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CLINICAL REVIEW
Imaging

Imaging residual inflammatory cardiovascular risk

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Targeting residual cardiovascular risk in primary and secondary prevention, would allow deployment of novel therapeutic agents, facilitating precision medicine. For example, lowering vascular inflammation is a promising strategy to reduce the residual inflammatory cardiovascular risk in patients already receiving optimal medical therapy, but prescribing novel anti-inflammatory treatments will be problematic due to the lack of specific companion diagnostic tests, to guide their targeted use in clinical practice. Currently available tests for the detection of coronary inflammation are either non-specific for the cardiovascular system (e.g. plasma biomarkers) or expensive and not readily available (e.g. hybrid positron emission tomography imaging). Recent technological advancements in coronary computed tomography angiography (CCTA) allow non-invasive detection of high-risk plaque features (positive remodelling, spotty calcification, low attenuation plaque, and napkin-ring sign) and help identify the vulnerable patient, but they provide only indirectly information about coronary inflammation. Perivascular fat attenuation index (FAI), a novel method for assessing coronary inflammation by analysing routine CCTA, captures changes in the perivascular adipose tissue composition driven by inflammatory signals coming from the inflamed coronary artery, by analysing the three-dimensional gradients of perivascular attenuation, followed by adjustments for technical, anatomical, and biological factors. By detecting vascular inflammation, perivascular FAI enhances cardiovascular risk discrimination which could aid more cost-effective deployment of novel therapeutic agents. In this article, we present the existing non-invasive modalities for the detection of coronary inflammation and provide a practical guide for their use in clinical practice.

Keywords Inflammation • Coronary computed tomography angiography • Fat attenuation index • Perivascular fat • Cardiovascular risk

Introduction

Coronary artery disease (CAD) remains a leading cause of death and disability.[1] Current cardiovascular risk modification focuses on lifestyle interventions and the optimal control of traditional risk factors.[2–4] Newer treatments such as pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or canakinumab,[5] could also be administered in certain patients,[4] but their untargeted deployment is not cost-effective. It is therefore essential to develop new non-invasive diagnostic tests that would identify the vulnerable patient, going beyond current clinical risk scores,[6] which have moderate only performance, systematically overestimate the actual risk for cardiovascular events,[7] and are inappropriate for assessing risk in special groups of patients, such as those with autoimmune chronic diseases (e.g. psoriasis, rheumatoid arthritis) or HIV, known to be at high cardiovascular risk.[8] As many acute coronary syndromes (ACS) occur in individuals without obstructive atherosclerotic plaques,[9,10] new tests should focus on identifying the vulnerable coronary plaques, rather than the degree of luminal stenosis they cause.

Vascular inflammation is a critical factor involved not only in atherosclerotic plaque formation, but also in the triggering of plaque rupture. The role of inflammation in atherosclerosis has been recognized for decades,[11] and its importance in human coronary atherosclerosis is further supported by epidemiological evidence and Mendelian randomization studies.[11,12] Recently, the CANTOS trial provided the first clinical evidence that reducing systemic inflammation by the intereleukin-1b inhibitor canakinumab significantly lowers the risk of major adverse cardiovascular events.[5] Therefore, the assessment of 'residual inflammatory risk' has been proposed as a rational strategy for enhancing risk prediction and guiding the deployment of cost-effective, precision treatments for cardiovascular disease prevention.[5] These concepts are summarized in *Figure 1*.

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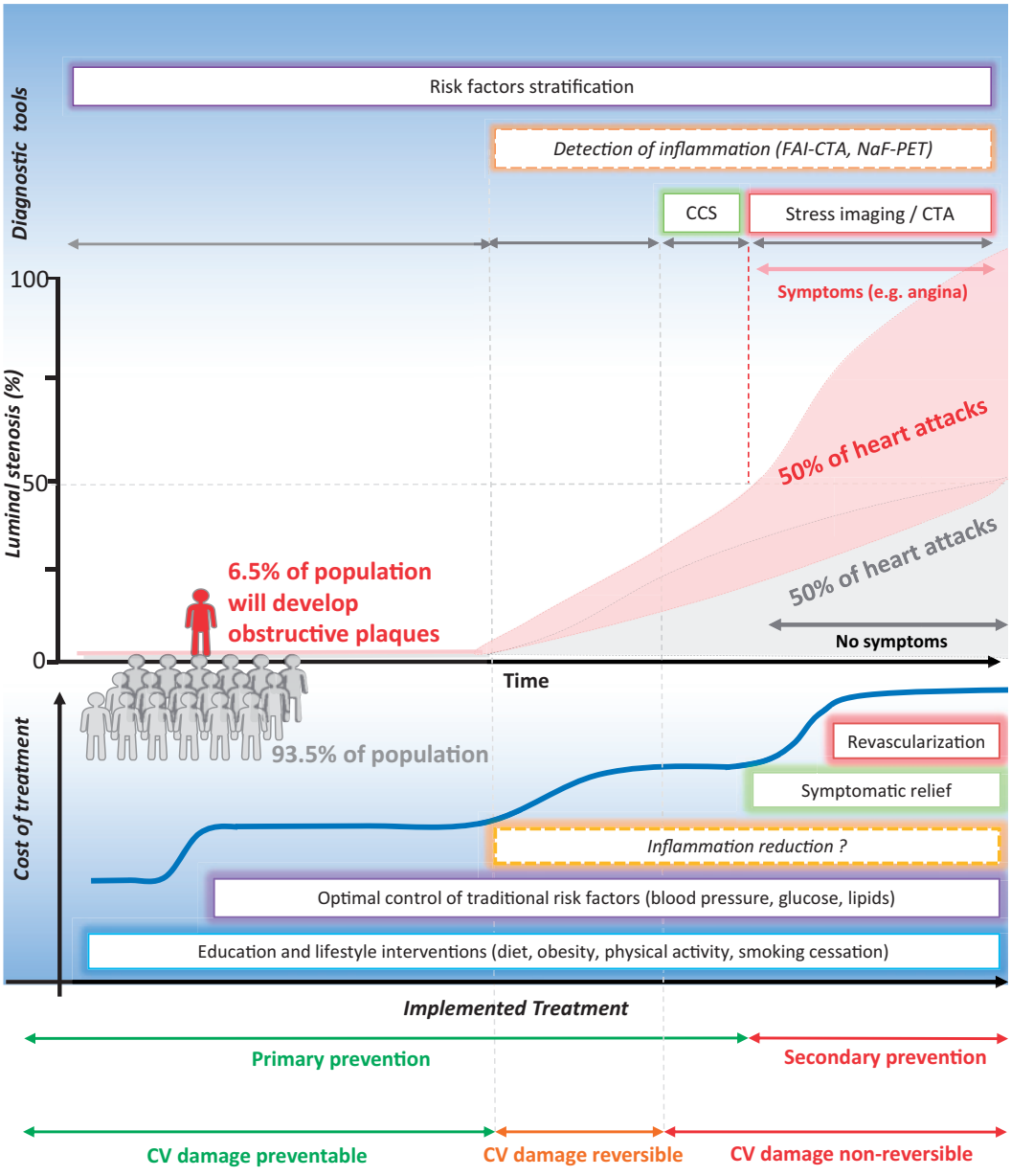


Figure 1 Current landscape in cardiovascular risk stratification. A schematic representation of coronary luminal stenosis over ageing (chronological or biological) is shown at the top. It is estimated that ~6.5% of the general population will develop obstructive coronary artery disease during their lifetime. At the early stages of disease, before the clinical manifestations of atherosclerosis, cardiovascular risk stratification is based on the assessment of the clinical profile and the use of risk scoring systems (which usually have modest predictive accuracy). In asymptomatic subjects, risk prediction can be further enhanced by coronary calcium scoring. Non-invasive diagnostic assessment of symptomatic subjects relies on functional stress imaging or anatomical assessment by coronary computed tomography angiography. However, ~50% acute coronary syndrome occur in patients without any obstructive plaques,[69] for whom usual functional imaging tests are of limited diagnostic value. Novel, accurate, and cost-effective ways for cardiovascular risk discrimination (e.g. assessment of coronary inflammatory burden) would allow the deployment of more effective prevention treatment strategies and save lives, but appropriate screening tools for the detection of coronary inflammation have been lacking.

