tanja od 65 µm ima važnu ulogu.[27] Debljina fibrozne kapice inverzno je povezana s veličinom centralne nekroze i rupturirani plakovi u usporedbi s nerupturiranima imaju veće centralne nekrotične jezgre.[20,28,29] Infiltracija fibrozne

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 patients 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

kapice makrofagima smanjuje debljinu fibrozne kapice, što povećava rizik od rupture.[29]

Kod vulnerabilnog plaka često je pozitivno remodeliranje.[21] Pod tim pojmom razumijevamo rast plaka prema van s poštedom lumena od suženja, a praćeno je neovaskularizacijom i stvaranjem vaza vazorum koja destabilizira plak jer zbog nezrelosti stijenke uzrokuje krvarenje.[30,31]

Za razliku od kalcificiranih plakova koji se smatraju stabilnima, mikrokalcifikacije ili točkaste kalcifikacije osobito u fibroznoj kapici, specifična su obilježja vulnerabilnog plaka.[32,33] Treba naglasiti da su pozitivno remodeliranje, centralna nekrotična jezgra i točkaste kalcifikacije kod vulnerabilnog plaka prvotno dokazani na patohistološkim uzorcima koji su godinama analizirani isključivo *post mortem*. Tek je u novije vrijeme razvoj IVUS-a omogućio njihov prikaz na bolesnicima, međutim, invazivnost te pretrage i visoka cijena ograničavaju njezinu širu dostupnost. Danas su tehnološki napredni i neinvazivni MSCT uređaji šire dostupni, a omogućuju vizualizaciju plakova uz malu dozu ionizirajućeg zračenja i mali volumen kontrastnoga sredstva. Primjenu te pretrage ograničava nedostatak školovanih stručnjaka iz područja KV oslikavanja, inženjera i specijalista radiologije koji znaju primijeniti prikladne tehnike snimanja.

Obilježja vulnerabilnog plaka na višeslojnoj kompjutoriziranoj koronarografiji

U najnovijim preporukama CAD-RADS 2.0 - 2022 (engl. *Coronary Artery Disease-Reporting and Data System*) naziv vulnerabilni plak promijenjen je u plak visokog rizika (engl. *high-risk plaque*).[22] Međutim, budući da se prvotni naziv vulnerabilni plak uvriježio u medicinskoj zajednici, primjenjuje se i u ovom članku. Na MSCT koronarografiji jasno su vidljiva sljedeća obilježja te vrste plaka: (i) pozitivno remodeliranje, (ii) plak niske atenuacije, (iii) točkasta kalcifikacija i (iv) znak prstena za salvete. Prevalencija navedenih obilježja relativno je visoka i procjenjuje se na oko 30 %. U najnovijim preporukama osobito je naglašena važnost standardnog načina pisanja i preporučuje se opisati sva navedena obilježja aterosklerotskoga plaka.[22] U pisanom nalazu potrebno je dodati oznaku HRP (engl. *high-risk plaque*), kao oznaku modifikatora kada su prisutna dva ili više prije navedenih obilježja.

Pozitivno remodeliranje

Pozitivno remodeliranje najčešće se vidi u kliničkoj praksi. Riječ je o širenju stijenke krvne žile prema van na mjestu aterosklerotskoga plaka, zbog čega je lumen na mjestu suženja koronarne arterije djelomično očuvan[34] **(slika 1, 2)**. Kvantifikacija ovoga obilježja moguća je s pomoću indeksa remodeliranja prvotno predloženog u istraživanjima s IVUS-om. Kod IVUS-a se indeks modeliranja izračunava kao omjer površine poprečnoga presjeka na najužemu mjestu suženja i površine poprečnoga presjeka krvne žile proksimalno i distalno od mjesta suženja[35] **(slika 3)**. Na MSCT koronarografiji njegove se vrijednosti često precjenjuju i one veće od 1,1 smatraju se klinički značajnima **(slika 4)**. Bolesnici s AKS-om imaju veće vrijednosti indeksa od bolesnika sa stabilnom anginom, kao i od onih sa *culprit* plakovima.[36,37] Izračun indeksa remodeliranja na MSCT-u označuje omjer vanjskoga promjera žile na mjestu plaka i prosjeka normalnog promjera žile proksimalno i distalno od stenoze. Isto tako, plakovi s pozitivnim remodeliranjem na MSCT koronaplaques.[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: (i) positive remodeling, (ii) low attenuation plaque, (iii) spotty calcification, and the (iv) 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

