Does FFR_{CT} have proven utility as a gatekeeper prior to invasive angiography?

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For decades, invasive coronary angiography (ICA) in the catheterization lab has remained the gold standard for evaluation of symptoms of possible coronary artery disease (CAD). However, because catheter angiography is expensive, uncomfortable, and associated with a small, but nonzero, incidence of major complications, indirect means of evaluating CAD have been sought. Physiologic methods of evaluating CAD began with simple exercise stress testing and later added stress nuclear imaging, stress echocardiography, and even stress MRI, all of which have evolved and improved in spatial resolution and diagnostic accuracy with progressive technological advances.¹ More recently, noninvasive coronary computed tomography angiography (CTA) has become technically feasible since the 1990s using ECG-gated coronary computed tomography. With the arrival of 64 multi-detector and even more advanced CT scanners, utilization of coronary CTA has increased exponentially in a relatively short time frame.²

The accuracy of coronary CTA has been established using ICA as a reference standard.³ The prognostic utility of coronary CTA for the prediction of coronary events has also been demonstrated.⁴ Furthermore, given the large proportion of patients evaluated by ICA who have no significant stenosis,⁵ noninvasive coronary CTA has been evaluated observationally and in clinical trials as a gatekeeper prior to coronary angiography.⁶

Guidelines support the use of either a physiologic or anatomic means for evaluation and treatment decisions for patients with CAD.^{1,7} In a landmark series of experiments beginning over 40 years ago, Dr. Gould and

colleagues demonstrated that coronary flow reserve is not determined by anatomic coronary stenosis alone.⁸ Lesion length, plaque morphology and biochemical composition, endothelial factors, and microvascular health are among the determinants beyond diameter stenosis that contribute to coronary flow reserve.¹

Multiple randomized trials have tested whether to treat coronary stenosis by revascularization guided by either anatomic stenosis or demonstration of physiologic flow impairment via fractional flow reserve. In the multicenter, randomized DEFER trial, 325 patients scheduled for percutaneous coronary intervention (PCI) underwent fractional flow reserve (FFR) evaluation by invasive pressure wire, and if FFR ≥ 0.75 the patients were randomized to either PCI or medical management (deferral of PCI). In 2001, the 1, 3, 6, 12, and 24 months of follow-up were reported demonstrating no difference in mortality or recurrent angina for patients with FFR ≥ 0.75 who either underwent PCI vs. those with deferred PCI.⁹ At fifteen-year follow-up, mortality was similar for subjects with FFR ≥ 0.75 whose coronary stenoses were deferred vs. underwent PCI (33.0% mortality in the defer group vs. 31.1% in the PCI group, $P = 0.79$). Interestingly, the incidence of myocardial infarction was lower in the defer group (2.2%) vs. PCI group (10.0%), with a relative risk of 0.22 (95% CI 0.05–0.99, $P = 0.03$).¹⁰ Next, the Fractional Flow Reserve vs. Angiography for Multivessel Evaluation (FAME) trial evaluated angiography-based PCI vs. FFR-guided PCI among patients referred for coronary angiography. Among 1005 patients in this multicenter randomized controlled trial, there was a significant clinical outcomes benefit to FFR-guided PCI vs. angiographically guided PCI at 1 year, 67 (13.2%) patients in the FFR-group experience combined death/MI/repeat revascularization vs. 91 patients (18.3%) in the angiographically guided group ($P = 0.02$). There was no difference in freedom from angina at 1 year.¹¹ More recently, the Fractional

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Flow Reserve vs. Angiography for Multivessel Evaluation 2 (FAME 2) trial evaluated angiographic vs. FFR-guided PCI in 1220 subjects with stable CAD and was halted early due to a significant difference favoring use of FFR for reduction of a combined endpoint, although the FFR was not blinded to patients or their treating clinicians and the outcomes difference was entirely driven by urgent revascularization.¹² In summary, the available basic science data when combined with randomized trial outcomes clearly support a physiologic rather than a purely anatomic evaluation prior to coronary revascularization.

