HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography

Medical technologies guidance
Published: 13 February 2017
Last updated: 19 May 2021

www.nice.org.uk/guidance/mtg32

Contents

1 Recommendations

1.1 The case for adopting HeartFlow FFR$_{CT}$ for estimating fractional flow reserve from coronary CT angiography (CCTA) is supported by the evidence. The technology is non-invasive and safe, and has a high level of diagnostic accuracy.

1.2 HeartFlow FFR$_{CT}$ should be considered as an option for patients with stable, recent-onset chest pain who are offered CCTA in line with the NICE guideline on chest pain. Using HeartFlow FFR$_{CT}$ may avoid the need for invasive coronary angiography and revascularisation. For correct use, HeartFlow FFR$_{CT}$ requires access to 64-slice (or above) CCTA facilities.

1.3 Based on the current evidence and assuming there is access to appropriate CCTA facilities, using HeartFlow FFR$_{CT}$ may lead to cost savings of £391 per patient **[2021]**. By adopting this technology, the NHS in England may save a minimum of £9.4 million by 2022 through avoiding invasive investigation and treatment **[2021]**.

2   The technology

Description of the technology

2.1   HeartFlow FFR$_{CT}$ (developed by HeartFlow) is coronary physiology simulation software used for the qualitative and quantitative analysis of previously acquired computerised tomography DICOM data. The software provides a non-invasive method of estimating fractional flow reserve (FFR) using standard coronary CT angiography (CCTA) image data. FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in a normal artery. FFR is currently measured invasively using a pressure wire placed across a narrowed artery.

2.2   After a clinician decides to request a HeartFlow test, anonymised data from a CCTA scan (of at least 64 slices) are sent from the local imaging system, by secure data transfer to HeartFlow's central processing centre in the US. A case analyst employed by the company then uses the image data to create 3D computer models of the coronary arteries, incorporating coronary flow characteristics. The results are presented in a report which is sent, by secure data transfer, to the referring clinician within 48 hours. The report includes both 3D images of the coronary anatomy and calculated functional information, including the estimated FFR values (known as FFR$_{CT}$ values). Clinicians can then use the report to help guide the management of suspected coronary artery disease.

2.3   HeartFlow FFR$_{CT}$ is intended for use in patients with stable, recent-onset chest pain and suspected angina. Because the safety and effectiveness of FFR$_{CT}$ analysis has not been evaluated in other patient subgroups, HeartFlow FFR$_{CT}$ is not recommended in patients who have an acute coronary syndrome or have had a coronary stent, coronary bypass surgery or myocardial infarction in the past month.

2.4   The company first received a CE mark in July 2011, covering all 1.X versions of the technology, including the current version, 1.7.

2.5   HeartFlow FFR$_{CT}$ costs £700 per test. A higher price of £888 is used in the company submission and assessment report. The cost was reduced in May 2015.

2.6   The claimed benefits of HeartFlow FFR$_{CT}$ in the case for adoption presented by the company were as follows:

- Analysis is done using standard CCTA scans, without the need for additional imaging, radiation or medication.

- It provides the same accuracy in excluding coronary artery disease as CCTA, and characterises the coronary arteries from both functional and anatomical perspectives, differentiating between ischaemic and non-ischaemic vessels in a way that CCTA cannot.

- It allows physicians to evaluate anatomical coronary artery disease and accurately determine which coronary lesions are responsible for myocardial ischaemia, avoiding unnecessary invasive diagnostic or therapeutic procedures and related complications.

- It reduces the need for revascularisation in patients after identifying anatomical stenosis by invasive coronary angiography (ICA) alone, by more accurately identifying if those stenoses are ischaemic.

- It improves the diagnostic accuracy for coronary artery disease compared with CCTA alone against the gold standard of invasive FFR, and provides both functional and anatomical assessment of coronary arteries.

- It has better diagnostic performance than CCTA alone, or other non-invasive or invasive tests (such as nuclear myocardial perfusion, magnetic resonance perfusion, stress echocardiography, exercise treadmill testing, invasive angiography or intravascular ultrasound) for detecting and excluding coronary artery lesions that cause ischaemia.

- It reduces costs arising from inconclusive or inaccurate diagnostic tests.

- It avoids staff and procedure costs for unnecessary ICAs.

- It avoids staff and procedure costs for unnecessary interventions (such as angioplasty).

- It provides a more effective use of high-cost invasive procedure suites, providing the opportunity to reduce waiting times for these facilities and increase patient turnaround.

Current management

2.7 The NICE guideline on chest pain recommends diagnostic testing for people in whom stable angina cannot be excluded by clinical assessment alone.

2.8 The guideline recommends offering 64-slice (or above) CCTA as the first-line diagnosis test when clinical assessment indicates typical or atypical angina; or non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves.

2.9 Subsequent diagnostic tests can be requested dependent on the CCTA results. The guideline recommends offering non-invasive functional imaging for myocardial ischaemia if 64-slice (or above) CCTA has shown coronary artery disease of uncertain functional significance, or is non-diagnostic. Non-invasive functional imaging includes:

- myocardial perfusion scintigraphy with single-photon emission CT (MPS with SPECT)

- stress echocardiography

- first-pass contrast-enhanced MR perfusion

- MR imaging for stress-induced wall motion abnormalities.

  ICA should be offered as a second-line investigation when the results of non-invasive functional imaging are inconclusive.

