National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing coronary stenosis during invasive coronary angiography

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be used with NICE's final scope for the assessment and the diagnostics assessment report. A glossary of terms can be found in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of assessing the functional significance of coronary stenosis (that is, whether it causes inadequate blood supply) using QAngio XA 3D/QFR (Medis) and CAAS vFFR (Pie Medical Imaging) imaging software.

Angina is chest pain caused by insufficient blood supply to the heart (myocardial ischaemia). Stable angina is brought on by physical activity or emotional stress and goes away with rest. It is the key symptom of coronary artery disease, one of the main causes of morbidity and mortality in economically developed countries. Options for managing stable angina include lifestyle advice, drug treatment and revascularisation using percutaneous (stent placement during percutaneous coronary intervention) or surgical techniques (such as coronary artery bypass surgery). Choosing the appropriate management option depends on correctly detecting and

characterising coronary stenosis. Therefore, the diagnostic pathway for stable angina:

- confirms a diagnosis of stable angina
- defines the severity of coronary stenosis, which provides prognostic information and identifies people who are likely to benefit from myocardial revascularisation, in addition to optimal medical therapy.

Tests for people who might need revascularisation include coronary computed tomography angiography and other non-invasive tests to identify blocked arteries. If these tests are inconclusive, further tests such as invasive coronary angiography (ICA) are needed. ICA shows whether the arteries are blocked or narrowed, and the degree of stenosis. It is usually used as a third-line investigation for stable angina or during initial stages of percutaneous coronary intervention.

Visual assessment of angiograms taken during ICA, however, has limited ability to differentiate between functionally significant and non-significant (not substantially affecting blood supply) coronary stenosis. People with functionally significant stenosis may benefit from revascularisation (using percutaneous or surgical techniques), while functionally non-significant stenosis should be treated medically. If it is necessary to more accurately understand the functional significance of a stenosis, fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) measurements can be done during ICA. These invasive techniques require use of a pressure wire with or without a vasodilator drug, such as adenosine, and can only be done in interventional catheter laboratories.

QAngio XA 3D/ QFR (QAngio QFR) and CAAS vFFR are analytical software that can be used during ICA to assess the functional significance of coronary stenosis. They use angiographic images taken during the ICA and can be used in diagnostic-only or in interventional catheter laboratories. It is claimed that they are more accurate than ICA alone for indicating whether

intermediate stenoses are functionally significant and thus could improve clinical decision making relating to revascularisation. In a diagnostic setting they could help avoid unnecessary referrals for invasive FFR or iFR and/or revascularisation (percutaneous and surgical). In interventional catheter laboratories, they could help avoid unnecessary FFR/iFR measurement of coronary stenosis, and also help prioritise lesions for treatment.

By avoiding unnecessary invasive measurement of FFR/iFR, the risks associated with passing the pressure wire to the coronary arteries, and with adenosine infusion could be avoided.

Provisional recommendations on the use of these technologies will be made by the diagnostics advisory committee at the committee meeting on 3 September 2020.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does QAngio XA 3D/QFR and CAAS vFFR imaging software for non-invasively assessing the functional significance of coronary obstructions (stenoses) during invasive coronary angiography (ICA) represent a clinically and cost-effective use of NHS resources?
Populations	People with stable angina undergoing ICA whose angiograms show intermediate coronary obstructions (stenoses). An intermediate stenosis is defined as any lesion stenosis identified by ICA where there is clinical uncertainty about its functional significance and the potential appropriateness of revascularisation. When data permit, the following subgroups may be considered: • people with multivessel coronary artery disease • people with diffuse coronary artery disease • people with microvascular dysfunction (for example, caused by diabetes) • people with chronically occluded vessels. If possible, the analysis should also consider the impact of sex and ethnicity on outcomes.
Interventions	Clinical decision making based on QAngio XA 3D/QFR

	imaging software (used during ICA), alongside clinical judgement. Clinical decision making based on CAAS vFFR workflow (used during ICA), alongside clinical judgement.
Comparator	Clinical decision making based on visual interpretation of the angiographic images taken during ICA, alongside clinical judgement. Reference standard is invasive fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) measurement.
Healthcare setting	Diagnostic-only catheter laboratories. Interventional catheter laboratories.
Intermediate outcomes	Intermediate measures for consideration may include: • measures of diagnostic accuracy • proportion of patients who need invasive functional assessment of stenosis (FFR or iFR) • proportion of patients who need revascularisation (percutaneous and surgical) • number of vessels with stent placements • inter-observer variability • proportion of angiograms that were poor quality and unsuitable for quantitative flow ratio (QFR) or vessel-FFR (vFFR) (QFR/vFFR analysis not attempted) • failure rate (because of poor angiogram quality or other reasons) • rate of inconclusive results • time to results • radiation exposure.
Clinical outcomes	Clinical outcomes for consideration may include: • rates of major adverse cardiac events (definition may vary from study to study but usually includes cardiovascular death, myocardial infarction, stroke, and need for urgent revascularisation) • adverse events (related to diagnostic intervention) • adverse events (related to revascularisation) • mortality.
Patient-reported outcomes	Patient-reported outcomes for consideration may include health-related quality of life (related to the diagnostic interventions and treatment outcomes for stable angina).

Costs	Costs will be considered from an NHS and personal social services perspective. Costs for consideration may include: • costs of diagnostic interventions (including software costs [per patient or annual license cost], time to process results, software installation, maintenance and staff training costs) • cost of referral to interventional catheter laboratory (applicable to diagnostic-only centres) • costs of invasive functional assessment of stenosis (FFR or iFR) • costs of revascularisation (percutaneous and surgical) • costs of drug treatment (optimal medical therapy) • costs of managing major adverse cardiac events • costs of managing side effects related to invasive functional assessment of stenosis (FFR or iFR) • costs of managing side effects related to revascularisation (percutaneous and surgical). The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparator, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review to evaluate the diagnostic accuracy, clinical effectiveness and implementation of QAngio XA 3D/QFR (QAngio QFR) and CAAS vFFR. There were 41 unique studies that met the selection criteria for inclusion in the review (see pages 34 to 36 of the diagnostics assessment report for the selection criteria). Of the included studies, 39 evaluated QAngio

QFR, 3 evaluated CAAS vFFR and only 1 study directly compared QAngio QFR with CAAS vFFR. There were 2 studies that did not report diagnostic accuracy data but included other eligible outcomes. Seventeen of the studies were conference abstracts only, 15 of which were included in the diagnostic accuracy review.

Fifteen of the studies were done in multiple centres. Most studies were done in Asia, including 33 with sites in Japan, 5 in China, 4 in South Korea and 1 site in Singapore. A total of 22 studies had sites in Europe, 3 of which were in the UK. Two of the studies had sites in the US and 2 separate single studies had sites in Brazil and Australia.

The inclusion criteria for the systematic review of diagnostic accuracy included diagnostic accuracy and correlation studies in which quantitative flow ratio (QFR) using any version of the QAngio system or CAAS vFFR was done in addition to invasive fractional flow reserve (iFFR) as the reference standard, in the same patients.

The clinical effectiveness and implementation review included experimental or observational studies in which QAngio QFR or vessel-FFR (CAAS vFFR; with or without invasive FFR) had been used and which reported relevant clinical outcomes. Relevant publications reporting implementation issues, or practical advice on QAngio QFR or CAAS vFFR and their use in clinical practice were also eligible. Case reports, and studies focusing only on technical aspects of QAngio QFR or CAAS vFFR (such as technical descriptions of the testing process or specifications of machinery and software) were excluded (see pages 34 to 36 of the diagnostics assessment report for further details on selection criteria).

Study quality

The EAG used the QUADAS-2 tool to assess the risk of bias and applicability for the 24 diagnostic accuracy studies reported in full text manuscripts. The 15

conference abstracts were not formally quality assessed because of insufficient reporting.

Of the 22 QAngio QFR studies, 11 were at low risk of bias . The main source of bias was related to patient selection:

- 4 studies were considered at high risk of patient selection bias because of patient exclusions or significant exclusion of potentially harder to diagnose patients
- 3 studies did not provide sufficient information on patient selection to assess risk of selection bias (unclear risk).

There were concerns over the applicability of the index test, with a high number of studies being done retrospectively (offline use of QAngio QFR) rather than as part of invasive coronary angiography (ICA) and before FFR.

The risk of bias was generally low in relation to the reference standard and the patient flow. However, there were concerns over 3 studies at high risk of bias because of the conduct of the index test or reference standard. One study was at high risk of bias because of patient flow concerns.

Of the CAAS vFFR studies, all carried out CAAS vFFR analyses retrospectively (offline), and 2 were done at a single centre. One study was funded by the CAAS vFFR manufacturer. Only the ILUMIEN I study had a full text manuscript. This study was considered at high risk of selection bias because of the large percentage of lesions excluded.

The results of the QUADAS-2 assessment are summarised in table 2 of the diagnostics assessment report (see pages 53 to 54).

Diagnostic test accuracy

CAAS vFFR

The review identified 4 publications reporting the diagnostic accuracy of CAAS vFFR. Only 1 of the studies (ILUMIEN I) reported a 2×2 table of diagnostic

accuracy, and only 1 presented a Bland-Altman plot (FAST; Masdjedi et al. 2019) from which data were extracted to calculate diagnostic accuracy. Two of the studies were conference abstracts and only reported sensitivity and specificity without confidence intervals (Jin et al. 2019 and FAST EXTEND).

There was notable heterogeneity across this small number of studies. The ILUMIEN I study found considerably lower sensitivity and specificity than the FAST studies, and the Jin et al. study found lower sensitivity, but slightly higher specificity. A summary of the properties of the CAAS vFFR studies is presented in table 8 of the diagnostics assessment report.

The EAG noted that the meta-analyses of the CAAS vFFR studies should be interpreted with caution because imputation of data was needed for 2 studies on the prevalence of FFR results below and above the cut-off of 0.80 or less, and because of the high heterogeneity across studies. The results of these bivariate meta-analyses are summarised in table 2.

Table 2 Bivariate meta-analysis of CAAS vFFR studies

Analysis	Sensitivity	95% confidence intervals	Specificity	95% confidence intervals
Using FAST (Masjedi)	75.98	66.86 to 83.22	74.38	51.32 to 88.89
Using FAST EXTEND	84.86	61.76 to 95.11	72.20	50.30 to 86.95

Only 1 study, reported as a conference abstract, directly compared CAAS vFFR with QAngio QFR. It concluded that diagnostic performance of CAAS vFFR was poorer than for QAngio QFR, with area under the curves (AUCs) of 0.719 (95% confidence interval [CI] 0.621 to 0.804) for CAAS vFFR and 0.886 (95% CI 0.807 to 0.940) for contrast QFR (cQFR).

There were insufficient data to do any subgroup or sensitivity analyses for CAAS vFFR.

QAngio QFR

The EAG did a meta-analysis of the included studies, focusing on the diagnostic accuracy of QAngio QFR to detect lesions or vessels needing intervention (defined as having an FFR of 0.8 or less). Two approaches were used. The primary analysis consisted of a meta-analysis of reported diagnostic accuracy data from studies in which these data were reported, or could be derived from reported estimates of sensitivity and specificity. The secondary analysis used a data extraction approach in which FFR and QAngio QFR values from published plots were extracted and used to calculate diagnostic accuracy. This second approach allowed for a wider range of analyses.

