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QAngio XA 3D/Quantitative Flow Ratio (QFR) and CAAS vFFR imaging software for assessing coronary obstructions: a systematic review, meta-analysis and economic evaluation

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List of abbreviations

AUC	Area under the curve
BCIS	The British Cardiovascular Intervention Society
CCTA	Coronary computed tomography angiography
CI	Confidence interval
cQFR	Contrast-flow quantitative flow ratio
DICOM	The Digital Imaging and Communication in Medicine
ECG	Electrocardiogram
HSROC	Hierarchical summary receiver operating characteristic
ICA	Invasive coronary angiography
ICER	Incremental cost-effectiveness ratio
iFR	Instantaneous wave-free ratio
IPD	Individual participant data
FN	False negative
FP	False positive
FFR	Fractional flow reserve
fQFR	Fixed-flow quantitative flow ratio
MACE	Major Adverse Cardiac Event
MPS	Myocardial perfusion
NICE	National Institute for Health and Care Excellence
PCI	Percutaneous Coronary Intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
QCA	Quantitative coronary angiography
QoL	Quality of life
QFR	Quantitative flow ratio
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
RR	Relative risk
SPECT	Scintigraphy with single-photon emission computed tomography
TP	True positive
TN	True negative
vQFR	Vessel quantitative flow ratio

Glossary

CAAS vFFR: None invasive imaging technology produced by Pie Medical Imaging

Cost-effectiveness analysis: An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling: A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

False negative: Incorrect negative test result – number of diseased persons with a negative test result.

False positive: Incorrect positive test result – number of non-diseased persons with a positive test result.

Incremental cost-effectiveness ratio: The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test: The test whose performance is being evaluated.

Markov model: An analytic method particularly suited to modelling repeated events or the progression of a chronic disease over time.

Meta-analysis: Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression: Statistical technique used to explore the relationship between study characteristics and study results.

Negative predictive value: Proportion of patients who tested negative on the test that do not have the condition of interest.

Opportunity costs: The cost of forgone outcomes that could have been achieved through alternative investments.

Percutaneous Coronary Intervention: A non-surgical procedure that uses a to place a small structure called a stent to open up blood vessels in the heart that have been narrowed by plaque build-up.

Positive predictive value: Proportion of patients who tested positive on the test that have the condition of interest

Receiver operating characteristic curve: A graph which illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold.

Reference standard: The best currently available diagnostic test against which the index test is compared.

Sensitivity: Proportion of people with the target disorder who have a positive test result.

Specificity: Proportion of people without the target disorder who have a negative test result.

True negative: Correct negative test result – number of non-diseased persons with a negative test result.

True positive: Correct positive test result – number of diseased persons with a positive test result.

QAngio XA 3D/QFR: Non-invasive imaging software produced by Medis

Abstract

Background

QAngio XA 3D/QFR imaging software (produced by Medis) and CAAS vFFR (produced by Pie Medical Imaging) are two non-invasive technologies that could replace invasive fractional flow reserve (FFR) assessment of the functional significance of coronary stenoses.

Objectives

To determine the clinical and cost-effectiveness of QAngio and CAAS vFFR.

Methods

We performed a systematic review of all evidence on QAngio and CAAS vFFR including: diagnostic accuracy, clinical effectiveness, implementation, and economic analyses. We searched MEDLINE and other databases to January 2020 for studies where either technology was used and compared to FFR in patients with intermediate stenosis. Risk of bias was assessed with QUADAS-2.

Meta-analyses of diagnostic accuracy were performed, using bivariate analyses of aggregate data and data extracted from study plots. Clinical and implementation outcomes were synthesised narratively. A simulation study investigated the clinical impact of using QAngio.

We developed a *de novo* decision analytic model to estimate the cost-effectiveness of QAngio and CAAS vFFR relative to the comparators of pressure wire FFR/iFR or clinical decision making based on visual interpretation of ICA alone in the UK NHS. Scenario analyses were undertaken to explore the robustness of the results to variation in the sources of data used to populate the model and alternative assumptions.

Results

39 studies (5440 patients) of QAngio and three of CAAS vFFR (500 patients) were included.

QAngio had good diagnostic accuracy to predict functionally significant FFR (≤0.80 cut-off); cQFR had a sensitivity of 85% (95% CI 78 to 90) and specificity of 91% (95% CI 85 to 95). QAngio, was highly correlated with FFR (r=0.8).

Data on the diagnostic accuracy of CAAS vFFR was limited and a full meta-analysis was not feasible.

There was very little data on other clinical and implementation outcomes, although QAngio appears feasible as part of ICA examination. The simulation found that QFR slightly increased the

revascularisation rate when compared to FFR, from 40.2% to 42.0%. Using a grey zone strategy increased it to 43.2%. All three strategies had similar numbers of resulting coronary events.

The base case cost-effectiveness results showed that the test strategy with the highest net benefit was ICA with confirmatory FFR/iFR. The next best strategies were QAngio and CAAS vFFR (without FFR/iFR). However, the difference in net benefit between this best strategy and the next best was small, ranging from 0.007 – 0.012 QALYs (or equivalently £140 - £240) per patient diagnosed at a cost-effectiveness threshold of £20,000 per QALY.

Limitations

Diagnostic accuracy evidence on CAAS vFFR, and on the clinical impact of QFR, were limited.

Conclusions

QFR as measured by QAngio has good agreement and diagnostic accuracy against FFR and is preferable to standard ICA alone. It appears to have very similar cost-effectivness to using FFR and therefore, pending further evidence on general clinical benefits and specific subgroups, could entirely replace FFR.

The clinical and cost-effectiveness of CAAS vFFR is uncertain. RCT evidence evaluating the effect of QFR on clinical and patient-centred outcomes is needed.

Plain English Summary

(250 words)

Stable angina is a type of chest pain; left untreated, it can lead to heart failure, heart attack, and sudden death. To avoid these, patients may require surgical intervention to open constricted arteries, known as “revascularisation”.

Patients who might need revascularisation undergo tests to identify blocked arteries. The last line of testing is called invasive fractional flow reserve (FFR) assessment. This consists of an invasive measurement of blood flow, by inserting a wire into the artery, after giving drugs to dilate the artery. It carries some risks and may have substantial side effects.

Non-invasive tests have been proposed to precede or replace invasive FFR. These include the QAngio XA 3D/QFR imaging software (produced by Medis) and CAAS vFFR (produced by Pie Medical Imaging).

This project investigated whether these technologies can provide accurate assessments of blood flow, and if they are a reasonable use of NHS resources. A thorough review of all the literature on the technologies was performed. All data were combined and re-analysed to determine whether the tests accurately predict the need for revascularisation and to consider their clinical benefits. An economic analysis was conducted to investigate whether using either of these technologies is economically viable.

The project found that QAngio can accurately measure blood flow, and pending more evidence on benefits to patients’ health, could replace FFR, and is a reasonable use of NHS resources. The current evidence for CAAS vFFR is too limited to draw any firm conclusions.

1 Scientific Summary

1.1 Background

People with stable angina may require intervention to open constricted arteries, known as "revascularisation". QAngio XA 3D/QFR imaging software (produced by Medis) and CAAS vFFR (produced by Pie Medical Imaging) are two non-invasive technologies used as adjunct to invasive coronary angiography that estimate the quantitative flow ratio (QFR) of coronary lesions to assess the functional significance of coronary stenoses. There is potential for these technologies to partially or wholly replace invasive fractional flow reserve (FFR) assessment as the last-line test to inform revascularisation decisions.

1.2 Objectives

This project aimed to evaluate the clinical and cost-effectiveness of non-invasive assessment of the functional significance of coronary stenoses, using QAngio XA 3D/QFR (Medis) and CAAS vFFR (Pie Medical Imaging) imaging software.

1.3 Methods

1.3.1 Systematic review

A systematic review of the diagnostic accuracy, clinical efficacy and practical implementation of QAngio XA 3D/QFR and CAAS vFFR software for assessing the functional significance of coronary obstructions in people with intermediate coronary stenosis was conducted.

Comprehensive bibliographic searches including MEDLINE and Embase and supplementary sources were conducted up to 2nd of January 2020 for published and unpublished literature.

Diagnostic accuracy and correlation studies in which QFR were performed using any version of the QAngio system or CAAS vFFR in addition to invasive FFR (or iFR) as a reference standard in the same patients were included. Empirical studies of QFR or vFFR (with or without invasive FFR) that reported relevant clinical outcomes (including morbidity and mortality) or issues related to implementation of QFR or vFFR and their use in clinical practice were also eligible. Patients with intermediate stenosis referred for Invasive coronary angiography (ICA) to assess coronary stenosis and the need for revascularisation were eligible for inclusion.

Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and of all full-text papers subsequently obtained for assessment. Data extraction and quality assessment were conducted by at least one researcher and checked by a second. Risk of bias of diagnostic accuracy studies was assessed using QUADAS-2.

For diagnostic accuracy outcomes, bivariate models were fitted to calculate summary estimates of sensitivity and specificity with 95% confidence intervals (CIs) using aggregate data and data extracted from study plots. Additional diagnostic accuracy results that could not be pooled in a meta-analysis and clinical effectiveness and implementation outcomes were synthesised narratively. Data from figures reported in studies were digitized to simulate the accuracy of a 'grey-zone strategy', whereby confirmatory FFR is only performed in patients with a QFR between 0.78 and 0.84.

1.3.2 Economic analysis

Cost-effectiveness literature on QAngio and CAAS vFFR was reviewed. The titles and abstracts of all reports identified by the bibliographic searches were screened independently by two researchers. A subsequent pragmatic review of existing decision models evaluating ICA and/or FFR/iFR was also conducted by one researcher, and key findings were summarised narratively.

A decision analytic model was developed to estimate the cost-effectiveness of QAngio XA 3D/QFR and CAAS vFFR used during ICA for assessing the functional significance of coronary stenosis in patients with stable angina whose angiograms show intermediate stenosis. Five diagnostic strategies were considered: (i) strategy 1 of ICA alone, (ii) strategy 2 of ICA followed by confirmatory FFR/iFR (reference standard), (iii) strategy 3 of ICA with QFR, (iv) strategy 4 of ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive, and (v) strategy 5 of ICA with vFFR.

The decision model had two components: a diagnostic element and a prognostic element. The diagnostic component was used to link the diagnostic accuracy of QFR and vFFR to short-term costs and consequences (e.g., the impact on the proportion of patients who need revascularisation [percutaneous or surgical], the proportion of patients who need 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), while the prognostic component was used to link the short-term consequences to longer-term costs and consequences (e.g., the risk of major adverse cardiovascular events including myocardial infarction, sudden cardiac death and need for urgent/unplanned revascularisations) to ensure that differences in costs, life years gains, and QALYs were appropriately quantified over a lifetime horizon.

1.4 Results

A total of 41 studies were included in the systematic review, of which 39 (5440 patients) evaluated QAngio and three (500 patients) assessed CAAS vFFR. Only one study directly compared QAngio with CAAS vFFR. Seventeen studies were only reported as conference abstracts.

Most studies included a mix of patients with stable and unstable angina. Stenosis severity varied widely across studies; mean/median FFR ranged from 0.75 to 0.88, and mean percentage diameter

stenosis from 37% to 66%. Only seven studies were conducted prospectively, and eleven studies (all of QAngio) were at low risk of bias.

1.4.1 Diagnostic accuracy

QFR, as measured by QAngio, was highly correlated with FFR (r=0.8), with the average difference between them being 0.01. 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.

QAngio had good diagnostic accuracy to predict FFR (≤0.80 cut-off); cQFR mode had a sensitivity of 85% (95% CI 78 to 90) and specificity of 91% (95% CI 85 to 95); fQFR mode had a sensitivity of 82% (95% CI 68 to 91) and specificity of 89% (95% CI 77 to 95). Where reported, QAngio had significantly higher diagnostic accuracy than standard ICA. Data on how diagnostic accuracy may vary by key patient characteristics was too limited to draw any firm conclusions.

Using data extracted from figures, simulating a 'grey-zone' strategy, where only patients with a QAngio QFR between 0.78 and 0.84 receive confirmatory FFR, improved diagnostic accuracy compared to using QFR alone to a sensitivity of 93.1% (95% CI 90.1 to 94.9) and a specificity of 92.1% (88.3% to 94.5%). 20.1% of patients fell in the grey zone and would receive confirmatory FFR. However, only 30.4% of patients with QAngio results in the grey zone had results that were discordant with their FFR.

Only three retrospective studies of CAAS vFFR were available, limiting the scope for reliable meta-analysis. Only one conference abstract directly compared the diagnostic accuracy of QAngio and CAAS vFFR against FFR, and found that QAngio had higher overall diagnostic accuracy, with AUCs of 0.719 (95% CI 0.621 to 0.804) for vFFR and 0.886 (95% CI 0.807 to 0.940) for cQFR.

1.4.2 Clinical effectiveness

No evidence was found on the effectiveness of QFR on major cardiovascular events and death. Three studies that reported clinical outcomes found that QAngio may predict long-term major cardiovascular adverse events. QAngio evidence suggests that the technology is applicable in a clinical context.

A simulation study based on the results of the meta-analysis found that replacing using QFR in place of FFR may slightly increase the number of revascularisations (from 40.2% to 42%) with a possible small increase in the number of coronary events (an extra 1 MACE per 1000 patients). Using a grey-zone approach of performing a confirmatory FFR where QFR is close to 0.8 might further increase revascularisations rates (to 43.2%) but with no impact on incidence of MACE.

1.4.3 Cost-effectiveness

No full cost-effectiveness studies of QAngio or CAAS vFFR were identified by the systematic review. The pregamatic review identified 21 relevant reports of which two studies were selected to inform the conceptualisation of the *de novo* decision model.

The base case cost-effectiveness results showed that the test strategy with the highest net benefit (most cost-effective strategy) was ICA followed by confirmatory FFR/iFR (strategy 2), at a cost-effectiveness threshold 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 (or equivalently £140) per patient diagnosed for ICA with QFR (strategy 3), 0.012 QALYs (or equivalently £240) per patient diagnosed for ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive (strategy 4), and 0.011 QALYs (or equivalently £220) per patient diagnosed for ICA with vFFR (strategy 5). The cost-effectiveness results for strategy 5 must be interpreted with caution due to very limited data available from diagnostic accuracy studies of vFFR.

1.5 Discussion

This review includes a comprehensive systematic review of all the published literature on QFR as assessed by QAngio and CAAS vFFR and has been conducted following recognised guidelines to ensure high quality. The review identified a substantial literature on the diagnostic accuracy of QAngio, so the findings of the analysis of diagnostic accuracy are likely to be conclusive.

Although there is substantial evidence diagnostic accuracy of QFR assessment using QAngio, it remains largely unclear which patient or lesion characteristics might significantly affect the diagnostic accuracy of QAngio.

The clinical value of QAngio to support decision making on revascularisation remains uncertain, particularly what impact it might have on preventing or causing future coronary events, and whether the 0.8 cut-off, or the proposed grey zone, are clinically appropriate. However, it appears unlikely that its clinical value or use will differ substantially from widespread use of FFR.

The key drivers of cost-effectiveness were: (i) the diagnostic sensitivity of test results (rather than specificity) because “true positive” test results translated into higher QALY gains than mismanagement of “false negative” test results; (ii) the procedural QALY loss associated with FFR/iFR; (iii) the magnitude and duration of the QALY gains associated with revascularisation; and (iv) the additional costs associated with confirmatory testing with FFR/iFR.

1.6 Conclusions

QFR measured using QAngio has good agreement and diagnostic accuracy compared with FFR and is more accurate than standard ICA for the evaluation of functionally significant stenoses. Due to limited evidence the clinical effectiveness of CAAS vFFR is currently uncertain.

The high correlation between QFR and FFR, and the high diagnostic accuracy of QFR, suggest that, pending further evidence on clinical benefits, QFR assessment could potentially replace FFR entirely, and hence remove the need for invasive pressure wire and adenosine use. The cost-effectiveness of QAngio suggests that it is a reasonable use of NHS resources as it is only marginally less cost-effectiveness than FFR.

Evidence on the CAAS vFFR technology was limited to three studies. This prevented any full meta-analyses of diagnostic accuracy for CAAS vFFR, or any assessment of its clinical effectiveness. The cost-effectiveness results for CAAS vFFR should be interpreted with caution due to the limited diagnostic information available.

1.6.1 Recommendations for research

The substantial existing evidence for diagnostic accuracy of QAngio suggests that further studies of diagnostic accuracy are not required. Large, multi-centre prospective studies are required to assess the diagnostic accuracy and clinical feasibility of CAAS vFFR. Ideally these should compare CAAS vFFR to ICA assessment, and if possible, to QFR.

Large ongoing randomised trials will hopefully inform decision makers on the clinical value of QFR compared with angiography- and FFR-guided revascularisation.

1.6.2 Study registration

The protocol for this review is registered on PROSPERO CRD42019154575

2 Background

2.1 Description of the health problem

Stable angina is a type of chest pain caused by insufficient blood supply to the heart, brought on by physical activity or emotional stress, which goes away with rest. It is the key symptom of coronary artery disease, which remains one of the main causes of morbidity and mortality in high-income countries. Complications include unstable angina, heart failure, myocardial infarction, and sudden death.

To alleviate symptoms, patients may receive revascularisation to open damaged, constricted or blocked arteries. This most commonly consists of inserting a small tube or "stent" into the artery to keep it open and allow blood flow. Patients who might need revascularisation undergo a number of tests to identify blocked arteries, including coronary computed tomography angiography (CCTA) and other non-invasive tests. If these tests are inconclusive, more invasive tests are needed, for example invasive coronary angiogram (ICA), where a contrast medium is injected through the catheter and X-ray images (angiograms) are taken.

As assessment of angiograms have limited ability to differentiate between arteries with inadequate blood supply (which need revascularisation) and those with adequate supply which do not need treatment, the procedure may be combined with an invasive measurement of blood flow, such as invasive fractional flow reserve (FFR) assessment. During this procedure, the blood flow is measured by inserting a wire into the artery, after giving drugs to dilate the artery. The procedure is invasive and therefore, carries some risks and may have substantial side effects.

The 2017 Health Survey for England reported that the prevalence among all adults of ever having ischemic heart disease (including myocardial infarction and angina), was 4%.[1] Prevalence was higher among men (6%) compared with women (3%) and increased with age (3% among people aged 45-54, 16% in people aged 75 and over). Prevalence of angina and history of angina among all adults was 3%.

2.2 Description of the technologies under assessment

Non-invasive imaging tests have been proposed to precede or replace invasive FFR, by using the existing angiograms to determine blood flow, without inserting a wire.

2.2.1 QAngio XA 3D/ QFR

QAngio XA 3D/QFR (Medis) imaging software is used to perform QFR assessment of coronary artery obstructions. It is designed to be used with all invasive coronary angiography (ICA) systems; biplane or monoplane. It uses two, standard 2D X-ray angiographic projections, taken at least 25

degrees apart – and ideally between 35 and 50 degrees apart – to create a 3D-reconstruction of a coronary artery; this shows the QFR values across the artery. QFR is an assessment (by frame count) of the pressure (blood flow velocity) drop over the artery, with a value of 1 representing a normally functioning artery with no pressure drop. A 20% or more drop in blood pressures (QFR value of 0.8 and less) is considered a significant obstruction where revascularisation should be considered. QAngio XA 3D/QFR software is installed on a laptop or workstation that is connected to the ICA system. The Digital Imaging and Communication in Medicine (DICOM) data from ICA projections are immediately uploaded and viewable on the connected workstation. The total time for data acquisition and analysis is about 4 to 5 minutes (as reported by the company). AngioPlus (Pulse Medical Imaging Technology, Shanghai, China) is an equivalent CE-marked version marketed in Asia.

The QAngio software offers two different flow models to calculate QFR:

- Fixed flow QFR, using fixed flow velocity
- Contrast QFR, using contrast frame count in an angiogram without hyperaemia.

Fixed flow QFR is faster to compute, but may be less accurate than contrast QFR.

Furthermore, the QAngio software provides 4 different QFR indices along the analysed coronary segment:

- Vessel QFR: the QFR value at the distal location of the analysed vessel segment
- Index QFR: a point which can be moved along the QFR pullback curve
- Lesion QFR: the contribution to the QFR drop by the selected lesion alone
- Residual vessel QFR: an indication of the vessel QFR, if the selected lesion is resolved.

2.2.2 CAAS vFFR

CAAS vessel-FFR workflow builds a 3D reconstruction of a coronary artery based on 2 standard X-ray angiograms, assesses the pressure drop across the stenosis, and determines a vessel FFR value. It gives both anatomical and functional assessment of the stenosis, and can be integrated into catheter laboratories. The total time for analysis is approximately 2 minutes per artery according to the company.

All available versions of CAAS (8.0, 8.1, 8.2) use the same algorithm for calculating vFFR. The CAAS workstation provides various modules (for example, quantitative coronary arteriography and left ventricular analysis), and the vFFR module can be added to the CAAS workstation. In addition to the vFFR, CAAS vFFR provides measurements at the end of the lesion and at a chosen position in the coronary artery.

2.3 Comparators

ICA may differentiate between arteries with inadequate blood supply (which need revascularisation) and those with adequate supply which do not need treatment.

During an ICA procedure, a coronary diagnostic catheter is inserted into an artery, usually in the arm pit or groin, and moved up the aorta and into the coronary arteries. A special type of dye called contrast medium is injected through the catheter and X-ray images (angiograms) are taken. Although providing valuable information on coronary artery anatomy, visual assessment of angiograms taken during ICA has limited ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses.

When ICA is inconclusive, it may be combined with the invasive measurement of FFR. In these procedures FFR is assessed invasively by advancing a pressure wire towards the stenosis and measuring the ratio in pressure between the two sides of the stenosis during maximum blood flow (induced by adenosine infusion). This is associated with risks related to the passage of a guide wire, side effects of adenosine, and additional radiation exposure. The invasive FFR measurement is also associated with increased procedural time and costs, compared with ICA alone. As an alternative to invasive FFR, instantaneous wave-free ratio (iFR) may be used. This also uses inserted pressure wires to assess flow, but does not require vasodilator drugs such as adenosine.

2.4 Current service provision and care pathways

Patients who experience chest pain and may need revascularisation will be assessed for angina, and other cardiovascular conditions. Where clinical assessment alone is insufficient for a diagnosis patient are referred for 64-slice or above coronary CT angiography (CCTA) as the first-line diagnostic test when clinical assessment suggests typical or atypical angina, or non-anginal chest pain, but 12-lead resting electrocardiogram (ECG) has been done and shows ST-T changes or Q waves.

Patients may go on to further diagnostic testing. NICE guidance 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. This could include:

- myocardial perfusion scintigraphy with single-photon emission computed tomography (MPS with SPECT)
- stress echocardiography
- first-pass contrast-enhanced MR perfusion
- MR imaging for stress-induced wall motion abnormalities.

In addition, NICE's medical technologies guidance 32 recommends that HeartFlow FFRCT should be considered as an option for patients with stable, recent onset chest pain who are offered 64-slice (or above) CTCA. It provides both functional and anatomic assessment of coronary arteries, and has better diagnostic performance than CTCA alone, or other non-invasive or invasive tests.

If these tests are also inconclusive ICA is offered as a third-line diagnostic tool.

A diagnosis of stable angina are made when clinical symptoms are present and:

- significant coronary artery disease is found during ICA or 64-slice (or above) CTCA. This is usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.
- reversible myocardial ischaemia is found during non-invasive functional imaging.

ICA is also sometimes used to guide treatment strategy for people with a confirmed diagnosis of stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment (OMT), and so may require revascularisation. ICA may differentiate between arteries with inadequate blood supply (which need revascularisation) and those with adequate supply which do not need treatment.When ICA is used to determine the presence and severity of coronary stenosis and it is inconclusive, it may be combined with the invasive measurement of FFR using a pressure wire, as recommended by the European Society of Cardiology and American College of Cardiology[2 3]. Lesions with an FFR of 0.80 or less are functionally significant and revascularisation may be considered. Should iFR be used, a measure of 0.89 or less is considered functionally significant.

ICA is either performed in diagnostic-only ICA laboratories, or in interventional catheter laboratories as part of the initial stenosis assessment prior to percutaneous coronary intervention. In diagnostic-only laboratories patients where ICA alone is inconclusive might be referred to an interventional laboratory for an FFR or iFR assessment. In interventional laboratories an FFR or iFR assessment can be performed immediately after ICA, if needed.

The British Cardiovascular Intervention Society (BCIS) audit reports 244,332 invasive coronary angiography (ICA) procedures took place in the UK in 2017/18 in NHS and private facilities, with 35,017 procedures performed in diagnostic-only catheter laboratories.

There is substantial regional variation in the diagnostic pathway for stable angina, due in part by availability of imaging modalities at each centre, and experience (or preferences) of the cardiologists referring for the test. Clinical advisors noted that the pathway recommended by NICE is widely recognised as current best practice.

2.5 Position of the technology in the diagnostic pathway

QFR or vFFR could potentially replace pressure-wire FFR, or iFR, by providing a non-invasive means to assess FFR as part of an ICA assessment in people with stable chest pain of recent onset. Visual assessment of angiograms taken during ICA may be limited in its ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses. Alternatively, they may be used as a precursor to invasive FFR, with the invasive procedure used when QFR or vFFR is inconclusive.

QFR may also be used in other aspects of decision-making, including whether to stent more than one vessel, or to select a stent type or other interventional device for revascularisation.

QAngio and CAAS vFFR could also be used in diagnostic-only laboratories, possibly reducing the need for referrals to interventional laboratories.

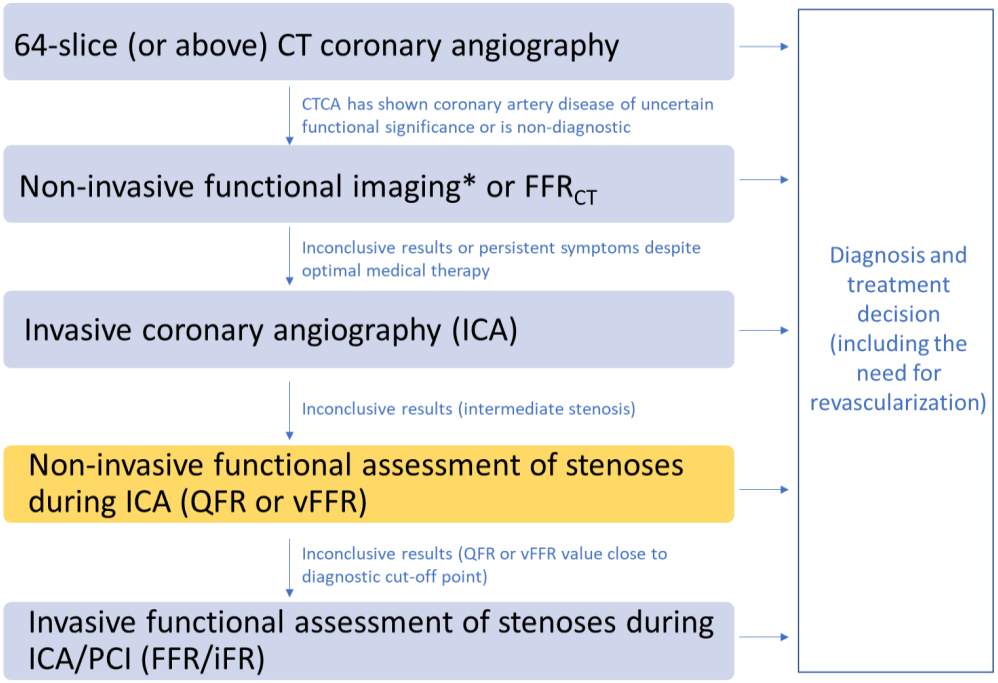
The QAngio instructions recommend the following approach:

- QFR below 0.78: treat the patient in the catheter laboratory;
- QFR above 0.84: follow the patient medically;
- QFR between 0.78 and 0.84 ('grey-zone'): verify by invasive FFR measurement.

Following request for clarification, Pie Medical stated they recommend the same hybrid approach.

The likely pathway leading to invasive FFR, and including the probable placement of QFR, is summarised in Figure 1.

Figure 1: Diagnostic pathway for stable angina, including QFR or vFFR (from NICE DAP 48 final scope)



3 Aims and objectives

The aim of the project is to determine the clinical and cost-effectiveness of non-invasive assessment of the functional significance of coronary stenoses, using the QAngio XA 3D/QFR (Medis) and CAAS vFFR (Pie Medical Imaging) imaging software.

To achieve this, the following objectives were set:

i) Clinical effectiveness

- To perform a systematic review and meta-analysis of the diagnostic accuracy and, where feasible, clinical efficacy of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, used during ICA for assessing the functional significance of coronary obstructions in people with stable chest pain whose angiograms show intermediate coronary stenosis.

- To perform a narrative systematic review of the clinical efficacy and practical implementation of QAngio and CAAS vFFR. This includes assessment of the associated revascularisation rates, mortality and morbidity, patient-centred outcomes, adverse events, and acceptability to clinicians and patients.

ii) Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, for assessing the functional significance of coronary stenosis in people with stable chest pain whose angiograms show intermediate stenosis.

- To develop a decision model to estimate the cost-effectiveness of the QAngio XA 3D/QFR and CAAS vFFR imaging software used during ICA to indicate whether coronary obstructions are functionally significant. Consideration will be given to differences in the cost-effectiveness of the technologies in diagnostic-only or in interventional catheter laboratories.

- The decision model will link the diagnostic accuracy of QFR derived from the QAngio XA 3D/QFR imaging software, and vFFR derived from the CAAS vFFR software, to short-term costs and consequences (e.g., the impact on the number of revascularisations needed, the proportion of people who need invasive functional assessment of stenosis, time to test results, and associated risks of the diagnostic intervention). It will then link the short-term consequences to potential longer-term costs and consequences (e.g., major

cardiovascular events such as myocardial infarction and sudden cardiac death, adverse events related to revascularisation and diagnosis, mortality) using the best available evidence.

4 Assessment of Clinical Effectiveness

4.1 Methods for reviewing effectiveness

The systematic review was conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance and reported in accordance with the (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [4]

4.1.1 Searches

Comprehensive searches of the literature were conducted to systematically identify all studies relating to the QAngio technology and to CAAS vFFR.

The searches were carried out during October 2019, with a further updated search undertaken on 2nd January 2020. The following databases were searched: MEDLINE, PubMed, Embase, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Health Technology Assessment (HTA) Database and EconLit.

Ongoing and unpublished studies were identified by searches of ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations & Theses A&I, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. Abstracts from any recent conferences which are thought to be relevant to the review were also consulted.

A search strategy for Ovid MEDLINE is reported in Appendix 10.1. The MEDLINE strategy was translated to run appropriately on the other databases and resources. No language or date restrictions were applied to the searches. No study design search filters were used.

Reference lists of relevant recent reviews [5] were checked in order to identify additional potentially relevant reports.

Database searches were carried out to identify cost-effectiveness studies where invasive coronary angiography (alone and/or with FFR) was one of the interventions under comparison. The following databases were searched, EconLIT, Embase, HTA database MEDLINE, NHS EED. The search strategies for EconLIT, Embase and MEDLINE are reported in Appendix 10.1.

Pragmatic supplementary PubMed and Google Scholar searches were carried out to identify studies of diagnostic data on ICA vs. FFR.

4.1.2 Contact with study authors and manufacturers and request for IPD

An individual participant data (IPD) meta-analysis of four studies that has previously been performed was eligible for this review. [5] The EAG contacted the authors, prior to commencing this assessment and authors agreed, in principle, to share the collected IPD with the EAG for the purposes of this work. However, due to slow response from the study authors, the IPD could not be supplied in time for this report, and the decision was made not to pursue an IPD analysis. Instead, published data and data presented in figures was used. Where possible, IPD-equivalent data were extracted from plots using a digitising software, see Section 4.1.4 for further detail.

4.1.3 Selection criteria

Two reviewers (AL and RW) independently screened all titles and abstracts. Full papers of any titles and abstracts that were thought to be relevant were obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements were resolved by consensus or by consulting a third reviewer (MS). Conference abstracts were included where sufficient data were reported to confirm eligibility. Authors were contacted when insufficient data were reported to confirm inclusion (for instance, to clarify what index test was used in the study, or to provide complete 2x2 data) and where it was unclear whether the same diagnostic accuracy results were presented in more than one report (e.g. conference abstracts linked to a publication).

Diagnostic accuracy

Included were: diagnostic accuracy and correlation studies in which QFR using any version of the QAngio system or CAAS vFFR were performed in addition to invasive FFR (or iFR) as a reference standard in the same patients.

Clinical effectiveness/implementation

Included were: experimental or observational studies where QFR or vFFR (with or without invasive FFR) have been used and which report relevant clinical outcomes as detailed. Relevant publications reporting issues related to implementation of, or practical advice for, QFR or vFFR and their use in clinical practice were also eligible. Case reports, and studies focusing only on technical aspects of QFR or vFFR (such as technical descriptions of the testing process or specifications of machinery and software) were excluded.

Participants

Patients with intermediate stenosis (however defined) who are referred for ICA to assess coronary stenosis and the need for revascularisation were included. Although the main focus of this assessment

was on patients with stable chest pain (either suspected stable angina or confirmed angina that is not adequately controlled by treatment), patients with all types of angina (including unstable, non-specific and atypical) were eligible for inclusion. Patients with acute MI (STEMI and NSTEMI <72 hours) were also included provided QFR was performed in non-culprit vessels.

Interventions

All versions of QAngio XA 3D/QFR (Medis) (including AngioPlus) and CAAS vFFR imaging software (Pie Medical Imaging) used in conjunction with ICA to allow simulation of FFR were included.

All sub-measurements of QFR were eligible, including contrast-flow QFR (cQFR) and fixed-flow QFR (fQFR). Eligible healthcare settings were diagnostic-only and interventional catheter laboratories.

Reference standard

The reference standard was FFR assessed using an invasive pressure wire with or without adenosine. Instantaneous wave-free ratio (iFR), which was found to be non-inferior to FFR for predicting cardiovascular events and all-cause mortality,[6] was also accepted as a reference standard.

Outcomes

The eligible outcome measures relating to diagnostic accuracy were:

- Sensitivity and specificity of QAngio XA 3D/QFR, CAAS vFFR
- Positive and negative predictive values
- Estimates of difference in measurements between QFR or vFFR and invasive FFR/iFR
- Correlation between QFR or vFFR and invasive FFR/iFR measurements (including Bland-Altman assessments)

Some studies reported difference or concordance between QFR or vFFR and invasive FFR/iFR in numerous ways, including inter and intra-rater differences in measurements, mean differences, correlation coefficients, sensitivity and specificity or ROC curves. All relevant outcome definitions and cut-offs were extracted and their applicability to the decision problem accounted for when presenting the results. Diagnostic accuracy results of ICA alone was considered if reported alongside QAngio or CAAS.

In addition, the following clinical outcomes were eligible:

- Morbidity, mortality and major adverse events (e.g. myocardial infarction, heart failure)

- Adverse events related to the diagnostic procedure (e.g. pressure wire damage, adenosine side effects, stroke)
- Adverse events related to revascularisation
- Distress, anxiety and similar harms caused by QFR, vFFR, invasive FFR or iFR
- Subsequent use of invasive pressure-wire FFR or iFR
- Subsequent revascularisation procedures performed (including unscheduled revascularizations)
- Number of vessels with stent placements
- Health related quality of life
- Radiation exposure
- Test failure rates
- Inconclusive test rates
- Inter-observer variability

Eligible outcomes related to the implementation of the interventions of interest and related practical issues included:

- Acceptability of QFR, vFFR and invasive FFR (to clinicians and patients)
- Timing of results from data acquisition
- Referral times
- Patient satisfaction
- Training requirements
- Uptake and compliance

4.1.4 Data extraction

A standardised data extraction form was developed, piloted and finalised to data extract study and patient characteristics and eligible outcomes. For studies reporting diagnostic accuracy data the number of true-positive, true-negative, false-positive and false-negative results were extracted for each index test evaluated in each study, along with sensitivity and specificity data, the area under the curve (AUC) and 95% confidence intervals and positive and negative predictive values. Whether diagnostic accuracy was determined per patient, vessel or lesion was recorded.

Where not reported, sensitivity and specificity were calculated if data allowed. Further data were requested from study authors where required. Correlation and mean difference between vFFR and FFR were recorded along with reasons for any excluded, failed or inconclusive results and any other relevant clinical outcomes from the studies.

As IPD could not be supplied, digitised data were extracted using WebPlotDigitizer software, to approximately reconstruct the individual-level data from included studies. Data were extracted for all studies that presented a Bland-Altman or correlation plot. Bland-Altman plots were preferred for extraction, as these were found to be generally clearer and easier to extract. The extracted averages

and differences between QFR and FFR were converted into QFR and corresponding FFR values for each study. For some studies, the quality of published figures was not sufficient to extract data.

Data were extracted by one reviewer (RW) using a standardised data extraction form and independently checked by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer (MS) where necessary. Data from relevant studies with multiple publications were extracted and reported as a single study. The most recent or most complete publication was used in situations where we could not exclude the possibility of overlapping populations across separate study reports.

4.1.5 Critical appraisal

The quality of the diagnostic accuracy studies was assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies). QUADAS-2 evaluates both risk of bias (associated with the population selection, index test, reference standard and patient flow) and study applicability (population selection, index test and reference standard) to the review question.

The quality assessments was performed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus, and where necessary, by consulting a third reviewer (MS).

4.1.6 Methods of data synthesis

The results of data extraction were presented in structured tables and as a narrative summary, grouped by population and test characteristics. The diagnostic accuracy was calculated for each study based on extracted data, using the usual index test of QFR ≤ 0.8 and reference standard of FFR ≤ 0.8 as defining patients in need of stenting. Where sufficient clinically and statistically homogenous data were available, data was pooled using appropriate meta-analytic techniques. Studies that did not report sufficient information to derive 2x2 data (from tables, text or plots) were not included in the meta-analysis and synthesised narratively. Statistical analysis of diagnostic accuracy

4.1.6.1 Meta-analysis using 2x2 diagnostic data

The primary meta-analyses in this report were based on studies that reported 2x2 diagnostic data, or where data could be reconstructed from tables was conducted. Both univariate meta-analysis and bivariate meta-analysis of sensitivity and specificity was performed and compared, categorised according to “Mode” of QFR used: either fQFR, cQFR or unspecified, referred to as ‘QFR’. These analyses included all patients, vessels and lesions. Results are reported in forest plots and summarised in tables and ROC plots.

Separate (univariate) meta-analyses were performed for each diagnostic outcome (sensitivity, specificity, PPV, NPV, diagnostic odds ratio, area under ROC curve, correlation between QFR and FFR and mean difference between QFR and FFR) and presented in forest plots.

A hierarchical bivariate model described by Reitsma et al. was fitted which calculates summary estimates of sensitivity and specificity and the associated 95% confidence intervals (CIs). [7] The hierarchical summary ROC (HSROC) model was also fitted to produce summary ROC curves. [8, 9] Results of both models are presented in ROC plots. Unless otherwise specified, all analyses used a cut-off for the index test of QFR ≤ 0.8 and reference standard of FFR ≤ 0.8 as defining patients in need of revascularisation.

As some studies reported data on two or more tests (e.g. QFR and ICA or fQFR and cQFR) the bivariate model was extended to include diagnostic accuracy parameters for multiple tests which allowed for formal comparison between models in terms of specificity and diagnostic odds ratio. [9]

Investigation of heterogeneity and subgroup analyses

For diagnostic accuracy data, we visually inspected the forest plots and ROC space to check for heterogeneity between study results. To assess the impact of patient factors we performed meta-regressions of sensitivity, specificity and diagnostic odds ratio against key patient parameters reported in papers.

Where available, we considered the following factors as potential sources of heterogeneity:

- Type and severity of stenosis (e.g. high percentage diameter stenosis)
- multivessel coronary artery disease
- diffuse coronary artery disease
- multiple stenoses in one vessel
- microvascular dysfunction (for example, caused by diabetes)
- chronic total occlusion
- diabetes
- sex
- age
- ethnicity (or study location as a proxy for ethnicity)
- results of previous non-invasive tests
- use of fixed flow QFR vs. contrast QFR (QAngio XA 3D)
- previous MI

For these analyses fQFR was not been separated from cQFR, but one test per study (cQFR for preference) was analysed, to maximise data. This was judged reasonable given that diagnostic accuracy did not appear to vary substantially according to type of QFR used.

Where studies reported the factors of interest separately by subgroup, these subgroup results were compared; however, these were too sparsely reported to permit any meta-analysis. For patient factors where data did not allow for meta-regression, a narrative synthesis of the impact of covariates has been provided.

Sensitivity analyses

We conducted sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS-2 domain results (for example, risk of incorporation bias) and study design (for example, in-procedure versus retrospective evaluation of index test results) for diagnostic accuracy studies. ROC plots of sensitivity and specificity according to risk of bias were produced to visually assess possible bias. Where feasible, bivariate meta-analyses were repeated, subgrouped according to the assessed risk of bias.

4.1.6.2 Meta-analysis of data extracted from figures

Using data extracted from figures, estimates of sensitivity and specificity was calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. These were compared to the diagnostic accuracy results from 2x2 table to investigate whether the extracted data could be used for analysis. The bivariate meta-analyses performed using 2x2 data were repeated using the extracted figure data.

4.1.6.3 "Grey zone" analysis

Extracted figure data was used to conduct an analysis where testing includes a "grey-zone" of intermediate QFR values for which an FFR would be performed as a confirmatory test. The "grey-zone" diagnostic procedure considered, following the QAngio instructions, was:

1. Perform QFR
2. If QFR >0.84 continue without stenting/bypass [test negative]
3. If QFR ≤0.78 proceed to stenting/bypass [test positive]
4. If QFR is between 0.78 and 0.84, perform an FFR test and proceed to stenting/bypass if FFR≤0.80 [the grey zone]

For the grey zone analysis, it was assumed that anyone within the grey zone has perfect diagnostic accuracy (because all received a 'gold-standard' FFR test), therefore false positive and negatives are only present in patients outside the grey zone. The impact of using the grey zone on the diagnostic accuracy of QAngio was assessed. The effect of using different FFR thresholds on the diagnostic accuracy of QAngio was also assessed. Due to lack of guidance on CAAS vFFR grey-zone cut-offs no such analyses were performed for this technology.

4.1.6.4 Narrative synthesis

Evidence related to clinical effectiveness and implementation of QFR, vFFR and invasive FFR were too limited to allow meta-analysis. Results were tabulated and presented narratively. Conclusions of these studies, suggested consequences for QFR and ICA, recommendations for practice and suggested needs for further research were summarised.

Narrative summaries were used for any diagnostic accuracy outcomes where meta-analyses or other statistical analyses were not feasible. This included tabulating or plotting results as reported in studies, and narratively describing and comparing these results.

4.1.6.5 Statistical analysis of clinical effectiveness

The systematic review identified very little published data on the clinical impact of using QFR and QAngio screening. In particular, very little data was found on the impact QFR (with or without a grey zone) might have on future incidence and prevention of coronary events. Therefore, to investigate what the clinical impact of using QFR testing might be, a simulation study was performed to seek to identify the impact QFR and invasive FFR assessment might have on the number of revascularisations performed, and on morbidity and mortality and other longer-term outcomes. This simulation used two key sources of data:

1. The data on FFR and QFR measurements extracted from published Bland-Altman figures was used as a representative population of patients with intermediate stenosis, with FFR and QFR measurements for each patient.
2. The IRIS-FFR study reported the association between FFR and coronary events in patients who are revascularised and in patients where revascularisation is deferred. [10] These data were used to calculate the risk of coronary events, and then to simulate events for each patient in our sample population (from point 1), given their observed FFR measurement.

Combining these two data sources produced a simulated data set where each patient had the following data:

1. An FFR measurement
2. The associated QFR measurement
3. The risk of a coronary event if revascularisation were performed
4. The risk of a coronary event if revascularisation were deferred
5. Whether the patient had a coronary event (if revascularised)
6. Whether the patient had a coronary event (if deferred)

Three strategies for deciding on whether to revascularize were considered:

1. FFR only: perform FFR on all and revascularize if FFR ≤ 0.8
2. QFR only: perform QFR on all revascularize if QFR ≤ 0.8, without FFR measurement
3. Grey zone (GZ): perform a QFR and:
    a. revascularize if QFR ≤ 0.78,
    b. defer if QFR > 0.84
    c. If QFR is between 0.78 and 0.84, perform FFR and revascularize if FFR ≤ 0.8

Applying these strategies to the simulated data set, the following data were calculated for each strategy:

1. The proportion of patients who would be revascularised
2. The total number of coronary events
3. The proportion with unnecessary revascularisation (i.e. revascularised, but would not have had an event if revascularisation were deferred)
4. The proportion where revascularisation prevented and event (i.e. are revascularised, and would have had an event if revascularisation were deferred)
5. The proportion where revascularisation caused an event (i.e. have an event when revascularised, but would not have had an event if revascularisation were deferred)

These results were then compared across strategies to investigate how the differing strategies might alter the incidence of coronary events.

Detailed simulation methods

The sample population for the simulation was taken to be the data extracted from published Bland Altman figures. For this analysis fQFR data were excluded and only cQFR or non-specified QFR data used, making a total of 3,193 patients, each with an FFR measurement and its associated QFR measurement. Since these data were extracted from figures, they may not be a perfect representation of the actual study patients (see Section 4.1.4). The simulation did not differentiate between studies, so the patients are treated as if they came from a single "mega-study".

To predict coronary outcome in this sample population the results of the recent IRIS-FFR registry report were used, representing 5846 patients who were either "revascularized" (stent or bypass surgery) or "deferred" (continued with current management without surgery) based on their measured FFR result. The IRIS-FFR study used major cardiovascular events (MACE, a composite of cardiac death, myocardial infarction and repeated/emergency revascularization) as its primary outcome. The mean incidence rate from MACE in deferred patients was 1.44 events per 100-lesion years. For simplicity, it was assumed that each person has one lesion, equating to a 1.44% risk in one year. Based on data reported in the publication this equated to a risk of 0.64% at an FFR of exactly 1. According to IRIS-FFR most of these events are later revascularizations. The hazard ratio for MACE

was estimated as 1.06 per 0.01 decrease in FFR. It was been assumed that the 1-year risk ratio is the same as this hazard ratio. In patients with revascularizations the mean risk of MACE was 2.4% in one year with a hazard ratio of 1 (so risk is the same regardless of FFR value).

Based on those risks, the predicted risk of MACE for every person in the sample population was calculated using their reported FFR measurement (this means that risk is not dependent on QFR). A risk of event if revascularised and a risk if deferred was calculated. A Monte Carlo simulation was then used to simulate whether each person had a MACE event if they were "deferred" or if they were revascularized, based on the calculated risks. Therefore, the incidence of simulated events is solely a function of FFR values, and knowing the QFR has no impact on risk of MACE events. The simulation process was repeated 10,000 times, to produce a reasonable sample of plausible simulations.

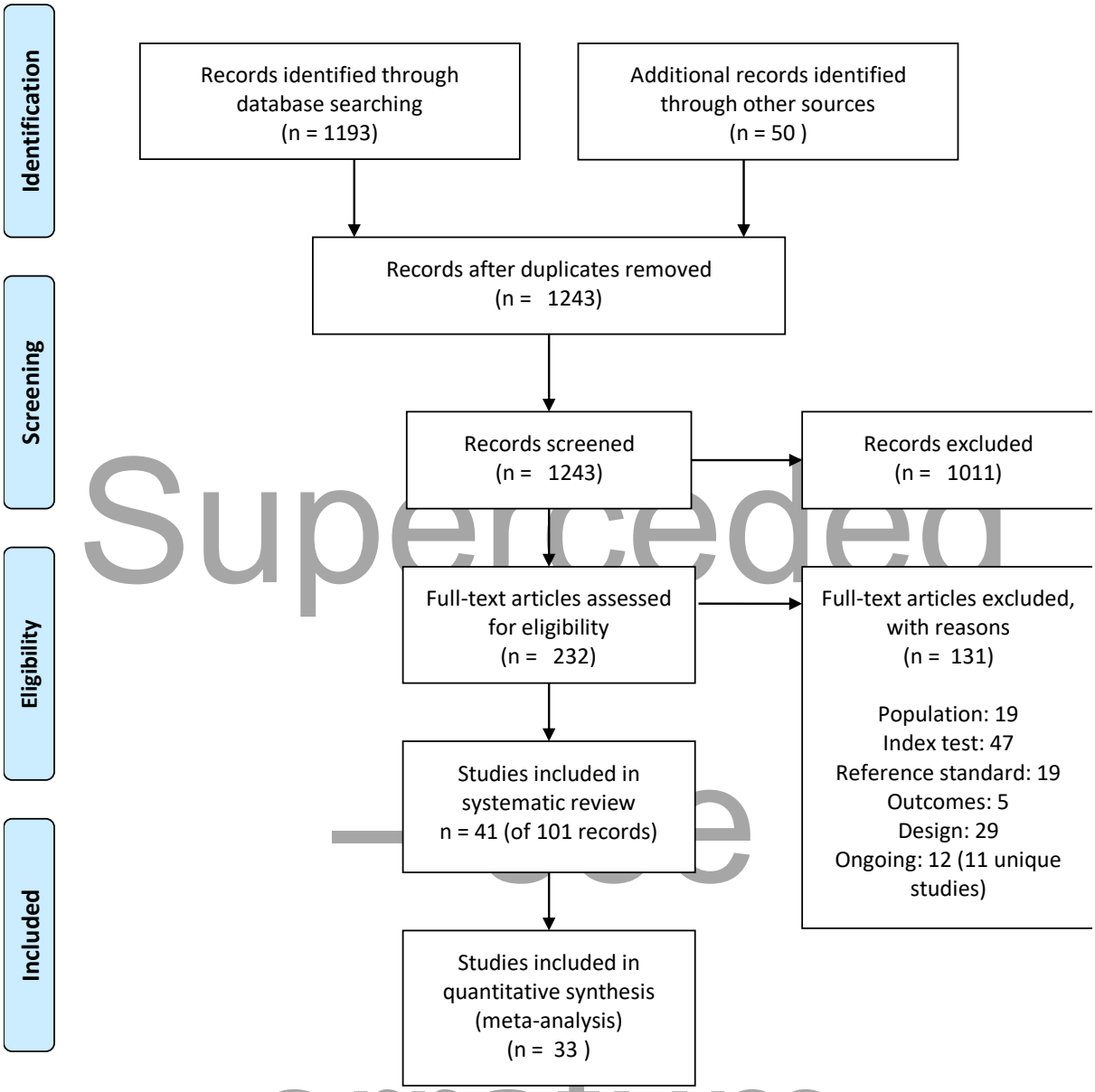
For each simulated sample who would and would not be revascularised was determined for each of the three strategies listed above. Given that, and the known MACE status for each patient, the five statistics in the list above were calculated. Results were pooled across simulations to find median values across simulations, and to plot distributions across all simulations. All statistical analyses were conducted in R software.

4.2 Quantity and quality of evidence available

A total of 41 unique studies were included in the systematic review.[11-51] Thirty-nine studies evaluated QAngio, [11-14, 17-52] and three studies evaluated CAAS vFFR.[15, 16, 23] One study directly compared CAAS vFFR with QAngio.[23]

Two studies did not report diagnostic accuracy data, but included other eligible outcomes.[22, 27] All other studies were included in the diagnostic accuracy review, of which 33 were included in a meta-analysis.[12-18, 20, 21, 23-29, 31, 32, 34, 36-43, 45-51] Seventeen were conference abstracts.[11, 13, 15, 19, 22-28, 32, 33, 35, 36, 41, 51] Figure 2 presents an overview of the study selection process and presents the list of all included studies.

Figure 2 Study selection process (PRISMA flow diagram)



4.2.1 Characteristics of included studies

Table 1 presents the characteristics of the studies included in the systematic review. Only seven studies used QFR prospectively as part of the ICA examination preceding FFR.[11, 41, 45-49] Fifteen studies were conducted in multiple centres.[12, 19, 21, 23, 31, 34, 35, 38, 42-44, 47, 48 49]

Most studies were conducted in Asia, including Japan (33 studies),[17-21, 23-49 50] China (five studies)[11, 23, 43, 49 42] South Korea[19, 21, 31, 34] and Singapore.[13]

Twenty-two studies were conducted in Europe, including Belgium,[12, 42, 43] Canada,[44] Denmark,[11, 47, 48] France,[35] Germany,[39, 43, 47] Hungary,[42] Italy,[38, 43, 47] Lithuania,[51] Netherlands,[12, 15, 32, 34, 37, 38, 40, 43-45, 47] Poland,[29, 30, 47] Spain,[12, 19, 31, 34, 38, 47] and the UK,[12, 23, 44] Two studies were conducted in the USA,[16, 43] one in Brazil[24] and one in Australia.[33] Eleven studies included an international cohort.[11, 12, 19, 23, 31, 34, 38, 42-44, 47]

QAngio studies analysed a total of 5440 patients (over 6524 vessels or lesions), and CAAS vFFR studies analysed a total of 500 patients (over 519 vessels or lesions). Most studies included a mixed population of stable and unstable CAD, although eleven studies focused on patients with stable CAD only.[20, 24, 28-30, 32, 41, 43, 45, 46, 50] Three studies evaluated non-culprit vessels in patients with MI,[14, 25, 38] two focused exclusively on patients with three-vessel disease,[12, 20] one only included patients with intermediate left main stenosis (mostly left-main bifurcation),[19] and one focused specifically on in-stent restenosis.[31] Where reported, mean age ranged from 59 to 72.5 years and most participants were male (60% to 93%). Patient history and stenosis severity varied widely across studies. Prevalence of diabetes ranged from 6% to 48%, rates of previous MI from 4% to 58%, and previous PCI 4% to 65% (not accounting for one study with 100% in-stent restenosis).[31] Mean/median FFR ranged from 0.75 to 0.88, and mean %DS from 37% to 66%.

Table 1 Characteristics of studies included in the systematic review

Main studies	Single/multicentre	Country	Population	N patients (vessels or lesions)#	Mean age (SD)	%Male	Diabetes %	% acute MI	FFR Mean(SD) or median (IQR)	Mean %DS	%stable angina	%stable CAD	%previous MI	%Previous PCI
QAngio studies														
Cliff (2019)[13] Conference abstract	Single	Singapore	Acute MI and non-acute	33 (41)	59(20)	69%	30%	58%	NR	NR	NR	NR	NR	NR
Cortés (2019)[14]	Single	Spain	STEMI, >50% DS in non-culprit arteries	10 (12)	70(9)	75%	NR	100%	0.87(0.06)	NR	NR	0%	NR	NR
Emori (2018)A[17]	Single	Japan	Intermediate stenosis, prior/non-prior MI related	75 (75)	70(9)	77%	47%	0%	0.79(0.11)*/0.76(0.13)~	53(14)*/54(14)~	NR	NR	50%	51%
Emori (2018)B[18]	Single	Japan	Intermediate stenosis	100 (100)	70(10)	71%	48%	NR	0.75(0.10)	55(10)	NR	NR	22%	NR
FAVOR II China Xu (2017)[49]	Multi	China	CAD (suspected or known)	308 (332)	61(10)	74%	86%	14%	0.82(0.12)	46.5(11.3)	23%	34%	48%	65%
FAVOR II Europe-Japan Westra (2018)[47]	Multi	Italy, Netherlands, Germany, Poland, Spain, Japan, Denmark	Stable angina or secondary evaluation post MI	272 (317)	67(10)	72%	29%	2%	0.83(0.09)	45(10)	NR	NR	NR	40%

FAVOR Pilot Tu (2016)[43]	Multi	Belgium, Italy, Netherlands, Germany, China, Japan, United States	Stable angina, referred for ICA & FFR	73 (84)	66(9)	84%	27%	0%	0.84(0.08)	64.5(4.5)	100%	100%	32%	38%
Goto (2019)[19] Conference abstract	Multi	Spain, Japan, South Korea	Intermediate left main stenosis. Mostly LM bifurcation (85%)	62 (NR)	NR	NR	NR	NR	0.76(0.11)	44.1(11.1)	NR	NR	NR	NR
Hamaya (2019)[20]	Single	Japan	Stable CAD, 3-vessel disease	NR (154)	68(10)	76%	38%	0%	NR	36.8(14.4)	NR	100%	23%	NR
Hwang (2019)[21]	Multi	South Korea	Intermediate stenosis, stable angina or acute MI (non-culprit lesions)	264 (358)	61(13)	77%	33%	31%	0.80(0.13)	0.531	NR	69%	6%	NR
Kajita (2019)[24] Conference abstract	Single	Brazil	Stable CAD, intermediate lesions	24 (34)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kameyama (2016)[25] Conference abstract	Single	Japan	ACS, emergency ICA, non-culprit lesions	25 (26)	NR	NR	NR	100%	NR	NR	NR	NR	NR	NR
Kanno (2019)A[26] Conference abstract	Single	Japan	Intermediate stenosis	95 (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kanno (2019)B[27] Conference abstract	Single	Japan	Intermediate stenosis, de novo, deferred revascularisation	212 (NR)	NR	NR	NR	NR	0.87 (0.84-0.90)	NR	NR	NR	NR	NR

Kirigaya (2019)[28] Conference abstract	Single	Japan	Stable CAD	95 (NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Koltowski (2018)[29]	Single	Poland	Stable CAD	268 (306)	66(10)	72%	28%	0	0.80(0.10)	51.3(10.2)	NR	100%	48%	59%
Kleczynski (2019)[30]	Single	Poland	Stable angina, intermediate stenosis	50 (123)	66(9)	72%	NR	0	0.82(0.10)	44.2(11.7)	100%	100%	NR	NR
Liontou (2019)[31]	Multi	Spain, Japan, South Korea	Intermediate in-stent restenosis	73 (78)	68(11)	81%	30%	6%	0.79(0.09)	51(9)	69%	69%	58%	100%
Liu 2017[32] Conference abstract	Single	Netherlands	Stable angina	NR (45)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mehta (2019)[33] Conference abstract	Single	Australia	NR	NR (85)	NR	NR	NR	NR	0.86(0.09)	NR	NR	NR	NR	NR
Mejia-Renteria (2019)[34]	Multi	Spain, South Korea, Netherlands	Intermediate stenosis, stable angina and acute ACS (incl. MI patients, non-culprit arteries in staged procedure)	248 (300)	64(10)	76%	38%	17%	0.80(0.11)	52(12)	70%	70%	14%	NR
Neylon (2016)[35] Conference abstract	Multi	France	NR	36 (38)	64(18)	66%	NR	NR	0.88(0.11)	NR	NR	NR	NR	NR

Sato (2018)[36] Conference abstract	Single	Japan	Intermediate stenosis	68 (70)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smit (2019)[37]	Single	Netherlands	Referred for FFR following ICA in diagnostic-only setting.	290 (334)	67(9)	69%	24%	0%	0.85(0.01)	43.1(8.5)	NR	NR	16%	33%
Spitaleri (2018)[38] (Reproducibility cohort)	Multi	Italy	ACS, multivessel disease, staged procedure	31 (34)	64(12)	81%	10%	100%	NR	59(13)	NR	NR	10%	19%
Spitaleri (2018)[38] (Diagnostic accuracy cohort)	Multi	Italy	STEMI, multivessel disease	45 (49)	62(11)	80%	9%	100%	0.84(0.11)	66(10)	NR	0%	4%	4%
Spitaleri (2018)[38] (clinical outcomes cohort)	Multi	Italy, Spain, Netherlands	STEMI, multivessel disease	110 (NR)	64(12)	81%	22%	100%	NR	62(11)	NR	NR	8%	6%
Stahli (2019)[39]	Single	Germany	Intermediate and less severe stenosis (%DS 40-70%), stable and unstable angina	436 (516)	72	68%	23%	4.1% (NSTEMI)	0.88 (0.82-0.92)	41% (median)	NR	72%	33%	55%
SYNTAX II Asano (2019)[12]	Multi	Belgium, Netherlands, Spain, UK	3-vessel disease	386 (836)	67(10)	93%	32%	NR	0.78 (0.73-0.84)	NR	NR	NR	13%	NR
Ties (2018)[40]	Single	Netherlands	Stable and unstable CAD	96 (101)	64(10)	60%	25%	16.7% (NSTEMI)	0.87(0.08)	43.4(8.4)	NR	51%	NR	24%
Toi (2018)[41] Conference abstract	Single	Japan	Stable angina, intermediate stenosis	50 (NR)	69(11)	78%	43%	NR	0.81(0.09)	NR	NR	NR	NR	NR

Tu (2014)[42]	Multi	Belgium, Hungary, China	Stable and unstable CAD, intermediate stenosis, de novo lesions	68 (77)	62(9)	69%	29%	0%	0.82(0.11)	46.6(7.3)	77%	87%	NR	32%
Van Diemen (2019)[44] Conference abstract	Multi	Netherlands, Canada, UK	NR	NR (286)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
van Rosendael (2017)[45]	Single	Netherlands	Non acute, eligible for FFR.	NR (15)	64(11)	71%	6%	0%	NR	38.7(8.6)	NR	100%	6%	24%
Watari (2019)[46]	Single	Japan	Stable CAD, intermediate stenosis.	121 (150)	71(11)	68%	36%	3% (NSTE MI/unstable angina)	0.81(0.12)	49(9)	35%	97%	21%	36%
WIFI II Westra (2018)[48]	Multi	Denmark	CAD, Referred from CTA	172 (240)	61(8)	67%	10%	NR	0.82(0.11)	50(12)	31%	NR	NR	NR
WIFI Prototype study Andersen (2017)[11] Conference abstract	NR	Denmark (+China and Netherlands?)	Stable angina and secondary evaluation after acute MI	93 (NR)	NR	NR	NR	NR	0.81(0.09)	47(9)	NR	NR	NR	NR
Yazaki (2017)[50]	Single	Japan	Stable angina and asymptomatic CAD	142 (151)	73(10)	70%	29%	0.7% (NSTE MI/unstable angina)	0.84(0.08)	48.8(8.2)	51%	99%	21%	41%
Ziubryte (2019)[51] Conference abstract	Single	Lithuania	Intermediate stenosis.	62 (69)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CAAS vFFR studies														

FAST EXTEND Daemen (2019)[15]	Single	Netherlands	Stable or unstable angina or NSTEMI	303 (NR)	65(11)	67%	NR	NR	0.84(0.07)	NR	NR	NR	NR	NR
ILUMIEN I Ely Pizzato (2019)[16]	Single	USA	Stable CAD, unstable angina and non-STEMI undergoing PCI. FFR measured pre and post-PCI	115 (115)	65(10)	76%	37%	11%	0.76(0.12)	53.3(18.2)	63%	67%	24%	NR
Jin (2019)[23] Conference abstract	Multiple	China, UK	Intermediate stenosis	82 (101)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[#]Analysed population; *prior MI subgroup; ~no prior MI subgroup

4.2.2 Quality of diagnostic accuracy studies.

Table 2 summarises the results of the risk of bias and applicability assessment for QFR for the 24 diagnostic accuracy studies reported in a full text manuscript, with further details reported in Appendix Table 69 and Table 70. The risk of bias from the 15 studies included in the diagnostic accuracy review that were only reported as conference abstracts was not formally assessed due to insufficient reporting.[11, 13, 15, 19, 22-28, 32, 33, 35, 36, 41, 51] As FAST-EXTEND, the extension of FAST-STUDY was reported as conference abstract only, only the quality of the earlier FAST-STUDY was assessed. [53]

Eleven out of 22 QAngio studies were at low risk of bias across all domains.[17, 18, 34, 38, 39, 42, 43, 46-49] The main source of bias was related to study participant selection; four studies were considered at high risk of patient selection bias, due to large rates of patient exclusions or significant exclusion of potentially harder to diagnose patients.[14, 20][21, 29][12], and three studies did not provide sufficient information on patient selection to assess risk of selection bias (unclear risk). [31, 40, 45] Exclusion rates and reasons are reported in Appendix Table 78. Risk of bias was generally low for other domains, although three studies were at high risk of bias due to the conduct of the index test or reference standard (e.g. no reporting of blinding between QFR and FFR results) [30, 45, 50] and one study was at high risk of bias due to patient flow concerns, as FFR was only performed in iFR grey-zone patients.[12]

ILUMIEN-I was the only CAAS vFFR complete study with a full text manuscript. The study was considered at high risk of bias due to the large percentage of lesions excluded from the study (65%). In an earlier published report of the FAST-EXTEND study, Masdjedi (2019)[53] also reported a large rate (54%) of exclusions. Although most of these failed tests appear to have been due to angiographic image processing issues rather than limitations inherent to CAAS vFFR (see 4.9.5), the large exclusion rates reported mean that the risk of selection bias cannot be excluded.

Only three studies raised no concerns about their applicability to the review question.[45-47] The main concern about applicability related to the retrospective (offline) use of QFR retrospectively (offline), rather than as part of the ICA examination and before FFR; only five studies (all of QAngio) were conducted prospectively and raised no significant concerns regarding the applicability of the index test.[45-49] There were no significant concerns regarding the applicability of the reference standard in any of the studies. Twelve of the 22 assessed QAngio studies did not raise significant concerns about the applicability of their population to the review question; [20, 29, 30, 34, 37, 39, 42, 43, 45-47, 50] concerns about study population applicability were primarily related to the under-representation of patients with stable CAD. We note that as only patients with an FFR measurement could be included in the diagnostic accuracy review, a subset of patients with intermediate stenosis (including those examined in a diagnostic-only setting, or with a counter-indication to adenosine) are not represented in the included evidence.

Seven studies of QAngio[11, 12, 38, 42, 45, 48, 49] and one of CAAS[15] reported a conflict of interest with their respective manufacturer.

Table 2 Risk of bias and applicability of diagnostic accuracy studies (QUADAS-2)

Study	Patient selection (RoB)	Index test (RoB)	Reference standard (RoB)	Flow (RoB)	Patient selection (applicability)	Index test (applicability	Reference standard (applicability
Cortés (2019)[14]	-	+	+	?	-	-	+
Emori (2018)A[17]	+	+	+	+	?	-	+
Emori (2018)B[18]	+	+	+	+	?	-	+
FAVOR II China Xu (2017)[49]	+	+	+	+	-	+	+
FAVOR II Europe-Japan Westra (2018)[47]	+	+	+	+	+	+	+
FAVOR Pilot Tu (2016)[43]	+	+	+	+	+	-	+
Hamaya (2019)[20]		+	+	+	+	-	+
Hwang (2019)[21]	-	+	+	+	-	-	+
Kleczynski (2019)[30]	+	-	+	+	+	-	+
Koltowski (2018)[29]	-	+	+	+	+	-	+
Liontou (2019)[31]	?	+	+	+	-	-	+
Mejia-Renteria (2019)[34]	+	+	+	+	+	-	+
Smit (2019)[37]	+	-	-	+	+	-	+
Spitaleri (2018)[38] (Cohort B, diagnostic accuracy)	+	+	+	+	-	-	+
Stahli (2019)[39]	+	+	+	+	+	-	+
SYNTAX II Asano (2019)[12]	+	+	+	-	-	-	+
Ties (2018)[40]	?	+	+	+	-	-	+
Tu (2014)[42]	+	+	+	+	+	-	+
van Rosendael (2017)[45]	?	-	-	?	+	+	+
Watari (2019)[46]	+	+	+	+	+	+	+

WIFI II Westra (2018)[48]	+	+	+	+	-	+	+
Yazaki (2017)[50]	+	+	-	+	+	-	+
CAAS vFFR							
ILUMEN-I Ely Pizzato (2019)[16]	-	+	+	+	+	-	+
FAST Masdjedi et al. 2019[53] CAAS vFFR	-	+	+	+	+	-	+

RoB: Risk of bias.
+low risk of bias or no significant concerns about applicability to the review question;
- high risk of bias or significant concerns about applicability;
?: unclear risk of bias or unclear about applicability

4.3 Overview of the meta-analyses (QAngio)

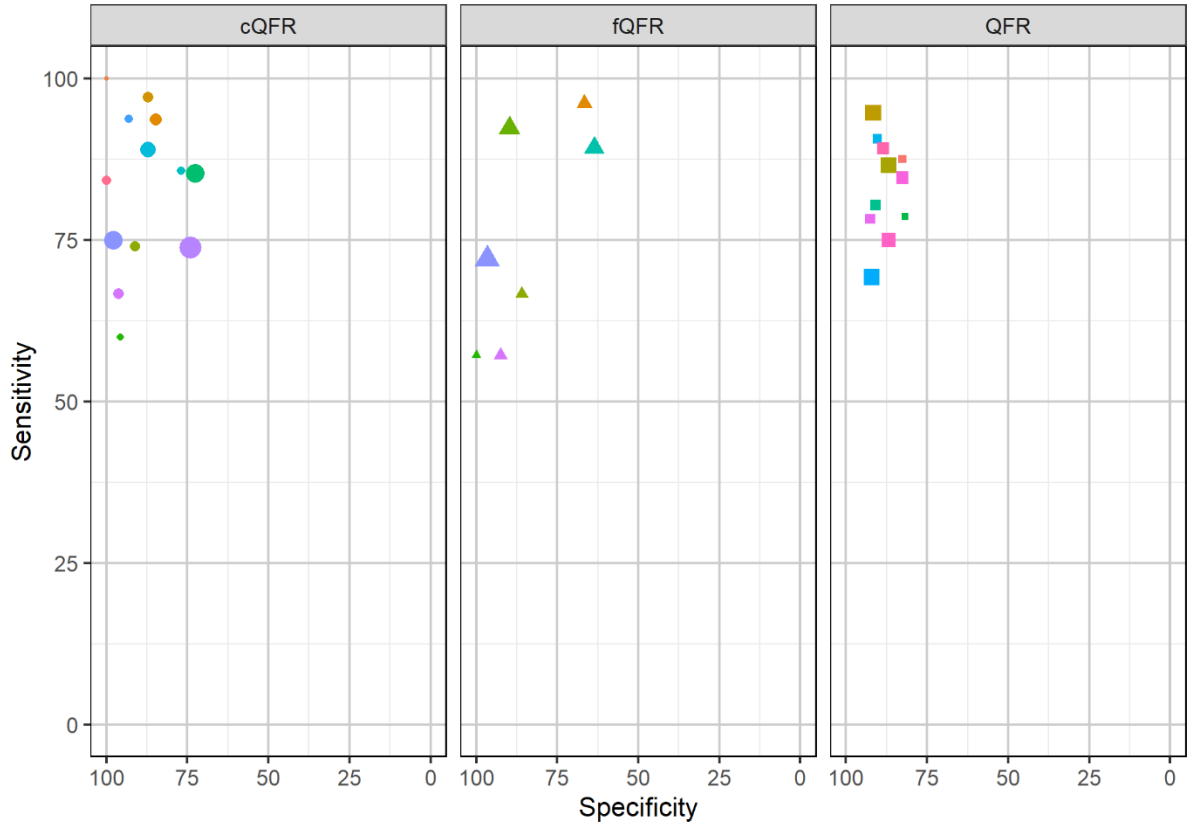
Meta-analysis of the included studies is focussed on the diagnostic accuracy of QFR to detect lesions or vessels requiring intervention (defined as having an FFR ≤ 0.8). There were insufficient data to perform meta-analyses of any clinical outcomes; these are discussed in Section 4.9.

Diagnostic accuracy of QFR was analysed in two ways. The first, and primary, analysis consists of a meta-analysis of reported diagnostic accuracy data (true positives, true negatives, false positives, false negatives) in studies where these data were reported, or could be derived from reported estimates of sensitivity and specificity. The second approach was to extract data on FFR and QFR values in each study from published Bland-Altman plots, or plots of FFR vs QFR, and to use these to calculate diagnostic accuracy. This approach may be less accurate, because extracting data from figures is imperfect, but it allowed for a wider range of analyses, such as considering different QFR and FFR cut-offs, and the impact of using a "grey zone" where patients with intermediate QFR values go on to receive confirmatory FFR. This second approach is considered in Section 4.7.

Of all QAngio included studies, 26 reported sufficient diagnostic accuracy data to be included in the primary meta-analysis of diagnostic accuracy (four studies[20, 31, 41, 45] were only included in analyses of data extracted from plots). These are divided into three "modes" of QFR: fixed-flow QFR (fQFR), contrast QFR (cQFR) and studies where the type of QFR was not specified (listed as QFR or non-spec. QFR). Most studies included in the primary analysis used FFR as the reference standard for determining whether intervention was required, all of these used a cut-off FFR of 0.8. One study[46] used iFR as the reference standard.

Figure 3 shows the general sensitivity and specificity estimates for each study, assuming an index test cut-off of QFR ≤ 0.8 and a reference standard curt-off of FFR ≤ 0.8. Results are plotted separately for each "mode" of QFR testing. This suggests that specificity is uniformly high and generally above 75% (except for two fQFR studies). Sensitivity is more heterogeneous, but is also above 75% in most studies (except for fQFR). There are no immediately apparent differences in accuracy between the three modes.

Figure 3 Sensitivity and specificity estimates for each study, by mode of QFR



4.4 Univariate meta-analyses (QAngio)

Figure 4 shows the forest plot for the univariate meta-analysis of sensitivity, and Figure 5 the same for specificity.

For the random-effect analyses, these show high sensitivity (82% - 85%) and high specificity (89% - 91%) for all three models of QFR. 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 QFR had a sensitivity of 84% (95% CI 78 to 89) and specificity of 89% (95% CI 87 to 91).

Across-study heterogeneity was moderate to high (e.g. for cQFR sensitivity $I^2 = 81\%$), but there does not appear to be any clear evidence that mode of QFR (fQFR vs cQFR) makes a difference to diagnostic accuracy.