Because of the common occurrence of an anatomic-physiologic disconnect, cardiologists have cautioned to avoid the “oculostenotic reflex”—that is a decision to perform coronary revascularization based upon visual assessment of anatomic stenosis alone without physiologic evaluation either by stress testing or invasive FFR.¹³ Nevertheless, today over 90% of PCI are undertaken without assessment of FFR.¹⁴

The experience to date with coronary CTA has only reproduced and reinforced prior evidence of an anatomic-physiologic disconnect; for example, when compared to invasive FFR in the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study,¹⁵ the specificity of anatomic stenosis by CTA for FFR <0.8 was 42%. Due to the reliably suboptimal specificity of visual coronary stenosis determined either by invasive angiography or by coronary CTA, ongoing work has sought to incorporate physiologic information along with coronary CTA. Such methods have included hybrid imaging (CTA-SPECT), rest coronary CTA with pharmacologic stress CT perfusion imaging, evaluation of coronary contrast gradients, or mathematical modeling such as by FFR_{CT}.¹⁶ However, each of these methods involves trade-offs of either additional time, ionizing radiation exposure, cost (CTA-SPECT, stress CT perfusion) or additional post-processing time that, while semi-automated, often requires considerable manual correction of center lines and artifacts (transluminal gradients).

Thus, the potential to extract physiologic data from an otherwise routine coronary CTA dataset at the lowest financial and time expenditure has universal appeal and offers a possible “holy grail” of combined anatomic with physiologic coronary evaluation from a single exam. This is the goal of FFR_{CT}, which applies mathematical modeling to estimate an invasive FFR from a coronary CTA dataset.

How does FFR_{CT} estimate FFR? The current FFR_{CT} product with United States and European approval for clinical use is marketed by HeartFlow (Redwood City, CA). CTA data are transferred from an

end-user to HeartFlow’s processing center, where a series of fluid dynamic equations are applied via a confidential, proprietary algorithm using a super-computer. FFR_{CT} essentially estimates an FFR based upon the myocardial territory supplied by an arterial segment, the size of the coronary artery, the presence and plaque and degree of anatomic stenosis.¹⁷ In so doing, FFR_{CT} software can estimate a lesion specific invasive FFR (Figure 1). Some authors have further used this technology to perform “virtual stenting”—that is, to estimate how a post-PCI FFR might improve based upon pre-procedural CTA data (Figure 2).¹⁸ Aside from HeartFlow, several other groups are independently developing their own technique for simulating physiology from either rotational ICA or CTA datasets, including some products such as Siemens that may be incorporated into a clinical workstation software rather than sending data to a processing center for analysis as with Heartflow.

In spite of the appeal, however, there are several limitations to FFR_{CT} worth noting. First and most importantly, unlike invasive FFR, FFR_{CT} does not involve physiologic hyperemia with adenosine and thus is not a physiologic test. Rather FFR_{CT} is a mathematical model that estimates physiology. Secondly, as with any modeling estimate, FFR_{CT} may demonstrate accuracy in large groups of patients but its utility at the individual patient level remains uncertain. Third, nearly all of the research into FFR_{CT} has been industry supported or published by researchers with industry support, which introduces bias. Fourth, although FFR_{CT} has demonstrated trends toward accuracy, the utility at the individual patient level is limited by imprecision. Thus, for an FFR_{CT} estimate of invasive FFR of 0.74 and based upon the reported confidence intervals from the initial large accuracy studies of FFR_{CT}, the 95% CI will range from a highly significant 0.60 to a nonflow limiting 0.88.¹⁹ Thus, extremely flow-limiting or non-flow limiting lesions boost the accuracy statistics of FFR_{CT}, but the wide confidence interval hampers the utility of FFR_{CT} for intermediate lesions of individual patients, the real lesions of clinical interest.

