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Research paper

Non-invasive fractional flow reserve derived from coronary computed tomography angiography in patients with acute chest pain: Subgroup analysis of the ROMICAT II trial

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ABSTRACT

Background: Non-invasive fractional flow reserve (FFR_{CT}) derived from coronary computed tomography angiography (CTA) permits hemodynamic evaluation of coronary stenosis and may improve efficiency of assessment in stable chest pain patients. We determined feasibility of FFR_{CT} in the population of acute chest pain patients and assessed the relationship of FFR_{CT} with outcomes of acute coronary syndrome (ACS) and revascularization and with plaque characteristics.

Methods: We included 68 patients (mean age 55.8 ± 8.4 years, 71% men) from the ROMICAT II trial who had ≥50% stenosis on coronary CTA or underwent additional non-invasive stress test. We evaluated coronary stenosis and high-risk plaque on coronary CTA. FFR_{CT} was measured in a core laboratory.

Results: We found correlation between anatomic severity of stenosis and $FFR_{CT} \leq 0.80$ vs. $FFR_{CT} > 0.80$ (severe stenosis 84.8% vs. 15.2%; moderate stenosis 33.3% vs. 66.7%; mild stenosis 33.3% vs. 66.7% patients). Patients with severe stenosis had lower FFR_{CT} values (median 0.64, 25th-75th percentile 0.50–0.75) as compared to patients with moderate (median 0.84, 25th-75th percentile, $p < 0.001$) or mild stenosis (median 0.86, 25th-75th percentile 0.78–0.88, $p < 0.001$). The relative risk of ACS and revascularization in patients with positive $FFR_{CT} \leq 0.80$ was 4.03 (95% CI 1.56–10.36) and 3.50 (95% CI 1.12–10.96), respectively. $FFR_{CT} \leq 0.80$ was associated with the presence of high-risk plaque (odds ratio 3.91, 95% CI 1.55–9.85, $p = 0.004$) after adjustment for stenosis severity.

Conclusion: Abnormal FFR_{CT} was associated with the presence of ACS, coronary revascularization, and high-risk plaque. FFR_{CT} measurements correlated with anatomic severity of stenosis on coronary CTA and were feasible in population of patients with acute chest pain.

1. Introduction

Coronary computed tomography angiography (CTA) has become a standard method for the evaluation of patients who present to the emergency department (ED) with symptoms suggestive of acute coronary syndrome (ACS).[1–3] Coronary CTA permits rapid evaluation of

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patients with decreased time to diagnosis and discharge as compared to standard work-up with stress testing.[1–3] The major strength of coronary CTA is its high negative predictive value for the exclusion of significant coronary stenosis and ACS. However, the positive predictive value, especially in patients with intermediate stenosis, is only moderate. In patients with suspected ACS in the ED, this may result in higher rates of invasive coronary angiography (ICA) and coronary revascularization among patients who undergo coronary CTA as compared to stress testing.[1–3]

Supplemental analyses of coronary CTA datasets, such as the assessment of coronary plaque, first-pass perfusion and resting wall motion abnormalities, have been proposed to improve specificity and positive predictive value of the test for stenosis and ACS.[4–6] More recently, non-invasive fractional flow reserve calculation from coronary CTA (FFR_{CT}) has been developed. Using computational fluid dynamics, FFR_{CT} can provide accurate assessment of fractional flow reserve with standard coronary CTA acquisition and no need for adenosine infusion. The measurements of FFR_{CT} correlated closely with invasive FFR measurements.[7,8] The evaluation of hemodynamic significance is important as there is frequent discordance between anatomic severity of stenosis and its hemodynamic significance.[9,10] Furthermore, coronary revascularization guided by the hemodynamic assessment with invasive FFR lead to improved outcomes as compared to the anatomic assessment only.[11] Management strategy of coronary CTA with FFR_{CT} was demonstrated to be feasible and safe alternative of ICA, with overall lower rate of ICA and equivalent clinical outcomes with lower cost at 1-year follow-up.[12,13] FFR_{CT} was also a better predictor of need for revascularization and future major adverse cardiovascular events when compared to anatomic stenosis detected by coronary CTA.[14] There is growing evidence that abnormal FFR_{CT} is not only related to anatomic severity of stenosis, but also to coronary plaque characteristics and burden.[15–18]

The majority of FFR_{CT} studies has been performed in stable chest pain patients in the outpatient setting. The feasibility and performance of FFR_{CT} in the acute chest pain setting has not been studied. Therefore, we analyzed data from the Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT) II trial and performed FFR_{CT} measurements in a subgroup of patients to determine the feasibility and performance of the technique in the population of acute chest pain patients in the ED. We also performed advanced coronary plaque analyses to assess the relationship between plaque characteristics and FFR_{CT} and their relation to ACS outcomes.

