

Review Article



The Role of Perivascular Fat in the Diagnosis and Prognosis of Atherosclerosis

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ABSTRACT

Cardiovascular diseases are the leading cause of morbidity and mortality globally, with obesity serving as a significant yet complex risk factor in this regard. Obesity represents a heterogeneous set of conditions that consist of interactions between metabolic physiology, genetic- as well as environmental-factors. Recent advances in adipose tissue biology have provided greater understanding into the distinct structures and functions of different adipose tissue depots. This includes perivascular adipose tissue, which has been shown to engage in bi-directional paracrine-, vasocrine- and endocrine-signalling with the vascular wall that regulates the vascular redox state and atherogenesis. This has implications for how we approach the treatment of cardiometabolic disease, where novel insulin-sensitising agents might reduce the risk of atherosclerosis through pleiotropic effects on the vascular wall, both directly and indirectly through modulating the adipose tissue secretome. Importantly, clinical imaging modalities for visualisation of peri-vascular adipose tissue now exist that allow for more accurate cardiovascular risk-stratification and raise the possibility of more targeted therapeutic approaches in selected patients. In particular, the perivascular Fat Attenuation Index (an artificial intelligence enhanced cardiac computed tomography biomarker) has allowed for the detection of inflammatory changes in perivascular adipose tissue that holds significant potential to improve secondary risk management. Consequently, this review summarises how perivascular adipose tissue biology contributes to the development of atherosclerosis, in addition to discussing how these developments can be detected using novel cardiovascular imaging techniques.

Keywords: Atherosclerosis; Adipose tissue; Oxidative stress; Metabolic syndrome; Computed tomography angiography

INTRODUCTION

Globally there are over 550 million people living with cardiovascular disease (CVD), which consists of a broad range of associated disease states.¹⁻³ Included in this is coronary artery disease (CAD), a manifestation of atherosclerosis, which is the single largest cause of death worldwide with over 9 million (or 1 in 6) deaths annually as of 2019.³ Of those with myocardial infarction (MI), a complication of CAD, one in four patients develop heart failure (HF)

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Conflict of Interest

C.A. is founder, shareholder, and director of Caristo Diagnostics, a CT image analysis company. The other authors declare no competing interests. The imaging technologies discussed in this manuscript are subject to University of Oxford patent US10,695,023B2 and patent applications PCT/GB2017/053262, GB2018/1818049.7, GR20180100490 and GR20180100510, licensed through exclusive license to Caristo Diagnostics.

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which is associated with a 5-year mortality of up to 50%, exacting a significant cost on the healthcare system.⁴ In the United States, for example, there were 1.1 million hospitalisations due to MI in 2010 alone contributing to a total direct and indirect cost due to CVD of US \$450 billion, which is projected to increase to over US \$1 trillion by 2030.^{5,6}

In this regard, obesity is an established but complex CVD risk factor, with adipose tissue (AT) location and the underlying metabolic state having a significant impact on its biological variability and contribution to overall cardiovascular risk.⁷ A considerable body of evidence now exists to support the understanding of AT as an active endocrine organ, secreting a range of bioactive molecules known as adipokines into the circulation that can affect the cardiovascular system.^{8,10} Additionally, perivascular adipose tissue (PVAT) is known to have direct, paracrine effects on the underlying vascular wall, making this depot a critical regulator of vascular function.^{7,9} Previous work has also demonstrated that paracrine inflammatory signals from the vascular wall drive the expression of adipogenic genes, adipocyte size and lipid accumulation in AT.¹¹ Here, pericoronary AT contains, on average, smaller adipocytes and larger numbers of immature adipocyte precursors making this depot sensitive to the underlying pathological changes in atherosclerotic vessels.¹¹ The consequent inflammation-induced lipolysis that occurs in pericoronary AT can now be detected using novel cardiovascular imaging techniques, allowing for better cardiovascular risk prediction in patients at risk of atherosclerosis.¹¹

As a result, in this review we will discuss the role of PVAT in the development of atherosclerosis and consider how the latest advances in AT imaging can assist in identifying patients with atherosclerosis in order to mitigate their risk of adverse cardiovascular events.

THE STRUCTURE AND FUNCTION OF ADIPOSE TISSUE

AT can be broadly delineated on the basis of anatomical location into subcutaneous adipose tissue (ScAT) and visceral adipose tissue (VAT), with VAT in turn consisting of a number of distinct depots.^{7,12} As it pertains to the heart, these include intramyocardial AT (fat within the myocardium), epicardial adipose tissue (EpAT; fat adjacent to the epicardium surrounding the heart and within the visceral pericardium), pericardial AT (fat surrounding the heart that is outside the visceral pericardium but within the parietal pericardium), and paracardial AT (fat within the thorax that is outside the pericardial sac).^{9,12} Together these encompass the VAT depots within the chest wall and are termed intrathoracic adipose tissue (ThAT).¹² Included in but not limited to this group is PVAT, which is defined as the fat surrounding a vessel outside the adventitial sheath that falls within a radial distance equal to the diameter of the vessel from the outer aspect of the vessel wall.^{12,13} When discussing coronary PVAT this depot is considered part of EpAT.¹⁰

AT can also be defined based on function, phenotype and expression profile as either white adipose tissue (WAT) or brown adipose tissue (BAT).^{14,15} BAT is a thermogenic organ which generates heat in response to cold ambient temperatures, and is characterised by the expression of uncoupling protein 1 (UCP1), which is activated in response to fatty acids and results in the uncoupling of oxidative phosphorylation from ATP production, driving heat production.^{14,16} WAT on the other hand is the primary site of lipid storage and adipokine release, functioning as a regulator of whole-body metabolism including insulin signalling.^{14,16} Once thought in humans to be found exclusively in infants and children, functional BAT depots have been more

recently described in adults and it is now recognised that brown-like or beige adipocytes can be recruited into WAT depots with resultant thermogenic properties.^{14,16}

In addition to adipocytes, within the stromal fraction of AT lie various other cell types including fibroblasts, macrophages, lymphocytes, eosinophils as well as vascular cells and multipotent adipocyte precursor stem cells; these all contribute to the overall phenotype of the specific AT depot, which will in turn have a depot-specific secretomic profile that reflects its autocrine, paracrine and endocrine functions.⁷ Studies also reveal a distinct variation in the transcriptomic and proteomic profiles of different depots.⁷ In general, VAT expansion is associated with increased CVD risk whilst ScAT harbours a neutral or cardioprotective risk profile; however, there is considerable heterogeneity that exists here.⁷ For example, abdominal ScAT displays an adverse metabolic profile similar to that of VAT when compared to gluteal ScAT, yet even within abdominal ScAT the deeper layers are more closely associated with insulin resistance and CVD risk than the superficial layers.⁷

