

Usefulness of FFR-CT to exclude haemodynamically significant lesions in high-risk NSTEMI-ACS

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ABSTRACT

BACKGROUND: Coronary computed tomography angiography (CCTA) and fractional flow reserve (FFR) derived from CCTA (FFR-CT) may provide a means of reducing unnecessary invasive coronary angiography (ICA) in patients with suspected non-ST-elevation acute coronary syndromes (NSTEMI-ACS).

AIMS: The aim of this study was to evaluate the capacity of FFR-CT and CCTA to rule out significant lesions in high-risk NSTEMI-ACS patients, using ICA with invasive FFR as the gold standard.

METHODS: High-risk NSTEMI-ACS patients admitted to 4 European centres were enrolled in this single-arm, prospective core lab-adjudicated study. Patients underwent CCTA with FFR-CT analysis, followed by ICA with invasive FFR.

RESULTS: Out of the 250 initially planned NSTEMI-ACS patients, 168 were included, of whom 151 (92%) had sufficient CCTA image quality to undergo CCTA and FFR-CT analysis. The median high-sensitivity troponin T level at 1 hour post-hospitalisation was 5.3 (interquartile range: 1.8-18.6) times the upper reference limit. At the patient level, the diagnostic performance of FFR-CT was numerically higher as compared to CCTA though not statistically significant (sensitivity: 94% vs 93%, specificity: 63% vs 54%, positive predictive value: 83% vs 79%, negative predictive value: 85% vs 80% and accuracy: 83% vs 79%; $p=0.58$), suggesting an enhanced capability to avoid unnecessary ICA. At the lesion level, the ability of FFR-CT to detect significant lesions was significantly better than that of CCTA (receiver operating characteristic curves: 0.84 vs 0.65 respectively; $p<0.01$).

CONCLUSIONS: In patients with high-risk NSTEMI-ACS, FFR-CT offers better diagnostic accuracy – though not statistically significant – and a higher ability to rule out haemodynamically significant stenoses as compared to CCTA. This indicates that FFR-CT can reduce unnecessary invasive procedures by more accurately identifying patients requiring further intervention.

KEYWORDS: ACS/NSTEMI-ACS; MSCT; non-invasive imaging; NSTEMI

Whilst ST-elevation myocardial infarction (STEMI) can typically be diagnosed based on electrocardiogram (ECG) criteria alone, non-ST-elevation acute coronary syndrome (NSTEMI) can represent a diagnostic challenge. The combination of a clinical assessment and ECG criteria is often insufficient for an accurate diagnosis. In addition, although biomarkers such as troponin have a high positive predictive value for the diagnosis of myocardial infarction when markedly raised, the advent of high-sensitivity troponin (hs-Tn) has led to an increase in the number of patients with mildly raised hs-Tn, which has less discriminative power. This results in a significant number of patients being referred for invasive coronary angiography (ICA) who are ultimately found to have no significant epicardial stenoses. This proportion has been reported to be as high as 50% among patients with an increase in troponin of ≤ 3 times the upper range limit (URL)¹.

Coronary computed tomography (CT) angiography (CCTA) has been widely studied in the context of low- to intermediate-risk chest pain, demonstrating an excellent capacity to rule out the presence of significant coronary artery disease. Similarly, fractional flow reserve (FFR) derived from CCTA (FFR-CT) has also been extensively studied as a tool to avoid invasive assessment of intermediate coronary lesions in a stable setting². However, to date, no study has evaluated the potential benefit of CCTA and FFR-CT in the setting of high-risk, troponin-positive NSTEMI-ACS.

Accordingly, in the present study, we investigated whether, in patients with high-risk NSTEMI-ACS, CCTA and FFR-CT were able to exclude the presence of haemodynamically significant coronary stenoses.

Methods

STUDY POPULATION

The detailed methodology of the study has been described previously³. It is important to note that recruitment was slower than expected during the COVID-19 pandemic, as many centres temporarily prohibited the inclusion of non-COVID studies to prioritise pandemic management. Additionally, CT scanners were heavily used for COVID patients, limiting their availability for this study. As a result, the study was extended to 3 additional centres following a similar study protocol. Thus, in total, the study recruited patients from 4 European centres (Lausanne, Switzerland; Monzino, Italy; Aalst, Belgium; and UZB, Belgium) between August 2019 and April 2022. Patients presenting to the hospital with symptoms of ischaemia and in whom a rise and/or fall of high-sensitivity troponin T (hs-TnT) was detected with at least 1 value above the 99th percentile of the URL were screened for inclusion¹.

Impact on daily practice

This preliminary multicentre, international, core lab-adjudicated study suggests that fractional flow reserve (FFR) derived from coronary computed tomography angiography (FFR-CT) may help reduce unnecessary coronary angiographies in high-risk acute coronary syndrome patients. However, before being widely implemented, these findings need further confirmation. The successful application of this approach in hospitals requires well-established protocols and close collaboration with radiology departments, as both tests must be completed within 24 hours. Additionally, although rare in our study, there is a potential limitation if FFR-CT analysis is not feasible. While this strategy adds approximately 80 cc of contrast for patients who ultimately undergo coronary angiography, it provides a complete analysis of the coronary tree, reducing the need for additional contrast use for FFR measurements in non-culprit vessels. It also simplifies the procedure overall, as it begins with a wealth of information from the FFR-CT. For patients with a negative FFR-CT, this algorithm allows for early discharge, saving contrast and optimising hospital resources.

