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FASTTRACK CLINICAL RESEARCH
Imaging

Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry

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Aims Non-invasive assessment of stable chest pain patients is a critical determinant of resource utilization and clinical outcomes. Increasingly coronary computed tomography angiography (CCTA) with selective CCTA-derived fractional flow reserve (FFR_{CT}) is being used. The ADVANCE Registry, is a large prospective examination of using a CCTA and FFR_{CT} diagnostic pathway in real-world settings, with the aim of determining the impact of this pathway on decision-making, downstream invasive coronary angiography (ICA), revascularization, and major adverse cardiovascular events (MACE).

Methods and results A total of 5083 patients with symptoms concerning for coronary artery disease (CAD) and atherosclerosis on CCTA were enrolled at 38 international sites from 15 July 2015 to 20 October 2017. Demographics, symptom status, CCTA and FFR_{CT} findings, treatment plans, and 90 days outcomes were recorded. The primary endpoint of reclassification between core lab CCTA alone and CCTA plus FFR_{CT}-based management plans occurred in 66.9% [confidence interval (CI): 64.8–67.6] of patients. Non-obstructive coronary disease was significantly lower in ICA patients with FFR_{CT} ≤0.80 (14.4%) compared to patients with FFR_{CT} >0.80 (43.8%, odds ratio 0.19, CI: 0.15–0.25, $P < 0.001$). In total, 72.3% of subjects undergoing ICA with FFR_{CT} ≤0.80 were revascularized. No death/myocardial infarction (MI) occurred within 90 days in patients with FFR_{CT} >0.80 ($n = 1529$), whereas 19 (0.6%) MACE [hazard ratio (HR) 19.75, CI: 1.19–326, $P = 0.0008$] and 14 (0.3%) death/MI (HR 14.68, CI 0.88–246, $P = 0.039$) occurred in subjects with an FFR_{CT} ≤0.80.

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Conclusions In a large international multicentre population, FFR_{CT} modified treatment recommendation in two-thirds of subjects as compared to CCTA alone, was associated with less negative ICA, predicted revascularization, and identified subjects at low risk of adverse events through 90 days.

Keywords FFRCT • Coronary CT angiography • Fractional flow reserve • Invasive coronary angiography

Introduction

Coronary computed tomography angiography (CCTA) has been shown to be an effective non-invasive test in the diagnosis and treatment planning for patients with stable chest pain and suspected coronary artery disease (CAD).[1–4] Coronary computed tomography angiography is excellent at ruling out CAD, but its utility is diminished by the limited ability to predict physiologically significant CAD as defined by an abnormal invasive fractional flow reserve (FFR).[5,6] Coronary computed tomography angiography-derived fractional flow reserve (FFR_{CT}) is a non-invasive physiological test that can assess flow limitation across coronary stenoses with high diagnostic accuracy and good correlation to invasive FFR.[7] In addition, FFR_{CT} has been shown to reduce the incidence of negative referrals to invasive coronary angiography (ICA) post-CCTA, thus increasing the eventual revascularization rate.[8–10] However, to date most of the data have been limited to single centre populations and trial settings and there remains concerns regarding the clinical application of FFR_{CT}, especially in areas of 'greyzone' uncertainty, where diagnostic accuracy may be lower.

The Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care (ADVANCE) registry was designed to observe the 'real-world' utility and impact of using FFR_{CT} in a broad variety of healthcare settings, geographical regions, and patient populations. The study aimed to determine how the incremental information of an anatomical combined with functional FFR_{CT} would change clinical decision-making, patient management, clinical outcomes, and resource utilization.

Methods

Patients being investigated for clinically suspected CAD with documented atherosclerosis >30% degree stenosis (DS) on CCTA were prospectively enrolled at 38 sites in Europe, North American, and Japan from 15 July 2015 to 20 October 2017. All subjects were clinically stable symptomatic patients diagnosed with CAD by CCTA who met the following eligibility criteria: age >18 years, ability to provide informed consent, and CAD diagnosed on a diagnostic standard CCTA. Exclusion Criteria included: poor quality CCTA, life expectancy <1 year, and an inability to comply with follow-up requirements. All patients provided written informed consent following Institutional Review Board review and approval. Demographics, symptom status, CCTA and FFR_{CT} findings, treatment plans, and clinical outcomes through 90 days were recorded.

Management strategies

The site investigators were asked to report an initial management plan and treatment strategy based on CCTA alone for each subject in accordance with local guidelines for the practice and interpretation of CCTA. The decision to further investigate CCTA results with FFR_{CT} was directed by the physician interpreting the scan with a recommendation to consider FFR_{CT} for stenoses in the 30–90% range. All FFR_{CT} analyses were performed in a single centre (HeartFlow, Redwood City, CA, USA). Once the FFR_{CT} result was made available, the site investigators were asked to re-determine the treatment strategy based on the new information of the CCTA combined with the locally interpreted FFR_{CT} result. A positive FFR_{CT} was deemed to be a value ≤0.80 in accordance with the previous published invasive and non-invasive literature.[11] Subsequent clinical management decisions such as revascularization or medical therapy rested at the discretion of the referring physician. The registry did not dictate interpretation or management decisions.

A core laboratory [Duke Clinical Research Institute (DCRI), Durham, NC, USA] blinded to clinical information, symptom status, and outcomes, reviewed all CCTA and declared an independent management plan based on CCTA alone. Coronary computed tomography angiography-derived fractional flow reserve analyses were then made available to the core lab, who then re-determined the subject specific treatment strategy for each patient based on the CCTA and FFR_{CT} results. This involved adjudication of vessel- and lesion-specific ischaemia, measuring the FFR_{CT} 2 cm distal to focal lesions.

Management plan treatment strategies for both site and core laboratory consisted of the following options: (i) optimal medical therapy, (ii) percutaneous coronary intervention (PCI), (iii) coronary artery bypass grafting (CABG) surgery, or (iv) additional diagnostic testing required. If revascularization was selected, vessel segments to be revascularized were specified and the interpreter was asked to recommend either PCI or CABG. In instances of high-risk anatomy such as; three-vessel disease, or two vessel involving the left anterior descending (LAD) artery or left main stem disease, a consensus reading of two reviewers determined the appropriate revascularization strategy.

