Noninvasive Cardiovascular Imaging in Rheumatoid Arthritis: Current Modalities and the Emerging Role of Magnetic Resonance and Positron Emission Tomography Imaging

Victoria Furer, MD,* Zahi A. Fayad, PhD,† Venkatesh Mani, PhD,† Claudia Calcagno, MD, PhD,† Michael E. Farkouh, MD,‡ and Jeffrey D. Greenberg, MD, MPH*

Objectives: Rheumatoid arthritis (RA) is associated with premature atherosclerosis and increased prevalence of cardiovascular disease. The objective of this review is to summarize current and emerging imaging modalities for the evaluation of subclinical atherosclerosis in RA, with an emphasis on potential application of novel modalities, high-resolution magnetic resonance imaging and positron emission tomography, as screening tools for early cardiovascular disease risk stratification.

Methods: A PubMed literature search was undertaken using the search terms "rheumatoid arthritis" AND "cardiovascular disease" OR "atherosclerosis" OR "plaque" and including all relevant terms for imaging modalities.

Results: Two noninvasive imaging modalities have been widely adopted for direct visualization of arterial wall: carotid ultrasonography and cardiac computed tomography. Published studies in the RA population using these 2 modalities are reviewed. Novel cardiovascular imaging modalities are described, with an emphasis on high-resolution magnetic resonance imaging and positron emission tomography. Emerging research tools in vascular imaging, including dynamic and cardiac stress perfusion contrast-enhanced magnetic resonance imaging, are presented. The incremental imaging capabilities to characterize plaque composition and vessel wall inflammation as well myocardial abnormalities and published studies are systematically reviewed.

Conclusions: An increasing number of cardiovascular imaging modalities with improved characterization of features associated with plaque vulnerability have been developed. Given the heightened cardiovascular risk profile of the RA population, these novel imaging modalities offer promise for risk stratification and drug safety evaluation.

 Semin Arthritis Rheum 41:676-688

Keywords: *atherosclerosis, plaque, vessel wall, inflammation, cardiovascular imaging, ultrasonography, cardiac computed tomography, magnetic resonance imaging, positron emission tomography, rheumatoid arthritis*

*Division of Rheumatology, New York University Hospital for Joint Diseases, New York, New York.
†Translational and Molecular Imaging Institute, Mount Sinai School of Medicine, New York, New York.
‡Mount Sinai Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York.

Dr Furer received partial support by the Arthritis Foundation New York City Chapter Grant; partial support was provided to Dr Fayad by NIH/NHLBI R01 HL071021, R01 HL078667; and Dr Greenberg received partial support by the Arthritis National Research Foundation Grant.

Address reprint requests to Victoria Furer, MD, Division of Rheumatology, NYU Hospital for Joint Diseases, 301 East 17th Street, New York, NY 10003. E-mail: Victoria.Furer@alumni.med.nyu.edu.

 0049-0172/12/$-see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.semarthrit.2011.08.007

Cardiovascular disease (CVD) is an important extra-articular comorbidity in patients with rheumatoid arthritis (RA), with a 2- to 3-fold increased prevalence compared with the general population (1,2). Early CVD identification, along with ongoing CV risk factor monitoring and management, has been advocated to be incorporated as part of the standard of care for RA patients (3). Proposed mechanisms for acceleration of atherosclerosis include traditional cardiovascular (CV) risk factors (4-7) and systemic inflammation-related mechanisms (8). Multiple studies have supported the latter hypothesis, demonstrating markers of RA severity and inflammation to predict the incidence of CV events (7,9-14).

The Framingham risk score (15) and other risk scoring models apply a combination of clinical risk factors to predict risk of future CV events in the general population. These clinical risk factors ("traditional" CV risk factors) typically include age, gender, hypertension, hyperlipidemia, diabetes, and smoking status. These prediction models do not account for any RA-related risk factors, and their utility has not been validated for the RA population. Indeed, application of the Framingham score in patients with RA has been suggested to markedly underestimate CV risk (16). The Reynold's risk score may improve CV risk prediction for RA patients, because it also includes high-sensitivity C-reactive protein (CRP) and family history of premature CVD (17). However, most large cohort studies conducted in RA do not have complete Framingham and Reynold's risk score variables measured at baseline.

Atherosclerosis is a progressive, multifocal disease of the arterial wall, initiated by lipid accumulation in the intima layer, sustained by chronic inflammation, and resulting in plaque formation. The underlying molecular and immunological mechanisms of atherosclerosis share similarities with those of RA (18). Patients with RA have been observed to have distinct characteristics of morphological and functional vascular abnormalities compared with non-RA patients. Histologic evidence in patients with CVD reveals increased inflammation in the walls of coronary arteries and increased prevalence of vulnerable plaque characteristics in RA patients compared with non-RA controls (19). Patients with RA have a higher prevalence and severity of subclinical atherosclerosis, detected by different vascular imaging and functional modalities, compared with healthy controls with similar CV risk profiles (20). Because plaque rupture is the most frequent cause of arterial thrombosis, identification of rupture-prone or "vulnerable" plaques represents a promising screening strategy for patients with subclinical atherosclerosis. Key features of the vulnerable plaque include a lipid-rich necrotic core, a thin fibrous cap, inflammatory cellular infiltrate, and plaque neovascularization (21,22).

Noninvasive atherosclerotic plaque imaging and visualization of vascular inflammation are new potential surrogates of CV risk that open novel opportunities for studying the biology and mechanisms of CVD in rheumatic diseases (23). In this article, we review the currently available noninvasive techniques for evaluation of atherosclerotic plaque. We then introduce emerging molecular imaging techniques, including positron emission tomography (PET), high-resolution magnetic resonance imaging (HR-MRI), dynamic contrast-enhanced (DCE) MRI, stress perfusion contrast-enhanced MRI (CMR), followed by a discussion of their potential applicability to patients with rheumatic diseases. Emerging data from our group and others suggest that blocking proinflammatory cytokines, particularly tumor necrosis factor, may reduce CV risk in RA (24,25). Thus, identification of clinical subsets with evidence of plaque inflammation and other characteristics of plaque instability may help to refine stratification and intervention strategies.

METHODS

A PubMed literature search was undertaken for studies published between 1963 and June 2011, using the following index terms, alone or in combination: "rheumatoid arthritis," "cardiovascular disease," "atherosclerosis," "plaque," and including all relevant imaging terms for carotid ultrasound, Doppler, carotid intima media thickness, ankle-brachial index, computed tomography, coronary calcification, Agatston score, magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI, stress perfusion MRI, positron emission tomography, and fluorodeoxyglucose (FDG). Preference was given to clinical studies, meta-analyses, and guidelines. References noted in relevant articles were also assessed.