Given the requirement for the iodinated contrast administration for both CCTA and ICA, patients with a glomerular filtration rate (GFR) below 45 ml/min were not included. Pregnant and breastfeeding women, patients with prior coronary stenting, coronary artery bypass grafting (CABG), and patients with known severe heart failure (ejection fraction below 30%) were also excluded. Additionally, patients were excluded if they presented with STEMI or NSTEMI-ACS with 1 or more very high-risk criteria requiring urgent ICA, as per current European⁴ and American guidelines⁵. In accordance with these guidelines, NSTEMI-ACS patients were deemed high risk when they presented with a positive troponin level, showing a dynamic rise or fall, along with symptoms of ischaemia.

STUDY DESIGN AND PROCEDURE

The present study is a single-arm, double-blinded, core laboratory-adjudicated prospective trial. Patients admitted with high-risk NSTEMI-ACS and who agreed to participate in the study underwent CCTA followed by ICA within a recommended time window of 24 hours, as per guidelines. In parallel, patients benefitted from guideline-recommended medical management including cardiac monitoring and antithrombotic therapy.

Abbreviations

ACS	acute coronary syndrome	FFR-CT	FFR derived from coronary CT angiography	NSTEMI	non-ST-elevation myocardial infarction
CABG	coronary artery bypass grafting	hs-Tn	high-sensitivity troponin	PCI	percutaneous coronary intervention
CCTA	coronary computed tomography angiography	MI	myocardial infarction	QCA	quantitative coronary angiography
CT	computed tomography	NSTEMI-ACS	non-ST-elevation acute coronary syndrome	STEMI	ST-elevation myocardial infarction
FFR	fractional flow reserve			URL	upper range limit

CT SCAN ACQUISITION

CT acquisition was performed on a 256-slice multidetector CT (Revolution CT [GE HealthCare] or equivalent). Beta blockers (molecule and dosage left to the physician's discretion) were administered before image acquisition, aiming for a heart rate <65 bpm. Additionally, one dose of sublingual nitroglycerine (400-800 mg)⁶⁻⁸ was administered. Parameters used for CT acquisition were as follows⁹: 80-100 kVp/550 mA for body mass index (BMI) <25 kg/m² (high definition mode), 100 kVp/550 mA for BMI between 25 and 30 kg/m², 120 kVp/600 mA for BMI >30 kg/m² (standard definition mode). For the CCTA acquisition, 80 ml of iodinated contrast was used. A lesion was defined as significant if it had a quantitative coronary angiography (QCA) lumen area stenosis >50%^{10,11} (see Core-laboratory analysis section).

FFR-CT ANALYSIS

FFR-CT was computed offline by blinded investigators in a central FFR-CT core laboratory (HeartFlow, Redwood City, CA, USA). A haemodynamically significant lesion was defined as a lesion with an FFR-CT value of ≤ 0.80 . Of note, the FFR-CT value was taken at the same arterial position as the invasive FFR measurement.

ICA AND FFR

ICA was performed following local and international best practices. FFR was measured in all lesions with a visual diameter stenosis $\geq 30\%$ using the PressureWire X Guidewire (Abbott) using the following protocol: equalisation of the pressure wire and the aortic pressure was performed at the tip of the guide catheter prior to all measurements. The pressure wire was then advanced distal to the stenosis. Hyperaemia was obtained using intracoronary adenosine (100 μg for the right coronary artery and 200 μg for the left coronary artery). At the end of the procedure, the absence of drift was confirmed by pulling back the pressure wire to the initial equalisation site.

BLINDING

Patients, as well as physicians performing ICA, were blinded to the results of CCTA. For obvious ethical reasons, relevant extracardiac findings were communicated to the treating physician to ensure adequate follow-up and/or treatment.

CORE LABORATORY ANALYSIS

In order to guarantee adequate blinding and provide high-quality standardised analysis, all data from ICA, CCTA, and FFR-CT were collected and analysed in a central core laboratory (CoreAalst BV, Aalst, Belgium). ICA images were analysed with three-dimensional (3D) QCA software (CAAS 8.2 Workstation [Pie Medical Imaging]). For ICA, a haemodynamically significant lesion was defined as a lesion with an FFR value of ≤ 0.80 . FFR was not measured in case of very severe stenosis (>90%) or an occluded vessel. In this case, an arbitrary value of 0.50 was attributed to the vessel as previously described¹². CCTA data were analysed using validated software (QAngio CT [Medis Medical Imaging]) by the core laboratory. Measurements were automatically generated by the software, and the analyst manually adjusted luminal contours when necessary. A significant lesion was

defined as a QCA lumen area stenosis >50%. For FFR-CT, a haemodynamically significant lesion was defined as a lesion with an FFR-CT value of ≤ 0.80 . A final database with each vessel analysed with each modality (ICA, CCTA and FFR-CT) was then generated by the core laboratory. For the purpose of simplicity, the coronary anatomy was segmented into three main vessels: left anterior descending artery, left circumflex artery and right coronary artery. Each side branch was adjudicated as pertaining to the main branch.

