ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

HeartFlow FFR_{CT} for the Diagnosis of Coronary Artery Disease

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Summary of Key Points

- Coronary artery disease (CAD) is a common heart condition and is the second leading cause of death in Singapore.
- Computed tomography coronary angiography (CTCA) is an imaging modality used for the diagnosis of CAD. It is limited to the anatomical depiction of coronary arteries. Fractional flow reserve (FFR) is the gold standard for the functional assessment of the haemodynamic significance of CAD, and is measured during an invasive coronary angiography (ICA) procedure.
- HeartFlow FFR_{CT} (HeartFlow, Inc.) is an artificial intelligence (AI)-based technology that allows the non-invasive assessment of FFR_{CT} value in patients with suspected CAD, using previously acquired CTCA images.
- Overall, HeartFlow FFR_{CT} was found to be safe and likely clinically effective.
    - There were no major safety issues.
    - Using invasive FFR as the reference standard, HeartFlow FFR_{CT} demonstrated a good diagnostic accuracy (sensitivity, 84% to 85%; specificity, 73% to 76%) and was more specific than CTCA alone in detecting obstructive CAD.
    - Compared to standard care, HeartFlow FFR_{CT} reduced time to definitive investigation (28 *vs.* 44 days, p=0.004), changed clinical management in 22.4% to 66.9% of patients and reduced unnecessary ICA in 22% to 91% of patients. In addition, the rate of ICA showing no obstructive CAD was reduced across studies by 52% to 61%.
    - Despite reduced ICA procedures, similar revascularisation rates were reported between FFR_{CT}-guided and standard care, indicating that patients with significant CAD were not underdiagnosed.
    - HeartFlow FFR_{CT} resulted in similar short-term (up to one year) rate of cardiac events compared to standard care.
- At the healthcare system level, HeartFlow FFR_{CT} may potentially reduce the need for invasive ICA and increase the availability of diagnostic facilities and services.
- The cost-effectiveness of HeartFlow FFR_{CT} remains uncertain in the local setting, with mixed findings of cost savings (S$637 per patient) reported by the National Institute for Health and Care Excellence (NICE) to cost incurring (S$435 per patient) reported in the FORECAST randomised controlled trial based on US cost data.
- HeartFlow FFR_{CT} costs £700 (S$1,140) per test in addition to an average CTCA cost of S$1,300.
- Key implementation considerations include the need for adequate scan quality, appropriate data security measures and clinical governance, and oversight of AI medical devices.
- There has been a growing adoption of HeartFlow FFR_{CT} across various healthcare systems and clinical guidelines, including a positive recommendation by NICE.

I. Background

Coronary artery disease (CAD) is a heart condition characterised by the formation of atherosclerotic plaque in the coronary arteries, leading to impairment of blood flow and oxygen supply to the myocardium.[1] CAD varies in signs, symptoms and severity, and may manifest as stable ischemic heart disease or acute coronary syndrome.[1,2] If not managed, it can progress into congestive heart failure and predisposes to sudden cardiac death.[1] Symptoms of CAD include shortness of breath, angina and pain in the neck, jaw, throat, upper abdomen or back.[2]

In Singapore, CAD is the second leading cause of death, accounting for 20% of all deaths in 2021.[3,4] Across Southeast Asia, the age-standardised prevalence of CAD was reported to be 1,470.5 per 100,000 population.[5] Despite a substantial decline in the age-standardised disability-adjusted life years (from 2,683 in 1990 to 923 in 2017), CAD remains a main contributor to cardiovascular disease (CVD) burden locally.[6] CAD also presents a significant economic burden with an estimated annual cost of over US$200 billion to the US healthcare system.[1]

For patients with chest pain syndrome, computed tomography coronary angiography (CTCA) is an imaging modality widely used for diagnosing CAD.[7] However, conventional CTCA is limited to the anatomical depiction of coronary arteries. It does not allow for functional assessment of the haemodynamic significance of CAD, which is important to determine the prognostic benefit of myocardial revascularisation.[7,8] Fractional flow reserve (FFR) is the gold standard to determine the haemodynamic severity of coronary lesions, although the measurement traditionally involves an invasive coronary angiography (ICA) procedure that incurs additional resource, procedural time, risk of complications and patient discomfort.[9] Therefore, there remains a clinical need for a simple and non-invasive haemodynamic assessment of coronary lesions to aid clinical decision-making.

II. Technology

HeartFlow FFR_{CT} Analysis (HeartFlow, Inc.), hereinafter referred to as HeartFlow FFR_{CT}, is an artificial intelligence (AI)-based technology that uses deep learning to generate a patient-specific, digital three-dimensional (3D) model of the coronary arteries based on previously acquired high-quality CTCA images.[8] The software calculates the FFR_{CT} value using simulated metrics such as pressure, velocity and blood flow.[10] This information contributes to the functional evaluation of CAD in a patient.[10] To request for a HeartFlow test, anonymised CTCA Digital Imaging and Communications in Medicine (DICOM) data of at least 64 slices are sent to HeartFlow's central processing centre in the US for analysis.[11] The report, containing the personalised 3D modelling and estimated FFR_{CT} values, are sent back to the ordering clinician within 48 hours.[11]

Data from the HeartFlow FFR_{CT} software can also inform the HeartFlow Planner, a pre-procedural, interactive planning tool. Using a color-coded model of the patient's coronary arteries, the Planner allows clinicians to identify haemodynamically significant blockages and explore various treatment scenarios by virtually modifying the vessel to understand the impact of each treatment strategy in real time.[12] Figure 1 depicts the 3D model of HeartFlow FFR_{CT} visualised on the HeartFlow Planner tool.

Figure 1. Illustration of HeartFlow FFR_{CT}. Image adapted from https://www.heartflow.com/heartflow-ffrct-analysis/

HeartFlow FFR_{CT} represents a novel technology that allows determination of the haemodynamic significance of coronary lesions in a non-invasive manner, providing clinicians with insights into the extent of arterial blockage as well as its impact on coronary blood flow. When used in tandem with the HeartFlow Planner, it may further enable multiple interventional strategies to be trialled *in-silico* before delivery of treatment *in-vivo*.[7] HeartFlow FFR_{CT} technology may allow improved clinical decision-making in managing patients with varying degree of coronary stenosis, potentially avoiding unnecessary invasive FFR and its associated cost, radiation and complications.[7]

III. Regulatory and Subsidy Status

HeartFlow FFR_{CT} was Conformité Européene (CE) marked since July 2011 and cleared by the US Food and Drug Administration (FDA) through the De Novo pathway (DEN130045) in November 2014. Based on the FDA database (as of April 2023), the latest approved version of the software is FFR_{CT} v3.plus with no difference in the core technology from the primary predicate device.