Residual inflammatory risk can be quantified either by measuring circulating inflammatory biomarkers [e.g. high sensitivity C-reactive protein (hsCRP)] or by imaging [e.g. positron emission tomography/computed tomography (PET/CT)]. However, circulating biomarkers lack specificity for vascular inflammation, while PET/CT is expensive and not widely available. Coronary calcium score measured by CT, is a rational biomarker for risk stratification in low/intermediate risk individuals, but it is increased by risk-modifying treatments such as statins, limiting its use in secondary prevention. We have recently developed[13] and validated[14] a new method for the non-invasive

quantification of coronary inflammation by analysing the changes of perivascular adipose tissue (PVAT) attenuation (or radiodensity) in coronary computed tomography angiography (CCTA). This new biomarker, called perivascular fat attenuation index (FAI), overcomes many of the limitations of existing biomarkers,[13,14] and could be a valuable tool for the quantification of residual inflammatory risk and cardiovascular risk stratification.

In this article, we discuss the existing non-invasive modalities for the detection of coronary inflammation with special focus on CCTA assessment and the newly developed FAI technology.

Inflammation in vascular disease pathogenesis

Types of inflammation and relevance to the cardiovascular system

The links between the immune system and atherogenesis are well established.[11] Resident immune cells may become activated in a non-specific way by pathogens as a generic host defence (innate immunity) leading to the respiratory burst of macrophages, activation of mast cells, neutrophils, and the complement system cascade.[15] Activation of toll-like receptors (TLRs) on immune cells also triggers pro-inflammatory signalling responses and dendritic cell activation, which cross-link innate and adaptive immunity. The latter is a highly organized defence mechanism, more relevant to atherosclerosis, via the interactions between antigen presenting cells (dendritic cells, B cells, macrophages) and naive T cells, leading to T-cell responses, and antibody secretion. T-cell activation leads to production of interferon-γ and pro-inflammatory interleukins that perpetuate T-cell responses.[15]

Atherosclerosis is a state of systemic low-grade inflammation associated with immune system activation in the presence of classic risk factors (i.e. diabetes mellitus, dyslipidaemia, hypertension), but also related to other conditions (e.g. periodontitis).[16] This chronic low-grade inflammation is different to the severe chronic inflammatory state associated with autoimmune conditions e.g. psoriasis, rheumatoid arthritis, *per se* leading to a 1.5- to 2.0-fold increase in the risk of cardiovascular events.[17] Acute inflammation e.g. associated with systemic infections/sepsis also leads to pro-inflammatory cytokine production, but this is less relevant to atherosclerosis.

Inflammation in atherosclerotic plaque formation and rupture

Low-grade inflammation leads to endothelial dysfunction and loss of nitric oxide bioavailability,[18] followed by the expression of cell adhesion molecules and selectins, a process which is induced by pro-inflammatory cytokines, and attracts circulating leukocytes into arterial intima (*Figure 2*).[19] Pro-inflammatory mediators trigger the production of reactive oxygen species that oxidize LDL in the sub-endothelial space. Oxidized-LDL is taken up by macrophages who are turned into foam cells, initiating plaque development.[19] Activated T-lymphocytes and smooth muscle cells (SMC) are also involved in the inflammatory response, which results in SMC proliferation and migration to the intima. At this stage, regulated differentiation of SMC to osteoblasts can lead to intimal/medial arterial calcification and plaque stabilization.[20] However, excess plaque inflammation and extracellular matrix degradation by matrix-metalloproteinases results in tissue remodelling and cap destabilization[11,21] ultimately leading to plaque rupture, coronary thrombosis, and ACS.[19]

Perivascular adipose tissue and plaque inflammation

Evidence suggests that PVAT secretes pro-inflammatory cytokines and other bioactive mediators which diffuse into the adjacent vascular wall, promoting atherogenesis in a paracrine manner ('outside-in' signalling).[22,23] However, reverse signalling from vessels to the surrounding fat also takes place. Wire-injury of the vascular wall leads to pro-inflammatory changes in PVAT phenotype via tumour necrosis factor (TNF)-α signalling.[24] In humans, vascular oxidative stress triggers vasoprotective responses in PVAT[25–27] (as a local defence mechanism), and arterial inflammation induces well-described morphological changes in PVAT.[13] In our previous studies using human vessels, we have demonstrated that inflammatory molecules (e.g. TNF-α, interleukin-6) released from the inflamed arterial wall, diffuse into the perivascular space inducing lipolysis and supressing adipogenesis,[13] in a model that resembles a local 'cachexia-type' response of PVAT to vascular inflammation. This response reduces adipocyte size and leads to a gradient of the lipophilic phase of PVAT around the vascular wall.[13,26] Therefore, reported differences in epicardial fat biology[28] or volume[29] in the presence of coronary atherosclerosis could be the result of vascular inflammation rather than the cause of vascular disease. Following the discovery that vascular inflammation drives phenotypic changes in PVAT in a paracrine way (via inside-out signals), an experimental study using a porcine model demonstrated a striking increase of fluorodeoxyglucose (FDG) uptake by PVAT following angioplasty injury.[30] This study confirmed the concept that inflammatory events in the vascular wall induce changes in PVAT, contrary to the belief of an exclusively 'outside-in' signalling (i.e. from PVAT to the vascular wall). Whether adipose tissue 'browning' is included among vascular inflammation-induced changes in PVAT remains to be seen.[31] The interactions between vascular inflammation and PVAT in atherogenesis are summarized in *Figure 2*.

