Imaging the event-prone coronary artery plaque

Andreas A. Giannopoulos, MD,[a] Dominik C. Benz, MD,[a] Christoph Gräni, MD,[a] and Ronny R. Buechel, MD[a]

[a] Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland

Received Jun 13, 2017; accepted Jun 19, 2017
doi:10.1007/s12350-017-0982-0

Acute coronary events, the dreaded manifestation of coronary atherosclerosis, remain one of the main contributors to mortality and disability in the developed world. The majority of those events are associated with atherosclerotic plaques-related thrombus formation following an acute disruption, that being rupture or erosion, of an event-prone lesion. These historically termed vulnerable plaques have been the target of numerous benchtop and clinical research endeavors, yet to date without solid results that would allow for early identification and potential treatment. Technological leaps in cardiovascular imaging have provided novel insights into the formation and role of the event-prone plaques. From intracoronary optical coherence tomography that has enhanced our understanding of the pathophysiological mechanisms of plaque disruption, over coronary computed tomography angiography that enables non-invasive serial plaque imaging, and positron emission tomography poised to be rapidly implemented into clinical practice to the budding field of plaque imaging with cardiac magnetic resonance, we summarize the invasive and non-invasive imaging modalities currently available in our armamentarium. Finally, the current status and potential future imaging directions are critically appraised. (J Nucl Cardiol 2019;26:141–53.)

Key Words: Coronary artery disease • acute coronary syndromes • computed tomography (CT) • PET/CT imaging • vulnerable atherosclerotic plaque

Abbreviations

TCFA	Thin cap fibroatheroma
OCT	Optical coherence tomography
ESS	Endothelial shear stress
IVUS	Intravascular ultrasound
NIRS	Near-infrared spectroscopy
CCTA	Coronary computed tomography angiography
ACS	Acute coronary syndrome
PET	Positron emission tomography
CMR	Cardiac magnetic resonance
CAD	Coronary artery disease

INTRODUCTION

The majority of acute cardiac events occur in the context of plaque-related thrombus formation.[1] Our improved understanding of the pathophysiology of coronary atherosclerosis together with our potentials to deliver targeted treatment of coronary plaques through percutaneous coronary interventions (PCI) has naturally led to tremendous efforts devoted to identifying what

Electronic supplementary material The online version of this article (doi:10.1007/s12350-017-0982-0) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

Reprint requests: Ronny R. Buechel, MD, Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Ramistrasse 100, 8091 Zurich, Switzerland; *ronny.buechel@usz.ch*

1071-3581/$34.00

Copyright © 2017 American Society of Nuclear Cardiology.

has been described as the event-prone or *vulnerable* plaque. To this end, our aim has shifted from identifying patients at risk for future events to *the particular lesion at risk* worth treating in order to prevent the occurrence of adverse events. However, and despite substantial research efforts paralleled by impressive technological advances in various fields of invasive and non-invasive imaging over the past years, when rationally observed, we have not yet come forth with the ideal imaging modality that can accurately pinpoint the vulnerable plaque with satisfying certainty. It may be argued that it is largely due to basic flaws in our current understanding of the pathophysiological processes that has led to the vulnerable plaque hypothesis, including the common negligence or at least imperfect integration of extrinsic contributors to vulnerability such as patient-related factors (e.g., rheological effects) or—even more important—the chronology of stabilizing and destabilizing intra-plaque processes. Such yet unresolved issues may render exact identification of the vulnerable plaque at any single given point in time extremely difficult and potentially misleading when seeing the forest for the tree. However, it is beyond the scope of the present review to discuss in depth the reasons for these shortcomings. By contrast, we aim to present an overview of the most relevant clinically available techniques to date and some very promising approaches for identification of what might be best described as the *event-prone* coronary plaque.

HISTOPATHOLOGICAL FEATURES AND BIOMECHANICAL MILIEU OF THE EVENT-PRONE PLAQUE

Distinct anatomical, rheological, and biomechanical factors are implicated in the formation of the vulnerable plaque as well in the initiation of an acute coronary event with thrombus formation that results in total or partial luminal occlusion. The event-prone coronary plaque has been historically defined from pathology studies as the precursor lesion of an acute coronary syndrome and described as the thin cap fibroatheroma (TCFA) which is characterized by a thin fibrous cap (measured thinner than 65 μm) over a large necrotic core (usually pertaining more than one-fourth of the plaque area), presence of macrophages and smooth muscle cells desolation.[2,3] These culprit plaques are most frequently observed in the proximal segments of the coronaries and are often non-stenotic lesions demonstrating positive outward remodeling.[3] Weakening of the fibrous cap is considered to be the critical point leading to plaque rupture or plaque erosion, and fibrous cap thickness has been shown to be the main plaque characteristic discriminating ruptured plaques from TCFA and fibroatheromas.[4,5]

The most frequent pathophysiological mechanism of an acute coronary event remains plaque rupture while the frequency of plaque erosion is considered to steadily increase.[6,7] Lifestyle modifications implemented into clinical medicine of today as well as the widespread use of lipid-lowering medication have altered the natural history of atherosclerosis and we evidence a shift in the underlying cause of thrombus formation. Contemporary data suggest further that only a small proportion of the TCFA rupture lead to coronary events thereby challenging the concept of the event-prone vulnerable plaque.[8] Yet current imaging modalities do not allow for the detection of plaque erosion (with the exception of optical coherence tomography, OCT) and our focus still remains on the identification of the event-prone TCFA lesions.

Elegant research studies have shown that local and global hemodynamic factors play a role in the formation of vulnerable plaques and in triggering the acute event. Among them, endothelial shear stress (ESS) and wall stress hold a prime position. ESS has been intensively studied and the proatherogenic role of low shear stress has been demonstrated in animal and human studies.[9–11] Blood perturbation and flow stagnancy induce a low ESS microenvironment that increases vascular inflammation, activates degrading mechanisms and promotes the transition of stable plaques to rupture-prone, TCFAs. Local wall stress is determined primarily by blood pressure, local tissue composition, and local geometry. Plaque rupture is considered to occur when the local wall stress exceeds the strength of the fibrous cap. A dynamic interplay between local ESS, local tissue stiffness, and local wall stress during plaque development and at the time of rupture/erosion is considered to be the event trigger.[9,12] With the advance of imaging modalities, including research approaches combining anatomical and physiological information,[13] the improvement of our knowledge on the biomechanical mechanisms implicated on plaque rupture is expected to shed light on this fine equilibrium and the loss of it.

INTRAVASCULAR CORONARY IMAGING

Moving on from the two-dimensional luminography that invasive coronary angiography provides, a number of intravascular imaging modalities have enabled enhanced visualization of the coronary lumen and wall

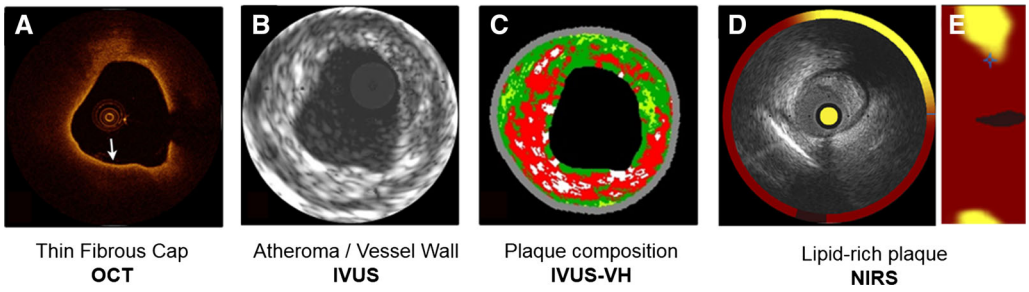


Figure 1. Intravascular Imaging. Intracoronary multimodality imaging of a vulnerable plaque using optical coherence tomography (**A**), gray-scale intravascular ultrasound (**B**), and intravascular ultrasound-virtual histology (**C**). Optical coherence tomography (**A**) shows a signal-rich layer and an underlying signal-poor region with high light attenuation, suggestive of lipid/necrotic core with an overlying fibrous cap with minimal thickness 40 μm (*arrow*), consistent with a thin-capped fibroatheroma. The substantial proportion of necrotic core (*red color*) with confluence at the luminal site for >30° is consistent with an intravascular ultrasound-virtual histology thin-caped fibroatheroma (**C**). In a different vulnerable plaque, intravascular ultrasound image (**D**) depicts a lesion containing a lipid pool, noted by the *yellow color* in the surrounding *circle* with the corresponding chemogram by near-infrared spectroscopy (**E**) Adapted with permission from Oxford University Press from Ref. 33.

