MR Imaging of Coronary Arteries and Plaques

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ABSTRACT

Cardiac magnetic resonance offers the promise of radiation-free imaging of the coronary arteries, providing information with respect to luminal stenosis, plaque burden, high-risk plaque characteristics, and disease activity. In combination, this would provide a comprehensive, individualized assessment of coronary atherosclerosis that could be used to improve patient risk stratification and to guide treatment. However, the technical challenges involved with delivering upon this promise are considerable, requiring sophisticated approaches to both data acquisition and post-processing. In this review, we describe the current status of this technology, its capabilities, its limitations, and what will be required in the future to translate this technology into routine clinical practice. (J Am Coll Cardiol Img 2016;9:306–16) © 2016 by the American College of Cardiology Foundation.

Myocardial infarction (MI) is a leading cause of death and a major health resource burden that by 2030 is estimated to cost the global economy more than U.S. $1 trillion per year (1). The majority of these events occur as a consequence of atherosclerotic plaque rupture. Identifying plaques at risk of rupture is challenging, however—in particular because these lesions are frequently nonobstructive on antecedent angiography and therefore also missed with conventional ischemia imaging. Interest has therefore developed in novel strategies for improving the prediction of cardiovascular risk in patients. Measures of plaque burden, such as computed tomography (CT) calcium scoring, offer some improvements, particularly in low-risk populations, whereas advances in scanner technology now allow measurement of disease activity and the visualization of high-risk plaque characteristics. A single imaging modality that can assess each of these parameters of coronary atherosclerosis would potentially be a major advance. Specific imaging protocols could then be tailored to different patient populations and combined protocols designed to provide complementary information and to maximize the technique’s prognostic capability. Ideally such a scan would be safe, widely available, and repeatable, allowing us to track coronary atherosclerosis during a patient’s lifetime. This review investigates the promise that cardiac magnetic resonance (CMR) holds in imaging coronary atherosclerosis, with a particular focus on magnetic resonance angiography (MRA), assessments of plaque burden and plaque characteristics alongside evolving molecular technologies that target disease activity (Central Illustration). We examine some of the technical challenges facing CMR, its current capabilities, and how in the future it may become the imaging modality of choice for investigating coronary atherosclerosis.

RATIONALE FOR CMR IMAGING OF THE CORONARY ARTERIES

Magnetic resonance has become a routine clinical imaging investigation used to assess a wide range of...

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tissues and pathophysiological conditions. Although its application to the heart was delayed compared with stationary structures, technological advances in software and hardware components have now lead to its widespread clinical adoption for imaging the myocardium. Applying CMR to the coronary arteries offers further challenges because of both their small caliber and complex motion. As a consequence, coronary CMR has to date lagged behind CT. However, CMR holds several key advantages over CT that might ultimately see it become the imaging modality of choice for assessing the coronary vasculature. First, CMR offers superior soft-tissue contrast, potentially allowing improved detection of high-risk plaque characteristics such as intra-plaque hemorrhage, thrombus, and positive remodeling (Figure 1). Second, CMR is not affected by the calcium blooming that hampers CT and frequently renders luminal assessments impossible in patients with advanced atheroma. Finally and, perhaps most importantly, CMR does not involve exposure to ionizing radiation. This makes it attractive as a screening modality, allows multiple vascular beds to be imaged simultaneously, and renders serial imaging to track disease progression feasible. Moreover, there is the opportunity to image younger patients so that we can better understand the early stages of atherosclerosis and how subjects transition from health to disease. Indeed, it is worth noting that these various advantages have seen CMR, not CT, emerge as the imaging modality of choice for assessing the carotid and peripheral arteries. The challenge therefore is to successfully apply these various techniques to the coronary arteries.

TECHNICAL CHALLENGES AND SOLUTIONS. The coronary arteries are small tortuous structures, have variable 3-dimensional (3D) branches and cover a large volume. A clinically useful assessment requires visualization of the proximal and mid-vessels, which often only measure 3 to 4 mm in diameter (smaller vessels and side branches are less important in guiding patient management) and is made even more difficult by the rapid movement of these arteries with the cardiac cycle and breathing. The requirements for both high spatial resolution and complex motion correction are highly challenging for any imaging modality, but in CMR create a particular tension with respect to scanning times and data acquisition. Although most strategies to improve spatial resolution generate exponential increases in the scanning time required, current motion correction approaches discard large amounts of data while the heart is moving. The future challenge is therefore to find fast CMR techniques capable of high spatial resolution without compromising motion correction and vice versa.

