Curr Cardiol Rep (2014) 16:520
DOI 10.1007/s11886-014-0520-5

Recent Advances in Visualizing Vulnerable Plaque: Focus on Noninvasive Molecular Imaging

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Published online: 25 July 2014

Abstract Traditional imaging methods in atherosclerosis have focused primarily on anatomic information. Imaging approaches that visualize molecular targets rather than anatomic structures may emphasize biologic aspects of atherosclerosis. Molecular imaging of atherosclerotic lesions has become a crucial experimental tool and is now emerging in the clinical arena. In this review, we briefly highlight the rationale and fundamental principles of molecular imaging. We then discuss the promising imaging modalities, along with their potential limitations, and the molecular targets being investigated in experimental research. Finally, we summarize the most important clinical studies recently performed in humans.

Keywords Atherosclerosis · Vulnerable plaque · Molecular imaging · Nuclear molecular imaging · CT · MRI

Introduction

Despite a considerable decrease during the past few decades, acute cardiovascular events remain the leading cause of mortality and morbidity in the United States and Western Europe [1]. Atherosclerosis and its complications are responsible for most of these events. Until now, identifying patients at high risk for an acute cardiovascular event relied mainly on risk factors and biomarker measurement [2, 3]. Although relatively effective in large cohorts of subjects, clinical risk factors and biomarkers may underestimate the future risk of an acute event at the individual level, especially in young patients [4, 5].

Traditionally, imaging of atherosclerosis has focused on anatomically or physiologically based features at advanced stages of disease, either by directly revealing luminal stenosis or by evaluating the functional consequences of the stenosis. However, most plaques that cause acute coronary syndromes may originate from non-flow-limiting lesions and may be related to thrombosis and obstruction [6]. Autopsy studies indicate that rupture of the atherosclerotic plaque and subsequent thrombosis account for approximately 70 % of fatal acute myocardial infarctions and/or sudden coronary deaths [7]. Less often, acute coronary syndromes may be caused by plaque erosion or calcified nodule with a sudden narrowing of the lumen [7]. To date, clinical risk factors and available biomarkers have been disappointing in predicting plaques leading to acute events. Therefore, better modalities clearly are needed to detect "vulnerable atherosclerotic plaques" (i.e., those likely to cause an acute vascular event).

During the past decade, development of new tools to identify vulnerable plaques has received much attention. Several intravascular imaging modalities, such as intravascular ultrasound, optical coherence tomography, and near-infrared spectroscopy, currently are being evaluated as potential tools to detect vulnerable plaque [8]. However, the invasive nature of these techniques limit their use to patients undergoing invasive coronary angiography and are not suitable for identifying patients who are asymptomatic but at high risk for future acute vascular events.

This article is part of the Topical Collection on *Lipid Abnormalities and Cardiovascular Prevention*

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On the other hand, in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, a combination of a higher baseline plaque burden, a smaller lumen, and the presence of an intravascular ultrasound–derived thin-cap fibroatheroma were the imaging predictors of subsequent cardiovascular events, albeit in less than 20 % of the patients [9].

The discord among the frequency of observed plaque rupture, symptoms, and clinical events may be explained by silent plaque ruptures and healing (with lesion growth), a process that may be phasic rather than linear and therefore difficult to predict [10]. The subclinical nature of this process suggests that current attempts to prospectively identify specific morphologic features of plaque segments that predispose to future rupture, erosion, and clinical events remain a difficult challenge.

Molecular imaging aims to look beyond anatomy by allowing visualization and measurement of biologic processes at the molecular and cellular levels. It therefore has emerged as a novel tool to identify biologic aspects of atherosclerotic plaques in addition to anatomic imaging.

In this review, we focus on noninvasive molecular imaging of atherosclerosis. We first discuss the fundamental principles of molecular imaging and the promising imaging modalities for investigating high-risk atherosclerosis. Next, we highlight the key biologic processes and molecular targets currently being investigated in preclinical research. We also summarize some recent clinical studies based on molecular imaging. Finally, we address the potential limitations and challenges in translating this emerging field of research into clinical practice.

General Principles of Molecular Imaging

Molecular imaging requires three components (Fig. 1): 1) the selection of an appropriate molecular or cellular target, 2) an imaging probe that recognizes the molecular target, and 3) the corresponding imaging modality.