over the last decades, delivering novel insights into the pathophysiological mechanisms of the atherosclerotic process and the event-prone plaque. Among those modalities, the most prominent and well investigated include OCT, intravascular ultrasound (IVUS), IVUS-Virtual Histology (IVUS-VH), and near-infrared spectroscopy (NIRS) (Figure 1).

Intracoronary OCT is a light-based imaging modality that generates high-resolution cross-sectional, histology-like images of the coronary lumen.[14,15] On account to the latter, OCT can provide superb and detailed characterization of the internal structures of the arterial wall[16] and has excellent accuracy for vulnerable plaque detection vs. histology, tethered however with a significant number of false-positive results.[17] Primarily due to light scattering phenomenon, the penetration depth (1.5 mm) of OCT is restricted, thereby not allowing for the estimation of plaque burden and plaque remodeling patterns as well as the geometrical distribution of the plaque. OCT is superior to other intravascular imaging modalities with regards to the identification of coronary plaques bearing the fingerprints of vulnerability and the sole one to visualize the thin fibrous cap.[18,19] The latter has been defined in several OCT studies with a thickness <65 μm (similar to histopathological findings),[16,20] whilst others have incorporated a threshold of <85 μm.[21] OCT can visualize the necrotic core and several other features such as macrophage accumulation,[22] neoangiogenesis,[23] plaque rupture, and/or erosion as well as microcalcifications.[16] Of note, the ability of OCT to evaluate coronary plaques is considered to be more useful in plaques at the later stages of atherosclerotic progression.[24] Although large-scale serial studies are lacking, a recent prospective OCT study has shown that the presence of lipid-rich plaques and importantly those with longer lipid length, wider arc, and greater luminal narrowing have predictive value for future cardiovascular events compared to non-culprit plaques.[25]

Being a robust invasive imaging technique that is well implemented into clinical practice, IVUS allows for accurate visualization of the vessel lumen and atherosclerotic plaque characteristics such as plaque remodeling, plaque burden, and the presence of lipid core and calcifications.[26] The lack in spatial resolution compared to OCT (~ 80-120 μm vs. ~ 10 μm for OCT) can be partially compensated with the aid of post-acquisition (off-line) spectral analysis of radiofrequency backscattered signals (RF-IVUS).[27] The latter provide additional information (to a certain extent) and permit for characterization of different tissue components with notable examples including IVUS Virtual Histology (IVUS-VH), the proprietary iMAP-IVUS (Boston Scientific, Santa Clara, CA, USA), and integrated backscatter IVUS (IB-IVUS). Studies that have prospectively assessed the natural history of coronary atherosclerosis have implemented IVUS and/or its daughter post-processing techniques as for example the PROSPECT study that incorporated, a signal radiofrequency analysis of the IVUS backscatter, establishing that IVUS can identify plaques with a risk of events at 3 years.[28] Similarly, in smaller single-center trials also using IVUS technologies,[29,30] IVUS-VH was able to identify plaques at increased risk of subsequent events.

NIRS integrates emission of infrared light into tissue and subsequently measures the proportion of the reflected light over a wide range of optical wavelength (800-2,500 nm).[31] Based on the differential absorption of light by organic molecules, it allows for the chemical characterization of biological tissues and can be used to assess lipid and protein content in atherosclerotic plaques. Detection of lipid core-baring plaques has been demonstrated vs histology; [32] however, NIRS cannot pinpoint TCFAs in the absence of anatomical information.[33] To this end, the ability of NIRS to identify fibroatheromas is modest but enhanced when combined with IVUS.[34] Prospective studies have shown an increased risk of major adverse events in patients with NIRS-detected plaques pertaining high lipid burden (i.e., a maximal lipid-core burden index greater than median values) at 1-year follow-up.[35] Moreover, NIRS was able to identify lipid-rich lesions with an increased likelihood of periprocedural myocardial infarction after stent implantation.[36]

Novel approaches include a combination of the above-mentioned imaging technologies and improvement in the spatial resolution of some of them. For example, catheters combining OCT and IVUS [37] or advancements in OCT technology such as micro-OCT [38] or post-processing advancements such as tissue signal attenuation OCT.[39] Lastly, hybrid imaging incorporating ESS or fractional flow reserve computationally can provide further insight into the event-prone lesions.[13,40] Several other experimental modalities have been proposed, such as intravascular elastography (palpography), intravascular magnetic resonance, thermography, and angioscopy, yet none of them have been extensively studied in large-scale clinical trials and are beyond the scope of the current review article.

Collectively, and although they have facilitated great advances in our understanding of the pathophysiological mechanisms of the plaques with characteristics of vulnerability, it is evident that none of the currently available intracoronary imaging modalities can assess at the same time point all the characteristics of the event-prone coronary plaques. Furthermore, intravascular assessment of a single vessel will inevitably detect only a minority of high-risk plaques[41] and multi-vessel imaging as well as serial imaging is rather cumbersome and certainly not clinically indicated in all patients undergoing catheterization. Further advancements in both interventional techniques as well as intravascular imaging modalities and image processing are necessary aiming to improve the easiness and the implementation of such techniques into the clinical practice and management of a patient with event-prone lesions.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

The accuracy of coronary computed tomography angiography (CCTA) to identify coronary stenosis is well established, and the evidence for its prognostic value is staggering.[42,43] Recent studies, however, suggest that the non-invasive evaluation of plaque morphology and composition might outperform traditional detection of luminal stenosis for predicting adverse cardiac events.[44–46] Several groups have demonstrated the added prognostic value of total plaque burden over clinical risk factors and conventional CT reading on a patient level.[47] On a lesion level, several morphological hallmarks have been described that may identify event-prone lesions: low CT attenuation plaques, napkin-ring sing, positive remodeling, and spotty calcifications.