To suppress cardiac motion, data are currently only acquired during end-systolic or mid-diastolic standstill. These periods vary for different coronary arteries and between patients but are around 70 ms for most patients and can be lengthened by reducing heart rate with beta-blockade (2). To suppress respiratory motion, images can be obtained during breath-holding; however, this limits scan time to <20 s and therefore the data that can be acquired. As a consequence, the 3D coverage of these scans is limited to a thin slab with a spatial resolution of ~0.7 × 0.7 × 4 to 5 mm. Alternatively, more detailed images can be obtained during free breathing, using navigator sequences, which measure the position of the diaphragm and only allow data acquisition when the diaphragm is close to a predefined position. Such scans take much longer, between 10 and 15 min. For small deviations of the diaphragmatic position, corrections can be applied; however, even then this approach remains highly wasteful given the amount of data that is discarded. Recent advances in self-navigated techniques measure displacement of the heart directly and then attempt to correct the data for motion rather than discarding it. This has the potential to greatly improve scanner efficiency and to increase spatial resolution (3). This coupled with parallel imaging, higher field strengths, dedicated multichannel receiver coils, fully digital systems, and compressed sensing techniques promise rapid improvements in the image quality associated with coronary magnetic resonance.

MAGNETIC RESONANCE ANGIOGRAPHY. The standard assessment of the coronary vasculature remains the coronary angiogram, which focuses on delineating the arterial anatomy and detecting focal narrowings in its lumen. Various sequences are available for performing coronary MRA (Figure 1). In the cerebral and peripheral arteries, MRA is now clinically established. Translating these successes into reliable coronary MRA has been a focus of research for 25 years since the first reports by Edelman (4) and Manning (5). This section describes current state-of-the-art techniques and some of the more clinically focused research validating coronary MRA against CT and invasive coronary angiography.

For coronary MRA, rapid sequences are essential and most centers use either spoiled gradient echo
(e.g., TurboFLASH) or balanced steady-state free precession (SSFP) (e.g., TrueFISP) sequences. The former requires contrast to generate bright blood angiograms, the latter does not. At higher field strengths, however, SSFP sequences are suboptimal because of longer repetition times (mandated by specific absorption rate limitations), susceptibility to off-resonance effects, and the need for higher flip angles. At 3-T or 7-T, gradient echo imaging with contrast is therefore frequently preferred. Additional preparatory techniques such as frequency selective fat suppression, magnetization transfer contrast, or T-2 pre-pulses may also be used to enhance contrast between the vessel and the surrounding fat, myocardium, or venous blood.

Chelated gadolinium-based contrast agents are most commonly used in contrast-enhanced MRA, shortening the T1 relaxation times of the blood pool. This enhances the coronary lumen compared with surrounding tissue, facilitating improved resolution and discrimination. Gadolinium contrast agents are renally excreted and redistribute into surrounding tissue rapidly so that a time frame of only 10 to 15 min is available for coronary imaging. Nevertheless, this

Cardiac magnetic resonance potentially allows multifaceted imaging of the coronary arteries, providing information with respect to luminal stenosis on angiographic images, plaque burden on black-blood imaging, high-risk plaque characteristics including high-intensity plaques, and disease activity with hybrid positron emission tomography/magnetic resonance imaging.
appears sufficient to generate anatomical images of the coronary arteries and to delineate luminal stenosis, with an accuracy approaching that of CT and invasive coronary angiography (Figure 2). The main 2 disadvantages of current contrast agents are the rapid leakage from the visual lumen into the surrounding tissue, reducing signal-to-noise and the concomitant signal increase in the coronary venous system that can cause overlap with the circumflex artery in particular.