The same can be said for EpAT, where there is evidence to show that atrial-, ventricular- and coronary depots have differing transcriptomic signatures.⁷ For EpAT there is evidence to suggest multiple roles in: local energy storage, protection from free fatty acid (FFA)-induced lipotoxicity (owing to its adipogenic capacity), protection from hypothermia (owing to its thermogenic capacity), as well as serving as a site for ganglia innervation of the myocardium and having mechanical insulation properties.¹² Additionally, the fact that EpAT shares a microcirculation with the myocardium and derives from the same embryological origin as omental and mesenteric AT, which are known to be sources of adipokines, suggests that EpAT has further endocrine and paracrine functions as well.⁹

Similarly, PVAT maintains multiple functions and it plays a crucial role in paracrine signalling to the underlying vasculature, regulating aspects of vascular physiology such as vasoconstriction and the arterial redox state.^{13,17} PVAT also engages in vasocrine signalling, where secreted adipokines diffuse through the vascular wall and into the downstream microcirculation of associated vascular beds.^{7,17} Additionally, PVAT secreted adipokines (along with those of other remote VAT depots) can have effects on both the myocardium and the vasculature through endocrine mechanisms.¹⁷ In this regard, PVAT is particularly important in the relationship between redox-signalling, metabolic derangements and atherosclerosis, owing to the bidirectional cross-talk that occurs between PVAT and the underlying vasculature (**Figure 1**).¹⁸

CROSS-TALK BETWEEN AT AND THE CARDIOVASCULAR SYSTEM

Under physiological conditions, PVAT serves to protect the cardiovascular system against oxidative stress and the development of atherosclerosis through the release of adipokines such as adiponectin.^{17,18} Adiponectin plays a role in glucose metabolism and is protective against obesity-related insulin resistance as well as having both antioxidant and antiatherogenic properties.^{2,8} Specifically, adiponectin inhibits the phosphorylation and membrane translocation of p47^{phox} as well as the activation and membrane translocation of Rac1 in a 5' adenosine monophosphate-activated protein kinase dependent manner, crucial aspects of NADPH-oxidase activation.^{17,18} Additionally, adiponectin has been shown to stimulate NO production in endothelial cells and reduce endothelial nitric oxide

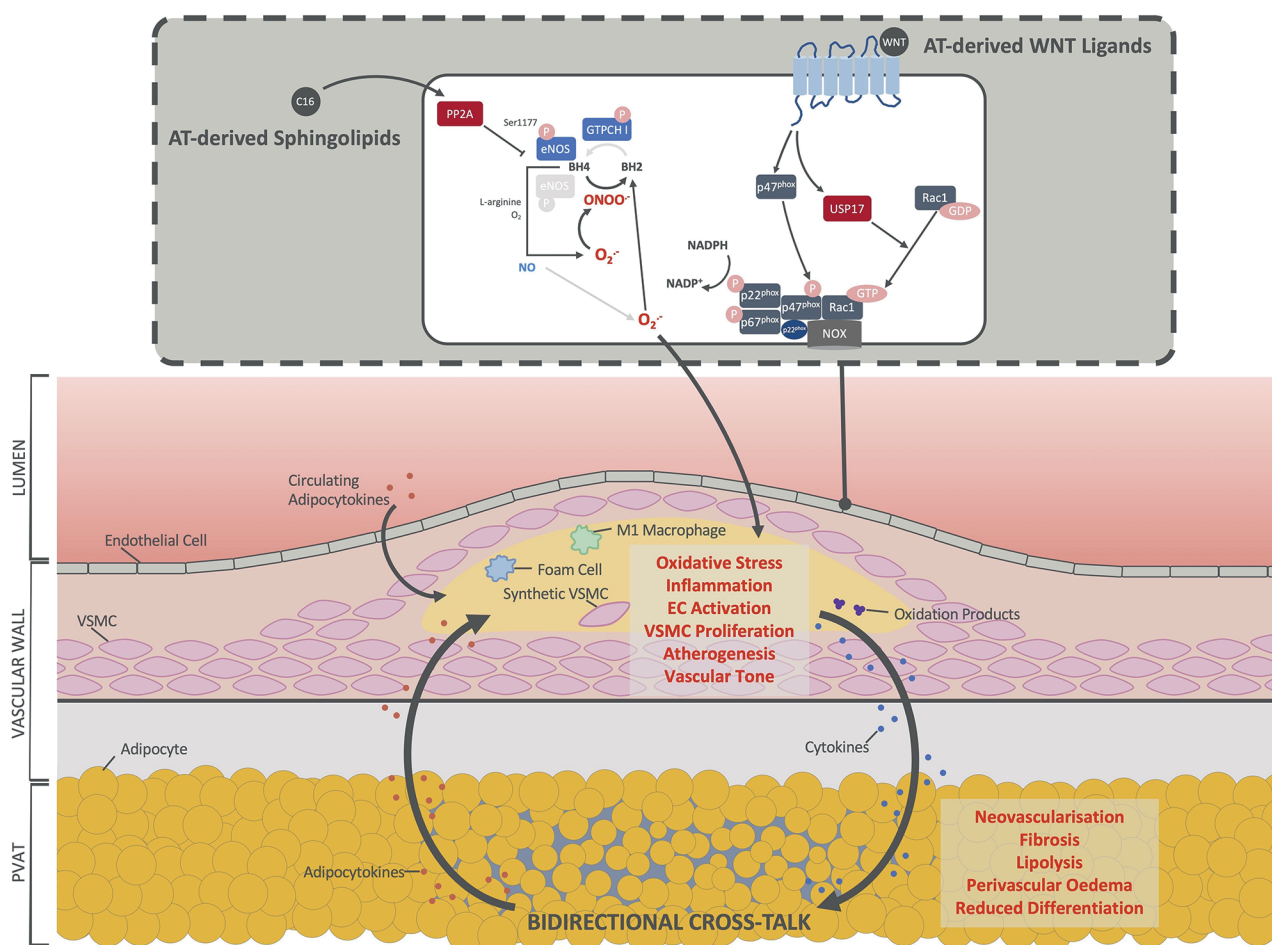


Figure 1. Cross-talk between adipose tissue and the vascular wall.