The technology has been publicly reimbursed by the United Kingdom (UK) National Health Service (NHS) England, US Centers for Medicare and Medicaid Services and the Japanese Ministry of Health, Labour and Welfare.[13-15]

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

In line with the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines (see Figure A1 in Appendix A),[16] the local diagnostic pathway for patients with stable chest pain first involve clinical risk assessment of their likelihood of CAD. This includes pre-test probability scoring, assessment of patients' cardiovascular risk factor and other test results. While no further testing is necessary for low-risk patients, those in the intermediate to high-risk groups may undergo other assessment such as CTCA or cardiac stress testing depending on the patient's age, exercise capacity and resting electrocardiographic abnormalities. Patients with obstructive CAD on CTCA, or with moderate to severe ischemia on stress testing, may undergo further diagnostic confirmation with ICA. ICA is also recommended when findings from both CTCA and stress tests are inconclusive and the patient remains symptomatic (Personal communication, Senior Consultant from National University Heart Centre Singapore, 20 March 2023).

Of note, variations in local clinical practice exist, where patients with a high risk of CAD may be directly referred for ICA (Personal communication, Senior Consultant from National Heart Centre Singapore, 28 March 2023). This practice is in line with that of the European Society of Cardiology (ESC) guideline.[17] As highlighted by Weiting et al. (2022),[18] reference of local testing regimens to both ACC/AHA and ESC guidelines allows for considerable variation in the investigation of chest pain in local setting.

Introducing HeartFlow FFR_{CT} into local clinical pathways as an addition to standard CTCA would allow the functional significance of stenosis to be determined at the point of CTCA. It may also replace the need for stress testing or invasive FFR measurement with ICA, especially in patients with moderate coronary artery stenosis on CTCA, where further evaluation is often necessary to determine the haemodynamic significance of the stenosis.

VI. Summary of Evidence

The assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria presented in Table 1. Literature searches were conducted in health technology assessment (HTA) databases, Cochrane Library, PubMed and Embase. The key evidence base consists of two HTA reports from the National Institute for Health and Care Excellence (NICE; MTG32)[11] and the US Veterans Affairs Evidence Synthesis Program (VA ESP)[8] initially published in 2017 and 2019, respectively, and both updated in 2021. Several comparative studies published following the last search date of the updated HTA reports were also included, comprising one systematic review with meta-analysis (SRMA),[19] two studies[20,21] based on the FORECAST randomised controlled trial (RCT) and two real-world studies[22,23].

Two other studies served as supplementary evidence: the FDA Summary of Safety and Effectiveness Data (SSED) document;[10] and one economic evaluation[24] reporting on cost-effectiveness of FFR_{CT} not specific to HeartFlow. The study design and characteristics of the key and supplementary evidence sources are presented in Tables B1 and B2 (Appendix B).

Table 1: Summary of PICO criteria

Population	Symptomatic patients suspected of CAD
Intervention	HeartFlow FFR_{CT}

Comparator	Other diagnostic strategies for CAD, including CTCA alone, stress testing, ICA and invasive FFR
Outcome	Safety, clinical- and cost-effectiveness

Abbreviations: CAD, coronary artery disease, CTCA, computed tomography coronary angiography; FFR, fractional flow reserve; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiogram.

Safety

Overall, HeartFlow FFR_{CT} was found to be safe with no major safety issues. As HeartFlow FFR_{CT} analyses previously acquired CTCA images, NICE MTG32 (2021)[11] reported no adverse events (AEs) associated with the technology. Risks identified by FDA SSED,[10] are associated with diagnostic decisions made based on incorrect FFR_{CT} findings (e.g., false positive or false negative results), which may adversely affect the clinical management of a patient. Other risks such as delayed delivery of the analysis report and improper interpretation of FFR_{CT} findings by healthcare professionals were also noted.[10]

Effectiveness

Accuracy

Findings from two HTAs reported that HeartFlow FFR_{CT} has a good diagnostic accuracy, with higher specificity than CTCA alone in the detection of obstructive CAD.[8,11] Compared to the gold standard of invasive FFR, findings across three SRMAs summarised in VA ESP (2021)[8] showed a good vessel-level sensitivity of 84% to 85% and moderate specificity of 73% to 76%, with an area under the receiving operator curve (AUC) of 0.87 to 0.89 (Table 2). Notably, HeartFlow FFR_{CT} outperformed CTCA alone, demonstrating higher specificities and AUCs in identifying obstructive CAD with invasive FFR as the reference standard (see Table 2).[8,11] These findings suggest that the additional functional information provided by HeartFlow FFR_{CT} improved the accuracy of detecting patients without functionally significant obstructive CAD.[8] Moreover, NICE concluded that the sensitivity and specificity of HeartFlow FFR_{CT} were similar or better than its comparators, such as stress testing and CTCA alone (see Table C1 in Appendix C).[11]

Table 2: Diagnostic accuracy of HeartFlow FFR_{CT} and CTCA compared to a reference standard of invasive FFR

Systematic review*	Celeng et al. (2018)	Hamon et al. (2019)	Pontone et al. (2020)
Index test: HeartFlow FFR_{CT}			
Sensitivity† (95% CI)	85% (81% to 90%)	84% (80% to 88%)	85% (81% to 88%)
Specificity† (95% CI)	73% (61% to 82%)	76% (73% to 79%)	75% (72% to 78%)
AUC	0.87	0.89	0.89
Index test: CTCA			
Sensitivity† (95% CI)	87% (84% to 91%)	86% (85% to 88%)	88% (85% to 90%)
Specificity† (95% CI)	61% (54% to 68%)	64% (63% to 66%)	64% (61% to 66%)
AUC	NR	0.82	0.82

* Each systematic review included a subset of 9 studies on HeartFlow. † Per-vessel.

