



Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER325
Topic:	CaRi-Heart, a standardised measurement of coronary inflammation using coronary computed tomography angiography (CCTA) in the investigation and management of coronary artery disease (CAD) risk.
Summary of findings:	<p>People with suspected heart problems, such as CAD or chest pain, may be referred for a CCTA. CCTA is usually the reference standard in the investigation of suspected coronary artery disease (CAD). CAD is caused by the narrowing of the arteries that supply the heart. However, earlier risk factors for CAD may be missed with CCTA alone. CaRi-Heart is a novel method of detecting the earlier risk factors, namely, changes in perivascular fat attenuation. Earlier detection of these risk factors could in theory lead to earlier diagnosis and intervention in people with CAD.</p> <p>CaRi-Heart is a cloud-based CE-marked medical device (Caristo Diagnostics Ltd, Oxford UK) which measures coronary inflammation through the mapping of perivascular fat attenuation index (FAI) for people undergoing CCTA for chest pain assessment. The FAI-Score is then incorporated into a risk prediction algorithm with clinical risk factors and CCTA-derived coronary plaque metrics to generate the 'CaRi-Heart risk'.</p> <p>Researchers at HTW have identified two clinical guidelines about the management and/or diagnosis of chest pain, one meta-analysis on the measurement of vascular inflammation biomarkers, including the mapping of perivascular FAI and three primary studies about the measurement of coronary inflammation using CCTA.</p> <p>We did not identify any studies that evaluated the cost-effectiveness of CaRi-Heart.</p>

Introduction and aims

Health Technology Wales researchers searched for evidence on the use of CaRi-Heart and more generally, the measurement of coronary inflammation using coronary computed tomography angiography (CCTA), and any evidence on how measurement of these factors predicts CAD risk and guides future patient management.

CaRi-Heart is a digital health technology and was determined to be a Tier C technology according to the [Evidence Standards Framework for Digital Health Technologies](#). Tier C evidence standards apply to digital health technologies that function as interventions. This includes technologies that are designed to calculate, i.e., a calculator that impacts on treatment, diagnosis, or care. For technologies of this classification, it is recommended that the best practice standard to demonstrate effectiveness would be to draw on randomised controlled studies carried out in a setting relevant to the UK health and social care system, comparing the digital health technology with a relevant comparator. The studies should demonstrate consistent benefit including clinical outcomes in the target population, in addition to using validated condition-specific outcome measures.

Evidence overview

Guidance

We identified relevant guidance relating to the management of stable angina from SIGN in 2018 (SIGN 2018) and earlier advice relating to the assessment and diagnosis of recent-onset chest pain of suspected cardiac origin from NICE in 2010 (NICE 2010). Both publications make no specific reference to the CaRi-Heart device or include information about the measurement of coronary inflammation using coronary computed tomography angiography (CCTA).

NICE highlight that significant coronary artery disease (CAD) found during CT coronary angiography is 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery. However, information from the topic proposer suggests that more than 75 percent of people undergoing a CCTA do not have evidence of significant CAD and are therefore not identified as high risk, and that a high proportion of patients presenting with an acute coronary syndrome go on to have non-obstructive coronary artery disease.

Evidence reviews

We identified one meta-analysis (Antonopoulos et al. 2021) which aimed to explore the added value of common biomarkers of vascular inflammation for cardiovascular prognostication. The authors searched for published cohort studies on the prognostic value of common biomarkers of vascular inflammation groups in people without known CAD. Common circulating inflammatory biomarkers included C-reactive protein, interleukin-6 and tumour necrosis factor- α , arterial positron emission tomography/computed tomography and CCTA-derived biomarkers of vascular inflammation, including anatomical high-risk plaque features and perivascular fat imaging. The authors used data from 39 cohort studies in their analysis.

The concordance statistic/index (c-index) was selected by the authors as the metric of choice to assess the performance of each biomarker. A c-statistic gives the probability of a person who experienced an event i.e., major adverse cardiovascular events (MACEs) or mortality, having a higher risk score than a person who has not experienced an event, ranging from 0 – 1. In their subgroup analysis when predicting MACEs and mortality, CCTA with high-risk plaque features (HRP) displayed a c-index of 0.61 (95% CI, 1.5-10.6) with a P value of less than 0.001. CCTA with perivascular adipose tissue (PVAT) displayed a c-index of 0.82 (95% CI, 4.0-12.5).