Figure 4 Univariate meta-analysis of sensitivity

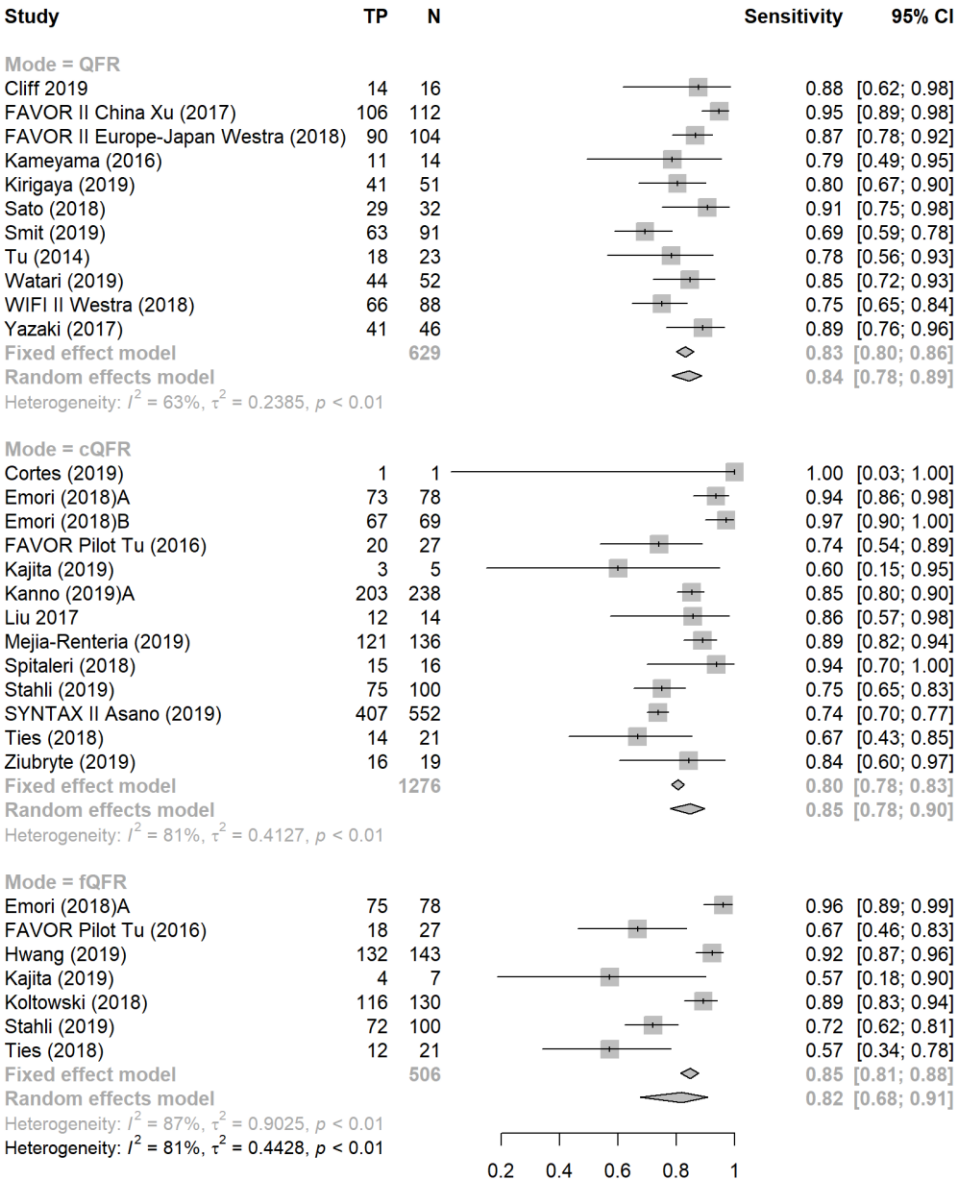
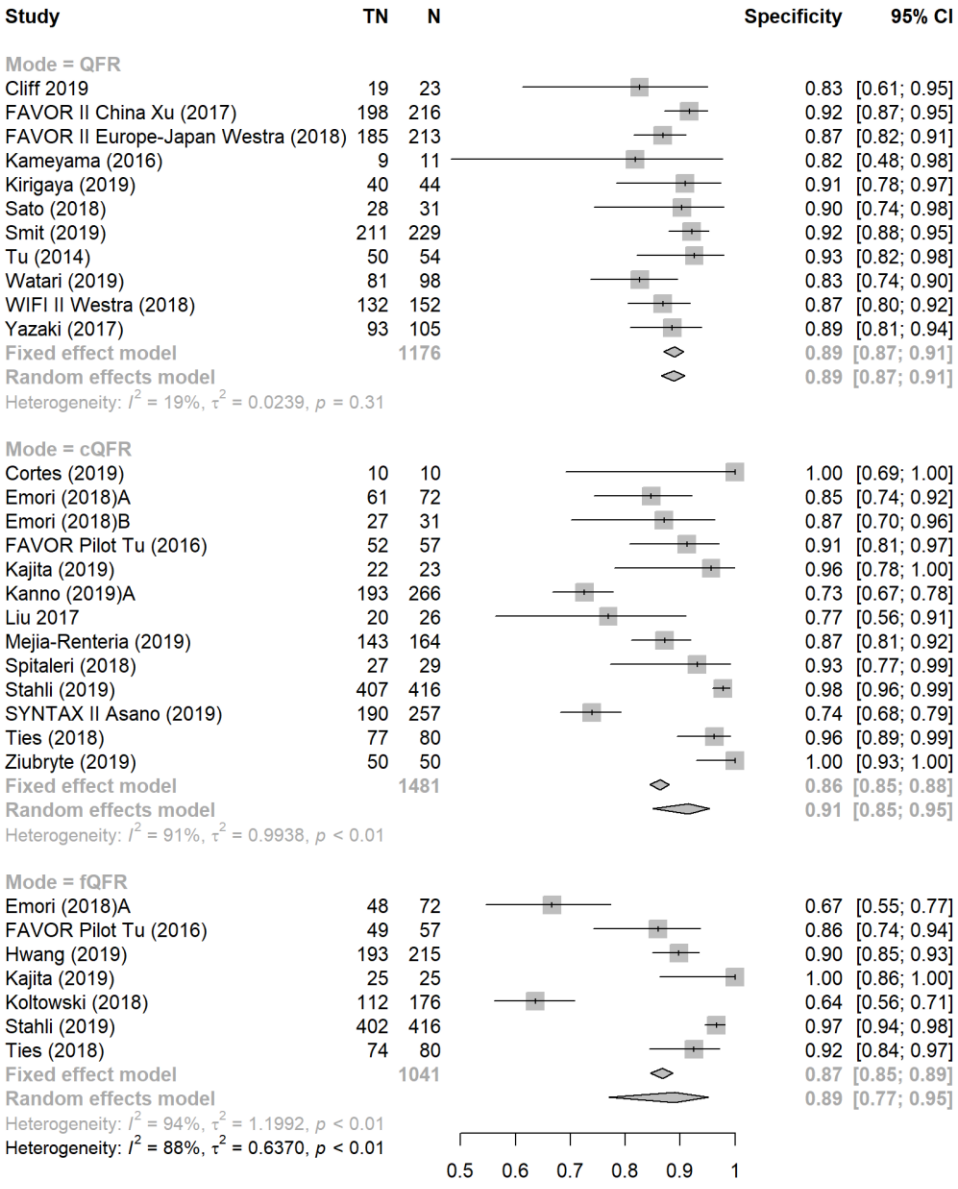


Figure 5 Univariate meta-analysis of specificity



Meta-analyses of area under the curve (AUC), and diagnostic odds ratio (DOR) were also performed (see Appendix Figure 29 and Figure 30). Summary AUCs were 87% (95% CI 83 to 92) for cQFR, 89% (95% CI 86 to 92) for fQFR and 92% (95% CI 90 to 94) for non-specified QFR. Summary diagnostic odds ratios were 3.51 (95% CI 2.71 to 4.30) for fQFR, 3.76 (95% CI 3.01 to 4.52) for cQFR and 3.71 (95% CI 3.27 to 4.15) for non-specified QFR.

Summary positive predictive values (see Appendix Figure 27) 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 QFR. Summary negative predictive values (see Appendix Figure 28) 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 QFR.

As both FFR and QFR are continuous measurements, it is also important to consider the agreement between FFR and QFR, in terms of the mean difference between them, and their correlation. We meta-analysed reported mean differences between FFR and QFR measurements and reported correlations. Where studies did not report the standard deviation of the mean difference it was imputed by taking the average value from studies that did report standard deviations.

The mean difference between QFR and FFR was almost exactly zero for all three modes of QFR testing (see Appendix Figure 31) [MD 0 (95% CI -0.05 to 0.06) for fQFR, -0.01 (95% CI -0.06 to 0.04) for cQFR and 0.01 (95% CI -0.03 to 0.05) for non-specified QFR]. FFR and QFR were highly correlated in all studies (see Appendix Figure 32): correlation coefficient 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 QFR.

4.5 Bivariate meta-analysis (QAngio)

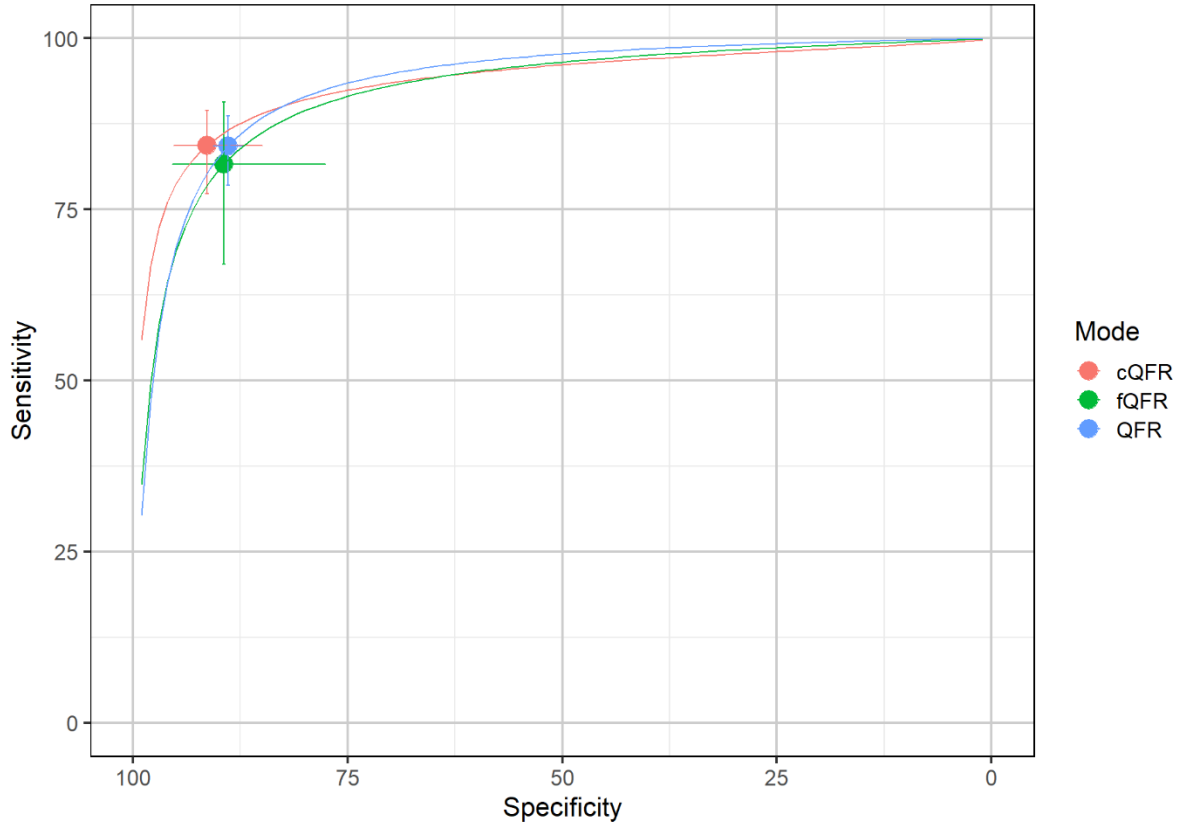
The results of the full bivariate meta-analysis are summarised in Figure 6 and Table 3. Results are almost identical to the univariate analyses, with no evidence of difference between fQFR and cQFR.

In order to include all studies in a single meta-analysis, and given the similarity of results across modes of QFR, we performed a further bivariate meta-analysis which combined all studies using only a single “mode” of QFR from each. In practice, this meant combining studies with cQFR results with studies not specifying how QFR was performed (and as a result, excluding fQFR assessments). This might be expected to give the most “optimistic” estimate of diagnostic accuracy, because fQFR is excluded. The results for this combined analysis are also in Table 3. The results are, inevitably, very similar to those for cQFR or non-specified QFR, but with narrower confidence intervals. We note that this arguably represents the best summary of the diagnostic accuracy of QFR, as it based on the maximum number of studies, but it is a post-hoc analysis not specified in the protocol.

Table 3 Results of bivariate meta-analysis

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

Figure 6 ROC plot of bivariate meta-analysis



The summary results and HSROC curves in Figure 6 demonstrate the high diagnostic accuracy of QFR and the similarity between the three analysed modes. The HSROC curve for fQFR lies consistently below that for cQFR, suggesting a possibility that fQFR may have slightly inferior diagnostic accuracy, but this difference is well within the bounds of uncertainty. This is in line with the expected use of QFR, where cQFR is calculated when the fQFR is in the range of 0.70 to 0.85

4.5.1 Meta-analysis of ICA studies

Five studies included in the meta-analysis also reported 2x2 table data on the diagnostic accuracy of using ICA alone, using 50% diameter stenosis as the cut-off with FFR < 0.8 as the reference standard. These five studies are summarised in Table 4. We note that reporting of diagnostic data on ICA may be subject to selection bias, as only a small subset of studies reported it, and they are likely to do so to demonstrate the superiority of using QFR over relying on ICA alone.

Table 4 Diagnostic accuracy of included ICA studies

Study	2D or 3D	N	Sensitivity			Specificity		
				95% CI			95% CI	
FAVOR II China Xu (2017)	2D	332	62.5	53.5	71.5	58.2	51.7	64.7
FAVOR II Europe-Japan Westra (2018)	2D	317	44.2	34.7	53.8	76.5	70.8	82.2
FAVOR Pilot Tu (2016)	3D	84	44.4	25.7	63.2	78.9	68.4	89.5
Mejia-Renteria (2019)	3D	300	69.9	62.1	77.6	70.7	63.8	77.7
Stahli (2019)	3D	516	34.0	24.7	43.3	91.6	88.9	94.3

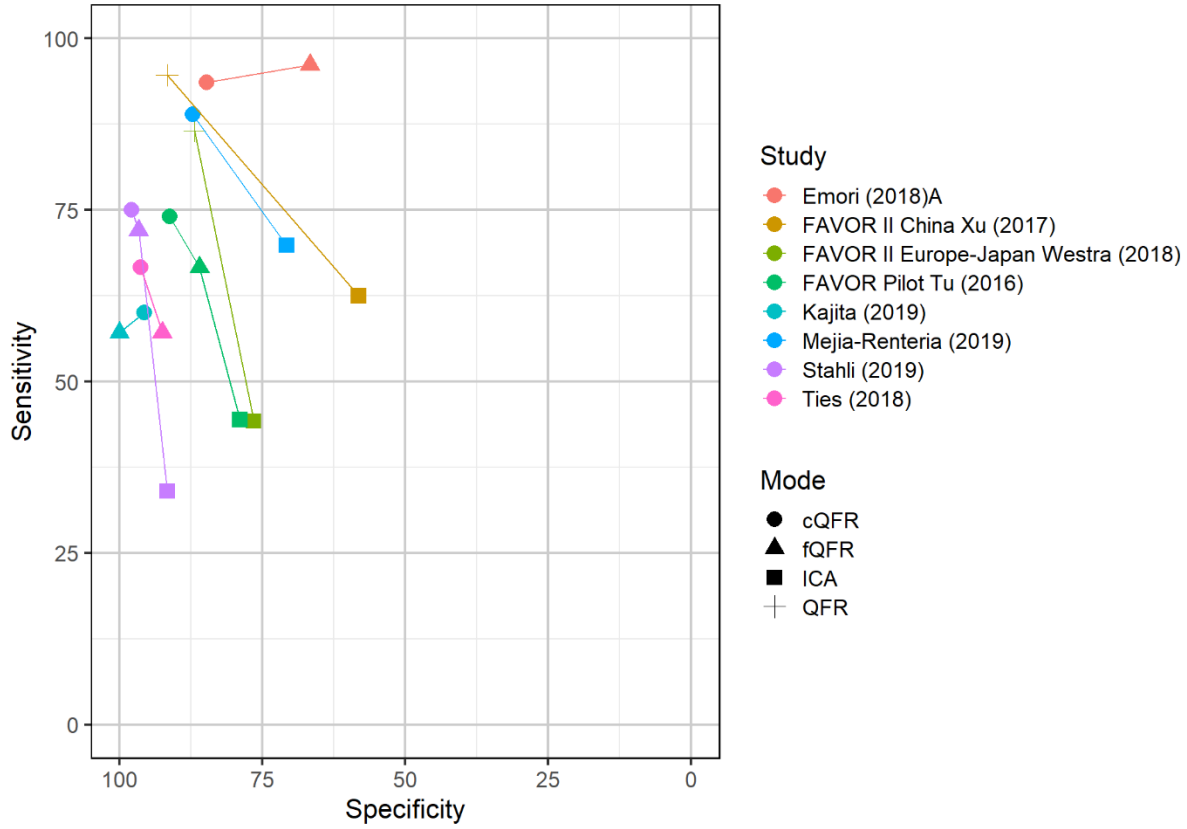
Given the limited number of studies, and because 2D and 3D ICA may have very different performance, no bivariate meta-analysis of these data is presented here. Based on the results of individual studies, the diagnostic accuracy of ICA appears poorer than QFR.

Twelve included studies reported area under the curve (AUC) estimates for diagnostic accuracy of using ICA alone. A meta-analysis of these studies gave a summary AUC fror 3D ICA of 0.71 (95% CI 0.66 to 0.76). For 2D ICA the summary AUC was 0.63 (95% CI 0.59 to 0.67). Both have lower AUC values than QFR, and it appears that 2D ICA may be inferior to 3D ICA.

4.5.2 Bivariate meta-analysis to compare tests

Eight studies in the meta-analysis compared two or more testing approaches: five of these compared using 2D or 3D ICA to QFR and five compared fQFR to cQFR. An ROC plot of results from studies reporting two or more tests is shown in Figure 7. In all five studies, ICA performed more poorly than QFR, with lower sensitivity and specificity. Differences between fQFR and cQFR were more mixed, with three studies suggesting cQFR has slightly higher sensitivity than fQFR, but the other two were not consistent with this.

Figure 7 ROC plot of studies comparing ICA, fQFR and cQFR



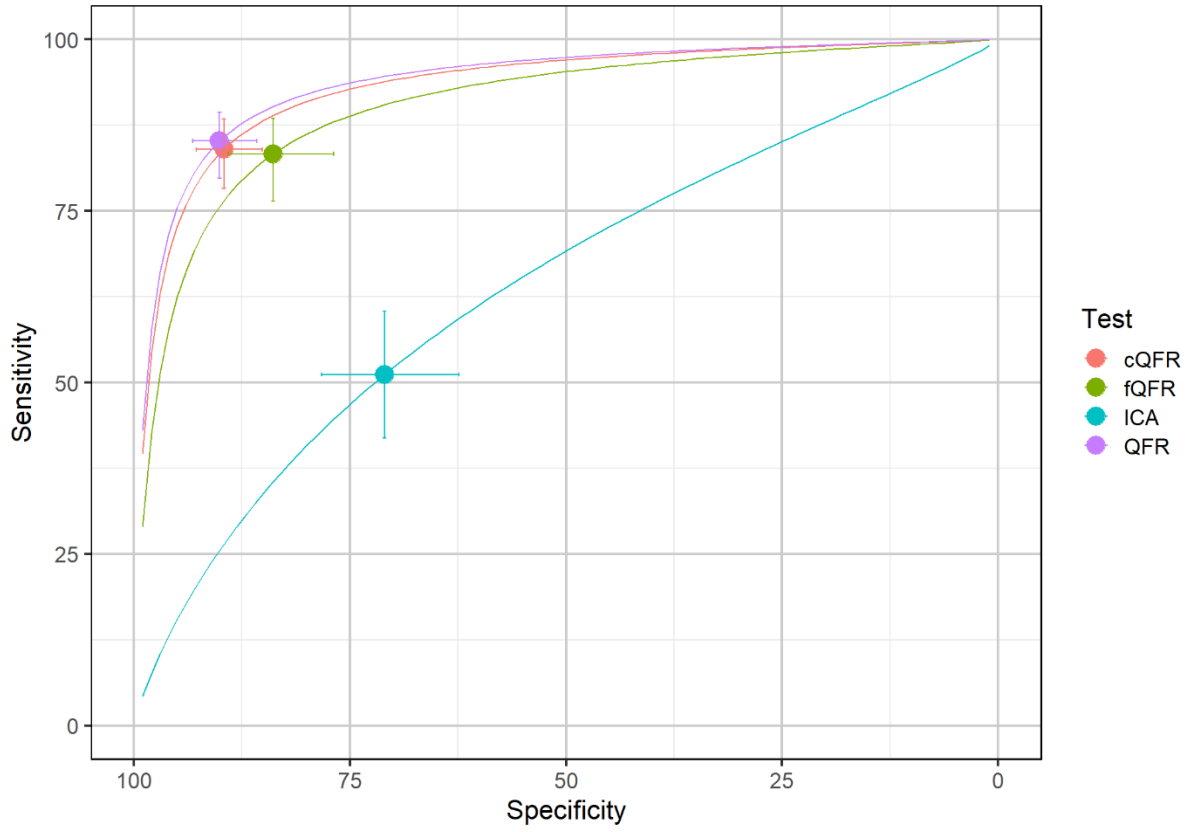
An indirect comparative bivariate meta-analysis accounting for these comparisons between studies is presented in Table 5 and Figure 8. These analyses show the clear inferiority of using ICA alone when compared to FFR as a reference standard. It is clearly inferior to using QFR in both sensitivity and specificity, with a sensitivity of only 51.2% and a specificity of 71.0%.

Unlike the earlier bivariate meta-analysis (Figure 6) the comparative analysis suggests that fQFR is slightly inferior to cQFR, mainly due to an inferior specificity (83.9% instead of 89.6%). This suggests that fQFR produces slightly too many false-positive results (where QFR ≤ 0.8 but FFR > 0.8). This might suggest that if an initial fQFR produces a result less than 0.8 it should be followed up by a confirmatory cQFR.

Table 5 Results of bivariate meta-analysis with comparison of tests

Mode	Sensitivity	95% CI		Specificity	95%CI	
cQFR	83.97	78.32	88.37	89.59	85.15	92.82
fQFR	83.32	76.42	88.50	83.91	76.91	89.08
QFR	85.20	79.76	89.38	90.09	85.80	93.19
ICA	51.16	41.86	60.38	70.99	62.39	78.30

Figure 8 ROC plot of bivariate with comparisons of tests



4.6 Impact of patient and study characteristics (QAngio)

4.6.1 Impact of study characteristics

ROC plots differentiating between studies reporting at patient, vessel or lesion level found no evidence that this affects diagnostic accuracy. There was no evidence of difference in diagnostic accuracy between prospective and retrospective analyses of QFR (see Appendix Figure 33 and Figure 34).

4.6.2 Impact of patient factors

Few studies reported diagnostic accuracy data in any form according to different patient characteristics (such as distinguishing between people with and without diabetes, or with and without multivessel disease). The limited evidence reported is discussed in section 4.9.

Given this lack of evidence, in order to investigate the impact on diagnostic accuracy of key patient factors, we have performed meta-regressions of sensitivity, specificity and diagnostic odds ratio against the mean value of these factors, where reported in papers. These analyses are obviously limited by being meta-regression of study-level proportions, rather than true analyses of patient-level data, and because of limited reporting of these factors across studies. For these analyses we did not separate fQFR from cQFR, but use one test per study (cQFR for preference), to maximise data. This was considered reasonable given that diagnostic accuracy does not strongly depend on mode of QFR used.

Table 6 shows the p-values from these meta-regression analyses. For most parameters there is no evidence of any association with diagnostic accuracy. However, this may be due to a lack of data rather than no association.

Four patient factors (diabetes, stable coronary artery disease, multivessel disease, and mean FFR) suggest a possibility of association, as all have at least one p-value below 0.05. Plots of the proportions of patients with these factors, against estimated sensitivity, specificity and log DOR are shown in Appendix Figure 35 to Figure 38.

The association between diabetes and diagnostic accuracy is partly driven by one study where nearly all patients had diabetes, but the trend for studies with more diabetic patients to have higher sensitivity and DOR remains even if that study is removed. There is a trend for specificity and DOR to decline as higher proportions of patients have stable coronary artery disease. Conversely, specificity and DOR increase as more patients have multivessel disease (although this is based on only five studies).

There is evidence that the lower the average FFR in a study, the higher the sensitivity and lower the specificity (but with no impact on the overall accuracy in terms of the DOR). We might therefore also expect some variation in diagnostic accuracy with any factor that lowers FFR (%DS, medical history etc.), but the data are too limited to confirm this

Table 6 P-values from meta-regression analyses

	DOR	Sensitivity	Specificity
Mean age	0.822	0.936	0.813
Sex	0.501	0.538	0.207
Diabetes	0.136	0.044	0.901
Mean %DS	0.753	0.149	0.466
Stable angina	0.574	0.266	0.345
Stable CAD	0.014	0.898	0.151
Previous MI	0.899	0.579	0.437
Acute MI	0.719	0.495	0.963
Multivessel disease	0.016	0.712	0.076
Diffuse CAD	0.307	0.868	0.472
Previous PCI	0.848	0.216	0.195
Mean FFR	0.988	0.008	0.019
% with FFR below 0.8	0.595	0.026	0.012

4.6.2.1 Subgroup analyses

Twelve studies reported diagnostic accuracy results stratified by patient or vessel characteristics [18, 26, 39, 54] [17, 21, 29, 35, 39, 48, 49, 55] and four studies reported results of multivariate regression analyses of predictors of QFR/FFR discrepancies.[12, 34, 47, 48] All studies were of QAngio.

The number of subgroup analyses was too small to allow meta-analysis and results are summarised narratively, and in figures. None of the analyses reported in the included studies were pre-specified in a prospectively registered protocol. All patient characteristics for which subgroup data were reported were specified in the review protocol (high/lowIMR, small/non-small vessel diameter, multiple/single lesion, diabetes/no diabetes, MI history), except three (LAD/no LAD vessel, CKD and acute MI), which are presented for the sake of completion.

Appendix Figure 39 shows an ROC plot for five studies reporting sensitivity and specificity by subgroups, and Appendix Figure 40 shows the diagnostic odds ratios for the same studies. Results of subgroup analyses reported in included diagnostic accuracy studies are summarised in Appendix Table 75 and Table 76.

Microcirculatory resistance

Two studies explored the effect of microcirculatory resistance on the accuracy of QAngio and showed inconsistent results.[26, 54] In both studies, patient populations were stratified according to microcirculatory status, defined by the index of microcirculatory resistance (IMR), the product of hyperemic T_{mn} and hyperemic distal arterial pressure and measured by pressure wire. Microirculatory dysfunction was defined as ≥23U (predefined as 75th centile of IMR values) in one study[54] and as ≥25U in the other.[26] Results differed significantly between the two studies. Although both found a statistically significant difference in diagnostic accuracy between high and low IMR groups, one study found that QAngio's accuracy was reduced in patients with high-IMR compared with low-IMR (sensitivity 86% vs. 90%; specificity 69% vs. 94%; AUC 0.88 vs. 0.96, OR of misclassification: OR 1.05 95% CI 1.02-1.08),[34] whilst the other found QAngio had higher sensitivity but lower specificity in the high IMR group (sensitivity 96.7% vs. 81.5%; specificity 64.2% vs. 77.2%).

Vessel characteristics and location

There was limited evidence that vessel characteristics and location were associated with different rates of QFR/FFR discrepancies, although two studies reported vessels with bifurcation/trifurcation lesions were associated with poorer diagnostic accuracy compared with other vessels. SYNTAX found that bifurcation/trifurcation were independent predictors for the increased incidence of false negative QFR (OR 1.81 95%CI 1.10 to 2.98) and one small study of 38 vessels reported that bifurcations lesions accounted for five out of six (83.3%) false measurements.[35] One study that included only patients with left main stenosis (85% left main bifurcation) had high sensitivity (84.8%) and moderate specificity (68.2%) (AUC 0.82 95% CI 0.71-0.93). No other studies reported on the potential impact of left main stenosis on diagnostic accuracy.

Results from studies evaluating the effect of small vessel disease on diagnostic accuracy were mixed. One study found higher sensitivity and AUC for cQFR in patients with small vessel disease (≤2.8mm

reference diameter) compared with other patients (sensitivity: 80.0% vs. 65.7%; specificity 98.5% vs. 97.2%; AUC: 0.89 95% CI 0.85 - 0.93 vs. 0.81 95% CI 0.76 - 0.86),[56]) whilst another study found that small vessel disease (≤2.5mm reference diameter) was associated with an increased incidence of false negative QFR (OR 1.67, 95%CI: 1.14 to 2.44) in a multivariate analysis. [12]

One study found that found no significant differences in QAngio accuracy between subgroups with LAD and non-LAD coronary arteries,[18] although a multivariate analysis from SYNTAX II found a non-statistically significant trend suggesting LAD may be associated with a higher rate of false positives (OR 0.53 95% CI 0.27-1.04), and that lesions located in side branches were associated with a higher rate of false positive QFR (OR 2.07, 95%CI: 1.14 to 3.76) and false negatives (OR 0.47, 95% CI 0.28-0.81).

One study found no significant difference in mean differences between QFR and FFR per lesion in patients with single and multiple lesions.[48], and multivessel disease was not a significant predictor of QFR/FFR discrepancy in a multivariate analysis conducted by another study.[34] FAVOR II-China found that accuracy of QAngio in patients with %DS 40-80% did not differ from the whole study population results.

Comorbidities and other patient characteristics

There was also limited evidence on the impact of patient comorbidities on the accuracy of QAngio. Two studies found no difference in diagnostic accuracy in subgroup analyses comparing patients with and without diabetes.[39, 55] Smit (2019) [55] found similar accuracy in diagnostic accuracy between diabetics and non-diabetics (sensitivity 71.0% vs. 69.0%, specificity 95.0% vs. 91.0%, AUC 0.91 vs. 0.93, per-vessel analysis). Results of per-patient analyses were also not statistically significant. Stahli (2019)[39] also found no statistically significant difference in AUC between patients with and without diabetes (0.84, 95% CI 0.76-0.90 vs. 0.87, 95% CI 0.83-0.90). On the other hand, FAVOR II Europe-Japan found in a multivariate regression that diabetes was associated with an increased chance of discrepancy between QFR and FFR (OR 2.88 95% CI 1.30-6.46).[47] One study found a higher mean discrepancy between QFR and FFR in a small subgroup of 21 patients with diabetes (MD=–0.059 ±0.07) compared with 173 non-diabetics (MD=–0.027 ±0.074);[29] the difference between the subgroups was statistically significant (p=0.039), although no further diagnostic accuracy results were reported.

One study that compared results for vessels of stable CAD patients with non-culprit vessels in MI patients found no significant difference in diagnostic accuracy between the two groups (sensitivity 90.1% vs. 96.2%, specificity 89.5% vs. 90.6%; AUC 0.946 vs. 0.967).[21] However, in a multivariate analysis another study found that acute coronary syndrome was associated with a significantly higher rate of misclassification between QFR and FFR (OR 3.97 95% CI 1.78–8.86). [34] One study

retrospectively compared single vessels in groups of 75 patients with and without prior MI found no significant difference for cQFR and fQFR between the two groups.[17] One study found a statistically significant difference in AUC between patients with and without CKD (0.67 95% CI 0.46 -0.88 vs. 0.89 95% CI 0.84 - 0.94, p=0.05).

No subgroup data were reported for the following review protocol variables: diffuse coronary artery disease, multiple stenosis in one vessel, chronic total occlusion, sex, age, ethnicity, and results of previous non-invasive tests, although sex, age and chronic total inclusion were reported as non-significant variables in reported regression analyses (see Appendix Table 77).

Overall, results from subgroup and regression analyses were limited by the number of studies and design issues such as small sample size and risk of confounding and should therefore be interpreted with caution. There was some evidence suggesting that diagnostic accuracy of QFR is reduced in bifurcation/trifurcation lesions. However, due to limited and sometimes inconsistent data there is insufficient evidence to conclude that patient or lesions characteristics significantly affect the diagnostic accuracy of QAngio.

4.6.2.2 Sensitivity analyses

We performed a number of sensitivity analyses to examine the impact of QUADAS risk of bias assessment and other potential causes of bias on the diagnostic accuracy meta-analyses.

As noted in section 4.6.1 there was no evidence that diagnostic accuracy varied by whether studies collected data prospectively or retrospectively, or whether the analysis was performed at patient, vessel or lesion level.

Repeating the main bivariate meta-analyses (as in section 4.5) by whether the QUDAS assessment was high risk of bias, low risk of bias or unclear (note: all conference abstracts were classified as unclear in this analysis) for each QUADAS category found no evidence of bias in diagnostic accuracy (see Appendix Figure 41).

4.7 Meta-analyses of data extracted from figures (QAngio)

In order to further investigate the diagnostic properties of QFR we digitally extracted data from all papers that presented either a plot of FFR against QFR, or a Bland-Altman plot of QFR and FFR. We preferred Bland-Altman plots for extraction, as these were found to be generally clearer and easier to extract. All extraction was performed by a single reviewer using the WebPlotDigitizer software.

We used digitised data extraction to reconstruct, approximately, the individual-level data for all included studies that presented a suitable figure. The extracted averages and differences between QFR and FFR from Bland-Altman plots were converted into their equivalent QFR and FFR values. This

extraction generated, approximately, the FFR and corresponding QFR for each participant in each study.

The extraction could not be perfect: the digitally extracted points were placed with some, minor error; overlap between points, or low image quality, meant that the number of extracted points was fewer than the total number of participants. We note also that the set of studies is not the same as in previous sections, because some studies presented diagnostic accuracy results, but no figure, or vice-versa. In all analyses, we focus on cQFR or non-specified QFR: fQFR is excluded.

Figure 9 shows the complete extracted data for QFR vs FFR, and Figure 10 a Bland-Altman plot of all data. The pattern of data is similar to that observed in most individual studies, with FFR and QFR being highly correlated; the correlation coefficient across all data being 0.803. The distribution of data appears homogeneous across studies (each colour on the plot represents a separate study), the data are centred around the line where FFR = QFR (red line on the figure). The data seem to broadly fit a highly correlated bivariate normal distribution, truncated at QFR and FFR values of 1.

The upper left pink region shows the “false-negatives” where QFR > 0.8 but FFR ≤ 0.8; The lower-right pink region shows the “false positives” where QFR ≤ 0.8 but FFR > 0.8. Only a minority of patients fall in these regions, and for most of these the difference between FFR and QFR is less than 0.1, confirming the consistency between FFR and QFR measurements.

The Bland-Altman plot shows that QFR and FFR values are generally very similar: 95% of QFR values are within 0.14 of the FFR; 90% are within 0.11, and 50% are within 0.04. The average difference between QFR and FFR is 0.001.

Figure 9 FFR against QFR for data extracted from figures

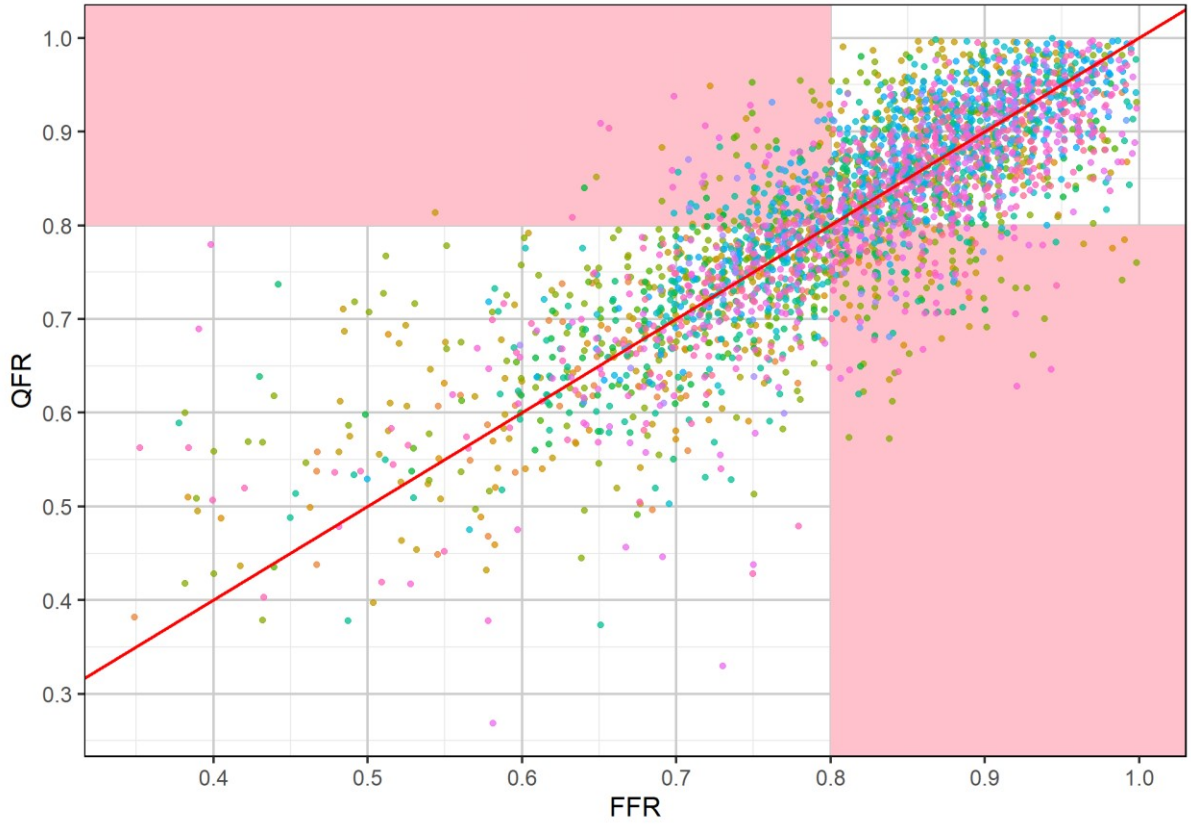
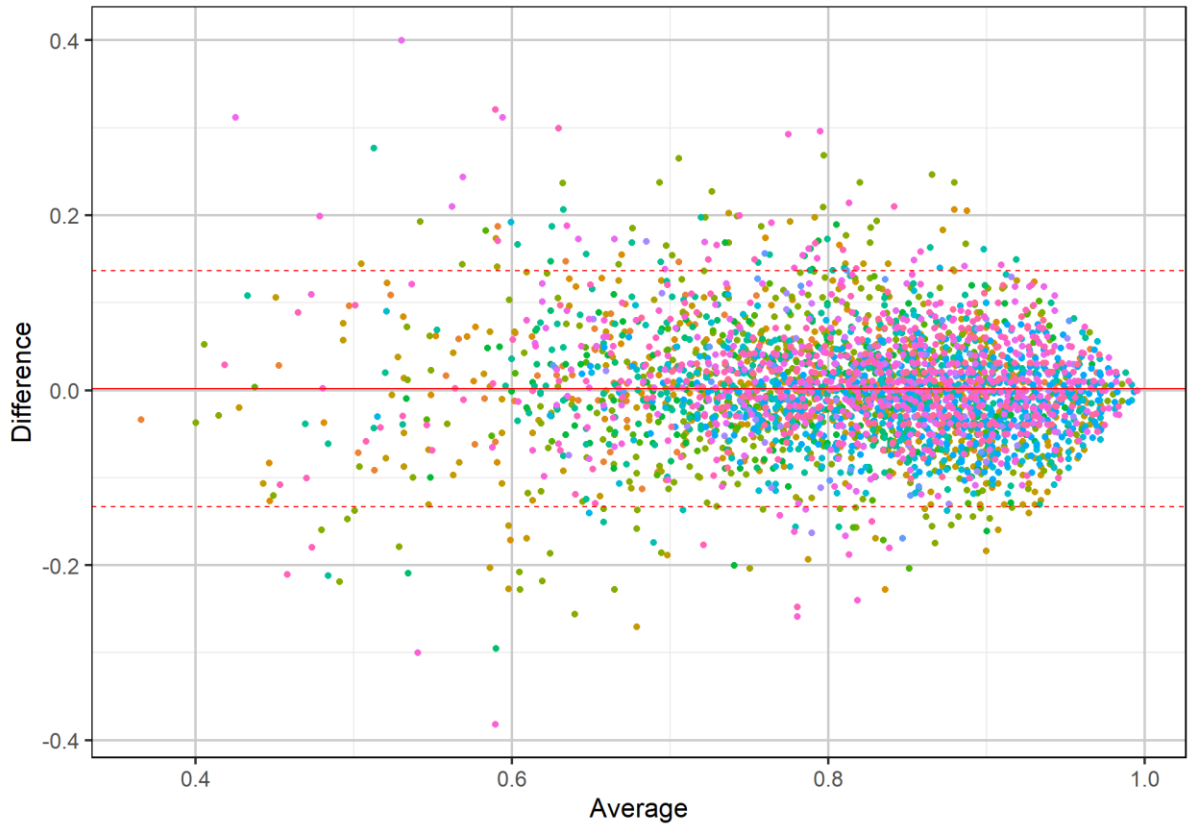


Figure 10 Bland-Altman plot for data extracted from figures



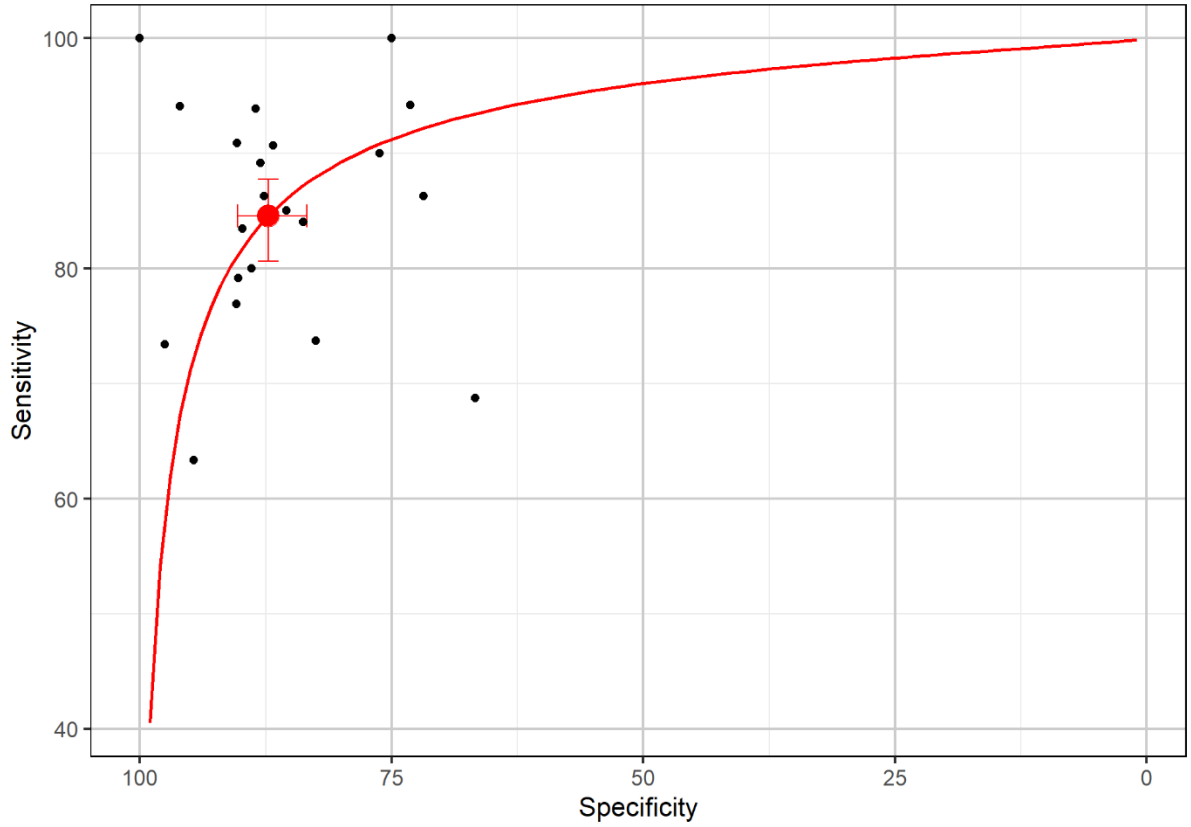
4.7.1 Meta-analysis of diagnostic accuracy

We calculated the diagnostic accuracy for each study based on extracted data, using the usual index test of QFR ≤ 0.8 and reference standard of FFR ≤ 0.8 as defining patients in need of coronary intervention. To investigate whether the extracted data could be used for analysis, we compared these diagnostic accuracy results to the results from 2x2 tables (used in previous meta-analyses in Section 4.5). The extracted sensitivity and specificity estimates are summarised in Appendix Table 71. Overall, 30 studies reported either 2x2 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.

In general, the number of data points from the extracted figure data were smaller than that reported in the studies. This is to be expected, as overlapping points will be missed when extracting from figures. There is mostly good agreement in diagnostic accuracy between the data sources, expect for a few cases where the figure data has lower sensitivity and mostly lower specificity (FAVOR II China, Hwang, Koltowski, Smit). Only one study (Kameyama) had better diagnostic accuracy when using data extracted from figures. This consistency suggests that using the extracted figure data for diagnostic analysis is reasonable, even though it represents a smaller sample size. The results of performing a bivariate meta-analysis for diagnostic accuracy using the extracted figure data is shown in Figure 11. The black points are the results in each study and the red dot is the result of the meta-analysis (with its HSROC curve). The summary sensitivity is 84.6% (95% CI 80.7 to 87.8) and specificity is 87.2% (83.4 to 90.3). This is similar to the results from the main analysis when cQFR and non-specified QFR were combined [sensitivity 84.3%; specificity 89.8%], albeit with slightly lower specificity, further confirming that analysing the extracted figure data is reasonable.

We note that this bivariate meta-analysis is presented to confirm that the extracted data reasonably represent the properties of the included studies: the bivariate meta-analyses in Section 4.5 should be taken as the primary analyses.

Figure 11 Bivariate meta-analysis of extracted figure data



4.7.2 Grey zone analysis

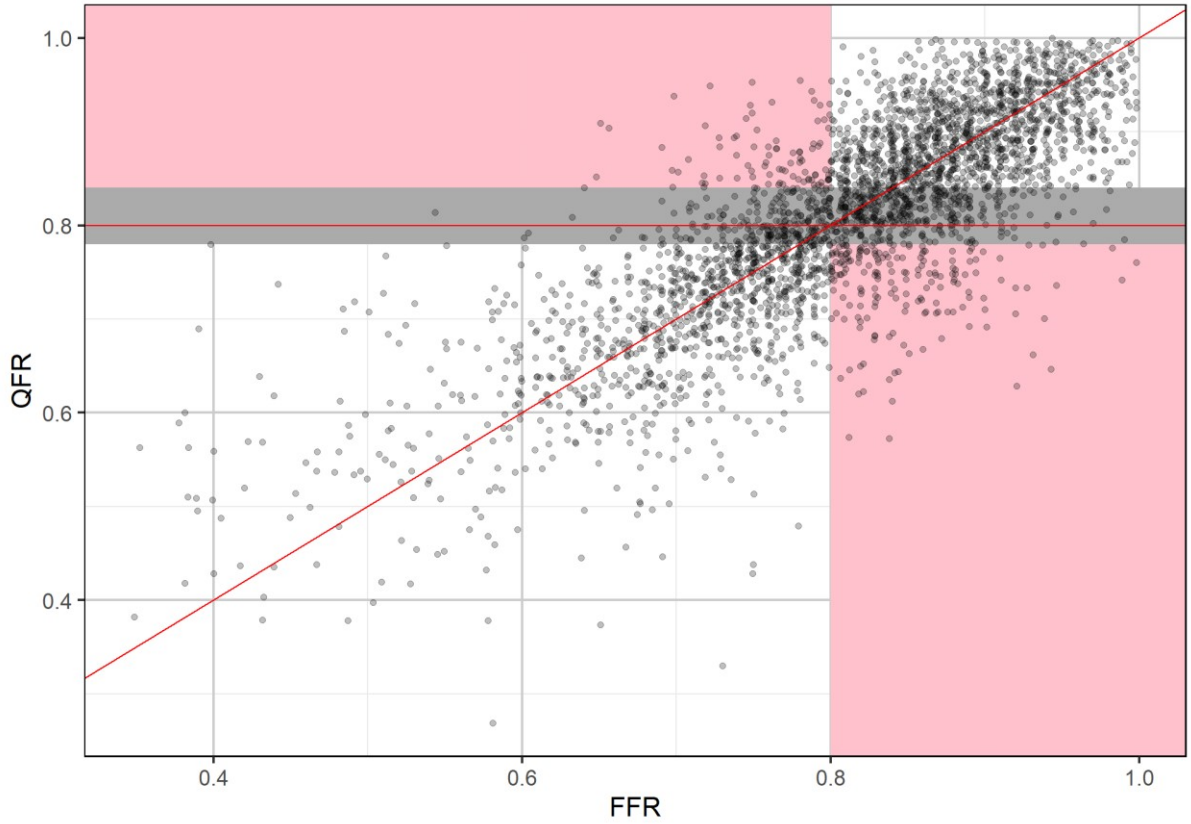
The main purpose of extracting data from figures is to permit an analysis where testing includes a "grey zone" of intermediate QFR values for which an FFR would be performed as a confirmatory test. The "grey zone" diagnostic procedure is:

5. Perform QFR
6. If QFR > 0.84 continue without stenting/bypass and defer FFR [test negative]
7. If QFR ≤ 0.78 proceed directly to stenting/bypass without FFR [test positive]
8. Otherwise perform an FFR and proceed based on that result (at 0.8 cut-off) [the grey-zone]

This means that for anyone within the grey zone there is perfect diagnostic accuracy, so false positive and negatives occur only in patients outside the grey zone.

Figure 12 shows the FRR and QFR data again, with the proposed grey zone highlighted. In total, across studies, 20.1% of all patients lie within the grey zone (accordingly up to 79.9% of patients would theoretically have a wire-free and adenosine-free procedure in this scenario). Of these grey-zone patients, 19.1% are "true positives" where both QFR and FFR are below 0.8; 50.2% are true negatives, with both tests above 0.8. Only 18.3% are false negatives and 12.4% false positives. Hence, only 30.4 % of patients in the grey-zone have discordant FFR and QFR results (relative to the 0.8 threshold).

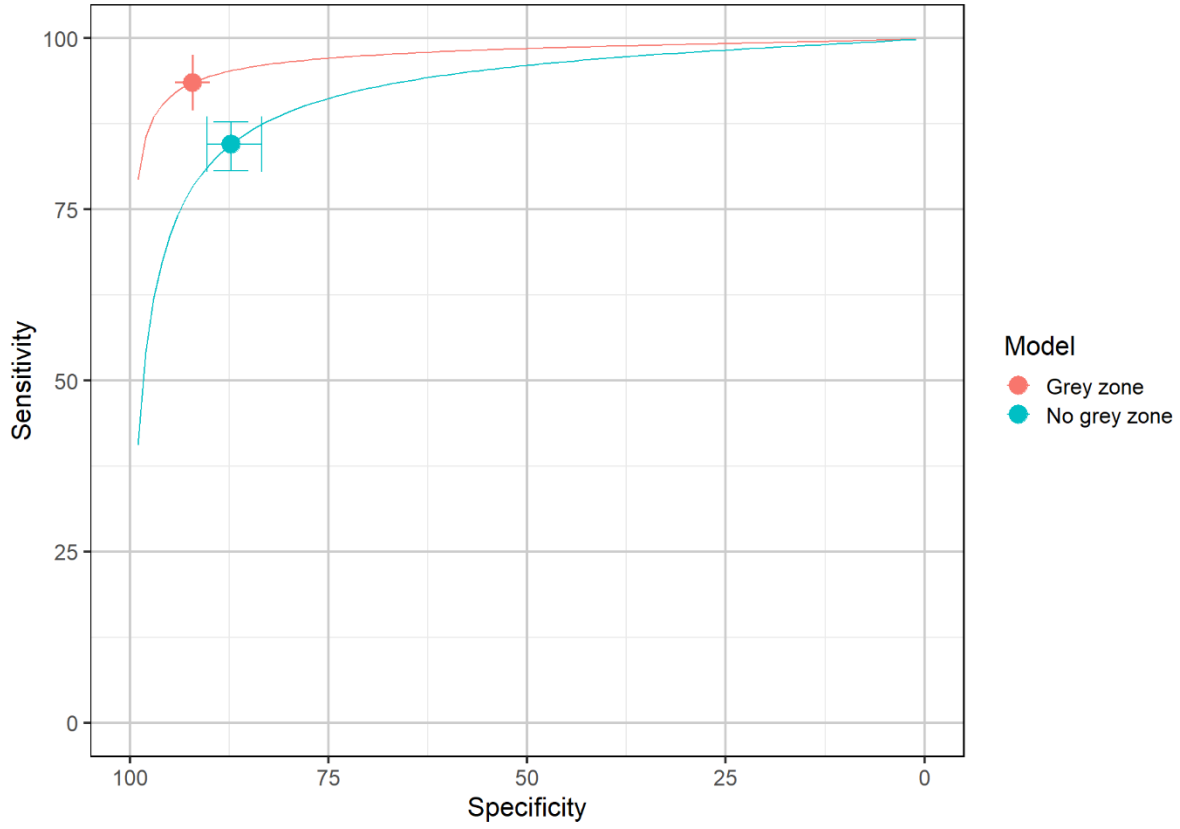
Figure 12 FFR and QFR data showing QFR grey zone between 0.78 and 0.84



Within the grey zone, differences between FFR and QFR are small. This is shown in Appendix Figure 42, categorised by true positives, false positives etc. Very few patients in the grey zone differ in test values by more than 0.1, and most by 0.05 or less.

The diagnostic accuracy when using the grey zone improves, as would be expected, to a sensitivity of 93.1% (95% CI 90.1 to 94.9) and a specificity of 92.1% (88.3% to 94.5%). Figure 13 shows the result of this meta-analysis (with its HSROC curve) compared to the meta-analysis without the grey zone presented in Section 4.5. Clearly using the grey zone improves diagnostic accuracy compared to QFR alone, due to the 3.7% of patents reclassified from test negative to positive and 2.5% who are reclassified in the opposite direction. However, this improvement depends on assuming that the 0.8 threshold of FFR genuinely separates those who need intervention from those who do not.

Figure 13 Diagnostic accuracy of QFR with and without using the grey zone



As an alternative to using the manufacturer-specified grey-zone, we also examined what grey zone thresholds would be required to achieve a sensitivity and specificity of 90 and 95%. This is summarised in Table 7. This suggests that the manufacturer-recommended grey zone favours high sensitivity over high specificity.

Table 7 Approximate grey zone thresholds required for sensitivity and specificity of 90 or 95%

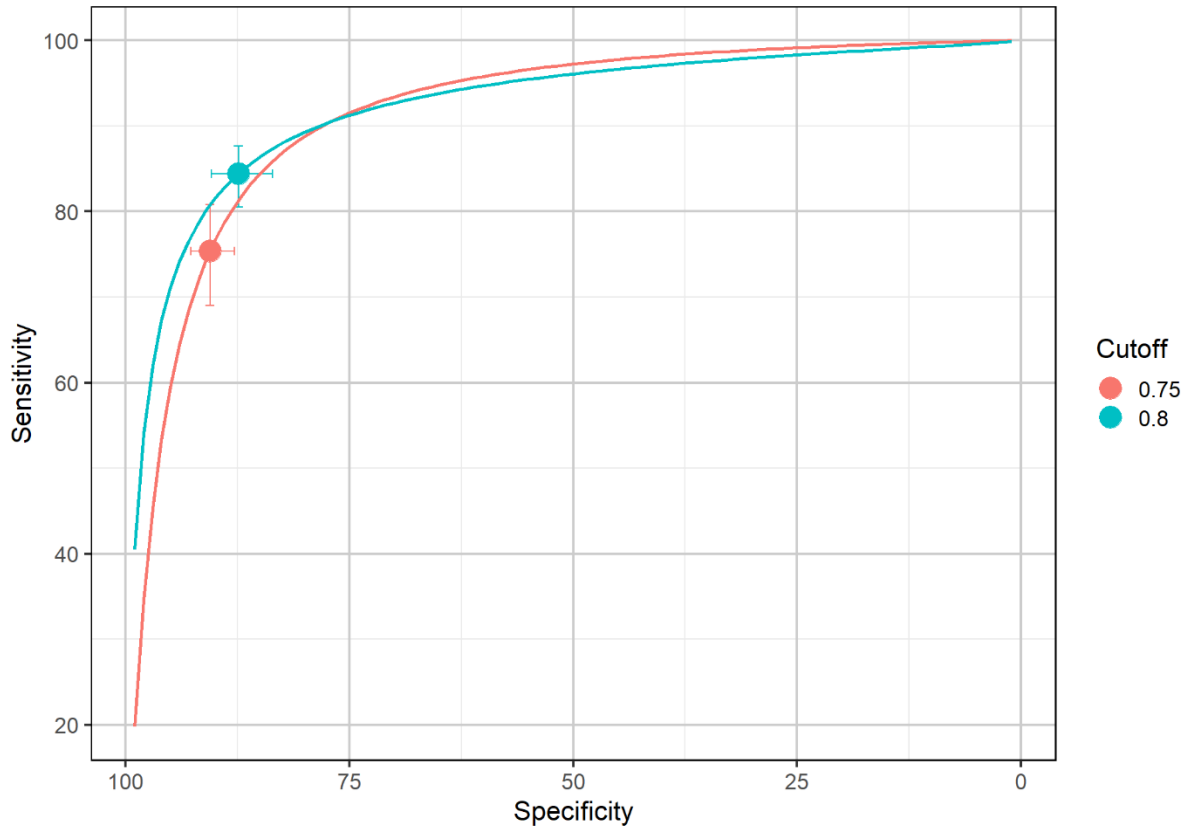
For sensitivity of:	For specificity of:	Lower grey-zone threshold	Upper grey zone threshold
90%	90%	0.78	0.82
90%	95%	0.75	0.82
95%	90%	0.78	0.85
95%	95%	0.75	0.85

4.7.3 Alternative FFR thresholds

The IRIS-FFR study[10] found that only for FFR ≤ 0.75 did the risk of major adverse cardiac events become significantly lower in patients with revascularized lesions than in those where revascularization was deferred. This suggests that the current threshold of 0.8 for planning revascularization may not be clinically appropriate. Using the extracted figure data, we can

investigate the diagnostic accuracy of QFR vs FFR at other thresholds. For example, if the threshold for both QFR and FFR is 0.75 then the diagnostic accuracy becomes sensitivity 75.4% (69.0 to 80.8) and specificity 90.6% (87.9 to 92.7). This is compared to the previous meta-analysis at the threshold of 0.8 in Figure 14. Using a 0.75 threshold leads to slightly lower sensitivity, but higher specificity. The two ROC curves, however, are almost identical, suggesting no overall change in diagnostic accuracy.

Figure 14 Diagnostic meta-analysis using FFR/QFR thresholds of 0.75 and 0.8



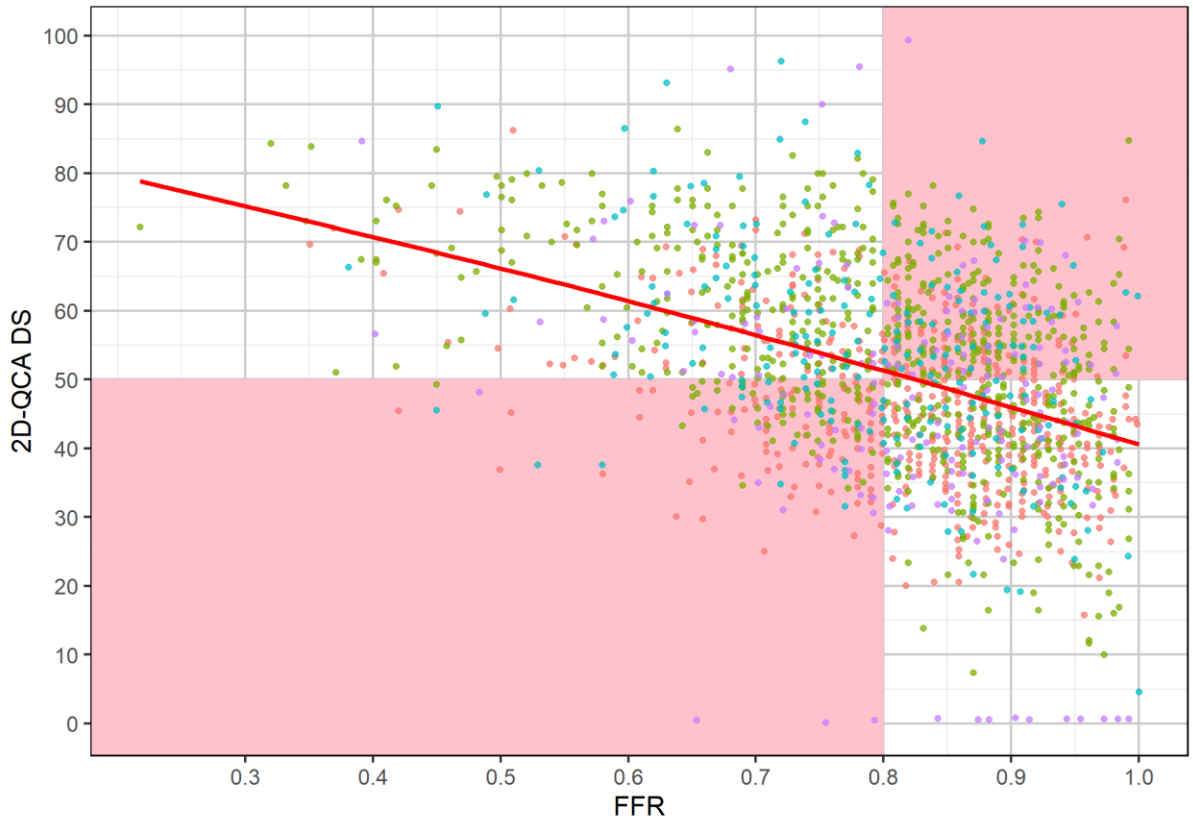
4.7.4 Meta-analysis of extracted figure data for 2D ICA

In order to inform the economic analyses an additional pragmatic search for studies that compared 2D ICA to FFR assessment was performed to identify studies that presented sufficient granular data (such as scatter plots or Bland-Altman plots) from which ICA and FFR data could be extracted. This search identified four such studies (see Appendix Table 72).[57-60]

Figure 15 shows the plot off all extracted data from these four studies. It can be seen that, when compared to the equivalent figure for QFR (Figure 9), 2D ICA is much more weakly correlated with FFR (correlation coefficient -0.432). There are many false negatives (bottom left pink region) and

false positives (top right pink region) when using 50% diameter stenosis and the index test and FFR ≤ 0.8 as the reference standard.

Figure 15 Extracted data on 2D ICA compared to FFR



We performed a bivariate meta-analysis of these extracted data, using the same approach as for QAngio. The summary sensitivity was 62.6% (95% CI 51.5 to 72.5) and specificity was 61.6% (95% CI 53.1 to 69.4). This is a substantially lower diagnostic accuracy than for QAngio.

4.7.5 QAngio: studies not included in meta-analysis

Appendix Table 73 presents results from the six studies of QAngio that reported diagnostic accuracy results but were not included in the meta-analysis due to insufficient data.[11, 19, 30, 33, 35, 44] All studies were reported as conference abstracts only (although one was subsequently published after the cut-off date for conducting meta-analyses).[30] One QAngio prototype study recorded QAngio analyses prospectively (on-site analysis), and re-ran analyses retrospectively after 'essential modifications' (no further details reported). All other studies were retrospective and did not report which version of QAngio was used.[19, 30, 33, 35, 44]

Results broadly reflected the findings of the meta-analysis. All studies reported moderate to high diagnostic accuracy for QAngio compared with FFR. There was significant heterogeneity in reported diagnostic accuracy estimates. Sensitivity ranged from 64.0% to 91.8%, and specificity from 68.2% to

97.3%. Where reported, PPV estimates ranged from 74.0% to 84.8% and NPV from 68.2% to 93.0%. AUC ranged from 0.77 (95% CI 0.67 - 0.87) to 0.99 (95% CI 0.97-1.00). Correlation coefficients (r) also varied significantly, ranging from 0.578 to 0.801.

The WIFI prototype study reported moderate sensitivity (0.64 (95% CI 0.48-0.77)) and specificity (0.8 (95% CI 0.66-0.89)) in its initial analyses. Following 'essential modifications' (no further details reported) a blinded in-center core laboratory reanalysis was performed and improved both sensitivity (0.66, 95% CI 0.51-0.79) and specificity (0.86, 95%CI 0.73-0.93).

4.7.6 QAngio: other modes

Three studies reported results for QAngio modes other than cQFR and fQFR.[29, 43, 45] Their results are presented in Appendix Table 74. Two small studies (n=15 and 84 vessels) reported results for aQFR,[43, 45] and one larger study (n=306 lesions) tested iQFR, lQFR and vQFR.[29] Sensitivity of aQFR per vessel ranged from 78% to 100%, and specificity from 91% to 93%; one study reported a high AUC (0.90, 95% CI 0.81-0.96) for aQFR, and similar results in per-patient analyses. One study found that iQFR had higher diagnostic accuracy overall (sensitivity 83.3%, specificity 86.6%, AUC 0.936) compared with vQFR (sensitivity 90.5%, specificity 69.7%, AUC 0.900) and lQFR (sensitivity 91.1%, specificity 71.7%, AUC 0.822).

4.8 CAAS vFFR

The review identified four publications reporting the diagnostic accuracy of CAAS vFFR.[15, 16, 23, 53] One is the original FAST study of vFFR, one is a conference abstract reporting an update to FAST (FAST EXTEND). There were two other independent studies, one of which has only been published as a conference abstract.[23] All studies performed CAAS vFFR analyses retrospectively (offline), and two were conducted in a single centre,[15, 16] One study was funded by CAAS vFFR manufacturer.[15] All studies compared CAAS vFFR against FFR as reference standard.[15, 16] One study was funded by CAAS vFFR manufacturer (Pie Medical Imaging);[15] Two studies included a mixed population of stable angina, unstable angina or NSTEMI.[15, 16]

We only included studies that explicitly reported that the CAAS system was used, or where this was confirmed by the authors. Other studies of vessel-FFR were identified, but are not included if other technologies were used or the precise technology used could not be determined. Further details on excluded studies are reported in Appendix Table 68. Only one of the studies[16] reported a 2x2 table of diagnostic accuracy, and only one[53] presented a Bland-Altman plot which we digitally extracted to calculate diagnostic accuracy. The two conference abstracts reported only sensitivity and specificity without confidence intervals. In order to construct approximate confidence intervals we assumed that the proportion of patients with FFR ≤ 0.8 was 29% (the rate observed in the Masjedi FAST study), and constructed 2x2 diagnostic data under that assumption.

The sensitivity and specificity from all publications is summarised in Figure 16. There is notable heterogeneity across even this small number of studies. In particular, the ILUMIEN 1 study found considerably lower sensitivity and specificity that the FAST studies, and the Jin (2019) study had lower sensitivity, but slightly higher specificity. Only one of the studies16 reported a 2x2 table of diagnostic accuracy, and only one53 presented a Bland-Altman plot which we digitally extracted to calculate diagnostic accuracy. The two conference abstracts reported only sensitivity and specificity without confidence intervals. In order to construct approximate confidence intervals we assumed that the proportion of patients with FFR ≤ 0.8 was 29% (the rate observed in the Masjedi FAST study), and constructed 2x2 diagnostic data under that assumption.

The sensitivity and specificity from all publications is summarised in Figure 16. There is notable heterogeneity across even this small number of studies. In particular, the ILUMIEN 1 study found considerably lower sensitivity and specificity that the FAST studies, and the Jin (2019) study had lower sensitivity, but slightly higher specificity.

Table 8 summarises the properties of the CAAS vFFR studies. Only one of the studies[16] reported a 2x2 table of diagnostic accuracy, and only one[53] presented a Bland-Altman plot which we digitally extracted to calculate diagnostic accuracy. The two conference abstracts reported only sensitivity and

specificity without confidence intervals. In order to construct approximate confidence intervals we assumed that the proportion of patients with FFR ≤ 0.8 was 29% (the rate observed in the Masjedi FAST study), and constructed 2x2 diagnostic data under that assumption.

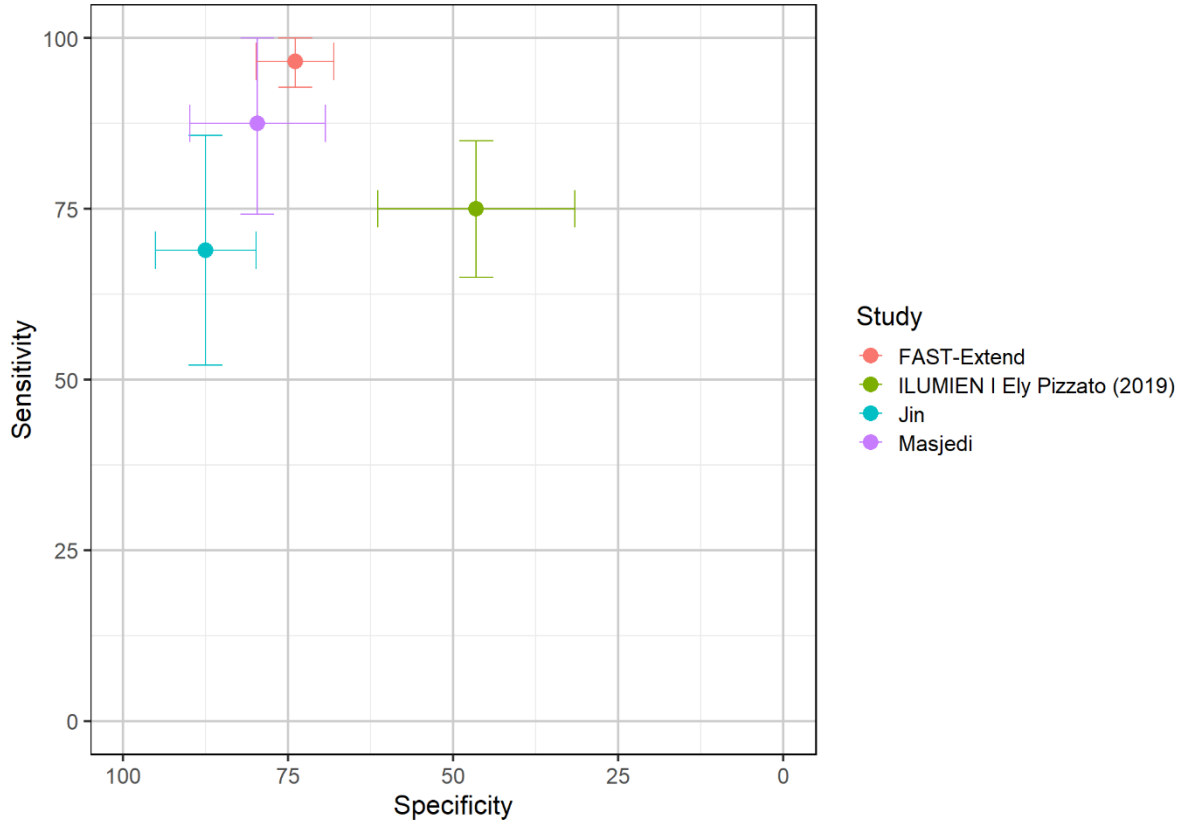
The sensitivity and specificity from all publications is summarised in Figure 16. There is notable heterogeneity across even this small number of studies. In particular, the ILUMIEN 1 study found considerably lower sensitivity and specificity that the FAST studies, and the Jin (2019) study had lower sensitivity, but slightly higher specificity.

Table 8 Properties of the CAAS vFFR studies

Study	N	Test	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Correlation
Jin (2019)[23] conference abstract	101 vessels (82 patients)	CAAS vFFR	68.2%	87.3%	NR	NR	0.719 (0.621-0.804)	NR
		QAngio (cQFR)*	83.5%	31.9%	NR	NR	0.886 (0.807-0.940)	NR
		QAngio (fQFR)*	72.7%	89.9%	NR	NR	0.882 (0.803-0.938)	NR
ILUMIEN I (2019)[16]	115 lesions (115 patients)	CAAS vFFR 8.1	75.0%*	46.5%	70.1%*	52.6%*	NR	r=0.449 (95% CI 0.290 to 0.584 p<0.0001)
FAST Masdjedi et al. 2019[53]	100 patients	CAAS vFFR	NR	NR	NR	NR	0.93 0.88 - 0.97	r=0.89
		3D ICA (%DS)	NR	NR	NR	NR	0.66 0.55 - 0.77	
FAST EXTEND[15] conference abstract	303 patients	CAAS vFFR 8.0	97%	74%	85%	89%	0.95 (0.93-0.98)	r=0.89
		3D ICA (%DS)	NR	NR	NR	NR	0.63 (0.55-0.67)	NR

* ICA at lower radiation saved mode of 7.5 frames/second

Figure 16 Sensitivity and specificity of CAAS vFFR studies



4.8.1 Bivariate meta-analysis (CAAS vFFR)

The results of bivariate meta-analysis of these studies are presented in Table 9. As the FAST and FAST-Extend studies overlap we report meta-analysis using each of these (and excluding the other). While diagnostic accuracy is reasonable in both analysis, confidence intervals are wide, reflecting the limited data and high heterogeneity. In both cases, specificity is lower than estimated for QFR (around 89%). When using FAST-Extend sensitivity is similar to QFR (around 84%), but when using the earlier FAST study sensitivity for CAAS vFFR is lower than for QFR. These meta-analyses should be interpreted with caution, because they required imputation of data for two studies on the prevalence of FFR results below and above the cut-off of ≤0.80, and because of the high heterogeneity across studies.

Table 9 Bivariate meta-analysis of CAAS vFFR studies

Analysis	Sensitivity	95% CI		Specificity	95%CI	
Using FAST [Masjedi]	75.98	66.86	83.22	74.38	51.32	88.89
Using FAST-Extend	84.86	61.76	95.11	72.20	50.30	86.95

Only one study[23] has directly compared CAAS vFFR with QFR, and this is currently reported only as a conference abstract. That study concluded that diagnostic performance of vFFR was poorer than for QFR, with AUCs of 0.719 (95% CI 0.621 to 0.804) for vFFR and 0.886 (95% CI 0.807 to 0.940) for cQFR.

