# Advances in the Use of Coronary Computed Tomographic Angiography in the Evaluation of Coronary Artery Disease in the Emergency Department

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## Clinical Question:

Is there a way to improve the performance of standard coronary computed tomographic angiography (CCTA) in ruling out clinically significant coronary ischemia as the cause of chest pain in the emergency department?

## Introduction:

Compared to other non-invasive coronary imaging modalities, CCTA has consistently shown higher sensitivity and negative predictive value in determining the presence of coronary stenosis,[1-3] even supporting its use in the evaluation of low-risk chest pain presenting to the emergency department (ED).[4,5] Fractional flow reserve (FFR) has traditionally been performed during invasive coronary angiography (ICA) by inserting a wire across a stenotic vessel to calculate pressure differences caused by vessel narrowing as a marker of flow limitation – thus risk stratifying need for further intervention. Advances in computational fluid dynamics have allowed for noninvasive CT-derived FFR (FFRCT) assessment,[6] but whether this adds to the ED evaluation of chest pain is unclear.

### Koo BK, Andrejs E, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW. *J Am Coll Cardiol*. 2011;58(19):1989-97. doi: 10.1016/j.jacc.2011.06.066.

This landmark study set out to evaluate the diagnostic performance of a novel noninvasive method of calculating FFR by using computational fluid dynamics to determine lesion-specific ischemia on CCTA, comparing it to the gold standard of invasive FFR measured during ICA.

The study included patients from four different facilities in Seoul, Korea, Riga, Latvia, Goyang, Korea, and Palo Alto, California. Included patients were ≥18 years of age with CCTA findings of ≥50% stenosis in a major coronary artery ≥2.0 mm diameter and planned ICA with FFR. Notable exclusion criteria included noncardiac illness with life expectancy <2 years, pregnancy, iodinated contrast allergy, serum creatinine ≥ 1.7 mg/dl, significant arrhythmia, heart rate ≥100 beats/min, systolic blood pressure ≤90 mmHg, contraindication to beta-blockers, nitroglycerin, or adenosine, prior coronary artery bypass grafting (CABG), Canadian Cardiovascular Society class IV angina or non-evaluable CCTA as determined by the CTA core laboratory.

A total of 103 patients were included, all of whom underwent both CCTA and ICA with FFR. All patients received metoprolol to reach a heart rate <65 beats/min and 0.2 mg sublingual nitroglycerin immediately before acquiring CCTA. Images were obtained of coronary vessels, left ventricle and proximal ascending aorta. 3-dimensional image analysis was performed in a blinded fashion. Coronary segments with densities > 1 mm2 were considered to meet criteria for atherosclerosis. Lesion-related luminal diameter stenosis was quantified as none (0%), mild (1-49%), moderate (50-69%) or severe (≥70%). Diagnosis of obstructive coronary artery disease was based on the presence of ≥50% or ≥70% stenosis depending on the vessel. ICA and FFR were done per normal standards, with a FFR ≤0.80 considered diagnostic for ischemia. FFRCT was calculated using reconstructed CCTA images to obtain values for coronary flow, resistance and pressure. As with invasive FFR, FFRCT ≤0.80 was considered diagnostic for stenosis-related ischemia.

Compared to CCTA alone, FFRCT performed similarly with respect to sensitivity, negative predictive value (NPV), and negative likelihood ratio (NLR) for the diagnosis of lesion-specific ischemia. FFRCT, however, also had statistically significant improvements in accuracy, specificity, positive predictive value (PPV) and positive likelihood ratio (PLR). Additionally, FFRCT showed good correlation to FFR with Spearman's rank correlation = 0.717, p<0.0001; Pearson's correlation coefficient = 0.678, p<0.0001. At the per-vessel level there was slight underestimation by FFRCT as compared to measured FFR (mean difference 0.022 ± 0.116, p<0.016), with similar values and no systematic differences at the per-patient level (mean difference 0.019 ± 0.128, p<0.131).

Limitations of this study include a smaller study size, which limited the power of per-patient performance of FFRCT vs CCTA; the study was adequately powered, however, for per-vessel calculations. Another limitation is that all of the study subjects had clinical indications for ICA, exposing the study to selection bias and limiting the ability to assess the diagnostic performance of FFRCT in consecutive all-comer patients undergoing CCTA. Lastly, patients with prior CABG were excluded from this study, precluding performance evaluation in this high-risk population.