Non-invasive approaches to detect coronary inflammation

Circulating markers of inflammation

Anti-inflammatory interventions (such as statins[32] or canakinumab[5]) reduce cardiovascular risk. On the other hand, administering non-specific anti-inflammatory treatments to patients with normal hsCRP (e.g. methotrexate)[33] has no impact on clinical outcomes. Measurement of circulating levels of pro-inflammatory mediators (e.g. hsCRP, interleukin-6, interleukin-1b, or interleukin-1 receptor antagonist and lipoprotein-associated phospholipase A2 etc.), is a widely used strategy to quantify residual inflammatory risk.[5,12,32,34–36] Both circulating hsCRP and interleukin-6 are independently associated with cardiovascular events [for upper CRP tertile hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.1–1.3; per 2 SD increase in plasma IL6 odds ratio 1.6, 95% CI 1.4–1.8],[37,38] but they provide only modest predictive information (c-statistic in the range of 0.61–0.65)[37,39] and may overestimate risk in the primary prevention

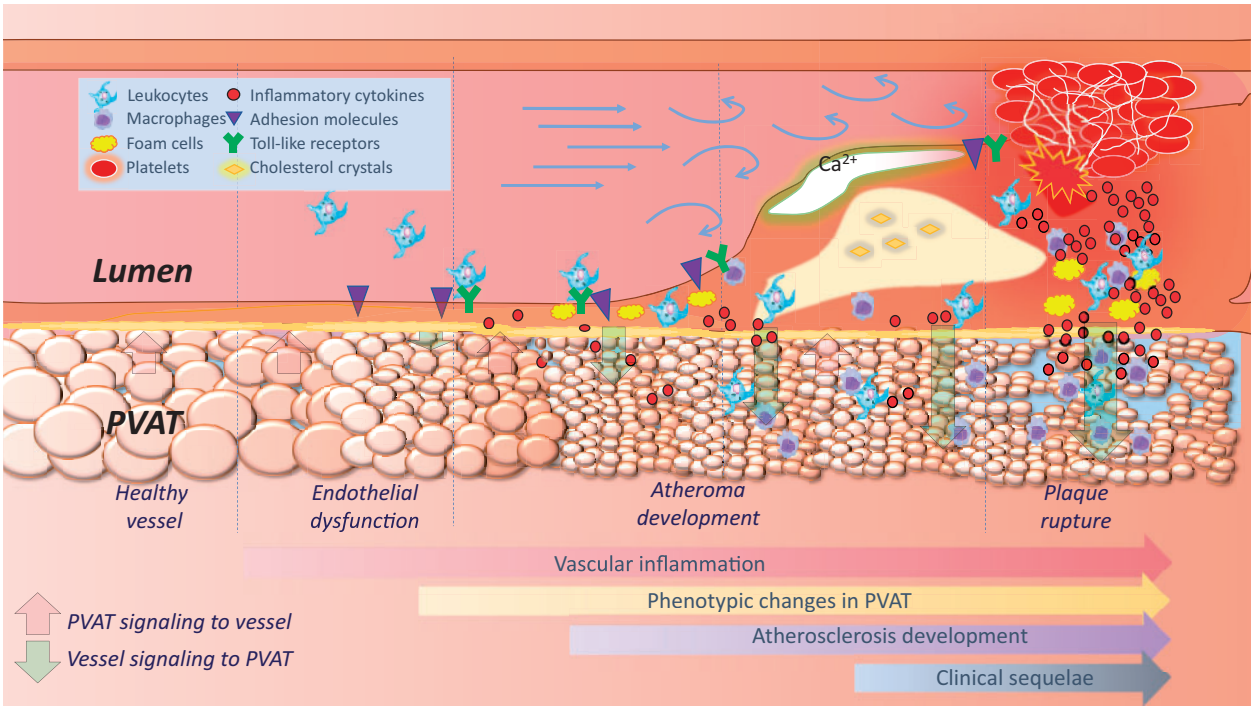


Figure 2 The role of inflammation and perivascular adipose tissue in atherosclerosis. Pro-inflammatory mechanisms are involved in early endothelial dysfunction and the recruitment of inflammatory cells and lipoproteins into the vascular intima, which contribute to a vicious cycle of lipid accumulation, foam cell formation, fatty streak development, and perpetuate vascular wall inflammation, leading to plaque formation and rupture, local thrombosis, and acute coronary syndrome. Phenotyping of coronary plaques by coronary computed tomography angiography can detect anatomical high-risk plaque features that independently predict plaque rupture events. Perivascular adipose tissue adipocytes regulate aspects of vascular biology via secretion of active adipokines, but also receive inflammatory stimuli from the underlying vessel, which inhibit adipocyte differentiation and intracellular lipid accumulation. A shift in perivascular adipose tissue phenotype as the result of vascular inflammation takes place at the early stage of vascular disease, before the development of any vascular lesions, while in advanced atherosclerosis and/or after a plaque rupture event, high levels of vascular inflammation lead to the loss of fat droplets in perivascular adipocytes and a shift in the lipid:aqueous phase of perivascular adipose tissue. PR, positive remodelling.

setting.[34] For example, based on hsCRP levels, it is estimated that almost ~60% of subjects in the secondary prevention setting could be classified as having 'high residual inflammatory risk'.[34] The profiling of circulating non-coding RNAs are alternative approaches for cardiovascular risk stratification,[40,41] but their accurate measurement is problematic, and their clinical value unclear.

Gut microbiota is implicated in the pathogenesis of atherosclerosis and the development of arterial hypertension. Microbiota may induce systemic inflammation via microbial colonization and/or the release of active, pro-inflammatory metabolites in the plasma.[42] These pro-inflammatory mediators can trigger tissue inflammatory pathways, such as inflammasome activation in epicardial adipose tissue and possibly within the vascular wall.[42] Plasma levels of both trimethylamine N-oxide (TMAO) (a pro-atherogenic and pro-thrombotic metabolite produced from gut microbiota) and its precursor trimethyllysine, have independent value in predicting major adverse cardiovascular events in patients with ACS (c-index 0.76–0.80).[43,44] Whether biomarkers of gut microbiota can be used as surrogates for vascular inflammation is unknown, but findings from recent studies suggest that these biomarkers may be useful in cardiovascular risk stratification.

Hybrid positron emission tomography imaging of vascular inflammation

Positron emission tomography/computed tomography and PET/magnetic resonance (MR) are non-invasive imaging modalities that co-register PET images with CT or MR anatomical data. The most widely used radioactive tracer, 18-fluorodeoxyglucose (^{18}F-FDG) is taken up by metabolically active cells (such as macrophages) and can monitor inflammation in the human arterial wall (e.g. of carotid arteries or aorta),[45] albeit not directly informative about the inflammatory burden of coronary arteries (due to increased background noise and high ^{18}F-FDG uptake by the myocardium). The predictive value of arterial (i.e. aortic) ^{18}F-FDG uptake for future cardiovascular events is only modest (c-statistic 0.66)[46] and does not detect ruptured coronary plaques in >50% of ACS patients.[47]

Other tracers, such as e.g. sodium fluoride 18F (^{18}F-NaF) or Gallium 68 (^{68}Ga)-DOTATATE have better specificity for coronary inflammation. ^{18}F-NaF is taken up by areas of active microcalcification that correspond to vascular inflammation and active vascular disease.[48] Uptake of ^{18}F-NaF is significantly increased in ruptured

coronary plaques,[48] although the predictive value of such measurements is unexplored. Use of 68Ga-DOTATATE imaging, a somatostatin receptor subtype-2 (SST2)-binding PET tracer, tracks M1-primed pro-inflammatory macrophages, and is increased in culprit lesions of ACS patients.[49] Other PET imaging systems, such as CXC-motif chemokine receptor 4 (CXCR4) imaging using 68Ga-pentoxifaxor tracer,[50] PET/MR imaging systems of oxidation-specific epitopes using a zirconium-89 (^{89}Zr)-labelled tracer (^{89}Zr-LA25)[51] or choline-based tracers and others[52] could be also useful tools for imaging of inflamed atherosclerotic lesions, but more data are needed on their diagnostic and predictive performance. Despite the unique information on the links between immunology and vascular inflammation provided by PET/CT or PET/MR, these methods remain expensive, with limited clinical availability and high radiation exposure.

