Molecular and Cellular Imaging of Atherosclerosis
Emerging Applications
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Molecular imaging studies have shed light on important biological aspects of atherosclerosis, and are now entering the clinical arena for the detection of clinical atheroma. This review first discusses fundamental principles regarding the rationale for and development of molecular imaging technologies for investigating atherosclerosis. Next, we highlight clinically promising imaging strategies that illuminate key biological aspects of atherosclerosis, including macrophage activity, protease activity, lipoprotein presence, apoptosis, and angiogenesis. We envision that several molecular imaging approaches will become important adjuncts to the clinical management of high-risk atherosclerosis.


Molecular imaging is a rapidly evolving discipline that aims to develop imaging agents and technologies to visualize specific molecular processes in vivo. With a considerable track record in the biological sciences and drug discovery (1–7), molecular imaging is now poised to make significant contributions to clinical imaging of atherosclerosis (8). Advances in atherosclerosis biology (9–13), imaging agent chemistry (nanotechnology, chemical biology screens), and imaging platforms (magnetic resonance imaging [MRI], integrated nuclear-computed tomography imaging, optical imaging, and ultrasound imaging) continue to drive this progress from bench to bedside.

In this review, we present recent developments in molecular and cellular imaging of atherosclerotic vascular disease. The discussion comprises several sections. First, we provide a rationale for employing molecular imaging strategies in the detection of clinical atheromata. Next, we provide a biological framework for designing atherosclerosis-targeted imaging agents, and briefly summarize various technical aspects of molecular agent development. We then consider a few clinically promising applications of molecular imaging for high-risk atherosclerosis.

Molecular Imaging: Detection of Atherosclerosis Beyond Anatomy

Via its sequelae of myocardial infarction and stroke, atherosclerotic vascular disease threatens to become a leading cause of death worldwide by the year 2020 (14). As high-risk or vulnerable plaques are often unrecognized before causing clinical events, there is an unmet need to identify these plaques before the onset of symptoms (15–17). This recognition has motivated the development of a number of noninvasive and invasive diagnostic imaging strategies to permit identification of high-risk individuals, based on the presence of high-risk anatomical or structural features of plaques (18–20). Recognizing that the multiplicity of so-called vulnerable plaques necessitates both local and global treatment strategies (21), the present discussion emphasizes the role of atherosclerosis imaging in the identification and management of the high-risk patient rather than solely individual lesions.

In contrast with existing imaging approaches that primarily aim to assess structural components of atherosclerosis (e.g., fibrous cap thickness, the size of the lipid core), molecular and cellular imaging aims to image biological properties of atherosclerotic plaques in vivo (6–8, 22–27). The fundamental motivation for this approach stems from the recognition that molecular and cellular processes govern all phases of atherogenesis, including plaque progression and plaque rupture (10). The ability to visualize specific biological aspects of atherosclerotic lesions could have utility in a number of different clinical scenarios, such as: 1) providing new diagnostic imaging capabilities for detecting high-risk plaques before symptom onset; 2) offering the potential of personalized medicine (28) to guide the initiation and titration of molecularly based atherosclerotic therapies (e.g., a measure of plaque macrophage activity could direct novel antimacrophage molecular therapies); and 3) supplying imaging end points for clinical trials to assess the efficacy of novel atherosclerotic therapeutics, as a prelude to...
lipid, macrophages produce and/or secrete a number of proteases, such as cathepsins and matrix metalloproteinases (MMP) that can degrade the extracellular matrix comprising the fibrous cap. Macrophages also secrete various reactive oxygen species (e.g., products of NAD[P]H oxidases or myeloperoxidase [MPO]) that can further modify lipoproteins, setting up a vicious cycle of additional monocyte/macrophage recruitment. Finally, autopsy studies have demonstrated prominent macrophage accumulation in ruptured atherosclerotic lesions (30). These findings underscore a key role for macrophages in plaque complications (15).

The endothelium also contributes importantly to athero-
genesis. Via their recruitment of monocytes, endothelial cells regulate early lesion development. Under inflammatory conditions, endothelial cells express adhesion molecules such as vascular cell adhesion molecule (VCAM)-1; VCAM-1 can mediate the recruitment both monocytes and T lymphocytes into the nascent atheroma to foster lesion evolution (10). In addition, the fragile endothelium in angiogenic vessels, typically associated with α/β3 integrin (31), can promote lesion progression via intraplaque hemorrhage (32) and may produce plaque complications (15).