Overall, this study demonstrated that FFRCT correlated well with invasive FFR and provided increased diagnostic accuracy of lesion-specific ischemia and lower false positives when compared to CCTA alone.

### Coenen A, Lubbers MM, Kurata A, et al. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology.* 2015 Mar;274(3):674-83. doi: 10.1148/radiol.14140992.

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In this study, Coenen et al. looked to validate a new computational algorithm which could perform calculations both quickly and locally in the same hospital while maintaining the diagnostic potential of the results. In a single center retrospective observational study, they looked to compare CCTA and computationally derived FFR with invasive coronary angiography and invasively-measured FFR. They included 122 consecutive patients with known or suspected CAD between 2007 and 2013 who had a CCTA performed based on clinical factors and an invasive angiogram with invasive FFR performed within 50 days of the CCTA. They excluded patients with prior CABG, PCI of the vessel of interest, or a cardiac event between the two imaging methods.

In total, 106 total patients were included with 189 unique vessels analyzed. Baseline characteristics of the population included an average age of 61.4 ± 9.2 years and a largely male population (77%). Most of the patients had hypertension (59%), dyslipidemia (59%), and almost half had a family history of CAD (48%). A total of 14 patients had a history of MI with 11 patients with prior PCI, but not in the vessel considered for this study. Patients were routinely given sublingual nitroglycerin prior to the studies, with beta blockers used in those with a fast heart rate. The median time between CTA and invasive measurements was 16 days. Anatomic stenosis > 50% and FFR < 0.80 was considered significant as defined in previous studies.

A total of 42.3% of vessels were found to have hemodynamically significant stenosis by invasive FFR, the gold standard test for this study. Anatomic CCTA characterized 70.4% of vessels as significant stenosis while invasive anatomic angiography characterized 46.0% of vessels as such. This led to a sensitivity and specificity of CCTA for hemodynamically significant stenosis of 81.3% and 37.6%, respectively, compared to the sensitivity and specificity of invasive ICA, 73.8% and 74.3%, respectively. Computational FFR using this new locally processed and faster algorithm had the same sensitivity as CCTA with improved specificity (65.1%). Furthermore, increasing the FFR cutoff for significance from 0.80 to 0.82 improved the sensitivity to 90% but did not alter the specificity (similar at 64%). Computational time ranged from 30 minutes to 2 hours, a significant improvement on prior outsourced computational methods. Finally, the overall correlation between computational FFR and invasive FFR was moderate to good with a Pearson correlation coefficient of 0.59.

This study largely served as evidence that computational FFR can reliably be performed locally and efficiently in a hospital without having the wait long hours and high costs associated with prior outsourced server-based computation of FFR. It also further validated the growing evidence for use of computational FFR as a reliable metric for the prediction of functionally significant coronary artery disease. A few major limitations of this study include the predominantly male patient population, and the exclusion of vessels with prior PCI, extremely high coronary calcium scores, and the patients with acute cardiac events.

**Chinnaiyan KM, Safian RD, Gallagher ML, et al. Clinical Use of CT-Derived Fractional Flow Reserve in the Emergency Department. *JACC Cardiovasc Imaging.* 2020;13(2 Pt 1):452-61. doi: 10.1016/j.jcmg.2019.05.025.**

In clearly minimal or severe atherosclerosis, CCTA can safely expedite disposition either to ED discharge or admission for planned ICA. Patients with intermediate (50-70%) stenosis, calcifications impairing study quality, or complex plaque morphology are not as reliably risk-stratified, however, leading to additional invasive testing and increased cost. To evaluate the utility of FFRCT in patients with acute chest pain (ACP), Chinnaiyan et al. performed a retrospective analysis of prospectively enrolled institutional CCTA registry. They sought to evaluate the feasibility, clinical outcomes, and costs associated with the use of FFRCT in patients experiencing ACP and undergoing CCTA.

Inclusion criteria were the presence of ACP, no known history of coronary artery disease (CAD), and presence of stenosis >25% on CCTA. Patients were excluded if they had a heart rate >100 bpm, renal insufficiency, or other contraindication to iodinated contrast. Patients received beta blockers to target a heart rate <60 bpm, as well as 0.8 mg sublingual nitroglycerin prior to CCTA. In the original registry, patients were selected for CCTA if they had no clinical evidence of acute coronary syndrome by electrocardiogram or cardiac biomarkers. Only a subset of those patients undergoing CCTA also underwent FFRCT, which was pursued by recommendation from the physician interpreting the CCTA on the basis of discovering: 1) coronary stenosis >50%, 2) dense coronary calcification obscuring the lumen, or 3) high-risk plaque features in coronary stenoses <50%.