PVAT interacts with the vascular wall in a bidirectional manner. AT-derived adipocytokines, gaseous messengers, microRNAs and lipid mediators diffuse into the underlying vasculature and are released into the systemic circulation, thereby engaging in both paracrine and endocrine signalling. This constitutes the “outside-to-inside” axis of the interplay between PVAT and the vascular wall, with certain Wnt ligands (such as WNT5A) and sphingolipid species (including CerC16 and its glycosylated derivatives) acting as examples of AT-derived bioactive molecules that regulate the vascular redox state through the modulation of NOX activity and eNOS coupling respectively. In the context of metabolic disease, dysfunctional AT thereby facilitates atherogenesis through the propagation of oxidative stress, type-I inflammation, EC activation, and VSMC proliferation in the vascular wall. Cytokines or oxidative products in the vascular wall can then diffuse back into the underlying PVAT and activate pro-inflammatory pathways in what is termed “inside-to-outside” signalling. Dark arrows indicate active pathways. Light arrows indicate inactive pathways. Lines with flat ends indicate inhibition.

AT = adipose tissue; BH2 = dihydrobiopterin; BH4 = tetrahydrobiopterin; CerC16 = ceramide-C16:0; EC = endothelial cell; eNOS = endothelial nitric oxide synthase; NOX = NADPH oxidase; O₂⁻ = superoxide; ONOO⁻ = peroxynitrite; PVAT = perivascular adipose tissue; VSMC = vascular smooth muscle cell; Wnt = Wingless-related integration site.

synthase (eNOS)-derived O₂⁻, through improving eNOS coupling by increasing PI3K/Akt-mediated phosphorylation and BH4 bioavailability.¹⁷ This comprises only part of what is termed “outside-to-inside” signalling, so when considering the interplay between PVAT and the cardiovascular system, apart from adipokines such as adiponectin and leptin it is important to note the other bioactive compounds that are released in this manner including: cytokines and chemokines; hydrogen sulfide, nitric oxide (NO) and other gaseous exchange messengers; fatty acids; reactive oxygen species (ROS) as well as microRNA-containing microparticles and extracellular vesicles (Figure 1).^{7,12,19}

These secreted PVAT-derived products have pleiotropic effects on the vascular wall which, under physiological conditions, alter the inflammatory and transcriptomic milieu of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) in the vascular wall, protecting against

atherogenesis.⁷ In this regard, it is now understood that changes in the underlying vasculature can also affect surrounding AT depots—constituting an “inside-to-outside” signalling arm of this bidirectional cross-talk (**Figure 1**).^{17,18} This was first explored in murine studies where, in response to vascular injury, pro-inflammatory adipokines were found to be upregulated in PVAT whereas anti-inflammatory adipokines, such as adiponectin, were downregulated.⁷ Our group then demonstrated that, in the presence of increased vascular oxidative stress, lipid peroxidation products such as 4-hydroxynonenal (4HNE) are released from the vasculature and diffuse into the surrounding PVAT depots in a paracrine way, thereby activating adiponectin (ADIPOQ) in a peroxisome proliferator-activated receptor (PPAR)- γ -dependent manner and increasing AT-derived adiponectin secretion, which then diffuses into the adjacent vascular wall and exhibits antioxidant effects as part of a protective feedback mechanism.^{7,17,18}

Importantly, in the context of metabolic disease such as visceral obesity or insulin resistance prior to the onset of advanced CVD, ROS-induced inflammation has a suppressive effect on PPAR- γ activity resulting in reduced expression and release of ADIPOQ and adiponectin from VAT depots; this contributes to the environment of oxidative stress that results in the development of early-stage CVD, highlighting how AT dysfunction can serve to propagate atherosclerosis.^{17,18}

THE BASIC MECHANISMS OF AT DYSFUNCTION IN ATHEROSCLEROSIS

There are a number of factors which contribute to the cardiometabolic complications that typify the CVD risk associated with excess visceral adiposity.²⁰ A major component here is AT dysfunction, characterised by adipocyte hypertrophy and impaired adipogenesis, reduced FFA uptake and triglyceride synthesis, as well as the development of resistance to the effects of insulin in inhibiting lipolysis, AT fibrosis, AT immune cell infiltration and the secretion of pro-inflammatory adipocytokines.²⁰ In this regard, the association between AT dysfunction and the metabolic syndrome can be in part explained by regional differences in adipogenesis, immune-mediated pericellular fibrosis, and FFA-derived lipotoxicity.²⁰

Under physiological conditions, the expansion of fat mass occurs through either hypertrophy (the accumulation of lipid in existing adipocytes) or hyperplasia (the differentiation of precursor cells to form new adipocytes).²⁰ In VAT, this occurs primarily through hypertrophy owing to its comparatively reduced adipogenic capacity, as opposed to ScAT in which hyperplasia predominates.²⁰ Here, bone morphogenic protein 4 (BMP4) initiates the commitment of mesenchymal progenitor cells to an adipogenic lineage, with zinc finger proteins-521 (ZFN521) and -423 (ZFN423) acting as important additional regulators of early adipogenesis.²¹ Specifically, ZFN521 is key in maintaining the proliferative and uncommitted nature of adipocyte precursors in human ScAT and has an inverse relationship with BMP4, whereas ZFN423 functions as a BMP4-regulated activator of PPAR- γ transcription, which is the principal coordinator of adipocyte differentiation in AT.^{21,22} PPAR- γ also contributes to triglyceride synthesis through FFA uptake and trapping, thereby serving to reduce circulating FFA levels and limiting the potential lipotoxicity experienced by other insulin-sensitive tissues.^{21,22}

In dysfunctional AT however, adipogenic capacity is reduced, a key mechanism of which is the development of cellular senescence in adipocyte progenitors, leading to permanent cell cycle arrest, inhibited adipocyte differentiation, as well as the secretion of senescence-associated secretory phenotype factors which further antagonise physiological adipocyte

differentiation in the affected tissue.²¹ Cellular senescence in turn, is induced by both telomere-dependent or -independent DNA damage as well as cellular stress, including oxidative stress and inflammation.²¹ Additionally, this pattern of low-grade inflammation that accompanies oxidative stress can lead to immune cell infiltration in AT and subsequent alterations in adipose-derived inflammatory cytokines.²⁰ This causes deleterious extracellular matrix remodelling that culminates in pericellular fibrosis, inhibiting the lipid-storage and expansion capacities of AT and contributing to AT dysfunction.²⁰ This ultimately leads to non-esterified fatty acid spillover and subsequent flux of FFA into lean tissues, inducing lipotoxicity and the storage of triglycerides at ectopic sites such as the vascular wall.²⁰ Accumulated LDL at these sites is then oxidised by ROS to form oxLDL, indicating how the significantly increased CVD risk seen with visceral adiposity compared to subcutaneous adiposity can be attributed to the pro-inflammatory milieu propagated by oxidative stress.^{20,23}

