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## EDITORIAL

# Imaging Vulnerable Plaque in a Modern School of Cardiology – the PlaqueImage Project

Theodora Benedek

Editor-in-Chief, Journal of Interdisciplinary Medicine

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Vulnerable plaques are atheromatous lesions with particular features that make them prone to rupture. Plaque rupture leads to the formation of an intracoronary thrombus, in most of the cases associated with an acute coronary syndrome.

The detection of vulnerable plaques is one of the main goals of modern cardiac imaging, and coronary computed tomography angiography remains the reference technique for plaque characterization due to its noninvasive nature associated with the possibility to provide complex information about plaque morphology and composition.

The PlaqueImage project started in 2015 with the aim to train a team of researchers in the modern imaging of coronary plaques, making them highly qualified in multimodality cardiac imaging. Along with the progress recorded in understanding the complex mechanisms related to plaque vulnerabilization and rupture, the PlaqueImage project also had the role to train PhD students in modern research methodology. As a result, 14 PhD theses were completed, and a large number of publications on imaging vulnerable plaques were finalized. From the studies initiated by the PhD students, 8 have been published on the clinicaltrials.gov platform in order to validate them from a methodological point of view, and many study protocols of these trials have been published in the form of study designs. Some of them have been finalized, and some of them are still ongoing.

The ATHERODENT trial [NCT03395041] aimed to investigate the link between periodontal disease, inflammation, and atherosclerosis progression.<sup>1</sup> The STAFF study investigated the association between in-stent flow hemodynamics and the risk of stent failure following bioresorbable vascular scaffold implantation.<sup>2</sup> The CT-STENT study provides a cost-effectiveness perspective on provisional CT follow-up for MACE reduction after coronary stent implantation. The VIP trial [NCT03606330] investigated the association between systemic, pancoronary, and local plaque vulnerability for image-based prediction of acute coronary syndromes.<sup>3</sup> The GEOMETRY study [NCT03702764] performed a computational assessment of plaque geometry in high-risk coronary lesions,<sup>4</sup> while the STRESS study investigated the role of shear stress derived from im-

aging-based computer modelling for the prediction of atherosclerotic plaque vulnerability. Hybrid 3D imaging has been developed by the HYBRIDHEART<sup>5</sup> [NCT04397198] and FUSE-HEART<sup>6</sup> [NCT04680689] studies, which used complex 3D CT/CMR hybrid imaging models for complex assessment of myocardial viability and ventricular contractility after myocardial infarction. Systemic inflammation as a major driver of major cardiac events has been tested in the VIABILITY study [NCT03830944] (aiming to study inflammatory and CMR-imaging based biomarkers for the assessment of ventricular remodeling and viability in the post-infarction period),<sup>7</sup> the INFLAMAP study (aiming to identify inflammatory and imaging-based predictors of atrial fibrillation recurrence after pulmonary vein isolation),<sup>8</sup> and the FIBROS study (aiming to identify imaging-derived biomarkers associated with atrial fibrosis, structural remodeling, and the risk of cardioembolic events).<sup>9</sup> These are the main studies derived from the PlaqueImage project and coordinated by the research team of PlaqueImage.

The main results of PlaqueImage are also illustrated in the current issue of JIM. This focus issue presents the main features associated with plaque vulnerability in light of the principal results of the PlaqueImage project. For exemplification, spotty calcium, low-density atheroma, positive remodeling, and the napkin ring sign were identified as the most specific features associated with the risk of infarction. Also, serum biomarkers, such as matrix metalloproteases or inflammatory mediators, are associated with increased patient vulnerability, which adds significant risk on top of the plaque-related risk. Invasive cardiac imaging provides relevant information about vulnerability features as well, but its use is limited by the invasive nature of optical coherence tomography (OCT) and intravascular ultrasound (IVUS) techniques.

All these data have been extensively studied during the five years of PlaqueImage development, and the expertise accumulated during the project allowed the research team to identify the most relevant features associated with an increased risk of myocardial infarction, with a tremendous impact on public health and society. Altogether, the PlaqueImage project successfully demonstrated the role of a modern school of cardiology in the progress of science for the benefit of the patient.

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## CONFLICT OF INTEREST

Nothing to declare.

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# Positive Remodeling – a Major Feature of Vulnerability in Patients with Non-Obstructive Coronary Artery Disease

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## ABSTRACT

The most common cause of acute coronary syndrome is thrombosis of an atheromatous plaque. Positive remodeling is the compensatory dilatation of the plaque-containing section of the vessel wall. Plaques are most commonly characterized as vulnerable when possessing some of the following features: fibrous cap thickness  $<65\ \mu\text{m}$ , large necrotic lipid core, high degrees of inflammatory infiltrates, positive remodeling, intraplaque hemorrhage, or neoangiogenesis. The presence of these plaque features is associated with high cardiovascular risk. In the initial stage of vasculopathy, due to positive remodeling, lumen reduction is not typical; it only develops in the advanced phase of the disease, due to which, based on a lumenogram, the vascular system may appear intact. Therefore, coronary angiography can easily miss the diagnosis or underestimate its extent, since it does not inform us of the composition of the arterial wall, because the contrast agent is just filling the vessel lumen. Coronary CT angiography may fill this diagnostic gap, since changes of the vessel wall can directly be visualized. To increase diagnostic accuracy, invasive coronary angiography can be completed by intravascular ultrasound and optical coherence tomography.

**Keywords:** vulnerable plaque, acute coronary syndrome, cardiac computed tomography angiography, optical coherence tomography, virtual histology intravascular ultrasound

## INTRODUCTION

The most common cause of acute coronary syndrome is thrombosis of an atheromatous plaque. In the past, studies have suggested that the primary cause of acute coronary syndromes is coronary stenosis caused by the thickening of the plaque, which decreases blood flow, leading to ischemia. But recent data suggest that the stenosis is due to rupture or erosion of a vulnerable plaque, while calcified plaques are less common. To avoid advanced coronary disease, it is important to recognize in time the features that predispose to plaque vulnerability.<sup>1,2</sup>

Plaques are most commonly characterized as vulnerable when possessing some of the following features: fibrous cap thickness  $<65\ \mu\text{m}$ , large necrotic lipid

core, high degrees of inflammatory infiltrates, positive remodeling, intraplaque hemorrhage, or neoangiogenesis.<sup>3,4</sup>

Positive remodeling represents the compensatory dilatation of the plaque-containing section of the vessel wall, so that the lumen diameter does not change, no significant narrowing develops, and the patient does not have any symptoms. The presence of these plaque features is associated with high cardiovascular risk.<sup>5</sup>

The mechanism of arterial remodeling was first described in 1953 by Crawford and Levene, who stated that “ordinary atheromatous plaques do not project into the lumen but lie in a depression in the media, which may bulge outwards.”<sup>6</sup> Glagov *et al.* showed a significant positive correlation between the area of the internal elastic lamina and that of the plaque, pointing out that only the expansion of the external elastic membrane could be observed until the lesion has reached 40% area stenosis.<sup>7</sup> In the early 90s, *in vivo* studies demonstrated through intravascular ultrasound (IVUS) a similar correlation between early plaque accumulation and compensatory enlargement of vessel size.<sup>8</sup> Further histologic and IVUS studies demonstrated that arterial remodeling could be bidirectional. “Positive remodeling”, as observed by Glagov *et al.*, describes an expansion in the external elastic membrane area and “negative remodeling” describes a reduction of the external elastic membrane area at the lesion site.<sup>4</sup>

A histopathological study conducted by Varnava *et al.* in the early 2000s sought to determine the association between plaque composition and coronary remodeling.<sup>9</sup> By this time, several studies have discussed that the outward dilation of the vessel wall is not an advantage but rather dangerous, as marked compensatory remodeling can make the plaque vulnerable,<sup>7,10</sup> while vessel shrinkage may appear more stable.<sup>11,12</sup>

Varnava *et al.* have shown that coronary artery plaques that have undergone positive remodeling have a significantly larger lipid core, higher macrophage numbers, and eccentric distribution that may undergo a more regionalized restructuring of the vessel wall, allowing outward expansion. The vessel narrows where it has a low index of vulnerability to plaque rupture (low lipid content and low macrophage number), and it is associated with a more circumferential distribution of the plaque and adventitial thickening.<sup>9</sup>

## DEFINITIONS OF REMODELING

The definition of remodeling varies among studies.<sup>13</sup> Remodeling can be quantified using the remodeling index (RI). RI was defined as the external elastic membrane (EEM) at the minimal lumen area (MLA) divided by the

average of the proximal and distal reference external elastic membrane areas at the cross sectional areas (CSA).<sup>10,14–19</sup> Positive RI cut points vary in studies between 1.00 and 1.05, while a negative RI is generally considered <0.88, and an intermediate RI between 0.88 and 1.00.<sup>14,17</sup>

## DIAGNOSTIC METHODS

Invasive coronary angiography (ICA) has been the only available method for to imaging assessment of coronary arteries, and it is still the gold standard.<sup>20</sup> In the initial stage of vasculopathy, due to positive remodeling, lumen reduction is not typical. It only develops in the advanced phase of the disease, due to which, based on a lumenogram, the vascular system may appear intact. ICA can easily miss the diagnosis or underestimate its extent, and it does not provide information regarding the composition of the arterial wall, since the contrast agent is just filling the vessel lumen.<sup>20</sup>

### Coronary CT Angiography

A frequent feature associated with plaque rupture is the thin-cap fibroatheroma (TCFA), which is characterized by a necrotic core with an overlying thin-ruptured fibrous cap (measuring less than 65  $\mu\text{m}$  in thickness) infiltrated by macrophages and lymphocytes.<sup>21,22</sup> TCFA is frequently associated with expansive remodeling.<sup>20</sup>

These changes cannot be assessed by ICA because the vessel wall is not detectable; only the lumen becomes visible, which may appear normal.

Coronary CT angiography (CCTA) may fill this diagnostic gap, since changes of the vessel wall can be directly visualized using this modern technique.<sup>20</sup> CCTA is the preferred test in the exclusion of coronary artery disease in patients with a lower range of clinical likelihood of coronary artery disease, no previous diagnosis of coronary artery disease, and characteristics associated with a high likelihood of good image quality.<sup>23,24</sup> Noninvasive functional imaging or anatomical imaging using CCTA is recommended in patients with suspected or newly diagnosed coronary artery disease and may be used as the initial test to rule out or establish the diagnosis.<sup>24–27</sup>

Traditionally, plaque analysis is done visually, subjectively, but diagnostic accuracy can be significantly improved by using automated analysis software. In CCTA imaging, in addition to the degree of lumen narrowing and the calcium content of atherosclerotic plaques, lesion characteristics, such as plaque morphology, plaque load, and plaque remodeling can also be assessed more accurately.

In a follow-up study, Motoyama *et al.* analyzed previous CCTA recordings of individuals with acute coronary syndrome. The risk of acute coronary syndrome was higher in individuals with positive remodeling and low-attenuation plaque.<sup>28,29,30</sup>

Another study from 2020, which included 1,005 patients, demonstrates that adverse plaque characteristics (defined as the presence of positive remodeling, low-attenuation plaque, or spotty calcification) are associated with a higher cardiovascular risk, at the same time being linked with an accelerated progression of new adverse plaque characteristics.<sup>31</sup>

The clinical utility of CCTA was revealed by post-hoc analyses of the SCOT-HEART data, a study that investigated the extent of adverse coronary artery plaque characteristics on CCTA and their association with subsequent clinical outcomes. The presence of positive remodeling or low-attenuation plaque (defined as adverse plaque) was associated with a greater risk of death from coronary heart disease and non-fatal myocardial infarction in non-obstructive and obstructive coronary artery disease. Importantly, the study demonstrated that the characterization of plaque morphology had a prognostic value for high-risk vulnerable plaques, and it may help risk stratification and guide the intensity of therapy.<sup>32,33</sup>

## Intravascular Ultrasound

The development of modern imaging technologies, such as intravascular ultrasound (IVUS), has made it possible to study coronary arterial remodeling *in vivo*.<sup>34</sup>

IVUS allows the visualization of the entire vessel wall structure and morphology. The use of IVUS allows the calculation of eccentricity and symmetry indices and the evaluation of subsequent vascular lumen remodeling.<sup>35,36</sup>

Early *in vivo* studies of human coronary arteries using IVUS imaging found a correlation between the area of the atheroma and that of the EEM.<sup>8</sup>

Positive remodeling has been observed in the coronary arteries in acute coronary syndromes. It is generally associated with vulnerable plaques and high thrombus burden, leading to distal embolization.<sup>9,10</sup>

A small clinical study examined non-culprit, non-obstructive lesions, using IVUS to assess the implications of plaque composition and morphology in the mechanism of vascular remodeling. In lesions showing positive remodeling, the size of the lipid core was significantly larger, whereas the fibrotic burden was significantly and inversely correlated with the remodeling index. Positively remodeled lesions have a higher risk phenotype to rupture, as

they contain a thin-cap fibroatheroma. In contrast, lesions with negative remodeling were found to have intima thickening, a more stable phenotype.<sup>16</sup>

The European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound (ATHEROREMO-IVUS) study was designed to investigate the associations between genetic profile, coronary atherosclerosis phenotype, and vulnerability determined by IVUS. The study observed that single-nucleotide polymorphism Rs6932 is associated with remodeling and is near the SLC22A25 gene, in addition to being strongly associated with IVUS-derived vulnerability indicators in or near eight different genes.<sup>37</sup>

At the same time, the AtheroRemo-IVUS study pointed out the significant association between the necrotic core in the imaged coronary segment and major acute cardiovascular events, suggesting that imaging biomarkers are useful clinical tools in assessing the future risk of major cardiovascular complications in patients with coronary artery disease.<sup>38</sup>

Coronary slow flow following stent implantation is an important complication associated with poor prognosis in patients with acute coronary syndrome.<sup>39</sup> Several studies examined the characteristics of the culprit lesion in ST-elevation myocardial infarction and the role of plaque volume in the pathogenesis of slow flow, and found that the presence of IVUS parameters (lesion of the external elastic membrane at the cross-section area, plaque area, plaque volume, and remodeling index) was significantly higher in the slow flow group compared to the normal flow group.<sup>15,40–42</sup>

IVUS can also be used for evaluation before and after stent placement, and to identify the presence of in-stent restenosis. A recent study demonstrated the importance of assessing the severity of remodeling using IVUS, indicating that an IVUS-guided strategy is more effective for stent implantation than angiography alone. IVUS-guided procedures were associated with significantly higher rates of optimal stent expansion and decreased risk of stent underexpansion, malposition, and residual stenosis.<sup>13</sup>

IVUS is an essential clinical method for studying arterial remodeling *in vivo*<sup>43</sup>; however, this is not relevant to the use of IVUS in daily clinical practice because IVUS analysis of three vessels is more time consuming and may increase the risk of complications.<sup>38</sup>

## Optical Coherence Tomography

The use of optical coherence tomography (OCT) is becoming increasingly important in the investigation of coronary artery disease. OCT offers high-resolution images that re-

veal the nature and composition of the plaque. We usually draw a parallel between IVUS and OCT, but in reality, they use two different technologies to produce intracoronary images. Both investigations have their advantages and disadvantages and should be seen as complementary to each other. The axial resolution of OCT is better, superior for the examination of calcified plaques, visualization of fibrous cap and intima morphology, and detection of macrophages. In contrast, IVUS has a higher tissue penetration and is better in identifying plaque burden and evaluating vascular remodeling, but it lacks the spatial resolution needed for small features, for example to identify details of the intima and biochemical changes associated with the formation of an atherosclerotic plaque.<sup>44-46</sup>

### THE IMPACT OF TYPE 2 DIABETES ON CORONARY ARTERY REMODELING

Several studies have addressed the association between negative coronary artery remodeling and type 2 diabetes.<sup>47</sup> Jensen *et al.* showed that in patients with associated diabetes, compensatory vessel enlargement is less common, in contrast to coronary artery narrowing.<sup>48</sup> The study also showed that the presence of diabetes was associated with greater atherosclerotic progression and damage to the compensatory remodeling of the artery wall. Also, inadequate compensatory remodeling was more evident in insulin-treated patients. As the vessel wall reacts negatively to insulin, the proliferation of smooth muscle and fibrous tissue increases wall stiffness, thereby impairing its compensatory expansion capacity.<sup>49,50</sup> However, increased insulin resistance was significantly associated with a higher remodeling index and positive coronary artery remodeling.<sup>51</sup> Serum levels of glycated albumin were elevated but serum endogenous secretory receptor for advanced glycation end-products (esRAGE) levels were decreased in diabetic patients with negative remodeling.<sup>50</sup> A recent study published in 2020 showed that some of the glucose-related variables, such as HbA1c, are significantly and positively associated with negative coronary artery remodeling.<sup>52</sup>

### CONCLUSION

Excluding the presence of the coronary heart disease or determining the extent of disease plays an important role in the study of patients with chest pain. As a noninvasive imaging method, coronary computed tomography angiography is able to provide accurate data of the coronary artery wall and to assess the presence and components of

an atherosclerotic plaque, even in non-flow-limiting coronary artery disease. Over the next few years, the number of coronary computed tomography angiography examinations is likely to increase significantly, and its role as a “gatekeeper” prior to invasive angiography will be further strengthened. To increase diagnostic accuracy, invasive coronary angiography can be associated with intravascular ultrasound and optical coherence tomography.