4.8.2 Subgroup and sensitivity analyses (CAAS vFFR)

There was insufficient data to conduct any subgroup analyses or meta-regressions to investigate whether the diagnostic accuracy of CAAS vFFR varied with patient or study characteristics. Sensitivity analyses according to study quality were not feasible.

As only one study presented a figure with extractable data, analyses of these data were not performed. No further data suitable for narrative review or synthesis was identified.

4.9 Clinical outcomes

4.9.1 Morbidity, mortality and major adverse events

Three cohort studies reported mortality or major clinical outcomes in eligible patients with QFR (QAngio) measurements.[27, 38] All found that a clinically significant QFR was associated with a higher incidence of long-term major cardiovascular adverse events. No data were reported for CAAS vFFR. Results are summarised in Appendix Table 79 and below.

Spitaleri (2018)[38] included patients with multivessel disease who underwent revascularisation as part of a large randomised trial of PCI in 1498 STEMI patients where at least one non-culprit lesion (NCL) was left untreated.[61] QFR was calculated in NCLs in a subgroup of 110 patients following revascularization. Patients with QFR values >0.80 in all NCLs were classified as having functional complete revascularization (n=54), and those with at least one NCL with QFR value ≤0.80 were classified as having 'functional incomplete' revascularization (n=56). Patient-oriented cardiac events (POCE, defined as cumulative occurrence of all-cause death, any myocardial infarction, and any coronary revascularization) were measured at 5-year follow-up. A total of 39 (35%) patients experienced an adverse event. The cumulative incidence of patient-oriented cardiac events was higher in the group with QFR value ≤0.80 (46%) compared with the group with >0.80 QFR (24%) (HR 2.3 (95% CI 1.2-4.5), p=0.01). Further individual POCE outcomes are reported in Appendix Table 79.

Kanno (2019)B[27] (conference abstract only) evaluated 212 de novo intermediate coronary lesions in 212 patients with deferred revascularization based on FFR values above 0.80. Baseline and physiological indices including cQFR were compared between patients with and without major adverse cardiovascular event-MACE (cardiovascular death, non-fatal MI, target vascular revascularization, and non-target vascular revascularization) during 4-year follow-up. MACE incidence at four years follow-up was 5.7%. In patients with MACE, cQFR was lower than that in

patients without MACE (mean or median 0.80 vs 0.88, p=0.030). On logistic regression analysis, cQFR≤0.8 was a significant predictor of MACE (OR 5.60, 95% CI 1.69-18.6, p=0.005).

Hamaya (2019)[20] included a population of 549 patients with stable 3-vessel disease who underwent cQFR. At median 2.2 years follow-up, patients with MACE had lower cQFR in all three vessels than those without MACE (2.76 [2.64-2.88] vs. 2.64 [2.49-2.73], p<0.001), and 3-vessel cQFR was a statistically significant predictor of MACE in multivariate analyses (HR 0.97, 95% CI 0.96-0.99). cQFR was also a better predictor of remote revascularisation (≥3 months) compared with %DS (AUC 0.73, 95% CI: 0.65-0.79 vs. AUC 0.66, 95% CI: 0.56-0.74, p=0.043).

4.9.2 Subsequent use of invasive pressure-wire FFR

No studies of QFR prospectively evaluated the impact of QFR use and subsequent reductions in use of adenosine and pressure-wire procedures. However, five 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.[26, 34, 37, 47, 48]

Results are summarised in Table 10. None of these studies used the grey zone boundaries recommended by the manufacturer (0.78-0.84), and only two studies used the same grey-zone.[37, 47] All studies derived their grey-zone boundaries from their own cohort, except one[37] which used boundaries defined by another study.[47] Diagnostic accuracy criteria of QFR against FFR used to derive grey-zone boundaries varied across the studies (e.g. minimum sensitivity and specificity of the grey-zone was above 95% in one study,[47] and above 90% in another).[48] Each study retrospectively modelled a QFR–FFR hybrid strategy using QFR as the main diagnostic method and only performing FFR measurements in their defined grey zone. Despite the variety of choice of grey-zones and how they were defined, all are broadly similar, to each other and to the manufacturer specified definition used in the meta-analysis in Section XX.

All simulated grey-zone strategies were associated with a large percentage of adenosine/FFR procedures (hypothetically) avoided, ranging from 42% to 68%. The widest grey-zone area (0.71-0.90)[48] was associated with the lowest proportion of adenosine/FFR-free procedures (42%), and the narrowest boundaries (0.77-0.86, 0.78-0.87) associated with the highest proportion of procedures avoided (61% to 68%)[37, 47, 48] None of the simulations modelled the clinical impact of delayed FFR in patients with an FFR below 0.8.

Table 10 Adenosine & 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/FFR procedures avoided
FAVOR II Europe-Japan Westra (2018)[47]	0.77-0.86	Sensitivity & specificity >95%	64%

Kanno (2019) (A)[26] (conference abstract)	0.73-0.84	PPV & NPV>90%	52%
Mejia-Renteria (2019)[34, 62]	0.74-0.84	>95% agreement	59%
Smit (2019)[37]	0.77-0.86	Sensitivity: 95%, specificity: 92.5%	61%
WIFI II [48]	0.78-0.87 0.71-0.90	Sensitivity & specificity >90% Sensitivity & specificity >95%	68% 42%

4.9.3 Inter-observer variability

Eight studies reported outcomes data on reproducibility of QFR readings between two different analysts (Appendix Table 80). One study directly compared QAngio and CAAS vFFR,[23] six studies evaluated QAngio only[14, 21, 22, 24, 30, 42] and one CAAS vFFR only.[53] Three studies were only reported as conference abstracts.[22-24] The number of single measurements analysed ranged from 10 to 101 vessels. All QFR measurements were performed and compared retrospectively (offline) where reported. Only two studies explicitly reported blinding analysts to each other's readings.[42, 53]

QFR was found to have moderate to high level of inter-rater reliability. Two studies of QAngio reported mean differences ≤0.01 in repeated QFR measurements between analysts.[21, 42] One study reported a moderate correlation between three separate raters (mean intra-class correlation (ICC) 0.614 (95% CI 0.464-0.728)). Two studies reported high ICC results, one in stable angina patients (r=0.990)[30] and the other in non-culprit lesions of STEMI patients (r=0.991).[14] Another study found that inter-rater reliability was higher for cQFR (R^2=0.82) than fQFR (R^2=0.70) and ICA %DS (R^2=0.67).[24] One study found high inter-rater repeatability for QAngio (fQFR: 0.001 (SD0.036) and cQFR: 0.001 (SD0.049)) as well as CAAS vFFR (0.005 (SD0.037)) and no statistically significant differences between raters' measurements. Inter-rater reliability was also high in the FAST study across 100 repeated CAAS vFFR measurements (r=0.95).[53]

4.9.4 Intra-observer variability

Eight studies reported outcomes data on intra-observer reproducibility of QFR readings (Appendix Table 81). Seven studies evaluated QAngio only[13, 14, 22, 24, 30, 42, 51] and one study directly compared QAngio and CAAS vFFR.[23] Five studies were only reported as conference abstracts.[13, 22-24, 51] Where reported all measurements were performed retrospectively (offline). The time gap between initial and repeated measurements was reported in four studies and ranged from three days to two weeks.[13, 24, 42, 51]

All studies except one[22] reported a high level of intra-rater reliability for QFR. One study that assessed QFR readings independently by 3 analysts twice among 100 vessels reported a moderate

ICC coefficient (r=0.428). Where reported, r coefficients for QAngio in other studies ranged from 0.958 to 0.997, and mean differences between repeat measurements from 0.00 (SD 0.03) to 0.016 (SD 0.06). One study found that R^2 were higher for fQFR (0.91) and cQFR (0.94) than %DS measured by ICA (0.76).[24] One study that evaluated both QAngio and CAAS vFFR found high levels of repeatability and no statistically significant changes between repeated tests (cQFR: MD 0.009±0.053, p=0.230; fQFR: MD 0.016±0.060, p=0.066; vFFR: MD 0.008±0.040, p=0.175).

4.9.5 Test failures: rates and reasons

Appendix Table 82 reports rates of exclusions from diagnostic accuracy studies and reasons for exclusion. Sixteen studies did not report rates of patient exclusions or reasons for exclusion.[11, 13, 19, 20, 22, 26, 28, 30, 41, 45] [15, 32, 33, 35, 36, 51] Exclusion rates varied widely, from 6% to 92%, although this is partly due to differences in patient selection criteria, reporting and methods of calculating exclusions rates (e.g. out of total population considered for eligibility vs. out of total number of patients with FFR). This limits the comparability of exclusion rates across the studies.

Issues with acquisition and quality of angiographic images (e.g. lack of at least two projections with 25% degree angle in between, or poor image quality) were the most reported cause of exclusion, with 15 studies reporting it as their main reason for excluding patients from QFR analyses.[14, 17, 18, 21, 25, 43, 46, 47] [12, 29, 34, 39, 40, 53] [16] Anatomical features of arteries (e.g. excessive overlapping or foreshortening, ostial lesions, severe tortuosity) were the second most commonly listed reason for exclusion. Rates of exclusions 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 QFR.

Both CAAS vFFR that reported reasons for exclusion reported high exclusion rates (63% and 65%) although both studies were retrospective.[16, 53] In both studies the majority of exclusions were explained by angiographic image processing issues (rather than directly due to CAAS vFFR). For instance, 83% of exclusions in ILUMIEN were due to lack of at least two angiographic projections, table movement during ICA or pixel resolution incompatibility. ILUMIEN concluded that careful adaptions in acquisitions of ICA images could reduce test failure.

4.9.6 Other outcomes

No evidence was reported in QAngio and CAAS vFFR studies for any of the following protocol-specified outcomes: impact of QFR on the rate revascularisation procedures, adverse events related to the diagnostic procedure, adverse events related to revascularisation, distress, anxiety and similar harms caused by QFR, vFFR, invasive FFR or iFR, number of vessels with stent placements, health related quality of life and radiation exposure.

4.9.7 Simulation study of clinical effectiveness

Given the very limited data on clinical effectiveness of QAngio reported in publications, we performed a simulation study to investigate the possible impact of using QAngio, compared to FFR, on actual coronary outcomes. The full methods are set out in Section 4.1.6.5, but briefly:

This simulation study treats the complete data extracted from figures (3192 observations) as a representative sample from the true population of FFR and QFR measurements. To predict coronary outcomes we used the results of the recent IRIS-FFR registry report, representing 5846 patients who were either "revascularized" (stent or bypass surgery) or "deferred" (continued with current management without surgery) based on their measured FFR result.

The IRIS-FFR study used major cardiovascular events (MACE, a composite of cardiac death, myocardial infarction and repeated/emergency revascularization) 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 we simulated whether each person had a MACE event if they were "deferred" or if they were revascularized. Note that this assumes that risk is solely a function of FFR values, and that knowing the QFR has no impact on risk of MACE events.

We investigated three strategies for deciding on whether to revascularize:

1. FFR only: perform FFR on all and revascularize if FFR ≤ 0.8
2. QFR only: perform QFR on all and revascularize if QFR ≤ 0.8, without FFR measurement
3. Grey zone: perform a QFR and:
    a. revascularize if QFR ≤ 0.78,
    b. defer if QFR > 0.84
    c. If QFR is between 0.78 and 0.84, perform FFR and revascularize if FFR ≤ 0.8

4.9.7.1 Results of the simulation study

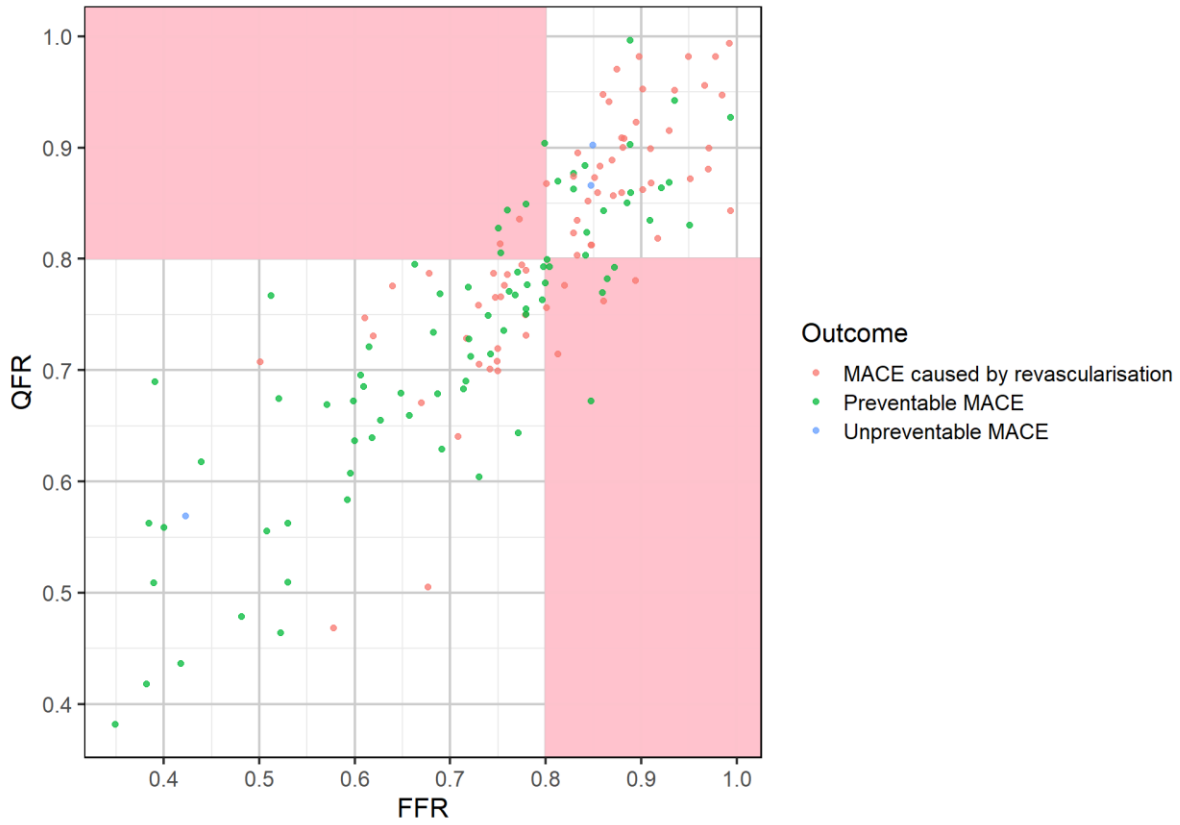
Figure 17 presents an example simulation, showing the distribution of simulated MACE events according to FFR and QFR. For ease of interpretation, the majority of patients who have no MACE are excluded and only patients with MACE are shown. Preventable MACE events (i.e. patients who would have a MACE event if not revascularised) are evenly distributed across both FFR and QFR ranges. MACE events caused by revascularization (i.e. where MACE occurs if revascularized, but would be avoided if deferred) are concentrated above values of 0.75 for both FFR and QFR, in line with the suggestion in IRIS-FFR that deferral is preferable for FFR over 0.75.

Most events occur in the white regions, where the same revascularisation decision would be made using either FFR or QFR. There are few patients, and hence few MACE, in the "false-negative" region (upper-left pink area), where patients would be revascularised based on FFR, but not if using

QFR. Hence using QFR would miss out on preventing some events in this region (green dots) but equally would avoid causing MACE events due to revascularisation (red dots).

In the "false-positive" region (lower-right pink area), where patients would be revascularised based on QFR, but not if using FFR, there are also few events. QFR preventing some events in this region (green dots) that would be missed by FFR, but equally would cause MACE events due to revascularisation (red dots). The "preventable" and "caused" events in these two regions approximately balance each other out.

Figure 17 MACE events from an example simulation



Based on the data extracted from figures if using the "FFR only" strategy 40.2% of patients would be revascularized; using the "QFR only" strategy 42.0% would be revascularized; using the "grey zone" strategy 43.2% would be revascularized. So using QFR moderately increases the revascularization rate, and using it in combination with a "grey zone" increases it further.

Table 11 summarise the key results of the simulation. FFR is slightly more effective at preventing MACE, but QFR leads to only about 1 extra unprevented MACE event per 1,000 patients. If the grey-zone is used the total number of MACE events is closer to that of using FFR for everyone. Using QFR results in around 1.3 to 1.6 more revascularisations to prevent one MACE event.

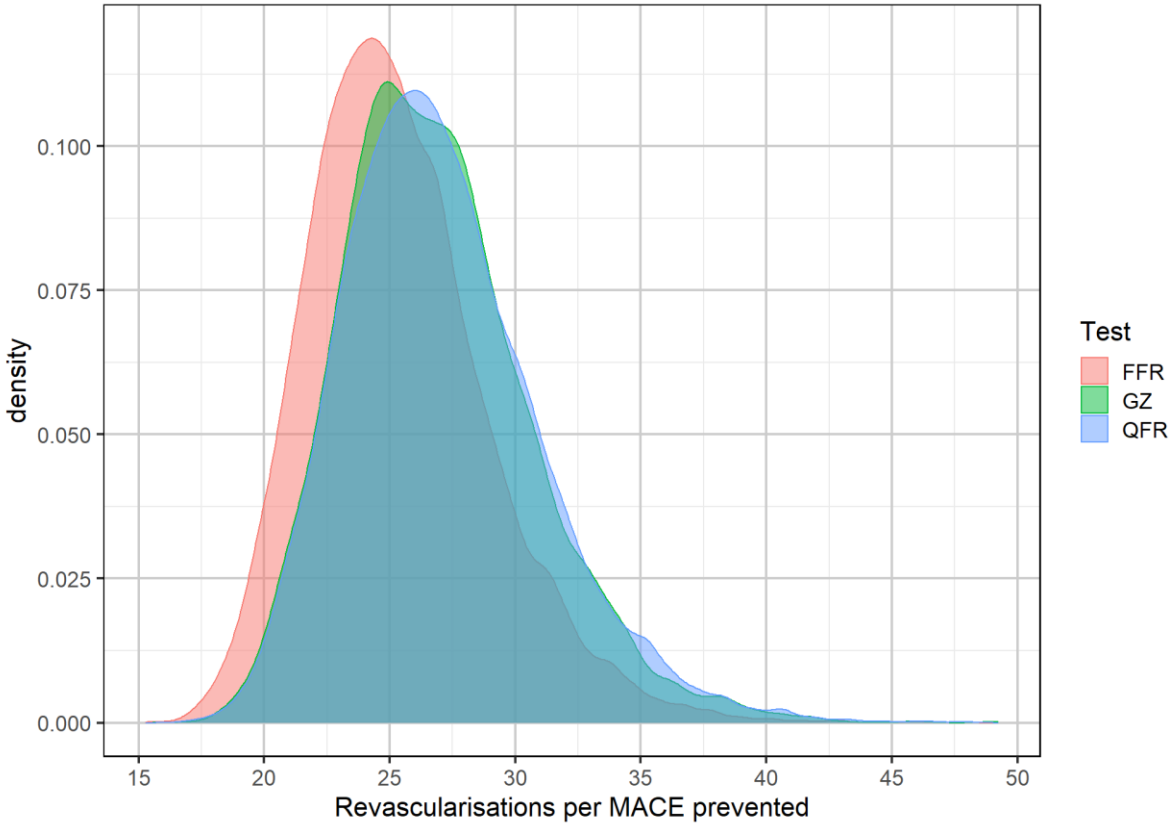
Using QFR with or without with a "grey zone" leads to more revascularizations, and so more MACE events caused by revascularisation (6 or 9 per 10,000 more, respectively) so leading to a higher number of revascularizations per MACE prevented.

Table 11 Key results of the simulation study

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

Table 11 presents only the median values across all simulations. Figure 18 shows the distribution of revascularisations per MACE prevented. Appendix Figure 43, Figure 44 and Figure 45 show the prevented and unprevented events, and events caused by revascularisation across all simulations. These show the substantial overlap between the distributions, so although the results in Table 11 suggest some difference between strategies, it is not clear if these are genuine differences that would be observed in actual clinical practice.

Figure 18 Estimated revascularizations per MACE prevented across all simulations



Overall, these simulations suggest that there is little conclusive clinical difference between using QFR and FFR to make revascularisation decisions. 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 increases the number of revascularisations performed, without substantially improving the number of MACE prevented.

The simulation has numerous limitations as a result of its assumptions. Most important is 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 QFR as well as FFR might alter the predicted risk. The IRIS-FFR risks may not match the risks in the UK population eligible for FFR or QFR. The simulation is also based only on the data extracted from figures, which is a small sample and may not represent the patients seen in practice. The simulation only considers a single lesion per patient, when QFR may be used to assess multiple stenoses in a patient.

4.10 Implementation evidence

4.10.1 Timing of results from data acquisition

Six studies of QAngio reported measuring the time required to complete QFR analysis.[11, 29, 42, 47, 49, 50] Results are summarised in Appendix Table 83. Two studies were prospective, [11, 49] and one was only reported as a conference abstract.[11] Sample size ranged from 68 to 268 patients. Reporting of methods for calculating time to QFR acquisition differed among the studies. For instance, only two studies specified that calculations included time required to select appropriate angiographic images for generating 3D images.[47, 50]

Time to QFR data acquisition ranged from an average of 2 min 7seconds to 10 min (SD 3min). One study of 268 patients reported that time to image acquisition significantly decreased with the number of ICAs analysed, from 5 min 59s to 2 min 7s between the first and last 50 cases. One conference abstract of an earlier prototype version of QAngio reported a mean total time to QFR of 10 min (SD 3 min). The study reported that the application required essential modifications during the study and retrospective reanalysis of ICA and QFR was performed with the final version of QFR, though it was not clear which analysis was used to derive mean time to data acquisition.

4.10.2 Other outcomes

No evidence was found for on any of the following review protocol-specified implementation outcomes: acceptability of QFR, vFFR and invasive FFR (to clinicians and patients), referral times, patient satisfaction, training requirements, test uptake and compliance.

4.10.3 Conclusions and recommendations for research from included studies

Most studies concluded that QAngio had good diagnostic accuracy for detecting significant coronary stenosis and good correlation and agreement with both wire-based FFR[50 29, 34, 37, 42, 43, 47-49 11, 12, 17, 18, 20, 21, 23-27, 31-33, 35, 36, 38-41, 45, 51, 53, 63] and iFR[13, 18, 21, 33, 46], and is able to improve angiographic assessment for evaluation of intermediary coronary artery stenosis.[11, 47, 49]

CAAS studies also concluded QFR had good correlation and agreement with wire-based FFR [15, 16, 21, 53] although one concluded that only one-third of routinely acquired coronary angiographic images were appropriate for retrospective vFFR analysis.[16]

Studies conducted in patients with acute coronary syndrome concluded that QFR was safe and accurate in assessment of non-culprit vessels.[14, 25, 28, 38] Some studies suggested that diagnostic accuracy of QFR may be affected by specific clinical characteristics namely small vessels [29 12], presence of bifurcated lesions and trifurcated lesions [12 35], left main stenosis,[19] prior-MI related coronary arteries [17] and microvascular function.[26, 38]

Several studies concluded that QFR may be a good alternative tool for identifying significant coronary stenosis in various clinical settings or may complement invasive wire-based options;[20, 28, 34, 46] it is applicable to patients allergic to adenosine and ATP vasodilators and may avoid procedural risks or patient discomfort associated with invasive wire-based options.[20, 49] Some studies noted that QFR may reduce procedure time, be associated with reduced cost and allow for wider adoption of functional assessment of coronary stenosis. [20, 30, 43]

Some studies recommended using a hybrid approach to reduce the need for invasive FFR, although there was no consensus on an optimal grey zone. [13 30 40] In some cases, patients may be unsuitable for evaluation of stenosis severity using angiography, including diffuse tandem disease, tandem lesions, lesions with angiographic haziness caused by calcification or thrombus, lesions with ulceration cause by plaque rupture.[17] Diagnostic accuracy could be affected in patients with bifurcation lesion [29 47], patients with prior MI-related coronary arteries [17] and patients with left main location of stenoses[19]. Some studies suggested that confirmation with FFR may be required close to values of 0.8.[30, 50] One CAAS study noted that careful adaptations in image acquisition will be required to reduce the risk of test failures if used in daily clinical practice.

Further prospective online investigation into the clinical benefit of QFR-based revascularisation was recommended by multiple studies [14, 34, 39, 40, 42, 43, 45, 47] including using appropriately powered RCTs with relevant clinical end-points before implementing the device as a definite alternative to invasive FFR, [21, 29, 34, 37, 47] such as the ongoing FAVOR III China trial.(FAVOR III China, NCT03656848) Some recommended further testing of modelled hybrid QFR/FFR approaches.[48]

A number of studies recommended that that testing of the diagnostic accuracy and feasibility of QFR in clinical practice in different settings is needed [14, 29, 33, 35, 40, 46 42, 45 37 34].

Further investigation of diagnostic precision and the application of the current QFR methodology in patients with different lesions subtypes [35] including bifurcation lesion [29 47], patients with prior MI-related coronary arteries [17] and patients with left main location [19] was recommended.

4.11 Clinical Effectiveness Summary and Conclusions

The diagnostic accuracy of QAngio has been widely studied in 39 studies to date with a total of 5949 patients (7034 vessels or lesions).

QFR at a cut-off of 0.8 has good diagnostic accuracy to predict FFR (also at a cut-off of 0.8) with sensitivity around 84% and specificity around 89%. Although this means there is some discordance between QFR and FFR most false positive or false negatives arise near the boundary (e.g. where one is 0.81 and the other 0.79), and the discordance may not be clinically meaningful. Data on how this accuracy may vary by key patient characteristics was very limited, and no conclusive variation could be found. QFR, as measured using QAngio, is highly correlated with FFR measured with an invasive pressure wire. On average, there is no difference between the two values, and values rarely differ by more than 0.1, and, in 50% of patients, by less than 0.04.

The use of a "grey zone", where patients with intermediate QFR values go on to have confirmatory FFR, was found to increase diagnostic accuracy. Around 20% of patients fall in the grey zone and would receive confirmatory FFR. Of these, only around 30% have discordant FFR and QFR results, so the confirmatory FFR is unnecessary for the majority of patients in the grey zone.

Diagnostic accuracy data for CAAS vFFR was limited to only three studies. Results from the studies were heterogeneous limiting meta-analysis and a full evaluation of CAAS vFFR. Hence its diagnostic value is currently uncertain, but it may be potential alternative to QAngio.

This report did not perform a full systematic review of 2D or 3D ICA, but in those studies that we did identify the diagnostic accuracy of ICA was substantially inferior to QAngio, with diameter stenosis from ICA being poorly correlated with FFR.

There was very little reported data on clinical effectiveness and implementation outcomes when using QAngio, as nearly all studies published to date have focussed on diagnostic accuracy. What data there is suggests that QAngio QFR results of 0.80 or below may be significant predictors of subsequent MACE, and that a grey-zone strategy is likely to lead to substantial reductions in adenosine and FFR procedures. Timing of results, inter-rater and intra-rater reliability were generally acceptable for QAngio, indicating that the technology is feasible in a clinical context. Feasibility of CAAS vFFR is uncertain notably due to lack of evidence on repeatability within and between-raters and the high rate of patient exclusions from retrospective evidence.

The simulation study to investigate the clinical impact of using QAngio found that QAngio may lead to a slight increase in revascularisations compared to using FFR, but both methods prevent broadly the same number of MACE events. Up to 1 person in 1000 may have a MACE event if using QAngio that could have been prevented with FFR, but this is highly uncertain. Using a grey zone seems to

lead to an increase in the number of revascularisations, but with no improvement in MACE prevented compared to using FFR alone or QFR alone.

Overall, this review suggests that making decisions on revascularisation in patients with intermediate stenosis using QFR as measured by QAngio is a reasonable diagnostic strategy, and so QFR assessment could potentially replace use of invasive FFR entirely. The trade-off appears to be a balance between avoiding the side effects of FFR (particularly adenosine use) at a cost of possibly slightly more revascularisation procedures. The use of QFR appears to be conclusively preferable to using diameter stenosis measured by standard ICA alone.

The review did not find a strong case for consistently using FRR in patients where QFR is borderline (around 0.8, the "grey zone" approach). This seems to place too strong an emphasis on patients close to the 0.8 threshold. Most patients in this region have similar FFR and QFR results (within 0.05), and so any discordance between QFR and FFR may not be clinically meaningful. A large proportion of people who go on to receive FFR have the same conclusion as their original QFR, exposing them to a potentially harmful, unnecessary test. This conclusion, however, does not prevent the use of FFR where clinicians might think it necessary for reasons other than the QFR being close to 0.8.

Data on CAAS vFFR are currently too limited and heterogeneous to draw any useful conclusions on its clinical value.

5 Assessment of existing cost effectiveness evidence

This section provides an overview of existing cost-effectiveness evidence on the use of the QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing the functional significance of coronary obstructions in patients with suspected stable chest pain whose angiograms show intermediate stenosis and who may require revascularisation. Given that the two technologies under assessment have only recently been commercialised, it was anticipated that there would be a dearth of relevant economic evidence. Therefore, to inform the development of a new decision-analytic model, a review of published cost-effectiveness studies evaluating ICA (alone and/or with FFR) in the management of coronary artery disease was conducted.

5.1 Methodology of the cost-effectiveness review of QAngio and CAAS vFFR imaging software

5.1.1 Searches

The bibliographic search detailed in Section 4.1.1 was used to identify studies reporting on the cost-effectiveness of QAngio and CAAS vFFR imaging software.

5.1.2 Selection process

The review considered a broad range of economic studies including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. The inclusion criteria considered were full economic evaluations comparing two or more alternatives and considering both costs and consequences (i.e. cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses).

The protocol for the selection of relevant studies defined two selection stages: i) assessment and screening for possible inclusion of titles and abstracts identified by the search strategy, and ii) acquisition and screening for inclusion of the full texts of potentially relevant studies. Two researchers (RW and AL) independently screened the titles and abstracts of all reports identified by the bibliographic searches. Full-text papers were to be subsequently obtained for assessment and screened by at least two researchers, with any disagreement resolved by consensus.

5.2 Results cost-effectiveness review of QAngio and CAAS vFFR imaging software

The initial search identified a total of 1,243 records (after deduplication). No studies were identified as potentially relevant from their titles and/or abstracts, as none evaluated the cost-effectiveness of either QAngio and CAAS vFFR imaging software.

5.3 Methodology of the review of decision models evaluating ICA

Given the lack of cost-effectiveness studies evaluating QAngio and CAAS vFFR imaging software used during ICA, a review of published cost-effectiveness studies evaluating ICA (alone and/or with

FFR) in the management of CAD was conducted. The search targeted cost-effectiveness studies where ICA was one of the interventions under comparison. The aim of the review was to help inform the conceptualisation of the decision problem and identify any relevant sources of evidence. In particular, the review aimed to assess how the link between short-term diagnostic outcomes and longer-term impact and subsequent prognosis associated with the diagnostic pathways in the management of CAD and associated costs and outcomes had been established in the literature.

5.3.1 Searches

The searches were conducted in October 2019 in the following databases: MEDLINE ALL (includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), EconLit, EMBASE, NHS Economic Evaluation Database (NHS EED), and HTA database. Search strategies are detailed in Appendix 10.1.

5.3.2 Study selection

Cost-effectiveness studies where ICA (alone and/or with FFR) was one of the interventions under comparison, published after 2000 were considered for inclusion. Only cost-effectiveness, cost-utility and cost-benefit analyses were considered eligible. Studies that presented results as a cost per diagnose were not considered for inclusion. The patient population of this review was defined as patients with stable chest pain and suspected or known CAD. Studies in patients with acute coronary syndromes (ACS) and non-ST elevation MI (NSTEMI) as primary diagnosis were excluded. The inclusion criteria further specified that only titles in English would be considered eligible. Titles that were books, editorials, letters to the editor, and reviews that did not include a *de novo* model were excluded from the review.

One researcher (AD) conducted the two-step selection process consisting of screening for inclusion i) the titles and abstracts of studies identified by the bibliographic searches, and ii) the full-text articles identified at the previous step as potentially relevant.

5.4 Results of the review of decision models evaluating ICA

A total of 1,740 records were identified during the initial search of economic databases of which 1,264 remained after deduplication. The first step of screening identified 25 titles as potentially relevant based on their titles and/or abstracts. After the full text articles of these records were obtained and assessed for eligibility, 21 studies[64-74,75, 76, 77, 78, 79, 80, 81, 82, 83, 84] were considered to meet the selection criteria and included in the review. The studies are summarised in detail in Appendix Table Table 86. Results of the searches and the list of excluded studies are presented in Appendix Table 84 and Table 85.

Given the aim of the review, a formal assessment using checklists to assess the quality of the included cost-effectiveness studies was not conducted. Instead, a narrative review of key model features, including testing and management strategies, and assumptions to support the conceptualisation and development of a *de novo* analytical model is presented below.

The majority of studies [64-66, 71, 77, 79, 81, 82, 84 67 68, 73, 75] 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. Two studies used microsimulation models[70, 78] that also combined a decision tree structure to model diagnostic outcomes followed by a lifetime disease progression state transition model. Of the 5 studies which modelled the full time horizon with a decision tree model, three models [67, 69, 76] only captured short-term outcomes (1 year time horizon), while two others comprised longer time horizons (10 years [80]and lifetime[83]). One study[74] used a Bayesian mathematical model based on two equations to estimate costs and QALYs for each strategy under comparison over a 10-year time horizon. The equations appear to be equivalent to the calculations in a decision tree's rollback algorithm.

Of the 21 studies, two models [73] were considered to be good examples of alternative ways to evaluate diagnostic strategies in patients with suspected stable angina. These studies were selected on the basis that they encompassed many of the features identified in the other studies. The two models differed in terms of how they modelled the diagnostic pathway and subsequent long-term risks of major cardiovascular related events and associated costs and outcomes. The first study[73] was a cohort model that estimated outcomes for an average patient in clinical practice, while the second study [70] was a microsimulation model that estimated outcomes for hypothetical patients at different levels of disease severity (defined in terms number of coronary vessels affected and whether patients have ischemia). A key difference of the two models was the approach taken to assess the long-term impact of the diagnostic strategies on the risk of major cardiovascular events. In one study [73], the model transition probabilities were based on risk prediction equations and patient covariates from a previously published model on angina, which allowed estimation of the occurrence of a primary cardiovascular event (with risk conditioned on factors such as age and gender) and of subsequent events conditional on having and surviving a first cardiovascular event. In contrast, the second study (2015)[70] estimated the risk of primary and subsequent cardiovascular events, dependent on disease severity, based on the rates of major cardiac adverse events (MACEs) from the literature. A summary of both models is presented below.

Walker et al, 2011

Walker and colleagues[73] developed a decision tree and Markov model structure to evaluate the cost-effectiveness of eight alternative testing sequences, including different combinations of exercise

treadmill testing, single-photon emission computed tomography, cardiovascular magnetic resonance and coronary angiography, to identify patients with angina who require revascularisation (i.e. those with significant stenosis) derived from the CE-MARC study.[85] The study population included patients with angina (with and without significant stenosis) and those without angina, based on characteristics of patients in the CE-MARC study. The base-case analysis considered a population comprised of a 60-year-old male, classified as grade 2 on the Canadian Cardiovascular Society (CCS) scale, with a prior likelihood of significant stenosis requiring revascularisation of 39.5%. Patients with angina were assumed to have had no previous MI. The Markov model had a 50 year time horizon with a three-month cycle length. The perspective of the study was NHS and Personal Social Services and health outcomes were measured in terms of QALYs. Costs were expressed in terms of 2010/11 pound sterling, and costs and health outcomes were discounted at a rate of 3.5% per annum.

The aim of the diagnostic testing was to identify patients with significant coronary artery stenosis who require revascularisation (either PCI or CABG). It was assumed that all patients suspected of having significant coronary stenosis would undergo coronary angiography as a definitive test before revascularisation. ICA was considered the reference standard test with perfect sensitivity and specificity. Since ICA was performed on all patients indicated for revascularisation, the model did not consider any false positive test results. The diagnostic component of the model divided the patient cohort according to their underlying disease status based on characteristics of patients in the CE-MARC study, survival to interventional and diagnostic procedures, test results, and subsequent clinical management conditional on test results. All patients with positive and inconclusive test results progressed to a further test in the sequence, although the type of the next test depended on whether the result was positive or inconclusive for some strategies (e.g., in strategy 8 a positive exercise treadmill test result would be followed by ICA, while inconclusive test results would receive single-photon emission computed tomography test) . Patients whose overall testing sequence resulted in a positive result were managed with either PCI or CABG. The relative proportion of patients who underwent each type of revascularisation was sourced from UK clinical registries. Patients who tested negative at any point in the test sequence were managed with optimal medication if they had angina, or no further medical therapy for those without angina. The decision tree captures mortality associated with both invasive tests and revascularisation, and separately applies procedure-specific mortality rates for ICA, PCI and CABG. At the end of the decision tree, patients with significant stenosis could be classified as TP, FN or dead. Patients without significant stenosis could be TN with angina, TN without angina or dead. All testing strategies are assumed to take the same time, and do not account for delays to revascularisation resulting from strategies that involve more tests.

The diagnostic accuracy estimates for the different tests considered in the alternative strategies were conditional on positive/inconclusive results in previous tests in the strategy, thus accounting for

correlations between tests within diagnostic strategies. This is only possible with access to individual patient data (IPD) from studies that include all the tests used across the full set of diagnostic strategies, as was the case for the CE-MARC study, which informed diagnostic accuracy in this model. However, the people interpreting each test were blinded to the results of previous tests in each diagnostic sequence, so the data would not have captured the influence of knowledge on previous tests on the diagnostic accuracy estimates of subsequent tests.

The long-term model is composed of three submodels. Patients with significant stenosis enter one submodel at either the TP or FN state. The key difference between TP and FN, is that TP have undergone revascularisation. In the base-case analysis, the treatment effect of revascularisation is limited to a reduction from angina symptoms with improved HRQoL for TP compared to FN, while the same baseline risk of cardiovascular events is applied for TP and FN. A proportion of FN are assumed be correctly diagnosed over time (conditional on their CCS grade), and transition to the TP health state. Patients can remain event free, have a primary non-fatal cardiovascular event, die from cardiovascular event or other causes. Patients who survive a primary non-fatal cardiovascular event transition to the non-fatal cardiovascular event state and have an increased risk of further cardiovascular events for 12 months after which they transition to the non-fatal event post 12 months state. The risk of cardiovascular events in this state is lower than in the non-fatal event post 12 months state, but higher than the baseline risk (TP and FN states). Patients in all health states are subject to a mortality risk from non-cardiovascular death, which is sourced from UK life tables (with cardiovascular deaths removed to avoid double counting). A similar submodel to the one described above this is used to estimate the cost and health outcomes of TN with angina. TN without angina go into a two health states (alive and dead) submodel that derived transition probabilities from sex and age adjusted UK life tables for all-cause mortality.

The probabilities of fatal and non-fatal cardiovascular events in the submodels for patients with angina were estimated based on risk equations from the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA).[86] This study estimated risk equations to predicts i) the risk of a first primary event, cardiovascular death, MI or
cardiac arrest (equation 1), ii) the odds of that event being fatal (equation 2), and iii) the risk of a further primary event in the first year after a first non-fatal event (equation 3). The equations allow for the adjustment the rate of events dependent on the patient characteristics (age, gender, medication, comorbidities, etc.) and, importantly, accounting for the occurrence of previous MI. Walker et al, 2011 applied a fourth equation to model the risk of secondary cardiovascular events, which captures the excess cardiovascular risk for patients who had had a previous MI.

The model also considers cancer related mortality due to radiation exposure during some testing procedures (ICA and single-photon emission computed tomography [SPECT]) and PCI (assumed to be performed at the same time as ICA). The model quantified the average radiation exposure in each test sequence, these radiation dosages were then combined with and cancer incidence and mortality from the literature to calculate lifetime incidence and mortality conditional on the patient's age when they were tested. The costs and morbidity associated with cancer were not modelled.

HRQoL in the model was dependent on age, gender, CCS grade and whether patient had undergone revascularisation. EQ-5D utility weights by CCS grade from a study in angina were combined with UK population norm EQ-5D estimates by age and gender to obtain age and CCS specific HRQoL estimates. The underlying assumption was that the relative impact of CCS grade on HRQoL compared to the population is the same across all age groups.

One important base case assumption of the Walker et al, 2011 model is that revascularisation has no impact on the risk of cardiovascular events, but only provides relief from angina symptoms (captured by change in CCS score). HRQoL scores for patients with angina (with and without significant stenosis) are based on age and gender adjusted UK population scores with a relative adjustment made based on CCS grade. Data from a RCT comparing coronary angioplasty with medical management was used do link CCS score at baseline and 6 months after intervention with the two treatments. Patients with angina and significant stenosis who receive revascularisation (TP) are attributed the HRQoL based on the average CCS grade of those following treatment with angioplasty conditional on initial CCS grade. Patients with angina and significant stenosis who are misclassified (FN) are attributed the HRQoL based on the average CCS grade of those following treatment with medical management conditional on initial CCS grade. It was assumed that angina patients without significant stenosis received the same HRQoL as FN patients, while the other TN without angina were based on age and gender adjusted UK population scores.

Costs included the model were those of tests and interventional procedures, treatment costs in the long-term model and health state costs, namely: fatal and non-fatal cardiovascular events, and other cause mortality. Treatment and health state costs were also sourced from the EUROPA trial (with a price year inflation adjustment). Background treatment costs were the same for all patients with angina and an additional background cost was applied for patients after a cardiovascular event. Patients without angina were assumed to have no costs in the long-term model.

The authors considered uncertainty by performing probability sensitivity analysis and scenario analysis where they varied assumptions on baseline characteristics (CCS grade, gender and age), prior likelihood of coronary heart disease requiring revascularisation, re-diagnose rate of FN, clinical

management of TP the impact of radiation exposure on cancer (risk assumed to be zero), risk of cardiovascular events following revascularisation (treatment effect from EUROPA), HRQoL decrements and the cost of diagnostic tests. The model was sensitive to prior likelihood of disease, reducing the starting age and increasing baseline CCS grade in the model, use of absolute HRQoL decrements by CCS grade, allowing for a proportion of TP to not receive revascularisation, re-identification rate of FN, and costs of tests. The prior likelihood of coronary heart disease requiring revascularisation was considered a key driver of cost-effectiveness.

Genders et al, 2015

The model developed by Genders and colleagues[70] was 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 chest pain. The base-case population consisted of 60-year-old patients with and a 30% pretest probability of obstructive CAD (defined as ≥50% stenosis on at least one vessel), who had never undergone revascularisation procedures and had no prior history of CAD. The study presents cost-effectiveness results for the separate jurisdictions. We refer here to inputs and results specific to the analyses under the UK NHS perspective, as they are more relevant to our study. Costs were calculated as pound sterling (2011 price year), and health outcomes as QALYs. Both costs and QALYs were discounted at an annual rate of 3.5%.

The diagnostic strategies in the model are evaluated under two different diagnostic workups. In the invasive workup, patients with obstructive CAD on coronary CT angiography (CCTA) and patients with inducible ischemia on cardiac stress imaging were referred for ICA prior to a decision regarding medical management. In the conservative workup, only patients identified as having higher CAD severity by CCTA or cardiac stress imaging would be referred to ICA and patients with milder forms of the disease managed with OMT. Patients with normal arteries or mild CAD (<50% stenosis) receive no further testing under either diagnostic workup.

The decision tree starts by classifying patients according to 8 categories of disease severity based on percentage stenosis, number of vessels affected, location of lesion (left main trunk or not) and severity of inducible stenosis (where present). Patient distribution across disease severity categories was sourced from hospital records for patients who had undergone CCTA and ICA. Diagnostic accuracy estimates derived from published meta-analyses were then applied to split patients according to the test results for each diagnostic strategy. For the purpose of applying these estimates, patients who were considered correctly classified with a negative result had normal coronary arteries or mild CAD (<50% stenosis). Patients correctly identified with a positive result had moderate CAD, severe CAD, or 3-vessel disease/left main coronary stenosis. The model did not consider inconclusive test results. The authors assumed independence of diagnostic accuracy estimate for CCTA and cardiac stress

imaging, and further assumed that FP results were only possible for mild CAD and mild inducible ischemia (under the conservative diagnostic workup). Patients with FP results are assumed to receive unnecessary optimal medication for the full time horizon, incurring a treatment cost and utility decrement in the long-term model. Similarly to Walker et al, 2011, [73] adverse events from testing and revascularisation procedures were also considered. However, in this model adverse events are not limited to procedural mortality, but also include non-fatal MI with ICA. This adverse event had a cost attributed to it, but did not translate into an increased risk of further events in the long-term model.

The decision tree splits the patient population according to disease severity, test results and survival to testing (ICA and FFR) and revascularisation procedures. It also allows quantifying the average exposure to radiation with the different tests and PCI.

In the ICA strategy, all patients were tested with ICA. Those who tested negative received risk factor management, those who tested positive would be tested with FFR to decide treatment. ICA is assumed to be a perfect test, and FFR appears to allow prefect distinction between disease severity categories, although this is not explicitly stated in the paper. OMT was then given to patients with mild ischemia and moderate to severe CAD, PCI for patients with severe CAD and severe ischemia; and CABG for patients with 3-vessel or left main coronary stenosis. Revascularised patients would also receive OMT, and all individuals in the model received risk factor management.

Subsequently to the decision tree, patients entered a state transition model comprising three health states: alive, post-MI and dead. Patients enter the model via the alive state, where they could remain until death or suffering a non-fatal MI. Patients who suffered a non-fatal MI would transition to the post-MI state where they could remain or transition to the dead state. The transition probabilities were derived from published trial data that reported risk of MACE (cardiovascular death, non-fatal MI and repeated revascularisation) in patients treated with CABG, PCI and OMT. The rates of MACE were dependent on disease severity and whether patients were treated with optimal medication or revascularisation. All FN were assumed to be correctly identified and treated by the end of the first year, with the exception of those with moderate CAD without ischemia of whom only 25% were re-diagnosed. Patients who experienced a primary cardiovascular event would have a higher risk of subsequent cardiovascular events, which was modelled by applying a hazard ratio of 1.44 to their baseline risk. The model also considered mortality from non-cardiovascular causes. This was estimated based on age and sex specific general mortality data from which deaths attributed to cardiovascular causes had been removed to avoid double counting. The mortality, morbidity and costs due to cancer incidence were not modelled, although the model calculated cumulative radiation exposure over the time horizon.

The risk of MACE was estimated from the trial data separately for the i) first year and ii) all subsequent years to allow for a higher event rate in the first year after starting treatment. The rates were estimated based on the CABG arm of the SYNTAX trial [87] for patients with 3-vessel disease or left main coronary stenosis, and the optimal medication and PCI arms of the COURAGE trial [88] for the patients with suspected or mild inducible ischemia and moderate to severe CAD (treated with optimal medication) and patients with severe CAD and severe inducible ischemia (treated with PCI). The reciprocal of the treatment hazard ratio (HR) was applied to this risk to estimate the baseline probability of cardiovascular events for untreated patients (FN), who does have a higher rate of events until they are correctly diagnosed. A single treatment effect hazard for optimal medication, PCI and CABG (HR=0.70) sourced from three meta-analyses of OMT comparing treatment to no treatment, but it is unclear how this estimate was calculated. The rates of MACE applied in the model are summarised in Table 12.

Table 12 Annual rates of MACE in Genders et al, 2015

	Annual rate of MACE			**Treatment received***
	No treatment	**Treatment**		
		1st year	**Subsequent years**	
Normal coronary arteries	0.0008	0.0008	0.0008	RF
Mild CAD	0.025	0.025	0.025	RF
Moderate CAD				
No inducible ischemia	0.025	0.025	0.025	RF
Mild inducible ischemia	0.246 (Rate × (1/HR)	0.172	0.071	RF+OMT
Severe CAD				
Mild inducible ischemia	0.246 (Rate × (1/HR)	0.172	0.071	RF+OMT
Severe inducible ischemia	0.157 (Rate × (1/HR)	0.110	0.043	RF+OMT+PCI
3-vessel/LM				
Mild inducible ischemia	0.137 (Rate × (1/HR)	0.096	0.031	RF+OMT+CABG
Severe inducible ischemia	0.137 (Rate × (1/HR)	0.096	0.031	RF+OMT+CABG
* if correctly identified; HR, hazard ratio;RF, risk factor management				

We note that the MACE rates without treatment seem counterintuitive (e.g., higher MACE rate for untreated moderate CAD with mild ischemia compared to untreated severe CAD with severe ischemia). The authors did not comment on the MACE rates.

If the treatment effect applied in the model is indeed the same for optimal medication and revascularisation, this is similar to the absence of a treatment effect of revascularisation in addition to optimal medication in Walker et al, 2011.[73] This is an important interpretation of the clinical evidence

on the treatment effect of revascularisation, and one that is discussed further in Section 6.5.5.2. In previous studies where a treatment effect on the rate of cardiovascular events for revascularisation compared to optimal medication was considered explicitly for comparable patients (e.g., same disease severity) 7 models included the existence of a treatment effect [64, 65, 72, 79, 81, 82, 84], while 6 studies did not [66-68, 75, 80, 83] in line with Walker et al,2011, and Genders et al, 2015.[73] [70]

HRQoL in the model was assigned to individuals according to disease severity and treatment received. Patients without CAD or inducible ischemia were assumed to have the HRQoL of the general population based on age and sex specific EQ-5D estimates for the US population. For patients with CAD and inducible ischemia who underwent active treatment (optimal medication or revascularisation), mapped EQ-5D utility decrements were applied to the general population HRQoL estimates. In the first year of treatment, the utility decrements of treatment relative to the general population were derived from on the average utility decrement as observed in the same trial data that informed the rates of MACE for treated patients, while for subsequent year the last observed value in the trials was carried forward. The authors state that a disutility was considered for patients with FP results. It was not clear how the utility decrements for FN were estimated. Table 13 summarises the utility values for the start age in the model conditional on treatment and disease severity. The HRQoL estimates for the first year and subsequent years of treatment are presented for the same age solely for ease of comparison.

Table 13 Base-case utility estimates for an individual aged 60 years in Genders et al, 2015

	No treatment		**Treatment**				**Treatment received***
			1st year		**Subsequent years**		
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	
Normal coronary arteries	0.851	0.824	0.851	0.824	0.851	0.824	RF
Mild CAD	0.851	0.824	0.851	0.824	0.851	0.824	RF
Moderate CAD							
No inducible ischemia	0.851	0.824	0.851	0.824	0.851	0.824	RF
Mild inducible ischemia	0.699	0.677	0.734	0.711	0.749	0.726	RF+OMT
Severe CAD							
Mild inducible ischemia	0.699	0.677	0.734	0.711	0.749	0.726	RF+OMT
Severe inducible ischemia	0.699	0.677	0.740	0.716	0.760	0.736	RF+OMT+PCI
3-vessel/LM							
Mild inducible ischemia	0.659	0.638	0.740	0.716	0.820	0.794	RF+OMT+CABG
Severe inducible ischemia	0.659	0.638	0.740	0.716	0.820	0.794	RF+OMT+CABG
* if correctly identified							

The model considers costs of tests, test adverse events, medication, MI in the long-term model, and incidental findings from CCTA. Unit costs were mostly sourced from UK published data. Based on the description of the unit cost selected for PCI, this procedure was assumed to take place in an outpatient setting. It is not, however, clear what assumptions were made regarding the setting for ICA, CABG and treatment of non-fatal MIs. The unit cost for FFR was sourced from a previous cost-effectiveness study in a US setting.[83] An annual cost of medication was included in the model according to disease severity and treatment received (OMT, PCI or CABG). The resource use assumed for patients who received optimal medication alone and in addition to PCI was sourced from the COURAGE trial[88], while for those who received CABG and optimal medication it was taken from the SYNTAX trial.[87] The distribution of medication use applied in the model is shown in Table 14.

Table 14 Medication use in Genders et al, 2015

	Medication use (%)			
Medication class	Platelet inhibitor	Statin	Nitrate	ACE inhibitor
Drug & dosage/ day	Aspirin, 80mg	Simvastatin, 40mg	Isosorbide mononitrate, 60mg	Enalapril, 20mg
Baseline	48	22	0	0
No CAD	12	17	1	7
Mild CAD	32	31	5	11
Moderate CAD w/o inducible ischemia	73	72	11	27
OMT*	95	92	61	62
PCI + OMT*	95	93	47	64
CABG + OMT*	83	86	8**	53
* at 3 years unless otherwise stated; **at 1 year				

Model parameters were entered as distributions, and probabilistic sensitivity analysis was performed to incorporate joint parameter uncertainty. Scenario analysis was performed to test assumptions on diagnostic accuracy of stress echocardiography, cost of tests, alternative diagnostic pathways, probability of CAD, time to re-diagnose of FN, and treatment effect of optimal medication for FP. A subgroup analysis by gender was also performed. The authors do not identify any drivers of cost-effectiveness, but note that the assumption that FP will remain misclassified over the time horizon and FN will be re-diagnosed after 1 year is likely to have biased results again strategies with low specificity.

5.5 Conclusions of the assessment of existing cost effectiveness evidence

The review did not identify any studies that evaluated the cost-effectiveness of QAngio or CAAS vFFR. A supplementary review of published cost-effectiveness studies evaluating ICA (alone and/or with FFR/) in the management of CAD identified 21 relevant studies. Two studies were considered to be particularly good examples of alternative modelling approaches to establish the link between short-

term diagnostic outcomes and the longer-term impact and subsequent prognosis associated with the diagnostic pathways in the management of CAD and associated costs and outcomes. The modelling approaches identified in Section 5.4 were used to inform the conceptualisation of the de novo model described in Section 6.4, and allowed identifying relevant evidence sources to inform model inputs and assumptions.

6 Independent economic assessment: York model

6.1 Overview

The review of cost-effectiveness studies in Section 5 identified no studies evaluating the cost-effectiveness of QAngio and CAAS vFFR imaging software for assessing the functional significance of coronary stenosis. Therefore, a *de novo* decision analytic model was developed to formally estimate the cost-effectiveness of QAngio and CAAS vFFR imaging software for assessing the functional significance of coronary obstructions during invasive coronary angiography in patients with stable angina and intermediate stenosis, relative to the comparators of invasive FFR or iFR measurement or clinical decision making based on visual interpretation of ICA alone, alongside clinical judgement, in the UK NHS.

In developing and populating the decision model three issues are considered central to the approaches and methods employed:

1. The need to link the diagnostic accuracy of QFR and vFFR to short-term costs and consequences (e.g., the impact on the proportion of patients who need revascularisation (percutaneous or surgical), the proportion of patients who need invasive functional assessment of stenosis using FFR or iFR, and adverse event rates and health-related quality of life associated with the diagnostic interventions).

2. The need to link the short-term consequences to potential longer-term costs and consequences (e.g., the risk of major adverse cardiovascular events such as myocardial infarction, sudden cardiac death and need for urgent/unplanned revascularisations) using the best available evidence to ensure that differences in costs, life years gains, and QALYs are appropriately quantified over a lifetime horizon.

3. The need to ensure that the data inputs and assumptions are relevant to inform current NHS practice, with particular consideration given to any differences in the cost-effectiveness of the technologies in diagnostic-only laboratories or interventional catheter laboratories.

The decision analytic model provides a framework for combining the diagnostic outcomes and the subsequent prognosis associated with the diagnostic outcomes over the long-term, and other inputs reflecting current NHS practice. The model evaluates costs from the perspective of the NHS and Personal Social Services (PSS), expressed in UK £ sterling at a 2018/19 price base. Outcomes in the model are expressed in terms of quality-adjusted life years (QALYs). Both costs and outcomes are discounted using a 3.5% annual discount rate, in line with current NICE guidelines.[89] The model is developed using Microsoft Excel.

The model is probabilistic in that uncertainty in input parameters are reflected through the use of appropriate probability distributions, rather than using fixed mean estimates for input parameters [90]. Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in order to capture the uncertainty in overall results. Scenario analyses are undertaken to explore the robustness of the cost-effectiveness results to changes in the parameter inputs and assumptions of the model.

The following sections outline the decision problem, the structure of the model, and provide an overview of the key assumptions and data used to populate the model.

6.2 Decision problem and population

The decision problem addressed by the model relates to the cost-effectiveness of QAngio and CAAS vFFR imaging software used during ICA for assessing the functional significance of coronary stenosis in patients with stable angina whose angiograms show intermediate stenosis.

The model considers this in the context of the NICE Clinical Guideline Pathway (2020)[91], where ICA is used to guide treatment strategy for patients with a confirmed diagnosis of stable CAD of uncertain functional significance and whose symptoms are not satisfactorily controlled with OMT and so may require revascularisation.

QAngio and CAAS vFFR imaging software can be used in the same clinical settings where ICA is performed. These settings include diagnostic-only laboratories, or in interventional catheter laboratories. One key difference between the two settings is that assessments with FFR/iFR are only performed on interventional catheter laboratories. When patients assessed in a diagnosis-only lab require an FFR/iFR measurement due to inconclusive ICA results, they have to be referred to an interventional catheter laboratory. Therefore, inconclusive results obtained with QAngio and CAAS vFFR imaging software that require confirmation with FFR/iFR would also need to be referred to an interventional catheter laboratory. In contrast an FFR/ iFR assessment can be performed immediately after ICA, QAngio or CAAS vFFR in an interventional catheter laboratory if needed.

The target population of the model consists of patients with stable CAD whose angiograms taken during ICA show intermediate stenosis. Although various definitions of intermediate stenosis exist, the modelled population considers intermediate stenosis to be any stenosis where there is clinical uncertainty about its functional significance and the potential appropriateness of revascularisation.

No subgroup data are available to permit a separate consideration of subpopulations.

6.3 Diagnostic strategies

The aim of diagnostic testing is to identify patients with functionally significant coronary stenosis who would benefit from revascularisation (PCI or CABG), in addition to OMT. Since ICA is required to show intermediate stenosis, the starting diagnostic test is visual assessment with ICA. In the absence of other tests, clinical decision making would be based on visual interpretation of the angiographic images taken during ICA, alongside clinical judgement. However, ICA alone is not sufficient to indicate whether anatomical obstructions are functionally significant or functionally non-significant; therefore, confirmatory FFR or iFR is considered the reference standard test for functional assessment of coronary obstructions. Because FFR/iFR is regarded as the 'gold standard' diagnostic test for assessing functional significance of stenosis, it is assumed to have perfect sensitivity and specificity of 100%. This means that all patients would receive an appropriate treatment based on the results of FFR/iFR (either revascularisation for true positive test results or OMT for true negative test results). The comparator diagnostic tests for the QAngio and CAAS vFFR imaging software are: ICA alone (without the functional assessment of coronary obstructions) or ICA, followed by invasive FFR/iFR measurement using pressure-wire.

The interventions are clinical decision making based on: i) QAngio and ii) CAAS vFFR imaging software (used during ICA), alongside clinical judgement. These technologies are alternatives to pressure-wire FFR/iFR and provide a non-invasive means to simulate FFR measurement during ICA assessment. The technologies may also be used as a precursor to invasive FFR/iFR, with the invasive pressure-wire FFR/iFR only used as a confirmatory procedure when QFR or vFFR test results are inconclusive.

The decision model evaluates the following five diagnostic strategies:

1) ICA alone, i.e., visual interpretation of angiographic images taken during ICA without additional testing to assess the functional significance of intermediate stenosis;
2) ICA, followed by confirmatory FFR/iFR (reference standard);
3) ICA with QFR using QAngio imaging software;
4) ICA with QFR using QAngio imaging software, followed by confirmatory FFR/iFR if QFR is inconclusive;
5) ICA with vFFR using CAAS vFFR imaging software.

The strategy of ICA alone, referred herein as strategy 1, is based on the use of a diagnostic threshold of 50% diameter stenosis (DS) to define the need for revascularisation (i.e., 50% or more DS in the left main coronary artery, alongside clinical judgement, is sufficient to indicate the need for revascularisation). Strategy 1 means that treatment decisions based on % DS and clinical judgement alone are used to stratify treatment decisions. However, it is widely accepted that %DS has only

modest correlation with physiologic indexes of myocardial ischaemia such as FFR/iFR. Therefore, the more appropriate comparator strategy for the new technologies is ICA followed by confirmatory FFR/iFR, referred herein as strategy 2. The diagnostic threshold for strategy 2 is an FFR value of 0.8, where revascularisation can be safely deferred for stenoses with an FFR above 0.8, while stensoses with an FFR ≤0.8 are functionally significant and should be considered for revascularisation.

The strategy of ICA with QFR, referred herein as strategy 3, is based on the use of a single diagnostic threshold of 0.8 to define functionally significant and non-significant stenoses. A QFR value of ≤0.8 is considered a significant obstruction and revascularisation should be considered, while stenoses with a QFR value >0.8 are considered to be functionally non-significant and revascularisation can be deferred (i.e., patients receive OMT alone).

The strategy of ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive, referred herein as strategy 4, is considered an alternative strategy to strategy 3. In strategy 4 a dual threshold is used to represent a 'hybrid' approach of QFR, followed by FFR when the test results of QFR are inconclusive (grey zone). A QFR value below 0.78 is considered to have sufficiently high accuracy to indicate functionally significant stenosis and revascularisation should be considered, while a QFR value above 0.84 is considered to have sufficiently high accuracy to indicate functionally non-significant stenosis and revascularisation may be deferred (i.e., patients receive OMT alone). QFR values that are inconclusive and lie in the grey zone region [0.78 – 0.84] should be verified by invasive FFR/iFR measurement before a decision is taken on the need for revascularisation. This strategy uses the same grey zone region as described in the QAngio XA 3D/QFR instructions, and corresponds to Medis' recommended use of the technology.

The strategy of ICA with vFFR, referred herein as strategy 5, is the same as strategy 3 but with the alternative technology CAAS vFFR rather than QAngio XA 3D/QFR. A vFFR value of ≤0.8 is considered a significant obstruction and revascularisation should be considered, while stenoses with a vFFR value >0.8 are considered to be functionally non-significant and revascularisation can be deferred.

Note that it is not possible to consider a sixth strategy using CAAS vFFR, followed by confirmatory FFR/iFR when vFFR is inconclusive because there is no diagnostic accuracy data available to inform this strategy (and it is not possible to infer diagnostic information from the very limited diagnostic data available for vFFR) (see Section 4.8).

6.4 Model structure

The model is made up of two components: a diagnostic element, which characterises the diagnostic outcomes and costs and consequences associated with diagnostic testing and revascularisation, and a longer-term prognostic element, which considers the subsequent prognosis associated with the diagnostic outcomes and associated costs and consequences of treatment over the remaining lifetime of a patient.

The period represented by the diagnostic element (referred herein as diagnostic model) takes account of the diagnostic accuracy of the non-invasive functional tests (QAngio and CAAS vFFR used during ICA) relative to the reference standard measurement using the invasive test of FFR/iFR (assumed to have a sensitivity and specificity of 100%). Patients correctly identified as having functionally significant stenosis ("true positive" result, TP) will progress to revascularisation, in addition to OMT, while patients correctly identified as having functionally non-significant stenosis ("true negative" result, TN) will receive OMT without the need for revascularisation. Patients incorrectly identified as having functionally significant stenosis ("false positive" result, FP) will undergo unnecessary revascularisation, while patients incorrectly identified as not having functionally significant stenosis ("false negative" result, FN) will not receive an appropriate revascularisation procedure. The non-invasive tests may also lead to inconclusive results about the functional significance of stenosis, which leads to further invasive testing with pressure-wire FFR/iFR in order to confirm whether or not there is a need for revascularisation.

The longer-term prognostic element of the model (referred herein as prognostic model) takes account of the impact and subsequent prognosis associated with the diagnostic outcomes and models the risk of major adverse cardiovascular events such as MI, sudden cardiac death and need for urgent/unplanned revascularisation, as well as adverse events related to revascularisation and MI. The costs and HRQoL implications of treatment is modelled over a lifetime horizon.

6.4.1 Diagnostic model

Diagnostic outcomes are modelled with a decision tree, which takes account of the diagnostic accuracy of the tests and subsequent treatment pathway. The decision tree is constructed to compare the TP, FP, TN and FN rates of the alternative diagnostic strategies.

The decision tree starts with the alternative diagnostic strategies that are used to diagnose the functional significance of stenosis. The outcomes of each strategy are governed by the sensitivity and specificity of the particular test strategy. The accuracy of the tests is defined independent of disease prevalence (i.e., underlying prevalence of functionally significant stenosis in the population); however, the expected proportion of tests with positive and negative results in the population is dependent on the underlying prevalence. Therefore, for all strategies, patients are separated into their

"true" status of either functionally significant stenosis or functionally non-significant stenosis based on the distribution of the population with an FFR value ≤0.8. Patients with functionally significant stenosis requiring revascularisation are allocated to one of three outcome states as a result of the diagnostic strategy: (i) TP, who are correctly identified and treated with revascularisation, (ii) FN, who are misidentified and do not receive revascularisation, and (iii) death as a result of the mortality risks associated with the diagnostic and revascularisation procedures. Patients without functionally significant stenosis who do not require revascularisation are also allocated to one of three outcome states as a result of the diagnostic strategy: (i) TN, who are correctly identified and treated with OMT, (ii) FP, who are misidentified and receive an inappropriate revascularisation, and (iii) death as a result of the mortality risks associated with the diagnostic and revascularisation procedures. For revascularisation, a proportion of patients are assumed to be treated with either PCI or CABG, in addition to OMT.

A schematic of the diagnostic model for each of the five strategies is shown in Figure 19 to Figure 23 (with outcome of death not shown on the figures for simplicity). Strategies 1 (ICA alone), 3 (ICA + QFR) and 5 (ICA + vFFR) have four possible diagnostic test results of TP, FN, FP and TN based on the diagnostic accuracy of the tests relative to the reference standard test of FFR ≤0.8. Strategy 2 is the reference standard test (ICA + FFR) and TP and TN are the only diagnostic outcomes under this strategy because FFR/iFR is assumed to be a perfect test (100% sensitivity and specificity). Strategy 4 is the hybrid approach of QFR where the possible diagnostic outcomes are TP, FN, FP and TN for those considered to have conclusive QFR (values outside the grey zone), while TP and TN are the only possible outcomes for those with inconclusive QFR (grey zone) because these patients undergo confirmatory FFR/iFR. Death can occur as a result of the diagnostic and revascularisation procedures.

The model assumes that all diagnostic tests in each strategy are performed in the same medical appointment, and that revascularisation procedures are either performed immediately after testing or without a delay that might lead to a deterioration of the patient condition. Therefore, the base-case analysis is more representative of an interventional setting. The assumption that all diagnostic tests in each strategy are performed in the same medical appointment is relaxed in a scenario analysis, so as to explore the cost-effectiveness of the strategies in a diagnostic-only setting.

For the diagnostic model, costs are incurred according to the type of diagnostic test, adverse events associated with FFR, and treatment received. Procedural health-related quality of life loss is included for FFR and revascularisation. Costs, health-related quality of life, and mortality effects associated with ICA are excluded from the model because these are incurred equally across all strategies.

The diagnostic model represents the start of the long-term prognostic model. The proportion of patients starting in the health states in the prognostic model is based on the expected proportion of tests with positive and negative results in the population (TP, TN, FP, FN).

Figure 19 Strategy 1 of ICA alone, without additional testing to assess the functional significance of stenosis

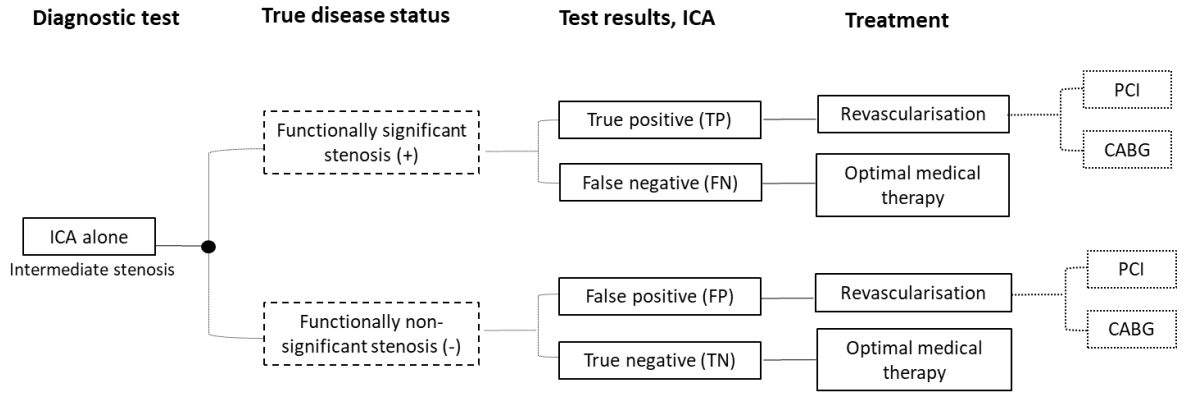


Figure 20 Strategy 2 of ICA, followed by confirmatory FFR/iFR

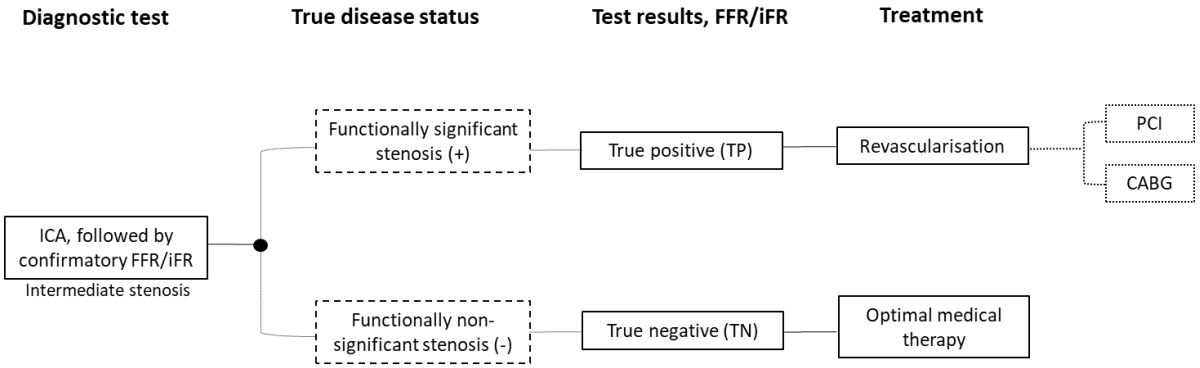


Figure 21 Strategy 3 of ICA with QFR

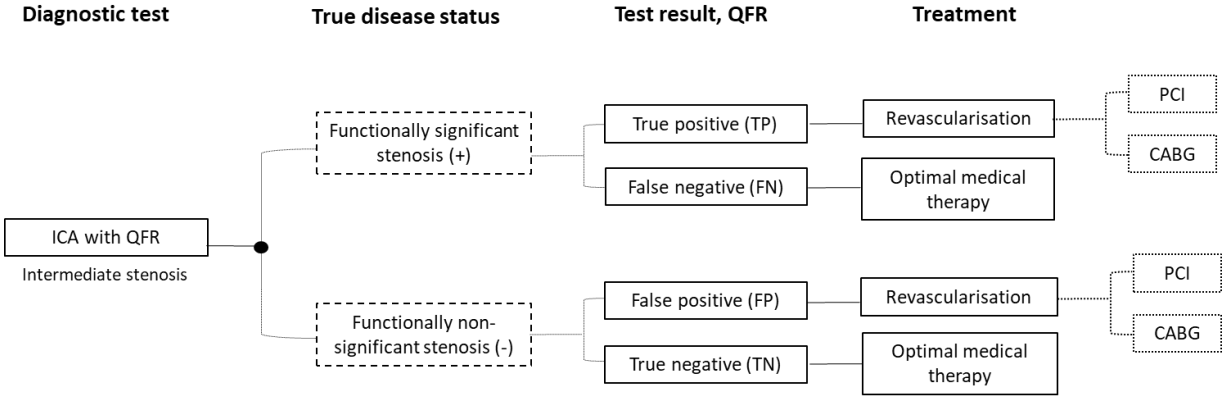


Figure 22 Strategy 4 of ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive

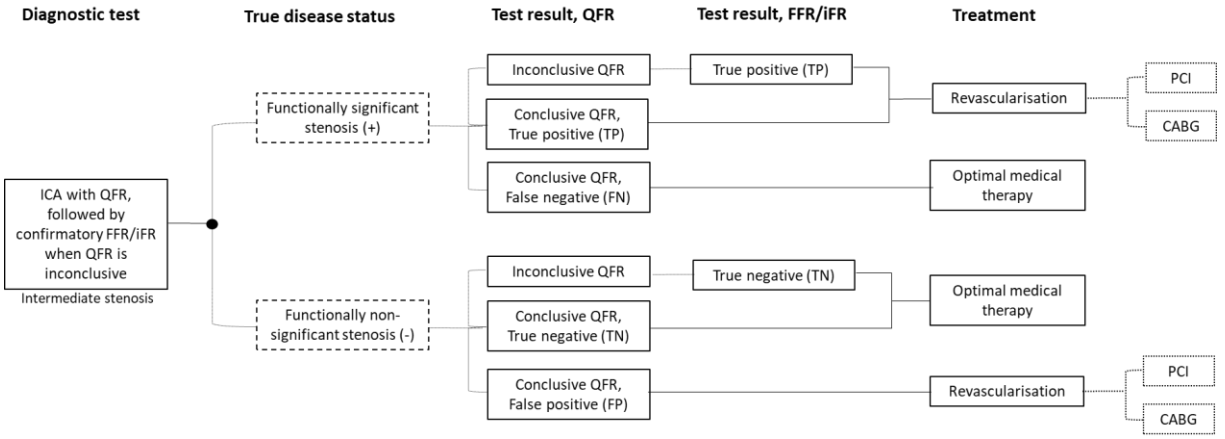
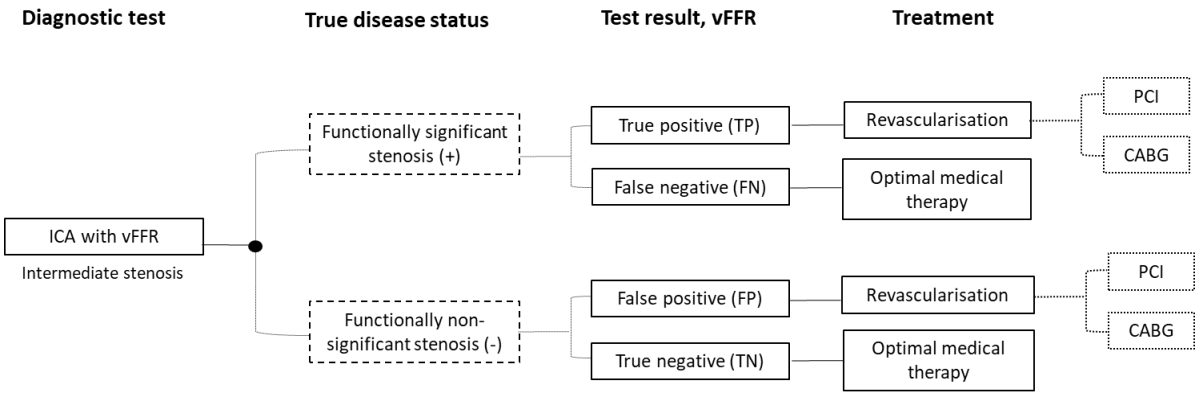


Figure 23 Strategy 5 of ICA with vFFR



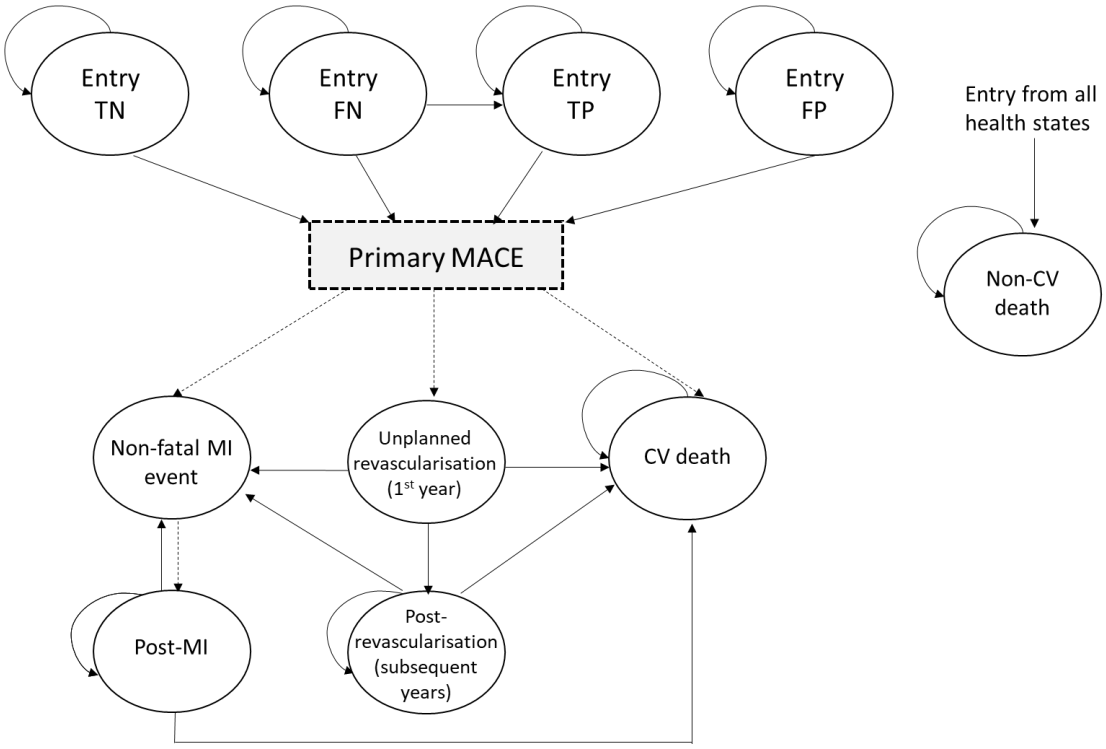
6.4.2 Prognostic model

The prognostic implications of receiving treatment (either revascularisation in addition to OMT or OMT alone) based on being in one of the four diagnostic outcome states (TP, FN, FP or TN) is quantified using a Markov model, which captures the progression of disease through the risk of major adverse cardiovascular events and associated costs and consequences, and risk of death from non-cardiac causes, over a lifetime horizon. A cycle length of one year is used in the model. A schematic of the model structure is shown in Figure 24.