Thus, biological insights provide the foundation for the development of atherosclerosis-targeted imaging agents (Fig. 1, Table 1). The past two decades have witnessed tremendous growth in atherosclerosis imaging, and recent review articles summarize some of the experimental data (6–8, 22–27). Many promising imaging agents, already undergoing experimental validation, may emerge in the clinical arena.

### NEW ATHEROSCLEROSIS IMAGING AGENTS: WINDOWS INTO IN VIVO BIOLOGY

A molecular imaging agent (or imaging reporter) typically consists of two components: 1) a detection moiety, such as a radioisotope, magnetic compound, fluorochrome, or sonic

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**Table 1.** Current High Priority Imaging Targets in Atherosclerosis

<table>
<thead>
<tr>
<th>Biological Process</th>
<th>Class</th>
<th>Specific Molecular Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage activity</td>
<td>Surface receptors</td>
<td>SRA, CD36, dextran receptor (magnetic nanoparticles-MRI), others</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hexokinase, GLUT-1 (FDG-PET)</td>
<td></td>
</tr>
<tr>
<td>Peroxidases</td>
<td>MMP (1, 8, 9, 13), cathepsins-NIRF* (B, S, K)</td>
<td></td>
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<tr>
<td>Modified lipoproteins</td>
<td>MPO</td>
<td></td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>OxLDL, others</td>
<td></td>
</tr>
<tr>
<td>Increased vascularity and leakage</td>
<td>Perfusion markers</td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td>VCAM-1, α/β3* (angiogenesis-MRI), E-selectin</td>
<td></td>
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<tr>
<td>Apoptosis</td>
<td>Cell membrane</td>
<td></td>
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<tr>
<td>Enzymes</td>
<td>Phosphatidylserine (Annexin A5–SPECT)</td>
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<tr>
<td>Cell trafficking</td>
<td>Monocytes</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Caspases, scramblases</td>
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<tr>
<td>Stem cells</td>
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**Boldfaced** agents have been clinically tested in human subjects. *Agents that are expected to undergo clinical evaluation within the next 3 to 5 years.

FDG = fluorodeoxyglucose; GLUT-1 = glucose transporter-1; MMP = matrix metalloproteinase; MPO = myeloperoxidase; MRI = magnetic resonance imaging; NIRF = near infrared fluorescence imaging; OxLDL = oxidized low-density lipoprotein; PET = positron emission tomography; SPECT = single-photon emission computed tomography; SRA = scavenger receptor A; VCAM = vascular cell adhesion molecule.
enhancer; and 2) a molecule-specific or cell-specific affinity ligand, such as an antibody, peptide, or small molecule (e.g., derived from diversity oriented synthesis). Clinically useful molecular imaging agents report on specific biological processes, generate a strong signal (ideally when recognized by its target), possess favorable pharmacokinetics and biodistribution, and exhibit an excellent safety profile. For these reasons not all biomarkers associated with atherosclerosis (29) furnish promising imaging targets. For example, secreted proteins or stationary receptors with low abundance are difficult to target. Conversely, internalizing receptors, abundant extracellular markers, and low-background enzyme-sensing quenched substrates can provide high-yield imaging strategies (Table 1).

Reporter imaging agent technology has dovetailed advances in chemical biology, and now incorporates screening approaches using phage-display (33–35), nanoparticle libraries (36), and combinatorial chemistry (37). Equally important, amplification strategies can enhance target signal generation and/or minimize background signal (6,38). Such “smart” agents (e.g., protease-activatable [39–42], or incorporating oligomerization of signal-producing substrates [43], cellular trapping of phosphorylated substrates [44], and covalent binding [45]) can provide high contrast-to-noise ratios and thus prove particularly well suited for in vivo imaging.

EMERGING CLINICAL APPLICATIONS

With the recent advances in biology and imaging technology, molecular imaging studies now offer the ability to visualize key biological signatures of atherosclerosis in vivo. We anticipate that molecular imaging studies of atherosclerosis will prove useful in the following four clinical scenarios: 1) identifying patients at high-risk for cardiovascular events (death, myocardial infarction, stroke) not identified by routine clinical evaluation (e.g., history, physical exam, electrocardiogram, lipid profile, C-reactive protein, exercise treadmill testing); 2) characterizing the vulnerability of lesions in high-risk areas of the coronary vasculature (e.g., the proximal third of each of the coronary arteries [46])—lesions deemed particularly high-risk could eventually justify novel local therapies such as intracoronary drug-eluting stents; 3) evaluating novel atherosclerotic therapies that target biology rather than the lipid profile (e.g., peroxisome proliferator-activated receptors [47]); and 4) selecting individualized treatment strategies based on the molecular profile of vulnerable plaques identified in particular patients. Several promising atherosclerosis-targeted imaging agents have already undergone testing in the clinic or are on the clinical horizon (Table 1).

