Evaluating coronary inflammation in the absence of plaque using FAI Score: a powerful tool for risk stratification

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We thank our colleagues for their interest in our Article.[1] In response to Zhao et al, the original method of measuring Fat Attenuation Index (FAI)) was corrected for scan parameters (weighted attenuation).[1] However, translation to a clinically-applicable tool required rigorous standardization[2] for technical, anatomical and biological factors, now captured by FAI-Score,[3] which is embedded into a prognostic model (AI-Risk) as previously described.[3] These algorithms were evaluated by the regulatory bodies in Europe, UK and Australia, and the "locked" algorithms were cleared as a Medical Device. Accordingly, the study[4] did not develop any new AI model, but rather validated an existing "locked" commercial medical device in a new cohort, so further evaluation of the device's parameters was beyond the scope of this study. Establishing safe and secure pipelines for scans/data anonymization and transfer, standardised central image analysis under appropriate quality management systems, secure data linkage, internal auditing trail and continuous monitoring of new AI algorithms by the national regulatory bodies are all important for healthy ethical standards in AI research. The ORFAN study has pioneered the development of such a framework (https://oxhvf.com/orfan/overview/) and can be used as an exemplar for its strict ethical and legal standards in AI research.

In response to Nurmohamed et al, FAI is a "thermometer" of inflammation in the adjacent artery,[1,2] capturing pathways such as IL6, TNF-a and IFNγ.[1] Deeper radiotranscriptomic phenotyping of perivascular fat provides more precise assessment of specific vascular inflammatory pathways.[5] FAI responds to anti-inflammatory treatments including anti-TNFa, anti-IL12/anti-IL23/anti-IL17 (but not methotrexate)[6], statins[7] anti-ox-LDL[8] and closely tracks "cooling" of the inflamed coronaries after acute MI.[9] FAI-Score is a standardised metric capturing vascular inflammation for the proximal segment of each coronary artery,[3] and in the absence of local atherosclerotic plaques in the analysis segment, it provides an excellent biomarker to describe arterial inflammation. This is why it predicts stroke

(capturing peripheral arterial inflammation) and heart failure (identifying people prone to ischaemic cardiomyopathy after a future STEMI or due to progressive microvascular disease in the heart). However, before claiming that FAI Score is more/less predictive of stroke HR(95%CI):5.95(2.6-13.63), heart failure 4.28(2.46-7.43), or MI 1.96(1.2-3.2) (Table S7),[4] the overlapping confidence intervals need to be taken into account, as these effect sizes are statistically indistinguishable. Regarding the interaction with risk factors, most of them cause vascular inflammation.[10] Even after they are optimally treated, there is residual inflammatory risk related to the same risk factors as well as other emerging/unknown factors. Clinically, the most actionable readout of inflammatory risk for the patient is the FAI Score (HR=20.2(11.5-35.5) for Q4vsQ1, Table S6), that is targeted by intensive risk factors modification plus anti-inflammatory treatments. Correction for risk factors is an academic exercise (reducing HR to 7.83(4.33-14.2) for Q4vsQ1, Table S6), representing only the part of residual inflammatory risk not related with the risk factors, which is practically indistinguishable from the overall residual inflammatory risk targeted by anti-inflammatory treatments.

In response to Chuanhui Xu, the ability of FAI Score to predict risk in autoimmune diseases and its relationship with systemic inflammatory biomarkers like hsCRP is the focus of separate ORFAN sub-studies, which are expected to report in the coming months. What we know is that, in patients with psoriasis, FAI score responds well to clinically used[6] and novel[8] biologics, and can be used to select candidates/track their responsiveness to these treatments.

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