Primary analysis

The EAG identified 26 studies with sufficient diagnostic accuracy data to be included in the primary meta-analysis. Both univariate and bivariate meta-analyses of sensitivity and specificity were done and compared and these were divided into 3 modes of QAngio QFR: fixed-flow QFR (fQFR), contrast QFR (cQFR) and studies in which the type of QAngio QFR was not specified. Most studies included in the primary analysis used FFR as the reference standard, using a cut-off of 0.8, although 1 study used iFR as the reference standard. The EAG noted that there was no evidence of difference between cQFR and fQFR.

In the univariate meta-analysis for the random-effect analysis, QAngio QFR at a cut-off of 0.8 had good diagnostic accuracy to predict FFR (also at a cut-off of 0.8). cQFR had a sensitivity of 85% (95% CI 78 to 90) and specificity of 91% (95% CI 85 to 95); fQFR had a sensitivity of 82% (95% CI 68 to 91) and specificity of 89% (95% CI 77 to 95). Studies that did not specify the mode of QAngio QFR had a sensitivity of 84% (95% CI 78 to 89) and specificity of 89% (95% CI 87 to 91). The results are summarised in figures 1 and 2.

Figure 1 Univariate meta-analysis of sensitivity

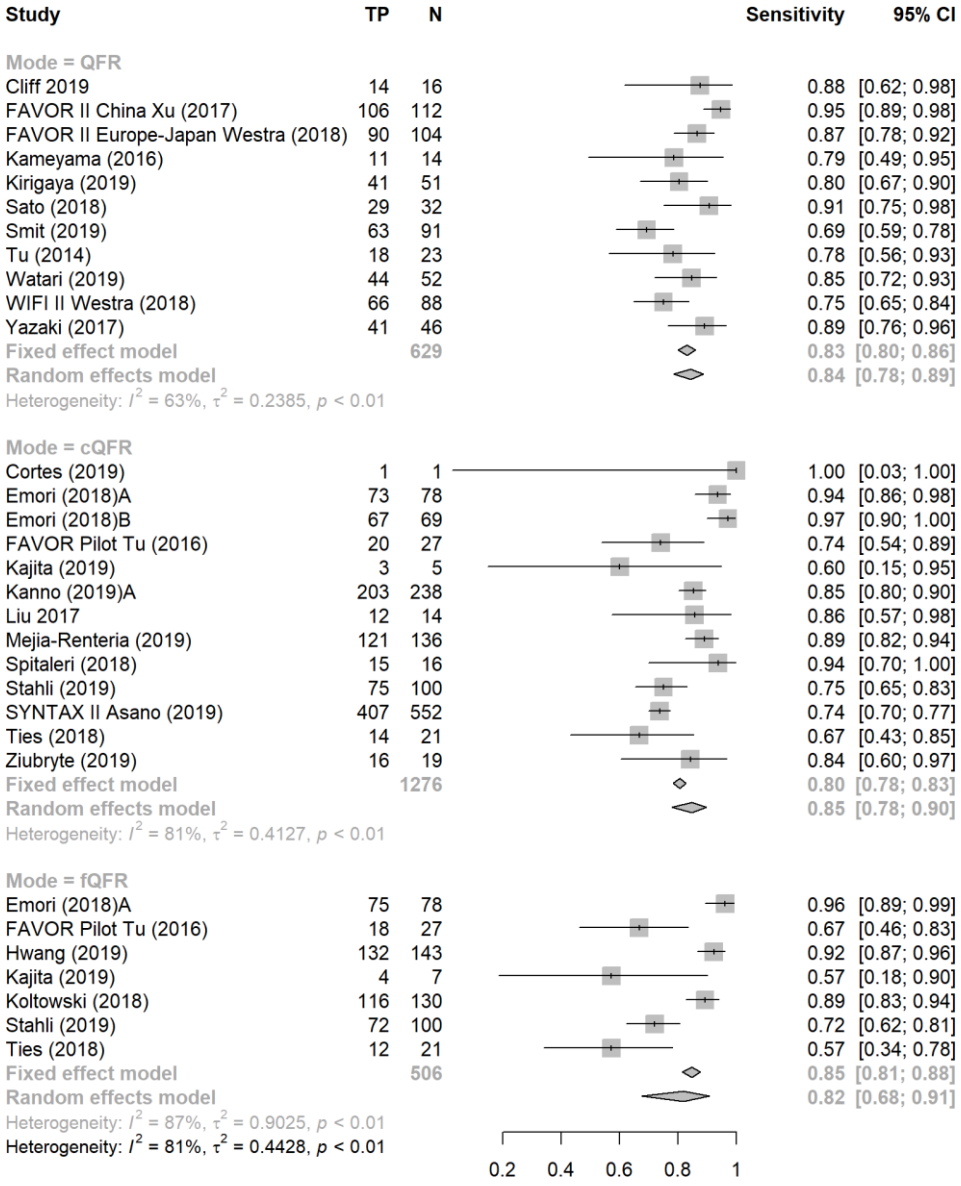
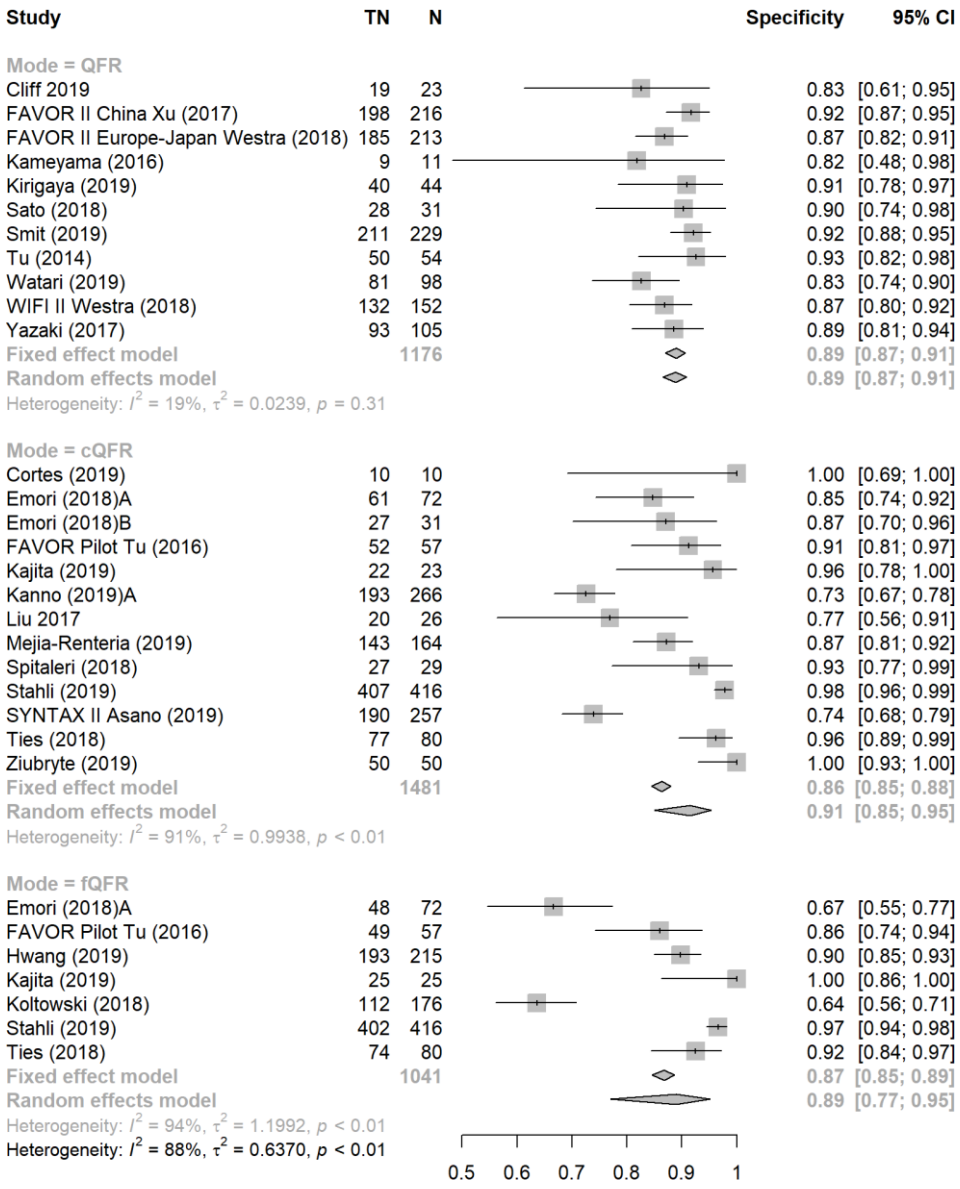


Figure 2 Univariate meta-analysis of specificity



Summary positive predictive values were 77% (95% CI 69 to 83) for fQFR, 85% (95% CI 80 to 89) for cQFR and 80% (95% CI 76 to 84) for non-specified QAngio QFR (see figure 27 in the appendix of the diagnostics assessment

report). Summary negative predictive values were 92% (95% CI 89 to 94) for fQFR, 91% (95% CI 85 to 94) for cQFR and 91% (95% CI 87 to 93) for non-specified QAngio QFR (see figure 28 in the appendix of the diagnostics assessment report).

The results of the bivariate meta-analysis were almost identical to the univariate analyses, with no evidence of difference between fQFR and cQFR (see pages 59 to 60 of the diagnostics assessment report). The results of this analysis are summarised in table 3.

Table 3 Results of bivariate meta-analysis

Mode	Sensitivity	95% confidence intervals	Specificity	95% confidence intervals
cQFR	84.32	77.29 to 89.48	91.4	84.96 to 95.24
fQFR	81.61	66.97 to 90.66	89.43	77.58 to 95.38
Non-specified QFR	84.25	78.51 to 88.68	88.95	87.02 to 90.61
cQFR or non-specified QFR	84.34	80.04 to 87.85	89.80	86.36 to 92.45

Abbreviations: QFR, quantitative flow ratio; cQFR, contrast QFR; fQFR, fixed-flow QFR

Because both FFR and QAngio QFR are continuous measurements, it is also important to consider the agreement between FFR and QAngio QFR, in terms of the mean difference between them, and their correlation. A meta-analysis was done of the reported mean differences between FFR and QAngio QFR measurements and reported correlations.

The mean difference between QAngio QFR and FFR was almost exactly zero for all 3 modes of QAngio QFR testing (see figure 31 in the appendix of the diagnostics assessment report). For fQFR the mean difference was 0 (95% CI -0.05 to 0.06), for cQFR the mean difference was -0.01 (95% CI -0.06 to 0.04) and for non-specified QAngio QFR the mean difference was 0.01 (95% CI -0.03 to 0.05). FFR and QAngio QFR were highly correlated in all studies with

correlation coefficients of 0.78 (95% CI 0.72 to 0.82) for fQFR, 0.78 (95% CI 0.70 to 0.85) for cQFR and 0.79 (95% CI 0.73 to 0.83) for non-specified QAngio QFR (see figure 32 in the appendix of the diagnostics assessment report).