The accuracy of FFR_{CT} has been evaluated in three randomized studies (Table 1). The Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW) study¹⁹ evaluated 159 vessels in 103 patients and found that the accuracy, sensitivity, and specificity of CTA improved from 58.5%, 91.4%, 39.6% to 84.3%, 87.9%, 82.2% with FFR_{CT}. However, the 95% CI for limits of agreement was wide at ± 0.24 . Similarly, the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study¹⁵ determined that among 252 patients with stable CAD, the

Figure 1. Example of computed tomography-derived fractional flow reserve analysis added to coronary computed tomography angiography to assess the hemodynamic significance of moderate stenosis. A 52-year-old male with hypertension and dyslipidemia was referred to coronary computed tomography angiography for evaluation of exertional chest pressure. Coronary computed tomography angiography demonstrated a moderate amount of noncalcified plaque associated with positive remodeling (*arrow*), resulting in moderate (50%–69%) stenosis. Computed tomography-derived fractional flow reserve across the lesion was 0.85, suggesting that it is unlikely to be hemodynamically significant. The patient was treated with medical therapies and 7 years later remains asymptomatic and without any cardiac events. Reprinted from.¹⁶

per-patient accuracy sensitivity, and specificity of CTA improved from 64%, 84%, and 42% to 73%, 90%, and 54% which did not meet the pre-specific primary endpoint for significant difference between FFR_{CT} and CTA alone. Lastly, the Diagnostic performance of noninvasive fractional flow reserve derived from coronary CT angiography in suspected coronary artery disease (NXT) trial²⁰ evaluated FFR_{CT} among 254 patients and determined that per-patient CT accuracy, sensitivity, and specificity improved from 81%, 94%, 34% for CTA to 90%, 86%, and 79% for FFR_{CT}. The limits of agreement for FFR_{CT} improved but remained wide at ± 0.16 . In summary, although a slight improvement over CTA in accuracy studies, the results to date for FFR_{CT} accuracy leave continued room for improvement.

There are limited cost studies of FFR_{CT}, but Dr. Hlatky et al²¹ used a modeling approach to apply FFR_{CT} use to data from invasive FFR randomized trials. In this cost analysis, an approach to CAD by ICA and PCI based upon visual stenosis evaluation was more costly than CTA plus FFR_{CT} and ICA as needed (\$10 702 vs. \$7674). The use of CTA plus FFR_{CT} and ICA as needed rather than the currently most commonly employed approach of ICA with visual stenosis assessment in this modeled analysis was concluded to reduce cost by 30% in addition to 12% fewer downstream adverse events. However, the

limitation for such an analysis is the use of theoretical cost modeling rather than real world outcomes and application of outcome reductions due to invasive FFR to noninvasive FFR_{CT}, which may not be identical.

Based upon this background and the need for further clinical and cost-outcomes data, the Prospective Longitudinal Trial of FFR_{CT} (Outcomes and Resource Impacts) or PLATFORM study was undertaken. Although commonly mistaken for a randomized trial, the PLATFORM study design was observational cohort. The initial findings were published in 2015 and evaluated 584 subjects of mean age 61 years with stable symptoms of suspected CAD.²² The patients were divided into sequential cohorts without randomization, such that half of the 380 of the patients who were referred clinically for invasive angiography would undergo FFR_{CT} and half of the 204 of the patients referred clinically for noninvasive testing would undergo FFR_{CT}. Thus, 100 patients underwent standard noninvasive testing and 104 FFR_{CT}. 187 subjects underwent ICA and 193 FFR_{CT}. The primary endpoint was percent with less than 50% stenosis at invasive angiography within 90 days. Secondary endpoints included death, myocardial infarction, and unplanned coronary revascularization. The study demonstrated that those evaluated first by FFR_{CT} had a 12% incidence of

Figure 2. Invasive and noninvasive functional assessment before and after revascularization: (A) Noninvasive fractional flow reserve (FFR) from coronary computed tomographic angiography data (FFR_{CT}) of the left anterior descending (LAD) coronary artery was 0.72. Invasive coronary angiography and FFR confirmed the functionally significant LAD stenosis. (B) FFR_{CT} demonstrated no ischemia in the LAD after virtual stenting, with a computed value of 0.86. Invasive FFR after stent implantation was 0.90. Reprinted from.¹⁸

Table 1. Key studies of computed tomography-derived fractional flow reserve accuracy. Reprinted from¹⁶