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.

rografiji imaju veću nekrotičnu jezgru i češće ih se na IVUS-u opisuje kao fibroaterome s tankom fibroznom kapicom (TFCA), dok indeks pozitivnog remodeliranja kod fibroateroma s TFCA mjeren MSCT-om pokazuje veće vrijednosti nego pri mjerenju OCT-om (engl. *optical coherence tomography*).[38,39]

Plak niske atenuacije

Pod pojmom plak niske atenuacije razumijevamo nekalcificirani plak čija jezgra ima vrijednosti atenuacije manje od 30 Hounsfieldovih jedinica (H. j.) u bilo kojem vokselu mjerenja.[22] U kliničkoj je praksi važno razlikovati plak niske atenuacije od pozitivnog remodeliranja jer su vrijednosti atenuacije pri pozitivnom remodeliranju često veće od 30 H. j. Treba naglasiti da je prag od 30 H. j. općenito prihvaćen u kliničkoj praksi zbog visoke osjetljivosti i specifičnosti za detekciju plakova bogatih lipidima[40] **(slika 4)**. Manje vrijednosti, u pravilu, odgovaraju nekrotičnom sadržaju jezgre, dok veće vrijednosti promjera jezgre povećavaju rizik od AKS-a **(slika 1, 2)**. Plakovi s lipidnim sadržajem na MSCT koronarografiji u usporedbi s očitanjima na IVUS-u u prosjeku bilježe niže atenuacijske vrijednosti.[40,41] Međutim, u istraživanjima i kliničkoj praksi razlikovanje mekog plaka lipidnog sadržaja i fibroznog plaka na MSCT-u otežava preklapanje denziteta između navedenih entiteta[40,42] **(slika 2)**. Također, u usporedbi s OCT-om, plakovi niske atenuacije na MSCT-u povezuju se s nalazom TFCA na OCT-u.[43] Usprkos otežanom razlikovanju lipidnih plakova od fibroznih, čak 88 % rupturiranih plakova kod AKS-a ima atenuacijske vrijednosti niže od 30 H. j. u odnosu prema samo 18 % kod stabilnih plakova. Automatizirana softverska rješenja pri očitanju MSCT koronarografije omogućuju pouzdaniju kvantifikaciju plakova niske atenuacije.[44,45]

Točkasta kalcifikacija

U većine preminulih od iznenadne srčane smrti histopatološki uzorci plakova sadržavaju mikrokalcifikacije koje se ne prikazuju na MSCT koronarografiji, za razliku od pouzdanog prikaza točkastih kalcifikacija.[34] Točkaste su kalcifikacije sitne kalcifikacije unutar mekog nekalcificiranog plaka. Atenuacija im je veća od 130 H. j. i dijele se u sljedeće kategorije: male (<1 mm), srednje (1 – 3 mm) i masivne (>3 mm)[46-48] **(slika 4)**. Povezuju se s plakovima koji uzrokuju AKS, a istraživanja MSCT koronarografijom pokazala su da je ovo obilježje vulnerabilnog plaka usporedivo s nalazima dobivenima IVUS-om[37,48,49] **(slika 3)**.

Znak prstena za salvete

Znak prstena za salvete jedinstveno je obilježje vulnerabilnog plaka vidljivo na poprečnim presjecima nekalcificiranoga plaka. Sastoji se od zone nekrotične jezgre niske atenuacije koja graniči s lumenom i okružena je prstenastom zonom veće atenuacije koja odgovara fibroznom tkivu[50,51] **(slika 1)**. To je obilježje pouzdano pri detekciji TFCA-a i u skladu je s patohistološkim i nalazima OCT-a.[39,51,52] Tehnološki razvoj MSCT uređaja početkom prošlog desetljeća omogućio je provođenje istraživanja u kojima je znak prstena za salvete uspoređivan s ostalim obilježjima prisutnima kod invazivnih kardioloških dijagnostičkih metoda i patohistoloških nalaza. Dijagnostička su istraživanja prethodila istraživanjima usmjerenima na procjenu prognostičke vrijednosti obilježja vulnerabilnog plaka za neželjene kardijalne događaje.