Promising targets include those that are involved in the pathobiologic process of atherosclerosis and have well-known clinical importance for the detection of high-risk atherosclerotic plaques. These targets are reviewed in a separate section.

The imaging probe typically consists of a high-affinity and -specificity ligand for a target attached to a signal-generating moiety. It also should have favorable kinetics to allow sensitive and fast detection. These ligands should be conjugated easily with a signal-generating moiety, such as radioisotopes for radionuclide imaging, paramagnetic and superparamagnetic agents for magnetic resonance imaging (MRI), microbubbles for ultrasound imaging, and fluorochromes for near-infrared fluorescence (NIRF) imaging. As imaging probes, monoclonal antibodies have been used against diverse targets in experimental studies. Although specific, their larger size does not allow for high target-to-background ratios, because they remain in the circulation for a long time. Antibodies have limitations related to their size, immunogenicity, and production difficulties; therefore, the use of smaller molecules, such as nanobodies, peptides or synthetic structures is preferred.

Imaging Modalities

Nuclear Imaging Modalities

Nuclear imaging techniques, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are the modalities of choice for studying biologic processes and molecular imaging. The main advantage of nuclear imaging is its high sensitivity in detecting molecular targets within the picomolar range, which makes it possible to use low doses of contrast agents. PET is more appropriate for clinical use because of its superior spatial resolution compared with SPECT (3–5 mm vs. 10–15 mm) and more accurate quantification. This quality makes it particularly suitable for molecular imaging in atherosclerosis, in which targets commonly are small and sparse. However, these modalities have relatively poor spatial resolution and provide limited information about anatomic details. The use of hybrid imaging with either computed tomography (CT) or MRI overcomes this problem and offers the opportunity to combine targeted PET images with high-resolution anatomic images.

The availability and ongoing development of new radiotracers will further expand the feasibility of this imaging modality and its use in clinical practice. Nevertheless, a major limitation still is the repeated radiation exposure, which probably will limit its use in asymptomatic patients with atherosclerotic risk factors. The cost, availability, and stability of these agents in a short period are other potential drawbacks.

MRI

MRI has the advantages of providing a high degree of spatial resolution and soft tissue contrast with excellent structural information and a lack of ionizing radiation. However, for targeted molecular imaging applications, MRI has a lower sensitivity than nuclear imaging. Therefore, molecular MRI often requires the delivery of relatively high doses of target-specific contrast agents. The most commonly used classes of agents are gadolinium chelates (which increase the signal on T1-weighted images) and superparamagnetic iron oxide nanoparticles (which reduce the signal on T2-weighted images), including ultrasmall (USPIO) and micron-sized particles.

Imaging of coronary arteries with magnetic resonance remains more difficult and challenging because of their small size and continuous motion during data acquisition.