Patients with stable CAD and intermediate stenosis enter the model in one of four diagnostic outcome health states: TN (functionally non-significant stenosis with FFR >0.8 and received OMT), FN (functionally significant stenosis with FFR ≤0.8 and received OMT), TP (functionally significant stenosis with FFR ≤0.8 and have undergone revascularisation), FP (functionally non-significant stenosis with FFR >0.8 and have undergone revascularisation) or death.

All patients alive may remain in their initial health state over time with no major adverse cardiovascular events, or have a primary major adverse cardiovascular event (MACE). The primary MACE event is defined as cardiovascular death, non-fatal myocardial infarction (MI) and unplanned (urgent) revascularisation, where the risk differs between the first year and subsequent years from model entry. If the primary MACE is fatal, the patient enters an absorbing state of cardiovascular death. If the event is a non-fatal MI, they enter the post-MI health state where the risk of a subsequent cardiovascular event (cardiovascular death or MI) is increased as a result of having had a previous MI. If the primary MACE is an unplanned revascularisation, it is assumed that patients will receive an appropriate revascularisation procedure, with the associated costs and risks as those patients who entered the model in the TP state (i.e., it is assumed that patients who require a subsequent targeted revascularisation have the same risk of MACE as patients who enter the model in the TP state, under the assumption that the need for urgent revascularisation is indicative of functionally significant stenosis with FFR ≤0.8). Patients enter the unplanned revascularisation event state for one cycle only and, for the following 12 months, are at an increased risk, compared to subsequent years, of cardiovascular death or MI. Those that have a cardiovascular death or non-fatal MI during this period enter the cardiovascular death state or post-MI state, respectively. If no event occurs in 12 months following an unplanned revascularisation the patient moves into the post-revascularisation health state, where the risk of cardiovascular death or MI relates to the risk post-12 months from the TP state. From any of the states in the model where patients are alive, there is a competing risk of a non-cardiovascular death.

Figure 24 Schematic of prognostic model



6.5 Model input parameters

6.5.1 Patient population

The population consists of patients with stable CAD whose angiograms taken during ICA show intermediate stenosis. The age and gender distribution varies across the studies informing the diagnostic accuracy of the technologies (mean age ranging from 61 to 72 years old and proportion of males from 67 to 81%). The IRIS-FFR registry is the largest registry to investigate the prognosis of coronary stenosis assessed by FFR. The mean age and proportion of males in the IRIS-FFR registry [10] was 64 years and 72%, respectively. These values are within the range reported in the diagnostic accuracy studies and the patient populations of the largest RCTs undertaken to evaluate clinical outcomes of revascularisation for patients with stable CAD (e.g., ISCHEMIA, [92] mean age 64 years and 77% male; BARI 2D,[93] mean age 62 years and 70% male; and COURAGE,[88] mean age 62 years and 85% male). These studies, however, were mainly or wholly undertaken outside the UK. The smaller ORBITA trial,[94] which enrolled patients with stable angina and angiographically severe single-vessel coronary artery disease at five UK sites had a mean age of 66 years and 73% male. IRIS-FFR includes mostly patients with stable angina (76%), although 18% had unstable angina and nearly 6% had NSTEMI/STEMI.

Given that the IRIS-FFR registry is the largest registry to investigate the prognosis of coronary stenosis assessed by FFR and that the mean age and proportion of males is very similar to the ORBITA trial, this is used to inform the base case population in the model (mean age 64 years and 72% male).

6.5.1.1 Prevalence of functionally significant stenosis

The prior likelihood of functionally significant stenosis in the population is based on the distribution of FFR values ≤0.8 in the recreated individual level patient data used to inform the diagnostic accuracy of QFR compared with FFR (See Section 4.7). In the absence of alternative individual level data to provide the underlying distribution of FFR/iFR values in the population, the analysis assumes that the population in the QAngio studies is reflective of the UK population in terms of underlying prevalence of functionally significant stenosis for which the technologies (QAngio and CAAS vFFR) would be used.

In the base-case analysis, the FFR distribution is based on the subset of studies that jointly reported values of FFR and cQFRor non-specified QFR to be consistent with the set of studies informing the diagnostic accuracy for strategy 4, which considers QFR, followed by FFR when the test results of QFR are inconclusive (see Section 6.5.3.1). This distribution of FFR values suggest a prior likelihood of functionally significant stenosis of 40.2% based on the proportion of participants who had an FFR measurement of 0.8 or less.

6.5.1.2 Patient throughput

The cost of the diagnostic tests (QAngio and CAAS vFFR) per patient depends on the average annual throughput per centre. In order to estimate this throughput, assumptions about patient eligibility for testing with FFR/iFR is combined with data from the British Cardiovascular Intervention Society (BCIS) audit return (data from the 2017/18 BCIS audit return[95] is used as the information in the 2018/19 audit[96] are only partially reported).

Patients with stable CAD are expected to constitute approximately one third of patients who undergo ICA in the UK (Dr Gerald Clesham, personal communication). Table 15 shows the average annual number of patients who undergo ICA in the NHS, and the average number of ICA procedures per centre.

Table 15 ICA procedures in the UK NHS

	Number of centres	ICA procedures		Source
		Total number	Average per centre*	
NHS interventional centre	98	205,085	2,093	BCIS audit returns[95]
Diagnostic only centre	60	35,017	584	
Total	158	240,102	1,520	
*Calculated based on number of centres and ICA procedures				

Under a very broad definition of intermediate stenosis, i.e., all stable CAD patients would undergo confirmatory testing with FFR/iFR, the average annual throughput for an NHS interventional centre could be as much as one third of the average number of ICA procedures per centre, which would yield an expected upper bound of 698 patients per centre for annual throughput in an NHS interventional setting (which is the setting considered in the base-case analysis; see Sections 6.4.1 and 6.5.2).

A more realistic assumption would be to consider that only patients with stable CAD who currently undergo FFR/iFR have intermediate stenosis. According to the BCIS audit returns[95], 21,098 pressure wire procedures were performed annually in the UK in 2017/18 (11,726 for diagnostic-only purposes and the rest followed by PCI). This gives an average of 215 pressure wire procedures per intervention centre per year. In the base case analysis, it is assumed that the majority of these procedures are performed in stable CAD in patients with intermediate stenosis. An average annual throughput of 200 patients per centre is assumed in the base case. Alternative throughput assumptions are considered in a scenario analysis.

6.5.2 Setting

In UK clinical practice, ICA can be used in two settings: diagnostic-only and interventional catheter laboratories. QAngio and CAAS vFFR can be used in the same settings as ICA, whereas FFR/iFR is currently only performed in an interventional setting.

The base-case analysis assumes that the tests in each of the five diagnostic strategies are all performed at the same medical appointment, and, which implicitly assumed an interventional setting. While the large majority of ICA procedures in the NHS are conducted in an interventional setting (see Table 15),[95] it is important to consider the differences between settings that may impact on the cost-effectiveness of the strategies under comparison.

The key difference between diagnostic-only and interventional catheter laboratories is that FFR/iFR can only be performed in the latter. In a diagnostic-only setting, strategies that include FFR/iFR in the testing sequence (strategy 2 and 4) require that at least some patients undergo two separate diagnostic catheterisation procedures. The initial catheterisation corresponds to the ICA that is common to all

strategies in the model and is performed in the diagnostic-only catheter laboratory. Patients who have an inconclusive QFR measurement with QAngio (patients in the 'grey zone' for strategy 4) and all patients in strategy 2 are referred to an interventional catheter laboratory where they undergo a second catheterisation to obtain an FFR/iFR measurement. This is in contrast with how patients would be tested in an interventional setting, as all tests could be performed with a single catheterisation, and at the same point in time. One of the implications of conducting two separate catheterisations is that strategies that involve FFR/iFR will be more costly in a diagnostic-only setting compared to an interventional setting. Another potential consequence of this is that the condition of patients initially tested in a diagnostic-only setting deteriorates while waiting for the referral to the interventional catheter laboratory and subsequent clinical management with revascularisation where appropriate. However, the delays to patient management are unlikely to result in significant condition deterioration with impact on patients' health outcomes ((Dr Gerald Clesham, personal communication). This is supported by evidence of the ORBITA trial (see Section 6.5.5.2), which showed that PCI compared to placebo (mock PCI) did not statistically significant increase in the exercise time or change in HRQoL of patients with medically treated angina and severe coronary stenosis at a 6 weeks post-procedure.[94]

Another difference between settings, is the expected annual patient throughput in diagnostic-only compared to interventional catheter laboratories. Table 15 shows that on average 584 patients undergo ICA in diagnostic-only setting compared to 2093 in an interventional setting. However, the proportion of patients with stable CAD who undergo ICA in a diagnostic-only setting is likely to be higher than in an interventional catheter laboratory. The expected patient throughput in a diagnostic-only setting is unknow, but needs to be considered when evaluating the cost-effectiveness of the alternative diagnostic strategies as it determines the cost of the QAngio and CAAS vFFR tests. This is discussed further in Section 6.5.8.1.

It is possible that the diagnostic accuracy of QAngio and CAAS vFFR is also linked to diagnostic setting. The diagnostic accuracy studies identified in Section 4 do not provide evidence to ascertain whether there are any differences in diagnostic accuracy of these technologies across settings, as the patient population in the review may not represent patients examined in a diagnostic-only setting. This is because only patients with an FFR measurement could be included in the diagnostic accuracy review (see Section 4.1.3).

Finally, it is possible that there are additional training requirements for QAngio and CAAS vFFR in diagnostic-only catheter laboratories, as staff in these centres may need more training and support to correctly calculate and interpret the QFR and vFFR measurements. It is, however, uncertain, what resource use is associated with these additional training requirements, so this could not be reflected in the cost-effective analysis.

The base-case scenario assumes all diagnostic procedures take place in an interventional setting. The diagnostic-only setting is considered in scenario analyses, where the impact on cost-effectiveness estimates of i) additional costs due to the need to refer patients who require FFR/iFR measurements to an interventional catheter laboratory, and ii) alternative throughput assumptions are explored (see Section 6.7.2).

6.5.3 Diagnostic accuracy

The model considers the diagnostic accuracy of ICA, QFR and vFFR, while FFR/iFR is the reference standard test with 100% sensitivity and specificity. The diagnostic accuracy of iFR is assumed to be equivalent to that of FFR. The definition of functionally significant stenosis is based on an FFR value ≤0.8. The following sections present the diagnostic accuracy estimates used in the model.

6.5.3.1 QAngio and CAAS vFFR

For strategies 3 (QFR) and 5 (vFFR) that consider a single diagnostic threshold of 0.8, the test results are dichotomous (either positive or negative for functionally significant stenosis) based on the estimates of sensitivity and specificity of the tests relative to the reference standard of FFR ≤0.8. For strategy 4, where a hybrid QFR and FFR approach is considered, the QFR test results are no longer classified as dichotomous. Under this strategy, test results are classified as positive (QFR <0.78), negative (QFR >0.84) or inconclusive (0.78 ≤ QFR ≤ 0.84) based on the dual thresholds of 0.78 and 0.84. Diagnostic accuracy of QFR in strategy 4 is informed by the joint probabilities of having an FFR measurement below or above the 0.8 threshold and a QFR measurement within the intervals defined by the dual threshold (QFR <0.78, 0.78 ≤ QFR ≤ 0.84, QFR >0.84).

Single diagnostic threshold: Sensitivity and specificity estimates

The diagnostic accuracy of QFR for strategy 3 is informed by the results of the bivariate meta-analysis reported in Section 4.5, which combined results of studies that reported contrast mode (cQFR) or non-specified QFR mode. Alternative estimates for sensitivity and specificity based on studies reporting fixed-flow QFR mode (fQFR) only and cQFR mode only are considered in separate scenario analyses. Table 16 presents the diagnostic accuracy estimates for QFR in strategy 3 used in the base case analysis and alternative scenarios.

The diagnostic accuracy of vFFR for strategy 5 is informed by the sensitivity and specificity estimates of the FAST EXTEND study,[15] an update on the FAST study.[53] This study is chosen to represent the base-case analysis as it is the largest (n=303) of the four included CAAS vFFR diagnostic accuracy studies (see Section 4.8).[15, 16, 53] A pooled meta-analysis is not considered appropriate due to limited reported data, wide confidence intervals, and high heterogeneity across the limited number of vFFR studies. The limited number of vFFR studies means that the diagnostic accuracy estimates for strategy 5 are highly uncertain and the outcomes of this strategy must be interpreted with caution. The

robustness of the cost-effectiveness results to alternative estimates about the diagnostic accuracy of vFFR is considered in scenario analyses, whereby the estimates are informed by the remaining vFFR studies. Table 16 presents the diagnostic accuracy estimates for vFFR in strategy 5 used in the base case analysis and alternative scenarios.

Table 16 Diagnostic accuracy estimates for QAngio and CAAS vFFR

Test	Analysis	Sensitivity	Specificity	Source
QAngio	Base-case	84.34%	89.80%	Bivariate meta-analysis (Table 3) for combined cQFR and non-specified QFR "mode"
	Scenario	84.32%	91.40%	Bivariate meta-analysis (Table 3) for cQFR "mode"
	Scenario	81.61%	84.93%	Bivariate meta-analysis (Table 3) for fQFR "mode"
CAAS vFFR	Base-case	97.00%	74.00%	FAST EXTEND, 2019[15]
	Scenario	75.00%	46.50%	ILUMIEN I, 2019[16]
	Scenario	68.20%	87.30%	Jin et al, 2019[23]

The sensitivity and specificity estimates in the model are randomly drawn from probability distributions to reflect uncertainty in these parameters. Where diagnostic accuracy was sourced from meta-analyses, the log odds sensitivity and specificity (with confidence intervals), and the correlation between these two test accuracy dimensions were used to inform multivariate log-normal distributions from which the probabilistic estimates are drawn. For individual studies, beta-distributions were fitted to the sensitivity and specificity estimates. In order to preserve the correlation between sensitivity and specificity, the diagnostic accuracy 2x2 tables for each study were recreated (assuming a common prevalence for functionally significant stenosis of 0.402 [see Section 6.5.1.1]) and used to inform the alpha and beta parameters of the beta distributions.

Probability of QFR in the hybrid approach with confirmatory FFR

The diagnostic accuracy of QFR in strategy 4 was based on the joint distribution of QFR and FFR measurements in the extracted individual-level patient data (n=3,194) (See section 4.7.2)for the combined cQFR and non-specified QFR data. The probabilities of QFR test results being positive (QFR <0.78), negative (QFR >0.84) or inconclusive (0.78≤ QFR ≤0.84) was conditional on FFR values above and below 0.8. Table 17 presents the diagnostic accuracy estimates for strategy 4.

Table 17 QAngio diagnostic accuracy estimates for strategy 4

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

In the probabilistic analysis, the joint QFR and FFR probabilities in Table 17 were sampled from a set of 5,000 simulated values. These values were derived from 5,000 simulations of the joint distribution of FFR and QFR, generated by bootstrapping the extracted individual-level data from which the probabilities in Table 17 were derived.

The diagnostic accuracy of an equivalent hybrid diagnostic approach for vFFR was not possible due to data limitations. The diagnostic accuracy data for vFFR is very scarce (see Section 4.8), and only 81 data points for the joint FFR and vFFR distribution were available from one single study.[53] Furthermore, the underlying distribution of FFR values in this single study was considerably different from that of the data extracted for QFR (probability of FFR ≤0.80 was 0.296 in the single vFFR study compared to 0.402 across 3,194 data points in the QFR studies). Invasive coronary angiography

6.5.3.2 ICA

The diagnostic accuracy of ICA was informed by the bivariate meta-analysis of extracted data presented in Section 4.7.4. Table 31 presents the diagnostic accuracy estimates for ICA based on a threshold of 50% DS. Alternative sensitivity and specificity estimates based on a meta-analysis by Danad et al,2017, [97] for diagnostic performance of ICA compared with FFR is used in a scenario analysis.

Table 18 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)
	Scenario	71.00%	66.00%	Danad et al, 2017, [97] per vessel analysis

6.5.4 Procedural adverse events

Procedures involving catherisation for diagnostic testing (ICA and FFR/iFR) or revascularisation (PCI and CABG) have associated complications that may result in health care resource and health-related quality of life loss. The diagnostic model considers the impact of serious procedural complications from FFR/iFR and revascularisation. The procedural complications of ICA are excluded from the model because all patients undergo this procedure in all strategies and, therefore, procedural complications associated with ICA do not result in differences in costs and health-related quality of life across strategies.

The diagnostic pathway explicitly distinguishes between complications associated with invasive testing with FFR/iFR and revascularisation so that the potential benefits of less invasive testing can be captured (i.e., non-invasive testing with QFR and vFFR in strategies 3 and 5, respectively). However, revascularisation is often performed immediately after FFR/iFR and, therefore, the rates are often not reported separately in the literature by type of procedure.

6.5.4.1 Complications due to FFR/iFR

Three studies were identified that reported procedural complications rates in a format suitable to inform those associated with FFR/iFR alone (i.e., unrelated to the revascularisation procedure). The RIPCORD trial compared the clinical management (OMT alone or in addition to PCI or CABG) of patients with stable chest pain with ICA versus pressure-wire FFR assessment.[98] The placebo arm of the ORBITA trial[94] is also potentially relevant to inform the rates of FFR/iFR-related complications. In this study, patients were randomised to either PCI or a placebo procedure for angina relief, with all patients undergoing FFR/iFR prior to randomisation. Thus, patients who had serious peri-procedural complications in the placebo arm had undergone FFR/iFR but not PCI. The IRIS-FFR registry data also reports serious complications associated with FFR measurement.[10] The rates of serious events reported in the three studies are summarised in Table 19.

Table 19 FFR/iFR serious procedural complication rates

	ORBITA* **(N=95)**	**RIPCORD (N=200)**	**IRIS-FFR registry (N=8,633)**
Serious procedural complications	n (%)	n (%)	n (%)
Major bleeding	1 (1.05%)	-	-
Converted to PCI for procedural complication	4 (4.21%)	-	-
Pulmonary oedema	1 (1.05%)	-	-
Vessel occlusion	-	1 (0.5%)	-
Deep vein thrombosis	-	1 (0.5%)	-
Conduction disturbance requiring treatment	-	-	3 (0.03%)
Bronchospasm	-	-	2 (0.02%)
Coronary dissection	-	1 (0.5%)	3 (0.03%)
Ventricular arrhythmia**	-	1 (0.5%)	2 (0.02%)
Thrombus formation	-	-	1 (0.01%)
*Placebo arm of the trial, **Ventricular fibrillation in RIPCORD			

Data from the IRIS-FFR study[10] is used to inform the base-case analysis because this is considerably larger than the other studies, and is used as a source of baseline clinical effectiveness in the prognostic model (see Section 6.5.5.1). A scenario analysis uses the alternative source of data from

the RIPCORD study because this is a UK study and the patient population appears comparable to that of the base-case population (mean age 64 years old and 75% male).

The majority of complications reported in the ORBITA trial[94] appear to be related to ICA (major bleeding and pulmonary oedema) and not to FFR/iFR based on the description of the complications reported in the manuscript's supplementary materials. The conversion to PCI due to procedural complications in ORBITA appears to be due to coronary dissection caused by the pressure wire, and suggests a much higher rate for this complication than that reported in the IRIS-FFR registry. The patient population in ORBITA may represent a more severe population (mean baseline FFR: 0.69±0.16) compared to the IRIS-FFR registry (mean baseline FFR 0.83±0.11). Therefore, the rate of procedural adverse events in ORBITA is expected to be an overestimate of the complication rates in the base case population.

None of the studies above reported procedural mortality due to FFR/iFR. In the IRIS-FFR registry, deaths due to FFR may have been captured within the rates of major adverse cardiovascular events but this is unclear. A procedural death rate associated with FFR/iFR of 0.015% is included in the diagnostic model based on an estimate sourced from Fearon et al., (2004)[83], which was the only study identified in the review of decision models evaluating ICA (see Section 5.4) to include FFR-specific procedural death. The rates of FFR/iFR procedural complications applied in the base-case analysis are summarised in Table 20.

Table 20 Rates of FFR/iFR procedural complications in the model

Serious procedural complications	Rate	Source
Coronary dissection	0.03%	IRIS-FFR registry[10]
Venous occlusion	0%	IRIS-FFR registry [10]
Ventricular arrhythmia	0.02%	IRIS-FFR registry [10]
Conduction disturbance requiring treatment	0.03%	IRIS-FFR registry [10]
Bronchospasm	0.02%	IRIS-FFR registry [10]
Thrombus formation	0.01%	IRIS-FFR registry [10]
Death	0.015%	Fearon et al., 2003[83]

Note that while in ORBITA patients underwent iFR and FFR, all patients underwent FFR only in IRIS-FFR and RIPCORD. The base-case analysis assumes that there are no differences in the rates of procedural complications due to FFR and iFR, i.e., the complication rates associated with pressure wire FFR in IRIS-FFR are also reflective of the average rates of iFR as an alternative to FFR in UK clinical practice.

Probabilistic estimates of the FFR procedural complication rates were obtained by randomly sampling from independent beta distributions for each event rate.

6.5.4.2 Complications due to revascularisation

Death was the most common revascularisation complication reported in the cost-effectiveness models reviewed in Section 5.4. Two studies also considered non-fatal MI, but one reports complication rates jointly for ICA and revascularisation [70] and the other[84] sources complication rates from a very early 1996 study.

The IRIS-FFR registry [10] does not report procedural complications associated with revascularisation separate from the risk of major adverse cardiovascular events The rate of procedural deaths associated with revascularisation is sourced from UK audit data. A 0.99% death risk for non-emergency CABG [99] and 0.17% for in-hospital mortality for PCI[100] are applied in the diagnostic model. The mortality rate associated with revascularisation is estimated as a weighted average of the mortality rates for PCI and CABG, where the weights correspond to the relative proportion of PCI and CABG procedures. In the base-case analysis, 87% of revascularisation procedures are assumed to be PCI, while the remaining 13% are CABG based on BCIS audit returns.[95]

6.5.4.3 Other procedural adverse events: radiation exposure

Patients who undergo cardiac catheterisation are exposed to ionising radiation, which may increase the lifetime risk of malignancy and associated mortality. Some of the previous cost-effectiveness models of ICA[64, 67, 68, 70, 73, 75] reviewed in Section 5.4 considered radiation exposure due to ICA testing and revascularisation.

QAngio or CAAS vFFR may reduce the magnitude of radiation exposure by reducing the procedural time compared to FFR/iFR. However, radiation exposure even with FFR/iFR is expected to be very low and the reduction in exposure through the use of QFR or vFFR is expected to be very marginal (Dr Gerald Clesham, personal communication). Therefore, the impact of radiation exposure on cost-effectiveness is expected to be very minimal and is not quantified in the model. This is supported by the previous cost-effectiveness models, e.g., Walker and colleagues[73] explicitly modelled an increased risk of cancer death conditional on amount of radiation exposure for several different diagnostic strategies that included ICA and found that the cost-effectiveness results were robust to the exclusion of radiation effects.

6.5.5 Risk of MACE and treatment effects of revascularisation

6.5.5.1 Baseline risk of MACE

The benefits of treatment by correctly identifying patients suitable for revascularisation, or to have their ischaemia treated by OMT, are modelled through the impact on risk of MACE and health-related quality of life (HRQoL). The baseline risk of MACE in the absence of revascularisation depends on disease severity as measured by FFR/iFR, where lower FFR values are indicative of a higher cardiovascular event rate and higher FFR values of a lower cardiovascular event rate.[101] Thus, there is an inverse relationship between FFR value and subsequent outcomes.

The IRIS-FFR registry is the largest registry to prospectively evaluate the natural history of lesions after measurement of FFR in routine clinical practice.[10] Revascularisation was deferred in 6468 lesions (75%) and performed in 2165 lesions (25%) after FFR assessment. Treatment with revascularisation was generally recommended in participating centres when FFR was ≤0.75 and deferred when FFR was >0.8. For FFR values between 0.75 and 0.8, the decision regarding revascularisation was left to the operator's discretion. Of the deferred lesions, 85.1% had a FFR value >0.8, 9.2% had a FFR value of between 0.76 and 0.8, while 5.7% had a value of ≤0.75. The reasons for deferred lesions despite low FFR ≤0.75 included minimal coronary artery stenosis on ICA, diffuse disease without focal stenosis, no symptoms, small myocardial territory or not suitable for PCI.[10]

The primary endpoint in the IRIS-FFR registry was MACE arising from FFR-measured lesions, which was a composite of cardiac death, MI and repeat revascularisation. Cardiac death was defined as any death because of a proximate cardiac cause, including cardiac arrest, MI, and fatal arrhythmia. MI was defined as a non-fatal MI event within the first 48 hours of the procedure or ≥48 hours after the procedure accompanied by ischaemic symptoms. Repeat revascularisation was defined as any PCI or CABG of a lesion with an index FFR measurement.[10] The registry data provides a source of baseline risk of MACE according to FFR value in deferred lesions in the absence of revascularisation.

The overall incidence rate of MACE in the IRIS-FFR registry across the range of FFR values was 1.44% (95% CI, 1.15-1.73%) during the median follow-up of 1.9 years in deferred lesions. The corresponding incidence rates of clinical events were 0.09% for cardiac death, 0.14% for MI, and 1.34% for repeat revascularisation. When the 5.7% of deferred lesions with an FFR value of ≤0.75 were excluded, the overall incidence rate of MACE was 1.24% (95% CI, 0.96-1.52%).

The risk of MACE in deferred lesions increased significantly while FFR decreased. The adjusted hazard ratio for the risk of MACE when FFR was included as an independent predictor in deferred lesions was 1.06 (95% CI, 1.05-1.08) per 0.01 decrease in FFR (using FFR values ≥0.91 as a reference). The corresponding adjusted hazard ratios for the risk of clinical events were 1.06 (95% CI,

0.99-1.13) for cardiac death, 1.09 (95% CI, 1.05-1.14) for MI and 1.07 (95% CI, 1.06-1.09) for revascularisation.

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 provide an estimate of the baseline risk of MACE (i.e., MACE risk in the absence of revascularisation procedure) for the first year and subsequent years. The risk of MACE and the associated consequences in terms of health care resource use and HRQoL is modelled by stratifying patients into subgroups of FFR values, in order to take account of the relationship linking FFR value to subsequent prognosis. To adjust for competing risks across cardiac events, the rate of each MACE component was divided by the sum of the rates of the components. The resulting proportions (6% for cardiac death, 9% for MI and 85% for repeat revascularisation) were multiplied by the baseline rate of the composite MACE outcome for the reference group with FFR values ≥0.91, which resulted in rates adjusted for competing hazards from the MACE components.

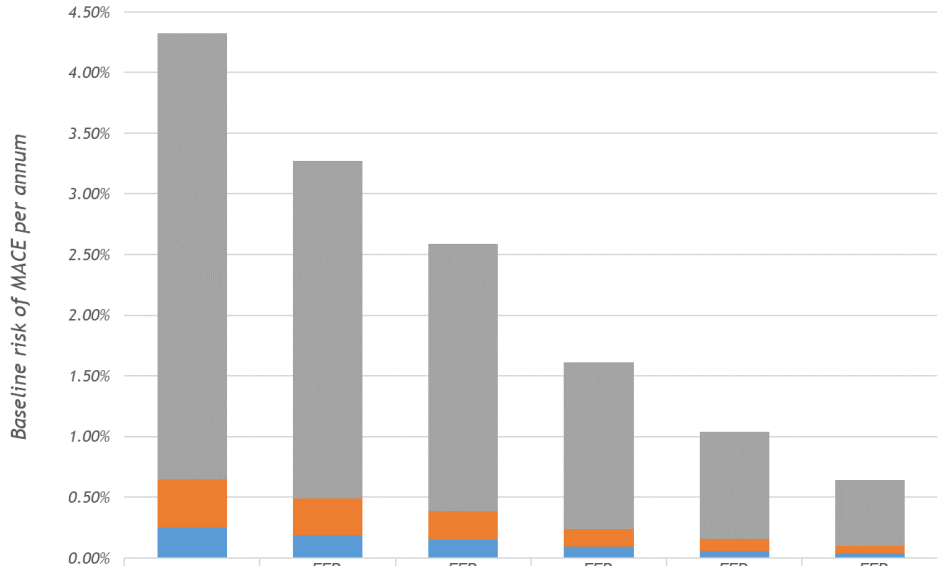
The baseline risk of MACE used in the model for individuals in the group with highest FFR values (FFR values ≥0.91) is 0.64% per annum in the first year and 0.32% per annum in subsequent years. This risk was used as a reference to compute the baseline risk of MACE components in categories with lower FFR values (<0.91), using the adjusted hazards ratios of 1.06, 1.09 and 1.07 per 0.01 decrease in FFR for cardiac death, MI and revascularisation, respectively. The corresponding annual baseline risk of MACE in deferred lesions by FFR value and by component of the composite outcome are shown in Figure 25 for the first year. The values for subsequent years are approximately half of the values for the first year.

This approach implies that the baseline risk of MACE used in the model is conditional on FFR value, while the distribution of FFR values differs by diagnostic strategy. Therefore, the baseline risk of MACE from the TN and FN entry states in the model (in the absence of revascularisation) for each diagnostic strategy is based on the joint conditional distribution of FFR values for the diagnostic strategy across the FFR categories in Figure 25, i.e., the expected proportion of TN outcomes with an FFR=[0.81-0.85], FFR=[0.86-0.90] and FFR≥0.91 and FN outcomes with an FFR=[0.76-0.80], FFR=[0.71-0.75] and FFR≤0.70 for each diagnostic strategy is dependent on the underlying distribution of FFR values across these categories in the population. The same approach is used to establish the risk of MACE following revascularisation for the TP and FP entry states in the model (see Section 6.5.5.2 below). An alternative assumption is considered in a scenario analysis where the risk of MACE is assumed to be completely independent of FFR and diagnostic test results.

The main limitation of using the IRIS-FFR registry data as a source of baseline risk of MACE for the model is that unobserved selection factors may have influenced the decision to perform or not to

perform revascularisation, which, in turn, may have exerted a modifying effect on outcomes. In addition, the registry is based outside the UK in participating centres in South Korea. In the absence of an alternative source of data that evaluates the natural history of lesions after measurement of FFR in routine UK clinical practice, the model assumes that any potential selection factors in the IRIS-FFR registry have no causal relation on outcomes and that any underlying reasons would not be expected to differ from UK practice.

Figure 25 Baseline risk of MACE by FFR value in the first year after FFR measurement.



	FFR<=0.70	FFR= [0.71-0.75]	FFR= [0.76-0.8]	FFR= [0.81-0.85]	FFR= [0.86-0.9]	FFR >=0.91
Unplanned revascularisation	3.68%	2.78%	2.20%	1.37%	0.88%	0.55%
Myocardial infarction	0.40%	0.30%	0.24%	0.15%	0.10%	0.06%
Cardiac death	0.25%	0.19%	0.15%	0.09%	0.06%	0.04%

6.5.5.2 Treatment effect of revascularisation

The treatment effect of revascularisation on MACE in patients with stable CAD is highly uncertain and has been an area of considerable debate over the past decades. Early RCTs examining the benefit of PCI and CABG surgery compared with OMT suggested a survival benefit for revascularisation. However, more recently, the benefits of revascularisation have been questioned as a result of similar rates of death and MI observed in patients that have been optimally pharmacologically managed without PCI.

Table 21 summarises the main findings of recent RCTs (post year 2000) in stable CAD that have compared revascularisation (in addition to OMT) versus OMT alone. The focus on studies post-2000 is due to the changes in interventions over the past decades. For example, PCI using bare metal stents or early generation drug-eluting stents have now been shown to be less safe and effective than

currently available second-generation stents,[102] while pharmacological interventions have changed over time.

The definition of MACE differs across the studies but it is generally defined as a composite of cardiovascular death (or all-cause mortality), MI, and hospital admission, with or without the need for revascularisation. The RCTs that showed a statistically significant difference in MACE between revascularisation and medical therapy were TIME,[103] MASS II[104] and BARI 2D[105] for CABG surgery, COURAGE[88] and FAME II [106] for repeat revascularisation, and DEFER[107] in low FFR (<0.75).

In the TIME trial, 305 patients aged 75 years and older with stable CAD of at least Canadian Cardiac Society Class II despite at least two antianginal drugs were randomly assigned to PCI, CABG or OMT.[103] A significant difference in MACE rate between the revascularisation (19%) and medical therapy (49%) group was observed over a mean follow-up of 184.4 days. This difference was mainly due to higher rates of hospital admission for acute coronary syndrome that required revascularisation.

In the MASS II trial, 611 patients with proximal multivessel stenosis and documented ischaemia were randomly assigned to PCI, CABG or OMT [104]. At 5-year follow-up, a significant difference in MACE was observed for CABG (21.2%) compared with PCI (32.7%) and OMT (36%). This difference suggests a protective effect of CABG but no significant difference in MACE was observed between PCI and OMT. The difference in MACE for CABG was due to a significant difference in the need for repeat revascularisation and MI, however there was no significant difference in overall mortality. In the BARI 2D trial, 2368 patients with stable CAD and type 2 diabetes were randomly assigned to PCI, CABG or OMT.[105] At 5-year follow-up, patients in the CABG stratum, who had more advanced CAD than those in the PCI stratum, had a significantly lower rate of MACE (22.4%) than the medical therapy group (30.5%), which was largely driven by fewer MIs.

In the COURAGE trial, 2287 patients with stable CAD were randomly assigned to PCI or OMT.[88] A statistically significant difference in the cumulative rate of additional revascularisation at 4.6 years was observed between PCI (21.1%) and OMT (32.6%). The corresponding hazard ratio was 0.60 (95% CI, 0.51 to 0.71). In the FAME II trial, 888 patients with stable CAD were randomly assigned to FFR-guided PCI for patients in whom at least one stenosis was functionally significant (FFR ≤0.80) or OMT. [106] At 2-year follow-up, a significantly lower rate of MACE was observed in the PCI group (8.1%) compared with OMT group (19.5%), which was largely driven by a lower rate of urgent revascularisation in the PCI group. The corresponding hazard ratio was 0.39 (95% CI, 0.26 to 0.57). In the DEFER trial, 325 patients with stable CAD and intermediate stenosis were randomly assigned to PCI for FFR ≥0.75, PCI for FFR <0.75 or OMT.[107] At 2-year follow-up, a significantly lower rate of MACE was observed in the PCI group with FFR <0.75 (78%) compared with OMT (89%) and PCI

with FFR ≥0.75 (83%), suggesting that FFR identifies those who will benefit the most from revascularisation in terms of MACE outcomes.

The RCTs that showed a non-statistically significant difference in MACE between revascularisation and medical therapy were MASS II[104] and BARI 2D[105] for PCI, COURAGE[88] for the outcomes of mortality and MI, JSAP,[108] and ISCHEMIA.[92]

In the MASS II trial at 5-year follow-up, there was no statistically significant difference in MACE between PCI (32.7%) and OMT (36%), while in the BARI 2D trial, there was no statistically significant difference in MACE between revascularisation group (77.2%) and OMT group (75.9%). In the COURAGE trial, there was no statistically significant difference in 4.6-year cumulative event rates for the composite endpoint of all-cause mortality and MI (hazard ratio of 1.05 for PCI, with 95% CI of 0.87 to 1.27).

In the JSAP trial, 384 patients with stable CAD and ≥75% coronary stenosis were randomly assigned to PCI or OMT.[108] At 3.3 year follow-up, there was no statistically significant difference in MACE between the PCI group (2.9%) and OMT group (3.9%). In the largest, and most recent, ISCHEMIA trial, 5179 patients with stable CAD and moderate or severe ischaemia were randomly assigned to a revascularisation group (74% PCI and 26% CABG) and OMT group.[92] Over a median follow-up of 3.2 years, 318 primary outcome events (composite of death from cardiovascular causes, MI, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest) occurred in the revascularisation group and 352 occurred in the OMT group. At 6 months, the cumulative event rate was 5.3% in the revascularisation group and 3.4% in the OMT group, while at 5 years the cumulative event rate was 16.4% in the revascularisation group and 18.2% in the OMT group. The trial findings were sensitive to the definition of MI and the timing of results; procedural MI was increased with revascularisation, while spontaneous MI was reduced with revascularisation, thus the net effect of MI was dependent on the time point at which it was measured. The evidence from the trial suggests that there is no statistically significant difference in MACE between revascularisation and OMT.

There have been several meta-analyses that have synthesised the results of trials examining the treatment effect of revascularisation on MACE in patients with stable CAD.[109-116] Of the most recent meta-analyses that include new generation stents, the following findings were identified:

- Pursnani et al (2012)[116] included RCTs comparing revascularisation with PCI to OMT in patients with stable CAD, dating from 1980 until 2012. When compared with OMT, PCI was associated with no statistically significant improvement in mortality (risk ratio [RR], 0.85; 95% CI, 0.71–1.01), cardiac death (RR, 0.71; 95% CI, 0.47–1.06), nonfatal MI (RR, 0.93;

95% CI, 0.70–1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76–1.14), with consistent results over different follow-up time points.

- Thomas et al (2013)[112] included RCTs comparing revascularisation with PCI to OMT in patients with stable CAD, dating from 1980 until 2011. When compared with OMT, PCI was associated with no statistically significant improvement in all-cause mortality (RR, 0.97; 95% CI, 0.84–1.12), cardiac death (RR, 0.91; 95% CI, 0.70–1.17) and nonfatal MI (RR, 1.09; 95% CI, 0.92–1.29).
- Stergiopoulos et al (2014)[115] included RCTs comparing revascularisation with PCI to OMT in patients with stable CAD, dating from 1970 until 2012. When compared with OMT, PCI was associated with no statistically significant improvement in all-cause mortality (odds ratio [OR], 0.90; 95% CI, 0.71-1.16), nonfatal MI (OR, 1.24; 95% CI, 0.99-1.56) and unplanned revascularisation (OR, 0.64; 95% CI, 0.35-1.17).
- Windecker et al (2014)[114] undertook a Bayesian network meta-analysis comparing revascularisation (PCI or CABG) with OMT among patients with stable CAD, dating from 1980 until 2013. CABG was associated with a survival benefit (RR, 0.80; 95% CrI 0.70 to 0.91) compared with OMT. New generation drug eluting stents (everolimus RR, 0.75; 0.59 to 0.96; zotarolimus (Resolute) RR, 0.65; 0.42 to 1.00) but not balloon angioplasty (RR, 0.85; 0.68 to 1.04), bare metal stents (RR, 0.92; 0.79 to 1.05), or early generation drug eluting stents (paclitaxel RR, 0.92; 0.75 to 1.12; sirolimus RR, 0.91; 0.75 to 1.10; zotarolimus (Endeavor) RR, 0.88; 0.69 to 1.10) were associated with improved survival compared with OMT. CABG reduced the risk of MI compared with OMT (RR, 0.79; 0.63 to 0.99), and everolimus eluting stents showed a trend towards a reduced risk of MI (RR, 0.75; 0.55 to 1.01). The risk of subsequent revascularisation was noticeably reduced by CABG (RR, 0.16; 0.13 to 0.20) followed by new generation drug eluting stents (zotarolimus (Resolute) RR, 0.26; 0.17 to 0.40; everolimus RR, 0.27; 0.21 to 0.35), early generation drug eluting stents (zotarolimus (Endeavor) RR, 0.37; 0.28 to 0.50; sirolimus: RR, 0.29; 0.24 to 0.36; paclitaxel: RR, 0.44; 0.35 to 0.54), and bare metal stents (RR, 0.69; 0.59 to 0.81) compared with OMT.
- Chacko et al (2020)[113] included RCTs comparing PCI to OMT in patients with stable and unstable CAD, dating from 1992 until 2019, which included the ISCHEMIA trial, to examine the effects on death and MI. For stable CAD, PCI did not show a statistically significant reduction in mortality (RR, 0.98; 95% CI 0.87-1.11), cardiac death (RR, 0.89; 95% CI 0.71-1.12) or MI (RR, 0.96; 95% CI 0.86-1.08).

The IRIS-FFR registry[10]prospectively evaluated the natural history of lesions after measurement of FFR in routine clinical practice in those revascularised (95.7% PCI, with the majority new generation drug-eluting stents (85.1%) and 4.3% CABG) compared with deferred lesions. The overall incidence rate of MACE in revascularised lesions was 2.4% compared with 1.44% in deferred lesions during the

median follow-up of 1.9 years. The corresponding incidence rates of clinical events were 0.71% for cardiac death or MI and 1.83% for repeat revascularisation compared with 0.21% and 1.34% in deferred lesions, respectively. However, unlike the deferred lesions, the risk of MACE was not associated with FFR measurement. After adjustment for independent predictors of MACE, the risk of MACE was not statistically significantly different between revascularised and deferred lesions for FFR values ≥0.76 (Hazard ratio [HR], 0.83; 95% CI 0.46-1.50 for FFR=[0.76-0.80] and HR, 1.21; 95% CI 0.44-3.36 for FFR=[0.81-0.85]). Revascularisation was associated with improved MACE rates compared with deferred lesions for lesions with an FFR ≤0.75 (HR, 0.47; 95% CI 0.24-0.89 for FFR=[0.71-0.75] and (HR, 0.47; 95% CI 0.26-0.84 for FFR≤0.70). The findings from the IRIS-FFR registry are consistent with the study by Johnson et al (2014), which examined the prognostic value of FFR on clinical outcomes. Johnson et al (2014) undertook a meta-analysis of study-level (9173 lesions) and patient-level (6961 lesions) data investigating prognosis of MACE outcomes after FFR measurement by revascularisation compared with OMT.[101] The study-level meta-regression indicated that revascularisation was associated with a lower normalised one-year MACE rate (composite of death, MI and repeat revascularisation) compared with OMT when FFR was ≤0.75. The corresponding patient-level meta-regression after adjustment for %DS indicated that revascularisation was associated with a lower one-year MACE rate compared with OMT when FFR was ≤0.76.

In summary, the treatment effect of revascularisation on MACE in patients with stable CAD is highly uncertain. The primary aim of the largest and most recent ISCHEMIA trial, which included UK centres, was to address the limitations of previous trials by determining whether revascularisation plus OMT compared with a conservative strategy of OMT alone would reduce the primary composite outcome of death from cardiovascular causes, MI, or hospitalisation for unstable angina, heart failure, or resuscitated cardiac arrest in patients with stable ischaemic heart disease with moderate or severe ischaemia.[92] As indicated above, the trial did not find evidence that revascularisation reduced the risk of MACE. Therefore, it seems appropriate for the base case analysis to consider that the benefits of the diagnostic tests in identifying the appropriateness for revascularisation confers no benefit on MACE outcomes. This means that in the base case analysis the risk of MACE following revascularisation for the TP and FP entry states in the model is the same as the baseline risk of MACE conditioned on FFR value, i.e., the expected proportion of TP outcomes with a FFR=[0.76-0.80], FFR=[0.71-0.75] and FFR≤0.70 and FP outcomes with a FFR=[0.81-0.85], FFR=[0.86-0.90] and FFR≥0.91 for each diagnostic strategy is dependent on the underlying distribution of FFR values across these categories in the population.

Alternative scenarios are considered in the model where revascularisation does confer a benefit on MACE outcomes compared with OMT. Three alternative scenarios are considered:

1. A significant reduction in MACE only for FFR below 0.76, in line with the findings of the IRIS-FFR registry. In this scenario, the HR for revascularisation is set equal to 0.47 (95% CI 0.24-0.89 for FFR=[0.71-0.75] and 95% CI 0.26-0.84 for FFR≤0.70) for all components of MACE for FFR≤0.75, while the HR is set equal to one for FFR>0.75.
2. A significant reduction in the component of MACE of unplanned revascularisation only and no reduction for cardiac death or MI. This is in line with the findings of the trials that found a positive effect of revascularisation on MACE outcomes but that this positive effect was largely determined by a reduction in number of repeat/emergency or unplanned revascularisations rather than cardiac death or MI. In this scenario, the HR is set equal to 0.26 (95% CrI 0.17 to 0.40) for repeat revascularisation from the meta-analysis by Windecker et al (2014) for new generation drug eluting stents, while the HR is set equal to 1 for cardiac death or MI.
3. A non-statistically significant reduction in MACE for all components. This is in line with the findings of the trials that found a modest improvement in MACE outcomes for revascularisation compared with OMT but this improvement was not statistically significant. In this scenario, the HR is set equal to 0.71 (95% CI, 0.47–1.06) for cardiac death, 0.93 (95% CI, 0.70–1.24) for non-fatal MI and 0.93 (95% CI, 0.76–1.14) for repeat revascularisation based on the meta-analysis by Pursnani et al (2012).

Additional sensitivity analyses using the results from the individual RCTs and meta-analyses reported above are considered to assess the impact of alternative assumptions about the treatment effect of revascularisation for MACE outcomes on the cost-effectiveness results.

Table 21 Summary of RCTs comparing revascularisation in addition to OMT vs OMT alone in stable CAD

Study Acronym, year	Region	Main inclusion criteria	N	Revascularisation procedure vs. OMT*	Follow-up, years	Primary end points	Main findings
DEFER, 2001[107]	Europe, Asia	SCAD, >50% DS, FFR≥0.75, no evidence of reversible ischemia by non-invasive testing in previous 2 months.	325	PCI for FFR≥0.75, performance group; PCI for FFR<0.75, reference group; OMT for FFR≥0.75, deferral group	2	MACE, defined as composite of all-cause mortality, MI, CABG, PCI, and any procedure-related complication necessitating major intervention or prolonged hospital stay	Event-free survival was similar between the deferral and performance groups (92% versus 89% at 12 months and 89% versus 83% at 24 months) but was significantly lower in the reference group (80% at 12 months and 78% at 24 months). → FFR identifies those who will benefit from PCI the most
TIME, 2001[103]	Switzerland	SCAD, age≥75 years, CCSC≥2 despite treatment with at least 2 antianginal agents	305	PCI, CABG, OMT	1	MACE, defined as composite of all-cause mortality, MI, hospital admission for ACS with or without the need for revascularisation. HRQoL at 6 months (SF-36, DASI, rose questionnaire for angina)	Significant difference in MACE between invasive group and medical therapy group (19% versus 49% at mean follow-up of 184.4 days). The difference was mainly due to higher rates of hospital admission for ACS. After 6 months, angina severity decreased and measures of HRQoL increased in both treatment groups; however, these improvements were significantly greater after revascularisation.

MASS II, 2007, 2006[104, 117, 118]	Brazil	SCAD, ≥70% proximal multivessel stenosis and documented ischemia	611	PCI, CABG, OMT	10	MACE, defined as composite of all-cause mortality, MI, refractory angina requiring revascularisation. [104] HRQoL at 6 months and 1 year follow-up (SF-36) [117]	At 5-year follow-up, significant difference in MACE for CABG (21.2%) compared with PCI (32.7%) and OMT (36%). No statistically significant difference in overall mortality among the 3 groups. Significant difference in repeat revascularisation procedures for CABG (3.9%) compared with PCI (11.2%) and OMT (9.4%). Significance difference in MI for CABG (8.3%) compared with PCI (11.2%) and OMT (15.3%). → Protective effect of CABG but no significance difference in MACE between PCI and OMT. The 10-year survival rates were 74.9% with CABG, 75.1% with PCI, and 69% with OMT. The 10-year rates of MI were 10.3% with CABG, 13.3% with PCI, and 20.7% with MT. The 10-year rates of additional revascularisations were 7.4% with CABG, 41.9% with PCI, and 39.4% with MT. 10-year rates of freedom from angina were 64% with CABG, 59% with PCI, and 43% with MT.

							HRQoL was better in both CABG and PCI groups compared to OMT after 1 year of follow-up. CABG group presented the greater and progressive improvement in HRQoL.
COURAGE, 2007, 2008[88, 119]	North America	SCAD, ≥70% in at least one proximal epicardial coronary artery and evidence of myocardial ischemia or at least one coronary stenosis of ≥80% and classic angina without provocative testing.	2287	PCI, OMT	4.6	Primary outcome was composite of all-cause mortality and MI. Secondary outcome was MACE, defined as all-cause mortality, MI, stroke and hospitalisation for unstable angina with negative biomarkers.[88] HRQoL at 1 year follow-up (SAQ)[119]	No statistically significant difference in 4.6-year cumulative primary-event rates between PCI group (19.0%) and OMT group (18.5%) (hazard ratio for the PCI group, 1.05; 95% CI, 0.87 to 1.27; P=0.62). No statistically significant difference between the PCI group and the OMT group in the composite of death, MI, and stroke (20.0% vs. 19.5%; hazard ratio, 1.05; 95% CI, 0.87 to 1.27; P=0.62); hospitalization for ACS (12.4% vs. 11.8%; hazard ratio, 1.07; 95% CI, 0.84 to 1.37; P=0.56); or MI (13.2% vs. 12.3%; hazard ratio, 1.13; 95% CI, 0.89 to 1.43; P=0.33). Statistically significant difference between PCI group (21.1%) and OMT group (32.6%) requiring additional revascularization (hazard ratio, 0.60; 95% CI, 0.51 to 0.71; P<0.001).

							Very modest improvement in SAQ score for PCI group compared to OMT group.
JSAP, 2008[108]	Japan	SCAD, ≥75% coronary stenosis	384	PCI, OMT	3.3	MACE, defined as composite of all-cause mortality, ACS, stroke, cerebrovascular accident and emergency hospitalisation.	No statistically significant difference in MACE between PCI group (2.9%) and OMT group (3.9%). However, the cumulative risk of death plus ACS was significantly smaller in PCI group.
BARI 2D, 2009, 2011 [105, 120, 121]	North and South America, Europe	SCAD + type 2 diabetes, ≥50% DS of a major epicardial coronary artery with positive stress test or ≥70% stenosis of a major epicardial coronary artery and classic angina	2368	PCI, CABG, OMT	5	MACE, defined as composite of all-cause mortality, MI and stroke [105]. Worsening of angina, freedom from angina, occurrence of new angina, and subsequent coronary revascularisation[120] HRQoL (DASI, RAND for Energy/Fatigue, Health Distress, and Self-Rated Health)[121]	No statistically significant difference in event-free survival between revascularisation group (77.2%) and OMT group (75.9%) in MACE. No statistically significant difference in overall mortality between revascularisation and OMT. In the CABG stratum, the rate of MACE was significantly lower in the revascularization group (22.4%) than in the medical-therapy group (30.5%). Statistically significant difference in worsening of angina (8% versus 13%), new angina (37% versus 51%), and subsequent coronary revascularizations (18% versus 33%) and a higher rate of angina-free status (66% versus 58%) in revascularisation

							group compared to OMT at 3 year follow-up. CABG had the greatest benefits from revascularisation. Compared with OMT, revascularization was associated with significantly greater improvements in Duke Activity Status Index (1.32 points), Energy (1.36 points), and Self-rated Health (1.77 points) but not Health Distress (0.47 points). These treatment effects were largely maintained over 4 years follow-up. The effect was significantly larger for CABG.
FAME II, 2014 [106, 122]	Europe, North America	SCAD, ≥50% DS, FFR<0.8	888	FFR-guided PCI for FFR≤0.8, PCI group; OMT for FFR>0.8, OMT group	2	MACE, defined as a composite of all-cause mortality, MI, or unplanned hospitalisation leading to urgent revascularisation within 2 years[106]. HRQoL (EQ-5D) by FFR at 1 month and 1 year follow-up[122]	Significantly lower rate of MACE in the PCI group compared to OMT group (8.1% vs. 19.5%; hazard ratio, 0.39; 95% CI, 0.26 to 0.57). This reduction was driven by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; hazard ratio, 0.23; 95% CI, 0.14 to 0.38; P<0.001), with no significant between-group differences in the rates of death and MI. HRQoL improved significantly after PCI in each abnormal FFR tertile, whereas it did not change in the OMT group. The lower FFR

							subgroups had the greater HRQoL improvement.
ORBITA, 2018 [94]	UK	SCAD, ≥70%DS single-vessel, FFR, iFR	200	PCI, OMT	6 weeks	HRQoL (SAQ, EQ-5D-5L)	No statistically significant difference in HRQoL for PCI compared to OMT. No detectable evidence of interaction with pre-randomisation based on FFR and iFR. PCI resulted in more patient-reported freedom from angina than placebo (49.5% versus 31.5%; odds ratio, 2.47; 95% CI, 1.30–4.72; P=0.006).
ISCHEMIA, 2019 [92, 123-125]	US	SCAD, ≥50% DS of a major epicardial coronary artery with positive stress test or ≥70% stenosis of a proximal or mid vessel	5179	PCI (74% of revascularisation group), CABG (26% of revascularisation group), OMT	3.2	MACE, defined as a composite of CV mortality, MI, hospitalisation for unstable angina, heart failure or resuscitated cardiac arrest [92, 123] HRQoL at 3, 12 and 36 months (SAQ) [124, 125]	No statistically significant difference in MACE between revascularisation group and OMT group. Very low rates of procedure-related stroke and death. Significant, durable improvements in angina control and HRQoL with revascularisation strategy compared to OMT

6.5.6 Other cause mortality

Mortality due to non-cardiovascular causes was estimated based on age and sex-specific UK life tables[126] and by deducting the mortality due to ischaemic heart disease (International Classification of Diseases [ICD] code 20-25)[127]. The age specific probability of death was estimated as a weighted average of male and female mortality.

6.5.7 Health-related Quality of Life

In order to estimate QALYs, it is necessary to quality-adjust the period of time for which the average patient is alive within the model using an appropriate utility or preference score. QALYs are calculated by summing the time spent in a health state weighted by the utility value associated with the health state. Additional adjustments are made to QALYs to reflect a decrement in utility associated with an acute or adverse event. The NICE methods guide advocates a preference for EQ-5D data with utility values using UK population weights when available.[89]

In the diagnostic model a one-off utility decrement is applied to patients undergoing invasive FFR/iFR and those who undergo revascularisation (known as procedural disutility). At the end of the diagnostic model, patients who survive enter the long-term prognostic model in one of the four health states of TP, FN, FP or TN. The implications on HRQoL of receiving treatment (either revascularisation in addition to OMT or OMT alone) based on being in one of the four diagnostic health states is quantified by attaching a utility value to each of the health states. A one-off utility decrement is also applied in the prognostic model to those who experience a non-fatal MI or require an unplanned revascularisation. To reflect a decrease in HRQoL for those with a history of MI, a separate utility decrement is applied to the post-MI health state. For those patients who experience an unplanned revascularisation, the utility value associated with the TP health state is applied based on the assumption that patients who undergo a targeted revascularisation achieve the same benefits of revascularisation, in terms of symptom relief, as patients who had a successful initial revascularisation procedure.

The utility values are used to calculate the expected number of QALYs for each diagnostic strategy over the duration of the model.

6.5.7.1 Procedural disutility

The model considers the procedural disutility associated with FFR/iFR, PCI and CABG. The disutility associated with ICA is not included because all patients undergo the procedure. Targeted literature searches were used to identify sources to inform procedural disutility parameters.

No studies reporting HRQoL loss associated with FFR/iFR were identified. However, FFR/iFR, particularly FFR which requires the administration of a hyperaemic agent, can cause discomfort to patients. The administration of the most commonly used hyperaemic agent used, adenosine, can result

in chest pain, dyspnoea, bronchospasm, conduction disturbances, facial flushes, headaches, and hypotension.[128,129-131]Patient discomfort can therefore arise from adverse events associated with the hyperaemic agent, but also relate to vasodilation that is a consequence of inducing a hyperaemic state to perform FFR. In the absence of suitable estimates to inform the disutility associated with FFR/iFR, a disutility equivalent to that of a PCI procedure is assumed (see below). Furthermore, this is assumed to apply to all patients undergoing FFR/iFR and not just to those who incurred procedural complications (See section 6.5.4.1). An additional disutility resulting from procedural complications was not included in the model to avoid double counting. It is expected that iFR is more tolerable to patients as it does not require the administration of a hyperaemic agent; however, a specific disutility estimate for iFR was not identified. Furthermore, the proportion of patients with intermediate stenosis who undergo iFR in the UK clinical practice is also unknown. Therefore, the base case analysis makes a simplifying assumption that the QALY loss estimate applied for FFR/iFR is 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). Bagust and colleagues[132] conducted a cost-effectiveness study comparing drug eluting stents compared with conventional stents for treatment of symptomatic CAD. The model considered the QALY loss per percutaneous transluminal coronary angioplasty (PTCA) and per CABG by combining EQ-5D data from two clinical trials in multivessel CAD which compared alternative revascularisation procedures (PTCA with bare and drug eluting stents, and CABG) with assumptions on the duration of the disutility. The disutility for each procedure was estimated as the difference in utility scores before and after the revascularisation procedure. The disutility was assumed to be incurred for one month for PTCA and six months for CABG, resulting in a QALY loss of 0.0056 and 0.033 QALYs per PTCA and CABG procedure, respectively. The authors noted, however, that the QALY losses may be an overestimate as all patients had multivessel disease. These QALY loss estimates are used to inform the base-case scenario. Table 22 summarises the QALY loss estimates associated with each procedure in the diagnostic model. The QALY loss associated with PCI and CABG is applied in the model as a weighted average, assuming 87% of revascularisation procedures are PCI and the 13% CABG (see Section 6.5.4.2). The QALY loss associated with revascularisation is also applied in the prognostic model to capture the HRQoL impact of unplanned revascularisation.

Table 22 QALY loss associated with testing and revascularisation procedures

Procedure	Mean QALY loss (95% CI)	Source
ICA	0	Assumed to cancel across strategies
FFR/iFR	0.0056 (0.0051-0.0062)	Assumed the same as for PCI
PCI	0.0056 (0.0051-0.0062)	Bagust et al, 2006[132]
CABG	0.033 (0.031-0.035)	Bagust et al, 2006[132]

Gamma distributions were fitted to the procedural HRQoL loss to generate probabilistic estimates.

6.5.7.2 Health state utilities

The benefits of the diagnostic tests in identifying the appropriateness for revascularisation can confer health benefits through greater symptom relief and, therefore, higher HRQoL. Given that the base case analysis assumes that there is no treatment effect of revascularisation on MACE, the improvement in symptom relief is the only benefit of revascularisation. Of the recent RCTs (post year 2000) in stable CAD that have compared revascularisation with OMT (see Table 21 in Section 6.5.5.2), there was a general trend towards significantly greater improvement in HRQoL after revascularisation. In the TIME trial, after 6 months, angina severity decreased and measures of HRQoL using the SF-36 instrument, Duke Activity Score Index (DASI) and Rose Angina Questionnaire showed a significantly greater improvement after revascularisation compared to OMT.[103] In the MASS II trial, HRQoL using the SF-36 instrument was better in both the CABG and PCI groups compared to OMT at 1 year follow-up, with the CABG group presenting the greater and progressive improvement in HRQoL.[117] In the COURAGE trial, HRQoL using the Seattle Angina Questionnaire (SAQ) showed a very modest improvement in SAQ score for the PCI group compared to OMT group at 1 year follow-up.[119] In the BARI 2D trial, HRQoL was reported using the DASI, RAND 36-Item Health Survey and self-rated health, and demonstrated that revascularisation compared with OMT was associated with significantly greater improvements in DASI, energy and self-rated health components but not health distress.[121]The HRQoL effects of revascularisation in BARI 2D were largely maintained over a 4 year follow-up. In the FAME II trial, HRQoL was measured using EQ-5D at 1 month and 1 year follow-up and reported based on patients' index FFR measurement.[122] The results of the trial showed that HRQoL improved significantly from baseline after PCI, with the largest marked improvement in those with a lower FFR value, whereas it did not change significantly in the OMT group. In the ISCHEMIA trial, HRQoL using the SAQ at 3, 12 and 36 months, showed a significant, durable improvement in angina control and HRQoL with revascularisation compared to OMT.[125] The smaller ORBITA trial, which reported HRQoL using SAQ and EQ-5D-5L visual analogue scale, was the only trial that demonstrated a non-statistically significant difference in HRQoL for PCI compared to OMT.[94]

In summary, the evidence from the most recent RCTs suggest that revascularisation has a significantly greater improvement in HRQoL than OMT alone. This is supported by a recent systematic review and meta-analysis summarising the evidence to determine the impact of coronary revascularisation on HRQoL, which showed that both PCI and CABG had significantly greater effects on HRQoL than medication but the effects of the revascularisation procedures did not differ significantly from each other.[133]

Of the most recent RCTs, only one trial, FAME II, measured improvement in HRQoL using EQ-5D. This trial was a subsequent RCT to the FAME I trial, which compared two different revascularisation strategies in patients with stable CAD and multivessel disease using standard ICA-guided revascularisation of lesions with >50 % DS and an FFR-guided revascularisation approach for lesions with an FFR ≤0.80[134] The FAME II trial was designed to clarify whether PCI of functionally significant stenoses (i.e., lesions with FFR ≤0.80) combined with OMT would be superior to OMT alone in patients with stable CAD. In a study by Nishi et al (2018), patient-level pooled analysis from the FAME I and II trials was used to assess whether the benefit in HRQoL after PCI depends on the severity of the stenosis as determined by FFR measurement.[122] The study is based on patients with stable CAD who underwent PCI with an FFR ≤0.80 from the FFR-guided arm of the FAME I trial and the PCI arm of the FAME II trial. The study reports the change from baseline in EQ-5D utility values by FFR=[0.70-0.80], FFR=[0.51-0.69] and FFR ≤0.50. The study also reports the change from baseline in EQ-5D utility values for lesions with FFR ≤0.80 who were treated medically from the OMT arm of the FAME II trial. The results of this study are directly relevant for informing the HRQoL improvement from revascularisation compared to OMT in the model.

Table 23 presents the change in EQ-5D utility values from baseline to one month and one year in the PCI (in addition to OMT) group and OMT group alone by FFR value based on Nishi et al (2018). The EQ-5D improved significantly from baseline after PCI in all FFR subgroups at both one month and one year follow-up, with a progressive improvement with lower FFR values. The EQ-5D improved slightly from baseline in the OMT group at both one month and one year, but this improvement was not statistically significant (note the results in Table 23 exclude crossovers to PCI in the OMT group).

Table 23 Change in EQ-5D utility values from baseline for PCI and OMT by FFR value (Nishi et al, 2018)

	Revascularisation, EQ-5D (95% CI)			OMT, EQ-5D (95% CI)
	FFR=[0.70-0.80]	FFR=[0.51-0.69]	FFR ≤0.50	FFR ≤0.80
At 1 month	0.039 (0.019 – 0.059)	0.056 (0.036 – 0.075)	0.080 (0.058 – 0.101)	0.003 (-0.012 – 0.017)
At 1 year	0.038 (0.013 – 0.063)	0.057 (0.037 – 0.078)	0.065 (0.040 – 0.089)	0.015 (-0.004 – 0.033)

The utility values in Table 23 are used to represent the change in baseline utility for the TP and FN health states. For the TP health state, the utility value for revascularisation is used to provide a weighted change in utility value based on the expected proportion of TP outcomes with a FFR=[0.70-0.80], FFR=[0.51-0.69] and FFR≤0.50, which differs by diagnostic strategy and is dependent on the underlying distribution of FFR values across these categories in the population. For the FN health state, the utility value for OMT for FFR ≤0.80 is used to provide the change in baseline utility. For

the FP and TN health states with FFR >0.80 (functionally non-significant stenosis), it is assumed that there is no change in baseline utility for patients with intermediate stenosis.

The underlying baseline utility for a 64 year old patient with stable CAD is also taken from Nishi et al (2018), where the average age of patients in the FAME trials was the same as the modelled population. In order to reflect the decreasing utility of patients as they age through the model, age and sex adjusted EQ-5D norms for the UK based on Ara et al, (2010) were adjusted to reflect the existence of stable CAD.[135] The adjustment factor was estimated by comparing the baseline utility of Nishi et al (2018) to the average utility of a 64 year old UK person, derived from a nationally representative UK sample using EQ-5D.

Patients who experience a non-fatal MI receive a one-off utility decrement, while those in the post-MI health state are subject to a decrease in HRQoL for the duration of time spent in this state. Both these utility decrements were sourced from Sullivan et al (2011), a study that estimated a catalogue of marginal disutilities for a wide range of health conditions based on UK specific health preferences.[136]In this study, marginal disutilities were estimated as EQ-5D index score decrements adjusted for patient characteristics (age, comorbidity, gender, ethnicity, income and education). The marginal disutility for 'acute MI' (International Classification of Diseases [ICD]-9 code410) informed the utility decrement for non-fatal MI events (-0.0626; S.E. 0.0132), while the estimate for previous MI informed the post-MI health state (-0.0368; S.E. 0.0252). Gamma distributions were fitted to the utility decrements for the uncertainty analysis.

6.5.8 Resource use and costs

This section details the resource use and costs applied in the model. The diagnostic model considers the costs of diagnostic testing, revascularisation, and treatment of procedural complications. The prognostic model considers the costs of OMT, health state and clinical events. Costs in the model are fixed estimates. Details by category of resource use and costs are presented in the sections below.

6.5.8.1 Test costs

QAngio costs

The costs of QAngio include the cost of the software license, and training and certification fees. These costs are summarised in Table 24 (adapted from the company's response to NICE's information request and additional EAG questions). Costs were originally reported in euro, and have been converted to pound sterling at an exchange rate of 0.86295 based on the average exchange rate between 25/08/2019 and 19/02/2020.[137]

Table 24 Summary of QAngio costs reported by Medis

	Software license fee*,**		Training and certification fee for up to 4 members of staff*	
Voucher	EURO	GBP	EURO	GBP
10 patients	€5,000	£4,314.75	€3,500	£3,020.33
50 patients	€25,000	£21,573.75	€3,500	£3,020.33
100 patients	€49,000	£42,284.55	Included in the license fee	
*Costs exclude VAT; **Vouchers also include the cost of customer support/service and software upgrades during the period of usage.				

Software license costs

The costs of QAngio software license are dependent on the number of patients tested (*"per-patient-study basis"*). The cost per patient of the software license is the same for the 10 and 50 patients' vouchers, while the 100 patients voucher offers a discount of £8.63 per patient compared to the other two options (assuming the same 100 patients are tested). To simplify cost calculations, it is assumed that annual throughput is a multiple of ten. It is further assumed that a NHS trust would purchase the least costly combination of vouchers that would allow covering the expected annual throughput. For example, if annual expected throughput was 180 patients, the trust would purchase one 100 patients' voucher and eight 10 patients' vouchers. For the base case annual throughput of 200 patients, the trust would purchase two 100 patients' vouchers, at a total cost of £84,569.10 (approximately £423 per patient).

Training costs

The cost of the 100 patients voucher also covers the training and certification of up to four QAngio users. The cost of the 10 and 50 patient vouchers does not include any training and certification. When training and certification are required and this cost is not covered by the voucher, a fee of £3,020 for up to four software users applies for both on-site and online training. It was assumed that for each 100 patients, 4 members of staff would require training, and that the training fee is, therefore covered by the voucher for an average annual throughput ≥100. It is only when annual throughput is lower than 100 patients, and therefore, the trust does not purchase at least one 100 patients' voucher, this cost will be incurred. In addition to the training and certification fees charged by the company, the staff time costs required for training activities should also be considered. According to Medis on-site training is currently only available for groups of a minimum of 10 participants, but that an e-learning platform is being developed to deliver training. E-learning is expected to be available before the fourth quarter of 2020. Another alternative for large research groups is to have training delivered over one and a half days at Leiden but travel and accommodation costs are not included. Medis states that

using the e-learning platform training should require 5 hours of staff time, while certification is done on a cloud-based solution and takes one to two hours. This training would be required by *"observer or technician in the cath lab, who actually uses the QFR software solution and carries out the analyses.* The company also has a shortened e-learning module for the interventional cardiologist that should take 30 minutes to complete. Since more detail has been provided for online training and on-site training appears to require a large number of participants, we have estimated costs of training assuming that this is delivered online.

It was assumed that for each group of four members of staff requiring training, one would be an interventional cardiologist and the other three cardiac physiologists. The cardiac physiologists are assumed to be the software operators, and, thus, undergo both the training and the certification module. The first module takes 5 hours to complete while the second requires one and a half hours (midpoint of the range of time provided by the company). Unit costs for staff time were taken from the Personal Social Services Research Unit (PSSRU) costs.[138] The cost per working hour of a surgical consultant was assumed to cost cardiologist time, and that of an allied professional (band 5) for cardiac physiologist time. Staff time and costs associated with NHS staff training and certification per 100 patients are shown in Table 25.

Table 25 QAngio - Staff time and costs associated with training and certification

Staff	Staff numbers	Time (hours)		Unit cost*	Source	Total cost
		Training	Certification			
Cardiologist	1	0.5	-	£109	Consultant: surgical, PSSRU 2019[138]	£54.50
Cardiac physiologist	3	5	1.5	£37	Allied professional (Band 5**) PSSRU 2019[138]	£721.50
Total	4	16.5	4.5	-	-	£776.00
*Per working hour; **Assumed the same as for radiographer						

It is assumed that the additional staff time and cost of that time will increase at the same rate as throughput, which corresponds to a staff cost per patient of £7.76. We assume the same staff cost per patient for an annual throughput lower than 100 patients. This simplifying assumption effectively implies that staff time is independent of throughput.

Total cost per patient tested

The costs of QAngio disaggregated by cost element are presented in Table 26 for the base-case throughput assumption of 200 patients per year. The cost per patient tested with QAngio is £430.61.

Table 26 Costs of QAngio 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 i) the software license, ii) training, and iii) annual maintenance. Pie Medical has two different pricing models for CAAS vFFR, which are summarised in Table 27 (adapted from the company's response to NICE's information request). Costs were originally reported in euro, and have been converted to pound sterling at the same exchange rate used to estimate the costs of QAngio XA 3D/QFR.[137]

Table 27 Summary of CAAS vFRR software license, annual maintenance and training costs reported by Pie Medical

Pricing model	Software license fee*			Annual maintenance fee*			Training fee*,**		
	EURO	GBP	Conditions	EURO	GBP	Starting from	Platform	EURO	GBP
1	€37,000	£31,929	Perpetual license	€5,500	£4,746	Year 2	e-learning	-	-
2	€200.00	£173	Per patient	€3,500	£3,020	Year 1	Webex	€250	£216
							On-site	€2,500	£2,157

*Costs exclude VAT, **Independent of pricing model

Software license costs

The cost per patient tested of the software license for CAAS vFFR varies according to the pricing model selected. Under pricing model 1, the software license costs £31,929 and is described as perpetual. The total number of tests covered by the license depends on the lifespan of the technology, which is unknown. For the purpose of determining a cost per patient tested, it is conservatively considered that the perpetual license covers the annual patient throughput independently of its size (i.e. the lifespan of the technology is one year). Under pricing model 2, the cost per patient tested is fixed at £172.59. Assuming that annual throughput is a multiple of 10 (as assumed for QAngio cost

calculations), the software license cost per patient is only lower for pricing model 2 compared to pricing model 2 when the annual throughput is lower or equal to 10 patients. For the base-case assumption of 200 patients per year, the software license cost per patient tested with pricing model 1 is £159.65.

