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ORIGINAL INVESTIGATIONS

1-Year Outcomes of FFR_{CT}-Guided Care in Patients With Suspected Coronary Disease

The PLATFORM Study

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ABSTRACT

BACKGROUND Coronary computed tomographic angiography (CTA) plus estimation of fractional flow reserve using CTA (FFR_{CT}) safely and effectively guides initial care over 90 days in patients with stable chest pain. Longer-term outcomes are unknown.

OBJECTIVES The study sought to determine the 1-year clinical, economic, and quality-of-life (QOL) outcomes of using FFR_{CT} instead of usual care.

METHODS Consecutive patients with stable, new onset chest pain were managed by either usual testing (n = 287) or CTA (n = 297) with selective FFR_{CT} (submitted in 201, analyzed in 177); 581 of 584 (99.5%) completed 1-year follow-up. Endpoints were adjudicated major adverse cardiac events (MACE) (death, myocardial infarction, unplanned revascularization), total medical costs, and QOL.

RESULTS Patients averaged 61 years of age with a mean 49% pre-test probability of coronary artery disease. At 1 year, MACE events were infrequent, with 2 in each arm of the planned invasive group and 1 in the planned noninvasive cohort (usual care strategy). In the planned invasive stratum, mean costs were 33% lower with CTA and selective FFR_{CT} ($8,127 vs. $12,145 usual care; $p < 0.0001$); in the planned noninvasive stratum, mean costs did not differ when using an FFR_{CT} cost weight of zero ($3,049 FFR_{CT} vs. $2,579; $p = 0.82$), but were higher when using an FFR_{CT} cost weight equal to CTA. QOL scores improved overall at 1 year ($p < 0.001$), with similar improvements in both groups, apart from the 5-item EuroQOL scale scores in the noninvasive stratum (mean change of 0.12 for FFR_{CT} vs. 0.07 for usual care; $p = 0.02$).

CONCLUSIONS In patients with stable chest pain and planned invasive coronary angiography, care guided by CTA and selective FFR_{CT} was associated with equivalent clinical outcomes and QOL, and lower costs, compared with usual care over 1-year follow-up. (The PLATFORM Study: Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts [PLATFORM]; NCT01943903) (J Am Coll Cardiol 2016;68:435–45) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomographic angiography

EQ-5D = 5-item EuroQOL scale

FFR_{CT} = fractional flow reserve using computed tomography

ICA = invasive coronary angiography

MACE = major adverse cardiac events

PCI = percutaneous coronary intervention

QOL = quality of life

SAQ = Seattle Angina Questionnaire

VAS = visual analog scale

Evaluation of chest pain is a common clinical problem, yet disagreement remains regarding optimal evaluation strategy, in part because of the many available testing options. Furthermore, most patients referred to elective invasive coronary angiography (ICA) are not found to have obstructive coronary artery disease (CAD) (1–4). The landmark PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial suggested that an evaluation strategy based on coronary computed tomographic angiography (CTA) was safe and clinically effective, but increased the rate of subsequent cardiac catheterization by almost 50% compared with functional testing (1). Moreover, despite a doubling of the rate of coronary revascularization after CTA, clinical outcomes in the PROMISE trial did not differ. In this context, it is notable that most interventions were performed without determining the functional significance of coronary stenoses, at variance with current practice guidelines (5).

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A new noninvasive method uses routinely acquired CTA data to provide both anatomic and functional data about coronary stenosis, accurately estimating fractional flow reserve using computed tomography (FFR_{CT}), on the basis of computational fluid dynamics and simulated maximal coronary hyperemia (6–9). In the PLATFORM (Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource Impacts) study, we prospectively applied this method and demonstrated that, compared with usual care, FFR_{CT} led to cancellation of 60% of planned ICA, a markedly lower rate of finding no obstructive CAD at ICA (from 73% to 12%) (10), and significantly lower 90-day costs of care in patients with a planned ICA (11). The present study tests the durability of these findings by comparing 1-year clinical, safety, economic, and quality-of-life (QOL) outcomes after FFR_{CT}-guided management versus usual care. We hypothesized that compared to usual care, an FFR_{CT}-guided strategy in patients with suspected CAD would continue to show low rates of major adverse cardiac events (MACE), similar QOL, and substantially lower medical resource utilization and cost.