Carotid Intima-Media Thickness (CIMT)

Carotid ultrasonography (US) is a noninvasive, accurate, and reproducible imaging modality that provides quantitative measurements of CIMT, widely used to identify subclinical vascular disease, evaluate cardiovascular risk, and monitor drug-related changes in clinical trials (26). Application of carotid US to clinical research began in the mid 1980s, when a histology study confirmed the feasibility of direct measurement of carotid artery wall thickness with in vivo B-mode real-time imaging (27). CIMT is defined as the distance between the inner and outer lines, corresponding to lumen-intima and media-adventitia interfaces, respectively. Current US technology is limited in distinction between intima and media layers.

CIMT can be measured at either the near (ie, closest to the transducer) or the far wall of the arterial segment at 3 anatomical locations: the extracranial common carotid artery (CCA), the most accessible and recommended approach (28); the bifurcation or carotid bulb; and the proximal internal carotid artery (ICA). CIMT can be expressed as a maximum thickness over a length or as a maximum thickness measured at the specific location (29). CIMT is influenced by age, sex, race, and systolic blood pressure, as well as anatomic location (30). Due to

different hemodynamics along the carotid tree, carotid bulb and ICA are more predisposed to atherosclerotic plaque formation rather than CCA (31). Although the cutoff point for abnormal CIMT varies, carotid plaque has been defined as an isolated CIMT of ≥1.5 mm or an isolated CIMT >50% of the surrounding intima-media thickness (IMT), regardless of the absolute dimension (32). In general, the presence of carotid plaque, or IMT ≥75th percentile for the patient's age, sex, and race, is indicative of increased CVD risk (28). To date, there is still no universally accepted carotid scanning protocol, resulting in heterogeneous data collection and analysis across published observational and intervention studies.

CIMT as a Surrogate Measure of General and Coronary Atherosclerosis in the General Population

Autopsy studies conducted in the 1960s revealed a moderate correlation between the extent of carotid and coronary atherosclerosis that was subsequently replicated by cross-sectional studies employing coronary angiography, intravascular US, and computed tomography (CT) (29). Prospective studies further established the association of CIMT with traditional CV risk factors, prevalent CVD, atherosclerosis in other arterial beds, and most importantly, future CV events (26). A landmark Cardiovascular Health Study prospectively followed 4476 asymptomatic adults aged 65 years and older using a composite measure of the maximal CCA and ICA IMTs (33). The cumulative 7-year rate of myocardial infarction (MI) or stroke was above 25% for subjects in the quintile with the highest IMT versus 5% for the lowest quintile (relative risk 3.87, 95% confidence interval 2.72–5.51). A systematic review and meta-analysis of 8 prospective studies, including a total of 37,197 subjects followed up for a mean of 5.5 years, showed that for an absolute CIMT difference of 0.1 mm, the future risk of MI increases by 10 to 15%, and stroke risk increases by 13 to 18% (34). However, the risk effect of CIMT for both end points decreased with adjustments for other CV risk factors. In view of these relationships, CIMT has been used as a surrogate endpoint for assessing the effect of pharmacological treatment on systemic atherosclerosis in clinical trials (35) with lipid-modifying, glucose-lowering, antihypertensive, and hormone-replacement therapies (26). Whether reduction of CIMT progression is a valid surrogate endpoint remains controversial.

Carotid US in Patients with RA

Carotid US has become the most commonly applied noninvasive imaging modality to detect subclinical atherosclerosis in patients with rheumatic diseases. A recent systematic review and meta-analysis concluded that CIMT is significantly increased in a wide spectrum of rheumatic diseases versus healthy controls, an overall absolute mean difference of 0.06 mm (95% confidence interval, 0.05–0.06 mm) (36). Specifically in RA patients, a new meta-analysis of 22 studies demonstrated an increased CIMT in RA patients versus controls (37). However, a variety of CIMT measurement protocols and lack of technical information related to the protocols used across the studies should be taken into account while interpreting the data. Overall, increased CIMT correlated with RA severity and duration (38–41). Conflicting results regarding plaque prevalence rates in RA were reported (11,40,42,43). Of particular note, a cross-sectional study of RA and control patients found that the prevalence of carotid plaque was 3-fold higher in RA versus controls, whereas CIMT was not increased (42). These findings might be explained by a more adverse profile of CV risk factors in the controls. Moreover, another study of RA patients versus healthy controls found comparable CIMT values between the groups (11). Of note, both carotid plaque presence and CIMT were associated with markers of systemic inflammation: erythrocyte sedimentation rate and CRP (11). A longitudinal follow-up of CIMT in RA patients, treated with a variety of nonbiologic DMARD regimens, revealed an increased annual CCA CIMT progression in RA patients versus healthy controls (44). The discordant results of CIMT measurements in RA suggest that vessel wall thickness progression may not be the primary mechanism by which RA incurs increased CV risk.

As in the general population, CIMT has been reported to predict the development of future CV events in the RA population. A small prospective study of RA patients, free of traditional CV risk factors at enrollment, examined incident CV events over a 5-year period (45). Patients who experienced CV events, 17% of the cohort, all had carotid plaques and significantly higher baseline CIMT than the rest of the cohort. The study concluded that CIMT >0.91 mm was independently associated with a high risk of subsequent CV event during the follow-up (45). Most recently, a prospective study of 636 RA patients confirmed that both CIMT and carotid plaque presence independently predict the incidence of acute coronary syndromes in RA (46). The incidence of new acute coronary syndromes was 2.3- and 4-fold higher for unilateral and bilateral plaque, respectively, compared with patients with no plaque.

Carotid US Limitations

Although carotid US is clearly helpful in identifying subclinical atherosclerosis, several important limitations must be acknowledged. Carotid US performance and interpretation is operator-dependent and, therefore, subject to intra- and interoperator measurement variability, making serial assessments of carotid US difficult, unless baseline and follow-up scans are read at the same time. US accessibility is anatomically limited to specific segments of the carotid tree. Although most CIMT measurements are acquired at the CCA, advanced atherosclerosis predominantly develops downstream from the ICA (47). US does

not differentiate smooth muscle hypertrophy or age-related sclerosis from the atherosclerotic process (47), does not directly inform about plaque burden, and does not define plaque composition (eg, presence of a necrotic core) or presence of vascular inflammation, both important for identification of vulnerable plaque.

In contrast to the general population, the extent of correlation between carotid US images and degree of histopathologic coronary atherosclerosis in RA patients has not been studied. Indeed, only a limited amount of information is available regarding the histopathology of atherosclerosis in RA patients. In 1 study, the features of coronary artery atherosclerosis in RA patients versus non-RA controls were examined postmortem (19). Overall, there was no difference in severity and extent of atherosclerosis between both groups, except for increased vessel wall inflammation observed in the RA group. In the subset of patients with established CVD, RA patients showed less severe CAD, reflected by extent of atherosclerosis and overall grade of stenosis, versus non-RA controls. However, RA patients with CVD were found to have a higher number of vulnerable plaques and more medial inflammation of the main coronary arteries. The results suggest that the phenotype of CVD in RA patients may be different than non-RA patients, and that simple anatomical imaging by US may not be adequate. New imaging techniques, able to provide more accurate information about plaque structure, composition, and metabolic activity, may therefore be required for risk stratification of early CVD in RA patients.