2.10 When ICA is used to determine the presence and severity of coronary stenosis, it may be combined with the invasive measurement of FFR using a pressure wire. Although the NICE guideline on chest pain does not consider FFR, other guidelines (such as those of the European Society of Cardiology and American College of Cardiology) state that lesions with an FFR of 0.80 or less are functionally significant and

revascularisation may be considered.

3 Clinical evidence

3.1   The key clinical outcomes for HeartFlow FFR$_{CT}$ presented in the decision problem were:

- measures of diagnostic accuracy (sensitivity and specificity, positive and negative likelihood ratios, area-under curve) using invasive fractional flow reserve (FFR) as the reference standard

- rates of diagnostic coronary angiography, percutaneous coronary intervention and coronary artery bypass surgery

- adverse events (test-related, major adverse cardiac events, radiation exposure and so on)

- quality of life

- mortality.

Summary of diagnostic accuracy evidence

3.2   The company conducted a literature search on the diagnostic accuracy of FFR$_{CT}$ and the existing tests in the current treatment pathway for patients with a 10% to 90% pre-test likelihood of coronary artery disease, against a reference standard of invasive FFR testing. This review identified 5 relevant meta-analysis studies and 23 individual studies, 1 of which was unpublished. Based on the 22 published studies, and using FFR as the reference standard, the company presented diagnostic accuracy per-patient results for HeartFlow FFR$_{CT}$ compared with:

- invasive coronary angiography (ICA)

- single-photon emission CT (SPECT)

- stress echocardiogram (ECHO)

- magnetic resonance imaging (MRI)

- coronary CT angiography (CCTA).

  If there were multiple studies for a test, the company conducted a meta-analysis; for example, 3 studies were included in the meta-analysis for HeartFlow FFR$_{CT}$ (Koo et al. 2011, Min et al. 2012 and Nørgaard et al. 2014). The methodology and results of the meta-analyses are reported as academic in confidence.

3.3 The external assessment centre (EAC) reviewed the company's selection of studies and considered that although they addressed the scope in terms of the comparators, reference test and outcomes, most included a mixture of patients with both high (over 90%) and intermediate (10% to 90%) pre-test likelihoods of disease. It also disagreed with the company's decision only to include studies that provided FFR measurements in more than 75% of blood vessels. The EAC considered this criterion not to be reflective of clinical practice, where visual assessment is sometimes used before proceeding with FFR measurements. The EAC also noted that this criterion did not reflect the company's proposed changes to the clinical pathway, where CCTA would be used to decide if HeartFlow FFR$_{CT}$ should be used.

3.4 To address these concerns, the EAC conducted a diagnostic literature search using extra keywords related to comparators and outcomes. It included only studies in which most patients had an intermediate pre-test likelihood of disease. The EAC identified 7 diagnostic studies, including 3 presented by the company (Bernhardt et al. 2012, Nørgaard et al. 2014 and Stuijfzand et al. 2014) and 3 that the company had identified but excluded (Danad et al. 2013, Kajander et al. 2010 and Ponte et al. 2014). Only 1 of these, Nørgaard et al. 2014, involved HeartFlow FFR$_{CT}$.

3.5 Nørgaard et al. (2014) reported on a multicentre study (the NXT trial) involving 2 UK centres, which compared HeartFlow FFR$_{CT}$ (v1.4) with CCTA for diagnosing myocardial ischaemia in 254 patients with suspected stable coronary artery disease scheduled to have ICA. Most patients in the study (87%) were considered to have an intermediate likelihood of coronary artery disease. Invasive FFR was measured in all vessels (n=484). The study reported the diagnostic performance of HeartFlow FFR$_{CT}$ and CCTA for diagnosing ischaemia compared with FFR

measured during ICA as the reference standard. The diagnostic accuracy of each test was presented on a per-patient and a per-vessel basis compared with the reference standard, an FFR value of ≤ 0.80. Per-vessel FFR$_{CT}$ was correlated to FFR (Pearson's correlation coefficient 0.82, p>0.001), with a slight underestimation of FFR$_{CT}$ compared with FFR. The authors concluded that HeartFlow FFR$_{CT}$ can identify functionally significant coronary artery disease with high sensitivity and specificity. Furthermore, adding FFR$_{CT}$ measurements to CCTA led to a marked increase in specificity.

3.6   The EAC identified 6 studies which both used the comparator tests and included patients with an intermediate likelihood of coronary artery disease. Bernhardt et al. (2012) compared the diagnostic performance of 1.5 T and 3 T MRI scanners using FFR as a reference standard in 34 patients with stable angina and suspected or known coronary artery disease. The authors studied an intermediate-risk population with a mean PROCAM score of 42.7 (a risk assessment metric which estimates the 10-year risk of developing a coronary event). Ponte et al. (2014) compared the diagnostic accuracy of CCTA and MRI for detecting functionally significant coronary artery disease in patients referred with suspected coronary artery disease, using ICA with FFR as the reference standard. The study included 95 patients with a 15% to 85% pre-test likelihood of coronary artery disease. Stuijfzand et al. (2014) evaluated CCTA and transluminal attenuation gradient compared with CCTA alone for diagnosing functionally significant lesions, using invasive FFR as the reference standard. The study included 85 patients (253 vessels) with an intermediate likelihood of coronary artery disease. Neglia et al. (2015) assessed the accuracy of several imaging techniques – CCTA, SPECT and ECHO – in 475 patients with an intermediate likelihood of coronary artery disease. Danad et al. (2013) evaluated the diagnostic accuracy of CCTA in 120 patients with suspected coronary artery disease who had cardiac positron emission topography (PET), CCTA and ICA. CCTA was done using a hybrid PET/CT scanner. Kajander et al. (2010) evaluated the diagnostic accuracy of PET and CCTA in 107 patients with a history of stable chest pain and a 30% to 70% pre-test likelihood of coronary artery disease. All patients had ICA independently of the non-invasive imaging results, and treatment decisions were based on both ICA and FFR.