Study endpoints

The primary endpoint was the reclassification rate between CCTA alone vs. CCTA and FFR_{CT}-based management plans as determined by the core laboratory. Secondary endpoints included: reclassification rate between CCTA-based and FFR_{CT}-based management plans as determined by the site; incidence of ICA demonstrating absence of obstructive CAD (no coronary stenosis >50%); percutaneous and surgical revascularization rates; and 90 days survival free from all cause or major adverse cardiovascular events (MACE) inclusive of myocardial infarction (MI), all-cause mortality or unplanned hospitalization for Acute Coronary Syndrome (ACS) leading to revascularization. Event adjudication was performed by an independent Clinical Events Committee using standard definitions, blinded to clinical, and computed tomographic data.

Statistical analysis

Continuous data are presented as mean (± standard deviation) or median (interquartile range, IQR), categorical data as frequency and percentage. Comparative statistics for net reclassification used the Mann–Whitney and Kruskal–Wallis tests as appropriate. Unpaired *t*-test was used to determine differences between anatomic severity and rates of positive FFR_{CT}. Univariable and multivariable logistic regression models using step-

Table 1 Demographics, coronary artery disease risk factors, and symptom status

	CTA only ($n = 346$)	FFR_{CT} ($n = 4737$)	Total ($n = 5083$)
Age (years)	64.3 (11.1)	66.1 (10.3)	66.0 (10.3)
Male gender	215 (62.1%)	3134 (66.2%)	3349 (65.9%)
Hypertension	210 (60.7%)	2835 (59.8%)	3045 (59.9%)
Diabetes mellitus	99 (28.6%)	1037 (21.9%)	1136 (22.3%)
Hyperlipidaemia	204 (59%)	2753 (58.1%)	2957 (58.2%)
Smoking			
Current smoking	46 (13.3%)	797 (16.8%)	843 (16.6%)
Ex-smoker	118 (34.1%)	1615 (34.1%)	1733 (34.1%)
Never smoked	141 (41.6%)	1973 (41.7%)	2117 (41.6%)
Unknown	38 (11.0%)	352 (7.4%)	390 (7.7%)
Angina status			
Atypical	175 (50.6%)	1727 (36.5%)	1902 (37.4%)
Typical	41 (11.8%)	1025 (21.6%)	1066 (21.0%)
Non-cardiac pain	8 (2.3%)	297 (6.3%)	305 (6.0%)
Dyspnoea	34 (9.8%)	472 (10.0%)	506 (10.0%)
None	73 (21.1%)	1164 (24.6%)	1237 (24.3%)
Unknown	15 (4.3%)	52 (1.1%)	67 (1.3%)
CCS angina class			
Grade 1	18 (43.9%)	254 (24.8%)	272 (25.5%)
Grade II	16 (39.0%)	561 (54.7%)	577 (54.1%)
Grade III	5 (12.2%)	111 (10.8%)	116 (10.9%)
Grade IV	0	23 (2.2%)	23 (2.2%)
Unknown	2 (4.9%)	76 (7.4%)	78 (7.3%)
CCTA rejection rate			160 (3.1%)
Diamond–Forrester risk	46.8 (±19.9)	51.6 (±20.3)	51.3 (±20.3)

CTA, computed tomography angiography.

wise selection were used to estimate the odds of revascularization where a *P*-value <0.1 was used for entry into the multivariable model. The fit of the final model was assessed using the Log Likelihood and Akaike Information Criterion. The χ^2 test of independence was used to assess if negative catheterization and MI/death were independent of or associated with minimum FFR_{CT} strata (>0.8/≤0.8); in cases of low (expected cell count <5) or zero cell counts, the Fisher's exact test was used. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated; in cases of zero cell counts, relative risk and associated 95% CIs were calculated. A two-sided level of $P < 0.05$ was considered significant.

Study funding, design, data gathering, and analysis

The ADVANCE Registry was funded by HeartFlow Inc., via individual Clinical Study Agreements with each enrolling institution and with the DCRI for Core Laboratory activities and Clinical Event Committee adjudication of adverse events. The trial database was housed in iMedNet. HeartFlow and the independent Clinical Research Organization (CRO) had access to iMedNet on the sponsor side. Principal Investigators, sub-investigators, and study co-ordinators at each site had access to iMedNet and were responsible for data entry. The Clinical Event Adjudication and core lab databases were housed in iMedNet. Duke Clinical Research Institute had access to this data for entry, resolving queries, and locking data. The CRO was able to query this data. HeartFlow did not have access to adjudication forms. The primary analysis was performed by the Principal Investigators including Drs Patel, Leipsic, Nieman, and Akasaka, as well as by Dr Fairbairn, with statistical and analytical support from Dr Rogers and Ms Mullen. The manuscript was drafted by the Principal Investigators and Dr Fairbairn. All authors reviewed the manuscript and approved of the submitted manuscript.

Results

Demographic, risk, and coronary artery disease risk factor distribution

Patient demographics and distribution of CAD computed tomography angiography (CTA) findings are provided in *Table 1*. A total of 5083 patients were enrolled, of whom 4893 had CCTA submitted for FFR_{CT} (96.2%). A total of 190 subjects did not have their CCTA examinations submitted for FFR_{CT} analysis at the site discretion: 111 because the invasive treatment decision was made due to the severity of the stenosis; 61 owing to minimal CAD; 9 because of multiple coronary stents; 2 because of CCTA exams not acquired in a fashion acceptable for FFR_{CT} analysis. Of the submitted CCTAs 4737 (96.8%) were of adequate quality for analysis. 3.2% were rejected from FFR_{CT} analysis because of image quality. Angina (typical or atypical) was the predominant symptom in 58%, with an average Diamond–Forrester pre-test probability for obstructive coronary disease of 51.6%. There