Secondary analysis

In this analysis the diagnostic accuracy for each study was calculated based on extracted data, using the index test of QAngio QFR of 0.8 or less and the reference standard of FFR of 0.8 to define need for coronary intervention. Overall, 30 studies reported either 2×2 table data or data that could be extracted from a figure. Nine studies did not present an extractable figure, and 3 studies presented a figure, but no summary data. The secondary analysis allowed for a wider range of analyses, such as considering different QAngio QFR and FFR cut-offs, and the effect of using a grey zone, in which patients with intermediate QAngio QFR values (between 0.78 and 0.84) go on to have confirmatory FFR.

A bivariate meta-analysis of diagnostic accuracy using data extracted from figures gave summary estimates for sensitivity and specificity of 84.6% (95% CI 80.7 to 87.8) and 87.2% (95% CI 83.4 to 90.3), respectively. This was similar to the results from the primary analysis when cQFR and non-specified QFR were combined.

QFR, as measured by QAngio, was highly correlated with FFR (r=0.8). In 50% of patients, QFR and FFR differed by no more than 0.04. In 95% of patients, values differed by no more than 0.1.

Grey-zone analysis

In the grey zone analysis:

- If QAngio QFR is more than 0.84: continue without stenting or bypass and defer FFR (test negative).

- If QAngio QFR is 0.78 or less: proceed directly to stenting or bypass without FFR (test positive).
- If QAngio QFR is between 0.78 and 0.84: do an FFR and proceed based on that result (at 0.8 cut-off).

This strategy increased diagnostic accuracy compared with using QAngio QFR alone. The sensitivity was 93.1% (95% CI 90.1 to 94.9) and the specificity was 92.1% (95% CI 88.3% to 94.5%). A total of 20.1% of patients were in the grey zone and would have confirmatory FFR. However, only 30.4% of patients with QAngio QFR results in the grey zone had results that differed from their FFR.

ICA

Primary analysis

The EAG identified 5 studies included in the meta-analysis that also reported 2×2 table data on the diagnostic accuracy of using 2D or 3D ICA alone. These studies used 50% diameter stenosis as the cut-off and FFR of 0.8 or less as the reference standard. Given the small number of studies, and because 2D and 3D ICA may have very different performance, no bivariate meta-analysis of these data was done. However the results of the individual studies showed that the diagnostic accuracy of ICA was significantly inferior to QAngio QFR.

Secondary analysis

To inform the economic analysis, the EAG did an additional pragmatic search for studies that compared 2D ICA with FFR assessment. This search identified 4 studies that had sufficient granular data (such as scatter plots or Bland-Altman plots) from which ICA and FFR data could be extracted. Compared with QAngio QFR, the correlation of 2D ICA with FFR was much weaker (correlation coefficient -0.432). A bivariate meta-analysis of these extracted data produced summary sensitivity and specificity estimates of 62.6% (95% CI 51.5 to 72.5) and 61.6% (95% CI 53.1 to 69.4), respectively. This is a substantially lower diagnostic accuracy than QAngio QFR.

Other intermediate outcomes

Test failure

A total of 16 studies did not report patient exclusion rates or reasons for exclusion. Exclusion rates varied widely, partly because of differences in patient selection criteria, reporting and methods of calculating exclusion rates. This limited the comparability of exclusion rates across the studies.

The most reported (15 studies) causes of exclusion were issues with image acquisition and quality (for example, lack of at least 2 projections with a 25 degree angle in between, or poor image quality). The second most reported reason for exclusion was anatomical features of arteries (for example, excessive overlapping or foreshortening, ostial lesions, severe tortuosity).

Exclusion rates were higher overall in retrospective studies (median 28%, range 6% to 92%) compared with prospective studies (median 17%, range 7% to 52%). This may be partly explained by the fact that ICA images in retrospective studies were less likely to have been collected following manufacturer instructions to acquire images suitable for QAngio QFR.

There were only 2 retrospective CAAS vFFR studies that reported exclusion rates, and these were both high at 63% and 65%. In both studies most exclusions were because of angiographic image processing issues (rather than directly because of CAAS vFFR). In ILUMIEN I, 83% of exclusions were because of a lack of at least 2 angiographic projections, table movement during ICA or pixel resolution incompatibility. ILUMIEN I concluded that careful adaptions in acquisitions of ICA images could reduce test failure.

The full list of exclusion rates and reasons for exclusion are shown in table 82 in the appendix of the diagnostics assessment report.

Variability

There were 8 studies that reported outcomes data on reproducibility of QAngio QFR readings between 2 different analysts (inter-observer variability). One directly compared QAngio QFR and CAAS vFFR, 6 evaluated QAngio QFR only and 1 evaluated CAAS vFFR only. QAngio QFR was found to have a moderate to high level of inter-observer reliability.

There were 8 studies that reported outcomes data on intra-observer reproducibility of QAngio QFR readings. Of these, 7 evaluated QAngio QFR only and 1 directly compared QAngio QFR and CAAS vFFR. All reported measurements were done retrospectively. The time gap between initial and repeated measurements was reported in 4 studies and ranged from 3 days to 2 weeks. Most studies reported a high level of intra-observer reliability for QAngio QFR. Further details on test variability are described in the diagnostics assessment report (pages 83 to 84).

Timing

There were 6 studies of QAngio QFR that reported measuring the time needed to complete QFR analysis. Of these studies, 2 were prospective and 1 was a conference abstract. Sample sizes ranged from 68 to 268 patients. The methods used for calculating the time to QFR acquisition varied between studies, with only 2 studies including the time taken to select appropriate images for 3D image generation.

Time to QFR data acquisition ranged from an average of 2 minutes 7 seconds to 10 minutes (standard deviation 3 minutes). One study of 268 patients reported that time to image acquisition significantly decreased with the number of ICAs analysed, from 5 minutes 59 seconds to 2 minutes 7 seconds between the first and last 50 patients. Further details are available in table 83 in the appendix of the diagnostics assessment report.

Clinical effectiveness

Morbidity, mortality and major adverse events

There were 3 cohort studies that reported mortality or major clinical outcomes in eligible patients with QAngio QFR measurements. All found that a clinically significant QAngio QFR was associated with a higher incidence of long-term major cardiovascular adverse events. No data were reported for CAAS vFFR.

Spitaleri et al. (2018) included patients with multivessel disease who had revascularisation as part of a large randomised trial of percutaneous coronary intervention (PCI). The trial included 1,498 ST-elevation myocardial infarction (STEMI) patients in whom at least 1 non-culprit lesion was left untreated. QAngio QFR was calculated in non-culprit lesions in a subgroup of 110 patients after revascularisation. Patients with QAngio QFR values of more than 0.80 in all non-culprit lesions were classified as having functional complete revascularisation (n=54), and those with at least 1 non-culprit lesion with QAngio QFR of 0.80 or less were classified as having functional incomplete revascularisation (n=56). Patient-oriented cardiac events, defined as cumulative occurrence of all-cause death, any myocardial infarction, and any coronary revascularisation, were measured at 5-year follow up. Patient-oriented cardiac events were higher in the group with QAngio QFR of 0.80 or less (46%) compared with the group with QAngio QFR of more than 0.80 (24%; HR 2.3 [95% CI 1.2 to 4.5], p=0.01).

Kanno et al. (2019 B) evaluated de novo intermediate coronary lesions in 212 patients with deferred revascularisation based on FFR values above 0.80. Baseline and physiological indices including cQFR were compared between patients with and without a major adverse cardiovascular event (MACE). MACE incidence at 4-year follow up was 5.7%. In patients with MACE, cQFR was lower than in patients without MACE (mean or median 0.80 compared with 0.88, p=0.030). On logistic regression analysis, cQFR of 0.8 or less was a significant predictor of MACE (OR 5.60, 95% CI 1.69 to 18.6, p=0.005).

Hamaya et al. (2019) included a population of 549 patients with stable 3-vessel disease who had cQFR. At a median 2.2-year follow up, patients with MACE had lower cQFR in all 3 vessels than those without MACE (2.76 [95% CI 2.64 to 2.88] compared with 2.64 [95% CI 2.49 to 2.73], p<0.001). Also, 3-vessel cQFR was a statistically significant predictor of MACE in multivariate analyses (HR 0.97, 95% CI 0.96 to 0.99). cQFR was also a better predictor of remote revascularisation (3 months or more) compared with percentage diameter stenosis (AUC 0.73, 95% CI 0.65 to 0.79 compared with AUC 0.66, 95% CI 0.56 to 0.74, p=0.043).

Subsequent use of invasive pressure-wire FFR

No studies of QAngio QFR prospectively evaluated the impact of QFR use and subsequent reductions in use of adenosine and pressure-wire FFR procedures. However, 5 studies included in the diagnostic accuracy review retrospectively derived a grey-zone strategy based on their diagnostic accuracy results to model a potential reduction in adenosine and FFR use. These results are summarised in table 4.

Table 4 Adenosine and FFR procedures reduced: grey-zone strategy models from included studies

Study	Grey zone	Diagnostic accuracy of grey-zone strategy (QFR vs. FFR)	Percentage of adenosine or FFR procedures avoided
FAVOR II Europe-Japan Westra (2018)	0.77–0.86	Sensitivity and specificity >95%	64%
Kanno (2019) (A) (conference abstract)	0.73–0.84	Positive predictive value and negative predictive value >90%	52%
Mejia-Renteria (2019)	0.74–0.84	>95% agreement	59%
Smit (2019)	0.77–0.86	Sensitivity: 95%, specificity: 92.5%	61%
WIFI II	0.78–0.87	Sensitivity and specificity >90%	68%
WIFI II	0.71–0.90	Sensitivity and specificity >95%	42%

Abbreviations: QFR, quantitative flow ratio; FFR, fractional flow reserve

Simulation study of clinical effectiveness

Because of the lack of published data on QAngio's clinical effectiveness, the EAG did a simulation study to investigate its possible impact on coronary outcomes, compared with FFR.

The sample population was taken to be the data extracted from published Bland-Altman figures. For this analysis fQFR data were excluded. Only cQFR or non-specified QAngio QFR data were used, for 3,193 patients, each with an FFR measurement and its associated QAngio QFR measurement. To predict coronary outcomes, the results of the recent IRIS-FFR registry report were used. This represented 5,846 patients who were either revascularised (stent or bypass surgery) or deferred (continued with current management without surgery) based on their measured FFR result.

The IRIS-FFR study used MACE as its primary outcome. The reported hazard of MACE events by FFR value was used to estimate the risk for each person in the extracted data. Based on those risks it was simulated whether each person had a MACE event if they were deferred or if they were revascularised. The EAG assumed that risk was solely a function of FFR values, and that knowing the QAngio QFR had no impact on risk of MACE events.

Three strategies for deciding whether to revascularise were investigated:

- FFR only: do FFR for all and revascularise if FFR is 0.8 or less.
- QAngio QFR only: do QAngio QFR for all and revascularise if QAngio QFR is 0.8 or less, without measuring FFR.
- Grey zone: do QAngio QFR for all and:
  - revascularise if QAngio QFR is 0.78 or less
  - defer if QAngio QFR is more than 0.84
  - if QAngio QFR is between 0.78 and 0.84, do FFR and revascularise if FFR is 0.8 or less.