Cellular imaging of macrophage activity. RECEPTOR-MEDIATED UPTAKE. Most clinically tested magnetic nanoparticles (MNP) have carbohydrate coatings (dextran or starch derivatives) that bind to and undergo endocytosis by macrophages, presumably through dextran receptors (48) or scavenger receptors. Long-circulating MNP that targeted tissue macrophages were first developed in the late 1980s (49) and subsequently proved biocompatible and able to effect strong MRI contrast (R2 > R1) in cells and in vivo (50,51). In atherosclerosis, preclinical studies with magnetofluorescent dextranated nanoparticles have demonstrated preferential uptake of dextranated MNP by lesional macrophages, with concomitant but much lower uptake by endothelial cells and smooth muscle cells (52). Recently, Kooi et al. (53) and Trivedi et al. (54) have demonstrated that long-circulating MNP (e.g., ferumoxtran, Advanced Mag-
netics, Cambridge, Massachusetts) can accumulate in macrophage-rich human carotid endarterectomy specimens. Symptomatic patients (n = 19) scheduled for carotid endarterectomy underwent pre-contrast carotid MRI and then received an intravenous injection of ferumoxtran (2.6 mg Fe/kg iron). After 24 h (and in one study serially up to 72 h), patients underwent repeat carotid MRI. Black-blood T2*-weighted imaging showed focal negative signal enhancement (darkening) within carotid atherosclerotic lesions (Fig. 2) (53,54). Histopathological correlation demonstrated colocalization between macrophages and iron deposition as detected by immunohistochemistry (Fig. 2) as well as electron microscopy. Slight uptake was noted in other cells such as smooth muscle cells and endothelial cells, and specimens from control patients without MNP showed minimal iron deposition (53). A recent experimental study extended these results by quantifying the cellular distribution of MNP in atherosclerosis using a multimodality MRI and near-infrared fluorescence (NIRF) magnetofluorescent nanoparticle (52).

Together these results demonstrate that MNP-enhanced MRI can identify macrophage-rich atheromata. To become useful for coronary plaque imaging, post-MNP magnetic resonance images will require higher resolution and signal-to-noise ratios, possibly via intravascular magnetic resonance coils (55,56) or novel pulse sequences (57). Alternatively, newer MNP, such as those that permit concomitant NIRF imaging (52), may allow sequential optical imaging of...
coronary plaque macrophages, possibly via intravascular NIRF catheters (58). Finally, newer derivatized MNP (i.e., those with affinity ligands conjugated to the dextran coat [35,59]) offer the potential to improve substantially the sensitivity and specificity of MNP uptake by activated macrophages (59).

METABOLISM. 18Fluorodeoxyglucose (18FDG), a positron emission tomography (PET) radiotracer, competes with glucose for uptake into metabolically active cells including macrophages in atheromata (44). Fluorodeoxyglucose is trapped inside cells after phosphorylation. Rudd et al. (44) employed 18FDG to image plaque inflammation in patients with symptomatic carotid atherosclerosis (Fig. 3). Patients (n = 8) who had experienced a recent carotid arterial ischemic event and had an internal carotid artery lesion >70% stenosis received an intravenous injection of 18FDG, and then underwent PET imaging 3 h later. Rigorous co-registration with subsequently acquired cranial computed tomography images demonstrated focal 18FDG uptake in carotid plaques (Fig. 3). Examination of the surgically resected plaque specimens demonstrated heavy macrophage infiltration. Corroborating microautoradiography experiments revealed focal uptake of tritiated deoxyglucose, an analog of 18FDG, into macrophage-rich plaque sections, with minimal uptake in other areas of plaques or in control sections. It still remains unsettled whether appreciable background 18FDG signal is present in other metabolically active arterial cells (e.g., smooth muscle cells) in vulnerable plaque.