ENDPOINTS

The primary endpoint was the ability of FFR-CT and CCTA to rule out the presence of significant lesions as defined by the invasive evaluation (i.e., the negative predictive value [NPV]) at the patient level. Secondary endpoints were the sensitivity, specificity, positive predictive value (PPV) and accuracy of FFR-CT and CCTA compared to the invasive evaluation at the patient level. Additionally, the misclassification rate for each strategy was calculated, and analyses were also conducted at a vessel level.

SAMPLE SIZE DETERMINATION AND STATISTICAL ANALYSIS

With the latest iteration of the FFR-CT software, the per-patient sensitivity and specificity were 86% (95% confidence interval [CI]: 77-92%) and 79% (95% CI: 72-84%), respectively¹³. In the VERDICT-EDI trial based on non-STEMI (NSTEMI) patients¹⁴, 12% had 3-vessel disease, 23% had 2-vessel disease (which included the left main), 34% had 1-vessel disease, and 30% had no significant disease. Thus, out of 100 patients with 300 coronary arteries, 116 (i.e., 36+46+34) vessels with a stenosis were expected in our study. Based on the FAMOUS NSTEMI trial¹⁵, 60% of invasive FFR measurements of stenoses were significant¹⁶. Thus, with a standard error of 0.05 and for a power of 80%, 204 patients were required. However, as it was expected that a proportion of CCTA images would not be suitable for analysis, a sample size of 250 patients was targeted. Statistical analyses were carried out with SPSS Statistics 25.0 software (IBM) and Stata, version 14.3 (StataCorp). Comparisons of diagnostic performance (sensitivity, specificity, accuracy) were performed using a paired McNemar test.

ETHICS

This project was approved by the local ethics board of each institution. The study was conducted in accordance with the study protocol, the Declaration of Helsinki, the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) as well as other locally relevant regulations.

Results

PATIENT POPULATION

Due to slower-than-expected enrolment related to the COVID-19 pandemic, study enrolment was stopped prematurely after reaching two-thirds of the planned sample size. In total, 168 patients presenting with high-risk NSTEMI-ACS were recruited between August 2019 and April 2022. The heart rate of 4 patients was too high to undergo adequate CCTA acquisition, and they were excluded. Due to insufficient image quality for CCTA¹² and/or FFR-CT analysis¹, 13 other

patients (8%) were excluded, leaving a total of 151 patients for the final analysis. In 12 cases, an FFR-CT analysis would have been possible, even though a CT-only analysis was not, but by study design, these patients were excluded.

Baseline patient characteristics are reported in **Table 1**. The mean age was 63±12 years, and 70% of patients were male. The vast majority of patients (96%) presented with chest pain, while shortness of breath and nausea were less common (29% and 10%, respectively). In total, 60% of patients had ECG changes consistent with ischaemia or bundle branch block. The median hs-TnT level at 1 hour post-hospitalisation was 5.3 (interquartile range: 1.8-18.6) times the URL.

ICA FINDINGS AND TREATMENT DECISION

A total of 99 patients (66.0%) had at least 1 significant lesion (either diameter stenosis >90% or with a diameter stenosis between 30% and 90% with an FFR ≤0.80). The remaining 52 patients (34.4%) either had no lesion with a diameter stenosis >30% on ICA or had a lesion with a diameter stenosis between 30% and 90% with an FFR >0.80). FFR was measured in a total of 106 lesions in 68 patients (45%). The majority of patients had 1- (34.4%) or 2-vessel (44.4%) disease. After ICA, 64% of patients were treated with percutaneous coronary intervention (PCI), 33% were managed conservatively, and 3% were referred for CABG surgery (**Table 2**).

PERFORMANCE OF FFR-CT AND CCTA AT THE PATIENT LEVEL

The ability of FFR-CT to rule out the presence of a significant lesion (NPV – predefined primary endpoint) was numerically higher than with CCTA (85% vs 80%, respectively). A similar trend was also observed for the other diagnostic parameters (secondary endpoints): 94% versus 93% for sensitivity, 63% versus 54% for specificity, 85% versus 80% for PPV, and 83% versus 79% for accuracy (**Figure 1**). However, this trend was not statistically significant (p=0.58).

Depending on the strategy used, the rate of misclassification varied notably. Using a guideline-based strategy with referral to ICA if appropriate, 34% of patients were assigned to undergo unnecessary ICA. Conversely, when employing a CCTA- or FFR-CT-based strategy, the rate of misclassification decreased to 21% and 17%, respectively (p<0.01) (**Figure 2**). A summary of the performance of CCTA and FFR-CT is shown in **Table 3**. Finally, the rate of potentially avoidable ICA (i.e., true negatives) would have been 19% with a CCTA-based strategy and 22% with an FFR-CT-based strategy.

PERFORMANCE OF CCTA AND FFR-CT AT THE VESSEL LEVEL

Figure 3 displays the percentage stenosis in terms of QCA according to modality (ICA vs CCTA). A total of 459 vessels were analysable in all 3 modalities (ICA, CCTA and FFR-CT). Overall, the performance of FFR-CT was better, mostly because of an increased specificity. On receiver operating characteristic analysis, the area under the curve was significantly higher for FFR-CT as compared with CCTA (0.85 vs 0.64; p<0.01) (**Central illustration**). At the vessel level, the NPV of FFR-CT and of CCTA were similar (92% vs

Table 1. Patients' baseline characteristics and clinical presentation.

