

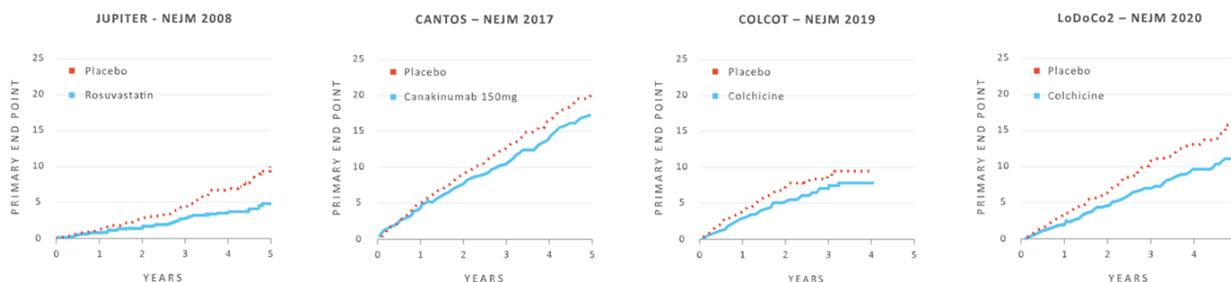
CARI-HEART® RISK IN THE TREATMENT OF CORONARY ARTERY DISEASE

The Unmet Need

Despite considerable progress in primary and secondary prevention, cardiovascular diseases (CVD) remain the leading cause of disease burden in the world with CVD deaths increasing from 12.1 million in 1990 to 18.6 million in 2019, Coronary Artery Disease (CAD) representing nearly half of this total (9.14 million).¹ In the era of precision medicine, there is an imperative need to move away from population-based risk factors and models towards an individualised assessment of cardiovascular biology and risk.

It is well established that atherosclerosis, the disease process that causes build-up of fatty material (plaque) inside the coronary arteries, is an inflammatory disease and that plaque rupture (which causes heart attacks) is also driven by vascular inflammation.^{2,3}

Figure 1.



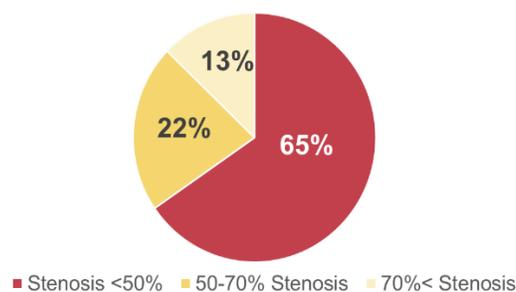
Several randomised controlled trials have established that treating inflammation reduces cardiovascular events, even in unselected populations.^{4,5,6,7} However, all current cardiac imaging tests for CAD (e.g. stress echocardiography, cardiac MRI, nuclear perfusion imaging) aim to detect narrowed arteries or the consequences of coronary narrowing (ischemia), and miss patients with 'invisible' but high-risk inflamed plaques: at least 50% of heart attacks occur in patients without major coronary artery narrowing (stenoses) or who didn't have any symptom.⁸

Coronary CT Angiography as a First-Line Investigation for Chest Pain

Coronary CT angiography (CCTA) received a Class 1A recommendation in the European Society of Cardiology (ESC) Guidelines as a first-line diagnostic test in the investigation of suspected CAD.⁹ In the UK, the 2016 NICE CG95 guidelines recommend CCTA as the first-line investigation for patients with stable chest pain.¹⁰ Like other cardiac imaging tests, CCTA focusses on stenosis severity and ischemia, but it also provides the ability to assess coronary plaque, if present, in addition to stenoses. Plaque characterisation and quantification is an area of active research, but is time consuming for clinicians.

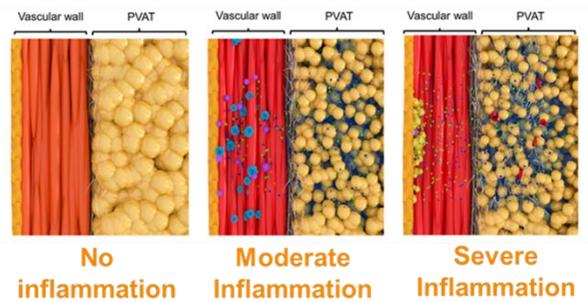
Although most CCTAs do not identify any obstructive CAD, nearly two thirds of heart attacks occur in patients without a significant coronary stenosis.^{11,12} Acute Coronary Syndromes (ACS) or even death are often the first manifestation of CAD, due to rupture of unstable plaques. Like other cardiac imaging tests, CCTA fails to identify inflammation that plays a key role in plaques rupture.³ A diagnostic test that accurately detects coronary inflammation would allow identification of people at risk of heart attacks who are currently missed, and permit initiation of appropriate personalised risk reduction strategies to the people who will benefit most, whilst preventing unnecessary costs and potentially harmful side-effects in people who will not benefit.