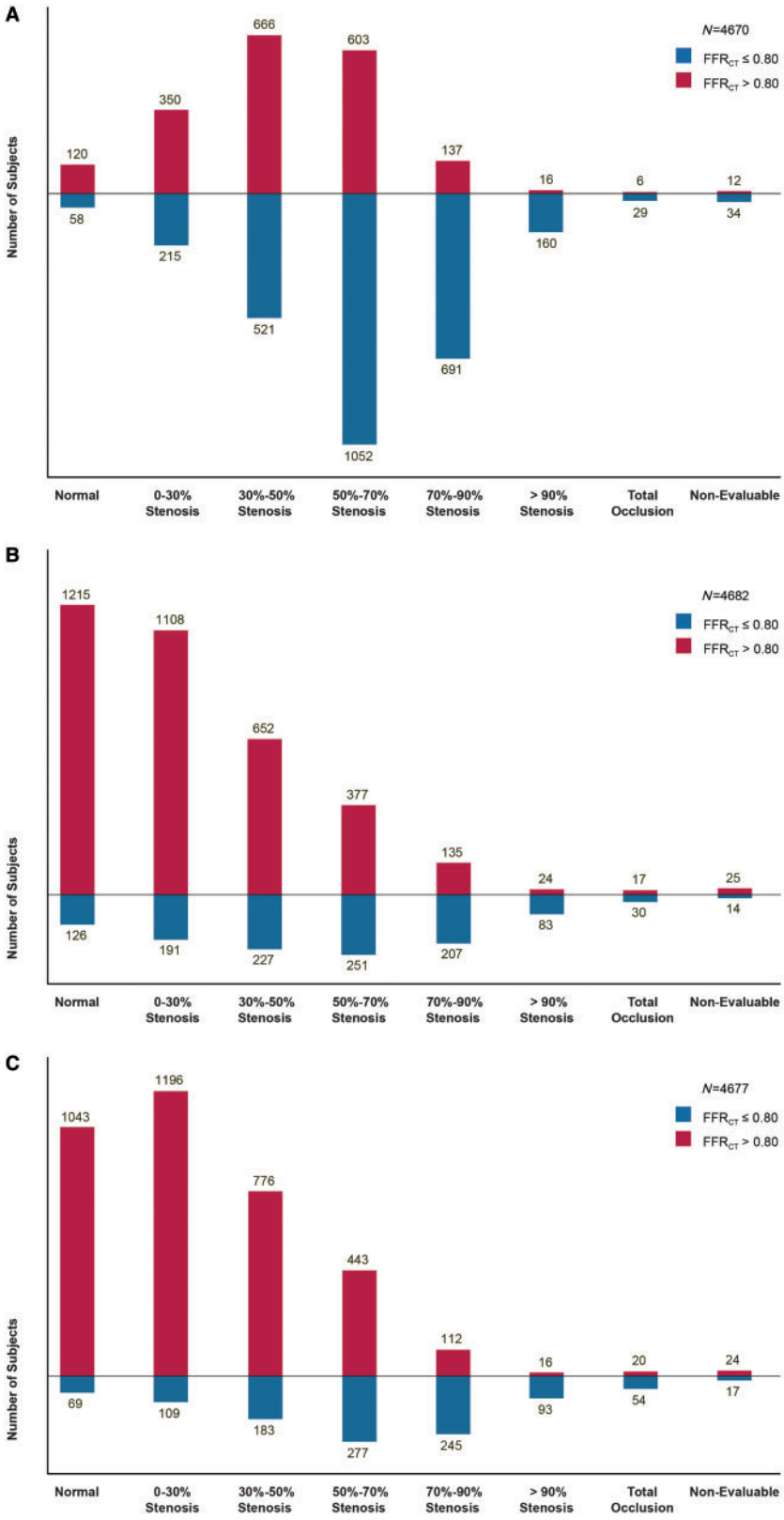


Figure 1 Degree of coronary artery disease (% stenosis) and coronary computed tomography angiography-derived fractional flow reserve positive/negative ratio stratified by coronary artery territory: (*A*) left anterior descending; (*B*) left circumflex, and (*C*) right coronary artery.

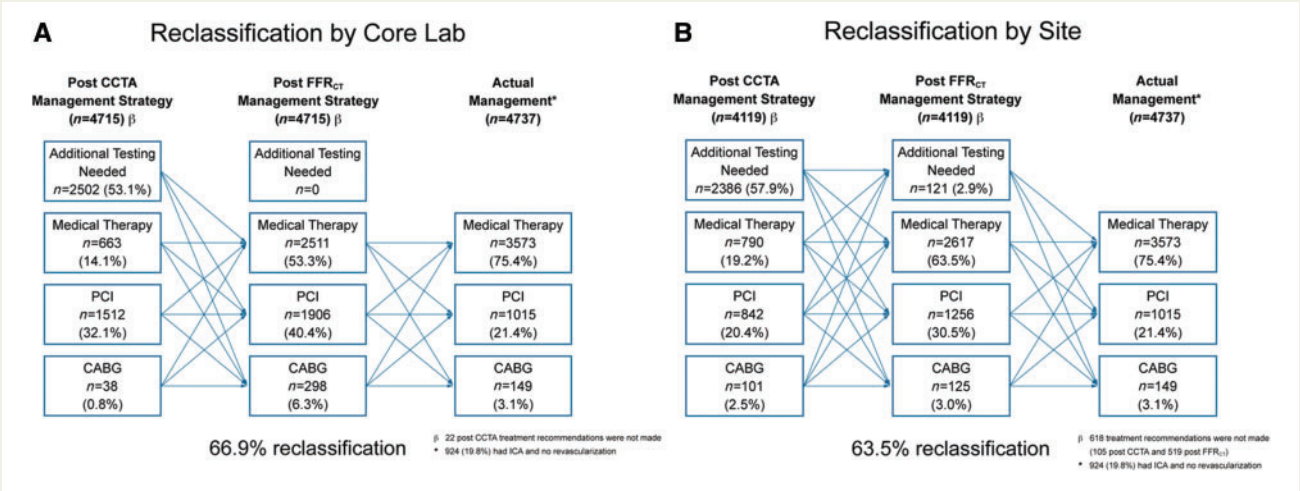


Figure 2 Clinical management strategies and reclassification of post-coronary computed tomography angiography, following coronary computed tomography angiography-derived fractional flow reserve and actual management at 90 days (*A* Core and *B* Site).

