QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing coronary stenosis during invasive coronary angiography (DAP 48)

Erratum to the EAG Diagnostic Assessment Report

Produced by: Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE), University of York

Completed on 22/09/2020

In response to the DAR consultation responses collated by NICE and sent to the EAG on 10/07/2020, the EAG provide the following erratum to the report. None of the amendments changed the overall conclusions of the report.

1. **Glossary:** In response to comment #2, the EAG added a missing term ("catheter) from the definition of Percutaneous Coronary Intervention, from:

"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."

To:

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

2. **Abstract:** In response to comment #17, QFR was incorrectly stated. The order of the following sentence:

"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."

Was replaced with:

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

3. **Section 2.2.1 (QFR description):** In response to comment #4, the EAG clarified that QAngio XA 3D/QFR (Medis) imaging provides both anatomical and functional assessment of coronary artery obstructions, from:

"QAngio XA 3D/QFR (Medis) imaging software is used to perform QFR assessment of coronary artery obstructions."

To:

"QAngio XA 3D/QFR (Medis) imaging software is used to perform QFR assessment of coronary artery obstructions. It gives both anatomical and functional assessment of the stenosis."

4. **Section 2.2.1 (QFR description):** In response to comment #3, the EAG added that QAngio was CFDA-approved, rather than CE-marked.

5. **Section 4.1.3:** In response to comment #12, in line with the protocol-specified population selection criteria which state that patients with intermediate stenosis who are referred for ICA to assess coronary stenosis and the need for revascularisation were eligible, the EAG added that Post-intervention assessment of revascularized vessels (whether using QFR, vFFR or FFR) was beyond the scope of this DAR, at the end of 4.1.3 Selection criteria/Participants:

"Follow-up or post-intervention examinations of revascularized vessels were excluded."

6. **Section 4.1.6 (Methods of data synthesis):** "QFR" was replaced by "QFR (or vFFR)" in the following places:
    a. Section 4.1.6, 2nd sentence
    b. Section 4.1.6.1, 2nd paragraph, last sentence
    c. Section 4.1.6.1, 3nd paragraph, last sentence

7. **Section 4.1.6.3:** In response to comment #19, the EAG corrected the following sentence:

*"*Due to lack of guidance on CAAS vFFR, grey-zone analyses were not performed for this technology."

With:

"Due to the limited data that could be extracted from figures of CAAS vFFR vs FFR, grey-zone analyses were not performed for the CAAS vFFR technology."

8. **Section 4.2.2:** "QFR" was replaced with "QFR and vFFR" in 1st paragraph, 1st sentence

9. **Section 4.8:** The EAG noticed there were repetitions and formatting problems that may have made this section unreadable. Paragraphs 4, 5 and 6 were removed:

"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 studies[16] 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 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."

These were replaced with:

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;the Jin (2019) study had lower sensitivity, but slightly higher specificity, although the study used ICA set at 7.5 frames per second (fps) rather than the manufacturer recommended setting of 12.5 fps, therefore its results may not be applicable.

10. **Section 4.8.1: In response to comment #14, the following sentences were added:**
    a. At the end of the last sentence in section 4.8:

"… although the study used ICA set at 7.5 frames per second (fps) rather than the manufacturer recommended setting of 12.5 fps, therefore its results may not be applicable."

    b. At the end of section 4.8.1:

"As noted above, the study used ICA set at 7.5 frames per second (fps) rather than the manufacturer recommended setting of 12.5 fps, therefore its results may not be applicable."

11. **Section 4.10.3:** The EAG inaccurately used QFR instead of vFFR in one sentence:

"CAAS studies also concluded that QFR had good correlation and agreement with wire-based FFR"

Was replaced with:

"CAAS studies concluded that vFFR had good correlation and agreement with wire-based FFR"

12. **Section 4.11, paragraph 2, sentence 3:** The EAG slightly nuanced the statement in view of the evidence:

"Data on how this accuracy may vary by key patient characteristics was very limited, and no conclusive variation could be found."

Was replaced with:

"Data on how this accuracy may vary by key patient characteristics was limited, and no conclusive variation could be found."