3.7   Table 1 summarises the EAC's analysis of diagnostic accuracy for HeartFlow FFR$_{CT}$ and its comparators at both per-vessel and per-patient levels, as shown in table 1. When there was more than 1 diagnostic accuracy study available, the EAC conducted a meta-analysis.

Table 1 Diagnostic accuracy: HeartFlow FFRCT and comparator tests

Type of analysis	Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Patient based	HeartFlow FFR$_{CT}$ (Nørgaard, 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
Patient based	CCTA (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
Patient based	ECHO (Neglia, 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
Patient based	ICA (Nørgaard, 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
Patient based	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
Patient based	SPECT (Neglia, 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

Type of analysis	Index test	N	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Vessel based	**HeartFlow FFR$_{CT}$** (Nørgaard, 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
Vessel based	**CCTA** (4 studies)	1,645	0.85 0.81 to 0.89	0.75 0.73 to 0.77	4.15 2.38 to 7.23	0.19 0.12 to 0.32
Vessel based	**ICA** (Nørgaard, 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
Vessel based	**MRI** (Bernhardt, 2012)	102	0.87 0.72 to 0.96	0.98 0.92 to 1.00	55.6 7.92 to 390	0.13 0.06 to 0.30

Abbreviations: CCTA, coronary CT angiography; CI, confidence interval; ECHO, stress echocardiogram; FFR$_{CT}$, fractional flow reserve CT; ICA, invasive coronary angiography; MRI, magnetic resonance imaging; SPECT, single-photon emission CT.

3.8   The EAC considered that despite the limitations associated with patients having a different reference test in some studies, all contributed to the decision problem and provided data for synthesis. It judged that the Nørgaard (2014) study had a low risk of bias for flow and timing, index and reference test. It noted that there was a risk of patient selection bias because an inclusion criterion was that patients had to have been referred for ICA, but it noted no other risks of bias or applicability concerns. Although it acknowledged that there were no studies directly comparing all the tests, it concluded that HeartFlow FFR$_{CT}$ has:

- similar sensitivity but higher specificity compared with CCTA

- higher sensitivity but lower specificity compared with ECHO

- similar sensitivity but lower specificity compared with MRI

- higher sensitivity and specificity compared with SPECT.

Summary of clinical-effectiveness evidence

3.9   The company conducted a literature search for evidence on the clinical outcomes specified in the decision problem for HeartFlow FFR$_{CT}$, and the existing treatments, against any comparator. It identified 16 studies of which 5 included HeartFlow FFR$_{CT}$, 1 published (Guar et al. 2014) and 4 unpublished (PLATFORM, Radiation FFR$_{CT}$, Real World Usage FFR$_{CT}$ and FFR$_{CT}$ RIPCORD).

3.10   The EAC included extra intervention and comparator keywords and identified 11 studies, 4 of which had already been identified by the company: 2 published studies (Hachamovitch et al. 2012 and Douglas et al. 2015) and 2 unpublished studies. The EAC noted that only the 2 unpublished studies fully matched the population, intervention, comparators and outcomes defined in the scope; the other 9 included various comparators but not HeartFlow FFR$_{CT}$. The 2 unpublished studies including HeartFlow FFR$_{CT}$ were PLATFORM (see section 3.18) and Radiation FFR$_{CT}$; the company provided both in the form of interim results for the former and an abstract for the latter. Two studies (Real World Usage FFR$_{CT}$ and FFR$_{CT}$ RIPCORD) included HeartFlow FFR$_{CT}$ but were excluded because they did not provide information on patients' pre-test likelihood of coronary artery disease.

3.11   Radiation FFR$_{CT}$ is a single-centre modelling study, based in Canada, investigating the potential effect of HeartFlow FFR$_{CT}$ on radiation dose exposure and downstream clinical event rate. In the modelling, a clinical pathway in which CCTA plus FFR$_{CT}$ was the initial diagnostic test was compared with 3 clinical pathways instead utilising SPECT, ECHO or CCTA as initial diagnostic tests. The model included 100 patients with suspected coronary artery disease, 34% of whom had intermediate disease. Patients were stratified into 3 categories of likelihood of disease: 50% low, 40% moderate and 10% high. No clinical outcomes were measured in this modelled population. The primary outcome was the estimated radiation dose and the secondary outcome was death or

myocardial infarction estimates at 1 year after the test. Of the 4 diagnostic pathways studied, ECHO had the lowest radiation dose (5.3 mSv) but had a higher clinical event rate related to both false-positive and false-negative findings. The FFR_{CT} pathway had lower cumulative radiation exposure (9.4 mSv) than SPECT (26.4 mSv) or CCTA (13.9 mSv) and also had the lowest clinical adverse event rate for low and intermediate-risk patients. For high-risk patients, the lowest clinical event rate was with ICA.