### CONFLICT OF INTEREST

Nothing to declare.

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# The Napkin-Ring Sign – the Story Behind Invasive Coronary Angiography

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## ABSTRACT

Coronary artery disease (CAD) represents one of the leading causes of morbidity and mortality across Europe. Most of the patients do not experience any warning sign before the coronary event develops, therefore screening this group of patients is essential to prevent major cardiac events. Coronary computed tomography angiography (CCTA) offers a noninvasive approach of the coronary arteries, providing information not only on the presence and severity of the coronary stenosis, but is also able to characterize the structure of the coronary wall. CCTA allows complex evaluation of the extension of CAD, and by assessing the structure of the atherosclerotic plaque, it can identify its degree of vulnerability. The napkin-ring sign (NRS) represents a ring-like attenuation of the non-calcified portion of the coronary lesion and has a high specificity (96–100%) for the identification of thin cap fibroatheroma (TCFA) or culprit lesion in acute coronary syndromes (ACS). It is also an independent predictor for ACS events and the strongest predictor for future ACS. Modern CCTA can provide submillimeter isotropic spatial resolution. Thus, CT attenuation-based tissue interpretation enables the assessment of total coronary plaque burden and individual plaque components, with a similar accuracy as intravascular ultrasound-based investigations. This review aims to present the important role of CCTA as a potent screening tool for patients with CAD, and the current evidences in the detection and quantification of vulnerable plaques.

**Keywords:** cardiovascular diseases, napkin-ring sign, culprit lesion, vulnerable plaque

## INTRODUCTION

Cardiovascular disease (CVD) is still one of the leading causes of morbidity and mortality in Europe, resulting in approximately 4 million deaths annually across the continent. The population of Eastern Europe is more likely to be affected by CVD, especially by coronary artery disease (CAD), which could progress to an acute coronary syndrome (ACS) turnout in myocardial infarction or unstable angina.<sup>1</sup> Atherosclerosis is a chronic inflammatory process, developing macro- and microstructural modifications of the artery wall, resulting in CVD. Lipid accumulation in the arterial intima, inflammation (local inflammatory reaction and macrophage infiltration of the affected arterial segment), foam cell formation, muscle cell proliferation, necrosis, calcification, and arterial wall fibrosis induce important functional and morphological changes and lead to plaque formation,

resulting in CAD.<sup>2</sup> The progression of CAD varies among patients, but generally it takes a long period of time until the first clinical manifestation of the disease appears.<sup>3</sup> The most common and dramatic manifestation of CAD is related to plaque rupture or erosion, followed by the activation of the coagulation cascade and subsequently intraluminal thrombosis. In a significant part of the cases, the first manifestation of CAD is acute myocardial infarction (AMI) or sudden cardiac death (in 50% of men and 64% of women).<sup>4</sup> Therefore, most of the patients presenting with ACS do not experience any symptoms or warning signs before the coronary event occurs. There are several methods to evaluate patients with stable chest pain. Coronary computed tomography angiography (CCTA) offers a noninvasive approach of the coronary arteries, being recommended as a screening tool, especially for patients with low to intermediate risk of CAD.<sup>5</sup> Conventional/invasive coronary angiography – ICA (considered the gold standard for the diagnosis of significant CAD) has a high specificity and sensibility to assess the obstructive lesions, but it is unable to characterize the plaque structure or to identify the high risk plaques, although it was demonstrated by several studies that a notable proportion of acute coronary events occur due to the rupture of mildly stenotic plaques.<sup>6,7</sup> Compared to conventional coronarography, CCTA can provide prognostic information from non-obstructive lesions by identifying vulnerable plaque parameters such as the napkin-ring sign, low attenuation, spotty calcification, and positive remodeling of the vessel. Moreover, non-contrast CT scans can assess epicardial adipose tissue (EAT) and by quantifying coronary artery calcification, using a score system (Agatston score), they can predict plaque progression and future coronary events beyond traditional risk factors.<sup>8,9</sup>

## BEYOND THE CORONARY PLAQUE MORPHOLOGY

Plaque rupture, followed by an ACS, has been related to the rupture or erosion of a vulnerable plaque with a lipid-rich necrotic core and a thin fibrous cap, followed by acute thrombosis and subsequently coronary occlusion.<sup>7,10</sup>

Currently, there are six types of atherosclerotic lesions, defined by the American Heart Association (AHA). Type I – initial lesion, characterized by intimal thickening and smooth muscle cell accumulation in the intima; Type II – “fatty streak” with luminal accumulation of foam cells, it usually regresses; Type III – preatheroma or progressive atherosclerotic lesion with extracellular lipid accumulation and pathologic intimal thickening; Type IV – atheroma; Type V – fibroatheroma, with thin fibrous cap, infiltrated

by macrophages and lymphocytes, with the presence of a necrotic core; Type VI – complicated plaque, without intact plaque surface and/or hematoma/hemorrhage and/or thrombotic deposit.<sup>11</sup> Based on the AHA classification, type I and type II plaques are reversible, capable to regress or to progress. Type III lesions are considered precursors of the fibroatheroma, described by pathological structural changes such as an escalated amounts of lipids and multiple smooth muscle cell layers near the lumen. These “proatheromas” are infiltrated with a great number of foam cells. Interestingly, 40% of these cells originate from smooth muscle cells and 60% from macrophages.<sup>12,13</sup> The progression of deep intimal thickening to pathologic intimal thickening depends on a complex interaction between retention and oxidation of lipids, as well as smooth muscle cell proliferation and inflammation.<sup>13</sup> Type IV lesions represent the first stage of advanced plaques, characterized by the appearance of the fibrous cap (containing collagen and proteoglycans, smooth muscle cells, macrophages, and lymphocytes), framing the necrotic core (with large extent of lipids, originating from extracellular lipid pools and insufficient efferocytosis of dead smooth muscle cells and macrophages). The evolved foam cells in this region will be damaged (mostly by apoptosis), subsequently releasing further inflammatory material.<sup>14,15</sup> From this stage of lesions, they can cause significant luminal narrowing and can progress to complicated plaque with surface erosion, thrombosis, and calcification. Based on the thickness of the fibrous cap, they are less or more prone to complication. Numerous studies showed that the fibrous cap thickness (TCAP) represents one of the best markers for vulnerable plaques, a cap thickness between 54–84  $\mu\text{m}$  being considered a vulnerable, high-risk plaque.<sup>16</sup> Postmortem assessment of coronary arteries, by examination of coronary cross-section layers, showed that 95% of ruptured plaques had a thickness of the fibrous cap lower than 65  $\mu\text{m}$ .<sup>17</sup> Optical coherence tomography (OCT) examination in patients with ACS determined a median cap thickness of 80  $\mu\text{m}$  in non-ruptured plaques.<sup>16</sup> Without an intact fibrous cap, the lipid-rich necrotic core can interact with the blood flow, facilitating platelet accumulation and thrombus formation in the affected segments. Histopathological partition distinguished three types of lesions prone to provoke acute coronary events: rupture, erosion, and calcified nodule.<sup>18</sup>

Ruptured plaques are characterized by a lipid-rich necrotic core, surrounded by a thin, fibrous cap with active inflammation. In most cases, the appearance of luminal thrombosis is caused by plaque rupture (approximately 60–70%), the rest of the cases resulting from plaque erosion, and about 5% being caused by thrombus formation

at the level of calcified nodules.<sup>19</sup> Plaque erosion is defined by a relatively intact intima, without cap disruption, where the blood flow comes into direct contact with the intimal surface due to lack of endothelial cells, favorizing thrombus formation.<sup>20</sup> Interestingly, autopsies revealed that a remarkable part of the thrombi in erosion (more than 85%) showed evidence of a healing process (acute inflammatory cell lysis, invasion by smooth muscle cells, organized layers of smooth muscle cells, proteoglycans with varying degrees of platelet/fibrin layering). On the other hand, a healing process was observed only in half of the ruptured plaques.<sup>21</sup> The examination of coronary cross-sections suggested that repeated plaque ruptures can initiate further plaque progression.<sup>22</sup>

The extension of the necrotic core also correlates with plaque complication. As the necrotic core extends outwards, causing thickening of the fibrous cap, concomitantly smooth muscle cells are depleted from the fibrous cap through cell apoptosis, therefore the cap thickness decreases.<sup>23,24</sup> Simultaneously with plaque progression, the vasa vasorum infiltrates the lesion and becomes leaky, provoking intraplaque hemorrhage.<sup>25</sup> The number of smooth muscle cells is inversely correlated with the progression of the atheroma because of migration and cell apoptosis.<sup>26</sup> There are numerous factors that induce smooth muscle cell apoptosis, thus the contribution of progressive cell loss to plaque stability is more complex and strongly affects the local milieu.<sup>27,28</sup> This milieu in atherosclerotic lesions inhibits the phagocytosis and defective efferocytosis of apoptotic cells, followed by secondary necrosis and leakage of intracellular contents, maintaining and exacerbating the inflammatory milieu.<sup>29</sup>

In conclusion, there are several morphological and functional changes that lead to the progression of a preatheroma to a vulnerable plaque. Vulnerable plaques prone to rupture contain a large necrotic core, active inflammation, and macrophage infiltration, a thin fibrous cap, and numerous vasa vasorum at the affected level.<sup>30</sup> The mechanisms of the rupture of a thin cap fibroatheroma are unclarified yet. Increased proteolytic activity, mechanical stress, and microcalcification of the fibrous cap are considered to be relevant factors.<sup>31–34</sup>

### **CAN WE PREVENT ACUTE MYOCARDIAL INFARCTION BY SCREENING FOR CORONARY ARTERY DISEASE?**

Prevention of acute coronary events seems to be the only potent strategy to reduce the rate of major acute cardiovascular events (MACE) and improve mortality and morbidity.<sup>35</sup> Although major efforts are ongoing to predict which plaque will cause MACE on an individual plaque level,

currently the diagnostic strategies target the detection of myocardial ischemia and hemodynamically significant luminal narrowing, but ignore the huge issue of a MACE occurring as the first (in half of the individuals) and only manifestation of CAD.

Based on the morphological characteristics of the fibroatheroma, there are several imaging features that aid the identification of vulnerable plaques. The rapid progression and development of cardiovascular imaging technologies in recent decades has enabled the introduction of several screening imaging procedures into clinical practice for the primary prevention or assessment of the extension of CAD, which could be useful to detect vulnerable lesions. However, in spite of these major developments, identifying vulnerable plaques remains a major challenge. The early diagnosis of CAD could promote physicians to initiate complex treatment for adequate primary prevention, thus reducing the incidence of acute coronary events.<sup>36</sup> There are several imaging methods to assess the coronary vessels, ICA being considered the gold standard for the diagnosis of CAD (both stable and ACS).<sup>37</sup> Although ICA can describe the anatomy of the coronary vessels and quantify the lumen-narrowing stenosis, it does not provide information about the wall structure of the coronary vessel or the composition of the atherosclerotic plaque, therefore being unable to identify the vulnerable plaques.<sup>38</sup> Additional invasive imaging methods could be used for a better evaluation of the extension of CAD and to identify the presence of a rupture-prone plaque. OCT can provide very high resolution (10–20  $\mu\text{m}$ ) images and is able to do a microscopic characterization of plaque morphology, therefore it can be used to evaluate plaque vulnerability by measuring the thickness of the fibrous cap, and to detect lipid content. Moreover, only OCT can detect the eroded plaques.<sup>39</sup>

Intravascular ultrasound (IVUS) represents another invasive intravascular imaging technique to improve the diagnostic accuracy of ICA. IVUS could be used for measuring the lumen area, plaque burden, and vascular remodeling. IVUS-based studies identified several imaging biomarkers in association with plaque vulnerability, such as the presence of an extensive necrotic core surrounded by a thin fibrous cap, with dense macrophage infiltration, large lipid pool, spotty calcification, and positive vascular remodeling.<sup>40,41</sup> Spectroscopy, thermography, angiography, and intravascular cardiac magnetic resonance also represent invasive imaging methods that could be used to provide additional information such as plaque temperature, plaque inflammation, and neoangiogenesis.

Although the previously presented invasive imaging markers could identify and precisely describe the

high-risk atherosclerotic plaques, they cannot be used as a screening method for primary prevention in a large population. Patel *et al.* found that among 398,978 elective invasive coronary angiographies, only 38% of the cases were positive for obstructive CAD, 62% of the patients had no obstructive disease, and 39% had normal coronary arteries.<sup>42</sup> Cardiac CCTA offers a noninvasive approach for CAD patients and can be used as a “gatekeeper” to reduce unnecessary invasive diagnostic procedures. Using at least 64-slice multidetector row has a sensitivity of 98% and a specificity of 90%. Due to the elevated sensitivity, CCTA investigations have a 95 to 100% negative predictive value to rule out obstructive CAD and an excellent negative predictive value for future events.<sup>43</sup> Multidetector computed tomography (MDCT) has the ability to describe and accurately localize the lumen-narrowing atherosclerotic plaques. By measuring local tissue attenuation, MDCT can assess the morphology and composition of these lesions with high temporal and spatial resolution. Moreover, in the guidelines for the diagnosis and management of chronic coronary syndrome published by the European Society of Cardiology, computed tomography angiography has a class I recommendation for diagnosing CAD in symptomatic patients.<sup>44</sup> Contrast-enhanced ultrasonography and high-resolution magnetic resonance imaging are also noninvasive investigations to characterize the coronary lesions, within their benefits and limits.