Characteristic	n=151
Age, years	63±12
Male	106 (70)
BMI, kg/m ²	28±2
Cardiac risk factors	
Active or former smoker	103 (68)
Hypercholesterolaemia	88 (58)
Hypertension	74 (49)
Diabetes	19 (13)
Peripheral artery disease	5 (3)
Clinical presentation	
Chest pain	145 (96)
Shortness of breath	44 (29)
Nausea/vomiting	15 (10)
ECG findings	
Normal ECG	45 (40)
ST depression	16 (14)
T wave inversion	34 (30)
RBBB	3 (3)
LBBB	10 (9)

1 hr troponin elevation (number of times above URL) 5.3 (1.8-18.6)

Values are expressed as n (%), mean±SD or median (Q1-Q3). BMI: body mass index; ECG: electrocardiogram; LBBB: left bundle branch block; Q: quartile; RBBB: right bundle branch block; SD: standard deviation; URL: upper range limit

Table 2. Coronary angiography findings and treatment.

Coronary angiography findings	n=151
Patients with at least one significant lesion	99 (66)
Extent of coronary artery disease	
None	52 (34.4)
Single vessel	67 (44.4)
Two vessels	23 (15.2)
Three vessels	9 (6.0)
Patients with at least 1 FFR measurement performed	68 (45)
Total number of FFR measurements performed	106
Mean FFR value	0.71±0.36
Treatment decision	
Conservative	49 (33)
PCI	97 (64)
CABG	5 (3)

Values are expressed as n (%), n, or mean±SD. CABG: coronary artery bypass grafting; FFR: fractional flow reserve; PCI: percutaneous coronary intervention; SD: standard deviation

92%). Sensitivity was slightly lower for FFR-CT compared to CCTA (83% vs 87%), while the other diagnostic parameters were all in favour of FFR-CT: 81% versus 70% for specificity, 67% versus 56% for PPV, and 82% versus 75% for accuracy (**Table 4**).

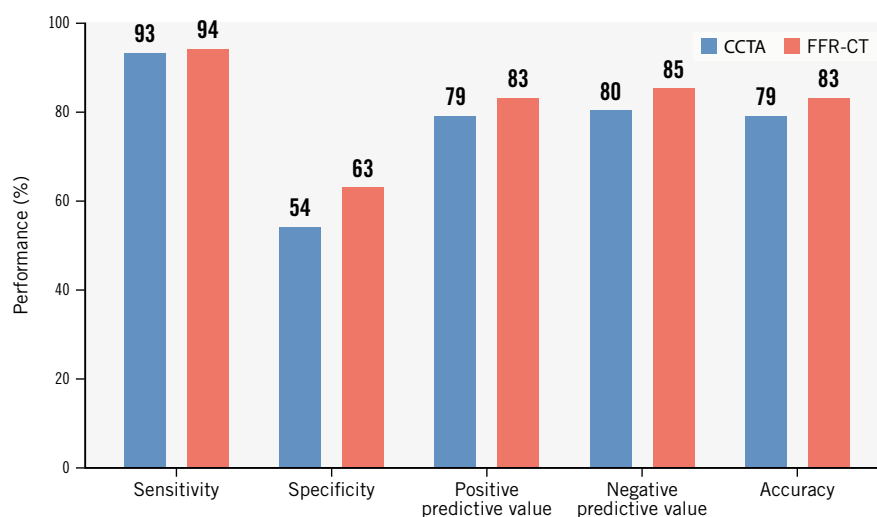


Figure 1. Diagnostic performance of CCTA (blue) and FFR-CT (red) at the patient level with invasive FFR as the gold standard. CCTA: coronary computed tomography angiography; FFR: fractional flow reserve; FFR-CT: FFR derived from CCTA

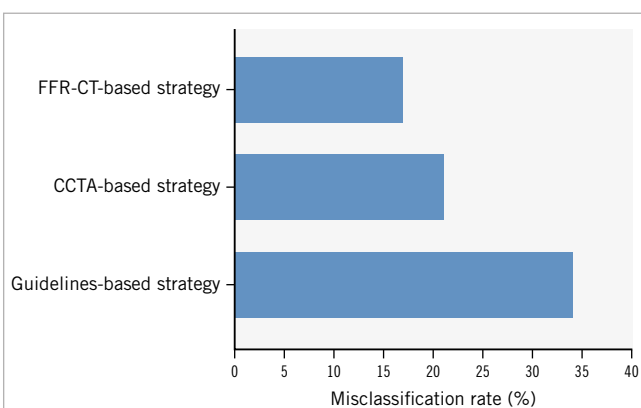


Figure 2. Percentage of misclassification (wrong positives and wrong negatives) of a guideline-based approach, a CCTA-based strategy, and an FFR-CT-based strategy. CCTA: coronary computed tomography angiography; FFR-CT: fractional flow reserve derived from CCTA

Table 3. Performance of CCTA and FFR-CT at the patient level (n=151).

	Angiography (gold standard)	CCTA	FFR-CT
True positive	99	92	93
True negative	52	28	33
False positive	-	24	19
False negative	-	7	6
Sensitivity, %	-	93	94
Specificity, %	-	54	63
Positive predictive value, %	-	79	83
Negative predictive value, %	-	80	85
Accuracy, %	-	79	83

Values are n, or % where indicated. CCTA: coronary computed tomography angiography; FFR-CT: fractional flow reserve derived from CCTA

Discussion

The present study is the first to systematically assess the performance of FFR-CT and CCTA, as compared with ICA with invasive FFR, in the context of high-risk, troponin-positive NSTEMI-ACS. The main findings can be summarised as follows (**Central illustration**): (1) in this high-risk population, 34.4% of patients were found to be without significant coronary artery disease; (2) both CCTA and FFR-CT demonstrated the capacity to avoid unnecessary ICA, but FFR-CT had a numerically higher – although statistically non-significant – diagnostic accuracy compared to CCTA, particularly in terms of its slightly higher NPV; and (3) at the vessel level, FFR-CT exhibited significantly better diagnostic accuracy as compared with CCTA alone.

