Perivascular Fat Attenuation Index Stratifies Cardiac Risk Associated With High-Risk Plaques in the CRISP-CT Study

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Abbreviations: CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CI: confidence interval; CRISP-CT: Cardiovascular Risk Prediction using Computed Tomography study; FAI: fat attenuation index; HR: hazard ratio; HRP: high-risk plaque; HU: Hounsfield units; LAD: left anterior descending artery; RCA: right coronary artery.
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Recommended tweet: *A post-hoc analysis of the CRISP-CT study demonstrates that perivascular FAI mapping stratifies the risk associated with high-risk plaques on #CCTA.*
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Research letter

Coronary computed tomography angiography (CCTA) is a first-line investigation in suspected coronary artery disease (CAD) (1,2). Further to the detection of luminal stenosis, CCTA can characterize distinct high-risk plaque (HRP) features associated with an increased risk of adverse events (3).

Coronary inflammation, a key driver of atherosclerotic plaque formation and rupture, inhibits lipid accumulation in adjacent adipocytes resulting in a three-dimensional gradient in the aqueous/lipid content of the perivascular adipose tissue (PVAT). These inflammation-induced changes can be quantified as perivascular attenuation gradients using the CCTA-derived Fat Attenuation Index (FAI) (4). Perivascular FAI has incremental prognostic value beyond traditional risk factors, as shown in the CRISP-CT (Cardiovascular Risk Prediction using Computed Tomography) study (5). However, it is unclear whether FAI provides incremental value to HRP.

We now present a post-hoc analysis in which we stratify the CRISP-CT population based: a) on the presence (HRP+) or absence (HRP-) of HRP (defined as ≥1 of the following: positive remodeling, low-attenuation plaque, spotty calcification or napkin-ring sign anywhere along the coronary tree) and b) high versus low perivascular FAI (**Figure 1A)**. Vessel-specific perivascular FAI mapping was performed around the proximal RCA and LAD using the CaRi-HEART algorithm as previously described (4,5), and the study population was split in high (FAI_{high}) vs low (FAI_{low}) groups based on validated FAI thresholds (5). As per our prior work (5), the left main stem was not analyzed because of its variable length/anatomy. The study was approved by the local institutional review boards (Cleveland Clinic IRB 17-915 & ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg).

Among 3912 patients undergoing clinically-indicated CCTA (mean age 55.7±13.7 years, 1608 [41.1%] females) followed over 5.3±2.1years, 74 cardiac deaths were recorded. For an RCA FAI cut-off of -70.1 HU (5), FAI_{high}/HRP+ patients had a 7.3-fold higher adjusted risk of cardiac mortality compared to the FAI_{low}/HRP- reference group after adjustment for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, epicardial obesity and modified Duke CAD index group (**Figure 1B**). A higher risk was also seen among FAI_{high}/HRP+ (HR[95%CI]: 7.33[3.22-16.67], P<0.001) and FAI_{high}/HRP- patients (5.65[2.65-12.03], P<0.001) compared to the FAI_{low}/HRP+ group. Similar trends were observed when stratifying the patient population based on the perivascular FAI around the LAD for a cut-off of -79.1HU; HR[95%CI]: 5.29[2.10-13.32], P<0.001, for FAI_{high}/HRP+; 3.92[1.69-9.23], P<0.001; for FAI_{high}/HRP- and 0.56[0.14-2.24], P=0.42, for FAI_{low}/HRP+ (reference: FAI_{low}/HRP-).

In a sensitivity analysis of 2040 patients from the Cleveland sub-cohort (mean age 51.6±14.0 years, 914 [44.8%] females) with available data on non-fatal myocardial infarction, the HR[95%CI] (vs FAI_{low}/HRP-) for a composite endpoint of cardiac mortality and non-fatal myocardial infarction (n=65 events over a mean follow-up of 4.47±2.28 years) was: 5.58[2.87-10.83], P<0.001, for FAI_{high}/HRP-; 3.59[1.56-8.27], P=0.003, for FAI_{high}/HRP+ and 0.83[0.38-1.80], P=0.64, for FAI_{low}/HRP+. Finally, in a subgroup analysis of 1415 patients with coronary artery calcium (CAC) scoring, FAI_{high}/HRP- remained associated with a significantly higher cardiac mortality risk (HR[95%CI]: 8.45[1.63-43.70], P=0.01) when compared to FAI_{low}/HRP- after further adjustment for CAC, highlighting the value of FAI mapping in the HRP- population.