Modern multislice computed tomography (MSCT) with increased spatial resolution permits a more complex characterization of non-calcified coronary plaques (defined as <130 Hounsfield units), assessing positive remodeling, low attenuation plaque, and spotty calcification.<sup>45</sup> Moreover, on CCTA images, several authors described a ring-like attenuation of the non-calcified portion of the coronary lesion, which was termed the napkin-ring sign.<sup>46,47</sup> Thus, non-calcified plaques are categorized into three different classes: homogenous plaque, non-napkin-ring sign heterogeneous plaques, and napkin-ring sign heterogeneous plaques.<sup>48</sup> The napkin-ring sign represents a large necrotic core – low attenuation core, surrounded by a thin-cap fibroatheroma – rim-like thin area of higher attenuation. Histopathological analyses on ex vivo donor heart demonstrated the correspondence between the napkin-ring sign and the presence of histological markers of a vulnerable plaque at that sequence.<sup>49</sup> Based on recent studies, besides the napkin-ring sign, the only independent predictors for future MACE were represented by fibrofatty plaque features, which were associated with events in short- and mid-term outcome periods.<sup>50–52</sup>

## THE NAPKIN-RING SIGN

As we mentioned before, the histopathological analysis of culprit and non-culprit thin-cap fibroatheromas (TCFAs) with identical luminal narrowing effect found that only fibrous cap thickness and necrotic core size are independent predictors of plaque rupture.<sup>53</sup> Furthermore, a large necrotic core cross-sectional area and the presence of macrophage infiltration are the best discriminators between a ruptured plaque or TCFAs and a stable atherosclerotic lesion.<sup>10</sup> Moreover, in 80% of the vulnerable plaques prone to rupture, the necrotic core area is >1 mm<sup>2</sup>.<sup>54</sup> Modern CCTA can provide submillimeter isotropic spatial resolution, thus the CT attenuation-based tissue interpretation enables the assessment of total coronary plaque burden and individual plaque components, with a similar accuracy as IVUS-based investigations.<sup>7,55</sup>

A ring-like CT attenuation pattern of non-calcified plaque was present in ACS culprit lesions and in plaques associated with slow-flow or no-reflow phenomenon during ICA.<sup>56,57</sup> There are two major qualitative components in the CT images of a vulnerable non-calcified plaque which fulfill the criteria of a napkin-ring sign: a center area of low CT attenuation tissue, apparently in contact with the lumen, and a higher attenuation plaque segment surrounding this central area (fibrous plaque tissue).<sup>48,49,58</sup> The necrotic core area represents an important factor compared with non-napkin-ring sign plaques, as it can be over twice the size in napkin-ring sign plaques (median 1.1 mm<sup>2</sup> versus 0.46 mm<sup>2</sup>).<sup>58</sup> Interestingly, the majority of these high-risk lesions have a necrotic core area over 1.0 mm<sup>2</sup>.<sup>30</sup> Based on CT images, the specificity of a napkin-ring sign for a vulnerable atherosclerotic lesion and TCFA is exceptional (98% and 94.1%), but unfortunately its specificity is relatively low.<sup>48,59</sup> In clinical investigations, the napkin-ring sign had a high specificity (96–100%) for the identification of TCFA or culprit ACS, being also an independent predictor for ACS events.<sup>46,60</sup> Studies also found that the napkin-ring sign was more frequent in TCFA compared with non-TCFA plaques (controlled by OCT).<sup>56</sup> Otsuka *et al.* found that the presence of the napkin-ring sign was the strongest predictor for future ACS [HR 5.55; 95% CI 2.10–14.70, *p* <0.001], independent of other high-risk criteria.<sup>46</sup> Furthermore, a long-term follow-up study of 7.8 years in a group of patients with CAD (including low-to-intermediate risk) evidenced an increased prevalence of the napkin-ring sign in patients with adverse events (63.4% vs. 2.8%, *p* <0.001). Moreover, the napkin-ring sign was the most important predictor of adverse events after the assessment of the conventional risk factors, stenosis severity, and plaque type.<sup>61</sup>

## THE POTENTIAL UTILITY OF CCTA AND THE CLINICAL IMPLICATIONS OF THE NAPKIN-RING SIGN

The constant upgrade of MSCT technology and new software features allow a more complex and more detailed noninvasive plaque characterization using morphological and functional data (CT-FFR and ESS). Combining morphological and functional characteristics of the atherosclerotic plaque results in a highly accurate detection of the vulnerable and stable lesions. This new feature has established CCTA as a first-line coronary assessment method in patients with low to intermediate risk of CAD.<sup>44,62</sup> In addition, the presence of inflammation at the coronary lesion could favor the atherosclerotic process. Given its use in the complex assessment of the perivascular adipose tissue, recently CCTA has been proposed as an effective tool for the quantification of coronary inflammation, which could be an important factor—besides the morphological and functional assessment of the coronary plaque—for an individualized coronary risk stratification.<sup>63,64</sup>

Using CCTA as a potential screening tool for low-to-intermediate risk of CAD could significantly reduce the unnecessary ICA; moreover, CCTA has an excellent negative predictive value and could be a good alternative to rule out the presence of CAD when pretest probability is intermediate.<sup>65</sup> In the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial, which compared the presence of CAD in patients with typical symptoms evaluated with CCTA versus functional testing, the rate of non-CAD was 28% in the CCTA group and 52% in the functional testing group.<sup>66</sup> Despite the availability of CCTA or functional testing, up to 45% of patients are directly referred for ICA without prior functional testing.<sup>67</sup> It is important to mention that although the technological improvement and the widely used radial access have reduced the complication rate of ICA, approximately 0.6–4.2% of the procedures have different type of complications.<sup>68</sup>

Based on the previously cited studies, CCTA can provide accurate characterization of the coronary arteries by detecting the obstructive plaques, and through its ability to visualize the coronary artery wall it could be used to assess plaque morphology. Thus, CCTA images could help to identify high-risk plaques, and by using a noninvasive imaging method the physician could initiate the adequate treatment. Moreover, CCTA may help to identify coronary artery lesion progression or regression, providing a good feedback and control of the chosen therapy.<sup>69,70</sup> Although it is not possible to control the therapeutic efficiency of a chosen intervention on the atherosclerotic plaque, repeated

CCTA examinations with direct monitorization of plaque progression may lead to a superior therapeutic modulation.<sup>71</sup>

Another revolutionary perspective of CCTA is the use of radiomics, a process where numerous quantitative features are extracted from the investigated region to create large data sets in which each abnormality is described by hundreds of parameters. The applicability of these features is still at an early stage, but the rapid progress encountered in the field of artificial intelligence will probably bring major changes in the way we integrate clinical, biological, and imaging information for a complex, individualized risk stratification and therapeutic decision-making.<sup>72</sup>

## CONCLUSION

The evolution and rapid progression of CT imaging technologies has changed the therapeutic approach of patients with suspected CAD, offering an early and accurate assessment of the coronary arteries. Due to the capability of CCTA to identify multiple high-risk features of atherosclerotic plaques, such as the napkin-ring sign, positive remodeling, low CT attenuation, low endothelial shear stress, and spotty calcification, this modern imaging technique may improve clinical evolution and lead to a more effective management of the cardiovascular patient.

## CONFLICT OF INTEREST

Nothing to declare.

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# The Impact of Coronary Artery Calcification on Long-Term Cardiovascular Outcomes

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## ABSTRACT

Decades of research and experimental studies have investigated various strategies to prevent acute coronary events. However, significantly efficient preventive methods have not been developed and still remains a challenge to determine if a coronary atherosclerotic plaque will become vulnerable and unstable. This review aims to assess the significance of plaque vulnerability markers, more precisely the role of spotty calcifications in the development of major cardiac events, given that coronary calcification is a hallmark of atherosclerosis. Recent studies have suggested that microcalcifications, spotty calcifications, and the presence of the napkin-ring sign are predictive vulnerable plaque features, and their presence may cause plaque instability.

**Keywords:** coronary atherosclerosis, vulnerable plaque, unstable plaque, coronary calcification

## INTRODUCTION

Cardiovascular diseases remain the leading cause of mortality worldwide despite recent major breakthroughs in invasive therapeutic procedures as well as in invasive and noninvasive diagnostic modalities. The mortality, morbidity, and socioeconomic influence of this disease makes its early diagnosis and prevention of the utmost importance.<sup>1</sup> The vast majority of cardiac deaths are from coronary artery disease (CAD), which is a complication of atherosclerosis, most often being represented by the rupture of an unstable coronary plaque.<sup>2</sup> Major advances in cardiovascular imaging made the assessment of coronary plaque characteristics possible. A vulnerable plaque is characterized by a build-up of lipids, fibrous tissue, and inflammation, and the presence of acute thrombosis. They can accumulate a few specific characteristics such as spotty calcifications, napkin-ring sign, positive remodeling, and low attenuation. Coronary computed tomography angiography (CCTA) has been proven as one of the most useful noninvasive imaging techniques assessing macrocalcifications, and it is useful predicting the global risk of acute events; however, it is not useful for identifying lesions prone to rupture. For the determination of plaque vulnerability and for the quantification of calcium within the plaque, intravascular ultrasound

(IVUS) or optical coherence tomography (OCT) are preferred. IVUS has high sensitivity and specificity for detecting dense calcific plaques and spotty calcifications. OCT can penetrate calcium and assess its other characteristics such as volume and thickness.<sup>3-8</sup> In this review, we focus on coronary artery calcification and its role in advanced atherosclerosis, given that many imaging modalities have proposed spotty calcifications to be one of the predictors of plaque instability and of future cardiac events.<sup>5</sup>

## IMAGING ATHEROSCLEROSIS AND VULNERABLE PLAQUE MORPHOLOGY

The prevention of major cardiac events is based on the identification of high-risk patients who may benefit from intensive preventive measures. Given that the majority of acute cardiovascular events is caused by the rupture of an unstable atherosclerotic plaque, the identification of these vulnerable coronary plaques is the main goal in prevention.<sup>9,10</sup>

Atherosclerosis is a chronic inflammatory state that results in the calcification of lipid-loaded plaques.<sup>11,12</sup> It begins with the accumulation of cholesterol and low-density lipoproteins in the sub-intimal region, causing irritation and inflammation, and attracting macrophages, which are trying to remove the lipoprotein complex. If the lesion continues to progress and not heal, a necrotic core will form with dying macrophages and with a rim of microcalcifications. That is why coronary artery calcification is a marker of atherosclerosis, developing as a healing response to local macrophage activity.<sup>13-15</sup> When the cap of this atheroma reaches a critical thinness, it is more likely to rupture, hence the term 'vulnerable plaque', leading to thrombus formation and occlusion.<sup>13,16,17</sup> Atherosclerotic lesions may be visualized via angiography, computed tomography (CT), CCTA, IVUS, or OCT, each providing different information. Characteristics associated with plaque instability are large plaque and necrotic core volume, thin-cap fibroatheroma (TCFA), napkin-ring sign, spotty calcification, low attenuation, positive vascular remodeling, and inflammation.<sup>8,13</sup> Some of these can be identified by noninvasive imaging (CCTA), others, such as cap thickness, may be identified with invasive methods like OCT.<sup>18</sup> Given that the size of microcalcifications and TCFA are below the CCTA scan spatial resolution, IVUS and OCT offer the possibility of plaque calcium quantification and arterial wall analysis.<sup>19,20</sup> In recent years, noninvasive imaging concentrates not only on plaque morphology but also on disease activity in the lesions, using complex techniques called metabolic imaging. These novel method-

ologies provide insight into the underlying inflammation, detected with positron emission tomography (PET) and magnetic resonance (MR).<sup>21</sup> Cardiac MR has the ability to identify some unstable plaque characteristics, based on uptake of gadolinium-based contrast associated with macrophage accumulation and hemorrhage within the plaque. The future of plaque imaging may be expanded by the recently developed hybrid scanners, which offer simultaneous metabolic and morphology imaging.<sup>22,23</sup>

## IMAGING CALCIUM DEPOSITS

Macroscopic vascular calcium deposits can be detected by CT angiography which has high sensitivity and specificity for detecting significant lumen stenosis. The assessment and quantification of calcium deposits is possible using the coronary artery calcification score (CAC scoring), a good marker of overall coronary plaque burden, which is also used to predict future coronary events. However, it is not as useful in describing vulnerable lesions, as recent studies have shown that the CAC score is a direct predictor of coronary artery disease, but it is inversely associated with acute coronary events.<sup>24-26</sup> The assessment of spotty calcifications may be possible using IVUS and OCT. IVUS provides high sensitivity and specificity in detecting large dense calcified lesions; however, its assessment is limited to arc and length.<sup>27</sup> OCT is able to penetrate calcium and assess its qualities, and it is also capable of quantifying macrophages, providing information about the level of plaque inflammation. OCT can provide information on morphological as well as disease activity characteristics that are equivalent to a histological examination, making the identification of higher risk patients more accessible.<sup>28,29</sup>

## CORONARY ARTERY CALCIFICATION

Coronary artery calcium presents a broad spectrum of shapes and sizes with regular or irregular borders. The deposits appear in different locations, and as suggested in recently published studies, these characteristics have a very important prognostic value.<sup>30</sup>

The extent of calcium in coronary arteries has different clinical implications. Traditionally, calcified plaques had been viewed as stable atheromas, but with the development of imaging technologies this view has evolved.<sup>31</sup> Based on the location of the calcium deposits we can differentiate between medial Mönckenberg calcification (often seen in old patients with diabetes and renal failure), intimal calcification (more common in atherosclerosis), and infantile calcification.

## MICROCALCIFICATIONS

Microcalcifications may represent an early, active stage in plaque calcification. They grow into larger masses and extend from deep within the necrotic core, forming a calcified sheet at the end.<sup>32</sup> The visualization of microcalcification may be possible with 18F-sodium fluoride (18F-NaF) PET imaging, which could help to identify active microcalcifications, because it accumulates in macrophages due to their high demand for glucose. An association between 18F-NaF-positive plaques and high-risk plaques has been demonstrated.<sup>33</sup> A few studies have investigated microcalcifications with the help of OCT and demonstrated to be related to mild stenosis with extensive inflammation and a large necrotic core.<sup>34</sup> Studies have shown that on a cellular level microcalcification may play a role in stress concentration (this effect is independent of size and location) and rupture of the plaque, because if two microcalcifications are located close to each other the stress concentration rises, and a whole region is exposed to high stress (high background stress being TCFA and cap shoulders).<sup>35,36</sup>

## SPOTTY CALCIFICATIONS

Spotty calcifications are small calcium deposits, in the range of 1–3 mm, some of them showing progressive calcification, turning into end-stage macroscopic calcifications.<sup>37–39</sup> In general, there are two explanations for the presence of spotty calcification.<sup>40</sup> It is mostly associated with unstable plaques with more extensive atherosclerosis and accelerated disease progression, playing an important role in plaque destabilization, or merely indicating the presence of an unstable plaque.<sup>41</sup> Recent studies found that spotty calcifications were more often found in fibroatheromas and more frequently present in ruptured plaques. Furthermore, culprit lesions in acute myocardial infarction were characterized by spotty calcifications, more often than in stable angina pectoris.<sup>42</sup>

Spotty calcifications show greater inflammation and may provoke greater pro-inflammatory factor expression, followed by macrophage-derived cytokine expression and vascular smooth muscle mineralization.