Ankle-Brachial Index

Ankle-brachial index (ABI) is a noninvasive, cost-effective test recommended by the American College of Cardiology/American Heart Association (ACC/AHA) for the diagnosis of peripheral artery disease (48), commonly applied in clinical practice for over 2 decades. The ABI represents a ratio of Doppler-recorded systolic blood pressure (BP) in the lower and upper extremities, measured in the posterior tibial and/or dorsalis pedis and brachial arteries, respectively. In addition to the assessment of peripheral artery disease, the ABI measured at rest has been shown to correlate with generalized and coronary atherosclerosis (49,50). In the general population, lower levels of the ABI (below 0.9) have been independently associated with an increased risk of all-cause and CVD-related mortality, MI, and stroke (51–54). A meta-analysis of 16 population-based studies found that ABI could improve the prediction of CV events when combined with the Framingham risk score (55).

In the RA population, a case-control study detected an increased prevalence of peripheral artery impairment measured by the ABI versus healthy controls (56). However, this difference was decreased with adjustment for inflammatory markers and joint damage. Interestingly, patients with an advanced RA (≥20 deformed joints) had more incompressible and obstructed arteries, independently of other covariates. Data from the Johns Hopkins RA cohort have also demonstrated a higher prevalence of arterial incompressibility in RA versus controls (57). Emerging evidence further suggests that application of the ABI in RA can be useful for CV risk stratification in patients with RA. Incompressibility of the peripheral arteries was found to be independently associated with an increased all-cause and CV mortality in a large prospective RA cohort (58).

The main advantages of the ABI examination include the fact that the test can be easily performed at the bedside or an outpatient setting. Among the limitations is the possibility of inaccurate BP measurements and calculation of the index that has been observed in the primary care setting (59). The ABI may be inaccurate when systolic BP cannot be abolished by BP cuff inflation, ie, in the elderly or patients with diabetes, or other diseases that result in arterial calcification.

Coronary Artery Calcification (CAC)

Electron beam CT (EBCT) and multidetector CT (MDCT) are fast CT methods designed to detect and assess CAC, a marker of subclinical CAD and a predictor of coronary events in the general population (60,61). CAC occurs almost exclusively in atherosclerotic arteries and seems to originate from the healing mechanism of subclinical plaque rupture events (62). Coronary calcification characterizes a late stage of atherosclerosis, corresponding to a healed plaque rather than to a vulnerable plaque (61). The rationale behind CAC measurement as a surrogate marker of atherosclerosis is based on a high correlation between CAC and total atherosclerotic plaque burden confirmed by histolopathologic, sonographic, and angiographic studies (63).

EBCT uses a rotating scanning electron beam to produce serial, thin-section scans, synchronized with the heart cycle (60). The design of EBCT permits acquisition of cross-sectional images of the heart with no constraints of mechanical motion. The most widely used method to quantify the amount of coronary calcium is the Agatston score, calculated by multiplication of the area of calcified coronary lesion and CT attenuation coefficient (64). The sum of the scores for all coronary-artery lesions represents the overall Agatston score (64). In recent years, EBCT has been replaced by an advanced mechanical high-resolution MDCT, capable of acquiring up to 128 slices simultaneously and producing high-quality images. Because EBCT preceded MDCT technology, the majority of studies to date on CAC and atherosclerosis have employed EBCT and reported the Agatston scores.

CAC as a Surrogate Measure of Coronary Atherosclerosis in the General Population

Large prospective studies, based on population cohorts, have demonstrated the incremental prognostic

value of CAC, beyond traditional risk factors (61). A meta-analysis of 4 studies published before 2003 examining asymptomatic subjects with baseline EBCT CAC score measurements and longitudinal follow-up of CV events incidence concluded that CAC score is an independent predictor of CHD events (65). A subsequent meta-analysis of 6 studies published between 2003 and 2005 showed that the presence of any CAC quantity increases CV events risk by 4-fold over 3 to 5 years (61). The Multi-Ethnic Study of Atherosclerosis, a population-based cohort of individuals without known CVD, found that a CAC score >300 was associated with a hazard ratio for future CHD events of nearly 10.4, and the independent predictive value of CAC was equal across ethnicities (66). CAC was found to predict not only CHD-related but also all-cause mortality (66–68). Currently, both American and European societies of cardiology support CAC screening in patients at intermediate risk of hard events (corresponding to Framingham score 6–20%) (60,69).

Coronary Arterial Calcium (CAC) Measurement in Patients with RA

A number of observational studies have determined a higher prevalence of CAC in the RA population versus healthy controls (70–73). Increased prevalence and severity of coronary calcification was detected by EBCT in patients with established (disease duration >10 years) but not early (disease duration <5 years) RA versus controls in a cross-sectional study (70). RA patients with coronary calcifications also had higher Framingham scores than patients with no calcifications, even after adjustment for age and gender (74). In addition, higher CAC scores were also correlated with the presence of metabolic syndrome (75) as well as serum tumor necrosis factor-alpha and interleukin-6 levels in the RA patients (76). The latter observation supports the concept of inflammation promoting CAC in RA patients. Other studies have demonstrated an association between RA duration and RA severity with CAC scores (72,77).

The prevalence, extent, and distribution of atherosclerosis have also been studied by MDCT in 85 RA patients and 85 controls, including imaging of the thoracic aorta and coronary and carotid arteries (73). RA cohort demonstrated earlier onset, greater prevalence, and more diffuse calcification over multiple vascular beds, as well as a preferential involvement of the thoracic aorta versus coronary arteries as compared with controls. Interestingly, discordance between measures of subclinical atherosclerosis in carotid and coronary arteries has been recently reported in RA (78). High CAC scores were found not only in RA patients with carotid plaque and increased CIMT but also in those without plaque and low CIMT. In contrast, a higher correlation between carotid measures and CAC score was found in non-RA controls.

In summary, visualization of coronary arteries by means of EBCT or MDCT has consistently demonstrated a higher prevalence and severity of CAC in longstanding RA as compared with healthy controls.