Taken together, the present data suggest that the use of CCTA (alone or in combination with FFR-CT) has the potential to optimise the management of NSTEMI-ACS by optimising patient selection for ICA.

Despite meeting all the criteria for NSTEMI-ACS including elevated troponin, a significant proportion of patients were found to be without significant obstructive coronary artery disease. This raises important questions regarding the limits of the current state-of-the-art diagnostic approach. Indeed, all the patients included in the present study met guideline-based indications for an early invasive strategy (i.e., within 24 hours). However, in more than one-third of these patients, this invasive strategy was not able to find an actionable coronary cause for their symptoms. This finding has important implications both in terms of unnecessary exposure to procedural risks and healthcare costs. As a consequence, the development of a non-invasive screening approach is highly relevant to current clinical practice.

In the present study, the use of CCTA or FFR-CT would have avoided between 54% and 64% of unnecessary invasive assessments. CCTA as an adjunctive diagnostic tool has already been studied in the past, albeit in different subpopulations. In a meta-analysis of 9 studies (n=1,349 patients), CCTA

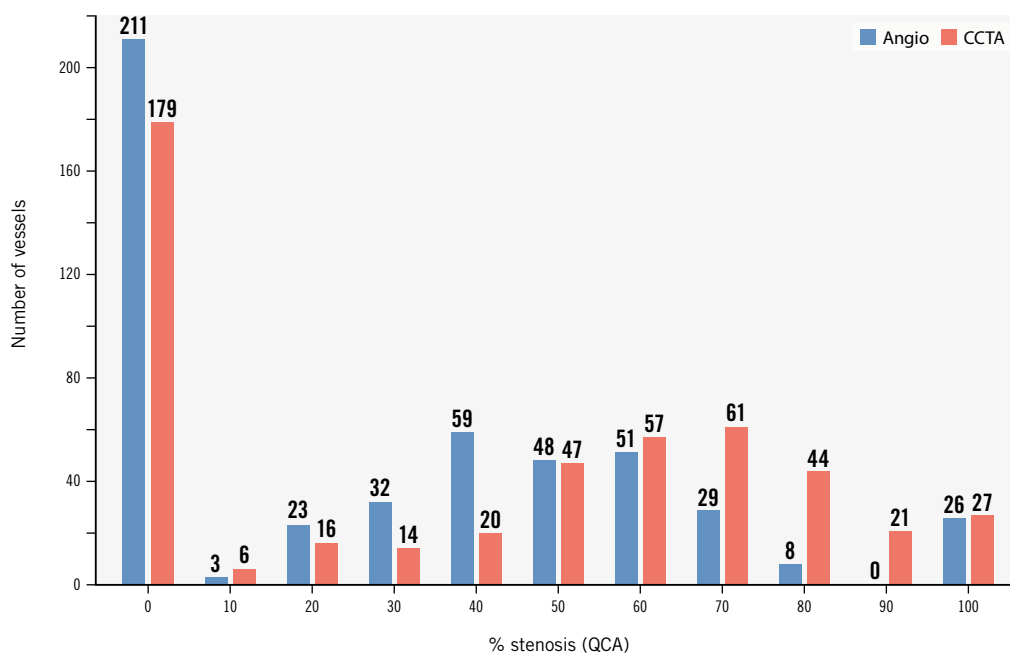


Figure 3. Percentage stenosis in terms of QCA according to modality (angiography in blue and CCTA in red). CCTA: coronary computed tomography angiography; QCA; quantitative coronary angiography

presented an overall high negative predictive value to exclude ACS in patients presenting to the emergency department with chest pain and suspected ACS¹⁷. The sensitivity of CCTA for NSTEMI-ACS diagnosis was 95% (95% CI: 88-100%), and specificity was 87% (95% CI: 83-92%), yielding a negative likelihood ratio of 0.06 (95% CI: 0-0.14) and a positive likelihood ratio of 7.4 (95% CI: 4.8-10.0). However, in these studies, patients were in the low-to-intermediate chest pain risk category with normal initial cardiac biomarkers, none had evidence of ischaemia on initial ECGs, and an NSTEMI-ACS was subsequently diagnosed in only 10% of patients (as opposed to 66% in the present cohort). Additionally, none of the previously published studies systematically evaluated the performance of CCTA and FFR-CT against FFR – the invasive gold standard in such a high-risk population. In the present patient population and similarly to prior studies, FFR-CT showed an increased specificity and ability to rule in significant lesions, thus, further limiting the number of patients sent unnecessarily for invasive evaluations¹³. Importantly, this did not come at the price of a lower sensitivity, and the number of false negative cases was similar for CCTA and FFR-CT (7 vs 6 patients). Of note, in the present study, CCTA data were adjudicated by a core laboratory. In the PROMISE study, the use of a core laboratory reclassified 16% of the patients compared to site-adjudicated results¹⁸. In comparison, FFR-CT analysis and reporting is an automated process with no reader-to-reader variability. Taken together, these two elements suggest that the actual difference between CCTA and FFR-CT performance might be larger in a real-world setting where CCTA can be adjudicated by physicians with varying degrees of expertise.

