

CaRi-Heart® Report

Instructions for Use



CaRi-Heart® Coronary Inflammation and Risk Report Instructions for Use

Intended Audience

This document is for use by healthcare professionals trained in cardiovascular health and patient care (including but not limited to Cardiologists, Radiologists and others) who will receive a CaRi-Heart Coronary Inflammation and Risk Report from Caristo Diagnostics.

Intended Use

CaRi-Heart is a software device used to produce analysis results to assist Healthcare Professionals in patient management. It helps operators assess vascular inflammation from coronary computed tomography angiography (CCTA) images and measure risk of cardiovascular mortality due to coronary inflammation and other clinical risk factors.

CaRi-Heart and its analysis results are indicated for adults from 30 to 80 years old who have been referred for CCTA imaging.

CaRi-Heart is to be used by trained operators. CaRi-Heart analysis results are to be used by Healthcare Professionals.

CaRi-Heart analysis results should be reviewed with other clinical information which may include, but is not limited to: the patient's original CT images, clinical history, symptoms, clinical risk factors, results of other diagnostic tests, and the clinical judgement of appropriately qualified Healthcare Professionals.

Indications for Use

CaRi-Heart is an image processing prescription software device intended to aid assessment of cardiovascular disease for adults from 30 to 80 years old who have been referred for CCTA imaging.

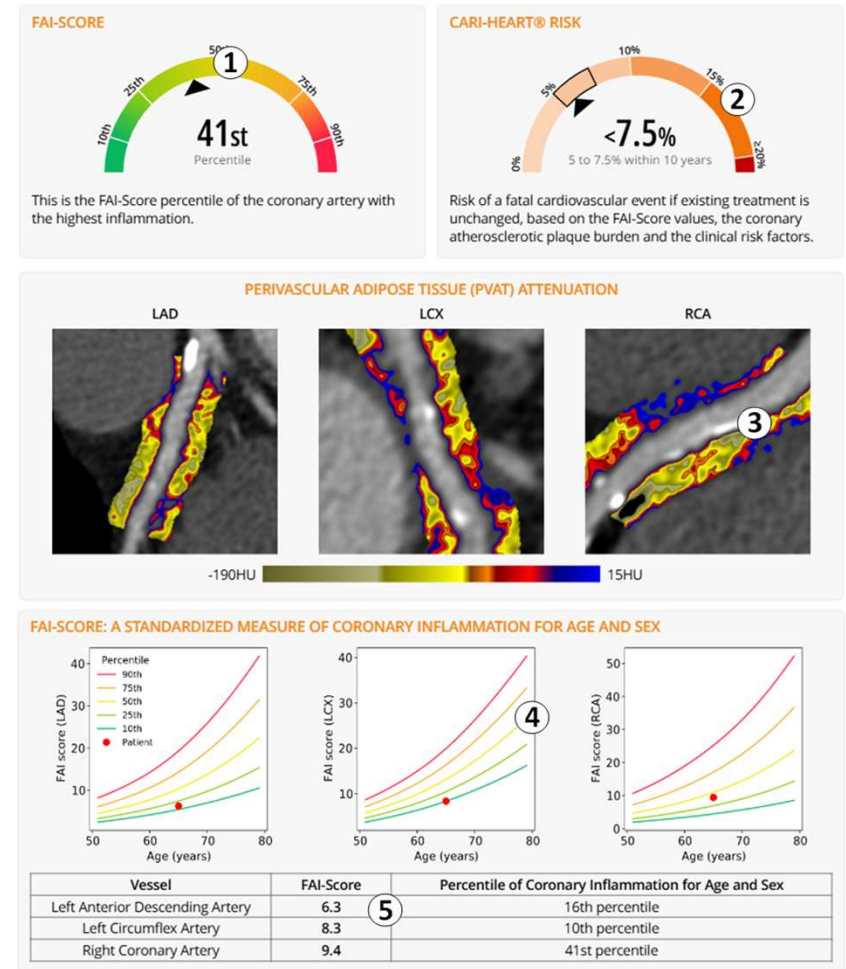
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CaRi-Heart Report Content