## LARGE CALCIFICATION

Extensive calcification or end-stage calcification is irreversible and may be more strongly associated with stable fibrotic plaques, increased mineralization, and limited inflammation, but the relationship between coronary ar-

tery calcification and plaque stability is not yet fully understood.<sup>24,43,44</sup> However, the CAC score is an independent predictor of major cardiac events, and calcified atherosclerosis in other vascular beds is associated with the risk of mortality.<sup>45–47</sup>

Several studies conducted in the last 10 years offer contradicting results. Plaque calcification, including volume and area, can be higher in asymptomatic patients. Other studies found that calcification volume is higher in patients with stroke, and a larger plaque may be associated with higher intraplaque hemorrhage.<sup>48</sup>

A study published in 2019, which followed patients with no previous coronary artery disease for 10 years after CCTA investigation, reported that the presence of spotty calcifications and napkin-ring sign provides prognostic value, allowing for better risk stratification. In addition, a long-term CT angiography study demonstrated that a vulnerable plaque has to continue to gather large necrotic core volumes to sustain plaque instability, because as previous observations have proven, a large percentage of the lesions identified as vulnerable at baseline diagnosis had stabilized over the following year.<sup>13,49</sup>

## ASSOCIATION BETWEEN CALCIFICATION NUMBER AND LOCATION AND PLAQUE VULNERABILITY

Atherosclerosis and calcification is an organized process, characterized by an irreversible and continuous build-up of plaque within the arterial wall.<sup>50</sup> Cardiac MR studies have classified lesions into single and multiple calcifications. Studies show that multiple calcifications are strongly associated with intraplaque hemorrhage and ulceration, making them more vulnerable. In addition, they may provoke a more activated inflammatory response, increasing the possibility of plaque rupture.<sup>51,52</sup> The increasing number of spotty calcifications shows a strong correlation with the incidence of ruptured plaques. The number of calcifications is higher in acute myocardial infarction and unstable angina, proving that multiple calcifications may lead to higher stress concentration and plaque rupture.<sup>53</sup>

A study exploring the spatial distribution of atherosclerosis and coronary artery flow patterns found that coronary plaques develop mainly at bifurcations and on the inner walls of curved coronary segments.<sup>30,54</sup> Several studies described a strong association between unstable lesions and calcium location, and an association between superficial calcification (calcium located closer to the lumen than to the adventitia) and plaque vulnerability has been dem-

onstrated. On the other hand, calcification located closer to the media-adventitia, away from the lumen, showed a higher risk for in-plaque hemorrhage but no impact on plaque destabilization.<sup>52,55,56</sup> A research group used OCT imaging to assess superficial calcium deposits and found no significant association with symptomatic plaques; however, sheet-like superficial calcium plates were present in a significant percentage at the culprit lesion site.<sup>57</sup> A study published in 2016 in Japan has enrolled approximately 100 patients with acute coronary syndrome who underwent OCT imaging of the culprit lesion, dividing them into two groups based on the presence of plaque rupture.<sup>58</sup> The study concluded that spotty calcifications were present more frequently in the group with plaque rupture. Also, these were smaller in size with shallow displacement, compared with the non-ruptured plaque. The study indicated that spotty calcifications may serve as an independent predictor of plaque rupture.<sup>59–62</sup>

A study published in 2020 assessed the correlation between features of plaque instability, calcification patterns and coronary artery disease, using CT angiography. The study concluded that large calcifications or denser lesions are associated with a higher stenosis and CAC score, and with lower plaque instability. The lesions with spotty calcifications had lower calcium score with lesser lumen stenosis and high instability score.<sup>63</sup> Furthermore, plaques with mixed calcification showed similar characteristics to the large calcification patterns, but the plaque instability score was closer to the average of those with spotty calcification. Another interesting observation was that spotty calcification with low density was mostly associated with low attenuation and napkin-ring sign, whereas large calcifications were present together with higher density and positive remodeling. The finding supports the theory that coronary artery events mainly result from the rupture of a mildly stenotic plaque, questioning the significance of the CAC score as a significant predictor of future events.<sup>64</sup> These recently published results are consistent with previous studies examining plaque calcification patterns, proving calcification is a good predictor of future coronary artery disease events. In accordance with previous evidence, we can conclude that spotty calcification is more frequently associated with the culprit lesion and plaque progression and instability, with a lower grade of coronary stenosis.

## CONCLUSION

Calcification is an important component of atherosclerosis. There is a proven correlation between calcification

and plaque progression and stability. Spotty calcifications may correlate with inflammation and instability, and may represent the active stage of vascular calcification. Plaque rupture is known to be the main cause of acute coronary syndromes. Therefore, its prediction is very important in the clinical setting, and identification of spotty calcifications in an atheromatous plaque at CCTA examination may indicate a higher degree of vulnerability.

## CONFLICT OF INTEREST

Nothing to declare.

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# Cardiovascular Imaging Techniques for Detection of Vulnerable Plaques

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## ABSTRACT

Various cardiovascular imaging techniques were developed for the detection of vulnerable atherosclerotic plaques, hoping to be able to predict a cardiovascular event. Plaque vulnerability results from compound pathophysiological mechanisms that lead to structural and morphological changes in lesions. The aim of this review is to present the most recent techniques for the assessment of vulnerable coronary plaques such as cardiac computed tomography angiography (CCTA), optical coherence tomography, or virtual histology intravascular ultrasound, based on literature data from the last 3 years. CCTA permits direct visualization of the intravascular lumen, together with characterization of the arterial wall. Recent studies maintain that low-attenuation plaques, spotty calcifications, positive vessel remodeling, and the napkin-ring sign are considered main markers of plaque vulnerability and instability. Emerging analytical techniques, such as machine learning or radiomics, will probably demonstrate useful as an auxiliary diagnostic tool for vulnerable plaque detection. The data from the two imaging techniques together provide useful information, especially in patients undergoing a PCI procedure for an acute coronary syndrome. Invasive and noninvasive imaging techniques are able to deliver a large amount of scientific data to assess vulnerable coronary atheromatous plaques. Recent studies demonstrated that information defined by the two techniques is complementary, and using both methods is essential for adequate diagnosis, therapeutic strategy, and prognostic assessment.

**Keywords:** vulnerable plaque, acute coronary syndrome, cardiac computed tomography angiography, optical coherence tomography, virtual histology intravascular ultrasound

## INTRODUCTION

Half of the cases of acute coronary syndrome (ACS) or sudden cardiac death are the primary consequences of coronary artery disease (CAD).<sup>1</sup> The aim to reduce the incidence of catastrophic cardiovascular events has taken several pathways in the last decades. The enforcement of aggressive protective efforts, lifestyle changes, and medical interventions with more efficient drugs has definitely contributed to the reduction in event rates. In another pathway, many cardiovascular imaging modalities were developed for the detection of vulnerable atherosclerotic plaques, hoping to be able to prognosticate an event.<sup>2-4</sup>

Most instances of ACS arise from thrombotic occlusion of a coronary artery caused by rupture of a thin-cap fibroatheroma (TCFA), characterized by a large lipid-rich necrotic core covered by an inflamed, thin rim of fibrous tissue.<sup>5</sup> Vulnerable plaques may be specified as plaque types that place patients at risk for ACS and sudden cardiac death in case of their destabilization. Plaque vulnerability results from compound pathophysiological mechanisms that lead to structural and morphological changes in lesions. In unstable coronary plaques the proportion of unstable components such as necrotic core or fatty tissue increases, while the volume of stable components such as calcific or fibro-fatty tissue decreases.<sup>6-8</sup> Vulnerable patients should be defined as subjects who are at threatening or high risk for similar events.<sup>9</sup>

Modifications in plaque structure, which refers to a vulnerable plaque, are detectable by using noninvasive imaging modalities such as cardiac computed tomography angiography (CCTA), or invasive imaging techniques including optical coherence tomography (OCT) and virtual histology intravascular ultrasound (VH-IVUS).

## **NONINVASIVE IMAGING TECHNIQUES FOR PLAQUE CHARACTERIZATION**

Detecting high-risk lesions at the earliest phase of CAD would facilitate in-time medical interventions to prevent the progression of coronary atherosclerosis and stymie several complications. In the era of precision medicine, it is crucial to move away from population-based risk factors or models and towards an individualized evaluation of cardiovascular risk. The role of noninvasive imaging methods is to ensure a significant influence on healthcare and patient outcomes, such methods being necessary to be safe, widely available, precise, and lastly cost-effective.<sup>10,11</sup>

In most cases, the atherosclerotic process is asymptomatic before it becomes sufficiently severe to cause ischemia. CCTA has developed into a powerful tool for detection and risk stratification of asymptomatic atherosclerosis, and at the same time for diagnosing CAD in patients with stable ischemic heart disease and ACS. CCTA not only describes the anatomy of the heart and coronary arteries in detail, but also permits direct visualization of the intravascular lumen and detection of the presence of an intraluminal stenosis, together with characterization of the arterial wall.<sup>12,13</sup>

As a result of many studies, the composition, morphology, and degree of inflammation of coronary plaques are more important than the degree of luminal stenosis.<sup>14</sup> It is essential to recognize precursor lesions of ACS, which is the result of abrupt intraluminal thrombosis that begins

from different pathologies.<sup>15</sup> The most common cause of thrombosis is plaque rupture, approximately 76% of all fatal coronary thrombi being caused by plaque rupture.<sup>16,17</sup>

CCTA imaging has been accurately compared with intravascular ultrasound (IVUS), and various studies demonstrated the existence of a significant correlation between CCTA and virtual histology.<sup>18</sup> The presence of noncalcified plaques (NCP), particularly low-attenuation plaques (LAP), spotty calcifications (SC), positive vessel remodeling (PR), and napkin-ring sign (NRS) has been considered as main markers of plaque vulnerability and instability.<sup>19</sup>

An important study by Motoyama *et al.* investigated the prevalence of CCTA plaque features in 1,059 patients presenting with ACS and stable angina (SA). The study was focused on characteristics such as plaque consistency and PR, described as a 10% growth in diameter at the plaque region compared to a normal reference segment of coronary artery.<sup>20</sup> Plaque consistency was evaluated and subdivided based on the presence of calcifications and their size (<3 mm in size defined as “spotty” vs. “large”). Noncalcified plaques were further subdivided into two types, plaques with low-attenuation core (LAC) <30 HU and plaques between 30 HU and 150 HU. The results show that PR, LAC, and SC were significantly more recognized in ACS than SA (PR: 87% vs. 12%,  $p < 0.001$ ; LAC: 79% vs. 9%,  $p < 0.001$ ; and SC: 63% vs. 21%,  $p = 0.0005$ ). In contrast, large calcifications were found more frequently in SA than ACS (55% vs. 22%,  $p = 0.004$ ).<sup>21</sup> Within a 12–50-month follow-up, the authors found that PR or LAC were independent predictors of future ACS, with a HR of 22.8 (95% CI 6.9–75.2;  $p < 0.001$ ) compared with patients presenting neither one of these features on CCTA.<sup>22</sup>

More recent analyses of large longitudinal multicenter trials have also confirmed the role of high-risk plaque features in predicting major adverse cardiovascular events (MACE). In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial 4,415 patients were randomized to a CCTA study to examine the ability of high-risk plaque features, such as PR, LAP, and SC, to predict a complex endpoint, including death and myocardial infarction. A total of 2.4% of patients presented a high-risk plaque, and 6.4% of patients defined with high-risk plaque experienced ischemic events during a follow-up of 25 months. In this study, vulnerable plaques were associated with higher event rates (HR 2.73; 95% CI 1.89–3.93).<sup>23,24</sup>

The SCOT-HEART (Scottish Computed Tomography of the HEART) study, one of the most recent trial of patients with stable chest pain, performed a plaque analysis

by CCTA. There were 1,769 randomized patients whose coronary segments were evaluated for 4 adverse plaque characteristics including LAP, PR, SC, and NRS. PR and LAP were the most feasible in predicting acute coronary events. Subjects with high-risk plaques and significant stenosis presented more frequently myocardial infarction or death due to coronary heart disease compared with those with normal cardiac CT (HR: 4.1;  $p = 0.100$ ). More specifically, in the group with high-risk plaque there was a 10-fold increase in the rate of CHD-related deaths or MI at 5 years of follow-up. PR and LAP were the most useful markers in predicting future coronary events. This study was specific because it also evaluated the coronary calcium (CAC) score as a predictor of future risk. A CAC score of above 1,000 Agatston units had a 13-fold increase in the same outcomes and hence performed better than the plaque characteristics.<sup>25-27</sup>

CCTA allows the identification of lipid-rich fibroatheroma of a vulnerable plaque that determines future clinical outcomes. The appearance of the “napkin-ring sign” on CCTA, which consists of a low-attenuation plaque core surrounded by a thin hyper-attenuating ring, allows non-invasive diagnosis of advanced, lipid-rich atheroma, which is highly specific. The overall level of the diagnostic precision of CCTA in this regard can be compared to invasive methods, such as IVUS or OCT.<sup>28-30</sup>

A study by Aleksandra *et al.*, based on a single-center prospective registry, analyzed 6,459 CCTA investigations to evaluate the prevalence, incidence, and evolution of the NRS in patients with suspected CAD. Their results showed that the NRS tends to colonize in proximal coronary segments and in clusters. This finding was described in a previous IVUS study, where the prevalent site of plaque rupture was also found within the proximal segment of the left anterior descending artery (LAD).<sup>31</sup> The distribution of the NRS in the coronary arteries was unequal, with more than half localized in the LAD, and more NRS were observed in the proximal coronary segments (proximal vs. distal: 39 vs. 14,  $p = 0.001$ ). At 34 months of follow-up, there were 68 NRS detected in 32 patients, as compared to 53 NRS in 22 patients at the baseline ( $p = 0.0736$ ). In 18 (20%) patients the evolution was observed with 23 additional NRS, including 10 (11%) patients without prior NRS ( $p < 0.001$ ).<sup>32</sup>

However, plaque analysis on CCTA is a time-consuming method that is not routinely quantitatively performed in clinical practice. Multiple studies are based on applying artificial intelligence (AI) and machine learning to detect vulnerable plaques using advanced deep learning techniques to assist in predicting outcomes.<sup>33,34</sup>

Radiomics uses mathematical formulas to calculate hundreds of shape-, attenuation-, and texture-related characteristics for a given anatomic volume or segmentation, having been recently applied in CCTA analysis. Qualitative parameters that may be operator-dependent, such as the NRS, can be detected through calculations of radiomic features, developing the evolution of automated scan interpretation.<sup>35-37</sup>