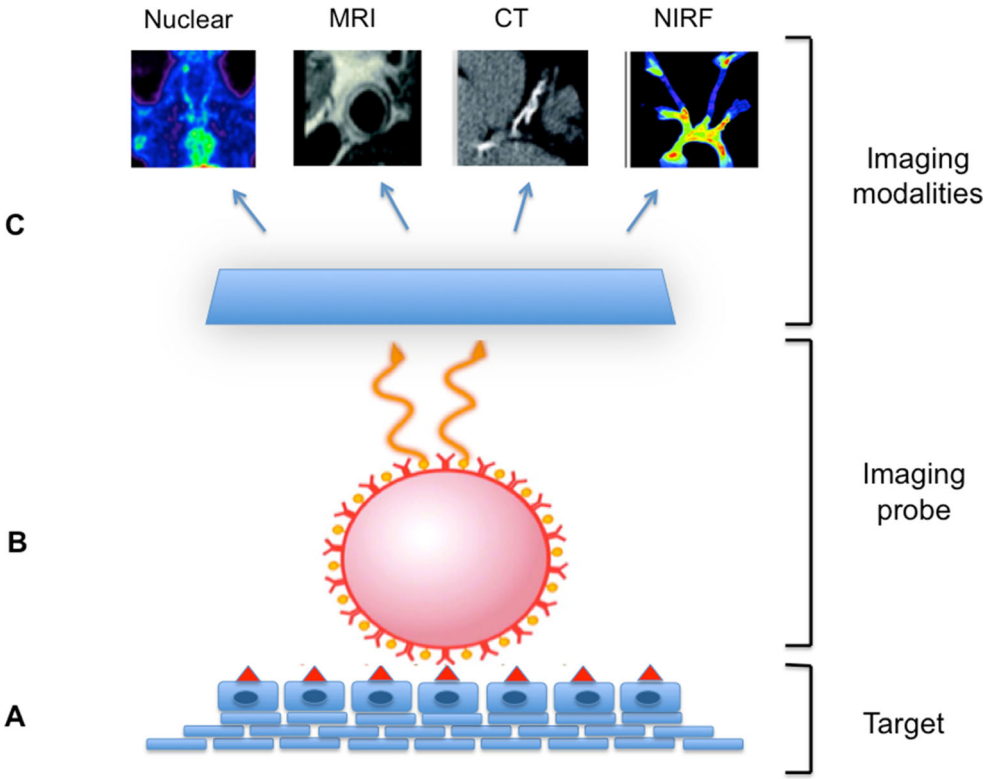

Fig. 1 Components required for molecular imaging. **a** Selection of an appropriate molecular or cellular target. **b** Imaging probe consisting of an affinity ligand recognizing the target conjugated with a signal-generating moiety. **c** The corresponding imaging modality for signal detection

Therefore, MRI has been used more often for studying large arteries, such as carotid arteries.

CT

CT is an anatomic imaging modality with high spatial and temporal resolution. It has an increasing clinical role as a tool for noninvasive characterization of coronary arteries, especially for identifying and characterizing plaque calcifications [11]. With the development of novel contrast agents, such as iodinated or gold nanoparticles, which selectively accumulate into macrophages, CT is showing promising preclinical results in the context of molecular imaging of intraplaque inflammation [12]. Like MRI, CT has low sensitivity for detecting contrast agents at the target level (compared with nuclear techniques); therefore, it requires high concentrations of these agents to generate enough contrast at the site of interest. Repeated radiation exposure and the need for high concentrations of contrast agents (with possible toxicity) remain critical limitations of molecular CT imaging.

Ultrasound

Ultrasound offers relatively low-resolution structural data but has the great advantages of being widely available, safe, inexpensive, and portable. Contrast-enhanced ultrasound-based molecular imaging is feasible by attaching the affinity ligand onto acoustically active gas-filled microbubbles [13]. Because of their size, microbubbles are constrained to the intravascular space, thereby limiting the selection of molecular targets to the endothelium.

Optical Imaging

Among the optical imaging techniques, NIRF is of particular interest for molecular imaging. It is performed by delivery of a NIRF probe that interacts with the target. The NIRF probe is excited at a given light wavelength and emits light at another wavelength. The light emission is detected by the NIRF imaging modality. At the NIRF wavelength range (650–900 nm), light can penetrate several centimeters into tissue, and tissue autofluorescence is minimal. NIRF molecular imaging offers high-sensitivity detection of fluorescent tracers and uses high-sensitivity agents that can be incorporated into small molecules without altering function or accessibility. Its main limitation is the low-depth penetration of light through tissues, and noninvasive NIRF imaging probably will remain in preclinical research. However, invasive (catheter-based) approaches are being developed [14].

Targets for Molecular Imaging in Atherosclerosis/Preclinical Research

Several biologic processes have been implicated in the development of plaque rupture, such as inflammation, proteolysis,

apoptosis, and neovascularization of the atherosclerotic plaque [15, 16] (Fig. 2).

Inflammation

Chemotaxis

During the course of atherosclerotic plaque formation, chemokines play a critical role by attracting inflammatory cells to the lesion and consequently keeping the inflammatory process progressing. Monocyte chemoattractant protein 1 (MCP-1) is a chemotactic agent that binds to the receptors on the cellular membrane of monocytes/macrophages, attracting these inflammatory cells to atherosclerotic plaque. Radiolabeled MCP-1 peptide (^{125}I and ^{99m}Tc) therefore has been used as a potential molecular imaging strategy in atherosclerotic plaque [17, 18].