CaRi-Heart® Coronary Inflammation and Risk Reports provide information about plaque, coronary-related inflammation and the inflammation-associated risk of cardiovascular mortality. The CaRi-Heart® Coronary Inflammation and Risk Report provides the following measures:

- 1 FAI-Score:** The highest percentile FAI-Score of vessels measured: a standardized modifiable measure of coronary inflammation reported per patient.
- 2 CaRi-Heart risk:** A modifiable measure of the risk of cardiovascular mortality within 10-years, taking into account coronary inflammation, atherosclerotic plaque, patient demographics and clinical risk factors.
- 3 PVAT Attenuation:** reported per vessel: a modifiable measure of coronary inflammation (perivascular adipose tissue attenuation).
- 4 FAI-Score charts:** Display of the percentile curves used to calculate the patient's FAI-Score percentiles from an age- and sex-matched population.
- 5 FAI-Score and percentile:** The per-vessel FAI-Score and percentile value.



Warnings, Cautions, and Notices

-  **CAUTION:** CaRi-Heart reports should not be used as a primary means of diagnosis.
-  **CAUTION:** CaRi-Heart reports are not a substitute for standard CCTA reports and do not contain incidental findings.
-  **CAUTION:** CaRi-Heart reports should be interpreted by a healthcare professional who retains the ultimate responsibility for making the pertinent diagnosis based on their standard practice.
-  **CAUTION:** Timeframes for analysis results provision are contractually defined and are subject to delay. CaRi-Heart reports should not be requested for patients with unstable coronary syndromes or in patients where urgent and timely workup and evaluation is critical.
-  **CAUTION:** Incorrect patient details will impact patient risk scores. Please ensure that the clinical risk factors and demographics sent to Caristo are correct.
-  **CAUTION:** Precision of FAI-Score percentile estimates is reduced at the lower and upper extremes of the indicated age range due to lower representation of these age groups within the reference population. This includes males younger than 35 years, females younger than 40 years, and all subjects aged 75 years and older. Results should be interpreted in the context of the overall clinical assessment.

-  **NOTICE:** The clinical end user is not able to routinely engage with the software or make precise edits or modifications.
-  **NOTICE:** CaRi-Heart uses tri-linear and tri-cubic interpolation in the display and rendering of evaluation and output images, this does not guarantee the absence of plaque which is at or below the resolution of the data provided as an input.
-  **NOTICE:** Measurement uncertainty may not only be from inter-operator variability but can also occur from image acquisition differences including but not limited to x-ray source kVp, image reconstruction kernel, and iodine concentration.

Variability in Quantitative Outputs

Inter-operator variability in the CaRi-Heart Risk Score at the patient level and FAI-Score at the main vessel level (LAD, LCX and RCA) were evaluated in a clinical performance testing study.

Inter-Operator Variability for CaRi-Heart Risk Scores and FAI-Scores

Quantitative Output	Bias	Lower LoA (95%)	Upper LoA (95%)
CaRi-Heart Risk Score (%)	0.30	-4.86	5.46
FAI-Score (LAD)	0.06	-2.31	2.42
FAI-Score (LCX)	-0.17	-3.07	2.73
FAI-Score (RCA)	0.22	-2.49	2.94

CaRi-Heart Risk Score Results

The CaRi-Heart Risk score is reported as a range representing the estimated 10-year risk of cardiovascular death following CCTA. Risk is presented in 2.5% intervals from 0% to 20%, with scores of 20% or greater reported as $\geq 20\%$. Risk score ranges are inclusive of the lower bound and exclusive of the upper bound.

Limitation

The CaRi-Heart Risk score is intended to provide an estimate of 10-year cardiovascular mortality risk. The score should be interpreted as a risk range rather than a precise point estimate. Differences within a reported risk range may not represent clinically meaningful differences in predicted risk.