If using the FFR only strategy 40.2% of patients would be revascularised. Using the QAngio QFR only strategy 42.0% would be revascularised, and using the grey-zone strategy 43.2% would be revascularised. Using QAngio QFR therefore moderately increased the revascularisation rate, and using it with a grey zone increased it further. The key results of the simulation study are shown in table 5 as median values across all simulations.

Table 5 Key results of the simulation study

Strategy	% with MACE	% with prevented MACE	% with MACE caused by revascularisation	% with unprevented MACE	Number of revascularisations per MACE prevented
FFR only	1.75	1.60	0.91	0.78	25.18
QFR only	1.85	1.57	0.97	0.81	26.80
Grey zone	1.82	1.63	1.00	0.75	26.50

Abbreviations: FFR, fractional flow reserve; QFR, quantitative flow ratio; MACE, major adverse cardiac event

These simulations suggest that using FFR may prevent slightly more MACE, at around 1 event per 1000 patients, but the overlap in simulated distributions means it is highly uncertain whether the difference is genuine. By contrast, the simulation suggests that QAngio QFR increases the number of revascularisations performed, without substantially improving the number of MACE prevented. Overall these simulations suggested that there was little conclusive clinical difference between using QAngio QFR and FFR to make revascularisation decisions.

The simulation study has numerous limitations because of its assumptions. Most important was that the risk of MACE depends only on a patient's FFR. The simulation could not account for any other key patient factors, and there is the possibility that knowing the QAngio QFR as well as FFR might alter the predicted risk. The IRIS-FFR study risks may not match the risks in the UK population eligible for FFR or QAngio QFR. Also, the simulation is based only on the data extracted from figures, which is a small sample and may not represent the patients seen in practice. The simulation also only considers a single lesion per patient, when QAngio QFR may be used to assess multiple stenoses in a patient.

2.2 Costs and cost effectiveness

The EAG did a search to identify studies investigating the cost effectiveness of using QAngio XA 3D/QFR (QAngio QFR) and CAAS vFFR imaging software to assess the functional significance of coronary stenosis during invasive coronary angiography. The EAG also constructed a de novo economic model to assess the cost effectiveness of the different testing strategies.

Systematic review of cost-effectiveness evidence

No studies were found that evaluated the cost effectiveness of either QAngio QFR or CAAS vFFR imaging software. Therefore, a review of published cost-effectiveness studies evaluating ICA (alone or with FFR) in managing coronary artery disease was done.

Study selection

Cost-effectiveness studies published after 2000 in which ICA (alone or with FFR) was one of the interventions under comparison were considered for inclusion. Only cost-effectiveness, cost-utility and cost-benefit analyses were considered eligible. The patient population was defined as patients with stable angina and suspected or known coronary artery disease. Studies in patients with acute coronary syndromes and non-ST elevation myocardial infarction (NSTEMI) as the primary diagnosis were excluded.

Results of the review of decision models evaluating ICA

The review identified 21 relevant studies. A formal assessment using checklists to assess the quality of the included cost-effectiveness studies was not done. Instead, the EAG did a narrative review of key model features, including testing and management strategies, and assumptions to support the development of a de novo analytical model.

Most studies used a decision tree to model the diagnostic pathway and short-term outcomes, and a long-term Markov model (or multiple Markov models) to characterise disease progression. Of the 21 studies, 2 models (Walker et al.

2011 and Genders et al. 2015) were good examples of alternative ways to evaluate diagnostic strategies in patients with suspected stable angina. Each study used a different approach to model the diagnostic pathway and subsequent long-term risks of major cardiovascular related events and associated costs and outcomes.

Walker et al. (2011) used a cohort model that estimated outcomes for an average patient in clinical practice. The model consisted of a decision tree and Markov model structure to evaluate the cost effectiveness of 8 alternative testing sequences. The model transition probabilities were based on risk prediction equations and patient covariates from a previously published model on angina. This allowed estimation of the occurrence of a primary cardiovascular event (with risk conditioned on factors such as age and sex) and of subsequent events based on surviving a first cardiovascular event.

Genders et al. (2015) used a microsimulation model comprising a decision tree and a lifetime state transition model to assess the cost effectiveness of invasive and non-invasive testing strategies for patients with stable angina. The model estimated outcomes for hypothetical patients at different levels of disease severity (defined in terms of the number of coronary vessels affected and whether patients had ischaemia). The estimated outcomes were the risk of primary and subsequent cardiovascular events based on the rates of major cardiac adverse events from the literature.

Further details of these 2 models are described on pages 95 to 103 in the diagnostics assessment report. The modelling approaches identified in these studies were used to develop a de novo economic model.

Economic analysis

The EAG developed a de novo economic model. It was designed to estimate the cost effectiveness of using QAngio QFR and CAAS vFFR during ICA to assess the functional significance of coronary stenosis in patients with stable angina whose angiograms showed intermediate stenosis. The cost

effectiveness of the software was compared with invasive FFR or iFR measurement or clinical decision making based on visual interpretation of ICA alone, alongside clinical judgement, in the NHS. Five diagnostic strategies were considered:

- strategy 1: ICA alone
- strategy 2: ICA followed by confirmatory FFR or iFR (reference standard)
- strategy 3: ICA with QAngio QFR
- strategy 4: ICA with QAngio QFR, followed by confirmatory FFR or iFR if QFR is inconclusive
- strategy 5: ICA with CAAS vFFR.

Model structure

The model consisted of a diagnostic model and a prognostic model. The diagnostic model was used to link the diagnostic accuracy of QAngio QFR and CAAS vFFR to short-term costs and consequences. These included the effect on the proportion of patients needing revascularisation, the proportion of patients needing invasive functional assessment of stenosis using FFR or iFR in strategy 4, and adverse event rates and health-related quality of life associated with the diagnostic interventions. There were slight differences in the decision tree structures, reflecting the possible test result outcomes for the 5 different diagnostic strategies (see pages 111 to 112 of the diagnostics assessment report).

Strategies 1, 3 and 5 had 4 possible results (true positive, false negative, false positive and true negative) based on the diagnostic accuracy of the tests relative to the reference standard. Strategy 2 was the reference standard test, with assumed perfect sensitivity and specificity, and therefore had only 2 possible test results (true positive and true negative). Strategy 4 was the hybrid approach of QAngio QFR with 4 possible test results (true positive, false negative, false positive and true negative) if QFR was conclusive. In this strategy, if QFR was inconclusive (grey zone) there were only 2 possible

outcomes (true positive and true negative) because patients have confirmatory FFR or iFR. The decision tree structures used for the different strategies are shown in figures 3 to 5.

The diagnostic model assumed that all tests in each strategy are done at the same appointment, and that revascularisation procedures are either done immediately after testing or without a delay that might cause the patient's condition to deteriorate. The EAG noted that this base-case analysis was more representative of an interventional setting.

The proportion of patients starting in the health states in the prognostic model was based on the expected proportion of tests with positive and negative results in the population.

The prognostic model was used to link the short-term consequences to longer-term costs and consequences (for example, the risk of major adverse cardiovascular events including myocardial infarction, sudden cardiac death and need for urgent or unplanned revascularisations). This would ensure that differences in costs, life years gained and quality-adjusted life years (QALYs) were appropriately quantified over a lifetime time horizon. The structure of the prognostic model is shown in figure 6.

Outcomes in the model were expressed as QALYs. The model evaluated costs from the perspective of the NHS and personal social services, expressed in UK pounds sterling at a 2018/19 price. A discount rate of 3.5% was applied to both costs and outcomes.

Figure 3 Diagnostic model used in strategies 1, 3 and 5

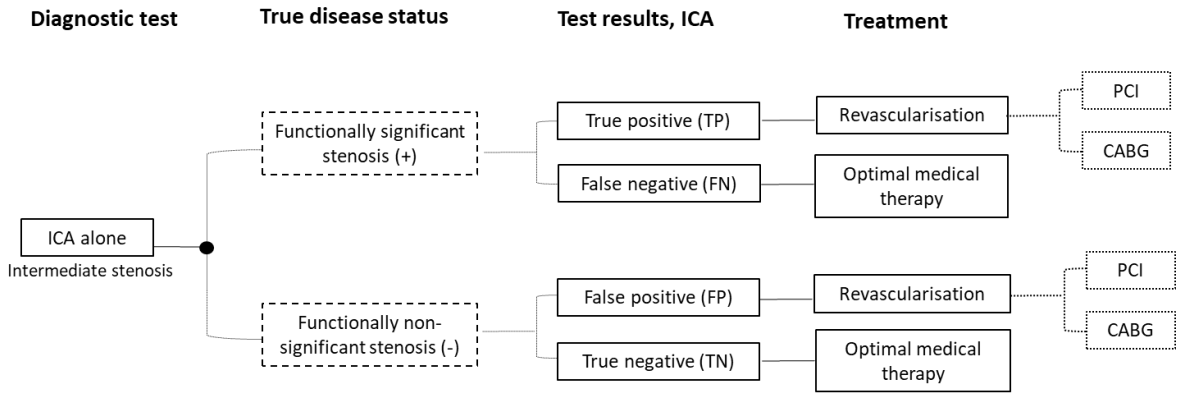


Figure 4 Strategy 2 of ICA, followed by confirmatory FFR or iFR

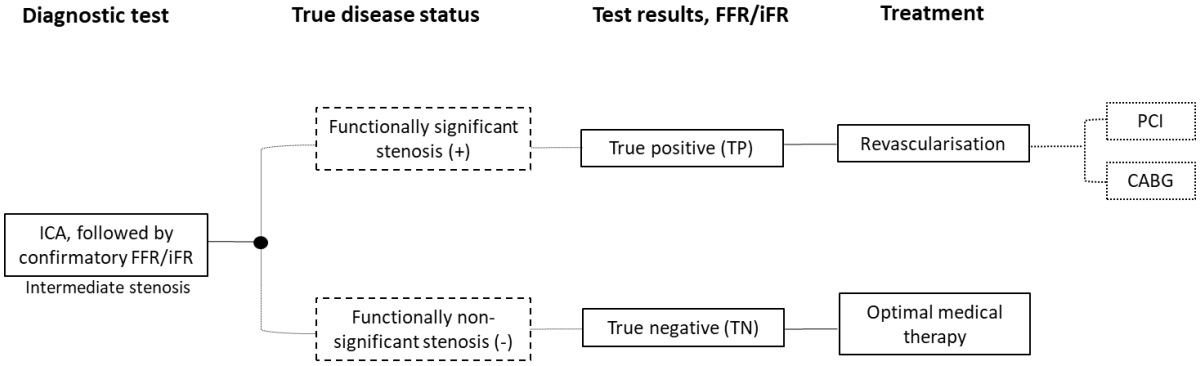


Figure 5 Strategy 4 of ICA with QFR, followed by confirmatory FFR or iFR when QFR is inconclusive