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 attenuation 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 scanners 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.

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.

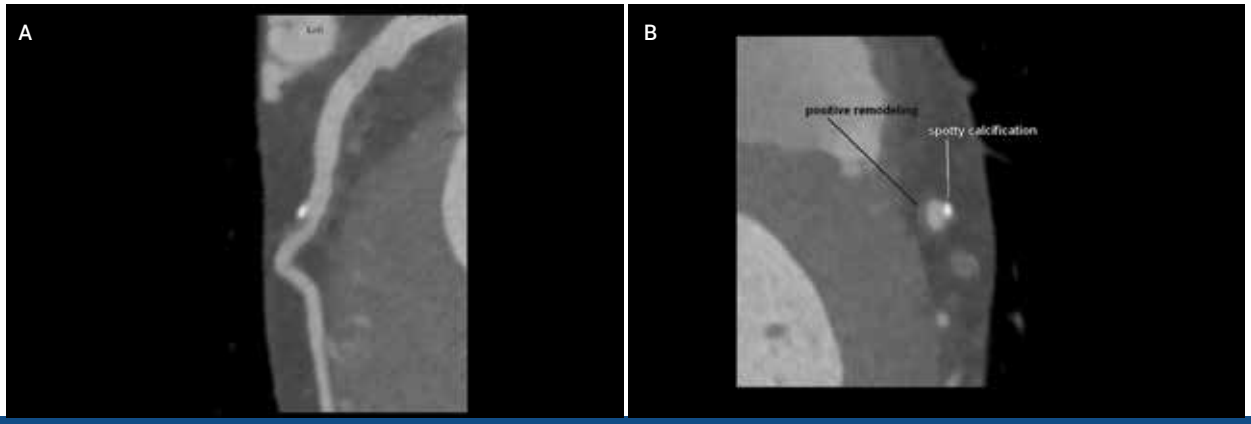

FIGURE 3. Female patient, 64 years old, referred to cardiac computed tomography angiography due to long- standing insufficiently regulated diabetes and multiple cardiovascular disease risk factors. Cardiac computed tomography angiography revealed diffuse non-obstructive coronary artery disease. Curved 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).

Prognostička vrijednost obilježja vulnerabilnog plaka na višeslojnoj kompjutoriziranoj koronarografiji

Rezultati istraživanja utemeljenih na invazivnim i neinvazivnim metodama oslikavanja koronarnih arterija upućuju na to da je većina bolesnika s AKS-om povezana s neopstruktivnim plakom (<50 %), a oni s neopstruktivnim KBS-om (u odnosu prema onima bez KBS-a) imaju mnogo veći rizik od kardijalne smrt i AKS-a.[9,53,54] Prijašnja istraživanja patohistoloških uzoraka dokazala su povezanost obilježja vulnerabilnog plaka s kliničkom slikom AKS-a. Dijagnostičke kardiološke i radiološke metode koronarnog oslikavanja omogućuju i kvantifikaciju rizika od neželjenih kardijalnih događaja. Većinu istraživanja usmjerenih na prognostičku vrijednost obilježja vulnerabilnog plaka uz razlike u dizajnu istraživanja i odabir populacija obilježavaju i različiti KV ishodi i vremena praćenja. Usprkos razlikama, gotovo je svima svojstven porast rizika od neželjenog događaja s povećanjem broja obilježja vulnerabilnoga plaka. Osim toga, pri nekim istraživanjima nije uzet u obzir nedvojbeno pozitivan utjecaj optimalne medikamentne terapije (OMT), što je, zasigurno, utjecalo na ishode. Vrijeme praćenja iznimno je važno jer pouzdana procjena prognostičkih vrijednosti pojedinih obilježja vulnerabilnog plaka zahtijeva duga vremena praćenja zbog njegove moguće stabilizacije. MSCT koronarografija u tom se smislu pokazala kao pouzdana metoda za praćenje prirodnog tijeka KBS-a, a poboljšanje prognostičke vrijednosti na razini plaka djelomično je pripisivo i novijim softverskim rješenjima koja omogućuju precizniju kvantifikaciju.[40,55,56] Jedno od prvih prospektivnih istraživanja prognostičkih vrijednosti plaka niske atenuacije, pozitivnog remodeliranja i točkaste kalcifikacije, u smislu predikcije neželjenih kardijalnih događaja nakon više od dvije godine praćenja izlučilo je plak niske atenuacije i pozitivno remodeliranje kao prediktore.[57] Isto tako, znak prstena za salvete pokazao se uz pozitivno remodeliranje i plak niske atenuacije kao prediktor AKS-a i kardijalne smrti nakon 2,3 godine praćenja.[58] Meta-analiza je dokazala značajan i 12,1

