The FISH&CHIPS Protocol

FFRCT In Stable Heart disease and Coronary Computed Tomography Angiography Helps Improve Patient care and Societal costs

Study Objective	The primary objective of FISH and CHIPS is to identify differences in health-related events, time to diagnosis and overall healthcare costs of a stable chest pain population undergoing Coronary Computed Tomography Angiography (CCTA) and Fractional Flow Reserve (FFR_{CT}), compared to a previous 'standard of care' diagnostic chest pain pathway of CCTA and non-invasive functional testing.
Study Design	This is a multi-centre, retrospective, observational analytic cohort study design. The study will utilise the electronic health record (EHR) data already collected by NHS England on all patients that underwent a CCTA for the assessment of coronary artery disease over a 2-year period (April 2017-April 2019). All patients were treated in accordance with the latest NICE clinical guidance (CG 95 2016). Healthcare data will be collected from 6 months prior to and 12 months following the index CCTA. Hospital admissions data collected will include inpatient hospital admissions, outpatient visits, cardiovascular diagnostic tests and procedures. All subsequent clinical events including myocardial infarction and all-cause death will be measured as clinical outcomes. Costs are determined from the NHS national tariff system.
Study Principal Investigator	Dr Timothy Fairbairn Liverpool Heart and Chest Hospital and the University of Liverpool, Thomas Drive, Liverpool, L14 3PE United Kingdom
Sponsor	Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool, L14 3PE United Kingdom

FISH&CHIPS MRC Medical Research Council Liverpool Centre for Cardiovascular Science

RESEARCH REFERENCE NUMBERS

IRAS Number:	285996
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Investigator Protocol Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I agree to allow the University of Liverpool monitors and auditors and their designees full access to all medical records at the research facility for participants entered in the study. I agree to comply with NHS England's information governance alliance (IGA) General Data Protection Regulation (GDPR) guidance.

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: 

Name: (please print): Jennifer Crooks Deputy Director of Research and Innovation

Chief Investigator:

Date: 22/6/22

Signature: 

Name: (please print): Dr Timothy Fairbairn

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Key Protocol Contributors	Dr Timothy Fairbairn, Chief Investigator Professor Rod Stables, CTU lead
Committees	Liverpool Heart and Chest hospital Research and Ethics Committee, Liverpool Health Partners (LHP) Single Point of Access to Research and Knowledge (SPARK) Joint Research Sponsorship Committee

1 Table of Contents

2 Abbreviations

CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCTA	Coronary Computed Tomography Angiography
CEC	Clinical Events Committee
DS	Degree Stenosis
FFR	Fractional Flow Reserve
FFR_{CT}-	CCTA-derived fractional flow reserve
ICA	Invasive Coronary Angiography
IHD	Ischemic Heart Disease
IRB	Institutional Review Board
LAD	Left Anterior Descending coronary artery
LCX	Left Circumflex coronary artery
LMS	Left Main Stem coronary artery
MACE	Major adverse cardiovascular events
MI	Myocardial Infarction
MT	Medical treatment
PCI	Percutaneous coronary intervention
RCA	Right coronary artery
SE	Stress echo
SPECT	Single-Photon Emission Tomography