Other methods for molecular imaging of inflammation in preclinical models

Contrast-enhanced ultrasound molecular imaging of vascular inflammation using microbubbles (e.g. targeted to vascular cell adhesion molecule-1)[53] has existed for more than a decade, but is not widely used in clinical practice. Short-tau inversion recovery T2-weighted cardiac magnetic resonance (CMR) imaging has been used to detect adventitial oedema and coronary inflammation in animal models.[54] Also studies with MR imaging of myeloperoxidase using novel paramagnetic sensors (Gd-5HT-DOTAGA) have yielded promising findings in experimental models of atherosclerosis.[55] Nonetheless the clinical application of MR angiography for detection of coronary inflammation remains limited.[54] Progress in hybrid fluorescence-mediated tomography co-registered with CT or MR could be a future alternative to the use of radiolabelled PET tracers for imaging vascular inflammation,[56] but to date these method lack clinical applicability.

Anatomical detection of high-risk plaque features using coronary computed tomography angiography

Another strategy to identify the vulnerable patient is by phenotyping atherosclerotic plaques for high-risk features.[14] Coronary computed tomography angiography informs not only on the presence of obstructive plaques and coronary plaque burden, but also on the presence of high-risk plaque (HRP) features, i.e. the napkin-ring sign, positive remodelling (remodelling index >1.1), low attenuation plaque, and spotty calcification.[57] HRP features are not a direct metric of inflammation, but are anatomical signs of plaque vulnerability and flag the risk of rupture (which is primarily driven by plaque inflammation).[57] HRP features provide incremental predictive value for coronary events on top of the extent of coronary atherosclerosis in patients undergoing diagnostic CCTA.[58,59] Certainly, the subjective assessment of HRP features, and the increase of vascular calcification by statins make the role of CCTA or non-contrast CCT in secondary prevention challenging. The risk reclassification value of HRP features is greatest in lower risk groups, such as younger patients, women and those with non-obstructive CAD,[59] and their reporting is recommended by the Society of Cardiovascular Computed Tomography (SCCT) as a 'vulnerability' modifier of the CAD-RADS score.[60]

Detecting coronary inflammation using perivascular fat attenuation index

Vascular inflammation (in particular TNF-α/IL-6 released from the inflamed vascular wall) triggers lipolysis and inhibits adipogenesis in PVAT, causing a gradient of adipocyte size in the first few millimetres around the inflamed coronary arterial wall (*Figure 3*). The gradient of PVAT adipocytes around the inflamed coronary artery leads to a respective gradient in PVAT's composition from a more aqueous/less lipophilic phase close to the inflamed artery to a less aqueous/more lipophilic phase in the non-PVAT within the epicardial fat depot.[13] Following this discovery, we designed an imaging tool to measure appropriately weighted gradients in the CT attenuation (or radiodensity) of coronary PVAT, captured by a new imaging biomarker, the perivascular FAI.[13] Perivascular FAI was developed via a radiotranscriptomic approach, and describes changes in the transcriptomic profile of PVAT in response to inflammatory signals from the adjacent coronary artery wall, as well as the changes in adipocyte size, adipogenesis, and lipolysis, all processes driven by coronary inflammation.[13] The proprietary algorithm used for this analysis (namely CaRi-HEART, Caristo Diagnostics, Oxford, UK) implements artificial intelligence (AI) to quantify a weighted measure of attenuation in concentric 1 mm-layers of perivascular tissue around the human arterial wall, capturing the gradient of perivascular weighted attenuation with increasing distance from the arterial wall, reflecting the changes in PVAT biology that occur as a result of vascular inflammation. FAI differs significantly between patients with obstructive CAD and non-atherosclerotic vessels and is positively associated with total coronary plaque burden.[13] Notably, perivascular FAI is only weakly correlated with HRP, suggesting that it captures different biological information than traditional HRP features. In addition, FAI can also be used for a 'plaque-specific' analysis, e.g. to identify culprit lesions in ACS patients, having an excellent classification performance for discriminating between stable and unstable plaques (area under the curve (AUC) 0.91, 95% CI 0.80–1.00).[13] By determining FAI in the reference proximal segments of the right coronary artery or left anterior descending artery, excellent surrogates of the background vascular inflammation of the entire coronary tree can be obtained, independently of the presence of specific plaques in other areas of the coronary vasculature. However, over and above the standardized FAI measurement in these coronary segments, FAI is increased around culprit lesions of ACS patients and dynamically responds to changes in local inflammatory status after plaque rupture events, returning back to 'normal' levels a few months after an ACS.[13] Given that the plaque-specific FAI analysis is a relative measurement of the signals on top of the overall vascular inflammatory burden, it has to be measured in relation to a reference coronary segment proximally to the lesion of interest. A shift of PVAT attenuation during ACS has been confirmed by various recent independent studies,[61–63] while a similar visual attenuation shift around spontaneous coronary arterial dissections has also been reported.[62] However, it should be noted that FAI is different to the crude 'mean CT attenuation (or radiodensity)' of PVAT, since it has to be appropriately corrected and weighted for parameters related to the obesity status, technical scanning parameters, and anatomical factors specific to the coronary