18Fluorodeoxyglucose uptake occurred variably in the contralateral asymptomatic plaques in six of eight patients, and did not occur in normal carotid arteries. These findings demonstrate that 18FDG PET could be useful in identifying inflamed subclinical carotid lesions. The advent of integrated PET-computed tomography scanners should further improve image quality with the 18FDG method. However, this approach will likely prove less suitable for detecting coronary atheromata due to high 18FDG cardiac uptake by metabolically active cardiomyocytes (25). Alternative PET tracers for imaging macrophages include the benzodiazepine receptor-targeted agent 11C(R)-PK11195 (60), as well as a number of experimental agents under development such as tagged affinity peptides.

Figure 3. Cellular imaging of macrophage metabolism using 18F-fluorodeoxyglucose (18FDG) (44). (A) Positron emission tomography (left), contrast computed tomography (middle), and offline co-registered positron emission tomography/computed tomography (right) images of a neurologically symptomatic patient who received an intravenous bolus of 18FDG (dose 370 Mbq). The positron emission tomography image demonstrates focal 18FDG uptake by a right carotid plaque (arrow), corroborated by the computed tomography angiogram and co-registered positron emission tomography/computed tomography images. (B) Relatively weaker 18FDG accumulation is seen in the carotid plaque of an asymptomatic patient. (C, D) A surgically resected carotid plaque from a symptomatic patient was incubated with tritiated deoxyglucose, an analogue of 18FDG. Autoradiography (C, original magnification x100) shows colocalization of silver grains with plaque macrophages (D, anti-CD68 antibody, x200) in areas of the fibrous cap and lipid core. Images provided courtesy of Dr. James Rudd and Dr. Peter Weissberg, Addenbrooke’s Hospital, Cambridge, United Kingdom. Reproduced by permission from reference 44.

Molecular imaging of protease activity. CATHEPSINS. The cathepsin family includes cysteine proteases overexpressed in human and experimental atherosclerosis (61). Produced by macrophages, endothelial cells, and smooth muscle cells, cathepsins S and K can degrade extracellular matrix via their elastase and/or collagenase properties and therefore may participate in plaque destabilization (62). Recently, Chen et al. (41) optically imaged cathepsin B activity in experimental atherosclerosis in vivo. The authors employed an NIRF-
activatable imaging agent that became brightly fluorescent after enzymatic cleavage by cathepsin B (39). Using noninvasive fluorescence-mediated tomography (63) co-registered with MRI, atherosclerotic lesions in mice became brightly fluorescent 24 h after receiving a systemic injection of the agent (Fig. 4). Ex vivo fluorescence reflectance imaging confirmed focal NIRF signal in atheroma, and correlative fluorescence microscopy revealed cathepsin B and macrophage colocalization with NIRF signal in microscopic sections.

This study demonstrated that protease activity could serve as a useful imaging biomarker for detecting inflammation in atherosclerosis. A version of this agent is under development for clinical trials (8), and may offer an approach to detect inflamed plaques. Although depth penetration limits certain optical imaging methods, near-infrared photons can be tomographically reconstructed, offering the potential for deep tissue imaging in vivo (38). In addition, NIRF imaging catheters (58) and handheld reflectance devices are undergoing rapid translation into the clinic. In concert with protease activatable imaging agents, these devices could identify inflamed coronary and carotid plaques in vivo. Additional protease-activatable NIRF agents, for example for cathepsin K (62), may provide new inflammatory readouts for atherosclerosis (64).

MMPs. Members of the MMP family of zinc-dependent endopeptidases can also degrade extracellular matrix macromolecules including elastin and collagen. Heightened activity of MMPs in human plaques and experiments in genetically altered mice suggest a causative role for MMPs in plaque destabilization, particularly in lesions with positive (expansive, outward, compensatory) remodeling (65–68). Recently, Schäfers et al. (69) performed an in vivo single-photon emission computed tomography (SPECT) biodistribution imaging study of a broad-spectrum MMP inhibitor. The 123I- or 125I-radiolabeled imaging agent derived from a compound that binds to the active catalytic site of MMPs (70). Using atherosclerotic apolipoprotein E-deficient (apo E−/−) mice, the authors demonstrated focal signal enhancement of carotid plaques in animals receiving an intravenous injection of the agent, validated by 125I autoradiography in situ. Animals pre-treated with the unlabeled MMP inhibitor parent compound showed minimal signal. Further studies may help to determine the precise relationship between the radiolabeled active site ligand and MMP activity.