Table 2 **FFR_{CT}-determined treatment plan and actual clinical management at 90 days**

Actual treatment	Site-determined post-FFR_{CT} treatment plan			
	Revascularization ($n = 1418$)	Medications ($n = 2679$)	Further diagnostics ($n = 121$)	Total ($n = 4737$)
MT	504 (35.5%)	2545 (95.0%)	92 (76.0%)	3573 (75.4%)
PCI	799 (56.3%)	115 (4.3%)	25 (20.7%)	1015 (21.4%)
CABG	115 (8.1%)	19 (0.7%)	4 (3.3%)	149 (3.1%)

Table 3 **Actual treatment at 90 days (medical therapy vs. revascularization) stratified by coronary computed tomography angiography-derived fractional flow reserve values (0.05 increments)**

Actual treatment	Site-determined post-FFR_{CT} treatment plan						
	<0.71 ($n = 1530$)	0.71–0.75 ($n = 615$)	0.76–0.8 ($n = 1000$)	0.81–0.85 ($n = 867$)	0.86–0.9 ($n = 595$)	>0.9 ($n = 130$)	Total ($n = 4737$)
Medical treatment	709 (46.3%)	468 (76.1%)	874 (87.4%)	820 (94.6%)	578 (97.1%)	124 (95.4%)	3573 (75.4%)
Revascularization	821 (53.7%)	147 (23.9%)	126 (12.6%)	47 (5.4%)	17 (2.9%)	6 (4.6%)	1164 (24.6%)

was no significant difference between subject group demographics or risk factors for those receiving CCTA alone vs. CCTA plus FFR_{CT}.

Extent and severity of coronary artery disease by coronary computed tomography angiography and coronary computed tomography angiography-derived fractional flow reserve

Coronary atheroma ≥50% DS was observed at CCTA in 72.1% of subjects ($n = 3398$) and >70% DS in 32% ($n = 1538$). Two- or three-vessel disease (≥50% DS) was present in 27.5% and 9.4%, respectively. Ischaemia (FFR_{CT} ≤0.80) in at least one coronary territory was present in 61.9% ($n = 3145$) of patients (*Figure 1*). The LAD was more likely to have anatomically severe (>70% DS), coronary disease (21.4%), and a positive FFR_{CT} ($n = 2760$, 58.3%) compared with other vessels: left circumflex (LCX) 23.8% ($n = 1260$), right coronary artery (RCA) 22.1% ($n = 1047$) ($P < 0.001$). The LAD exhibited significantly lower median FFR_{CT} values (0.79: IQR 0.71–0.85) compared with the LCX (0.88: IQR 0.81–0.92) and RCA (0.87: IQR 0.82–0.91), ($P < 0.001$). However, a positive FFR_{CT} in the mild-moderate (30–70%) stenosis range was more likely in the LAD (55.3%) compared with LCX (31.7%) and RCA (27.3%), ($P < 0.001$).

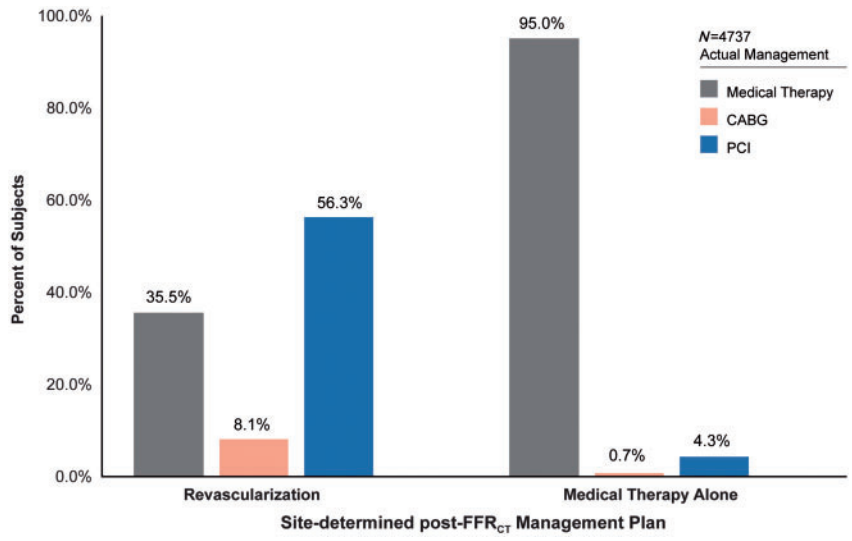


Figure 3 Actual treatment at 90 days (medical therapy, percutaneous intervention, and coronary bypass grafting) by post-coronary computed tomography angiography-derived fractional flow reserve treatment strategy.

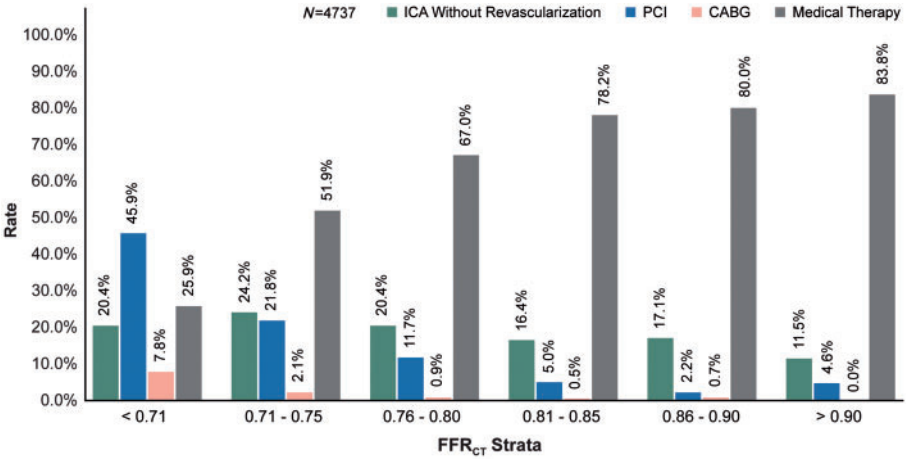


Figure 4 Actual treatment at 90 days (medical therapy, percutaneous intervention, and coronary bypass grafting) stratified by coronary computed tomography angiography-derived fractional flow reserve values (0.05 increments).