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. Cardiological and radiological 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 undoubtably 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 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 sig-

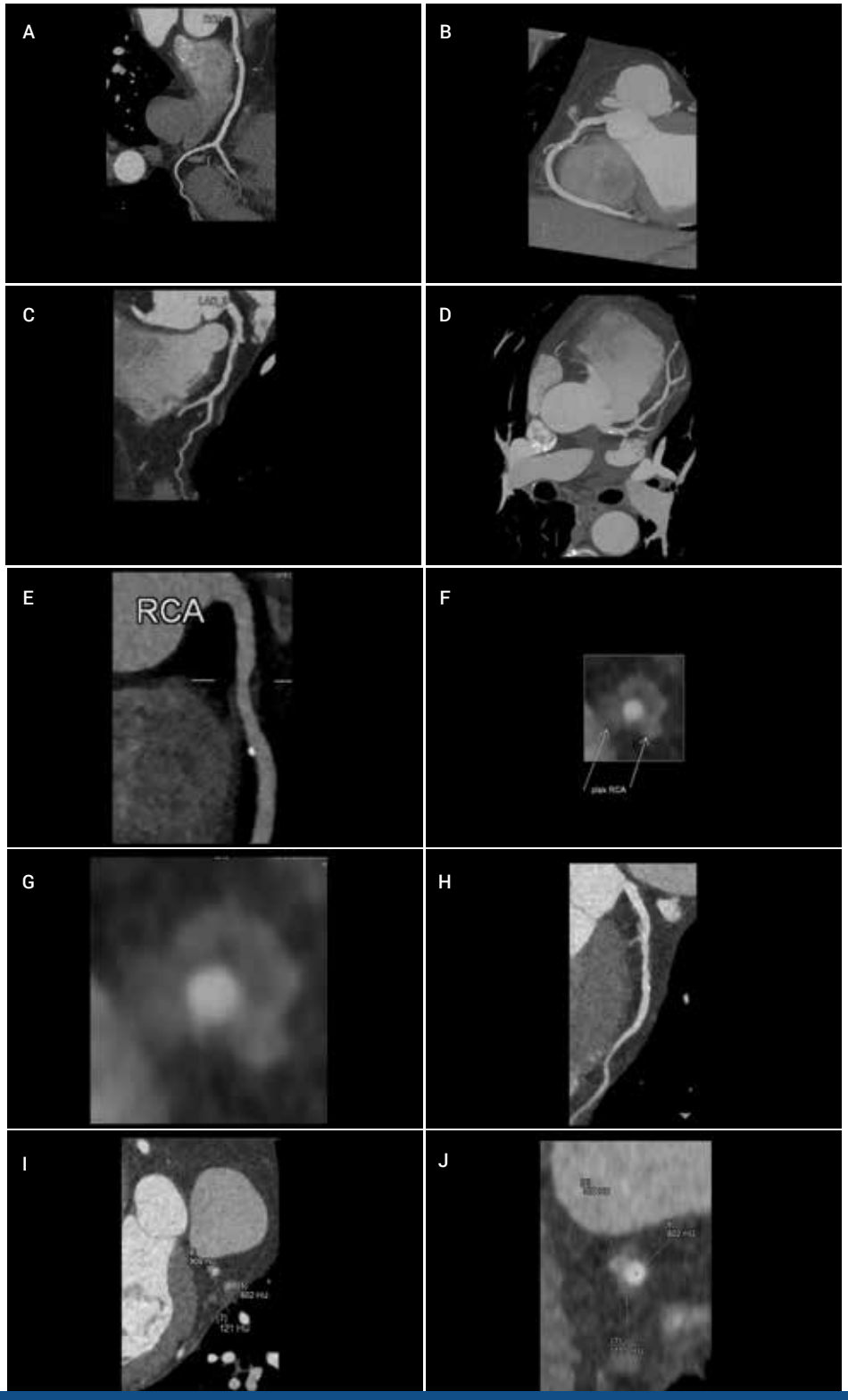

FIGURE 4. Male patient, 64 years old, with previously diagnosed non-obstructive coronary artery disease and low adherence to optimal medical therapy. Cardiac computed tomography angiography revealed non-obstructive non-calcified plaque in the proximal right coronary artery and proximal and mid left anterior 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.

puta veći omjer rizika u bolesnika s obilježjima vulnerabilnog plaka u odnosu prema onima sa stabilnim plakovima, kao i mnogo veći broj plakova niske atenuacije (<30 H. j.) kod AKS-a nasuprot broju plakova detektiranih u bolesnika sa stabilnom anginom.[37] S obzirom na prirodu pozitivnog remodeliranja od lumena prema van, vulnerabilni plakovi često uzrokuju neopstruktivnu stenozu i stoga je korist od OMT-a očekivana. U velikog udjela bolesnika upućenih na MSCT koronarografiju zbog sumnje na KBS postavi se dijagnoza neopstruktivne bolesti koja je povezana s većinom AKS-a. Prema rezultatima istraživanja *PARADIGM*, sama obilježja vulnerabilnog plaka ne utječu na dinamiku progresije neopstruktivnog plaka u opstruktivni nakon dvije godine praćenja, nego takvu ulogu imaju inicijalni postotni volumen ateroma i postotak promjera stenoze, koji su jedini značajni prediktori nastajanja opstruktivnih lezija.[59,60] Isto je istraživanje utvrdilo razlike po spolu i mnogo nižu prevalenciju i sporiju progresiju vulnerabilnih plakova u žena.[61] Nasuprot navedenima stoje rezultati istraživanja *PROSPECT* u kojemu je IVUS primijenjen za detekciju vulnerabilnog plaka u bolesnika s AKS-om, koji su potom praćeni 3,4 godine.