In clinical routine, CCTA allows for reliable and accurate characterization of plaques into calcified (CPs) and non-calcified (NCPs) at minimal expenses of time and cost. Interestingly, a recent meta-analysis—including 18 studies that investigated the plaque composition of culprit lesion—underlined the importance of plaque characterization as only NCPs but not CPs were associated with acute coronary syndromes (ACS).[47] Since histopathological studies have identified large necrotic/lipid-rich cores as a key feature of TCFA, a further fragmentation of NCPs into its fibrous, lipid-rich, and necrotic components was evaluated based on CT attenuation. Indeed, when TCFAs (as identified by OCT) were compared to stable lesions, CT attenuation was significantly lower (35 Hounsfield units [HU] vs. 62 HU).[48] Moreover, plaques with mean CT attenuation below 30 HU were associated with ACS.[49] However, since CT attenuation is influenced by numerous factors (e.g., the contrast agent protocol, tube voltage, slice thickness, or iterative reconstruction algorithms),[50–52] the thresholds that define low attenuation plaques vary substantially. Therefore, a reliable differentiation between the individual components of NCP is not yet clinically feasible, although spatial resolution would be sufficient for its quantification (down to 230 μm in latest-generation CT scanners).[53] Novel approaches include evaluation of the effective atomic number assessed from single-source dual-energy CT for classifying NCP into soft and fibrous plaques with promising results.[54,55] An alternative, more qualitative feature to describe TCFA in CCTA is the napkin-ring sign. It is defined by a central area of low CT attenuation in close contact with the vessel lumen (i.e., necrotic core) that is surrounded by an outer rim of higher CT attenuation (i.e., fibrous plaque tissue). Although the napkin-ring sign is a strong predictor of future cardiac adverse

events [56] and has very high specificity (96%) to detect event-prone lesions, its sensitivity (44%) is rather disappointing.[48] Therefore, most studies have aimed to identify more sensitive morphological features such as positive remodeling,[57] a compensatory enlargement of the vessel wall at the site of coronary artery disease (CAD) to preserve the luminal area—providing a rationale why two-thirds of myocardial infarctions evolve from non-obstructive lesions.[58] Since CCTA allows assessment not only of the lumen but also of the outer vessel wall, the remodeling index can be calculated by dividing the vessel area at the plaque site by the average area of the proximal and distal reference site.[59] A remodeling index threshold of ≥1.1 is considered abnormal. Lesions with positive remodeling are not only associated with a larger amount of necrotic core and a higher prevalence of event-prone lesions [60] but more importantly performed best among other high-risk plaque features in identifying culprit lesions in ACS.[49] In a clinical follow-up study, plaques with positive remodeling and low CT attenuation resulted in an adverse cardiac event in 1 out of 5 patients.[46] Another, more controversial, high-risk feature is spotty calcifications (with CT attenuation above 130 HU and size smaller than 3 mm). Although the effect of calcifications on plaque instability is debated and most microcalcifications causing acute plaque rupture are too small to be detected by CCTA,[61,62] spotty calcifications have been associated with culprit lesions in ACS.[49] Nevertheless, the feature has not been integrated into the definition of a high-risk plaque (HRP; i.e., positive remodeling ≥1.1 and/or low CT attenuation plaques ≤30 HU) in the largest clinical follow-up study to date.[63] The latter confirmed a high rate of ACS in patients with plaques featuring high-risk morphology compared to patients without (Figure 2) and highlighted the significance of plaque progression in patients: Patients with high-risk plaques at baseline who had plaque progression at serial CCTA analysis had shown an increase of 27% in the ACS rate over patients with a high-risk plaque at baseline but without plaque progression who did not experience any ACS. As evidence is unfolding, patients with high-risk plaques might be considered for a follow-up CCTA scan to estimate whether the vulnerable lesion evolves or stabilizes over time.

In conclusion, CCTA offers a variety of morphological features that have been shown to identify patients and plaques at particular risk for future adverse events. Fortunately, this information can be easily obtained from routine examinations without the need of any change in routine protocols or additional scans (Figure 3), paving the way for the clinical application of CT-based plaque characterization either alone or in combination with other modalities as part of hybrid imaging.

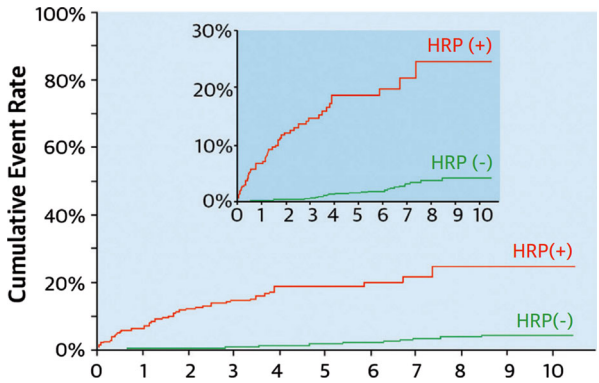


Figure 2. In the study of 3158 subjects, 294 (9.3%) had high-risk plaques (HRP, i.e., low attenuation <30 Hounsfield units and/or positive remodeling) and 2864 (90.7%) did not show HRP. Event rates were substantially higher for patients with HRP (*red*) as compared with those without HRP (*green*). On follow-up, 48 (16.3%) of the 294 HRP-carrying and 40 (1.4%) of 2864 non-HRP-carrying patients developed acute events. Reproduced with permission of Elsevier from Ref. 63.

POSITRON EMISSION TOMOGRAPHY

While morphological features serve as the basis of any attempt to identify event-prone lesion with intravascular imaging and CT, nuclear modalities such as positron emission computed tomography (PET) visualize active processes at the metabolic level, taking advantage of their superior sensitivity and inherent ability not only to detect picomolar tracer concentrations but also to provide quantification. In fact, virtually every aspect of atherosclerosis-related metabolic processes has been studied with PET. Among other aspects, detection and quantification of inflammation have repeatedly been used as an amenable target for PET imaging, and 18F-fluorodeoxyglucose (FDG) has been proven to be a tracer very well suited for imaging inflammation.[64] However, while FDG may be the most sensitive tracer, its specificity is hampered substantially and particularly in the setting of coronary artery assessment if physiological FDG uptake of the adjacent myocardium is not adequately suppressed by means of stringent patient preparation (i.e., a high-fat low-carbohydrate diet).[65] The FDG-PET signal indicates increased metabolic activity from macrophages [66,67] (Figure 4) which have been found to accumulate in event-prone plaques.[68]

FDG uptake seems highest during early stages of atherosclerosis, subsiding with increasing calcification.[69] Meanwhile, a number of studies have proven the validity of this concept and have shown high reproducibility.[70–73] Moreover, several studies have shown correlations between vascular FDG uptake and atherosclerotic risk factors [74,75] and several retrospective

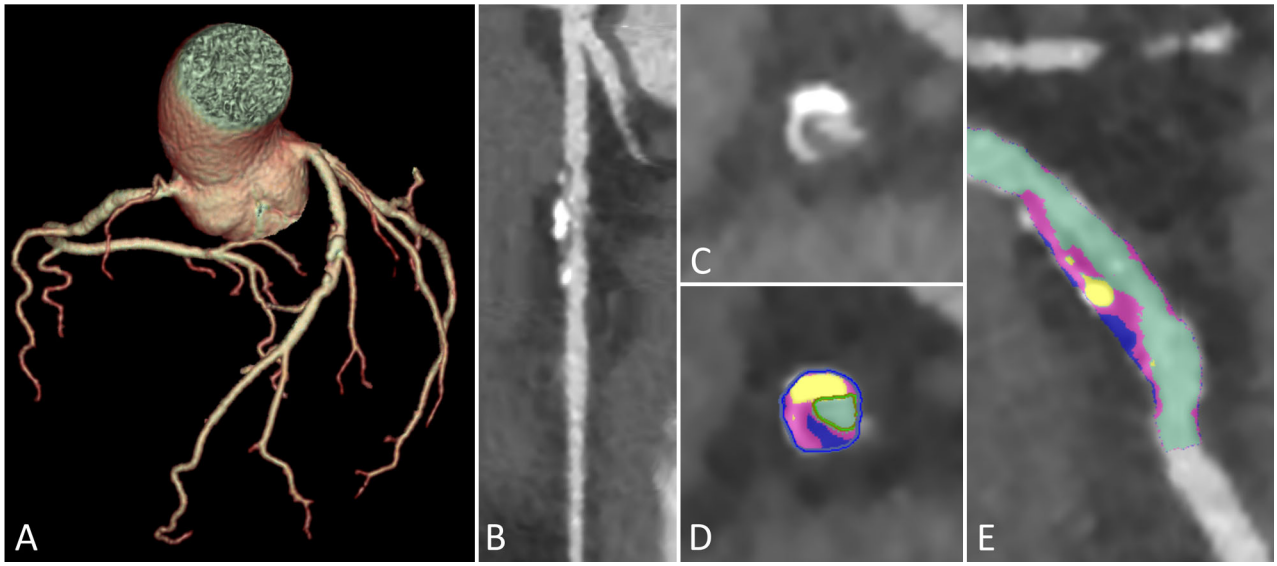


Figure 3. Routine CCTA of a 51-year-old female patient with atypical chest pain. Volume rendering (**A**) depicts a coronary lesion with a 60% stenosis in the proximal to mid left anterior descending artery with otherwise normal coronaries. Multiplanar curved (**B**) and cross-sectional reconstruction (**C**) show morphological features of a potentially event-prone plaque such as spotty calcifications, positive remodeling (remodeling index 1.7), while color-coded images (**D**, **E**) illustrate areas of low attenuation (*blue*, <30 Hounsfield units) adjacent to the vessel lumen (*green*), calcifications (*yellow* >130 Hounsfield units), and fibrous tissue (*purple*).