3 Summary

3.1 Professional Summary

Protocol Title	FFRCT In Stable Heart disease & CCTA Helps Improve Patient care and Spending
Investigation strategy	CCTA plus FFRCT reduces healthcare resource utilization and costs compared to a CCTA strategy alone.
Study Principal Investigator	Dr Timothy Fairbairn
Academic Research Organization	Liverpool Centre for Cardiovascular Science (LCCS), Liverpool Heart and Chest Hospital, Liverpool, UK
Sponsor	The University of Liverpool
Participants and Study sites	Approximately 100,000 patients from 25 sites who received a CCTA for the assessment of CAD in NHS England.
Study Planned Duration	36 months
Primary study objective	To determine whether a CCTA and FFRCT diagnostic pathway reduces health-related events, time to diagnosis and overall healthcare costs compared to a 'standard of care' CCTA diagnostic chest pain pathway.
Primary hypothesis	The addition of FFRCT into a CCTA diagnostic pathway will be safe with no difference in major adverse cardiovascular event rates or death whilst reducing the time to diagnosis, result in fewer downstream tests and reduce overall costs to the healthcare system.
Population	Chest pain patients with suspected stable coronary artery disease being clinically investigated with a CCTA in England.
Study Design and Methods	A pragmatic 'real world' multi-centre, retrospective, observational analytic cohort study design. All patients receiving a CCTA at institutions utilising FFRCT as part of NHS England's Innovation and Technology Payment (ITP) programme. Participants will be recruited from 1 year pre-ITP and the 2 years of the ITP programme. Patients will be followed up at a minimum of 24-months post CCTA for the pre-defined primary and secondary endpoints.
Primary Endpoint	Primary and secondary outcomes measured: 1. MI event rate, hospitalization for acute coronary syndrome, MI deaths and all-cause death. 2. Downstream testing: numbers of

	non-invasive functional tests, and invasive coronary angiograms without revascularisation performed following the index FFRCT. 3. Cost analysis: Total cost to the NHS of the index test and all downstream investigations and hospital admissions.
Secondary Endpoint	1. Time to diagnosis- Trust Referral to Treatment (RTT) time. 2. Qualitative assessment of the impact of the FFRCT health technology
Study follow up	Participants will be followed up to a minimum of 24 months

3.2 Plain English Summary

Chest pain may be a symptom that is related to a narrowing of the heart blood vessels (coronary artery disease [CAD]). This chest pain, known as angina, can result in a reduced quality of life and, if not diagnosed and managed appropriately, could result in a heart attack. Coronary disease remains the largest cause of death in the United Kingdom today, with one death every 4 minutes. Guidelines recommend the use of tests to help diagnose and manage chest pain 'angina' patients. Coronary computed tomography angiography (CCTA) is a test that takes images of the heart blood vessels. It is the main test for patients presenting with angina, as it is excellent at saying when the heart blood vessels are normal and can be reassuring for patients. However, when narrowing's are present CCTA lacks the ability to tell whether they are causing the patient's symptoms.

A new technology, CT-derived fractional flow reserve (FFRCT) uses the CCTA images to make a 3D model of the heart blood vessels that shows whether there is a limitation in the blood flow to the heart which is causing the symptoms. The National Institute for Health and Care Excellence (NICE) recommends the use of FFRCT in a chest pain pathway. However, use of this new technology remains limited due to funding restrictions and uncertainty as to its benefit in the NHS.

This study aims to determine the extent to which the new FFRCT technology is safe and reliable, provides a quicker time to diagnosis for the patient, reduces the need for further tests and thus does the investment in the test represent good value to the NHS.

4 Introduction

4.1 Background

The investigation of suspected stable coronary artery disease (CAD) should primarily be based on a non-invasive strategy (Knuuti *et al.*, 2020). In the United Kingdom Coronary Computed Tomography Angiography (CCTA) is now recommended as the first-line diagnostic test for patients with suspected angina and no prior CAD. (NICE, 2010) This recommendation by the National Institute for Health and Care Excellence (NICE) in 2016 was primarily driven by the very high sensitivity of CCTA to detect the presence or absence of coronary atheroma. (Nielsen et al., 2014; Meijboom et al., 2008) Given that the majority of patients with suspected angina turn out to have non-cardiac chest pain, and the majority of CCTA scans performed for this purpose show only minimal or no CAD, a significant proportion of patients can be immediately reassured by CCTA in the current NICE guidelines pathway. (Fordyce, Newby, & Douglas, 2016) However, in approximately a third of cases, CAD detected by CCTA is either indeterminate due to dense calcification or of intermediate severity which results in only modest specificity of CCTA to detect functionally significant 'ischaemic' CAD - and this remains its Achilles' heel. (Meijboom et al., 2008)