Oikonomou *et al.* applied the first study of radiomic techniques on CCTA scans for better detection of CAD processes. In this study, an AI algorithm named “fat radiomic profile” was applied to the SCOT-HEART trial. The method has significantly improved MACE prediction beyond traditional risk stratification, which included risk factors, coronary stenosis, coronary calcium score, and high-risk plaque features on CCTA.<sup>38</sup>

## INVASIVE IMAGING TECHNIQUES FOR PLAQUE CHARACTERIZATION

VH-IVUS is used in clinical practice for in vivo detection of vulnerable plaques.<sup>39</sup> Virtual histology segments are classified into four tissue types, the grayscale IVUS data permitting in vivo identification of different atherosclerotic plaque components: necrotic, fibrotic, fibro-fatty, and dense calcified tissue.<sup>40</sup> While VH-IVUS has provided a special possibility regarding the in vivo study of atherosclerotic plaques and offers a novel insight into plaque morphology, it still has a limited resolution of 150–250 microns, which does not make possible the assessment of thin plaque cap with thickness around 65  $\mu\text{m}$ , a threshold value quantified by histopathological studies.<sup>41</sup>

The direct association between lesions with TCFA and subsequent adverse events was first established in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study. It was a prospective, multicenter study which enrolled 697 patients with ACS after percutaneous coronary intervention (PCI) revascularization. The patients underwent angiography and IVUS imaging with a follow-up of 3.4 years, and MACE were equally attributable to the previously treated culprit and non-culprit lesions. The non-culprit lesions had a large plaque burden ( $>70\%$ ), a small luminal area (MLA)  $<4.0 \text{ mm}^2$ , and TCFA, which was associated with a more than 3-fold increase in the probability of later MACE (HR 3.35 [1.77–6.36],  $p < 0.001$ ).<sup>42,43</sup>

Schuurman *et al.*<sup>44</sup> reported on the 5-year outcomes of the AtheroRemo-IVUS study, in which IVUS was performed in a single nonstenotic segment of a coronary artery in 581 patients undergoing angiography for stable or

unstable CAD. During the follow-up, non-culprit lesion-related MACE, including unplanned revascularization, nonfatal ACS, and all-cause or cardiac death, were predicted on a patient level by this segment having an MLA  $<0 \text{ mm}^2$  and/or plaque burden  $>70\%$ , but not by TCFA. The authors remark that these long-term outcomes are in contrary to their earlier report from this study, in which TCFA was correlated with 1-year patient-level MACE.<sup>45</sup> They explain this discordance with the following reasons. First, it is known that atherosclerosis is a dynamic process, meaning that vulnerable plaques can suffer morphological changes. Prior IVUS studies demonstrated that in patients with AMI, there is a constant drive towards increased plaque vulnerability, with rare stabilization, at least in the first year.<sup>46</sup> Second, IVUS used alone is an imperfect tool to characterize TCFA, having suboptimal axial resolution ( $\sim 150 \mu\text{m}$ ) to distinguish the thin cap ( $<65 \mu\text{m}$ ) and cannot quantify the calcified plaque or visualize more distant noncalcific tissues because of acoustic shadowing. Finally, the study possibly had insufficient power to obtain the preferable relationship between TCFA and patient-level MACE. More invasive imaging studies will be required to obtain statistical correlations between lesion characteristics and patient-level events compared with lesion-level events.<sup>47,48</sup>

Intravascular OCT is superior to IVUS in detecting TCFA. Given the limited resolution of IVUS imaging (about  $150\text{--}200 \mu\text{m}$ ), it cannot obtain precise cap thickness quantifications. OCT has a  $15\text{--}20 \mu\text{m}$  depth resolution and is able to measure fibrous cap thickness more exactly and detect thin fibrous cap thickness  $<65 \mu\text{m}$ , plaque rupture, and other rupture-prone features.<sup>49,50</sup> The ability to assess and quantify these changes has allowed observation of new correlations such as a higher reduction in serum inflammatory markers with thickening of fibrous caps.<sup>51,52</sup> The high resolution of OCT has allowed detection of high-risk features such as increased vasa vasorum (micro-channel structures) and in vivo identification of histologic categories of vulnerable plaque (calcified nodules and plaque erosion).<sup>53,54</sup>

Francesco *et al.* enrolled in their study a total of 376 ACS patients who underwent pre-intervention OCT imaging of the culprit lesion. Subjects were divided into two groups according to the presence or absence of layered phenotype in the culprit plaque. Plaque rupture ( $64.8\%$  vs.  $53.0\%$ ;  $p < 0.039$ ) and lipid plaque ( $83.3\%$  vs.  $70.9\%$ ;  $p < 0.013$ ) presented more frequently in layered plaques than in non-layered plaques. TCFA prevalence was significantly higher ( $56.5\%$  vs.  $42.5\%$ ;  $p < 0.016$ ), and macrophage accumulation was also more frequently found

in layered plaques ( $79.6\%$  vs.  $56.3\%$ ;  $p < 0.001$ ). The incidence of MACE was similar between the two groups after one year of follow-up.<sup>55,56</sup>

Nevio *et al.* found that macrophage accumulations were more frequently present in culprit lesions ( $84\%$  vs.  $61\%$ ,  $p = 0.015$ ) in which they also had a higher circumferential extension than those observed in NCP in patients with ACS. Culprit plaques with thrombus presented a lower distance between macrophage accumulation and the luminal surface than the culprit plaque without thrombus ( $0.06 \text{ mm}$  vs.  $0.1 \text{ mm}$ ;  $p = 0.04$ ), confirming the key role of macrophages in facilitating plaque progression.<sup>57–59</sup>

Our team published a systematic review based on assessment of coronary plaque vulnerability using VH-IVUS and OCT techniques, including eleven studies in this systematic analysis. It analyzed 1,568 coronary lesions from 1,225 patients with ACS who underwent both IVUS and OCT investigations, determined plaque vulnerability by investigating plaques with TCFA versus those with thick cap fibroatheroma, ruptured vs. non-ruptured plaques, in culprit vs. non-culprit coronary lesions, and in lipid-rich vs. non-lipid-rich plaques. The review showed that IVUS-derived markers that significantly correlated with plaque vulnerability were the remodeling index, plaque burden, and quantity of necrotic core, while OCT-derived markers were the TCFA, macrophage accumulation, and the presence of intraluminal thrombus. Both IVUS and OCT can deliver essential information on coronary atheromatous plaque vulnerability by recognizing several plaque features that have been demonstrated to be significantly associated with plaque instability. The data from the two imaging techniques together provide useful information, especially in patients undergoing a PCI procedure for ACS.<sup>60</sup>

## CONCLUSION

Early identification of CAD, features of atherosclerotic process, assessment of ischemia concerning plaque characteristics, and assessment of vulnerable plaque are indispensable endpoints in order to achieve reduction of cardiovascular mortality. Invasive and noninvasive imaging techniques are able to deliver a large amount of scientific data to assess vulnerable coronary atheromatous plaques. Recent studies demonstrated that the information provided by the two imaging techniques is complementary and using both methods is essential for adequate diagnosis, therapeutic strategy, and prognostic assessment. Emerging technologies and analytical techniques, such as machine learning and radiomics, will probably provide a useful platform for future developments in coronary imaging.

## CONFLICT OF INTEREST

Nothing to declare.

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# Cardiovascular Risk Factors from Another Point of View

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## ABSTRACT

Cardiovascular diseases remain the main cause of death in western societies. This contributes to the appearance of new diagnostic and treatment methods addressed to reduce the burden of cardiovascular diseases. In the last decades new imaging methods have emerged; furthermore, routine biomarkers were found to be useful in cardiovascular risk stratification. Data reviewed in this article emphasize the multifactorial etiology of cardiovascular disease. The authors describe the role of inflammation in the precipitation and progression of atherosclerosis and atrial fibrillation. Affordable and well-known inflammatory markers can be used alone or in combination with new imaging methods for a better cardiovascular risk stratification. Coronary computed tomographic angiography findings and inflammatory markers are capable to identify patients with high risk of major adverse cardiovascular events or atrial fibrillation. Furthermore, they also have an important role in the choice of treatment strategy and follow-up.

**Keywords:** cardiovascular diseases, biomarker, risk factor

## INTRODUCTION

Europe's population is getting older. Population ageing is the most significant demographic and social trend of the 21st century, affecting every country in the world. The incidence of ischemic heart disease (IHD) and atherosclerosis increases with age, appearing 6–9 years earlier in men than in women. Each year, IHD causes millions of deaths worldwide, and atherosclerotic disease remains the most common cause of death in developed countries.<sup>1</sup> In the last decades, the mortality rate of cardiovascular disease has decreased significantly due to improved diagnosis and treatment methods and primary prevention.<sup>2</sup> Patients with coronary artery disease can be completely asymptomatic in the early phases, being diagnosed in advanced stages, when the treatment is difficult and the prognosis can be poor. In most cases the symptoms are caused by heart failure and different types of arrhythmias. In elderly patients, the onset of atrial fibrillation can be the first sign of myocardial hypoperfusion.<sup>3,4</sup> In addition to well-known risk factors, acute or chronic inflammatory states can lead to plaque instability, atherosclerosis progression, and adverse cardiovas-

cular events.<sup>5</sup> The most common causes of death in this group of patients are sudden death, acute heart failure, and malignant ventricular arrhythmias, caused by acute coronary syndrome (ACS) and myocardial infarction (MI).<sup>6</sup> These patients are very vulnerable to the slightest internal or external stimulus. For this reason, patients at high risk of atherosclerosis require regular screening and need to be diagnosed before the acute event. One of the most accurate methods is coronary computed tomography angiography (CCTA), which is capable to assess several aspects of coronary atherosclerosis such as the presence of atherosclerosis, stenosis, markers of potential plaque instability, and atheroma size.<sup>7</sup>

### **ASSESSMENT OF CORONARY ARTERY DISEASE**

In the last decade, the diagnosis of coronary artery disease has become easier, faster, and more accurate. In the past, electrocardiography was the only diagnostic and screening method. The appearance of coronary angiography contributed to the diagnosis of significant coronary stenosis but without providing any information about the structure of the plaques. Nowadays, this method is reserved for acute cases when angioplasty is needed, and it cannot be used widespread for screening and for the assessment of cardiovascular risk. Computed tomography has become an indispensable method in cardiology in the last decade. Numerous large-scale randomized studies have demonstrated that this method has an excellent diagnostic accuracy, in both symptomatic and asymptomatic patients.<sup>8,9</sup> Several trials, such as HEART (Scottish Computed Tomography of the Heart) and PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), demonstrated that the rate of MI can be significantly reduced using a CCTA-guided treatment strategy.<sup>10-13</sup> This noninvasive imaging method is able to diagnose patients with coronary atherosclerosis from the early stages and is able to determine long-term cardiovascular risk.

Another important feature of this investigation is that it is able to provide information about the structure of coronary plaques. This technique is capable to determine vulnerable plaque features, such as low-attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign.<sup>14-16</sup> In a meta-analysis (n = 13,977), Nerlekar *et al.* reported a strong correlation between high-risk plaque features and the incidence of major adverse cardiovascular events (MACE), the presence of two criteria increasing the risk of MACE 9-fold.<sup>17</sup>

### **CARDIOVASCULAR RISK IN PATIENTS WITH CHRONIC INFLAMMATORY DISEASES**

Atherosclerosis is the cause and the consequence of inflammation. This systemic disease is associated with a low-grade inflammation of the arterial wall at the level of medium- and large-sized arteries.<sup>18</sup> Galkina *et al.* showed in their review that inflammation has an important role in all phases of atherosclerosis.<sup>19</sup> Several studies demonstrated a positive correlation between chronic inflammatory state and atherosclerosis. We found several clinical trials in the literature dealing with the incidence of cardiovascular disease in patients with chronic inflammatory diseases. Literature data suggest that chronic inflammatory rheumatic diseases (CIRD), such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and seronegative SpA, are associated with significant cardiovascular (CV) morbidity and mortality.<sup>20</sup> In a meta-analysis, Aviña-Zubieta *et al.* concluded that CIRD patients have an increased prevalence of CV disease.<sup>21</sup> The ATHERODENT clinical trial showed a positive correlation between periodontal disease, atherosclerosis, and plaque vulnerability.<sup>22</sup> The correlation between atherosclerosis and chronic inflammatory disorders of the gastrointestinal tract is not elucidated.<sup>23,24</sup> Multiple cohort studies reported a significant correlation between inflammatory bowel disease (IBD) and the incidence of MACE.<sup>25-27</sup> In a French cohort study (n = 210,162), Kirchgesner *et al.* found an increased risk of acute arterial events in patients with IBD. Furthermore, they reported a high risk in young patients. In their group, the risk of MACE increased proportionally with the number, duration, and severity of acute events.<sup>28</sup> This finding was also confirmed by an Asian and Danish cohort study, where the authors described a strong correlation between cardiovascular morbidity and mortality in young patients with IBD.<sup>25,29</sup> Weissman *et al.* concluded in their review that IBD is a risk factor for atherosclerosis and MACE, especially in young and female patients.<sup>30</sup>

### **INFLAMMATION AND MAJOR CARDIOVASCULAR EVENTS**

Inflammation has also an important role in the precipitation of ACS, as the inflammatory state can lead to plaque disruption. The correlation between inflammation and MACE is complex and not fully understood.<sup>31</sup> Many types of inflammatory cells are involved in the mechanism of coronary plaque destabilization. Macrophages and neutrophils play an important role in plaque disruption and atherosclerosis progression.<sup>32</sup> These cells secrete matrix

metalloproteinase-9 (MMP-9). A disturbance in the ratio of MMP-9 and tissue inhibitors of matrix metalloproteinase (TIMP-1) leads to arterial extracellular matrix breakdown and eventually plaque rupture.<sup>33</sup> Several clinical trials demonstrated that patients with ACS have a significantly higher MMP-9 level.<sup>34-36</sup> The authors describe other types of MMPs, such as MMP-1 and MMP-2, which are also increased in patients with ACS. Wang *et al.*, in a recent review, concluded that the acquired immune system also contributes to coronary plaque vulnerability.<sup>31</sup> Helper T cells, especially Th1 cells, are characterized by the production of pro-inflammatory cytokines, such as interferon- $\gamma$  and tumor necrosis factor- $\alpha$ , which contributes to plaque disruption in ACS.<sup>37,38</sup> Researchers investigated the correlation between plaque vulnerability and different types of microorganisms but without finding a significant correlation.<sup>39</sup> Only a few studies reported that infection with *Chlamydia*, *Mycoplasma pneumoniae* and some viruses may have an additional higher cardiovascular risk.<sup>40-42</sup>

An acute inflammatory state can lead to ACS without the presence of any coronary artery occlusion. This indirect mechanism of ACS is characterized by the increased oxygen and metabolic needs of the myocardium, and it is called demand ischemia or myocardial infarction (MI) type 2.<sup>43,44</sup>

### THE ROLE OF C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

C-reactive protein (CRP) is a widely used inflammatory biomarker, its level being increased in every type of inflammatory disease. It is a valuable marker not only for diagnosis, but also for monitoring. Determination of CRP is easy, inexpensive, and highly available. Recently, the role of CRP in cardiology has been demonstrated. Studies suggest that there is a strong correlation between the level of high-sensitivity (hs)-CRP and MACE.