2. Methods

2.1. Patient population

The study population was selected from patients who were enrolled in the ROMICAT II trial, were randomized to the coronary CTA arm of the trial and underwent coronary CTA.[2] The ROMICAT II trial enrolled patients with acute chest pain and a low-to-intermediate suspicion for ACS. The local institutional review boards approved the study. In our retrospective study, we evaluated patients who had ≥50% stenosis as determined by the local site reads of coronary CTA or underwent an additional non-invasive cardiac stress test (Fig. 1).

2.2. Coronary CTA

Coronary CTA images were acquired using either retrospectively ECG-gated or prospectively ECG-triggered protocols. The investigators in the study used the scanners from three vendors (Siemens, General Electric, Toshiba) and different scanner generations (64-, 128-, 256-row, and dual source). Local physicians interpreted coronary CTA images and the presence of stenosis was categorized as severe (≥50% stenosis in the left main coronary artery or ≥70% in any coronary artery) or moderate (50%–70% stenosis in any coronary artery).

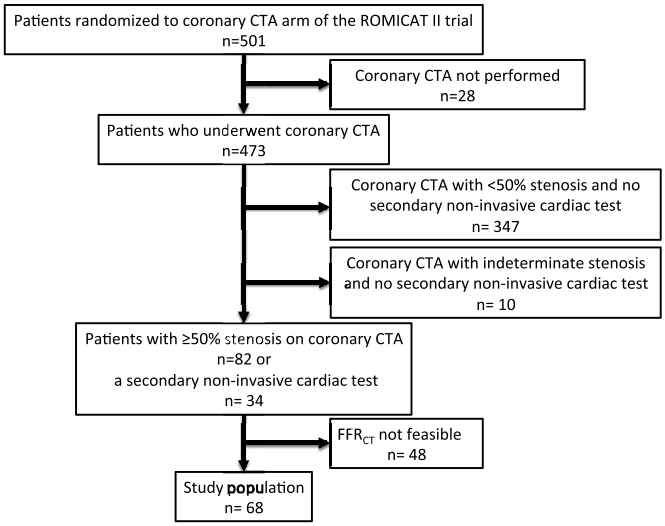

Fig. 1. Patient inclusions and exclusions.

Coronary CTA was deemed indeterminate if the readers were unable to rule out the presence of moderate or severe coronary stenosis.

2.3. Computation of FFR_{CT} from coronary CTA

The datasets submitted for the FFR_{CT} analysis met prospectively established inclusion criteria (field of view < 250 mm, slice thickness < 1 mm, administration of nitroglycerin). The FFR_{CT} implementation employed in this study was performed at a single core laboratory (HeartFlow Inc., Redwood City, California). CTA datasets meeting eligibility criteria were sent to the FFR_{CT} core laboratory. As previously validated, FFR_{CT} core laboratory applied a second set of quantitative criteria to determine whether image quality was adequate for FFR_{CT} analysis based on clear definition of coronary artery lumen and myocardial boundaries.[8] CTA datasets with inadequate image quality due to motion artifacts, severe calcium blooming artifacts or excessive image noise were excluded from the analysis.

FFR_{CT} was calculated blinded to all aspects of clinical care and clinical outcomes. The results of FFR_{CT} were not available to care providers. The techniques for calculation of FFR_{CT} have been detailed and accuracy against invasive FFR validated previously.[7,8] Briefly, 3-dimensional models of the coronary arterial tree and myocardium were segmented from the standard CTA images. Computational fluid dynamics techniques modeled coronary arterial flow under simulated maximal hyperemia. FFR_{CT} was calculated as the ratio of mean simulated pressure to aortic pressure at all coronary artery locations measuring ≥1.8 mm in diameter. Occluded vessels were assigned a value of 0.5. The lowest per-patient FFR_{CT} value was reported; a FFR_{CT} ≤0.80 at any coronary location constituted a per-patient "positive" result. We also reported per-vessel lowest FFR_{CT} value, which was used in per-vessel analysis. A FFR_{CT} ≤0.80 at any coronary location in a given vessel constituted a per-vessel "positive" result. Transfer of data, image segmentation, FFR_{CT} calculation and reporting typically requires less than 2 h with the current iteration of the technology.