Our hypothesis-generating analysis highlights a striking improvement in risk stratification when FAI is added on top of HRP features in routine CCTA interpretation. In the presence of low-FAI, HRP features are not associated with increased cardiac risk, while in the presence of high-

FAI, HRP flag a particularly high-risk group of patients. Future studies will focus on the mechanisms underlying these associations by exploring links with adverse plaque events (i.e. erosion versus rupture) while also adjusting for quantitative HRP metrics (i.e. low-attenuation plaque burden).

In summary, by detecting early signs of coronary inflammation which precede the development of atherosclerotic plaques, FAI may identify the "vulnerable" patient prior to the development of "vulnerable plaques". Including perivascular FAI in the routine interpretation of CCTA could provide new opportunities for personalized risk management in primary and secondary prevention.

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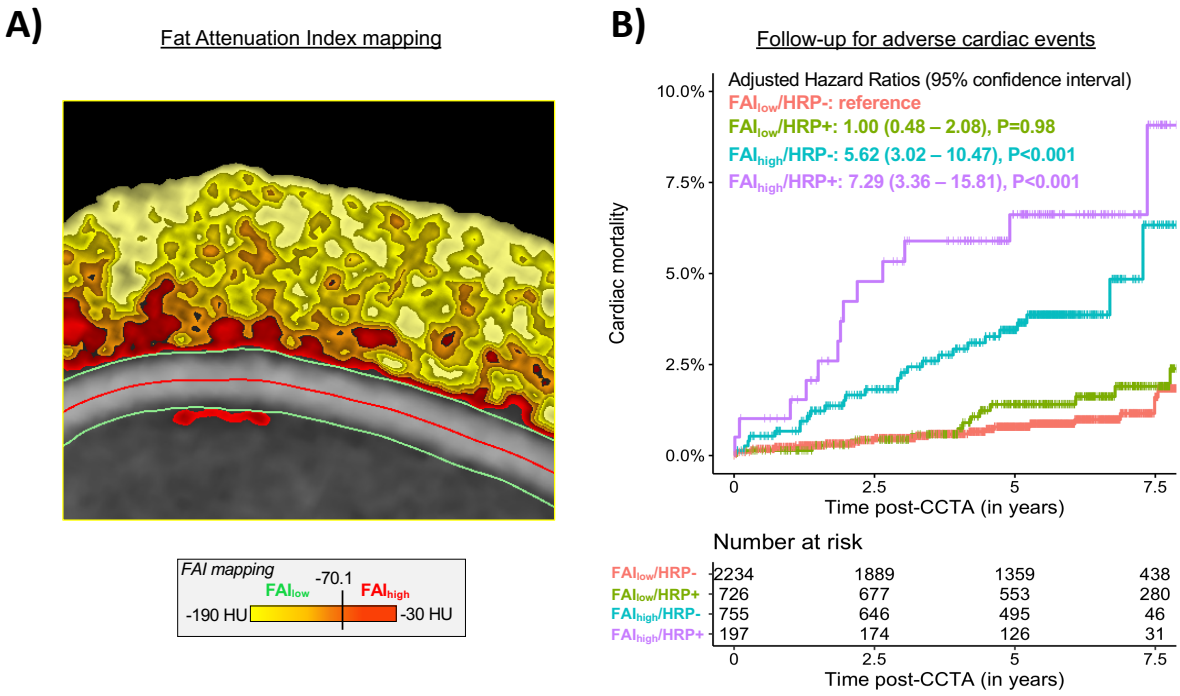

Figure legend. Perivascular Fat Attenuation Index (FAI) stratifies the risk associated with high-risk plaque features (HRP). (A) A visual example of pericoronary FAI mapping. **(B)** Unadjusted Kaplan-Meier curves with adjusted hazard ratios for patients stratified based on FAI around the right coronary artery (cutoff: -70.1 Hounsfield Units) and HRP presence, illustrating how FAI mapping identifies distinct risk groups among HRP+ and HRP- patients.