Recent advances in technology allow the use of raw CCTA images with computational fluid dynamic modelling to produce a 3D haemodynamic representation of the coronary tree flow limitation. (Lee et al., 2018) (Conte et al., 2017) (Taylor, Fonte, Min, City, & Angeles, 2013) This CT-Derived Fractional Flow Reserve (FFRCT) has developed rapidly since first concept and is now used in routine clinical practice. NICE, in a medical technology guidance (MTG 32), stated 'the clinical and cost effectiveness evidence justified FFRCT's use as a second line functional test for indeterminate or intermediate coronary stenoses'. The guidance also commented that 'based on the current evidence, using HeartFlow FFRCT may lead to cost savings of £214 per patient. By adopting this technology the NHS in England may save a minimum of £9.1 million by 2022 through avoiding invasive investigation and treatment'.

4.2 Study Rationale

The accurate diagnosis of CAD is important to allow the appropriate medical treatment and post-test risk stratification to identify patients that might benefit from revascularisation. FFR_{CT} is a non-invasive physiological test that can assess flow limitation across a coronary stenosis with high diagnostic accuracy and good correlation to invasive FFR.(Nørgaard *et al.*, 2017) FFR_{CT} has been shown in trials to reduce the total number of inappropriate invasive coronary angiograms (ICAs) post-CCTA, by reducing the number of cases with no obstructive coronary artery disease. This increases the revascularization treatment rate, which represents a more efficient use of the expensive catheter angiography laboratory.(Douglas *et al.*, 2015), (Jensen *et al.*, 2017), (Nørgaard *et al.*, 2014) Patients could therefore be receiving the test with the highest accuracy, improving diagnostic certainty, thereby reducing unnecessary downstream tests and the time to treatment.

The NHS should benefit by reducing the number of invasive tests and the wider economy will benefit from fewer lost working days. In addition, the ITP has allowed national coverage of FFR_{CT} which has the potential to remove regional variations in clinical practice and spending costs.

The existing evidence for the use of FFRCT is based on randomised controlled trials, registry studies and economic analysis from a US providers' perspective. There is no real-world comparative data, and no literature from the perspective of NHS practice, which differs from the more 'invasive' approach in the US. This research will answer whether an NHS FFRCT pathway is better for the patients in terms of safety, reducing unnecessary alternative tests and time to treatment compared to previous 'standard of care' diagnostic pathways (including CCTA alone, stress echocardiography, stress perfusion MRI and nuclear scintingraphy). The impact on the NHS will be determined by comparing costs of a CCTA and selective FFRCT pathway to those of a standard of care pathway as well as the number of hospital visits.

5 Study Objectives

5.1 Primary objective

The study aims to identify differences in health-related events, time to diagnosis and overall costs in a clinical population undergoing CCTA and FFR_{CT} for symptoms suggestive of stable CAD, compared to a previous 'standard of care' diagnostic chest pain pathway.

5.2 Secondary objective

5.3 Primary Endpoints:

1. Safety: Has the implementation of FFR_{CT} been safe?

   End points: Myocardial infarction event rate, hospitalization for acute coronary syndromes and mortality (all-cause and cardiovascular).

2. Time to Diagnosis: Does FFR_{CT} reduce the time to diagnosis and treatment?

   End points: Trust Referral to Treatment (RTT) time.

3. Downstream testing: Does FFR_{CT} reduce the number of downstream investigations and the number of overall invasive and non-invasive diagnostic tests?

   End points: numbers of non-invasive functional tests, and invasive coronary angiograms without revascularisation performed following the index FFR_{CT}.

4. Cost analysis: Does the technology represent value for money?

End point: Total cost to the NHS of the index test, all downstream investigations, hospital admissions and outpatient visits.

5.4 Exploratory Endpoints:

5.4.1 Qualitative Assessment

A qualitative survey of clinicians at the NHS trusts implementing a FFRCT pathway will be performed to assess the impact of a change in the service aligned with FFRCT. Factors assessed will include: ease of implementation (governance and IT), user friendliness, ease of clinical integration and practicality.