Interpretation

The CaRi-Heart Risk score should be interpreted in the context of the patient's overall clinical assessment, including CCTA findings, cardiovascular risk factors, symptoms, and other relevant clinical information. The CaRi-Heart Risk score is not intended to be used as a standalone determinant of patient management.

FAI-Score Percentiles

Limitation

FAI-Score reference percentiles are estimated using a continuous age- and sex-adjusted reference model derived from a reference population. The number of reference subjects at the lower and upper ends of the intended use population is smaller than in the central age range. As a result, FAI-Score percentile estimates for patients near the lower age limits of the intended use population (males <35 years and females <40 years) and the upper age limit (≥ 75 years) may be associated with greater statistical uncertainty than estimates for patients in more highly represented age groups.

Interpretation Guidance

FAI-Score percentile results should be interpreted in conjunction with the overall clinical assessment and should not be used as a standalone measure of patient risk. Small differences in percentile values, particularly for patients near the lower or upper bounds of the intended age range, may not represent clinically meaningful differences.

Performance Characteristics

Reports from CaRi-Heart are not intended to provide a diagnosis and are intended only to be used as an additional clinical data point as part of a wider diagnostic process. The software and/or its methodologies have been validated through clinical performance testing and peer-reviewed publications. A summary of the clinical performance testing along with a short sampling of the published data are provided overleaf.

Clinical Performance Testing

- The clinical performance of CaRi-Heart was evaluated as part of the PROVE-CT Study (“PROgnostic Value of the vascular inflammation in a multi-Ethnic cohort undergoing coronary CT Angiography”), a multi-center prospective observational cohort study. The study enrolled 6,528 consecutively sampled subjects from five U.S. sites (4,896 subjects; 75%) and two OUS sites (1,632 subjects; 25%) who had undergone CCTA as part of clinical care. All CCTA images were analyzed using the CaRi-Heart device to calculate the CaRi-Heart Risk score and FAI-Score per vessel (LAD, LCX, RCA), with all operators blinded to clinical outcome data. Median (IQR) follow-up time for the study subjects was 5.4 (2.7-10.3) years and included 359 cardiovascular deaths and 729 deaths in total (all cause).
- The mean (SD) age of the study population was 57.3 (11.9) years with 54.7% of subjects being male. 71.7% of the population identified as White, with 9.2% Black or African American, 7.5% Hispanic or Latino, 6.2% Asian and 12.8% unknown or other. 46.3% of subjects had hypertension, 37.1% had hypercholesterolemia, 16.5% had diabetes and 16.2% were current smokers. The study population included CCTA scans from at least 12 different scanner models from 4 different manufacturers, covering a representative range of tube currents, tube voltages and slice thicknesses.
- The pre-specified primary endpoint was the concordance between the CaRi-Heart Risk score and actual cardiovascular mortality (evaluated using the C-Index). The prespecified secondary endpoints were the concordance between the FAI-Score for each of the three main coronary arteries (LAD, LCX, RCA) and actual cardiovascular mortality (evaluated using the C-Index). Exploratory analyses included evaluation of model calibration (evaluated using Greenwood-Nam-D’Agostino) and subgroup analyses (e.g., U.S. vs OUS subjects). The results from these analyses are summarized below.

Clinical Performance Testing

Prognostic Performance of CaRi-Heart Risk score and FAI-Score

Quantitative Output	C-Index [95% CI] All Subjects	C-Index [95% CI] U.S. Subjects	C-Index [95% CI] OUS Subjects
CaRi-Heart Risk score	0.79 [0.76-0.83]	0.72 [0.66-0.80]	0.80 [0.78-0.84]
FAI-Score (LAD)	0.76 [0.72-0.80]	0.72 [0.68-0.78]	0.80 [0.76-0.82]
FAI-Score (LCX)	0.78 [0.73-0.81]	0.76 [0.69-0.81]	0.78 [0.75-0.81]
FAI-Score (RCA)	0.76 [0.70-0.82]	0.74 [0.67-0.80]	0.77 [0.73-0.80]