Adhesion Molecules

Activation of endothelial cells by local oxidative and enzymatic modifications of low-density lipoprotein (LDL) particles induces expression of leukocyte adhesion molecules that mediate recruitment of circulating leukocytes to evolving plaques. The attachment of inflammatory cells to activated endothelium is mediated by several cellular adhesion molecules, such as P-selectin, E-selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 (VCAM-1). Among these, VCAM-1 plays a central role in the recruitment of inflammatory cells. In advanced lesions, VCAM-1 also is expressed at the level of neovessels, indicating ongoing inflammation within the plaque. It also serves as a marker of neovascularization. Consequently, it has been studied most preferentially for the molecular imaging of plaque. Several imaging modalities, such as ultrasound [19–21], near-infrared

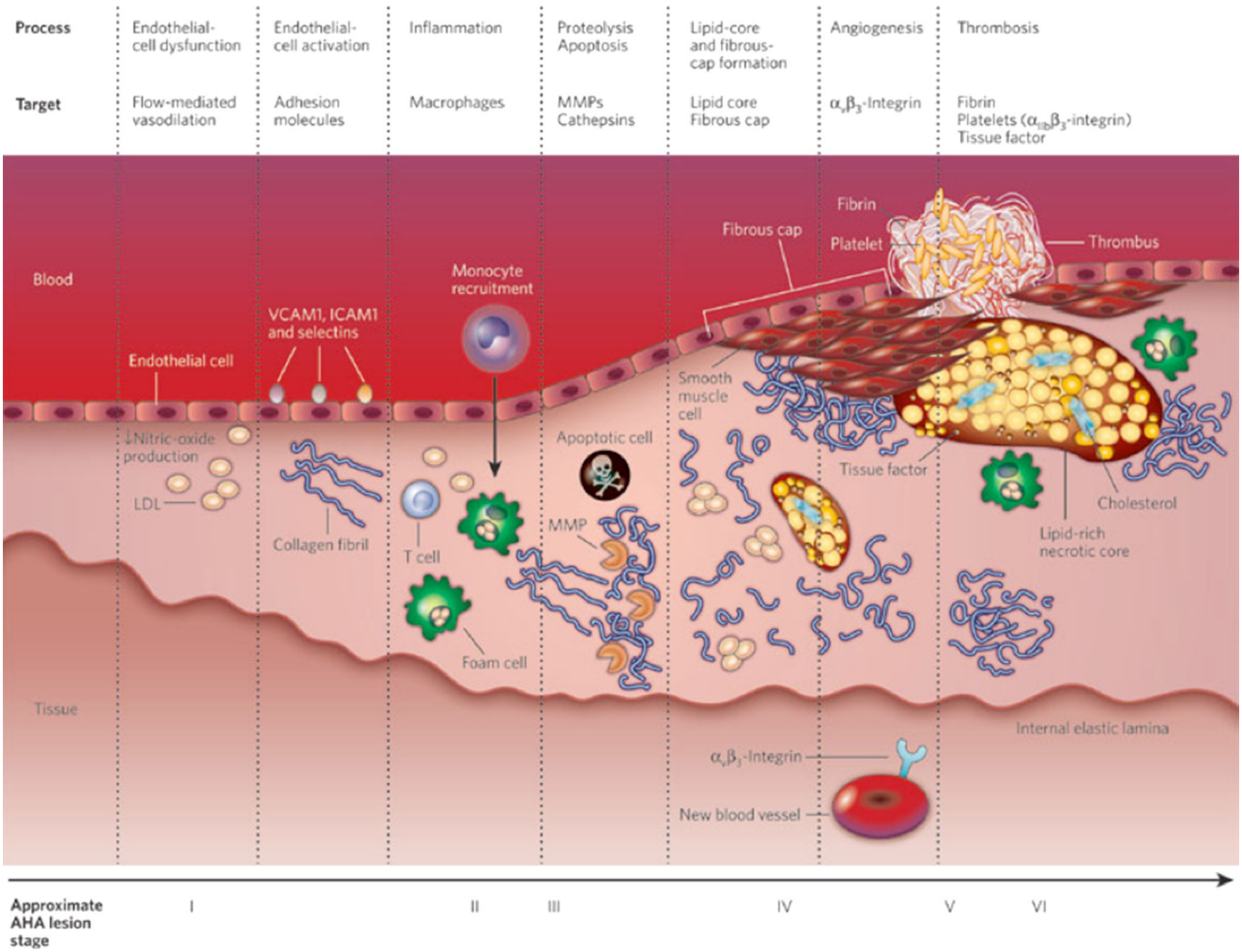

Fig. 2 The progression of an atherosclerotic lesion is shown in a simplified form, developing from a normal blood vessel (far left) to a vessel with an atherosclerotic plaque and superimposed thrombus (far right). Potential targets for molecular imaging at each stage are also listed. AHA, American Heart Association; ICAM1, intercellular adhesion molecule 1; LDL, low-density lipoprotein; MMP, matrix-metalloproteinase; VCAM1, vascular cell-adhesion molecule 1. (Reproduced with permission from: Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. Nature. 2008;451(7181):953-7. doi:10.1038/nature06803) [16]

[22], nuclear [21, 23], and magnetic resonance [24, 25], have been used to detect VCAM-1 expression.

Macrophages

Monocyte-derived macrophages, key effector inflammatory cells in atherosclerosis [26], produce cytokines, reactive oxygen species, and destabilizing proteases [26]. Macrophages are critically involved not only in atheroma initiation and propagation but also in plaque rupture, and they demarcate high-risk plaques [7]. Therefore, imaging of macrophages is an appealing approach to detect inflammation in plaques prone to clinical complications [27].

One strategy to visualize macrophages is based on their phagocytic activity. Nanoparticles such as dextran-coated magnetic and USPIO nanoparticles have been investigated for MRI-based molecular imaging [28, 29]. These nanoparticles accumulate rapidly in macrophages of atherosclerotic plaque. In addition to MRI, crystalline iodinated nanoparticles (N117) have been used for molecular CT imaging [30]. To combine the high spectral resolution of MRI with the high sensitivity of nuclear techniques and NIRF imaging, trimodality nanoparticles also have been developed for PET, MRI, and NIRF imaging [31].