5.4.2 Imaging biomarkers

Using the list of CCTA originally provided by the sites, the participating centres PACS teams will send the anonymised CCTA datasets to the CTU data storage for future linkage to the outcome data provided by NHS Digital. This process will ensure that anonymity is preserved while providing for a valuable resource in terms of a large database of anonymised imaging datasets with outcome data. There will also be the opportunity to repeat the data capture from NHS Digital in future years to establish medium and long-term outcomes. The purpose of creating this repository of anonymised outcome and imaging data is to allow for future research projects into image analysis of CTA including deep learning algorithms, radiomics analysis, and biomechanical modelling of coronary arteries all with the goal to improving future risk stratification to better target therapeutic interventions.

6 Study Design

This is a multi-centre, retrospective, observational analytic cohort study design.

This pragmatic 'real-world' trial, is designed to utilise big data to answer practical health questions and determine clinical outcomes in a timely fashion. Randomized clinical trials (RCT's) in comparative effectiveness research (CER) have been considered the gold standard. These are however, subject to several problems, including cost, patient selection bias and slow translation of knowledge into practice. (Angus, 2015) This study design removes any patient treatment heterogeneity effect seen in RCT's by assessing the impact of a new intervention on a whole population. (Longford, 1999) by utilising the electronic health record (EHR) data already collected by the NHS. This trial will thus represent a true assessment of the effectiveness of a new health technology on a population basis in the current NHS system and will enable the rapid translation of research into clinical and health care policy decisions.

Participants will include all individuals who had a CCTA performed at an institute participating in the NHSE FFRCT ITP during 2018-2020. All CCTA 12 months prior to and up to 24 months following the

start of a FFRCT programme (total study period 36 months) will be assessed. The cohort from this population that received an FFRCT will be separately identified, with linkage to the NHS digital data outcomes. HeartFlow will provide FFRCT-specific data.

NHS Digital's Data Access Request Service (DARS) will be queried to provide the patient episodes over the study period. NHSD collects national data sets containing details of all admissions, accident and emergency (A&E) attendances, and outpatient appointments at NHS hospitals in England. DARS will extract data from the following data sets:

- Emergency Care Data Set (ECDS)
- Hospital Episode Statistics Admitted Patient Care (HES APC)
- Hospital Episode Statistics Critical Care (HES CC)
- Hospital Episode Statistics Outpatients (HES OPC)
- Hospital Episode Statistics Accident and Emergency (HES AE)
- Diagnostic Imaging Dataset (DID)
- Medicines Dispensed in Primary Care Data Set (from NHS Business Authority)
- Civil Registration Deaths

These data sets will provide the following information:

- Patient demographics (such as age group, gender and ethnicity)
- Administrative information (such as dates and methods of admission and discharge)
- Geographical information; such as where patients are treated and the area where they live (post code).
- Medications (type, dose and whether processed)
- ICA and revascularisation data linked to patients.
- Incidence of downstream testing; stress echocardiograms, stress MRI or nuclear scintigraphy.

Costs will be calculated for all hospital attendances, diagnostic investigations and treatments from the published NHS England National Prices and Tariff workbook (2017-2019- HRG/OPEC codes) with the appropriate market forces factor applied. Health economic modelling will be performed by the University of Liverpool.

Referral to treatment (RTT) data is collected by each NHS trust for each patient. This data will be collected by the local research teams.

7 Study Population

7.1 Setting and Target Population

The study population will include all patients that received a CCTA for symptoms suggestive of CAD at a participating institute, 12 months prior to the institutes first FFRCT study and up to 24 months

following (total study period up to 36 months). The timeframe of study recruitment is dependent upon the starting time of each centre in the ITP programme. Centres that had a later start date (on-boarding) will have a shorter recruitment period, with a minimum of 12 months. These centres represent the 'real-world' NHS hospitals that are a mixture of secondary and tertiary referral centres (not dedicated academic or research sites) with clinical experience in CCTA who have met the minimum quality standards set out by NHS England. Thus, the study population represents a true reflection of the current CCTA practice in the national population, reducing the potential effect of selection bias seen in many RCT's.