Figure 2. Stenosis severity prior to ACS (ICONIC)



The Fat Attenuation Index (FAI): A New indicator of Coronary Inflammation

Scientific advances pioneered at the University of Oxford have shown that fat tissue surrounding the coronary artery “senses” the presence of inflammation: mediators released by an inflamed coronary artery cause changes in the size and composition of fat cells (adipocytes) surrounding the artery. These changes can occur before any atherosclerotic plaques are visible in the coronary artery itself.



It is these changes that Caristo’s technology captures, with the development of a novel imaging biomarker, the “Fat Attenuation Index” (FAI), applying Artificial Intelligence (AI) to the analysis of standard CCTA scans to calculate it.¹³

FAI is a Powerful Predictor of Cardiovascular Risk, including Death

FAI analysis has the potential to fundamentally disrupt the approach to diagnosis and treatment of coronary artery disease, by predicting heart attacks years before they happen.

The CRISP-CT study, involving over 4000 patients from Europe and the US, showed that patients with an abnormal FAI had a 6-9x higher risk for fatal heart attacks and 5x higher risk for non-fatal heart attacks. Importantly, this was after adjusting for all conventional risk factors (e.g., smoking, age, diabetes, hypertension, calcification).¹⁴

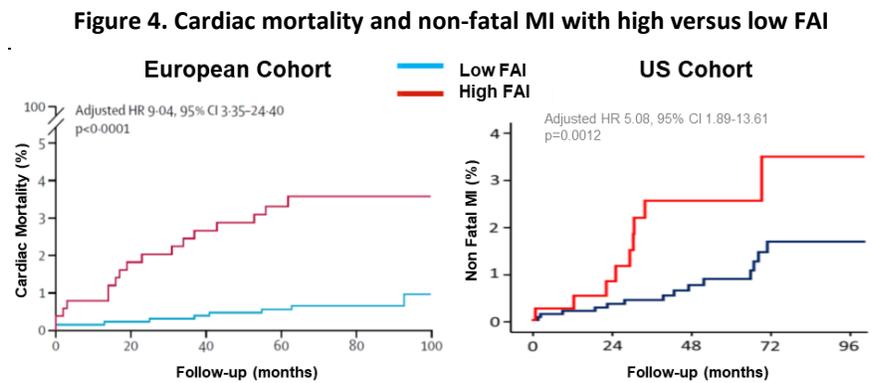
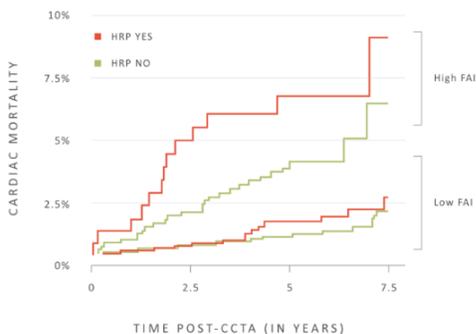


Figure 5. FAI vs. High Risk Plaque features



The striking predictive power of FAI was also independent of ‘high risk plaque features’, currently reported on CCTA scans: the presence of high-risk plaque features does not predict increased risk in people who have a low FAI, whereas people with a high FAI have a higher risk, even in the absence of high-risk plaque features.¹⁵

These findings have been hailed as “*game-changing*” by the British Heart Foundation.¹⁶

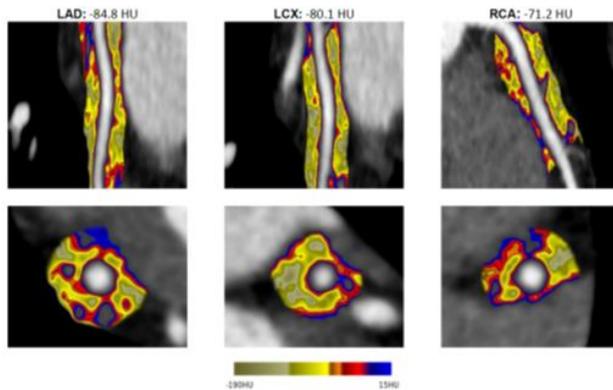
CaRi-Heart® Software: A CE-Marked Prognostic Cardiac Device

These scientific advances have been incorporated into **CaRi-Heart®**, a CE-marked software device approved under the new European Medical Device Regulations (MDR). CaRi-Heart® is device-agnostic, meaning all good quality CCTA scans from any manufacturer can simply be uploaded to the fully scalable cloud-based platform portal, securely transferred, analysed by Caristo and a report sent back to the referring physician.