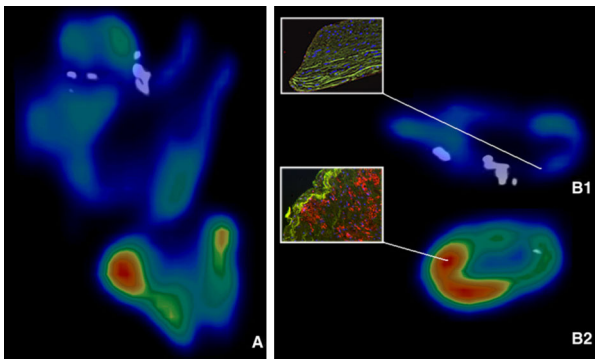
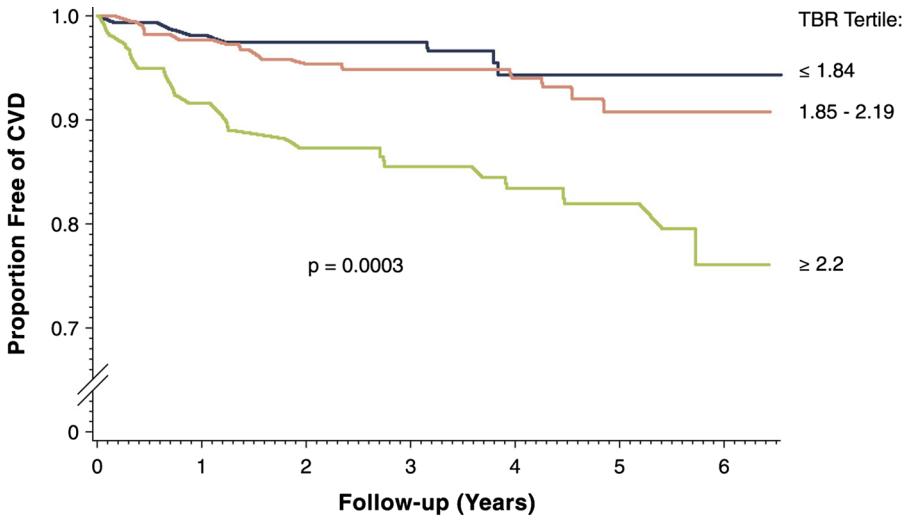


Figure 4. Ex-vivo FDG microPET/CT carotid plaque image in the coronal plane (**A**), transverse plane (**B**), and the corresponding histological results. The difference in FDG uptake in a transverse section of the cranial part of the plaque compared to the FDG uptake in a transverse section of the caudal part of the plaque (**B1**, **B2**). CD68 macrophage staining (*red*, *inlet* in **B2**) reflects inflammation in accordance with FDG uptake (**B2**). By contrast, no macrophages could be observed in the histological section that corresponds with **B1** (*inlet* in **B1**). Nuclei are depicted in *blue*. Reproduced with permission of Springer from Ref. 67.

analyses of PET imaging from patients with cancer suggest that arterial FDG uptake may constitute a useful prognostic biomarker for risk stratification.[76] Among them, Figueroa et al have demonstrated in 513 patients during a median follow-up period of 4.2 years that the degree of FDG signal intensity within an aortic lesion, as reflected by the target-to-background ratio (TBR), is positively associated with incident cardiovascular disease after adjustment for confounding clinical variables and seems inversely related to the time until incident cardiovascular disease (Figure 5).[77]

Moreover, FDG PET has been used to be a practical surrogate end point for clinical trials: Tahara et al have shown that FDG PET visualized aortic or carotid plaque inflammation and attenuation following treatment with simvastatin.[78] However, most of this evidence is obtained from studies using FDG PET for evaluation of large vessels such as the carotids (Figure 6) and the aorta, while studies aiming at coronary artery plaque assessment with FDG PET still remain scarce and limited to evaluation of the very proximal vessel segments.[73,79,80] Among them, the work by Singh et al is of particular interest as it has recently extended the use of FDG PET in a trial setting to the coronary level by evaluating the impact of atorvastatin on coronary plaque inflammation,[81] demonstrating the feasibility and clinical promise of this tracer for assessment of coronary plaque inflammation.

Aside from FDG, a number of other markers of inflammation, should be mentioned here although all are still in early phases of validation and feasibility assessment: 11C-PK11195, a selective ligand of the translocator protein (18 kDa) (TSPO) which is highly



Number at Risk:								Adjusted HR:
TBR Tertile 1:	167	160	149	120	75	36	10	1.0 (Referent)
TBR Tertile 2:	224	216	199	170	112	58	14	1.36 (0.55, 3.35)
TBR Tertile 3:	122	108	101	92	74	40	14	4.71 (1.98, 11.2)

Figure 5. The proportion of patients free of cardiovascular disease stratified by FDG arterial target-to-background ratio (TBR). Reproduced with permission of Elsevier from Ref. 77.

expressed by activated macrophages, has been shown to be able to distinguish between recently symptomatic and asymptomatic carotid plaques,[82] and 68Ga-DOTATATE uptake in the left anterior descending coronary artery, visualizing somatostatin receptors of subtype 2 (SSTR2) expressed by macrophages, has been shown to be higher in patients with prior cardiovascular events,[83] suggesting a role for this radiotracer as a potential biomarker for the identification of event-prone plaques.

A target that has recently been introduced in nuclear cardiac imaging is the cytokine receptor CXCR4 which has been known to play a role in promoting cancer growth and progression but has also been shown to be strongly expressed on the surface of inflamed cells, rendering it a potentially promising target for identifying event-prone plaques by PET, for example, using 68Ga-Pentixafor.[84] Currently, however, Pentixafor remains merely a potentially promising alternative to FDG as the concept of its utility for detection of inflammation in the vessel wall, namely the carotids, has been proven only in a very limited number of patients.

Contrary to the above-mentioned tracers, 18F-sodium fluoride (NaF) is not aimed at inflammation, but rather accumulates in regions of active micro-calcification which is commonly observed during the early stages of plaque formation. Dweck et al have shown that patients with increased coronary NaF uptake had higher rates of prior cardiovascular events, more often complained of angina, and had a higher cardiovascular risk.[85] In a subsequent clinical trial using FDG and NaF in 37 patients with myocardial infarction, the highest coronary NaF uptake was seen in the culprit plaque (Figure 7). By contrast, FDG uptake was commonly obscured by myocardial uptake despite a low-carbohydrate diet before undergoing FDG PET.[86]

While all the above-mentioned, relatively specific tracers with low background activity may be helpful in overcoming the problem of myocardial uptake that is inherent to the highly sensitive FDG, some other and potentially even more intricate technical limitations still apply. Among them, the issue of the small size of coronary plaques residing at the edge of the spatial resolution of PET (volume resolution of approx. 0.1 mL vs. a mean volume of 0.1 mL for significant plaques),[87] partial volume error, and the need for image acquisition over a relatively long time span resulting in cardiac and respiratory motion of the coronary tree remain perhaps the most challenging when it comes to PET imaging of the coronary arteries.