Abbreviations: AUC, area under the receiving operator curve; CI, confidence interval; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography; NR, not reported.

Table adapted from VA ESP (2021)[8].

Impact on clinical management

As evident from two HTA reports,[8,11] FORECAST[20,21] and a real-world study,[22] HeartFlow FFR_{CT} improved time to definitive investigation, reduced unnecessary ICA procedures and improved treatment efficiency. Compared to CTCA alone, the real-world NHS study[22] showed that the addition of FFR_{CT} to CTCA accelerated care pathways by reducing mean time to next investigation or definitive treatment (28 ± 4 *vs.* 44 ± 4 days, p=0.004) due to avoidance of follow-up tests. Similar findings were reported in FORECAST,[21] where compared with standard care, FFR_{CT}-guided care significantly reduced mean time to reach a definitive management plan (2.7 *vs.* 3 months, p<0.001). Further, compared to decisions made based on CTCA alone, HeartFlow FFR_{CT} led to a change in clinical management plans and reduced ICA that ranged from 22.4% to 66.9% and 22% to 91% of patients, respectively (see Table 3 and Table C2 in Appendix C).[8,11,20,22] In addition, similar rates of coronary revascularisation were reported between FFR_{CT}-guided and standard care (Table 3).[11,20] Based on this, NICE concluded that despite the lower rate of ICA performed, patients with functionally significant CAD were not underdiagnosed, indicating non-inferiority between the FFR_{CT} diagnostic strategy and its comparators.[11]

Of note, the wide ranges in the change in clinical management and ICA cancellations were likely attributed to variation in patient population and local clinical practices across studies.[8] While HeartFlow FFR_{CT} was found to lead to changes in clinical decisions, its impact on actual treatment received remains uncertain.[8] Moreover, unclear blinding of imaging results in several studies reviewed by VA ESP may lead to a bias in clinical decision-making.[8]

Table 3: Impact of HeartFlow FFR_{CT} on clinical management

Study	Rate (FFR_{CT} *vs.* standard care)		Rate of revascularisation (FFR_{CT} *vs.* standard care)
	Change in clinical management	Cancellation or reduction of ICA	
VA ESP (2021)[8]*	22.4% to 66.9%†	48% to 91%†	—
NICE MTG32 (2021)[11]*	—	44% to 77%†‡	23% *vs.* 24% (p=NS)§
Curzen et al. (2022)[20]	—	22% (p=0.01)	15% *vs.* 14% (p=0.69)
Graby et al. (2021)[22]¶	65% (p<0.001)	47%	—

* Refer to Table C2 in Appendix C for detailed findings for each study.

† Findings refer to a range of changes in clinical management, or cancellation or reduction in ICA.

‡ Findings reported by NICE that were not included in VA ESP (2021)[8].

§ Based on the planned invasive stratum of the PLATFORM trial reviewed by NICE.

¶ Based on comparison from clinicians presented with CTCA data and blinded *vs.* unblinded to FFR_{CT} analysis.

Abbreviations: CTCA, computed tomography coronary angiography; ICA, invasive coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; NICE, National Institute for Health and Care Excellence; NS, not significant; VA ESP, Veteran Association Evidence Synthesis Program.

Compared to standard care, HeartFlow FFR_{CT} reduced the rate of ICA showing no obstructive CAD by 52% to 61% (see Table C3 in Appendix C).[8,11,20] This indicated its potential for identification of patients who may not require an ICA, reducing unnecessary procedures. However, it should be noted that these findings depend on the criteria for ordering elective ICA, which may differ across various clinical practice.[8]

Clinical outcomes

Based on findings from two HTA reports[8,11] and FORECAST,[20] HeartFlow FFR_{CT} did not impact short term (up to 1 year) clinical outcomes when compared to standard care. As summarised in Table 4, FFR_{CT}-guided strategy showed similar major cardiac adverse event (MACE) at 1-year (PLATFORM; 0.7% *vs.* 1.0%) and major adverse cardiac and cerebrovascular event (MACCE) at 9 months (FORECAST; 10.2% *vs.* 10.6%).[8,11,20] These findings corroborated several single-arm studies reviewed by VA ESP (2021)[8], which generally reported low cardiac events in patients guided by HeartFlow FFR_{CT} up to a median follow-up of 4.7 years (see Table C4 in Appendix C). However, mixed findings on quality-of-life (QoL) were reported (Table 4).[8,11,20]

Table 4: Summary of clinical outcomes impacted by HeartFlow FFR_{CT} *vs.* usual care

Trial; Author (year)	N	Follow-up	Outcomes	Event rate	p-value
FORECAST; Curzen et al. (2022)[20]	1,399	9 months	MACCE*	10.2% *vs.* 10.6%	0.80
			QoL (EQ-5D)	0.6 *vs.* 0.6	0.61
			QoL (SAQ)	24.4 *vs.* 23.1	0.22
PLATFORM; Douglas et al. (2016)§	584	1 year	MACE	2 (0.7%) *vs.* 2 (1.0%)†	NR
			QoL (EQ-5D)‡	0.12 *vs.* 0.07	0.02

* Includes death, non-fatal MI, non-fatal stroke and cardiovascular hospitalisation.

† None of the patients whose ICA was cancelled based on HeartFlow results experienced serious clinical events.

‡ For patients in the non-invasive spectrum of the PLATFORM trial.

§ PLATFORM is reviewed by both NICE MTG32 (2021)[11] and VA ESP (2021)[8].

Abbreviations: AE, adverse event; EQ-5D, EuroQol-5 Dimension; MACCE, major adverse cardiac and cerebrovascular event; MACE, major adverse cardiac event; NR, not reported; SAQ, Seattle Angina Questionnaire; QoL, quality-of-life.

Besides, HeartFlow FFR_{CT} values were found to be a good prognostic indicator of cardiac outcomes. In a meta-analysis of five studies across 5,460 patients, compared to patients with a positive test result (FFR_{CT} ≤0.80), patients with a negative test result (FFR_{CT} >0.80) demonstrated a lower risk of unfavourable clinical outcomes at 12-month follow-up, including all-cause mortality (ACM), myocardial infarction (MI), MACE and unplanned revascularisation (see Table 5).[19] Notably, each 0.10-unit reduction in FFR_{CT} value was associated with a greater risk of ACM or MI (relative risk [RR], 1.67; 95% CI, 1.47 to 1.87; p<0.001).[19] This indicates the potential value of HeartFlow FFR_{CT} in avoidance of unnecessary ICA procedures.