13. **Similarly, section 7.1.1, paragraph 2, sentence 3:** The EAG slightly nuanced the statement in view of the evidence:

"Data on how this accuracy may vary by key patient characteristics was very limited, and no conclusive variation could be found."

Was replaced with:

"Data on how this accuracy may vary by key patient characteristics was limited, and no conclusive variation could be found."

14. **Section 4.11 – penultimate paragraph:** A typo error was amended, from from “FRR” to “FFR”

15. **Section 5.5, first sentence:** iFR was added to the first sentence:

From:

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.

To:

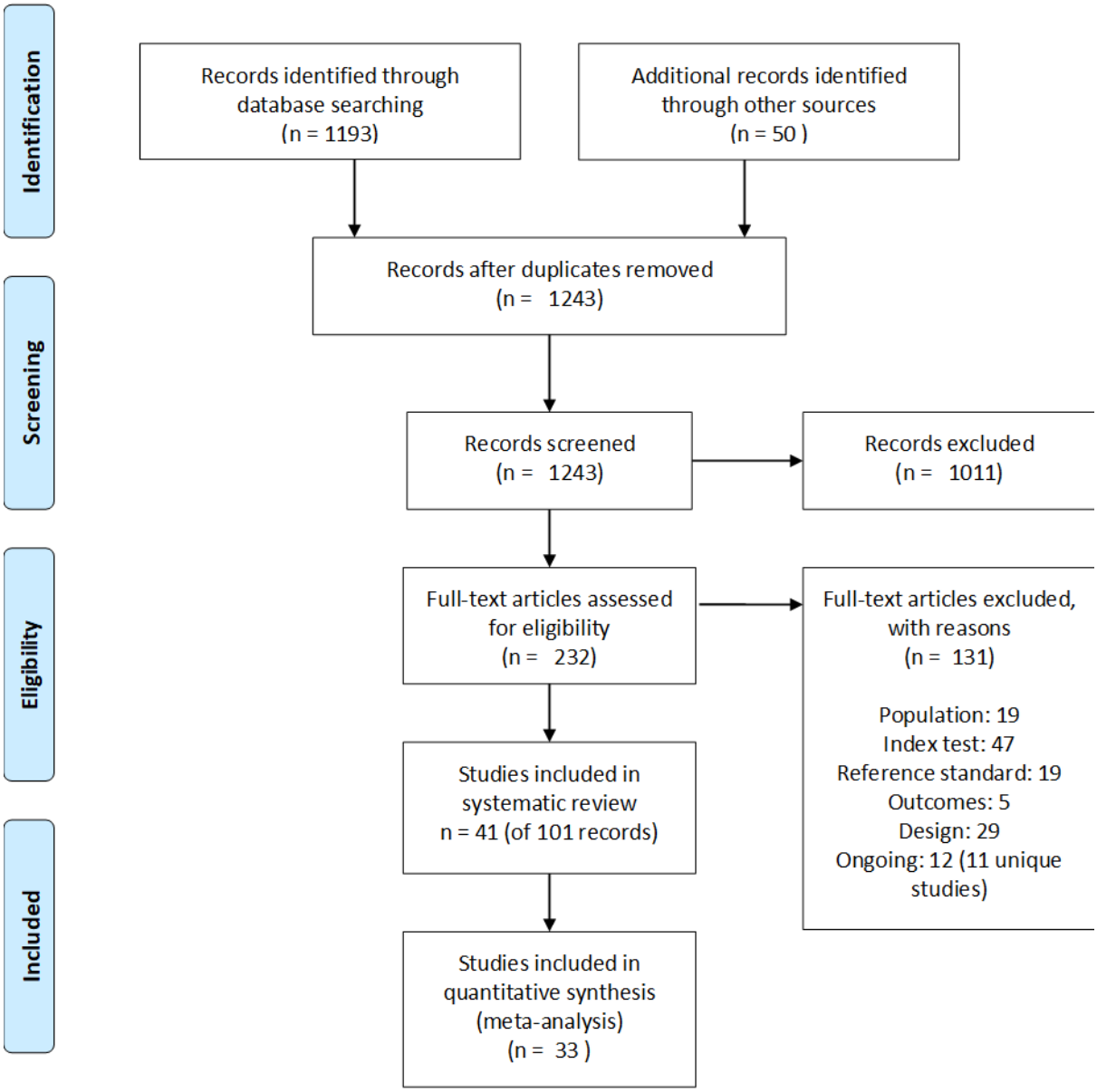
The review did not identify any studies that evaluated the cost-effectiveness of QAngio or CAAS vFFR. A supplementary review of published cost-effectiveness studies evaluating ICA (alone and/or with FFR/iFR) in the management of CAD identified 21 relevant studies.