Cardiac CT Limitations

Cardiac CT has been described to have limitations in identifying noncalcified and rupture-prone coronary plaques. Cardiac CT angiography based on 64-slice MDCT can be used to detect noncalcified plaques (79), but requires intravenous contrast agent injection and uses a significant dose of radiation. Exposure to ionizing radiation is an important limitation of cardiac CT. The estimated effective dose from a single CAC screening by MDCT widely varies from 0.8 to 10.5 mSv (1 mSv = 1 mGy in the case of radiographs), with the mean value of 3.1 mSv (80). This can be compared with an annual effective dose from natural background radiation in the USA of about 3 to 3.6 mSv (81). New imaging techniques aim to substantially reduce the radiation dose from cardiac CT. Finally, cardiac CT imaging is a more expensive procedure than carotid US (82).

High-Resolution Magnetic Resonance Imaging

HR-MRI has recently emerged as superior to other noninvasive modalities technology to characterize atherosclerotic plaque and depict arterial wall (83). MRI differentiates tissue structure on the basis of proton magnetic resonance properties with a wide range of image contrast, without using ionizing radiation. In vivo plaque image acquisition requires a multicontrast approach with black-blood and bright-blood sequences. In the black-blood technique, the signal from the flowing blood is suppressed and turned black to better image the adjacent vessel wall (84). (Fig. 1) The bright-blood sequence can be used to assess the thickness of the fibrous cap and the morphological integrity of atherosclerotic plaques (85). Advantages of HR-MRI include excellent soft-tissue contrast and sensitivity to flow, applicable to most vascular beds. However, the potential to image the human coronary artery wall is still limited, due to blood flow, motion, and spatial artifacts (86,87).

In large arteries such as the carotids, HR-MRI can provide comprehensive information about plaque size, composition, morphology, and biology (88). Most importantly from the clinical point of view, HR-MRI can reliably detect and quantify the key histopathologic correlates of plaque vulnerability: the presence of a lipid-rich necrotic core, fibrous cap thickness, intraplaque hemorrhage, calcification, and thrombus, with high resolution and reproducibility (85,89–94).

A close correlation between HR-MRI classification of the carotid atherosclerotic lesions and histologic findings, based on the American Heart Association classification, was confirmed in a study of 60 patients imaged before endarterectomy (95). This study demonstrated that HR-

Figure 1 High-resolution black-blood vessel wall magnetic resonance images of the carotids and thoracic aorta. Longitudinal view from a 3D acquisition is shown in the middle panel with corresponding color-coded cross-sectional slices around illustrating atherosclerotic plaque measures. A, anterior; P, posterior; R, right; L, left. White arrows in cross-sectional images indicate plaque. Calc, calcifications; Hem, intraplaque hemorrhage; LRNC, lipid-rich necrotic core. (Color version of figure is available online.)

MRI could distinguish advanced lesions from early and intermediate atherosclerotic plaque, with a high degree of sensitivity and specificity. A cross-sectional study of carotid MRI imaging in subjects with and without angiographically proven obstructive CAD revealed a distinct structure and composition of carotid artery walls in the disease group versus controls (96). Accordingly, HR-MRI has a broad range of potential applications, including atherosclerosis assessment from preclinical evaluation to clinical detection, diagnosis, and prognosis (97,98). A summary of vulnerable plaque histologic features and correlated imaging modalities outcomes is summarized in Table 1.

DCE-MRI offers an additional parameter for evaluating plaque vulnerability by providing information on plaque vascularity (99). Neovascularization, the formation of new capillaries within in the atherosclerotic plaque, is a hallmark of vulnerable atherosclerotic lesions (22). The presence of neovessels has been linked with extravasation and activation of inflammatory cells, as well as lipid deposition in the vessel wall (100). Neovessels also seem to play a key role in the progression of atherosclerotic plaques, plaque inflammation, and rupture.

DCE-MRI has been used extensively to study tumor vascularity. This technique takes advantage of the administration of a contrast agent (ie, Gadolinium chelates) to quantify the extent of blood supply and its associated physiological characteristics (99). Several gadolinium uptake parameters correlate with the extent of plaque vascu-

Table 1 Histologic Features of Vulnerable Plaque and Correlated Imaging Modalities Outcomes

Type of Lesion (Modified AHA Classification)	Plaque Characteristics	Histological Correlates	Expected Findings on Imaging (MRI and FDG-PET)
Type III	Intermediate lesion (pre-atheroma)	Pathological intimal thickening. SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis	Increased plaque burden on multicontrast MRI
Type IV	Early fibroatheroma	Increased macrophage content	Increased plaque burden on multicontrast MRI Increased SUV/TBR on PET
Type Va	Fibroatheroma (type V lesion)	Well-formed necrotic core with an overlying fibrous cap	Increased plaque burden on multicontrast MRI Increased SUV/TBR on PET Increases size of LRNC Fibrous cap thickness measured by multicontrast MRI (fibrous cap enhanced postcontrast)
		A thin fibrous cap infiltrated by macrophages and lymphocytes with rare SMCs and an underlying necrotic core	Changes in measures of DCE-MRI
Type Vb	Calcific lesion (type VII lesion)	Eruptive nodular calcification with underlying fibrocalcific plaque or collagen-rich plaque with significant stenosis usually contains large areas of calcification with few inflammatory cells; a necrotic core may be present	Increased plaque burden on multicontrast MRI Calcification size detected by CT or multicontrast MRI Increased plaque burden on multicontrast MRI Fibrous cap thickness measured by multicontrast MRI (fibrous cap enhanced postcontrast)
Type Vc	Fibrotic lesion (type VIII)	Thick fibrous cap	Changes in measures of DCE-MRI
Type VI lesion	Lesion with surface defect and/or hematoma/hemorrhage and/or thrombotic deposit	Fibroatheroma with cap disruption; luminal thrombus with or without communication with the underlying necrotic core; erosion	Increased plaque burden on multicontrast MRI Changes in measures of DCE-MRI Hemorrhage detected by multicontrast MRI

(Adapted from Stary HC, et al. Modified American Heart Association (AHA) Classification. Arterioscler Thromb Vasc Biol 1995;15:1512-31.)
LRNC, lipid rich necrotic core; SMC, smooth muscle cell; SUV, standardized uptake value; TBR, target-to-background ratio.

larity, macrophage burden, and neovessel density (confirmed by staining of histological specimens). The use of DCE-MRI in conjunction with standard approaches offers further insight into biologic processes associated with plaque vulnerability.

The noninvasive nature of HR-MRI facilitates serial assessments of atherosclerotic lesions in the setting of intervention trials. MRI has been shown to be useful in prospective quantification of changes in carotid atherosclerotic plaque size and morphology (101). Regression of carotid and aortic atherosclerosis lesions after lipid-lowering therapy with statin therapies has been demonstrated (97,98,102,103).

