Prediction of Coronary Revascularization in Stable Angina
Comparison of FFR_{CT} with CMR Stress Perfusion Imaging

Brief title: FFR_{CT} versus CMR in stable chest pain

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Abstract

Objectives

To compare, head-to-head, fractional flow reserve (FFR) derived from coronary CTA (FFR_{CT}) and cardiac magnetic resonance (CMR) stress perfusion imaging for prediction of standard of care guided coronary revascularization in patients with stable chest pain and obstructive coronary artery disease (CAD) by coronary CTA.

Background

FFR_{CT} is a novel modality for non-invasive functional testing. The clinical utility of FFR_{CT} compared to CMR stress perfusion imaging in symptomatic patients with CAD is unknown.

Methods

Prospective study of patients, n=110, with stable angina pectoris and $\geq$1 coronary stenosis $\geq$50% by coronary CTA. All patients underwent coronary angiography (ICA). Revascularization was FFR-guided in stenoses ranging from 30-90%. $FFR_{CT} \leq 0.80$ in $\geq$1 coronary artery or a reversible perfusion defect ($\geq$2 segments) by CMR categorized patients with ischemia. FFR_{CT} and CMR analysed by core laboratories blinded for patient management.

Results

A total of 38 patients (35%) underwent revascularization. Per-patient diagnostic performance for identifying standard of care guided revascularization, (95% confidence interval) yielded a sensitivity of 97% (86-100) for FFR_{CT} versus 47% (31- 64) for CMR, $p<0.001$; corresponding specificity was 42% (30-54) versus 88% (78-94), $p<0.001$; negative predictive value of 97% (91-100) versus 76% (67-85), $p<0.05$; positive predictive value of 47% (36-58) versus 67% (49-84), $p<0.05$; and accuracy of 61% (51-70) versus 74% (64-82), $p>0.05$, respectively.

Conclusions

In patients with stable chest pain referred to ICA based on coronary CTA, FFR_{CT} and CMR yielded similar overall diagnostic accuracy. Sensitivity for prediction of revascularization was highest for $FFR_{CT,}$ while specificity was highest for CMR.

Keywords

Stable angina, revascularization, FFR_{CT}, CMR stress perfusion imaging.

Abbreviations

CAD = Coronary Artery Disease
CMR = Cardiac Magnetic Resonance
CTA = Computed Tomography Angiography
CX = Circumflex Coronary Artery
FFR = Fractional Flow Reserve
FFR_{CT} = Coronary CTA derived Fractional Flow Reserve
LAD = Left Anterior Descending Coronary Artery
LM = Left Main Coronary Artery
MPI = Myocardial Perfusion Imaging
RCA = Right Coronary Artery.

Introduction

Current guidelines recommend myocardial perfusion imaging (MPI) as the frontline testing strategy in symptomatic patients with intermediate risk of coronary artery disease (CAD) (1,2) before referral to invasive coronary angiography and decision making on coronary revascularization. Meta-analyses (3,4) have indicated that stress perfusion imaging by cardiac magnetic resonance (CMR) is more accurate than commonly applied perfusion techniques by single photon emission computed tomography (SPECT) for the diagnosis of CAD. Still, CMR has not yet been generally implemented as a first-line testing strategy in patients with symptoms of stable CAD. Coronary computed tomography angiography (CTA) has evolved as an alternative due to a high diagnostic performance for exclusion of CAD (5). However, the hemodynamic significance of lesions cannot be assessed by coronary CTA. Computational fluid dynamics and individual image-based modelling now allows estimation of coronary blood flow and - pressure from standard acquired coronary CTA datasets (6). Subsequent processing of the data derived from computed tomography permits calculation of non-invasive fractional flow reserve (FFR_{CT}). The new metric, FFR_{CT}, has good diagnostic performance using invasive FFR as the reference standard (7, 8) and its utility in clinical practice has been demonstrated by improvements in diagnostic sensitivity compared to SPECT (9), diagnostic yield of coronary angiography (10) and prognosis (11).