[62] U tom je istraživanju na uzorku od 700 bolesnika pronađeno 596 TFCA-a, a od ukupno 74 neželjena zajednička kardijalna događaja samo je šest pripisivo kardijalnoj smrti i nefatalnom infarktu miokarda nakon nešto više od tri godine praćenja. I u drugim istraživanjima, kao što je primjerice *VIVA*, primijenjeni su IVUS i OCT i dobiveni slični rezultati.[63,64] Takvi rezultati dobiveni oslikavanjem koronarnih arterija, odnosno plakova djelomično se podudaraju s rezultatima patohistoloških istraživanja prema kojima ruptura plaka kod 10 - 20 % nesignifikantnih plakova nije praćena kliničkim simptomima.[65] Izgledno je da većina plakova rupturira i zacijeli bez uzrokovanja AKS-a. Ovakvi rezultati propituju sam koncept procjene rizika na temelju detekcije vulnerabilnog plaka kao i same termine „vulnerabilnost" i „visoki rizik" (engl. *high-risk plaque*). Navedeni su rezultati oprečni rezultatima MSCT istraživanja u kojemu se volumen nekalcificiranog plaka u bolesnika s neopstruktivnim lezijama i NSTEMI-jem pokazao kao značajan prediktor neželjenih kardijalnih događaja nakon 16 mjeseci praćenja.[66] U bolesnika s akutnom boli u prsištu obilježja vulnerabilnog plaka pokazala su se nakon učinjene MSCT koronarografije kao značajan prediktor AKS-a, neovisno i o stupnju stenoze.[49] Ova su istraživanja stvorila osnovu za implementaciju MSCT koronarografije u kliničku praksu hitnih službi sukladno preporukama iz Smjernica ESC-a za AKS.[5] Pouzdana procjena prognostičke vrijednosti vulnerabilnog plaka za neželjene kardijalne događaje neovisno o metodi oslikavanja podrazumijeva prilagodbe na ostale čimbenike rizika za nastanak AKS-a. Uz obilježja vulnerabilnog plaka istodobna ili asinkrona prisutnost sistemskih čimbenika poput protrombotskog miljea, upalnoga sistemskog ili lokaliziranog stanja i okolišnih proinflamatornih čimbenika utječe na rizik od nastanka AKS-a. Utjecaj OMT-a statinima, acetilsalicilatnom kiselinom i protuupalnim lijekovima dodatno modificira procjenu rizika od rupture vulnerabilnog plaka, što treba uzeti u obzir i u kliničkoj procjeni rizika bolesnika.