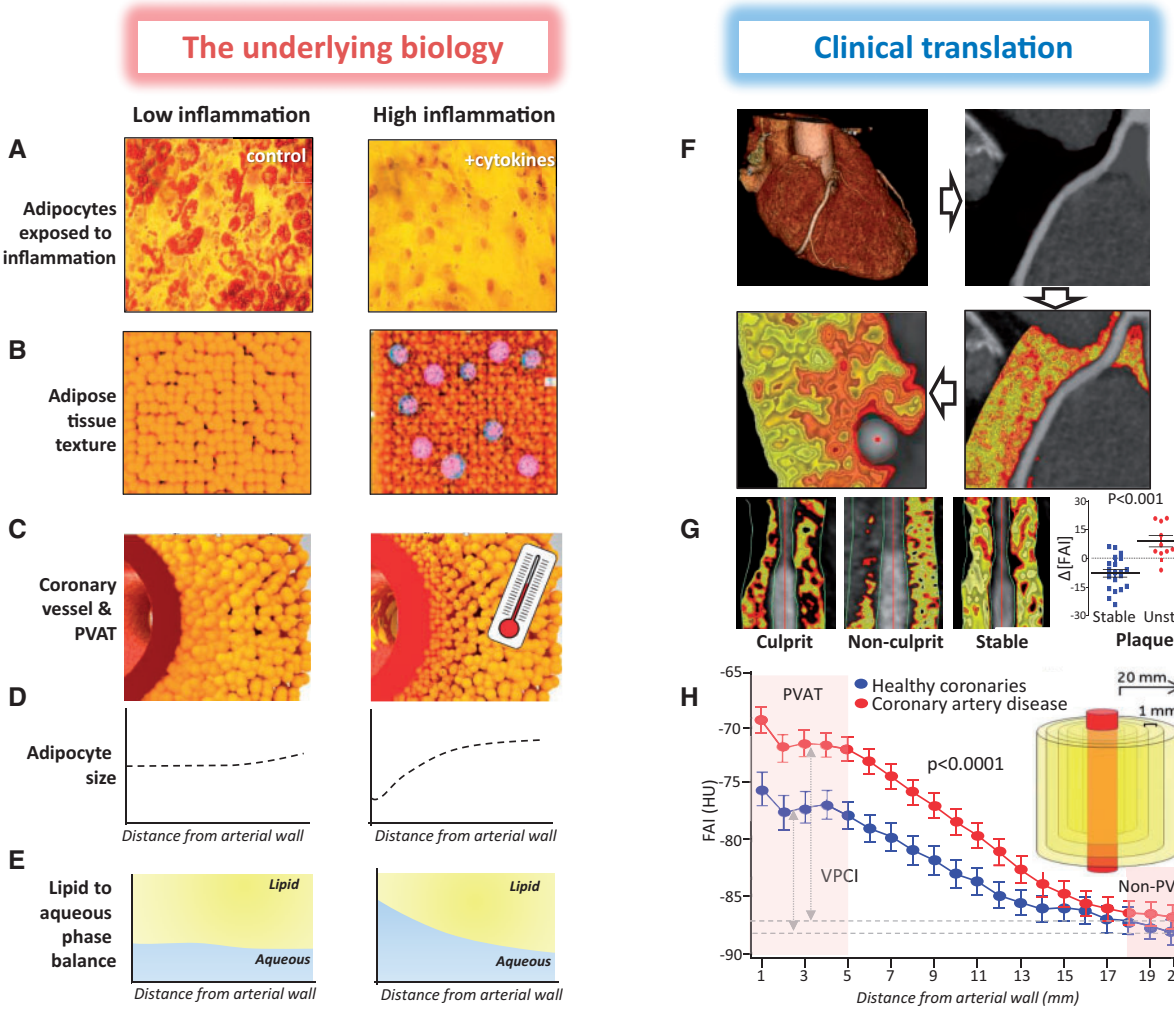


Figure 3 Schematic representation of the biology underlying the detection of coronary inflammation by imaging perivascular adipose tissue. Exposure of adipose tissue to exogenous inflammation leads to smaller adipocytes and low levels of intracellular lipids (*A*). Illustration of inflamed adipose tissue containing small adipocytes, with low intracellular fat levels, and high macrophage infiltration (*B*). Morphological appearance of perivascular adipose tissue surrounding inflamed coronary arteries (*C*). Vascular inflammation leads to a gradient in the adipocyte size (*D*) and the lipid:aqueous phase in perivascular adipose tissue (*E*), which can be detected by coronary computed tomography angiography. Standard-of-care routine coronary computed tomography angiography datasets can be used for fat attenuation index measurements (*F*). Perivascular fat attenuation index mapping can discriminate unstable (ruptured) from stable atherosclerotic plaques (*G*) and is increased in patients with atherosclerosis (*H*). Reproduced with permission from Antonopoulos *et al.*[13]; CP, culprit lesion, NCP, non-culprit lesion, VPCI, volumetric perivascular characterization index.

segment being examined, all information extracted by the CaRi-HEART algorithm from the CCTA DICOM files. For example, crude measurement of perivascular radiodensity or attenuation (ignoring the attenuation gradients generated around inflamed arteries), consistently underestimates coronary inflammation in obese individuals, as the global adipocyte size is larger in obesity (driving the radiodensity closer to -190 HU), while in lean individuals it overestimates inflammatory burden [as the small adipocyte drive attenuation (or radiodensity)] to higher values, even in the absence of local inflammation. FAI is weighted for the scanner, CT scan settings, reconstruction algorithms, and other technical parameters extracted from the CCTA DICOM files (proprietary artificial intelligence-enhanced algorithm CaRi-HEART, developed by the University of Oxford), making it hardware-agnostic, and analysable across different scanning settings and reconstruction algorithms. Notably, FAI is not affected by arterial calcification or lumen attenuation, thus having an advantage over coronary wall biomarkers, although the information provided is complementary to HRP features.[13] The concept of FAI is summarized in *Figure 3*. Due to its nature, perivascular FAI is a sensitive biomarker to detect coronary inflammation and FAI mapping can be used as an internal 'thermometer' of the entire coronary tree (when measured in non-diseased proximal coronary segments) or as a local biomarker of coronary plaque inflammation and vulnerability (as a relative measure around plaques under investigation). The predictive value of perivascular FAI was recently explored in the CRISP-CT (Cardiovascular RISk Prediction using Computed Tomography) study, which involved

standardized measurement of perivascular FAI around the proximal right coronary artery and the proximal left anterior descending (LAD) artery, in ~4000 individuals undergoing clinically-indicated diagnostic CCTA in two independent populations from Erlangen (Germany) and Cleveland (USA).[14] Perivascular FAI around the proximal segment of LAD or right coronary artery (RCA) was strongly predictive of all-cause and cardiac mortality, where its association with the former was driven by that with the later. A threshold in perivascular FAI of -70.1 HU around the proximal right coronary artery was defined as the cut-off, above which FAI was related with a six- to nine-fold increase risk for fatal heart attacks and five-fold increase risk for non-fatal myocardial infarction (*Figure 4*).[14] This predictive value was over and above the current state of the art in risk stratification, including risk factors (e.g. smoking, diabetes mellitus), extent of coronary atherosclerosis in CCTA, HRP features, and any other clinically relevant information available for these individuals. Perivascular FAI significantly improved discrimination and risk classification for both all-cause and cardiac mortality beyond traditional risk factors, HRP features and the extent of CAD (*Figure 4*).[14] Notably, although FAI around the LAD and RCA were similarly predictive of cardiac mortality, they were not identical. The variability between the two coronary arteries could potentially predict the coronary territory involved in a future ACS, but this information was not available in the CRISP-CT study.

Given the value of the FAI technology in predicting future fatal and non-fatal cardiac events, the obvious question is whether the risk identified by this method is modifiable by treatments. A definitive answer to this question can be given only by large randomized clinical trials, where individuals are randomized into treatment arms according to their baseline perivascular FAI. From the CRISP-CT study,[14] we have learned that perivascular FAI loses its predictive value for long-term cardiac mortality in individuals who initiated treatment with aspirin and/or statins after CCTA. On the other hand, individuals with elevated perivascular FAI that did not start any risk-modifying medication after CCTA have an 18-fold increased risk for fatal heart attacks, compared to those with perivascular FAI below the cut-off. Also, recent pilot data suggest that treatment of psoriasis patients with biologic agents (anti-TNFα, anti-IL12/23, or anti-IL17) lowers perivascular FAI.[64] These are strong observations, generating the need for appropriate clinical trials to evaluate this concept.

Another important question is the ability of perivascular FAI to track changes in coronary inflammation in response to treatment. Several randomized clinical trials examining this concept are ongoing, but initial evidence suggests that perivascular FAI measured around culprit lesions during ACS changes dynamically post-event, with significant changes being detectable as early as 5 weeks post-ACS and following the initiation of optimal secondary preventative therapies.[13]

As a dynamic and specific marker of coronary inflammation that is extracted from the post-processing of routine CCTA datasets, with independent prognostic discrimination and risk reclassification value, FAI overcomes many of the limitations of other existing modalities for vascular inflammation detection. FAI tracks low-grade vascular inflammation associated with cardiovascular risk factors including any type of inflammation leading to increased release of inflammatory cytokines by the vessel,[13] as well as vasculitis related with the chronic inflammation of autoimmune diseases such as psoriasis.[64] Perivascular FAI has prognostic value for cardiac mortality both in patients with and without obstructive CAD, and the biological processes captured by FAI could offer complementary information to other functional imaging tests or the routine anatomical information extracted from CCTA.

