Non-invasive imaging software to assess the functional significance of coronary stenoses: a systematic review and economic evaluation

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Scientific summary

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Background

People with stable angina may require intervention known as 'revascularisation' to open obstructed arteries. QAngio® XA 3D/QFR® (three-dimensional/quantitative flow ratio) (Medis Medical Imaging Systems BV, Leiden, the Netherlands) and CAAS® vFFR® (vessel fractional flow reserve) (Pie Medical Imaging BV, Maastricht, the Netherlands) imaging software are two non-invasive technologies used as adjuncts to invasive coronary angiography. QAngio XA 3D/QFR measures the quantitative flow ratio and CAAS vFFR measures the vessel fractional flow reserve 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 assessment as the last-line test to inform revascularisation decisions.

Objectives

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

Methods

Systematic review

A systematic review of the diagnostic accuracy, clinical efficacy and practical implementation of QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing the functional significance of coronary obstructions in people with intermediate coronary stenosis (i.e. stenoses where preceding tests have been insufficient to make a revascularisation decision) was conducted.

Comprehensive bibliographic searches, including of MEDLINE and EMBASE™ (Elsevier, Amsterdam, the Netherlands) and supplementary sources, were conducted up to 2 January 2020 for published and unpublished literature.

Diagnostic accuracy and correlation studies in which any version of QAngio XA 3D/QFR or CAAS vFFR were used, in addition to invasive fractional flow reserve (or instantaneous wave-free ratio) assessment as a reference standard in the same patients, were included. Empirical studies of quantitative flow ratio or vessel fractional flow reserve (with or without invasive fractional flow reserve assessment) that reported relevant clinical outcomes (including morbidity and mortality) or issues relating to implementation of quantitative flow ratio or vessel fractional flow reserve and their use in clinical practice were also eligible. Patients with intermediate stenosis referred for invasive coronary angiography 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. The risk of bias of diagnostic accuracy studies was assessed using quality assessment of diagnostic accuracy studies.

For diagnostic accuracy outcomes, bivariate models were fitted to calculate summary estimates of sensitivity and specificity with 95% confidence intervals 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 digitised to simulate the accuracy of a 'grey-zone' strategy, whereby confirmatory fractional flow reserve is performed only in patients with a quantitative flow ratio between 0.78 and 0.84.

Economic analysis

Cost-effectiveness literature on QAngio XA 3D/QFR 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 invasive coronary angiography and/or fractional flow reserve/invasive fractional flow reserve 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 invasive coronary angiography for assessing the functional significance of coronary stenosis in patients with stable angina whose angiograms show intermediate stenosis. Five diagnostic strategies were considered: (1) invasive coronary angiography alone, (2) invasive coronary angiography followed by confirmatory fractional flow reserve/invasive fractional flow reserve (reference standard), (3) invasive coronary angiography with quantitative flow ratio, (4) invasive coronary angiography with quantitative flow ratio, followed by confirmatory fractional flow reserve/invasive fractional flow reserve when quantitative flow ratio is inconclusive, and (5) invasive coronary angiography with vessel fractional flow reserve.

The decision model had two components: a diagnostic element and a prognostic element. The diagnostic component was used to link the diagnostic accuracy of quantitative flow ratio and vessel fractional flow reserve 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 fractional flow reserve or invasive fractional flow reserve in strategy 4, and adverse event rates and health-related quality of life associated with the diagnostic interventions], whereas 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-year gains and quality-adjusted life-years were appropriately quantified over a lifetime horizon.

Results

A total of 41 studies were included in the systematic review, of which 39 (5440 patients) evaluated QAngio XA 3D/QFR and three (500 patients) assessed CAAS vFFR. Only one study directly compared QAngio XA 3D/QFR with CAAS vFFR. A total of 17 included studies were reported only as conference abstracts.

Most studies included a mix of patients with stable and unstable coronary syndromes. Stenosis severity varied widely across studies; mean/median fractional flow reserve ranged from 0.75 to 0.88, and mean percentage diameter stenosis from 37% to 66%. Only seven studies were conducted prospectively, and 11 studies (all of QAngio XA 3D/QFR) were rated as being at low risk of bias.

Diagnostic accuracy

The average difference between quantitative flow ratio (measured using QAngio XA 3D/QFR) and fractional flow reserve was 0.01. In 50% of patients, quantitative flow ratio and fractional flow reserve differed by no more than 0.04; in 95% of patients, values differed by no more than 0.14. The quantitative flow ratio was highly correlated with the fractional flow reserve ($r = 0.8$).

The QAngio XA 3D/QFR quantitative flow ratio had good diagnostic accuracy to predict fractional flow reserve (≤ 0.80 cut-off point); contrast-flow quantitative flow ratio had a sensitivity of

85% (95% confidence interval 78% to 90%) and a specificity of 91% (95% confidence interval 85% to 95%); fixed-flow quantitative flow ratio mode had a sensitivity of 82% (95% confidence interval 68% to 91%) and a specificity of 89% (95% confidence interval 77% to 95%). Where reported, quantitative flow ratio had significantly higher diagnostic accuracy than standard invasive coronary angiography. Data on how diagnostic accuracy may vary by key patient characteristics were too limited to draw any firm conclusions.