In addition to its direct effects in promoting CVD, the type I inflammatory environment seen in dysfunctional AT is thought to play a causal role in the development of both local (AT) and systemic insulin resistance, which acts synergistically with metabolic inflammation through autocrine, paracrine and endocrine mechanisms as well as by exacerbating FFA spillover from AT to ectopic sites.²⁴ The underlying mechanisms here are not yet fully elucidated; however, this is currently thought to occur mostly as a result of the infiltration of type I immune cells in AT (mediated by cytokines including tumor necrosis factor [TNF]- α , interleukin [IL]-1 β , IL-6, and interferon [IFN]- γ) that potentiate a phenotypic switch of monocytes to pro-inflammatory M1-macrophages or a metabolically active mixed phenotype.²⁴ Along with type I inflammatory cytokines, ER-stress and FFA-flux are also thought to activate nuclear factor- κ B, c-Jun N-terminal kinase/mitogen activated protein kinase, and protein kinase C signalling pathways that induce serine or threonine phosphorylation of insulin receptor substrate-1 (IRS-1) or insulin receptor (IR), impairing downstream insulin signalling.²⁴ Additionally, IFN- γ and IL-6 activate the JAK-1/-2/STAT1 and STAT3 pathways respectively, which contribute to insulin resistance through suppressor of cytokines signalling (SOCS) molecules that repress IR tyrosine kinase activity and promote IRS degradation.²⁴ Concurrent to FFA spill over from AT, the altered substrate utilisation that accompanies insulin resistance in tissues like the myocardium results in an increased reliance on FFAs over glucose, culminating in lipotoxicity, increased ROS production, mitochondrial dysfunction and the activation of cell death pathways.^{24,25} This highlights how AT dysfunction, through oxidative stress and insulin resistance, is linked to the development of atherosclerosis and CVD.²⁴

INSULIN SENSITISATION AS A THERAPEUTIC STRATEGY IN ATHEROSCLEROSIS

Given the role of insulin resistance in AT dysfunction and vascular oxidative stress, compounds with insulin-sensitising effects offer an important paradigm for identifying novel therapeutic targets in atherosclerosis. Previous work by our group has shown that insulin sensitising agents such as dipeptidyl-peptidase-4 (DPP4) inhibitors restore vascular insulin sensitivity and reverse the insulin-induced production of superoxide in the vascular wall of patients with atherosclerosis.²⁶ We have also demonstrated a similar effect for canagliflozin, an sodium-glucose cotransporter-2 inhibitor, on the myocardium.²⁷ Yet in addition to identifying the direct effects of potential therapeutic agents on the vascular wall, it is also important to assess their indirect effects through understanding how such agents might modulate AT biology.

Wingless-related integration site (Wnt) signalling is an example of a complex signalling paradigm that has been linked to vascular disease, both directly as well as indirectly through increasing AT inflammation and insulin resistance.^{28,29} Here, our group has identified an obesity-associated imbalance between the non-canonical Wnt ligand WNT5A and secreted frizzled related protein 5, its negative regulator, in both PVAT and ThAT which promotes atherosclerosis via an NADPH oxidase (NOX)-dependent mechanism.²⁹ This work highlighted the WNT5A/USP17/NOX axis as a potential therapeutic target in obesity-associated vascular disease (**Figure 1**).

However, owing to the complexity of the bidirectional signalling that occurs between AT and the vasculature, in subsequent work our group has used an unbiased metabolomics approach to screen the secretomic profiles of distinct AT-depots from atherosclerotic patients with or without obesity. Here, we identified sphingolipid metabolism as the top dysregulated signalling pathway in the ThAT (compared to the ScAT) of patients with obesity.³⁰ Additionally, we showed that increased levels of C16:0-ceramide (CerC16) in the secretome of ThAT is causally linked to enhanced arterial superoxide production and a higher risk of cardiac mortality (**Figure 1**).³⁰ Subsequently, in a 52-week randomised trial liraglutide (a glucagon-like peptide 1 [GLP-1] analogue and substrate of DPP4) was demonstrated to mitigate the significant increase in plasma CerC16 and its glycosylated derivative C16:0-glucosylceramide (GlcC16) seen in a control group on a low-calorie diet, despite no significant changes in body mass index within either group.³⁰ Importantly, this confirmed ceramides as modifiable therapeutic targets in patients with obesity and indicates the importance of AT-derived bioactive molecules in the relationship between AT dysfunction and atherosclerosis.

IMAGING PVAT

All major clinical imaging modalities have been used for the assessment of AT within the pericardium, however only computed tomography has advanced to the targeted and clinically relevant assessment of PVAT for atherosclerotic disease assessment purposes.³¹⁻³³

Ultrasound

Given the anatomical and technical limitations on assessing the coronary arteries with ultrasound, there has been little progress in utilising cardiac echocardiography for the direct visualisation and assessment of PVAT. Despite this, there is significant work in the assessment of the broader EpAT (which includes PVAT) utilising transthoracic echocardiography. Although less specific than coronary PVAT, EpAT is strongly associated with atherosclerotic disease and is an underutilised biomarker of risk.³⁴ Evaluation of EpAT by transthoracic echocardiography has some advantages of being low cost, having no radiation exposure and a rapid assessment. Iacobellis et al first described the technique for echocardiographic assessment of EpAT.³⁵ They expressed EpAT as an echo-free space above the right ventricular free wall by transthoracic echocardiography and measured the thickness from the anterior aspect of the right ventricular free wall through parasternal long and short axis windows. There is conjecture as to what normal values for echo-assessed EpAT thickness are, with technical acquisition factors playing a significant role in the returned values, in particular the timing of the heart cycle.³⁶ Limitation on the use of echo for EpAT assessment include that this approach only partially measures EpAT in a single plane. In contrast, both EpAT thickness and volume can be measured by computed tomography (CT) and magnetic resonance imaging (MRI) more accurately than

echocardiography.³⁶ Echocardiographic measurements are not as reproducible as cardiac CT and MRI. Another limitation is the relatively poor inter-observer and intra-observer variability as compared with cardiac MRI and CT.

It is also important to note the role of associated ultrasound measurements that have become widely utilised in the assessment of atherosclerotic disease risk. The most commonly utilised in research clinical practice is the carotid artery intima-media thickness (cIMT). This measure is an index measure from high-resolution carotid artery ultrasound. cIMT increase is not synonymous with subclinical atherosclerosis but is related to it. There are European and American guidelines for the use of cIMT in clinical practice and cIMT screening can help the clinician to reclassify a substantial proportion of intermediate atherosclerotic cardiovascular risk patients into a lower or higher risk category.^{37,38}

Carotid artery extra-medial thickness (cEMT) has also been proposed as an ultrasound assessment of atherosclerotic disease risk that assesses adipose tissue deposition within the adventitia of arteries.^{39,40} cEMT has not been widely adopted in research or clinical practice.