3.12 The PROMISE study (Douglas et al. 2015) is a US-based multicentre randomised controlled trial involving over 10,000 patients, with a median follow-up of 25 months. Although the study did not include FFR_{CT}, the EAC considered it relevant to the decision problem because it provides further evidence on a diagnostic pathway based on CCTA. Patients with a mean pre-test likelihood of coronary artery disease of 53.3±21.4% were randomly assigned to either CCTA or functional imaging as a first-line diagnostic test. The composite primary end point was death, myocardial infarction, hospitalisation for unstable angina, or major procedural complication. Secondary end points included invasive cardiac catheterisation that did not show obstructive coronary artery disease and radiation exposure. Results showed that 164 of 4,996 (3.3%) patients in the CCTA group and in 151 of 5,007 (3.0%) in the functional testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; p=0.75) achieved the primary end point. CCTA was associated with fewer catheterisations showing no obstructive coronary artery disease than functional imaging (3.4% compared with 4.3%, p=0.02), although more patients in the CCTA group had catheterisation within 90 days of randomisation (12.2% compared with 8.1%). The median cumulative radiation exposure per patient was lower in the CCTA group than in the functional testing group (10.0 mSv compared with 11.3 mSv), but 32.6% of the patients in the functional testing group had no exposure. As such, overall exposure was higher in the CCTA group (mean 12.0 mSv compared with 10.1 mSv; p<0.001).

3.13 The EAC identified 9 published studies containing information on clinical outcomes in comparator diagnostic technologies. Further information about these studies can be found in the assessment report.

Chest pain guideline update: second literature search

3.14　During the assessment of HeartFlow FFR_{CT} for this guidance, <u>NICE updated its guideline on chest pain</u>. Because this included new recommendations for investigating chest pain, it became necessary to update the evidence and cost modelling for the HeartFlow FFR_{CT} assessment. The EAC repeated the evidence searches up to February 2016 and asked the company to identify any recent and ongoing studies. In total, the EAC assessed 7 new studies, 6 of which included HeartFlow FFR_{CT}.

3.15　Tanaka et al. (2016) is a technical study on a subgroup of the NXT study investigating the association between FFR_{CT} and invasive FFR in coronary arteries with serial lesions. The authors investigated patients (n=18 patients and 18 vessels) with stable angina and clinically suspected coronary artery disease. There was no clinical follow-up. The primary outcome was the per-segment correlation between FFR_{CT} and invasive FFR values, expressed as translesional delta (the difference between the proximal and distal FFR measurement of all sequential lesions). Values of translesional delta for FFR and FFR_{CT} were 0.10±0.09 and 0.09±0.10 in distal segments, and 0.17±0.10 and 0.22±0.13 in proximal segments respectively. The coefficient of correlation between translesional delta FFR and FFR_{CT} in each segment was 0.92 (p<0.001). The authors concluded that translesional delta FFR is highly correlated with FFR_{CT}.

3.16　Thompson et al. (2015) investigated the diagnostic performance of FFR_{CT} in relation to patients' sex and age, using invasive FFR measurements as the reference standard for a subgroup of the DeFACTO study. Previous evidence from DeFACTO was not considered eligible because it included patients with a high pre-test likelihood of coronary artery disease (Min et al. 2012). Thompson et al. (2015) was included because it reports results based on subgroup analyses for age and sex. The baseline pre-test likelihood did not differ in statistical significance within these subgroups, so it is not expected to bias the results. The authors investigated 252 patients (407 vessels) with stable angina, clinically suspected coronary artery disease and at least 1 coronary stenosis of 30% to 90%. For their analysis, the authors used a clinical rule that included all vessels

of diameter ≥2 mm and assigned an FFR value of 0.90 for vessels with stenoses <30% and an FFR value of 0.50 for vessels with stenoses >90%. There was no clinical follow-up. The primary outcome was per-patient and vessel diagnostic performance of FFR_{CT}. Using this clinical rule, diagnostic performance improved in both sexes with no statistically significant differences between them. There were no differences in the discrimination of FFR_{CT} after application of the clinical use rule when stratified by age ≥65 or <65 years. The authors concluded that FFR_{CT} had similar diagnostic accuracy and discriminatory power to FFR for ischaemia detection in men and women irrespective of age using a cut-off point of 65 years.

3.17   The other 4 studies on HeartFlow FFR_{CT} looked at clinical outcomes. The PLATFORM study (Douglas et al. 2015b and 2016) was presented to the committee as academic in confidence in June 2015 (Douglas et al. 2015a). The study included 584 patients recruited at 11 international centres. They were prospectively assigned to have either functional imaging (n=287) or CCTA/FFR_{CT} (n=297). Each cohort was subdivided into 2 groups based on the evaluation plan decided before enrolment in the study: non-invasive testing (any form of stress testing or CCTA without FFR_{CT}) or ICA (invasive testing).