In conclusion, while all PET tracers mentioned here have been proven valuable tools for advancing our understanding of the many facets that may define an event-prone coronary lesion, FDG currently remains the most widely used and validated PET tracer in atherosclerosis imaging. However, a variety of technical problems remains to be resolved prior to widespread

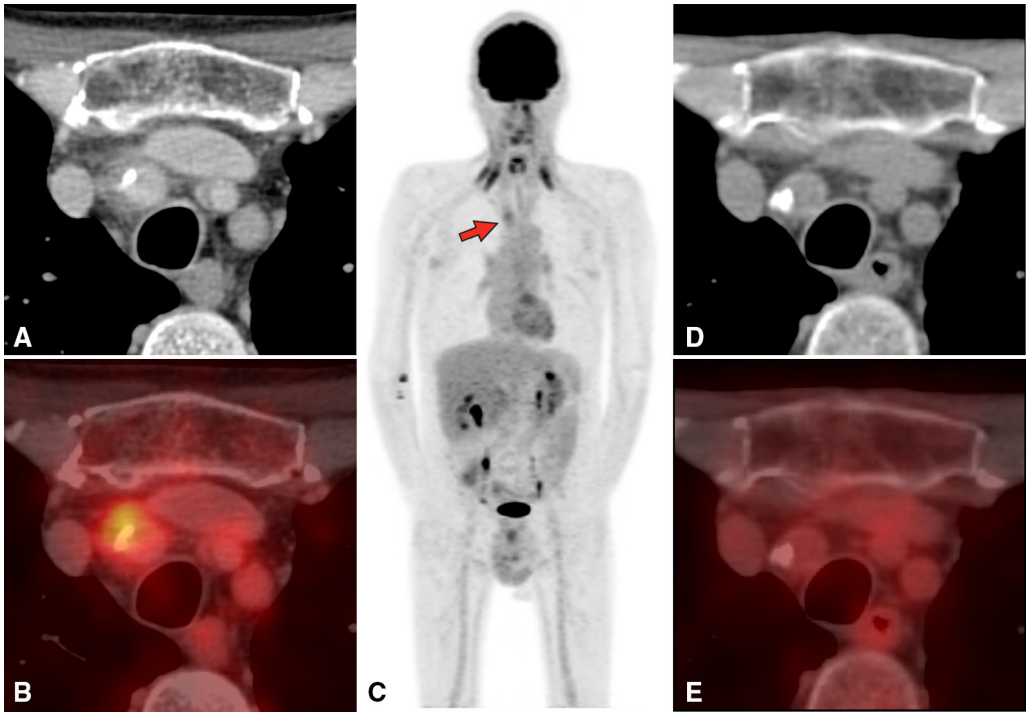


Figure 6. FDG PET/CT of a 59-year-old male patient depicts a plaque in the brachiocephalic artery (**A**) with focal FDG uptake (**B** and **C**) with a target-to-background ratio (TBR) of 2.1. Of note, however, in an FDG PET/CT study performed 11 months earlier the plaque (**D**) did not show any FDG uptake above background activity (**E**).

clinical application, particularly with regard to improvements in spatial resolution and cardiac and respiratory motion correction.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

The role for single-photon emission computed tomography (SPECT) in coronary artery plaque imaging is currently merely of experimental nature with only very limited literature on imaging of apoptosis using 99mTc-labeled Annexin 5,[88] or the detection of the proinflammatory molecule vascular cell adhesion molecule 1 [89] in animals. However, it may be hypothesized that the growing availability of high-resolution cadmium-zinc-telluride detector-based scanners may potentially revive the field in the near future.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance (CMR) imaging has become a clinical routine investigation tool in assessing a wide range of cardiac conditions including evaluation of significant CAD by use of perfusion imaging acquisition.[90] Visualizing coronary arteries by CMR, however, presents a number of challenges because of the small caliber of the vessels and the complex motion of

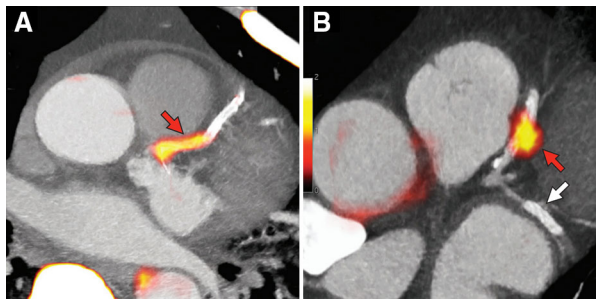


Figure 7. (**A**) NaF PET/CT of a patient with acute myocardial infarction with intense focal NaF uptake (tissue-to-background ratio 2.27) at the site of the culprit plaque (*red arrow*). (**B**) NaF PET/CT of a different patient with non-ST-segment elevation myocardial infarction with increased NaF uptake (tissue-to-background ratio 2.03) in the culprit lesion within the left anterior descending artery (*red arrow*). By contrast, the bystander non-culprit lesion within the left circumflex artery (*white arrow*) which was stented as well during the index admission did not show any increased NaF uptake. Modified and reproduced under the Creative Commons Attribution License (CC BY) from Ref. 86.

the coronary arteries with respect to scanning times and data acquisition.[91] Although CMR is able to image the presence of significant (>50%) stenosis, its diagnostic performance is disappointing compared to CCTA.[92] As the spatial resolution is directly proportional to scan time, the necessary high resolution for coronary imaging carries an inherent increased susceptibility to motion artifacts.[93] Therefore, using CMR for CAD plaque characterization in clinical routine has not been established. However, its potential has been proven in several experimental studies.[94] Key advantage features of CMR include high soft-tissue contrast enabling visualization and improved detection of high-risk plaque characteristics such as intra-plaque hemorrhage, thrombus, and positive remodeling.[95] Further, CMR is not affected by any blooming phenomenon that constitutes a common source of artifact in CCTA and might, in theory, allow for more accurate luminal and vessel wall assessment. In a promising experimental ex-vivo study, T1, T2, and ultrashort echo time by CMR were used to evaluate atherosclerotic plaques in fixed post-mortem human coronary arteries and proved to be highly sensitive and specific in the detection of calcification and lipid-rich necrotic cores with an excellent agreement with histological classification.[96] Finally, the introduction of macrophage-targeted superparamagnetic nanoparticles improved the capability of CMR to image macrophages as a specifically vascular target.[97] Morishige et al showed in an animal study that CMR was able to visualize disease activity by assessing vascular inflammation and therefore provide additional information to the anatomic description of CAD.[97]

In conclusion, CMR does not yet provide clinically relevant techniques for coronary artery plaque assessment, let alone vulnerable plaque detection, but it remains a promising tool with its inherent advantage of not exerting any radiation to the patient which may be important, particularly with chronology of event-prone plaques in mind that may eventually mandate serial follow-up scanning for assessment and monitoring of disease.