The role of hs-CRP in primary cardiovascular prevention is not so clear. Several large clinical trials demonstrated that an increased level of hs-CRP is associated with a higher cardiovascular risk. Ridker *et al.*, in several prospective studies, demonstrated that patients with elevated hs-CRP are prone to develop MACE.<sup>45-49</sup> They described that these patients, without cardiovascular disease, have a three times higher risk for myocardial infarction. They also emphasize that hs-CRP was the best predictor of CV risk among female patients after the onset of menopause. Other authors have also demonstrated this correlation.<sup>50,51</sup> However, others did not find a significant correlation.<sup>52-54</sup>

The level of hs-CRP has also an important role in patients with IHD. Studies have shown that hs-CRP is a marker of acute events in patients with IHD. Won-Woo *et al.* assessed the correlation between the level of hs-CRP and CCTA findings. They concluded that the combination of imaging and inflammatory markers contributes to a better CV risk stratification.<sup>55</sup> Takashi *et al.* found a significant correlation between the level of hs-CRP and the grade of necrosis of culprit lesion, assessed with IVUS.<sup>56,57</sup> Trans-lesion CRP gradient was calculated by Inoue *et al.*, and they found a higher level distal to the site of coronary plaque. They also reported a higher level in case of unstable plaques.<sup>58</sup> In the VISTA-16 trial (n = 5,145) the authors reported that elevated hs-CRP levels after an acute cardiovascular episode and subsequent level increases are associated with adverse outcomes.<sup>59</sup> Several other trials have confirmed this correlation.<sup>60,61</sup> In 2018, our research group reported that hs-CRP level is in correlation with infarct size in STEMI patients.<sup>62</sup>

### INFLAMMATION AND ATRIAL FIBRILLATION

Inflammation can be either a cause or a consequence of atrial fibrillation (AF). Data from the literature suggest that inflammation has an important role in the structural and electrical remodeling of the atrium. Inflammation causes atrial fibrosis, gap junction modulation, and calcium homeostasis disturbance. These modifications promote ectopic atrial activity and aberrant impulse conduction.<sup>63</sup> Studies describe a correlation between systemic inflammation and AF. Patients with IBD, CIRD, psoriasis, SLE or sclerosis are more predisposed to AF.<sup>64-67</sup> Local inflammatory conditions, such as myocarditis or pericarditis, are also associated with a high risk of AF.<sup>68</sup>

The determination of hs-CRP level can also be useful in patients with AF. There are studies that describe an increased level of this inflammatory marker in case of persistent AF, compared to paroxysmal AF.<sup>69</sup> Wu *et al.* demonstrated in a meta-analysis that a higher baseline hs-CRP level is associated with a higher risk of AF recurrence after catheter ablation and electrical cardioversion.<sup>70</sup> An elevated white blood cell (WBC) count is also in correlation with the incidence of AF, as confirmed by several studies such as the Framingham Heart Study.<sup>71</sup> Weymann *et al.*, in their meta-analysis, did not find any correlation between the onset of AF and WBC count. However, they suggest that WBC may have a predictive role in the recurrence of AF. Some authors consider that the determination of the neutrophil/lymphocyte ratio is more accurate.<sup>72,73</sup>

## CONCLUSIONS

In the last decade, due to the increased rate of cardiovascular diseases, further investigations were conducted to identify novel cardiovascular risk factors. Systemic inflammation is directly associated not only with ischemic heart disease, but also with the risk to develop atrial fibrillation. The pathophysiology of atrial fibrillation is multifactorial, inflammation being both a cause and a consequence of this condition. Inflammation can promote ectopic atrial activity and aberrant impulse conduction, and the level of circulating inflammatory markers may predict the risk of recurrence. Inflammatory biomarkers, especially in combination with imaging markers, can be used for a better stratification of cardiovascular risk.

## CONFLICT OF INTEREST

Nothing to declare.

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# Management of Culprit and Non-Culprit Lesions in Acute Coronary Syndrome

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## ABSTRACT

Multivessel coronary artery disease, defined by the presence of a significant stenosis ( $\geq 50\%$  diameter) in two or more epicardial coronary vessels, usually occurs in more than 50% of patients with ST-segment elevation myocardial infarction. The latest guidelines indicate revascularization of the non-culprit artery with a recommendation of class IIB. However, the management of non-culprit lesions in patients with acute coronary syndrome is still a matter of debate. This article presents the most recent concepts related to the management of culprit and non-culprit coronary lesions, based on advanced imaging approaches, in order to identify high-risk patients and prevent further acute coronary syndromes.

**Keywords:** multivessel coronary artery disease, culprit plaques, imaging techniques, PCI

## INTRODUCTION

Acute coronary syndrome (ACS) is still the leading cause of death globally despite the major improvements in interventional and pharmacological therapy of atherosclerotic heart disease in the last decade. ACSs are traditionally represented by three clinical entities including acute myocardial infarction with or without ST-segment elevation (STEMI, NSTEMI), unstable angina, and sudden coronary death. The main mechanism of producing this spectrum of coronary heart diseases develops from the presence of one or more underlying intra-luminary atherosclerotic plaques with thrombotic complications. In addition, there are some rare causes, such as coronary artery dissection, arteritis, myocardial bridging, thrombembolism, or coronary vasospasm, without other evident coronary artery disease. An atherosclerotic plaque rupture leads to acute myocardial infarction, due to total (STEMI) or partial occlusion (NSTEMI) of the vessel. In case of multiple obstructive coronary lesions, the identification of the one considered to be responsible for the acute coronary event (culprit) is essential to conduct proper treatment, drawing attention to the risk of complications treating a coronary artery with no plaque rupture (non-culprit). Non-culprit lesions in the setting of an ACS are also highly investigated. There are controversial opinions regarding the management of cul-

pruit and non-culprit lesions in the acute phase of a coronary event.

Noninvasive cardiac imaging techniques, including coronary computed tomography angiography (CCTA), magnetic resonance imaging (MRI), stress echocardiography, and echocardiography, play an important role in identifying patients at high risk for ACS. However, for patients with ACS considered at very high risk, the recommended strategy is immediate invasive approach, performed within 2 hours of hospital admission. Invasive coronary angiography (ICA), combined with modern imaging techniques including optical coherence tomography (OCT) and intravascular ultrasound (IVUS), are useful methods in identifying the anatomical characteristics of the coronary tree but they do not offer information about the hemodynamic consequences of the detected stenosis. The completeness of revascularization, especially in multivessel coronary artery disease, should be decided after evaluation of the functional significance of all lesions (particularly the non-culprit stenosis), left ventricular function, hemodynamical status, age, and comorbidities.<sup>1</sup>

### INVASIVE IDENTIFICATION METHODS OF CORONARY PLAQUE LESIONS

When multivessel obstruction is detected, the culprit lesion is defined as the lesion whose appearance is associated with the ECG changes, or as the lesion with the most obstructive luminal narrowing visible by coronary angiography. Therefore, endothelial dysfunction, elevated sympathetic activity, and its predisposition to thrombosis have a considerable impact on the blood flow dynamics of non-culprit lesions during myocardial infarction.<sup>2</sup> Intraluminal obstruction below 70% visible on CCTA or ICA in the coronary arteries are considered non-critical lesions, while critical lesions are defined by a narrowing larger than 70% of the lumen. However, ICA cannot reliably evaluate the functional severity of these lesions; furthermore, vulnerability features suggesting an increased risk of an acute ischemic event cannot be identified by this method.

The invasive functional assessment of the stenosis using fractional flow reserve (FFR) during the acute phase of an ACS is considered a reliable method to evaluate the ischemia in order to guide the percutaneous treatment. The safety and efficacy of FFR is shown by several randomized clinical trials. However, normal FFR values (>0.80) can lead astray due to submaximal hyperemia and incomplete response to adenosine.<sup>3</sup> Therefore, an alternative to FFR is iFR, performed in the so-called “wave-free period” in diastole. iFR is not influenced by intravascular pressure

alterations, can be performed without hyperemic stimulation, and is independent from adenosine response. Several randomized trials established FFR as the gold standard to assess a high-risk coronary artery lesion,<sup>4-8</sup> but other trials considered iFR to be non-inferior or even equivalent to FFR.<sup>9,33</sup> It is important to highlight that according to van de Hoeven *et al.*, non-culprit coronary artery flow reserve could be overestimated in the setting of STEMI due to altered hemodynamic forces.<sup>10</sup> However, the FFR-guided estimation of significant coronary artery stenoses compared to visual angiographic assessment leads to changes in decision-making for coronary intervention.<sup>8</sup>

Intravascular imaging techniques, including IVUS, OCT, or near-infrared spectroscopy (NIRS), are useful in detecting clinically relevant stenoses and high-risk atherosclerotic plaques. The position of the culprit lesion is determined by making cross-sectional images of the coronary arteries. The diagnostic accuracy of the mentioned techniques showed inferiority to physiological evaluation with FFR or even iFR. Similar studies showed a relatively high negative predictive value; however, a low positive predictive value indicates that IVUS and OCT detect plaque ruptures in approximately 50% of STEMI.<sup>8,11</sup>

CCTA-derived plaque characteristics, also named markers of vulnerability, including low-attenuation plaque, positive remodeling, the “napkin-ring” sign, and spotty calcification, carry predictive value for further adverse cardiac outcomes.<sup>12</sup> In the study by Myung *et al.*, culprit lesions in ACS were more frequently observed in the left anterior descending artery, with more severe stenosis, showing a higher incidence of vulnerability markers than non-culprit ones. Additionally, with a more severe degree of stenosis, there was a higher incidence of adverse plaque characteristics (APC) and worse hemodynamic parameters.<sup>13-15</sup> The identification of culprit lesions with the use of advanced imaging techniques, such as CCTA and FFR, could be useful in the risk stratification of patients and in the prediction of major cardiac events.<sup>16</sup> Furthermore, CT-FFR, developed by Taylor *et al.*, offers an approximated value of fractional flow reserve from standard coronary computed tomography images using advanced computational modeling of fluid dynamics. This technology has higher specificity and positive predictive value compared to standard CCTA and is being considered a “gatekeeper” strategy to the catheterization laboratory due to the potential rapid evaluation, noninvasive approach, and cost-effectiveness.<sup>8,12,17</sup> As previously described, functionally significant, lesion-specific ischemia is considered at a CT-FFR value  $\leq 0.80$ . Furthermore, von Knebel Doeberitz *et al.*<sup>12</sup> demonstrated that CT-FFR has higher discriminatory value over CCTA

and plaque markers, offering useful information regarding risk stratification. Additionally, Duguay *et al.* described CT-FFR as a better predictor of stenosis grade than ICA for the identification of further major adverse cardiovascular events (MACE) in the setting of non-culprit coronary lesions in ACS.<sup>18,32</sup>

### **REVASCULARIZATION STRATEGY: COMPLETE OR NOT?**

It is still unclear whether complete revascularization in multivessel coronary disease brings benefits or reduces the risk of future acute cardiovascular events. It is also still questionable whether complete revascularization compared with culprit-lesion-only percutaneous coronary intervention (PCI) has effects on the size of the affected myocardial territory, on left ventricular function, and on remodeling. There are several studies published in the last few years, which investigated the outcome of these two alternatives of coronary revascularization approach.

In a randomized trial, the DANAMI-3-PRIMUM study compared FFR-guided revascularization to culprit vessel-only PCI in patients with STEMI. They also investigated the size of infarction, left ventricular (LV) ejection fraction, and LV remodeling after the two types of revascularization strategy. They included 280 patients, 136 with culprit-only and 144 with complete FFR-guided intervention therapy. Revascularized patients underwent baseline CMR scans and repeated scanning 90 days later to reevaluate LVEF, LV volumes, and infarction size. Their results showed that complete FFR-guided revascularization in patients with STEMI and multiple obstructive coronary stenoses is not related to the size of affected myocardium, LV function, or remodeling compared with culprit-only PCI. However, the DANAMI-3-PRIMUM trial demonstrated the benefits of deferred FFR-guided complete revascularization, which was associated with the presence of 3-vessel disease and at least one non-culprit lesion with  $\geq 90\%$  stenosis. In these cases, FFR-guided complete revascularization significantly reduced adverse cardiac events from 41% to 8%, but the difference related to mortality and reinfarction remained nonsignificant.<sup>4,19</sup>

Furthermore, the Compare-Acute study randomly assigned 885 patients with STEMI and multivessel obstructive coronary disease who had undergone primary PCI of the culprit artery and complete FFR-guided revascularization in a ratio of 1:2. Accordingly to the results, the risk of composite cardiovascular outcome was lower among patients who had undergone FFR-guided complete revascu-

larization of non-infarct-related lesions and culprit lesions as well.<sup>6</sup>

The COMPLETE trial, published in 2019, used a sample of 4,041 patients with STEMI and multivessel coronary artery disease. The patients were randomized into two different groups: 2,016 patients who underwent complete revascularization including all significant coronary lesions, and 2,025 patients with culprit lesion-only PCI revascularization strategy. The staged non-culprit revascularizations for STEMI patients were considered within 72 hours during the index hospitalization after successful culprit-lesion PCI. After a 3-year follow-up period, cardiovascular death and myocardial infarction were significantly lower in the group of patients who underwent complete revascularization ( $p = 0.004$ ). Furthermore, the final results of the trial showed that among patients with STEMI and multivessel coronary artery disease a strategy of complete revascularization resulted in a 26% lower risk of death from cardiovascular causes or repeated myocardial infarction, compared with culprit-lesion-only PCI.<sup>20</sup>

A recent collaborative meta-analysis, assessing 11 non-randomized studies and 5,850 patients, investigated the outcome of multivessel PCI compared with culprit-only PCI in patients admitted for STEMI, complicated with cardiogenic shock and with multivessel disease. Despite the elevated risks of cardiogenic shock for poor outcome, the emergency revascularization of culprit and non-culprit coronary arteries seems to not influence neither the short-, nor the long-time survival of these patients. According to this study, there were no differences in cardiovascular death, reinfarction, or reduction of repeated revascularization.<sup>4</sup> Similarly, an updated meta-analysis of 14 studies by Amartya *et al.* demonstrated no significant difference in short- or long-term mortality between patients with multivessel PCI (MV-PCI) and culprit lesion-only PCI (CL-PCI) associated with cardiogenic shock.<sup>5</sup>

The CULPRIT-SHOCK trial by Thiele *et al.* evaluated the clinical outcomes of patients with acute myocardial infarction associated with cardiogenic shock and multivessel coronary artery disease one year after the acute event, after two different revascularization strategies: culprit-lesion-only PCI or immediate multivessel revascularization.<sup>20</sup> They also compared the need for renal replacement therapy in the first 30 days after PCI, and they recorded such an event in 11.6% of the patients in the culprit-only PCI group and 16.4% in the multivessel-PCI group. Furthermore, the rate of composite death, recurrent infarction, or acute heart failure needing reshospitalization did not differ significantly between the two groups.<sup>22</sup>

**TABLE 1.** Characteristics and outcomes of the most recent studies related to PCI of culprit and non-culprit lesions during ACS