3.18   Douglas et al. (2015b) report the study results at 3-month follow-up. The primary end point was the percentage of patients with planned ICA in whom no significant obstructive coronary artery disease (no stenosis ≥50% by core laboratory quantitative analysis or invasive FFR <0.80) was found at ICA within 90 days. Secondary end points included a composite measure of major adverse cardiac events consisting of death, myocardial infarction and unplanned revascularisation, all of which were independently and blindly assessed. Among patients with intended ICA (CCTA/FFR_{CT}=193; functional imaging=187), no obstructive coronary artery disease was found with ICA in 24 patients (12%) in the CCTA/FFR_{CT} arm and 137 patients (73%) in the functional imaging arm (risk difference 61%, 95% CI 53 to 69, p<0.0001). Among patients intended for non-invasive testing, the rates of finding no obstructive coronary artery disease with ICA were 13% in the CCTA/FFR_{CT} arm and 6% in the functional imaging arm (p=0.95). ICA was cancelled in 61% of patients after reviewing the CCTA/FFR_{CT} results. There were low numbers of

MACE and vascular complications in all groups.

3.19   Douglas et al. (2016) report outcomes from the same study at 1 year. The clinical end points measured were MACE and MACE plus vascular events within 14 days of procedure. Quality of life and resource use outcomes were also collected. There were 2 MACE events in each arm of the planned invasive group (risk difference -0.03 [CI -8.6 to 8.5]) and 1 in the planned non-invasive group (risk difference -1.00 [CI -12.7 to 10.7]). Cumulative 1-year radiation exposure in patients in the intended invasive evaluation cohort was similar between the usual care strategy (mean: 10.4 ± 6.7 mSv) and CCTA/FFR$_{CT}$-guided strategy (mean: 10.7 ± 9.6 mSv; p=0.21), whereas in the non-invasive testing cohort it was higher in patients with a CCTA/FFR$_{CT}$-guided strategy than usual care strategy (mean: 9.6 ± 10.6 mSv compared with 6.4 ± 7.6 mSv, p<0.001). Functional status and quality of life improved from baseline to 1-year follow-up in the planned non-invasive group (p<0.001 for all measures), with greater improvements on the EQ-5D in patients having CCTA/FFR$_{CT}$ compared with patients having functional imaging (mean change: 0.12 for CCTA/FFR$_{CT}$ compared with 0.07 for functional imaging, p=0.02).

3.20   Lu et al. (2015) used a subgroup analysis of the PROMISE trial (n=181) to investigate the added value of FFR$_{CT}$ compared with CCTA in improving efficiency of referral to ICA. End points for the subgroup analysis were rate of revascularisation and ICA that did not show obstructive coronary artery disease and MACE. Over a median follow-up of 25 months, the addition of FFR$_{CT}$ increased the rate of ICA with revascularisation from 49% to 61%. The rate of angiography without obstructive disease decreased from 27% to 11%. No patient with FFR$_{CT}$ >0.80 had an adverse event which ICA would have prevented.

3.21   Nørgaard (2016) reports on the real-world experience of using CCTA with FFR$_{CT}$ as gatekeeper to ICA in patients with stable coronary artery disease and intermediate-range coronary lesions (n=189). Patients were followed up for a median of 12 months. The primary end point was the impact of FFR$_{CT}$ on further downstream diagnostic testing. Other end points were the agreement between FFR$_{CT}$ and invasive FFR, and the short-term clinical outcome after FFR$_{CT}$ testing defined as the occurrence of MACE (death and acute myocardial infarction) or an angina episode

leading to hospital admission or visit in the outpatient clinic. The authors concluded that FFR$_{CT}$ testing is feasible in real-world scenarios involving patients with intermediate-range coronary stenosis determined by CCTA. They also concluded that implementing FFR$_{CT}$ for clinical decision-making may influence the downstream diagnostic workflow, and patients with an FFR$_{CT}$ >0.80 who are not referred for ICA have a favourable short-term prognosis. The authors highlight that in patients with FFR$_{CT}$ ranging between 0.76 and 0.80, a non-negligible number of false-positive results may be expected.

3.22   The EAC considered that the 1-year follow-up data from the PLATFORM study supported the company's claims about resource use, rates of ICA and percutaneous coronary intervention, and quality of life with HeartFlow FFR$_{CT}$. Additionally, the 1-year follow-up evidence from the PLATFORM supports the company's claim that MACE outcomes are equivalent between the current pathway and one that uses FFR$_{CT}$, whereas the PROMISE study showed that MACE outcomes at 1 year were equivalent between CCTA alone and functional testing. The EAC also considered that the evidence from the PLATFORM study showed higher 1-year radiation exposure in the HeartFlow FFR$_{CT}$ group in patients intended for non-invasive evaluation. However, this is to be expected because many patients in the non-invasive evaluation had a non-invasive test which did not need the use of radiation. The EAC concluded that the submitted evidence on clinical outcomes supports the value proposition of an FFR$_{CT}$-guided strategy compared with standard of care, mainly in patients with planned invasive investigation, with equivalent results between FFR$_{CT}$ and functional imaging in the non-invasive group.

Committee considerations

3.23   The committee considered that the evidence showed high diagnostic accuracy and increased specificity with HeartFlow FFR$_{CT}$ compared with CCTA alone. It also noted promising results from the PLATFORM study, in a population which closely matches that in the scope. The evidence was sufficient to conclude that HeartFlow FFR$_{CT}$ has a high diagnostic accuracy for coronary artery disease, and that its use has the potential to reduce the need for invasive coronary investigations.