METHODS

PLATFORM was a prospective, consecutive cohort study whose design (12) and 90-day outcomes have been previously reported (10,11). Briefly, 11 European sites enrolled symptomatic outpatients ≥18 years of age without known CAD who had an intermediate likelihood of obstructive CAD (20% to 80%) and whose physician had planned nonemergent cardiovascular testing to evaluate suspected CAD. Relevant institutional review boards approved the study protocol, and all patients provided written informed consent.

The PLATFORM study was funded by HeartFlow (Redwood City, California). DCRI independently performed quantitative coronary angiography, adjudicated clinical events, and performed the analysis of the primary and secondary endpoint determinations. There were no data confidentiality agreements. An Executive Committee oversaw trial design and study conduct, final data review, and presentation and publication of results, independently making the decision to publish. The investigators independently drafted the manuscript and take full responsibility for the accuracy and completeness of data analyses. Dr. Douglas received grants from HeartFlow during the conduct of the study; and has previously received other support from GE Medical Systems outside the submitted work. Dr. De Bruyne has received grants from Abbott, St. Jude Medical, and Medtronic; and other support from St. Jude Medical, Boston Scientific, Opsens, Omega Pharma, Siemens, Edwards, GE, Sanofi, HeartFlow, and Bayer outside the submitted work. Dr. Patel received grants from HeartFlow during the conduct of the study; has previously received grants from Janssen, Johnson & Johnson, AstraZeneca, Genzyme, NHLBI, and AHRQ; and personal fees from AstraZeneca, Bayer, and Otsuka outside the submitted work. Dr. Norgaard has received unrestricted institutional research grants from Siemens, Edwards Lifesciences, and HeartFlow. Dr. Byrne received grants from HeartFlow during the conduct of the study; has previously received grants from Boston Scientific; and lecture fees from B. Braun, Biotronik, and Boston Scientific outside the submitted work. Dr. Curzen has received grants from Boston Scientific and Medtronic; and grants and personal fees from HeartFlow, Haemonectics, and St. Jude Medical outside the submitted work. Dr. Gutberlet has received speaker honoraria from Siemens, Philips, Bracco, and Bayer. Dr. Feuchtner received grants from HeartFlow during the conduct of the study; and has previously received personal fees from St. Jude Medical and Boston Scientific outside the submitted work. Dr. Andreini has received grants and personal fees from GE Healthcare outside the submitted work. Dr. Jensen has received speaker honoraria from Bracco Imaging. Dr. Hadamitzky has received an unrestricted institutional research grant from Siemens Healthcare outside the submitted work. Dr. Chiswell received support from HeartFlow during the conduct of the study. Mr. Wilk is an employee of HeartFlow. Dr. Wang received personal fees and other support from HeartFlow during the conduct of the study. Dr. Rogers is an employee of and owns equity in HeartFlow; and received personal fees and other support from HeartFlow during the conduct of the study and previously outside the submitted work. Dr. Hlatky received grants from HeartFlow during the conduct of the study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Ronald Karlsberg, MD, served as Guest Editor for this paper.