A direct comparison of the clinical utility of FFR_{CT} and CMR as second-line sequential testing strategies has not previously been assessed. Consequently, the aim of this study was to compare, head-to-head, FFR_{CT} and CMR for predicting standard of care guided coronary revascularization in patients with new onset stable chest pain and obstructive CAD as determined by coronary CTA.

Methods

Study design and patient cohort

This study is a prespecified sub-study of the Dan-NICAD trial (12), which was designed to compare the diagnostic performance of SPECT and CMR in diagnosing invasively determined obstructive CAD in consecutive symptomatic patients having obstructive CAD as determined by coronary CTA. This sub-study represents a head-to-head comparison of the clinical utility of FFR_{CT} and CMR-testing for the prediction of standard of care guided coronary revascularization.

Coronary CTA is used as the recommended first-line testing strategy in patients with new onset stable chest pain in Denmark. In general, patients with a low-intermediate pre-test risk of having obstructive CAD and no prior revascularization, a body mass index <40 kg/m2, a glomerular filtration rate >45 ml/min and no persistent atrial fibrillation are eligible for coronary CTA. Consequently, the Dan-NICAD criteria for inclusion were new onset stable chest pain in low-intermediate risk patients referred for a first-line coronary CTA to rule-out CAD. This sub-study included patients randomized to the CMR-arm of the Dan-NICAD trial due to the presence of at least one coronary stenosis >50% as determined by coronary CTA. Exclusion criteria were known CAD, inability to undergo adenosine testing or CMR, allergy to iodinated contrast media, non-cardiac illness with life expectancy less than 2 years or pregnancy. All patients underwent subsequent coronary angiography. The decision on revascularization was guided by invasive FFR in stenosis ranging from 30-90% and was made at the discretion of the operator or the Heart Team. The study flow chart is illustrated in Figure 1.

FFR_{CT} and CMR assessments were performed at core-laboratories and test results were unknown to interventionalists and surgeons of the Heart Team. To mimic clinical practice, the CMR core-laboratory had information regarding symptoms, medicine, risk factors and the result of the coronary CTA; while the FFR_{CT} core-laboratory only had access to the coronary CTA-dataset.

Informed consent was obtained from all participants. The study was approved by The Central Denmark Region Committees on Health Research Ethics (S-20150085) and registered by the Data Protection Registry (2008-58-0035; 1563) of The Central Region of Denmark.

Coronary CTA

Coronary CTA was performed at two centres in Denmark. Both centres used a 320-slice volume CT scanner (Aquillion One, Toshiba Medical Systems, Japan) with prospective electrocardiographic (ECG) gating. Oral beta-blockers or ivabradine were administered if necessary, targeting a heart rate <60 beats/min. Administration of sublingual nitroglycerine was given to all patients without known side effects of this drug. An initial non-enhanced scan for calcium scoring was performed. Coronary CTA was assessed and graded visually by skilled CT cardiologists. Lesions were reported using an 18-segment model (13) and classified as proximal if located in segments 1, 2, 5, 6, 7, 11 or 13; all other lesion locations were classified as distal.

Invasive procedures and revascularization

Ingestion of caffeine was not allowed for 24 hours prior to invasive procedures. Coronary angiography was performed by standard techniques. FFR measurements (St. Jude Medical, MN, USA and Volcano, San Diego, CA, USA) were performed in coronary stenosis ranging from 30 to 90% (visual assessment by the treating physician) and a reference diameter ≥2mm. Maximal hyperaemia was induced by intravenous adenosine (140 mcg/kg/min). Recordings of aortic and distal coronary pressures were obtained during sustained hyperaemia (after 2 minutes of adenosine infusion). Patients were classified as having obstructive CAD, if ≥1 high-grade stenosis >90% (visual assessment) by invasive coronary angiography or if ≥1 coronary artery had an FFR-value ≤0.80 distal to stenosis ranging from 30-90%. Physicians responsible for downstream patient

management were blinded to the results of FFR_{CT} and CMR analyses, including those performing the ICA and FFR investigations. All patients revascularized by coronary artery by-pass surgery (CABG) or percutaneous coronary intervention (PCI) or a combination of the two were registered.