Imaging of MMP activity in atherosclerosis therefore offers another method for detecting inflamed atherosclerotic lesions. With the typical resolution of clinical SPECT systems (~10 mm), 125I scintigraphy of MMP-rich carotid plaques may prove feasible using Schäfers’ agent, particularly in concert with integrated SPECT-computed tomography systems. A gelatinase MMP-activatable NIRF agent (71) may furnish another option for imaging of MMP activity at higher resolution in vivo (72).

Imaging of MPO activity. Myeloperoxidase, a member of the heme peroxidase superfamily capable of generating the oxidant species hypochlorous acid, is biologically and clinically linked to atherosclerosis (73,74). Myeloperoxidase localizes within human atherosclerotic plaques (75,76), and its products may promote atherogenesis by modifying low-density lipoproteins (LDL) to an atherogenic form, functionally inactivating high-density lipoproteins, activating MMPs, causing endothelial cell apoptosis and tissue factor release, and inactivating nitric oxide (73,77). A number of MRI and nuclear imaging substrates for MPO are now...
available (78–82). Myeloperoxidase-induced oligomerization of these substrates produces high target-to-background signal levels via chemical amplification (e.g., enhanced relaxivity of paramagnetic [78–80] or superparamagnetic compounds [81]) and/or biological amplification (e.g., enhanced accumulation of larger substrates [82]) strategies. Ongoing investigation in atherosclerotic animals will determine the utility of these and novel MPO sensors.

**Imaging of lipoproteins. LDL.** Low-density lipoprotein contributes importantly to atherosclerosis initiation and progression (9,10), and the presence of a large lipid core is a high-risk feature of coronary plaques (15). When modified to an oxidized form (e.g., by MPO products, as discussed in the preceding text), oxidized LDL particles become proinflammatory and can promote recruitment and activation of monocytes in evolving atheromata. Low-density lipoprotein was recognized as a scintigraphic imaging target over 20 years ago, and reached clinical evaluation using 99mTc-labeled LDL (83). However, insufficient target-to-background ratios limited its applicability for coronary-sized lesions (24). Newer imaging targets include oxidized LDL epitopes, recently shown to be associated with coronary artery disease (84). Tsimikas et al. (85) have developed radiolabeled oxidation-specific antibodies to target oxidized LDL in experimental atheroma in vivo (86,87). Further studies will determine the potential of these agents (or perhaps magnetic and/or fluorescent analogs) and new lipoprotein-targeted agents (88,89) for the clinical detection of lipoprotein-rich plaques.

**Imaging of apoptosis.** Apoptosis or programmed cell death may contribute to atherosclerotic plaque vulnerability (10,15,90,91). During the process of apoptosis, phosphatidylserine, a phospholipid normally residing on the inner cell membrane of viable cells, becomes exteriorized and thus available to affinity ligands such as annexin V. Several scintigraphic imaging agents have been developed based on annexin V (e.g., 99mTc- and 123I-labeled annexin V for SPECT imaging, and 124I- and 18F-labeled annexin V for PET imaging). In an experimental atherosclerosis imaging study, Kolodgie et al. (92) demonstrated strong uptake of radiolabeled 99mTc annexin V in the balloon-injured aortas of cholesterol-fed rabbits. A good correlation was seen between lesional radiotracer uptake and macrophage content. In vivo however, annexin V can also bind necrotic cells and platelets, and can enter macrophages, thereby diminishing the specificity for apoptotic cells that the agent exhibits in vitro (93).

In a clinical extension of this work, Kietzelaer et al. (94) recently demonstrated in vivo uptake of radiolabeled annexin A5 (renamed from annexin V) into carotid plaques containing markers of instability, including macrophages, infiltrates, and intraplaque hemorrhage (Fig. 5). Two carotid plaques with stable histological features did not appreciably take up the imaging agent. Radiolabeled annexin A5 thus provides another clinical option for imaging carotid atheroma. For imaging of apoptotic coronary plaques, higher resolution imaging agents such as an annexin V magneto-

![Figure 5](image-url)
fluorescent nanoparticle for MRI (95) may offer additional apoptosis imaging capabilities.