16. **6.5.3.1 Last sentence:** The EAG deleted “Invasive coronary angiography” (misplaced heading)

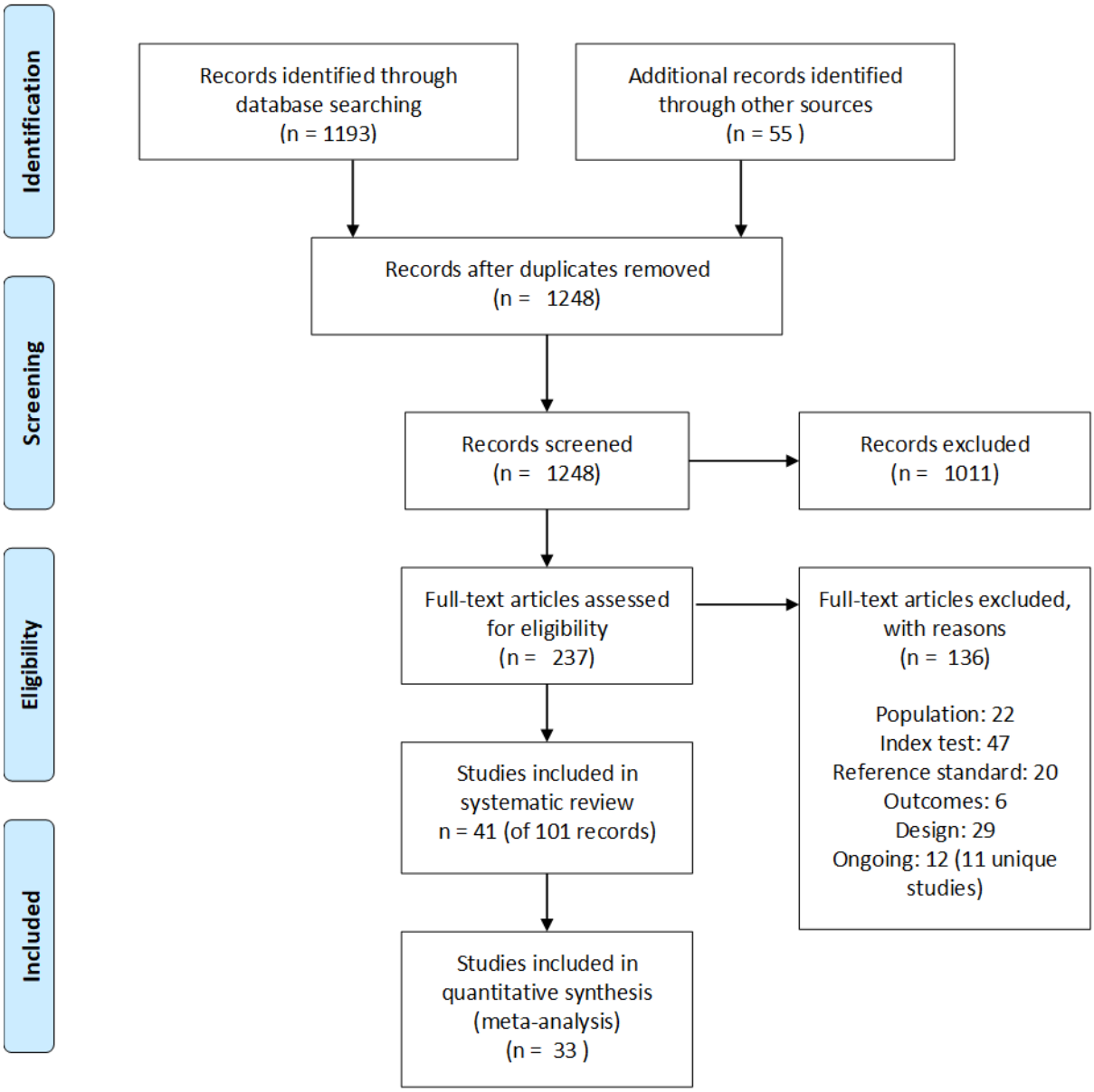
17. **6.5.4, table 20:** “Venous occlusion” was replaced with “Vessel occlusion”