Incorporating coronary computed tomography angiography-based measurement of coronary inflammation in clinical practice

Coronary computed tomography angiography radiation exposure is now down to approximately <5 mSv for most modern scanners and is readily available in most centres who investigate patients with chest pain.[65] Recent data from SCOT-HEART suggest that incorporation of standard CCTA in the chest pain management pathway is helpful for both guiding treatments and improving clinical outcomes.[66] High-risk plaque features in CCTA have low sensitivity but good specificity for future major adverse cardiac events.[59,67] Plaque characterization on top of CCTA and calcium score in subjects undergoing diagnostic CCTA is independently associated with ~10-fold higher risk of future cardiac events (HR 9.4, 95% CI 2.7–33.4) and substantially improves risk prediction on top of clinical profile and CCTA luminal assessment alone (c-statistic from 0.82 to 0.93).[68] More conservative were the results of the PROMISE trial in which the presence of HRP in patients with stable chest pain was independently associated with modestly increased risk for future events (HR 1.7, 95% CI 1.1–2.6) and contributed to patient reclassification.[59]

With the use of the new AI-enhanced technologies like perivascular FAI, the ability of CCTA to detect the 'vulnerable patient' can be significantly improved. In the CRISP-CT study,[14] 80% of the people undergoing CCTA for investigation of chest pain did not have obstructive CAD, and according to the current clinical guidelines they had no indication for changing their medical management. However, we know that ~50% of heart attacks occur in individuals without significant luminal stenosis,[9] due to rupture of non-obstructive, but presumably highly inflamed atherosclerotic plaques.[69] By performing HRP and perivascular FAI analysis, a new category of high-risk individuals without obstructive disease can be identified. Indeed, in the CRISP-CT study,[14] 43% of the population undergoing diagnostic CCTA had high cardiovascular risk as determined by perivascular FAI or HRP features (*Figure 4*). Among those individuals undergoing CCTA without flow-limiting coronary atherosclerosis, 15% had HRP and 24% abnormal perivascular FAI, while the overlap between the two was only 3%. In the same study, the existing state-of-the-art risk stratification by CCTA (risk factors, extent of atherosclerotic disease, and HRP) performed well in predicting cardiovascular mortality (c-statistic: 0.913, 95% CI 0.867–0.958 in the derivation and 0.763, 95% CI 0.669–0.858 in the validation cohort of study), and the addition of perivascular FAI significantly enhanced the predictive value of these models (increase in c-statistic by 0.049 and 0.075 for the derivation and validation cohorts, respectively).[14] These results confirm that the two approaches capture different pathologies, and they have complementary risk-prediction capacity (*Figure 4*).

In addition to those individuals without significant luminal stenosis on CCTA, ~20% of the individuals in CRISP-CT[14] had obstructive

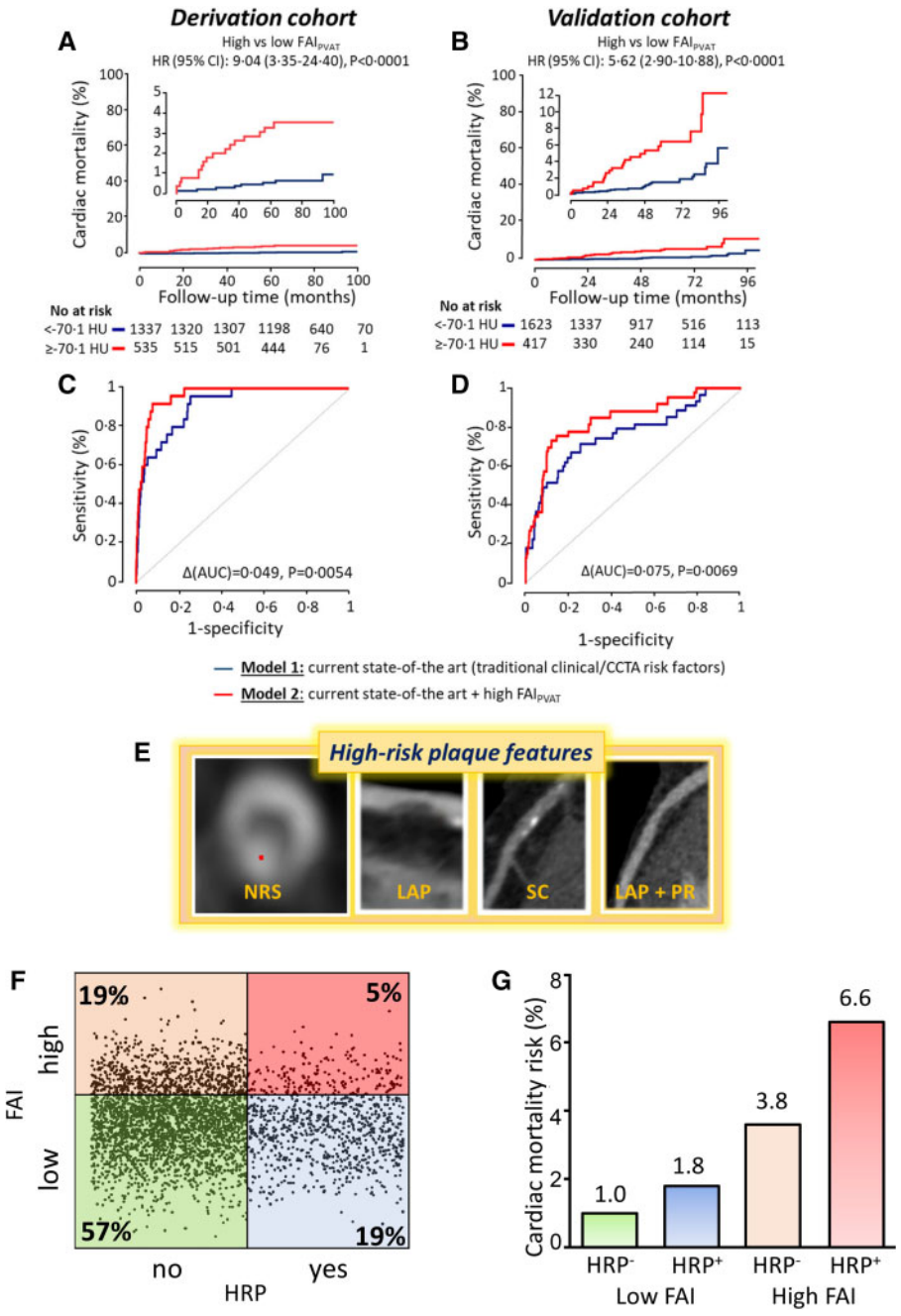


Figure 4 Prognostic value of perivascular fat attenuation index. In the CRISP-CT study,[14] which evaluated two prospective clinical cohorts of 3912 patients undergoing diagnostic coronary computed tomography angiography for clinical indications, perivascular fat attenuation index was predictive of cardiac mortality both in the derivation and validation cohorts (*A*, *B*). Fat attenuation index provided incremental prognostic value for cardiac mortality on top of traditional clinical risk factors, Duke coronary artery disease index and number of high-risk plaque features on coronary computed tomography angiography (*C*, *D*), (reproduced with permission from Oikonomou *et al.*[14]). High-risk plaque (HRP) features on coronary computed tomography angiography are defined as the napkin-ring sign (NRS), low attenuation plaque (LAP), spotty calcification (SC), and positive remodelling (SP) (*E*). Stratification of the pooled population of CRISP-CT based on the presence of high-risk plaque and high coronary inflammatory burden as determined by perivascular fat attenuation index and observed rates of cardiac mortality within each group (*F*, *G*). The combination of high-risk plaque and high fat attenuation index could be used to identify vulnerable patients at the highest risk that are eligible for aggressive prevention strategies; derived from *post hoc* data analysis of CRISP-CT data in the Oxford Academic Cardiovascular Computed Tomography (OXACCT) Core Lab.