3.24   The committee considered the technology to be innovative and understood that its adoption may serve to simplify a complex patient pathway. The committee heard from clinical experts that they had confidence in the diagnostic accuracy of HeartFlow FFR_{CT}, and that it could provide an effective early rule-out test for coronary artery disease. This would reduce the need for ICA and invasive FFR measurement, and potentially reduce radiation exposure.

3.25   The committee understood that there are differences in the local implementation of the patient pathway for diagnosing coronary artery disease. It was advised by clinical experts that the choice of functional imaging test depends on local access, available expertise and clinician preference. It heard that although HeartFlow FFR_{CT} has the potential to reduce the number of tests that are done, the other non-invasive functional imaging tests that are part of the current patient pathway offer different functionality and in some cases provide additional information. Overall, the committee concluded that HeartFlow FFR_{CT} should be considered for use as a non-invasive investigation for diagnosing angina in patients with stable, recent-onset chest pain of suspected cardiac origin, and that it provides the clinician with additional functional information to determine which coronary lesions are responsible for myocardial ischaemia. The committee considered that further clinical studies would be helpful to clarify the wider applicability of HeartFlow FFR_{CT} in routine clinical practice.

3.26   The committee considered the evidence from the PLATFORM study to be most relevant to the decision problem. It considered that the results demonstrate the potential of FFR_{CT} to avoid ICA and improve quality of life.

3.27   The committee discussed the relative importance of a per-patient or a per-vessel diagnosis. It heard from experts that per-patient diagnostic accuracy was more important for initial diagnosis, and that a per-vessel assessment provides additional information to inform patient management. The committee concluded that per-patient level figures were the most reliable and relevant to the diagnosis of coronary artery disease.

4 NHS considerations

System impact

4.1 The company's claimed system benefits included reduced costs from fewer inconclusive or inaccurate diagnostic tests and avoidance of unnecessary staff and procedure costs. It claimed that this would lead to more effective use of invasive procedure suites.

4.2 The company confirmed that, with specific reference to the updated NICE guideline on chest pain, the proposed place in the diagnostic pathway for HeartFlow FFR$_{CT}$ (to inform management following a positive coronary CT angiography [CCTA] result) was unchanged.

4.3 Conservative estimates by the NICE resource impact assessment team suggest that by 2021/22, when fully implemented, HeartFlow FFR$_{CT}$ will potentially be used in around 40,000 patients a year. This would equate to national savings of at least £9.1 million a year.

4.4 During selection and routing, the committee asked for additional information on compliance with data protection legislation, and the reproducibility of HeartFlow FFR$_{CT}$ analysis, especially in the face of an increasing workload which might be expected to arise from adoption of the technology in the NHS. The external assessment centre (EAC) produced a technical report that concluded:

- The company has a quality assurance process in place that fulfils data quality needs. This includes checks by different team members, and the separation of tasks to ensure that no single analyst is fully responsible for a diagnosis. After the procedure, a more experienced analyst reviews the process, focusing mainly on areas of stenosis. Expert clinician advice is also available should it be needed.

- Although the analytical process is largely automated, any part of it can be manually changed by the analyst. This may affect the fractional flow reserve CT (FFR$_{CT}$) estimate. Manual editing is part of the quality assurance process, negating the risk of spurious results generated from the automated analysis. Gaur et al. (2014) suggest that reproducibility is within acceptable 95% confidence interval limits of agreement. FFR$_{CT}$ reproducibility was found to be equivalent to invasive FFR reproducibility.

- The reproducibility of outlining the coronary artery lumen, part of the FFR$_{CT}$ computation analysis, decreases in the distal portion of the vessel (Gage repeatability and reproducibility=29.4%). This could be a result of different factors including lower CT quality, lower CT resolution, smaller vessel diameter at the distal end and higher disease burden.

- The company monitors FFR$_{CT}$ reproducibility by re-processing 5% of its case volume on a weekly basis. The company has confirmed that this has shown a reproducibility rate consistent with the literature (Gaur et al. 2014).

- The company fulfils regulatory approval standards for data confidentiality and integrity protection for remote processing. It offers NHS customers the option to upload fully anonymised DICOM data to comply with UK data protection law.

Committee considerations

4.5   The committee was satisfied with the EAC's conclusions on reproducibility (see section 4.4). It accepted that the company has protocols in place to manage an increased demand for HeartFlow FFR$_{CT}$.

4.6   The committee considered the protection and oversight of data transferred during the administration of HeartFlow FFR$_{CT}$ to be an important factor in the device's adoption. The committee was satisfied, on the basis of the information available, that the company's data transfer protocols meet regulatory requirements. The committee noted that patients should be informed when sending personal data outside the European Economic Area with HeartFlow FFR$_{CT}$, and that it may be necessary to obtain written consent.

4.7   The committee considered the availability of CCTA facilities. It understood that the cost model assumed access to CCTA facilities, but

heard from experts that access to CCTA varies across the NHS despite recommendations in NICE's previous guideline on chest pain. Furthermore, because CT scanners are used for many purposes, a constraint currently exists with regard to both the availability of scanners and scanning time. The committee heard from experts that a sizable investment would be needed for the wider implementation of HeartFlow FFR$_{CT}$, but acknowledged that this consideration was beyond the scope of the current assessment. It understood that adopting 64-slice CCTA was ongoing in the NHS, in line with the recommendations in the previous NICE guideline on chest pain.