Table 5: Meta-analysis of the prognostic value of HeartFlow FFR_{CT} on clinical outcomes

Endpoint	Total N	Percentage of patients		RR (95% CI)	p-value
		FFR_{CT} ≤0.80	FFR_{CT} >0.8		
Composite of ACM or any MI	5,460	1.4%	0.6%	2.31 (1.29 to 4.13)	0.005
MACE*		5.2%	1.9%	2.69 (1.91 to 3.78)	<0.001
Any MI		0.5%	0.2%	3.28 (1.33 to 8.06)	0.01
Spontaneous MI		0.4%	0.2%	2.63 (1.05 to 6.68)	0.038
Unplanned revascularisation		4.1%	1.3%	3.20 (2.13 to 4.80)	<0.001

* MACE was defined as a composite of ACM, any MI and unplanned revascularisation (PCI or CABG) performed >3 months from the CTCA investigation.

Abbreviations: ACM, all-cause mortality; CABG, coronary artery bypass graft; CI, confidence interval; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; MACE, major cardiac adverse event; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk.

Note: Table adapted from Norgaard et al. (2022)[19].

Healthcare system benefit

The ability of HeartFlow FFR_{CT} to improve clinical management and reduce unnecessary ICA procedures may free up diagnostic resources, including facilities and services such as magnetic resonance imaging (MRI) and nuclear medicine.[22] Further, compared to stress tests which require a separate clinic visit, HeartFlow FFR_{CT} allows functional assessment in a single patient visit and may reduce the delay and wait times between multiple tests.[23]

Cost-effectiveness

Five studies, including an economic model by NICE,[11] the FORECAST trial[20,21] and two real-world studies,[22,23] reported mixed findings (Table 6). Based on a decision-tree model from NICE MTG32 (2021)[11], HeartFlow FFR_{CT} was associated with cost savings of £391 (S$637)[a] per patient compared with current treatment pathway over a one-year time horizon. However, most other studies[20-23] suggested higher costs for FFR_{CT} (Table 6). In FORECAST,[20] the total cardiac cost at nine months between patients selectively referred for HeartFlow FFR_{CT} and the standard care group were £1,605 (S$2,615)[a] and £1,491 (S$2,429; p=0.10; mean difference, £114 [S$186]),[a] respectively. Despite substantial difference in resource costs between the UK and US, the application of US-specific cost data to the FORECAST data yielded similar conclusions, with higher cost of US$324 (S$435)[a] in the FFR_{CT}-guided compared to standard care.[21] Moreover, two real-world studies[22,23] conducted in the UK reported that a diagnostic strategy of FFR_{CT} was marginally more costly than CTCA alone by £39.44 to £44.97 (S$64 to S$73)[a] per patient in those with significant (≥50%) stenosis (see Table 6 and Tables C5 and C6 in Appendix C).

To highlight, the cost analysis by NICE[11] and the real world studies[22,23] were limited to the cost of investigations up to the point of diagnostic certainty and did not account for potential downstream cost savings arising from reduced time to diagnosis and avoidance of unnecessary investigative procedures. Variation in local practice with that of NICE's guideline, where CTCA is used as the first-line test for evaluation of patients with stable angina, may limit applicability of the predicted cost savings to the local context.

Table 6: Summary of cost-savings for HeartFlow FFR_{CT}

Study	Study design/model	Population	Comparison arms	Key findings
NICE MTG32 (2021)[11]; UK	Decision-tree model	People with SCP with possible CAD with intermediate PTP	HeartFlow FFR_{CT} *vs.* current treatment pathway	HeartFlow FFR_{CT} was associated with cost savings of £391 per patient
Curzen et al. (2021)[20]; UK	Randomised controlled trial	Patients attending RACPC for assessment of SCP	Patients selectively referred for HeartFlow FFR_{CT} *vs.* standard care*	Total cardiac cost £1,605 *vs.* £1,491 (p=0.10)
Hlatky et al. (2023)[21]; US				Total cardiac cost US$5,215 *vs.* US$4,891 (p=0.76)
Graby et al. (2021)[22]; UK	Real-world study	Patients undergoing routine clinical CTCA for assessment of CAD	CTCA + HeartFlow FFR_{CT} *vs.* CTCA alone	CTCA + FFR_{CT} costs £44.97 more per patient than CTCA alone†
Rasoul et al. (2021)[23]; UK		Patients referred for FFR_{CT}		CTCA + FFR_{CT} costs £39.44 more than CTCA alone†

[a] Based on the Monetary Authority of Singapore exchange rate as of 17 March 2023: £1=S$1.6292; US$1=1.3421. Figures were rounded to the nearest dollar.

* In the experimental group, all patients were referred for CTCA as the initial test and selectively referred for FFR_{CT} if the CTCA demonstrated a stenosis of ≥40% in a coronary artery segment or diameter suitable for revascularisation by either a coronary stent or coronary artery bypass graft surgery.

† In patients with ≥50% stenoses.

Abbreviations: CAD, coronary artery disease; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; PTP, pre-test probability; RACPC, rapid acute chest pain clinic; SCP, stable chest pain.

Although not specific to HeartFlow, a study reported that CTCA with FFR_{CT} dominated a diagnostic strategy of stress testing in a Markov microsimulation model over a lifetime time horizon, indicating cost-effectiveness of FFR_{CT} (see Table C7 in Appendix C).[24]

Ongoing trials

Five ongoing trials were identified from the ScanMedicine database (NIHR Innovation Observatory; Table 7), with majority of the studies investigating the diagnostic accuracy of FFR_{CT} against other diagnostic strategies.