Utjecaj terapije na vulnerabilni plak

Velika međunarodna istraživanja potvrdila su protektivni učinak OMT-a na neželjene kardijalne događaje. Osim toga, primjena MSCT koronarografije povećava propisivanje OMT-a

nificant 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 contrary 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

osobito u bolesnika s neopstruktivnim KBS-om.[67] Nakon ove pretrage medikamentna terapija promijenjena je u više od polovice bolesnika, dok je čak u tri četvrtine pacijenata ukinuta indikacija za invazivnu koronarografiju.[68] U prijašnjem istraživanju invazivnom koronarografijom utvrđeni su pozitivni učinci statina, kao što je primjerice umjerena regresija i stabilizacija plakova razvidna u redukciji nekrotične jezgre plaka i upalne komponente s manjom infiltracijom makrofaga te zadebljanjem fibrozne kapice.[69] Stabilizacija vulnerabilnih plakova i njihovih obilježja poboljšala je ishode liječenja bolesnika s AKS-om, što je potaknulo uvođenje atorvastatina u terapiju.[70] Slični su rezultati istraživanja *PARADIGM* čiji je cilj bio kvantifikacija utjecaja terapije statinima na plakove.[71] Naime, statini usporuju progresiju ukupnog volumena ateroskleroze, povećavaju kalcifikaciju plakova i do 35 % smanjuju pojavu novih vulnerabilnih plakova na kontrolnim MSCT koronarografijama u razdoblju duljem od dvije godine. Međutim, udio bolesnika s progresijom stenoze od neopstruktivne u opstruktivnu tijekom dvije godine nije se značajno razlikovao. U bolesnika s nestabilnom anginom pektoris visoka doza statina dovela je do zadebljanja fibrozne kapice fibroateroma, a u kombinaciji s ezetimibom smanjila je neželjene kardijalne događaja u usporedbi s terapijom isključivo statinima.[72,73] Spomenuta su istraživanja potvrdila veći utjecaj terapije statinima na meku komponentu plaka i smanjenje ukupnog volumena plaka s obzirom na stupanj suženja koronarne arterije, kao i pozitivan utjecaj na doživljenje smanjenjem učestalosti neželjenih kardijalnih događaja. Osim statina, učinkovito smanjenje upalne komponente zamijećeno je i kod drugih lijekova, kao što su primjerice inhibitori lipoprotein povezane fosfolipaze A2, kolcihin, metotreksat i antagonisti interleukina-1. Tako je inhibitor lipoprotein povezane fosfolipaze A2 bio učinkovit u usporivanju razvoja nekrotične jezgre vulnerabilnog plaka, međutim, u velikim randomiziranim istraživanjima nije dokazana korist u kliničkim ishodima.[74,75] Kolcihin u niskoj dozi (0,5 mg) nasuprot placebu u bolesnika s recentno preboljenim infarktom miokarda znatno je smanjio neželjene kardijalne događaje, uključujući i spontane infarkte miokarda nakon 2,5 godina praćenja.[76] Nasuprot tim rezultatima, metotreksat u niskoj dozi od 15 do 20 mg tjedno u usporedbi s placebom nije pokazao redukciju upalnih parametara ni smanjenje stope neželjenih kardijalnih događaja nakon 2,3 godine praćenja.[77] Monoklonalno protutijelo canakinumab u usporedbi s placebom znatno je smanjilo KV događaje nakon 3,7 godina praćenja u bolesnika s preboljelim infarktom miokarda.[78] Važnu ulogu upalnih parametara u etiologiji AKS-a dokazuju brojna istraživanja, a negativni rezultati pojedinih lijekova kojima je cilj bio dokazati korist od OMT-a više su pripisivi nedovoljno dobro određenim biokemijskim i patohistološkim mehanizmima djelovanja navedenih lijekova kod KBS-a nego propitivanju samoga koncepta redukcije lokalnih i sistemskih parametara upale. Za razliku od istraživanja vulnerabilnih plakova kojima je svrha bila dokazati korist od OMT-a, ponajprije statina, druga su istraživanja nastojala utvrditi korist od primjene perkutanih koronarnih intervencija. Za kvantifikaciju pojedinih parametara obilježja vulnerabilnog plaka i zbog svoje još uvijek superiorne rezolucije s obzirom na MSCT u brojnim su istraživanjima korišteni IVUS i OCT, međutim, ove invazivne metode oslikavanja relativno su slabo dostupne i zahtijevaju veća sredstva i iskustvo operatera. Već je napomenuto da vulnerabilni plakovi zbog pozitivnog remodeliranja često uzrokuju neopstruktivna suženja