	Discover-flow	Defacto	NXT
n, patients	103	252	254
n, vessels	159	408	484
Per patient			
CTA vs. FFR Sens, %	94 (85-99)	84 (77-90)	94 (86-97)
CTA vs. FFR Spec, %	25 (13-39)	42 (34-51)	34 (27-41)
CTA vs. FFR Accuracy, %	61 (51-71)	64 (58-70)	53 (47-57)
FFR _{CT} vs. FFR Sens, %	93 (82-98)	90 (84-95)	86 (77-92)
FFR _{CT} vs. FFR Spec, %	82 (68-91)	54 (46-63)	79 (72-84)
FFR _{CT} vs. FFR Accuracy, %	87 (79-93)	73 (67-78)	81 (76-85)
Per vessel			
CTA vs. FFR Sens, %	91 (81-97)	-	83 (74-89)
CTA vs. FFR Spec, %	40 (30-50)	-	60 (56-65)
CTA vs. FFR Accuracy, %	59 (50-66)	-	65 (61-69)
FFR _{CT} vs. FFR Sens, %	88 (77-95)	80 (73-86)	84 (75-89)
FFR _{CT} vs. FFR Spec, %	82 (73-89)	61 (54-67)	86 (82-89)
FFR _{CT} vs. FFR Accuracy, %	84 (78-90)	-	86 (83-89)

Sens sensitivity; Spec specificity

Cost Models Indexed as Percent of Real-World Cost

Figure 3. Cost as a function of increasing obstructive coronary artery disease (CAD) prevalence. With increasing prevalence of obstructive CAD (x axis), the cost of care after imaging by coronary computed tomographic angiography (cCTA) increases as a result of increased diagnostic tests and medical therapies (y axis). Depicted are the projected (modeled) costs for several large studies, including the first randomized trial of cCTA for acute chest pain in the emergency department,²⁷ Rule Out Myocardial Infarction Using Computer Assisted Tomography I (ROMICAT I),²⁸ Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT),²⁹ and ACRIN-PA³⁰ trials. cCTA findings of prevalence of obstructive CAD have not been reported yet for ROMICAT II. As prevalence of $\geq 50\%$ increases beyond 28% for the baseline scenario, 33% for alternative scenario A, 30% for alternative scenario B, and 28% for alternative scenario C, the triage scenarios using cCTA for initial triage of possible ACS increase cost compared with the actual data under usual care from the ROMICAT I study. Reprinted from.²⁵

no-obstructive CAD in comparison to 73% for those evaluated by ICA (61% absolute difference). On the other hand, those evaluated by FFR_{CT} vs. noninvasive testing had a 13% vs. 6% incidence of no-obstructive CAD ($P = 0.95$). Overall, the study, along with other studies, demonstrated a technical capability for CTA to serve as a gatekeeper to the catheterization lab, although the incremental value of FFR_{CT} was not reported and the CTA data alone likely provided most of the gatekeeper role through its high sensitivity.

A follow-up analysis based upon the PLATFORM data evaluated what the cost-impact of FFR_{CT} might be,

given the lack of real world cost studies with FFR_{CT}.²³ An important aspect of the design of the cost analysis was the decision to use a cost of zero for FFR_{CT} as a base case for the analysis:

“Because the Medicare reimbursement rate for FFRCT has not yet been determined, in the base case analysis we used a cost weight of zero to estimate the cost offset attributable to use of FFRCT—that is, the difference in subsequent costs between patients in the FFRCT strategy and in the conventional strategy.”²³ Thus, the abstract and primary outcomes report a base case of zero cost for FFR_{CT} although the test is not free.

Subsequently, the authors noted that “In sensitivity analyses, we recalculated 1-year costs after applying a series of cost weights for FFR_{CT} that were multiples of the cost weight for CTA.”²³ Given that most of the gatekeeper function will be performed by CTA alone without FFR_{CT}, the widespread use of FFR_{CT} at a cost higher than zero may raise health care costs. Unfortunately, it remains unclear which patients should be selected to undergo FFR_{CT} as part of a cost-effective multi-modality imaging evaluation. Furthermore, there was no difference in obstructive CAD in the noninvasive subgroup of the PLATFORM study vs. FFR_{CT} (13% vs. 6% no-obstructive CAD, $P = 0.95$), and the usual care group trended numerically superior vs. FFR_{CT}.