Training costs

CAAS vFFR training can be delivered via three alternative platforms: e-learning, webex or on-site training. The training fee depends on the delivery platform with e-learning offered at no cost, while webex and on-site training have a cost of £215.74 and £2,157.38, respectively. Pie Medical does not specify if there is a maximum number of NHS staff covered by the training fee. It is assumed that only one training session by either webex or on-site delivery would be required independent of annual throughput, and that any additional training would be delivered online at no additional cost. We calculated the cost of the training fee as the average between on-site and webex training costs (£1,186.56).

Pie Medical states that the same training should be delivered to staff using the CAAS vFFR software and the interventional cardiologist who interprets the result. Training delivered via e-learning and webex requires 2 hours per member of staff, while on-site training requires 4 hours. We made the same assumptions regarding numbers of members of staff who would require training as for QAngio XA 3D /FR, i.e. one cardiologist and three cardiac physiologists would require training for each 100 patients tested. We also assumed that the additional staff training time and cost of that time will increase at the same rate as the throughput. Thus, the cost per patients of staff time is independent of throughput, but depends on the training platform. The same unit costs were applied for the calculation of staff training costs as for QAngio XA 3D/QFR. Table 28shows the staff time cost per 100 patients tested with CAAS vFRR.

Table 28 CAAS vFRR - Staff time and costs associated with training

Staff	Staff numbers	Time (hours)		Unit cost*	Source	Total cost	
		Webex or e-learning	On-site			Webex or e-learning	On-site
Cardiologist	1	2	4	£109	Consultant: surgical, PSSRU 2019[138]	£218.00	£436.00
Cardiac physiologist	3	2	4	£37	Allied professional (Band 5**) PSSRU 2019[138]	£222.00	£444.00
Total	4	8	16	-	-	£440.00	£880.00
*Per working hour; **Assumed the same as for radiographer							

The staff training cost per patient is £4.40 when delivered online (webex or e-learning) and £8.80 when delivered on-site. In the base-case we assumed that the staff training costs per patient tested would correspond to £6.60, the average cost of online and on-site staff training.

Maintenance costs

Pie medical charges a fee for annual maintenance of CAAS vFFR. The cost of maintenance varies by pricing model. For pricing model 1, there is no maintenance cost in the first year, and an annual cost of £4,746.23 applies for subsequent years. For pricing model 2, there is an annual cost of £3,023.44 incurred every year. Since we have made a simplifying assumption that the lifespan of the technology is one year when considering the licence fee costs, we did not include annual maintenance cost for pricing model 1.

Total cost per patient tested

We assumed that the NHS trust would select the pricing model that would result in fewer costs according to the expected annual throughput. Pricing model 1 results in a lower cost per patient tested when annual throughput is greater than 10. The costs of CAAS vFFR broken down by cost element are presented in Table 29 for the base-case assumption of 200 patients per year. The cost per patient tested with CAAS vFFR is £172.18.

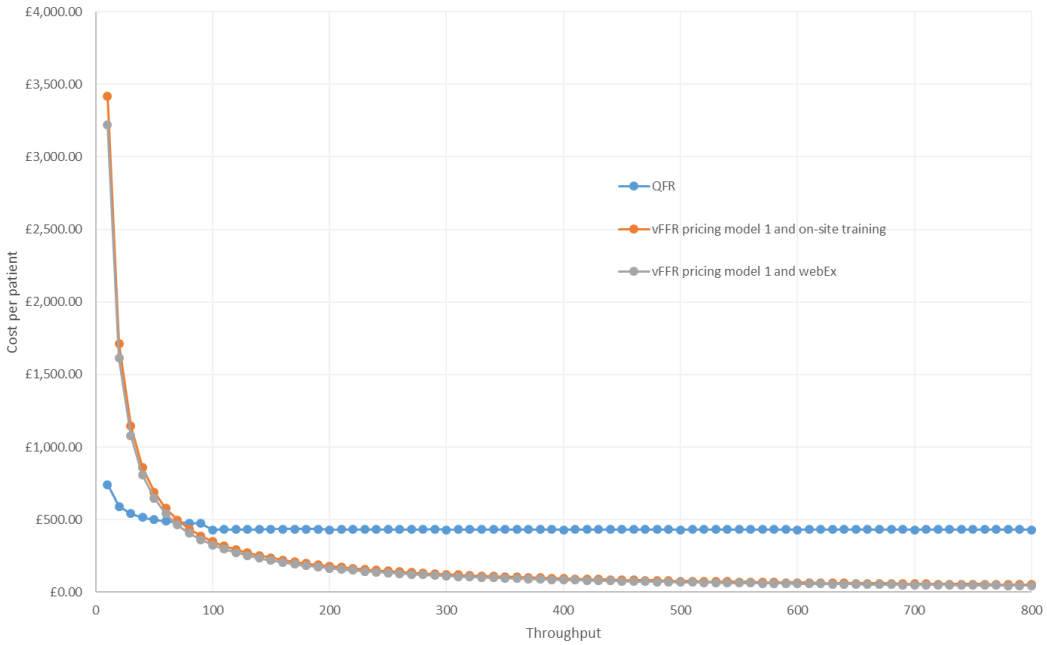
Table 29 Costs of CAAS vFFR for an annual throughput of 200 patients

Cost element	Total cost		Cost per patient tested*
	Webex or e-learning	On-site	
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
*Average of on-site and online learning			

Comparison of QAngio and CAAS vFFR testing costs

The cost per patient tested with QAngio and CAAS vFFR varies with annual throughput, as shown in Figure 26. The cost per patient tested of CAAS vFFR under pricing model 1 is more sensitive to alternative throughput estimates than QAngio XA 3D/QFR, especially for throughputs lower than 100 patients. The cost of QAngio is robust to alternative throughput estimates for throughputs greater than 100 patients. This cost is also consistently higher than that of CAAS vFFR for throughputs greater than 70 patients. Figure 26 shows two curves for the cost per patient tested with CAAS vFFR to illustrate the difference between assuming that training is delivered over webex or on-site. The cost per patient tested with CAAS vFFR seems consistently similar for the two modes of training delivered, therefore an average between the two modes was used to estimate the cost per patient tested for vFFR.

Figure 26 Comparison of QAngio and CAAS vFFR test cost at different throughputs



Invasive coronary angiography and fractional flow reserve

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[139]and uprated to 2018/19 prices[138]. The cost of ICA was calculated s the activity weighted average of the homogenous resource group (HRG) codes for simple catherization. However, the model did not consider a cost for ICA because all patients who enter the diagnostic model undergo this test. The unit cost for FFR/iFR was estimated as the difference between the activity weighted average of the HRG codes for complex and standard cardiac catheterisation (in line with the NICE scope). This difference represents the incremental cost of FFR/iFR compared to ICA alone. The unit costs used to estimate the cost of FFR/iFR are shown in Table 30.

Table 30 Cost of cardiac catheterisation tests

Cost category	Currency codes	Unit cost
Complex cardiac catheterisation	EY42A-D, across all HRG codes	£2,202.26
Standard cardiac catheterisation	EY43A-F, across all HRG codes	£1,765.46
FFR/iFR	Difference between complex and standard catheterisation	£436.80

The cost of iFR was not estimated separately, as it was assumed that this cost was already captured in the complex cardiac catheterisation HRG codes.

6.5.8.2 Revascularisation costs

Patients who test positive at the last step of each testing strategy undergo revascularisation with either PCI or CABG. The unit cost for these procedures was sourced from NHS reference costs 2017/18[139] and uprated to 2018/19 prices[138]. We estimated the activity weighted average cost of i) complex and standard percutaneous transluminal coronary angioplasty, and ii) complex major and standard CABG across all HRGs)to inform the unit cost of PCI and CABG, respectively. Costs applied in the model and the NHS currency codes used to inform these are presented in Table 31.

Table 31 Costs of revascularisation in the model

Cost category	Currency codes	Unit cost
PCI*	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*	ED26A-C, ED27A- and EY41A-D, across all HRG codes	£10,898.58
*Base-case assumption		

Since the cost of PCI and CABG were estimated across all HRGs, their unit cost reflects the cost of the procedures across all settings under which the procedures are performed in the NHS (adjusted by activity). We considered this to be the most appropriate assumption in the absence of clear evidence on the proportion of procedures per setting for patients in our study population. However, patients who are treated electively for stable angina do not usually require an overnight stay. Despite the NHS target to have at least 75% of elective PCIs performed as a day case, recent audit data shows that there is extremely wide variation in day case rates [140] and that only 30.4% of PCI is performed as a day case[95]. Some centres will perform PCI almost exclusively as a day case, while others will require patients to stay overnight in hospital following the procedure. Given the considerable variation in the NHS in terms of need for overnight stays following PCI, we only considered the cost of PCI to correspond to that of a day case admissionin a scenario analysis.

In the base-case scenario, patients revascularised after their index testing were assumed to incur a cost of £3,005 and £10,899 if they underwent PCI and CABG, respectively. This resulted on a cost per revascularisation of £4,031.22 assuming 87% of revascularisation procedures are PCI and 13% CABG (see Section 6.5.4.2).

6.5.8.3 Procedural complications costs

The cost of procedural complications for FFR/iFR were calculated based on the rates of complications in Table 19. Unit costs were sourced from NHS reference costs 2017/18[139] and uprated to 2018/19 prices[138]. These costs are summarised in Table 32.

Table 32 FFR serious procedural complications events

Procedural complication	Rate	Source	Unit cost	Currency codes/Assumptions
Coronary dissection	0.03%	IRIS[10]	£3,005.07	Activity weighted average of the PCI currency codes (EY40A-D and EY41A-D, across all HRG codes codes). It is assumed that PCI is required to repair coronary dissection. This cost is only incurred if patients do not subsequently undergo PCI due to testing positive for significant stenosis.
Ventricular arrhythmia	0.02%	IRIS[10]	£974.90	Activity weighted average of the arrhythmia or conduction disorders currency codes (EB07A-E, across all HRG codes codes).
Conduction disturbance requiring treatment	0.03%	IRIS[10]	£974.90	Activity weighted average of the arrhythmia or conduction disorders currency codes (EB07A-E, across all HRG codes codes).
Thrombus formation	0.01%	IRIS[10]	£928.12	Assumed average of unit cost of other complications, excluding coronary dissection
Bronchospasm	0.02%	IRIS[10]	£834.57	Activity weighted average of the asthma without interventions currency codes (DZ15N, P-R, across all HRG codes codes).
Death	0.015%	Fearon et al, 2003[83]	£0	Assumption

6.5.8.4 Optimal medical treatment costs

It was assumed that all patients in the prognostic model are treated with OMT for stable angina. NICE existing guidance was reviewed to define OMT. The NICE clinical guideline on the management of stable angina (CG126)[141] recommends that patients with stable angina receive a beta blocker or a calcium-channel blocker in either monotherapy or combination as first line of treatment. The alternative to the first line of treatment for patients who cannot tolerate it is monotherapy with a long-acting nitrate or one of the novel anti-ischemic drugs (ivabradine, nicorandil, or ranolazine). The use of three anti-angina drugs is not recommended unless patients are not satisfactorily controlled with two anti-angina drugs or are waiting for revascularisation or cannot undergo revascularisation. Drugs for secondary prevention of cardiovascular disease should also be considered for patients with stable angina. These drugs include aspirin, angiotensin-converting (ACE) inhibitors, other anti-hypertension drugs and statins. The guideline does not make specific recommendations regarding medication for patients who have undergone PCI or CABG, but revascularised patients will still need to receive anti-angina and secondary prevention drugs after the procedures. We have, thus, considered that OMT comprises both anti-angina secondary prevention drugs. Given that revascularisation will resolve or reduce some of the angina symptomology, it is likely that the composition of OMT varies depending on whether patients have received revascularisation and the type of procedure.

One of the models described in Section 5.4[70] assumed that the relative proportion of each drug class comprised by OMT would vary conditional on the patient's index treatment. We assumed the same, but sourced anti-angina medication use where available from Nishi et al. (2017)[122], the same study from which we sourced estimates of HRQoL (see Section 5.4). Nishi and colleagues reported anti-angina medication use at 1 year post diagnosis for patients treated with OMT in isolation (TN) or in addition to PCI (TP). This study also reported the use of these drugs for patients treated with OMT in isolation despite requiring revascularisation (FN). Since the study did not include patients who had undergone CABG, the medication use for these group (also TP) was taken from the same source used in Genders et al. (2015),[70] i.e. the SYNTAX trial.[87] Since Nishi et al (2017) did not report the use of secondary prevention drugs, medication use for these drugs was taken the SYNTAX trial [87] and the COURAGE trial[88](also used in Genders et al (2015).[70]

Cost of medication was estimated by combining the proportion of medication use for each type of treatment (OMT alone for patients who did not required revascularisation (TN) and those who did (FN), OMT for patients who underwent PCI (TP) and CABG (TP)) with unit costs from the British National Formulary [142]. Patients who underwent revascularisation without needing it (FP) were assumed to have the same medication use as the corresponding TP patients. The active substances and dosages selected, as well as proportion of medication use, were validated by the clinical adviser to the EAG. Medication use and estimated costs per annum of OMT conditional on patient clinical management after diagnosis are summarised in Table 33. These costs are applied in the prognostic model at each annual cycle, and it was assumed that if the patient underwent revascularisation in the model the cost of OMT would then correspond to OMT in addition of revascularisation regardless of the patient classification at the start of the prognostic model (TN, FN, TP or FP).

Table 33 Optimal medical treatment use and costs in the model

	Drug and dosage	Unit cost*	Source	Medication use							
				OMT	Source	PCI+OMT	Source	OMT FN	Source	CABG+OMT	Source
Anti-angina											
Beta blocker	Bisoprolol 5 mg/day	£ 0.17	BNF* [142]	75.0%	Nishi et al, 2018[122]	77.0%	Nishi et al, 2018[122]	81.0%	Nishi et al, 2018[122]	77.2%	SYNTAX [87]
Calcium-channel blocker	Amlodipine 5 mg/day	£0.17		40.0%		27.0%		32.0%		22.7%	
Long-acting nitrate	Isosorbide mononitrate 60 mg/day	£0.18		36.0%		23.0%		47.0%		8.0%	
Secondary prevention											
Aspirin	Aspirin 75 mg/day	£0.02	BNF* [142]	95.0%	COURAGE [88]	95.0%	COURAGE [88]	95.0%	Assumed the same as for OMT TN	83.3%	SYNTAX [87]
Statin	Atorvastatin 80 mg/day	£0.02		95.0%		93.0%		95.0%		85.5%	
ACE inhibitors	Ramipril 10 mg/day	£0.24		62.0%		64.0%		62.0%		52.5%	
Cost per year				**£163.63**		**£150.10**		**£169.68**		**£126.27**	

*Drug tariff value;

6.5.8.5 Health state and clinical event costs

The costs associated with health state membership and clinical events in the prognostic model are summarised in Table 34.

Table 34 Health state and clinical event costs

Health state/clinical event	Cost	Source
No event	£0	Assumption
MI	£2,317.53	Activity weighted average of HRG codes for actual or suspected MI (EB10A-E), across all HRG codes - NHS reference costs 2017/18[139]
Post MI	£0	Assumption
Unplanned revascularisation	£4,812.23	Activity weighted average of HRG codes for PCI and CABG (EY40A-D, EY41A-D, ED26A-C, ED27A-C and ED28A-C), non-elective long stays - NHS reference costs 2017/18[139]
Post Unplanned revascularisation	£0	Assumption
Cardiovascular death	£0	Assumption
Other cause death	£0	Assumption

It was assumed in the base-case analysis that only MI and unplanned revascularisation events would incur costs. This equates to assuming that all health care resource use other than anti-angina and secondary prevention medication use (see Section 6.5.8.4) is the same across health states. The unit costs of MI and unplanned revascularisation events were sourced from the NHS reference costs 2017/18[139] and uprated to 2018/19 price year.[138] These costs where estimated as activity weighted averages across the relevant HRG codes (

Table 86). The cost of unplanned revascularisation comprises the cost of PCI (activity weighted average of EY40A-D, and EY41A-D codes, £3,923), and CABG (activity weighted average of ED26A-C, ED27A-C and ED28A-C codes, £10,762) for non-elective long stays, and assumes that 87% of revascularisation performed is PCI (see Section 6.5.4.2).

6.6 Analytic Methods

6.6.1 Overview

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

Summarising cost-effectiveness using conventional incremental cost-effectiveness ratios (ICERs) requires consideration of which pairwise comparisons are appropriate when calculating incremental costs and effects. With multiple strategies, there are several different comparisons that could be made, each resulting in different incremental QALYs, costs and ICERs. In this case, a fully incremental ICER comparison is required to rule out any strategies based on the principles of dominance or extended dominance. However, even with a fully incremental ICER comparison strategies that are dominated and would not be considered cost-effective, may be 'better' than other non-dominated (but not cost-effective) strategies. The ICER comparison is also particularly sensitive to small differences between the strategies (e.g., small changes to the denominator in terms of QALY differences) may result in highly variable ICERs). For these reasons, the cost-effectiveness of the interventions is summarised in terms of net benefit, which applies a single unambiguous decision rule when there are multiple strategies: the cost-effective strategy is the one with the highest net benefit for a given cost-effectiveness threshold.

In this analysis, the net benefit is expressed in terms of Net Health Benefit (NHB), estimated by rearranging the ICER equation into the following equation:

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

Strategies are ranked in terms of NHB from highest to lowest, which is used to identify the cost-effective strategy (highest NHB) but is also used to interpret the next best choice (second highest NHB) and so on. A cost-effectiveness threshold of £20,000 per additional QALY is used in the analysis.

Uncertainty in the estimates of cost-effectiveness of the alternative strategies is reflected in probabilistic analysis and the probability that each strategy is more cost-effective than the others at the cost-effectiveness threshold of £20,000 per QALY is presented for the base case scenario.

6.6.2 Base-case analysis

The base-case parameters and associated assumptions are listed alongside their sources in Table 35.

Table 35 Base-case parameters

Parameter	Values	Source/Assumptions	Probabilistic model setup
Patient characteristics			
Age	64	IRIS-FFR[10]	NA
Proportion of male individuals	0.72	IRIS-FFR[10]	NA
Proportion with clinically significant stenosis (i.e. FFR<0.8)	0.402	Recreated individual level FFR measurements in the QAngio diagnostic accuracy studies (cQFR and non-specified QFR mode)	Calculated from each 5,000 bootstraped samples of the joint FFR and QFR distribution
Number of patients with stenosis of uncertain clinical significance			
Annual throughput	200	BCIS audit returns[95] and clinical opinion	NA
Diagnostic accuracy			
FFR/iFR			
Sensitivity	100%	Assumption	NA
Specificity	100%		
ICA			
Sensitivity	62.61%	Bivariate meta-analysis (Section 4.7.4)	Multivariate lognormal distribution fitted to log odds sensitivity and specificity
Specificity	61.59%		
QAngio			
Sensitivity	84.34%	Bivariate meta-analysis (Table 3) for combined cQFR and non-specified QFR mode	Multivariate lognormal distribution fitted to log odds sensitivity and specificity
Specificity	89.80%		
CAAS vFRR			
Sensitivity	97.00%	FAST – EXTEND[15]	Independent beta distributions fitted to the diagnostic accuracy 2x2 tables. Sensitivity: α=118, β=4 Specificity: α=47, β=134
Specificity	74.00%		

Joint probability of FFR and QFR			
QFR<0.78 & FFR≤0.80	0.744	Recreated individual level FFR and QFR measurements in the QAngio diagnostic accuracy studies (cQFR and non-specified QFR mode)	Calculated from each 5,000 bootstraped samples of the joint FFR and QFR distribution
QFR 0.78-0.84 & FFR≤0.80	0.188		
QFR≥0.84 & FFR≤0.80	0.069		
QFR<0.78 & FFR>0.80	0.095		
QFR 0.78-0.84 & FFR>0.80	0.212		
QFR≥0.84 & FFR>0.80	0.693		
Procedural adverse events			
FFR/iFR complications			
Conduction disturbance requiring treatment	0.03%	IRIS-FFR[10]	Beta distribution, α=3, β=8630
Bronchospasm	0.02%		Beta distribution, α=2, β=8631
Coronary dissection	0.03%		Beta distribution, α=3, β=8630
Ventricular arrhythmia	0.02%		Beta distribution, α=1, β=8631
Thrombus formation	0.01%		Beta distribution, α=1, β=8632
Death	0.015%	Fearon et al, 2003[83]	NA
Revascularisation complications			
PCI death	0.17%	NCAP 2019 annual report[100]	NA
CABG death	0.99%	ACS 2019 summary report[99]	NA
Revascularisation death	0.277%	Calculated	NA
Proportion per revascularisation procedure			
PCI	87%	BCIS audit returns[95]	NA
CABG	13%		NA
Clinical event rates			
Non-cardiovascular mortality	Age and sex dependent	ONS mortality data [126, 127]	NA

Baseline MACE rates	Dependent on underlying FFR distribution	IRIS-FFR[10]	The underlying FFR distribution was calculated from each 5,000 bootstraped samples of the joint FFR and QFR (or % DS where applicable) distribution
HR of revascularisation on MACE rates	1.0	Assumption of no treatment effect	NA
HRQoL			
Procedural disutility			
ICA	0	Assumption	NA
FFR/iFR	0.0056	Assumed same as PCI	Gamma distribution, mean=0.0056, SE=0.003
PCI	0.0056	Bagust et al, 2006[132]	Gamma distribution, mean=0.0056, SE=0.003
CABG	0.033	Bagust et al, 2006[132]	Gamma distribution, mean= 0.033, SE=0.001
Revascularisation	0.0092	Calculated	NA
Baseline utility in the prognostic model	Age and sex dependent	Calculated based on Ara and Brazier, 2010,[135] and Nishi et al, 2018[122]	Beta distribution fitted to reference group baseline utility, mean=0.821, SE=0.0112
Utility increments			
FN	0.015	Nishi et al, 2018[122]	Beta distribution; mean=0.015,SE=0.0094
TN	0.000	Calculated based on Nishi et al, 2018,[122]and underlying distribution of FFR	NA
FP	0.000		NA
TP	0		The underlying FFR distribution was calculated from each 5,000 bootstraped samples of the joint FFR and QFR (or % DS where applicable) distribution. Beta distributions were fitted to the utility increment by FFR category (see Table 23)
Health states and clinical events disutility			

MI	0.0626	Sullivan et al, 2011[136]	Gamma distribution, mean=0.0626, SE=0.0132
Post-MI	0.0368	Sullivan et al, 2011[136]	Gamma distribution, mean=0.0368, SE=0.0257
Unplanned revascularisation	0.0091	Calculated	NA
Costs			
Tests (per patient tested)			
Qangio XA	£430.61	Calculated	NA
CAAS vFFR	£172.18	Calculated	NA
FFR/iFR	£436.80	NHS reference costs 2017/18[139] uprated to 2018/19 costs[138]	NA
ICA	£0	Assumption	NA
Optimal medication treatment (annual cost)			
OMT only	£163.63	Calculated based on Nishi et al, 2018,[122]COURAGE,[88] SYNTAX,[87] and BNF[142]	NA
OMT only (FN)	£168.68		NA
OMT in addition to PCI	£150.10		NA
OMT in addition to CABG	£126.27		NA
OMT in addition to revascularisation	£147.00	Calculated	NA
Interventional procedures			
PCI	£3,005.07	NHS reference costs 2017/18[139] uprated to 2018/19 costs[138]	NA
CABG	£10,898.58		NA
Revascularisation	£4,031.22	Calculated	NA
Treatment of revascularisation complications			
Coronary dissection	£3,005.07	NHS reference costs 2017/18[139] uprated to 2018/19 costs[138]	NA
Ventricular arrhythmia	£974.90		NA
Conduction disturbance requiring treatment	£974.90		NA
Bronchospasm	£928.12		NA
Thrombus formation	£834.57	Assumed average of unit cost of other complications, excluding coronary dissection	NA

Death	£0	Assumption	NA
Health states and clinical events costs			
No event	£0	Assumption	NA
MI	£2,317.53	NHS reference costs 2017/18[139] uprated to 2018/19 costs[138]	NA
Unplanned revascularisation	£4,812.23		NA
Post MI	£0	Assumption	NA
Post unplanned revascularisation	£0	Assumption	NA
Death (cardiovascular and other causes)	£0	Assumption	NA

ACS, Adult Cardiac Surgery; NCAP, National Cardiac Audit Programme

6.6.3 Scenario analyses

A number of alternative scenarios are considered in which the assumptions used as part of the base case results are varied. These analyses are undertaken to assess the robustness of the base case results to variation in the sources of data used to populate the model and alternative assumptions.

Table 36 summarises the alternative scenarios considered. For each element, the position in the base case analysis is outlined, alongside the alternative assumption applied

Table 36 Details of the key elements of the base-case analysis and the variation used in the scenario analysis

Scenario	Element	Position in base case analysis	Variation in scenario analysis
Diagnostic accuracy			
1	Diagnostic accuracy of QAngio XA 3D/ QFR	Sensitivity and specificity estimates based on the bivariate meta-analysis for all studies using contrast-flow QFR mode (cQFR) or non-specified QFR	Sensitivity and specificity estimates based on studies reporting fixed-flow QFR mode (fQFR) only
2			Sensitivity and specificity estimates based on studies reporting contrast-flow QFR mode (cQFR) only
3			Perfect sensitivity and specificity for QFR (i.e. same as FFR)
4	Diagnostic accuracy of CAAS vFFR	Sensitivity and specificity estimates based on the largest study of vFFR (FAST EXTEND study)	Sensitivity and specificity estimates based on the ILUMIEN 1 (2019) study
5			Sensitivity and specificity estimates based on Jin (2019) study
6			Same sensitivity and specificity for vFFR and QFR
7	Diagnostic accuracy of ICA	Sensitivity and specificity estimates based on the bivariate meta-analysis of studies comparing 2D ICA with FFR	Sensitivity and specificity estimates based on meta-analysis by Danad et al (2017) for diagnostic performance of ICA compared with FFR
8	Diagnostic threshold of QFR and FFR	Diagnostic threshold of 0.8 used to define functionally significant stenosis for QFR and FFR	An alternative diagnostic threshold of 0.75 used for FFR and QFR based on the findings of the IRIS-FFR registry data (note it is not possible to explore an alternative diagnostic threshold for vFFR due to an absence of data)
9	Grey zone boundary for hybrid QFR + confirmatory FFR strategy	Grey zone boundary of 0.78 to 0.84 for QFR as recommended by the manufacturer of QAngio XA 3D/ QFR imaging software	A wider grey zone boundary of 0.70 to 0.90 for strategy 4 of QFR + confirmatory FFR when QFR is inconclusive

Risk of major adverse cardiovascular events			
10	Baseline risk of MACE	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	The baseline risk of MACE is independent of FFR and diagnostic test results
11	Treatment effect of revascularisation on MACE	No treatment effect of revascularisation on risk of MACE based on the findings of the ISCHEMIA trial	A significant reduction in the risk of MACE for revascularisation in FFR values below 0.76 based on the findings of the IRIS-FFR registry data
12			A significant reduction in the risk of unplanned revascularisation and no reduction for cardiac death or MI based on the findings of trials that showed a positive effect of revascularisation on MACE for repeat/emergency or unplanned revascularisation rather than cardiac death or MI
13			A reduction in the risk of MACE for all components based on the findings of trials that reported a modest (but non-statistically significant) improvement in MACE for revascularisation
Costs of diagnostic tests			
14	Patient throughput	Costs of QFR and vFFR based on an average annual throughput of 200	Alternative average annual throughput of 100 for QFR and vFFR
Costs of revascularisation			
15	Cost of PCI	Cost of PCI across all HRGs	Cost of PCI based on day cases only
16	Revascularisation procedure	Proportion of revascularisations assumed to be PCI in 87% of cases and CABG in 13% based on BCIS audit data	Alternative assumption of 75% PCI and 25% CABG
Health-related quality of life			

17	Duration of HRQoL benefits	HRQoL benefits of revascularisation and OMT observed at one year based on the findings of Nishi et al (2018) for the TP and FN health states applied for a lifetime duration	Alternative assumptions about the duration of HRQoL benefits of revascularisation and OMT
18	Magnitude of HRQoL benefits		No HRQoL benefits associated with treatment based on the findings of the ORBITA trial
19	Procedural disutility	Procedural disutility associated with FFR, equivalent to that of PCI	Higher procedural disutility associated with FFR, equivalent to that of CABG
Procedural complications associated with FFR			
20	FFR procedural death rate	Procedural death risk sourced from Fearon et al, 2004[83]	No procedural death risk from FFR
21	FFR adverse event rates	Adverse event rates sourced from IRIS-FFR registry [10]	Adverse event rates sourced from RIPCORD trial[98]
22			Adverse event rates sourced from ORBITA trial[94]
Setting			
23	Cost of FFR/iFR	Unit cost of FFR/iFR corresponds to the incremental cost of FFR/iFR compared to ICA alone (i.e., difference between a complex and a standard catheterisation)	Unit cost of FFR/iFR corresponds to the cost of a complex catheterisation
24	Patient throughput	Costs of QFR and vFFR based on an average annual throughput of 200	Costs of QFR and vFFR based on an average annual throughput of 500

6.6.4 Model validation

The model was developed in Excel by two analysts (AD and LS) and the programming checked by a third analyst (CR). As part of an overall quality assurance process, the internal validity of the model was assessed by extensively exploring logical consistency in the model results. A separate version of the prognostic model was also independently programmed by the third analyst (CR) to successfully replicate the base case results.

6.7 Results of the independent economic assessment

6.7.1 Results of the base-case scenario

Deterministic and probabilistic cost-effectiveness results expressed in terms of NHB at a cost-effectiveness threshold of £20,000 per additional QALY for the base case scenario are presented in Table 37 and Table 38, respectively. Strategy ranking from highest to lowest NHB is presented in both tables. The incremental NHB is calculated for each strategy relative to ICA alone. The probability that each strategy is cost-effective at a threshold of £20,000 per additional QALY is presented in Table 38 for the probabilistic analysis. The results are consistent for both the deterministic and probabilistic analysis.

Table 37 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 + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 38 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 + QFR	11.065	£4,813	10.824	0.020	2	0.218
4	ICA + QFR + confirmatory FFR (grey zone)	11.070	£5,020	10.819	0.015	4	0.199
5	ICA + vFFR	11.076	£5,119	10.820	0.016	3	0.204

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

The strategy with the highest NHB is strategy 2, ICA + FFR, but the difference between all the strategies is small. Strategy 2 is also the strategy with the highest probability of being cost-effective (27.8%). The least costly strategy is strategy 1, ICA alone, which also has the lowest QALY gain, while the most costly strategy is strategy 5, ICA + vFFR but this has the highest QALY gain. The incremental NHB per patient diagnosed for each of the strategies relative to ICA alone is 0.027 QALYs (or equivalently £544) for ICA + FFR, 0.020 QALYs (or equivalently £400) for ICA + QFR, 0.015 QALYs (or equivalently £298) for ICA + QFR + confirmatory FFR when QFR is inconclusive, and 0.016 QALYs (or equivalently £316) for ICA + vFFR.

In order to understand the difference in NHB between the alternative strategies, the disaggregated results for total expected costs and QALYs are informative. Table 39 shows the expected costs and QALYs for each strategy from the diagnostic and prognostic components of the model separately. The diagnostic model includes the costs of the diagnostic tests, revascularisation, and costs associated with treating adverse events related to FFR, while the prognostic model includes costs related to unplanned/repeat revascularisation, MI events and long-term OMT use. The diagnostic model includes a procedural disutility associated with invasive FFR/iFR and revascularisation, while the prognostic model includes the long-term symptom free benefits of revascularisation, a disutility associated with unplanned/repeat revascularisation, MI events and history of MI, applied to a baseline utility for patients with intermediate stenosis. Note that costs, adverse events and disutility associated with invasive ICA are excluded from the model as all strategies undergo ICA. The disaggregated costs and QALYs from the diagnostic component of the model are shown in Table 40, while the proportion of patients that enter the long-term prognostic model in each of the TN, FN, TP and FP entry states for each of the alternative strategies (based on the diagnostic accuracy results) is shown in Table 41.

For strategies with the highest diagnostic model costs this is due to a greater number of revascularisations. The percentage of revascularisation is dependent on the rate of TP and FP results. The positive predictive value (PPV) is highest for strategies involving QFR (strategies 3 [84.8%] and 4 [86.8%]) compared to vFFR (71.5%) or ICA alone (52.3%), while FFR is assumed to have perfect PPV. This means that there is a higher number of unnecessary revascularisations for vFFR and ICA alone compared to QFR or FFR, which increases the costs of revascularisation for these tests. Some of the total diagnostic model cost is offset by differences in costs of testing. The costs of the diagnostic tests are dependent on the level of patient throughput and for the base case scenario (throughput assumed to be 200), vFFR has lower costs (£172 per patient tested) compared to QFR (£431) and FFR (£437). The cost of adverse events associated with FFR increases the total cost of FFR but this is very marginal due to a low likelihood of adverse events occurring. The difference in total diagnostic model costs between strategies 2, ICA + FFR, and 3, ICA + QFR, is £15 per patient diagnosed, while the total diagnostic model cost for strategy 4, with the addition of FFR when QFR is inconclusive, increases the cost of a QFR strategy by £215 per patient due to a higher rate of TP results. The difference in total diagnostic model costs of strategy 5 relative to strategies 2 and 3 are £314 and £329 per patient, respectively, due to a higher percentage of revascularisation as a result of more FP test results. The procedural QALY loss associated with invasive FFR and revascularisation ranges from 0.0037 for ICA + QFR (no additional adverse events for QFR relative to ICA) to 0.0093 QALYs for ICA + FFR.

The difference in total costs between the strategies from the prognostic model is much smaller than the diagnostic model because the base case scenario assumes that there is no treatment effect associated with revascularisation on the rates of MACE. The only difference between the strategies in terms of costs associated with MACE is due to the inverse relationship between underlying FFR and subsequent risk of MACE, i.e., those with lower FFR have a higher risk of a cardiovascular event, while those with higher FFR have a lower risk of a cardiovascular event. The prognostic model also includes a difference in annual costs for OMT between those that receive OMT in addition to revascularisation (£150 for PCI and £126 for CABG) and those who receive OMT alone (£163 for TN and £169 for FN). Strategy 5, ICA + vFFR, and strategy 1, ICA alone, have the lowest prognostic costs, which is mainly due to the lower total costs of OMT associated with a greater number of revascularisations in these strategies. The difference in total prognostic costs between strategy 3, ICA + QFR, with the highest cost and strategy 5, ICA + vFFR, with the lowest cost is £22 per patient. The difference in total QALYs between the strategies from the prognostic model is largely due to the HRQoL gain associated with TP test results. The base case scenario assumes that there is no change in baseline HRQoL associated with TN and FP test results, while there is a small non-statistically significant change associated with FN test results. This means that the total expected QALYs is greater for strategies with more TP test results (better sensitivity), while there are no HRQoL benefits

associated with more TN test results (better specificity). As a result, strategies 2, ICA + FFR, and 5, ICA + vFFR, have the highest prognostic model QALY gains, while strategy 1, ICA alone, has the lowest. These QALY gains, however, are offset by the disutility associated with diagnostic testing that is highest for strategies 2 and 5 and lowest for strategy 1.

The benefits of revascularisation, in terms of improved HRQoL, means that the sensitivity of test results is a more important driver of cost-effectiveness than specificity because TP test results translate into higher QALY gains than mismanagement of FN results. The base case cost-effectiveness results are largely driven by the balance between the costs of the diagnostic tests and the costs and benefits of revascularisation.

Table 39 Total expected costs and QALYs from the diagnostic and prognostic model by strategy

		Diagnostic model		Prognostic model		Total model results	
Strategy	Identification	Costs	QALYs	Costs	QALYs	Costs	QALYs
1	ICA alone	£1,940	-0.0044	£2,757	11.043	£4,696	11.039
2	ICA + FFR	£2,059	-0.0093	£2,766	11.082	£4,825	11.073
3	ICA + QFR	£2,044	-0.0037	£2,769	11.069	£4,813	11.065
4	ICA + QFR + confirmatory FFR (grey zone)	£2,259	-0.0051	£2,761	11.075	£5,020	11.070
5	ICA + vFFR	£2,373	-0.0050	£2,747	11.081	£5,119	11.076

Table 40 Disaggregated costs and QALYs from the diagnostic model by strategy

		Costs			QALY loss	
Strategy	Identification	Testing	Revascularisation	Adverse events (FFR)	Testing (FFR)	Revascularisation
1	ICA alone	-	£1,940	-	-	-0.00440
2	ICA + FFR	£437	£1,620	£1.49	-0.00559	-0.00367
3	ICA + QFR	£431	£1,613	-	-	-0.00365
4	ICA + QFR + confirmatory FFR (grey zone)	£519	£1,739	£0.21	-0.00113	-0.00394
5	ICA + vFFR	£172	£2,199	-	-	-0.00498

Table 41 Diagnostic accuracy results by strategy

		Diagnostic accuracy						Percentage of Revascularisation
Strategy	Identification	TN	FN	TP	FP	PPV	NPV	
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 + vFFR	0.443	0.012	0.389	0.155	71.5%	97.3%	54.4%

6.7.2 Results of the alternative scenario analyses

6.7.2.1 Diagnostic accuracy

Scenarios 1-3: Using alternative sensitivity and specificity estimates for QFR

The sensitivity (84.3%) and specificity (89.8%) estimates for QFR, which are used to inform strategy 3 in the base case scenario, are based on the primary bivariate meta-analysis of Section 4.5 from all studies that reported diagnostic accuracy data for cQFR mode or non-specified QFR. Two separate scenarios consider the impact on cost-effectiveness of small differences in diagnostic accuracy by mode of QFR: scenario 1 uses sensitivity (81.6%) and specificity (89.4%) estimates for QFR based on studies that only report fQFR mode, while scenario 2 uses sensitivity (84.3%) and specificity estimates (91.4%) for QFR based on studies that only report cQFR mode. Table 42 and Table 43 present the cost-effectiveness results for scenarios 1 and 2, respectively.

Table 42 Deterministic cost-effectiveness results for scenario 1 - Sensitivity and specificity estimates based on fQFR mode only for strategy 3

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 + QFR	11.084	£4,778	10.845	0.019	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.
QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 43 Deterministic cost-effectiveness results for scenario 2 - Sensitivity and specificity estimates based on cQFR mode only for strategy 3

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 + QFR	11.088	£4,775	10.849	0.023	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.
QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

In scenario 1, there is a reduction in both the PPV (from 84.8% to 83.8%) and NPV (from 89.5% to 87.9%) for strategy 3, ICA + QFR, compared to the base case scenario. This results in a marginally smaller reduction in total QALYs (0.003 QALYs per patient) and decrease in total costs (£34 per patient) for strategy 3 compared to the base case, with no change in the overall ranking of NHB across strategies. In scenario 2, there is an increase in both the PPV (from 84.8% to 86.8%) and NPV (from 89.5% to 89.7%) for strategy 3 compared to the base case, due to more TN test results as a result of better specificity. This results in a marginally small increase in total QALYs (0.001 QALYs per patient) and decrease in total costs (£37 per patient) for strategy 3 compared to the base case scenario. This means that the sensitivity and specificity estimates used in scenario 2 are slightly more favourable for the cost-effectiveness of QFR compared to scenario 1 or the base case scenario; however, the more favourable estimates do not result in a change in NHB ranking across the strategies.

In order to understand the trade-off in diagnostic test costs and adverse events associated with FFR/iFR (strategy 2) compared with QFR (strategy 3), scenario 3 considers the impact on cost-effectiveness when QFR and FFR are assumed to be a perfect test, i.e., 100% sensitivity and specificity, and same underlying distribution of FFR values as used in the base case for strategy 2. Table 44 presents the cost-effectiveness results for strategies 2 (ICA + FFR) and 3 (ICA + QFR) under scenario 3. The total QALYs and costs for strategy 3 increase by 0.017 QALYs and £6 per patient from the base case scenario, which is largely due to a small increase in the number of revascularisations (from 39.9% to 40.2%). With QFR assumed to be a perfect test, strategy 3 now has higher NHB than strategy 2 (an increase of 0.008 QALYs per patient) and is ranked the most cost-effective strategy. The increase in NHB is largely due to greater total QALYs gained for strategy 3 compared to strategy 2, while the difference in total costs between the strategies is small (£7 per patient). The difference in total costs is small because QFR and FFR have similar costs of diagnostic testing (£431 for QFR vs. £437 for FFR/iFR), while the number of revascularisations is the same

under this scenario and the costs associated with treating adverse events of FFR/iFR are small (average of £1.49 per patient tested). The difference in total QALYs is due to the disutility associated with FFR/iFR and an increased risk of procedural mortality for FFR/iFR.

Table 44 Deterministic cost-effectiveness results for scenario 3 – Perfect sensitivity and specificity for QFR

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
2	ICA + FFR	11.096	£4,825	10.855	-	2
3	ICA + QFR	11.104	£4,818	10.863	0.008	1

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA + FFR.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 4-6: Using alternative sensitivity and specificity estimates for vFFR

The sensitivity (97.0%) and specificity (74.0%) estimates for vFFR, which are used to inform strategy 5 in the base case scenario, are based on the largest (303 patients) study of vFFR. As noted in Section 4.8, there are only three independent studies of CAAS vFFR, one of which has only been published as a conference abstract.[23] As reported in section 4.8.1, the bivariate meta-analysis of CAAS vFFR studies should be interpreted with caution due to limited data and high heterogeneity across studies. Therefore, this meta-analysis was not used to inform the economic model. Two scenarios consider the impact on cost-effectiveness of different diagnostic accuracy estimates for vFFR based on the two studies not included in the base case scenario: scenario 4 uses sensitivity (75%) and specificity (46.5%) estimates for vFFR based on the ILUMIEN 1 (2019) study,[16] while scenario 5 uses sensitivity (68.2%) and specificity (87.3%) estimates for vFFR based on the Jin et al (2019) conference abstract.[23] Table 45 and Table 46 present the cost-effectiveness results for scenarios 4 and 5, respectively.

Table 45 Deterministic cost-effectiveness results for scenario 4 - Sensitivity and specificity estimates based on the ILUMIEN 1 (2019) study for vFFR in strategy 5

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	-	4
2	ICA + FFR	11.096	£4,825	10.855	0.029	1
3	ICA + QFR	11.088	£4,775	10.849	0.023	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	3
5	ICA + vFFR	11.065	£5,412	10.795	-0.031	5

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 46 Deterministic cost-effectiveness results for scenario 5 - Sensitivity and specificity estimates based on the Jin (2019) study for vFFR in strategy 5

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 + QFR	11.088	£4,775	10.849	0.023	3
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	4
5	ICA + vFFR	11.068	£4,360	10.850	0.024	2

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

In scenario 4, there is decrease in both the PPV (from 71.5% to 48.5%) and NPV (from 97.3% to 73.5%) for strategy 5 compared to the base case scenario. This results in a substantial decrease in total QALYs (0.033 QALYs per patient) and an increase in total costs (£294 per patient) for strategy 5 compared to the base case. Strategy 5 is now ranked the least cost-effective strategy (lowest in terms of NHB) with lower NHB compared to strategy 1 of ICA alone (a reduction of 0.031 QALYs per patient, equivalent to £620 per patient diagnosed at a cost-effectiveness threshold of £20,000 per QALY). In scenario 5, there is an increase in the PPV (from 71.5% to 78.3%) but a decrease in the NPV (from 97.3% to 80.3%) for strategy, due to lower sensitivity and better specificity than the base case scenario. This results in a substantial decrease in both total QALYs (0.030 QALYs per patient) and total costs (£758 per patient) for strategy 5 compared to the base case scenario. Strategy 5, ICA + vFFR, now appears a more cost-effective strategy than strategies 3 and 4 based on QFR, and is ranked second in terms of NHB with FFR remaining the strategy with the highest NHB.

In order to understand the impact of differences in diagnostic test costs between vFFR and QFR, scenario 6 considers the impact on cost-effectiveness by assuming that both tests have the same diagnostic accuracy in strategies 3 and 5, i.e., the sensitivity and specificity for vFFR is set equal to the base case scenario for QFR. Table 47presents the cost-effectiveness results for scenario 6.

Table 47 Deterministic cost-effectiveness results for scenario 6 – Same sensitivity and specificity estimates for vFFR and QFR in strategies 3 and 5

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	2
3	ICA + QFR	11.087	£4,812	10.847	0.020	3
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.016	4
5	ICA + vFFR	11.087	£4,554	10.860	0.034	1

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

In scenario 6, the total QALYs and costs are reduced for strategy 5, largely due to a decrease in the number of revascularisations (from 54.5% to 40.0%). The only difference between strategies 5 and 3 is the difference in the costs of diagnostic testing of £258 less per patient for vFFR compared to QFR for the base case throughput assumption of 200 patients per year. This difference in the cost of testing between vFFR and QFR, under the scenario of equivalent diagnostic accuracy, is sufficient to change the ranking of NHB across the strategies, with strategy 5 now ranked with the highest NHB.

Scenario 7: Using alternative sensitivity and specificity estimate for ICA

The sensitivity (62.6%) and specificity (61.6%) estimates for ICA, which are used to inform strategy 1 in the base case scenario, are based on the bivariate meta-analysis in Section 4.7.4 from studies that reported diagnostic accuracy data for 2D ICA compared with FFR. Scenario 7 is used to assess the impact on cost-effectiveness of an alternative (higher) estimate of diagnostic accuracy for ICA based on a meta-analysis by Danad et al,2017,[97] for diagnostic performance of ICA compared with FFR (sensitivity, 71% and specificity 66% from per vessel analysis). Table 48 presents the cost-effectiveness results for scenario 7.

Table 48 Deterministic cost-effectiveness results for scenario 7 - Sensitivity and specificity estimates for ICA based on the meta-analysis by Danad et al (2017) in strategy 1

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.073	£4,726	10.837	-	5
2	ICA + FFR	11.096	£4,825	10.855	0.018	1
3	ICA + QFR	11.087	£4,812	10.847	0.010	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.006	3
5	ICA + vFFR	11.098	£5,118	10.842	0.005	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

In scenario 7, there is an increase in both the PPV (from 52.3% to 58.4%) and NPV (from 71.0% to 77.2%) for strategy 1 compared to the base case scenario. This results in an increase in total QALYs (0.012 QALYs per patient) and a marginal increase in total costs (£29 per patient) for strategy 1 but with no change in the NHB ranking, with ICA alone ranked the least cost-effective strategy.

Scenario 8: Using an alternative diagnostic threshold for FFR and QFR

The base case scenario uses a diagnostic threshold of FFR ≤0.8 to define functionally significant stenosis. In scenario 8, an alternative diagnostic threshold of FFR ≤0.75 is used to assess the impact on cost-effectiveness results for strategies 1, 2 and 3 compared to the base case scenario (note that there was insufficient diagnostic accuracy data for vFFR to inform an alternative diagnostic threshold for strategy 5, while strategy 4 uses a hybrid approach rather than a single diagnostic threshold). In scenario 8, the diagnostic accuracy of QFR is based on the estimates reported in Section 4.7.3 for this alternative threshold (sensitivity 75.4% and specificity 90.6%), while the diagnostic accuracy of ICA was estimated at FFR ≤0.75 and ≥50% DS using the approach described in Section 4.7.4 (sensitivity 74.0% and specificity 56.4%). The use of an alternative threshold also changes the prior probability of functionally significant stenosis from 40% in the base case scenario to 25% in scenario 8. This also means that the underlying distribution of FFR values for the different diagnostic outcomes (TN, FN, TP, and FP) shifts for these strategies, as the category of FFR=[0.76-0.80] is 'moved' from the distribution of FFR in patients with functionally significant stenosis (TP and FN) to those without (TN and FP). This shift in the FFR distribution also changes the utility increment for TP, increasing it slightly for all strategies (the size of the increment varies by strategy as it is dependent on the underlying FFR distribution). The utility increment for FN was assumed to remain the same, even though this increment was estimated in patients with FFR≤0.80 who did not receive revascularisation.

Table 49 presents the cost-effectiveness results for scenario 8. The NHB decreases for all three strategies but the ranking of strategies follows the same order as the base case scenario, with strategy 2 ranked the most cost-effective option. The total QALYs for all three strategies are reduced due to the reduction in prior probability of functionally significant stenosis which means that fewer patients are able to benefit from revascularisation. The proportion of patients who undergo revascularisation is reduced for both strategies 2 and 3 compared to the base-case scenario. The changes in diagnostic accuracy of strategy 3 (lower sensitivity and increased specificity) combined with lower prior probability of significant stenosis compared to the base-case results in a lower PPV (72.8% vs 84.8%) and higher NPV (91.7% vs 89.5%). In this scenario, the greater increase in FP results compared to FN ones for strategy 3, results in a greater number of revascularisations for this strategy compared to strategy 2 (25.9% vs 25%). The diagnostic accuracy of strategy 1 changes in the opposite way to strategy 3, i.e. the sensitivity increases while the specificity decreases. Despite the lower prior probability of functionally significant stenosis, this results in more revascularisation procedures overall (51.2% vs 48.1%) with associated higher costs and greater QALY loss compared to the base-case scenario. In the prognostic model, all three strategies accrue more costs and fewer QALYs compared to the base-case. The lower QALY gains and higher costs result from fewer patients with TP results entering the prognostic model in all three strategies, so fewer patients benefit from the utility increment and lower medication costs associated with a TP test result.

Table 49 Deterministic cost-effectiveness results for scenario 8 – Alternative diagnostic threshold (≤0.75) for QFR and FFR

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.018	£4,793	10.779	-	3
2	ICA + FFR	11.039	£4,248	10.826	0.048	1
3	ICA + QFR	11.029	£4,276	10.815	0.036	2

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenario 9: Using an alternative definition of the grey zone for strategy 4

In the base case scenario, a hybrid approach is used for strategy 4 with QFR followed by confirmatory FFR when the results of QFR are inconclusive (grey zone). The grey zone is defined based on the manufacturer's recommendation of 0.78≤ QFR ≤0.84. In scenario 9, an alternative wider definition is used for the grey zone of between 0.70 and 0.90 in order to assess the impact on the cost-effectiveness of strategy 4.

Table 50 presents the cost-effectiveness results for scenario 9.

The wider definition of the grey zone in scenario 9 increases the proportion of patients in the grey zone compared to base-case scenario from 20.2% to 61.6%, which changes the diagnostic accuracy of strategy 4 with more confirmatory FFR tests. The PPV and NPV of strategy 4 increases by 10.9% and 3.7%, respectively, compared to the base-case scenario. By widening the grey zone definition, more patients undergo FFR, which increases the costs of testing for strategy 4 by £181 compared to the base-case. However, an increase in FFR also results in fewer revascularisations compared to the base-case (reduced from 43.1% in the base case to 40.4% in scenario 9 for strategy 4) with a corresponding reduction in revascularisation costs of £108. The reduction in revascularisations also reduces the QALY loss due to this procedure compared to base-case, but this is offset by the increase in QALY loss due to FFR. In the diagnostic model, strategy 4 is more costly (£73 per patient) and incurs more QALY loss (0.0021 QALYs per patients) compared to the base-case scenario. The reduced misclassification and consequent improved clinical management of patients results in higher QALY gains (0.005 QALYs per patient) for strategy 4 in the prognostic model compared to the base-case. Overall, both the total QALYs (0.04 QALYs per patient) and total costs (£78 per patient) are higher for strategy 4 compared to the base-case scenario, which results in a small reduction in NHB (0.001 QALYs) compared to the base case, which leads to the same NHB for strategies 4 and 5.

Table 50 Deterministic cost-effectiveness results for scenario 9 – Alternative definition of the grey zone (0.70≤QFR≤0.90) for strategy 4

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 + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.097	£5,097	10.842	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

6.7.2.2 Risk of major adverse cardiovascular events (MACE)

Scenario 10: Baseline risk of MACE independent of FFR and diagnostic test results

The baseline risk of MACE in the base case scenario depends on disease severity as measured by FFR value, where lower FFR values are indicative of a higher cardiovascular event rate and higher FFR values of a lower rate, while the distribution of FFR values differs by diagnostic strategy. In scenario 10, the dependency on FFR is removed and the impact on cost-effectiveness is assessed by

considering the baseline risk of MACE to be completely independent of FFR and diagnostic test results.

Table 51 presents the cost-effectiveness results for scenario 10.

In scenario 10, the overall risk of MACE is 1.44% in the first year and 0.72% in subsequent years based on the IRIS-FFR registry data across all FFR values, whereas in the base case scenario it ranges from 4.33% for FFR values ≤0.70 to 0.64% for FFR values >0.90. In scenario 10 this results in an increase in total QALYs (0.048 for strategy 1, 0.080 for strategy 2, 0.067 for strategy 3, 0.075 for strategy 4, and 0.074 for strategy 5) and a decrease in total costs per patient for each strategy (£124 for strategy 1, £127 for strategy 2, £124 for strategy 3, £126 for strategy 4, and £139 for strategy 5) compared to the base case scenario. The corresponding NHB ranking changes because strategies 3, 4 and 5 now look very similar in terms of NHB (10.920 QALYs for strategy 3 and 10.923 QALYs for strategies 4 and 5), while strategy 2 remains the most cost-effective option and strategy 1 the least. The removal of dependency on FFR values appears to have the greatest impact on strategy 5, ICA + vFFR. This is largely because this strategy has more TP test results (better sensitivity) compared to strategies 3 and 4 using QFR. In scenario 10, the baseline risk of MACE is lower for FFR values ≤0.80, while it is greater for FFR values >0.80, compared to the baseline risk of MACE used in the base case scenario. This means that strategies with more TN test results (better specificity) are penalised with a higher risk of MACE, while strategies with more TP test results (better sensitivity) benefit from a lower risk of MACE. As a result, the NHB for strategy 5 improves more compared to strategies 3 and 4. This is in line with the base case conclusion that sensitivity of test results is a more important driver of cost-effectiveness than specificity because TP test results translate into higher QALY gains than mismanagement of FN results.

Table 51 Deterministic cost-effectiveness results for scenario 10 - The baseline risk of MACE is independent of FFR and diagnostic test results

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.109	£4,573	10.881	-	5
2	ICA + FFR	11.176	£4,698	10.942	0.061	1
3	ICA + QFR	11.154	£4,688	10.920	0.039	4
4	ICA + QFR + confirmatory FFR (grey zone)	11.168	£4,893	10.923	0.042	2
5	ICA + vFFR	11.172	£4,979	10.923	0.042	3

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 11-13: Treatment effect of revascularisation on MACE

The base case scenario assumes that there is no treatment effect associated with revascularisation on the risk of MACE based on the findings of the ISCHEMIA trial, i.e., revascularisation does not confer additional benefits over and above OMT on the risk of MACE. Three separate scenarios are used to consider the impact on cost-effectiveness of alternative assumptions about the benefits of revascularisation on MACE outcomes compared to OMT: scenario 11 considers a significant reduction in the risk of MACE for revascularisation in patients with an FFR value below 0.76, based on the findings of the IRIS-FFR registry data, which showed that there was only a statistically significant reduction in the risk of clinical outcomes for lesions with an FFR below 0.76; scenario 12 considers a statistically significant reduction in the risk of unplanned revascularisation, while there is no reduction for cardiac death or MI, based on the findings of trials that showed a positive effect of revascularisation on MACE for repeat/emergency or unplanned revascularisation rather than cardiac death or MI; and scenario 13 considers a reduction in the risk of MACE for all components (unplanned revascularisation, cardiac death or MI) based on the findings of trials that reported a modest (but non-statistically significant) improvement in MACE for revascularisation compared to OMT. Table 52, Table 53 and Table 54 present the cost-effectiveness results for scenarios 11, 12 and 13, respectively.

In scenario 11, the hazard ratio (HR) for revascularisation compared to OMT is set equal to 0.47 for the risk of MACE (across all components) for FFR values ≤0.75, while the HR is set equal to one for FFR values >0.75. Thus, strategies with more TP test results and a higher proportion of lower FFR values are expected to have better outcomes than the base case scenario. Scenario 11 results in an increase in total QALYs (0.019 for strategy 1, 0.022 for strategy 2, 0.021 for strategy 3, 0.021 for strategy 4, and 0.024 for strategy 5) and a decrease in total costs per patient for each strategy (£91 for strategy 1, £116 for strategy 2, £108 for strategy 3, £111 for strategy 4, and £125 for strategy 5) compared to the base case scenario. The corresponding NHB ranking switches for strategies 4 and 5, with strategy 5 appearing marginally more cost-effective than strategy 4. This is largely because strategy 5 has marginally more TP test results, which benefit from a lower risk of MACE compared to strategy 4.

In scenario 12, the HR for revascularisation compared to OMT for lesions with an FFR ≤0.8 is set equal to 0.26 for the risk of unplanned revascularisation, while the HR is set equal to 1 for cardiac death or MI. In this scenario, there is very little impact on total QALYs across strategies, while the total costs per patient decrease for each strategy (£155 for strategy 1, £235 for strategy 2, £203 for strategy 3, £220 for strategy 4, and £233 for strategy 5) compared to the base case scenario. The corresponding NHB ranking switches for strategies 4 and 5, with strategy 5 appearing marginally

more cost-effective than strategy 4. Again, this is largely because strategy 5 has marginally more TP test results, which benefit from a lower risk of revascularisation, compared to strategy 4.

In scenario 13, the HR for revascularisation compared to OMT for lesions with an FFR ≤0.8 is set equal to 0.71 for the risk of cardiac death, 0.93 for non-fatal MI and 0.93 for unplanned revascularisation. Scenario 11 results in an increase in total QALYs (0.012 for strategy 1, 0.016 for strategy 2, 0.014 for strategy 3, 0.015 for strategy 4, and 0.016 for strategy 5) and a decrease in total costs per patient for each strategy (£11 for strategy 1, £18 for strategy 2, £15 for strategy 3, £16 for strategy 4, and £17 for strategy 5) compared to the base case scenario. The corresponding NHB ranking switches for strategies 4 and 5, with strategy 5 appearing marginally more cost-effective than strategy 4. Again, strategies with more TP test results benefit most from improved clinical outcomes than strategies with more TN test results.

Table 52 Deterministic cost-effectiveness results for scenario 11 - A significant reduction in the risk of MACE for FFR values below 0.76 for revascularised lesions

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.080	£4,606	10.850	-	5
2	ICA + FFR	11.118	£4,709	10.882	0.032	1
3	ICA + QFR	11.108	£4,704	10.873	0.023	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.114	£4,908	10.869	0.019	4
5	ICA + vFFR	11.122	£4,993	10.872	0.022	3

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 53 Deterministic cost-effectiveness results for scenario 12 - A significant reduction in the risk of unplanned revascularisation following an index revascularisation procedure

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.062	£4,542	10.835	-	5
2	ICA + FFR	11.097	£4,590	10.868	0.033	1
3	ICA + QFR	11.088	£4,609	10.858	0.023	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.094	£4,799	10.854	0.019	4
5	ICA + vFFR	11.099	£4,885	10.855	0.020	3

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 54 Deterministic cost-effectiveness for scenario 13 - A modest reduction in the risk of MACE following an index revascularisation procedure

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.073	£4,686	10.838	-	5
2	ICA + FFR	11.112	£4,807	10.871	0.033	1
3	ICA + QFR	11.101	£4,797	10.861	0.023	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.108	£5,003	10.858	0.020	4
5	ICA + vFFR	11.114	£5,101	10.859	0.021	3

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenario 14: Costs of diagnostic tests

The cost per test of QFR and vFFR in the base case scenario is based on an average annual throughput of 200 per centre, which corresponds to an average cost of £431 per patient for QFR and £172 per patient for vFFR. Based on the base case assumptions, the average cost per test of QFR is constant for an annual throughput above 100, while it is expected to range from £473 (throughput of 90) to £741 (throughput of 10) per patient for throughput less than 100. For vFFR, the average cost per test varies for throughput below 200, with an average cost per test of £338 for throughput of 100 and increasing to £2,153 for throughput of 10 patients per centre. Scenario 14 considers the impact on cost-effectiveness of an alternative average annual throughput of 100 for QFR and vFFR. Table 55present the cost-effectiveness results for scenario 14.

Scenario 14 only results in an increase in the total costs of strategy 5, which is £166 per patient. The corresponding NHB ranking of strategies is unchanged. As an additional exploratory analysis, the average annual throughput for vFFR was varied to establish the point of indifference in NHB between strategies 3 and 5, with everything else held equal to the base case scenario. The NHB for strategies 3 and 5 are equal (and ranked second highest NHB across strategies after ICA + FFR) at an average annual throughput of 500 patients per centre, where the average cost per test of QFR is expected to be £431 while it is only £73 for vFFR.

Table 55 Deterministic cost-effectiveness results for scenario 14 – Throughput of 100 patients per year for QFR and vFFR

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 + QFR	11.087	£4,812	10.847	0.021	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,019	10.843	0.017	3
5	ICA + vFFR	11.098	£5,283	10.834	0.008	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 15-16: Costs of revascularisation

In the base case scenario, the costs of revascularisation for PCI and CABG are based on a weighted average of NHS reference costs across all HRGs, while the proportion of patients who undergo PCI and CABG as the index procedure is based on BCIS audit data. Two alternative scenarios are used to consider the impact on cost-effectiveness of a variation in the costs of revascularisation: scenario 15 considers a lower cost of PCI (reduced from £3,005 to £2,179 per patient) based on day cases only from NHS reference costs, while scenario 16 considers an alternative assumption of PCI in 75% of cases (reduced from 87% in the base case) and CABG in 25% of cases (increased from 13% in the base case), which increases the average cost of revascularisation from £4,031 to £4,978 per patient. Table 56 and Table 57Table 57 present the cost-effectiveness results for scenarios 15 and 16, respectively.

In scenario 15, the total QALYs are unchanged, while the total costs per patient for each strategy are reduced compared to the base case scenario (£346 for strategy 1, £289 for strategy 2, £287 for strategy 3, £310 for strategy 4, and £392 for strategy 5). The corresponding NHB ranking for strategies 3, 4 and 5 are changed, with strategy 5 appearing marginally more cost-effective than strategies 3 and 4. This is largely because strategy 5 has more TP and FP test results that benefit from a lower cost of revascularisation compared to strategies 3 and 4, which have more TN test results (better specificity).

In scenario 16, the total QALYs for each strategy are marginally reduced (ranging from 0.006 – 0.008 QALYs per patient) due to a higher procedural disutility associated with revascularisation as a result of an increase in CABG surgery, while the total costs for each strategy are increased as a result of higher costs associated with CABG compared to PCI (£521 for strategy 1, £449 for strategy 2, £447 for strategy 3, £476 for strategy 4, and £581 for strategy 5). The corresponding NHB ranking of strategies is unchanged.

Table 56 Deterministic cost-effectiveness results for scenario 15 – Cost of PCI based on day cases only

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,351	10.844	-	5
2	ICA + FFR	11.096	£4,536	10.869	0.025	1
3	ICA + QFR	11.087	£4,525	10.861	0.017	3
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£4,709	10.858	0.014	4
5	ICA + vFFR	11.098	£4,726	10.862	0.018	2

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 57 Deterministic cost-effectiveness results for scenario 16 – Proportion of revascularisations assumed to be PCI in 75% of cases and CABG in 25%

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.054	£5,218	10.793	-	5
2	ICA + FFR	11.090	£5,274	10.826	0.033	1
3	ICA + QFR	11.081	£5,259	10.818	0.025	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.087	£5,495	10.812	0.019	3
5	ICA + vFFR	11.090	£5,699	10.805	0.012	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 17-19: Health-related quality of life

In the base case scenario, improvement in symptom relief is the only benefit of revascularisation compared to OMT, which is assumed to be maintained over a lifetime duration. The HRQoL benefits in the FAME I and II trials observed at one year for the TP (revascularised with an FFR ≤0.8) and FN (OMT with an FFR ≤0.8) health states are applied in the model over a lifetime duration. Two separate scenarios are used to consider the impact on cost-effectiveness of both the duration and magnitude of HRQoL benefits of revascularisation: scenario 17 considers the impact on cost-effectiveness of the duration of HRQoL benefits by assuming that benefits are only maintained for a limited duration of 5 years and then return to baseline, while scenario 18 considers the impact of assuming no HRQoL benefits associated with revascularisation, over and above OMT, based on the findings of the ORBITA trial. Table 58and Table 59 present the cost-effectiveness results for scenarios 17 and 18, respectively.

Scenario 17 results in a significant reduction in total QALYs for each strategy compared to the base case scenario (0.158 QALYs for strategy 1, 0.183 QALYs for strategy 2, 0.172 QALYs for strategy 3, 0.178 QALYs for strategy 4 and 0.185 QALYs for strategy 5), while the total costs remain unchanged. The corresponding impact on NHB is a change in ranking, with strategy 3 now ranked marginally more cost-effective than strategy 2, while strategy 5 is ranked the least cost-effective strategy. In fact, the shorter the duration of HRQoL benefits, the more cost-effective strategy 3 appears relative to strategy 2. This is because the benefits of revascularisation need to be maintained for longer in order to offset the procedural disutility associated with FFR. The point of indifference in duration of HRQoL benefits between strategies 2 and 3, with everything else held the same as the base case scenario, is 7 years, i.e., strategy 2 only appears the most cost-effective strategy if the HRQoL benefits associated with revascularisation are maintained for at least 7 years in order to offset the procedural disutility associated with FFR.

Scenario 18 results in a significant reduction in total QALYs across all strategies compared to the base case scenario (0.218 QALYs for strategy 1, 0.256 QALYs for strategy 2, 0.240 QALYs for strategy 3, 0.249 QALYs for strategy 4 and 0.259 QALYs for strategy 5), while the total costs remain unchanged. The smallest reduction in QALYs is for strategies 1 and 3 because these strategies have the lowest proportion of TP test results compared with the other strategies. The corresponding impact on NHB is a change in ranking, with strategy 1 now ranked the most cost-effective strategy, followed by strategy 3, while strategy 5 is ranked the least cost-effective strategy. ICA alone appears the most cost-effective option because there are no benefits associated with revascularisation compared to OMT and, therefore, limited benefits associated with diagnostic testing to correctly identify patients suitable for revascularisation.

Table 58 Deterministic cost-effectiveness results for scenario 17 –HRQoL benefits associated with revascularisation and OMT maintained for 5 years only

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	10.903	£4,697	10.668	-	3
2	ICA + FFR	10.913	£4,825	10.672	0.004	2
3	ICA + QFR	10.915	£4,812	10.674	0.006	1
4	ICA + QFR + confirmatory FFR (grey zone)	10.915	£5,019	10.664	-0.004	4
5	ICA + vFFR	10.913	£5,118	10.657	-0.011	5

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 59 Deterministic cost-effectiveness results for scenario 18 – No HRQoL benefits associated with revascularisation

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	10.843	£4,697	10.608	-	1
2	ICA + FFR	10.840	£4,825	10.598	-0.010	3
3	ICA + QFR	10.847	£4,812	10.606	-0.002	2
4	ICA + QFR + confirmatory FFR (grey zone)	10.844	£5,019	10.593	-0.015	4
5	ICA + vFFR	10.839	£5,118	10.583	-0.025	5

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

An additional scenario 19 is used to assess the impact on cost-effectiveness of assuming a higher procedural disutility associated with FFR compared to the base case scenario. In the absence of identifying an estimate of EQ-5D disutility associated with FFR, the base case scenario assumes that the procedural disutility for FFR is equivalent to the disutility associated with PCI (a decrement of 0.0056 QALYs). In scenario 19, the impact on cost-effectiveness is assessed by considering a higher procedural disutility associated with FFR, which is equivalent to that of CABG surgery (a decrement of 0.0330 QALYs). Table 60 present the cost-effectiveness results for scenario 19.

Scenario 19 results in a change in the NHB of strategies 2 and 4 with FFR. The total QALYs for both strategies are reduced with the largest reduction as expected in strategy 2 (0.027 QALYs per patient for strategy 2 and 0.005 QALYs per patient for strategy 4). This changes the NHB ranking such that strategy 2 is now only marginally more cost-effective than strategy 1 of ICA alone, and strategy 3 is ranked the most cost-effective option. As an additional exploratory analysis, the procedural disutility associated with FFR was varied to establish the point of indifference in NHB between strategies 2 and 3, with everything else held equal to the base case scenario. The NHB for strategies 2 and 3 are equal (and ranked the highest across all strategies) at a procedural disutility of 0.014 QALYs for FFR, which is 2.5 times greater than the disutility associated with PCI but less than half the disutility associated with CABG.

Table 60 Deterministic cost-effectiveness results for scenario 19 – Higher procedural disutility associated with FFR

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	-	5
2	ICA + FFR	11.069	£4,825	10.828	0.002	4
3	ICA + QFR	11.087	£4,812	10.847	0.021	1
4	ICA + QFR + confirmatory FFR (grey zone)	11.088	£5,019	10.837	0.011	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	2

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 20-22: Using alternative sources to inform FFR/iFR procedural complication rates

The base-case scenario assumes that procedural death associated with FFR/iFR is 0.015% based on Fearon and colleagues,[83], and the rates of other adverse events associated with FFR/iFR are taken from the IRIS-FFR study.[10] Three separate scenarios are used to explore the impact on cost-effectiveness of alternative assumptions and data sources used to inform procedural complication rates of FFR/iFR: scenario 20 sets the procedural death rate equal to zero, while scenarios 21 and 22 uses the rates informed by the RIPCORD and ORBITA trial, respectively (both these studies were identified in Section 121 as potentially relevant data sources). In scenario 21, a procedural complication rate of 0.5% is assumed for the following adverse events: ventricular arrhythmia, vessel occlusion, coronary dissection and deep vein thrombosis. The unit cost applied for vessel occlusion is the same as for CABG (£10,896) because this was the procedure used to treat this adverse event in the RIPCORD trial.[98] For deep vein thrombosis, a unit cost of £997.40 was estimated based on the activity weighted average of currency codes for deep vein thrombosis (YQ51A-E) across all HRGs codes from NHS reference costs 2017/18[139] and uprated to 2018/19 prices.[138] All other adverse events use the same unit costs as the base-case scenario. Scenario 22 only considers a 4.21% rate of coronary dissection as observed in the ORBITA trial.[94] Table 61, Table 62 and Table 63 present the cost-effectiveness results for scenarios 20, 21 and 22, respectively.

Scenario 20 results in only a very small impact on the cost-effectiveness results. The NHB of strategies 2 and 4 increase by 0.002 and 0.0004 QALYs, respectively, compared to the base-case scenario because more patients survive FFR procedure to receive revascularisation. The small increase in revascularisations leads to more QALYs and costs accrued for both strategies compared to base-case scenario. These differences have no impact on the ranking of NHB across strategies.

Both scenarios 21 and 22 lead to an increase in the costs of adverse events for strategy 2 compared to the base-case scenario (£50 and £74 per patient, respectively), while the cost increase for strategy 4 compared to the base-case is £6 and £9 more for scenarios 21 and 22, respectively. Overall, this

translates into a small decrease in the NHB of strategies 2 and 4 with no change in the ranking of NHB across strategies.

Table 61 Deterministic cost-effectiveness results for scenario 20 – No procedural death with FFR/iFR

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	-	5
2	ICA + FFR	11.098	£4,825	10.857	0.030	1
3	ICA + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.094	£5,019	10.843	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 62 Deterministic cost-effectiveness results for scenario 21 – FFR/iFR complication rates from RIPCORD

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	£4,875	10.853	0.026	1
3	ICA + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,026	10.842	0.016	4
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 63 Deterministic cost-effectiveness results for scenario 22 – FFR/iFR complication rates from ORBITA

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	£4,899	10.851	0.025	1
3	ICA + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,029	10.842	0.016	3
5	ICA + vFFR	11.098	£5,118	10.842	0.016	4

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Scenarios 23-24: Diagnostic-only setting

Section 6.5.2, details key differences between diagnostic-only and interventional settings. Scenario 23 and 24 reflect the diagnostic-only setting by considering the i) additional costs due to the need to refer patients who require FFR/iFR measurements to an interventional catheter laboratory, and ii) alternative throughput assumptions.

In Scenario 23, the unit cost of FFR/iFR corresponds to the cost of a complex catheterisation (£2002) so as to account for the additional catheterisation that would be required under this scenario (see Section xxx). In the base-case scenario the cost of FFR/iFR only includes the incremental cost of FFR/iFR compared to ICA (£437), as a single catheterisation allows performing both procedures. Scenario 24 builds on the assumptions of scenario 23 on the cost of FFR/iFR and further assumes an average annual throughput of 500 patients per diagnostic-only centre. This is the average annual throughput value at which (with everything else held equal to the base case scenario) strategies 3 and 5 became equivalent in terms of NHB as identified by a previous exploratory analysis. This throughput estimate is also close to the average annual number of ICA procedures per diagnostic-only centre (584; see Section 6.5.1.2). Cost-effectiveness results for scenario 23 and 24 are presented in Table 64 and Table 65, respectively.

Table 64 Cost-effectiveness results for scenario 23 – Cost of FFR/iFR accounts for additional catheterisation in a diagnostic-only setting

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	-	3
2	ICA + FFR	11.096	£6,590	10.767	-0.060	5
3	ICA + QFR	11.087	£4,812	10.847	0.020	1
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,376	10.825	-0.002	4
5	ICA + vFFR	11.098	£5,118	10.842	0.016	2

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

Table 65 Cost-effectiveness results for scenario 24 – Throughput of 500 patients per year for QFR and vFFR, and cost of FFR/iFR accounts for additional catheterisation in a diagnostic-only setting

Strategy	Identification	Total QALYs	Total costs	NHB*	INHB*	NHB rank
1	ICA alone	11.061	£4,697	10.826	-	3
2	ICA + FFR	11.096	£6,590	10.767	-0.060	5
3	ICA + QFR	11.087	£4,812	10.847	0.020	2
4	ICA + QFR + confirmatory FFR (grey zone)	11.093	£5,376	10.825	-0.002	4
5	ICA + vFFR	11.098	£5,018	10.847	0.021	1

*At cost-effectiveness threshold of £20,000 per QALY. Incremental NHB is relative to ICA alone.