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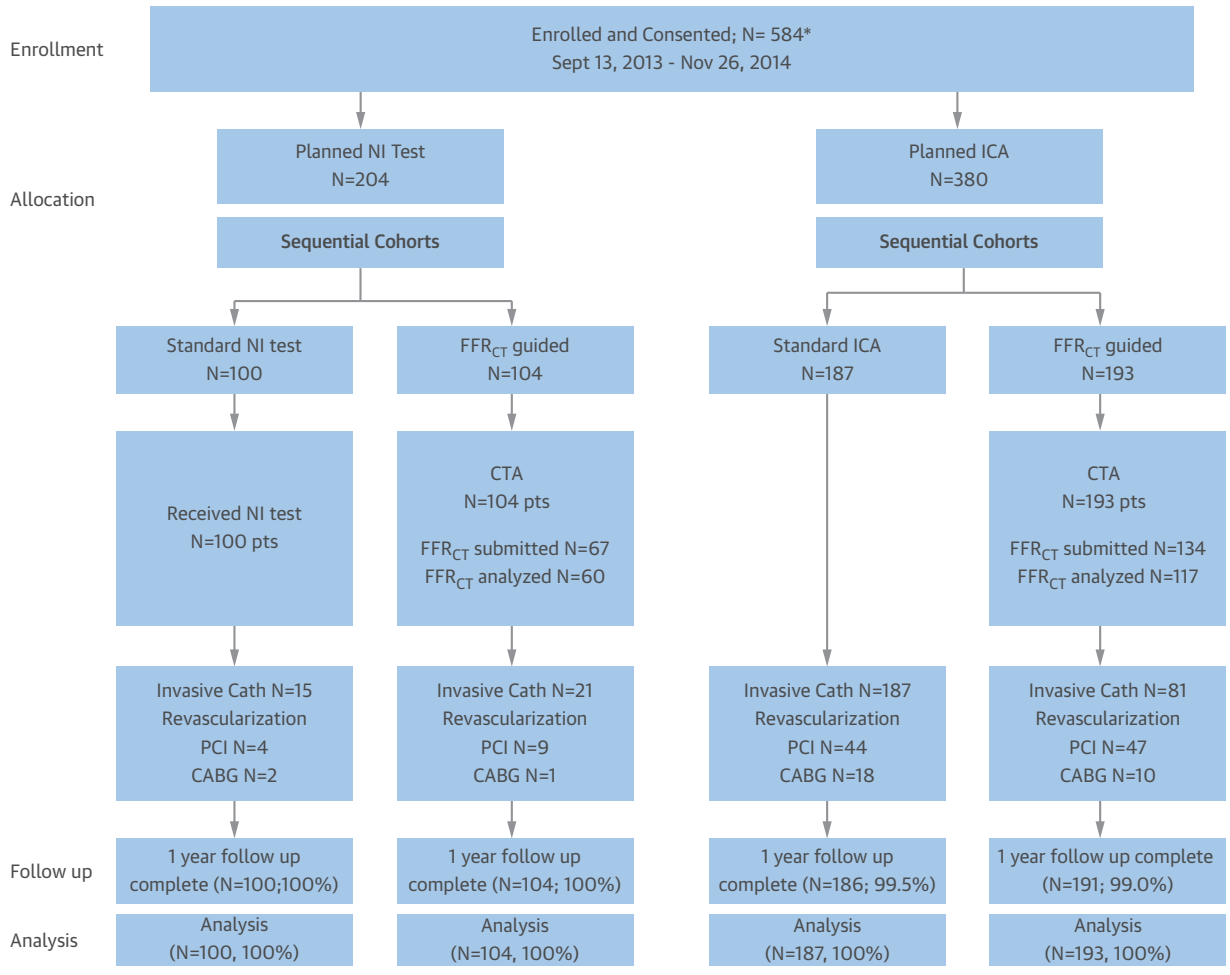
FIGURE 1 Study Flow



A total of 584 patients were allocated to noninvasive (NI) and invasive coronary angiography (ICA) cohorts. *One subject withdrew consent for use of any of his/her data. In keeping with relevant national law, this subject is not included in any data listing or analysis. CABG = coronary artery bypass grafting; CTA = computed tomography angiography; FFR_{CT} = fractional flow reserve using computed tomography; PCI = percutaneous coronary intervention.

Subjects in the first of 2 prospective cohorts received usual care testing as planned by their local clinicians, whether noninvasive or invasive (Figure 1). In the second, subsequently enrolled cohort, patients received CTA instead of planned noninvasive or invasive testing, followed by centrally performed FFR_{CT} analyses if the CTA revealed ≥30% stenosis or if the patient was referred to ICA. Noninvasive and invasive diagnostic testing was performed and interpreted locally (10,12). Independent core laboratories performed quantitative coronary angiography and FFR_{CT} measurements (7–9). Data provided to the clinical site included the lowest FFR_{CT} numeric value in each coronary distribution and color-scale representations of the coronary tree showing FFR_{CT} values in all vessels >1.8 mm in diameter (Online Figure 1). Local physicians made all subsequent clinical management decisions following standard practice including whether to alter care on the basis of FFR_{CT} results. Optimal medical therapy was encouraged in all groups.