2.4. Invasive and non-invasive tests

Investigators in the ROMICAT II trial prospectively collected information on ICA, revascularization procedures (percutaneous coronary intervention or coronary artery by-pass grafting) and additional non-invasive stress tests. Non-invasive stress tests included exercise treadmill electrocardiograms, nuclear myocardial perfusion imaging or stress echocardiograms. The tests were evaluated by local physicians and were reported positive if there was evidence of stress-induced ischemia.

2.5. Core laboratory assessment of coronary CTA

We performed additional core laboratory assessment of coronary CTA datasets. Three independent readers with level III experience in coronary CTA who were blinded to clinical care results evaluated coronary CTA on a per coronary segment basis using the model of the Society of Cardiovascular Computed Tomography.[19] Each segment was assessed for the presence of coronary stenosis and plaque. The severity of stenosis was categorized as: 0% = no stenosis, 1–49% = non-obstructive coronary artery disease (CAD), 50–69% = moderate stenosis, ≥50% stenosis in the left main coronary artery or ≥70% in any coronary artery = severe stenosis.

Qualitative assessment for high-risk coronary plaque was performed in all coronary segments with plaque. High-risk plaque was defined as the presence of at least one of the following features: positive remodeling (remodeling index > 1.1), presence of plaque with low CT attenuation of < 30 HU, napkin-ring sign and spotty calcium as described previously.[4]

Four independent readers with level III experience in coronary CTA performed quantitative coronary CTA analysis in coronary segments with visually detectable plaques. The images were analyzed on a dedicated workstation (QAngio CT RE 2.0, Medis, Leiden, the Netherlands). Readers performed automatic detection of the coronary arteries and segmentation of luminal and outer vessel boundaries followed by manual adjustments of the vessel centerline and boundaries as needed. Readers then determined the proximal and distal reference of the coronary plaque in the adjacent normal vessel. The final results of the coronary CTA analysis were reported per coronary artery. We measured total plaque volume, volume of plaque with < 30 HU and maximum remodeling index. The detailed description of the quantitative analysis was reported previously.[20]

2.6. Acute coronary syndrome definition

An independent clinical events committee adjudicated the presence of ACS during the index hospitalization as described previously.[2] ACS was defined as acute myocardial infarction or unstable angina pectoris according to the American College of Cardiology/American Heart Association Guidelines.[21]

2.7. Statistical methods

All statistical analyses were performed using Stata 13.1 (StataCorp LP, College Station, Texas). Continuous data are presented as mean ± standard deviation or median and 25th-75th percentile. Categorical and ordinal variables are presented as absolute and relative frequencies. Comparisons for unpaired data were performed with the use of an independent sample *t*-test or the Wilcoxon rank-sum test for continuous variables, the Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables. Binominal 95% confidence intervals (CI) were calculated using the 'exact' method, i.e. Clopper-Pearson intervals.[22] We performed multivariable multilevel mixed-effects logistic regression to evaluate the association between high-risk plaque (defined as any high-risk plaque by qualitative analysis) and FFR_{CT} after adjustment for stenosis severity at vessel level. At patient level, we used multivariable logistic regression models, in which we studied the association of high-risk plaque, FFR_{CT} and severe stenosis with the outcome of ACS during the index hospitalization. Based on these logistic regression models we calculated receiver operating characteristic (ROC) curves and corresponding areas under the receiver operating characteristics curve (AUC), which were compared using the DeLong algorithm.[23] For all analyses, a 2-tailed *P* value < 0.05 was required to reject the null hypothesis.

Table 1
Baseline characteristics of 68 subjects included in the study stratified by FFR_{CT} results.