FFR_{CT}

Standard acquired coronary CTA data sets were transmitted for core-laboratory analysis (HeartFlow Inc., Redwood City, California, USA). The principles behind FFR_{CT} computation have been described in detail previously (6). Any FFR_{CT} value in the major coronary arteries $\geq$1.8 mm in diameter, including side branches, were registered. Patients were classified as having obstructive CAD, if the per-patient lowest FFR_{CT}-value was $\leq$0.80 (distal-tip FFR_{CT}-value). In addition, patients were classified according to the per-patient lowest FFR_{CT}-value registered 2 cm distal to lesion (lesion-specific FFR_{CT}-value) using an identical threshold-value for ischemia (14). Occluded vessels were assigned an FFR_{CT}-value of 0.50. The distal-tip FFR_{CT}-value was used for the main comparisons with CMR.

CMR

Patients were instructed to stop ingestion of caffeine for 24 hours prior to stress studies. CMR scans were conducted using a 1.5 Tesla system (Siemens MAGNETOM Avanto, Siemens Healthcare GmbH, Erlangen, Germany) as previously described (15). In brief, stress perfusion imaging was conducted either after intravenous injection of 0.4 mg (5 ml) of Regadenoson (Lexiscan, Astellas Pharma, USA) or infusion of adenosine 140 mcg/kg/min over 4 min. Gadovist (Bayer Schering Pharma AG, Germany) or Dotarem (GD-DOTA, Guerbet LCC, USA), were used as contrast agents. CMR data were analyzed by a core laboratory (William Harvey Research Institute, Queen Mary University of London, London, UK). CMR-image quality was graded as high, medium or poor.

Stress-perfusion CMR images were evaluated according to a standard 16-segment model by visual analysis (16). Perfusion defects were defined as subendocardial or transmural signal changes by stress imaging or irreversible defects by late gadolinium enhancement (LGE) imaging. Abnormality of CMR studies were graded based on the number of segments involved: 0-1=normal; 2-4=small; 5-7=moderate; ≥8=large. Patients were classified as having obstructive CAD if reversible changes from rest to stress were registered in ≥2 contiguous segments.

Statistical analyses

This sub-study of the Dan-NICAD trial was planned and designed before the start of any data analysis in the main study (12). McNemar's test was used to compare the sensitivity, specificity and accuracy of FFR_{CT} and CMR as well was comparison of minimum distal-tip- and minimal lesion-specific FFR_{CT}-values in relation to classification of patient-level ischemia. Logistic regression using cluster robust standard errors was used to compare PPV and NPV. Fisher's exact test was used for comparison of proportions between subgroups. Associations between proportions of revascularized patients/proportions of patients with significant CAD and patient level minimum FFR_{CT} -values and size of CMR-perfusion defects, respectively, were tested using weighted linear regression with robust standard errors. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata software, version 15.1 (Stata Corp, College Station, Texas).

Role of the funding source and the core-laboratory at HeartFlow

The funders had no role in study design, data collection, analysis, interpretation, or writing of the report. HeartFlow only had access to the coronary CTA datasets and did not perform any data-

handling or data analysis, did not influence interpretation of data and did not participate in writing of the manuscript. The contract with HeartFlow on FFR_{CT}-analysis was made using the price at cost.

Results

Between September 2014 and March 2016, 1675 consecutive symptomatic patients were enrolled in the Dan-NICAD trial. A stenosis >50% was diagnosed by coronary CTA in 386 patients, of whom 197 patients were randomized to undergo CMR and invasive coronary angiography/FFR. Of these, 58 patients did not have a complete dataset, and 29 (21%) of coronary CTA datasets were rejected for FFR_{CT}-analysis, Figure 1. Basic characteristics of the 110 patients, who constituted the study cohort are shown in Table 1. Median (IQR) time delay between coronary CTA and coronary catheterization was 32 (25-39) days.