Study name	Authors	Patients enrolled	ACS event	Complete revascularization	Culprit-only revascularization	Follow-up period	Outcome (Mortality)
DANAMI-3-PRIMULTI substudy <sup>4</sup>	Kasper <i>et al.</i>	280	STEMI	144	136	90 days	Superiority of deferred MV-PCI
COMPLETE trial <sup>20</sup>	Shamir <i>et al.</i>	4,000	STEMI	2,016	2,025	3 years	Superiority of complete PCI
Meta-analysis of 11 non-randomized studies <sup>5</sup>	Dhacal <i>et al.</i>	5,850	STEMI + cardiogenic shock	1,157	4,693	In-hospital to 5 years	No differences
CvLPRIT- trial <sup>23</sup>	Anthony <i>et al.</i>	296	STEMI	150	146	12 months to 5,6 years	Superiority of complete PCI
CULPRIT-SHOCK trial <sup>22</sup>	Thiele <i>et al.</i>	706	AMI + cardiogenic shock	355	351	30 days and 1 year	No differences
Compare-Acute trial <sup>6</sup>	Smits <i>et al.</i>	885	STEMI	295	590	30 days, 12,24 and 36 months	Superiority of complete PCI

Similarly, the CvLPRIT study analyzed the rate of MACE after a 12-month period of follow-up in patients with complete versus infarct-related-only revascularization at the index admission. The rate of MACE involving all-cause death, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization was significantly lower in the complete revascularization group at 12 months and even after a median of 5.6 years of follow-up.<sup>23</sup>

## DISCUSSION

The conflicting data in the literature regarding to revascularization strategy and the difficulty of decision-making related to culprit-only or multivessel PCI in acute coronary syndromes draws attention to the importance of this topic. However, the estimated severity of non-culprit lesions is often exaggerated due to hemodynamic phenomena such as vasoconstriction, relative vasodilatation of the normal vessels, and intraprocedural changes in hemodynamics. Furthermore, the levels of catecholamine and other hormones with vasoconstrictive effect (serotonin, endothelin, thromboxan, and angiotensin) are elevated among STEMI patients; also, increased oxidative stress is lowering the vasodilator effect of nitric oxide, adenosine, and prostacycline.<sup>2,24,25</sup> Moreover, it should be emphasized that MV-PCI increases the complexity of the procedure, while also increasing the risk of myocardial injury and further hemodynamic deterioration from distal embolization, acute vessel occlusion, intrastent thrombosis, or loss of sidebranch.<sup>6,26</sup> Additionally, the minimal clinical benefit of MV-PCI in the acute phase of ACS can lead to unnecessary prolongation of PCI time, with fatal effects in hemodynamically instable patients.<sup>5</sup>

On the other hand, it is still unclear how early complete revascularization in multivessel coronary artery disease patients could lead to better outcome in long-term follow-up. Probably its major role is related to the improvement of collateral flow to the peri-infarcted myocardial territory due to prophylactic management of the non-infarct-related arteries.<sup>27</sup> Additionally, MV-PCI of non-culprit arteries may theoretically limit infarct size and preserve LV function, both of which are associated with improved survival in patients with ACS.

However, FFR remains the gold standard for the evaluation of the functional relevance of coronary artery stenosis.<sup>28,29</sup> In a group of STEMI patients with multivessel disease, revascularized with culprit-only PCI, FFR measured in the non-culprit lesions immediately after successful primary PCI showed a nonlinear and inverse risk continuum of MACE.<sup>30,31,34,35</sup>

## CONCLUSION

Our aim was to evaluate how the management of culprit and non-culprit lesions could improve ACS patient outcomes, both on short and long term after the acute event. Summarizing the most recent literature findings we may conclude that decision-making regarding culprit and non-culprit plaque management should be performed by integrating advanced cardiac imaging techniques. FFR investigation remains the gold standard for evaluating the functional relevance of coronary stenoses. FFR-guided complete revascularization of multivessel coronary artery disease in the acute phase of ACS could improve short-time outcomes, but long-time benefits of this strategy are still unproven.

## CONFLICT OF INTEREST

Nothing to declare.

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# Coronary Computed Tomography Angiography for Assessment of Stable Coronary Artery Disease – a Cost-effectiveness Perspective

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## ABSTRACT

Patients with chest pain presenting to the emergency room are currently investigated using either invasive coronary angiography (ICA) or noninvasive coronary computed tomography angiography (CCTA). ICA remains an expensive diagnostic tool and exposes patients to a high risk of periprocedural complication. Besides the currently available expansive economic evidence, there is still an important lingering issue: to establish, from the healthcare provider's point of view, which is the most cost-effective investigation tool for the detection of significant coronary artery disease. The aim of this article is to present the latest developments in the field of imaging tools for the detection of coronary atherosclerosis in patients with chest pain, from the perspective of a cost-effectiveness analysis.

**Keywords:** cost-effectiveness analysis, coronary CT angiography, stable coronary artery disease, stable chest pain, imaging

## BACKGROUND

Stable chest pain is still a frequent clinical presentation to medical clinics and emergency departments worldwide.<sup>1</sup> This leads to an increased number of invasive or noninvasive investigations with the primary aim to identify or dismiss the existence of flow-limiting coronary artery disease (CAD).<sup>2-4</sup> This results in a continuous resource-consuming problem for healthcare providers worldwide, given the fact that CAD continues to represent the most frequent cause of health-related deaths in the European Union (EU)<sup>5</sup> and contributes to a consistent decrease in the quality of life.<sup>6,7</sup> In the setting of such extensive charges, the accuracy of CAD diagnosis remains of great importance for the management of these patients.<sup>1</sup> Despite efforts to reduce cardiovascular mor-

tality in acute coronary syndrome (ACS) via advances in the management and implementation of up-to-date effective treatments, stable CAD continues to present high mortality rates. In the current clinical practice, invasive coronary angiography (ICA) has an essential role in the management of CAD subjects, being the current gold-standard for confirming the existence, location, and severity of CAD.<sup>8</sup> However, ICA remains an expensive diagnostic tool and exposes patients to a high risk of periprocedural complications.<sup>9-11</sup>

Driven by its ability to provide similar information regarding the coronary tree as conventional coronary angiography, coronary computed tomography angiography (CCTA) presented a widespread diffusion in the imaging field,<sup>12-20</sup> a fact supported by a substantial weight of clinical evidence.<sup>21-24</sup> In these terms, CCTA permits the visualization of coronary artery lumen and wall structure at a high image quality, at a low radiation dose,<sup>25</sup> but in a non-invasive fashion, with almost 100% accuracy in excluding significant CAD. Being typically performed in outpatient care, it is to be expected to prove less expensive as the conservative ICA, whose status as the gold standard investigation for CAD derives from its 100% diagnostic accuracy.

Currently, healthcare providers allocate significant efforts to provide the most appropriate management for stable CAD, one that is effective from both clinical and cost-effectiveness point of view.<sup>26</sup> As a large segment of the population increases in age and develops CAD, the treatment of ischemic heart disease should be sustainable for healthcare providers. This is the basis of the current agenda of cost-effectiveness analysis (CEA). CCTA seems to be the most suitable economic tool, given the differences expected both in terms of costs and outcomes for the common aim: to detect coronary stenosis. CEA investigates different diagnostic tests in order to equally examine costs and outcomes of diagnostic guidelines, with the main aim to optimize health outcomes considering existing resources.<sup>27</sup> Thus, CEA has the potential of promoting changes in healthcare systems based on quality-guided research.<sup>28,29</sup> Another key benefit of CEA is represented by the fact that cost savings are defined in the presence of equivalent outcomes; thus, cost fluctuation does not actually result in a decrease of quality received by the patients.<sup>30</sup>

Besides the currently available expansive economic evidence, there is still an important lingering issue: to establish, from the healthcare provider's point of view, the cost-efficiency of CCTA compared with the current guideline standard or other imaging techniques for the detection of significant coronary artery disease.<sup>31</sup>

## RISK STRATIFICATION, A CORNER MILESTONE

For patients presenting new symptoms of stable chest pain, it is of vital significance to implement a diagnostic workup in order to investigate the presence of CAD.<sup>32</sup> The current standard to diagnose functionally significant CAD is ICA. However, since this procedure is costly, invasive, and associated with a high risk for further major adverse events, ICA is recommended as initial test only for subjects with a high probability of CAD, as research has shown that obstructive CAD was identified in only 38–41% of these patients, a fact also clearly highlighted by registry data.<sup>33-38</sup> These facts are the basis for the necessity of improving screening tools for invasive strategies.<sup>39-41</sup> From this point of view emerges the need for a better previous risk stratification, a fact underlined by previous decision analysis indicating that the optimal diagnostic strategy in this segment of patients depends primarily on the prior probability for CAD.<sup>42-44</sup> Moreover, there is a need to implement the concept of gatekeepers for ICA, among which CCTA has gained an increasing popularity in recent research trials.

In patients with a low associated probability of CAD, a series of studies and trials (FAME 2, COURAGE, DIAD, FACTOR 46) showed the reduction of cardiac events as very unlikely, regardless of the test used, appropriate risk factor modification, and optimal medical therapy,<sup>45-48</sup> with no available randomized clinical trials to date to support an initial invasive strategy in order to reduce major cardiovascular end-points.<sup>49-51</sup>

A large body of evidence sustains the superiority of CCTA in low-to-intermediate risk patients, demonstrating that CCTA, either as the first or as a layering test, may represent a cost-effective initial strategy for patients with CAD prevalence of 10–50% for both near-term and long-term diagnostic periods.<sup>52,53</sup> The decision model tree of Dewey *et al.* proved CCTA as the most cost-effective approach to be implemented for the 10–50% pretest likelihood of CAD, while CCTA and ICA proved to be equally effective at a 60% likelihood. ICA proved to be the most cost-effective diagnostic tool only for a pretest likelihood greater than 70%.<sup>52</sup> The decision analytic model of Halpern *et al.* showed a cost reduction with CCTA depending on the prevalence of CAD, with overall costs reduced as long as the prevalence is under 85%.<sup>53</sup> However, in low-to-intermediate prior probability of significant CAD, the optimal diagnostic imaging test remains unclear, as a series of variables, such as costs, diagnostic test characteristics, prior calculated probability, local willingness-to-pay threshold, optimization criteria, availability, patient preference, or local team expertise, must be taken into consideration.<sup>32</sup>

Regarding patients with very high probability of CAD presenting stable chest pain, there is a large body of clinical trials suggesting diagnostic strategies involving ICA as the most cost-effective initial strategy for the diagnosis of stable chest pain, with a concomitant lack of clinical and health economic data in a large body of clinical trials (PROMISE, SCOT-HEART, EVINCI) to support the implementation of CCTA in subjects at high risk of CAD in real-world settings.<sup>31,53–55</sup> However, the same studies have shown that clinical estimates of prior probability are in fact grossly overinflated in real-world implementation. Therefore, in terms of real life, this group of subjects for whom direct ICA proved to be cost-effective compared to CCTA may not actually exist. Thus, these results should only be seen as a stimulus for further required research rather than furnishing definitive conclusions.

## UP-TO-DATE RESEARCH

If CCTA is to be considered a gatekeeper for ICA, correct CEAs are of great importance in the field of evidence-based science. Up to date, more than 10 large randomized clinical trials (including ACCURACY, Meijboom, CORE 64, EVINCI, PICTURE, Dewey, and the CONFIRM Registry) have compared CCTA with invasive angiography.<sup>56–66</sup>

The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry performed a direct comparison between CCTA and ICA. The results revealed that the use of CCTA, as a gatekeeper to ICA, resulted in lower rates of follow-up catheterization for subjects presenting no or mild CAD.<sup>67</sup>

In a study conducted by Budoff *et al.*, a 63.4% cost-saving was obtained when comparing ICA-confirmed CAD diagnosis costs with CCTA. In a similar manner, Halpern *et al.* obtained an overall reduction of costs when performing CCTA before ICA, at a prevalence of CAD below 85%. This trend persisted for the cases of CAD with a 50% prevalence as well.<sup>68</sup>

Another series of studies compared the cost-effectiveness of CCTA prior to ICA with direct ICA. Five studies were cost-utility analyses reporting beneficial measures in terms of gained QALYs, two of them scoring relatively high using the Drummond checklist.<sup>69–73</sup> The most important parameter driving the cost-effectiveness of CCTA is the probability test of CAD. In low-to-intermediate probability of CAD, CCTA proved to be more effective and less costly compared to the direct invasive approach. Conversely, in patients with higher probability of CAD, the direct invasive approach proved to be more effective and also associated with higher incremental cost-effectiveness

ratios that were above the thresholds typically considered good value for money.<sup>69,73</sup>

EVASCAN is one of the first large cost-effectiveness trials that included the largest population used for studying diagnostic accuracy in subjects with stable or suspected CAD to date. The trial included 705 patients from 40 centers and provided robust results, concluding what would become the cornerstone of further studies and guidelines.<sup>31</sup> The main conclusion of the trial stated that in patients with intermediate risk, CCTA is the best option to rule out CAD, especially in subjects who, for different reasons, cannot undergo ICA or present uncertain results from other diagnostic procedures.<sup>74–76</sup> The trial also assessed the benefits of CCTA triage for intermediate-risk as a cost-saving strategy compared with the conservative “ICA for all” approach. The trade-off for these potential monetary savings is the slight reduction in accuracy and a small increase in radiation dose.<sup>74</sup>

## CURRENT GUIDELINE RECOMMENDATIONS

With regard to the current recommendations of the guidelines of the European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American Heart Association (AHA) in the setting of chronic coronary syndromes (CCS), the latest ESC guideline from 2019 recommends the use of CCTA in the diagnostic and risk stratification of obstructive CAD amongst patients with stable chest pain on the basis of the pretest CAD probability, local team expertise and availability, and anticipated quality of the examination (I to IIa, B to C).<sup>77</sup> Less prioritized by the outdated 2012 ACC/AHA guideline, the use of CT angiography for CCS diagnosis is disadvantaged to the detriment of functional imaging tests as the choice to be made.<sup>78</sup> Current guidelines regarding the use of CCTA in patients with stable chest pain are predominantly derived from the results of the initial diagnostic accuracy studies.<sup>78</sup> In this setting, the main application of CCTA consists in acting as a gatekeeper for ICA and further revascularization, with further reduction in diagnostic work-up costs. On the other hand, in its 2016 guideline, the National Health Service (NHS) of the United Kingdom controversially recommended CCTA as the first-line investigation for all patients with angina and no prior CAD.<sup>79</sup> Also, previous pretest probability of obstructive CAD was no longer advised. The NHS recommendation is based on a surveillance review which included each imaging modality, on the basis of which a cost-effectiveness analysis was undertaken. CCTA emerged as having a very high diagnostic sensitivity as well as a lower cost in comparison with other

imaging investigations, particularly ICA.<sup>79</sup> Therefore, the analysis concluded that as a first-line investigation, CCTA offered a lower cost per correct diagnosis than any of the alternative strategies in all three risk groups of patients.