	FFR_{CT} ≤0.80 n = 40	FFR_{CT} > 0.80 n = 28	p value
Age - mean ± SD, years	57.1 ± 7.2	53.9 ± 9.7	0.154
Female gender - no. (%)	6 (15.0)	14 (50.0)	0.003
Cardiovascular Risk factors - no. (%)			
Hypertension	24 (60.0)	17 (60.7)	1.000
Diabetes mellitus	11 (27.5)	5 (17.9)	0.400
Dyslipidemia	24 (60.0)	18 (64.3)	0.803
Family history of premature CAD	8 (20.0)	11 (39.3)	0.103
Former or current smoker	28 (70.0)	14 (50.0)	0.129
Obesity (BMI ≥30 kg/m^2)	18 (45.0)	12 (42.9)	1.000
Medications			
Aspirin	13 (32.5)	8 (28.6)	0.794
Beta-blockers	9 (22.5)	9 (32.1)	0.413
ACE inhibitors/ARB	14 (35.0)	9 (32.1)	1.000
Calcium channel blocker	5 (12.5)	1 (3.6)	0.389
Statins	15 (37.5)	10 (35.7)	1.000

3. Results

3.1. Study population

Of the 501 patients randomized to coronary CTA, 473 patients underwent and completed CTA scan (Fig. 1). We included patients with ≥50% stenosis in at least one coronary artery (n = 82, 17.3%) based on the site reads of coronary CTA. We also included patients who underwent an additional non-invasive cardiac test (n = 34, 7.2%), among them 27 patients who had stenosis < 50% and 7 patients who had indeterminate stenosis severity. Total of 116 patients met inclusion criteria and their coronary CTA images were submitted for FFR_{CT} analysis. Out of 116 patients, 48 (41.4%) coronary CTA datasets were inadequate for FFR_{CT} analysis due to motion artifacts, severe calcium blooming artifacts or excessive image noise. The characteristics of 68 subjects included in the study stratified by FFR_{CT} results are summarized in Table 1. There were no significant differences in baseline demographics and cardiovascular risk factors between subjects with FFR_{CT} ≤0.80 and FFR_{CT} > 0.80 except for more men among those with abnormal FFR_{CT} ≤0.80. Compared to those patients in whom FFR_{CT} calculation was not feasible, there were no significant differences in baseline characteristics of patients with available FFR_{CT} measurements (Table S1).

3.2. Coronary CTA findings and FFR_{CT}

We observed association between abnormal FFR_{CT} ≤0.80 and the presence of severe stenosis defined as stenosis ≥70% in any artery or ≥50% stenosis in the left main coronary artery as assessed by site reads of coronary CTA (Table 2). Among 33 patients with severe stenosis on coronary CTA, 28 (84.8%) had FFR_{CT} ≤0.80 and 5 (15.2%) had FFR_{CT} > 0.80 (Fig. 2). Mild stenosis (< 50%) or moderate stenosis (50–69%) was more often found in patients with normal FFR_{CT} > 0.80 (Table 2). Patients with severe stenosis had lower FFR_{CT} values (median 0.64, 25th-75th percentile 0.50–0.75) as compared to patients with moderate (median 0.84, 25th-75th percentile 0.75–0.90, p < 0.001) or mild stenosis (median 0.86, 25th-75th percentile 0.78–0.88, p < 0.001) (Fig. 3).

3.3. Association of FFR_{CT} with ACS and coronary revascularization

ACS during the index hospitalization was diagnosed in 39.7% (27/68) patients (myocardial infarction n = 3, unstable angina pectoris n = 24). ACS was more often diagnosed in patients with FFR_{CT} ≤0.80 (23/40 patients, 57.5%) as compared to those with FFR_{CT} > 0.8 (4/28 patients, 14.3%; p < 0.001, Table 2). Subjects with FFR_{CT} ≤0.80 also

Table 2
Coronary CTA findings (site reads), acute coronary syndrome during index hospitalization and additional cardiac tests stratified by FFR_{CT} results.

	FFR_{CT} ≤0.80	FFR_{CT} > 0.80	p value
	n = 40	n = 28	
Coronary CTA stenosis – no. (%)			
Indeterminate	1 (2.5)	1 (3.6)	1.000
Mild (< 50%)	5 (12.5)	10 (35.7)	0.036
Moderate (50–69%)	6 (15.9)	12 (42.9)	0.013
Severe (≥70% or ≥50% left main)	28 (70.0)	5 (17.9)	< 0.001
Acute coronary syndrome – no. (%)	23 (57.5)	4 (14.3)	< 0.001
Myocardial infarction	3 (7.5)	0 (0.0)	
Unstable angina pectoris	20 (50.0)	4 (14.3)	
Invasive coronary angiography – no. (%)	21 (52.5)	9 (32.1)	0.137
Coronary revascularization – no. (%)	15 (37.5)	3 (10.7)	0.024
Percutaneous coronary intervention	12 (30.0)	3 (10.7)	
Coronary artery bypass	3 (7.5)	0 (0.0)	
Non-invasive stress test – no. (%)	15 (37.5)	17 (60.7)	0.084