Coronary CTA

Relevant preparation variables and Agatston scores are presented in Table 2.

Invasive procedures and revascularization

Overall 44 patients were diagnosed with obstructive CAD. Because of small vessel dimension, vessel tortuosity or paucity of symptoms at the time of angiography, 6 of these patients were not revascularized; 3 patients with obstructive stenosis (FFR $\leq$ 0.80 [range 0.76-0.80]) and 3 patients with an occluded coronary artery. The number of revascularized patients, n (%), was not significantly different in this sub-study, 38 (35), compared to the number of revascularizations performed in patients in the CMR-arm of the Dan-NICAD cohort, 25 (36), who were excluded due to missing data.

A total of 55 vessels were revascularized and distributed as follows, n (%): LM, 1 (2); LAD, 27 (49); CX, 9 (16); RCA 11 (20); side branches 7 (13). Revascularized lesions were located in proximal coronary segments in 34 (89%) patients. In 26 patients with a maximal stenosis >90%, 23 (88%) patients were revascularized, while 12 of these 26 patients had an FFR performed in another stenosis ranging from 30-90%. In 57 patients with a maximal stenosis ranging from 30-90%, 15 (26%) patients underwent revascularization. No patient with stenosis <30% was revascularized. Three out of 25 PCI-procedures were performed in chronic total occlusions; three out of 13 surgical procedures as off-pump coronary artery by-pass operations. An overview of invasive procedures and given treatments is presented in Table 3.

FFR_{CT}

The number, n (%), of patients classified with obstructive CAD, FFR_{CT}-value $\leq$0.80, was higher when classification was based on the per-patient minimum distal-tip - compared to per-patient minimum lesion-specific FFR_{CT}-value, 79 (72) versus 55 (50), respectively, p<0.001. The overall distributions of patient-level FFR_{CT}-values and the associations to the occurrence of significant CAD and revascularization are shown in Tables 4a and 4b. Of 55 revascularized vessels, 50 (91%) vessels had an FFR_{CT}-value $\leq$0.80. All occluded vessels were correctly identified by FFR_{CT}.

CMR

Stress studies were performed using regadenoson (n=48) or adenosine (n=62). Image quality was high in 90 (82%) patients and medium in 20 (18%). In 4 (4%) patients, no side effects to adenosine (dyspnoea, chest, pain, dizziness, or headache) were registered, of whom 1 patient had a reversible perfusion defect (RPD). Left ventricular ejection fraction, mean (SD), by CMR was 66 (10). Irreversible perfusion defects were identified in 4 (4%) patients, all of whom had an RPD as well.

Of 83 (75%) patients, who were classified as having a normal CMR test result, 82 (99%) had completely normal stress perfusion. An RPD was demonstrated in 27 (25%) patients (small RPD: 8/27 [30%]; moderate RPD: 13/27 [48%]; large RPD: 6/27 [22%]). The associations between the size of perfusion defects by CMR and the occurrence of significant CAD and revascularization are shown in Table 5. Of 8 patients diagnosed with an occluded coronary artery, 7 (88%) patients had an RPD by CMR.

Head-to-head comparison, FFR_{CT} versus CMR

The number of patients classified as having obstructive CAD, n (%), differed between the non-invasive modalities: FFR_{CT} 79 (72) versus CMR 27 (25), $p<0.001$. Concordant FFR_{CT} and CMR test results were found in 58 (53%) patients, of whom 27 (47%) patients had obstructive CAD by both tests and 31 (53%) patients normal test results by both FFR_{CT} and CMR. In the former group, revascularization was performed in 18 (67%) patients, in the latter 1 (3%), $p<0.001$. Discordant test results were seen in 52 (47%) patients, all having a normal test result by CMR and signs of obstructive CAD by FFR_{CT}, of whom 19 (37%) patients were revascularized. No patients were classified as abnormal by CMR and as normal by FFR_{CT}.

