VOL. 76, NO. 6, 2020
ISSN 0735-1097/$36.00

Letters

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

Coronary computed tomography angiography (CTA) is a first-line investigation in suspected coronary artery disease (1,2). Further to the detection of luminal stenosis, coronary CTA 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 3-dimensional gradient in the aqueous or lipid content of the perivascular adipose tissue. These inflammation-induced changes can be quantified as perivascular attenuation gradients using the coronary CTA-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 the FAI provides incremental value to HRP.

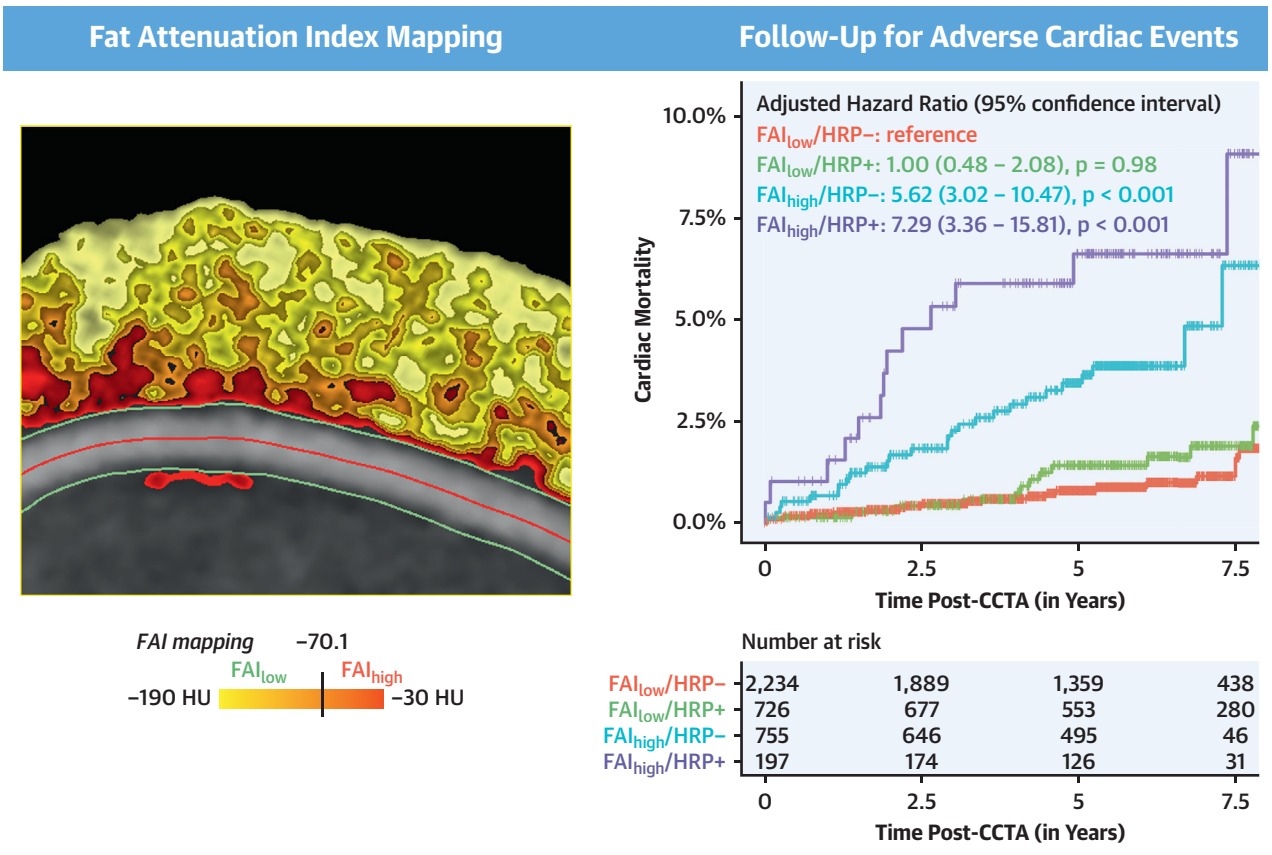
We now present a post hoc analysis in which we stratify the CRISP-CT study population based on: 1) the presence (HRP+) or absence (HRP-) of HRP (defined as ≥1 of the following: positive remodeling, low-attenuation plaque, spotty calcification or napkin-ring sign anywhere along the coronary tree); and 2) high versus low perivascular FAI (**Figure 1A**). Vessel-specific perivascular FAI mapping was performed around the proximal right coronary artery and left anterior descending artery using the CaRi-HEART algorithm as previously described (4,5), and the study population was split in high (FAI_{high}) versus 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 and anatomy. The study was approved by the local Institutional Review Boards (Cleveland Clinic Institutional Review Board 17-915 and ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg).