CONCLUSIONS AND FUTURE DIRECTIONS

Advanced invasive and non-invasive imaging modalities have undeniably proven to be valuable research tools that have certainly advanced our understanding of the various facets that define an event-prone coronary lesion. Admittedly, however, when it comes to clinical applicability no modality has yet proven true benefit nor is one close to being routinely used with this regard. Invasive imaging despite the high resolution and the insights it might provide cannot be routinely used or implemented into prevention guidelines due to their invasive nature. By contrast, CCTA and FDG PET imaging to date are the only non-invasive modalities that have been shown to be feasible for clinical application: high-risk morphological plaque features on routine CCTA can easily be appreciated and reported by any clinician as additional information in terms of risk stratification. Contrary to CCTA, the use of FDG PET for plaque assessment requires implementation of specific protocols including a stringent diet that mandates optimal patient cooperation and the same holds true for NaF PET. Nevertheless, alongside CCTA, it is PET imaging that currently remains the most promising technique for future clinical routine use. Lastly, although it is far from ready for clinical application in this setting, CMR with its inherent advantage of not being dependent radiation exertion, still deserves notion because it may be the preferable modality when it comes to serial imaging. This may be of importance against the background of an event-prone plaque hypothesis that is still in the process of (re-)formation, shifting from a focus on the state of a plaque, including rupture and erosion, towards a more integrative concept that incorporates extrinsic, that is patient-dependent, factors of vulnerability such as dynamic pressure and flow, and also the thrombotic state including concentrations of fibrinogen, endogenous inhibitors of fibrinolysis, and pro-coagulant microparticles.[98] While the presence of a plaque undeniably remains a conditio sine qua non, it is particularly the latter aspect that may be crucial for future attempts to identify the event-prone plaque because it implies that the factor time must be taken into account because neither the plaque nor the patient may necessarily be in a constant vulnerable/non-vulnerable state after a still-frame of the plaque characteristics has been captured. Hence, sequential imaging may be mandatory. The results by Motoyama et al to some extent corroborate this line of thinking by demonstrating that presence of plaque progression detected by serial CCTA is an independent predictor over the presence of high-risk plaque features.[63]

Furthermore, the advent of hybrid imaging in the form of PET/CCTA or—more recently—PET/CMR may pave the way for new applications, taking advantage of the synergistic information that is offered by combining morphological and metabolic information. In fact, several studies have used PET/MR for imaging atherosclerotic plaques in human carotid arteries,[99,100] demonstrating proof-of-concept for this approach (Figure 8). The potential of integrated molecular, functional, and anatomical imaging to expand our knowledge on the features that define the event-prone plaque and our understanding of the process that lead to its formation certainly merits further application of such hybrid imaging in a research setting. In theory, the alleged

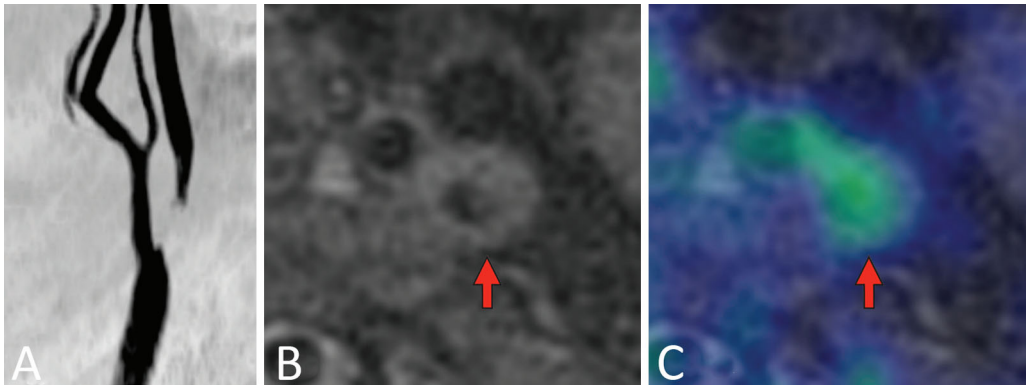


Figure 8. (**A**) MR angiography and (**B**) transverse MR imaging depict stenosis of the left internal carotid artery. PET/MR (**C**) shows increased FDG uptake in the internal carotid artery. Modified and reproduced under the Creative Commons Attribution License (CC BY) from Ripa RS, Kjær A. Imaging Atherosclerosis with Hybrid Positron Emission Tomography/Magnetic Resonance Imaging. Biomed Res Int. 2015; 914516.

added value from the synergy between PET and CCTA or PET and CMR may even justify its use in a clinical setting despite its higher cost and more complex management. However, a translation from experimental application to the clinical arena seems unlikely in the near future.

Any ongoing refinement or the combination of existing or novel imaging modalities is particularly welcome in the perspective of imaging's potential for early detection of event-prone plaques, enabling clinicians to improve risk stratification and thus paving the way for individualized therapy. However, potential implications with regard to optimal patient management based on such plaque characterization remain the foundation that has yet to be established for imaging of the event-prone plaque to claim its role in a real-world clinical setting.

Disclosure

The authors do not have any personal conflicts of interest to declare. However, the University Hospital Zurich holds a research agreement with GE Healthcare.

References

1. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017;376:2053-64.
2. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 2008;5:S2-S10.
3. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47:C13-C8.
4. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041-51.
5. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 2000;20:1262-75.
6. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004-13.
7. Libby P. Superficial erosion and the precision management of acute coronary syndromes: Not one-size-fits-all. Eur Heart J 2017;38:801-03.
8. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. Eur Heart J 2015;36:2984-87.
9. Kwak BR, Back M, Bochaton-Piallat ML, Caligiuri G, Daemen MJ, Davies PF, et al. Biomechanical factors in atherosclerosis: Mechanisms and clinical implications. Eur Heart J 2014;35:3013-20 20a-20d.
10. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: Molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379-93.
11. Koskinas KC, Chatzizisis YS, Baker AB, Edelman ER, Stone PH, Feldman CL. The role of low endothelial shear stress in the conversion of atherosclerotic lesions from stable to unstable plaque. Curr Opin Cardiol 2009;24:580-90.
12. Pedrigi RM, de Silva R, Bovens SM, Mehta VV, Petretto E, Krams R. Thin-cap fibroatheroma rupture is associated with a fine interplay of shear and wall stress. Arterioscler Thromb Vasc Biol 2014;34:2224-31.
13. Chatzizisis YS, Toutouzas K, Giannopoulos AA, Riga M, Antoniadis AP, Fujinom Y, et al. Association of global and local low endothelial shear stress with high-risk plaque using intracoronary 3D optical coherence tomography: Introduction of 'shear stress score'. Eur Heart J Cardiovasc Imaging 2016. doi: 10.1093/ehjci/jew134.
14. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. Circulation 2002;106:1640-45.
15. Giannopoulos A, Chatzizisis YS, Giannoglou GD. Optical coherence tomography: An arrow in our quiver. Expert Rev Cardiovasc Ther 2012;10:539-41.

16. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59:1058-72.
17. Fujii K, Hao H, Shibuya M, Imanaka T, Fukunaga M, Miki K, et al. Accuracy of OCT, grayscale IVUS, and their combination for the diagnosis of coronary TCFA: An ex vivo validation study. JACC Cardiovasc Imaging 2015;8:451-60.
18. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, et al. Expert review document part 2: Methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J 2012;33:2513-20.
19. Regar E, Schaar JA, Mont E, Virmani R, Serruys PW. Optical coherence tomography. Cardiovasc Radiat Med 2003;4:198-204.
20. Yonetsu T, Kakuta T, Lee T, Takahashi K, Kawaguchi N, Yamamoto G, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. Eur Heart J 2011;32:1251-59.
21. Prati F, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: Physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. Eur Heart J 2010;31:401-15.
22. Tearney GJ, Yabushita H, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Quantification of macrophage content in atherosclerotic plaques by optical coherence tomography. Circulation 2003;107:113-9.
23. Taruya A, Tanaka A, Nishiguchi T, Matsuo Y, Ozaki Y, Kashiwagi M, et al. Vasa vasorum restructuring in human atherosclerotic plaque vulnerability: A clinical optical coherence tomography study. J Am Coll Cardiol 2015;65:2469-77.
24. Otsuka F, Joner M, Prati F, Virmani R, Narula J. Clinical classification of plaque morphology in coronary disease. Nat Rev Cardiol 2014;11:379-89.
25. Xing L, Higuma T, Wang Z, Aguirre AD, Mizuno K, Takano M, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: A 4-year follow-up study. J Am Coll Cardiol 2017;69:2502-13.
26. Mintz GS, Garcia-Garcia HM, Nicholls SJ, Weissman NJ, Bruining N, Crowe T, et al. Clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound regression/progression studies. EuroIntervention 2011;6:1123-30.
27. Garcia-Garcia HM, Mintz GS, Lerman A, Vince DG, Margolis MP, van Es GA, et al. Tissue characterisation using intravascular radiofrequency data analysis: Recommendations for acquisition, analysis, interpretation and reporting. EuroIntervention 2009;5:177-89.
28. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35.
29. Calvert PA, Obaid DR, O'Sullivan M, Shapiro LM, McNab D, Densem CG, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: The VIVA (VH-IVUS in vulnerable atherosclerosis) study. JACC Cardiovasc Imaging 2011;4:894-901.
30. Cheng JM, Garcia-Garcia HM, de Boer SPM, Kardys I, Heo JH, Akkerhuis KM, et al. In vivo detection of high-risk coronary plaques by radiofrequency intravascular ultrasound and cardiovascular outcome: Results of the ATHEROREMO-IVUS study. Eur Heart J 2014;35:639-47.
31. Caplan JD, Waxman S, Nesto RW, Muller JE. Near-infrared spectroscopy for the detection of vulnerable coronary artery plaques. J Am Coll Cardiol 2006;47:C92-6.
32. Gardner CM, Tan H, Hull EL, Lisauskas JB, Sum ST, Meese TM, et al. Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. JACC Cardiovasc Imaging 2008;1:638-48.
33. Koskinas KC, Ughi GJ, Windecker S, Tearney GJ, Raber L. Intracoronary imaging of coronary atherosclerosis: Validation for diagnosis, prognosis and treatment. Eur Heart J 2016;37:524-35.
34. Kang S-J, Mintz GS, Pu J, Sum ST, Madden SP, Burke AP, et al. Combined IVUS and NIRS detection of fibroatheromas: Histopathological validation in human coronary arteries. JACC Cardiovasc Imaging 2015;8:184-94.
35. Oemrawsingh RM, Cheng JM, García-García HM, van Geuns R-J, de Boer SPM, Simsek C, et al. Near-infrared spectroscopy predicts cardiovascular outcome in patients with coronary artery disease. J Am Coll Cardiol 2014;64:2510-8.
36. Stone GW, Maehara A, Muller JE, Rizik DG, Shunk KA, Ben-Yehuda O, et al. Plaque characterization to inform the prediction and prevention of periprocedural myocardial infarction during percutaneous coronary intervention: The CANARY Trial (Coronary Assessment by Near-infrared of Atherosclerotic Rupture-prone Yellow). JACC Cardiovasc Interv 2015;8:927-36.
37. Li J, Li X, Mohar D, Raney A, Jing J, Zhang J, et al. Integrated IVUS-OCT for real-time imaging of coronary atherosclerosis. JACC Cardiovasc Imaging 2014;7:101-3.
38. Liu L, Gardecki JA, Nadkarni SK, Toussaint JD, Yagi Y, Bouma BE, et al. Imaging the subcellular structure of human coronary atherosclerosis using 1-μm resolution optical coherence tomography (μOCT). Nat Med 2011;17:1010-14.
39. Lee R, Foin N, Otsuka F, Wong P, Mari J-M, Joner M, et al. Intravascular assessment of arterial disease using compensated OCT in comparison with histology. JACC Cardiovasc Imaging 2016;9:321-2.
40. Toutouzas K, Chatzizisis YS, Riga M, Giannopoulos A, Antoniadis AP, Tu S. Accurate and reproducible reconstruction of coronary arteries and endothelial shear stress calculation using 3D OCT: Comparative study to 3D IVUS and 3D QCA. Atherosclerosis 2015;240:510-9.
41. Mintz GS. Predicting the vulnerable patient using intravascular imaging. J Am Coll Cardiol 2017;69:2514-6.
42. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: Results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724-32.
43. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 2011;58:849-60.
44. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings

for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041-51.
45. Ferencik M, Schlett CL, Ghoshhajra BB, Kriegel MF, Joshi SB, Maurovich-Horvat P, et al. A computed tomography-based coronary lesion score to predict acute coronary syndrome among patients with acute chest pain and significant coronary stenosis on coronary computed tomographic angiogram. Am J Cardiol 2012;110:183-9.
46. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49-57.
47. Thomsen C, Abdulla J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: A systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging 2016;17:120-9.
48. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovasc Imaging 2009;2:1412-9.
49. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol 2007;50:319-26.
50. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: Observations in an ex vivo model of coronary computed tomography angiography. Eur Radiol 2005;15:1426-31.
51. Achenbach S, Boehmer K, Pflederer T, Ropers D, Seltmann M, Lell M, et al. Influence of slice thickness and reconstruction kernel on the computed tomographic attenuation of coronary atherosclerotic plaque. J Cardiovasc Comput Tomogr 2010;4:110-5.
52. Benz DC, Grani C, Mikulicic F, Vontobel J, Fuchs TA, Possner M, et al. Adaptive statistical iterative reconstruction-V: Impact on image quality in ultralow-dose coronary computed tomography angiography. J Comput Assist Tomogr 2016;40:958-63.
53. Benz DC, Grani C, Hirt Moch B, Mikulicic F, Vontobel J, Fuchs TA, et al. Minimized radiation and contrast agent exposure for coronary computed tomography angiography: First clinical experience on a latest generation 256-slice scanner. Acad Radiol 2016;23:1008-14.
54. Nakajima S, Ito H, Mitsuhashi T, Kubo Y, Matsui K, Tanaka I. Clinical application of effective atomic number for classifying non-calcified coronary plaques by dual-energy computed tomography. Atherosclerosis 2017;261:138-43.
55. Shah NR, Cheezum MK, Motoyama S, Chatzizisis YS. Do we really need another individual coronary plaque characterization measurement? Atherosclerosis 2017;261:160-2.
56. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. JACC Cardiovasc Imaging 2013;6:448-57.
57. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-5.
58. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657-71.
59. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478-92.
60. Kröner ES, van Velzen JE, Boogers MJ, Siebelink HM, Schalij MJ, Kroft LJ, et al. Positive remodeling on coronary computed tomography as a marker for plaque vulnerability on virtual histology intravascular ultrasound. Am J Cardiol 2011;107:1725-9.
61. Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. Comprehensive plaque assessment by coronary CT angiography. Nat Rev Cardiol 2014;11:390-402.
62. Burke AP, Weber DK, Kolodgie FD, Farb A, Taylor AJ, Virmani R. Pathophysiology of calcium deposition in coronary arteries. Herz 2001;26:239-44.
63. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337-46.
64. Vallabhajosula S, Fuster V. Atherosclerosis: Imaging techniques and the evolving role of nuclear medicine. J Nucl Med 1997;38:1788-96.
65. Demeure F, Hanin FX, Bol A, Vincent MF, Pouleur AC, Gerber B, et al. A randomized trial on the optimization of 18F-FDG myocardial uptake suppression: Implications for vulnerable coronary plaque imaging. J Nucl Med 2014;55:1629-35.
66. Tawakol A, Migrino RQ, Hoffmann U, Abbara S, Houser S, Gewirtz H, et al. Noninvasive in vivo measurement of vascular inflammation with F-18 fluorodeoxyglucose positron emission tomography. J Nucl Cardiol 2005;12:294-301.
67. Masteling MG, Zeebregts CJ, Tio RA, Breek JC, Tietge UJ, de Boer JF, et al. High-resolution imaging of human atherosclerotic carotid plaques with micro 18F-FDG PET scanning exploring plaque vulnerability. J Nucl Cardiol 2011;18:1066-75.
68. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994;90:775-8.
69. Ogawa M, Nakamura S, Saito Y, Kosugi M, Magata Y. What can be seen by 18F-FDG PET in atherosclerosis imaging? The effect of foam cell formation on 18F-FDG uptake to macrophages in vitro. J Nucl Med 2012;53:55-8.
70. Dunphy MP, Freiman A, Larson SM, Strauss HW. Association of vascular 18F-FDG uptake with vascular calcification. J Nucl Med 2005;46:1278-84.
71. Rudd JH, Myers KS, Bansilal S, Machac J, Rafique A, Farkouh M, et al. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: Implications for atherosclerosis therapy trials. J Am Coll Cardiol 2007;50:892-6.
72. Rudd JH, Myers KS, Bansilal S, Machac J, Pinto CA, Tong C, et al. Atherosclerosis inflammation imaging with 18F-FDG PET: Carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. J Nucl Med 2008;49:871-8.
73. Wykrzykowska J, Lehman S, Williams G, Parker JA, Palmer MR, Varkey S, et al. Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. J Nucl Med 2009;50:563-8.
74. Rudd JH, Myers KS, Bansilal S, Machac J, Woodward M, Fuster V, et al. Relationships among regional arterial inflammation, calcification, risk factors, and biomarkers: A prospective fluorodeoxyglucose positron-emission tomography/computed tomography imaging study. Circ Cardiovasc Imaging 2009;2:107-15.
75. Kim TN, Kim S, Yang SJ, Yoo HJ, Seo JA, Kim SG, et al. Vascular inflammation in patients with impaired glucose