Prediction of revascularization, FFR_{CT} versus CMR

The per-patient diagnostic performance for identifying standard of care guided revascularization, (95% confidence interval) yielded a sensitivity of 97% (86-100) for FFR_{CT} versus 47% (31- 64) by CMR, $p < 0.001$; corresponding specificity was 42% (30-54) versus 88% (78-94), $p < 0.001$; negative predictive value 97% (91-100) versus 76% (67-85), $p<0.05$; positive predictive value 47% (36-58) versus 67% (49-84), $p<0.05$; and accuracy 61% (51-70) versus 74% (64-82), respectively, $p>0.05$, Central Illustration. The sensitivity of FFR_{CT} for predicting revascularization remained

constantly high in all tested strata, whereas the sensitivity of CMR was consistently low, Table 6. False-negative test results were more frequent by CMR, n=20, than classification of obstructive CAD by distal-tip FFR_{CT}-values, n=1, $p<0.001$, both amongst patients, n (%), undergoing multi-vessel revascularization: CMR 7 (50) versus FFR_{CT} 0 (0), $p<0.05$, patients treated by single-vessel revascularization: CMR 13 (54) versus FFR_{CT} 1 (4), $p<0.001$ and patients undergoing CABG: CMR 8 (62) versus FFR_{CT} 0 (0), $p<0.01$. Significantly more patients, n (%), with a false negative CMR test result compared to patients with a false negative FFR_{CT} test result underwent revascularization for proximal LAD-stenosis: CMR 17 (61) versus FFR_{CT} 0 (0), $p<0.001$, and had a stenosis severity >90% by ICA: CMR 14 (61) versus FFR_{CT} 1 (4), $p<0.01$. The only patient, who was falsely classified as normal by FFR_{CT} had a >90% stenosis of the RCA-1 and was treated directly with PCI.

The diagnostic sensitivity of CMR was not different among patients with analysable coronary CTA datasets compared to patients in whom CTA datasets were rejected for FFR_{CT}-analysis: 18 of 38 (47%) versus 4 of 7 (57%), $p>0.05$. No difference in the diagnostic performance of CMR, regadenosone versus adenosine, was demonstrated (Data not shown).

The specificity for predicting revascularization was significantly improved from 42% to 68%, $p<0.001$, by using lesion-specific FFR_{CT}-values rather than distal-tip FFR_{CT}-values for classification of obstructive CAD, which caused a non-significant decrease in test sensitivity of FFR_{CT} from 97% to 84%, $p>0.05$, Central Illustration and Table 7.

Discussion

This prospective clinical study comparing FFR_{CT} and CMR stress perfusion imaging in symptomatic stable patients with CAD as determined by coronary CTA did not show any difference in the diagnostic accuracy of FFR_{CT} and CMR in predicting standard of care guided coronary revascularization. However, a significant difference in sensitivity in favour of FFR_{CT} was

demonstrated, while the specificity of CMR was highest. The current study included patients in whom guidelines recommend adjunctive non-invasive functional testing. To avoid deferral from invasive investigation of obstructive coronary disease a high diagnostic sensitivity and negative predictive value of the second-line tests is essential. Accordingly, this first head-to-head comparison between second-line FFR_{CT} and CMR testing strategies is relevant.

In this study, patients undergoing revascularization were more often classified as having functional impairment by FFR_{CT} as compared to CMR. These results are in line with two recent studies, in which FFR_{CT} had a higher diagnostic sensitivity for prediction of revascularization compared to the severity of stenosis by coronary CTA (17) and compared to the occurrence of reversible perfusion defects by SPECT (9). Of note, clinical decision-making on revascularization in these studies was made independently of FFR_{CT}-analyses, as test results were unknown to the caregivers.