Model Calibration of CaRi-Heart Risk score

Quantitative Output	Slope [95% CI] All Subjects	Slope [95% CI] U.S. Subjects	Slope [95% CI] OUS Subjects
CaRi-Heart Risk score	0.88 [0.51-1.18]	0.94 [0.47-1.47]	0.94 [0.58-1.27]

The C-Indices for the CaRi-Heart Risk score and FAI-Score in each vessel (LAD, LCX, RCA) exceeded the pre-specified acceptance criteria (C-Index ≥ 0.70) in all subjects (primary and secondary endpoints) and both the U.S. and OUS subgroups. Furthermore, the CaRi-Heart Risk score was well calibrated in all subjects, along with both the U.S. and OUS subgroups with a slope of “1” (i.e., perfect calibration) lying within the 95% confidence intervals.

Clinical Performance Testing

Prognostic Performance of CaRi-Heart Risk score by Race/Ethnicity

Quantitative Output	C-Index [95% CI] White	C-Index [95% CI] Black / African American	C-Index [95% CI] Hispanic or Latino	C-Index [95% CI] Asian	C-Index [95% CI] Other or Unknown
CaRi-Heart Risk score	0.78 [0.74-0.81]	0.77 [0.67-0.84]	0.83 [0.72-0.92]	0.74 [0.63-0.85]	0.78 [0.70-0.88]
FAI-Score (LAD)	0.75 [0.71-0.78]	0.80 [0.71-0.87]	0.81 [0.70-0.91]	0.73 [0.60-0.84]	0.76 [0.66-0.83]
FAI-Score (LCX)	0.77 [0.71-0.82]	0.75 [0.67-0.83]	0.76 [0.66-0.88]	0.72 [0.56-0.81]	0.79 [0.70-0.86]
FAI-Score (RCA)	0.76 [0.69-0.79]	0.72 [0.63-0.82]	0.78 [0.69-0.90]	0.68 [0.53-0.75]	0.75 [0.64-0.84]

Model Calibration of CaRi-Heart Risk score by Race/Ethnicity

Quantitative Output	Slope [95% CI] White	Slope [95% CI] Black / African American	Slope [95% CI] Hispanic or Latino	Slope [95% CI] Asian	Slope [95% CI] Other
CaRi-Heart Risk score	0.87 [0.55-1.18]	1.21 [0.50-2.06]	1.47 [-0.12-3.50]	0.37 [-0.09-0.90]	1.20 [0.53-1.95]

The C-Indices for the CaRi-Heart Risk score and FAI-Score in each vessel (LAD, LCX, RCA) exceeded the pre-specified acceptance criteria for the primary and secondary endpoints (C-Index $\geq$ 0.70) in all race/ethnicity subgroups except for the FAI-Score (RCA) in the Asian subgroup. Note that the acceptance criteria were only pre-specified for the device performance on the whole population, with analyses by subgroups expected to increase variability into the C-Index measures due to the reduced number of events per subgroup. The CaRi-Heart Risk score was well calibrated in all race/ethnicity subgroups with a slope of “1” (i.e., perfect calibration) lying within the 95% confidence intervals for all except the Asian subgroup.

Clinical Performance Testing

Prognostic Performance of CaRi-Heart Risk score by Sex

Quantitative Output	C-Index [95% CI]	C-Index [95% CI]
	Male Subjects	Female Subjects
CaRi-Heart Risk score	0.80 [0.76-0.84]	0.73 [0.68-0.78]
FAI-Score (LAD)	0.75 [0.70-0.80]	0.74 [0.69-0.79]
FAI-Score (LCX)	0.77 [0.73-0.81]	0.73 [0.67-0.78]
FAI-Score (RCA)	0.77 [0.70-0.83]	0.71 [0.64-0.77]