Recent advances in the development of novel targeted molecular contrast agents, such as superparamagnetic iron oxide nanoparticles (SPION), significantly broaden the capabilities of vascular HR-MRI to identify specific cell types within atherosclerotic plaque. Experimental studies in animals have shown that SPIONs are internalized by macrophages and thus accumulate in high-risk plaques with a high macrophage content, inducing magnetic resonance signal changes (104). Application of

SPION-enhanced MRI permits not only measurement of macrophage burden in atherosclerotic plaque but also monitoring of statin-induced changes in plaque inflammation in animal models (105). A preliminary study employing SPION-enhanced MRI in 11 patients with carotid disease has confirmed the predominant accumulation of SPION in macrophages within prone-to-rupture or ruptured carotid plaques (106). This modality also shows promise in the functional imaging of atherosclerotic plaque.

In summary, HR-MRI has been shown to be a useful tool for clinical detection, diagnosis, and follow-up of atherosclerotic disease. Application of HR-MRI to study atherosclerosis in patients with RA and other rheumatic diseases would be promising for the study of atherosclerosis progression and evaluation of CV safety of new drugs.

In addition to vascular applications of HR-MRI, cardiac contrast-enhanced MRI (CMR) has been used to provide information about myocardial perfusion deficits, ventricular function, and myocardial viability. This modality has the advantage of high spatial and temporal resolution. Visualization of delayed contrast appearance in myocardial layers provides valuable diagnostic information. Late myocardial enhancement that appears as an area of high signal intensity localized to the subendocardial layer is the best current technique to discriminate scarred versus viable myocardium in patients with ischemic CAD (107). Different patterns and distribution of late enhancement might be helpful in diagnosing other myocardial diseases, including myocarditis (108). CMR with pharmacologically induced stress (eg, adenosine) has been established as a noninvasive diagnostic tool with high sensitivity and specificity for detecting subendocardial perfusion defects. This modality also permits the identification of microvascular dysfunction in the absence of significant coronary stenosis (109,110).

Myocardial abnormalities by stress perfusion CMR have been detected in a pilot study of 18 RA patients without history of cardiac disease (111). A high prevalence of delayed enhancement was observed and was associated with higher RA disease activity. Similar findings of a high prevalence of delayed enhancement on CMR were demonstrated in a study of 16 patients with Takayasu arteritis, suggesting the possibility of silent ischemia or myocardial scarring (112). These studies demonstrate the utility of late gadolinium enhancement and stress perfusion CMR in assessment of clinically silent myocardial disease in patients with rheumatic diseases. Further studies are required to validate these preliminary findings in larger RA cohorts.

^{18}F-Fluorodeoxyglucose-Positron Emission Tomography

FDG-PET is a metabolic technique that provides functional images of glycolytic activity to detect localized inflammation with high sensitivity and reproducibility (23,113,114). The primary clinical use of FDG-PET has been historically in the field of oncology, where FDG-PET in combination with CT (PET-CT) is the gold standard for monitoring tumor response to therapy. In the context of cardiovascular imaging, FDG-PET is an emergent modality for the identification of plaque inflammation (23,113).

In FDG-PET a radioactive tracer (FDG) is administered intravenously to circulate within the body and accumulate at the site of interest. FDG is a labeled modified glucose analog that transports into cells by glucose transporters and accumulates intracellularly. The degree of its cellular uptake is dependent on the cellular metabolic rate and the number of glucose transporters, which are upregulated in inflammatory conditions (113). Radiotracer uptake is semi-quantitatively expressed as a "standardized uptake value." To date, FDG has been the most commonly used PET agent in vascular imaging (114–116).

Histopathological data have confirmed the relationship between plaque inflammation and plaque rupture, including an abundance of macrophages within ruptured plaques (117,118). Correlations between the degree of arterial FDG uptake and the density of macrophages determined histologically have been documented in both animal models of atherosclerosis (119–121) and patients with carotid disease ($r = 0.70–0.85$) (116,122).

In 2002, FDG-PET was used for the first time to visualize and quantify human carotid plaque inflammation in patients scanned shortly after transient ischemic attack. A higher FDG uptake was recorded within "culprit" carotid plaques compared with their asymptomatic contralateral counterparts (116). Subsequent examination of the excised plaques showed FDG accumulation mainly in plaque macrophages (116). Subsequently, an FDG-PET study of 17 patients with severe carotid artery stenosis demonstrated a strong correlation between FDG uptake and plaque macrophage content (as determined from endarterectomy specimens) (122). Accordingly, FDG-PET was established as a noninvasive in vivo measure of carotid plaque inflammation severity. Another study reported that FDG-PET uptake in 1 vascular bed served as a biomarker for inflammation in other vascular beds, particularly when those beds were anatomically adjacent (123). No overlap between plaque inflammation and plaque calcification was found (123). Recently, FDG-PET was shown to be useful as a robust surrogate marker of efficacy in serial plaque imaging. Short scan time, small variability in plaque FDG uptake, and excellent intra- and interobserver agreement represent the multiple advantages of FDG-PET for interventional trials.

Several studies have demonstrated a correlation between measures of systemic inflammation, in particular, high-sensitivity CRP, and vascular inflammation detected by FDG-PET in the general population (123,124). In a pilot study conducted in patients with psoriasis, FDG-PET/CT detected diffusely increased inflammation of the

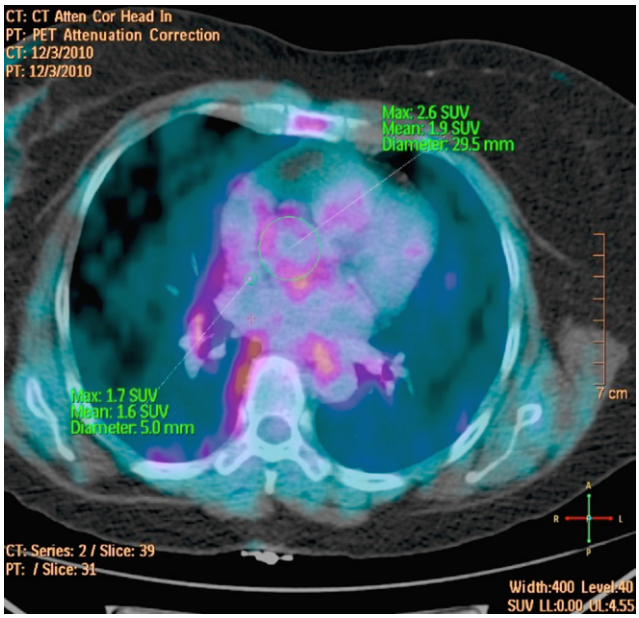

Figure 2 Sample FDG-PET/CT image from a longstanding RA patient with high FDG uptake in the thoracic aorta. (Color version of figure is available online.)

aorta that remained significant after adjusting for traditional CV risk factors and body mass index (125). To date, no published studies on application of the PET modality to image vascular inflammation in RA are available. An example of increased vessel wall inflammation on FDG-PET/CT is depicted in Figure 2 from a patient with longstanding RA from the New York University RA cohort.