## FURTHER QUESTIONS

As the most developed European countries lined up in implementing guidelines and country-specific organization recommendations, given the large grade of heterogeneity in the availability of CT scanners in other countries, the applicability of current recommendations in various healthcare systems may differ and remains to be explored. The implementation of these general indications for the assessment of stable CAD was estimated to be associated with a near 700% increase in the number of performed CCTA.<sup>80</sup> However, the utilization of CCTA remains sub-optimal related to the evidence proving its clinical efficiency, compared with other imaging techniques.<sup>81</sup> Thus, the potential implementation of these latest recommendations for the diagnostic management of stable CAD may involve a substantial investment in CCTA infrastructure and training. Besides the field of research or large clinical trials, the use of CCTA in routine clinical practice will inevitably generate a series of equivocal CCTA scans. Consequently, attending physicians may require further imaging tests in the diagnostic work-up in order to solve the doubt generated by the equivocal results, increasing the economic burden.<sup>25</sup>

64-slice CCTA has also been proven accurate for CAD diagnosis in most patients.<sup>82–85</sup> However, specific groups of patients may have low-quality images as a result of a difficult scanning process.<sup>86</sup> These groups of patients include those with tachycardic rhythm >65 bpm, arrhythmias, obesity, coronary calcium score (CCS) >400, previous percutaneous coronary interventions with stent implantation, intolerance to beta-blockers, or previous coronary artery bypass graft. Up-to-date ICA may be indicated in these difficult-to-image subjects. However, newer generation CCTA instruments may provide an alternative for these cases. According to a study conducted by Burgers *et al.*, the use of new-generation dual-source CCTA in case of difficult-to-image patients with CAD is equal in terms of effectiveness with ICA but at a cost-saving for both suspected and known CAD patients.<sup>85</sup> Therefore, this alternative is recommended to be implemented for the assessment of patients who prove to be difficult to assess using earlier CT scanners.

There are still great expectations from future research in order to more definitively apply cost data to healthcare policy decision-making.

## CONCLUSIONS

Given the current competitive economic environment, it is of great importance to understand expenditures correctly, as the increased costs of healthcare further lay the grounds for a necessary understanding of good value in healthcare.

Available economic analyses suggest the fact that with a high negative predictive value and a high diagnostic accuracy, CCTA seems to be an excellent cost-effective approach as a rule-out-test for CAD, prior to ICA, when applied to the appropriate population. However, further multicenter randomized trials are needed in order to determine the degree by which CCTA may improve clinical outcomes in patients with chest pain.

Finally, the implementation of CCTA for the evaluation of new-onset chest pain in the real world essentially depends on newly implemented health strategies, grounded on the reconfiguration of currently available assets and staffing levels.

Therefore, it becomes clear that CCTA is a definitely cost-effective imaging tool for the diagnosis of chest pain, confirming its key role in identifying the best clinical pathways that should be adopted to guarantee the optimal clinical outcome of CAD patients.

## CONFLICT OF INTEREST

Nothing to declare.

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# Acute Coronary Syndrome and Arrhythmia Induced by SARS-CoV-2 Infection in a Patient with Non-Significant LAD Lesion. A Case Report

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## ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) has emerged as a pandemic and public health crisis of an unprecedented effect. Clinical studies reported an association between COVID-19 and cardiovascular disease, whereas COVID-19 itself can induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism. **Case summary:** A patient diagnosed via screening coronary computed tomography angiography with non-obstructive coronary artery disease was hospitalized with non-ST elevation myocardial infarction and atrial flutter during a severe respiratory infection episode with SARS-CoV-2. After recovery from the infectious episode, fractional flow reserve-guided elective percutaneous coronary intervention with drug-eluting stent was performed. **Conclusions:** COVID-19 intercurrent in a cardiovascular patient with nonobstructive coronary artery disease triggered coronary plaque vulnerabilization with subsequent development of an acute coronary syndrome. SARS-CoV-2 proved to be involved via direct viral tissue involvement and concomitant mechanisms derived from systemic illness in the development of a severe supraventricular arrhythmic event.

**Keywords:** acute coronary syndrome, COVID-19, arrhythmic event, plaque vulnerability, elective PCI

## INTRODUCTION

Coronavirus disease (COVID-19), produced by a strain of coronavirus also identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly emerged as a global pandemic, showing disastrous unprecedented public health-related effects, while also having severe implications in social and economic activities.<sup>1</sup> Amongst respiratory changes, unrestrained COVID-19 disease could also generate a cytokine storm, circumstances in which pro-inflammatory substances, such as tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , or IL-6, are overproduced by the immune system, with consequential multiorgan impairment. Moreover, in

**TABLE 1.** Timeline

Time	Events
2019	<ul style="list-style-type: none"> <li>• First presentation: atypical chest pain</li> <li>• Cardiovascular risk factors: hypertension</li> <li>• MSCTA scan performed for screening: LAD 50% stenosis, mixed plaque, not all vulnerability criteria fulfilled</li> <li>• Cycle ergometer test: negative for ischemia, therefore long-term imaging follow-up, antiplatelet and lipid-lowering treatment recommended</li> </ul>
October 2020	<ul style="list-style-type: none"> <li>• Second presentation: typical chest pain, palpitation</li> <li>• ECG: atrial flutter, 160 bpm → synchronized electrical cardioversion</li> <li>• Elevated cardiac biomarkers: hs-cTnI and CK-MB</li> <li>• Biological inflammatory syndrome: leu 17.5 G/L, CRP 273 mg/L</li> <li>• Severe dyspnoea, persistent hypoxemia (SpO<sub>2</sub> 85%)</li> <li>• Naso-pharyngeal swab resulted positive for SARS-CoV-2</li> <li>• Due to respiratory and infectious status, invasive angiographic evaluation delayed for the moment</li> </ul>
January 2021	<ul style="list-style-type: none"> <li>• Coronary angiography: LAD 70% stenosis</li> <li>• FFR-guided elective PCI with DES</li> </ul>

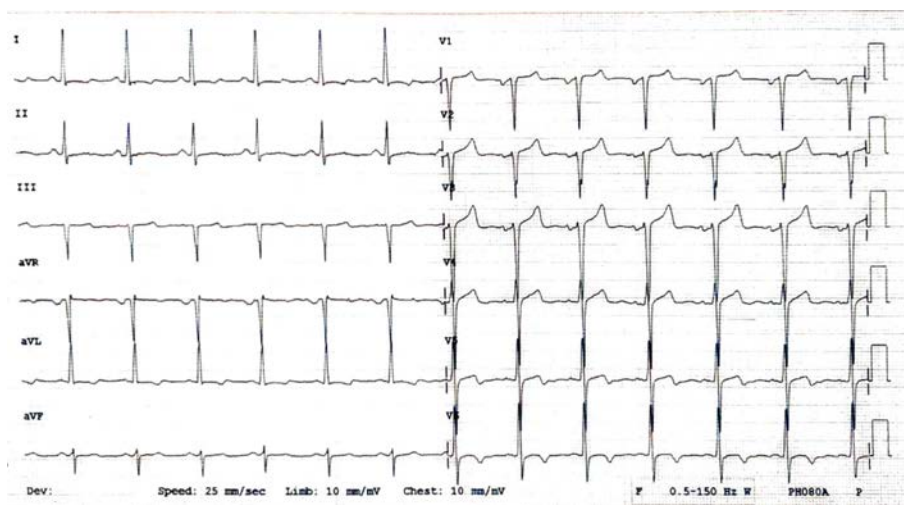
a substantial proportion of subjects, SARS-CoV-2 triggers a series of abnormalities in the coagulation cascade, which can lead to the development of thromboembolic events.<sup>2-4</sup> Recent clinical information denotes equally the vulnerability and the consequences of COVID-19 as being strongly associated with cardiovascular disease (CVD).<sup>5-9</sup> Besides the fact that CVD represents a mutual comorbidity reported among subjects infected with SARS-CoV-2, with a reported incidence of nearly 25%,<sup>5-7,10,11</sup> COVID-19 seems to stimu-

late the progression of CV conditions such as myocardial injury, myocarditis, type 1 or type 2 myocardial infarction, severe arrhythmias, acute heart failure, cardiogenic shock, and thromboembolic events.<sup>12-14</sup> The increased burden of inflammatory syndromes related to SARS-CoV-2 infection has been suggested to accelerate the progression of subclinical conditions or even cause de novo cardiovascular impairment.<sup>5-7</sup>

## CASE PRESENTATION

A 63-year-old male patient, with history of arterial hypertension under treatment (amlodipine, valsartan), presented to the emergency department after having experienced atypical chest pain for three days. The physical and cardiovascular clinical examination exposed no abnormalities. The chest pain was treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

The 12-lead electrocardiogram (ECG) performed at presentation in the emergency department identified subendocardial ischemia, with negative T waves in antero-lateral leads (V3-V6) (Figure 1). Bedside echographic examination showed no significant kinetic disturbance of the left ventricle, with preserved left ventricular ejection fraction (LVEF 50%). To exclude the possible cardiac origin of the complaints, a coronary computed tomography angiography (CCTA) was performed, which revealed no significant coronary obstruction. However, the CCTA scan showed a mixed plaque located on the left anterior descending coronary artery (LAD), with 50% luminal stenosis and not all imaging criteria fulfilled for vulnerability (Figure 2). Given the cardiovascular risk factors and associated symptoms, a

**FIGURE 1.** 12-lead electrocardiogram at first presentation



**FIGURE 2.** CTCA showing a mixed plaque on the left anterior descending coronary artery, with 50% luminal stenosis

cycle ergometer test was performed, with negative result for ischemia. Therefore, long-term imaging follow-up and treatment with antiplatelet and lipid-lowering agents was recommended at patient discharge.

On the second presentation to the emergency department, the patient presented for typical chest pain started 2 days before, accompanied by palpitations, respiratory signs, and mild fever (38.5 °C) within the last 4 days. At the

clinical examination the patient had altered status, shortness of breath, was tachypneic, with persistent hypoxemia (PaO<sub>2</sub> 58 mmHg) despite ventilation with a high oxygen concentration mask (6 L/min), and had crackles in both lung fields without any signs of congestion. The 12-lead ECG identified atrial flutter with a heart rate of 160 bpm and diffuse ST-T segment modifications (Figure 3). Given the symptoms and hemodynamic instability at presentation, synchronized electrical cardioversion was performed in the ER department.

Laboratory tests revealed significantly high values of high-sensitivity troponin I (upward of 11,000 pg/mL, reference range: 0.0–24.0 pg/mL) and creatine kinase MB (CK-MB) (98 U/L, reference range: 0–23 U/L). Therefore, a non-ST-elevation myocardial infarction was suspected. Moreover, a biological inflammatory syndrome was revealed, with leu: 17.5 G/L and CRP value of 273 mg/L.

Due to the systematic suspicion of COVID-19 in subjects presenting respiratory failure associated with fever, a polymerase chain reaction test was performed on a naso-pharyngeal swab, which returned positive for SARS-CoV-2. In the epidemiological and clinical circumstances stated above, invasive coronary angiography was delayed, while dual antiplatelet therapy (acetylsalicylic acid and clopidogrel), anticoagulation with LMWH, lipid-lowering agent, and a proton-pump inhibitor were immediately initiated.

After the acute respiratory distress syndrome has been treated, the patient was readmitted to cardiology in order to perform invasive angiographic reassessment and to establish the therapeutic strategy to follow. In the third admission, coronary angiography revealed a LAD coronary lesion with 70% stenosis. Fractional flow reserve (FFR)



**FIGURE 3.** 12-lead electrocardiogram at second presentation

measurements were performed guiding elective coronary angioplasty with drug-eluting stent for the LAD lesion. The patient gave informed consent allowing the publication of his data, and the institution where the patient had been admitted, approved the publication of the case.

## DISCUSSIONS

Currently available clinical data report both the susceptibility and the outcomes of SARS-CoV-2 as being related with cardiovascular disease.<sup>5-9</sup> This case further demonstrates the significant cardiovascular morbidity potentially caused by COVID-19. In this case report, the occurrence of SARS-CoV-2 in a subject with previous nonobstructive coronary artery disease led to the development of concomitant acute coronary syndrome and severe arrhythmia, therefore several issues arise.

First, a nonvulnerable coronary plaque has progressed to aggravation in spite of optimal anti-ischemic therapy. Given the interoccurrence of respiratory infection with SARS-CoV-2, the hypothesis of viral implication in triggering an increase in the vulnerability of a coronary lesion, with consequent increased risk of myocardial infarction, could be taken into consideration. Therefore, patients infected with SARS-CoV-2 may present an increased risk for conversion from an asymptomatic, sub-clinical coronary artery disease to an unstable status, characterized by multiple vulnerable coronary plaques, as a consequence of the immunopathology associated with the viral infection.<sup>15</sup> Although currently there is no information regarding the exact trigger responsible for plaque instability, “Kounis syndrome”, known as a myocardial infarction produced by the massive activation process of inflammation in anaphylactic conditions, could exemplify the correlation between a tremendous inflammatory trigger, coronary plaque instability, and the atherothrombotic process.<sup>16</sup> If this hypothesis is confirmed, it could also mean that in COVID-19 patients further protective measures are needed for plaque stabilization, such as cardiovascular treatment, including antithrombotic prevention,<sup>17</sup> and possibly therapy aiming the immunologic pathways involved in the infection.<sup>18</sup>

Second, the question arises whether the severe arrhythmia, considered as an equivalent for the cardiac stress test, developed as a result of persistent severe hypoxemia, or was the myocardial ischemia responsible for triggering the arrhythmic event? Our up-to-date understanding of the influence of SARS-CoV-2 on the development of arrhythmic events remains to progress as new records arise.<sup>5</sup> Arrhythmic events are considered common manifestations of

SARS-CoV-2, as recent records report heart palpitations as the first symptom in SARS-CoV-2 subjects after the most common fever or cough.<sup>20</sup> Nevertheless, the precise involvement of COVID-19 in the development of cardiac arrhythmic events is unclear given that they can be initiated by myocardial injury or even systemic factors such as fever, sepsis, hypoxia, or electrolyte imbalances.<sup>13,21</sup> A series of mechanisms could be involved in the escalation of risk for cardiac arrhythmias during SARS-CoV-2 infection. Arrhythmic events are not simply caused by the direct influence of COVID-19 infection, but rather are likely to be the outcomes of a systemic disorder.<sup>22</sup> This could be a direct result of hypoxemia stemming from the primary involvement of lung parenchyma, myocardial inflammation, or an abnormal systemic immune response, or it could be secondary to myocardial ischemia, myocardial strain caused by pulmonary hypertension, electrolyte imbalance, intravascular volume overload, or side effects of medical therapies.

Third, from the point of view of arrhythmia management, besides the rhythm and rate control via medical therapies, another question arises. From an electrophysiological point of view, given the current global epidemiological circumstances, what would be the indications for ablation in a cardiovascular patient with a history of SARS-CoV-2 infection? And if the patient presents indication for ablation, when would the optimal timing be?

## CONCLUSIONS

COVID-19 interoccurrence in a cardiovascular patient with nonobstructive coronary artery disease triggered coronary plaque vulnerabilization, with subsequent development of an acute coronary syndrome. SARS-CoV-2 proved to be involved via direct viral tissue involvement and concomitant mechanisms derived from systemic illness in the development of a severe supraventricular arrhythmic event.

## CONFLICT OF INTEREST

Nothing to declare.

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