MRI

MRI has not been widely utilised for the imaging of coronary PVAT, most likely due to its high cost, time consumption and lower image resolution compared to CT. MRI can be utilised for the global assessment of EpAT and has proven to be a very effective and reproducible method for EpAT volume quantification.^{41,42} The global nature of the EpAT assessment possible with MRI renders it a very useful marker with additional functional information beyond echocardiography by detecting deep regional AT that is not accessible with transthoracic or transoesophageal echocardiography. Limitations on the usage of MRI include cost, time required for the examination and difficulty in the segmentation of the region on the acquired scan. MRI approaches certainly yield superior reproducibility compared to ultrasound methods. Targeted assessment of AT in the perivascular space is possible on MRI but there has been little work focussed on the coronary arteries in this regard. Relevant related work includes assessment of AT thickness around the aorta and carotid arteries via MRI, however no such work has been carried out on the coronary arteries.⁴³

CT

It is with the use of cardiac CT that the assessment of PVAT has evolved from a purely research tool to be a biomarker relevant to clinical practice and at the frontier of technology for atherosclerotic CAD risk assessment.

Both contrast-enhanced and non-contrast-enhanced cardiac-gated multidetector CT can be utilised for the assessment of EpAT globally with excellent reproducibility, time efficiency and minimal radiation exposure. The combination of high spatial resolution, volume coverage of the entire heart and increasing availability of software analysis tools makes the use of CT to measure EpAT and specially PVAT ideal.⁴⁴ Automated assessment of EpAT utilising artificial intelligence approaches are also available, rendering EpAT volume quantification an entirely automated and almost instantaneous biomarker ready for applications in the radiology interpretation suite.⁴⁵

Cardiac CT offers the possibility of segmenting and analysing adipose tissue depots through application of pre-defined validated Hounsfield unit (HU) cut-offs (−190 to −30 HU for adipose tissue) as discrete segments.^{11,46} Coronary computed tomography angiography

(CCTA) in particular allows imaging of the vascular anatomy with the volumetric and qualitative characterisation of PVAT along the coronary vessels.

NOVEL TOOLS FOR THE STUDY OF ATHEROSCLEROSIS BY UTILISING CT IMAGING OF PVAT

The peri-coronary artery Fat Attenuation Index (FAI)

Translational efforts to unlock patient care benefits from the discoveries related to the effects of PVAT on atherosclerotic disease risk have been described and validated. The most clinically relevant novel CT-biomarker is the perivascular FAI, which tracks spatial changes in PVAT composition induced by inflamed coronary artery vessels.¹¹ Developed through a radiotranscriptomic approach that linked the CT phenotype of adipose tissue biopsies scanned ex vivo with their transcriptional profile, FAI relies on the concept that inflammation-induced changes in adipocyte size and lipid content are associated with a shift in CT attenuation towards a less negative HU range (towards -30 HU). The perivascular FAI (calculated by the CaRi-HEART algorithm developed by the University of Oxford) captures these gradients in the attenuation of the perivascular space, with high perivascular FAI linked to a higher inflammatory burden.¹¹ **Figure 2** demonstrates the pathobiological changes driving the inflammatory changes detected with the peri-coronary FAI. Our group has shown that atherosclerotic CAD is associated with higher perivascular FAI compared to healthy individuals.¹¹ Moreover, perivascular FAI is significantly increased around culprit/unstable lesions in patients presenting with acute MI.¹¹ Notably, perivascular FAI exhibits dynamic changes around the culprit lesions, decreasing significantly when measured five weeks after the index event.¹¹

PVAT attenuation, first described by Antonopoulos et al.,¹¹ has been found to be greater around atherosclerotic coronary segments compared to healthy segments, as assessed on IVUS.⁴⁷ Recently, Goeller et al.⁴⁸ independently confirmed that compared with non-culprit lesions, culprit lesions in acute coronary syndrome (ACS) patients are associated with significantly higher PVAT average radiodensity, a key component driving the FAI values. In further validation of the strong links between coronary inflammation and PVAT phenotype, higher perivascular fat radiodensity has been shown to strongly correlate with increased plaque inflammation as assessed by ¹⁸F-NaF uptake on positron emission tomography-CT imaging, as well as the progression of total and non-calcified atherosclerotic plaque burden in the adjacent vessel.^{49,50} Of note, in symptomatic patients undergoing cardiac CT the information captured by the perivascular FAI is independent of coronary calcification (when measured by coronary artery calcification) or systemic markers of inflammation, such as high sensitivity C-reactive protein.^{11,51}

The potential clinical value of pericoronary FAI assessment in improving cardiac risk prediction was explored in the Cardiovascular RiSk Prediction using Computed Tomography (CRISP-CT) study, a multi-centre study comprising two independent cohorts of up to 4,000 patients altogether undergoing clinically-indicated CCTA for stable chest pain investigation in two major centres in Europe and the USA with a follow-up up to 10 years after the scan.⁵¹ Higher perivascular FAI values around the proximal right coronary artery (RCA) and left anterior descending (LAD) arteries were linked to a higher adjusted risk of both all-cause and cardiac mortality.⁵¹ More importantly, FAI mapping offered incremental prognostic value for cardiac mortality beyond age, traditional risk factors, extent of CAD and presence of high-risk plaque features in both cohorts. In post-hoc analyses, a cut-off of -70.1 HU was ascertained and was associated with a 6- to 9-fold higher adjusted risk of future cardiac mortality in the two independent cohorts.⁵¹