Alternative contrast agents are being investigated. These demonstrate longer half-lives in the circulation, thereby providing more time for navigator-based sequences to acquire data. These include “intra-vascular” albumin-binding gadolinium compounds (e.g., gadofosveset) that are already approved for human use and appear to improve steady-state imaging of the vasculature, while also providing assessments of endothelial permeability and angiogenesis (6,7). Similarly, there is interest in performing coronary MRA using ultrasmall superparamagnetic particles of iron oxide (USPIO), although concerns have been raised about hypersensitivity reactions.

Current performance in the detection of coronary artery disease. Multiple studies have investigated the accuracy with which coronary MRA can detect and quantify coronary luminal stenoses. The first major report by Kim et al. (8) compared coronary MRA to invasive coronary angiography in 109 patients in a multicenter setting, demonstrating an overall diagnostic accuracy for coronary artery disease (CAD) of 72% with a sensitivity and specificity of 93% and 42%, respectively. There was, however, variation depending on the coronary artery being examined, with the tortuous left anterior descending and awkwardly situated circumflex arteries proving most troublesome. A more recent multicenter study demonstrated slightly better results with an overall accuracy of 79%, a sensitivity of 88%, a specificity of 72%, and an area under the curve of 0.87, again using invasive angiography as the gold standard (9). Many similar comparative reports have been published (10-13), culminating in a meta-analysis in 2010 demonstrating that, although MRA had an overall sensitivity of 87% and a specificity of 70% for obstructive coronary disease, CT performed better with values of 97% and 87%, respectively (14). Several advances and developments have been made since this meta-analysis with the latest studies reporting improved MRA results. For example Yonezawa et al. (15) used an unenhanced 3D whole-heart, free breathing, SSFP technique at 1.5-T and reported a sensitivity of 91% and specificity of 86%, with an area under the curve of 0.92. Although these data remain inferior to CT coronary angiography (itself a rapidly advancing technology), it suggests that the gap may be narrowing and that ultimately it might be closed with future technological advances.

Current recommendations. The most recent Appropriateness Criteria for coronary artery imaging recommended coronary MRA for the assessment of anomalies in the coronary arteries (class I) and aorto-coronary bypass grafts (class II) (16). MRA can robustly visualize anomalies of the coronary ostia and coronary aneurysms, helped by the large caliber and minimal motion of these particular abnormalities (16). Another major advantage is the avoidance of ionizing radiation in the young patients affected by these conditions, often making CMR the preferred imaging modality. Although the presence and patency of bypass grafts can be determined with coronary MRA (16), artefact from clips/sternal wires and difficulty in assessing the distal anastomosis mean that CT imaging is usually preferred.

Of note the use of coronary MRA for the assessment of native coronary arteries is currently not regarded as appropriate. However, niche areas are emerging for instance its use in combination with late gadolinium enhancement as a strategy for differentiating ischemic and dilated cardiomyopathies (16).
PLAQUE BURDEN. In addition to luminal assessments, CMR can provide detailed imaging of the arterial vessel wall allowing us to measure plaque thickness in 2-dimensions (2D) and plaque burden in 3D (Figure 1). Classically, this technique involves black-blood imaging sequences, using double inversion recovery pre-pulses to null signal in the arterial lumen followed by fast spin echo sequences to enhance signal within the plaque. More recently, flow-independent black-blood approaches have been suggested, which may be of particular value in the coronary arteries. Both approaches aim to maximize contrast between the vessel wall and the lumen, and addition of fat suppression techniques can then improve resolution between the outer vessel and the surrounding epicardium.

Using these approaches atherosclerotic plaque thickness and 3D plaque burden can be measured in the carotids, providing measures of the atherosclerotic burden that can assess treatment responses to novel therapies and predict major adverse cardiovascular outcomes. The feasibility of this approach to image coronary plaque was first demonstrated in 2000 with black-blood, breath-held, single-slice imaging. High resolution, cross-sectional images of the coronary arteries were obtained, allowing measurement of the coronary wall thickness. These plaque thickness measurements were increased in patients with established ischemic heart disease compared with healthy control subjects and have subsequently been shown to correlate with increasing numbers of cardiovascular risk factors. To date, the standard approach has been to perform 2D measurements of plaque wall thickness on cross-sectional images rather than a more global 3D assessment of plaque burden. These wall thickness measurements have a spatial resolution in the region of $0.7 \times 0.6 \times 3\, \text{mm}$ and scan-rescan reproducibility of $\sim 0.02 \pm 0.20\, \text{mm}$. They have been validated against intravascular ultrasound with mixed results.