Table 7: Ongoing clinical trials

Study (Trial ID)	Estimated enrolment	Brief description	Estimated completion date
THRONE (NCT04052256)	250	A prospective cohort study to evaluate disease progression in intermediate lesions (invasive FFR 0.81-0.90 at baseline) using FFR_{CT} at 2 years and determine whether CT characteristics may help to identify lesions that are more susceptible for FFR decline. Additionally, the study aims to correlate CT characteristics with coronary events up to 5 years after the baseline invasive FFR.	October 2023
AFFECTS (NCT02973126)	270	A diagnostic study to assess agreement between SPECT and FFR_{CT} in identifying vessel-specific, hemodynamically significant CAD in patients scheduled for ICA based on abnormal SPECT myocardial perfusion scans.	July 2022
FASTTRACK CABG (NCT04142021)	114	A prospective cohort study to assess the feasibility of CTCA and FFR_{CT} to replace ICA as a surgical guidance method for planning and execution of CABG in patients with 3-vessel disease with or without left main disease.	December 2022
FORTUNA (NCT03665389)	25	A diagnostic study to evaluate the relationship between FFR derived from FFR_{CT} before TAVR and FFR after TAVR to investigate if FFR_{CT} is useful for evaluating myocardial ischemia of severe AS.	March 2022
CONCORD (NCT04761991)	300	A prospective observational study evaluating the diagnostic accuracy of CMR and CT-FFR in patients with suspected CAD, using invasive FFR as the reference standard.	June 2025

Abbreviations: AS, aortic stenosis; CABG, coronary artery bypass graft; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; CT, computed tomography; CTCA, computed tomography coronary angiography; FFR, fractional flow reserve; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography; SPECT; single photon emission computerised tomography; TAVR, transcatheter aortic valve replacement.

Summary

Overall, HeartFlow FFR_{CT} was found to be safe and likely clinically effective. There were no major safety issues related to the use of the software. It demonstrated good sensitivity (84% to 85%), moderate specificity (73% to 76%), and was found to be more specific than CTCA alone in identifying obstructive CAD compared to a reference standard of invasive FFR. Compared to standard care, HeartFlow FFR_{CT} reduced the time to definitive investigation (28 ± 4 *vs.* 44 ± 4 days, p=0.004), changed clinical management and reduced unnecessary ICA procedures in 22.4% to 66.9% and 22% to 91% of patients, respectively. Use of this technology

also reduced the rate of ICAs reporting no obstructive CAD (52% to 61%, across studies). Despite reduced ICA procedures, similar revascularisation rates were reported between FFR_{CT}-guided and standard care, indicating that patients with significant CAD were not underdiagnosed. There was also no between-group differences in MACE and MACCE rates up to one year, suggesting its potential as a safe gatekeeper to ICA. Further, FFR_{CT}-guided care demonstrated good prognostic performance in predicting adverse cardiac events (1.67-fold increased risk of MI or ACM with every 0.10-unit reduction in FFR_{CT} value). The software may potentially benefit the healthcare system by freeing up diagnostic resources while allowing patient assessment in a single visit. Cost-effectiveness data remains limited, with mixed findings of cost savings (S$637 per patient) reported by NICE to cost incurring (S$435 per patient) reported in FORECAST based on US cost data.

Notably, findings from the evidence base should be interpreted with caution. Key limitations as reported by the HTAs include unbalanced baseline patient characteristics across studies, unclear impact on actual treatment decisions and lack of studies comparing longer term (>12 months) clinical outcomes. In addition, some studies were funded by HeartFlow Inc.

VII. Estimated Costs

NICE reported HeartFlow FFR_{CT} to cost £700 (S$1,140)[a] per test, while a more recent study has indicated a further cost reduction by the company to £530 (S$863)[a] in the UK.[11,23] This is in addition to an average local cost of around S$1,300 for CTCA.[18]

VIII. Implementation Considerations

As the FFR_{CT} analysis is based on previously acquired CTCA images, the need for adequate scan quality may be a potential barrier to adoption.[11] Consensus from experts consulted by NICE indicated that training is required to acquire high-quality CTCA images, with up to 25% of scans in clinical trials deemed unsuitable for FFR_{CT} analysis.[11]

Local expert shared that information technology (IT) challenges and privacy issues will be difficult to surmount and will incur further costs. There is a need to ensure medical confidentiality given that patient information is shared with HeartFlow for off-site FFR_{CT} analysis at their central processing centre in the US. To this end, adequate IT infrastructure is required to allow a secure and encrypted transmission of CTCA data to the company.[11] This may incur additional cost to integrate the technology into local IT systems and a need for compliance with the Transfer Limitation Obligation as outlined in the Personal Data Protection Act (PDPA). Briefly, organisations performing overseas transfer of medical information should ensure that the data is protected to a certain standard.[25] In addition, patient's consent for their CTCA images to be shared with an external party should also be sought.

As an AI technology, it would be necessary to exercise clinical governance and oversight over the adoption of HeartFlow FFR_{CT}. As outlined in the Ministry of Health (MOH) Artificial Intelligence in Healthcare Guidelines (AIHGle),[26] requirements include risk assessment to anticipate software failure and its mitigation measures, performance tracking to ensure similar performance in the local setting, and assessment of cybersecurity vulnerabilities,

among others. Following implementation, long-term monitoring of the software performance and ensuring that it remains clinically relevant is also required.

To add, local clinicians shared that patients with no or mild disease on CTCA should not undergo HeartFlow assessment on a routine basis due to cost issues, while a local validation study may be useful. If necessary, public healthcare institutions may consider conducting a local validation study for HeartFlow FFR_{CT} when the technology has received regulatory approval and is available for local use.

IX. Concurrent Developments

Multiple technologies similar to HeartFlow FFR_{CT}, that provide non-invasive estimation of FFR_{CT} values from previously acquired CTCA images, are in ongoing development (Table 8). Unlike HeartFlow FFR_{CT}, some of these technologies provide on-site measurement of FFR_{CT} values. Notably, one technology ($CT\text{-}FFR_B$) is locally developed at the National Heart Centre Singapore and is currently undergoing a trial to determine clinical and cost outcomes.