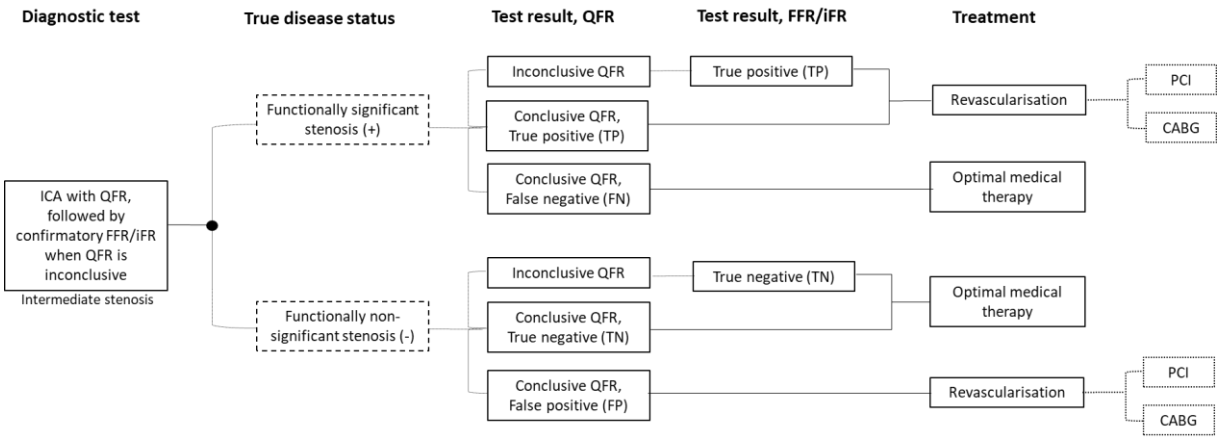
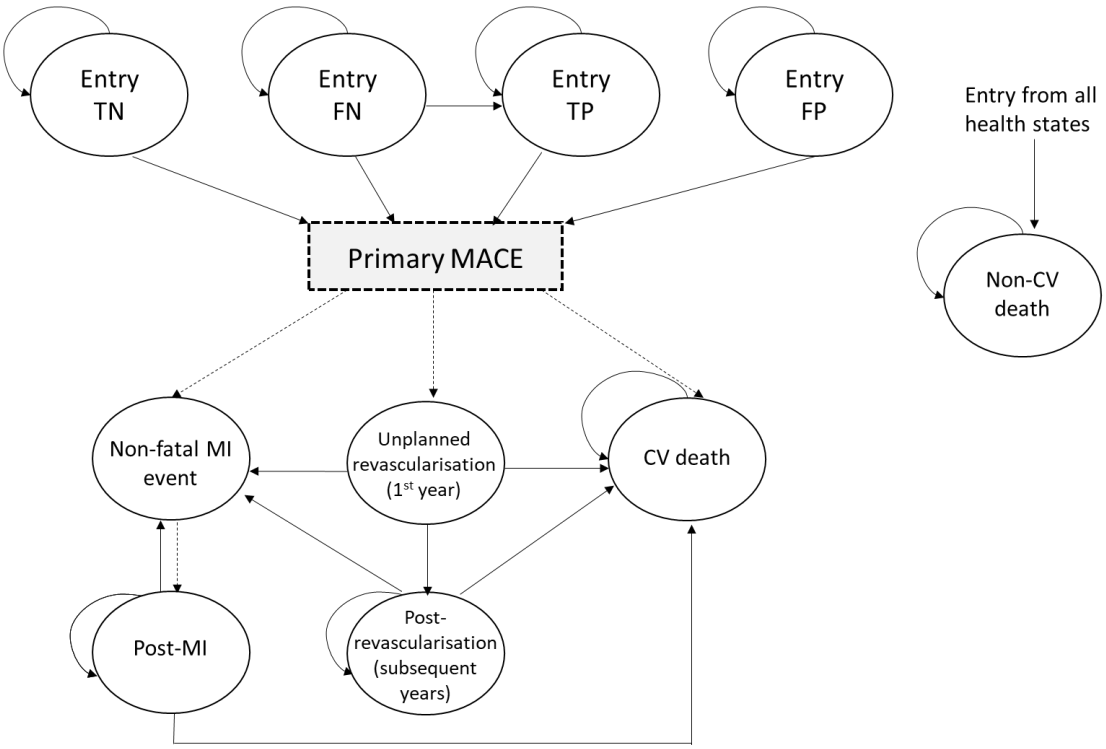


Figure 6 Schematic of prognostic model



Model inputs

Estimates for the model input parameters were obtained from the literature and from consulting experts. The diagnostic accuracy estimates were derived from the systematic review component of the assessment. The population consisted of patients with stable CAD whose angiograms taken during ICA showed intermediate stenosis. The age and sex distribution of the population was derived from the IRIS-FFR registry (mean age of 64 years and 72% men).

The prevalence of functionally significant stenosis in the population was based on studies that reported values of FFR and cQFR or non-specified QFR. It was assumed that the population in these QAngio QFR studies reflected the UK population. This suggested a prior likelihood of functionally significant stenosis of 40.2%, based on the proportion of people in the studies who had an FFR measurement of 0.8 or less.

To estimate the average annual patient throughput per centre, assumptions about patient eligibility for testing with FFR/iFR were combined with data from the British Cardiovascular Intervention Society audit return. This gave an assumed average annual throughput of 200 patients per centre in the base-case analysis. Alternative throughput assumptions were considered in the scenario analysis.

The base-case scenario assumed all diagnostic procedures took place in an interventional setting. The diagnostic-only setting was considered in scenario analyses.

Diagnostic accuracy

The model considered the diagnostic accuracy of ICA, QAngio QFR and CAAS vFFR, while FFR/iFR was the reference standard test with 100% sensitivity and specificity.

The proportion of people testing positive or negative when tested using the QAngio QFR or CAAS vFFR (strategies 3 and 5) was based on the estimated accuracy of the 2 tests. The diagnostic accuracy estimates for these 2 strategies are shown in table 6.

Table 6 Diagnostic accuracy estimates for QAngio QFR and CAAS vFFR

Test	Strategy	Analysis	Sensitivity	Specificity	Source
QAngio	3	Base case	84.34%	89.80%	Bivariate meta-analysis for combined cQFR and non-specified QFR mode
QAngio	3	Scenario	84.32%	91.40%	Bivariate meta-analysis for cQFR mode
QAngio	3	Scenario	81.61%	84.93%	Bivariate meta-analysis for fQFR mode
CAAS vFFR	5	Base case	97.00%	74.00%	FAST EXTEND (2019)
CAAS vFFR	5	Scenario	75.00%	46.50%	ILUMIEN I (2019)
CAAS vFFR	5	Scenario	68.20%	87.30%	Jin et al. (2019)

Abbreviations: QFR, quantitative flow ratio; cQFR, contrast QFR; fQFR, fixed-flow QFR

The diagnostic accuracy of QAngio QFR in strategy 4 was based on the joint distribution of QFR and FFR measurements in the extracted individual-level patient data. The probabilities of QAngio QFR test results being positive (QFR less than 0.78), negative (QFR more than 0.84) or inconclusive (QFR of 0.78 to 0.84) are shown in table 7.

Table 7 QAngio QFR diagnostic accuracy estimates for strategy 4

QAngio test result	Probability	Functionally significant stenosis (FFR≤0.80)	Non-significant stenosis (FFR>0.8)
Positive	QFR<0.78	0.744	0.095
Inconclusive (grey zone)	0.78≤ QFR ≤0.84	0.188	0.212
Negative	QFR>0.84	0.069	0.693

Abbreviations: QFR, quantitative flow ratio; FFR, fractional flow reserve

ICA diagnostic accuracy estimates are shown in table 8.

Table 8 Diagnostic accuracy estimates for ICA

Test	Analysis	Sensitivity	Specificity	Source
ICA	Base case	62.61%	61.59%	Bivariate meta-analysis of 6 studies (4.7.4 in the diagnostics assessment report)
ICA	Scenario	71.00%	66.00%	Danad et al. (2017) per vessel analysis

Abbreviations: ICA, invasive coronary angiography

Procedural adverse events

Procedures involving catheterisation for diagnostic testing (ICA and FFR/iFR) or revascularisation (percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]) have associated complications that may result in healthcare resource and health-related quality-of-life loss. The diagnostic model considered the impact of serious procedural complications from FFR/iFR and revascularisation. However, the procedural complications of ICA were excluded because all patients had this procedure in all strategies. The diagnostic pathway distinguished between complications associated with invasive testing (FFR/iFR) and revascularisation so that the potential benefits of less invasive testing could be captured.

Three studies that reported procedural complication rates were suitable to inform those associated with FFR/iFR alone: the RIPCORD trial, the placebo arm of the ORBITA trial and the IRIS-FFR registry. The rates of serious events reported in the 3 studies are summarised in table 19 of the diagnostics assessment report (page 121).

Data from the IRIS-FFR registry were used to inform the base-case analysis because this was considerably larger than the trials and was used as a source of baseline clinical effectiveness in the prognostic model. A scenario analysis used the alternative source of data from RIPCORD because this was a UK study and the patient population appeared comparable to that of the base-case population (mean age 64 years and 75% men).

The rates of FFR/iFR procedural complications applied in the base-case analysis are summarised in table 9.

Table 9 Rates of FFR/iFR procedural complications in the model

Serious procedural complication	Rate	Source
Coronary dissection	0.03%	IRIS-FFR registry
Venous occlusion	0%	IRIS-FFR registry
Ventricular arrhythmia	0.02%	IRIS-FFR registry
Conduction disturbance needing treatment	0.03%	IRIS-FFR registry
Bronchospasm	0.02%	IRIS-FFR registry
Thrombus formation	0.01%	IRIS-FFR registry
Death	0.015%	Fearon et al. (2003)

Complications due to revascularisation

Death was the most common revascularisation complication reported in the cost-effectiveness review. The IRIS-FFR registry does not report procedural complications associated with revascularisation separately from the risk of a major adverse cardiac event (MACE). The rate of procedural deaths associated with revascularisation was sourced from UK audit data, which gives a 0.99% death risk for non-emergency CABG and 0.17% for PCI. The mortality rate associated with revascularisation was estimated as a weighted average of the mortality rates for PCI and CABG, relative to the proportion of PCI and CABG procedures. In the base case, 87% of revascularisation procedures were assumed to be PCI, and 13% were CABG based on British Cardiovascular Intervention Society audit returns.

Other procedural adverse events

Patients who have cardiac catheterisation are exposed to ionising radiation, which may increase the lifetime risk of malignancy and associated mortality. QAngio QFR or CAAS vFFR may reduce radiation exposure by reducing the procedural time compared with FFR/iFR. However, radiation exposure with FFR/iFR is very low and the reduced exposure through using QAngio QFR or

CAAS vFFR is expected to be marginal. Therefore, the impact of radiation exposure on cost effectiveness was not quantified in the model.

Risk of MACE

The benefits of treatment, by correctly identifying patients whose condition is suitable for revascularisation or optimal medical therapy, were modelled through the impact on risk of MACE and health-related quality of life. The baseline risk of MACE in the absence of revascularisation depends on disease severity as measured by FFR/iFR.