18. **Section 6.5.7.2, final paragraph:** International Classification of Disease [ICD] was replaced with ICD

19. **Section 4.2, figure 2:** The EAG updated the PRISMA flow diagram as it did not contain reasons for exclusions of 5 references submitted by Pie Medical during the course of this assessment. Figure 1 (PRISMA flow diagram) was edited accordingly, from:


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1193)
Additional records identified through other sources (n = 50)
Records after duplicates removed (n = 1243)
Records screened (n = 1243)
Records excluded (n = 1011)
Full-text articles assessed for eligibility (n = 232)
Full-text articles excluded, with reasons (n = 131)
Population: 19
Index test: 47
Reference standard: 19
Outcomes: 5
Design: 29
Ongoing: 12 (11 unique studies)
Studies included in systematic review n = 41 (of 101 records)
Studies included in quantitative synthesis (meta-analysis) (n = 33)

to:



20. Section 6.7.2, table 62: In response to comment #9, NHB rank for strategy 5 was changed from 4 to 3.

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

was changed to:

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	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.

21. **Appendix 2, table 68:** In line with point 19. above, the EAG updated the appendix table of excluded studies as it did not contain reasons for exclusions of 5 references submitted by Pie Medical during the course of this assessment. Figure 1 (PRISMA flow diagram). The following 5 references were added to table 68:

Gigant C, Mizukami T, Sonck J, Nagum S, Tanzilli A, Bartunek J et al. Graft Patency and Progression of Coronary Artery Disease after CABG Assessed by Angiography-Derived Fractional Flow Reserve. Unpublished [academic in confidence].

Masdjedi K, Balbi MM, van Zandvoort LJC, Ligthart JMR, Nuis RJ, Vermaire A, et al. Validation of novel 3-Dimensional Quantitative Coronary Angiography based software to calculate Vessel Fractional Flow Reserve (vFFR) post stenting: Fast Assessment of STenosis severity POST stenting, The FAST POST-study. Conference: tct2018; San Diego, California USA.

Masdiedi K, Ligthart JMR, Witberg K, Tamoniak M, Vermaire A, Kardys I, et al. The Prognostic Value of Angiography-Based vessel-FFR after successful Percutaneous Coronary Intervention: The FAST Outcome study Unpublished [academic in confidence].

Tomaniak M, Masdiedi K, van Zandvoort L, Neleman T, Tovar MN, Vermaire A, et al. Correlation Between 3D-QCA based FFR and Quantitative Lumen Assessment by IVUS for Left Main Coronary Stenoses – the FAST Left Main Study Unpublished. [academic in confidence].

Tomaniak M. The impact of 3D-QCA based vessel fractional flow reserve (vFFR) on Heart Team decision making: a pilot reclassification study. Conference: EuroPCR 2019, Paris, France.

The following pages are numbered in accordance with the version of the report sent by NICE for comments.

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 catheter 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

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-effectiveness to using FFR and therefore, pending further evidence on general clinical benefits and specific subgroups, could entirely replace FFR.

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

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 gives both anatomical and functional assessment of the stenosis. 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 CFDA-appoved 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.

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. Follow-up or post-intervention examinations of revascularized vessels were excluded.