QALYs, quality-adjusted life years; NHB, net health benefit; INHB, incremental net health benefit.

In scenario 23, the cost of testing increases considerably for strategy 2 (£1,765) and strategy 4 (£357) compared to the base-case scenario. The sharp increase in cost for these strategies reduces their NHB with strategy 1 now having the lowest NHB followed by strategy 4. Under this scenario, strategy 3 has the highest NHB across all strategies.

In scenario 24, in addition to the changes to the testing costs of strategy 2 and 4 found for scenario 23, the increase of annual patient throughput reduces the testing costs of strategy 5 (£99 less compared to base-case) while the testing costs of strategy 3 remain £431. The difference in total costs between strategy 5 and strategy 3 is reduced to £206, which is offset by the QALY gains of strategy 5 compared strategy 3 (+0.011). Under this scenario, strategy 5 has the highest NHB across all strategies, but this result needs to be interpreted cautiously given the uncertainties in the diagnostic accuracy of CAAS vFFR.

6.8 Discussion of the independent economic assessment

The decision problem addressed by the model relates to the cost-effectiveness of QAngio and CAAS vFFR imaging software used during ICA for assessing the functional significance of coronary stenosis in patients with stable angina whose angiograms show intermediate stenosis. Five diagnostic strategies were addressed: strategy 1 of ICA alone (visual interpretation of angiographic images without additional testing to assess the functional significance of intermediate stenosis), strategy 2 of ICA followed by confirmatory FFR/iFR (reference standard), strategy 3 of ICA with QFR, strategy 4 of ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive, and strategy 5 of ICA with vFFR. The decision model considered the diagnostic accuracy of the non-invasive functional tests (QAngio and CAAS vFFR) and ICA relative to the reference standard of pressure wire FFR/iFR to determine whether patients were correctly (or incorrectly) identified as having functionally significant stenosis and should progress to revascularisation (in addition to OMT) or functionally non-significant stenosis and should receive OMT without the need for revascularisation. The short-term costs and consequences associated with diagnostic testing and revascularisation were considered. These short-term consequences were then linked to longer-term costs and consequences associated with the diagnostic outcomes and treatment by modelling the risk of major adverse cardiovascular events (myocardial infarction, sudden cardiac death and need for urgent/unplanned revascularisation) over a lifetime horizon.

The cost-effectiveness of the diagnostic strategies was assessed by ranking the strategies in terms of NHB from highest to lowest. The strategy with the highest NHB represents the cost-effective strategy, while the ranking is used to interpret the next best choice (second highest NHB) and so on. A cost-effectiveness threshold of £20,000 per additional QALY was used to determine cost-effectiveness. The strategy with the highest NHB was strategy 2 with FFR, while the strategy ranked with the lowest NHB was strategy 1 with ICA alone. The strategy with the second highest NHB was strategy 3 with QFR, while the next best strategies were either strategy 4 with QFR and confirmatory FFR or strategy 5 with vFFR. Strategy 2 was also the strategy with the highest probability of being cost-effective (27.8%) and strategy 1 had the lowest probability (10.0%), while strategies 3 to 5 had similar probabilities of cost-effectiveness (21.8% for strategy 3, 19.9% for strategy 4 and 20.4% for strategy 5).

The difference in NHB between strategies 2 (cost-effective) and 3 (next best strategy) was 0.007 QALYs, which is equivalent to £140 per patient diagnosed at a cost-effectiveness threshold of £20,000 per QALY gained. The diagnostic test costs for QFR and FFR were similar (£437 per test for FFR vs. £431 per test for QFR). The difference between the two strategies was largely driven by the trade-off in HRQoL between the procedural disutility associated with FFR/iFR and the HRQoL benefits associated with revascularisation. The procedural QALY loss associated with FFR/iFR was

not sufficient to offset the higher QALY gains associated with revascularisation for FFR due to more TP test results for strategy 2 compared to strategy 3.

The difference in NHB between strategies 3 and 4 was 0.005 QALYs, which is equivalent to £100 per patient diagnosed at a cost-effectiveness threshold of £20,000 per QALY gained. This difference was largely driven by the additional costs of testing for strategy 4 (£519 per patient tested with QFR followed by confirmatory FFR when QFR is conclusive) compared to strategy 3 (£431 per test for QFR without additional testing). The higher QALY gains associated with more TP test results for strategy 4 (due to the addition of confirmatory FFR in the inconclusive QFR test results) was not sufficient to offset the additional costs of testing with both QFR and FFR in strategy 4.

The difference in NHB between strategies 4 and 5 was minimal at 0.001 QALYs (or equivalently £20 per patient diagnosed at a cost-effectiveness threshold of £20,000 per QALY gained), while the difference in NHB between strategies 3 and 5 was 0.004 QALYs (or equivalently £80 per patient diagnosed). The diagnostic test costs for vFFR were smaller than QFR (£172 per test for vFFR vs. £431 per test for QFR), while the PPV was lower and the NPV higher in strategy 5 compared to strategy 3. The higher QALY gains associated with more TP test results, and the lower diagnostic testing costs, for strategy 5 compared to strategy 3 was not sufficient to offset the additional costs associated with unnecessary revascularisations due to a greater number of FP test results in strategy 5. Therefore, the benefits of improved test sensitivity of vFFR in strategy 5 are not sufficient to offset the better test specificity with QFR.

The cost-effectiveness results for strategy 5 should be interpreted with caution due to the limited availability of diagnostic accuracy studies for vFFR. The estimates of sensitivity and specificity for vFFR in strategy 5 were based on one study with 303 patients, whereas the diagnostic accuracy estimates for QFR were based on 26 studies and over 3,000 lesions, which was used to inform strategies 3 and 4.

A number of alternative scenarios were considered in which the assumptions used as part of the base case results were varied. These analyses were undertaken to assess the robustness of the base case results to variation in the sources of data used to populate the model and alternative assumptions. These alternative scenarios showed that the cost-effectiveness results for strategy 3 were robust to the mode of flow used for QFR measurement, contrast-flow QFR or fixed-flow QFR. The results were also robust to the use of an alternative diagnostic threshold of 0.75 for FFR and QFR in strategies 2 and 3, and to a wider definition of the grey zone region for confirmatory FFR in strategy 4. The use of different diagnostic accuracy estimates for vFFR based on two alternative studies highlighted the substantial uncertainty surrounding the cost-effectiveness of vFFR in strategy 5. In particular the diagnostic accuracy results reported for vFFR in a conference abstract were much more favourable

compared to the largest single study used in the base case analysis, which resulted in strategy 5 being ranked the second best cost-effective strategy after strategy 2.

In order to understand the trade-off in costs and benefits associated with strategies 2 (cost-effective) and 3 (next best strategy), a scenario was undertaken that considered both tests, FFR and QFR, to have the same diagnostic accuracy, i.e., both tests perfect with the same underlying distribution of FFR values. In this case, the total QALYs and costs for strategy 3 increased by 0.017 QALYs and £6 per patient from the base case scenario. Strategy 3 became cost-effective with the highest NHB (an increase of 0.008 QALYs per patient for strategy 3 compared to strategy 2). The increase in NHB was largely due to greater total QALYs gained for strategy 3 compared to strategy 2 with the difference mainly due to the procedural disutility associated with FFR/iFR and, to a lesser extent, the increased risk of procedural mortality for FFR/iFR.

In an additional exploratory scenario, the procedural disutility associated with FFR/iFR was also varied to establish the point of indifference in cost-effectiveness between strategies 2 and 3, with the diagnostic accuracy for QFR the same as used in the base case (and all other parameters the same as base case). The NHB for strategies 2 and 3 were equal (and ranked the highest across all strategies) at a procedural disutility of 0.014 QALYs for FFR/iFR, which is 2.5 times greater than the procedural disutility associated with PCI but less than half the disutility associated with CABG surgery.

A scenario was also undertaken to assess the impact on cost-effectiveness of the duration of HRQoL benefits associated with revascularisation. This scenario highlighted 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 cost-effective above strategy 3.

The benefits of revascularisation, in terms of improved HRQoL, suggests that the sensitivity of test results is a more important driver of cost-effectiveness than specificity because TP test results translate into higher QALY gains than mismanagement of FN test results. This was further supported by scenario analyses that included a benefit of revascularisation on the risk of MACE. Furthermore, strategy 1 only ever appeared cost-effective relative to the alternative strategies when it was assumed that there were no benefits of revascularisation, i.e., no impact on risk of MACE or HRQoL gain.

When considering a diagnostic-only setting, the large additional costs of repeating diagnostic catheterisation in a subsequent health care contact 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 (QFR alone) became the strategy with the highest net benefit, followed by strategy 5 (vFFR) alone.

6.9 Conclusions of the cost effectiveness section

The base case cost-effectiveness results showed that the test strategy with the highest net benefit (most cost-effective strategy) was ICA followed by confirmatory FFR/iFR, for a cost-effectiveness threshold of £20,000 per QALY gained. However, the difference in net benefit between this strategy and the next best strategies for the assessment of functional significance of coronary obstructions was relatively small at 0.007 QALYs (£140) for ICA with QFR, 0.012 QALYs (£240) for ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive, and 0.011 QALYs (£220) for ICA with vFFR. The cost-effectiveness results for the latter strategy of ICA with vFFR must be interpreted with caution due to very limited data available from diagnostic accuracy studies of vFFR. In addition, there was no diagnostic information available to inform a strategy of ICA with vFFR, followed by confirmatory FFR/iFR when vFFR is inconclusive.

The key drivers of cost-effectiveness were: (i) the sensitivity of the tests (rather than specificity) because TP test results translated into higher QALY gains than mismanagement of FN test results; (ii) the procedural QALY loss associated with FFR/iFR; (iii) the magnitude and duration of the QALY gains associated with revascularisation; and (iv) the additional costs associated with confirmatory testing with FFR/iFR.

7 Discussion

7.1 Statement of principal findings

7.1.1 Diagnostic accuracy

The diagnostic accuracy of QFR has been widely studied, with 39 studies in this review, including 5940 patients (over 7043 vessels or lesions). QFR, as measured using QAngio, is highly correlated with FFR measured with an invasive pressure wire. The average difference between FFR and QFR measurements is almost zero, and they rarely differ by more than 0.1, with about 50% of measurements differing by less than 0.04.

QAngio at a cut-off of 0.8 has good diagnostic accuracy to predict FFR (also at a cut-off of 0.8); cQFR mode had a sensitivity of 85% (95% CI 78 to 90) and specificity of 91% (95% CI 85 to 95); fQFR mode had a sensitivity of 82% (95% CI 68 to 91) and specificity of 89% (95% CI 77 to 95). . Although there is some discordance between QFR and FFR, most false positive or false negatives arise near the boundary (e.g. where one is 0.81 and the other 0.79), and the discordance may not be clinically meaningful. Data on how this accuracy may vary by key patient characteristics was very limited, and no conclusive variation could be found.

The use of a 'grey-zone' strategy, where patients with a QFR between 0.78 and 0.84 receive confirmatory FFR, improves diagnostic accuracy compared to using QFR alone to a sensitivity of 93.1% and specificity of 92.1%. However, this improvement is dependent on assuming the exact FFR cut-off of 0.8 is clinically meaningful. Most FFR and QFR values differ by 0.05 or less; therefore, the grey-zone approach is mainly identifying discordant FFR and QFR results very close to the 0.8 boundary; 30.4% of patients with QFR results in the grey zone have results that are discordant with their FFR.

Data on the diagnostic accuracy of CAAS vFFR was limited to only three studies. Due to variable reporting of results and apparent substantial heterogeneity in results across studies a full meta-analysis was not feasible.

Although assessing the diagnostic accuracy of using standard ICA alone was not the focus of this report, studies that reported data on ICA, and targeted searches for additional data, found that ICA alone had poor diagnostic accuracy when compared to FFR. All studies that compared QFR to ICA found QFR to be superior in diagnostic accuracy.

7.1.2 Clinical value and implementation

This review found limited evidence on the clinical impact of using QFR. The use of a grey zone could significantly reduce the proportion of adenosine and pressure-wire free procedures compared to

universal use of FFR, without significantly affecting diagnostic accuracy. Evidence on the applicability of QAngio suggests that the technology is applicable in a clinical context.

Given the limitations in the evidence, a simulation study was performed to investigate the impact of using QFR, with or without a grey zone, on future coronary events. The simulation found that using QFR slightly increased the revascularisation rate when compared to using FFR for all, from 40.2% to 42%. Using a grey zone strategy increased it further to 43.2%. However, all three strategies had similar numbers of resulting coronary events, suggesting all have a broadly similar benefit when making decisions as to who should receive revascularisation.

Although CAAS vFFR appears promising, its clinical value is currently uncertain due to limited evidence and lack of on-site prospective studies.

7.1.3 Cost-effectiveness

The base case cost-effectiveness results showed that the test strategy with the highest net benefit (most cost-effective strategy) was ICA followed by confirmatory FFR/iFR (strategy 2), at a cost-effectiveness threshold 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 (or equivalently £140) per patient diagnosed for ICA with QFR (strategy 3), 0.012 QALYs (or equivalently £240) per patient diagnosed for ICA with QFR, followed by confirmatory FFR/iFR when QFR is inconclusive (strategy 4), and 0.011 QALYs (or equivalently £220) per patient diagnosed for ICA with vFFR (strategy 5).

A number of alternative scenarios were considered in which the assumptions used as part of the base case results were varied. These alternative scenarios showed that the cost-effectiveness results were robust to the mode of QFR measurement (contrast-flow QFR or fixed-flow QFR), the use of an alternative diagnostic threshold of 0.75 for FFR and QFR, the use of a wider definition of the grey zone region for confirmatory FFR/iFR when QFR is inconclusive, throughput assumptions for QFR and vFFR, alternative estimates of procedural complication rates for FFR/iFR, and dependency of MACE risk on FFR. The scenarios were also used to identify the main drivers of cost-effectiveness. The key drivers identified were: (i) the sensitivity of test results (rather than specificity) because true positive test results translated into higher QALY gains than mismanagement of false negative test results; (ii) the procedural QALY loss associated with FFR/iFR; (iii) the magnitude and duration of the QALY gains associated with revascularisation; and (iv) the additional costs associated with confirmatory testing with FFR/iFR in strategy 4. Strategy 1 of ICA alone, without additional testing, only ever appeared cost-effective relative to the other strategies when it was assumed that there were no benefits of revascularisation.

7.2 Strengths and limitations of the assessment

7.2.1 Strengths

This review includes a comprehensive systematic review of all the published literature on QFR as assessed by QAngio and CAASS vFFR technologies, and has been conducted following recognised guidelines to ensure high quality.

The review identified a substantial literature on the diagnostic accuracy of QAngio (37 studies and over 5,000 patients), and despite evidence of heterogeneity and variable quality in the evidence, future research is unlikely to significantly change the overall diagnostic accuracy review findings. Study authors were contacted to provide additional data, and the review includes additional data from published studies and data from as yet unpublished studies.

This review has made best use of all available data, including extracting data from published figures, to maximise the range of analyses, including analysing the diagnostic impact of using a "grey zone" with QFR, and performing a simulation study to assess the criminal impact of QFR on future coronary events. This goes beyond any previous review or meta-analysis in the field.

This is the first study to assess the cost-effectiveness of QAngio and CAAS vFFR. The decision model comprehensively assessed both the short-term costs and consequences associated with diagnostic testing and also the longer-term impact of treatment on both costs and consequences to ensure that lifetime differences (e.g., the risk of major adverse cardiovascular events and health-related quality of life benefits associated with revascularisations) were appropriately quantified.

7.2.2 Limitations

Evidence on the CAAS vFFR technology was limited to four studies, which varied in their reporting, and appeared to have heterogeneous results. This prevented any full meta-analyses of diagnostic accuracy for CAAS vFFR, or any assessment of its clinical effectiveness.

There was insufficient data allowing exploration of 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.

As is common in reviews of diagnostic tests, data beyond basic diagnostic accuracy, such a data on the clinical impact of QAngio, or its practical implementation, was extremely limited and could not be fully reviewed. Although a simulation study was performed to address this, it was innately limited by having to make strong assumptions about the relevant population, and the risk of events, in that population.

The cost-effectiveness results for strategy 5 with vFFR must be interpreted with caution due to very limited data available from diagnostic accuracy studies of vFFR. The use of alternative diagnostic accuracy estimates for vFFR highlighted the substantial uncertainty surrounding the cost-effectiveness of vFFR. 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.

7.3 Uncertainties

Although there is substantial evidence diagnostic accuracy of QFR assessment using QAngio, it remains largely unclear which patient or lesion characteristics might significantly affect the diagnostic accuracy of QAngio.

The clinical value of QAngio to support decision making on revascularisation remains uncertain, particularly what impact it might have on preventing or causing future coronary events, and whether the 0.8 cut-off, or the proposed grey zone, is clinically appropriate. However, it appears unlikely that its clinical value or use will differ substantially from widespread use of FFR.

Prospective evidence for the clinical benefit of QFR-guided PCI is lacking. Results from the large RCTs FAVOR III Europe-Japan (non-inferiority trial comparing QFR with standard FFR guided PCI) and FAVOR III China (superiority trial comparing QFR with angiography-alone guided PCI), with a target recruitment of 2000 and 3860 and due to be completed in March 2022 and February 2023 respectively, will be informative.[143, 144]

Current evidence on CAAS vFFR is very limited, so its diagnostic accuracy,clinical value and cost-effectiveness are highly uncertain.

8 Conclusions

8.1 Implications for health care

8.1.1 Clinical implications

The results of this review suggest that making revascularisation decisions using QFR as measured with QAngio is preferable to making decisions based on diameter stenosis assessment using standard invasive coronary angiography alone.

The high correlation between QFR and FFR, and the high diagnostic accuracy of QFR, suggest that QFR assessment could potentially replace FFR entirely, and hence remove the need for invasive pressure wire and adenosine use. Simulations suggest that replacing FFR with QFR entirely might slightly increase the number of patients who are revascularised, but would have minimal or no impact on the incidence of coronary events.

The use of a "grey zone" where patients with borderline QFR values would proceed to an FFR assessment, would require around 20% of patients to have an FFR. However, for around 70% of these patients the FFR assessment would agree with the existing QFR assessment. The use of a grey zone might increase the number of patients being revascularised, but would appear to have almost the same future incidence of coronary events as if FFR had been used in all patients.

The current evidence on CAAS vFFR appears to be too limited for it to be used in clinical practice at this time.

8.1.2 Economic implications

The economic evidence suggests small differences in net benefit at a cost-effectiveness threshold of £20,000 per QALY between ICA followed by confirmatory FFR/iFR (strategy 2), and ICA with QFR (strategy 3) in an interventional setting. In a diagnostic-only setting, ICA with QFR may yield a higher net benefit at a cost-effectiveness threshold of £20,000 per QALY than ICA followed by confirmatory FFR/iFR, provided that the diagnostic accuracy of QAngio is comparable across settings. The use of QAngio in line with strategy 3 is potentially a good use of NHS resources, particularly in a diagnostic-only setting.

8.2 Suggested research priorities

The substantial existing evidence for diagnostic accuracy of QAngio suggests that further studies of diagnostic accuracy are not required. However, further prospective investigation of the diagnostic accuracy of QAngio in patients with different lesions subtypes, including bifurcation lesion and left main location stenoses, or with three-vessel disease, may be needed to confirm trends reflected in existing evidence.

Large, prospective studies are required to assess the diagnostic accuracy and clinical feasibility of CAAS vFFR. Ideally these should compare CAAS vFFR to ICA assessment, and if possible, to QFR.

Randomised controlled trials are required to investigate whether the use of QFR-guided PCI (with or without a “grey zone”) results in improved clinical outcomes. Such studies should follow up patients for all key coronary events, including events caused by unnecessary revascularisation and report rates of and reasons for test failure in a clinical setting and in a wide range of patients with intermediate stenosis. Results from the FAVOR III Europe-Japan and FAVOR III China will be informative.

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10 Appendices

10.1 Appendix 1: Clinical review literature search strategies

Appendix 1: Literature search strategies
Search strategy for MEDLINE
Database: Ovid MEDLINE(R) ALL <1946 to September 25, 2019>
Search Strategy:
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1 QANGIO$.ti,ab,kw. (8)
2 quantitative flow ratio$.ti,ab,kw. (36)
3 QFR.ti,ab,kw. (82)
4 "3D/QFR".ti,ab,kw. (1)
5 aQFR.ti,ab,kw. (2)
6 adenosine-flow QFR.ti,ab,kw. (2)
7 cQFR.ti,ab,kw. (6)
8 contrast-flow QFR.ti,ab,kw. (7)
9 fQFR.ti,ab,kw. (5)
10 fixed-flow QFR.ti,ab,kw. (5)
11 iQFR.ti,ab,kw. (1)
12 index QFR.ti,ab,kw. (1)
13 LQFR.ti,ab,kw. (4)
14 lesion QFR.ti,ab,kw. (1)
15 vQFR.ti,ab,kw. (1)
16 vessel QFR.ti,ab,kw. (1)
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (99)
18 vessel FFR.ti,ab,kw. (11)
19 vFFR.ti,ab,kw. (8)
20 CAAS vFFR.ti,ab,kw. (0)
21 18 or 19 or 20 (19)
22 17 or 21 (118)
23 animals/ not (humans/ and animals/) (4586208)
24 22 not 23 (107)
25 "quinol:fumarate reductase".ti,ab. (29)
26 24 not 25 (88)

10.2 Appendix 2: Included, excluded and ongoing studies

Table 66 All studies included in the systematic review of clinical effectiveness

Main studies	Linked studies
Cliff (2019)[13] Conference abstract	145
Cortés (2019)[14]	146-148
Emori (2018)A[17]	149
Emori (2018)B[18]	150-152
FAST EXTEND Daemen (2019)[15] Conference abstract	53, 153
FAVOR II China Xu (2017)[49]	57, 154-156
FAVOR II Europe-Japan Westra (2018)[47]	157
FAVOR Pilot Tu (2016)[43]	158, 159
Goto (2019)[19] Conference abstract	
Hamaya (2019)[20]	160
Hwang (2019)[21]	161, 162
ILUMIEN I Ely Pizzato (2019)[16]	163
Ishihara (2019)[22] Conference abstract	
Jin (2019)[23] Conference abstract	
Kajita (2019)[24] Conference abstract	164
Kameyama (2016)[25] Conference abstract	
Kanno (2019)A[26] Conference abstract	165-167
Kanno (2019)B[27] Conference abstract	
Kirigaya (2019)[28] Conference abstract	
Koltowski (2018)[29]	168-170
Kleczynski (2019)[30]	52
Liontou (2019)[31]	
Liu 2017[32] Conference abstract	
Mehta (2019)[33] Conference abstract	171
Mejia-Renteria (2019)[34]	54, 59, 62, 172-176
Neylon (2016)[35] Conference abstract	

Sato (2018)[36] Conference abstract	
Smit (2019)[37]	55, 177-182
Spitaleri (2018)[38]	
Stahli (2019)[39]	56, 183-185
SYNTAX II Asano (2019)[12]	186-188 189
Ties (2018)[40]	
Toi (2018)[41] Conference abstract	
Tu (2014)[42]	
Van Diemen (2019)[44]	63
van Rosendael (2017)[45]	190
Watari (2019)[46]	
WIFI II Westra (2018)[48]	191, 192
WIFI Prototype study Andersen (2017)[11] Conference abstract	193, 194
Yazaki (2017)[50]	195
Ziubryte (2019)[51] Conference abstract	

Table 67 Ongoing studies

Setting	Recruitment years	Interventions	Main indications	Responsible Party	Registration number	N
RCTs						
FAVOR III Europe-Japan Multi-centre	NR Estimated start date Nov 2018 Last updated May 2019-recruiting Est. completion March 2022	QFR-guided revascularisation vs. ICA & FFR – guided revascularisation	Coronary Artery Disease	E.H. Christiansen Aarhus University Hospital Skejby	NCT03729739	Target: 2000
FAVOR III China Multi-centre	NR Actual start date Dec 2018 Last updated Feb 2020-Active not recruiting Est. completion Feb 2023 Est. completion March 2022	QFR- Vs ICA alone	Coronary Artery Disease Myocardial Ischaemia Coronary Circulation Coronary Stenosis Percutaneous Coronary Intervention	Bo Xu, China National Center for Cardiovascular Diseases	NCT03656848	Actual 3860
China	NR Registration date: May-2017	QFR+virtual stenting vs. FFR+real stent	Major epicardial coronary artery stenosis, multivessel and long lesions	X. Qu Shanghai Chest Hospital	ChiCTR-INR-17011360	Target: 100
FAVOR IV Multi-centre China	NR Actual start date Aug 2019 Last updated Aug 2019 recruiting	QFR-guided strategy Vs. CAG-guided strategy	Primary valvular heart disease with Comorbid CAD, planned elective on-pump valve surgery due to primary mitral and/or aortic valvular heart disease	Qiang Zhao,MD, Ruijin Hospital	NCT03977129 2018CR001	Target 792
Single arm diagnostic accuracy studies						

China	NR Registration date: Jan- 2018	Index test: cQFR Reference standard: FFR	Coronary artery stenosis	Z. Zhang Department of cardiovascular medicine, Hospital of Third Military Medical University	ChiCTR1800014516	Target: 200
FORTRESS China	NR Estimated start date Feb-2018 Est. completion date: Feb 2019 Last updated Jan 2018- Not yet recruiting	Index test: QFR Reference standard: FFR	Stable and unstable angina or secondary evaluation of stenosis after acute MI	Pulse Medical Imaging Technology (Shanghai) Co., Ltd	NCT03405506 CARDIAC201701	Target: 69
DETECT-ISCHEMIA Germany	NR Estimated start date July 2017 Last updated Feb 2018- recruiting	Index test QFR Reference standard: FFR& iFR	CAD, intermediate stenosis	C. Jensen Contilia Clinical Research Institute	NCT03420131 U1111-1199-4364 DRKS00012757	Target: 250-280
Korea Multi-centre	Jan 2012- Sep 2019 Completed	Index test QFR Reference standard: FFR	Ischemic Heart Disease	C. Kiyuk, Seoul St. Mary's Hospital	NCT04102917 XC18REDI0035	Actual: 915
Dan-NICAD 2	NR Actual start date Jan 2018 Last updated Dec 2019 recruiting	Index test QFR Reference standard: FFR	Angina Pectoris Atherosclerosis Coronary Artery Disease Myocardial Ischemia	University of Aarhus	NCT03481712	Target 2000
Multi-center Korea	NR Actual start date April 2016 Last updated Jan 2020 active not recruiting	Index test QFR Reference standard: FFR	Ischemic Heart Disease	Joo Myung Lee, Samsung Medical Center	NCT03791788	Target 524

QIMERA-I Multi- centre Spain	NR Estimated start date Jan 2020 Last updated Dec 2019 not yet recruiting	Index: QFR Reference: standard dPRRFR and FFR	Coronary Occlusion	Carlos Baladron, PhD, Hospital Clínico Universitario de Valladolid	NCT04200469 CASVE-PI-19-1515	Target 100

FFR: Fractional flow reserve; RFR: resting full-cycle ratio; dPR: diastolic pressure ratio

Table 68 Excluded studies from systematic review of clinical effectiveness at full text screening stage

Not eligible population
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10.3 Appendix 3: Risk of bias and applicability assessment (QUADAS-2)

Risk of bias assessment

Signalling question (SQ)1: Was a consecutive or random sample of patients enrolled?

SQ2: Did the study avoid inappropriate exclusions? (note exclusion of tandem lesion and %)

RoB (Participant selection): Could the selection of patients have introduced bias?

SQ3: Was QFR performed during the same exam as angiography (i.e. online)?

SQ4: Was the same cut-off used for the index test and FFR?

SQ5: Was interpretation of QFR blinded to FFR? NOTE: if done prospectively, and if FFR done by separate staff/in separate room, then fine.

RoB (Index test): Could the conduct or interpretation of the index test have introduced bias?

SQ6: Is the reference standard likely to measure FFR accurately enough?

SQ7: Was interpretation of FFR blinded to QFR?

RoB (Reference standard): Could the conduct or interpretation of the reference std test have introduced bias?

SQ8: Did all patients analysed receive both the index test and FFR? (or some received iFR only)

SQ9: Were all or nearly patients included in the analysis?

SQ10: Were QFR and FFR measured during the same examination?

RoB (Flow and timing): Could the patient flow have introduced bias?

Table 69 Risk of bias assessment with justifications

	Comments	SQ1	SQ2	RoBPS	SQ3	SQ4	SQ5	RoBIT	SQ6	SQ7	RoBRS	SQ8	SQ9	SQ10	RoBFT
Cortés (2019)[14]	Very small sample of 12 patients with FFR. Retrospective offline QFR. Exclusions and reasons for exclusion not reported. Only 12 patients included. Exclusion of patients not reported. FFR blinded because performed before QFR (retrospective)	N	UC	-	N	Y	Y	+	Y	Y	+	Y	N	N	?
Emori (2018)A[17]	If lesions in multiple arteries, only 1 (most severe stenosis) was selected as target vessel. FFR blinded because performed before QFR (retrospective). 15% excluded (reasons provided).	Y	Y	+	N	Y	Y	+	Y	Y	+	Y	Y	N	+
Emori (2018)B[18]	Retrospective but consecutive with few exclusions (reasons provided). FFR blinded because performed before QFR (retrospective).	Y	Y	+	N	Y	Y	+	Y	Y	+	Y	Y	N	+
FAST Masdjedi et al. 2019[53] CAAS vFFR	Large number (118) and proportion (total included n=100) excluded Ntably due to: lack of 2 adequate orthogonal views (58), overlap or foreshortening (35), inadequate pressure waveform (25). FFR blinded because performed before QFR (retrospective).	Y	UC	-	N	Y	Y	+	Y	Y	+	Y	N	N	+
FAVOR II China Xu (2017)[49]	Consecutive, prospective. No significant concerns.	Y	Y	+	Y	Y	Y	+	Y	Y	+	Y	Y	Y	+
FAVOR II Europe-Japan Westra (2018)[47]	UC if consecutive.	UC	Y	+	Y	Y	Y	+	Y	Y	+	Y	Y	Y	+
FAVOR Pilot Tu (2016)[43]	Excluded ostial left main or ostial right: UC how many.	N	UC	+	N	Y	Y	+	Y	Y	+	Y	Y	Y	+
Hamaya (2019)[20]	Retrospective selection of subgroup of 154 vessels with FFR (out of 549 patients with 1,595 vessels). Large proportion excluded due to anatomy: 140 vessels excluded due to small (<2mm), RCA (right coronary artery) or LCx (left circumflex coronary artery) (52), arrhythmia during ICA (32), ineligible coronary anatomy (98), insufficient image quality (10). FFR blinded because performed before QFR (retrospective). Large proportion excluded due to anatomy.	N	UC	-	N	Y	Y	+	Y	Y	+	Y	N	N	+
Hwang (2019)[21]	Large number of excluded vessels (124; 25.7%), including due to calibration failure (49), ostium lesion (35), insufficient projection (25). FFR blinded because performed before	Y	N	-	N	Y	Y	+	Y	Y	+	Y	N	N	+

	Comments	SQ1	SQ2	RoBPS	SQ3	SQ4	SQ5	RoBIT	SQ6	SQ7	RoBRS	SQ8	SQ9	SQ10	RoBFT
	QFR (retrospective). 25.7% excluded (reasons provided).														
ILUMIEN I Ely Pizzato (2019)[16]	Large percentage (65%) of lesions excluded. FFR blinded because performed before QFR (retrospective).	UC	UC	-	N	Y	Y	+	Y	Y	+	Y	N	N	+
Kleczynski (2019)[30]	The analysis was conducted twice by two analyzers and the mean value (from four calculations) was used for further analysis. This may have reduced the risk of inter and intra-rater variability. Results per analyzer NR.	Y	UC	+	N	Y	Y	-	Y	Y	+	Y	UC	N	+
Koltowski (2018)[29]	Retrospective selection, large number excluded, including 299 due to lack of proper ICA projections (34.9%), bifurcation lesions (5%), tandem lesions (2.5%), ostial lesion (3%)	N	Y	-	N	Y	Y	+	Y	Y	+	Y	N	N	+
Liontou (2019)[31]	Large number (124/202 or 61.4%) of vessels excluded for study, reasons provided. UC how many ostial lesions, overlapping and tortuous vessels were excluded. FFR blinded because performed before QFR (retrospective)	UC	N	?	N	Y	Y	+	Y	Y	+	Y	N	N	+
Mejia-Renteria (2019)[34]	Retrospective, large number of exclusions (101), incl. ostial in LM or RCA (10), grafted target vessels (2), inadequate projections (28), significant overlapping (17), inadequate ICA quality (19), resting haemodynamic data N available (6) contrast filling Nt optimal for TIMI frame count analysis (15)	N	Y	+	Y	Y	Y	+	Y	Y	+	Y	N	N	+
Smit (2019)[37]	Retrospective but consecutive. 13.5% vessels excluded but reasons reported and acceptable. Unlikely blinded. Mean time between ICA and invasive FFR was 22.8± 25.1 days. The majority of patients included in our study (97%) underwent FFR measurement within 3months after the initial ICA. 13% patients excluded.	Y	Y	+	N	Y	UC	-	Y	UC	-	Y	N	N	+
Spitaleri (2018)[38] (Cohort B, diagnostic accuracy)	Vessels with diffuse disease excluded, but relatively low (n=8, for a total sample of 76, i.e. 11% of otherwise eligible patients) and no other significant concerns. FFR blinded because performed before QFR (retrospective).	Y	N	+	N	Y	Y	+	Y	Y	+	Y	N	N	+
Stahli (2019)[39]	Retrospective, but limited exclusions with acceptable reasons reported. All pressure tracings were reviewed for high signal quality, and FFR and resting Pd/Pa ratio analyzed offline by experienced investigators blinded to QFR. 8.7% excluded (reasons provided)	Y	Y	+	N	Y	Y	+	Y	Y	+	Y	Y	N	+

	Comments	SQ1	SQ2	RoBPS	SQ3	SQ4	SQ5	RoBIT	SQ6	SQ7	RoBRS	SQ8	SQ9	SQ10	RoBFT
SYNTAX II Asano (2019)[12]	Large percentage (29%) of lesions excluded due to lack of appropriate projections, but N other significant concerns. FFR blinded because performed before QFR (retrospective). FFR only performed in iFR grey zone patients (0.86-0.93).	N	UC	+	N	Y	Y	+	UC	Y	+	N	N	N	-
Ties (2018)[40]	Very large proportion of excluded vessels (69.6%), mostly due to "lack of basic requirements" (insufficient details). FFR blinded because performed before QFR (retrospective). 69.7% excluded (reasons provided).	UC	N	?	N	Y	Y	+	Y	Y	+	Y	N	N	+
Tu (2014)[42]	3 were excluded, reasons included: 1) the interrogated vessel had too much overlap or foreshortening (>90%); 2) the image quality of the hyperemic projection was Nt sufficient to evaluate by frame count; and 3) the mean pressure of the guiding catheter or blood hematocrit value was Nt documented.	Y	UC	+	N	Y	Y	+	Y	Y	+	Y	Y	N	+
van Rosendael (2017)[45]	Prospectively recruited. N Ntes on how many were excluded (and reasons for exclusion). Very small sample (n=17 patients). No reporting of blinding. No reporting on number excluded and reasons for exclusion	UC	UC	?	Y	Y	UC	-	Y	UC	-	Y	UC	Y	?
Watari (2019)[46]	Consecutive, prospective. iFR was the only reference standard.	Y	N	+	Y	Y	Y	+	UC	Y	+	N	Y	Y	+
WIFI II Westra (2018)[48]	Intention on excluding as few as possible based on impaired angiographic quality	Y	Y	+	Y	Y	Y	+	Y	Y	+	Y	Y	Y	+
Yazaki (2017)[50]	Consecutive, prospective	Y	Y	+	Y	Y	Y	+	Y	UC	-	Y	Y	Y	+

SQ: Signalling question; PS: Patient selection; IT: Index test; RS: Reference standard; FT: Flow and timing; Y: yes; N: no: ?: insufficient information to decide; + low risk of bias; - high risk of bias; UC: unclear risk of bias

Applicability assessment

Applicability concern 1: Are there concerns that the included patients do not match the review question?

Applicability concern 2: Are there concerns that the index test, its conduct, or interpretation differ from the review question? E.g. QFR cut-off not 0.8, unusual QFR mode used for main analysis?

Applicability concern 3: Are there concerns that the reference standard, its conduct, or interpretation differ from the review question?

Table 70 Applicability assessment with justifications

Study	Comments	Patient selection	Index test	Reference standard
Cortés (2019)[14]	Minority with intermediate stenosis and stable CAD. 100% STEMI with >50% DS in non-culprit arteries. Offline assessment.	-	-	+
Emori (2018)A[17]	% stable CAD unknown, only most severe arteries selected in case of multiple lesions. Offline assessment.	?	-	+
Emori (2018)B[18]	% stable CAD unknown. Offline assessment.	?	-	+
FAST Masdjedi et al. 2019[53] CAAS vFFR	Majority with intermediate stenosis and stable CAD. 60% stable CAD, 26% acute, intermediate stenosis. Large number of exclusions. Offline assessment.	-	-	+
FAVOR II China Xu (2017)[49]	Minority with intermediate stenosis and stable CAD. 34% stable CAD, 61% unstable angina. Online assessment.	-	+	+
FAVOR II Europe-Japan Westra (2018)[47]	Majority with intermediate stenosis and stable CAD. Online assessment.	+	+	+
FAVOR Pilot Tu (2016)[43]	Majority with intermediate stenosis and stable CAD. All stable angina. Offline assessment.	+	-	+
Hamaya (2019)[20]	Majority with intermediate stenosis and stable CAD. 100% stable CAD, only 10% with 3-vessel disease. Offline assessment.	+	-	+
Hwang (2019)[21]	Majority with intermediate stenosis and stable CAD. 69% stable CAD, 31% acute. However the large rate of exclusion is potentially concerning. Offline assessment.	-	-	+
ILUMIEN I Ely Pizzato (2019)[16]	Majority with intermediate stenosis and stable CAD. 63% stable angina, 22.1% unstable, 10.9 STEMI. Offline assessment.	+	-	+
Kleczynski (2019)[30]	Majority with intermediate stenosis and stable CAD. Offline assessment.	+	-	+
Koltowski (2018)[29]	Majority with intermediate stenosis and stable CAD. 100% stable CAD. Offline assessment.	+	-	+
Liontou (2019)[31]	Majority with intermediate stenosis and stable CAD. Different population: All in-stent restenosis, ≥50% DS in-stent, although 69% had stable angina (26% unstable angina, 6% acute MI). Offline assessment.	-	-	+
Mejia-Renteria (2019)[34]	Majority with intermediate stenosis and stable CAD. 70% stable angina, 30% ACS. Offline assessment.	+	-	+

Smit (2019)[37]	Majority with intermediate stenosis and stable CAD. All referred from diagnostic-only setting, so likely to be stable. All intermediate stenosis (30-90%). Offline assessment.	+	-	+
Spitaleri (2018)[38] (Cohort B, diagnostic accuracy)	Minority with intermediate stenosis and stable CAD. All STEMI with multivessel disease patients (assessment of non-culprit vessels). Offline assessment.	-	-	+
Stahli (2019)[39]	Majority with intermediate stenosis and stable CAD. 72% stable CAD, 4% acute, most/all other unstable angina. All intermediate stenosis. Offline assessment.	+	-	+
SYNTAX II Asano (2019)[12]	All 3 vessel disease (potentially harder to diagnose). Stable or unstable angina, or atypical chest pain (n/% NR). Offline assessment.	-	-	+
Ties (2018)[40]	Majority with intermediate stenosis and stable CAD. 51% stable CAD, 16.7% acute (NSTEMI). Most patients excluded. Offline assessment.	-	-	+
Tu (2014)[42]	Majority with intermediate stenosis and stable CAD. 76.5% stable angina, 8.8% silent ischemia -64% bifurcation lesions. Offline (China, Hungary) and online (Belgium) assessment.	+	-	+
van Rosendael (2017)[45]	Majority with intermediate stenosis and stable CAD. All stable CAD, though %DS is low (38.7(8.6)). Online assessment.	+	+	+
Watari (2019)[46]	Majority with intermediate stenosis and stable CAD. Online assessment.	+	+	+
WIFI II Westra (2018)[48]	Minority with intermediate stenosis and stable CAD. 31% stable angina, 34% atypical angina, 31% nonspecific angina. Online assessment.	-	+	+
Yazaki (2017)[50]	Majority with intermediate stenosis and stable CAD. 50.7% stable angina, 99.3% CAD. Offline assessment.	+	-	+

AC: Applicabilty concern; + no significant concern; - significant concern; ? insufficient information to assess

10.4 Appendix 4: Further meta-analysis results

Figure 27 Meta-analysis of positive predictive values

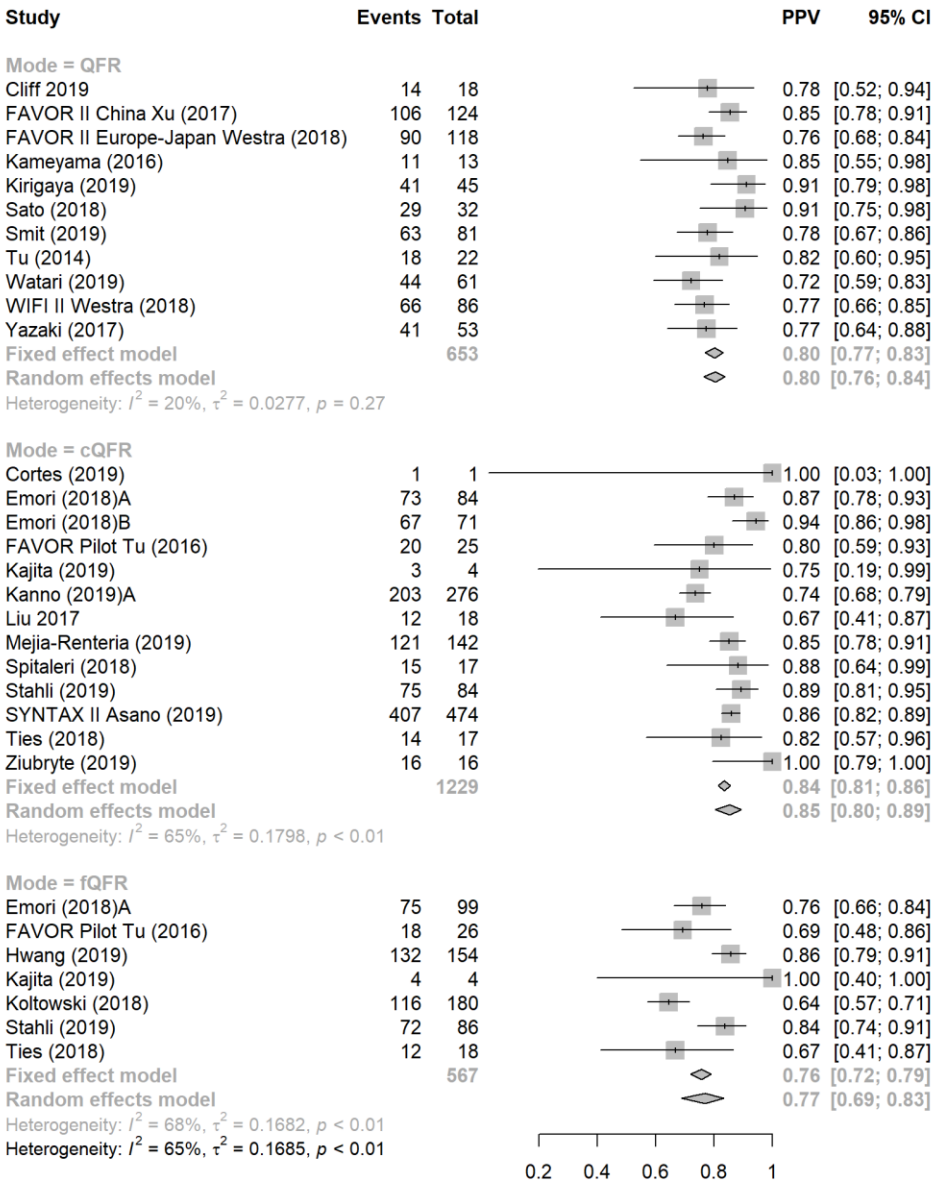


Figure 28 Meta-analysis of negative predictive values

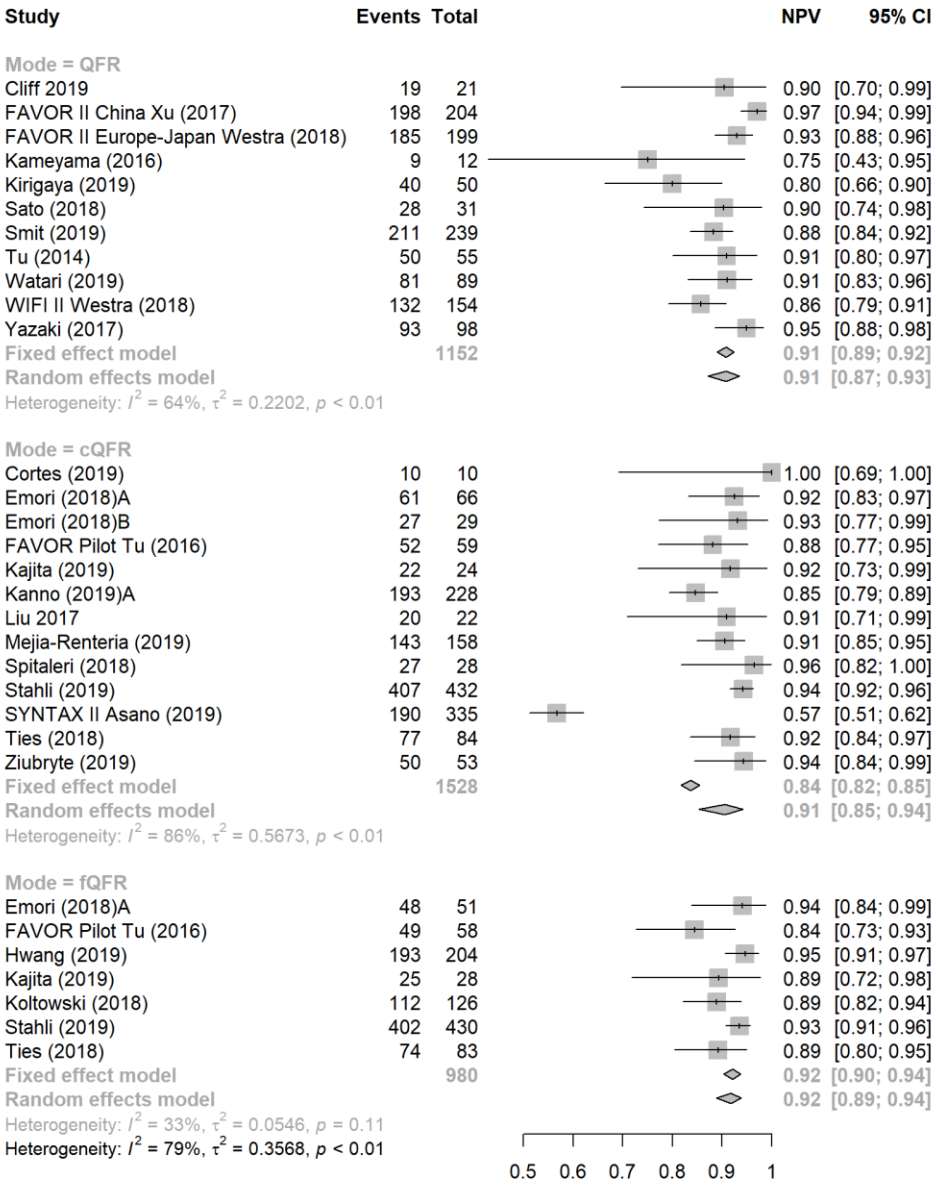


Figure 29 Meta-analysis of diagnostic odds ratios

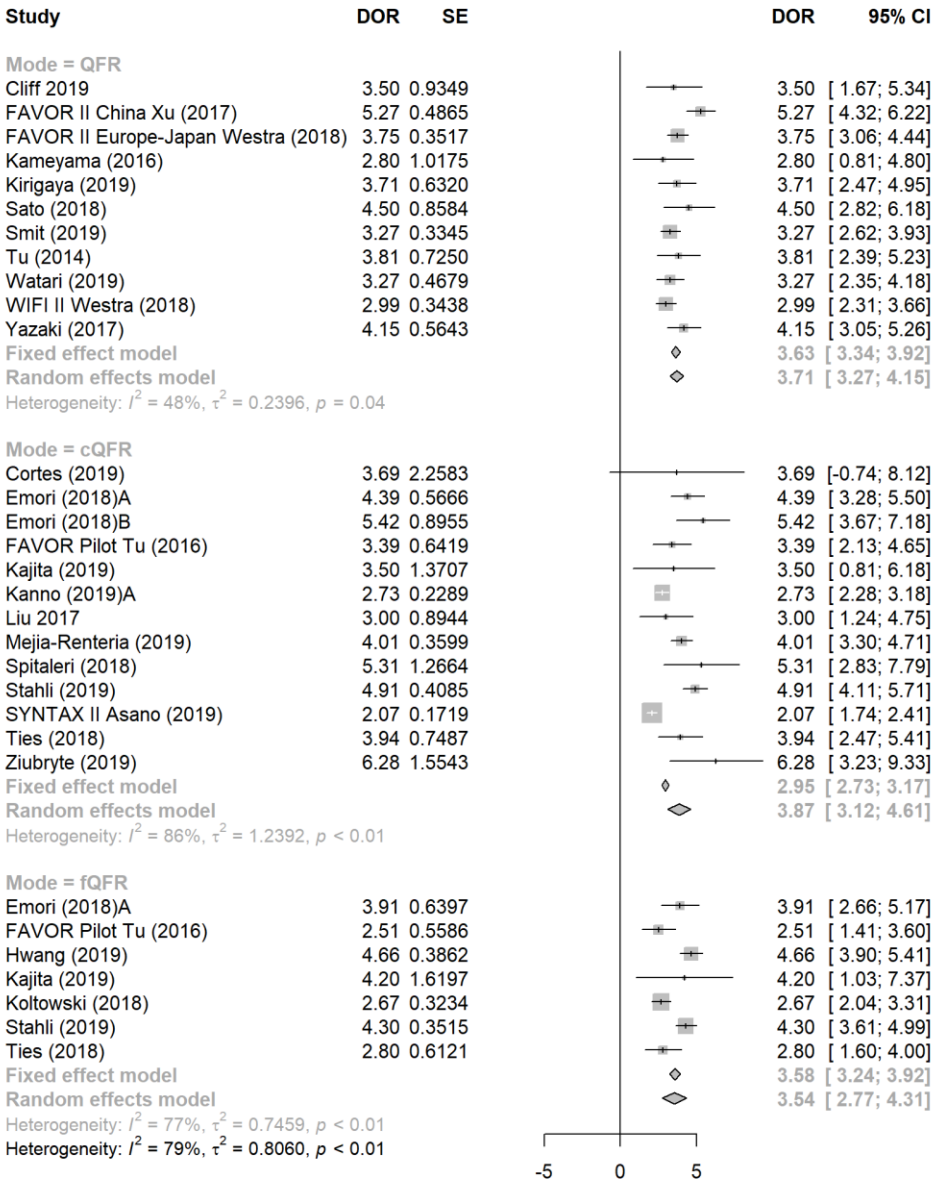


Figure 30 Meta-analysis of area under the curve (AUC)

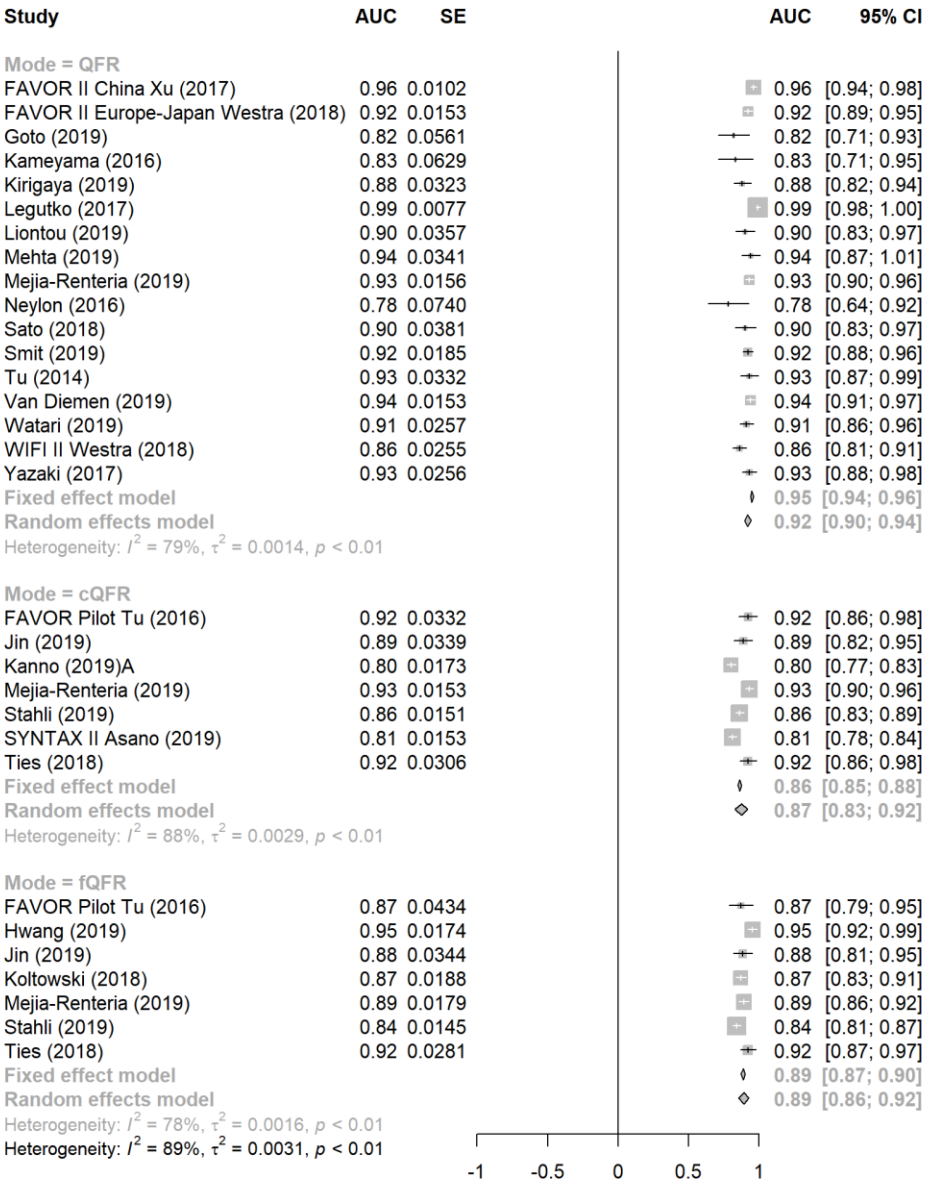


Figure 31 Meta-analysis of mean difference between FFR and QFR

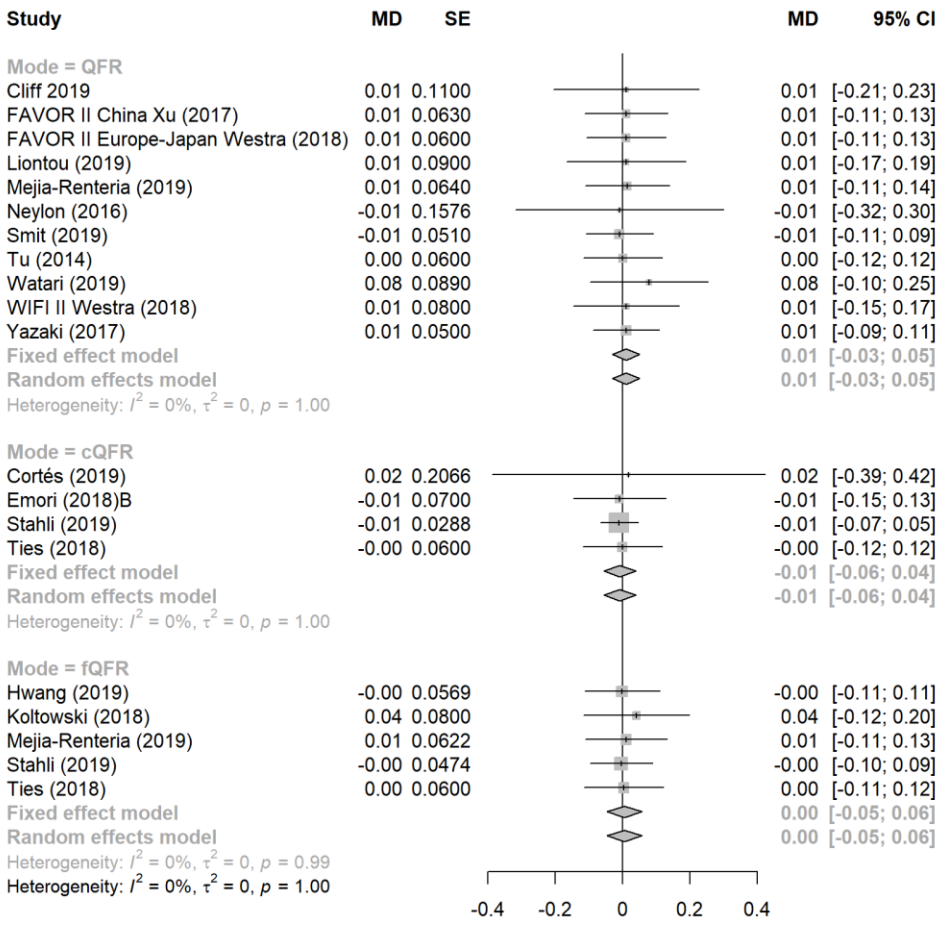


Figure 32 Meta-analysis of correlation between QFR and FFR

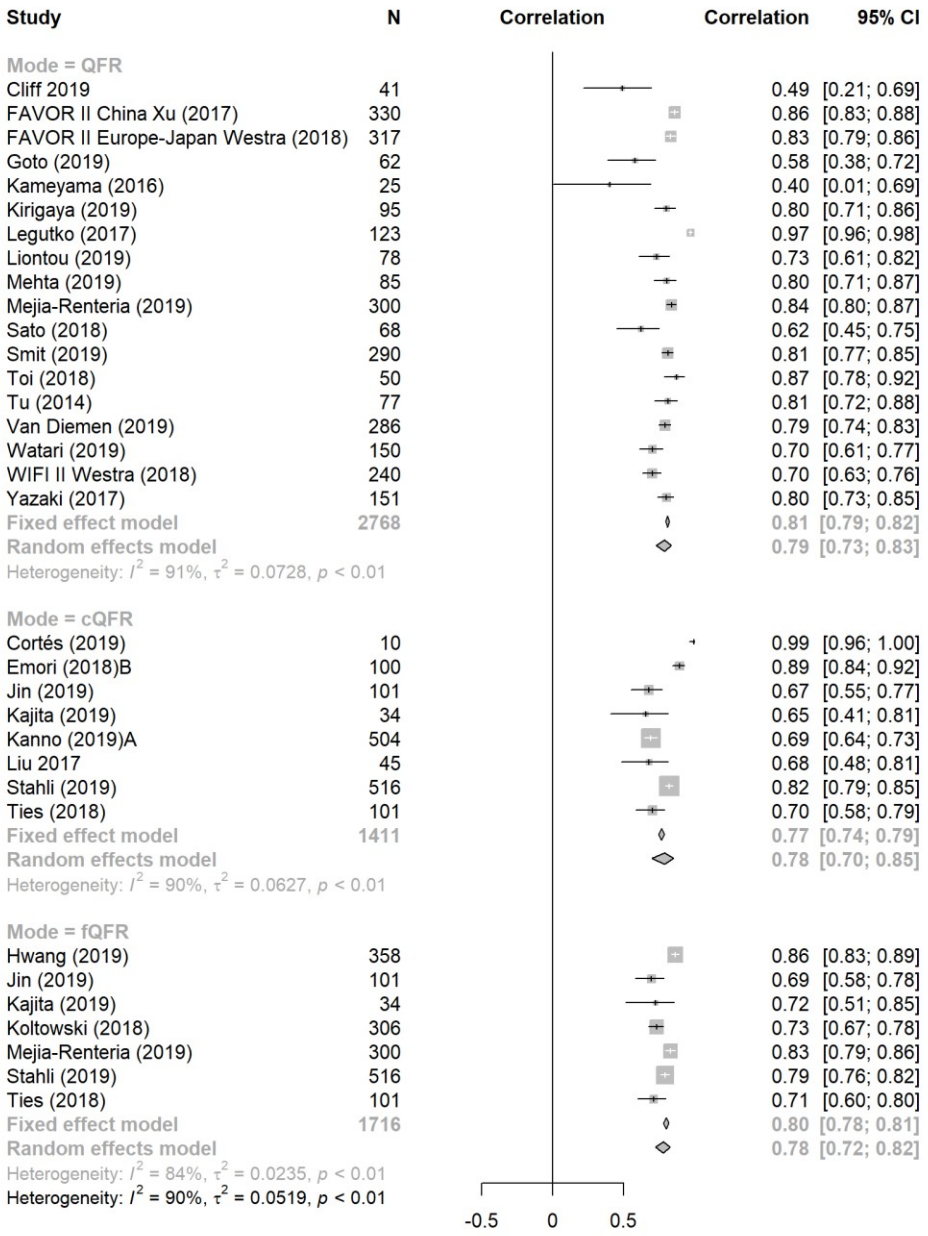


Figure 33 Bivariate meta-analysis, by study type

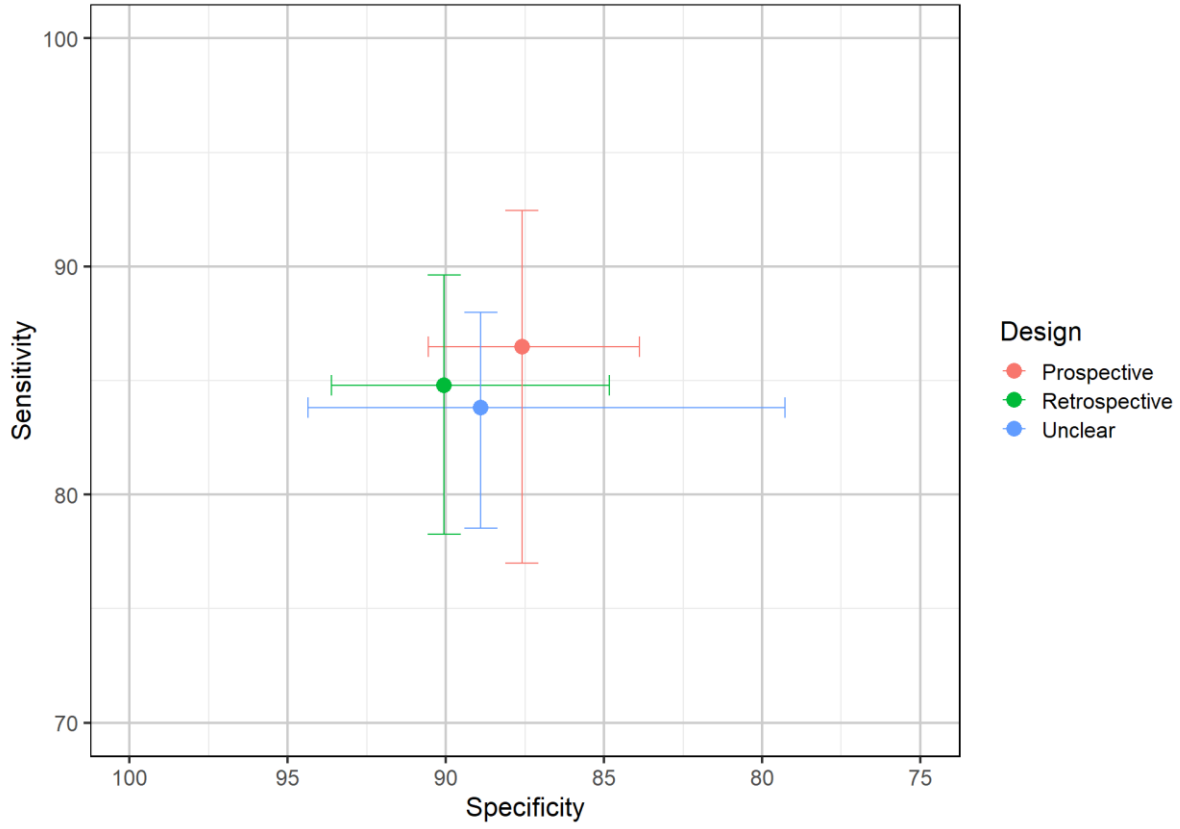


Figure 34 Bivariate meta-analysis, by unit of analysis

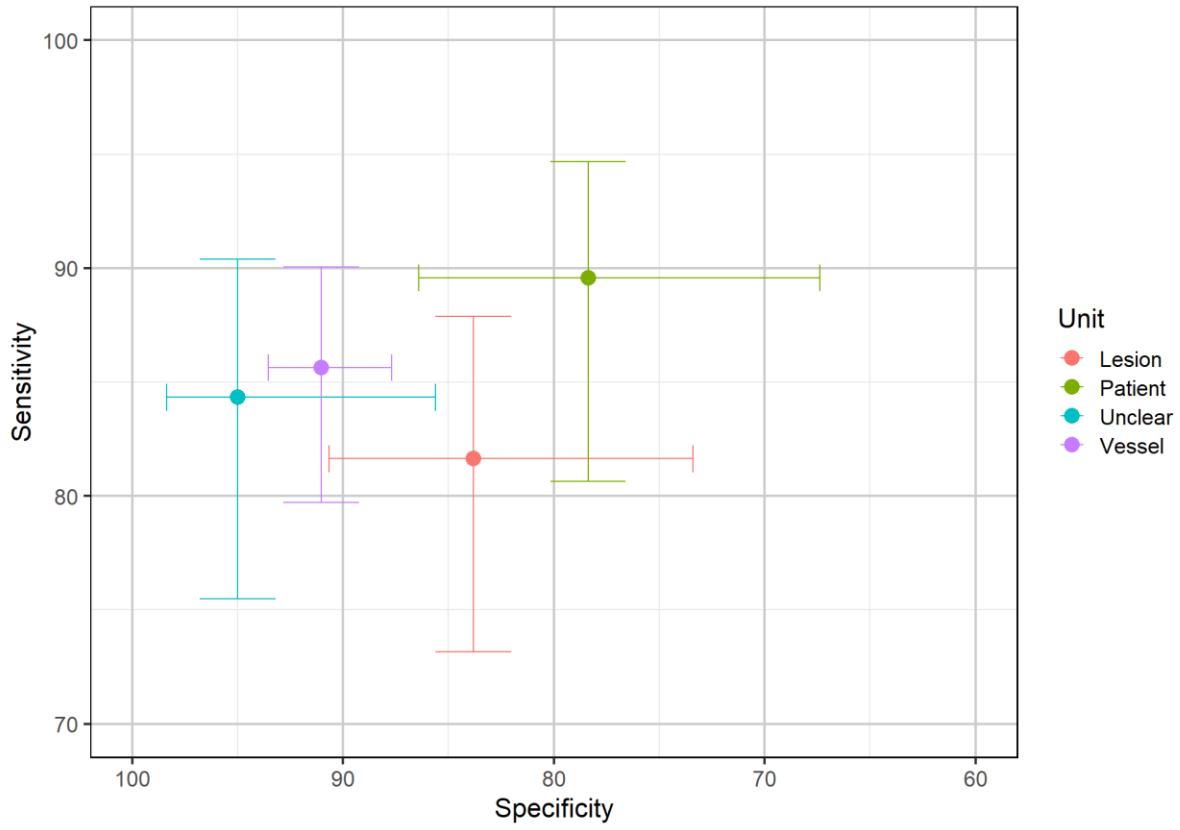


Figure 35 Meta regression of sensitivity, specificity and DOR by proportion with diabetes

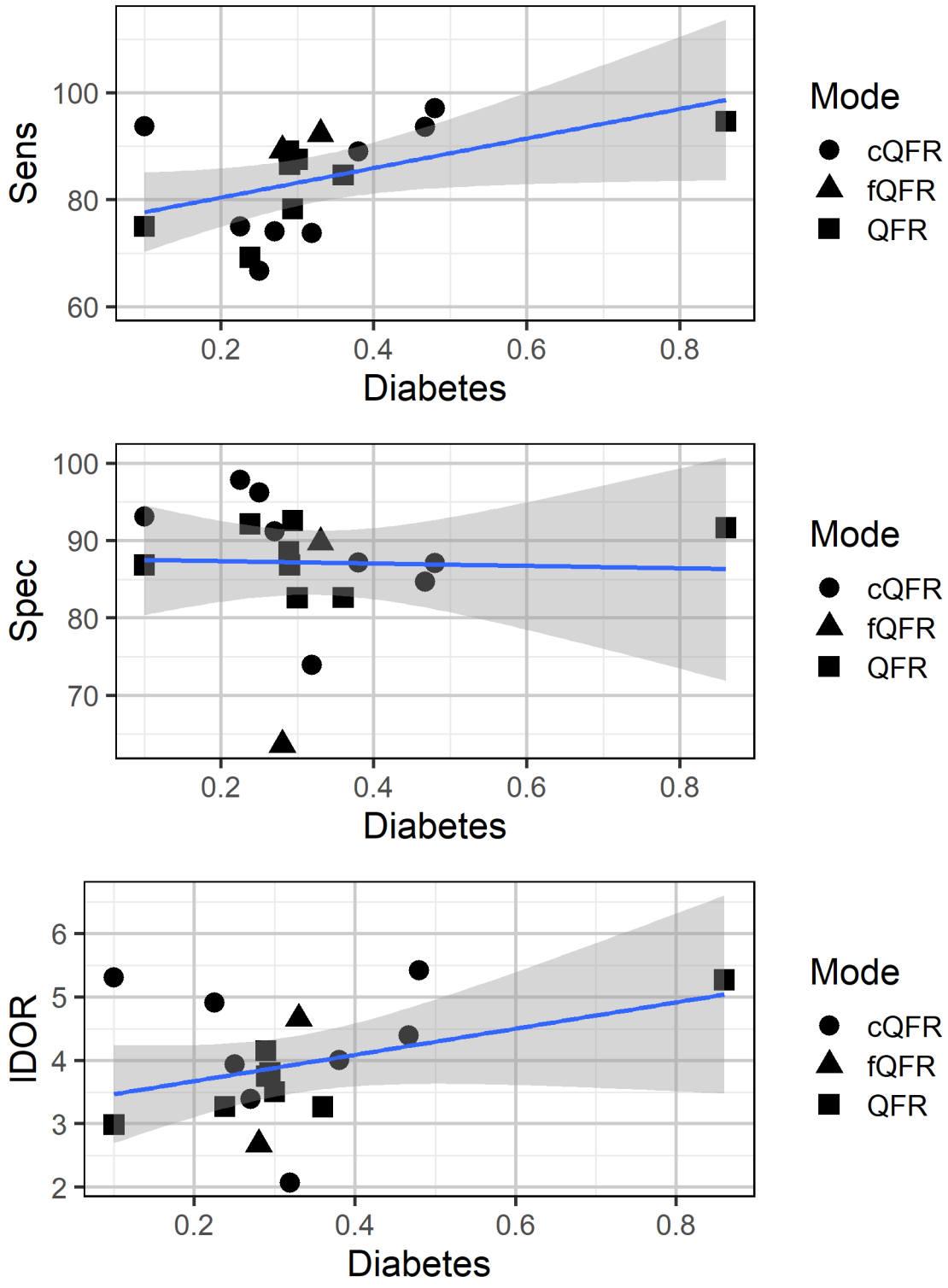


Figure 36 Meta regression of sensitivity, specificity and DOR by proportion with stable CAD

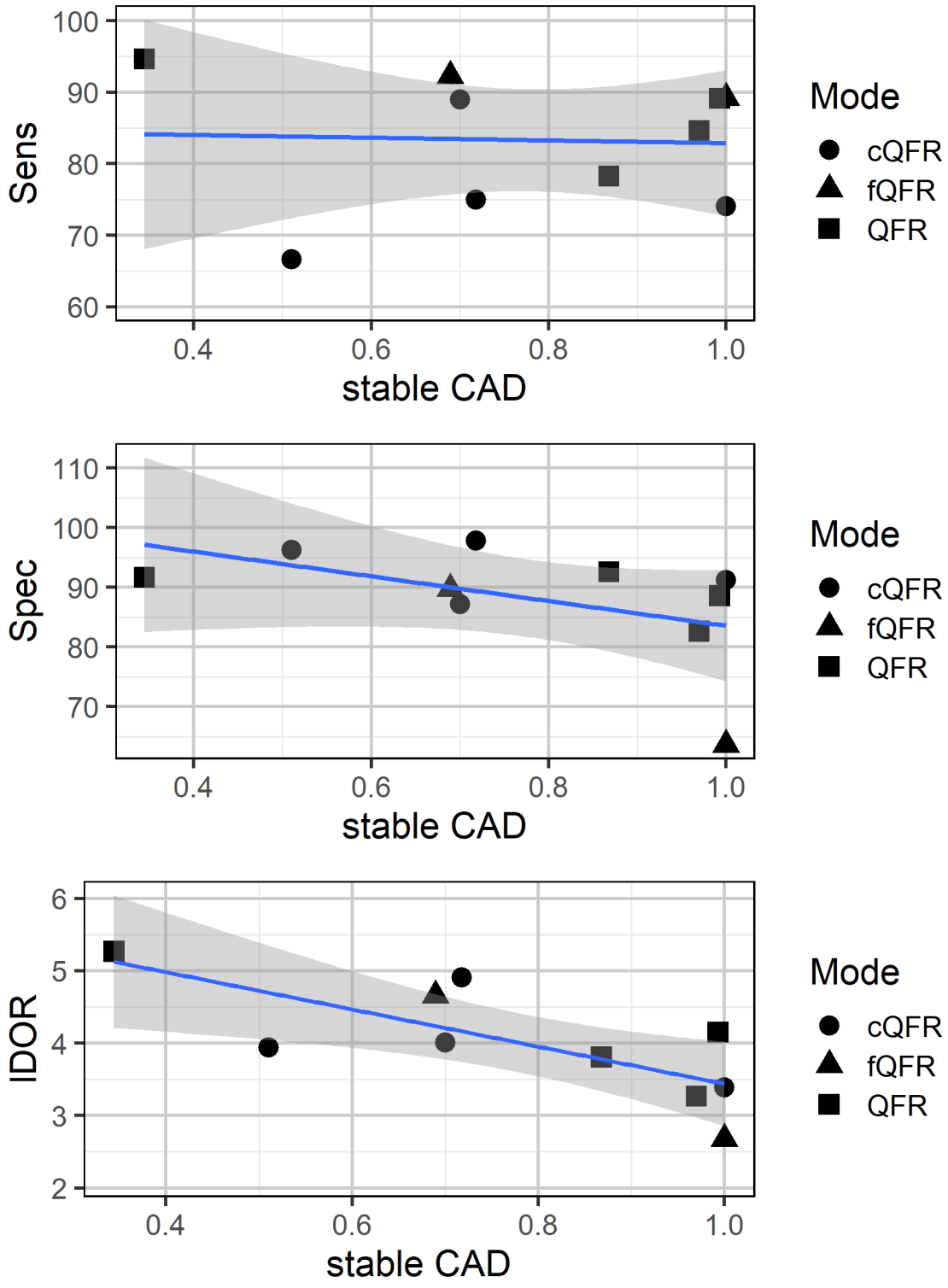


Figure 37 Meta regression of sensitivity, specificity and DOR by proportion with multivessel disease