**Imaging of angiogenesis.** VCAM-1. Due to their potential to promote intraplaque hemorrhage and subsequent cholesterol deposition and plaque growth (96), plaque neovessels may mark plaque vulnerability (15,90). Microvessels in human atheromata can overexpress the leukocyte adhesion molecule VCAM-1, a ligand for the α5β1 integrin very late antigen-4, and indicate ongoing inflammation within plaques (97). Recently, two new VCAM-1–targeted imaging agents have been investigated in atherosclerosis (35,98). Kelly et al. (35) identified a novel VCAM-1–peptide affinity ligand from phage display that is actively internalized by cells expressing VCAM-1. Conjugation of the ligand to a magnetofluorescent nanoparticle enabled direct MRI and NIRF imaging of VCAM-1 expression in murine atherosclerosis, validated by correlative NIRF microscopy and immunohistochemistry. Hamilton et al. (98) synthesized VCAM-1–targeted chogenic immunoliposomes using a commercially available VCAM-1 antibody as an affinity ligand. Intravascular ultrasound imaging of the VCAM-1–targeted agent in balloon-injured carotid arteries of cholesterol-fed swine demonstrated intimal signal enhancement after agent injection. Further studies may determine its specificity for atheroma compared to nondiseased arterial segments (99).

**INTEGRIN α5β3.** Neovascular endothelial cells also characteristically express integrin α5β3, a heterodimeric protein that localizes to human atherosclerotic plaques, particularly within the vasa vasorum and intraplaque microvessels (100). To image α5β3 expression in early atherosclerosis, Winter et al. (101) conjugated an arginine-glycine-aspartic acid (RGD) peptidometic to a gadolinium-coated (>90,000 molecules) perfluorocarbon. Using cholesterol-fed rabbits with intimal hyperplasia, the α5β3–targeted agent showed durable plaque signal enhancement on in vivo MRI. Histological examination revealed colocalization of α5β3 with endothelial cells lining the vasa vasorum. Magnetic resonance imaging of α5β3 expression may therefore permit detection of atherosclerotic lesions with abundant neovessels. Further investigation to determine whether the augmented α5β3 signal in atherosclerotic plaques suffices to distinguish plaques from normal coronary arteries that express α5β3 at baseline (100). Other α5β3–targeted imaging agents have been designed for ultrasound (102), PET (103), SPECT (104,105), NIRF (106), and MRI (107), and could also be applied to atherosclerosis. Finally, another promising strategy for imaging angiogenesis targets the extra-domain B of fibronectin, an extracellular matrix protein found in advanced atherosclerotic lesions (108).

**OUTLOOK**

Molecular imaging studies can now elucidate biological aspects of atherosclerosis in vivo, and the field is moving rapidly toward the clinical detection of high-risk atheroma (Table 1). Targeted and activatable imaging agents now under development use a variety of imaging platforms including MRI, nuclear, NIRF, and ultrasound. To achieve clinical utility for the evaluation of atherosclerotic plaques, molecular imaging studies must: 1) provide outcome information beyond that of clinical (e.g., Framingham risk score) and emerging biomarker (e.g., C-reactive protein) risk assessments; 2) be compared to imaging methods that address plaque anatomy (e.g., noncontrast-enhanced MRI, intravascular ultrasound, optical coherence tomography, near infrared spectroscopy); and 3) accurately report on the biological process targeted by the agent. These requirements will undoubtedly require prospective clinical trials that evaluate novel imaging agents with histological end points (e.g., carotid endarterectomy specimens retrieved after agent injection), imaging end points (e.g., statin-mediated reductions in macrophage or protease activity), and, ultimately, clinical end points (e.g., new-onset angina, myocardial infarction, stroke, or death).

Patients likely recruited for such trials include those with indications for invasive procedures such as carotid endarterectomy (atheroma specimen retrieval) and cardiac catheterization (nonculprit lesion assessment after culprit lesion percutaneous coronary intervention) as well as patients with very high Framingham risk scores (e.g., 10-year risk of nonfatal myocardial infarction or death >20%), particularly if noninvasive molecular imaging options are available. Initial molecular imaging trials likely will focus on imaging agent validation in atheroma specimens, primarily by correlated plaque imaging signals with the histological presence of the expected biological target. Secondary trials will then determine the ability of a given molecular imaging agent to predict cardiovascular risk in outcome-driven, natural history studies of vulnerable plaques.

Although likely to require substantial effort and cost, completion of such trials will be of pivotal importance to patients and apparently healthy individuals at high risk for the consequences of atheroma progression and rupture. If predictive beyond conventional risk assessment, we envision that molecular imaging of atherosclerosis, in concert with anatomical imaging techniques, will prove instrumental in guiding the detection, risk stratification, systemic therapy (e.g., optimal medications and doses), and local treatment (e.g., intracoronary stenting) of this disease.

**REFERENCES**


APPENDIX

For a glossary of terms, please see the online version of this article.