Model Calibration of CaRi-Heart Risk score by Sex

Quantitative Output	Slope [95% CI]	Slope [95% CI]
	Male Subjects	Female Subjects
CaRi-Heart Risk score	0.92 [0.58-1.26]	0.78 [0.38-1.19]

The C-Indices for the CaRi-Heart Risk score and FAI-Score in each vessel (LAD, LCX, RCA) exceeded the pre-specified acceptance criteria for the primary and secondary endpoints (C-Index ≥ 0.70) in both the male and female subgroups. Furthermore, the CaRi-Heart Risk score was well calibrated in both the male and female subgroups with a slope of “1” (i.e., perfect calibration) lying within the 95% confidence intervals.

Clinical Performance Testing

Prognostic Performance of CaRi-Heart Risk score by Scanner Manufacturer

Quantitative Output	C-Index [95% CI] Siemens	C-Index [95% CI] GE	C-Index [95% CI] Philips	C-Index [95% CI] Unknown
CaRi-Heart Risk score	0.81 [0.76-0.83]	0.80 [0.73-0.91]	0.73 [0.64-0.83]	0.69 [0.59-0.89]
FAI-Score (LAD)	0.77 [0.74-0.82]	0.63 [0.52-0.76]	0.70 [0.60-0.82]	0.68 [0.56-0.81]
FAI-Score (LCX)	0.78 [0.74-0.82]	0.73 [0.64-0.86]	0.69 [0.61-0.76]	0.74 [0.56-0.84]
FAI-Score (RCA)	0.77 [0.70-0.83]	0.74 [0.60-0.85]	0.74 [0.64-0.82]	0.78 [0.62-0.89]

Model Calibration of CaRi-Heart Risk score by Scanner Manufacturer

Quantitative Output	Slope [95% CI] Siemens	Slope [95% CI] GE	Slope [95% CI] Philips	Slope [95% CI] Unknown
CaRi-Heart Risk score	0.80 [0.52-1.13]	1.13 [-0.37-3.03]	0.78 [-0.29-2.26]	1.32 [0.58-2.22]

The C-Indices for the CaRi-Heart Risk score and FAI-Score in each vessel (LAD, LCX, RCA) exceeded the pre-specified acceptance criteria for the primary and secondary endpoints (C-Index ≥ 0.70) for all scanner manufacturer subgroups except for the FAI-Score (LAD) in GE, FAI-Score (LCX) in Philips and CaRi-Heart Risk score and FAI-Score (LAD) in subjects where the scanner manufacturer was unknown. Note that the acceptance criteria were only pre-specified for the device performance on the whole population, with analyses by subgroups expected to increase variability into the C-Index measures due to the reduced number of events per subgroup. The CaRi-Heart Risk score was well calibrated in all race/ethnicity subgroups with a slope of “1” (i.e., perfect calibration) lying within the 95% confidence intervals.

Clinical Performance Testing

Prognostic Performance of CaRi-Heart Risk score by Obstructive vs. Non-Obstructive Disease

Quantitative Output	C-Index [95% CI]	C-Index [95% CI]
	Obstructive Disease	Non-Obstructive Disease
CaRi-Heart Risk score	0.67 [0.59-0.74]	0.74 [0.70-0.78]
FAI-Score (LAD)	0.68 [0.61-0.75]	0.74 [0.70-0.77]
FAI-Score (LCX)	0.71 [0.64-0.77]	0.73 [0.69-0.76]
FAI-Score (RCA)	0.72 [0.63-0.77]	0.71 [0.67-0.75]

Model Calibration of CaRi-Heart Risk score by Obstructive vs. Non-Obstructive Disease

Quantitative Output	Slope [95% CI]	Slope [95% CI]
	Obstructive Disease	Non-Obstructive Disease
CaRi-Heart Risk score	0.82 [0.01-1.75]	0.72 [0.41-1.03]