The authors of the meta-analysis note several limitations within their methodology. The study did not use other model performance metrics to explore the clinical value of introducing biomarkers in risk prediction models such as the net clinical benefit. Therefore, the cost effectiveness of a risk stratification strategy based on inflammatory biomarkers is unclear.

Primary studies

Health Technology Wales researchers identified three primary studies relating to the measurement of coronary inflammation using CCTA (Hoshino et al. 2020, Oikonomou et al. 2021, Oikonomou et al. 2018). Both Oikonomou et al (2021) and Oikonomou et al. (2018) gathered data from the CRISP-CT study (Cardiovascular Risk Prediction using Computed Tomography).

Oikonomou et al. (2018) aimed to quantify the perivascular FAI in baseline coronary CTA scans from two prospective cohorts who underwent CTA in the EU and the US with a median follow up of 6 years and 4.5 years, respectively. The clinical indication for coronary CTA was based on local clinical practice, which varied between the two cohorts. The CRISP-CT study proposed a cut-off of -70.1 HU (Hounsfield units) as a critical threshold to identify high-risk individuals, which flags high-risk individuals with a fivefold to ninefold higher adjusted risk for cardiac death. Cardiac mortality was defined as any death due to proximate cardiac causes (e.g., myocardial infarction, low-output heart failure, and fatal arrhythmia). A post-hoc analysis of the same study reported that in the presence of low FAI, high-risk plaque features are not associated with increased cardiac risk, while in the presence of high FAI, high-risk plaque features flag a particularly high-risk group of patients (Oikonomou et al. 2020).

From the same study, Oikonomou et al. (2021) aimed to retrospectively report the performance of CaRi-Heart. One of the outputs of CaRi-Heart is the 'CaRi-Heart Risk' representing the individualised patient risk of a fatal cardiac event at eight years. The study provides a re-classification table where a negative predictive value of a 'CaRi-Heart Risk' of more than 10% for a fatal cardiac event at eight years was reported as 99.3%. Across the population, CaRi-Heart reclassified 611 (15.6%) patients to a higher risk category and 662 (16.9%) were reclassified to a lower risk category compared to using a clinical risk factor-based approach such as the ESC-SCORE. When compared to a baseline risk model consisting of variables such as age, sex and smoking, the CaRi-Heart Risk significantly improved risk discrimination with a c-statistic of 8.5%, $P=0.01$ in the US Cohort and 14.9%, $P<0.001$ in the European cohort.

Hoshino et al. (2020) conducted a retrospective study which aimed to investigate the association between FAI and whole vessel and lesion plaque quantification on CCTA in 187 people with intermediate epicardial stenosis evaluated by fractional flow reserve (FFR), although the study did not aim to evaluate CaRi-Heart specifically. The authors found an association between FAI and FFR, CCTA-derived two-dimensional and three-dimensional lumen and plaque quantification and cardiac mass.

On-going studies

HTW researchers identified three on-going systematic reviews and/or meta-analysis relating to imaging biomarkers and/or fat attenuation, although the protocols do not make specific reference to CaRi-Heart (Sagris et al. 2021; Antonopoulos, 2020; Shaowei et al. 2021). These studies are briefly described in the Literature Search Results section.

CaRi-Heart is being assessed as a Phase 3 project as part of the [AI in Health and Care Award](#). This project is intended to support first real-world testing in health and social care settings to develop evidence of efficacy and preliminary proof of effectiveness.

Areas of uncertainty

There is evidence that changes in perivascular FAI can correlate with CAD risk, although not all the evidence identified makes specific reference to CaRi-Heart; the availability of differing methods of assessing FAI is beyond the scope of this report. Furthermore, most of the evidence is based on retrospective analysis of patients with known CAD/CAD risk, with little or no evidence of what difference this would make to patient management decisions. It is also unclear at this stage whether CaRi-Heart could be beneficial in all people having CCTA, or whether there are specific groups of people who could benefit from its use.