Another strategy for imaging plaque macrophages is detection of metabolic activity in the plaque by fluorine-18–radiolabeled fluorodeoxyglucose (18F-FDG). FDG already is established in clinical practice for imaging tumors and assessing myocardial viability. Therefore, because this substance is readily available, its use is an attractive approach, especially for imaging carotid atherosclerotic lesions, and several FDG-based studies have been carried out [32–34]. The myocardial uptake of 18F-FDG remains a major limitation in imaging coronary arteries; therefore, other tracers that have less myocardial uptake, such as 18F-labeled fluorocholine (FCH), also have been investigated [35]. FCH is taken up by the cell via a choline-specific transporter, undergoes phosphorylation by choline kinase, and then is incorporated into the cell membrane. Hence, FCH uptake also may reveal metabolic activity. However, with this metabolic approach, distinguishing among the different subtypes of macrophages is not possible and is rather unspecific. Because each of these subpopulations plays a different role in the atherosclerotic process, more targeted approaches are being investigated [36].

Modified LDL plays a critical role in atherogenesis [37] and is internalized by macrophages via scavenger receptors, including CD36 and lectin-like oxidized LDL receptor 1 (LOX-1) [38]. Targeted imaging of these scavenger receptors has been used as an alternative approach for imaging macrophages. Here too, gadolinium nanoparticles targeting scavenger receptors have provided contrast enhancement in experimental atherosclerosis [39]. Other tracers visualizing LOX-1 expression by SPECT [40] or SPECT/CT and MRI [41] also have been described.

Apoptosis

In advancing atheroma, lipid-laden macrophages may die as the result of a high rate of apoptosis, expanding the formation of a "necrotic," lipid-rich core, which demarcates plaques at risk for future complications [7]. During apoptosis, the cell membrane expresses phosphatidylserine. Annexin A5 is a protein that binds with high affinity to phosphatidylserine. Accordingly, radiolabeled annexin A5 (^{123}I, ^{124}I, ^{99m}Tc, and ^{18}F) [42] has been used as a strategy to image apoptotic cells in atherosclerosis.