Although plaque thickness may provide a surrogate of plaque burden, they will always be prone to sampling error. The ongoing challenge will therefore be to develop rapid methods for imaging the coronary vessel wall in 3D, providing comprehensive plaque burden estimates that can compete with the simplicity of CT calcium scoring. Encouragingly, studies have suggested that 3D black-blood imaging of individual coronary arteries is feasible in patients.
with nonobstructive disease (29) and, further, that whole heart black-blood imaging of the coronary vessels in healthy subjects is possible with a novel flow-independent i-T2prep sequence (17). Simultaneous advances in image analysis will also be required to accurately segment the arterial wall, allowing for rapid plaque burden quantification.

**HIGH-RISK ANATOMICAL PLAQUE CHARACTERISTICS.**

Histological studies have indicated that culprit plaques responsible for MI have certain pathological characteristics, including a large necrotic core, positive remodeling, a thin fibrous cap, angiogenesis, intraplaque hemorrhage, inflammation, and microcalcification (Figure 2). Each of these represents a potential imaging target that might be used to refine our ability to identify high-risk coronary lesions. To better predict an individual person’s risk, it will be important to measure not just the plaque burden but also the high-risk plaque burden. Indeed, emerging data have suggested that identification of such characteristics using CT can improve current patient risk stratification models (30). In the next section, we will review the ability of CMR to identify the specific characteristics that define high-risk plaques.

**POSITIVE REMODELING.**

Individual atherosclerotic lesions with eccentric plaque formation and positive remodeling can be identified using the black-blood CMR measurements of lumen diameter and plaque thickness previously discussed (Figure 1). These measures of increased plaque eccentricity in the aorta and carotids have been shown to predict adverse cardiovascular outcomes (22). Positive remodeling is also detectable in the coronary arteries. In an analysis of 179 patients participating in the MESA (Multi-Ethnic Study of Atherosclerosis) study, 365 cross-sectional black-blood images were sampled. A total of 129 of these images were not interpretable, but, in the remainder, 2D measurements were made of the lumen, the plaque wall, and the epicardial diameter. As coronary plaque wall thickness increased, the overall vessel size increased at a greater rate than the change in lumen area, indicating that the coronary vessel size enlarged to compensate for atherosclerotic change (i.e., positive remodeling) (31). In a similar study, positive remodeling was observed in the right coronary artery of 223 asymptomatic subjects >60 years of age. Again, around one-third of studies were not interpretable, but in the remaining, wall thickness correlated with increased vessel area consistent with positive remodeling and with the degree of coronary calcification (32). CMR studies relating positive remodeling in the coronary arteries to clinical outcomes are awaited.

**PLAQUE HEMORRHAGE AND LUMINAL THROMBUS.**

Met-hemoglobin is an intermediate breakdown product of hemoglobin that is formed 12 to 72 h following hemorrhage and therefore represents a key component of acute thrombus. It is associated with a high signal and short T1, allowing detection of fresh thrombus using magnetic resonance imaging (MRI) in a range of conditions, including deep venous thrombosis and pulmonary embolism. More recently, this approach has been used in atherosclerosis to visualize regions of both endothelial thrombus related to plaque rupture/erosion and intraplaque hemorrhage. In the carotid arteries, noncontrast T1-weighted echo gradient sequences, incorporating fat and blood suppression, can detect high-intensity signal in the culprit plaques of patients who have suffered a recent stroke (33,34). The same authors went on to provide histological validation of this direct thrombus imaging approach in 63 patients who underwent MRI before carotid endarterectomy. They demonstrated that such high-intensity plaques had negative and positive predictive values of 70% and 93%, respectively, for the detection of complex carotid lesions with evidence of surface rupture and intraluminal or intraplaque hemorrhage (35).