The reported 1-year and long-term (up to 3 years) cumulative incidence of MACE in the IRIS-FFR registry for deferred lesions is used in the model to estimate the baseline risk of MACE for the first year and subsequent years. The baseline risk of MACE used in the model for people in the group with the highest FFR values (FFR values of 0.91 or more) was 0.64% in the first year and 0.32% per year in subsequent years. This risk was used as a reference to compute the baseline risk of MACE components in categories with lower FFR values (less than 0.91), using the adjusted hazard ratios of 1.06, 1.09 and 1.07 per 0.01 decrease in FFR for cardiac death, myocardial infarction and revascularisation, respectively.

Treatment effects of revascularisation

The treatment effect of revascularisation on MACE in patients with stable CAD is highly uncertain. The largest and most recent ISCHEMIA trial, which included UK centres, aimed to address the limitations of previous trials. It determined whether revascularisation plus optimal medical therapy compared with optimal medical therapy alone reduced the primary composite outcome of death from cardiovascular causes, myocardial infarction, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest in patients with stable ischaemic heart disease with moderate or severe ischaemia. The trial did not find evidence that revascularisation reduced the risk of MACE. Therefore, in the base-case analysis, by identifying the appropriateness for revascularisation, the diagnostic tests confer no benefit on MACE outcomes.

Health-related quality of life

In the diagnostic model a one-off utility decrement was applied for patients having invasive FFR/iFR and for those who had revascularisation (known as procedural disutility). At the end of the diagnostic model, patients who survived entered the long-term prognostic model in 1 of the 4 health states of true positive, false negative, false positive or true negative. A utility value was attached to each of the 4 health states to quantify the effect on health-related quality of life of having treatment in 1 of these states.

In the prognostic model, a one-off utility value was also applied for patients who had a non-fatal myocardial infarction or needed an unplanned revascularisation. A separate utility decrement was applied to the post-myocardial infarction health state, to reflect a decrease in health-related quality of life for those with a history of myocardial infarction. For those who had unplanned revascularisation, the utility value associated with the true positive health state was used, reflecting the assumption that patients had the same benefits of revascularisation in terms of symptom relief as patients who had a successful initial revascularisation procedure.

The base-case analysis made a simplifying assumption that the QALY loss estimate applied for FFR/iFR was representative of both types of pressure wire procedures. One UK study was identified as relevant to inform the procedural disutility of revascularisation (PCI and CABG). The QALY loss estimates associated with each procedure in the diagnostic model are summarised in table 10. The QALY loss associated with revascularisation was also applied in the prognostic model to capture the impact of unplanned revascularisation on health-related quality of life.

Table 10 QALY loss associated with testing and revascularisation procedures

Procedure	Mean QALY loss (95% confidence interval)	Source
ICA	0	Assumed to cancel across strategies
FFR/iFR	0.0056 (0.0051 to 0.0062)	Assumed the same as for PCI
PCI	0.0056 (0.0051 to 0.0062)	Bagust et al. (2006)
CABG	0.033 (0.031 to 0.035)	Bagust et al. (2006)

Abbreviations: ICA, invasive coronary angiography; FFR/iFR, invasive fractional flow reserve or instantaneous wave-free ratio; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; QALY, quality-adjusted life year

All the input parameters for the decision tree and prognostic models are reported in the diagnostics assessment report from page 114.

Costs

For a full breakdown of all test costs, please refer to the diagnostics assessment report, pages 142 to 154.

QAngio QFR costs

The costs of QAngio QFR include the cost of the software license, and training and certification fees. These costs as applied to the base-case analysis are summarised in table 11, with a cost per patient tested of £430.61.

Table 11 Costs of QAngio QFR for an annual throughput of 200 patients

Cost element	Total cost	Cost per patient tested
Software license fee	£84,569.10	£422.85
Training and certification fee	–	–
Training and certification staff costs	£1,552.00	£7.76
Total	£86,121.10	£430.61

CAAS vFFR costs

The costs of CAAS vFFR cost include the cost of the software license, training, and annual maintenance. The costs of CAAS vFFR, broken down by cost element for the base-case analysis, are summarised in table 12, with a cost per patient of £172.18.

Table 12 Costs of CAAS vFFR for an annual throughput of 200 patients

Type of cost	Total cost (online learning)	Total cost (on-site)	Cost per patient tested (average of on-site and online learning)
Software license fee	£31,929.15	£31,929.15	£159.65
Training fee	£215.74	£2,157.38	£5.93
Staff training costs	£440.00	£880.00	£6.60
Maintenance cost	–	–	–
Total	£32,584.89	£34,966.53	£172.18

Invasive coronary angiography and fractional flow reserve costs

The unit costs used to estimate the costs of catheterisation tests currently used in NHS clinical practice were sourced from NHS reference costs 2017/18 and inflated to 2018/19 prices. The model did not consider a cost for ICA because all patients who entered the diagnostic model had this test. The unit cost for FFR/iFR was estimated as the difference between the activity weighted average of the healthcare resource group (HRG) codes for complex and standard cardiac catheterisation (£436.80). This difference represented the incremental cost of FFR/iFR compared with ICA alone. The unit costs used to estimate the cost of FFR/iFR are shown in table 30 of the diagnostics assessment report.

Revascularisation costs

Patients who had a positive test at the last step of each testing strategy had revascularisation with either PCI or CABG. The unit cost for these procedures was sourced from NHS reference costs 2017/18 and inflated to 2018/19

prices. The costs of revascularisation used in the model and the NHS currency codes used to inform these are shown in table 13. The cost per revascularisation was £4,031.22, assuming that PCI and CABG accounted for 87% and 13% of revascularisation procedures, respectively.

Table 13 Costs of revascularisation in the model

Cost category	Currency codes	Unit cost
PCI (base-case assumption)	EY40A-D and EY41A-D, across all HRG codes	£3,005.07
PCI as day case	EY40A-D and EY41A-D, day case	£2,178.95
CABG (base-case assumption)	ED26A-C, ED27A- and EY41A-D, across all HRG codes	£10,898.58

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft

Procedural complication costs

The costs of procedural complications for FFR/iFR were calculated based on the rates of complications shown in table 9. Unit costs were sourced from NHS reference costs 2017/18 and inflated to 2018/19 prices. These are summarised in table 14. Assumptions around these costs can be found in the diagnostics assessment report (page 151).

Table 14 FFR serious procedural complications

Procedural complication	Rate	Source	Unit cost
Coronary dissection	0.03%	IRIS	£3,005.07
Ventricular arrhythmia	0.02%	IRIS	£974.90
Conduction disturbance needing treatment	0.03%	IRIS	£974.90
Thrombus formation	0.01%	IRIS	£928.12
Bronchospasm	0.02%	IRIS	£834.57
Death	0.015%	Fearon et al, 2003	£0

Optimal medical treatment costs

It was assumed that all patients in the prognostic model had treatment with optimal medical therapy for stable angina. NICE's clinical guideline on managing stable angina recommends that patients have either a beta blocker or a calcium-channel blocker alone or together as first line of treatment.

Medication use for each type of treatment was as follows:

- Optimal medical therapy alone for patients who did not need revascularisation (true negative).
- Optimal medical therapy alone for patients who did need revascularisation (false negative).
- Optimal medical therapy for patients who had PCI and/or CABG (true positive).
- Patients who had revascularisation without needing it (false positive) were assumed to have the same medication use as patients who were true positive.

The cost of medication was estimated by combining the proportion of medication use for each type of treatment with unit costs from the BNF. The active substances and dosages selected, as well as the proportion of medication use, were validated by a clinical adviser. Medication use and estimated costs per year of optimal medical therapy depending on clinical management after diagnosis are summarised in table 33 of the diagnostics assessment report (page153). These costs were applied in the prognostic model at each annual cycle.

Health state and clinical event costs

The base-case analysis assumed that only myocardial infarction and unplanned revascularisation events would incur costs. The costs associated with the different health states and clinical events in the prognostic model are summarised in table 15.

Table 15 Health state and clinical event costs

Health state or clinical event	Cost	Source
No event	£0	Assumption
Myocardial infarction	£2,317.53	NHS reference costs 2017/18
Post myocardial infarction	£0	Assumption
Unplanned revascularisation	£4,812.23	NHS reference costs 2017/18
Post unplanned revascularisation	£0	Assumption
Cardiovascular death	£0	Assumption
Other cause of death	£0	Assumption

Analytical methods

The cost effectiveness of the QAngio QFR and CAAS vFFR imaging software used during ICA for assessing the functional significance of a coronary obstruction in patients with intermediate stenosis was evaluated. The total expected costs and QALYs were compared with those obtained using pressure-wire FFR/iFR measurement or visual interpretation of angiographic images alone.

The EAG summarised the cost effectiveness in terms of net benefit rather than an incremental cost effectiveness ratio (ICER). In this analysis, net benefit is estimated using:

$$Net\ Health\ Benefit\ (NHB) = QALYs - \frac{Costs}{Cost - effectiveness\ threshold}$$

The most cost-effective strategy has the highest net health benefit (NHB) when strategies are ranked from highest to lowest NHB.

Base-case assumptions

For decision making, the NHB at a maximum acceptable ICER of £20,000 per QALY gained will be considered. The base-case parameters and their associated sources and assumptions are as follows:

- A diagnostic threshold of 0.8 was used to define functionally significant stenosis for QAngio QFR and FFR.
- A grey-zone boundary of 0.78 to 0.84 for QAngio QFR was used as suggested by the manufacturer of QAngio QFR.
- The baseline risk of MACE in the absence of revascularisation depends on disease severity as measured by FFR, while the distribution of FFR values differs by diagnostic strategy.
- There is no treatment effect of revascularisation on risk of MACE, based on the findings of the ISCHEMIA trial.
- Costs of QAngio QFR and CAAS vFFR were based on an average annual throughput of 200.
- The proportion of revascularisations was assumed to be PCI in 87% of people and CABG in 13%, based on British Cardiovascular Intervention Society audit data.
- Health-related quality-of-life benefits of revascularisation and optimal medical therapy observed at 1 year for the true positive and false negative health states applied for a lifetime duration.
- Procedural disutility associated with FFR was equivalent to that of PCI.

Base-case results

The deterministic and probabilistic cost-effectiveness results for the base-case analysis, expressed in terms of NHB at a maximum acceptable ICER of £20,000 per QALY gained, are shown in tables 16 and 17, respectively. The

incremental NHB was calculated for each strategy compared with ICA alone. The results are consistent for both the deterministic and probabilistic analysis.

