Pericoronary adipose tissue imaging and the need for standardised measurement of coronary inflammation:

translating PCAT attenuation gradients into FAI Score for clinical use

Kenneth Chan[1] MRCP, Charalambos Antoniades[1] MD PhD FRCP FMedSci

1. Acute Multidisciplinary Imaging & Interventional Centre, British Heart Foundation (BHF) Centre of research Excellence, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

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Correspondence to:
Professor Charalambos Antoniades MD PhD FRCP FMedSci,
BHF Chair of Cardiovascular Medicine University of Oxford
Acute Multidisciplinary Imaging & Interventional Centre (AMIIC),
University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU
e-mail: Charalambos.antoniades@cardiov.ox.ac.uk

Inflammation is a critical process driving atherogenesis and the instability of vulnerable, predominantly non-calcified plaques(1). Recently, the prospect of modulating inflammation to improve cardiovascular outcomes is becoming evident from large-scale clinical trials using specific anti-inflammatory agents (anti-IL-1β in CANTOS)(2) and broad anti-inflammatory effects with colchicine (LoDoCo2 and COLCOT trials)(3,4), although intervening with an anti-inflammatory agent early post an acute coronary syndrome may be less beneficial (CLEAR SYNERGY)(5). Importantly, inflammatory risk is not entirely captured by known clinical risk factors, and significant cardiovascular events occurred among patients who have achieved target low-density lipoprotein control as well as those without obstructive coronary artery stenosis(6,7). While systemic inflammatory biomarkers such as C-reactive protein (hsCRP) have some prognostic value, their specificity to vascular inflammation remains unclear. Identifying patients with elevated inflammation therefore remains an unmet need.

Imaging of the peri-coronary coronary adipose tissue (PCAT) emerges as a valuable biosensor of dynamic inflammatory processes within the coronary vasculature (8). We have previously shown that inflamed coronary arteries and plaques release lipolytic and inflammatory mediators into the surrounding PCAT, with smaller adipocytes (lower lipid phase) and higher aqueous phase as approaching the vascular wall, altering its radiological texture and composition(8). These alterations of the lipid-water balance within PCAT, result in increased x-ray attenuation values towards the higher end of the typical adipose range (-190 to -30 Hounsfield units), as approaching closer to the outer vascular wall of the inflamed artery. These three-dimensional changes within PCAT, are detectable through mapping of x-ray attenuation gradients from routine coronary CT angiograms (CCTA), and provide an imaging biomarker of coronary artery inflammation (8). Averaging the attenuation within the PCAT, provides a crude but still useful marker of coronary inflammation, and it correlates

strongly with positron emission tomography (PET) NaF uptake (r=0.68, P<0.001) (9). Importantly, it does not rely on the degree of coronary stenosis, coronary calcium score or high-risk plaque features, which opens up an opportunity for risk stratification of epicardial coronary artery disease by capturing inflammatory risk(10). However, average PCAT mean attenuation is significantly influenced by the hardware and scan parameters (e.g. tube voltage, vendor and imaging platform used etc)(11); it is also applicable primarily to vessel segments without branches and with predictable local anatomy, like the proximal right coronary artery (RCA). These factors can significantly limit the reproducibility and clinical validity of PCAT mean attenuation(11). However, when appropriate corrections are applied (for the scanner/technical variability and handling of the local anatomy), the resulting Fat Attenuation Index (FAI) provides stronger prognostic value(10). For the clinical translation of this technology, further standardization was needed taking into account further technical parameters including segment standardization and patient's age and sex (FAI Score), while the interpretation of the results is performed in age and sex nomograms (11). The FAI score is generated by a proprietary algorithm, reproducible across platforms and different geographical areas/ethnicities, providing consistent prognostic value when measured across any of the three coronary arteries(7). However, due to the easier access to the various tools measuring PCAT mean attenuation, a plethora of studies has yield various prognostic associations for this particular metric, highlighting both the biological relevance of the concept as well as the need for standardization for clinical translation.

In this issue of *JACC: Cardiovascular Imaging*, Tan *et al* (12) reviewed and meta-analysed 17 studies involving >8,000 individuals with PCAT imaging and MACE outcomes. Pooling quantitative analyses without access to the source data, leads to significant heterogeneity and makes it very difficult to extract robust conclusions. Given that only a few studies reported findings with FAI measurements, these studies were excluded from the

quantitative pooled analysis, which inadvertently disregarded the largest outcomes studies published in this field.