A study population of 85,292 patients received either CCTA analysis alone (standard of care group, n=75,361) or CCTA and Heartflow FFRCT analysis (FFRCT group, n=9,799) during the two years of the new technology being available to each site. The total study population over the 36 months is likely to be over 100,000.

7.2 Inclusion Criteria

7.2.1 Site eligibility:

- Sites within NHS England with a FFRCT ITP programme commencing between April 1st 2018-March 31st 2020
- Sites must have performed a minimum number of ≥50 FFRCT within 1 year of their programme commencing

7.2.2 Individual eligibility:

- Age ≥18 years
- CCTA for the assessment of coronary artery disease (CAD)

7.3 Exclusion Criteria

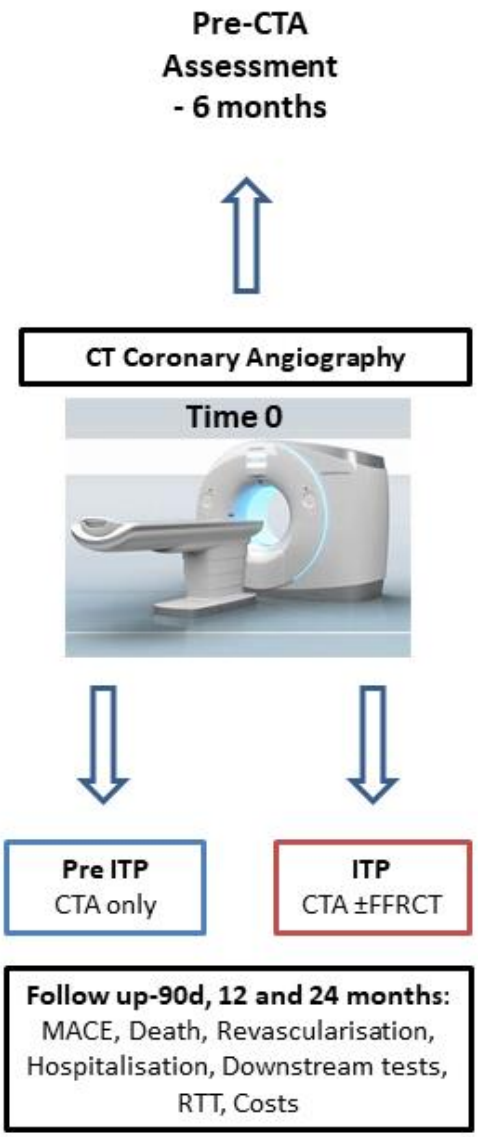
- Age <18 years
- Coronary artery calcium scoring alone
- CCTA in addition to a second CT investigation for a non-coronary indication (CT TAVI, CT aorta)
- Previous CCTA within 6 months
- Prior CABG / MI
- Entry into a separate FFRCT research study during the study timeframe

7.4 Follow up

Patient data will be collected up to a minimum of 24 months post-CCTA. Clinical data will also be analysed for the 6 months pre-CCTA to ensure no cross over between diagnostic pathways and prior testing (including CCTA) within 6 months (Figure 1).

Longitudinal long-term follow-up (>2 years) at 5 and 10 years would be feasible and cost effective using the same methodology of HES downloads and data analysis. This would provide a true long-term perspective of health care resource use in a stable angina population

Figure 1 Study Design Overview



8 Statistical Methodology

8.1 Sample size and Power calculation

As an observational analytic cohort study design, this trial requires no power calculation for estimates of effect. However, multiple previous studies have guided the sample size and estimates of expected clinical outcomes. Disease prevalence at CCTA can be estimated from SCOTHEART (n=4778), where the coronary arteries were normal in 37%, non-obstructive CAD in 38% and obstructive CAD in 25% of a UK population. The CONFIRM registry study showed in a contemporary US population of over 5000 patients investigated by CCTA that the annual event rate varied between 0.31% for normal coronary arteries to 2.06% in the instance of obstructive CAD (Leipsic et al., 2013). The international ADVANCE registry study of a patient population being investigated with FFRCT had cardiovascular event rates of 1.16% at 1 year. Thus, it is possible to estimate expected clinical outcome event rates and compare to actual observed events across the pathways to determine the safety of a UK CCTA pathway.