CLINICAL, ECONOMIC, AND QOL ENDPOINTS. The 1-year clinical endpoints were: 1) a composite of MACE (all-cause mortality, myocardial infarction [MI], and unplanned hospitalization for chest pain leading to urgent revascularization); and 2) MACE plus vascular events within 14 days of procedures. An independent clinical events committee adjudicated all MACE events in a blinded fashion using standard, prospectively determined definitions (13). Cumulative radiation exposure from all cardiovascular tests and invasive procedures was determined over the 1 year after enrollment, as previously described (10).

Use of key medical resources was tabulated from enrollment through 1 year, including CTA, noninvasive stress tests, invasive tests, coronary revascularization procedures, selected cardiac medications (aspirin, statins, antiplatelet medications), and clinical events. QOL was assessed at baseline, 90 days, and 1 year using the 7-item Seattle Angina Questionnaire (SAQ) (14), the 5-item EuroQOL scale (EQ-5D) with index calculation weighted for the United States (15), and the EuroQOL visual analog scale (VAS) (with 0 = worst and 100 = best health).

Cumulative medical costs over 1 year were calculated on a per-patient basis by multiplying a standardized cost weight for each medical resource by the number of times that resource was used (11). The 2015 Medicare reimbursement rates (national average of technical and professional fees) and online pharmacy costs for drugs were used as cost weights (Online Table 1). We did not discount costs over 1-year follow-up. Because the Medicare reimbursement rate for FFR_{CT} 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 FFR_{CT}—that is, the difference in subsequent costs between patients in the FFR_{CT} strategy and in the conventional strategy. 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. We calculated "downstream costs" (i.e., those induced by the initial diagnostic test) by setting to zero the costs of the intended initial test (invasive stratum: ICA in the usual care arm or initial CTA in the FFR_{CT} arm; noninvasive stratum: initial CTA or stress test).

STATISTICAL ANALYSIS. Endpoints were compared between the FFR_{CT}-guided and usual care management strategies separately in the planned noninvasive testing stratum and in the planned invasive testing stratum. Results were also compared in propensity-matched subpopulations created independently for the planned invasive and noninvasive groups using age, sex, diabetes, smoking status, and type of angina as predictors, applying a greedy matching algorithm (10,11).

Baseline characteristics were summarized and compared across usual care and FFR_{CT}-guided care cohorts. Continuous variables were described as mean ± SD or median (interquartile range), and compared using the nonparametric Wilcoxon rank sum test. Categorical variables were summarized as counts (percentages) and compared using the Pearson chi-square test or Fisher exact test if cell frequencies were insufficient.

For economic analyses, unadjusted costs were compared in each stratum between strategies using the nonparametric Wilcoxon rank sum test on all patients and in the propensity-matched cohorts. A 95% confidence interval (CI) for the difference in mean per-patient cost between usual care and FFR_{CT}-guided care cohorts was determined using empirical bootstrap resampling with 100,000 replicates. Additional information regarding the statistical analysis is in the Online Appendix.

All statistical assessments were independently performed by statisticians at the Duke Clinical Research Institute, and all patients were analyzed as allocated. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All preplanned comparisons of the secondary endpoints of this study are reported here, with no adjustment of the type 1 error rate made for multiple comparisons.

RESULTS

The 584 patients enrolled and consented in the PLATFORM study were followed for 12 months, including 204 in the planned noninvasive testing stratum (usual care noninvasive testing: n = 100; CTA followed by selective FFR_{CT}: n = 104), and 380 in the planned invasive testing stratum (usual care [ICA]: n = 187; CTA followed by selective FFR_{CT}: n = 193) (10). Patients averaged 60.9 years of age, and 40% were women. Other characteristics included diabetes (14%), hypertension (54%), history of smoking (54%), and dyslipidemia (35%) (Online Table 2). The mean pre-test probability of obstructive CAD was 49 ± 17%. Clinical characteristics were generally similar between the usual care and FFR_{CT}-guided care cohorts and within the planned noninvasive and invasive test groups. One-year follow-up was obtained in 581 participants (99.5%), by clinic visit in 97.4%, and chart review in 2.1% (**Figure 1**). FFR_{CT} data were measureable in 88% of studies; motion and misalignment accounted for 75% of failures, heavy calcification 13%, and missing data 13%. Comparison of FFR_{CT} and invasively measured FFR in the 50 vessels in 29 patients for which both were available yielded an overall accuracy of 84.0% (95% confidence interval [CI]: 70.9% to 92.8%), similar to that reported in the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial (9) (Online Table 3).

