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Review article

# New methods to image unstable atherosclerotic plaques

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ABSTRACT

Atherosclerotic plaque rupture is the primary mechanism responsible for myocardial infarction and stroke, the top two killers worldwide. Despite being potentially fatal, the ubiquitous prevalence of atherosclerosis amongst the middle aged and elderly renders individual events relatively rare. This makes the accurate prediction of MI and stroke challenging. Advances in imaging techniques now allow detailed assessments of plaque morphology and disease activity. Both CT and MR can identify certain unstable plaque characteristics thought to be associated with an increased risk of rupture and events. PET imaging allows the activity of distinct pathological processes associated with atherosclerosis to be measured, differentiating patients with inactive and active disease states. Hybrid integration of PET with CT or MR now allows for an accurate assessment of not only plaque burden and morphology but plaque biology too. In this review, we discuss how these advanced imaging techniques hold promise in redefining our understanding of stable and unstable coronary artery disease beyond symptomatic status, and how they may refine patient risk-prediction and the rationing of expensive novel therapies.



## 1. Introduction

Atherosclerotic plaque rupture is the primary mechanism responsible for two of the biggest killers worldwide: myocardial infarction and stroke [1]. In 2015, 423 million people were estimated to be living with cardiovascular disease, and it caused an estimated 18 million deaths. Whilst the clinical effects of atherosclerotic plaque rupture can be devastating, the development of atheromatous plaque is itself a silent and for many a benign process. Indeed, atherosclerosis is an almost ubiquitous finding in older patients the majority of whom will never suffer a cardiovascular event. Perhaps, the major challenge facing contemporary cardiovascular researchers is therefore to develop methods of accurate risk prediction without over medicalizing the population as a whole. In this review, we will briefly discuss the pathophysiology of atherosclerosis before investigating novel non-invasive imaging methods aimed at detecting unstable atherosclerotic plaque and measuring disease activity in the coronary arteries and large vessels. These advanced imaging techniques hold promise in redefining our understanding of stable and unstable coronary artery disease beyond a patient's symptomatic status with the potential to improve our pathological understanding, to refine patient risk-prediction and to appropriately target expensive novel therapies.

### 1.1. Pathophysiology of atherosclerosis

Atherosclerosis is a smouldering immunoinflammatory disease fuelled by lipids [2]. It is characterised by focal thickening of the arterial intima (plaque formation) in medium and large sized arteries. Within the plaques lipid, inflammatory infiltrates, smooth muscle cells and connective tissues are found. An injury to the plaque cap known as a plaque rupture results in exposure of its core contents to the blood, causing acute thrombus formation and either partial or complete occlusion of the vessel lumen [3]. Atherothrombosis from plaque rupture is the most common cause of fatal myocardial infarction, accounting for approximately three quarters of cases, with plaque erosion accounting for the remaining quarter [4]. However, the majority of coronary plaque rupture events appear to be clinically silent, resulting in plaque growth rather than myocardial infarction.

Atherosclerosis begins in a hypercholesterolaemic state where low-density lipoproteins (LDL) infiltrate the endothelial wall. Subsequent oxidation of LDL molecules causes an inflammatory response with infiltration of T-lymphocytes and macrophages that consume LDL and form foam cells. This is initially protective, but

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with further LDL accumulation, macrophage cell death is ultimately triggered, contributing to further inflammation and the development of a necrotic core of soft unstable atheroma. Plaque inflammation also triggers smooth muscle cell loss and the production of matrix metalloproteinases (MMP) that weaken the fibrous cap, predisposing it to plaque rupture [2,5]. The thick necrotic acellular lipid core becomes increasingly hypoxic, stimulating angiogenesis, with the formation of immature microvessels prone to intra-plaque haemorrhage (IPH) [6–8].

Similar to tuberculosis [9], calcification of atherosclerotic plaque is thought to be a healing response to intense necrotic plaque inflammation characterised by two distinct stages. In the latter stage of macrocalcification, the healing process is complete and the plaque stabilised [10–12]. By contrast, the earlier stage of microcalcification is a common feature of ruptured and unstable plaques where healing is incomplete, inflammation remains active and the fibrous cap weakened by the tiny calcific deposits [13–15].

Unstable plaques at risk of rupture, therefore, have certain pathological features, including a large necrotic core, thin fibrous cap, inflammation, hypoxia, haemorrhage and microcalcification. By contrast, stable plaques at low risk of rupture have different characteristics, including a thick fibrous cap and macroscopic calcification. Advanced imaging now allows us to identify these plaque characteristics *in vivo* and determine whether patients predominantly have stable or unstable atheroma. Development of hybrid molecular imaging allows us to measure disease activity in the coronary arteries, directly. These developments hold promise in altering how we define stable and unstable atherosclerosis and in refining risk prediction beyond standard approaches. However, it should be noted that the plaque characteristics and pathophysiology underlying plaque erosion remain poorly understood, representing an important limitation of this approach.