The authors established CCTA and FFRCT groups for comparison by looking at all those undergoing FFRCT and identifying a CCTA group with similar degree of stenosis, indicating a likely attempt at propensity-matching the cohorts, though the statistical details of this effort were not elaborated upon. Patients were followed for 90 days after index scan. Specifically, safety was defined as absence of death, nonfatal MI, and unplanned revascularization therapy in patients with negative FFRCT.

A total of 327 patients were referred to FFRCT, with 24 excluded due to either normal or occluded arteries and six excluded due to insufficient study quality, leading to inclusion of 297 patients compared to 258 in the CCTA arm. Arms were well matched for age, sex, hypertension, hyperlipidemia, smoking, and familial history of early CAD, although a significantly higher portion of typical angina was seen in the CCTA group (11% vs. 2%, p<0.001). There was no statistically significant difference in 90-day major adverse cardiac events (MACE) between CCTA and FFRCT groups (4.3 vs 2.7%, p=0.31). In the CCTA group there was one death, three myocardial infarctions (MI), and six patients with unexpected percutaneous coronary intervention (PCI), five of whom were found to have severe disease on coronary angiography despite CCTA results indicating only 26-50% stenosis. There were four late unexpected

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revascularizations in the FFRCT-negative group (FFR >0.80), with no death or MI. When confirmed by findings on ICA, nonobstructive CAD was higher in those with negative FFRCT (56.5%) compared with those with positive FFRCT (8%) or CCTA alone (22.9%) (p<0.001). Costs were lower in the negative FFRCT group compared to positive FFRCT, and compared to the CCTA-only group for stenoses >50%, with no difference between groups in hospitalization or subsequent ED visits, and no increase in ED length of stay.

There were some limitations. This was a prospective trial based on an institutional coronary CTA registry which limits generalizability to an all-comers approach. Moreover, the decision of who underwent FFRCT was a function of the previous trial, and not established *a priori*, possibly introducing unclear bias into the results. The authors indicated patients with similar stenoses on CCTA were selected for matching but did not elaborate on the statistical method of choosing these patients, a possible source of bias. Patients with ACS as determined by ECG or cardiac biomarker abnormalities were excluded, limiting the evaluation of CCTA and FFRCT accuracy and utility in this patient population.

Within every stenosis category negative FFRCT was associated with higher rates of nonobstructive CAD on ICA compared with negative FFRCT or CCTA, indicating a possibly higher sensitivity for hemodynamically-significant disease. The authors conclude that deferral of revascularization is safe with negative FFRCT on the basis of lower obstructive disease on invasive angiography. We agree that this study serves as an important proof-of-concept and that prospective studies of FFRCT-guided triage algorithms in the ED are warranted.

### Shiono Y, Matsuo H, Kawasaki T, et al. Clinical Impact of Coronary Computed Tomography Angiography-Derived Fractional Flow Reserve on Japanese Population in the ADVANCE Registry. *Circ J.* 2019;83(6):1293-1301. Doi: 10.1253/circj.CJ-18-1269.

The ADVANCE registry (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care) is an international prospective registry of individuals with at least 30% coronary stenosis on CCTA who undergo FFRCT. This retrospective secondary analysis of the ADVANCE registry evaluated 1,758 Japanese patients with FFRCT data to determine the effect of adding FFRCT data on treatment strategy allocation and association with 90-day MACE.

An initial management plan of optimal medical therapy, percutaneous coronary intervention (PCI), or CABG was determined by site investigators based on initial CCTA imaging results. FFRCT data was then provided and used by the investigators to guide their management plan. The same CCTA and FFRCT data were also sent to a blinded independent laboratory where subject management plans were made in the same stepwise fashion. Primary endpoints included rate of reclassification in management plan with the addition of FFRCT data, incidence of ICA without obstructive CAD (<50% stenosis), surgical and percutaneous revascularization rates, and 90-day survival free from MACE.