PLANNED INVASIVE COHORTS. In the planned invasive testing stratum receiving FFR_{CT}-guided care, CTA was performed in 100% of patients, submitted for FFR_{CT} in 134 cases (69%), and analyzed in 117 (60%). Among the 60% of patients who had a planned ICA cancelled, investigators reported that FFR_{CT} data were considered in the treatment decision in 79%,

including 55% of decisions based solely on FFR_{CT}. Revascularization was performed in 28%, including coronary artery bypass grafting (CABG) in 5%. In comparison, in the usual care group, 100% had ICA as planned, resulting in a similar rate of 90-day revascularization (32%) and CABG (9%). The primary endpoint of catheterization without obstructive CAD at 90 days occurred in 12% of FFR_{CT}-guided care and 73% of usual care patients, yielding a risk difference of 61% (95% CI: 53.0% to 68.7%; $p < 0.0001$) (10). Results were similar in the roughly one-half of patients in each strategy who had prior noninvasive functional testing before study enrollment: among those managed using FFR_{CT}, the rates of no obstructive disease were 10% and 15% with and without prior functional testing, respectively; among those in the usual care group, the rates were 78% and 70%, respectively, including 79% for treadmill testing, 67% for stress echocardiography, and 84% for nuclear stress testing. Results were similar when analysis was limited to patients with typical angina or atypical angina (data not shown). Of note, at the time of revascularization, data regarding the functional significance of coronary stenosis were available in 95% of the FFR_{CT}-guided group (56 of 59 revascularizations) versus 49% (32 of 65) of the usual care group.

Clinical outcomes and safety. During 1-year follow-up, 2 MACE events occurred in the FFR_{CT}-guided care group, both within 90 days (1 periprocedural MI, and 1 hospitalization for urgent revascularization while awaiting CABG) (Table 1). Importantly, there were no events during 1 year of follow-up in the 117 patients whose planned ICA was cancelled on the basis of the CT/FFR_{CT} findings, only 4 of whom underwent ICA during 1-year follow-up. Of these, 3 had no hemodynamically significant CAD at ICA and did not undergo revascularization, and 1 had percutaneous coronary intervention (PCI) for a circumflex lesion that had progressed to total occlusion over 9 months from an initial 50% to 70% lesion on CTA that had an FFR_{CT} of 0.88. Of those who did have an initial ICA, 6 required a repeat ICA over the next 9 months, including 2 repeat PCIs. In contrast, in the usual care group, there were 10 repeat ICAs and 3 new revascularizations (2 PCI, 1 CABG). Vascular complications were infrequent (5 total).

In the usual care group, 2 MACE events (1 unexplained death and 1 nonfatal MI during cardiac surgery) and 2 vascular complications occurred over 1 year. The risk difference between the groups was nearly zero; however, there was insufficient evidence to conclude noninferiority due to low power (Table 1). The relative rates of MACE and vascular

TABLE 1 1-Year Clinical Outcomes

	Planned Noninvasive Test (n = 204)			Planned Invasive Test (n = 380)		
	Usual Care Strategy (n = 100)	FFR_{CT}-Guided Strategy (n = 104)	p Value	Usual Care Strategy (n = 187)	FFR_{CT}-Guided Strategy (n = 193)	p Value
Invasive catheterization without obstructive CAD*						
Patients	6 (6.0)	13 (12.5)	0.95	137 (73.3)	24 (12.4)	<0.001
Risk difference, %	-6.5 (-14.4 to 1.4)†			60.8 (53.0 to 68.7)†		
MACE						
Patients	1	0		2	2	
Percentage	1.00 (0.03–5.45)†	0.00 (0.00–3.48)†		1.07 (0.13–3.81)†	1.04 (0.13–3.69)†	
Risk difference, %	-1.00 (-12.67 to 10.68)‡			-0.03 (-8.55 to 8.47)‡		
MACE components						
All-cause death	0 (0.0)	0 (0.0)		1 (0.5)	0 (0.0)	
Nonfatal MI	1 (1.0)	0 (0.0)		1 (0.5)	1 (0.5)	
Hospitalization with urgent revascularization	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.5)	
MACE or vascular complications						
Patients	1	1		4	7	
Percentage	1.00 (0.03–5.45)†	0.96 (0.02–5.24)†		2.14 (0.59–5.39)†	3.63 (1.47–7.33)†	
Risk difference, %	-0.04 (-11.73 to 11.62)‡			1.49 (-7.05 to 9.95)‡		
Cumulative radiation exposure			<0.001			0.21
Mean ± SD, mSv	6.42 ± 7.47	9.55 ± 10.56		10.36 ± 6.69	10.72 ± 9.62	
Median (IQR), mSv	2.57 (0.00–10.58)	4.91 (2.49–12.37)		7.00 (7.00–15.00)	7.94 (2.67–17.32)	