More recently, unenhanced T1-weighted 3D imaging sequences (this time incorporating navigator sequences and electrocardiogram gating) have been used to identify intracoronary thrombus. A major advantage of this technique is that it can be used to acquire information across the entire volume of the heart, ensuring that sampling error is not an issue. However, T1-weighted imaging of the coronary arteries does not provide detailed anatomical information and so has to be fused with coronary MRA scans, similar to the approach employed for hybrid positron emission tomography (PET) imaging (Figure 3). This technique appears effective in the coronary vasculature, with a recent study suggesting a sensitivity and specificity of ~90% for thrombus at the site of culprit plaque rupture in patients after MI (36). Similarly, in a multimodality imaging study of patients with angina, high-intensity plaques on these T1 imaging sequences were associated with multiple high-risk imaging features including subclinical intracoronary thrombus on optical coherence tomography (37), positive remodeling on ultrasound, and low attenuation plaque on CT (38).

Unenhanced T1-weighted imaging also appears to provide important prognostic information. The presence of high-intensity plaques in the carotid arteries predicted cardiac events, outperforming carotid intimal medial thickness and traditional cardiovascular risk factors (39). This finding has since been corroborated in a recent meta-analysis of 8 studies.
incorporating 689 patients, which demonstrated a 6-fold increase in cerebrovascular events in patients with high-intensity carotid plaques (40). In the coronary arteries, a case report first described a high-intensity coronary plaque going on to rupture and cause MI (41). Subsequently, a large study demonstrated high-intensity plaques in 159 of 568 patients with known or suspected CAD. Forty-one of these subjects subsequently went on to have a coronary event with the presence of a high-intensity plaque acting as an independent predictor on multivariate analysis (hazard ratio: 3.96; 95% confidence interval: 1.92 to 8.17) (42). Most recently, high-intensity plaques in patients with stable CAD were predictive of periprocedural MI at the time of percutaneous intervention (43). These emerging prognostic data, coupled with the ability to image the entire coronary vasculature, place noncontrast T1-weighted imaging as perhaps the most promising CMR approach for identifying high-risk coronary atheroma.

**INFLAMMATION AND ANGIOGENESIS.** Atherosclerosis is an inflammatory condition characterized at almost every stage by the actions of macrophages, T helper cells, and an array of pro-inflammatory cytokines. In particular, inflammation plays a pivotal role in the precipitation of acute MI, with macrophages secreting matrix metalloproteinases that weaken the fibrous cap, predisposing the plaque to rupture. Angiogenesis is another key process that is triggered by the hypoxic environment within the necrotic core and therefore commonly observed in high-risk lesions. The new vessels that develop are immature, leaky, and associated with intraplaque hemorrhage, which in turn can trigger abrupt plaque growth and/or rupture. Inflammation and angiogenesis therefore both represent key high-risk plaque characteristics with several novel CMR approaches demonstrating early promise in their detection.

Late gadolinium enhancement has become widely used for detecting regions of extracellular expansion in the myocardium. Similarly, in carotid atheroma, gadolinium has been shown to accumulate in areas of interstitial edema, angiogenesis, and fibrosis. Although this technique can be used to image the fibrous cap, late enhancement toward the adventitia relates to deeper regions of inflammation and angiogenesis. In particular, the rate of contrast enhancement on dynamic MRI has been shown to correlate strongly with histological evidence of plaque angiogenesis and macrophage content (44), whereas in a retrospective study, such late enhancement was observed in the culprit lesions of patients post-stroke. Attempts have been made to move this technology into the coronary arteries, with late gadolinium enhancement of these vessels correlating with the severity of atherosclerosis (45) and with vasculitic inflammatory conditions such as systemic lupus erythematosus (46).

Short-tau inversion recovery (STIR) imaging provides T2-weighted images that are sensitive to the increased water content in regions of inflammation. The feasibility of detecting coronary inflammation was first demonstrated in a pig model of coronary balloon injury and validated against histology (47). Subsequent studies have demonstrated an increased STIR signal in the culprit coronary artery of a patient sustaining MI (48) and in regions of persistent inflammation after percutaneous coronary intervention (49). Further work is now required to test whether both late gadolinium enhancement and
STIR imaging can reliably identify coronary plaque inflammation and differentiate stable from unstable atherosclerotic lesions.