Table 16 Deterministic cost-effectiveness results for base-case scenario

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	–	5
2	ICA + FFR	11.096	£4,825	10.855	0.029	1
3	ICA + QAngio QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QAngio QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	3
5	ICA + CAAS vFFR	11.098	£5,118	10.842	0.016	4

*At a maximum acceptable ICER of £20,000 per QALY. Incremental NHB is relative to ICA alone. Abbreviations: ICA, invasive coronary angiography; FFR fractional flow reserve; QFR, quantitative flow ratio; vFFR, vessel-FFR; QALY, quality-adjusted life year; NHB, net health benefit; INHB, incremental NHB

Table 17 Probabilistic cost-effectiveness results for base-case scenario

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank	Probability cost-effective at £20,000/QALY
1	ICA alone	11.039	£4,696	10.804	–	5	0.100
2	ICA + FFR	11.073	£4,825	10.831	0.027	1	0.278
3	ICA + QAngio QFR	11.065	£4,813	10.824	0.020	2	0.218
4	ICA + QAngio QFR + confirmatory FFR (grey zone)	11.070	£5,020	10.819	0.015	4	0.199
5	ICA + CAAS vFFR	11.076	£5,119	10.820	0.016	3	0.204

*At a maximum acceptable ICER of £20,000 per QALY. Incremental NHB is relative to ICA alone. Abbreviations: ICA, invasive coronary angiography; FFR fractional flow reserve; QFR, quantitative flow ratio; vFFR, vessel-FFR; QALY, quality-adjusted life year; NHB, net health benefit; INHB, incremental NHB

Strategy 2 (ICA plus FFR) had the highest NHB and the highest probability of being cost effective, although the differences between all the strategies were small. Strategy 1 (ICA alone) was the cheapest and had the lowest QALY gain, while strategy 5 (ICA plus vFFR) was the most expensive and had the highest QALY gain.

To understand the difference in NHB between the alternative strategies, the disaggregated costs and QALYs from the diagnostic component of the model are shown in table 40 of the diagnostics assessment report (page 167).

The proportion of patients who entered the long-term prognostic model in each of the true negative, false negative, true positive and false positive entry states for each of the alternative strategies (based on the diagnostic accuracy results) are shown in table 18. Strategies 3 and 4 had the highest positive predictive values at 84.4% and 86.8%, respectively. The positive predictive values for strategies 1 (ICA alone) and 5 (vFFR) were lower at 52.3% and 71.5% respectively, and therefore would lead to more unnecessary revascularisations compared with QAngio QFR and FFR. Strategy 2 (FFR), as the reference standard, was assumed to have a perfect positive predictive value.

The difference in QALYs between strategies in the prognostic model was because of the health-related quality-of-life gain associated with true positive results. Therefore, strategies with higher sensitivities (2 and 5) were associated with higher QALY gains. The benefits of revascularisation, in terms of improved health-related quality of life, means that the sensitivity of test results is a more important driver of cost effectiveness than specificity. The base-case cost-effectiveness results were largely driven by the balance between the costs of the diagnostic tests and the costs and benefits of revascularisation.

Table 18 Diagnostic accuracy results by strategy

Strategy	Identification	TN	FN	TP	FP	PPV (%)	NPV (%)	Revascularisations (%)
1	ICA alone	0.368	0.150	0.251	0.229	52.3	71.0	48.0%
2	ICA + FFR	0.598	0.000	0.401	0.000	100	100	40.1%
3	ICA + QFR	0.537	0.063	0.338	0.061	84.8	89.5	39.9%
4	ICA + QFR + confirmatory FFR (grey zone)	0.541	0.028	0.373	0.057	86.8	95.2	43.0%
5	ICA +	0.443	0.012	0.389	0.155	71.5	97.3	54.4%

	vFFR							

Abbreviations: ICA, invasive coronary angiography; FFR fractional flow reserve; QFR, quantitative flow ratio; vFFR, vessel-FFR; TN, true negative; FN, false negative; TP, true positive; FP, false positive; PPV, positive predictive value; NPV, negative predictive value

Analysis of alternative scenarios

Several alternative scenarios were considered to assess the robustness of the base-case results. These are shown in table 36 of the diagnostics assessment report and summarised below.

Diagnostic accuracy alternative scenarios

- Using alternative sensitivity and specificity estimates for QAngio QFR (scenarios 1 to 3).
- Using alternative sensitivity and specificity estimates for CAAS vFFR (scenarios 4 to 6).
- Using alternative sensitivity and specificity estimates for ICA (scenario 7).
- Using an alternative diagnostic threshold for FFR and QAngio QFR (scenario 8).
- Using an alternative definition of the grey zone for strategy 4 (scenario 9).

Risk of major adverse cardiovascular events alternative scenarios

- Baseline risk of MACE independent of FFR and diagnostic test results (scenario 10).
- Treatment effect of revascularisation on MACE (scenarios 11 to 13.)

Costs of diagnostic tests alternative scenarios

- Using an alternative average annual throughput of 100 for QAngio QFR and CAAS vFFR (scenario 14).

Costs of revascularisation alternative scenarios

- Using a lower cost of PCI based on day case costs only from NHS reference costs (scenario 15).

- Using an alternative assumption of the proportion of patients having PCI and CABG (scenario 16).

Health-related quality-of-life alternative scenarios

- Alternative assumptions about the duration of health-related quality-of-life benefits of revascularisation and optimal medical therapy (scenario 17).
- No health-related quality of life benefits associated with treatment based on the findings of the ORBITA trial (scenario 18).
- Higher procedural disutility associated with FFR, equivalent to that of CABG (scenario 19).

Procedural complications associated with FFR alternative scenarios

- No procedural death risk from FFR (scenario 20).
- Adverse event rates from the RIPCORD trial (scenario 21).
- Adverse event rates from the ORBITA trial (scenario 22).

Setting alternative scenarios

- Unit cost of FFR/iFR corresponds to the cost of a complex catheterisation (scenario 23).
- Costs of QAngio QFR and CAAS vFFR based on an average annual throughput of 500 (scenario 24).

The results from the scenario analyses showed that the base-case results were generally robust when alterations were made to the sources of data used in the model and when different assumptions were made. However, sometimes these alterations resulted in significant changes to the NHB rankings of the different strategies.

In the base case, the diagnostic accuracy estimates for vFFR were based on the FAST EXTEND study (sensitivity 97.0% and specificity 74.0%), the largest study of vFFR (330 patients). Accuracy estimates from ILUMIEN I reduced the cost effectiveness of vFFR, but estimates from Jin et al. 2019 increased it. This resulted in vFFR being the second most cost-effective strategy. This

highlighted the substantial uncertainty surrounding the cost effectiveness of vFFR in strategy 5.

When QAngio QFR was considered to have the same diagnostic accuracy as FFR (that is, perfect sensitivity and specificity), the total QALYs and costs for strategy 3 increased by 0.017 QALYs and £6 per patient from the base-case scenario. In this scenario strategy 3 became cost effective with the highest NHB, largely because of greater total QALYs gained for strategy 3 compared with strategy 2. This difference was mainly because of the procedural disutility associated with FFR/iFR.

In a scenario where the procedural disutility of FFR was increased over that used in the base case, the NHB of strategies 2 and 4 were most affected. The total QALYs for both strategies were reduced, resulting in strategy 2 becoming the second least cost effective. In this scenario, strategy 3 was the most cost effective. By varying the procedural disutility associated with FFR, the EAG identified that an FFR disutility of 0.014 QALYs resulted in an equal NHB for strategies 2 and 3. This procedural disutility was 2.5 times greater than that associated with PCI, but less than half the disutility associated with CABG.

In terms of the impact on cost effectiveness of the duration of health-related quality of life, scenario analysis showed that the benefits need to last for at least 7 years to offset the disutility associated with FFR/iFR in the base case for strategy 2 to remain more cost effective than strategy 3.

The benefits of revascularisation, in terms of improved health-related quality of life, suggested that the sensitivity of test results was a more important driver of cost effectiveness than specificity because true positive test results translated into higher QALY gains than mismanagement of false negative test results.

In a diagnostic-only setting, the large additional costs of repeating diagnostic catheterisation at a subsequent appointment in an interventional laboratory for

strategies involving an FFR/iFR measurement (strategies 2 and 4) meant that strategies without this testing component were more cost effective. Strategy 3 (QAngio QFR alone) became the strategy with the highest net benefit, followed by strategy 5 (CAAS vFFR alone).

The other scenario analyses had a lesser impact on the results. Full details of the results of the scenario analyses are available in the diagnostics assessment report (pages 168 to 187).

3 Summary

Clinical effectiveness

The EAG identified 41 studies that matched the inclusion criteria for the review, 39 of which evaluated QAngio QFR and 3 evaluated CAAS vFFR. Only 1 study directly compared QAngio QFR with CAAS vFFR.

A meta-analysis of the QAngio QFR diagnostic accuracy studies showed that QAngio QFR at a cut-off of 0.8 had good diagnostic accuracy to predict FFR (also at a cut-off of 0.8) with sensitivity around 84% and specificity around 89%. This was the case for all 3 modes of QAngio QFR (fQFR, cQFR and non-specified QFR).

QAngio QFR was highly correlated with FFR measured with an invasive pressure wire (r=0.8). In 50% of patients, QAngio QFR and FFR differed by no more than 0.04; in 95% of patients, values differed by no more than 0.1.

When patients with intermediate QAngio QFR values (between 0.78 and 0.84) went on to have confirmatory FFR (the grey zone strategy) diagnostic accuracy increased. Around 20% of patients were in the grey zone and would have confirmatory FFR. Of these, only around 30% have discordant FFR and QAngio QFR results.

Only 5 studies included in the meta-analysis reported the diagnostic accuracy of using 2D or 3D ICA alone. Results of these individual studies indicated that

the diagnostic accuracy of ICA was significantly inferior to QAngio QFR, with diameter stenosis from ICA being poorly correlated with FFR.

The review identified very little reported data on clinical effectiveness and implementation outcomes when using QAngio QFR. Three cohort studies suggested that QAngio QFR results of 0.80 or less may be significant predictors of a subsequent major adverse cardiac event (MACE). QAngio QFR with or without a grey-zone strategy was likely to lead to substantial reductions in adenosine and FFR procedures. Timing of results, inter- and intra-observer reliability were generally acceptable for QAngio QFR, indicating that the technology could be used in a clinical context.

A simulation study found that QAngio QFR may lead to a slight increase in revascularisations (42.0% using QAngio QFR compared with 40.2% using FFR only), but both methods prevented broadly the same number of MACE events. The revascularisation rate was increased further (43.2%) if QAngio QFR was used in a grey-zone strategy but with no improvement in preventing MACE events compared with using FFR alone or QAngio QFR alone.

Diagnostic accuracy data for CAAS vFFR were reported in only 3 studies. Results from these studies were heterogeneous, limiting meta-analysis and a full evaluation of CAAS vFFR. The feasibility of CAAS vFFR in clinical practice was also uncertain, because of a lack of evidence on repeatability within and between observers and the high rate of patient exclusions from retrospective evidence.

Cost effectiveness

The EAG found no studies that evaluated the cost effectiveness of either QAngio QFR or CAAS vFFR imaging software. However, 21 studies were found for ICA (alone or with FFR), 2 of which were used to inform the model. The EAG developed a de novo economic model, consisting of a diagnostic component and a longer-term prognostic component. Five diagnostic strategies were evaluated: ICA alone (strategy 1), ICA with confirmatory

FFR/iFFR (strategy 2), ICA with QAngio QFR (strategy 3), ICA with QAngio QFR, followed by confirmatory FFR/iFR if QFR is inconclusive (strategy 4) and ICA with CAAS vFFR (strategy 5).

The base-case cost-effectiveness results showed that the test strategy with the highest net benefit (most cost-effective strategy) was strategy 2, for a maximum acceptable ICER of £20,000 per QALY gained. However, the difference in net benefit between this strategy and the next best strategies was relatively small at 0.007 QALYs (£140) per patient diagnosed for strategy 3 , 0.012 QALYs (£240) per patient diagnosed for strategy 4, and 0.011 QALYs (£220) per patient diagnosed for strategy 5.