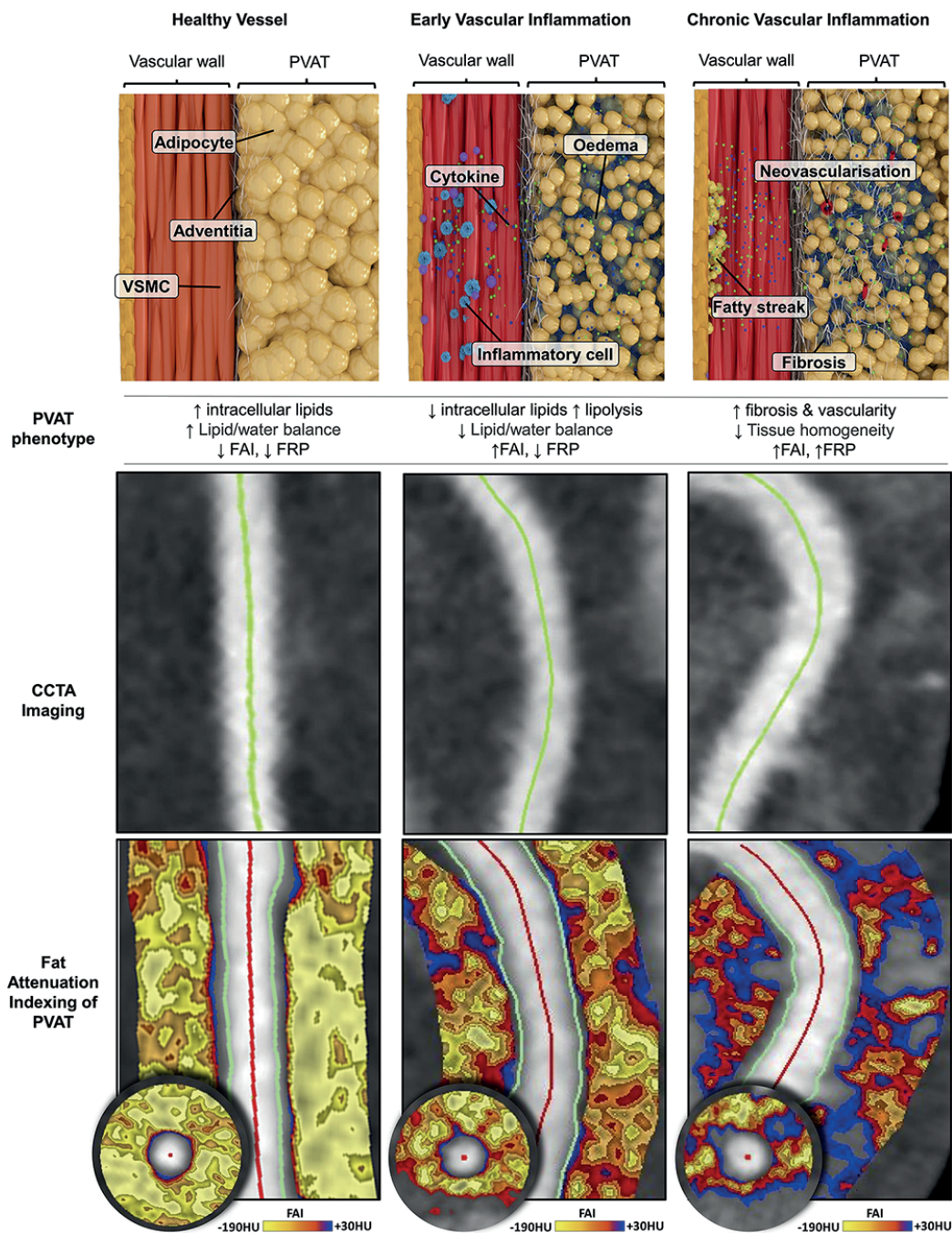


Figure 2. Schematic representation of the biology underlying the coronary artery FAI.

Coronary inflammation drives phenotypic changes in PVAT, including decreased adipocyte size, differentiation, and intracellular lipid content. Lipolysis and inflammatory infiltration lead to early inflammatory changes within the coronary PVAT and subsequent neovascularisation and PVAT fibrosis worsen with chronic vascular states. The novel CT-derived FAI captures weighted 3-dimensional attenuation values reflecting the biological phenotypic gradients inherent to coronary inflammation, while typical interpretation of the CT images (as shown in middle section 'CCTA imaging') fail to recognise the presence of inflammation. Persistence of vascular inflammation and atherosclerotic disease may lead to further, irreversible changes in PVAT composition, characterised by increased extracellular fibrosis and neomicrovascularisation. Those changes can be detected by radiomic phenotyping of PVAT using the novel signature FRP. ↑ indicates an increase. ↓ indicates a decrease. This figure is reproduced with permission following publication in "Cardiac computed tomography. In: Libby P, Bonow R, Mann D, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Volume 1. 12th ed. Philadelphia (PA): Elsevier; 2022. p.348."

CCTA = coronary computed tomography angiography; CT = computed tomography; FAI = Fat Attenuation Index; FRP = Fat Radiomic Profile; HU = Hounsfield unit; PVAT = perivascular adipose tissue.

Perivascular FAI is yet to be tested in a clinical trial to assess the reversibility of coronary PVAT inflammation, as measured by FAI, in response to statin therapy, new anti-inflammatory agents (e.g., canakinumab) or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.⁵² Such a trial is needed to understand the clinical benefits of atherosclerotic disease risk reduction with FAI assessment. Despite this, there is good data to demonstrate that perivascular FAI is modifiable and may track the effects of anti-inflammatory interventions (**Figure 3**). In patients who received advice to commence treatment with statins or aspirin after CCTA, the perivascular FAI (measured before deployment of the new treatment) was no longer predictive of cardiac mortality (adjusted hazard ratio [HR], 2.85; $p=0.25$). In contrast, among those who did not receive any recommendations for change of management after CCTA, the predictive value of high perivascular FAI values for cardiac mortality was retained (adjusted HR, 18.71; $p=0.01$).⁵¹ Notably, in a recent prospective cohort study of patients with moderate to severe psoriasis, anti-inflammatory treatment with novel biologics (anti-TNF- α , anti-IL-17, and anti-IL-12/23) was associated with a significant reduction in perivascular FAI at one year, whereas no significant change was observed in individuals treated with topical or ultraviolet B phototherapy.⁵³ This study is the best evidence to date that novel perivascular imaging techniques can be utilized to track response to interventions for coronary disease. Further, 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.¹¹ This was seen in a small sub-study of the original development cohort of the perivascular FAI, with 5 patients who underwent CTCA at the time of MI and a follow-up scan 5-weeks following the event matched with controls with stable plaque but no MI were also analysed 5 weeks following their initial scan. There was a significant ($p=0.04$) reduction in FAI at the culprit lesion 5 weeks after the event, whereas there was no change in FAI around the stable atherosclerotic plaques. We have also shown that the predictive power of peri-coronary artery FAI is even more powerful when it is added on top of coronary artery high risk plaque (HRP) features. In the presence of low peri-coronary FAI, HRP features are

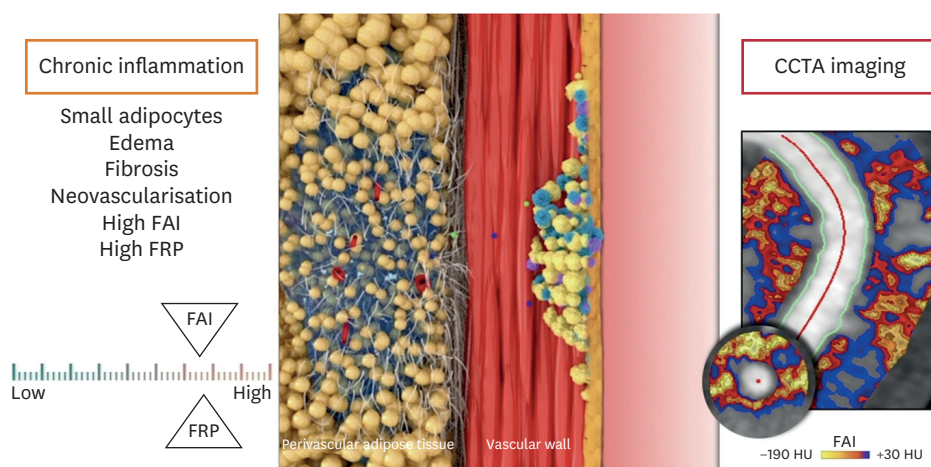


Figure 3. Detecting biological changes to PVAT using the coronary artery FAI.