5   Cost considerations

Cost evidence

5.1   The company conducted a search of the health economics literature on HeartFlow FFR_{CT} and the comparators specified in the decision problem. They identified a total of 174 studies, 24 of which it considered relevant to the decision problem.

5.2   The external assessment centre (EAC) reviewed this search, and considered that most of the studies included neither an appropriate patient population nor a treatment pathway. Only 1 published study, Rajani et al. (2015), was considered by the EAC to be relevant to the decision problem. It conducted a further review of the literature up to February 2016 and identified an additional relevant published study, Hlatky et al. (2015).

5.3   Rajani et al. (2015) was a single-centre retrospective cost analysis of 410 patients referred to a rapid-access chest pain clinic in Guy's and St Thomas' Hospital, London, from April 2012 to March 2013. Patients were grouped into pre-test likelihood categories and diagnostic imaging was done based on standardised protocols as recommended in the previous NICE guideline on chest pain. A standardised unit cost for each test and procedure was taken from the NHS National Tariff 2013/14. A decision-tree economic model was used to evaluate the cost of 1,000 patients passing through the current treatment pathway compared with the same 1,000 patients after incorporating HeartFlow FFR_{CT}. The authors found that introducing HeartFlow FFR_{CT} to the pathway resulted in cost savings of £200 per patient. The EAC noted that although the derivation of costs in the study is explicit, details of the decision model structure are unclear.

5.4   Hlatky et al. (2015) investigated the quality-of-life and economic outcomes of fractional flow reserve CT (FFR_{CT}) in the PLATFORM study (see [section 3.17](#)). Cumulative medical costs were measured over 90 days for each patient by multiplying a standardised cost weight for

each medical resource by the number of resources used by the patient. Medicare reimbursement rates (the national average of technical and professional fees in the US) from 2015 were applied because cost weights and online pharmacy costs were used for drugs. Patients were prospectively assigned to either functional imaging (usual care, n=287) or coronary CT angiography (CCTA)/HeartFlow FFR_{CT} (n=297). In the planed invasive group, mean costs were \$7,343 among the CCTA/FFR_{CT} patients and \$10,734 among functional imaging patients (p<0.0001). In the planned non-invasive group, mean costs were not significantly different (p=0.26) between the CCTA/FFR_{CT} patients (\$2,679) and the functional imaging patients (\$2,137). Overall, each quality-of-life (EQ-5D) score improved at 90 days compared with baseline in the study population (p<0.0001), and scores improved more in CCTA/FFR_{CT} patients than in functional imaging patients. In the invasive group, quality-of-life improvements were similar in both arms.

5.5   Douglas et al. (2016) published data on the 1-year economic outcomes of FFR_{CT} in the PLATFORM study. Costs were calculated in the same manner as the 90-day results in Hlatky et al. (2015). In the planned invasive arm, the mean per-patient cost was \$8,127 in FFR_{CT} patients and \$12,145 for usual care patients (p<0.0001). The cost savings at 1 year increased by 1.5% from the cost savings at 90 days. In the non-invasive arm, mean costs were not significantly different (p=0.82) between the FFR_{CT} patients (\$3,049) and the usual care patients (\$2,579).

Economic model

5.6   The company presented a decision-tree model based on integrating HeartFlow FFR_{CT} into the existing diagnostic pathway at the time of its submission. A theoretical population of 1,000 patients with suspected coronary artery disease was allocated to either the current treatment pathway (based on the previous NICE guideline on chest pain) or the company's revised pathway, which included HeartFlow FFR_{CT}. The cost consequences of the treatment pathways were compared based on the mix of diagnostic technologies used in each. The model had a 1-year time horizon, included the impact of different testing strategies, and relevant clinical outcomes.

5.7 The proportion of patients eligible for CCTA as a first-line test and their probability of having coronary artery disease were taken from Rajani et al. (2015). In the model, 10% of patients were assumed to be ineligible for invasive coronary angiography (ICA), have an inconclusive CCTA result and have an uncertain single-photon emission CT (SPECT) result.

5.8 The diagnostic accuracy of HeartFlow FFR_{CT} and its comparators in the company's model were based on per-patient level results reported in selected papers, as follows:

- HeartFlow FFR_{CT}: sensitivity 86%, specificity 79% (Nørgaard et al. 2014)

- SPECT: sensitivity 76%, specificity 38% (Melikian et al. 2010)

- CCTA: sensitivity 94%, specificity 48% (Meijboom et al. 2008)

- ICA: sensitivity 69%, specificity 67% (Meijboom et al. 2008).

  The cost of HeartFlow FFR_{CT} (£888) was based on the company's original list price. Costs for comparator tests were based on 2014/15 hospital resource group (HRG) tariffs, as follows:

- SPECT: £220 (HRG code RA37Z, nuclear medicine category 3)

- CCTA: £136 (HRG code RA14Z, CT scan, more than 3 areas)

- Calcium scoring: £77 (HRG code RA08Z, CT scan, 1 area, no contrast)

- ICA: £1,241 (HRG code EA36A, catheter 19 years and over)

- Percutaneous coronary intervention (PCI): £2,832 (weighted average of 2 tariffs, assuming that 25% of patients needing PCI will need more than 2 stents. HRG codes EA31Z [£2,704] and EA49Z [£3,216]).

5.9 The company's base-case results reported an average per-patient cost of £2,239 using the current pathway and £2,080 using the adapted pathway with HeartFlow FFR_{CT}, representing an average saving of £159 per patient.