Table 8: Similar technologies in development

Technology (Manufacturer)	Brief description	Status
cFFR (Siemens Healthineers)	A machine learning-based software that provides on-site measurement of CT-FFR value based on previously acquired CTCA images.	For research use and not yet commercially available
Toshiba CT-FFR (Toshiba Medical Systems)	Using an on-site workstation, Toshiba CT-FFR calculates coronary flow and pressures by accounting for structural changes in the coronary artery lumen and aorta during the diastolic phase of the cardiac cycle.	
$CT\text{-}FFR_B$ (National Heart Centre Singapore)	A locally developed software that computes CT-FFR values based on 3D coronary artery tree model reconstructed with a CFD simulation.	Undergoing clinical trial
Elucid PlaqueIQ (Elucid, Inc.)	Elucid's PlaqueIQ is an analysis software that objectively quantifies plaque morphology and, with an investigational tool, derives FFR_{CT} from these plaque measurements.	FFR_{CT} tool remains investigational
Shukun-FFR (Shukun Technology Inc.)	A software that computes CT-FFR values using coronary arteries segmentation model and the CFD simulation model.	Approved by China's NMPA
CT-FFR (Heartcentury co., Ltd.)	A software that computes CT-FFR values using anatomic model construction and the CFD simulation model.	Undergoing clinical trial
DEEPVESSEL FFR (Keya Medical)	A software that processes CTCA images semi-automatically, generates a 3D model of the coronary artery tree, and computes non-invasive DVFFR values.	NMPA approved, FDA cleared and CE marked
CardioSimFFRct Analysis software (Shengshi Technology, Co., Ltd)	A non-invasive method to determine FFR which computes the hemodynamic significance of CAD (FFR_{CT}) from CCTA data using CFD.	Undergoing clinical trial
RuiXin-FFR (Raysight Medical)	A non-invasive method to determine FFR which computes the RuiXin-FFR value from CCTA data using CFD.	Approved by China's NMPA
Abbreviations: CAD, coronary artery disease; CFD, computational fluid dynamics; CTCA, computed tomography coronary angiography; FDA, US Food and Drug Administration; FFR, fractional flow reserve; FFR_{CT}, fractional flow reserve computed tomography; NMPA, National Medical Products Administration.		

X. Additional Information

In addition to the regulatory approval and reimbursement of HeartFlow FFR_{CT} in multiple regions, there has been a growing adoption of FFR_{CT} technology across various healthcare systems. As mandated by the NHS, HeartFlow FFR_{CT} has been implemented in 62 NHS England hospitals with over 15,000 patients scans referred for HeartFlow Analysis (as of 31 December 2020).[11,27] According to the company, the technology is also available at over 360 medical practices across North America.[28] Further, there has also been various guideline-driven adoption of HeartFlow FFR_{CT}, including a positive recommendation by NICE (Table 9).

Table 9: Guideline-driven adoption of FFR_{CT} technologies

Guideline	Recommendation
NICE MTG32 (2021)[11]	• HeartFlow FFR_{CT} is recommended as an option for patients with stable, recent-onset chest pain who are offered CTCA.
SHTG adaptation (2021)[29]	• HeartFlow FFR_{CT} may be considered as an option alongside a set of complementary diagnostic tools for patients with stable, recent onset chest pain symptoms who have undergone CTCA with adequate image quality on a 64-slice (or above) CT scanner.
ACC/AHA Joint Guideline for the Evaluation and Diagnosis of Chest Pain (2021)[16]	• FFR_{CT} may be useful for the diagnosis of vessel-specific ischemia and to guide decision-making regarding the use of coronary revascularisation in intermediate to high-risk patients with coronary stenosis of 40% to 90%
CAD-RADS (2022)[30]	• Include the use of FFR_{CT} for the functional assessment of patients with CAD-RADS 3 (moderate stenosis).
Abbreviations: ACC, American College of Cardiology; AHA, American Health Association; CAD-RADS, Coronary Artery Disease Reporting and Data System; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; NICE, National Institute for Health and Care Excellence; SHTG, Scottish Health Technologies Group.	

It is also important to consider findings from the recent ISCHEMIA trial which may potentially change clinical practice for the management of CAD.[31] Findings from the ISCHEMIA trial (n=5,179) suggest that patients with stable CAD and moderate to severe ischemia can be safely managed using a conservative strategy of medical therapy based on CTCA findings, without the need for further functional assessment.[23,31] Although this questions the place of HeartFlow FFR_{CT} in clinical practice, as functional haemodynamic information such as FFR_{CT} may not be required for patient management, further investigation is warranted.

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Appendix

Appendix A: Clinical pathway for the management of patients with stable chest pain

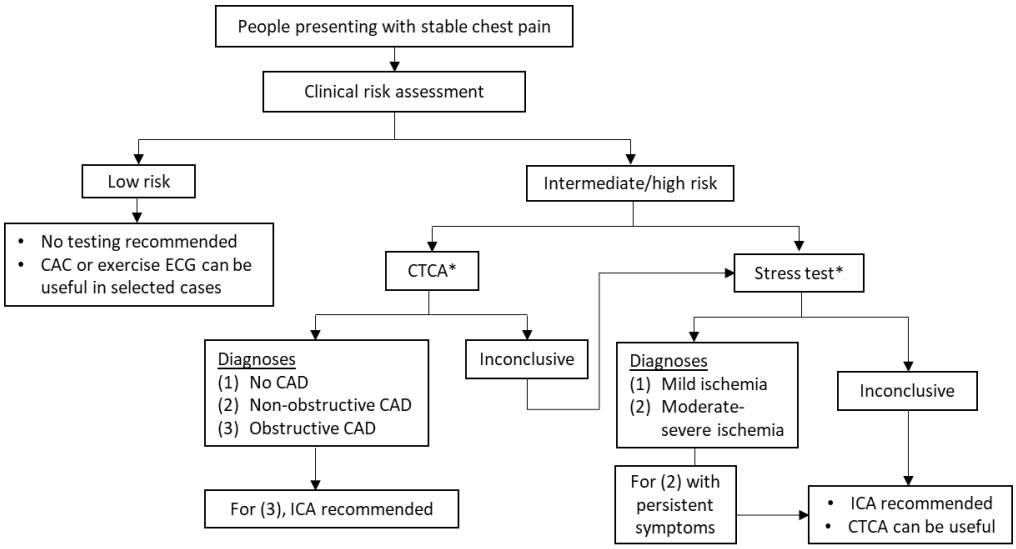

Figure A1: Diagnostic pathway for patients with stable chest pain and no known CAD. Adapted from the 2021 AHA/ACC Joint Guidelines for the Evaluation and Diagnosis of Chest Pain.[16]

Note: * Test choice guided by patient's exercise capacity, resting electrocardiographic abnormalities; CTCA preferable in those <65 years of age and not on optimal preventive therapies; stress testing favored in those ≥65 years of age (with a higher likelihood of ischemia).