One important limitation of FDG-PET/CT application is the exposure to radiation (126). New protocols strive to reduce the effective dose of radiation, permitting more widespread use of this modality. Other limitations relate to the specificity of FDG uptake, and the precision of the quantification of FDG signal (23).

CV risk stratification is an important part of the clinical management of RA. Current European League Against Rheumatism (EULAR) recommendations for CV risk management in patients with RA and other forms of inflammatory arthritis include annual CV risk assessment according to national guidelines developed for the general population and aggressive treatment of systemic inflammation (3). These guidelines recommend monitoring more closely RA patients with seropositivity, disease duration above 10 years, and presence of certain extra-articular features. There are no evidence-based guidelines regarding the use of imaging modalities for CV risk stratification in RA. The preferred modality for detecting subclinical atherosclerosis in patients with rheumatic diseases has not been determined. In current clinical practice, 2 noninvasive imaging modalities are available for direct visualization of atherosclerotic plaque: carotid US and cardiac CT. Carotid US indirectly evaluates for the presence of coronary atherosclerosis via CIMT measurement and is considered a simple, safe, and inexpensive test, with no ionizing radiation involved. In comparison, cardiac CT visualizes coronary arteries calcification and involves ionizing radiation. Both tests have limited utility in evaluating plaque characteristics and detecting vulnerable plaque features. In the general population, CAC (Agatston score) seems to be a better predictor for subsequent CV events than CIMT (127). However, CIMT might be more sensitive than CAC score for evaluation of CV risk in young and middle-age adults (128). In patients with rheumatic diseases, no direct comparison between the 2 modalities has been conducted. Extrapolating from the guidelines targeted to the general population, carotid US to evaluate for the presence of carotid plaque and CIMT measurement and/or cardiac CT to assess CAC seems a reasonable approach to refine the CV risk in patients at intermediate CVD risk (28,60). However, the definition of intermediate risk in RA patients has not been clearly defined as in the general population (where it corresponds to Framingham risk score of 6%-20% without established CVD) and should require further study and validation.

In recognition of the need for better risk stratification, alternative imaging modalities have been developed over the last decade. Valid and reliable data on plaque inflammation and burden, correlating with vulnerable plaque characteristics on a histopathological level, can be obtained through FDG-PET and MRI, respectively. Early experience further supports a multimodality imaging approach (129). In RA, these new technologies appear to be promising for the detection of early subclinical CVD, and for monitoring the CV effects of antirheumatic therapies. Future studies will clarify the role of these novel modalities and their utility for clinical research and patient care.

REFERENCES

1. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44(12):2737-45.
2. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003; 107(9):1303-7.
3. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69(2):325-31.
4. Dessein PH, Joffe BI, Stanwix AE. Inflammation, insulin resistance, and aberrant lipid metabolism as cardiovascular risk factors in rheumatoid arthritis. J Rheumatol 2003;30(7):1403-5.
5. Choi HK, Seeger JD. Lipid profiles among US elderly with untreated rheumatoid arthritis—the Third National Health and Nutrition Examination Survey. J Rheumatol 2005;32(12): 2311-6.
6. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis 2009;68(9):1395-400.

7. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010;69(11):1920-5.
8. Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. Am J Med 2008;121(10 Suppl 1):S21-31.
9. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol 1999;26(12):2562-71.
10. Jacobsson LT, Turesson C, Hanson RL, Pillemer S, Sievers ML, Pettitt DJ, et al. Joint swelling as a predictor of death from cardiovascular disease in a population study of Pima Indians. Arthritis Rheum 2001;44(5):1170-6.
11. Del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis Rheum 2003;48(7):1833-40.
12. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year follow up study of a primary care-based inception cohort. Arthritis Rheum 2005;52(8):2293-9.
13. Turesson C, McClelland RL, Christianson TJ, Matteson EL. Severe extra-articular disease manifestations are associated with an increased risk of first ever cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66(1):70-5.
14. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med 2008;121(10 Suppl 1):S9-14.
15. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97(18):1837-47.
16. Dessein PH, Joffe BI, Veller MG, Stevens BA, Tobias M, Reddi K, et al. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. J Rheumatol 2005;32(3):435-42.
17. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA 2007;297(6):611-9.
18. Pasceri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. Circulation 1999;100(21):2124-6.
19. Aubry MC, Maradit-Kremers H, Reinalda MS, Crowson CS, Edwards WD, Gabriel SE. Differences in atherosclerotic coronary heart disease between subjects with and without rheumatoid arthritis. J Rheumatol 2007;34(5):937-42.
20. Stamatelopoulos KS, Kitas GD, Papamichael CM, Chryssohoou E, Kyrkou K, Georgiopoulos G, et al. Atherosclerosis in rheumatoid arthritis versus diabetes: a comparative study. Arterioscler Thromb Vasc Biol 2009;29(10):1702-8.
21. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006;47(Suppl 8):C13-8.
22. Moreno PR, Purushothaman KR, Zias E, Sanz J, Fuster V. Neovascularization in human atherosclerosis. Curr Mol Med 2006; 6(5):457-77.
23. Rudd JH, Hyafil F, Fayad ZA. Inflammation imaging in atherosclerosis. Arterioscler Thromb Vasc Biol 2009;29(7):1009-16.
24. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005;32(7):1213-8.
25. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2007; 56(9):2905-12.
26. O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J 2010;31(14):1682-9.
27. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74(6):1399-406,.
28. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21(2): 93-111; quiz 89-90.
29. Bots ML, Baldassarre D, Simon A, de Groot E, O'Leary DH, Riley W, et al. Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations? Eur Heart J 2007; 28(4):398-406.
30. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (The Bogalusa Heart Study). Am J Cardiol 2002;90(9):953-8.
31. Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 1983;53(4):502-14.
32. Roman MJ, Naqvi TZ, Gardin JM, Gerhard-Herman M, Jaff M, Mohler E. American society of echocardiography report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Vasc Med 2006;11(3):201-11.
33. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340(1):14-22.
34. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115(4):459-67.
35. Revkin JH, Shear CL, Pouleur HG, Ryder SW, Orloff DG. Biomarkers in the prevention and treatment of atherosclerosis: need, validation, and future. Pharmacol Rev 2007;59(1): 40-53.
36. Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. Rheumatic disease and carotid intima-media thickness: a systematic review and meta-analysis. Arterioscler Thromb Vasc Biol 2010;30(5):1014-26.
37. van Sijl AM, Peters MJ, Knol DK, de Vet HC, Gonzalez-Gay MA, Smulders YM, et al. Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. Semin Arthritis Rheum 2011;40(5):389-97.
38. Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. Arthritis Rheum 2002;46(7): 1714-9.
39. Grover S, Sinha RP, Singh U, Tewari S, Aggarwal A, Misra R. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol 2006;33(2):244-7.
40. Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum 2002;46(6):1489-97.
41. Del Rincon I, O'Leary DH, Freeman GL, Escalante A. Acceleration of atherosclerosis during the course of rheumatoid arthritis. Atherosclerosis 2007;195(2):354-60.

42. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 2006;144(4):249-56.
43. Kobayashi H, Giles JT, Polak JF, Blumenthal RS, Leffell MS, Szklo M, et al. Increased prevalence of carotid artery atherosclerosis in rheumatoid arthritis is artery-specific. J Rheumatol 2010; 37(4):730-9.
44. Nagata-Sakurai M, Inaba M, Goto H, Kumeda Y, Furumitsu Y, Inui K, et al. Inflammation and bone resorption as independent factors of accelerated arterial wall thickening in patients with rheumatoid arthritis. Arthritis Rheum 2003;48(11):3061-7.
45. Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay MA. Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. Semin Arthritis Rheum 2009;38(5):366-71.
46. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'Leary DH, Del Rincon I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011;63(5):1211-20.
47. Finn AV, Kolodgie FD, Virmani R. Correlation between carotid intimal/medial thickness and atherosclerosis. A point of view from pathology. Arterioscler Thromb Vasc Biol 2010;30(2):177-81.
48. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery. Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47(6):1239-312.
49. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation 1993; 88(3):837-45.
50. Papamichael CM, Lekakis JP, Stamatelopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, et al. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. Am J Cardiol 2000;86(6):615-8.
51. Ogren M, Hedblad B, Isacsson SO, Janzon L, Jungquist G, Lindell SE. Non-invasively detected carotid stenosis and ischaemic heart disease in men with leg arteriosclerosis. Lancet 1993; 342(8880):1138-41.
52. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ 1996;313(7070): 1440-4.
53. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation 2004;109(9):1089-94.
54. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003;163(16):1939-42.
55. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300(2):197-208.
56. del Rincon I, Haas RW, Pogosian S, Escalante A. Lower limb arterial incompressibility and obstruction in rheumatoid arthritis. Ann Rheum Dis 2005;64(3):425-32.
57. Chung CP, Giles JT, Szklo M, Post W, Petri MA, Blumenthal R, et al. Interleukin-6 levels are associated with elevated ankle brachial index in rheumatoid arthritis [Abstract]. Arthritis Rheum 2010;62(Suppl 10):S950.
58. Ramirez C, Escalante A, Sahai M, Battafarano D, Pogosian S, Del Rincon I. Prediction of 10-year cardiovascular and all-cause mortality in rheumatoid arthritis using the ankle-brachial index [Abstract]. Arthritis Rheum 2010;62(Suppl 10):S437.
59. Nicolai SP, Kruidenier LM, Rouwet EV, Bartelink ML, Prins MH, Teijink JA. Ankle brachial index measurement in primary care: are we doing it right? Br J Gen Pract 2009;59(563):422-7.
60. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention. Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. Circulation 2006;114(16):1761-91.
61. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation 2007;115(3):402-26.
62. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92(5):1355-74.
63. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association Writing Group. Circulation 1996;94(5):1175-92.
64. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15(4):827-32.
65. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med 2004;164(12):1285-92.
66. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358(13):1336-45.
67. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology 2003;228(3): 826-33.
68. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49(18):1860-70.
69. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003; 24(17):1601-10.
70. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheuma-

toid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;52(10):3045-53.
71. Kao AH, Wasko MC, Krishnaswami S, Wagner J, Edmundowicz D, Shaw P, et al. C-reactive protein and coronary artery calcium in asymptomatic women with systemic lupus erythematosus or rheumatoid arthritis. Am J Cardiol 2008; 102(6):755-60.
72. Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison with the multi-ethnic study of atherosclerosis. Arthritis Res Ther 2009;11(2):R36.
73. Wang S, Yiu KH, Mok MY, Ooi GC, Khong PL, Mak KF, et al. Prevalence and extent of calcification over aorta, coronary and carotid arteries in patients with rheumatoid arthritis. J Intern Med 2009;266(5):445-52.
74. Chung CP, Oeser A, Avalos I, Gebretsadik T, Shintani A, Raggi P, et al. Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther 2006;8(6):R186.
75. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis 2008;196(2):756-63.
76. Rho YH, Chung CP, Oeser A, Solus J, Asanuma Y, Sokka T, et al. Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. Arthritis Rheum 2009;61(11): 1580-5.
77. Kao AH, Krishnaswami S, Cunningham A, Edmundowicz D, Morel PA, Kuller LH, et al. Subclinical coronary artery calcification and relationship to disease duration in women with rheumatoid arthritis. J Rheumatol 2008;35(1):61-9.
78. Giles JT, Post W, Szklo M, Blumenthal RS, Petri M, Gelber A, et al. Discordance in the association of carotid with coronary atherosclerosis in rheumatoid arthritis compared with controls [Abstract]. Arthritis Rheum 2009;60(Suppl 10):S601.
79. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/ SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Cardiovasc Comput Tomogr 2010;4(6):407e1-33.
80. Kim KP, Einstein AJ, Berrington de Gonzalez A. Coronary artery calcification screening: estimated radiation dose and cancer risk. Arch Intern Med 2009;169(13):1188-94.
81. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008;248(1):254-63.
82. Kaul P, Douglas PS. Atherosclerosis imaging: prognostically useful or merely more of what we know? Circ Cardiovasc Imaging 2009;2(2):150-60.
83. Fayad ZA. MR imaging for the noninvasive assessment of atherothrombotic plaques. Magn Reson Imaging Clin N Am 2003;11(1):101-13.
84. Fayad ZA, Fuster V, Fallon JT, Jayasundera T, Worthley SG, Helft G, et al. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. Circulation 2000;102(5):506-10.
85. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 2000;102(9):959-64.
86. Botnar RM, Stuber M, Kissinger KV, Kim WY, Spuentrup E, Manning WJ. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. Circulation 2000; 102(21):2582-7.
87. Desai MY, Lai S, Barmet C, Weiss RG, Stuber M. Reproducibility of 3D free-breathing magnetic resonance coronary vessel wall imaging. Eur Heart J 2005;26(21):2320-4.
88. Sanz J, Fayad ZA. Imaging of atherosclerotic cardiovascular disease. Nature 2008;451(7181):953-7.
89. Toussaint JF, LaMuraglia GM, Southern JF, Fuster V, Kantor HL. Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. Circulation 1996;94(5):932-8.
90. Yuan C, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 2001;104(17):2051-6.
91. Itskovich VV, Samber DD, Mani V, Aguinaldo JG, Fallon JT, Tang CY, et al. Quantification of human atherosclerotic plaques using spatially enhanced cluster analysis of multicontrast-weighted magnetic resonance images. Magn Reson Med 2004; 52(3):515-23.
92. Fuster V, Fayad ZA, Moreno PR, Poon M, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: Part II: approaches by noninvasive computed tomographic/magnetic resonance imaging. J Am Coll Cardiol 2005;46(7):1209-18.
93. Briley-Saebo KC, Mulder WJ, Mani V, Hyafil F, Amirbekian V, Aguinaldo JG, et al. Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. J Magn Reson Imaging 2007;26(3):460-79.
94. Anderson RW, Stomberg C, Hahm CW, Mani V, Samber DD, Itskovich VV, et al. Automated classification of atherosclerotic plaque from magnetic resonance images using predictive models. Biosystems 2007;90(2):456-66.
95. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multicontrast magnetic resonance imaging. Circulation 2002;106(11):1368-73.
96. Underhill HR, Yuan C, Terry JG, Chen H, Espeland MA, Hatsukami TS, et al. Differences in carotid arterial morphology and composition between individuals with and without obstructive coronary artery disease: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2008;10:31.
97. Corti R, Fayad ZA, Fuster V, Worthley SG, Helft G, Chesebro J, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. Circulation 2001; 104(3):249-52.
98. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Smith D, et al. Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. Circulation 2002; 106(23):2884-7.
99. Calcagno C, Mani V, Ramachandran S, Fayad ZA. Dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) of atherosclerotic plaque angiogenesis. Angiogenesis 2010;13(2): 87-99.
100. Fleiner M, Kummer M, Mirlacher M, Sauter G, Cathomas G, Krapf R, et al. Arterial neovascularization and inflammation in vulnerable patients: early and late signs of symptomatic atherosclerosis. Circulation 2004;110(18):2843-50.
101. Saam T, Yuan C, Chu B, Takaya N, Underhill H, Cai J, et al. Predictors of carotid atherosclerotic plaque progression as measured by noninvasive magnetic resonance imaging. Atherosclerosis 2007;194(2):e34-42.
102. Corti R, Fuster V, Fayad ZA, Worthley SG, Helft G, Chaplin WF, et al. Effects of aggressive versus conventional lipid-lowering therapy