Values are n (%) or n, unless otherwise indicated. *By core lab quantitative coronary angiography (at 90 days). †95% confidence interval. ‡90% confidence interval.

CAD = coronary artery disease; FFR_{CT} = fractional flow reserve using computed tomography; IQR = interquartile range; MACE = major adverse cardiac events; MI = myocardial infarction.

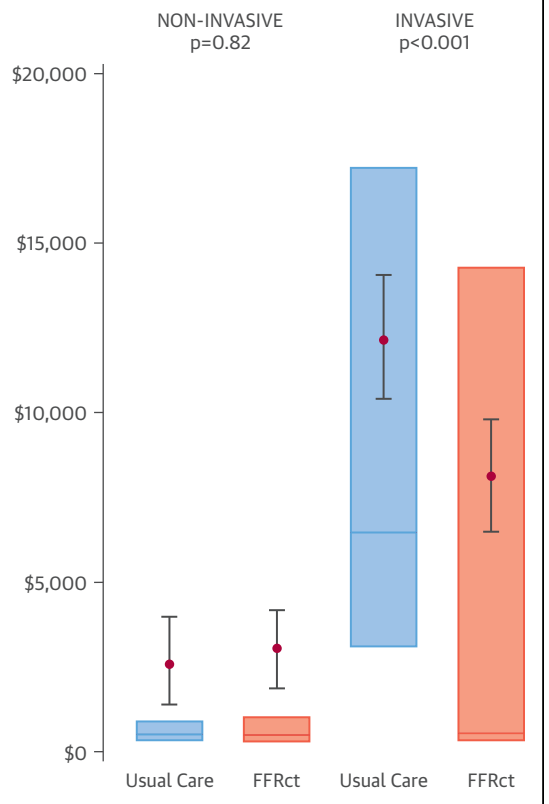
TABLE 2 Resource Use Over 12 Months After Enrollment

	Planned Noninvasive Test (n = 204)		Planned Invasive Test (n = 380)	
	Usual Care Strategy (n = 100)	FFR_{CT}-Guided Strategy (n = 104)	Usual Care Strategy (n = 187)	FFR_{CT}-Guided Strategy (n = 193)
Noninvasive tests				
Stress electrocardiography	11	9	17	19
Stress echocardiography	29	2	5	6
Stress nuclear	17	8	6	3
Magnetic resonance imaging	3	3	6	3
Coronary CT angiography	62	104	1	194
FFR_{CT}	0	60	0	117
Invasive procedures				
Diagnostic ICA	11	13	159	44
ICA with PCI	5	9	44	55
FFR_{INV}	0	5	12	29
Intravascular ultrasound	3	2	8	5
Optical coherence tomography	0	0	3	1
Coronary revascularization				
PCI	5	9	49	55
Bypass surgery	2	1	18	10
Total hospital days	43	57	514	283
Clinic visits	56	48	162	111

Values are n.

CT = computed tomography; FFR_{CT} = fractional flow reserve using computed tomography; FFR_{INV} = fractional flow reserve determined by invasive coronary angiography; ICA = invasive coronary angiography; PCI = percutaneous coronary intervention.