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)

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 (or vFFR) ≤ 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 (or vFFR) and FFR and mean difference between QFR (or vFFR) 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 (or vFFR) ≤ 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 the limited data that could be extracted from figures of CAAS vFFR vs FFR, grey-zone analyses were not performed for the CAAS vFFR 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:

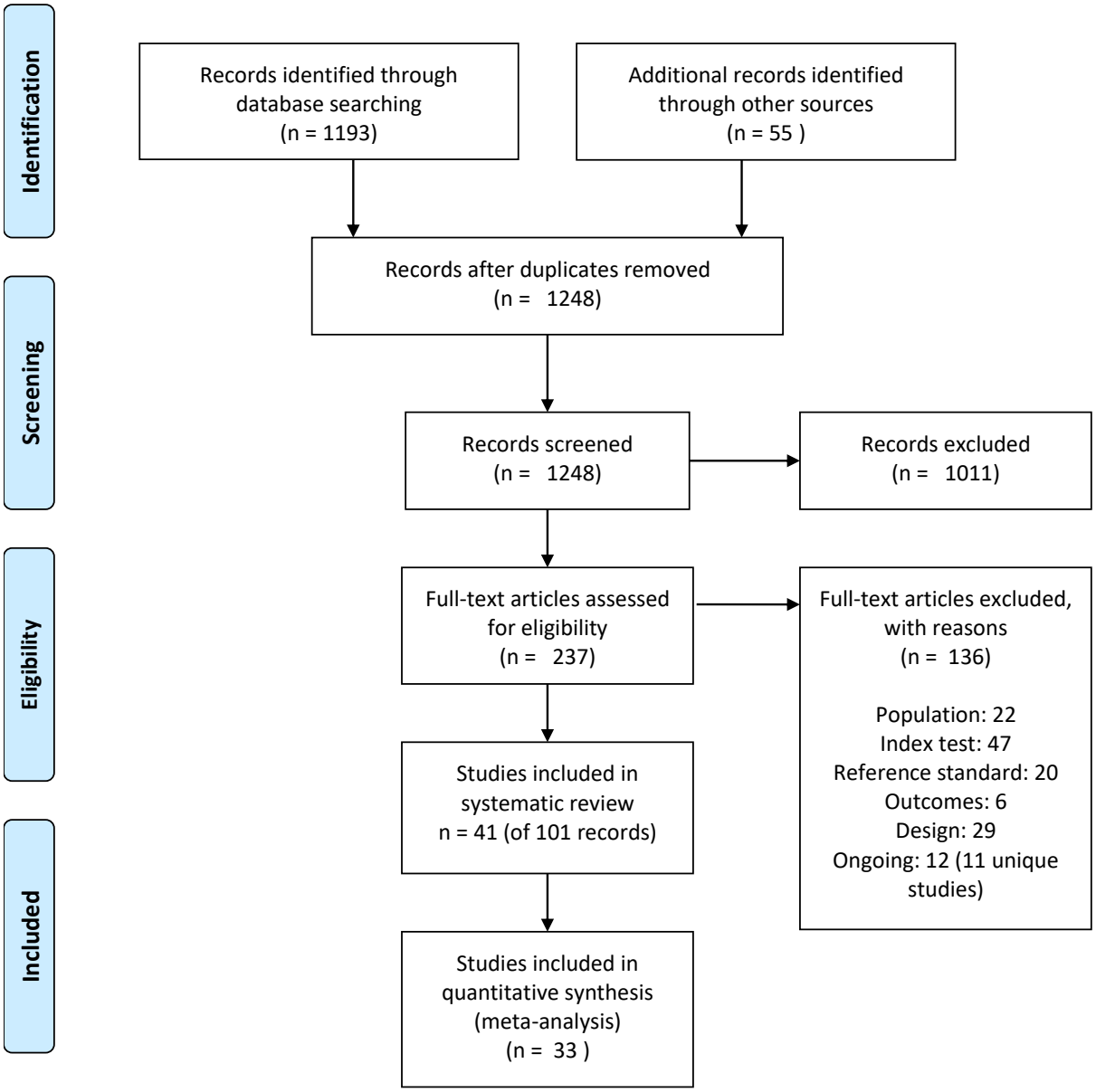
1. The data on FFR and QFR measurements extracted from published Bland-Altman figures was used as a representative population of patients with intermediate stenosis, with FFR and QFR measurements for each patient.
2. The IRIS-FFR study reported the association between FFR and coronary events in patients 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)

Three strategies for deciding on whether to revascularize were considered:

Figure 2 Study selection process (PRISMA flow diagram)



4.2.2 Quality of diagnostic accuracy studies.

Table 2 summarises the results of the risk of bias and applicability assessment for QFR and vFFR 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.