**FUTURE TECHNIQUES.** The lipid-rich necrotic core consists largely of oxidized lipid, apoptotic cells, cell debris, and associated inflammation. In the carotid arteries, efforts have been made to image the lipid within these regions. Both fibrous tissue and lipid-rich necrotic core have similar T2 properties and proton densities, making their differentiation difficult. However, late gadolinium enhancement can improve their distinction because, although the atherosclerotic fibrous cap enhances with gadolinium, the necrotic core lacks its own vasculature and appears hypointense. This approach has therefore been used to estimate both the carotid fibrous cap thickness and the size of its necrotic core (50). Importantly, this approach can also be used to identify regions of carotid plaque rupture or ulceration (51) that may or may not be clinically apparent (52).

Translation of these approaches into the coronary arteries has to date not proved feasible and presents a major challenge given the necessary spatial resolution. With further technical advances, identification of coronary lesions with a large necrotic core or a thick fibrous cap may yet still be possible, both of which would be of potential clinical utility. However, CMR is unlikely to provide sufficient resolution to accurately identify thin-capped coronary fibroatheroma, given that these are defined by a cap thickness of <50 μm.

**Microcalcification.** Like CT, CMR can resolve regions of macroscopic calcium that have a hypointense signal on most CMR sequences and are generally associated with plaque stability. By contrast, CMR is unable to resolve the areas of microcalcification that are associated with increased plaque vulnerability, although hybrid imaging with 18F-fluoride PET holds great potential in this regard. Mechanical stress and shear stress appear to have an important role in driving both the development of atherosclerotic lesions; for example, in areas of low shear stress such as bifurcations, and also the propensity to plaque rupture at sites of increased mechanical stress. Both can be modeled using finite element analysis on the basis of anatomical imaging provided by CMR and may therefore be of use in better understanding the pathophysiology leading to clinical events (53). Similarly, assessments of coronary flow may provide assessment of hemodynamic obstruction associated with individual coronary lesions and measurement of the coronary flow reserve (54,55).

**DISEASE ACTIVITY**

The ability to study the activity of specific pathological processes is now with us, heralding the dawn of a new era of cardiovascular molecular imaging. CMR sits at the center of that capability with the availability not only of specific magnetic resonance tracers, but also with the emergence of hybrid PET and MRI systems that can harness the unrivaled sensitivity and availability of PET imaging agents.

**CMR-BASED TRACERS.** Alongside their potential as intravascular contrast agents, the powerful T2* effects of USPIOs have been used to target a wide range of molecular processes. In humans, USPIOs have been used off-label to study vascular inflammation. After intravenous administration, USPIOs become engulfed by activated monocytes resulting in a reduced CMR signal in tissue subsequently infiltrated by these cells. This technique has been used to monitor vascular macrophages in carotid atheroma, demonstrating increased USPIO uptake in culprit carotid plaques post-stroke compared with contralateral lesions (56) and reduction in this signal with statin therapy (57). Translation of these imaging agents in to coronary atheroma is keenly awaited, although it should be noted that the strong blood-pool signal provided by USPIOs may make identification of signal in the coronary wall challenging.

At the pre-clinical level, USPIOs have been incorporated into a wide range of imaging nanoparticles that can then be targeted to different pathophysiological processes. The iron oxide then allows these nanoparticles to be tracked in vivo using T2-weighted MRI. Similarly, other MRI contrast agents can be used. For example, lipid micelle nanoparticles targeting oxidized lipid have been labeled with gadolinium (58), iron oxide (59), and manganese (60) and used to image murine atheroma. We have also used USPIOs to label modified high-density lipoprotein particles. These particles evade the immune system and naturally migrate to lipid-rich murine atheroma with the potential of providing important diagnostic and mechanistic information (61). Moreover, the center of these particles can be loaded with pharmacological agents, transforming them into drug delivery systems, targeting the most active and inflamed plaques (62). If this nanotracer technology can be translated in to humans, it might potentially allow us to both image and treat high-risk plaques with a level of specificity not previously possible.