Additionally, for patients who ultimately undergo ICA, the prior implementation of an FFR-CT-based strategy has the

potential to streamline the invasive evaluation. By providing detailed insights into the haemodynamic significance of specific coronary lesions, FFR-CT may reduce or even eliminate the need for additional invasive FFR measurements.

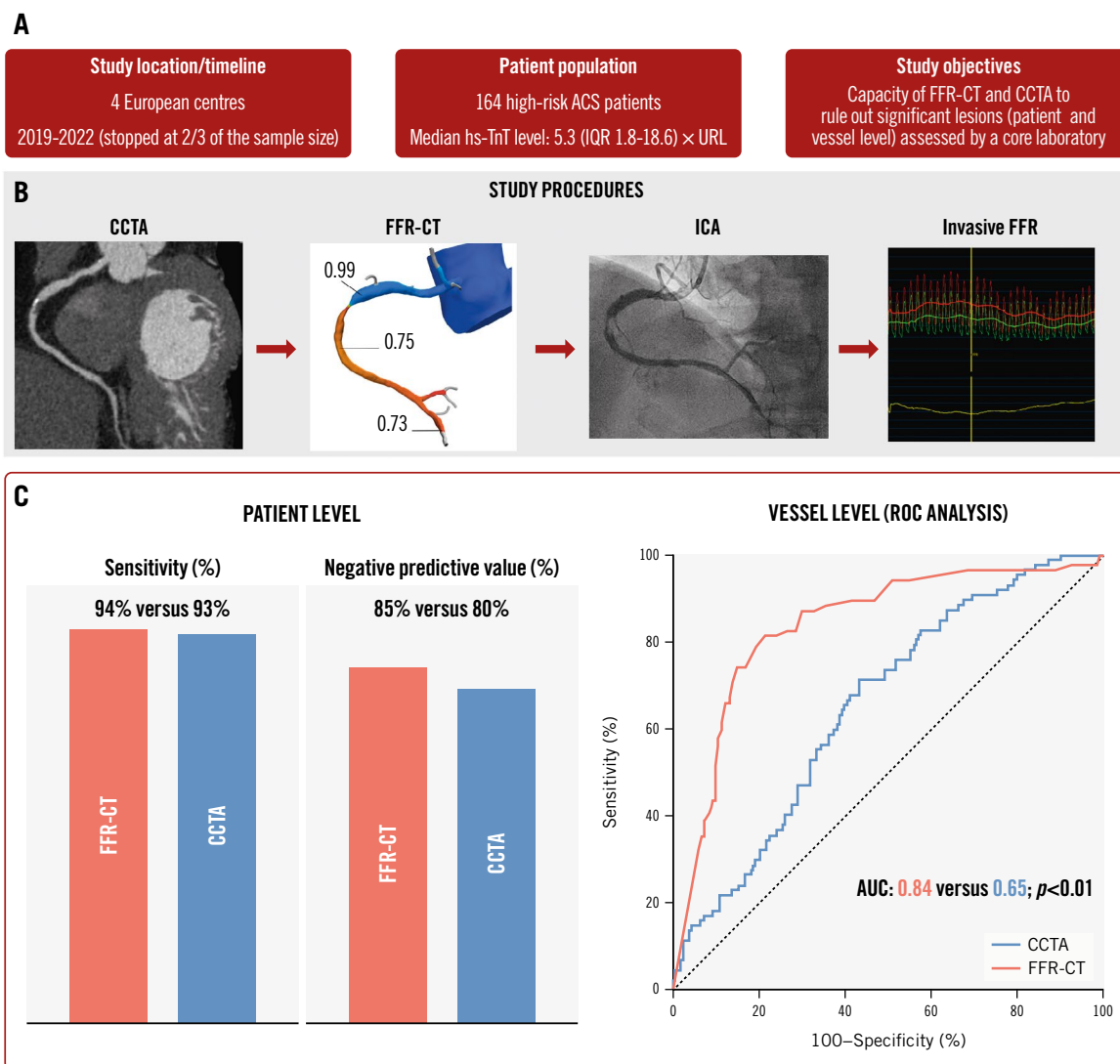
The current results also show that, despite being challenging (as illustrated by the slow enrolment rate), a strategy of CCTA first followed by ICA is feasible within the guideline-recommended window of 24 hours. However, this requires a strong collaboration between emergency, radiology and cardiology departments.

The results of the present study pave the way for future larger studies that should aim at clarifying the group of patients in which a first-line strategy of CCTA+FFR-CT is most effective and safe. Ultimately, a randomised trial assessing the impact of a CCTA-first strategy, compared to usual care, on hard clinical endpoints in patients with high-risk NSTEMI-ACS will be needed. Finally, the cost-effectiveness of such an approach will need to be evaluated. However, this is a complex aspect since, beyond the avoidance of unnecessary ICA, CCTA+FFR-CT also offer the possibility of avoiding invasive physiological measurements in intermediate lesions. Moreover, CCTA is gaining interest as a tool for effective PCI planning¹⁹⁻²¹.