Several factors might influence the only modest diagnostic sensitivity of CMR stress perfusion imaging demonstrated in the present study. First, it should be recognized that studies included in recent meta-analyses (3,4) used CMR as a first line rule-out in patients with chest pain, while the current applied CMR as a second-line testing strategy solely in those patients who had documented CAD by coronary CTA. Second, the disease prevalence in the current study was lower than in previous studies. In the CE-MARC study 11 % of patients had a previous myocardial infarction or had undergone revascularization (18). In the MR-IMPACT-II study 39% sustained a previous infarction and 31% had been treated by coronary angioplasty in the past (19), while patients with known CAD were excluded in our study. Third, an anatomic/physiological mismatch is well-known (17, 20), implying that a number of lesions in prior studies presumably would have been re-classified, if physiologic measurements by FFR instead of morphologic degree stenosis by ICA had been used as the reference. Fourth, it might be argued that 3T scanners yielding higher spatial resolution and giving the potential for quantification of perfusion might have increased the

diagnostic sensitivity of CMR. However, 3T scanners have not been documented to yield superior results compared to 1.5 T systems and the latter scanner type is by far the most prevalent system used for CMR stress perfusion studies. Furthermore, quantitative measures of perfusion by CMR has not yet been fully established. Fifth, the threshold for a reversible perfusion defect by CMR stress perfusion imaging in this study was defined as $\geq$2 segments in accordance with international guidelines. Applying a lower threshold for test positivity would not have changed test sensitivity for CMR, as 82 out of 83 patients (99%) had completely normal CMR stress perfusion scans. Although a small myocardium-at-risk may be a reason for a false negative CMR scan (21), it is unlikely to explain the demonstrated low sensitivity of CMR, as 89% of treated lesions were located proximal in the coronary arteries. Moreover, the modest diagnostic sensitivity of CMR was demonstrated across subpopulations. Finally, the low diagnostic sensitivity of CMR in this study are unlikely to be caused by inappropriate CMR stress testing or data analysis, as 96% of patients had adverse effects during pharmacological stress testing and as 82% of CMR datasets had a good image quality.

The low rate of patients classified with obstructive CAD by CMR may seem in contrast to the medium-to high burden of coronary atherosclerosis seen in patients in this study as illustrated by 40% of patients having an Agatston score above 400, 24% having a stenosis severity >90% and 35% undergoing revascularization of whom 37% were treated due to multi-vessel disease and 34% were treated by CABG.

The modest per-patient FFR_{CT} specificity detected in this study may in part be explained by the use of distal-tip FFR_{CT}-value rather than lesion-specific FFR_{CT}-value (22). The increase in test specificity by applying lesion-specific FFR_{CT} for categorizing patients was achieved with a non-significant decrease in test sensitivity, which is in accordance with a recent study (14). Still, the specificity of CMR remained significantly higher than that of FFR_{CT}.

Similarities between the vessel specific approach elaborated by FFR and FFR_{CT} as opposed to evaluation by myocardial perfusion by CMR would be in favour of FFR_{CT} and an explanation for the difference in the diagnostic performance. However, FFR_{CT} modelling and principles underlying computational fluid dynamics are fundamentally different from FFR. In addition, revascularization was guided not only by FFR-assessments but by angiography in 48% of patients in our study.

How the differences of second-line FFR_{CT} and CMR test performance influence outcomes in terms of prognosis/costs for societies is at the moment unsettled. However, testing strategies using either first-line CMR (23,24,25) or selective FFR_{CT} (11) have both indicated a favorable prognosis considering death and myocardial infarction in stable patients with a normal test result and also a more favorable resource utilization compared to usage of first-line coronary angiography (26,27). The importance of choosing a first-line testing strategy with the ability to provide direct visualization of atherosclerotic coronary lesions has recently been demonstrated in the SCOT-HEART randomized trial (28), in a sub-study of the Prospective Multicentre Imaging Study for Evaluation of Chest Pain (PROMISE) trial (29) and by a meta-analysis (30), as the incidence of major adverse cardiovascular events was significantly lower following anatomic assessment by coronary CTA than following first-line functional testing strategies.