5.10 The company conducted 1-way sensitivity analyses on the sensitivity and specificity of HeartFlow FFR_{CT} and the comparator tests, as well as

the costs of HeartFlow FFR$_{CT}$. The analyses showed that HeartFlow FFR$_{CT}$ continued to be cost saving until its price reached £1,126. With regard to changes in the sensitivity and specificity, HeartFlow FFR$_{CT}$ remained cost saving for nearly all the values tested when considered in the context of the entire patient population.

Revisions by the external assessment centre

5.11 The EAC incorporated the changes to the updated NICE guideline on chest pain in the company economic model. In this context, the EAC assumed that HeartFlow FFR$_{CT}$ would be used following an initial CCTA, and that non-invasive functional imaging tests would subsequently be used only if the CCTA result were uncertain or non-diagnostic. The EAC reviewed the parameters and costs used in the company's model. It revised the company's sensitivity and specificity parameters for the comparator diagnostic tests, based on its own analyses of diagnostic accuracy (see table 1).

5.12 The EAC used the company's revised list price of £700 for HeartFlow FFR$_{CT}$, instead of £888 as used in the company's model.

5.13 The EAC used the updated NICE guideline on chest pain to determine the costs of all comparator tests except MRI, to ensure that they were consistent with 2014/15 reference costs. The cost of MRI was taken from the Payment by Results tariff, because the chest pain guideline committee determined this to be more representative of the true cost. These costs were as follows:

- SPECT: £367 (RN21Z, myocardial perfusion scan, stress only)

- CCTA: £122 (RD28Z, complex CT scan)

- ECHO: £271 (EY50Z, complex echocardiogram)

- ICA: £1,685 (EY43A to EY43F, standard cardiac catheterisation)

- MRI: £515 (RA67Z, cardiac MRI scan, pre and post contrast)

- PCI: £2,865 (weighted average of 2 tariffs, assuming that 25% of patients needing PCI will need more than 2 stents. HRG codes EA31Z [£2,704] and EA49Z [£3,216]). Includes an estimated annual cost of £33 for medication following a PCI [aspirin and clopidogrel, British national formulary (2015)].

5.14 The EAC noted that the company's model did not include costs of drug therapy for patients having PCI. It consulted the NICE guideline on stable angina and estimated an annual drug treatment cost for these patients of £33 based on British national formulary (2015) prescription costs for aspirin and clopidogrel, and used a cost of £2,865 (PCI tariff with drug costs) in its revised model.

5.15 The EAC included a cost for optimal medical therapy. It obtained expert advice that optimal medical therapy usually consists of aspirin, statins, nitrates and beta blockers. Based on this information it estimated an annual cost of £84 (aspirin, simvastatin, glyceryl trinitrate and propranolol hydrochloride) from the British national formulary (2015) and used it in the revised model.

5.16 Using these updated assumptions, the EAC found a base-case cost saving of £214 per patient for HeartFlow FFR_{CT} compared with the current treatment pathway for all functional imaging tests (SPECT, MRI and ECHO).

5.17 The EAC ran a number of sensitivity analyses, varying: the price of HeartFlow FFR_{CT}; the diagnostic accuracy of the functional imaging tests, HeartFlow FFR_{CT}, ICA and CCTA; and the proportion of uncertain CCTA and functional imaging tests. It also used estimates of diagnostic accuracy for CCTA and ICA from the updated NICE guideline on chest pain. In all instances, HeartFlow FFR_{CT} remained cost saving.

Committee considerations

5.18 The committee considered the cost modelling done by the EAC to be both appropriate and plausible. The committee heard from experts that percutaneous or surgical revascularisation is only offered to patients following ICA, and sometimes a confirmatory invasive FFR. The availability of data from HeartFlow FFR_{CT} may help to plan treatment in

individual vessels and patients.

5.19   For the guidance review, the EAC revised the model to reflect 2021 costs. There were no changes to the cost of the technology. The main parameter change was the cost of comparator tests. Further details of the 2021 revised model are in the cost update in the review decision.

5.20   Based on the 2021 guidance review updated cost model, the EAC found a base-case cost saving of £391 per patient for HeartFlow FFR$_{CT}$ compared with the current treatment pathway for all functional imaging tests (SPECT, MRI and ECHO). This cost saving will increase if the cost of HeartFlow FFR$_{CT}$ is reduced.

6 Conclusions

6.1 The committee concluded that the evidence suggests that HeartFlow FFR$_{CT}$ is safe, has high diagnostic accuracy, and that its use may avoid the need for invasive investigations.

6.2 The committee concluded that cost savings of £214 per patient are plausible and likely to be realised in practice, providing that sites adopting HeartFlow FFR$_{CT}$ have access to 64-slice (or above) coronary CT angiography.

7   Committee members and NICE project team

Committee members

This topic was considered by the medical technologies advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the topic) and a technical adviser or senior technical analyst.

Neil Hewitt
Technical analyst

Paul Dimmock
Technical analyst (evaluations)

Jae Long
Project manager

Update information

January 2022: Minor change to redirect NICE Pathways link

May 2021: We updated this guidance to reflect 2021 costs. Details of the changes are explained in the review decision. The update also includes revised cost-saving estimates. New evidence and updated costs identified during the guidance review are marked **[2021]**.

ISBN: 978-1-4731-2333-5

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