Using data extracted from figures, simulating a grey-zone strategy, where only patients with a QAngio XA 3D/QFR quantitative flow ratio between 0.78 and 0.84 receive confirmatory fractional flow reserve, improved diagnostic accuracy compared with quantitative flow ratio alone to a sensitivity of 93.1% (95% confidence interval 90.1% to 94.9%) and a specificity of 92.1% (95% confidence interval 88.3% to 94.5%). A total of 20.1% patients fell in the grey zone and would receive confirmatory fractional flow reserve. However, only 30.4% of patients with quantitative flow ratio results in the grey zone had results that were discordant with their fractional flow reserve.

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 XA 3D/QFR and CAAS vFFR with fractional flow reserve. The abstract reported that QAngio XA 3D/QFR quantitative flow ratio had a higher overall diagnostic accuracy, with areas under the curve of 0.719 (95% confidence interval 0.621 to 0.804) for vessel fractional flow reserve and 0.886 (95% confidence interval 0.807 to 0.940) for contrast-flow quantitative flow ratio.

Clinical effectiveness

No evidence was found on the effectiveness of QAngio XA 3D/QFR on major cardiovascular events and death. Three studies that reported clinical outcomes found that QAngio XA 3D/QFR may predict long-term major cardiovascular adverse events.

A simulation study based on the results of the meta-analysis found that using quantitative flow ratio in place of fractional flow reserve may slightly increase the number of revascularisations (from 40.2% to 42.0%), with a possible small increase in the number of coronary events (an extra one major adverse cardiac event per 1000 patients). Using a grey-zone approach of performing a confirmatory fractional flow reserve where the quantitative flow ratio is close to 0.8 might further increase revascularisations rates (to 43.2%) but with no impact on incidence of major adverse cardiac events.

Cost-effectiveness

No full cost-effectiveness studies of QAngio XA 3D/QFR or CAAS vFFR were identified by the systematic review. The pragmatic 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 invasive coronary angiography followed by confirmatory fractional flow reserve/instantaneous wave-free ratio (strategy 2), at a cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained. However, the difference in net benefit (i.e. the additional health gains net of health losses in the health-care system due to additional costs, expressed in health or monetary terms) between this strategy and the next best strategies was relatively small at 0.007 quality-adjusted life-years (or equivalently £140) per patient diagnosed for invasive coronary angiography with quantitative flow ratio (strategy 3), 0.012 quality-adjusted life-years (or equivalently £240) per patient diagnosed for invasive coronary angiography with quantitative flow ratio, followed by confirmatory fractional flow reserve/instantaneous wave-free ratio when quantitative flow ratio is inconclusive (strategy 4), and 0.011 quality-adjusted life-years (or equivalently £220) per patient diagnosed for invasive coronary angiography with vessel fractional flow reserve (strategy 5). The cost-effectiveness results for strategy 5 must be interpreted with caution because of very limited number of data available from diagnostic accuracy studies of vessel fractional flow reserve.

Discussion

This review includes a comprehensive systematic review of all the published literature on quantitative flow ratio as assessed by QAngio XA 3D/QFR 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 XA 3D/QFR, so the findings of the analysis of diagnostic accuracy are likely to be conclusive.

Although there is substantial evidence demonstrating the good diagnostic accuracy of quantitative flow ratio assessment using QAngio XA 3D/QFR overall, it remains largely unclear which patient or lesion characteristics might significantly affect the diagnostic accuracy of QAngio XA 3D/QFR.

The clinical value of QAngio XA 3D/QFR to support decision-making on revascularisation remains uncertain, particularly regarding what impact it might have on preventing or causing future coronary events, and whether the 0.8 cut-off point 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 fractional flow reserve.

The key drivers of cost-effectiveness were (1) the diagnostic sensitivity of test results (rather than specificity) because 'true-positive' test results translated into higher quality-adjusted life-year gains than mismanagement of 'false-negative' test results, (2) the procedural quality-adjusted life-year loss associated with fractional flow reserve/instantaneous wave-free ratio, (3) the magnitude and duration of the quality-adjusted life-year gains associated with revascularisation and (4) the additional costs associated with confirmatory testing with fractional flow reserve/instantaneous wave-free ratio.

Conclusions

Quantitative flow ratio measured using QAngio XA 3D/QFR has good agreement and diagnostic accuracy compared with fractional flow reserve and is more accurate than standard invasive coronary angiography for the evaluation of functionally significant stenoses. The good association between quantitative flow ratio and fractional flow reserve, and the high diagnostic accuracy of quantitative flow ratio, suggest that, pending further evidence on clinical benefits, quantitative flow ratio assessment could represent a reasonable alternative to invasive fractional flow reserve, particularly where fractional flow reserve is not available. The cost-effectiveness of QAngio XA 3D/QFR suggests that it is a reasonable use of NHS resources, as it is only marginally less cost-effective than invasive fractional flow reserve assessment.

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 because of the limited diagnostic information available.

Recommendations for research

The substantial existing evidence for diagnostic accuracy of QAngio XA 3D/QFR suggests that further studies of diagnostic accuracy are not required. Large, multicentre prospective studies are required to assess the diagnostic accuracy and clinical feasibility of CAAS vFFR. Ideally these should compare CAAS vFFR with invasive coronary angiography assessment and, if possible, with quantitative flow ratio.

Large ongoing randomised trials will hopefully inform decision-makers of the clinical value of quantitative flow ratio compared with angiography and fractional flow reserve-guided revascularisation.

Study registration

This study is registered as PROSPERO CRD42019154575.

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This report

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