Among 3,912 patients undergoing clinically indicated coronary CTA (mean age 55.7 ± 13.7 years, 1,608 [41.1%] women) followed over 5.3 ± 2.1 years, 74 cardiac deaths were recorded. For a right coronary artery FAI cutoff of -70.1 Hounsfield units (5), FAI_{high}/HRP+ patients had a 7.3-fold higher adjusted risk of cardiac mortality compared with the FAI_{low}/HRP- reference group after adjustment for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, smoking, epicardial obesity, and modified Duke Coronary Artery Disease Index group (**Figure 1B**). A higher risk was also seen among FAI_{high}/HRP+ patients (hazard ratio [HR]: 7.33; 95% confidence interval [CI]: 3.22 to 16.67; $p < 0.001$) and FAI_{high}/HRP- patients (HR: 5.65; 95% CI: 2.65 to 12.03; $p < 0.001$) compared with the FAI_{low}/HRP+ group. Similar trends were observed when stratifying the patient population based on the perivascular FAI around the left anterior descending artery, for a cutoff of -79.1 Hounsfield units (for FAI_{high}/HRP+ patients, HR: 5.29; 95% CI: 2.10 to 13.32; $p < 0.001$; for FAI_{high}/HRP- patients, HR: 3.92; 95% CI: 1.69 to 9.23; $p < 0.001$; for FAI_{low}/HRP+ patients, HR: 0.56; 95% CI: 0.14 to 2.24; $p = 0.42$) (reference: FAI_{low}/HRP-).

In a sensitivity analysis of 2,040 patients from the Cleveland subcohort (mean age 51.6 ± 14.0 years, 914 [44.8%] women) with available data on nonfatal myocardial infarction, the HR (vs. FAI_{low}/HRP- patients) for a composite endpoint of cardiac mortality and nonfatal myocardial infarction ($n = 65$ events over a mean follow-up of 4.47 ± 2.28 years) was 5.58 for FAI_{high}/HRP- patients (95% CI: 2.87 to 10.83; $p < 0.001$), 3.59 for FAI_{high}/HRP+ patients (95% CI: 1.56 to 8.27; $p = 0.003$), and 0.83 for FAI_{low}/HRP+ patients (95% CI: 0.38 to 1.80; $p = 0.64$). Finally, in a subgroup analysis of 1,415 patients with coronary artery calcium scoring, FAI_{high}/HRP- remained associated with a significantly higher cardiac mortality risk (HR: 8.45; 95% CI: 1.63 to 43.70; $p = 0.01$) when compared with FAI_{low}/HRP- after further adjustment for coronary artery calcium, highlighting the value of FAI mapping in the HRP- population.

JACC VOL. 76, NO. 6, 2020
AUGUST 11, 2020:755–61

FIGURE 1 Perivascular FAI Stratifies the Risk Associated With HRP Features



(A) A visual example of pericoronary Fat Attenuation Index (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 HU) and high-risk plaque (HRP) presence, illustrating how FAI mapping identifies distinct risk groups among HRP+ and HRP− patients. CCTA = coronary computed tomography angiography.

Our hypothesis-generating analysis highlights a striking improvement in risk stratification when FAI is added on top of HRP features in routine coronary CTA interpretation. In the presence of FAI_{low}, HRP features are not associated with increased cardiac risk, while in the presence of FAI_{high}, HRP features 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 vs. rupture) while also adjusting for quantitative HRP metrics (i.e., low-attenuation plaque burden).

In summary, by detecting early signs of coronary inflammation that 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 coronary CTA could provide new opportunities for personalized risk management in primary and secondary prevention.