Proteolysis

In response to ongoing inflammatory stimuli, macrophage foam cells produce proteinases, such as matrix metalloproteinases (MMPs), cysteine protease, and cathepsin K, that can digest extracellular matrix proteins and may contribute to the degradation of the protective fibrous cap of atherosclerotic plaques [37]. Activation of these enzymes represents an attractive target for molecular imaging. An elegant approach has been developed to sense proteinase activity by using activatable fluorescent probes that are quenched in their uncleaved form and become strongly fluorescent after proteolysis. Several activatable near-infrared probes have been designed to detect cysteine protease [43], MMP [44], and cathepsin K [45] activity by NIRF imaging. Another approach for detecting MMP activity is the use of MMP inhibitors as a targeting moiety conjugated to gadolinium chelates [46] or radioisotopes [47, 48].

Neovessel Formation and Intraplaque Hemorrhage

In atherosclerosis, because of arterial wall thickening, the passive diffusion of oxygen to the deeper layers of the wall becomes inefficient. The resulting hypoxia stimulates the growth of neovessels into the arterial wall from the vasa vasorum to meet metabolic demands. These neovessels are fragile and prone to leakage and therefore may promote intraplaque hemorrhage, which intensifies the inflammatory process and further destabilizes the atheroma. In particular, integrin $\alpha v\beta 3$ has been recognized as a key mediator of angiogenesis and represents an important target to identify neovessel formation [49]. Cyclic peptides containing the Arg-Gly-Asp (RGD) attachment site have been conjugated to imaging moieties for magnetic resonance [50], PET [51], and optical imaging [52]. These tracers have detected plaque burden efficiently in animal models of atherosclerosis.

Thrombus Formation

Plaque rupture or erosion initiates the coagulation cascade. Fibrin deposition does not necessarily lead to occlusive thrombus formation but may indicate the risk of further complications. Accordingly, fibrin deposition may be a useful target for identifying complicated atherosclerotic lesions. Most experience with targeting fibrin formation has been obtained with the small-molecular Gd-based fibrin-specific MRI contrast agent EP2104R [53, 54]. Additional approaches to exploring thrombus formation include imaging factor XIII by using peptide substrates for factor XIII and by using optical imaging [55] or MRI [56].

Molecular Imaging in the Clinical Arena

18F-FDG PET Imaging of Plaque Inflammation

Early observations of 18F-FDG uptake in the arterial wall were reported in the large arteries of patients undergoing PET for cancer staging [57]. Further studies showed that FDG signal correlates with macrophage infiltration; therefore, 18F-FDG uptake might reflect plaque inflammation [32]. Observational studies suggest that 18F-FDG imaging may be used for risk stratification in atherosclerosis. FDG uptake in the vessel wall demonstrated a high correlation with components of the metabolic syndrome. In an observational follow-up study in 932 cancer patients, 18F-FDG uptake in large arteries was an independent predictor of future cardiovascular events, and it was a stronger predictor than conventional risk factors [58]. Retrospective studies in cancer patients undergoing PET provide evidence that FDG uptake in the carotid arteries and aortic arch correlates with subsequent stroke [59]. In a small prospective study, Marnane et al. [60••] investigated the recurrence of stroke in 60 patients with recent stroke, transient ischemic attack, or retinal embolism and ipsilateral carotid stenosis (≥50 %). This study showed that 18F-FDG uptake independently predicted early stroke recurrence, regardless of the severity of the ipsilateral stenosis. Stroke recurred in 22 % of patients within 90 days. Of these patients, 80 % had a mean above-threshold 18F-FDG uptake in the carotid artery (>2.14 g/mL; $P<0.0001$). Moreover, molecular imaging has the potential to assess the effects of pharmacotherapy. The anti-inflammatory effects of statins have been recognized, unrelated to LDL cholesterol reduction [61]. 18F-FDG has been used to evaluate the in vivo anti-inflammatory effects of statins on atherosclerotic plaque of large arteries. Tahara et al. [62] demonstrated that the use of simvastatin attenuates the FDG plaque uptake in large arteries 3 months after initiation of therapy. In another study, Tawakol et al. [63•] compared the effect of low-dose (10 mg) versus high-dose (80 mg) atorvastatin on aortic or carotid artery plaque inflammation in 67 patients by FDG PET during a 12-week intervention. They showed that both the low and high statin dosages reduced FDG uptake in the target vessel, and the reduction was more effective in the patient group receiving the high-dose statin.