In the context of chronic inflammation and metabolic disease, cytokines and oxidative products from both the vascular wall and the circulation diffuse into PVAT in a paracrine and endocrine manner respectively. This induces biological changes in PVAT including lipolysis, oedema, fibrosis, neovascularisation and the impaired differentiation of adipocyte precursors. These changes are reflected through an increase in the FAI and FRP which can be detected using CCTA imaging. The accompanying video illustrates the process of how early vascular inflammation affects PVAT biology, which can be detected on CCTA through changes in the FAI, as well as how this develops in the setting of chronic inflammation to include changes in the FRP which can also be imaged using CCTA: weblink to the video animation. This figure and video are reproduced with permission following publication in “Kotani CP, Antoniadou C. Perivascular fat imaging by computed tomography (CT): a virtual guide. *Br J Pharmacol* 2021;178:4270-90.”

CCTA = coronary computed tomography angiography; FAI = Fat Attenuation Index; FRP = Fat Radiomic Profile; PVAT = perivascular adipose tissue.

not associated with increased cardiac risk, while in a high FAI setting, HRP features flag a particular high-risk group of patients.⁵⁴

Recent data from a post-hoc analysis of the multicentre Scottish Computed Tomography of the Heart (SCOT-HEART) trial has shown similar predictive results. Tzolos et al.⁵⁵ investigated the associations between the risk of future fatal or nonfatal MI and PVAT average radiodensity measured from CTCA. They found that coronary artery PVAT radiodensity had marked and complementary predictive value for the risk of fatal or nonfatal MI: Coronary PVAT attenuation of the RCA was predictive of MI (HR, 1.55; $p=0.017$, per 1 standard deviation increment). In multivariable analysis, adding RCA attenuation of ≥ -70.5 HU to an model that include low-attenuation non-calcified plaque burden led to improved prediction of future MI (HR, 11.7; $p<0.0001$).

The coronary artery fat radiomic profile

The latest advance in coronary artery PVAT assessment relies on radiomics and provides a different snapshot of PVAT inflammatory burden—a biomarker for static and long-term change (**Figure 2**). Through mathematical extraction of the spatial distribution of signal intensities and pixel interrelationships, radiomics quantifies textural information in CT images by using analysis methods from artificial intelligence (AI) such as machine learning.^{56,57} It is possible to extract radiomic features from any defined segment of a CT, including PVAT. Given that inflammation can induce structural changes in PVAT, we sought to identify biomarkers with lower variability than the perivascular FAI through CCTA-based radiomic phenotyping of coronary PVAT.

Coronary PVAT CT radiomic features were linked to markers of inflammation, fibrosis and vascularity using gene expression studies. Using an AI powered approach, 1,391 radiomic features from 101 patients who had major adverse cardiac events (MACE) within 5 years of having a CCTA and from 101 healthy controls were used to develop an algorithm known as the Fat Radiomic Profile (FRP) to distinguish between cases and controls. The FRP signature was subsequently validated using CCTA scans from 1,575 patients enrolled in the SCOT-HEART trial and was shown to significantly improve the predictive value of traditional risk-prediction tools for MACE.⁵⁸ The capacity of the FRP to detect unstable coronary plaques was also assessed. The FRP was significantly higher in patients with acute MI and remained unchanged 6 months after the index event, unlike the FAI, which decreased dramatically after AMI, suggesting that FAI is a more dynamic biomarker of inflammation, whereas FRP captures more static changes (**Figure 3**). The discovery that culprit coronary artery lesions have distinct radiomic signatures compared to non-culprit lesions in MI and lesions in stable coronary artery disease was confirmed recently by Lin et al.,⁵⁹ albeit not an analysis including PVAT. They reported that lesion radiomic features provided incremental value for discriminating culprit lesions when added to a machine learning model containing high risk plaque features and plaque volumes (area under the receiver operating characteristic curve [AUC], 0.86 vs. 0.76; $p=0.004$). More relevant to PVAT, in a prospective case-control study, 60 patients with acute MI underwent CCTA shortly after admission and before invasive angiography.⁶⁰ These patients were matched to patients with stable CAD and with controls (no CAD) and the peri-coronary PVAT radiomic features of the RCA and around culprit and non-culprit lesions in patients with MI. It was found that 20.3% of the radiomic features differed significantly between MI patients and controls, and 16.5% differed between patients with MI and stable CAD (critical $p<0.0006$); whereas none differed between patients with stable CAD and controls. Using machine learning, a model integrating clinical features, coronary PVAT attenuation, and radiomic parameters provided superior

discrimination of acute MI (AUC, 0.87) compared with a model with clinical features and coronary PVAT attenuation (AUC, 0.77; $p=0.001$) or clinical features alone (AUC, 0.76; $p<0.001$).

USING PVAT IMAGING IN CLINICAL PRACTICE

Obesity is a well-established risk factor behind the development of cardiovascular disease, with adipose tissue known to secrete a range either pro- or anti-atherogenic adipokines that exert both endocrine and paracrine effects on the cardiovascular system.^{17,18,61,62} Despite this, in a number of large epidemiological studies obese patients with CAD have been found to exhibit a paradoxical reduction in risk of all-cause and cardiovascular mortality, and although there are a number of inherent methodological limitations in these studies, they bring to question the validity of body weight as a therapeutic target in secondary prevention for cardiovascular disease.^{61,63} In fact, only marked reductions in body weight afforded by bariatric surgery have been shown to result in a significant reduction in all-cause and cardiovascular mortality, with one multicentre, randomised controlled trial (RCT) failing to demonstrate any effect to this end in patients with type 2 diabetes mellitus (T2DM).⁶⁴⁻⁶⁸