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.

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;the Jin (2019) study had lower sensitivity, but slightly higher specificity, although the study used ICA set at 7.5 frames per second (fps) rather than the manufacturer recommended setting of 12.5 fps, therefore its results may not be applicable.

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; [#] calculated

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. As noted above, the study used ICA set at 7.5 frames per second (fps) rather than the manufacturer recommended setting of 12.5 fps, therefore its results may not be applicable.

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

4.9.7 Simulation study of clinical effectiveness

Given the 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

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 vFFR 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]

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 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 a 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 FFR 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.

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/iFR) 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

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).

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 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]
Vessel 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.

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' (ICD-9 code 410) 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]

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	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 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.

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 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

Table 68 Excluded studies from systematic review of clinical effectiveness at full text screening stage

Not eligible population
Adjedj J, Hyafil F, Aminfar F, Farnoud A, Rubimbura V, Fournier S, et al. Hemodynamic and clinical impact in adult patients with anomalous aortic origin of the coronary artery evaluated with quantitative flow reserve. *Eur Heart J* 2019;40 (Supplement 1):1687.
Adjedj J, Hyafil F, Muller O, Aubry P. Hemodynamic and clinical impact in adult patients with anomalous aortic origin of the right coronary artery evaluated with Quantitative Flow Ratio *EuroPCR* 2019.
Biscaglia S. *Prognostic value of QFR measured immediately after successful stent implantation: The international multicenter prospective HAWKEYE study*. In: EuroPCR; 2019.
Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, et al. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. *Jacc: Cardiovascular Interventions* 2019;21:21.
ChiCTR1800017985. *Effect of QFR-guided Revascularization on 30-day mortality in Patients Undergoing Valve Surgery With Concomitant Coronary Artery Disease*. In; 2018.
Gigant C, Mizukami T, Sonck J, Nagum S, Tanzilli A, Bartunek J et al. Graft Patency and Progression of Coronary Artery Disease after CABG Assessed by Angiography-Derived Fractional Flow Reserve. Unpublished [academic in confidence].
Ishibashi Y, Grundeken MJ, Nakatani S, Iqbal J, More MA, Genereux P, et al. In vitro validation and comparison of different software packages or algorithms for coronary bifurcation analysis using calibrated phantoms: Implications for clinical practice and research of bifurcation stenting. *Catheter Cardiovasc Interv* 2015;85:554-63.
Masdjedi K, Ligthart J, Witberg K, Tomaniak M, Zandvoort L, Diletti R, et al. The Prognostic Value of Angiography-Based Vessel-FFR After Successful Percutaneous Coronary Intervention: The FAST Outcome Study. *J Am Coll Cardiol* 2019;74:B110-B10
Masdjedi K, Balbi MM, van Zandvoort LJC, Ligthart JMR, Nuis RJ, Vermaire A, et al. Validation of novel 3-Dimensional Quantitative Coronary Angiography based software to calculate Vessel Fractional Flow Reserve (vFFR) post stenting: Fast Assessment of Stenosis severity POST stenting, The FAST POST-study. Conference: tct2018; San Diego, California USA.
Masdiedi K, Ligthart JMR, Witberg K, Tamoniak M, Vermaire A, Kardys I, et al. The Prognostic Value of Angiography-Based vessel-FFR after successful Percutaneous Coronary Intervention: The FAST Outcome study Unpublished [academic in confidence].
NCT02811796. *Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation*. In; 2016. Available from: https://clinicaltrials.gov/show/NCT02811796
NCT03780335. *Early Prediction of QFR in STEMI-I*. In; 2018. Available from: https://clinicaltrials.gov/show/NCT03780335
Ozaki Y, Gonzalo N, Salazar CH, Kuku KO, Mejia-Renteria H, Hideo-Kajita A, et al. Comparison of quantitative flow ratio value of left anterior descending and circumflex coronary artery in patients with Takotsubo syndrome. *Int J Cardiovasc Imaging* 2019;01:01.
Rubimbura V, Guillon B, Fournier S, Amabile N, Chi Pan C, Combaret N, et al. *Validation of Quantitative Flow Reserve and residual quantitative flow reserve to predict FFR post-stenting from the Does Optical Coherence Tomography Optimize Results of Stenting study (DOCTORS) population*. In: EuroPCR; 2019.