The effect of a cholesteryl ester transfer protein inhibitor, dalcetrapib, was assessed by multimodality imaging in the phase 2b randomized, double-blind, placebo-controlled dal-PLAQUE (A Study of the Effect of Dalcetrapib on Atherosclerotic Plaque in Patients with Coronary Heart Disease) trial [64•]. In this study, end points were also plaque characterization by MRI (plaque size, composition, and contrast-enhanced–based plaque neovascularization) and 18F-FDG PET imaging. The MRI-derived change in total vessel area showed a relative reduction compared with baseline at 24 months. PET imaging demonstrated a modest nonsignificant tendency toward decreased carotid FDG activity compared with placebo. Unfortunately, the main clinical outcome with dalcetrapib was not reached, because it did not demonstrate any cardiovascular benefit. Another single-center, double-blind, placebo-controlled, randomized trial of 56 patients with diabetes compared the anti-inflammatory effects of pioglitazone with those of glimepiride by FDG imaging [65]. The pioglitazone-treated group showed a significantly greater reduction of FDG carotid and aortic plaque inflammation compared with the glimepiride group.

Losmapimod is a novel anti-inflammatory agent that inhibits p38 mitogen-activated protein kinase intracellular inflammation pathways. The anti-inflammatory effects of losmapimod on vascular inflammation were assessed by 18F-FDG in stable atherosclerotic patients receiving statin therapy. This phase 2 randomized, double-blind, placebo-controlled study showed that the use of losmapimod for 3 months reduced vascular inflammation in the most inflamed regions while decreasing inflammatory biomarkers [66].

FDG PET imaging of plaque inflammation usually is limited to large arteries, such as the carotid arteries and aorta. Imaging of coronary arteries remains difficult and challenging because of intense tracer uptake in the adjacent myocardium, cardiac and respiratory motion artifacts, and partial volume effect due to small vessel size. Despite these challenges, however, PET/CT coronary imaging has been shown to be relatively feasible by suppressing myocardial glucose uptake due to a high-fat low-carbohydrate diet prior to imaging [67, 68]. Ongoing efforts are aimed toward developing cardiac gating and breath-hold techniques that may help eliminate artifacts [69].

Sodium 18F-Fluoride PET Imaging of Active Plaque Calcification

Calcification is a key process in atherosclerosis and an independent predictor of future cardiovascular events [70].

Although CT can detect calcifications, it cannot measure active mineralization and calcification or reliably detect microcalcifications that may lead to microfractures and acute thrombosis [71•]. Hydroxyapatite, the essential structural component of vascular calcification, is prominent during active stages of mineralization. PET/CT using 18F sodium fluoride (18F-NaF) is a novel strategy for imaging active mineralization in atherosclerosis and has been used for years in detecting bone metastasis in patients. The uptake of 18F-NaF relies on the exchange mechanism of hydroxyl ions in the hydroxyapatite crystal.