The study population had a Diamond-Forrester pretest probability for obstructive CAD of 55%. CCTA found ≥50% stenosis in 77.9% of subjects, and >70% stenosis in 46.9% of patients, with multivessel disease in 33.7%. A majority of patients (71%) had FFRCT-positive lesions; the left anterior descending artery (LAD) more frequently had anatomically severe and physiologically significant stenoses compared to the left circumflex or right coronary artery. Addition of FFRCT data led to reclassification in patient treatment strategy in 55.8% and 56.9% of cases by the site investigators and independent laboratory analysis, respectively. The majority of reclassifications were de-escalations to optimal medical therapy (58.5%) as opposed to selection of PCI (22.1%) or CABG (2.5%). Only 22.6% of FFRCT-negative patients received invasive coronary angiography as opposed to 61.7% of FFRCT-positive patients. There was a trend toward a higher rate of 90-day MACE in the FFRCT-positive group compared to the FFRCT-negative group (five vs. zero, respectively). The five events in the FFRCT-positive group included two hospitalizations for acute coronary syndrome and three deaths.

This study again demonstrated the importance of augmenting anatomic evaluation with physiologic assessment. The addition of FFR data allowed the reclassification of many anatomically concerning lesions as physiologically less concerning, leading to a reduction in unnecessary invasive testing, as supported by the zero MACE event rate in the FFRCT-negative group. It is important to note that because this study was a sub-analysis of the ADVANCE registry, statistical significance was not achieved. However, these trends follow those seen in the full prospective analysis of the ADVANCE registry which was appropriately powered for statistical significance. Additionally, while the MACE rate at 90 days is certainly relevant in the acute setting, further study with more longitudinal follow-up would be ideal to further assess the potential benefits of FFRCT use.

### Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-Year Impact on Medical Practice and Clinical Outcomes of FFRCT: The ADVANCE Registry. *JACC Cardiovasc Imaging.* 2020;13(1 Pt 1):97-105. doi:10.1016/j.jcmg.2019.03.003.

An observational study using patients from the ADVANCE registry was used to determine 1-year clinical events for patients who underwent evaluation of their chest pain via CCTA and FFRCT if indicated.

Data for 5,083 patients undergoing CCTA with FFRCT from 38 international sites were reviewed for treatment plans and 1-year clinical outcomes including MACE (ACS, MI, and death). Of the 5,083 patients, 190 did not have FFRCT after CCTA and 156 had FFRCT unable to be analyzed. Approximately 5.5% of patients were lost to follow up. The total number of patients who had CCTA followed by positive versus negative FFRCT was 2,860 and 1,428 patients, respectively. 1-year clinical data was reviewed for the patients with CCTA followed by FFRCT. Major adverse cardiac events occurred in 55 patients, 43 in those with positive FFRCT and 12 in those with negative FFRCT (RR 1.91, 95% CI:

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0.96-3.43). Time to first event occurred more often in patients with positive FFRCT versus those with negative FFRCT. At 1-year, only 0.19% of patients with FFRCT >0.80 had an MI and none died from cardiovascular related death. Additional 1-year data was collected on those with positive FFRCT; analysis demonstrated increasing rates of MACE with decreasing FFRCT, with the highest rates in patients with FFRCT <0.71.

Limitations of this study include those listed previously, and that the data was collected from a registry, which is inherently subject to referral bias. Additionally, because it is an observational review of a registry instead a randomized study, treatment recommendations are unable to be made.

## Conclusion

The primary advantage of adding FFRCT to CCTA is the decreased need for additional and/or more invasive diagnostics for anatomically higher-grade stenoses that do not significantly limit perfusion. The benefit of this advantage to the evaluation of chest pain in the ED remains unclear. As in previous CCTA-only studies,[4,5] rates of major adverse cardiac events seen in the ADVANCE registry were low overall, limiting the real-word utility of a diagnostic test whose purpose is to rule out adverse events, and the addition of FFRCT did not greatly improve sensitivity for hemodynamically-significant stenoses over CCTA alone. The avoidance of unnecessary admission and/or invasive cardiac angiography and decreased overall costs remain attractive and could potentially balance the reservations regarding the use of ionizing radiation.

## Answer

For those who already choose to utilize CCTA in low-risk chest pain, FFRCT seems to be a good addition, but the current data on FFRCT is not enough to mandate significant change in clinical practice at this time for emergency medicine physicians. ●

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