**HYBRID PET/CMR IMAGING.** The advent of hybrid PET/CMR imaging has presented the opportunity to harness the molecular imaging available with PET...
alongside established CMR techniques. To date, coronary PET studies have exclusively been fused with CT, but CMR has multiple advantages, such as motion correction and soft-tissue contrast that are likely to see it increasingly used. To date, 2 tracers in particular have been used to target disease activity and high-risk atherosclerotic plaques: 18F-fluorodeoxyglucose (18F-FDG) and 18F-fluoride. 18F-FDG is a glucose analog that has been widely used as a marker of vascular inflammation in the carotid arteries on the basis that macrophages use more glucose than surrounding cells. Indeed, 18F-FDG uptake in the carotids correlates closely with macrophage burden, localizes to culprit plaque following stroke, and is modifiable with statin therapy (63). Studies using this tracer in the coronary arteries have had mixed results, predominantly because glucose is also the predominant energy source of the myocardium, with uptake in the heart muscle often obscuring coronary activity (64,65).

18F-fluoride has recently been shown to preferentially bind regions of vascular microcalcification activity beyond the resolution of CT (66). In contrast to the macroscopic calcium deposits detected by CT that impart stability, microcalcification is consistently associated with high-risk coronary lesions and increased risk of rupture (67). 18F-fluoride uptake in the coronary arteries has now been described in 2 clinical trials. In the first, increased uptake could be localized to individual coronary plaques and identified high-risk patients with increased Framingham risk scores (68). In the second, increased activity colocalized to individual coronary plaques in patients with stable angina, with multiple high-risk features including a large necrotic core, microcalcification, and positive remodeling. A parallel cohort of patients post-MI 18F-fluoride localized to the culprit coronary plaque in 37 of 40 subjects, demonstrating that at least retrospectively 18F-fluoride can identify the individual lesions responsible for adverse coronary events (65) (Figure 3). The ability of this technique to prospectively identify high-risk patients at risk of MI is currently being tested in a large prospective multicenter study (PREFUR [Prediction of Recurrent Events With 18F-Fluoride]; NCT02278211).

What role then might PET/CMR play in the rapidly developing field of coronary plaque imaging? Perhaps the 2 major obstacles to the widespread adoption of these PET techniques are that of cardiac motion and radiation exposure. PET/MRI offers potential solutions to both. In particular, the novel self-navigation CMR techniques described earlier can be used to correct both MRI and PET images without discarding any data, and thereby improving the efficiency of scanning (69). Moreover, PET/MRI promises to reduce radiation doses by as much as 75% compared with PET/CT. This would allow cardiac PET to be performed using 3 to 4 mSv, making this a potentially acceptable clinical tool and facilitating serial imaging to investigate how disease activity changes with time or with novel therapeutic interventions.

**FUTURE APPLICATIONS: IDENTIFYING THE VULNERABLE PATIENT**

CAD is a complex, multifaceted, and continuously evolving disease process, making the identification of patients at high risk of future MI challenging. Accurate risk prediction is likely to require a similarly multifaceted approach, playing to one of the key strengths of CMR. Indeed, in a single scan, CMR can potentially assess luminal stenosis, plaque burden, high-risk plaque characteristics, and disease activity (Central Illustration). Data to date suggest that high-risk plaques are fairly ubiquitous in the coronary vasculature and that the majority will not go on to cause clinical events (70). First, many of these plaques will heal rather than rupture and, second, even when rupture does occur then it is usually subclinical. This has raised doubt as to whether the positive predictive value of identifying individual high-risk plaques will ever be great enough to warrant intervention (71). A patient-level approach may therefore be more effective, perhaps combining markers of plaque burden, ischemia, high-risk plaque characteristics, and disease activity to identify the vulnerable patient (72). Such patients might then benefit from systemic rather than plaque directed intervention. Indeed, with the advent of novel, expensive, and potentially toxic treatments such as Ticagrelor and PCS-K9 inhibitors, an imaging strategy that can target these medications to patients at the highest risk would be of real clinical utility. CMR would appear well positioned to assume such a role in the future if the technical challenges associated with imaging the coronary arteries can be overcome.

**CONCLUSIONS**

CMR has the potential to provide a multiparametric assessment of coronary atherosclerosis incorporating key information related to plaque burden, high-risk plaque characteristics, and disease activity alongside more conventional assessments of luminal stenosis. Considerable technical challenges remain in reliably translating these techniques in to the coronary arteries; however, if these can be met, then CMR holds real promise in improving our understanding of CAD, identifying patients at increased cardiovascular risk,
and in delivering the promise of truly personalized health care for CAD.

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