underwent revascularization during the index hospitalization more often: 15/40 (37.5%) patients vs. 3/28 (10.7%) patients (p = 0.024). The relative risk of ACS and revascularization in those with FFR_{CT} ≤0.80 as compared to those with FFR_{CT} > 0.8 was 4.03 (95% CI 1.56–10.36) and 3.50 (95% CI 1.12–10.96), respectively.

3.4. Potential effects of FFR_{CT} on downstream testing

ICA was performed in 44.1% (30/68) patients (Table 2). Among them, 73.3% (22/30) had severe stenosis on coronary CTA. Moderate stenosis was found in 20.0% (6/30) and mild stenosis in 6.7% (2/30) patients on coronary CTA. In patients with FFR_{CT} > 0.8 who underwent ICA, 37.5% (3/8) patients had severe stenosis on ICA. Among 8 patients with moderate or mild stenosis on coronary CTA, 7 patients had normal FFR_{CT} > 0.8 and only one patient with normal FFR_{CT} was diagnosed with ACS.

Additional non-invasive stress test after coronary CTA was performed in 47.1% (32/68) patients. Among these patients, ACS was diagnosed in 18.8% (6/32). Abnormal FFR_{CT} ≤0.80 was detected in 46.9% (15/32) patients. In the group of patients with FFR_{CT} ≤0.80, 26.7% (4/15) patients were diagnosed with ACS. Normal FFR_{CT} > 0.80 was found in 53.1% (17/32) patients. The result of non-invasive stress test was positive for ischemia in 17.7% (3/17) patients with FFR_{CT} > 0.80. Two patients from this group were diagnosed with ACS

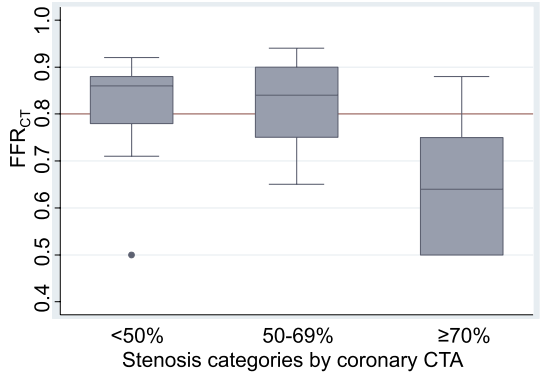

Fig. 3. Box and whisker plot of per patient FFR_{CT} by categories of coronary CTA stenosis.

(11.8%, 2/17, p = 0.383 as compared to abnormal FFR_{CT}). Coronary CTA showed severe stenosis in 5.9% (1/17) patients. The remaining patients had moderate (29.4%, 5/17), mild (58.8%, 10/17) or indeterminate (5.9%, 1/17) stenosis. Only one patient without severe stenosis on coronary CTA and FFR_{CT} > 0.8 was diagnosed with ACS. FFR_{CT} could potentially decrease the need for additional non-invasive testing in half of patients (16/32 with less than severe stenosis on coronary CTA and normal FFR_{CT}).

3.5. Core laboratory evaluation of high-risk plaque and FFR_{CT}

We performed additional analysis with core laboratory assessment of coronary CTA. Among 16 patients with severe stenosis on coronary CTA, all 16 (100%) patients had positive FFR_{CT} ≤0.80 (Table S2). In patients with moderate stenosis, positive FFR_{CT} ≤0.80 was found in 9/11 (81.2%) patients. Overall, 25/27 (92.6%) patients had positive FFR_{CT} ≤0.80 among patients with moderate or severe stenosis by core laboratory reads. In contrast, only 34/51 (66.7%) patients with moderate or severe stenosis by site reads had positive FFR_{CT} ≤0.80. Among patients with mild stenosis by core laboratory reads, 26/41 (63.4%) had negative FFR_{CT} > 0.80, which was similar to site reads (10/15 patients, 66.7%).