Limitations

This study has limitations related to its non-randomised design, relatively small sample size and the fact that it had to be stopped before reaching the targeted sample size. Moreover, the present cohort represents a relatively select population as patients with low GFR, prior PCI/CABG and severe heart failure were excluded. The prevalence of patients with no significant coronary artery disease in our study may indicate that, while meeting the high-risk ACS criteria,

Usefulness of FFR-CT in patients with high-risk NSTEMI-ACS.



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A) Study summary; (B) study procedures; and (C) patient- and vessel-level results. In patients with high-risk NSTEMI-ACS, FFR-CT offers better diagnostic accuracy and a higher ability to rule out haemodynamically significant stenoses as compared to CCTA, with the potential to reduce unnecessary invasive procedures. ACS: acute coronary syndrome; AUC: area under the curve; CCTA: coronary computed tomography angiography; FFR: fractional flow reserve; FFR-CT: FFR derived from CCTA; ICA: invasive coronary angiography; IQR: interquartile range; NSTEMI-ACS: non-ST-elevation acute coronary syndrome; ROC: receiver operating characteristic; URL: upper range limit

they were potentially at slightly lower risk than in other studies¹⁵. However, these limitations are compensated by the multicentric nature of the study and the core laboratory adjudication of all imaging data, ensuring proper blinding and high-quality data. Finally, this study focused on physiological assessment, and it cannot be excluded that systematic use of intravascular imaging might have occasionally identified plaque erosion or rupture in patients without FFR-significant lesions, thus, unmasking an occult culprit lesion.

Conclusions

In high-risk NSTEMI-ACS, FFR-CT not only offers improved diagnostic accuracy as compared to CCTA but also exhibits the capacity to rule out significant lesions. It demonstrates greater specificity and positive predictive value, significantly surpassing CCTA at the lesion level. This suggests that FFR-CT could reduce unnecessary invasive procedures (and simplify these) by more accurately identifying patients requiring further intervention. However, these findings need

Table 4. Performance of CCTA and FFR-CT at the vessel level (n=459).

	Angiography (gold standard)	CCTA	FFR-CT
True positive	141	123	117
True negative	318	222	259
False positive	-	96	59
False negative	-	18	24
Sensitivity, %	-	87	83
Specificity, %	-	70	81
Positive predictive value, %	-	56	67
Negative predictive value, %	-	92	92
Accuracy, %	-	75	82

Values are n, or %, where indicated. CCTA: coronary computed tomography angiography; FFR-CT: fractional flow reserve derived from CCTA

to be confirmed in larger studies or in a randomised trial as this study was prematurely stopped with a smaller patient population than initially planned, thus, limiting the statistical power of its findings.

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Conflict of interest statement

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References

1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-69.
2. DISCHARGE Trial Group; Maurovich-Horvat P, Bosserd M, Kofoed KF, Rieckmann N, Benedek T, Donnelly P, Rodriguez-Palomares J, Erglis A, Štěchovský C, Šakalyte G, Čemerlić Adić N, Gutberlet M, Dodd JD, Diez I, Davis G, Zimmermann E, Kępka C, Vidakovic R, Francone M, Ilnicka-Suckiel M, Plank F, Knuuti J, Faria R, Schröder S, Berry C, Saba L, Ruzsics B, Kubiak C, Gutierrez-Ibarluzea I, Schultz Hansen K, Müller-Nordhorn J, Merkely B, Knudsen AD, Benedek I, Orr C, Xavier Valente F, Zvaigzne L, Suchánek V, Zajančauskiene L, Adić F, Woinke M, Hensey M, Lecumberri I, Thwaite E, Laule M, Kruk M, Neskovic AN, Mancone M, Kuśmierz D, Feuchtner G, Pietilä M, Gama Ribeiro V, Drosch T, Delles C, Matta G, Fisher M, Szilveszter B, Larsen L, Ratiu M, Kelly S, Garcia Del Blanco B, Rubio A, Drobni ZD, Jurlander B, Rodean I, Regan S, Cuéllar Calabria H, Boussousou M, Engström T, Hodas R, Napp AE, Haase R, Feger S, Serna-Higuera LM, Neumann K, Dreger H, Rief M, Wieske V, Estrella M, Martus P, Dewey M. CT or Invasive Coronary Angiography in Stable Chest Pain. *N Engl J Med*. 2022;386:1591-602.
3. Meier D, Skalidis I, De Bruyne B, Qanadli SD, Rotzinger D, Eeckhout E, Collet C, Muller O, Fournier S. Ability of FFR-CT to detect the absence of hemodynamically significant lesions in patients with high-risk NSTEMI-ACS admitted in the emergency department with chest pain, study design and rationale. *Int J Cardiol Heart Vasc*. 2020;27:100496.
4. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, Gilard M, Hinterbuchner L, Jankowska EA, Jüni P, Kimura T, Kunadian V, Leosdottir M, Lorusso R, Pedretti RFE, Rigopoulos AG, Rubini Gimenez M, Thiele H, Vranckx P, Wassmann S, Wenger NK, Ibanez B; ESC Scientific Document Group. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-826.
5. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354-94.
6. Pontone G, Baggiano A, Andreini D, Guaricci AI, Guglielmo M, Muscogiuri G, Fusini L, Fazzari F, Mushtaq S, Conte E, Calligaris G, De Martini S, Ferrari C, Galli S, Grancini L, Ravagnani P, Teruzzi G, Trabattoni D, Fabbiochi F, Lualdi A, Montorsi P, Rabbat MG, Bartorelli AL, Pepi M. Stress Computed Tomography Perfusion Versus Fractional Flow Reserve CT Derived in Suspected Coronary Artery Disease: The PERFECTION Study. *JACC Cardiovasc Imaging*. 2019;12:1487-97.
7. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, Marwan M, Naoum C, Norgaard BL, Rubinshtein R, Schoenhagen P, Villines T, Leipsic J. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr*. 2016;10:435-49.
8. Takx RA, Suchá D, Park J, Leiner T, Hoffmann U. Sublingual Nitroglycerin Administration in Coronary Computed Tomography Angiography: a Systematic Review. *Eur Radiol*. 2015;25:3536-42.
9. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, La Meir M, Miyazaki Y, de Mey J, Gaemperli O, Ouda A, Moreira JP, Mandry D, Camenzind E, Macron L, Doenst T, Teichgraber U, Sigusch H, Asano T, Katagiri Y, Morel MA, Lindeboom W, Pontone G, Lüscher TF, Bartorelli AL, Serruys PW. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. *Eur Heart J*. 2018;39:3689-98.
10. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, Chieffo A, Christodorescu RM, Deaton C, Doenst T, Jones HW, Kunadian V, Mehilli J, Milojevic M, Piek JJ, Pugliese F, Rubboli A, Semb AG, Senior R, Ten Berg JM, Van Belle E, Van Craenenbroeck EM, Vidal-Perez R, Winther S;

ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J*. 2024 Aug 30. [Epub ahead of print].

11. Driessen RS, Danad I, Stuijzand WJ, Raijmakers PG, Schumacher SP, van Diemen PA, Leipsic JA, Knuuti J, Underwood SR, van de Ven PM, van Rossum AC, Taylor CA, Knaapen P. Comparison of Coronary Computed Tomography Angiography, Fractional Flow Reserve, and Perfusion Imaging for Ischemia Diagnosis. *J Am Coll Cardiol*. 2019;73:161-73.
12. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
13. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, De Bruyne B, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S; NXT Trial Study Group. 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). *J Am Coll Cardiol*. 2014;63:1145-55.
14. Kofoed KF, Kelbæk H, Hansen PR, Torp-Pedersen C, Høfsten D, Kløvgaard L, Holmvang L, Helqvist S, Jørgensen E, Galatius S, Pedersen F, Bang L, Saunamaki K, Clemmensen P, Linde JJ, Heitmann M, Wendelboe Nielsen O, Raymond IE, Kristiansen OP, Svendsen IH, Bech J, Dominguez Vall-Lamora MH, Kragelund C, Hansen TF, Dahlggaard Hove J, Jørgensen T, Fornitz GG, Steffensen R, Jurlander B, Abdulla J, Lyngbæk S, Elming H, Therkelsen SK, Abildgaard U, Jensen JS, Gislason G, Køber LV, Engstrøm T. Early Versus Standard Care Invasive Examination and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *Circulation*. 2018;138:2741-50.
15. Layland J, Oldroyd KG, Curzen N, Sood A, Balachandran K, Das R, Junejo S, Ahmed N, Lee MM, Shaikat A, O'Donnell A, Nam J, Briggs A, Henderson R, McConnachie A, Berry C; FAMOUS-NSTEMI investigators. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J*. 2015;36:100-11.
16. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. *J Biomed Inform*. 2014;48:193-204.
17. Samad Z, Hakeem A, Mahmood SS, Pieper K, Patel MR, Simel DL, Douglas PS. A meta-analysis and systematic review of computed tomography angiography as a diagnostic triage tool for patients with chest pain presenting to the emergency department. *J Nucl Cardiol*. 2012;19:364-76.
18. Lu MT, Meyersohn NM, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Foldyna B, Mueller ME, Hearne S, Yang C, Achenbach S, Truong QA, Ghoshhajra BB, Patel MR, Ferencik M, Douglas PS, Hoffmann U. Central Core Laboratory versus Site Interpretation of Coronary CT Angiography: Agreement and Association with Cardiovascular Events in the PROMISE Trial. *Radiology*. 2018;287:87-95.
19. Andreini D, Collet C, Leipsic J, Nieman K, Bittencourt M, De Mey J, Buls N, Onuma Y, Mushtaq S, Conte E, Bartorelli AL, Stefanini G, Sonck J, Knaapen P, Ghoshhajra B, Serruys PW. Pre-procedural planning of coronary revascularization by cardiac computed tomography: An expert consensus document of the Society of Cardiovascular Computed Tomography. *EuroIntervention*. 2022;18:e872-87.
20. Collet C, Sonck J, Leipsic J, Monizzi G, Buytaert D, Kitslaar P, Andreini D, De Bruyne B. Implementing Coronary Computed Tomography Angiography in the Catheterization Laboratory. *JACC Cardiovasc Imaging*. 2021;14:1846-55.
21. Ko B, Ohashi H, Mizukami T, Sakai K, Sonck J, Nørgaard BL, Maeng M, Jensen JM, Ihdahid A, Tajima A, Ando H, Amano T, De Bruyne B, Koo BK, Otake H, Collet C. Stent sizing by coronary CT angiography compared with optical coherence tomography. *J Cardiovasc Comput Tomogr*. 2024;18:337-44.