CaRi-Heart® provides both personalised assessment of coronary inflammation and an estimate of the cardiovascular risk for a given patient: the **CaRi-Heart® Risk**. This information allows physicians to make more informed treatment decisions for an individual patient.

CaRi-Heart® Risk provides a Personalized Cardiovascular Risk Prediction

Figure 6. Images provided by CaRi-Heart®



The CaRi-Heart® report includes an individualised quantification of coronary inflammation in the 3 main epicardial coronary arteries, adjusted for age and gender, the **FAI Score**, and an estimate of the **absolute risk** of a fatal cardiac event within the next 8 years, the **CaRi-Heart® Risk**, based on the FAI-Score, the coronary atherosclerotic plaque burden and clinical risk factors.

The FAI-Score represents the **relative risk** of a patient. By quantifying coronary artery inflammation, FAI-Score provides a measure of disease activity, with a high FAI score indicating an

increased future cardiovascular risk, if left untreated. FAI-Score is particularly useful in younger patients, where traditional cardiovascular risk scores usually report a low absolute risk, as adverse events usually occur later in life.

Current international clinical guidelines on CAD evaluation recommend the assessment of total CAD risk using an appropriate risk scoring system. ESC guidelines state that *“the estimation of CAD risk remains the cornerstone of these guidelines and thus appears at the forefront of the proposed management schemes”*.¹⁷ CaRi-Heart® Risk significantly improves risk discrimination over clinical risk factor-based models (such as the ESC-SCORE, QRisk, Framingham or Pooled Cohort Equations risk scores), and has a consistent net clinical benefit on decision curve analysis across the full spectrum of cardiac risk.¹⁸

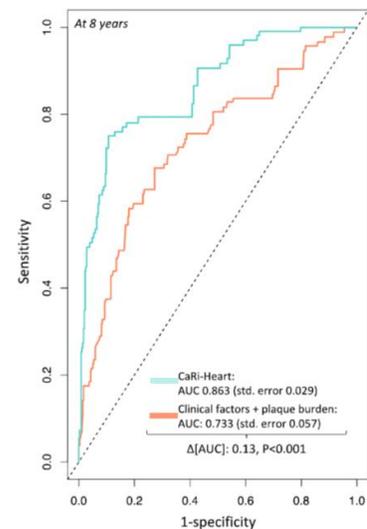
This may be used by clinicians to:

- identify individuals at risk despite a “negative” CCTA, or a low absolute cardiovascular risk, to guide early deployment of targeted intensive measures of primary prevention;
- assess residual risk in patients with established coronary atherosclerosis despite optimum treatment, to guide targeted deployment of novel (and typically expensive) drugs for secondary prevention.

For example: patients with known coronary artery disease already receiving optimum treatment (eg: antiplatelet and statin therapy) who present with abnormally high FAI-Score could be candidates for treatment with new anti-inflammatory agents or PCSK9 inhibitors to target their residual cardiovascular and inflammatory risk.

Caristo’s biomarkers are dynamic, meaning they change in response to drug treatments. Therefore physicians will be able, for the first time, to monitor the effect of therapeutic interventions in modifying an individuals’ cardiovascular risk from a standard CCTA.^{19,20} The frequency of reassessment using CaRi-Heart® is left to the individual clinician, but in the absence of symptom changes, annual follow-up may be appropriate.

Figure 7. comparison of a clinical risk factors based model with CaRi-Heart®¹⁸



Intended Use

CaRi-Heart® is intended to be used for the analysis of clinically indicated CCTAs. In others words, the decision to undertake CCTA has already been made by the healthcare professional and is not dependent on CaRi-Heart® analysis. The results provided by a CaRi-Heart® analysis are intended to aid clinical decision making.

Certification

CaRi-Heart® received CE Mark, under the new MDR process, in February 2021.

Futhermore Caristo received ISO 27001 certification for information security management, an important requirement for patients' data privacy as CaRi-Heart® involves the transfer of Cardiac CT images.

Caristo also holds ISO 13485 and ISO 9001 certifications.

Summary

By detecting early signs of coronary inflammation which precede the development of atherosclerotic plaques, CaRi-Heart® allows identification of the “vulnerable” patient to allow personalised risk management in primary and secondary prevention.

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