8.2 Statistical Analysis

Analysis of the primary end-point is based on the rate of adverse events (MACE) as a composite of all-cause death, myocardial infarction and invasive coronary angiography without revascularization. Event rates over time will be calculated using Kaplan-Meier methodology from the time of the CCTA. Cox proportional hazard ratios will be used to determine the odds ratio (OR) of receiving revascularization post FFRCT compared to other tests.

Time to diagnosis will be compared using an 'intention to diagnose analysis' by analysing groups according to their investigative test (FFRCT vs CCTA alone).

The primary cost analysis will include total patient pathway costs at 12 months, with comparison between the two testing strategies. The mean cost difference with 95% confidence intervals and P value will be calculated. Sub-analysis will categorise the total costs breakdown as; Investigations, hospital stay, procedural costs.

Cost sensitivity analyses will be applied to the modelling, looking at different cost utilities in the UK and regional variability.

9 Good Clinical Practice

9.1 Ethical Conduct

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). Ethical approval will be sought from the Health Regulatory Authority (HRA), the trial will comply with the principles set out in the declaration of Helsinki and the UK policy framework for health and social care research.

9.1.1 Informed Consent

As a retrospective study we will be accessing confidential patient information without consent in England. Therefore, consent was approved on the basis of health and social care research in the public interest (National Health Service Act 2006 -s251 - 'Control of patient information'. , through an application to the Confidentiality Advisory Group (CAG) and ethical approval from the Health Regulatory Authority (HRA)

Patient information will be kept to a minimum needed for the purposes of the research project and will be kept securely for the duration of the study and up to 15 years post study completion. Data will be linked to health records using the NHS number by NHS Digital. All research sites and the clinical trials unit will comply with the UK General Data Protection Regulation (GDPR).

9.1.2 Good Clinical Practice (GCP)

Members participating in the study will be encouraged to complete their GCP training.

9.2 Data Management and Confidentiality

9.2.1 Data Collection

The data will be collected from 25 NHS trusts participating in the NHS England ITP FFRCT programme, a life science industry (HeartFlow) and the national data collection institute (NHS Digital).

The sponsor and principal investigators are responsible for the handling, processing, accuracy and quality assurance of data collection. The study teams will be familiar with the study protocol and requirements. Data will be recorded in a confidential manner. The study staff will comply with the Data Protection Act 2018 with regards to collection, storage, processing and disclosure of data. All data will be stored within the NHS trust framework with password protection and external server backup. The legal basis for processing data will be based on the General Data Protection Regulation Article 6 (1) (e) and General Data Protection Regulation Article 9 (2) (j).

Publication of the study results will not include any patient identifiable data. Data will be archived and stored for 15 years.

9.2.2 FFRCT Data

Patient data was anonymised prior to sending to HeartFlow as part of the clinical service in accordance with local and national clinical governance regulations. Data linkage to the hospital

episodes statistics will be performed using a non-identifiable, anonymised methodology. Patient data will remain anonymised and personal information will remain in the hands of NHS organisations.

9.2.3 Trial Management

The study will be conducted by a team of researchers including the principal investigator, co-investigators and a dedicated trial team at Liverpool Heart and Chest Hospital Clinical Trials Unit (CTU). A Trial Steering Committee will be formed and study oversight will be co-ordinated by the sponsors' research committee, with quarterly progress reports. All records will be made available to the sponsor and ethics committee for review or as part of an audit of the study.

10 References

Angus, D. C. (2015). Fusing randomized trials with big data: The key to self-learning health care systems? JAMA - Journal of the American Medical Association, 314(8), 767–768.

BHF. (2018). UK Factsheet. British Heart Foundation, https://ww(August).

Collet, C., Onuma, Y., Andreini, D., Sonck, J., Pompilio, G., Mushtaq, S., … Serruys, P. W. (2018). Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. European Heart Journal, 39(41), 3689–3698.