Recommended clinical management strategies following coronary computed tomography angiography-derived fractional flow reserve

Coronary computed tomography angiography-derived fractional flow reserve resulted in revision of the clinical management plan as determined by the site investigators in 63.5% of patients (CI: 62.0–65) when compared with initial CCTA-based treatment plan. Under core laboratory analysis, FFR_{CT} changed management plans in 66.9% of patients (CI: 64.8–67.6). Reclassification patterns are shown in *Figure 2*. Of 2386 (59.7%) patients in whom further information was required after CCTA, FFR_{CT} reclassified 70.0% ($n = 1671$) to medical treatment (MT), 24.4% ($n = 570$) to PCI, 2.1% ($n = 49$) to CABG, and only 2.6% ($n = 121$) were assigned to downstream testing. An initial management decision for MT was assigned to 19.2% ($n = 790$), and this assignment remained unchanged after FFR_{CT} in 93% of cases, with only 5.4% changing to revascularization (*Table 2* and *Figure 3*). However, among the 22.9% of subjects ($n = 943$) for whom the CCTA-based management plan indicated revascularization, 22.3% were reclassified to MT alone after FFR_{CT} analysis (PCI to MT 20.9%, $n = 198$; CABG to MT 1.4%, $n = 12$). A positive FFR_{CT} (≤0.80)

occurred in 61.9% of subjects, yet only 34.4% (site) and 46.8% (core) of cases were recommended for revascularization despite the majority of these patients, 69.5% ($n = 984$) having anatomically significant disease (>50% DS) on CCTA. Over half of the deferrals from ICA, 53.9% ($n = 762$) had an FFR_{CT} between 0.75 and 0.8, with patients with lower FFR_{CT} more likely to be recommended for ICA (*Table 3*).

Rate of non-obstructive angiography and revascularization

The rate of anatomically defined 'non-obstructive' disease at ICA (no stenosis >50% at ICA) was significantly lower in patients with FFR_{CT} ≤0.80 (14.4%) vs. FFR_{CT} >0.80 (43.8%), (OR 0.19, CI 0.15–0.25, $P < 0.001$) (*Figure 3*).

When stratified by 0.05 categorical FFR_{CT} increments, subjects were significantly more likely to undergo ICA with decreasing FFR_{CT} (FFR_{CT} ≤0.70: 73.8% vs. FFR_{CT} >0.80: 20.5%) and to be revascularized at ICA (FFR_{CT} ≤0.70: 72.5% vs. FFR_{CT} >0.80: 20.4% $P < 0.001$), (Supplementary material online). In multivariable analysis, stenosis >70%/occluded vessel (OR 5.85–6.36, $P < 0.00105$) and FFR_{CT} <0.80 (OR 5.88, $P < 0.001$) were significant predictors of revascularization (*Table 4* and *Figure 4*), as were the presence of typical/atypical symptoms and male gender.

Major adverse cardiovascular events, myocardial infarction, and death

No death or MI occurred within 90 days in any subject whose FFR_{CT} was >0.80 ($n = 1592$). Conversely, in patients with at least one FFR_{CT} value ≤0.80 ($n = 3145$) there were 19 (0.6%, $P < 0.01$) MACE events; 4 MI, 5 urgent unplanned hospitalizations for ACS and urgent revascularization and 10 deaths. These events predominantly occurred in the lower FFR_{CT} ranges below 0.76 (18 of 19), indicating that an FFR_{CT} ≤0.80 increased the risk of an adverse event [MACE, hazard ratio (HR) 19.75, CI 1.19–326], $P = 0.0008$ and 14 death/MI, HR 14.68, CI 0.88–246, $P = 0.039$], (*Figure 5A* and *B*).

Table 4 Multivariable logistic regression analysis of univariate predictors of revascularization amongst subjects with coronary computed tomography angiography-derived fractional flow reserve performed as compared to those subjects who did not undergo revascularization

Covariates	Estimates of effect	Odds ratio	*P*-value
Age (≥65)	-0.0433	0.96 (0.81–1.14)	0.6189
Female gender	-0.2953	0.74 (0.62–0.90)	0.0023
Hyperlipidaemia	0.3036	1.35 (1.14–1.61)	0.0005
Diabetes mellitus	0.0990	1.10 (0.91–1.33)	0.3066
Smoking	0.1150	1.12 (0.89–1.41)	0.3189
Symptom status			
Typical angina	0.9898	2.69 (2.14–3.38)	<0.0001
Atypical angina	0.2808	1.32 (1.06–1.61)	0.0129
Non-cardiac pain	0.1223	1.13 (0.76–1.89)	0.5400
Dyspnoea	0.3204	1.38 (1.00–1.89)	0.0472
Coronary stenosis >70%	1.7666	5.85 (4.95–6.91)	<0.0001
FFR_{CT} ≤0.8	1.8959	5.88 (4.43–7.80)	<0.0001

Intercept parameter estimate: -3.8806, $P < 0.0001$. Reference categories for covariates: (i) age: '≤65 years', (ii) 'male sex', (iii) 'no hyperlipidaemia', (iv) 'no diabetes mellitus', (v) 'no smoking', (vi) no 'typical angina', 'atypical angina', 'non-cardiac pain', or 'dyspnoea', (vii) coronary stenosis: '≤70%', and (viii) FFR_{CT}: '>0.8'.

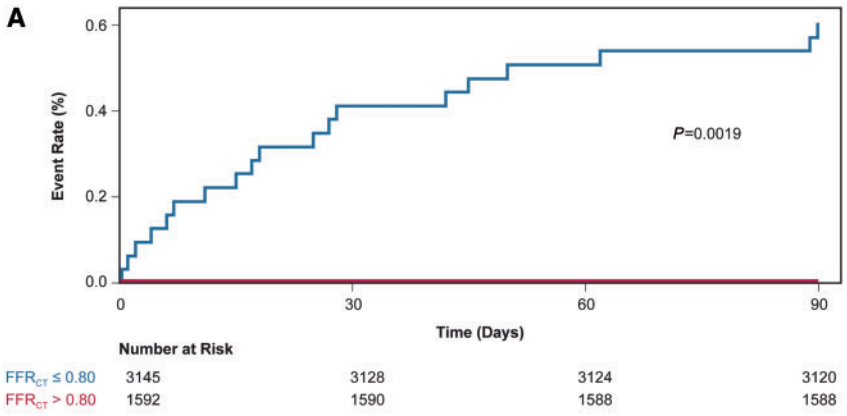
Discussion

In this large prospective international multicentre registry, FFR_{CT} changed management recommendations from CCTA-based plans in approximately two out of three subjects. A negative FFR_{CT} was associated with a low rate of invasive angiography or revascularization within 90 days and with freedom from MI or death. In addition, there was an inverse relationship between FFR_{CT} and the likelihood of downstream ICA, revascularization, and MACE.