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CAC, coronary artery calcium; CAD, coronary artery disease; CTCA, computed tomography coronary angiography; ECG, electrocardiogram; ICA, invasive coronary angiography.

Appendix B: Studies identified and study design

Table B1: List of included studies

Type of study	Key evidence base	Supplementary evidence base
Health technology assessment report	2	—
Systematic reviews with meta-analysis	1	—
Randomised controlled trial	1 (2 studies)	—
Real-world study	2	—
Economic evaluation	—	1
FDA Summary of Safety and Effectiveness Data	—	1

Note:

1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   b. Studies only available in the abstract form.

Table B2: Design and characteristics of included studies

Study	Study design	Number of studies/patients	Population
Key evidence base			
NICE MTG32 (2021)[11]	HTA	39 studies*	People with stable chest pain who require investigation for possible CAD, and have a pre-test likelihood of CAD in the range of 10-90%.
VA ESP (2021)[8]	HTA	24 studies in 33 publications	Adult candidates for non-invasive evaluation for coronary disease or invasive coronary angiography.
Norgaard et al. (2022)[19]	SRMA	5 studies of 5,460 patients	Studies comparing FFR_{CT}>0.80 vs ≤0.80 in non-emergent patients with stable chest pain.
Curzen et al (2022)[20]	RCT (FORECAST)	1,399 patients	Patients at least 18 years old and were attending a Rapid Access Chest Pain Clinic for assessment of stable chest pain.
Hlatky et al (2023)[21]			
Graby et al. (2021)[22]	Real-world study	98 patients	Patients (aged >18 years old) undergoing routine clinical CTCA for assessment of CAD (deemed clinically indicated by the referring consultant cardiologist), who had ≥1 stenosis of ≥25%.
Rasoul et al (2021)[23]	Real-world study	125 patients	Patients undergoing CT-FFR.
Supplementary evidence base			
FDA SSED[10]	—	—	—
Karady et al. (2020)[24]	Economic evaluation	10,003 patients	Patients with low-risk stable chest pain.

* Studies identified by NICE's External Assessment Centre in the original and updated HTA report in 2016 and 2021, respectively.

Abbreviations: CAD, coronary artery disease; CTCA, computed tomography coronary angiography; CT-FFR, computed tomography fractional flow reserve; FDA, US Food and Drug Administration; FFR_{CT}, fractional flow reserve computed tomography; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SHTG, Scotland Health Technology Group; SRMA, systematic review with meta-analysis; SSED, Summary of Safety and Effectiveness Data; VA ESP, Veteran Affairs Evidence Synthesis Program.

Appendix C: Supplementary tables and figures

Table C1: Diagnostic accuracy of HeartFlow FFR_{CT} and comparators

Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Patient-based					
HeartFlow FFR_{CT} (Norgaard et al. 2014; NXT trial)	254	0.86 (0.77 to 0.93)	0.79 (0.72 to 0.85)	4.07 (3.02 to 5.49)	0.18 (0.10 to 0.31)
CTCA (6 studies)	1,136	0.95 (0.92 to 0.97)	0.68 (0.65 to 0.71)	3.18 (1.56 to 6.47)	0.09 (0.05 to 0.16)
ECHO (Neglia et al. 2015)	261	0.45 (0.33 to 0.57)	0.90 (0.85 to 0.94)	4.52 (2.74 to 7.45)	0.61 (0.49 to 0.76)
ICA (Norgaard et al. 2014)	254	0.64 (0.52 to 0.74)	0.83 (0.76 to 0.88)	3.70 (2.57 to 5.33)	0.44 (0.33 to 0.59)
MRI (2 studies)	129	0.89 (0.78 to 0.95)	0.91 (0.82 to 0.97)	8.59 (4.12 to 17.9)	0.13 (0.07 to 0.26)
SPECT (Neglia et al. 2015)	293	0.73 (0.63 to 0.81)	0.67 (0.60 to 0.74)	2.20 (1.74 to 2.79)	0.41 (0.29 to 0.57)
Vessel-based					
HeartFlow FFR_{CT} (Norgaard et al. 2014)	484	0.84 (0.76 to 0.91)	0.86 (0.82 to 0.89)	5.97 (4.60 to 7.75)	0.18 (0.12 to 0.29)
CTCA (4 studies)	1,645	0.85 (0.81 to 0.29)	0.75 (0.73 to 0.77)	4.15 (2.38 to 7.23)	0.19 (0.12 to 0.32)
ICA (Norgaard et al. 2014)	484	0.55 (0.45 to 0.65)	0.90 (0.87 to 0.93)	5.56 (3.92 to 7.89)	0.50 (0.40 to 0.62)
MRI (Bernhardt et al 2012)	102	0.87 (0.72 to 0.96)	0.98 (0.82 to 1.00)	55.6 (7.92 to 390)	0.13 (0.06 to 0.30)

Note: Based on the data, while acknowledging that there were no studies directly comparing all the tests, NICE concluded that HeartFlow FFR_{CT} has (i) similar sensitivity but higher specificity compared to CTCA, (ii) higher sensitivity but lower specificity compared with ECHO, (iii) similar sensitivity but lower specificity compared with MRI and (iv) higher sensitivity and specificity compared with SPECT.

Abbreviations: CI, confidence interval; CTCA, computed tomography coronary angiography; ECHO, echocardiography; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography.

Table adapted from NICE MTG32[11].