In a per vessel analysis, we found good correlation between coronary stenosis and FFR_{CT} as assessed by the core laboratory (Table 3). Vessels with abnormal FFR_{CT} ≤0.8 had higher prevalence of high-risk plaque (any high-risk plaque and individual high-risk plaque features of positive remodeling, low CT attenuation plaque, napkin-ring sign and spotty calcium) as detected by qualitative analysis. Similar results were

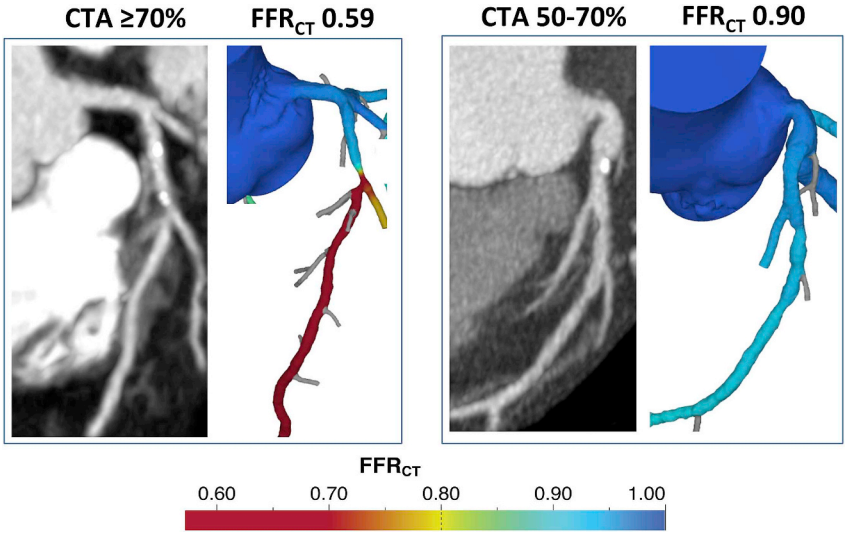

Fig. 2. Representative cases of coronary CTA and FFR_{CT}. *Left panel:* 64-year-old man with acute chest pain diagnosed with unstable angina. Coronary CTA demonstrated 70–99% stenosis of the left anterior descending coronary artery at the origin of the first diagonal branch. FFR_{CT} was abnormal (0.59). Invasive coronary angiography confirmed ≥70% stenosis and patient underwent stent placement. *Right panel:* 61-year-old woman diagnosed with non-cardiac chest pain. Coronary CTA demonstrated 50–70% stenosis in mid left anterior descending coronary artery. FFR_{CT} was normal (0.90). Invasive coronary angiography showed 30–50% stenosis.

Table 3
Results of core laboratory assessment for stenosis, qualitative high-risk plaque and quantitative plaque stratified by FFR_{CT} results (per vessel analysis).

	FFR_{CT} ≤0.80 n = 71	FFR_{CT} > 0.80 n = 175	p value
Stenosis – no. (%)			
Mild (< 50%)	37 (52.1)	170 (97.1)	< 0.001
Moderate (50–69%)	13 (18.3)	4 (2.3)	< 0.001
Severe (≥70% or ≥50% LM)	21 (29.6)	1 (0.6)	< 0.001
Qualitative plaque – no. (%)			
Any high-risk plaque	48 (67.6)	52 (29.7)	< 0.001
Positive remodeling	23 (32.4)	9 (5.1)	< 0.001
Low HU plaque	15 (23.1)	5 (2.9)	< 0.001
Napkin-ring sign	13 (18.3)	2 (1.1)	< 0.001
Spotty calcium	41 (57.8)	50 (28.6)	< 0.001
Quantitative plaque – mean ± SD			
Total plaque volume, mm^3	198.5 ± 188.8	43.2 ± 79.7	< 0.001
Plaque Volume < 30 HU, mm^3	4.7 ± 7.6	1.1 ± 4.7	< 0.001
Remodeling index	1.24 ± 0.29	1.05 ± 0.14	< 0.001

found in per patient analysis (data not shown). In quantitative plaque analysis, we observed higher remodeling index, total plaque volume and low CT attenuation (< 30 HU) plaque volume in vessels with abnormal FFR_{CT} ≤0.8. In multivariable multilevel mixed-effects logistic regression, the association between high-risk plaque (defined as any high-risk plaque by qualitative analysis) and FFR_{CT} ≤0.8 was independent of stenosis severity (odds ratio 3.91, 95% CI 1.55–9.85, p = 0.004). In the multivariable model at patient level, the addition of high-risk plaque (odds ratio 16.47, 95%CI 1.13–240.81, p = 0.041) and FFR_{CT} (odds ratio 1.67, 95%CI 0.40–7.09, p = 0.483) to stenosis (odds ratio 40.18, 95%CI 3.44–469.36, p = 0.003) improved discriminatory capacity for ACS as compared to stenosis only (AUC: 0.87, 95%CI 0.79–0.95 vs. 0.77, 95%CI 0.67–0.86; p = 0.003; Fig. S1).