Coronary computed tomography angiography is now considered a reasonable or preferred first line investigation for patients with suspected CAD,[12–14] as studies have suggested improved clinical outcomes for patients managed based on initial CCTA rather than alternative non-invasive tests.[4] While, CCTA has been proven to be an effective diagnostic tool, there remain concerns regarding fairly high rates of downstream ICA and resource utilization as well as the lack of physiological information available to guide treatment decision-making.[2,15,16] FFR_{CT} has been proposed as a diagnostic tool to help determine more appropriately who should proceed for ICA following CCTA.[7,8,15,17] The PROMISE FFR_{CT} retrospective sub-study highlighted the potential of FFR_{CT} to reduce ICA referral and enrich the appropriateness of the population referred for ICA.[17,18]

Our findings based on prospective utilization of FFR_{CT} after positive CCTA represent the first real-world multicentre evaluation of the utility and safety of FFR_{CT}. FFR_{CT} led to a recommendation of ICA in only 40% of subjects in a cohort with an anatomic obstructive disease rate of 72%, and subjects referred for ICA downstream were significantly more likely to have obstructive disease at ICA if they had a positive FFR_{CT}.[19–21]

Management reclassification by FFR_{CT} as expected occurred in all directions. There was, however, a clear directed benefit in instances of physician uncertainty expressed by the need for 'further testing', as the majority of subjects (70%) were safely deferred to medical management alone. Importantly only in a very small minority of cases (0% by core lab and 2.6% by site) was further testing deemed necessary to determine CAD significance, thereby highlighting the improved diagnostic certainty and the opportunity to reduce further downstream testing. Importantly, this approach of test layering not only results in increased costs and at times additional radiation exposure, it may not help discriminate those patients likely to benefit from revascularization. In the recently published PACIFIC trial, hybrid testing with a CTA/SPECT approach did not enhance on the accuracy for the detection of lesions specific ischaemia beyond CCTA or SPECT alone.[22] In instances, when the physician recommendation was for revascularization post-CCTA alone, FFR_{CT} redirected management to medical therapy in close to 25% of cases, offering the potential to avoid unnecessary ICA. This observation supports the concept that CCTA alone could result in increased ICA without revascularization.[6] Interestingly a positive FFR_{CT} (≤0.80) was not

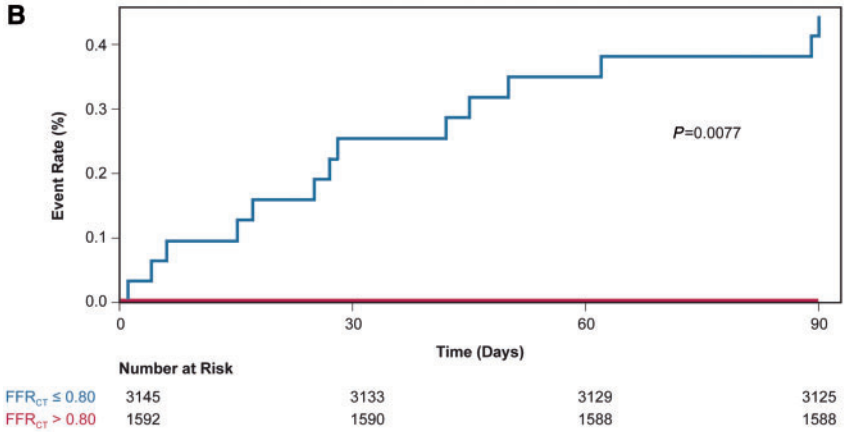


Number at Risk

$FFR_{CT} \leq 0.80$	3145	3128	3124	3120
$FFR_{CT} > 0.80$	1592	1590	1588	1588

Subjects for whom no event was recorded were censored at 90 days post-cCTA unless data was recorded on the Registry Completion CRF page, in which case the subject was censored at the minimum of the date of participation completion or discontinuation and 90 days post-cCTA.

	K-M Event Rate% (standard error)		
	30 Days	60 Days	90 Days
$FFR_{CT} \leq 0.80$	0.41%(0.11%)	0.51%(0.13%)	0.60%(0.14%)
$FFR_{CT} > 0.80$	0.00%(0.00%)	0.00%(0.00%)	0.00%(0.00%)



Number at Risk

$FFR_{CT} \leq 0.80$	3145	3133	3129	3125
$FFR_{CT} > 0.80$	1592	1590	1588	1588

Subjects for whom no event was recorded were censored at 90 days post-cCTA unless data was recorded on the Registry Completion CRF page, in which case the subject was censored at the minimum of the date of participation completion or discontinuation and 90 days post-cCTA.

	K-M Event Rate% (standard error)		
	30 Days	60 Days	90 Days
$FFR_{CT} \leq 0.80$	0.25%(0.09%)	0.35%(0.11%)	0.45%(0.12%)
$FFR_{CT} > 0.80$	0.00%(0.00%)	0.00%(0.00%)	0.00%(0.00%)

Figure 5 Major adverse cardiac events (*A*) (all-cause mortality, myocardial infarction, unplanned hospitalization with urgent revascularization) and (*B*) myocardial infarction/all-cause mortality alone at 90 days for coronary computed tomography angiography-derived fractional flow reserve positive (≤0.80) and negative values (>0.80).

followed by either ICA or revascularization in up to half of cases, despite the majority having evidence of anatomical (>50% DS) significant disease. This perhaps reflects nuanced management decisions regarding factors such as diffuse atherosclerosis and the absence of lesion specific ischaemia or other factors such as anatomical location, comorbidities, and symptom severity. It is also important to recognize that follow-up is limited to 90 days at present and longer term follow-up will be valuable to assess whether these medically managed FFR_{CT}-positive patients will end up needing revascularization over time is uncertain. These findings should also be placed into the context of recent guidelines highlighting the importance of guiding revascularization decision-making based on anatomy and physiology emphasizing the value of FFR_{CT} to enable meaningful Heart Team discussions in a fashion that CTA alone cannot.[23,24]

There is also growing awareness that while in a trial setting FFR and FFR_{CT} have been evaluated using a binary cut-off, in practice the benefit from revascularization seems to increase with lower FFR values.[21,25,26] Predictors of revascularization in this study were lesion specific ischaemia by FFR_{CT}, diameter stenosis ≥70% and angina