Thus, median costs were lower in the invasively referred subgroup of the PLATFORM study for FFR_{CT} vs. ICA ($P < 0.001$), but not different for the noninvasively referred patients ($P = 0.82$). For the invasive subgroup, there was a 33% decreased cost (\$8,127 vs. \$12,145, $P < 0.001$) and CTA+FFR_{CT} was associated with a 61% lower incidence of catheterization having no-obstructive CAD. But, there was no difference in quality of life or safety outcomes, and the authors provided no analysis for CTA vs. CTA+FFR_{CT} in order to demonstrate the incremental value of FFR_{CT}. With regard to the noninvasively referred patients, the authors noted, “1-year costs of FFR_{CT}-guided management became significantly higher in sensitivity analyses when the cost weight of FFR_{CT} was set equal to or above the CTA cost weight.”²³ In spite of the important details of these results, the PLATFORM study is frequently summarized as establishing the cost-effectiveness of FFR_{CT} vs. usual care.²⁴ Most patients today are referred initially to noninvasive testing, and FFR_{CT} demonstrated no cost-difference for the base case cost of zero (FFR_{CT} for free).

Much of the gatekeeper role of CTA may be driven by the sensitivity of CTA alone without the need for added cost of FFR_{CT}. Of course, the cost of CTA and subsequent FFR_{CT} will vary according to the disease prevalence, or pretest probability as has been demonstrated comparing CTA alone to usual care emergency room evaluation from ROMICAT I study data (Figure 3).²⁵ Because only a minority (29% in a pooled analysis of 18 studies)⁴ of patients referred to CTA in most studies have obstructive CAD, use of CTA alone has been proposed based upon observational datasets and evaluated as a gatekeeper to ICA in the Computed Tomographic Angiography for Selective Cardiac Catheterization (CONSERVE) trial. Results were recently presented as a conference abstract and are in press.⁶ In that study, 1503 patients referred for nonemergent ICA were randomized to CTA vs. ICA. The trial demonstrated that CTA could reduce the need for

invasive angiography by 78% (22% ICA after CTA vs. 100% ICA first). Coronary revascularization was reduced in the CTA first subgroup by 41% (10% vs. 17%), and cost reduced by 50% (mean per patient \$3338 vs. \$6740, $P < 0.001$). Thus, the gatekeeper role proposed using FFR_{CT} as in PLATFORM could likely be almost entirely performed safely and more cost-effectively by CTA alone. However, it is important to note conflicting observational data from a large Medicare registry among older patients with a higher prevalence of CAD, in which the use of CTA compared with SPECT was associated with 2× increase in ICA, 2.5× increase in PCI, 3× increase in CABG, and increased healthcare cost.²⁶ Thus, the cost-effectiveness data for CTA and FFR_{CT} remain limited and conflicting to date.

In conclusion, anatomy alone cannot provide the only basis to justify coronary revascularization. Physiologic evaluation of coronary function remains crucial to understanding ischemia and prognosis. FFR_{CT} estimates physiology but is not a physiologic test. Although the PLATFORM study demonstrated that FFR_{CT} is associated with reduced cost among patients referred directly to invasive angiography, most CAD patients are referred initially to noninvasive testing. Furthermore, other studies suggest that CTA alone or other noninvasive testing options provide at least some gatekeeper role prior to the catheterization lab. As the authors of the PLATFORM cost analysis noted, “Further testing in larger randomized settings in both groups is warranted to fully understand the impact of FFR_{CT}-guided care in patients being evaluated for suspected CAD.”²³ Although clinicians should seek to improve upon current practice, whereby a large percentage of patients referred to invasive angiography have no-obstructive CAD, the outcomes or cost benefit of FFR_{CT} beyond CTA alone or noninvasive testing has not been demonstrated by the PLATFORM or any study. Further evaluation of the optimal workflow and cost-effectiveness of FFR_{CT} is warranted.