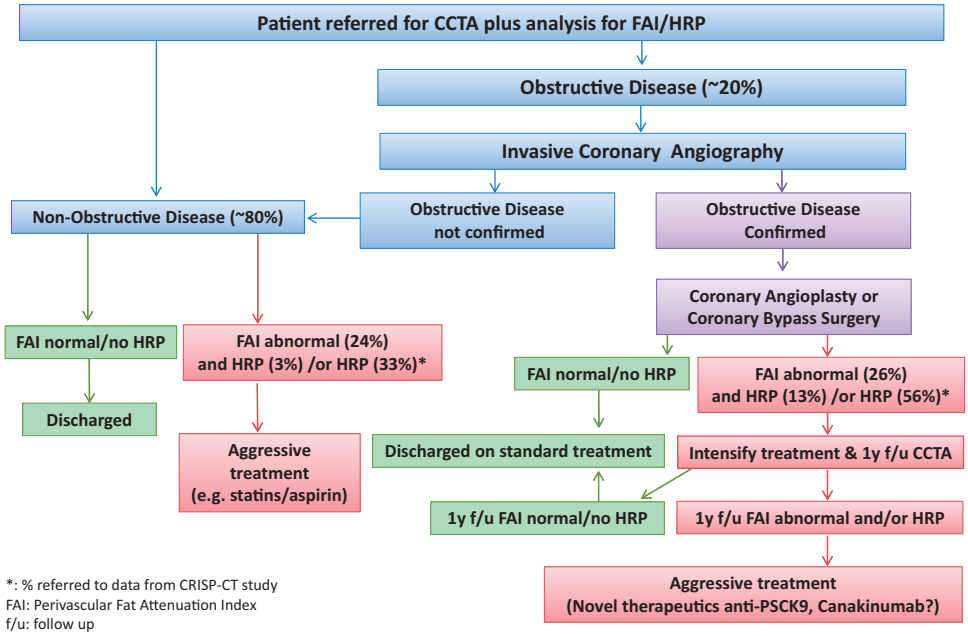


Figure 5 Vision for implementing fat attenuation index (FAI) and high-risk plaque features (HRP) in clinical practice. CAD, coronary artery disease; CV, cardiovascular; OMT, optimal medical treatment; anti-PCSK9, pro-protein convertase subtilisin/kexin type 9 inhibitors.

CAD, with many undergoing additional interventions (percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG)). Among those patients with established coronary atherosclerosis, 56% had HRP and 26% abnormal perivascular FAI, while the overlap between the two was 13%. The use of HRP and perivascular FAI analyses was complementary for risk prediction, as the observed 5-year cardiac mortality in CRISP-CT was 1.8% in people with low FAI/HRP^{+}, 3.8% in those with abnormal perivascular FAI/HRP^{-}, and 6.6% in those with both abnormal perivascular FAI and HRP^{+} (*Figure 4*). This suggests that incorporating both perivascular FAI and HRP in a combined risk assessment model would add major value to risk stratification in secondary prevention.

This could potentially be supplemented by measurement of hsCRP, given that the correlation between perivascular FAI and hsCRP levels is poor, suggesting that the information captured by perivascular FAI is different to systemic inflammatory burden. FAI analysis could be used as a companion diagnostic test in secondary prevention, allowing the personalized deployment of high cost treatments (such as canakinumab or PCSK9-inhibitors) to only a small proportion of CAD patients who are poor responders to the current state-of-the art treatment and have persistently high levels of coronary inflammation. A proposed pathway for the deployment of these new technologies to medical practice is presented in *Figure 5*.

Defining coronary inflammation using perivascular FAI alone or in combination with HRP features comes with certain limitations, which need to be considered. HRP features are operator-dependent and are relatively rare in populations with chest pain without flow-limiting coronary stenosis; perivascular FAI measurement is time consuming and its reliable calculation is complex, requiring AI solutions. Off-site platforms would offer global solutions to the clinician if they are cost-effective, user friendly, strictly managed, and regulated (i.e. have the appropriate regulatory and quality approvals, such as a CE-mark in Europe or Food and Drug Administration (FDA) clearance in the USA). Certainly, the need for contrast CCTA that involves radiation exposure will limit the deployment of these solutions in primary prevention, although their use as part of a standard CCTA reporting armamentarium will give an entirely new dimension to the management of

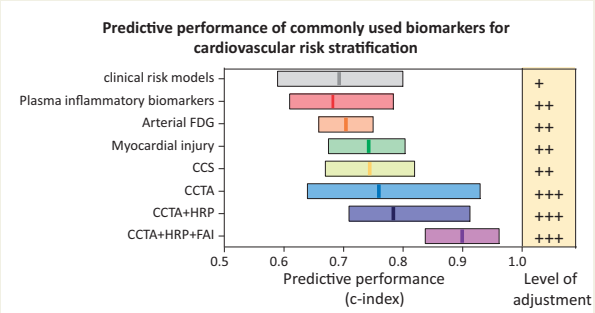
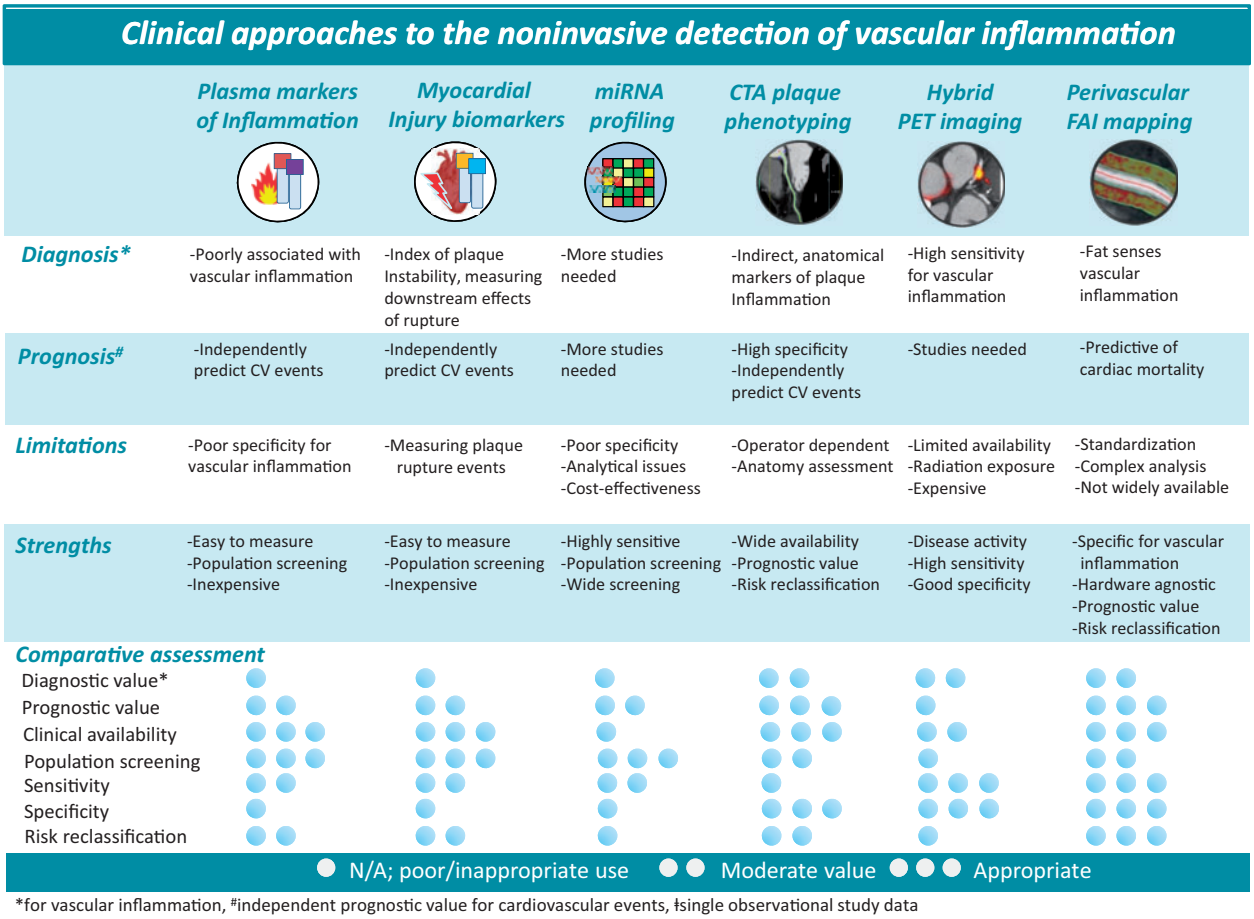