The topic developer has informed HTW that there are several on-going economic evaluations, although HTW did not identify any on-going economic studies through database searches relating to CaRi-Heart or the measurement of coronary inflammation when compared to current practice in the UK.

Literature search results

Health technology assessments and guidance

NICE. (2010). Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis. Clinical guideline [CG95] Published: 24 March 2010.: The National Institute for Health and Care Excellence. Available at: <https://www.nice.org.uk/guidance/cg95> [Accessed 15 December 2021].

SIGN. (2018). SIGN 151 - Management of Stable Angina. A national clinical guideline. Health Improvement Scotland, Scottish Intercollegiate Guidelines Network (SIGN). Available at: <https://www.sign.ac.uk/our-guidelines/management-of-stable-angina/> [Accessed 15 December 2021].

Evidence reviews and economic evaluations

Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. (2021). Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. JACC. Cardiovascular imaging. doi: [10.1016/j.jcmg.2021.09.014](https://doi.org/10.1016/j.jcmg.2021.09.014)

Individual studies

Hoshino M, Yang S, Sugiyama T, et al. (2020). Peri-coronary inflammation is associated with findings on coronary computed tomography angiography and fractional flow reserve. J Cardiovasc Comput Tomogr. 14(6): 483-9. doi: <https://doi.org/10.1016/j.jcct.2020.02.002>

Oikonomou EK, Antonopoulos AS, Schottlander D, et al. (2021). Standardized measurement of coronary inflammation using cardiovascular computed tomography: integration in clinical care as a prognostic medical device. Cardiovascular Research. 117(13): 2677-90. doi: <https://doi.org/10.1093/cvr/cvab286>

Oikonomou EK, Marwan M, Desai MY, et al. (2018). 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 (London, England). 392(10151): 929-39. doi: [10.1016/S0140-6736\(18\)31114-0](https://doi.org/10.1016/S0140-6736(18)31114-0)

Evidence submitted by the topic proposer

Oikonomou EK, Desai MY, Marwan M, et al. (2020). Perivascular Fat Attenuation Index Stratifies Cardiac Risk Associated With High-Risk Plaques in the CRISP-CT Study. Journal of the American College of Cardiology. 76(6): 755-7. doi: <https://doi.org/10.1016/j.jacc.2020.05.078>

Ongoing research

Peri-coronary adipose tissue attenuation index (FAI) - A new imaging biomarker and its diagnostic and prognostic utility: A systematic review and meta-analysis. PROSPERO 2021 CRD42021229491 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=229491

An on-going systematic review with an anticipated completion date of 07 July 2021 (although at the time of writing this report we were unable to find it published), which will aim to investigate the association between perivascular fat attenuation index (FAI) and adverse cardiovascular events as well as plaque stabilisation. Outcomes include the hazard ratio for all-cause mortality, cardiac mortality, myocardial infarction, or MACEs of people with high FAI vs low FAI.

Alexios Antonopoulos. Prognostic value of plasma and imaging biomarkers to identify residual inflammatory risk and the vulnerable patient at risk for cardiovascular events. PROSPERO 2020 CRD42020181158 Available from:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=181158

An on-going review with an anticipated completion date of 31 August 2020 (although at the time of writing this report we were unable to find it published), which aimed to study the prognostic accuracy of commonly used plasma biomarkers.

Main outcomes will include mortality, cardiac mortality, myocardial infarction, and stroke.

Shaowei Ma, Min Jiang, Ke Zhou. Does increased peri-coronary fat attenuation associated with myocardial ischemia: a systemic review and meta-analysis. PROSPERO 2021 CRD42021297228

Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=297228

An on-going systematic review and meta-analysis with an anticipated completion date of 31 January 2022. The Main outcomes aim to create a relationship between peri-coronary fat attenuation and myocardial ischemia.

Date of search:

14 December 2021

Concepts used:

CaRi-Heart, coronary artery disease, fat attenuation index, coronary computed tomography angiography (CCTA), artery inflammation, coronary inflammation, vascular inflammation, measurement of coronary inflammation.