Disclosures

The opinions and assertions contained herein are the author's alone and do not reflect the views of the Walter Reed National Military Medical Center, the US Army, or the Department of Defense.

References

1. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, et al. Anatomic versus physiologic assessment of coronary artery disease. *J Am Coll Cardiol*. 2013;62:1639–53.

2. Otero HJ, Steigner ML, Rybicki FJ. The “post-64” era of coronary CT angiography: understanding new technology from physical principles. *Radiol Clin North Am.* 2009;47:79–90.
3. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol.* 2008;52:1724–32.
4. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;57:1237–47.
5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. *New Engl J Med.* 2010;362:886–95.
6. Lee S-E, Lin FY, Lu Y, Chang H-J, Min JK. Rationale and design of the conserve trial: coronary computed tomographic angiography for selective cardiac catheterization: relation to cardiovascular outcomes, cost effectiveness and quality of life. *Am Heart J.* 2016;186:48–55.
7. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2014;130:1749–67.
8. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. *Am J Cardiol.* 1974;34:48–55.
9. Bech GJW, De Bruyne B, Pijls NHJ, de Muinck ED, Hoorntje JCA, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis. A Randomized Trial. 2001;103:2928–34.
10. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. 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;36:3182–8.
11. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.
12. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med.* 2014;371:1208–17.
13. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. *Circulation.* 1995;92:2333–42.
14. Dattilo PB, Prasad A, Honeycutt E, Wang TY, Messenger JC. Contemporary patterns of fractional flow reserve and intravascular ultrasound use among patients undergoing percutaneous coronary intervention in the United States: insights from the National Cardiovascular Data Registry. *J Am Coll Cardiol.* 2012;60:2337–9.
15. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic ct angiography. *JAMA.* 2012;308:1237–45.
16. Hulten E, Blankstein R, Di Carli MF. The value of noninvasive computed tomography derived fractional flow reserve in our current approach to the evaluation of coronary artery stenosis. *Curr Opin Cardiol.* 2016;31:970–6.
17. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow ReserveScientific Basis. *J Am Coll Cardiol.* 2013;61:2233–41.
18. Kim K-H, Doh J-H, Koo B-K, Min JK, Erglis A, Yang H-M, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC: Cardiovasc Interv.* 2014;7:72–8.
19. Koo B-K, Erglis A, Doh J-H, Daniels DV, Jegere S, Kim H-S, 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 (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) study. *J Am Coll Cardiol.* 2011;58:1989–97.
20. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol.* 2014;63:1145–55.
21. Hlatky MA, Saxena A, Koo BK, Erglis A, Zarins CK, Min JK. Projected costs and consequences of computed tomography-determined fractional flow reserve. *Clin Cardiol.* 2013;36:743–8.
22. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA et al. 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 FFRCT: outcome and resource impacts study. *Eur Heart J* 2015; 36(47):3359–67.
23. Hlatky MA, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. *J Am Coll Cardiol.* 2015;66:2315–23.
24. Lim GB. Imaging: cost-effectiveness of FFRCT-guided care. *Nat Rev Cardiol.* 2016;13:506.
25. Hulten E, Goehler A, Bittencourt MS, Bamberg F, Schlett CL, Truong QA et al. Cost and resource utilization associated with use of computed tomography to evaluate chest pain in the emergency department the rule out myocardial infarction using computer assisted tomography (ROMICAT) study. *Circ: Cardiovasc Qual Outcomes* 2013;6:514–24.
26. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *Jama.* 2011;306:2128–36.
27. Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol.* 2007;49:863–71.
28. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol.* 2009;53:1642–50.
29. Goldstein JA, Chinnaiyan KM, Abidov A, Achenbach S, Berman DS, Hayes SW, et al. The CT-STAT (coronary computed tomographic angiography for systematic triage of acute chest pain patients to treatment) trial. *J Am Coll Cardiol.* 2011;58:1414–22.
30. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entriokin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. *N Engl J Med.* 2012;366:1393–403.