Smit JM, Koning G, Van Rosendael AR, Dibbets-Schneider P, Mertens BJ, Delgado V, et al. The relationship between contrast-flow quantitative flow ratio and ischemia assessed by SPECT MPI. Eur Heart J 2017;38 (Supplement 1):825
Smit JM, Koning G, van Rosendael AR, Dibbets-Schneider P, Mertens BJ, Jukema JW, et al. Relationship Between Coronary Contrast-Flow Quantitative Flow Ratio and Myocardial Ischemia Assessed by SPECT MPI. Eur J Nucl Med Mol Imaging 2017;44:1888-96
Smit JM, Van Rosendael AR, Koning G, Reiber JH, Dibbets-Schneider P, Mertens BJ, et al. The relationship between contrast-flow QFR and ischemia assessed by SPECT MPI. European Heart Journal Cardiovascular Imaging 2017;18 (Supplement 1):i45-i46
Suetomi T, Okamura T, Nakao F, Yamada J, Oda T, Mochizuki M, et al. Impact of jailing configuration and bifurcation angle on incomplete stent apposition after single crossover stenting with final kissing balloon dilatation, assessed by three-dimensional OCT. EuroIntervention. Conference: EuroPCR 2015
Takahashi K, Kogame N, Tomaniak M, Chichareon P, Chang CC, Modolo R, et al. TCT-326 Diagnostic Performance of Angiography-Based Quantitative Flow Ratio With Respect to Fractional Flow Reserve Derived From Computed Tomography Angiography: Insight From the SYNTAX III Trial. J Am Coll Cardiol 2019;74 (13 Supplement):B324
Tomaniak M, Masdiedi K, van Zandvoort L, Neleman T, Tovar MN, Vermaire A, et al. Correlation Between 3D-QCA based FFR and Quantitative Lumen Assessment by IVUS for Left Main Coronary Stenoses – the FAST Left Main Study Unpublished. [academic in confidence].
Tomaniak M, Masdjedi K, Zandvoort L, Neleman T, Tovar M, Vermaire A, et al. TCT-331 Correlation Between 3D-QCA-Based FFR and Quantitative Lumen Assessment by IVUS for Left Main Coronary Stenoses: The FAST Left Main Study. J Am Coll Cardiol 2019;74 (13 Supplement):B329
Westra J, Winther S, Tu S, Nissen L, Gormsen L, Petersen S, et al. Comparison of quantitative flow ratio and fractional flow reserve to identify myocardial ischemia: Validation with myocardial perfusion scintigraphy and cardiovascular magnetic resonance. J Am Coll Cardiol 2017;70 (18 Supplement 1):B30.
No eligible outcome
Kanno Y, Hoshino M, Sugano A, Kanaji Y, Yamaguchi M, Sumino Y, et al. Optical Coherence Tomography-Defined Plaque Vulnerability in Relation to Functional Stenosis Severity Stratified by Fractional Flow Reserve and Contrast Quantitative Flow Ratio. *J Am Coll Cardiol* 2019;73 (9 Supplement 1):1172.
Kanno Y, Hoshino M, Sugiyama T, Kanaji Y, Yamaguchi M, Hada M, et al. Impact of subtended myocardial mass on the assessment of functional ischemia as evaluated by FFR and QFR. *Eur Heart J* 2019;40 (Supplement 1):1654.
Kleczynski P, Dziewierz A, Wiktorowicz A, Bartus S, Rzeszutko L, Bagienski M, et al. Contrast medium Pd/Pa ratio in comparison to fractional flow reserve, quantitative flow ratio and instantaneous wave-free ratio - a comprehensive assessment. *Postepy w Kardiologii Interwencyjnej* 2017;13 (4):356.
Sejr-Hansen M, Westra J, Thim T, Christiansen EH, Eftekhari A, Kristensen SD, et al. Quantitative flow ratio for immediate assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction-An iSTEMI substudy. *Catheterization & Cardiovascular Interventions* 2019;25:25.