4. Discussion

We performed analysis of non-invasive FFR_{CT} in patients from the ROMICAT II trial who underwent coronary CTA and had moderate or severe coronary stenosis or required additional non-invasive stress test. We demonstrated the feasibility of FFR_{CT} analysis in acute chest pain population in multicenter, multivendor setting. Our study showed that severity of stenosis on coronary CTA correlated with FFR_{CT} measurements. Patients with abnormal FFR_{CT} were also more likely diagnosed with ACS and more often required revascularization. In coronary plaque analysis, we observed association of the presence of high-risk plaque features with abnormal FFR_{CT} values, which persisted after adjustment for stenosis severity.

4.1. Feasibility of FFR_{CT} in acute chest pain population

Prior studies reported good correlation of FFR_{CT} with invasive FFR as well as relationship to outcomes in populations of outpatients with stable chest pain.[7,8,12–14,24] Large multicenter trials reported that 71–89% of coronary CTA datasets were of sufficient images quality for FFR_{CT} analysis.[7,8,13] The results from clinical practice with focused image optimization required for FFR_{CT} showed event better results with 97–99% of coronary CTA having image quality sufficient for FFR_{CT} analysis.[25,26] In our study, we demonstrated that the evaluation of FFR_{CT} in patients with acute chest pain in the ED was feasible. We selected a population with high prevalence of CAD and patients who required additional testing. Despite the challenging population characteristics, we observed that FFR_{CT} was feasible in 59% of patients. This was possible despite the fact that coronary CTA scans were not acquired with the goal to perform FFR_{CT} and were acquired before 2011, i.e. with older CT equipment. The FFR_{CT} acceptance was similar to the analysis from the PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), in which 67% of coronary CTA datasets were evaluable.[14] In the future prospective studies of FFR_{CT} in acute chest pain populations, the investigators will have to pay attention to obtain high image quality necessary for the analysis. Rapid evaluation in the core laboratory with turnaround time of a few hours will be necessary for the implementation of FFR_{CT} into the ED workflow. In addition to FFR_{CT} performed as an off-site analysis, which may require longer processing times, on-site FFR_{CT} solutions tested in smaller, single center studies have been demonstrated to provide results that compare favorably with invasive FFR and have been feasible in patients with suspected ACS.[17,24,25] Considering on-site assessment may be more time efficient, especially in the setting of acute chest pain where efficient time management is crucial, but future studies will be needed to evaluate this concept.

4.2. Correlation of FFR_{CT} with stenosis and ACS outcomes

Prior studies showed correlation of FFR_{CT} with stenosis severity,[14] which was confirmed in our study. However, there was still substantial disagreement. Mild or moderate stenosis was found on coronary CTA in 28% (11/40) patients with abnormal FFR_{CT} ≤0.8. There were 18% (5/28) patients with severe stenosis as assessed by site coronary CTA reads who had normal FFR_{CT} > 0.8. Therefore, overall there was disagreement in 24% (16/68) patients. These findings are similar to the results from the PROMISE trial, in which there was 31% of patients with disagreement between coronary CTA and FFR_{CT} and 29% of patients with disagreement between ICA and FFR_{CT}.[14] The disagreement was higher in the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) trial, in which the investigators observed disagreement between coronary CTA and FFR_{CT} in 47% of patients.[8] Our results are also in line with experience comparing invasive evaluation of ICA with FFR, which showed discrepancy rate of 25% in the Fractional Flow Reserve Versus Angiography in Multivessel Evaluation (FAME) trial.[10]

An interesting observation from our study is the difference in the agreement between coronary CTA and FFR_{CT} when core laboratory evaluation was used. We found that all patients graded as having severe stenosis on coronary CTA by core laboratory readers were also found to have FFR_{CT} ≤0.8. Overall, we found lower grading of stenosis severity in core laboratory reads. The results are in concordance with the recent analysis from the PROMISE trial that showed lower prevalence of significant stenosis in core laboratory CTA reads as compared to the site reads.[26] Less conservative assessment of stenosis severity (i.e. less patients with significant stenosis) did not affect the predictive accuracy of CTA for the future majors adverse cardiovascular events.[26] These results suggest that combined “less conservative” evaluation of coronary CTA for stenosis with detection of hemodynamically significant lesions using FFR_{CT} is a concept that will need to be prospectively evaluated.