by simvastatin on human atherosclerotic lesions: a prospective, randomized, double-blind trial with high-resolution magnetic resonance imaging. J Am Coll Cardiol 2005;46(1):106-12.
103. Zhao XQ, Yuan C, Hatsukami TS, Frechette EH, Kang XJ, Maravilla KR, et al. Effects of prolonged intensive lipid-lowering therapy on the characteristics of carotid atherosclerotic plaques in vivo by MRI: a case-control study. Arterioscler Thromb Vasc Biol 2001;21(10):1623-9.
104. Ruehm SG, Corot C, Vogt P, Kolb S, Debatin JF. Magnetic resonance imaging of atherosclerotic plaque with ultrasmall superparamagnetic particles of iron oxide in hyperlipidemic rabbits. Circulation 2001;103(3):415-22.
105. 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(17):1707-15.
106. Kooi ME, Cappendijk VC, Cleutjens KB, Kessels AG, Kitslaar PJ, Borgers M, et al. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. Circulation 2003;107(19):2453-8.
107. Saraste A, Nekolla S, Schwaiger M. Contrast-enhanced magnetic resonance imaging in the assessment of myocardial infarction and viability. J Nucl Cardiol 2008;15(1):105-17.
108. Hunold P, Schlosser T, Vogt FM, Eggebrecht H, Schmermund A, Bruder O, et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol 2005; 184(5):1420-6.
109. Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002;346(25):1948-53.
110. Bernhardt P, Levenson B, Albrecht A, Engels T, Strohm O. Detection of cardiac small vessel disease by adenosine-stress magnetic resonance. Int J Cardiol 2007;121(3):261-6.
111. Kobayashi Y, Giles JT, Hirano M, Yokoe I, Nakajima Y, Bathon JM, et al. Assessment of myocardial abnormalities in rheumatoid arthritis using a comprehensive cardiac magnetic resonance approach: a pilot study. Arthritis Res Ther 2010;12(5):R171.
112. Keenan NG, Mason JC, Maceira A, Assomull R, O'Hanlon R, Chan C, et al. Integrated cardiac and vascular assessment in Takayasu arteritis by cardiovascular magnetic resonance. Arthritis Rheum 2009;60(11):3501-9.
113. Schillaci O, Danieli R, Padovano F, Testa A, Simonetti G. Molecular imaging of atherosclerotic plaque with nuclear medicine techniques. Int J Mol Med 2008;22(1):3-7.
114. 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(9):892-6.
115. Yun M, Yeh D, Araujo LI, Jang S, Newberg A, Alavi A. F-18 FDG uptake in the large arteries: a new observation. Clin Nucl Med 2001;26(4):314-9.
116. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation 2002;105(23):2708-11.
117. Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med 1984; 310(18):1137-40.
118. Jander S, Sitzer M, Schumann R, Schroeter M, Siebler M, Steinmetz H, et al. Inflammation in high-grade carotid stenosis: a possible role for macrophages and T cells in plaque destabilization. Stroke 1998;29(8):1625-30.
119. Ogawa M, Ishino S, Mukai T, Asano D, Teramoto N, Watabe H, et al. (18)F-FDG accumulation in atherosclerotic plaques: immunohistochemical and PET imaging study. J Nucl Med 2004;45(7):1245-50.
120. 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(3):294-301.
121. Zhang Z, Machac J, Helft G, Worthley SG, Tang C, Zaman AG, et al. Non-invasive imaging of atherosclerotic plaque macrophage in a rabbit model with F-18 FDG PET: a histopathological correlation. BMC Nucl Med 2006;6:3.
122. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermylen D, Cury RC, et al. In Vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. J Am Coll Cardiol 2006;48(9):1818-24.
123. 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(2):107-15.
124. Yoo HJ, Kim S, Park MS, Yang SJ, Kim TN, Seo JA, et al. Vascular inflammation stratified by C-reactive protein and low-density lipoprotein cholesterol levels: analysis with 18F-FDG PET. J Nucl Med 2011;52(1):10-7.
125. Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, et al. Systemic and vascular inflammation in patients with moderate to severe psoriasis as measured by [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT): a pilot study. Arch Dermatol 2011; 147(9):1031-9.
126. Huang B, Law MW, Khong PL. Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. Radiology 2009;251(1):166-74.
127. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168(12):1333-9.
128. Lester SJ, Eleid MF, Khandheria BK, Hurst RT. Carotid intima-media thickness and coronary artery calcium score as indications of subclinical atherosclerosis. Mayo Clin Proc 2009;84(3):229-33.
129. 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(1):139-43.