Evangelos K. Oikonomou, MD
Milind Y. Desai, MD
Mohamed Marwan, MD
Christos P. Kotanidis, MD, MSc
Alexios S. Antonopoulos, MD, PhD
David Schottlander, DPhil
Keith M. Channon, MD
Stefan Neubauer, MD
Stephan Achenbach, MD
***Charalambos Antoniades, MD, PhD**

*Division of Cardiovascular Medicine
John Radcliffe Hospital
University of Oxford
Oxford OX3 9DU
United Kingdom
E-mail: charalambos.antoniades@cardiov.ox.ac.uk
Twitter: @Charis_Oxford

https://doi.org/10.1016/j.jacc.2020.05.078

Please note: The authors acknowledge the contribution of all members of the CRISP-CT study. The study was funded by the British Heart Foundation (FS/16/15/32047 and TG/16/3/32687 to Dr. Antoniades) and the National Institute for Health Research Oxford Biomedical Research Centre (Oxford, United Kingdom). The methods for analysis of the perivascular fat attenuation index described in this report are subject to patent PCT/GB2015/052359 and patent applications PCT/GB2017/053262, GB2018/1818049.7, GR20180100490, and GR20180100510, licensed through exclusive license to Caristo Diagnostics. Drs. Channon, Neubauer, and Antoniades are founders and shareholders of Caristo Diagnostics, a CT image analysis company. Drs. Antonopoulos and Oikonomou have served as consultants for Caristo Diagnostics. Dr. Schottlander is an employee of Caristo Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

REFERENCES

1. Adamson PD, Williams MC, Dweck MR, et al. Guiding therapy by coronary ct angiography improves outcomes in patients with stable chest pain. J Am Coll Cardiol 2019;74:2058–70.

2. Blaha MJ, Cainzos-Achirica M. Coronary CT angiography in new-onset stable chest pain: time for U.S. guidelines to be NICEr. J Am Coll Cardiol 2019;73:903–5.

3. Williams MC, Moss AJ, Dweck M, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. J Am Coll Cardiol 2019;73:291–301.

4. Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat. Sci Transl Med 2017;9:eaal2658.

5. Oikonomou EK, Marwan M, Desai MY, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet 2018;392:929–39.

Relationship of Altmetric Attention Score to Overall Citations and Downloads for Papers Published in *JACC*

Dissemination of scientific content has been amplified with increasing use of social media (SoMe) in cardiovascular (CV) medicine (1). Traditionally, the performance of a scholarly journal paper is measured by the number of times it is cited. A newer metric, the Altmetric Attention Score (AAS), is a real-time, automatically calculated, weighted count of the online attention a research output receives. AAS thus provides information around impact and performance of a paper on social media platforms, news or media outlets, blog-spots, and podcasts.

The objective of this study was to determine whether there was a correlation between AAS and its components, with citations and overall article downloads published in the *Journal of the American College of Cardiology (JACC)*.

All papers published in the *Journal* from January 2016 through December 2017 were included in our analysis. For each paper, the number of citations and AAS were recorded as of December 2018. The full text of every paper was examined for article type and topic. We examined the Pearson's correlation between each component of AAS and total downloads/citations. We fit a linear regression model with total paper download count from onlinejacc.org or citation count as the outcome, with AAS (and its components), months since publication, and type of article as covariates. Because total downloads/citations and the AAS (and components) are non-negative, we log-transformed these variables (adding 1 to each before transformation because log [0] is not defined). The degree of association was interpreted using the linear regression coefficients with their corresponding 95% confidence intervals (CIs). As paper metrics did not contain patient information, institutional review board approval was not required.

There were in total 773 *Journal* papers included in the analysis; of these, 472 (61.1%) were original articles. Median AAS was 42 (interquartile range [IQR]: 20 to 78), whereas the median number of citations was 19 (IQR: 10 to 34). The median downloads and twitter mentions were 1,381 (IQR: 775 to 2,454) and 42 (IQR: 20 to 88), respectively.

The Pearson's correlation between overall AAS and downloads was 0.138 ($p < 0.001$). Correlation between overall AAS and citations was 0.159 ($p < 0.001$). Across all AAS components, Twitter mentions, and policy documents numerically had the highest Pearson's correlation with article downloads of 0.257 ($p < 0.001$) and 0.458 ($p < 0.001$), respectively.

The adjusted associations between log(AAS + 1) and log(twitter mentions + 1) with log(downloads + 1) for the included studies are shown in **Figure 1**. Overall, a unit increase in log(AAS + 1) increased the log(downloads + 1) by 0.261 (95% CI: 0.206 to 0.316), and increased the log(citations + 1) by 0.208 (95% CI: 0.154 to 1.825), while a unit increase in log(twitter mentions + 1) increased log(downloads + 1) by 0.375 (95% CI: 0.324 to 0.425) and increased the log(citations + 1) by 0.191 (95% CI: 0.137 to 0.245), demonstrating a positive association between these metrics.

This is the first study to examine the relationship of AAS and its components with download and citations for the papers published in the *Journal*.

This study shows that, for papers published in the *Journal*, there was correlation between AAS and