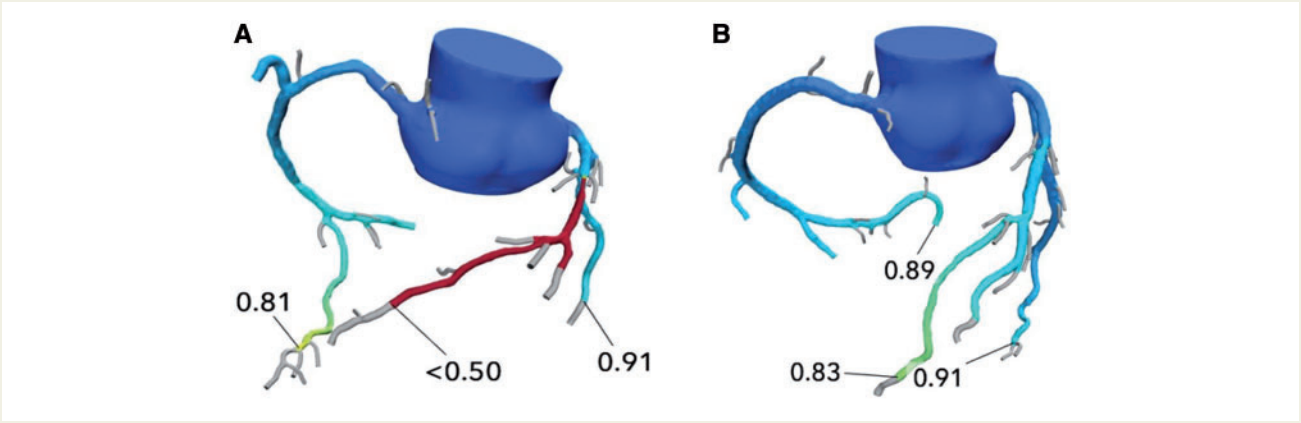


Figure 6 Three-dimensional coronary computed tomography angiography-derived fractional flow reserve pressure model of (*A*) a 59-year-old male with a 50–70% mid left anterior descending coronary artery stenosis yet severe ischaemia (coronary computed tomography angiography-derived fractional flow reserve ≤0.50) who experienced an NSTEMI in follow-up. (*B*) In comparison, a 71-year-old male with a more severe stenosis (70–90%) in the mid-left anterior descending without lesion specific ischaemia (coronary computed tomography angiography-derived fractional flow reserve 0.83) who was clinically well through 90 days follow-up.

symptoms. FFR_{CT}, like all test results, needs to be integrated into the overall clinical presentation including severity of symptoms. There was a difference noted between site and core management plans in the setting of positive FFR_{CT}, with site management strategies being more conservative in recommending ICA and revascularization (34.4%), supporting the theory that there is a significant role in the interpretation and clinical context of the FFR_{CT} result, as sites were privy to greater information of the clinical history and co-morbidities whereas the core lab was not.

This international real-world registry has also highlighted patterns of physician referral behaviour. The majority of lesions referred for further investigation were in the LAD, which is greater than the observed proportions of LAD disease burden in ICA studies,[19] and likely reflects heightened clinical concerns owing to the prognostic importance of LAD disease. The varied correlation between degree of stenosis and ischaemia is well known from studies such as FAME and RIPCORD,[27,28] which may result in a higher degree of uncertainty and desire to know more information. The increased likelihood of FFR_{CT}-determined ischaemia in the mild-moderate (30–70%) degree of anatomical stenosis in the LAD compared to other vessels is of particular diagnostic use and given the high frequency in our patient population (55.3%), justifies clinicians' vigilance in referring these lesions to ICA.[24,25]

Beyond defining the clinical use and role of FFR_{CT}, our data provide meaningful insight into the potential prognostic value of FFR_{CT} in clinical practice. Importantly, a negative FFR_{CT} was associated with an excellent short-term prognosis, as none of the 1592 subjects with negative FFR_{CT} experienced death, MI, or unplanned hospitalization for ACS and urgent revascularization. All MACE events occurred in subjects with FFR_{CT} ≤0.80, with the majority of events in subjects with an FFR_{CT} ≤0.75. This clustering of events in subjects with more significant ischaemia is interesting, however, long-term clinical follow-up is needed to determine if there is a relationship between the severity of FFR_{CT} reduction and adverse clinical outcomes. Our results mirror the invasive physiology experience where lower FFR values have been consistently shown to predict all-cause mortality and increased likelihood of MI and urgent revascularization.[29]

Limitations

Our analysis is not without limitations. To start, while including a broad sampling of patients undergoing FFR_{CT} across many countries and healthcare systems, ADVANCE is a registry, and therefore, we cannot exclude some element of referral bias. As well, while sites provided their treatment strategies on the basis of CCTA, virtually all subjects had FFR_{CT} available and therefore what their downstream treatment would have been in absence of FFR_{CT} cannot be determined with complete certainty. As such, while we report the change in clinical recommendations following FFR_{CT} as compared to CCTA alone, through 90 days not all site recommendations were followed clinically, highlighting the multifaceted nature of clinical decision-making. In addition, while detailed case/incident reports were submitted detailing all events, like many registries, a central event adjudication committee was not used. Finally, the Follow-up reported represents only the first 90 days, and although most adverse events and invasive management strategies occur within this time, longer term follow-up is essential particularly for MACE, and therefore is planned through 3 years in the ADVANCE registry.