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

(<50 %), no usprkos tomu smatra ih se visokorizičnima. Recentno istraživanje *PROSPECT-ABSORB* nije pokazalo značajnu redukciju neželjenih kardijalnih događaja u bolesnika s vulnerabilnim plakovima liječenima bioresorptivnim stentovima nasuprot OMT-u nakon četiri godine kliničkog praćenja.[79] Slični su rezultati i istraživanja *PECTUS*, u kojemu je za detekciju neopstruktivnog vulnerabilnog plaka rabljen OCT, međutim, zbog povlačenja bioresorptivnih stentova s tržišta, ona je prekinuta.[80] Mali broj bolesnika obuhvaćen tim istraživanjem umanjuje njegovu znanstvenu korist. Rezultati trenutačnih istraživanja, poput *PREVENT* (NCT02316886) i *VULNERABLE* (NCT0559906), imaju za cilj dokazati dobrobit PCI-ja kod neopstruktivnih vulnerabilnih plakova i zasigurno će pojasniti korist od ovakvog pristupa u bolesnika s AKS-om. Rezultati dosadašnjih istraživanja ne upućuju na značajnu korist PCI-ja s obzirom na OMT u smislu smanjenja neželjenih kardijalnih događaja u bolesnika s vulnerabilnim plakovima dijagnosticiranima invazivnim ili neinvazivnim metodama.

Zaključak

Koronarna bolest srca vodeći je javnozdravstveni problem u Republici Hrvatskoj, u čijoj se dijagnostici primjenjuje invazivna i MSCT koronarografija. MSCT koronarografija zbog neinvazivnosti ima brojne prednosti, ali se također ističu njezine dijagnostičke performanse koje omogućuju jasan prikaz kvalitativnih i kvantitativnih obilježja aterosklerotskih plakova. Prikaz navedenih obilježja dobio je na kliničkoj važnosti jer ruptura većine stabilnih i vulnerabilnih plakova nije praćena kliničkim simptomima. Tako trenutačne smjernice ističu da je obilježja vulnerabilnog plaka, kao što su primjerice pozitivno remodeliranje, plak niske atenuacije, točkaste kalcifikacije i znak prstena za salvete, potrebno navesti u nalazima da bi se omogućila procjena rizika od rupture, odnosno AKS-a. U procjeni prognostičke vrijednosti za neželjene kardijalne događaje obilježja vulnerabilnog plaka na MSCT-u potvrdila su pozitivan smjer, međutim, potrebna je viša razina znanstvenih dokaza kako bi ova pretraga postala metoda izbora za procjenu rizika. Rezultati randomiziranih kliničkih istraživanja nedvojbeno pokazuju pozitivan učinak statina na stabilizaciju vulnerabilnog plaka, ali i na redukciju sistemskih i lokalnih upalnih parametara. Optimalna medikamentna terapija pokazala je sličnu terapijsku učinkovitost u smislu redukcije neželjenih kardijalnih događaja kod vulnerabilnih plakova kao i metodološki siguran invazivni perkutani pristup. Međutim, treba naglasiti da je trenutačno teško dati jednoznačan odgovor na ovaj terapijski izazov koji sve češće susrećemo u svakodnevnoj kardiološkoj praksi.

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.

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