Figure 6 Predictive performance of commonly used biomarkers for cardiovascular risk stratification in stable patients. CCS, coronary calcium score; CCTA, coronary computed tomography angiography; FAI, fat attenuation index; FDG, fluorodeoxyglucose uptake; HRP, high-risk plaque features; myocardial injury biomarkers: high sensitivity cardiac troponin I/T; systemic inflammation: plasma levels of C-reactive protein and interleukin-6; bar graphs represent low-high (and mean) value for the predictive performance of each biomarker (i.e. c-index, more details provided in the Supplementary material online, *Appendix to Figure 6*).



*for vascular inflammation, #independent prognostic value for cardiovascular events, ǂsingle observational study data

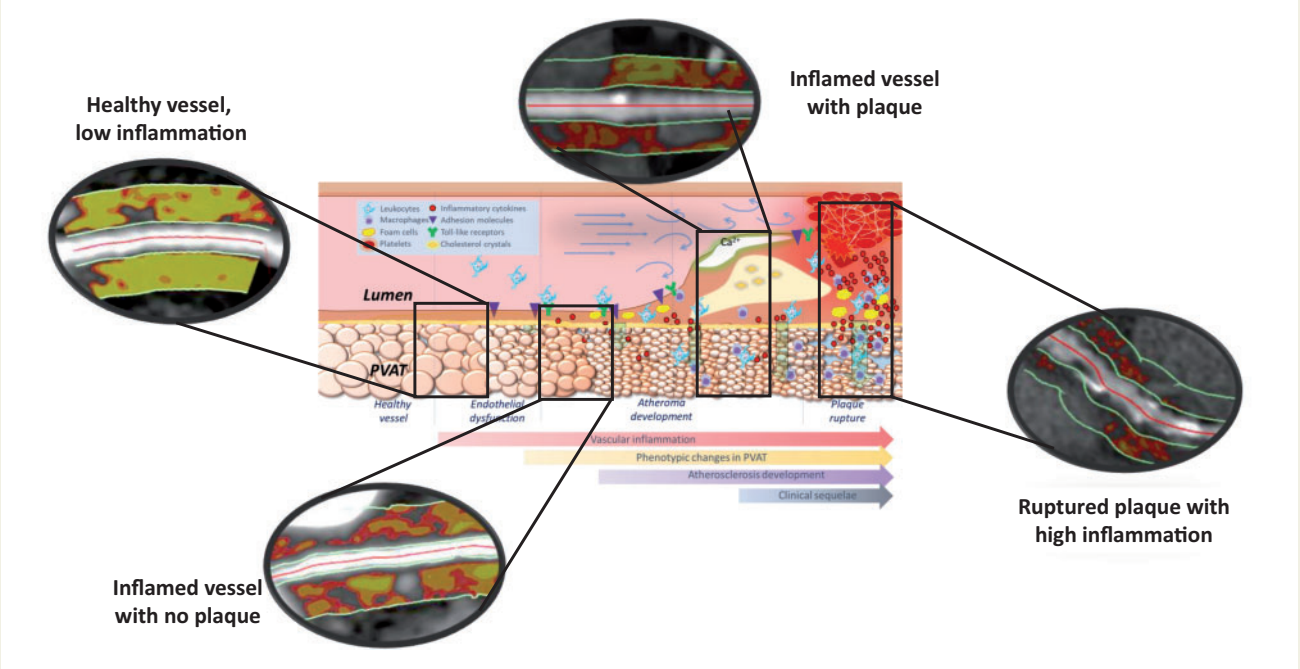
Figure 7 Overview and comparative assessment of existing approaches for the detection of coronary inflammation. CTA, computed tomography angiography; FAI, fat attenuation index; PET, positron emission tomography.

patients with chest pain. Finally, the results of randomized clinical trials will interrogate the responsiveness of these new methods to treatments that modify cardiovascular risk, while future outcomes clinical trials will explore whether the risk identified by these new measures of coronary inflammation is modifiable by established treatments in primary prevention or by emerging therapeutic strategies over and above the current secondary prevention measures.

Conclusions

The role of inflammation in the development of atherosclerosis and plaque rupture leading to ACS is now well established. Despite the advancement of medical pharmacotherapy in primary and secondary prevention, residual inflammatory risk is neither adequately identified nor managed. Therefore, the development of methods to detect the inflamed coronary artery, flagging the 'vulnerable patient', remains an unmet need. The value of the most commonly used biomarkers for risk stratification in stable patients is summarized in *Figure 6*, while a schematic on the strengths and limitations of each approach for the detection of coronary inflammation is provided in *Figure 7*.

The lack of any plasma biomarkers specific for coronary inflammation has shifted the focus to non-invasive imaging. While PET/CT offers good solutions for the imaging of coronary inflammation, it expensive and difficult to implement in routine clinical practice. Conversely, standard CCTA allows the identification of HRP features, which are useful for risk stratification, despite their qualitative nature. The recently developed perivascular FAI, captures the changes in the composition of PVAT around the inflamed coronary arteries by using a composite measure of the perivascular attenuation gradients around the coronary arteries (*Take home Figure*). This new way to measure inflammation, using images acquired from a standard CCTA, can be used both prospectively and retrospectively (in already obtained scans) to allow risk reclassification. The combination of HRP and perivascular FAI in an integrative fashion has the potential to change the landscape in precision medicine, guiding the deployment of standard as well as novel therapeutics in both primary and secondary prevention.



Take home figure Computed tomography (CT) imaging of coronary inflammation by fat attenuation index mapping. PVAT, perivascular adipose tissue.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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