Corrected metrics of inflammation (FAI and the most recent FAI Score) have generally demonstrated predictive value for MACE, cardiac mortality, non-fatal MI and heart failure, reproducible across all three coronary arteries(7,10,11), compared to uncorrected metrics like PCAT mean attenuation that provides lower predictive value and it is reproducible in vessel segments with simple anatomy like the proximal RCA (**Figure**)(10). Indeed, an important confounder in the interpretation of the results from the PCAT literature, is also the variable reporting of the prognostic value of the metric. Some studies reported HR per one standard deviation (SD) increase in PCAT mean attenuation(13), while others used changes per Hounsfield unit or even compared values above and below an attenuation cutoff. These different approaches are problematic when combined in the meta-analysis without having access to the source data, limiting the interpretation of the pooled effect size(14,15). Additionally, the definition of MACE varied across the studies. Two of the larger studies including all-cause death, raising the question of whether all events in these studies could be attributed to the cardiovascular system(14,15). This might have partly explained the lack of prognostic associations in these studies. Despite these limitations, the meta-analysis showed an overall significant association between RCA PCAT mean attenuation and MACE, reflecting the strong biological associations between clinical outcomes and phenotypic changes in PCAT in response to inflamed coronary artery. However, the effect size of the pooled result should be interpreted with caution given the significant heterogeneity between studies.

Another important consideration is the site of PCAT measurement. Pooled analysis was possible using data from just three studies that included PCAT mean attenuation measurements for the left anterior descending (LAD) and left circumflex arteries (LCX) in

addition to the RCA, compromising the pooled analysis with the studies that measured PCAT mean attenuation only around the RCA. Indeed, a consistent anatomical definition of perivascular adipose tissue is important, as highlighted in the European Society of Cardiology (ESC) clinical consensus statement(16). Indeed, the original perivascular FAI assessments were measured around the proximal segment of the RCA, over a 40 mm section, at a radial distance from the arterial wall equivalent to the artery's diameter. This location on the RCA is anatomically preserved across individuals, with consistent orientation relative to its neighbouring structures, enabling consistency of PCAT mean attenuation measurements in the RCA compared to the LAD and LCX(16). This becomes even more relevant when measuring PCAT attenuation in segments other than the proximal segments of the three arteries, as the reference values/cutoffs are different for each segment of the coronary tree, making comparisons of PCAT mean attenuation measurements impossible between the different studies presented in the meta-analysis. Indeed, validation studies were necessary to develop separate algorithms for calculating coronary inflammation using perivascular FAI Score around the proximal RCA, LAD and LCX (11), while there is still no clinically available model measuring FAI Score in the mid or distal vessels.

A notable finding from the current meta-analysis is the association between PCAT imaging and different plaque types. Despite variations in the definitions and qualitative assessment of high-risk plaques (HRP) across studies, the pooled analysis demonstrated increased odds of HRP in the presence of increased PCAT attenuation, confirming the original observation that plaque-specific FAI measurements can differentiate stable from unstable plaques with AUC=0.91(8), while it is significantly elevated around ruptured plaques (17). Additionally, significant associations were observed with non-calcified plaque components, but not with calcified plaques, a finding further confirmed by previous observations that only perivascular FAI around non-calcified plaques (but not around

calcified plaques) changes in response to statin treatment(18). These findings highlight the relevance of inflammation in high-risk, non-calcified plaques that are vulnerable to rupture. Indeed, it was previously shown that patients with HRP had a significantly increased risk of MACE in the presence of elevated coronary inflammation (11), and elevated systemic inflammation accelerates progression of non-calcified plaque(1). It also supports the notion that while coronary calcification describes the burden of stable atherosclerotic disease, it might not adequately capture the inflammatory risk that drives acute coronary events.