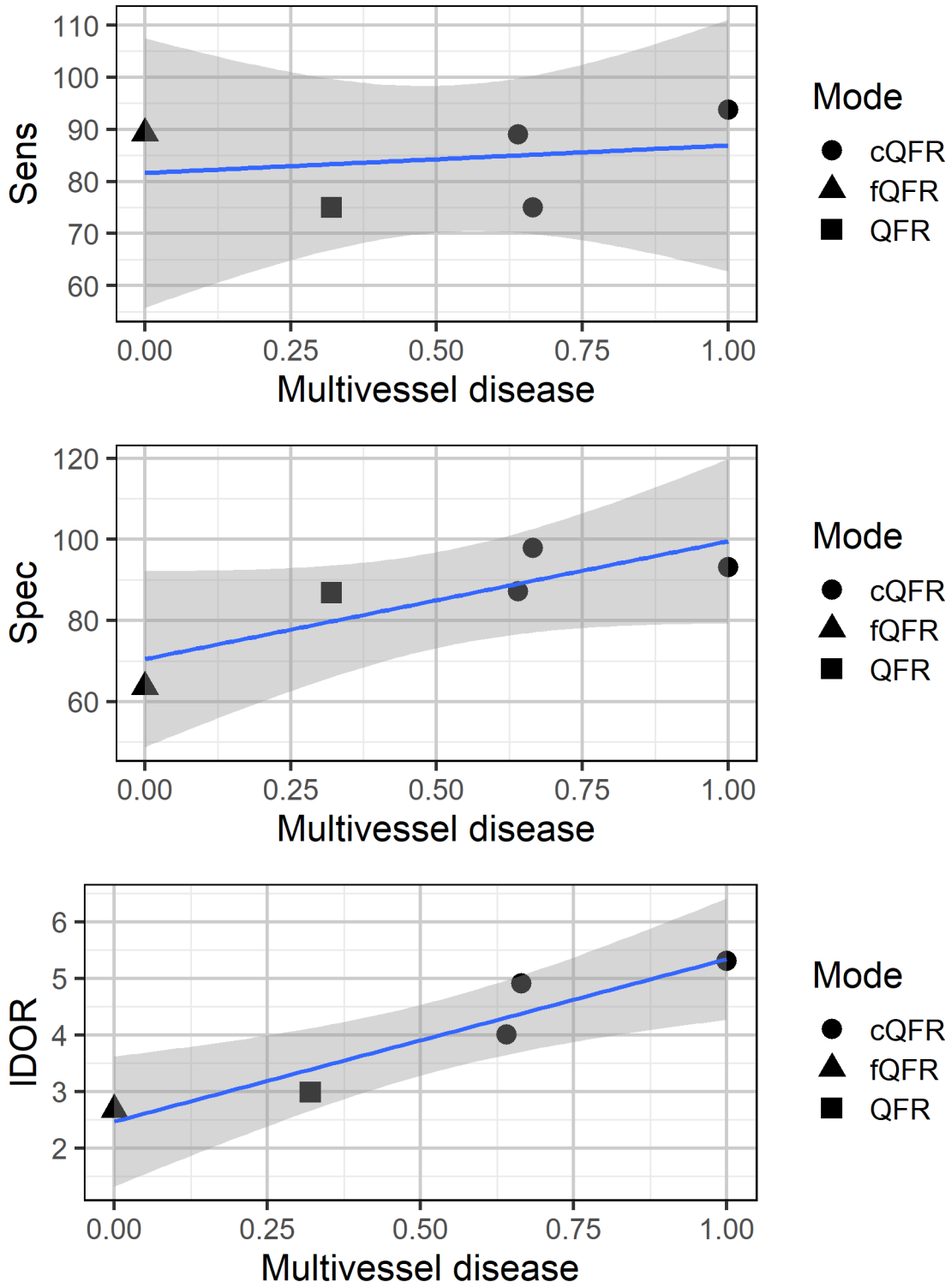


Figure 38 Meta regression of sensitivity, specificity and DOR by mean FFR

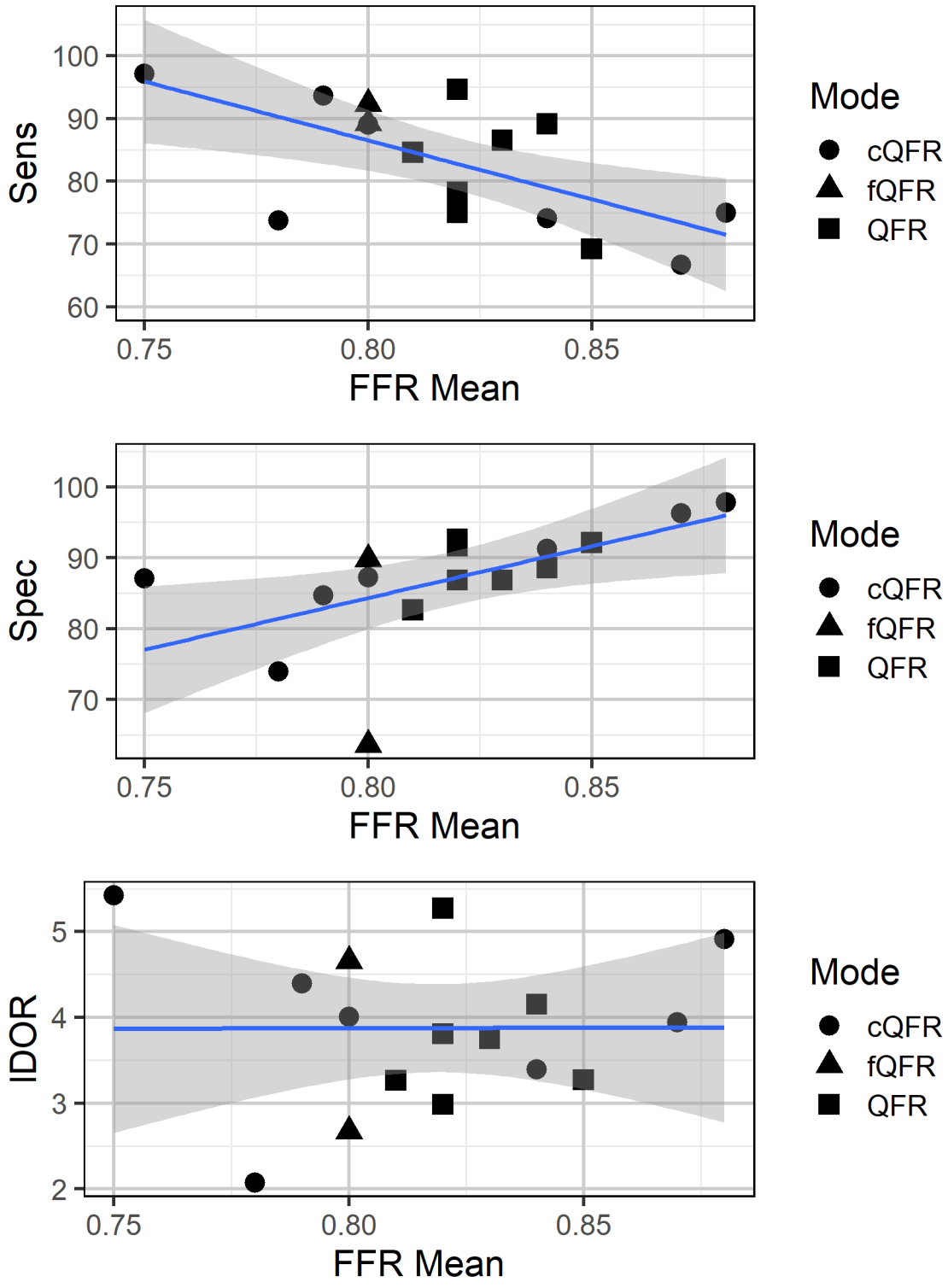


Figure 39 Sensitivity and specificity by patient subgroups

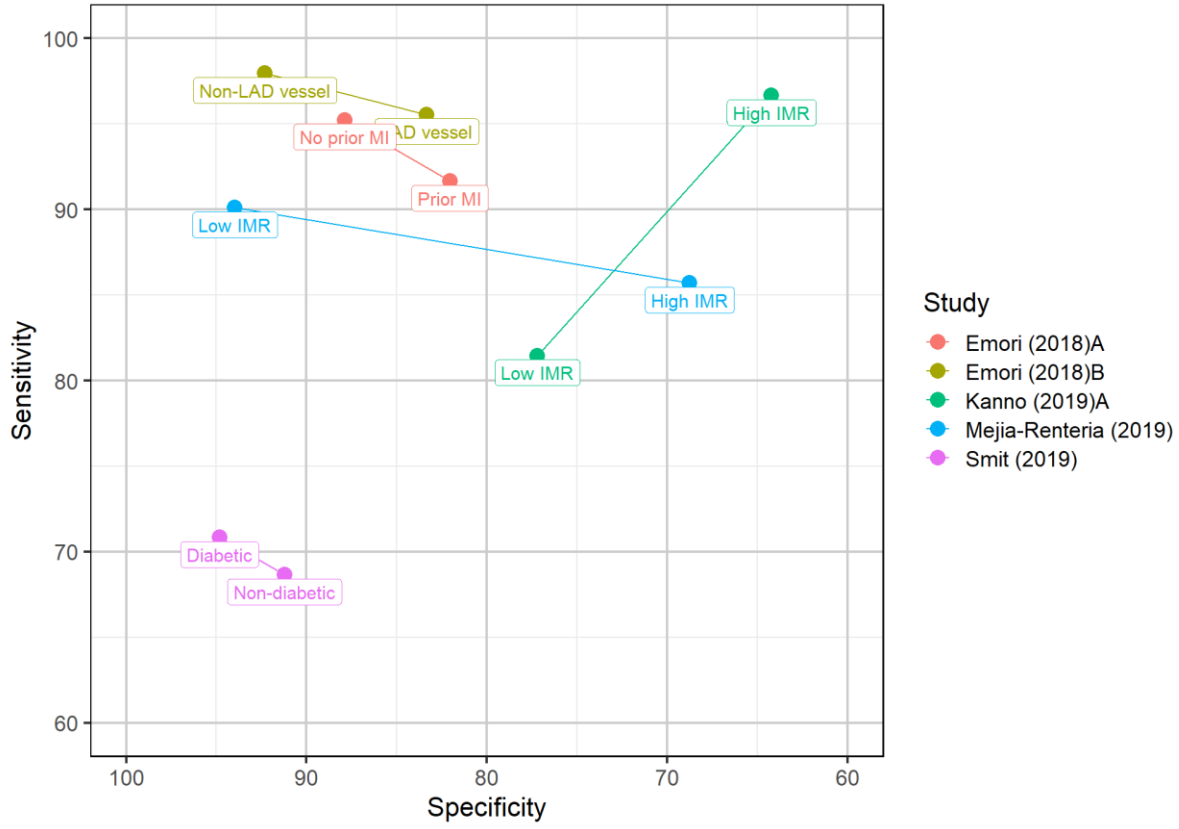


Figure 40 Diagnostic odds ratios by patient subgroups

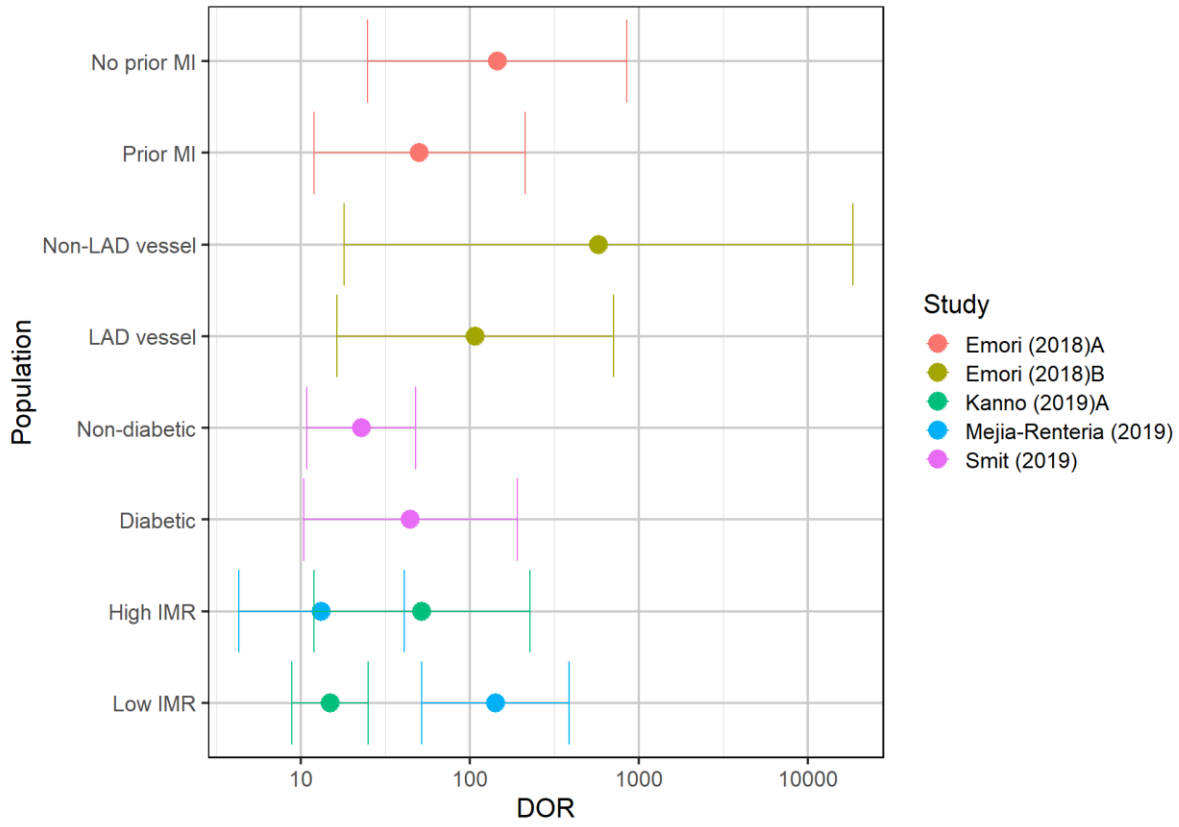


Figure 41 Bivariate meta-analyses according to QUADAS2 classification

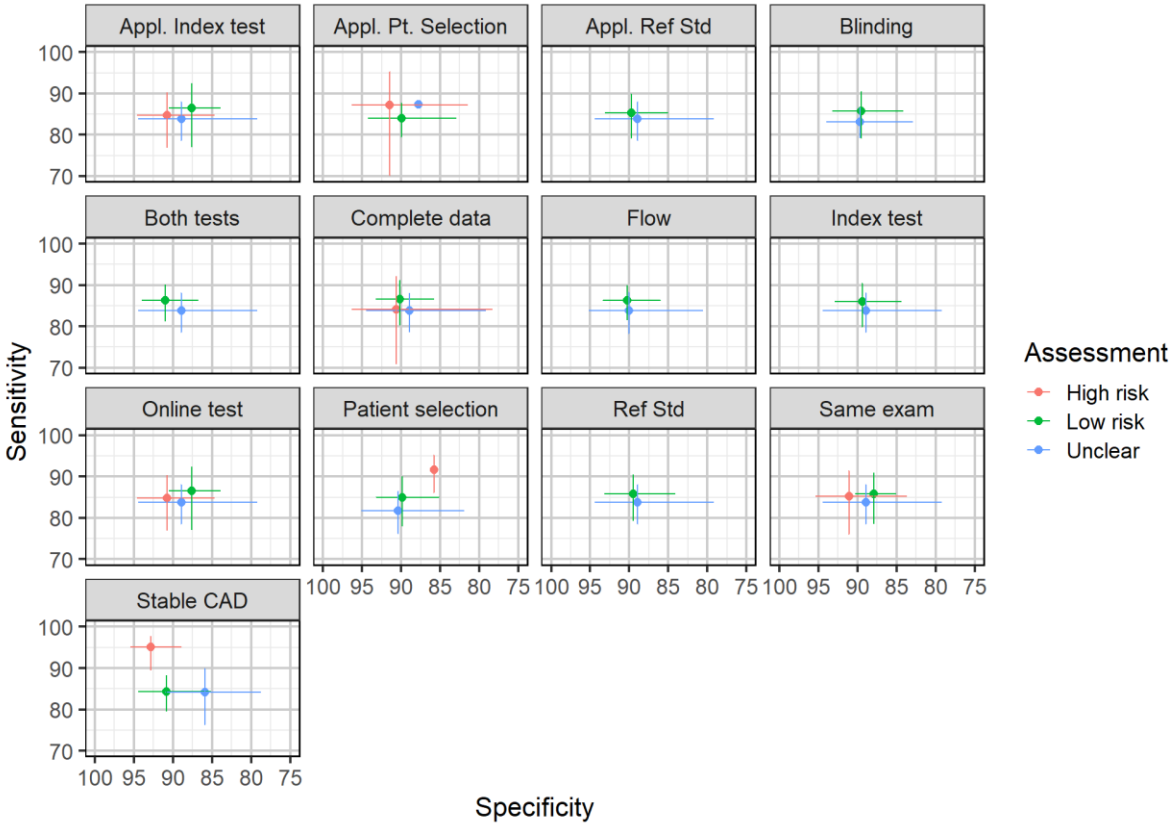


Table 71 Comparison of diagnostic accuracy based on figure data and tabulated data

Study	Extracted from B-A figure			From text/tables		
	N	Sensitivity	Specificity	N	Sensitivity	Specificity
Cliff 2019				39	87.50	82.61
Cortes (2019)	15	100.00	100.00	11	100.00	100.00
Emori (2018)A	143	93.90	88.52	150	93.59	84.72
Emori (2018)B				100	97.10	87.10
FAVOR II China Xu (2017)	252	90.70	86.75	328	94.64	91.67
FAVOR II Europe-Japan Westra (2018)	238	85.06	85.43	317	86.54	86.85
FAVOR Pilot Tu (2016)				84	74.07	91.23
Hamaya	136	94.20	73.13			
Hwang (2019)	274	83.46	89.80	358	92.31	89.77
Kajita (2019)				28	60.00	95.65
Kameyama (2016)	24	80.00	88.89	25	78.57	81.82
Kanno (2019)A	381	86.29	71.84	504	85.29	72.56
Kirigaya (2019)	89	79.17	90.24	95	80.39	90.91

Koltowski (2018)	205	84.04	83.78	306	89.23	63.64
Liontou	72	90.00	76.19			
Liu (2017)				40	85.71	76.92
Mejia-Renteria (2019)	278	86.29	87.66	300	88.97	87.20
Sato (2018)	64	90.91	90.32	63	90.63	90.32
Smit (2019)	240	63.38	94.67	320	69.23	92.14
Spitaleri (2018)	42	94.12	96.00	45	93.75	93.10
Stahli (2019)	267	73.44	97.54	516	75.00	97.84
SYNTAX II Asano (2019)				809	73.73	73.93
Ties				101	66.67	96.25
Toi	34	68.75	66.67			
Tu (2014)	78	76.92	90.38	77	78.26	92.59
van Rosendael	26	100.00	75.00			
Watari (2019)				150	84.62	82.65
WIFI II Westra (2018)	206	73.75	82.54	240	75.00	86.84
Yazaki (2017)	129	89.19	88.04	151	89.13	88.57
Ziubryte (2019)				69	84.21	100.00

Figure 42 Difference between FFR and QFR values in the grey zone

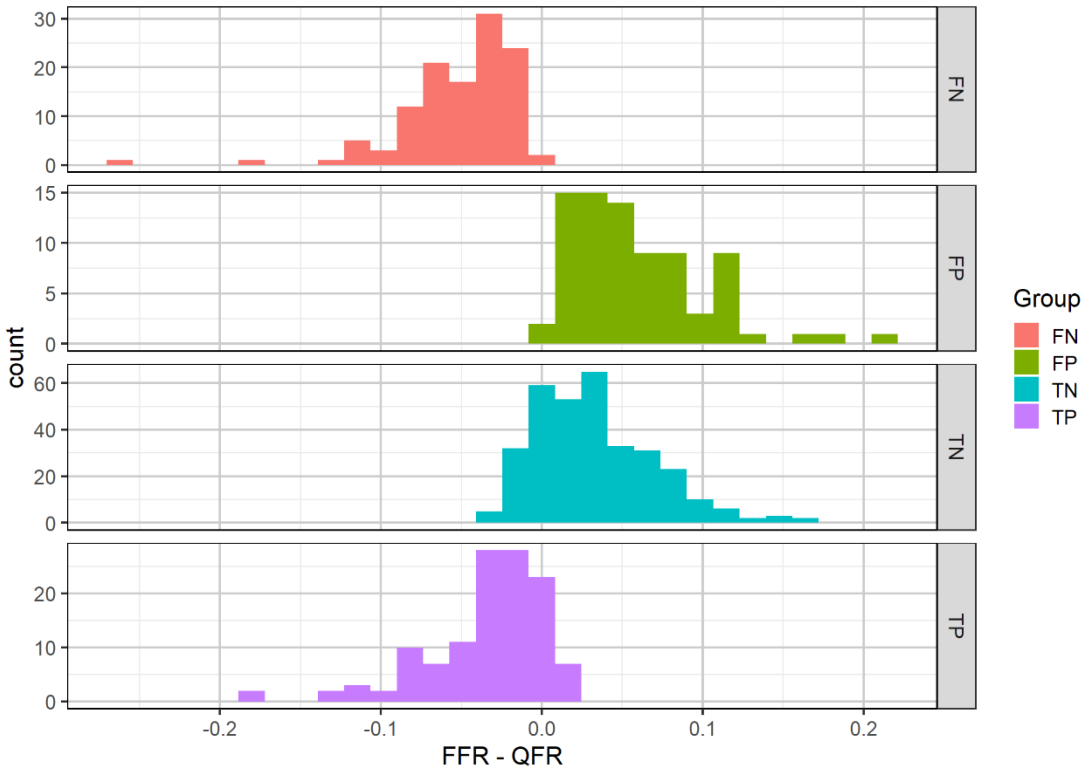


Table 72 Studies included in the meta-analysis 2D ICA

Study	N patient (vessel/lesion)	Population	Unit of analysis*	Sens*	Spec*	AUC*	Correlation*	ICA cut-off	FFR cut-off
FAVOR II China & CHINA II Europe-Japan Ding (2019)[57]	576 (645)	SA, CAD, post-MI	Vessel	47.1% (95% CI: 40.5-53.6%)	74.4% (95% CI: 70.2-78.6%)	0.66 (95% CI: 0.62-0.71)	r=0.59	≥50%	≤0.80
Kim (2016)[58]	463 (724)	SA: 69.2%; UA: 19.4%; SI: 11.4%	Vessel	78% (95% CI 72-82)	48% (95% CI 43-53)	NR	r=0.49	≥50%	<0.80

Mejia (conference abstract) [59]	196 (246)	Intermediate stenosis, SA & acute ACS	Vessels	82%	41%	0.67 (95% CI 0.61-0.74)	r=-0.39	≥50%	≤0.80
DAN-NICAD Serj-Hansen[60]	176 (232)	TA: 31%; AA: 35%; other: 34%	Patient	NR	NR	NR	Rho:0.30	≥50%	≤0.80

* As reported in studies; CCTA: coronary computed tomography angiography; SA: stable angina; UA: unstable angina; SI: silent ischemia; ACS : acute coronary syndrome ; *non-anginal chest pain, dyspnea or arrhythmia

10.5 Appendix 5: Further narrative synthesis results

Table 73 Results of QAngio studies not included in the meta-analysis

Study	Population	Design	Test	Unit of analysis	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Correlation	MD
WIFI Prototype study Andersen (2017)[11] Conference abstract	Stable angina and secondary evaluation after acute MI N=93 patients	Prospective	XA 3D/QFR (prototype)	Patient	0.64 (95% CI 0.48-0.77)	0.8 (95% CI 0.66-0.89)	74.0%	71.0%	0.77 (0.67 - 0.87)	NR	MD (FFR-QFR)=-0.02(0.12)
		Retrospective *Reanalysis with the final QFR application*	XA 3D/QFR (modified prototype)	Patient	0.66 (95% CI 0.51-0.79)	0.86 (95%CI 0.73-0.93)	81.0%	74.0%	0.87 (0.79 - 0.94)	NR	MD (FFR-QFR)=0.0(0.07)
		NR	ICA (3D %DS)	Patient	NR	NR	NR	NR	0.75 (0.65-0.85)	NR	NR
Neylon (2016)[35] Conference abstract	NR N=38 vessels (36 patients)	Retrospective	XA 3D/QFR	Lesion	NR	NR	NR	NR	0.78 (0.67-0.96)	NR	MD (FFR-QFR)=-0.01(NR)

Goto (2019)[19] Conference abstract	Intermediate left main stenosis. Mostly LM bifurcation (85%) N=62 patients	Retrospective	XA 3D/QFR	NR	84.8%	68.2%	84.8%	68.2%	0.82 (0.71-0.93)	r=0.578	NR
Kleczynski (2019)[30]	Intermediate stenosis N=123 vessels (50 patients)	Retrospective	XA 3D/QFR	Vessel	91.8%	97.3%	NR	NR	0.98 (0.94-1.00)	NR	NR
Mehta (2019)[33] Conference abstract	NR N=85 vessels	Retrospective	XA 3D/QFR	Lesion	84%	92%	76%	95%	0.94	R=0.801	NR
Van Diemen (2019)[44] Conference abstract	NR N=152 (fQFR) N=140 (cQFR)	Retrospective	XA 3D/QFR	Vessel	fQFR: 76% (59-89)* cQFR: 71% (53-86)*	fQFR: 94% (88-98)* cQFR: 93% (86-97) *	fQFR: 79% (64-89) * cQFR: 74% (59-85) *	fQFR: 93% (88-96) * cQFR: 92% (86-95) *	NR	NR	NR

Table 74 Results for alternative QAngio modes (aQFR, iQFR, LQFR, vQFR)

Study	Population	Design	Test	Unit of analysis	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	Correlation	MD
Koltowski (2018)[29]	Stable CAD. 268 patients, 306 lesions	Retrospective	vQFR	Lesion	90.5%	69.7%	68.8%	90.8%	0.900	r=0.78	MD (FFR-QFR)= 0.03(0.07)
			lQFR	Lesion	48.6%	96.5%	91.1%	71.7%	0.822	r=0.7	MD (FFR-QFR)=-0.06(0.07)
			iQFR	Lesion	83.8%	86.6%	82.2%	87.9%	0.936	r=0.85	MD (FFR-QFR)=-0.002(0.054)
FAVOR Pilot Tu (2016)[43]	73 patients, 84 vessels	Retrospective	aQFR	Patient	78.0%	89.0%	80.0%	88.0%	0.90 (0.81-0.96)	NR	NR
			aQFR	Vessel	78.0%	91.0%	81.0%	90.0%	0.91 (0.83-0.96)	r=0.72	MD (QFR-FFR)=-0.001(0.065)
Van Rosendael (2017)[45]	15 vessels, non-acute CAD	Retrospective	aQFR (observer 1)	Vessel	100%	92.9%	50%	100%	NR	NR	MD (QFR-FFR) 0.01(0.04)
			aQFR (observer 1)	Vessel	100%	92.3%	50%	100%	NR	NR	NR

Table 75 Subgroup analyses from QAngio studies stratified by vessel characteristics

Study	Subgroup	N*	Test	Sens	Spec	PPV	NPV	AUC	Correlation
Kanno (2019)A[26~]	High IMR	155 patients	cQFR	96.7%	64.2%	63.0%	96.8%	NR	NR
Kanno (2019)A[26]	Low IMR	349 patients	cQFR	81.5%	77.2%	78.8%	80.0%	NR	NR
Mejia-Renteria (2019)[34 54]	High IMR	83 vessels	cQFR	86%	69%	67%	87%	0.88 (NR)	0.77
Mejia-Renteria (2019)[34 54]	Low IMR	217 vessels	cQFR	90%	94%	93%	92%	0.96	0.86
Stahli (2019)[39,56]	Small vessel disease (≤2.8mm reference diameter)	225 vessels	cQFR	80.0%	98.5%	94.6%	94.0%	0.89 0.85 - 0.93	r = 0.84
Stahli (2019)[39]	Small vessel disease (≤2.8mm reference diameter)	225 vessels	fQFR	73.9%	96.6%	87.3%	92.1%	NR	r = 0.83
Stahli (2019)[39]	No small vessel disease	154 vessels	cQFR	65.7%	97.2%	79.3%	94.5%	0.81 0.76 - 0.86	r = 0.77
Stahli (2019)[39]	No small vessel disease	154 vessels	fQFR	68.6%	96.7%	77.4%	94.9%	NR	r = 0.74
WIFI II Westra (2018)[48]	multiple lesions	81 lesion	QAngio (NS)	NR	NR	NR	NR	NR	MD=0.01±0.09

WIFI II Westra (2018)[48]	single lesion	174 lesions	QAngio (NS)	NR	NR	NR	NR	NR	MD=0.01±0.07
FAVOR II China Xu (2017)[49]	%DS 40-80%	273 patients	QAngio	92.2%	92.3%	82.6%	96.8%	NR	NR
FAVOR II China Xu (2017)[49]	%DS 40-80%	272 patients	ICA (2D %DS)	54.5%	60.0%	50.5%	22.9%	NR	NR
Emori (2018)B[18]	LAD[#]	63 vessels	cQFR	95.0%	83.0%	93.0%	88.0%	NR	NR
Emori (2018)B[18]	Non LAD[#]	37 vessels	cQFR	100.0%	92.0%	96.0%	100.0%	NR	NR

*****Unit used in analyses. *IMR, LAD, CAD, CKD, MI, DS.* ~data from personal communication; [#]not review protocol-specified.

Table 76 Subgroup analyses from QAngio studies stratified by comorbidities

Smit (2019) [55]	diabetic	66 patients	QAngio (NS)	75.0%	95.0%	90.0%	97.0%	NR	NR
	non-diabetic	193 patients	QAngio (NS)	69.0%	88.0%	75.0%	85.0%	NR	NR
	diabetic	82 vessels	QAngio (NS)	71.0%	95.0%	85.0%	89.0%	0.91 0.84 - 0.99	r=0.74
	non-diabetic	238 vessels	QAngio (NS)	69.0%	91.0%	74.0%	88.0%	0.93 0.89 - 0.96	r=0.83
Stahli (2019)[39]	Diabetes	98 patients	QAngio (NS)	NR	NR	NR	NR	0.84 (0.76-0.90)	r=0.82
Stahli (2019)[39]	No diabetes	338 patients	QAngio (NS)	NR	NR	NR	NR	0.87 (0.83-0.90)	r=0.81
Koltowski (2018)[29]	Diabetes	21	QAngio (NS)	NR	NR	NR	NR	NR	MD=–0.059 ±0.07
Koltowski (2018)[29]	No diabetes	173	QAngio (NS)	NR	NR	NR	NR	NR	MD=–0.027 ±0.074
Emori (2018)A[17]	Prior MI	75 patients/vessels	fQFR	94.0%	62.0%	69.4%	92.3%	0.90 (0.81 - 0.95)	r=0.84
Emori (2018)A[17]	Prior MI	75 patients/vessels	cQFR	92.0%	82.0%	82.5%	91.4%	0.93 (0.86 - 0.97)	r=0.88
Emori (2018)A[17]	No prior MI	75 patients/vessels	fQFR	98.0%	73.0%	82.0%	96.0%	0.97 (0.93 - 0.99)	r=0.91
Emori (2018)A[17]	No prior MI	75 patients/vessels	cQFR	95.0%	88.0%	90.9%	93.5%	0.97 (0.93 - 0.99)	r=0.94
Hwang (2019)[21]	Stable CAD[#]	253 vessels	fQFR	90.1%	89.5%	82.8%	94.2%	0.946	r=0.86

Hwang (2019)[21]	MI non-culprit[#]	105 vessels	fQFR	96.2%	90.6%	90.9%	96.0%	0.967	r=0.88
Koltowski (2018)[29]	CKD[#]	32 patients	QAngio (NS)	NR	NR	NR	NR	0.67 (0.46 - 0.88)	r=0.63
Koltowski (2018)[29]	No CKD[#]	170 patients	QAngio (NS)	NR	NR	NR	NR	0.89 (0.84 - 0.94)	r=0.79

[#]Not review protocol-specified

Table 77 Results from multivariate regression analyses

	FAVOR II Europe-Japan Westra (2018)[47]	Mejia 2018 [54], Mejia[34]	WIFI II Westra (2018)[48]	SYNTAX II Asano (2019)[12]
%DS	NO	NO	NO	
ACS/acute MI (not previous MI)		OR 3.97 95% CI (1.78–8.86)*		
Adenosine route	NO			
Age	NO		NO	NO
Bifurcation/trifurcation				OR 1.81 95%CI (1.10 to 2.98)*
BMI	NO		NO	
Chronic total inclusion (main vessel)				NO
Diabetes	OR 2.88 95% CI (1.30-6.43)*			NO
EF Ejection fraction				
eGFR				
FFR	NO		R=-1.17 (SE 0.53)[£]	
Hypertension			NO	
IMR (index microcirulatory resistance)		OR 1.05 95%CI (1.02-1.08)*		
LAD (left anterior decending)				NO***
LCx (left circumflex artery)				NO
Left marginal artery			NO	
Lesion length	NO			
Lesion location				
LM/LCA/LMCA (Left main coronary artery)				
MI history/previous MI				NO
MLD		NO		
Multi-vessel disease		NO		
Pa		NO		
Previous PCI	NO			
Proximal/mid-segment location		NO		
RCA (right coronary artery)				

Reference diameter				NO **
Sex	NO		NO	NO
Side branch location				OR 2.07 95%CI (1.14 to 3.76)*
Small vessel				OR 1.67 95% CI (1.14 to 2.44)*
Smoker	NO	NO		
Vessel	NO		NO	

Table 78 Patient and vessel exclusions and test failures from diagnostic accuracy studies

Study	N failed/ excluded	%	Unit	Reasons (n or %)
QAngio (prospective studies)				
FAVOR II Europe-Japan Westra (2018)[47]	57	17%	Patient	Lesion >90% and no additional lesions with FFR measurement (8), no lesions >30% apart (6), AF (1), acute MI (1), ostial RCA (1), stepdown (1), protocol violation (7), FFR not measured (2), overlap (1), poor image quality (3), projection <25% apart (1), technical issue (1), drift (9), damping (15). The authors stated bifurcation lesions were excluded but numbers were not reported.
Toi (2018)[41] (conference abstract)	NR	NR	NR	NR
Van Rosendael (2017)[45]	NR	NR	NR	NR
Watari (2019)[46]	11	7%	Vessel	Non-optimal angiographic projections for QFR analysis (9) or incomplete pressure-wire measurement (2).
WIFI Prototype study Andersen (2017)[11] (conference abstract)	NR	NR	NR	NR
FAVOR II China Xu (2017)[49]	29	9%	patients	2 enrolled patients (3 vessels, including data for QFR (2), poor image quality (1)). Withdrew informed consent (4), atrial fibrillation during coronary angiography (1), total occlusion lesion (1), lesion diameter stenosis <30% or >90% in all vessels (9), ineligible for diagnostic intervention or FFR examination (12)
WIFI II Westra (2018)[48]	190	52%	Patient	Lesion >90% and no FFR measurement (51), no confirmed lesion with %DS>30%(86), FFR not measured (34), drift (4), dampening (5), no sign of adenosine effect (1), other angiographic or procedural criteria (9) Lesions excluded due to unsuccessful QFR computation (15), including: overlap at the lesion segment of interest (6), excessive foreshortening in stenotic segments (7), insufficient contrast flow quality (1), and inability to contour a tight stenosis because of poor contrast filling (1)
QAngio (retrospective studies)				
Cliff 2019 [13] (conference abstract)	NR	NR	NR	NR
Cortés (2019)[14]	134	92%	Patient	Suboptimal angiographic images (46, of which 13 were primary, 33 staged procedure), retrospective (88)
Emori (2018)A[17]	13	8%	Patient	Incomplete CAG (9), ostial lesions (3), collateral donor artery (1)
Emori (2018)B[18]	6	6%	Patient	Incomplete coronary angiography (4), ostial lesion (1), collateral donor artery (1)
FAVOR Pilot Tu (2016)[43]	15	17%	Patient	Excessive overlap of vessels (5), incomplete data (3), excessive pressure wire drift (3), noisy angiograms (2), <25 degrees apart (1), no sign induced hypermia (1)

Goto (2019)[19] (conference abstract)	NR	NR	NR	NR
Hamaya (2019)[20]	140	20%	Patient	Small (<2mm) RCA (right coronary artery) or LCx (left circumflex coronary artery) (52), arrhythmia during ICA (32), ineligible coronary anatomy (98), insufficient image quality (10)
Hwang (2019)[21]	127	35%	Vessel	Calibration failure (49), ostium lesion (35), insufficient projection (25), tortuous vessel (7), overlapped vessel (7), inadequate contrast filling (3), no iFR (1)
Ishihara (2019)[22] Conference abstract	NR	NR	NR	NR
Jin (2019)[23] (conference abstract)	20	20%	Patients	unsuitable coronary anatomy, invalid FFR measurements, poor image quality and lack of 2 projections ≥25° apart (20 total)
Kajita (2019)[24] (conference abstract)	NR	NR	NR	NR
Kameyama (2016)[25] (conference abstract)	9	26%	Vessel	Poor angiographic images (9)
Kanno (2019)A[26]	NR	NR	NR	NR
Kanno (2019)B[27]	NR	NR	NR	NR
Kirigaya (2019)[28] (conference abstract)	NR	NR	NR	NR
Kleczynski (2019)[30]	NR	NR	NR	NR
Koltowski (2018)[29]	551	64%	Lesion	Lack of proper angiographic projections (n=299). Other reasons: bifurcation lesion (n=43), AF (41), vessel overlap/shortening (37), low image quality (28), ostial lesion (26), tandem lesion (21), collateral (18), bypass grafting (15)
Liontou (2019)[31]	124	61%	Vessels	History of CABG, ostial left main or ostial right coronary artery lesions, occlusive restenosis, bioresorbable scaffolds, incompatibility of angiographic images (n=90). Lack of at least two angiographic projections >25 degrees apart, severe vessel tortuosity and/or overlap limiting QFR analysis (n=34).
Liu 2017[32] (conference abstract)	NR	NR	NR	NR
Mehta (2019)[33] (conference abstract)	NR	NR	NR	NR
Mejia-Renteria (2019)[34]	101	26%	Vessel	Ostial in LM or RCA (10), grafted target vessels (2), inadequate projections (28), significant overlapping (17), inadequate ICA quality (19), resting haemodynamic data no available (6) contrast filling not optimal for TIMI frame count analysis (19)
Neylon (2016)[35] (conference abstract)	NR	NR	NR	NR
Sato (2018)[36] (conference abstract)	NR	NR	NR	NR
Smit (2019)[37]	52	13%	Vessels	Insufficient image quality (n= 17), presence of a coronary stent (n = 4), excessive overlap and/or foreshortening of coronary arteries

				(n = 18), absence of angiographic views with projection angles >_25 apart (n= 6), ostial stenosis (n= 5), or aneurysm (n= 2)
Spitaleri (2018)[38]	31	41%	Patients	No successful PCI on culprit lesion (3), diffuse disease in non-culprit vessel (8), severe tortuosity (2), vessel <2.5mm (2), operator preferred not to perform FFR (16)
Stahli (2019)[39]	43	9%	Patients	Lack of 2 projections 25degrees apart (24), insufficient image quality (12), vessel overlap/shortening (10), low contrast filling (7), technical issues (4). +14 patients with incomplete FFR measurement.
SYNTAX II Asano (2019)[12]	341	29%	Vessel	No two appropriate projections (311), lumen diameter <2.0mm (12), ostial lesion near aorta (4), other (14)
Ties (2018)[40]	232	70%	Vessel	Lack of basic requirements (200), insufficient image quality (17), inappropriate reference diameter function (8), overlap/foreshortening (5), no perpendicularity (1), true bifurcation (1)
Tu (2014)[42]	3	4%	Vessel	Too much overlap or foreshortening (>90%), insufficient image quality, mean pressure of the guiding catheter or blood hematocrit value not documented.
Van Diemen (2019)[44] (conference abstract)	266	48%	Vessels	No FFR (72). QFR analysis succeeded in 286 (52%) of the remaining 552 arteries. No further details reported
WIFI II Westra (2018)[48]	190	52%	Patient	Lesion >90% and no FFR measurement (51), no confirmed lesion >30% (86), FFR not measured (34), drift (4), dampening (5), no sign of adenosine effect (1), other angiographic or procedural criteria (9) Lesions excluded due to unsuccessful QFR computation (15), including: overlap at the lesion segment of interest (n=6), excessive foreshortening in stenotic segments (n=7), insufficient contrast flow quality (n=1), and inability to contour a tight stenosis because of poor contrast filling (n=1)
Yazaki (2017)[50]	20	12%	Vessel	Lacking two optimal angiographic projections at least 25° apart, overlapping vessels), no preferred references in proximal or distal vessels, insufficient contrast, target lesion at ostium of left or right artery.
Ziubryte (2019)[51] (conference abstract)	NR	NR	NR	NR
CAAS vFFR				
FAST EXTEND Daemen (2019)[15]	NR	NR	NR	NR
FAST Masdjedi et al. 2019[53] CAAS vFFR	170	63%	Patients	Inadequate pressure waveform (25), STEMI (16), bypass graft (3), left main lesion (2), collaterals (5), lack of 2 adequate orthogonal views >30 degrees (58), overlap or foreshortening (35), no invasive blood pressure available (15), unknown position of FFR pressure wire (11)
ILUMIEN I Ely Pizzato (2019)[16]	405 (pre- and post-PCI)	65%	Lesions	Unavailability of at least 2 angiographic projections (172, 42.5%), table movement while acquiring angiographic images (104, 25.7%), angiography pixel/resolution incompatibility (61, 15%), <30 degrees angle between projections (26, 6.4%), multiple reasons (21, 5.2%), other (calibration issues, missing SID value, CABG, occluded vessel, total 21, 5.2%).

Table 79 Mortality, morbidity and major cardiovascular outcomes from QAngio studies

Study	Population	Outcomes
Spitaleri (2018)[38]	NCL lesions in STEMI patients N=110. QFR≤0.80 group: at least one untreated NCL with QFR≤0.80 (n=56) QFR>0.80 group: all untreated NCL with QFR>0.80 (n=54)	<u>POCE (5 yr)</u> QFR≤0.80: 46% QFR>0.80: 24% HR 2.3 (95% CI 1.2-4.5), p=0.01 <u>Cardiovascular death (at 5 yr)</u> QFR≤0.80: 18% QFR>0.80: 6% , p=0.09 <u>All-cause mortality (at 5 yr)</u> QFR≤0.80: 21% QFR>0.80: 9%, p=0.1 <u>Any reinfarction (at 5 yr)</u> QFR≤0.80: 1% QFR>0.80: 1%, p<0.9 <u>Any revascularization (at 5 yr)</u> QFR≤0.80: 25% QFR>0.80: 14%, p<0.9
Hamaya (2019)[20]	Stable CAD, 3 vessel-disease N= 549	<u>MACE (median 2.2 yrs)</u> Patients with MACE had lower cQFR in all three vessels than those without MACE (2.76 [2.64-2.88] vs. 2.64 [2.49-2.73], p<0.001). 3-vessel cQFR was statistically significant predictor of MACE in multivariate analyses (HR 0.97, 95% CI 0.96-0.99). Other statistically significant predictors: diabetes (HR 1.68, 95%CI 0.97-2.91) previous MI (HR 1.89, 95% CI 1.07-3.28) hs-cTnI (HR 1.48, 95% CI 1.13-1.91) multivessel disease (1.33, 95% CI 0.57-3.00) Gensini score (HR 0.996, 95% CI 0.98-1.01 <u>Remote revascularisation (≥3 months)</u> cQFR: AUC 0.73 (95% CI: 0.65-0.79) % DS : AUC 0.66 (95% CI: 0.56-0.74), p=0.043
Kanno (2019)(B)[27] Conference abstract	Intermediate stenosis, de novo, deferred revascularisation (FFR>0.8), N=212 Median FFR & cQFR: 0.87 cQFR: 22.2%	<u>MACE (4 yrs)</u> 5.7% overall Baseline cQFR in MACE: mean or median* 0.80 Baseline cQFR in non-MACE: 0.87 Odds of MACE in cQFR≤0.8: OR 5.60, 95% CI 1.69-18.6, p=0.005

*NR; NCL: non-culprit lesion

Table 80 Inter-observer reliability results

Study	Index test	N observations/observers Blinding	Results
Cortés (2019)[14]	XA 3D/QFR 'Prototype'	20 selected patients assessed by 2 analysts. No blinding reported.	r=0.991 (95% CI 0.960-0.997)
FAST Masdjedi et al. 2019[53] CAAS vFFR	CAAS vFFR	100 vessels assessed independently by 2 blinded analysts	r=0.95 MD 0.004(0.0236)
Hwang (2019)[21]	QAngio XA 3D/QFR 1.2	30 randomly selected vessels assessed independently by 2 analysts.	MD 0.002 (0.792 (SD 0.107) versus 0.794 (SD 0.109), p=0.919)
Ishihara (2019)[22] Conference abstract	QAngio (no further details)	100 vessels (94 patients) assessed independently by 3 analysts twice.	ICC (mean value of 3 raters)= 0.614 (0.464-0.728)
Jin (2019)[23] Conference abstract	XA 3D/QFR CAAS vFFR	101 vessels independently analysed by 2 analysts.	fQFR: MD=0.001±0.036, p=0.847; cQFR: MD=−0.001±0.049; p=0.910, vFFR: MD=−0.005±0.037, p=0.393
Kajita (2019)[24] Conference abstract *(data from [164])*	QAngio XA 3D/QFR 1.0	34 vessels analysed by 2 analysts.	fQFR: R^2=0.70 cQFR: R^2=0.82 %DS: R^2=0.67
Kleczynski (2019)[30]	QAngio XA 3D/QFR 2.1.12.2	NR	ICC: 0.990 (95% CI 0.987–0.992)
Tu (2014)[42]	QAngio XA 3D/QFR 1.0	10 randomly selected vessels assessed independently by 2 blinded analysts	MD 0.01 (SD 0.03)

MD: mean difference; CI: confidence interval; DS: diameter stenosis; ICC: intra-class correlation

Table 81 Intra-observer reliability results

Study	Index test	N observations/observers	Results
Cliff 2019 [13] Conference abstract	XA 3D/QFR	17 anonymized lesions reanalysed after 2 weeks	MD=0.01 (0.05)
Cortés (2019)[14]	XA 3D/QFR 'Prototype'	20 lesions assessed by 2 independent analysts reanalysed once*	r=0.958 (95% CI 0.877-0.984)
Ishihara (2019)[22] Conference abstract	QAngio (no further details)	100 vessels (94 patients) assessed independently by 3 analysts twice.	ICC per rater: 1: 0.695 (95% CI 0.579-0.784) 2: 0.820 (0.733-0.879) 3: 0.479 (0.313-0.617) Average of all 3 raters: ICC 0.806 (0.711-0.869) Intra-rater reliability of measurements: ICC=0.428
Jin (2019)[23] Conference abstract	XA 3D/QFR CAAS vFFR	101 vessels assessed by 2 independent analysts reanalysed once*	cQFR: MD 0.009±0.053, p=0.230 fQFR: MD 0.016±0.060, p=0.066 vFFR: MD 0.008±0.040, p=0.175
Kajita (2019)[24] Conference abstract (hideo kajita) *(data from [164])*	QAngio XA 3D/QFR 1.0	34 vessels reanalysed after 1 week	fQFR: R^2= 0.91 cQFR: R^2= 0.94 %DS: R^2=0.76
Kleczynski (2019)[30]	QAngio XA 3D/QFR 2.1.12.2	NR	ICC: 0.991 (95% CI 0.988–0.993)
Tu (2014)[42]	QAngio XA 3D/QFR 1.0	10 randomly selected vessels reanalysed after 1 week.	mean 0.00 (SD 0.03)
Ziubryte (2019)[51] Conference abstract	XA 3D/QFR	69 lesions measured three times with 3 days intervals between measurements	r=0.997 (p<0.001)

*Duration between measurements and actual number of measurements analysed NR; MD: mean difference; CI: confidence interval; DS: diameter stenosis; ICC: intra-class correlation

Table 82 Patient and vessel exclusions and test failures from diagnostic accuracy studies

Study	N failed/ excluded	%	Unit	Reasons (n or %)
QAngio (prospective studies)				
FAVOR II Europe-Japan Westra (2018)[47]	57	17%	Patient	Lesion >90% and no additional lesions with FFR measurement (8), no lesions >30% apart (6), AF (1), acute MI (1), ostial RCA (1), stepdown (1), protocol violation (7), FFR not measured (2), overlap (1), poor image quality (3), projection <25% apart (1), technical issue (1), drift (9), damping (15). The authors stated bifurcation lesions were excluded but numbers were not reported.
Toi (2018)[41] (conference abstract)	NR	NR	NR	NR
Van Rosendael (2017)[45]	NR	NR	NR	NR
Watari (2019)[46]	11	7%	Vessel	Non-optimal angiographic projections for QFR analysis (9) or incomplete pressure-wire measurement (2).
WIFI Prototype study Andersen (2017)[11] (conference abstract)	NR	NR	NR	NR
FAVOR II China Xu (2017)[49]	29	9%	patients	2 enrolled patients (3 vessels, including data for QFR (2), poor image quality (1)). Withdrew informed consent (4), atrial fibrillation during coronary angiography (1), total occlusion lesion (1), lesion diameter stenosis <30% or >90% in all vessels (9), ineligible for diagnostic intervention or FFR examination (12)
WIFI II Westra (2018)[48]	190	52%	Patient	Lesion >90% and no FFR measurement (51), no confirmed lesion with %DS>30%(86), FFR not measured (34), drift (4), dampening (5), no sign of adenosine effect (1), other angiographic or procedural criteria (9) Lesions excluded due to unsuccessful QFR computation (15), including: overlap at the lesion segment of interest (6), excessive foreshortening in stenotic segments (7), insufficient contrast flow quality (1), and inability to contour a tight stenosis because of poor contrast filling (1)
QAngio (retrospective studies)				
Cliff 2019 [13] (conference abstract)	NR	NR	NR	NR
Cortés (2019)[14]	134	92%	Patient	Suboptimal angiographic images (46, of which 13 were primary, 33 staged procedure), retrospective (88)
Emori (2018)A[17]	13	8%	Patient	Incomplete CAG (9), ostial lesions (3), collateral donor artery (1)
Emori (2018)B[18]	6	6%	Patient	Incomplete coronary angiography (4), ostial lesion (1), collateral donor artery (1)
FAVOR Pilot Tu (2016)[43]	15	17%	Patient	Excessive overlap of vessels (5), incomplete data (3), excessive pressure wire drift (3), noisy angiograms (2), <25 degrees apart (1), no sign induced hypermia (1)

Goto (2019)[19] (conference abstract)	NR	NR	NR	NR
Hamaya (2019)[20]	140	20%	Patient	Small (<2mm) RCA (right coronary artery) or LCx (left circumflex coronary artery) (52), arrhythmia during ICA (32), ineligible coronary anatomy (98), insufficient image quality (10)
Hwang (2019)[21]	127	35%	Vessel	Calibration failure (49), ostium lesion (35), insufficient projection (25), tortuous vessel (7), overlapped vessel (7), inadequate contrast filling (3), no iFR (1)
Ishihara (2019)[22] (conference abstract)	NR	NR	NR	NR
Jin (2019)[23] (conference abstract)	20	20%	Patients	unsuitable coronary anatomy, invalid FFR measurements, poor image quality and lack of 2 projections ≥25° apart (20 total)
Kajita (2019)[24] (conference abstract)	NR	NR	NR	NR
Kameyama (2016)[25] (conference abstract)	9	26%	Vessel	Poor angiographic images (9)
Kanno (2019)A[26]	NR	NR	NR	NR
Kanno (2019)B[27]	NR	NR	NR	NR
Kirigaya (2019)[28] (conference abstract)	NR	NR	NR	NR
Kleczynski (2019)[30]	NR	NR	NR	NR
Koltowski (2018)[29]	551	64%	Lesion	Lack of proper angiographic projections (n=299). Other reasons: bifurcation lesion (n=43), AF (41), vessel overlap/shortening (37), low image quality (28), ostial lesion (26), tandem lesion (21), collateral (18), bypass grafting (15)
Liontou (2019)[31]	124	61%	Vessels	History of CABG, ostial left main or ostial right coronary artery lesions, occlusive restenosis, bioresorbable scaffolds, incompatibility of angiographic images (n=90). Lack of at least two angiographic projections >25 degrees apart, severe vessel tortuosity and/or overlap limiting QFR analysis (n=34).
Liu 2017[32] (conference abstract)	NR	NR	NR	NR
Mehta (2019)[33] (conference abstract)	NR	NR	NR	NR
Mejia-Renteria (2019)[34]	101	26%	Vessel	Ostial in LM or RCA (10), grafted target vessels (2), inadequate projections (28), significant overlapping (17), inadequate ICA quality (19), resting haemodynamic data no available (6) contrast filling not optimal for TIMI frame count analysis (19)
Neylon (2016)[35] (conference abstract)	NR	NR	NR	NR
Sato (2018)[36] (conference abstract)	NR	NR	NR	NR
Smit (2019)[37]	52	13%	Vessels	Insufficient image quality (n= 17), presence of a coronary stent (n = 4), excessive overlap and/or foreshortening of coronary arteries

				(n = 18), absence of angiographic views with projection angles >_25 apart (n= 6), ostial stenosis (n= 5), or aneurysm (n= 2)
Spitaleri (2018)[38]	31	41%	Patients	No successful PCI on culprit lesion (3), diffuse disease in non-culprit vessel (8), severe tortuosity (2), vessel <2.5mm (2), operator preferred not to perform FFR (16)
Stahli (2019)[39]	43	9%	Patients	Lack of 2 projections 25degrees apart (24), insufficient image quality (12), vessel overlap/shortening (10), low contrast filling (7), technical issues (4). +14 patients with incomplete FFR measurement.
SYNTAX II Asano (2019)[12]	341	29%	Vessel	No two appropriate projections (311), lumen diameter <2.0mm (12), ostial lesion near aorta (4), other (14)
Ties (2018)[40]	232	70%	Vessel	Lack of basic requirements (200), insufficient image quality (17), inappropriate reference diameter function (8), overlap/foreshortening (5), no perpendicularity (1), true bifurcation (1)
Tu (2014)[42]	3	4%	Vessel	Too much overlap or foreshortening (>90%), insufficient image quality, mean pressure of the guiding catheter or blood hematocrit value not documented.
Van Diemen (2019)[44] (conference abstract)	266	48%	Vessels	No FFR (72). QFR analysis succeeded in 286 (52%) of the remaining 552 arteries. No further details reported
WIFI II Westra (2018)[48]	190	52%	Patient	Lesion >90% and no FFR measurement (51), no confirmed lesion >30% (86), FFR not measured (34), drift (4), dampening (5), no sign of adenosine effect (1), other angiographic or procedural criteria (9) Lesions excluded due to unsuccessful QFR computation (15), including: overlap at the lesion segment of interest (n=6), excessive foreshortening in stenotic segments (n=7), insufficient contrast flow quality (n=1), and inability to contour a tight stenosis because of poor contrast filling (n=1)
Yazaki (2017)[50]	20	12%	Vessel	Lacking two optimal angiographic projections at least 25° apart, overlapping vessels), no preferred references in proximal or distal vessels, insufficient contrast, target lesion at ostium of left or right artery.
Ziubryte (2019)[51] (conference abstract)	NR	NR	NR	NR
CAAS vFFR				
FAST EXTEND Daemen (2019)[15]	NR	NR	NR	NR
FAST Masdjedi et al. 2019[53] CAAS vFFR	170	63%	Patients	Inadequate pressure waveform (25), STEMI (16), bypass graft (3), left main lesion (2), collaterals (5), lack of 2 adequate orthogonal views >30 degrees (58), overlap or foreshortening (35), no invasive blood pressure available (15), unknown position of FFR pressure wire (11)
ILUMIEN I Ely Pizzato (2019)[16]	405 (pre- and post-PCI)	65%	Lesions	Unavailability of at least 2 angiographic projections (172, 42.5%), table movement while acquiring angiographic images (104, 25.7%), angiography pixel/resolution incompatibility (61, 15%), <30 degrees angle between projections (26, 6.4%), multiple reasons (21, 5.2%), other (calibration issues, missing SID value, CABG, occluded vessel, total 21, 5.2%).

Table 83 Timing of QFR results

Study	Design	Population	Index test	Data acquisition duration
WIFI Prototype (2017)[11] Conference abstract*	Prospective/retrospective	N=93 Unselected, consecutive population referred to FFR	QAngio Prototype	Mean total time to QFR: 10 min (SD3)*
Koltowski (2018)[29]	Retrospective	N=306 lesions (268 patients) Stable CAD, intermediate stenosis	XA 3D/QFR (model NR)	'Substantially decreased with number of analysed cases' First 50 cases: mean 5 min 59 s (IQR 5 min 5 s–6 min 43 s) Last 50 cases: mean 2 min 7 s (IQR 1 min 47 s–2 min 28 s)
Tu (2014)[42]	Retrospective	N=77 vessels (68 patients)	XA 3D/QFR 1.0	The complete analysis took <10 min, including approximately 1 min per bifurcation reconstruction including the time required by user interaction, 1 min was to generate the interior meshes after 3D, and 5 min for the CFD simulation on a workstation.
FAVOR II China[49]	Prospective	N=330 vessels (306 patients)	QAngio (AngioPlus)	4.36(2.55) min (including 3-dimensional angiographic reconstruction and frame count analysis)
Yazaki (2017)[50]	Retrospective	N=151 vessels (142 patients)	XA 3D/QFR	Median 4.43 min (IQR, 3.01–5.53) including time selecting 2 angiographic images
FAVOR II Europe-Japan Westra (2018)[47]	Prospective	N=295 lesions	XA 3D/QFR	Median 5.0 min (IQR 3.5-6.1), vs. FFR: 7.0 min (5.0-10.0), p<0.001 Including time for selection of a different view where needed, and excluding transfer time from angiographic equipment to the QFR workstation. FFR time excluded time for preparing and zeroing pressure system.

* The application required essential modifications during the study and blinded in-center core laboratory (QFR and 3D QCA) reanalysis was performed with the final version of QFR. It was not clear which analysis informed these results.

10.6 Appendix 6: Further simulation study results

Figure 43 Simulation study: MACE events prevented

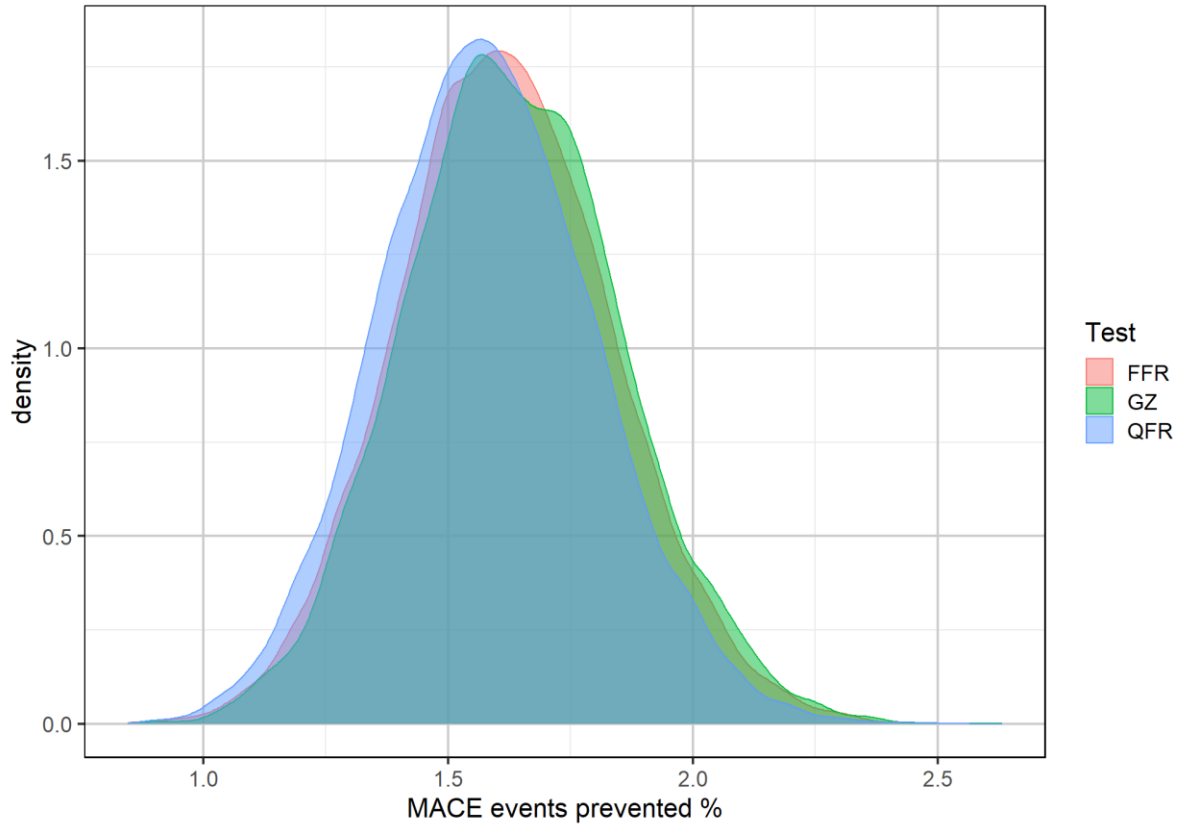


Figure 44 Simulation study: MACE events not prevented

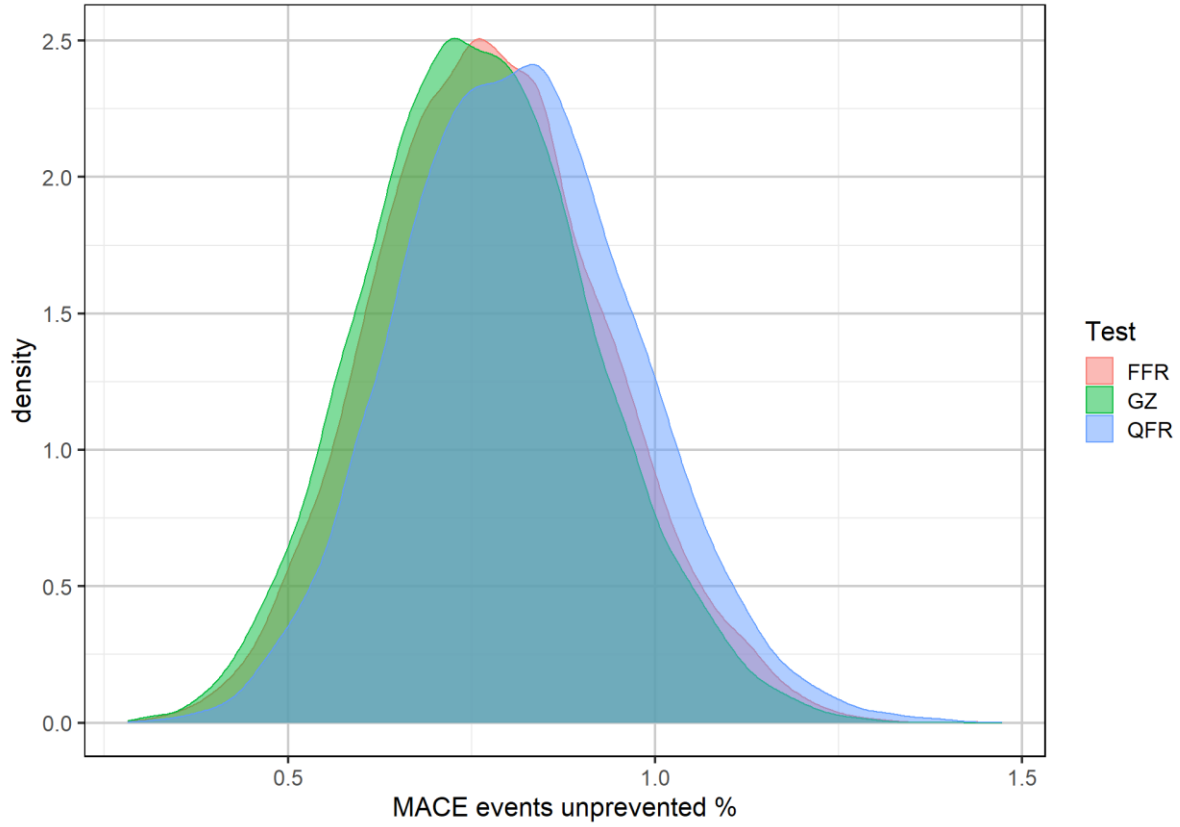
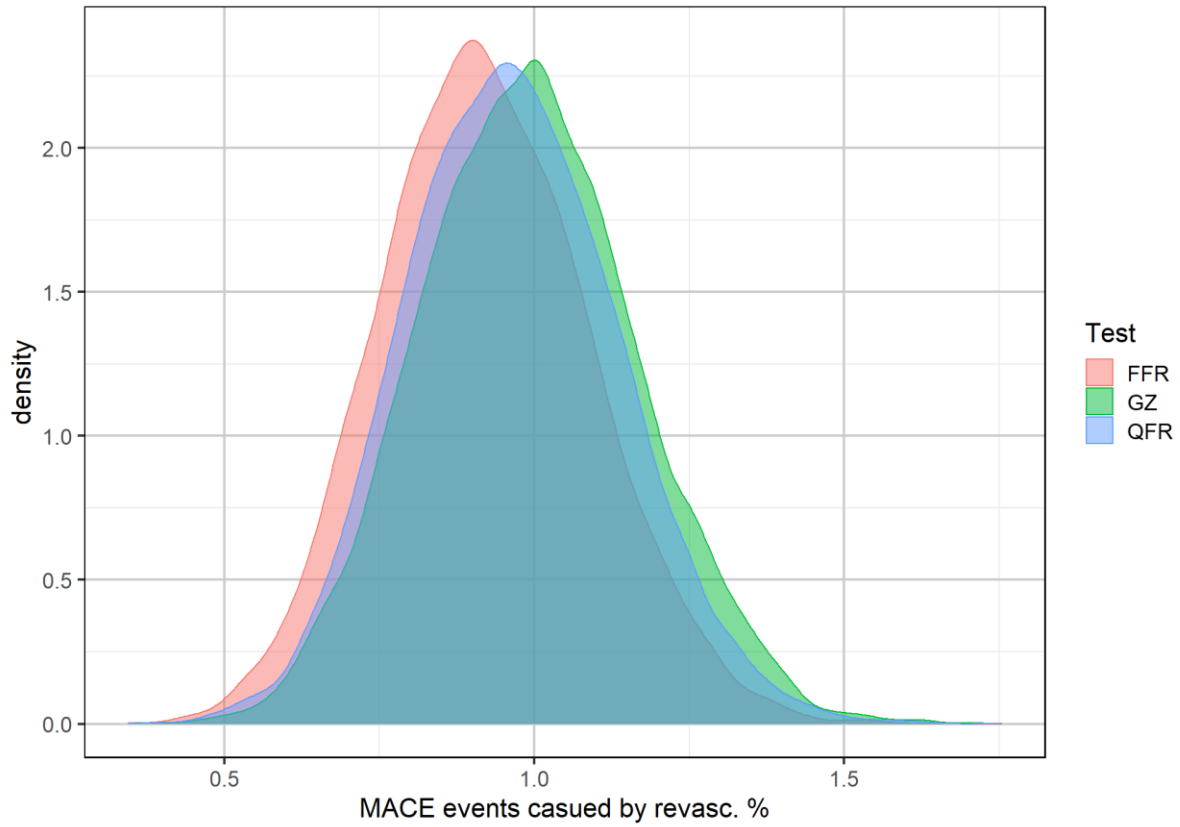


Figure 45 Simulation study: MACE caused by revascularisation



10.7 Appendix 7: Review of decision models evaluating ICA

QANGIO literature searching cost effectiveness 18th October 2019

Database search strategies
Database searches were carried out to identify cost-effectiveness studies where invasive coronary angiography (alone and/or with FFR) was one of the interventions under comparison.
Databases searched: EconLIT, Embase, HTA database MEDLINE, NHS EED
Total number of records identified=1740
Total number of records identified after deduplication in EndNote X.9.2 bibliographic software=1264

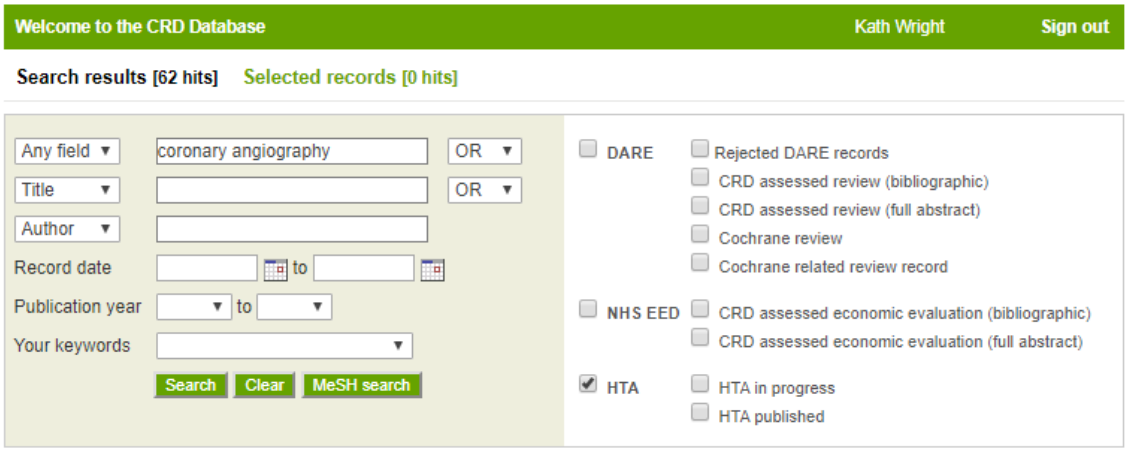
EconLIT
Via OVID
Search date=18th October 2019
Records retrieved=2
Econlit <1886 to October 03,2019>
1 coronary angiograph$.mp. (2)

Embase
Via OVID
Search date=18th October 2019
Records retrieved=858
Embase <1974 to 2019 October 17>

1 *Coronary Angiography/ (3060)
2 coronary angiography.ti,ab. (50830)
3 1 or 2 (51869)
4 Economics/ (234606)
5 Cost/ (57396)
6 exp Health Economics/ (818928)
7 Budget/ (27893)
8 budget*.ti,ab,kw. (37185)
9 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. (268523)
10 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (382513)
11 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. (216418)
12 (value adj2 (money or monetary)).ti,ab,kw. (3124)
13 Statistical Model/ (157315)
14 economic model*.ab,kw. (4585)
15 Probability/ (97263)
16 markov.ti,ab,kw. (27735)
17 monte carlo method/ (37601)
18 monte carlo.ti,ab,kw. (46807)
19 Decision Theory/ (1711)

20 Decision Tree/ (11762)
21 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. (31964)
22 or/4-21 (1560379)
23 3 and 22 (1858)
24 limit 23 to yr="2000 -Current" (1596)
25 limit 24 to embase (858)

HTA database
Via CRD website https://www.crd.york.ac.uk/CRDWeb/
Search date=18th October 2019
Records identified=62



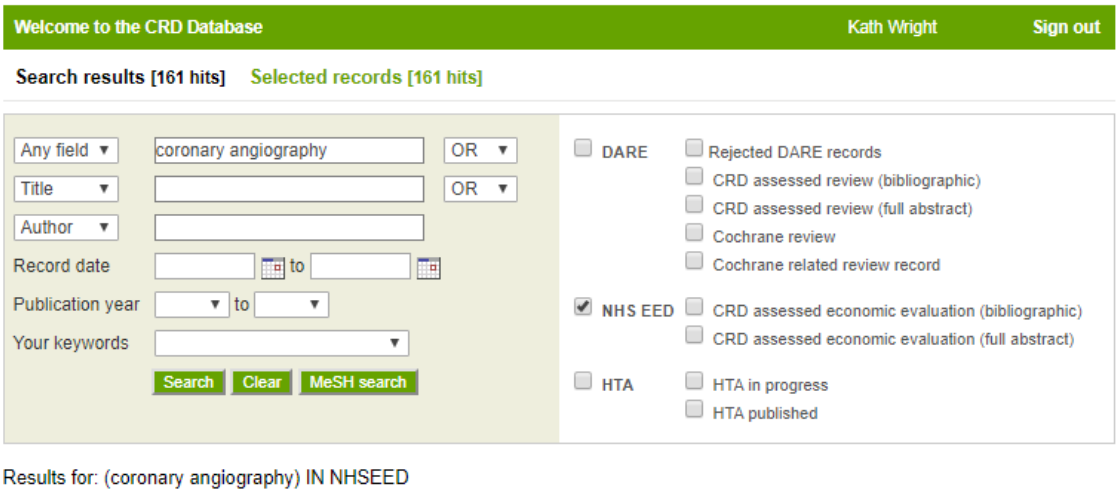
Results for: (coronary angiography) IN HTA

MEDLINE
Via OVID
Search date=18th October 2019
Records identified=665
Ovid MEDLINE(R) ALL <1946 to October 17, 2019>

1 *Coronary Angiography/ (18583)
2 coronary angiography.ti,ab. (30052)
3 1 or 2 (41395)
4 Economics/ (27093)
5 exp "Costs and Cost Analysis"/ (229217)
6 Economics, Nursing/ (3994)
7 Economics, Medical/ (9035)
8 Economics, Pharmaceutical/ (2894)
9 exp Economics, Hospital/ (23942)
10 Economics, Dental/ (1908)
11 exp "Fees and Charges"/ (29932)
12 exp Budgets/ (13585)
13 budget*.ti,ab,kf. (28234)

14 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (218635)
15 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (272429)
16 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (152531)
17 (value adj2 (money or monetary)).ti,ab,kf. (2256)
18 exp models, economic/ (14432)
19 economic model*.ab,kf. (3128)
20 markov chains/ (13736)
21 markov.ti,ab,kf. (21125)
22 monte carlo method/ (27269)
23 monte carlo.ti,ab,kf. (46880)
24 exp Decision Theory/ (11629)
25 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (22091)
26 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (696909)
27 3 and 26 (855)
28 limit 27 to yr="2000 -Current" (665)

NHS EED database
Via CRD website https://www.crd.york.ac.uk/CRDWeb/
Search date=18th October 2019
Records identified =161



Results for: (coronary angiography) IN NHSEED

Table 84 Results of the search

Database	**Number of records retrieved before deduplication**	**Number of records after deduplication**
MEDLINE **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)**	665	660
EMBASE Ovid	858	468
EconLit Ovid	2	1
NHS EED CRD databases	161	87
HTA	62	48
Total in EndNote	1740	1264

Table 85 Summary of excluded studies

Study	**Reason for rejection**
Bosch et al, 2005	Different patient population (acute coronary syndrome)
Goehler et al, 2011	Different patient population (acute chest pain) and does not include long-term outcomes
Kent et al, 2013	Different patient population (NSTEMI)
Nam et al, 2015	Different patient population (NSTEMI)

Full references of the excluded studies are available upon request.