Yamaguchi M, Hoshino M, Horie T, Yuki H, Kanno Y, Hirano H, et al. Evaluation of Non-Culprit Lesions in Acute Coronary Syndromes Using Quantitative Flow Ratio. *J Am Coll Cardiol* 2019;73 (9 Supplement 1):1473.
Not eligible study design
Accuracy of angiography-derived fractional flow reserve: a systematic review and meta-analysis. PROSPERO 2017 CRD42017084512 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017084512
Anonymous. Corrigendum to: Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. *Eur Heart J* 2019;40:356.
Asano T, Katagiri Y, Collet C, Tenekecioglu E, Miyazaki Y, Sotomi Y, et al. Functional comparison between BuMA Supreme biodegradable polymer sirolimus-eluting and durable polymer zotarolimus-eluting coronary stents using Quantitative Flow Ratio: PIONEER QFR Substudy. *Eurointervention* 2017;14:e570-e79
Chahour K, Aboulaich R, Habbal A, Abdelkhirane C, Zemzeme N. NUMERICAL SIMULATION OF THE FRACTIONAL FLOW RESERVE (FFR). *Mathematical Modelling of Natural Phenomena* 2018;13.
Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. *Eur Heart J* 2018;39:3314-21
Dan K, Shinoda A, Tsuzura D, Garcia-Garcia HM. Triple coronary vessel disease including double vessel chronic total occlusion: Quantitative flow ratio minimizes injury of the single vessel that provides collaterals. *Cardiology Journal* 2019;26:407-09
Collet C, Onuma Y, Sonck J , Asano T, Vandeloo B et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis (vol 39, pg 3314, 2018). *Eur Heart J* 2019;40:356-56.
Erbay A, Abdelwahed YS, Stahli BE, Landmesser U, Leistner DM. The danger lurks dastardly in the coronary vessel wall: spotlight on patients' vulnerability. *Eur Heart J* 2018;39:1656
esaro A, Gragnano F, Di Girolamo D, Moscarella E, Diana V, Pariggiano I, et al. Functional assessment of coronary stenosis: an overview of available techniques. Is quantitative flow ratio a step to the future? *Expert Review of Cardiovascular Therapy* 2018;16:951-62
Giddens DP. Computing Fractional Flow Reserve During Coronary Angiography: How Good Is Good Enough? *JACC Cardiovasc Interv* 2016;9:2036-38
Guillon B, Rubimbura V, Fournier S, Eeckhout E, Schiele F, Muller O, et al. Validation of quantitative flow reserve and residual quantitative flow reserve to predict fractional flow reserve post stenting from the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study population. *Kardiovaskulare Medizin. Conference: Joint Annual Meeting* 2019;22
Hirshfeld JW, Jr., Nathan AS. QFR and FFRCT: Accurate Enough? *Jacc: Cardiovascular Interventions* 2019;12:2060-63.
Howard JP, Murthy VL. A Song of Pressure and Flow, or There and Back Again. *JACC Cardiovasc Interv* 2018;11:754-56.
Lansky AJ, Pietras C. Fractional flow reserve from 3-dimensional quantitative coronary angiography: fresh light through an old window. *JACC Cardiovasc Interv* 2014;7:778-80.
Mejia-Renteria H, Tu S, Macaya F, Escaned J. Influence of coronary microcirculatory dysfunction on FFR calculation based on computational fluid dynamics. *Eur Heart J Cardiovasc Imaging* 2017;18:1066