tolerance and type 2 diabetes: Analysis with 18F-fluorodeoxyglucose positron emission tomography. Circ Cardiovasc Imaging 2010;3:142-8.
76. Paulmier B, Duet M, Khayat R, Pierquet-Ghazzar N, Laissy JP, Maunoury C, et al. Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events. J Nucl Cardiol 2008;15:209-17.
77. Figueroa AL, Abdelbaky A, Truong QA, Corsini E, MacNabb MH, Lavender ZR, et al. Measurement of arterial activity on routine FDG PET/CT images improves prediction of risk of future CV events. JACC Cardiovasc Imaging 2013;6:1250-9.
78. Tahara N, Kai H, Ishibashi M, Nakaura H, Kaida H, Baba K, et al. Simvastatin attenuates plaque inflammation: Evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 2006;48:1825-31.
79. Cheng VY, Slomka PJ, Le Meunier L, Tamarappoo BK, Nakazato R, Dey D, et al. Coronary arterial 18F-FDG uptake by fusion of PET and coronary CT angiography at sites of percutaneous stenting for acute myocardial infarction and stable coronary artery disease. J Nucl Med 2012;53:575-83.
80. Alexanderson E, Slomka P, Cheng V, Meave A, Saldana Y, Garcia-Rojas L, et al. Fusion of positron emission tomography and coronary computed tomographic angiography identifies fluorine 18 fluorodeoxyglucose uptake in the left main coronary artery soft plaque. J Nucl Cardiol 2008;15:841-3.
81. Singh P, Emami H, Subramanian S, Maurovich-Horvat P, Marincheva-Savcheva G, Medina HM. Coronary plaque morphology and the anti-inflammatory impact of atorvastatin: A multicenter 18F-fluorodeoxyglucose positron emission tomographic/computed tomographic study. Circ Cardiovasc Imaging 2016;9:e004195.
82. Gaemperli O, Shalhoub J, Owen DR, Lamare F, Johansson S, Fouladi N, et al. Imaging intraplaque inflammation in carotid atherosclerosis with 11C-PK11195 positron emission tomography/computed tomography. Eur Heart J 2012;33:1902-10.
83. Rominger A, Saam T, Vogl E, Ubleis C, la Fougere C, Forster S, et al. In vivo imaging of macrophage activity in the coronary arteries using 68Ga-DOTATATE PET/CT: Correlation with coronary calcium burden and risk factors. J Nucl Med 2010;51:193-7.
84. Hyafil F, Pelisek J, Laitinen I, Schottelius M, Mohring M, Doring Y, et al. Imaging the Cytokine Receptor CXCR4 in atherosclerotic plaques with the radiotracer 68Ga-pentixafor for PET. J Nucl Med 2017;58:499-506.
85. Dweck MR, Chow MW, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial 18F-sodium fluoride uptake: A novel marker of plaque biology. J Am Coll Cardiol 2012;59:1539-48.
86. Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: A prospective clinical trial. Lancet 2014;383:705-13.
87. Otsuka M, Bruining N, Van Pelt NC, Mollet NR, Ligthart JM, Vourvouri E, et al. Quantification of coronary plaque by 64-slice computed tomography: A comparison with quantitative intracoronary ultrasound. Invest Radiol 2008;43:314-21.
88. Johnson LL, Schofield L, Donahay T, Narula N, Narula J. 99mTc-annexin V imaging for in vivo detection of atherosclerotic lesions in porcine coronary arteries. J Nucl Med 2005;46:1186-93.
89. Liu C, Zhang X, Song Y, Wang Y, Zhang F, Zhang Y, et al. SPECT and fluorescence imaging of vulnerable atherosclerotic plaque with a vascular cell adhesion molecule 1 single-chain antibody fragment. Atherosclerosis 2016;254:263-70.
90. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): A prospective trial. Lancet 2012;379:453-60.
91. Sharif F, Lohan DG, Wijns W. Non-invasive detection of vulnerable coronary plaque. World J Cardiol 2011;3:219-29.
92. Hamdan A, Asbach P, Wellnhofer E, Klein C, Gebker R, Kelle S, et al. A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis. JACC Cardiovasc Imaging 2011;4:50-61.
93. Scott AD, Keegan J, Firmin DN. Motion in cardiovascular MR imaging. Radiology 2009;250:331-51.
94. Kramer CM, Narula J. Atherosclerotic plaque imaging: The last frontier for cardiac magnetic resonance. JACC Cardiovasc Imaging 2009;2:916-8.
95. Larose E, Yeghiazarians Y, Libby P, Yucel EK, Aikawa M, Kacher DF, et al. Characterization of human atherosclerotic plaques by intravascular magnetic resonance imaging. Circulation 2005;112:2324-31.
96. Karolyi M, Seifarth H, Liew G, Schlett CL, Maurovich-Horvat P, Stolzmann P, et al. Classification of coronary atherosclerotic plaques ex vivo with T1, T2, and ultrashort echo time CMR. JACC Cardiovasc Imaging 2013;6:466-74.
97. Morishige K, Kacher DF, Libby P, Josephson L, Ganz P, Weissleder R, et al. High-resolution magnetic resonance imaging enhanced with superparamagnetic nanoparticles measures macrophage burden in atherosclerosis. Circulation 2010;122:1707-15.
98. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. Eur Heart J 2015;36:2984-7.
99. Saito H, Kuroda S, Hirata K, Magota K, Shiga T, Tamaki N, et al. Validity of dual MRI and F-FDG PET imaging in predicting vulnerable and inflamed carotid plaque. Cerebrovasc Dis 2013;35:370-7.
100. Silvera SS, Aidi HE, Rudd JH, Mani V, Yang L, Farkouh M, et al. Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries. Atherosclerosis 2009;207:139-43.