Conte, E., Annoni, A., Pontone, G., Mushtaq, S., Guglielmo, M., Baggiano, A., … Andreini, D. (2017). Evaluation of coronary plaque characteristics with coronary computed tomography angiography in patients with non-obstructive coronary artery disease : a long-term follow-up study. European Heart Journal Cardiovascular Imaging, 18, 1170–1178.

Curzen, N. P., Nolan, J., Zaman, A. G., Norgaard, B. L., & Rajani, R. (2016). Does the Routine Availability of CT – Derived FFR In fl uence Management of Patients With Stable Chest Pain Compared to CT Angiography Alone? JACC. Cardiovascular Imaging, 9(10), 1188–1194.

Danad, I., Van Rossum, A. C., Knaapen, P., Van De Ven, P. M., Van Royen, N., Raijmakers, P. G., … Taylor, C. A. (2018). 1185Head-to-head comparison of FFR-CT against coronary CT angiography and myocardial perfusion imaging for the diagnosis of ischaemia. European Heart Journal, 39(suppl_1).

Douglas, P. S., Pontone, G., Hlatky, M. A., Patel, M. R., Norgaard, B. L., Byrne, R. A., … De Bruyne, B. (2015). Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRct: outcome and resource impacts stud. European Heart Journal, 36(47), 3359–3367.

Fairbairn, T. A., Nieman, K., Akasaka, T., Nørgaard, B. L., Berman, D. S., Raff, G., … Patel, M. R. (2018). Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve : lessons from the ADVANCE Registry. European Heart Journal, 0(August), 1–11.

Fordyce, C. B., Newby, D. E., & Douglas, P. S. (2016). Diagnostic Strategies for the Evaluation of Chest Pain. Journal of the American College of Cardiology, 67(7), 843–852.

Hlatky, M. A., De Bruyne, B., Pontone, G., Patel, M. R., Norgaard, B. L., Byrne, R. A., … Douglas, P. S. (2015). Quality-of-Life and Economic Outcomes of Assessing Fractional Flow Reserve with Computed Tomography Angiography: PLATFORM. Journal of the American College of Cardiology, 66(21), 2315–2323.

Izzat, L., & Knight, E. (2011). Copyright Medinews (Cardiology) Limited Reproduction Prohibited Copyright Medinews (Cardiology) Limited Reproduction Prohibited Copyright Medinews (Cardiology) Limited Reproduction Prohibited Copyright Medinews (Cardiology) Limited Reproduction Pr. British Journal of Cardiology, 18(2), 2009–2012.

Jensen, J. M., Bøtker, H. E., Mathiassen, O. N., Grove, E. L., Øvrehus, K. A., Pedersen, K. B., … Nørgaard, B. L. (2017). Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris : influence on downstream rate of invasive coronary angiography. European Heart Journal Cardiovascular Imaging, 0, 1–10.

Knuuti, J. *et al.* (2020) '2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes', *European Heart Journal*, 41(3), pp. 407–477.

Lee, S.-E., Sung, J. M., Rizvi, A., Lin, F. Y., Kumar, A., Hadamitzky, M., & Kim, Y.-J. (2018). Quantification of Coronary Atherosclerosis. Circulation. Cardiovascular Imaging, 14(July), 1–10.

Leipsic, J., Taylor, C. M., Heilbron, B. G., Mancini, G. B. J., Achenbach, S., Berman, D. S., … Min, J. K. (2013). Cardiovascular Risk among Stable Individuals Suspected of Having Coronary Artery Disease with No Modifiable Risk Factors : Results from an International Multicenter Study of 5262 Patients 1. Radiology, 267(3), 718–726.

Longford, N. T. (1999). Selection bias and treatment heterogeneity in clinical trials. Statistics in Medicine, 18(12), 1467–1474.

Lu, M. T., Ferencik, M., Roberts, R. S., Lee, K. L., Ivanov, A., Adami, E., … Hoffmann, U. (2017). Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. JACC: Cardiovascular Imaging, 10(11), 1350–1358.