In this regard, our group has previously shown that PVAT is a major regulator of vascular oxidative stress and redox signalling in humans via paracrine tissue-tissue interactions.^{17,18} As such, therapeutic modalities that shift the PVAT secretome towards an anti-inflammatory milieu might have pleiotropic effects on the human vascular wall and regulate mechanisms of atherogenesis. GLP-1 analogues are one such potential modality, with large-scale clinical trials such as LEADER demonstrating that treatment with liraglutide led to a significant reduction in cardiovascular risk compared to placebo in patients with T2DM (beyond that which was attributable to either weight loss or improvement of glycaemic control alone).⁶⁹ Pre-clinical studies have also suggested that GLP-1 analogues modulate vascular inflammation, preventing the development and progression of atherosclerosis.⁷⁰⁻⁷² Furthermore, whilst GLP-1R agonists seem to exert direct anti-inflammatory actions on adipocytes resulting in adipose tissue remodelling in mice and promoting adiponectin upregulation in cultured adipocytes, it is still not known whether GLP-1 analogues exert vasoregulatory actions through modifying this cross-talk between PVAT and the vascular wall.⁷³⁻⁷⁵ Thus, whilst further work is conducted into understanding the effects of insulin-sensitising agents on PVAT biology, the ability to non-invasively identify pro-atherogenic changes in PVAT is of critical importance in order to proactively identify patients at high-risk of atherosclerosis.

On this point, how the FAI can be incorporated into clinical practice has been explored, and it is expected that automated approaches to PVAT assessment and atherosclerotic disease risk prognostication will begin to be adopted in practice beyond highly specialized and academic centers.⁵² This integration is through a regulated medical device, CaRi-Heart®, which is a novel CCTA-based risk stratification medical device, which combines the peri-coronary artery FAI mapping with traditional cardiovascular risk factors and multi-dimensional, comprehensive CCTA coronary plaque analysis. The prognostic output produced by CaRi-Heart® demonstrates significant net clinical benefit in two large and independent CCTA populations (the CRISP-CT Study⁷⁶) over and above traditional cardiovascular risk factors.⁷⁷

The FAI-Score

There is significant difficulty in applying raw peri-coronary FAI values into the clinical environment. FAI values have served well as a research tool but the translation of the values

into clinical practice is complicated by technical considerations such as scan tube voltage, biological factors such as background adipocyte volume, and anatomical factors related to the segment of the coronary artery that is imaged. To overcome these difficulties the FAI-Score was developed to correct raw FAI values to the technical, biological/anatomical and patient specific anatomical factors.^{77,78} FAI-Score facilitates a standardisation of FAI values for the influence of background peri-coronary inflammation for all three of the coronary arteries. The FAI-Score is the only regulatory cleared CCTA metric of coronary inflammation in Europe and is interpreted in arbitrary units upon gender and age adjusted nomograms for each coronary artery.

The weighted FAI as used in the CRISP-CT study came from Cox-regression models which is not useful in clinical practice. The FAI-Score resolves this issue and provides greater usability with powerful prognostic ability. A FAI-Score above the 75th percentiles in both the RCA and the LAD gives a relative risk that is 2.4 times greater for fatal cardiac events, while over the 95th percentile is linked to with 3–5 times higher risk.⁷⁸

FAI-Score should be interpreted alongside traditional risk factors, plaque burden and high-risk plaque features. Such assessment has been investigated in prognostic models in the US population of the CRISP-CT Study, with external validation in the European arms. Reclassification of some 20% of the clinical CCTA patients to a higher and a similar number to a lower risk group for cardiac death was achieved.⁷⁸ The implementation of technology such as the FAI-Score alongside European Society of Cardiology Score may provide more accurate risk assessment in with CCTA information available. The detection of patients with significant (i.e., up to 2.5-fold increased relative risk) for fatal cardiac events may warrant escalation of statin or anti-inflammatory therapies. The personalisation of risk assessment tools through merging imaging data (such as PVAT assessment and plaque characteristics) will see their value increase massively, however regulatory approval will be required before clinical implementation is possible as such tools combine imaging as well as prognostic modelling. CaRi-HEART® medical device is the only regulatory cleared risk calculator (in Europe and Australia), that takes into account FAI-Score, the presence of coronary atherosclerotic plaque from CCTA and the patient's clinical risk factors, providing a very accurate calculation of the absolute risk of the patient for a fatal cardiac event.⁷⁸ This new calculated absolute risk, is now recalibrated in a large multi-ethnic multi-national study the Oxford Risk Factors And Non Invasive Imaging (ORFAN) study, in 100,000 participants, linked with 10 years outcomes data through national registries, expected to deliver in the coming year.

With the uptake of AI-enhanced technologies such as CaRi-Heart® the ability to detect the vulnerable patient at risk of atherosclerotic disease events will be significantly improved. It is proposed that the peri-coronary FAI could be incorporated into practice as a companion diagnostic test in secondary prevention, thereby unlocking the targeted deployment of high-cost treatments such as canakinumab or PCSK9-inhibitors to only a small proportion of atherosclerotic disease patients who are poor responders to the current state-of-the-art treatment and have persistently high levels of coronary inflammation, as detected in the PVAT. This is a solution for ensuring we give the right therapy to the right patient at the right time.

It is most likely that off-site platforms (software as a service approach, such as the CaRi-Heart® device) will be the most effective means to deploy technology into clinical environments as this would offer global solutions to the clinician and patient that are cost-effective, user friendly (possibly mobile application driven), strictly managed, and tightly

regulated (i.e., have the appropriate regulatory and quality approvals, such as a Conformité Européenne [CE] mark in Europe or Food and Drug Administration [FDA] clearance in the USA). Currently, the need for a contrast enhanced CT scan that involves radiation exposure will limit the deployment of CT technologies in primary prevention settings, although their use as part of a standard CCTA reporting protocols will give an entirely new dimension to the management of patients with atherosclerotic coronary disease.

CONCLUSION

In this review article, we have introduced the concept of PVAT as an active endocrine organ that is dynamically involved in the development of a pro-atherogenic inflammatory milieu, while it engages in bidirectional communication with the vascular wall. Indeed, the ability of PVAT to sense inflammatory and other signals from the vascular wall, and the subsequent phenotypic changes it undergoes as a result, make it a plausible “biosensor” of vascular inflammation. Modern imaging technologies that analyse the CT attenuation changes within PVAT provide quantitative metrics of vascular inflammation (the FAI-Score) which is now used to calculate the residual cardiovascular inflammatory risk in clinical practice. Beyond its use as a source of diagnostic biomarkers relevant to risk prediction, PVAT can also be targeted therapeutically to prevent or treat atherosclerosis. Although this is an attractive concept, delivery of interventions specifically to PVAT is not straightforward. Future studies are needed to facilitate the development of such therapeutic strategies that will unlock PVAT’s potential as a powerful therapeutic target in cardiovascular therapeutics.

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