To evaluate the clinical utility of PCAT imaging to quantify coronary inflammation, perhaps greater emphasis should be placed on the robust external validation of standardised measurement rather than statistical pooling of studies with heterogeneous designs and technical measurement. Recognizing the need for consistent and clinically applicable metrics of coronary inflammation, FAI Score was developed as a standardized, clinically interpretable measure that adjusts for technical, anatomical, and biological factors, and is interpreted using age- and sex-specific nomograms(11), as described in a recent ESC clinical consensus statement(16) (**Figure**). The quantitative measure was initially derived from the USA and European populations(11), and recently validated externally in the UK arm of the ORFAN cohort, which has demonstrated strong prognostic value for both fatal and non-fatal cardiac events(7). Importantly, even in individuals with minimal or no atheroma, elevated coronary inflammation, as detected by the FAI Score, was associated with a significantly increased risk of cardiovascular events, reinforcing its potential utility in early risk stratification and prevention. Finally, the ability of FAI Score measured in any of the three epicardial coronary arteries predicts not only fatal and non-fatal myocardial infraction but also the development of ischaemic heart failure (**Figure**), suggests that inflammation expands from the main arteries to the small coronary vessels and possibly the microcirculation, and FAI Score

reflects the inflammatory status of the entire artery, not only the proximal coronary segments where it is measured.

In summary, Tan *et al* (12) confirmed the value of measuring PCAT mean attenuation as a way to study coronary inflammation, while highlighting the need of standardization to improve its reproducibility across all coronary arteries in order to facilitate clinical translation. These issues have been addressed by metrics like FAI Score, that take into account not only the scan-related/technical variability, but also the local anatomical and biological variability, producing measurements of coronary inflammation that are reproducible and applicable for clinical decision making in practice.

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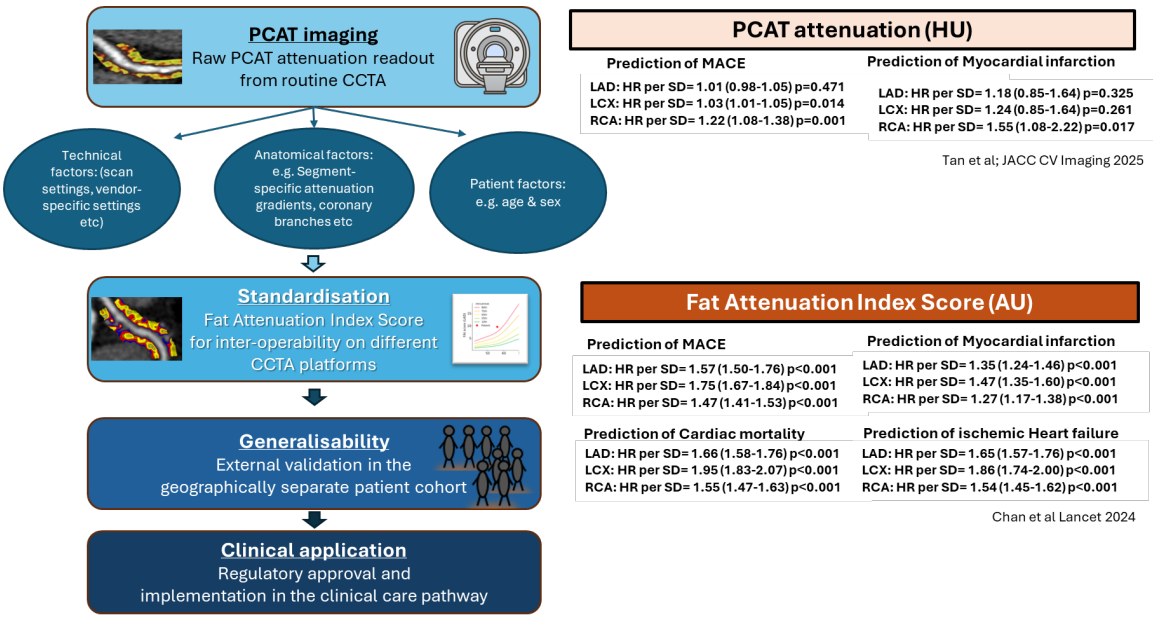

CCTA, Coronary computed tomography angiography; CI , confidence interval; FAI, Fat attenuation index; HR, Hazard ratio; MACE, major adverse cardiovascular events; PCAT, Pericoronary adipose tissue; SD, standard deviation

Figure: Translating PCAT imaging to clinical application of quantifying coronary inflammation. Hazard ratios are presented as per 1 standard deviation increment in FAI Score as a continuous variable. By taking into account technical, anatomical and patient factors, FAI Score measured in all 3 coronary vessels demonstrated more consistent associations with MACE compared to PCAT attenuation. Further external validation is a critical step to ensure generalisability and implementation into clinical application.

CCTA, Coronary computed tomography angiography; CI , confidence interval; FAI, Fat attenuation index; HR, Hazard ratio; MACE, major adverse cardiovascular events; PCAT, Pericoronary adipose tissue

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