Table C2: Impact of HeartFlow FFR_{CT} on clinical management

Author (year)	N	Population	Change in clinical management
Studies reviewed in VA ESP (2021)[8]			
Baggiano et al. (2020)	291	Symptomatic patients scheduled for ICA + invasive FFR	28% (95% CI, 22.8% to 31.2%)
Curzen et al. (2016)	200	Patients with suspected CAD with at least one stenosis (30 to 90%) on CTCA undergoing non-emergent ICA	36% (95%, 29.3% to 42.7%)
Fairbairn et al. (2018)	5,083	Patients with suspected CAD with documented atherosclerosis (>30%) on CTCA	66.9% (95% CI, 68.4% to 67.6%)
Fares et al. (2019)	207	Patients with suspected CAD referred for FFR_{CT}	24% (95% CI, 17.4% to 30.6%)
Jang et al. (2016)	75	Patients with suspected CAD undergoing CTCA and referred for ICA	55% ICA cancellation: 48%

Jensen et al. (2018)	774	Patients with suspected CAD referred to non-emergent ICA or CTCA	ICA cancellation: 75% (high-risk), 91% (low-intermediate risk)
Norgaard et al. (2017)	1,248	Patients with suspected CAD undergoing CTCA	ICA cancellation: 66% (95% CI, 59% to 73%)
Shiono et al. (2019)	1,829	Japanese patients with suspected CAD with documented atherosclerosis (>30%) on CTCA	55.8% (95% CI, 53.5% to 58.1%)
Rabbat et al. (2020)	431	Patients with obstructive CAD (>1 vessel with ≥50% diameter stenosis	Compared to CTCA alone, CTCA + FFR_{CT} reduced the rates of ICA (45% vs. 80%) for those with obstructive CAD.
Additional studies reviewed in NICE MTG32 (2021)[11]			
PROMISE	271	Patients with stable chest pain without known CAD	PROMISE findings suggested that reserving ICA for patients with an FFR_{CT} of ⩽0.80 could decrease ICA by 44%.
PLATFORM	584	Symptomatic patients with suspected CAD	In two separate reports from PLATFORM, ICA was cancelled in 77% of patients having CTCA + FFR_{CT} in one report and it was cancelled in 61% of the cases after receiving CTCA + FFR_{CT} results in another report.
Abbreviations: CAD, coronary artery disease; CI, confidence interval; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography.			

Table C3: Impact of HeartFlow FFR_{CT} on the rate of ICA showing no obstructive CAD

Study	Key findings
Douglas et al. (2015); PLATFORM*	The use of HeartFlow FFR_{CT} as an alternative diagnostic strategy to guide care in patients planned for ICA resulted in a significantly lower rate of angiography showing no obstructive CAD compared to usual care (12% vs. 73%, p<0.0001; risk difference: -61%, 95% CI, -53% to -69%), with NICE indicating superiority of the FFR_{CT} pathway to standard pathway.
Curzen et al. (2021)[20]; FORECAST	The number of ICA showing no obstructive epicardial lesion was 52% lower in the FFR_{CT} group compared to standard care.
* Reviewed in NICE MTG32 (2021)[11] and VA ESP (2021)[8] Abbreviations: CAD, coronary artery disease; CI, confidence interval; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography; NICE, National Institute for Health and Care Excellence.	

Table C4: Evidence supporting the clinical outcomes with a diagnostic strategy of HeartFlow FFR_{CT}

Author (year)	Trial	Follow-up	Type of AE reported	Event rate
Fairbairn et al. (2018)	ADVANCE registry	90 days	MACE	19 (0.4%)
Nous et al. (2021)		1 year		59 (1.2%)
Ihdayhid et al. (2019)	—	4.7 years (median)		20 (9.7%)
Jang et al. (2016)	—	1 year	CVD events	Data not reported†
Jensen et al. (2018)	—	90 days	Clinical AEs	14 (1.8%)*
Norgaard et al. (2017)	—	90 days	Cardiac AEs	0 cardiac SAE‡
* None of the patients whose ICA was cancelled based on HeartFlow results experienced serious clinical events. † No significant difference in CVD events between patients with changed and unchanged management with HeartFlow ‡ Including in patients whose ICA was cancelled based on HeartFlow results. Abbreviations: AE, adverse event; CVD, cardiovascular disease; FFR_{CT}, fractional flow reserve computed tomography; MACE, major adverse cardiac event; SAE, serious adverse event. Table adapted from VA ESP (2021)[8].				

Table C5: Cost analysis per year of HeartFlow FFR_{CT} and CTCA alone based on the 2020/2021 HRG tariff by Graby et al. (2022)[22]

Year	Pathway cost (£)			
	CTCA only	CTCA + FFR_{CT}		
		≥25% stenosis	≥50% stenosis	50% to 90% stenosis
Total	137,809	161,149	149,096	149,747
Per patient	549.04	650.00	594.01	596.58
Difference*	—	+101.96	+44.97	+47.54

* Relative to CTCA only.

Abbreviations: CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography.

Table C6: Cost analysis of HeartFlow FFR_{CT} and CTCA alone based on the study by Rasoul et al. (2021)[23]

Scenario	CTCA, n (£)	CTFFR, n (£)	ICA, n (£)	Invasive FFR, n (£)	Total cost, £	Per patient cost, £
CTCA + FFR_{CT}	125 (27,500)	125 (66,250)	44 (44,000)	24 (8,064)	145,814	1,166.51
CTCA + FFR_{CT} (<50% stenosis excluded)	125 (27,500)	81 (42,930)	43 (43,000)	24 (8,064)	121,494	971.95
CTCA + ICA	125 (27,500)	0	81 (81,000)	24 (8,064)	116,564	932.51

Abbreviations: CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; ICA, invasive coronary angiography.

Table C7: Cost-effectiveness data from the Markov microsimulation model by Karady et al. (2020)[24]

Strategy	Cost (95% CI)		QALY (95% CI)		Discounted ICER ($/QALY) †	Life-years gained (95% CI), years
	Undiscounted	Difference*	Undiscounted	Difference*		
Functional	$7,989 ($7,958 to 8,020)	–	24.68 (24.66 to 24.70)	–	Dominated‡	26.51 (26.48 to 26.53)
CTCA with FFR_{CT}	$7,222 ($7,192 to $7,252)	-$767 (-$805 to -$729)	25.14 (25.12 to 25.17)	0.46 (0.44 to 0.49)	–	27.01 (26.99 to 27.04)

Note: A lifetime time horizon was used in the Markov model.

* Differences in cost and QALY are expressed in reference to functional strategy.

† Discount rate of 3% applied.

‡ A strategy is considered dominated by the other if the other strategy has lower cost and higher QALY.

Abbreviations: CI, confidence interval; CTCA, computed tomography coronary angiography; FFR_{CT}, fractional flow reserve computed tomography; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.