18F-NaF uptake has been described in the aorta and carotid arteries and is believed to reflect active vascular calcification [72, 73]. In a retrospective study of 296 cancer patients, Derlin et al. [73] observed a significant correlation between 18F-NaF uptake in carotid arteries and the degree of atherosclerotic calcification on CT imaging. 18F-NaF uptake was significantly associated with risk factors such as age, male sex, hypertension, hypercholesterolemia, and cumulative smoking exposure. Additionally, the prevalence of radiotracer uptake increased strongly with the number of atherogenic risk factors present. The same group performed a second, retrospective study to compare 18F-FDG and 18F-NaF uptake in carotid plaques in 45 cancer patients who underwent both 18F-FDG and 18F-NaF PET scans within a 6-month period [74]. Remarkably, colocalization of both 18F-NaF and 18F-FDG uptake was observed in only 6.5 % of the arterial lesions with radiotracer accumulation. These findings emphasize that 18F-FDG and 18F-NaF allow evaluation of distinct pathophysiologic processes in atherosclerotic lesions. Dweck et al. [71•] demonstrated that 18F-NaF PET imaging allows detection of active mineralization in coronary atherosclerotic disease. Coronary 18F-NaF and 18F-FDG were evaluated in a prospective study of 119 patients with and without aortic valve disease. In this study, 18F-NaF uptake was associated with symptomatic coronary disease, atherosclerotic risk factors, and prior cardiovascular events. Compared with 18F-FDG, quantification of coronary 18F-NaF uptake was not hampered by myocardial activity. Recently, a prospective clinical trial compared coronary 18F-NaF and 18F-FDG uptake in patients with myocardial infarction and stable angina [75••]. The greatest coronary 18F-NaF uptake was observed in the culprit lesions. In contrast, 18F-FDG imaging could not distinguish between culprit and nonculprit plaques, probably because of myocardial uptake. Moreover, in patients with stable coronary disease, lesions with greater 18F-NaF plaque uptake were associated with more high-risk features on intravascular ultrasound (positive remodeling, microcalcification, and necrotic core). 18F-NaF uptake also was compared with histology in carotid endarterectomy samples from patients with symptomatic carotid disease. Elevated 18F-NaF uptake was associated with histologic evidence of active calcification, macrophage infiltration, apoptosis, and necrosis. This technique appears to be a promising strategy for identifying high-risk and ruptured plaque. However, larger prospective studies are needed to determine whether 18F-NaF uptake can predict a cardiovascular event.

Imaging of Inflammation with [^{11}C]PK11195

Another PET tracer, [^{11}C]PK11195, targeting activated macrophages by specifically interacting with the macrophage translocator protein, has been used to determine intraplaque inflammation. In a pilot study, Gaemperli et al. [76] recruited 32 patients with symptomatic and asymptomatic carotid artery stenoses. This study showed that symptomatic patients (those with recent ipsilateral stroke or transient ischemic attack) had increased [^{11}C]PK11195 uptake compared with patients with asymptomatic stenosis; however, this was a proof-of-principle study. The value of [^{11}C]PK11195 PET/CT imaging needs to be investigated in larger prospective studies. An important question is whether elevated [^{11}C]PK11195 signals can predict cerebrovascular events in asymptomatic patients.

MRI of Plaque Inflammation

Imaging of atherosclerotic plaque inflammation also has been realized with USPIO, a magnetic resonance contrast agent. USPIOs are phagocytized by macrophages and therefore reflect inflammation within the plaque. Early studies showed that carotid plaque inflammation can be identified with USPIO-enhanced MRI and that USPIOs accumulate predominantly in macrophages in ruptured and rupture-prone human carotid atherosclerotic lesions [28, 77]. The prospective trial ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) demonstrated that USPIO-enhanced MRI may be used to measure the dose–response of atorvastatin on plaque inflammation [78]. This study showed that the use of atorvastatin 80 mg significantly reduced plaque inflammation after 3 months compared with baseline, whereas this was not observed with atorvastatin 10 mg. These findings suggest that USPIO-enhanced MRI might be a promising approach for assessing therapeutic response to "anti-inflammatory" interventions in patients with atherosclerotic lesions.

Conclusions

A better understanding of the biologic basis of plaque disruption has led to the identification of molecular and cellular targets that extend the scope of imaging beyond anatomy. Substantial technologic developments in the field of molecular imaging have made it possible to visualize these targets. Molecular imaging approaches have the potential to improve assessment of risk for acute complications and to monitor

therapeutic strategies in high-risk individuals. Despite substantial preclinical research in the development of new imaging probes and targeting of different biologic processes, only a few of these probes currently are used in daily clinical practice. Each molecular imaging modality has its own strengths and limitations. Acute coronary events may be related to triggers, not only to the presence of vulnerable plaques [79]. However, there are some data suggesting that potential stressors may trigger events only among a relatively few susceptible individuals [80].

Prospective, long-term, large studies still are needed to determine whether molecular imaging can provide better outcome information beyond the traditional risk factor assessment.

Acknowledgments Funding sources for this article include Willy Gepts Research Funds and Universitair Ziekenhuis Brussel.

Compliance with Ethics Guidelines

Conflict of Interest Gezim Bala and Bernard Cosyns declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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