The C-Indices for the CaRi-Heart Risk score and FAI-Score in each vessel (LAD, LCX, RCA) exceeded the pre-specified acceptance criteria for the primary and secondary endpoints (C-Index ≥ 0.70) in both obstructive and non-obstructive disease subgroups except for the CaRi-Heart Risk score and FAI-Score (LAD) in the obstructive disease subgroup. Note that the acceptance criteria were only pre-specified for the device performance on the whole population, with analyses by subgroups expected to increase variability into the C-Index measures due to the reduced number of events per subgroup. The CaRi-Heart Risk score was well calibrated in both the obstructive and non-obstructive disease subgroups with a slope of “1” (i.e., perfect calibration) lying within the 95% confidence intervals.

Clinical Performance Testing

In summary, all primary and secondary endpoints achieved the predetermined acceptance criteria (C-Index ≥ 0.70) demonstrating excellent prognostic performance for cardiovascular death. Bland-Altman analysis of each of these metrics demonstrated good inter-operator performance and the CaRi-Heart Risk score was well calibrated. Subgroup analyses by U.S. vs OUS, sex, race/ethnicity, manufacturer and obstructive vs non-obstructive disease did not reveal any clinically meaningful bias in performance.

Selected Peer-Reviewed Publications

1. Kenneth Chan*, Elizabeth Wahome*, Apostolos Tsiachristas, Alexios S Antonopoulos, Parijat Patel, Maria Lyasheva, et al.: Inflammatory risk and cardiovascular events in patients without obstructive coronary artery disease: the ORFAN multicentre, longitudinal cohort study. [www.thelancet.com](https://doi.org/10.1016/S0140-6736(24)00596-8). *Lancet* 2024; [https://doi.org/10.1016/S0140-6736\(24\)00596-8](https://doi.org/10.1016/S0140-6736(24)00596-8)
2. Oikonomou EK, Antonopoulos AS, Schottlander D, et al. Standardized measurement of coronary inflammation using cardiovascular computed tomography: integration in clinical care as a prognostic medical device. *Cardiovasc Res* 2021; 117: 2677–90
3. 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(10151):929-939
4. Antoniades C, Shirodaria C. Detecting Coronary Inflammation With Perivascular Fat Attenuation Imaging: Making Sense From Perivascular Attenuation Maps. *JACC Cardiovasc Imaging* 2019;12(10):2011-2014
5. Antonopoulos AS, Sanna F, Sabharwal N, et al. Detecting human coronary inflammation by imaging perivascular fat. *Sci Transl Med* 2017;9(398).

Imaging Pre-requisites

	Coronary Inflammation Analysis
Patients	Patient should be between 30 to 80 years old for inflammation evaluation. Patient should not have coronary artery bypass grafts (CABG).
Scan field of view	Images should include the pulmonary artery bifurcation cranially and fully include the apex of the heart caudally. 10cm to 50cm extents.
Scanner	Images should be acquired using a CCTA protocol on a 64-slice scanner or above
Scan protocol	For non-photon-counting scanners, images should be acquired at peak energies of 70, 80, 90, 100, 110, 120, or 140 kVp. The SIEMENS NAEOTOM photon counting scanner is supported for the following acquisition settings: • Spectral – 140 kVp tube voltage and a 67 or 100 keV virtual monoenergetic image with a QR44 Filter for reconstruction. • UHR - 120 kVp tube voltage and (THRESHOLD MODE) image with a QR44 Filter for reconstruction.
Reconstruction resolution	Images have a slice thickness and in-plane resolution of at or below 1mm.
Data	12-16 bit pixel data.
Reconstruction deep learning	Deep-learning or AI-based reconstruction or filtering are not supported by default for inflammation evaluations.
Reconstruction matrix size	Between 512x512 and 1024x1024.

Device Information

Device: CaRi-Heart 2.11
Reference: 2493
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R_x Only

A report can be re-requested by contacting Caristo Diagnostics at support@caristo.com
A Technical Security Whitepaper can be provided upon request by contacting support@caristo.com