In this context, it is worth noticing that a number of obstructive lesions in the current study would have remained undiagnosed by CMR perfusion imaging, if invasive angiography had not been performed, which is of special importance because first-line CMR have indicated more favourable resource utilization than first-line coronary angiography. We did not include any follow-up data on either symptomatic relief or incidence of coronary events in our study, so it remains unknown how the reported discrepancy in diagnostic performance of second-line FFR_{CT} and CMR following a first-line coronary CTA impact resource utilization and patient outcomes.

Limitations

The number of patients included in this prospective study is relatively small, which may give rise to spurious non-significant results. However, as our sample size was sufficient to detect significant differences between the main effect parameters, the diagnostic sensitivity and specificity of the two tests being compared, the risk of spurious non-significant results is not an issue for our primary outcomes.

A number of patients were unable to complete all planned series of tests. Our rejection rate for FFR_{CT}-analysis was 21%, and was higher than reported in previous studies, where CTA scan protocols were optimized for FFR_{CT}-analysis (9, 10), but at the same level as in a study without pre-scheduled FFR_{CT}-analysis (17). As the proportion of patients undergoing revascularization and the diagnostic sensitivity of CMR were similar in drop-outs and in the study population, we do not believe this had any impact on the result of this study.

The results of this study only apply to patients in whom coronary CTA testing is appropriate.

Conclusion

In patients with stable chest pain and documented CAD by coronary CTA adjunctive non-invasive functional testing by FFR_{CT} and CMR yielded similar overall accuracy for prediction of coronary revascularization. However, a significant difference in diagnostic sensitivity in favour of FFR_{CT} was demonstrated, while the specificity of CMR was highest.

Clinical Perspective

To the best of our knowledge, this prospective study is the first of its kind to compare the novel physiologic metric, FFR_{CT}, with CMR stress perfusion imaging for prediction of standard of care

guided coronary revascularization in real-world practice. The current study in stable symptomatic patients with coronary lesions as determined by coronary CTA did not show any difference in the overall accuracy of FFR_{CT} and CMR in predicting revascularization. However, FFR_{CT} had a significantly higher diagnostic sensitivity than CMR in identifying patients undergoing revascularization, while the specificity was highest for CMR. Randomized prospective trials are warranted to clarify, whether the reported discrepancy between the applied adjunctive functional testing strategies in selecting patients for invasive procedures will have significant impact on patient outcomes.

Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE

Functional testing is recommended prior to referral to invasive angiography in patients with stable chest pain and obstructive CAD as determined by coronary CTA. A direct comparison of the clinical utility of FFR_{CT} and CMR as second-line sequential testing strategies has not previously been assessed. In this study we found a similar diagnostic accuracy of the two non-invasive testing strategies for prediction of standard of care guided coronary revascularization. However, the diagnostic sensitivity was significantly higher for FFR_{CT} compared to CMR, while the specificity was highest for CMR.

TRANSLATIONAL OUTLOOK

The reported diagnostic performance of second-line FFR_{CT} and CMR following a first-line coronary CTA in patients with stable chest pain relates to prediction of standard of care guided revascularization. Large prospective studies are warranted to evaluate if the reported discrepancy impact resource utilization and patient outcomes.

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Legends

Figure 1. Flowchart.

This study represents a sub-study of the Dan-NICAD-trial (Danish Study of Non-Invasive testing in Coronary Artery Disease (12).

*CMR = Cardiac magnetic resonance; #CTA = Computed tomography angiography; §FFR_{CT} = Fractional flow reserve derived from coronary CTA; †ICA = Invasive coronary angiography.

Central Illustration. **FFR_{CT} compared with CMR stress perfusion imaging for prediction of standard of care guided coronary revascularization in patients with stable chest pain.**

FFR_{CT} defined as the per-patient lowest FFR_{CT}-value in coronary vessels ≥1.8 mm in diameter. The results of core laboratory FFR_{CT} analysis and CMR test assessments had no impact on referral to invasive angiography and were blinded to decision makers.

‡NPV = Negative predictive value; †PPV = Positive predictive value. Other abbreviations as in Figure 1.