Meijboom, W. B., Van Mieghem, C. A. G., van Pelt, N., Weustink, A., Pugliese, F., Mollet, N. R., … de Feyter, P. J. (2008). Comprehensive Assessment of Coronary Artery Stenoses. Computed Tomography Coronary Angiography Versus Conventional Coronary Angiography and Correlation With Fractional Flow Reserve in Patients With Stable Angina. Journal of the American College of Cardiology, 52(8), 636–643.

Min, J. K., Leipsic, J., Pencina, M. J., Berman, D. S., Koo, B. K., Van Mieghem, C., … Mauri, L. (2012). Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA - Journal of the American Medical Association, 308(12), 1237–1245.

Nakazato, R., Park, H. B., Berman, D. S., Gransar, H., Koo, B. K., Erglis, A., … Min, J. K. (2013). Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity results from the DeFACTO study. Circulation: Cardiovascular Imaging, 6(6), 881–889.

NICE. (2010). Chest pain of recent onset: assessment and diagnosis. NICE Guidance, (March 2010). Retrieved from https://www.nice.org.uk/guidance/cg95/chapter/guidance

Nielsen, L. H., Ortner, N., Nørgaard, B. L., Achenbach, S., Leipsic, J., & Abdulla, J. (2014). The diagnostic accuracy and outcomes after coronary computed tomography angiography vs.

conventional functional testing in patients with stable angina pectoris: a systematic review and meta-analysis. European Heart Journal Cardiovascular Imaging, 15(9), 961–971.

Nørgaard, B. L., Hjort, J., Gaur, S., Hansson, N., Bøtker, H. E., Leipsic, J., … Jensen, J. M. (2017). Clinical Use of Coronary CTA–Derived FFR for Decision-Making in Stable CAD. JACC: Cardiovascular Imaging, 10(5), 541–550.

Nørgaard, B. L., Leipsic, J., Gaur, S., Seneviratne, S., Ko, B. S., Ito, H., … Achenbach, S. (2014). Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: The NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). Journal of the American College of Cardiology, 63(12), 1145–1155.

Nørgaard, B. L., Terkelsen, C. J., Mathiassen, O. N., Grove, E. L., Bøtker, H. E., Parner, E., … Jensen, J. M. (2018). Coronary CT Angiographic and Flow Reserve-Guided Management of Patients With Stable Ischemic Heart Disease. Journal of the American College of Cardiology, 72(18), 2123–2134.

Rajani, R., Webb, J., Marciniak, A., & Preston, R. (2015). Comparative efficacy testing - Fractional flow reserve by coronary computed tomography for the evaluation of patients with stable chest pain. International Journal of Cardiology, 183, 173–177.

Roel S. Driessen, MDa, Ibrahim Danad, MDa, Wijnand J. Stuijfzand, MDa, Pieter G. Raijmakers MD, PhDb, Stefan P. Schumacher, MDa, Pepijn A. van Diemen, MDa, Jonathon A. Leipsic, Md., Juhani Knuuti, MD, PhDd, S. Richard Underwood, MD, PhDe, Peter M. van de Ven, P., & Albert C. van Rossum, MD, PhDa, Charles A. Taylor, PhDg, Paul Knaapen, MD, P. (2019). Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. Journal of the American College of Cardiology, (2), 161–173.

Stewart, S., Murphy, N., Walker, A., McGuire, A., & McMurray, J. (2003). The current cost of angina pectoris to the National Health Service in the UK. Heart, 89(8), 848–853.

Taylor, C. A., Fonte, T. A., Min, J. K., City, R., & Angeles, L. (2013). Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve Scienti fi c Basis. Journal of the American College of Cardiology, 61(22), 2233–2241.

Williams, M. C., Hunter, A., Shah, A. S. V, Assi, V., Lewis, S., Smith, J., … Newby, D. E. (2016). Use of Coronary Computed Tomographic Angiography to Guide Management of Patients with Coronary Disease. Journal of the American College of Cardiology, 67(15), 1759–1768.