We evaluated the association of FFR_{CT}, which was not used for the clinical decision-making in the ROMICAT II trial, with the outcome of ACS during the index hospitalization. There was a strong association between abnormal FFR_{CT} and the diagnosis of ACS. Among 27 patients with the diagnosis of ACS, 23 (85%) patients had FFR_{CT} ≤0.8. This observation showed that hemodynamic significance of coronary lesions is important predictor of ACS in acute chest pain setting. Our results mirror the prior experience from stable chest pain population. In the PROMISE trial, the association of FFR_{CT} with revascularization and major adverse cardiovascular events was significantly stronger than for severe stenosis on CTA (hazard ratio 4.31 vs. 2.90, p = 0.033), a notable result as stenosis guided the clinical decision for coronary revascularization, whereas FFR_{CT} was not available to caregivers in the trial.[14]

Four out of 28 patients with FFR_{CT} > 0.8 were diagnosed with ACS. These discrepant results, reflect clinical practice, in which further testing may be driven by clinical presentation in acute chest pain.

Furthermore, prior studies showed remaining discordance of FFR_{CT} results with invasive FFR, especially around the threshold of 0.8, and between FFR_{CT} and functional stress testing.[27,28]

4.3. FFR_{CT} and coronary plaque characteristics

The presence of high-risk plaque features, such as positive remodeling, low CT attenuation, napkin-ring sign and spotty calcium, on coronary CTA is associated with the presence of ACS in acute setting and increased risk of future cardiovascular events in stable chest pain patients.[4,29] In a secondary analysis of Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) trial of stable chest pain patients, qualitative and quantitative measures of coronary plaque were independently associated with lesions causing ischemia as confirmed by invasive FFR.[16] Similar observations were made by the investigators in the NXT trial who found association of significant stenosis, non-calcified and low CT attenuation plaque volume with abnormal $FFR_{CT} \leq 0.8$.[15] The volume of low CT attenuation plaque and FFR_{CT} was incremental to stenosis in prediction of lesion specific ischemia as assessed by invasive FFR. The incremental value of plaque assessment and FFR_{CT} was also present in patients with non-significant stenosis on coronary CTA. We extended this novel observation of the association between high-risk plaque features and total and low CT attenuation plaque volume with hemodynamic significance as assessed by FFR_{CT}, which was independent of the presence of significant stenosis, in the acute chest pain population. Our results provide an additional piece of evidence supporting the notion that coronary plaque characteristics are an important determinant of hemodynamic significance of coronary stenosis.

4.4. Limitations

We performed FFR_{CT} analysis in a subgroup of patients in the ROMICAT II trial. This approach may introduce selection bias. The results of coronary CTA based on site reads affected the clinical decisions and were also used to select the patients included in our substudy. Only 3 out of 22 patients diagnosed with ACS had myocardial infarction. Remaining 19 patients were diagnosed with unstable angina. This limits our ability to study relationship between stenosis detected by site reads and FFR_{CT} with respect to the prediction of ACS. The estimates of decreased need for secondary testing and ICA are affected by those limitations as well. Further prospective studied will be necessary to evaluate whether implementation of FFR_{CT} in the evaluation of patients with acute chest pain in the ED can decrease the rates of secondary testing. Invasive FFR was not performed routinely in the ROMICAT II trial. Therefore, we were unable to confirm the results of FFR_{CT} with invasive FFR in patients who underwent ICA. A fairly high proportion of coronary CTAs were not suitable for FFR_{CT} analysis, which is reflective of older generations of CT scanners and image acquisition not being optimized for FFR_{CT}.

5. Conclusions

We showed that FFR_{CT} measurements correlated with the anatomic severity of stenosis on coronary CTA. Abnormal FFR_{CT} was associated with the presence of ACS and coronary revascularization. We found association between the presence of high-risk plaque and FFR_{CT}, which was independent of stenosis severity.

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Appendix A. Supplementary data

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