Conclusions

In a large international multicentre population, FFR_{CT}-modified treatment recommendation in up to two-thirds of subjects as compared to CCTA alone, was associated with fewer ICA without obstructive disease, and predicted revascularization, while helping discriminate subjects at lower risk of adverse events at 90 days.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. SCOTHEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–2391.
2. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–1300.
3. Shaw LJ, Hausleiter J, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Kim YJ, Cheng VY, Chow BJW, Cury RC, Delago AJ, Dunning AL, Feuchtner GM, Hadamitzky M, Karlsberg RP, Kaufmann PA, Leipsic J, Lin FY, Chinnaiyan KM, Maffei E, Raff GL, Villines TC, Labounty T, Gomez MJ, Min JK. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter confirm (coronary CT angiography evaluation for clinical outcomes: an international multicenter) registry. *J Am Coll Cardiol* 2012;**60**:2103–2114.
4. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJR, Timmis AD, Newby DE. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;**67**:1759–1768.
5. Budoff MJ, Nakazato R, Mancini GBJ, Gransar H, Leipsic J, Berman DS, Min JK. CT angiography for the prediction of hemodynamic significance in intermediate and severe lesions head-to-head comparison with quantitative coronary angiography using fractional flow reserve as the reference standard. *JACC Cardiovasc Imaging* 2016;**9**:559–564.
6. Meijboom WB, van Mieghem CA, Van Pelt N, Weustink A, Pugliese F, Mollet NR, Boersma E, Regar E, van Geuns RJ, de Jaegere PJ, Serruys PW, Krestin GP, de Feyter PJ. 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. *J Am Coll Cardiol* 2008;**52**:636–643.
7. Nørgaard BL, Hjort J, Gaur S, Hansson N, Bøtker HE, Leipsic J, Mathiassen ON, Grove EL, Pedersen K, Christiansen EH, Kaltoft A, Gormsen LC, Mæng M, Terkelsen CJ, Kristensen SD, Krusell LR, Jensen JM. Clinical use of coronary CTA–derived FFR for decision-making in stable CAD. *JACC Cardiovasc Imaging* 2017;**10**:541–550.
8. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U, Schuchlenz HW, Feuchtner G, Gilard M, Andreini D, Jensen JM, Hadamitzky M, Chiswell K, Cyr D, Wilk A, Wang F, Rogers C, de Bruyne B. 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 FFR_{ct}: outcome and resource impacts stud. *Eur Heart J* 2015;**36**:3359–3367.
9. Jensen JM, Bøtker HE, Mathiassen ON, Grove EL, Øvrehus KA, Pedersen KB, Terkelsen CJ, Christiansen EH, Maeng M, Kaltoft A, Jakobsen L, Sørensen JT, Thim T, Kristensen SD, Krusell LR, Nørgaard BL. Computed tomography derived fractional flow reserve testing in stable patients with typical angina pectoris: influence on downstream rate of invasive coronary angiography. *Eur Heart J Cardiovasc Imaging* 2018;**19**:405–414.
10. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, Jensen JM, Mauri L, Bruyne BD, Bezerra H, Osawa K, Marwan M, Naber C, Erglis A, Park SJ, Christiansen EH, Kaltoft A, Lassen JF, Bøtker HE, Achenbach S. 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**:1145–1155.
11. Tonino PAL, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, MacCarthy PA, van't Veer M, Pijls NHJ. Angiographic versus functional severity of coronary artery stenoses in the FAME Study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;**55**:2816–2821.
12. Fordyce CB, Newby DE, Douglas PS. Diagnostic strategies for the evaluation of chest pain. *J Am Coll Cardiol* 2016;**67**:843–852.
13. Williams MC, Moss A, Nicol E, Newby DE. Cardiac CT improves outcomes in stable coronary heart disease: results of recent clinical trials. *Curr Cardiovasc Imaging Rep* 2017;**10**:14.
14. NICE. *Chest Pain of Recent Onset: Assessment and Diagnosis*. NICE Guidelines; 2010. www.nice.org.uk/guidance/cg95.
15. Blankstein R, Bittencourt MS, Bhatt DL. Coronary CTA in the evaluation of stable chest pain. *J Am Coll Cardiol* 2017;**69**:1771–1772.
16. Nielsen LH, Ortner N, Nørgaard BL, Achenbach S, Leipsic J, Abdulla J. 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. *Eur Heart J Cardiovasc Imaging* 2014;**15**:961–971.
17. Nørgaard BL, Jensen JM, Blanke P, Sand NP, Rabbat M, Leipsic J. Coronary CT angiography derived fractional flow reserve: the game changer in noninvasive testing. *Curr Cardiol Rep* 2017;**19**:
18. Lu MT, Ferencik M, Roberts RS, Lee KL, Ivanov A, Adami E, Mark DB, Jaffer FA, Leipsic JA, Douglas PS, Hoffmann U. Noninvasive FFR derived from coronary CT angiography: management and outcomes in the PROMISE trial. *JACC Cardiovasc Imaging* 2017;**10**:1350–1358.
19. Johnson LW, Krone R. Cardiac catheterization 1991: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1993;**28**:219–220.
20. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate use criteria for coronary revascularization and trends in utilization, patient selection and appropriateness of percutaneous coronary intervention: trends in appropriateness of PCI HHS public access. *JAMA* 2015;**314**:2045–2053.
21. Krone RJ, Johnson L, Noto T. Five year trends in cardiac catheterization: a report from the registry of the society for cardiac angiography and interventions. *Cathet Cardiovasc Diagn* 1996;**39**:31–35.
22. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P, Min JK. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. *Eur Heart J* 2017;**38**:991–998.
23. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S;Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
24. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery

(EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
25. Zimmermann FM, Ferrara A, Johnson NP, Nunen LXV, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon H, Remkes WS, Stella PR, Schaardenburgh PV, Bech GJW, Bruyne BD, Pijls NHJ. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015;**36**:3182–3188.
26. Kang DY, Ahn JM, Lee CH, Lee PH, Park DW, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park SJ. Deferred vs. performed revascularization for coronary stenosis with grey-zone fractional flow reserve values: data from the IRIS-FFR registry. *Eur Heart J* 2018;**39**:1610–1619.
27. De Bruyne B, Fearon WF, Pijls NHJ, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;**371**:1208–1217.
28. Curzen NP, Nolan J, Zaman AG, Norgaard BL, Rajani R. Does the routine availability of CT—derived FFR in fluence management of patients with stable chest pain compared to CT angiography alone? *JACC Cardiovasc Imaging* 2016;**9**:1188–1194.
29. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen S-L, Di Serafino L, Domínguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jiménez-Navarro MF, Katritsis DG, Kocaman SA, Koo B-K, López-Palop R, Lorin JD, Miller LH, Muller O, Nam C-W, Oud N, Puymirat E, Rieber J, Rioufol G, Rodés-Cabau J, Sedlis SP, Takeishi Y, Tonino PAL, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NHJ, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014;**64**:1641–1654.