### 1.2. Atherosclerotic plaque imaging

Direct imaging of coronary atherosclerotic plaque is now possible with CT calcium scoring (CACs) and coronary computerised tomography angiography (CCTA). This has permitted more accurate determination of coronary plaque burden, the presence of both obstructive and non-obstructive disease and assessments of plaque composition. Magnetic resonance (MR) whilst not as advanced as CT can provide similar information without radiation exposure, whilst novel PET approaches allow, for the first time, assessment of coronary disease activity. These plaque-imaging techniques are developing rapidly and, in the case of CT, starting to enter routine clinical practice. They are discussed in greater detail below and illustrated in Fig. 1.

### 1.3. Measures of plaque burden

Atherosclerotic plaque burden can be measured in different vascular beds using multiple different modalities, including ultrasound, CT and MR. Regardless of the methodology, plaque burden assessments provide powerful prognostic information, based upon the rationale that the greater number of plaques, the more likely a plaque is to rupture and cause an event.

CT calcium scoring is the best studied technique having been incorporated in to clinical guidelines [16] and providing prognostic information of incremental value to standard risk factor assessments [17]. However, most patients with high CT calcium scores will never suffer a clinical event. This may be because whilst CT calcium provides a surrogate of global plaque volume, it actually targets stable macrocalcific plaques, not the unstable plaques at highest risk of rupture. Moreover, CT calcium scoring cannot differentiate stable burnt-out disease from active unstable

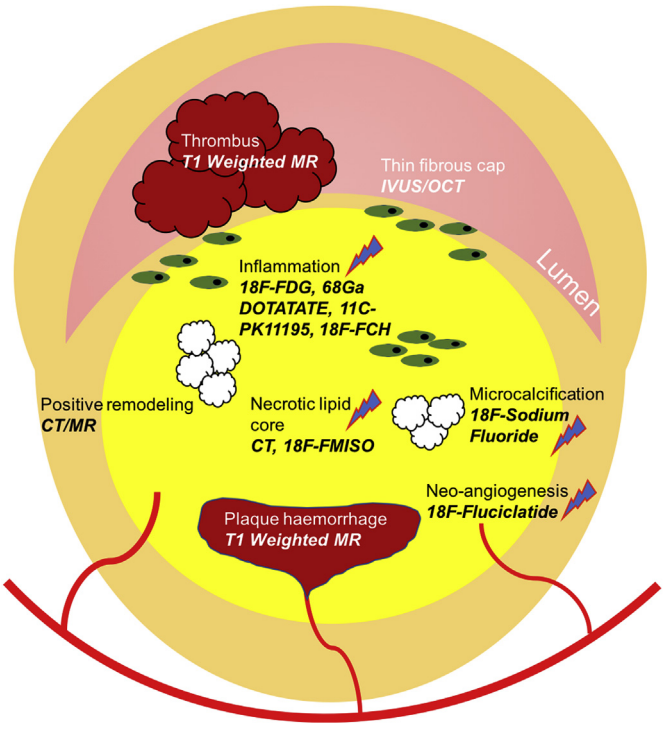


**Fig. 1.** Schematic representation of morphological and biological targets for unstable plaque imaging.

atheroma. Methods that can directly quantify unstable plaque and assess disease activity are therefore required.

### 1.4. Plaque morphological characteristics

Culprit plaques that have ruptured and caused an event have certain histological characteristics. Indeed, many retrospective and pathological studies have demonstrated the thin capped, fibro-fatty atheromatous (TCFA) plaque as the cause for the majority of myocardial infarctions and strokes [15,18–20]. Other recognised features of potentially unstable plaques are microcalcification, positive remodelling, inflammation and plaque haemorrhage [21], each representing a potential imaging target to improve the identification of high risk patients. As with plaque burden, multiple imaging modalities have been employed to better characterise plaque morphology.

IVUS can assess plaque burden, positive remodelling and lipid core. Moreover, virtual histology IVUS (VH-IVUS) allows direct detection of the VH-IVUS TCFAs in the coronary vasculature [22–24]. However, in the PROSPECT study of the 695 patients, whilst 595 VH-IVUS TCFAs were identified, only 6 MIs were observed over a 3-year period [25]. Comparable findings were reported in the VIVA study [26], suggesting low predictive value of these supposedly high-risk plaques [27,28]. We, therefore, prefer the term unstable plaque characteristics.

The other main invasive assessment of unstable plaque is OCT. This technique is particularly good at imaging the fibrous plaque, with the ability to identify thin caps and both plaque rupture and erosion [29,30]. Emerging OCT techniques offer assessment of further unstable plaque characteristics including plaque macrophages and angiogenesis [31–33]. However, similar to VH-IVUS, OCT-defined unstable plaques only rarely cause clinical events, so that plaque directed therapies cannot be recommended [34].

Contrast coronary CT angiography (CCTA) offers major