10.8 Appendix 8: Supplementary review of ICA models results

Table 86 Summary of included studies

Study, country	Testing (and management) strategies	Patient population (base-case where clearly stated)	Model type	Health states	Key assumptions/comments
Amemiya et al, 2009 [65] Brazil	1. No examination and no treatment – patients only receive testing and treatment when a cardiac event occurs that require revascularization or conservative treatment (medication). 2. Medication; all patients receive medication for CAD, but undergo no tests, and are not revascularised until a cardiac event occurs. 3. Routine ICA followed by optimal treatment including elective revascularisation; all patients undergo ICA and those with a positive test result receive medication for CAD. All patients with LM require revascularization. For other vessel diseases, 14.5% underwent elective revascularisation within the 1st year. 4. CCTA; all patients undergo CCTA and those with a positive test result receive medication for CAD, some of whom go on to elective revascularisation. If revascularisation is planned, the patient will have ICA for further evaluation as a work-up study; 12% of CCTA-positive patients would also undergo ICA, but not revascularization.	Males aged 60 years with a history of chest pain, but without a definitive diagnosis of CAD. Pretest probability of CAD: 50%	Decision tree + Markov model Lifetime horizon	Decision tree classifies patients in each strategy according to disease severity category (no CAD, 1-vessel, 2-vessel or 3-vessel/LM), test given to all patients (none, ICA or CCTA) and attributes a treatment (no medication, medication, medication/revascularisation). Patients enter the Markov model after treatment. Markov model: healthy (no CAD), angina, angina free, post MI, post PCI/CABG with or without angina, and dead.	People without CAD remain healthy until death For patients who undergo revascularisation, those with 1- or 2-vessel disease receive PCI, while those with 3-vessel or left main trunk disease receive CABG. For patients with CAD the risks of death, nonfatal MI and revascularisation, and proportion of patients with relief of angina are modified to different extents by medication. PCI and CABG are assumed more effective than medication for up to 10 years. Annual rates of cardiac events after revascularisation are calculated separately for the 1st year and for the following 9 years. All live patients had health state utility of 1, except those in the angina and post MI states who had a utility of 0.88. A probability of ICA complications is reported, but it is unclear if this has an impact on costs or HRQoL. Misclassification is not modelled.
Bertoldi et al, 2016 [64] Brazil	1. Ex-ECG + Stress ECHO + ICA 2. Ex-ECG + CCTA + ICA 3. Ex-ECG + SPECT + ICA 4. Ex-ECG + ICA	Patients aged 60 years old at risk of stable CAD	Decision tree + Markov model	The decision tree classifies patients into CV risk categories, based on the results of testing strategy, and	ICA is a perfect test. No indeterminate results from the last test in the strategy.

	5. SPECT + ICA 6. Stress ECHO + ICA 7. Stress ECHO + CCTA + ICA 8. Stress CMR + ICA 9. CCTA + ICA 10. ICA + Stress ECHO 11. ICA + SPECT Patients progress to the next test if results of the previous one are positive or inconclusive. ICA is the reference test. A positive result at the last test in the sequence classifies the patient as moderate (1- or 2-vessel CAD) or high risk (3-vessel or associated left ventricular dysfunction). Patients who test negative are classified as low risk (without significant CAD). Treatment is not specified based on risk category, but rates of revascularisation (PCI and CABG) vary across risk categories.	Pretest probability of CAD: 50%	Lifetime horizon	whether they were correctly classified in their risk category. The risk categories are high risk, moderate risk, low risk, high risk with FN, moderate risk with FN and low risk with FP. Markov model: stable, CV event, PCI or CABG, CV death, cancer death, and other cause death.	10% of initially misdiagnosed cases are correctly rediagnosed in the 1st year, with increasing numbers until the 10th year, by which all have been properly rediagnosed. TN have a low risk of CV events and of revascularisation; TP have a higher risk of CV events and lead to more revascularisation procedures. FN have a high risk of CV events but are misdiagnosed as low-risk; which further increases CV risk but results in fewer revascularisation procedures. FP have low risk of CV events, but misdiagnosis leads to more revascularization procedures. Procedure related mortality is considered for PCI and CABG. The proportion of patients who undergo CABG amongst those who receive revascularisation is assumed to vary across risk categories. Disutility is incurred when patients have PCI, CABG and MI. CCTA, SPECT, and ICA are assumed to have an average radiation dose of 10mSv that increases the lifetime risk of cancer after a 10 years latency period.
Boldt et al, 2013 [74] Germany	1. CMR +ICA 2. SPECT+ ICA 3. ICA Patients progress to the next test if results of the previous one are positive or inconclusive. ICA is the reference test.	Patients with suspected CAD Pretest probability of CAD: 10-100%	Bayesian mathematical model 10 years horizon	Two sets of equations allow estimating the mean total costs and incremental QALY. No health states are defined.	ICA is a perfect test. A correct diagnosis of CAD is assumed to increase the number of QALYs by 3 years over the time horizon. The annual mortality rate varies according to the tests received by the patient and whether CAD positive patients were incorrectly classified as negatives. Complications associated with test procedures include death and MI. Procedural related death are assumed to subtract 10 years of life, while deaths caused by FN (missed CAD) subtract 5 years.

					A disutility of 0.1 was applied annually for complications caused by test and missed CAD. Only short-term costs associated with tests and test procedural complications (MI) are included.
Burgers et al, 2017 [67] Westwood et al, 2013 [75] UK	1. ICA 2. NGCCT 3. NGCCT+ ICA–only NGCCT positive patients undergo further testing with ICA	Patients with known or suspected of CAD, who are difficult to image: obese, coronary calcium score>400, arrhythmias, previous revascularisation, heart rate>65 beats per minute, and intolerance of beta-blockers. The two populations (known CAD and suspected CAD) are evaluated separately. Pretest probability of CAD: 10-29% for suspected CAD and 39.5% for known CAD	Decision tree + 4 Markov models Lifetime horizon	The decision tree divides the patient cohort according to classification according to 'true' disease status, test results, treatment options, and immediate complications from revascularisation and testing procedures. Patients with suspected CAD then enter the: 1. CAD progression model if they are true positives or false negatives, and have not suffered a stroke due to ICA or revascularisation. 2. Stroke model if they have a procedure related stroke 3. General population model if they are TN or FP, and have not suffered a stroke due to the tests. This model only accrues QALYs. For the known CAD population, the key difference is that TN all have CAD and enter the CAD progression model if they have not suffered a stroke due to the tests. All patients accrue costs and disutility due to radiation-induced cancer based on the radiation dose of the diagnostic tests and	ICA is a perfect test. Rates of revascularisation subsequently to tests for patients with CAD were assumed the same as for a previous study, despite the differences between study populations. The suspected CAD population had three treatment options (PCI, CABG and medication), whereas the known CAD population could only be treated with CABG or a PCI. The proportion of patients undergoing each treatment was based on expert opinion. The baseline probabilities in the CAD progression model are dependent on treatment received (medication, CABG or PCI). The probability of non-fatal CV events varies in time. Risk equations are derived from the EUROPA trial and adjusted to reflect the study populations. 4 equations allow estimating the probabilities of (1) any event that will occur in a cycle (3 months); (2) that event being fatal; (3) a subsequent event in the first year after a first non-fatal event and (4) a subsequent event after 1 year. A proportion of the FN are identified as TP every cycle in the CAD progression model, and are treated accordingly. Their prognosis is the same as for TP who were identified directly by the diagnostic test. The diagnostic accuracy estimates differ for the different difficult-to-image groups.

				treatments, through the radiation model. CAD progression model: start, CV death, 'non-fatal primary event in current year (MI/cardiac arrest), history of non-fatal event, and non-CV death. Stroke model: alive or dead Radiation model: no health states. The model keeps track of cumulative radiation exposure and estimates risk of cancer and cancer related death. The model also estimates the costs and QALYs for patients who develop cancer. General population: alive or dead	The baseline characteristics used to parameterise risk equations in the CAD progression model were informed by the patient characteristics in the diagnostic accuracy studies. These characteristics differed by population and difficult-to-image groups. The model distinguishes between ICA and revascularisation complication rates. When a PCI is performed after an ICA, the mortality of PCI only is used (PCI is assumed to be performed at the same time as ICA). HRQoL in the model was based on age, gender, baseline CCS classification and whether or not the patient had undergone treatment. A utility decrement was assumed for non-fatal events.
Espinosa and Annapragada, 2013 [72] US	1. ICA only 2. CCTA using conventional iodine-based contrast agent + ICA 3. CCTA using a BPCA + ICA Patients progress to the next test if results of the previous one are positive. ICA is the reference test. Treatment conditional on test results is not considered in th emodel.	Males aged 55 years with a history of chest pain, presenting at an emergency department with acute chest pain, normal cardiac enzyme levels, and either non-diagnostic or normal ECG results. Pretest probability of CAD: 30%	Decision tree 1 year time horizon	The decision tree splits patients according to testing complications, and then by classification according to 'true' disease status and test results.	ICA is a perfect test. CAD positivity was defined as luminal stenosis of 50% or greater. The diagnostic accuracy of CCTA with BPCA was assumed the same as with a conventional contrast agent. It was assumed that patients were not screened for renal comorbidities prior to testing. The complications from ICA include MI, stroke, ventricular, arrhythmias, local vascular injury, contrast agent reactions, or nephropathy. However, only mortality seems to be considered in the model. CV

					events over the follow-up period are considered and conditional on patient classification (TP, FP, FN or TN). Patients who have a CV event have an additional mortality risk over the time horizon. Utility weights were attributed to patients according to their classification as TP, FP, FN or TN, with a disutility incurred by those who experience a CV event. It is unclear when events are assumed to incur (and thus, for how long is disutility applied).
Fearon et al, 2003 [83] US	1. Nuclear stress imaging 2. FFR 3. No testing (Stent all intermediate lesions) All patients undergo ICA (not reference test). Strategy 1 implies delaying PCI until the test is performed while the other two strategies do not impose further delays to revascularisation Strategy 3 does not consider any further testing, with all patients receiving PCI. Patients tested with nuclear stress imaging receive PCI if ischemia is detected and have to return to cath lab; those without ischemia are treated with medication.	55 year old patients with chest pain who underwent coronary angiography before stress perfusion imaging, and who had an intermediate coronary lesion of unclear physiologic significance. The population only includes patients with 1-vessel disease. Pretest probability of functional ischemia: 40%	Decision tree Lifetime horizon	The decision tree illustrates the diagnostic pathway and subsequent treatment. Patients who are tested with FFR receive PCI if FFR<0.75 and medication otherwise.	It is unclear what the reference test is. Nuclear stress imaging is assumed to have the same diagnostic accuracy as FFR (88% sensitivity and 96% specificity). Deferral of PCI due to nuclear imaging results in additional hospital costs, but not to prognostic changes. The model assumes that 30% of patients would have angina relief with medical therapy and 70% of patients with PCI. Angina relief would be maintained for 4 years, and the quality-of-life adjustment for living with angina was 0.9. A risk of death was assumed for PCI, regardless of whether it was deferred or performed immediately. FFR also had increased the risk of death. It is assumed that survival of patients remains the same, regardless of treatment. However, HRQoL is higher for those who obtain angina relief. The quality-adjusted survival benefits are considered in the model as a QALY pay-off. Life-time costs are considered in a similar manner.

Genders et al, 2009 [79] UK, US, The Netherlands	1. CCTA+ICA 2. ICA In strategy 1, only patients with positive CCTA undergo ICA. Patients who test positive in the last test in the sequence, are treated with a combination of medication, PCI and CABG.	Patients with suspected CAD Pretest probability of CAD: <40%	Decision tree + Markov model Lifetime horizon	The decision tree splits patients according to whether they survive the test, and then by classification according to 'true' disease status and test results. Markov model: alive, CV event, post CV event, CV death, non CV death. CV events included coronary death, MI, coronary insufficiency, angina, stroke, cardiac arrest, peripheral arterial disease, and heart failure	ICA is a perfect test. Diagnostic accuracy was assumed to be independent of age, sex, risk factors, and presentation. Significant CAD was defined as a luminal diameter reduction ≥50%. Risk of CV events and death. Treatment is assumed to reduce the rates of CV events. The model allows for reintervention, but it is not clear what this consists of or how it is implemented in the model. Untreated CAD patients (false negatives) have higher rates of CV events and lower HRQoL due to angina. False negatives are assumed to remain undiagnosed and untreated until they have a CV event (after which they would be correctly diagnosed and treated as FP). CV events are associated with a utility decrement.
Genders et al, 2015[70] UK, US, The Netherlands	1. No imaging 2. CCTA(+FFR) 3. CSI 4. CCTA+CSI 5. ICA (+FFR) In strategy 4, only patients with positive CCTA follow through to CSI. In all strategies, FFR is only performed if CSI was not done before CAG. All strategies were analysed as both conservative and invasive diagnostic work-ups. In the invasive diagnostic work-up, patients	60-year-old patients with stable chest pain and without a history of CAD, PCI or CABG. Pretest probability of CAD: 30%	Microsimulation model comprising a decision tree + state-transition model Lifetime horizon	Decision tree divides the cohort according to disease severity, test results and subsequent treatment. State transition model: alive, post-MI, dead	ICA is a perfect test. The MACE (revascularisation, non-fatal MI, and cardiac death) risk was dependent on disease severity and modified by treatment. FN patients were assumed to return to their physicians with persistent symptoms, have additional testing, and began receiving appropriate treatment within the 1st year (except for patients with moderate CAD without ischemia, for whom it was assumed that only 25% returned).

	with obstructive CAD on CCTA (≥50% stenosis in ≥1 vessel, regardless of severity) and patients with inducible ischemia CSI (regardless of severity) were referred for ICA. In the conservative diagnostic work-up, patients with moderate CAD on CCTA or mild inducible ischemia on CSI received OMT without referral to ICA. CSI includes CMR, SPECT and stress ECHO. Treatment was dependent on disease severity: risk factor management in patients with normal coronary arteries, mild CAD, and moderate CAD without ischemia; OMT for patients with mild ischemia and moderate to severe CAD; PCI for patients with severe CAD and severe ischemia; and CABG for patients with 3-vessel or LM.				Patients without obstructive CAD and without inducible ischemia had age and sex adjusted general population HRQoL. Patients with CAD and on treatment had treatment specific utility values sourced from clinical trial data. The model considered procedural complications (death and MI), but does not distinguish between test and treatment related complications. The model estimates cumulative radiation exposure for each pathway, but does not model the effects of radiation exposure. CCTA was assumed to produce incidental findings of indeterminate clinical importance that resulted in additional radiation exposure, decreased HRQoL, and increased diagnostic costs (due to follow-up testing).
Goeree et al, 2013 [71] Canada	1. CCTA+ICA 2. ICA In strategy 1, only patients with positive CCTA undergo ICA. All patients identified with CAD receive treatment.	Patients with suspected CAD Pretest probability of CAD: 30%	Decision tree + Markov model Lifetime horizon	The decision tree splits patients according to whether they survive the test, and then by classification according to 'true' disease status and test results. Markov model: no event, CV event (MI 1st year), subsequent CV event (MI), death.	ICA is a perfect test Treatment is assumed to be a combination of medication, CABG and PCI, and to reduce the rate of CV events. Testing is assumed to have no impact on HRQoL, but both tests have an associated mortality risk. CV events and mortality rates depend on on age, gender, whether the patient had been diagnosed with CAD and was treated or is still receiving treatment, whether the patient was misdiagnosed and did not received treatment for CAD, and whether the patient had a previous MI and is at increased risk of a subsequent MI and death.

					The 'no event' health state considers different HRQoL estimates depending on whether patients had CAD or not, and if they had CAD whether they were receiving treatment (controlled symptoms) and or not (undiagnosed CAD). Occurrence of CV events result on disutility.
Hayashino et al, 2004 [84] US	1. no screening; 2. Ex-ECG+ICA 3. Exercise ECHO+ICA 4. SPECT+ICA For all strategies involving two tests, only patients who test on the 1st test receive the second test in the sequence. Patients who tested negative or were not screened received no specific therapy. Treatment conditional on ICA results was PCI for patients with 1- or 2-vessels CAD on angiography underwent and CABG for patients with 3-vessel or LM.	Asymptomatic 55 year old men with diabetes, two additional atherogenic risk factors (smokers and hypertension), without a history of angina/MI, and suspected CAD Pretest probability of CAD: 23.5%	Decision tree + Markov model 30 years horizon	The decision tree structure is not described, but the model appears to split patients according to disease severity (no CAD, 1-vessel, 2-vessel, 3-vessel/LM), and consider whether the patients have silent ischemia (not treated under the strategy 1). Markov model: normal (no CAD), silent ischemia, symptomatic ischemia, history of MI, post-PCI, post-CABG, and death.	All patients received aspirin and simvastatin. Patients with MI develop relevant symptoms and receive the appropriate treatment, and patients with silent myocardial ischemia do not receive specific therapy. Patients with silent myocardial ischemia detected by initial screening and patients with symptomatic myocardial ischemia developing in the years following screening received PCI or CABG. Patients with false negative results by screening tests and those with silent myocardial ischemia developing in the years following do not receive specific therapy. PCI and CABG reduces late MI with revascularisation, and annual risk of revascularisation. CABG also reduces the risk of death. The model considers procedural complications (death and nonfatal MI) for ICA, PCI and CABG. The rate of complications is independent of number of vessels involved for ICA, but not for PCI.

Hernandez and Vale, 2007 [81] Mowatt et al, 2004 [82] UK	1. Ex-ECG + SPECT + ICA 2. Ex-ECG + ICA 3. SPECT + ICA 4. ICA Patients progress to the next test if results of the previous one are positive or inconclusive. ICA is the reference test. Treatment is not specified based on risk category, but rates of revascularisation (PCI and CABG) vary across risk categories.	Patients age 60 years old with chest pain and suspected CAD Pretest probability of CAD: 10.5%	Decision tree + Markov model 25 years time horizon	The decision tree classifies patients into CV risk categories, based on the results of testing strategy, and whether they were correctly classified in their risk category. The risk categories are low risk; medium risk; high risk; FN (high risk); FN (medium risk); FP (medium risk). It also accounts for death due to either tests or revascularisation procedures for patients identified as being at high or moderate risk. Markov model: low risk; medium risk; high risk; FN (high risk); FN (medium risk); FP (medium risk); revascularisation; MI; death.	ICA is a perfect test. All misclassified patients correctly diagnosed over a 10-year period as a result of an additional scan or a non-fatal MI. Mortality and MI risk varies by risk category. Procedure related mortality is considered for PCI and CABG. The proportion of patients who undergo CABG amongst those who receive revascularisation is assumed to vary across risk categories. PCI and CABG reduce mortality and MI risk, but to different extents. It is assumed that patients who have an MI or are revascularised will lose some HRQoL for the three subsequent months. Revascularisation does not result in an improvement of HRQoL.
Kreisz et al, 2009 [80] Australia	1. CCTA+ICA 2. ICA Patients progress to the next test if results of the previous one are positive. ICA is the reference test. Treatment is not specified based on test results.	Individuals with suspected significant obstructive CAD Pretest probability:10-90%	Decision tree 10 years time horizon	The decision tree splits the cohort according to the results of CCTA, and whether they were correctly classified (TN, FN, TP or TP). Patients who undergo ICA (directly, as a confirmatory test (TP and FP with strategy 1) or as a late referral (FP for strategy 1) are split into three categories: no complications, complications and death.	ICA is a perfect test ICA complications include acute MI, major vascular complications requiring surgery, transient ischaemic attack, major and minor stroke, and death. Although the risk of complications is stated to be associated with pretest probability of CAD in the study populations, the authors assumed the same rate of complications to be independent of CAD pretest probability in the base-case. Patients with CAD who are correctly diagnosed are assumed to have a higher HRQoL for the full time horizon due to appropriate treatment. FN have 3 months

					with a lower HRQoL, after which they are assumed to be tested with ICA and receive appropriate treatment. The model does not appear to account for any long-term differences in mortality between strategies. The majority of complications from ICA cause temporary disutility. Major stroke is the only complication that causes a permanent loss in utility. It is unclear what utility weight is attributed to individuals who are TN.
Ladapo et al, 2009 [78] US	1. CCTA + ETT 2. ETT + CCTA 3. CCTA 4. ETT 5. Stress ECHO 6. SPECT 7. ICA 8. No diagnostic testing In Strategy 1, all patients are tested with CCTA, and those identified as having severe CAD (3-vessel or LM, are tested with ICA. Positives on ICA are treated with aggressive medical therapy and revascularised (PCI or CABG). Patients with evidence of 1- or 2-vessel CAD on CCTA are tested with Ex-ECG, and those who test positive and markedly abnormal on ETT are treated with aggressive medical therapy and revascularised after confirmatory ICA. Those with CCTA evidence of 1- or 2-vessel CAD whose stress test results are positive but not markedly abnormal are initially managed with aggressive medical therapy alone. Patients with no evidence of significant CAD on CCTA receive no additional therapies beyond baseline care. When the results of the CCTA differ from those of the ETT are treated with aggressive medical therapy only patients with a Bayesian post-test probability of disease exceeding 50% are treated.	55-year-old individuals with stable chest pain and suspected CAD Pretest probability: 30 and 70% (men and women, respectively)	Microsimulation Lifetime horizon	The simulation model tracks patients through the diagnostic pathways defined by each strategy. Patients then enter a natural history model, where they can experience nonfatal adverse (MI and stroke) events, medical and surgical interventions, and death. The model also considers incidental findings of pulmonar nodes with CCTA.	ICA is a perfect test. Patients were assumed to have no prior history of CAD, MI, atrial fibrillation, diabetes mellitus, or LM. The distribution of CAD, proportion of mildly stenosed arteries, number and position of vessels affected was assumed to vary depending on gender. CAD is defined as a ≥50% stenosis in the left main coronary artery or ≥70% stenosis in any other coronary artery. The model considers mortality risks associated with testing procedures, PCI, CABG, repeat revascularisation and pulmonary procedures (follow-up on incidental findings). Rates of revascularisation were higher for patients managed initially with aggressive medical therapy alone or with bare-metal stent–based PCI, while these were lower for patients managed with drug-eluting stents and CABG. The model assumes that patients with CAD who are FN have a constant 5% annual probability of being correctly diagnosed.

	In Strategy 2 (Fig. 2), all patients are tested with ETT. Patients with markedly abnormal results are tested with ICA, and positives are treated with aggressive medical therapy and revascularisation. Patients whose ETT is positive but not markedly abnormal are tested with CCTA, and those with evidence of severe CAD are further tested with ICA and positives are treated as above. Patients with CCTA evidence of 1- or 2-vessel CAD are initially treated with aggressive medication alone. Patients with no evidence of CAD receive baseline care. In strategy 3, all patients are tested with CCTA, and those with evidence of significant CAD are tested with ICA. Patients with 1- or 2-vessel CAD on receive aggressive medical therapy alone; those with 3-vessel and LM receive aggressive medical therapy + revascularisation. Patients with no evidence of CAD receive baseline care. In strategy 4, all patients whose ETT is positive but not markedly abnormal are treated aggressively with medication alone. Those who test positive and markedly abnormal on Ex-ECG are treated with aggressive medical therapy and revascularised after confirmatory ICA. Strategies 5 and 6 are similar to Strategy 4 but use stress ECHO and SPECT, respectively. Strategy 7 tests all patients with ICA, and treats based on that test as per other strategies. In strategy 8 patients are not evaluated for CAD and receive no therapies beyond baseline care.				Treatment for CAD reduces mortality and rate of CV events compared to untreated CAD. Treatment effects on mortality are dependent on the number of vessels and location of stenosis. It was assumed that lung nodes had no direct impact on survival. HRQoL estimates were dependent on whether patients had CAD and its severity, as well as the incidence of nonfatal CV events and angina relief from treatment. The combination of aggressive medical therapy with PCI or CABG was assumed more effective in relieving angina symptoms, than aggressive medical therapy alone, and that CABG was marginally more effective than PCI.

Lee et al, 2015 [69] South Korea	1. CCTA + 2nd test (ICA or SPECT) 2. SPECT + 2nd test (ICA or CCTA) In all strategies patients with a positive on the first test were referred to ICA or a second noninvasive test. ICA was the reference test. The pathway for patients who have inconclusive test results is not clear. Patients could be treated with: observation without medication, medication only, PCI, or CABG. Only patients with a positive ICA result could undergo revascularisation. The other treatment options were possible for all patients regardless of testing strategy and test results.	Individuals with chest pain and suspected CAD Pretest probability of CAD:10-90% (this was stratified into 3 subgroups (10-29%, 30-60%, and 61-90%), which were evaluated separately	Decision tree 1 year time horizon	The decision tree split the cohort according to test results, underlying disease status and subsequent treatment, and considered the following one-year outcomes: no event, event, or death related to CAD.	ICA is not a perfect test. Diagnostic accuracy was estimated based on a retrospective cohort study, with a correction to sensitivity and specificity. The correction was necessary because not all patients underwent ICA in the study, and clinicians were more likely to refer patients with positive non-invasive test results to ICA. Positive ICA defined as any luminal stenosis ≥70% in any of the major coronary arteries. The events considered in the model were MI and unstable angina requiring hospital admission. HRQoL was assumed to depend on whether patients received appropriate treatment and re-experienced CAD during the 1-year follow-up. Transition probabilities were estimated based on data from the same retrospective study that informed the diagnostic accuracy data.
Min et al, 2010 [77] US	1. CCTA + ICA for positive or inconclusive findings 2. CCTA + ICA for positive findings and SPECT for inconclusive findings 3. SPECT + ICA for positive or inconclusive findings 4. SPECT + ICA for positive findings and CCTA for inconclusive findings 5. ICA ICA is the reference test. Individuals received no treatment if identified as having no CAD, were treated with medical therapy if they had CAD of any severity. In addition, patients with	55-year-old male with chest pain and no prior history of CAD Pretest probability of CAD: 30%	Decision tree (although not described as such) + Markov model Lifetime horizon	The decision tree splits the cohort according to test results, underlying disease status and severity of disease. Markov model: No CAD (No treatment); Mild CAD (no treatment); Moderate CAD (no treatment); Severe CAD (no treatment); No CAD (treatment); Mild CAD (treatment); Moderate CAD (treatment); Severe CAD (treatment); death.	ICA is a perfect test Obstructive CAD defined as a luminal stenosis severity ≥ 50% in the left main coronary artery or ≥ 70% in any other major epicardial artery. Baseline risks in the Markov model depend on disease severity. Medication, PCI and CABG reduce risks of death and CV events. 90% of patients with CAD that were not diagnosed by the initial test are assumed

	moderate CAD received PCI, and those with severe CAD, CABG.			Patients in the Markov model could suffer MI events and revascularisation/repeat revascularisation.	to be correctly diagnosed within 10 years in the model. HRQoL varies according to CAD severity with MI and revascularisation events imposing a disutility. ICA, PCI and CABG have an associated immediate mortality risk. CCTA is assumed to produce incidental findings which impose a one off cost.
Min et al, 2017 [66] US	1. ETT + ICA for positive or inconclusive findings 2. ETT + Stress ECHO for inconclusive findings and ICA for positive findings 3. ETT + MPS for inconclusive findings and ICA for positive findings 4. ETT + CCTA for inconclusive findings and ICA for positive findings 5. Stress ECHO + ICA for positive or inconclusive findings 6. Stress ECHO + CCTA for inconclusive findings and ETT 7. MPS + ICA for positive or inconclusive findings 8. MPS + CCTA for inconclusive findings and ICA for positive findings 9. CCTA + ICA for positive or inconclusive findings 10. CCTA + Stress ECHO for inconclusive findings and ICA for positive findings 11. CCTA +MPS for inconclusive findings and ICA for positive findings 12. ICA ICA is the reference tests. Individuals received no treatment if identified as having no CAD, were treated with medical therapy if they had mild CAD of any severity. Patients with moderate CAD were managed with medical therapy (50%) or PCI + medical therapy	55-year-old male with chest pain and no prior history of CAD Pretest probability of CAD: 20%	Decision tree (although not described as such) + Markov model Lifetime horizon	The decision tree splits the cohort according to test results, underlying disease status and severity of disease. The model accounts for outcomes and costs of treatment for those correctly diagnosed with CAD, diagnosis of FN, and clinical events such as revascularisation, MI and death. However, the model states are not clearly described or depicted.	ICA is a perfect test Mild CAD - non-obstructive stenosis 1-69% in all affected vessels, not including the left main artery. Moderate CAD - ≥70% stenosis in one or two major epicardial coronary artery vessels, not including the left main artery. Severe CAD - ≥50% stenosis in the left main artery or ≥70% stenosis in any other major epicardial artery. Patients experiencing post-test MI were also considered to have severe CAD. ICA, PCI and CABG have an associated immediate mortality risk. Baseline risks in the Markov model depend on disease severity. Medication, PCI and CABG reduce risks of death and CV events. HRQoL depended on whether individuals had CAD and the severity of pain for those that had CAD. Patients who underwent revascularisation had a temporary improvement in their HRQoL. MI events impose a disutility.

	(50%). Patients with severe CAD were managed with PCI + medical therapy (50%) or CABG + medical therapy (50%).				20% of patients with CAD that were not diagnosed by the initial test are assumed to be correctly diagnosed within 5 years in the model.
Pletscher et al, 2016 [68] Switzerland	1. ETT + ICA 2. Stress echo+ICA 3. SPECT+ICA 4. CCTA+ ICA 5. CCTA + SPECT for intermediate or indeterminate scans + ICA For strategies 1 to 6, all positive and inconclusive test results progress to the next test in the sequence. ICA is the reference test. Patients who test positive in their overall diagnostic sequence are managed with revascularisation. Patients with CAD but no significant stenosis are managed with medical therapy.	60-year-old males with suspected CCS grade 2 CHD and a prior likelihood of stenosis of 39.5%			The model is equivalent to the model developed by Walker et al, 2011 [73] with updated parameters to reflect the Swiss health care system context.
Priest et al, 2011 [76] US	6. ETT + ICA 7. Stress echo+ICA 8. SPECT+ICA 9. CCTA+ ICA 10. CCTA + SPECT for intermediate or indeterminate scans + ICA Positive results with any test require confirmation with ICA, which is the reference test. There is no explicit link between test results and treatment (not explicitly modelled). CV event rates are dependent on testing strategy alone.	Patients presenting to an emergency department with chest pain and at low risk of CAD Pretest probability of CAD: 2-30%	Decision tree 1 year time horizon	The decision tree splits the cohort according to test results and underlying disease status. It also captures the occurrence of CV events (death, MI) during the time horizon.	ICA is a perfect test. TP have an increased risk of CV events compared to patients who had negative results. Patients with positive diagnostic tests who subsequently tested negative on ICA were assumed to have an annual risk of a CV event compared with patients with normal test results. Patients with negative test results on the initial screen had CV event rates were conditional on tests undertaken. TN were assumed to have the population norm HRQoL, while TP had a lower HRQoL (equivalent to patients with angina). FP incurred disutility from stress associated with misdiagnose and for undergoing ICA unnecessarily. Patients

					who have a MI are subject to a reduction in HRQoL too. It is unclear what is the HRQoLof FN.
Walker et al, 2011 [73] UK	1. ICA 2. ETT + ICA 3. ETT + CMR + ICA 4. ETT + SPECT + ICA 5. CMR + ICA 6. SPECT + ICA 7. ETT+ ICA if positive or CMR if ETT inconclusive + ICA 8. ETT+ ICA if positive or SPECT if ETT is inconclusive + ICA For strategies 1 to 6, all positive and inconclusive test results progress to the next test in the sequence. ICA is the reference test. Patients who test positive in their overall diagnostic sequence are managed with revascularisation. Patients with CAD but no significant stenosis are managed with medical therapy.	60 year old males referred to cardiologists with suspected CAD (CSS2) Pretest probability of significant stenosis requiring revascularisation: 39.5%	Decision tree + Markov model 50 years time horizon	The decision tree groups individuals into 3 groups according to test results, their underlying disease status, and whether they suffer procedural death from ICA or revascularisation: TP, FN, TN with angina, TN without angina, and death. Markov model is composed of 3 sub-models for patients: 1. with significant stenosis – entry FN, entry TP, non fatal CV event, non fatal CV event post 12 months, CV death, non CV death. 2. without significant stenosis but with angina – entry TN with angina non fatal CV event, non fatal CV event post 12 months, CV death, non CV death. 3. without significant stenosis or angina: alive and dead.	ICA is a perfect test Diagnostic accuracy estimates for all tests were calculated conditional on positive/uncertain results in earlier tests in the strategy based on a single study. These allowed accounting for correlations between tests within diagnostic strategies. The proportion of patients with significant stenosis receive PCI or CABG was sourced from the literature. Risks of long-term CV mortality and CV events (including increased risk of further CV events during 1 year after a CV event) was estimated based on risk equations from the EUROPA study. The model accounted for cancer related mortality conditional on radiation exposure associated with tests and revascularisation procedures (ICA, SPECT and PCI). The proportion of FN assumed to be diagnosed (and subsequently receive appropriate revascularisation) within one year in the model was informed by expert elicitation and is conditional on CCS grade. HRQoL for patients with CAD varies by age, gender, initial CCS grade and treatment status. HRQoL reductions for patients experiencing angina are assumed to be a fixed proportion of the HRQoL of the general population by age. Revascularisation is assumed to improve

					HRQoL, through angina relief but have no effect on the risk of CV events.

BPCA, blood-pool contrast agent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian cardiovascular society; CMR, cardiovascular magnetic resonance; CSI, cardiac stress imaging; CCTA, coronary computed tomography angiography; CV, cardiovascular; ECHO, echocardiography; ETT, exercise treadmill testing; Ex-ECG, exercise electrocardiography; FFR, fractional flow reserve; FN, false negative; FP, false positive; HRQoL. Health-related quality of life; ICA, invasive coronary angiography; LM, left main trunk disease; MACEs, major adverse cardiac events; MI, myocardial infarction; MPS, myocardial perfusion scintigraphy; NGCCT, new generation dual-source coronary CT with>64 slices; PCI, percutaneous coronary intervention; SPECT, single-photon emission computed tomography; TN, true negative; TP, true positive.

10.9 Appendix 9: Systematic review protocol

Title of the project

QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing coronary obstructions: a systematic review and economic evaluation

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Plain English Summary

Stable angina is a type of chest pain caused by insufficient blood supply to the heart, brought on by physical activity or emotional stress, which goes away with rest. If left untreated, it can lead to complications such as unstable angina, heart failure, heart attack, and sudden death.

To avoid these complications, patients may require intervention to open damaged, constricted or blocked arteries, known as "revascularisation". This most commonly consists of inserting a small tube or "stent" into the artery to keep it open and allow blood flow.

Patients who might need revascularisation undergo a number of tests to identify blocked arteries, including coronary computed tomography angiography (CCTA) and other non-invasive tests. However, these tests are often inconclusive, in which case more invasive tests are needed.

The last line of testing consists of an invasive coronary angiogram (ICA). During an ICA procedure, a catheter is inserted into an artery and moved into the coronary arteries. A special type of dye called contrast medium is injected through the catheter and X-ray images (angiograms) are taken. Visual assessment of these angiograms has limited ability to differentiate between arteries with inadequate blood supply (which need revascularisation) and those with adequate supply which do not need treatment. When an angiogram is inconclusive it may be combined with the invasive measurement of blood flow, measured by inserting a wire into the artery, after giving drugs to dilate the artery. This is called invasive fractional flow reserve (FFR) assessment. Because this procedure is invasive it carries some risks and may have substantial side effects.

Non-invasive imaging tests have been proposed to precede or replace invasive FFR, by using the existing angiograms to determine blood flow, without inserting a wire. These include the QAngio XA 3D/QFR imaging software (produced by Medis) and CAAS vFFR (produced by Pie Medical Imaging).

This project will investigate whether the QAngio and CAAS vFFR technologies can provide accurate assessments of blood flow. The project will consider whether these technologies can improve on using visual assessment of the angiograms alone, and be used to make reliable decisions on whether revascularisation is needed, and so reduce the need for invasive FFR. It will also investigate whether using these technologies is a reasonable use of NHS resources.

To do this a thorough review of all the literature on the QAngio and CAAS vFFR technologies will be performed. Any data from studies of these technologies will be re-analysed to determine whether it accurately predicts the need for revascularisation and consider its clinical benefits. An economic

analysis will be conducted to investigate whether using either of these technologies is economically viable.

Decision problem

The purpose of this assessment is to investigate non-invasive technologies for assessing the functional significance of coronary stenoses during invasive coronary angiography (ICA). This may be either quantitative flow ratio (QFR) assessment using the QAngio XA 3D/QFR (Medis) imaging software or vessel-fractional flow reserve using the CAAS vFFR system (Pie Medical Imaging). The assessment will consider whether these are clinically useful and cost-effective as alternatives to, or in addition to, using standard ICA alone, with or without invasive assessment of fractional flow reserve.

Interventions

Non-invasive imaging techniques for the assessment of the functional significance of coronary obstructions (stenoses) avoid the need for a pressure wire or adenosine. They could be used in people with stable chest pain of recent onset who are referred for invasive coronary angiography (ICA). Visual assessment of angiograms taken during ICA may be limited in its ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses.

QAngio XA 3D/ QFR

QAngio XA 3D/QFR (Medis) imaging software is used to perform QFR assessment of coronary artery obstructions. It is designed to be used with all invasive coronary angiography (ICA) systems; biplane or monoplane. It uses 2, 2D X-ray angiographic projections, taken at least 25 degrees apart – and ideally between 35 and 50 degrees apart – to create a 3D-reconstruction of a coronary artery; this shows the QFR values across the artery. QFR is an assessment (by frame count) of the pressure (blood flow velocity) drop over the artery, with a value of 1 representing a normally functioning artery with no pressure drop. A 20% or more drop in blood pressures (QFR value of 0.8 and less) is considered a significant obstruction where revascularisation should be considered. QAngio XA 3D/QFR software is installed on a laptop or workstation that is connected to the ICA system. The Digital Imaging and Communication in Medicine (DICOM) data from ICA projections are immediately uploaded and viewable on the connected workstation. The total time for data acquisition and analysis is about 4 to 5 minutes (as reported by the company). AngioPlus (Pulse Medical Imaging Technology, Shanghai, China) is an equivalent CE-marked version marketed in Asia.

The QAngio software offers two different flow models to calculate QFR:

- Fixed flow QFR, using fixed flow velocity

- Contrast QFR, using contrast frame count in an angiogram without hyperaemia.

Fixed flow QFR is faster to compute, but may be less accurate than contrast QFR.

Furthermore, the QAngio software provides 4 different QFR indices along the analysed coronary segment:

- Vessel QFR: the QFR value at the distal location of the analysed vessel segment
- Index QFR: a point which can be moved along the QFR pullback curve
- Lesion QFR: the contribution to the QFR drop by the selected lesion alone
- Residual vessel QFR: an indication of the vessel QFR, if the selected lesion is resolved.

CAAS vFFR

CAAS vessel-FFR workflow builds a 3D reconstruction of a coronary artery based on 2 standard X-ray angiograms, assesses the pressure drop across the stenosis, and determines a vessel FFR value. It gives both anatomical and functional assessment of the stenosis, and can be integrated into catheter laboratories. The total time for analysis is approximately 2 minutes per artery according to the company.

All available versions of CAAS (8.0, 8.1, 8.2) use the same algorithm for calculating vFFR. The CAAS workstation provides various modules (for example, quantitative coronary arteriography and left ventricular analysis), and the vFFR module can be added to the CAAS workstation. In addition to the vFFR, CAAS vFFR provides measurements at the end of the lesion and at a chosen position in the coronary artery.

Diagnostic technologies and pathways

The main alternatives to using QAngio or CAAS vFFR , are:

a) Visual interpretation of the angiographic images created during invasive coronary angiography (ICA) (including assessment of percentage diameter stenosis), without invasive flow assessment (FFR or iFR).

b) Visual interpretation of the angiographic images, followed by invasive flow assessment (FFR or iFR) if ICA alone is inconclusive.

Therefore, when adding the option to use QAngio or CAAS vFFR , four diagnostic pathways might be used to decide on whether to proceed to revascularisation, namely:

1. Visual assessment of ICA alone (without QFR or FFR/iFR)
2. ICA, followed by FFR/iFR if ICA is inconclusive
3. ICA, followed by QFR or vFFR if ICA is inconclusive (without using FFR/iFR)
4. ICA, followed by QFR or vFFR if ICA is inconclusive, with subsequent FFR/iFR if results remain inconclusive

The clinical and cost-effectiveness of each of these four diagnostic pathways will be investigated and compared.

Population and relevant subgroups

The population of interest is individuals with suspected stable angina who may need revascularisation, who have been referred for ICA because any previous non-invasive testing has not resolved whether revascularisation is required.

According to NICE guidance, ICA should be a third-line assessment: following CT coronary angiography and/or other non-invasive functional imaging, where these have not resolved whether revascularisation is required. However, ICA may also be used as a first or second-line assessment where CT coronary angiography is unavailable, or if patients are deemed at sufficiently high risk for revascularisation to justify immediate ICA.

The particular focus is on patients whose ICA results show intermediate stenoses. Various definitions of intermediate stenosis exist, with lower limits ranging from 30% to 50% and upper limits from 70% to 90%. This assessment will therefore not, initially, use any specific definition, instead considering an intermediate stenosis to be any stenosis where uncertainty remains before or after ICA as to whether revascularisation should be performed.

The accuracy of QFR or vFFR in identifying individuals who may require revascularisation may depend on some clinical and lesion characteristics such as age, gender, history of cardiovascular disease, previous PCI, lesion length and location. Previous MI and presence of microcirculatory disease have been identified as variables that may be associated with reduced accuracy of QFR.[196-198]

The subgroups relevant to this appraisal can be defined as people at higher (and lower) risk of requiring revascularisation.

Place of the intervention in the care pathway

Angina is a type of chest pain caused by insufficient blood supply to the heart (myocardial ischemia). 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 which remains one of the main causes of morbidity and mortality in high-income countries. If left untreated, it can lead to cardiovascular complications such as, unstable angina, myocardial infarction, heart failure and sudden cardiac death.

The diagnostic pathway for stable angina aims to confirm the diagnosis of stable angina, and define the severity of coronary stenosis to identify people who may benefit from revascularisation in addition to OMT.

Patients who experience chest pain will be assessed for angina, and other cardiovascular conditions. Where clinical assessment alone is insufficient for a diagnosis patients should be referred for 64-slice or above coronary CT angiography (CCTA) as the first-line diagnostic test when clinical assessment suggests typical or atypical angina, or non-anginal chest pain, but 12-lead resting electrocardiogram (ECG) has been done and shows ST-T changes or Q waves.

Patients may go on to further diagnostic testing. NICE guidance 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. This could include:

- myocardial perfusion scintigraphy with single-photon emission computed tomography (MPS with SPECT)
- stress echocardiography
- first-pass contrast-enhanced MR perfusion
- MR imaging for stress-induced wall motion abnormalities.

If these tests are also inconclusive ICA is offered as a third-line diagnostic tool.

A diagnosis of stable angina should be made when clinical symptoms are present and:

- significant coronary artery disease is found during ICA or 64-slice (or above) CTCA. This is usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.

- reversible myocardial ischaemia is found during non-invasive functional imaging.

ICA may also be used to guide treatment strategy for people with a confirmed diagnosis of stable angina whose symptoms are not satisfactorily controlled with OMT, and so may require revascularisation.

During an ICA procedure, a coronary diagnostic catheter is inserted into an artery, usually in the arm pit or groin, and moved up the aorta and into the coronary arteries. A special type of dye called contrast medium is injected through the catheter and X-ray images (angiograms) are taken. Although providing valuable information on coronary artery anatomy, visual assessment of angiograms taken during ICA has limited ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses.

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. NICE guideline on chest pain does not currently consider FFR; however other guidelines (such as those of the European Society of Cardiology and American College of Cardiology) do recommend its use, and state that lesions with an FFR of less than 0.80 are functionally significant and revascularisation may be considered. FFR is assessed invasively by advancing a pressure wire towards the stenosis and measuring the ratio in pressure between the two sides of the stenosis during maximum blood flow (induced by adenosine infusion). This is associated with risks related to the passage of a guide wire, side effects of adenosine, and additional radiation exposure. The invasive FFR measurement is also associated with increased procedural time and costs, compared with ICA alone.

As an alternative to invasive FFR, instantaneous wave-free ratio (iFR) may be used. This also uses inserted pressure wires to assess flow, but does not require vasodilator drugs such as adenosine. An iFR of 0.89 or less is considered functionally significant.

ICA can be performed either in diagnostic-only ICA laboratories, or in interventional catheter laboratories as part of the initial stenosis assessment prior to percutaneous coronary intervention. In diagnostic-only laboratories patients where ICA alone is inconclusive might be referred to an interventional laboratory for an FFR or iFR assessment. In interventional laboratories an FFR or iFR assessment can be performed immediately after ICA, if needed.

QFR or vFFR could potentially replace pressure-wire FFR, or iFR, by providing a non-invasive means to assess FFR as part of an ICA assessment. Alternatively, they may be used as a precursor to invasive FFR, with the invasive procedure used when QFR or vFFR is inconclusive. The QAngio instructions recommend the following approach:

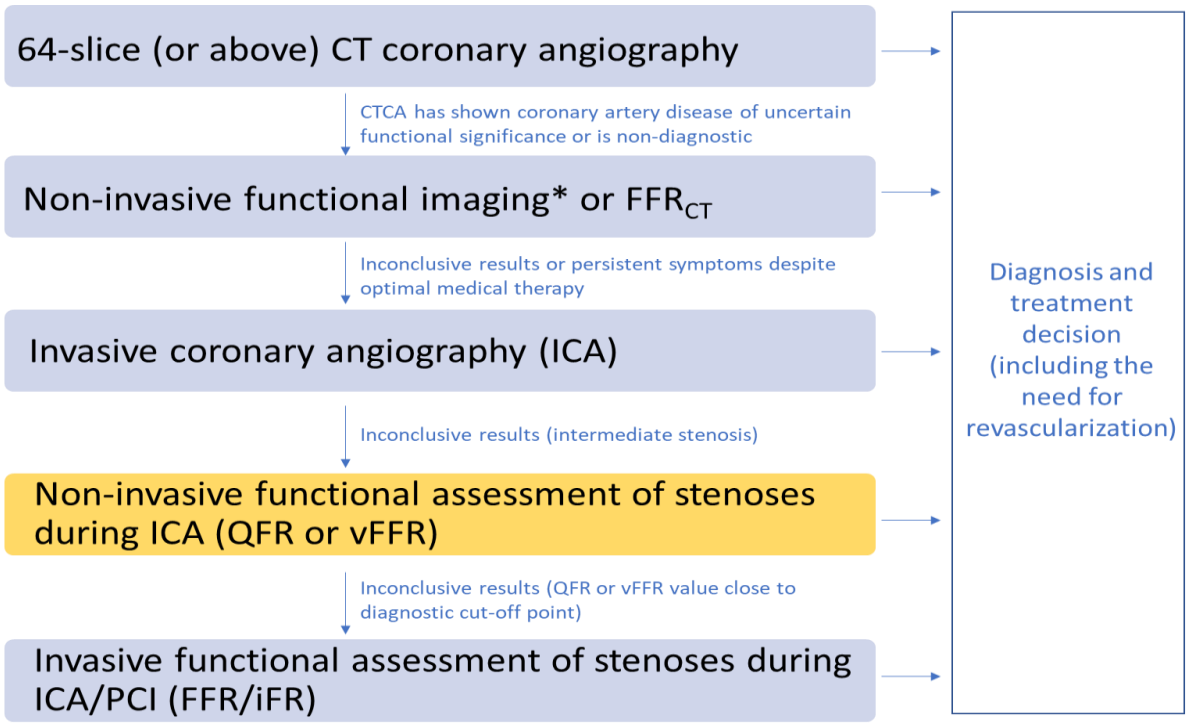
- QFR below 0.78: treat the patient in the catheter laboratory;
- QFR above 0.84: follow the patient medically;
- QFR between 0.78 and 0.84: verify by invasive FFR measurement.

QFR could also potentially be used in other aspects of decision making, including whether to stent more than one vessel, or to select a stent type or other interventional device for revascularisation.

QAngio and CAAS vFFR could be used in diagnostic-only laboratories, possibly reducing the need for referrals to interventional laboratories.

The likely pathway leading to invasive FFR, and including the probable placement of QFR, is summarised in Figure 1.

Figure 1 Diagnostic pathway for stable angina, including QFR or vFFR (from NICE DAP 48 final scope)



A diagnosis of stable angina should be made when:

- significant coronary artery disease is identified during ICA or 64-slice (or above) CTCA, usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.
- reversible myocardial ischaemia is found during non-invasive functional imaging

There is substantial regional variation in the diagnostic pathway for stable angina, due in part by availability of imaging modalities at each centre, and experience (or preferences) of the cardiologists referring for the test. Clinical advisors noted that the pathway recommended by NICE is widely recognised as current best practice.

Objectives

The aim of the project is to determine the clinical and cost-effectiveness of non-invasive assessment of the functional significance of coronary stenoses, using the QAngio XA 3D/QFR (Medis) and CAAS vFFR (Pie Medical Imaging) imaging software.

To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review and meta-analysis of the diagnostic accuracy and, where feasible, clinical efficacy of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, used during ICA for assessing the functional significance of coronary obstructions in people with stable chest pain whose angiograms show intermediate coronary stenosis.
- To perform a narrative systematic review of the clinical efficacy and practical implementation of QAngio and CAAS vFFR. This will include assessment of the associated revascularisation rates, mortality and morbidity, patient-centred outcomes, adverse events, and acceptability to clinicians and patients.

Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, for assessing the functional significance of coronary stenosis in people with stable chest pain whose angiograms show intermediate stenosis.

- To develop a decision model to estimate the cost-effectiveness of the QAngio XA 3D/QFR and CAAS vFFR imaging software used during ICA to indicate whether coronary obstructions are functionally significant. Consideration will be given to differences in the cost-effectiveness of the technologies in diagnostic-only or in interventional catheter laboratories.

- The decision model will link the diagnostic accuracy of QFR derived from the QAngio XA 3D/QFR imaging software, and vFFR derived from the CAAS vFFR software, to short-term costs and consequences (e.g., the impact on the number of revascularisations needed, the proportion of people who need invasive functional assessment of stenosis, time to test results, and associated risks of the diagnostic intervention). It will then link the short-term consequences to potential longer-term costs and consequences (e.g., major cardiovascular events such as myocardial infarction and sudden cardiac death, adverse events related to revascularisation and diagnosis, mortality) using the best available evidence.

- The cost-effectiveness of the QAngio XA 3D/QFR and CAAS vFFR imaging software compared with visual assessment of ICA alone, or ICA followed by FFR/iFR if ICA is inconclusive, will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

Methodology

Systematic review of diagnostic accuracy and clinical effectiveness

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.

Literature searching

Comprehensive searches of the literature will be conducted to identify all studies relating to the QAngio technology and to CAAS vFFR.

Focused searches will be used to identify literature on invasive FFR more generally, to identify key papers and reviews of the clinical effectiveness and implementation of invasive pressure-wire FFR and iFR.

The following databases will be searched: MEDLINE, PubMed, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Health Technology Assessment (HTA) Database and EconLit.

Ongoing and unpublished studies will be identified by searches of ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations & Theses A&I, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. Abstracts from any recent conferences which are thought to be relevant to the review will also be consulted.

A search strategy for Ovid MEDLINE is included in Appendix 1. The MEDLINE strategy will be translated to run appropriately on the other databases and resources. No language or date restrictions will be applied to the searches. A study design search filter will not be used.

Reference lists of relevant reviews will be scanned in order to identify additional potentially relevant reports.

Searches for studies for cost and quality of life data will also be undertaken, as determined by the economic model.

Pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence and during the development of the model.

IPD and contact with study authors and manufacturers

An individual participant data (IPD) meta-analysis of four studies likely to be eligible for this review has previously been performed.[199] The EAG have contacted the authors, and they have agreed, in principle, to share the collected IPD with the EAG for the purposes of this assessment.

Given this agreement, the authors of any other diagnostic accuracy studies deemed eligible for the review may also be contacted and IPD for their study requested. However, given the short timelines of this project, IPD requests will be restricted to larger studies of most relevance to UK. It is also anticipated that authors may not be able to provide IPD, and published data will be used. IPD will not be sought for studies of clinical outcomes.

It is anticipated that many studies may not report sufficient data in publications to perform full syntheses or fully populate the economic model. Therefore, study authors may be contacted to seek detailed diagnostic and other clinical data as appropriate, where they are unable to provide suitable

IPD. Manufacturers may similarly be contacted to seek more detailed data, and to identify unpublished studies or data sources.

Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any titles and abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements will be resolved by consensus or, where necessary, by consulting a third reviewer. Conference abstracts will be eligible and attempts will be made to contact authors for further data.

The following eligibility criteria will be used to identify relevant studies:

Participants

Patients with stable chest pain (either suspected stable angina or confirmed angina that is not adequately controlled by treatment), who are referred for ICA to assess coronary stenosis and the need for revascularisation. Studies without patients with intermediate stenosis (however defined) will be excluded.

Interventions

QAngio XA 3D/QFR (and AngioPlus) and CAAS vFFR imaging software used in conjunction with ICA to allow simulation of FFR.

The two sub-measurements of contrast-flow QFR (cQFR) and fixed-flow QFR (fQFR) that are offered by the QAngio software will be included. Eligible healthcare settings include diagnostic-only and interventional catheter laboratories.

Reference standard

The reference standard is FFR assessed using an invasive pressure wire with or without adenosine.

Instantaneous wave-free ratio (iFR), which was found to be non-inferior to FFR,[200] will also be accepted as a reference standard.

Outcomes

The eligible outcome measures relating to diagnostic accuracy are:

- Sensitivity and specificity of QAngio XA 3D/QFR, CAAS vFFR

- Positive and negative predictive values
- Estimates of difference in measurements between QFR or vFFR and invasive FFR/iFR
- Correlation between QFR or vFFR and invasive FFR/iFR measurements (including Bland-Altman assessments)

Some studies may report difference or concordance between QFR or vFFR and invasive FFR/iFR in numerous ways, including inter and intra-rater differences in measurements, correlation coefficients, sensitivity and specificity or ROC curves. All relevant outcome definitions and cut-offs will be extracted and their applicability to the decision problem will be accounted for when presenting the results. Diagnostic accuracy results of ICA alone will be considered if reported alongside QAngio or CAAS.

In addition, the following clinical outcomes will be eligible:

- Morbidity, mortality and major adverse events (e.g. myocardial infarction, heart failure)
- Adverse events related to the diagnostic procedure (e.g. pressure wire damage, adenosine side effects, stroke)
- Adverse events related to revascularisation
- Distress, anxiety and similar harms caused by QFR, vFFR, invasive FFR or iFR
- Subsequent use of invasive pressure-wire FFR or iFR
- Subsequent revascularisation procedures performed
    - Including unscheduled revascularisations
- Number of vessels with stent placements
- Health related quality of life
- Radiation exposure
- Test failure rates
- Inconclusive test rates

- Inter-observer variability

Eligible outcomes related to the implementation of the interventions of interest and related practical issues include:

- Acceptability of QFR, vFFR and invasive FFR (to clinicians and patients)
- Timing of results from data acquisition
- Referral times
- Patient satisfaction
- Training requirements
- Uptake and compliance

Study designs

Diagnostic accuracy and correlation studies

Eligible study designs will be studies in which QFR using the QAngio system, or CAAS vFFR are performed alongside invasive FFR (or iFR) as a reference standard in the same patients.

Clinical effectiveness/implementation

Eligible study designs will be any experimental or observational study where QFR or vFFR (with or without invasive FFR) have been used and which report relevant clinical outcomes as listed above. We will also include relevant publications reporting issues related to implementation of, or practical advice for, QFR or vFFR and their use in clinical practice.

The following types of publication will be excluded: case reports, and studies focusing only on technical aspects of QFR or vFFR (such as technical descriptions of the testing process or specifications of machinery and software).

Data extraction

Data on study and patient characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. If time constraints allow, attempts will be made where possible to contact authors and/or manufacturers for

missing data and original raw data (IPD). Data from relevant studies with multiple publications will be extracted and reported as a single study. The most recent or most complete publication will be used in situations where we cannot exclude the possibility of overlapping populations.

Where IPD cannot be supplied, data may be extracted from published figures using suitable data extraction software.

Collection of IPD

In order to obtain IPD a data sharing agreement will be established between study authors and the EAG (see draft version in Appendix 2) to permit formal transfer of data. Data will be requested on results of QFR, invasive FFR, and ICA, sufficient to calculate diagnostic accuracy, along with data on key subgroup characteristics (see below), where available; however the EAG will accept any data the authors may have. The EAG will accept data in any electronic form. Data supplied must be anonymised and transferred to the EAG by secure means. The data will be held securely at York, accessible only to the EAG, and will not be transferred to other computers or portable devices. IPD will be deleted after the end of the project, in agreement with study authors.

Quality assessment strategy

The quality of the diagnostic accuracy studies will be assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies), modified as necessary to incorporate review-specific issues. QUADAS-2 evaluates both risk of bias and study applicability to the review question. Suitable quality assessment tools such as ROBINS-I will be used based on the availability of other eligible clinical outcomes and study designs.

The quality assessments will be performed by one reviewer and independently checked by a second reviewer. Disagreements will be resolved through consensus, and where necessary, by consulting a third reviewer.

Synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by population and test characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques.

Statistical analysis of diagnostic accuracy

Using extracted diagnostic accuracy data from 2 x 2 tables, from IPD, or extracted from figures, estimates of sensitivity and specificity will be calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. Positive and negative predictive values will also be calculated and presented in figures and tables. Where three or more studies are available the hierarchical bivariate model described by Reitsma et al. will be fitted which calculates summary estimates of sensitivity and specificity and the associated 95% confidence intervals (CIs). The hierarchical summary ROC (HSROC) model will also be fitted to produce summary ROC curves. Results of both models will be presented in ROC plots.

While diagnostic accuracy analysis will be the preferred method of meta-analysis, if this is not feasible meta-analysis of correlation coefficients and meta-analyses of differences in measurements will also be performed.

Sensitivity analyses will be performed to assess the possible impact of uncertainty in diagnostic accuracy, differences across patient subgroups, and the impact of failed or inconclusive QFR assessment.

Statistical analysis of clinical effectiveness

Data on clinical outcomes will be tabulated or plotted. Where there are sufficient studies reporting the same clinical outcomes, results will be synthesised using standard random-effects meta-analyses.

If sufficient data are available, statistical models (such as simulation studies) will be generated to assess the impact of QFR, vFFR and invasive FFR/iFR assessment on the number of revascularisations performed, and on morbidity and mortality and other longer-term outcomes. The four diagnostic pathways:

1. Visual assessment of ICA alone (without QFR or FFR/iFR)
2. ICA, followed by FFR/iFR if ICA is inconclusive
3. ICA, followed by QFR or vFFR if ICA is inconclusive (without using FFR/iFR)
4. ICA, followed by QFR or vFFR if ICA is inconclusive, with subsequent FFR/iFR if results remain inconclusive

will be compared in terms of their impact on morbidities, mortality and adverse events.

All statistical analyses will be conducted in R and/or Stata software, as appropriate.

Investigation of heterogeneity and subgroup analyses

For diagnostic accuracy data, we will visually inspect the forest plots and ROC space to check for heterogeneity between study results. To investigate sources of heterogeneity, we will incorporate relevant covariates in the bivariate and HSROC models, where possible. Subgroup analyses will be conducted, by performing separate bivariate and HSROC models in defined subgroups of studies.

Where possible, for diagnostic accuracy data and clinical outcomes reviews, we will consider the following factors as potential sources of heterogeneity:

- Type and severity of stenosis (e.g. high percentage diameter stenosis)
- multivessel coronary artery disease
- diffuse coronary artery disease
- multiple stenoses in one vessel
- microvascular dysfunction (for example, caused by diabetes)
- chronic total occlusion
- diabetes
- sex
- age
- ethnicity (or study location as a proxy for ethnicity)
- results of previous non-invasive tests
- use of fixed flow QFR vs. contrast QFR (QAngio XA 3D)
- previous MI

Sensitivity analyses

We will carry out sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS-2 domain results (for example, by excluding studies with high risk of incorporation bias) and study design (for example, in-procedure versus retrospective evaluation of index test results) for diagnostic accuracy studies.

Where participants from several studies are recruited from the same cohorts and significant overlap is suspected, data from only one study with the most reliable reporting will be included in the main analyses. The impact of studies where substantial overlap is suspected, or where only a composite outcome is reported, will be explored by including/excluding them from the main analyses.

Narrative synthesis

For outcomes related to clinical effectiveness and implementation of QFR, vFFR and invasive FFR, and where meta-analysis is not feasible, we will perform a narrative synthesis. For this we will extract summary information on the findings of included studies that relate to the clinical and implementation outcomes and summarise and harmonise these across studies. Also considered will be: the conclusions of these studies, suggested consequences for QFR and ICA, recommendations for practice and suggested needs for further research. These results will be tabulated and summarised.

Narrative summaries will be used for any outcomes where meta-analyses or other statistical analyses are not feasible. This will include tabulating or plotting results as reported in studies, and narratively describing and comparing these results.

Additional clinical evidence

Depending upon the findings from the clinical and cost-effectiveness review, it may be necessary to undertake additional targeted searches to inform the risks of major cardiovascular events and associated costs and outcomes in order to properly inform and conduct the economic model. If this is considered necessary, the review will, initially, be restricted to published cost-effectiveness models that assess the long-term impact of diagnostic strategies in the management of coronary artery disease (CAD) and/ or predict costs and outcomes in CAD from a UK perspective. If data gaps are still evident, a pragmatic approach will be used, supplementing findings with targeted searches for systematic reviews, long-term RCTs with clinical outcomes and/or prospective cohort studies.

Systematic review of cost-effectiveness evidence and development of decision model

Relevant cost-effectiveness evidence on the use of the QAngio XA 3D/ QFR imaging software and CAAS vFFR (Pie Medical Imaging) for the assessment of coronary obstructions will be systematically identified, appraised for quality and narratively summarised. The aim of the review will be to examine any existing decision-analytic models used to assess the cost-effectiveness of QAngio XA 3D/ QFR and CAAS vFFR against any comparator(s), in order to identify key issues and areas of uncertainty that could be addressed in the development of a new decision-analytic model for this assessment.

Systematic review of cost-effectiveness evidence

The results of the searches carried out for the systematic review of clinical effectiveness and diagnostic accuracy of the QAngio XA 3D/ QFR and CAAS vFFR imaging software will be used to identify any relevant studies of the cost-effectiveness of the technology against its relevant comparators. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside clinical trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the text of the report. In particular, information will be extracted on the comparators, study population and setting, main analytic approaches (e.g. patient-level analysis / decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the current decision problem and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

Initial scoping searches indicate that the existing cost-effectiveness literature for the QAngio XA 3D/ QFR and CAAS vFFR imaging software is likely to be limited. Therefore, to further inform the development of a new decision-analytic model, we will also undertake a targeted literature search to identify cost-effectiveness studies evaluating ICA in people with stable chest pain of recent onset. The inputs and assumptions in these studies may be important to consider as part of the conceptualisation and development of a new decision model. These studies will not be subject to a formal assessment but will be used, as necessary, to assist in the overall development of a new decision-analytic model for the evaluation of QAngio XA 3D/ QFR and CAAS vFFR imaging software. In particular, they will be used to identify important parameter estimates and source of data inputs, as well as highlighting key areas of uncertainty.

Development of a de-novo economic model

Following the review of existing cost-effectiveness evidence, a decision-analytic model will be developed. This will aim to estimate the cost-effectiveness of the QAngio XA 3D/ QFR and CAAS vFFR imaging software used during ICA for the assessment of coronary obstructions in people with stable chest pain whose angiograms show intermediate stenosis. Consideration will be given to differences in the cost-effectiveness of the technologies in diagnostic-only or in interventional catheter laboratories. The population, comparator technologies and reference standards are as set out above.

The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g., health-related quality of life utility values), routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Services and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and quality-adjusted life years discounted at a rate of 3.5% per annum.

General structure of the model

Diagnostic outcomes will be modelled with a decision tree, which takes account of the diagnostic accuracy of the non-invasive tests (ICA without the functional assessment of coronary obstructions and QAngio XA 3D/ QFR and CAAS vFFR used during ICA) relative to the reference standard test of invasive FFR/iFR measurement using pressure-wire (assumed to have a sensitivity and specificity of 100%). Patients correctly identified as having functionally significant stenosis (“true positive” result)

will progress to revascularisation, while patients correctly identified as having non-significant coronary stenosis ("true negative" result) will receive OMT without the need for revascularisation. However, patients incorrectly identified as having functionally significant stenosis ("false positive" result) will lead to unnecessary revascularisations, while patients incorrectly identified as not having functionally significant stenosis ("false negative" result) will not receive an appropriate revascularisation procedure and, as a result, may experience reduced quality of life and increased risk of major cardiovascular event or death until their disease is correctly managed. The tests may also lead to inconclusive results about the functional significance of stenosis, which can lead to further invasive testing with pressure-wire FFR/iFR in order to confirm whether or not there is a need for revascularisation.

Establishing a direct link between diagnostic test accuracy and clinical outcomes is unlikely to be feasible due to limited or no formal evidence. The longer-term impact and subsequent prognosis associated with the diagnostic outcomes will be modelled using the best available evidence on the risk of major cardiovascular events such as myocardial infarction and sudden cardiac death, as well as adverse events related to revascularisation, surgery and diagnosis. The model will also consider how specific patient baseline characteristics and risk affect the likelihood of experiencing further cardiovascular events and need for revascularisation.

Consideration will be given to modelling the harmful effects associated with radiation exposure from invasive FFR measurement. The robustness of the analysis will depend on the availability of evidence linking radiation exposure to cancer risk, as well as the effect of cancer on quality-adjusted life expectancy. This will be informed using targeted literature searches to identify the increased risk of cancer as a result of ionising radiation from ICA with pressure-wire FFR/iFR and revascularisation procedures.

It will also be important to consider patient throughput and its impact on the cost per patient for the use of the QAngio XA 3D/ QFR and CAAS vFFR imaging software. The implication of variation in patient throughput is likely to be explored using sensitivity and threshold analysis. It will also be important to consider whether the provision of the non-invasive FFR/iFR measurement might influence physician practice and referral behaviour in the management of stable angina and any possible implications for throughput.

Model parameters

Further details of the model structure and data to be used to populate the model will be dependent on the findings from the systematic searches of the literature. However, it is expected that particular consideration will be given to the following key variables:

- Diagnostic accuracy of the different technologies;
- Time to QFR, vFFR and FFR/iFR measurement;
- Resource utilisation and costs for the different technologies (including acquisition costs, consumables, maintenance, staff and training costs);
- Size of the relevant population and anticipated throughput for each technology;
- The number of revascularisations;
- The risks of major cardiovascular events (including myocardial infarction and sudden cardiac death);
- The short- and long-term costs and consequences of stable angina (including related cardiovascular events);
- Adverse events related to both diagnostic and treatment interventions;
- The link between radiation exposure and cancer risk and mortality;
- Health related quality of life impact resulting from the different technologies.

Costs and resource utilisation

Resource utilisation and costs will be estimated for the QAngio XA 3D/ QFR and CAAS vFFR imaging software and pressure-wire guided FFR measurement, including hyperemia inducing agents, as well as costs of treatment intervention, managing major adverse cardiac events and other adverse events. The costs are expected to include:

- Costs of QAngio XA 3D/ QFR and CAAS vFFR imaging software (including purchase price of software, software installation, support, maintenance and training costs, and potential need for a new workstation, time to process results)
- Costs of invasive functional assessment of stenosis (including pressure wires and hyperemia inducing agents)
- Costs of revascularisation (including PCI and CABG)
- Costs of drug treatment for OMT

- Costs of managing major adverse cardiac events (including MI and sudden cardiac death)
- Costs of managing adverse side effects related to invasive functional assessment, medical therapy, revascularisation (PCI or CABG) and radiation exposure.

Data for the cost analysis will be obtained from routine NHS sources, published studies and information provided by the manufacturers of the devices.

Economic analysis objectives

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of QAngio XA 3D/ QFR and CAAS vFFR imaging software during ICA for the functional assessment of coronary obstructions for people with stable angina, whose angiograms show intermediate coronary stenosis.
- To populate the model using the most appropriate data, identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts and manufacturers.
- To relate intermediate outcome measures of diagnostic accuracy to subsequent revascularisation decisions and to final health outcomes, including morbidity and mortality associated with revascularisation and major cardiovascular events. Final health outcomes will be evaluated in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to their additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the incremental cost-effectiveness of the QAngio XA 3D/ QFR and CAAS vFFR imaging software during ICA compared with visual assessment of ICA alone, or ICA followed by FFR/iFR if ICA is inconclusive, based on an assessment of the long-term NHS and Personal Social Service costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes. The final specification of the model will be determined during the review and model conceptualisation stage.
- To characterise the uncertainty in the data used to populate the model and to present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the

use of appropriate probability distributions, rather than as a fixed parameter input. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves, which show the probability that an intervention is expected to be cost-effective for a given estimate of health opportunity costs (cost-effectiveness threshold).

- To undertake sensitivity, scenario and/ or threshold analysis to explore the robustness of the cost-effectiveness results to changes in the parameter inputs (e.g., impact of increasing/ decreasing sensitivity and specificity of the diagnostic images), structural assumptions of the model and the time horizon.

It is anticipated that the model will be developed in either Microsoft Excel or the statistical programming language of R (or a combination of both e.g., separate software may be used for the diagnostic and treatment elements of the model); the choice of software will depend on the final conceptualisation of the model.

iii) Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturers or study analysts and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers or study analysts will be highlighted in yellow and underlined in the assessment report.

If confidential information is included in economic models then a version using dummy data or publically available data in place of confidential data will be provided.

iv) Competing interests of authors

None of the authors have any conflicts of interest.

v) Timetable/milestones

Milestone	**Date to be completed**
Submission of final protocol	3 October 2019
Submission of progress report	3 January 2020

Submission of draft Diagnostic Assessment Report	28 February 2020
Submission of final Diagnostic Assessment Report	27 March 2020

Search strategy for MEDLINE

Database: Ovid MEDLINE(R) ALL <1946 to September 25, 2019>
Search Strategy:
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1 QANGIO$.ti,ab,kw. (8)
2 quantitative flow ratio$.ti,ab,kw. (36)
3 QFR.ti,ab,kw. (82)
4 "3D/QFR".ti,ab,kw. (1)
5 aQFR.ti,ab,kw. (2)
6 adenosine-flow QFR.ti,ab,kw. (2)
7 cQFR.ti,ab,kw. (6)
8 contrast-flow QFR.ti,ab,kw. (7)
9 fQFR.ti,ab,kw. (5)
10 fixed-flow QFR.ti,ab,kw. (5)
11 iQFR.ti,ab,kw. (1)
12 index QFR.ti,ab,kw. (1)
13 LQFR.ti,ab,kw. (4)
14 lesion QFR.ti,ab,kw. (1)
15 vQFR.ti,ab,kw. (1)
16 vessel QFR.ti,ab,kw. (1)
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (99)
18 vessel FFR.ti,ab,kw. (11)
19 vFFR.ti,ab,kw. (8)
20 CAAS vFFR.ti,ab,kw. (0)
21 18 or 19 or 20 (19)
22 17 or 21 (118)
23 animals/ not (humans/ and animals/) (4586208)
24 22 not 23 (107)
25 "quinol:fumarate reductase".ti,ab. (29)
26 24 not 25 (88)