The base-case assumptions were varied in several different scenario analyses. In these scenarios the cost-effectiveness results were robust to the mode of QAngio QFR measurement (cQFR or fQFR), the use of an alternative diagnostic threshold of 0.75 for FFR and QFR, the use of a wider definition of the grey zone for confirmatory FFR/iFFR, throughput assumptions for QAngio QFR and CAAS vFFR, alternative estimates of procedural complication rates for FFR/iFR, and dependency of MACE risk on FFR.

Two scenario analyses also considered a diagnostic-only setting. In this setting, large additional costs of repeating diagnostic catheterisation in an interventional laboratory for strategies involving an FFR/iFR measurement (strategies 2 and 4) favoured the cost effectiveness of strategies without this testing component. Strategy 3 (QAngio QFR alone) became the strategy with the highest net benefit, followed by strategy 5 (CAAS vFFR alone).

The key drivers of cost effectiveness were:

- the sensitivity of the tests (rather than specificity) because true positive results translated into higher QALY gains than mismanagement of false negative results
- the procedural QALY loss associated with FFR/iFR

- the magnitude and duration of the QALY gains associated with revascularisation and
- the additional costs associated with confirmatory testing with FFR/iFR.

4 Issues for consideration

Clinical effectiveness

Most of the studies in the review of diagnostic accuracy evaluated QFR as assessed by QAngio. However, the evidence available on the diagnostic accuracy of CAAS vFFR was limited. This prevented any full meta-analyses of diagnostic accuracy for CAAS vFFR, or any assessment of its clinical effectiveness.

There were insufficient data to explore the impact of key patient characteristics (such as multivessel disease or diabetes) on diagnostic accuracy or clinical effectiveness, so these could not be fully investigated. It remains largely unclear which patient or lesion characteristics might significantly affect the diagnostic accuracy of QAngio QFR.

Prospective evidence for the clinical benefit of QAngio QFR-guided treatment is lacking. Results from the large randomised controlled trials FAVOR III Europe-Japan (non-inferiority trial comparing QAngio QFR with standard FFR guided PCI) and FAVOR III China (superiority trial comparing QAngio QFR with angiography-alone guided PCI) will be informative. They have a target recruitment of 2,000 and 3,860 patients and are due to be completed in March 2022 and February 2023, respectively.

The simulation study that investigated the clinical impact of using QAngio QFR, compared with FFR, on actual coronary outcomes, was limited by the strong assumptions made about the relevant population and their risk of events. Most important was that the risk of MACE in the simulation depends only on a patient's FFR value.

Using a grey-zone strategy improved diagnostic accuracy compared with using QAngio QFR alone. However, this improvement relies on the assumption that the exact FFR cut-off of 0.8 is clinically meaningful. Because most FFR and QAngio QFR values differ by 0.05 or less, the grey-zone approach mainly identifies discordant FFR and QAngio QFR results very close to the 0.8 boundary. Of those patients with QAngio QFR results in the grey zone, 30.4% are discordant with their FFR.

Cost effectiveness

FFR/iFR can cause discomfort to patients and are associated with the risk of coronary artery dissection. FFR uses vasodilator drugs to increase blood flow, such as adenosine, which are associated with a high rate of side effects (up to 30% of patients), including chest pain and shortness of breath. These are usually transient but can be very traumatic for patients. As there were no suitable estimates to inform the disutility associated with FFR/iFR, a disutility equivalent to that of a PCI procedure was assumed. It is uncertain whether this accurately captures the discomfort experienced by patients during FFR/iFR.

The cost-effectiveness results were very sensitive to the procedural disutility assumed in the model for FFR/iFR and the duration of health-related quality-of-life benefits associated with revascularisation.

There were very limited data available from diagnostic accuracy studies of CAAS vFFR. In addition, using alternative diagnostic accuracy estimates for CAAS vFFR highlighted the uncertainty surrounding its cost effectiveness. Therefore, the cost-effectiveness results for strategy 5 with CAAS vFFR must be interpreted with caution.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

The risk of significant coronary artery disease and its presentation are related to age, sex and ethnicity. Because of this, women and people from some ethnic groups have coronary artery disease that is potentially underdiagnosed and undertreated in current practice. An objective measurement of the functional significance of stenosis such as using QAngio QFR or CAAS vFFR could help address this and promote equality.

NICE is not aware of any variation in the accuracy of QAngio QFR or CAAS vFFR according to age, sex, ethnicity or other protected characteristic. The clinical effectiveness of QAngio QFR or CAAS vFFR may be different in people with microcirculatory dysfunction, for example related to diabetes. Some people with diabetes may be covered under the disability provision of the Equality Act (2010).

Angina can sometimes have a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities. Therefore, some people with stable angina may be covered under the disability provision of the Equality Act (2010).

6 Implementation

Evidence of clinical utility

The clinical utility of QAngio QFR and CAAS vFFR to guide revascularisation decisions and improve clinical outcomes compared with standard care is uncertain. Clinical experts indicated that this was the biggest barrier to adoption.

Training and certification

Staff who would use QAngio software (for example, cardiac physician, laboratory technician, radiographer, cardiologist) would need training and certification. All staff need to successfully process 8 to 10 analyses to gain certification. The training could be shortened if analyses were to be completed and reviewed online later. The company is also developing an online training course.

Diagnostic-only catheter laboratories currently do not do invasive FFR measurements so staff in these centres may need more training and support to correctly calculate and interpret the QAngio QFR.

Depending on the QAngio QFR volume of analyses expected (purchased upfront), there may be an additional cost related to the staff training.

Training for CAAS vFFR is provided online via e-learning or webex or can be delivered on-site. It takes 2 hours to complete.

Unclear commissioning and reimbursement in the NHS

Current HRG codes split cardiac catheterisation into 2 categories; EY43 standard (£1,726) and EY42 Complex (£2,153). Invasive FFR is included in the latter tariff but because QAngio QFR does not complicate the catheterisation, trusts may not be reimbursed for it under the current HRG coding. However, they may need to see offsets in the number of patients per session and reduction in the cost of consumables.

Diagnostic-only catheter laboratories wishing to adopt QAngio QFR or CAAS vFFR software may have to bear the additional cost of the software and the analysis time, while the potential cost savings of avoided referrals to interventional centres may be realised in a different commissioning catchment area. This may be a barrier to adoption in diagnostic-only centres.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by the Centre for Reviews and Dissemination and Centre for Health Economics, University of York.

    - Duarte A, Llewellyn A, Walker R et al. (2020) QAngio XA 3D/Quantitative Flow Ratio (QFR) and CAAS vFFR imaging software for assessing coronary obstructions: a systematic review, meta-analysis and economic evaluation.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers of technologies included in the final scope:

- Medis Medical Imaging Systems BV
- Pie Medical Imaging

Other commercial organisations:

- Boston Scientific
- Abbott
- Medtronic Ltd

Professional groups and patient/carer groups:

- British Cardiovascular Intervention Society
- Royal College of Physicians
- Royal College of Radiologists

Research groups:

- University of Sheffield

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)
- NHS England
- Royal Cornwall Hospital
- Welsh Government

Appendix B: Glossary of terms

Adenosine

A drug used to induce maximal blood flow (vasodilator drug).

Angiography

Angiography (also referred to as arteriography) is a medical imaging technique used to visualise the lumen (central space where blood flows) of blood vessels and organs of the body, with particular interest in the arteries, veins, and the heart chambers. See also computed tomography coronary angiography and invasive coronary angiography.

Chronically occluded vessel

A complete or almost complete blockage of a coronary artery for 30 or more days.

Computed tomography coronary angiography

A non-invasive test that uses X-rays to give detailed pictures of the heart and the blood vessels, including information about the degree of stenosis (obstruction) in the coronary arteries.

Coronary artery bypass graft

A surgical procedure used to treat coronary heart disease. It diverts blood around narrowed or clogged parts of the major arteries to improve blood flow and oxygen supply to the heart.

Coronary artery disease

A disease (also referred to as coronary heart disease or ischaemic heart disease) in which blood flow to the heart muscle is reduced, usually because of the build up of plaque in the arteries of the heart. It is the most common of the cardiovascular diseases.

Coronary artery dissection

A split or a tear in the wall of the artery, which compresses or compromises the lumen of the artery reducing blood flow.

Coronary artery stenosis (obstruction, narrowing)

A narrowing of the coronary artery leading to reduced blood flow, often because of the build up of plaque (fatty deposits) in the wall of the arteries.

Diffuse coronary artery disease

Usually defined as significant obstruction (stenosis) involving the whole length of the coronary artery, significant stenosis 2 cm or longer, or presence of 3 or more significant stenoses in the same artery (tandem stenoses).

Fractional flow reserve

A technique used in coronary catheterisation to measure pressure differences across a coronary artery stenosis. It is used to determine the likelihood that the stenosis results in reduced blood (and oxygen) delivery to the heart muscle (myocardial ischaemia).

Functional imaging

Functional imaging (or physiological imaging), is a medical imaging technique of detecting or measuring changes in physiological activities within a certain tissue or organ, for example, changes in blood flow.

Invasive coronary angiography

An invasive diagnostic test that provides anatomical information about the degree of stenosis (obstruction or narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of X-rays. It is considered the gold standard for providing anatomical information about coronary artery stenosis.

Microvascular dysfunction

A type of coronary artery disease that affects the small vessels (arterioles and capillaries) of the heart. It is also known as coronary small vessel disease, microvascular angina, or non-obstructive coronary disease.

Multivessel coronary artery disease

When significant coronary artery obstructions (stenoses) are present in more than 1 coronary artery.

Myocardial ischaemia

Happens when blood flow to the heart is reduced, preventing it from getting enough oxygen. The reduced blood flow is usually the result of a partial or complete blockage of coronary arteries.

Myocardial revascularisation

Restores blood flow to the heart after myocardial ischaemia. It is usually done by percutaneous coronary intervention or coronary artery bypass grafting.

Percentage diameter stenosis

Percentage of the lumen reduction caused by the stenosis. For example, 30% diameter stenosis is a stenosis that compromises 30% of the normal artery lumen.

Percutaneous coronary intervention (coronary angioplasty)

A non-surgical procedure used to treat stenosis (obstruction, narrowing) of the coronary arteries of the heart. It uses a balloon catheter and a stent (a short wire-mesh tube) to dilate the artery and keep it open. The stent can be coated with a drug that reduces the risk of future blockages (drug-eluting stent) or an uncoated stent (bare-metal stent).

Pressure wire

A special guide wire that has a small sensor at its tip to measure blood pressure in the artery before and after stenosis. Comparing the 2 measurements can show if, and to what extent, the stenosis is limiting blood flow.

Quantitative flow ratio

A novel index of the functional severity of coronary stenosis, which can be calculated from 3-dimensional quantitative coronary angiography. It is a potential non-invasive alternative to fractional flow reserve.

Stable angina

A type of chest pain that results from reduced blood flow. It is usually triggered by physical activity or emotional stress and resolves with rest.