FIGURE 2 1-Year Costs by Stratum and Evaluation Strategy



Median costs (indicated by the **line within the boxes**) were lower with fractional flow reserve using computed tomography (FFR_{CT}) versus usual care using an invasive strategy ($p < 0.001$) but similar with a noninvasive strategy ($p = 0.82$). The **top of each box** indicates the 75th percentile and the **bottom** the 25th percentile. Mean costs are indicated by the **point**, with **error bars** indicating the ±95% confidence interval.

complications were unchanged in both groups in the propensity-matched cohort. Changes in medication use from enrollment to 1 year were similar in the 2 arms for aspirin ($p = 0.56$) and statins ($p = 0.76$) but were greater in the FFR_{CT}-guided care than in usual care for $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, and ticagrelor; $p = 0.006$). Cumulative 1-year radiation exposure in patients with an intended invasive evaluation was similar in the 2 cohorts (usual care mean: 10.4 ± 6.7 mSv vs. FFR_{CT} cohort mean: 10.7 ± 9.6 mSv; $p = 0.21$).

Resource utilization. The mean 1-year per-patient cost of medical care was significantly lower in the FFR_{CT}-guided strategy than in the usual care strategy ($8,127 vs. $12,145; $p < 0.0001$ [95% CI on the $4,018 difference: $1,590 to $6,577]). See **Table 2** for resource use tabulation. Mean per-patient "downstream costs," excluding the costs of the initial tests, were $7,831 for the FFR_{CT} group and $9,864 in the usual care group ($p < 0.0001$). More patients in the FFR_{CT}-guided group had low costs (median = $546) than in the usual care group (median = $6,472) (**Figure 2**). The pattern of mean 12-month costs was similar whether patients had prior noninvasive testing ($8,534 vs. $11,228; $p < 0.001$) or did not ($7,680 vs. $13,033, $p < 0.001$). The cost difference at 12 months was slightly, but not significantly, greater among patients with atypical angina (interaction $p = 0.16$) (Online Table 4).

The difference in 12-month costs was similar in the propensity-matched cohort. The mean per-patient cost of the FFR_{CT} strategy was 33% lower in the entire population and was also 33% lower in the 148 propensity score-matched patient pairs ($7,837 vs. $11,741; $p < 0.001$). In sensitivity analyses, we assigned a series of cost weights to FFR_{CT} that were multiples of the cost weight for CTA. When the cost weight for FFR_{CT} was set to 3 times the cost weight of CTA, the FFR_{CT}-guided strategy had significantly lower costs in the invasive stratum ($8,812 vs. $12,145; $p < 0.001$). The FFR_{CT}-guided strategy still had significantly lower costs at 1 year even when the cost weight for FFR_{CT} was set to 15 times the cost weight of CTA ($10,861 vs. $12,145; $p = 0.014$).

QOL. Functional status and QOL improved from baseline to 12 months of follow-up in the planned invasive group, including mean increments of 21 units on the SAQ ($p < 0.001$), 0.07 units on the EQ-5D ($p < 0.001$), and 4.1 units on the VAS ($p < 0.001$). However, the improvements were similar in the patients in the FFR_{CT} strategy and usual care groups (**Figure 3**). Findings were unchanged in the propensity score-matched population (data not shown).

PLANNED NONINVASIVE COHORTS. In the planned noninvasive testing stratum managed by FFR_{CT}-guided care, CTA was performed in 100%, submitted for FFR_{CT} in 67 patients (64%), and analyzed in 60 (58%). Catheterization was performed in 19 patients and revascularization in 10, compared to 12 and 5, respectively, in the usual care group. Catheterization without obstructive CAD at 90 days was found in 12.5% of FFR_{CT}-guided care and 6.0% of usual care patients, a risk difference of -6.5 (95% CI: -14.4 to 1.4; $p = 0.95$) (**Table 1**). Results were similar when analyzed only in those patients with typical or atypical angina (data not shown).

Clinical outcomes and safety. One MACE event (a nonfatal MI) occurred in the usual care planned noninvasive group compared to none in the FFR_{CT}-guided group over 12-month follow-up (**Table 1**), and only 1 patient had an ICA that was not performed as part of initial evaluation, due to myocarditis. In the FFR_{CT}-guided group, 1 additional patient required an ICA after 90 days and 1 required repeat ICA; there were no additional revascularizations. In the usual care group, 3 additional patients required ICA and 1 PCI. Vascular complications were infrequent in both groups. The risk difference for MACE or vascular complications between groups was small; however, there was not significant evidence to determine noninferiority due to low power. Changes in medication use from enrollment to 1 year were similar in the 2 arms for aspirin, statins, and $P2Y_{12}$ inhibitors (all $p > 0.10$). Cumulative 12-month radiation exposure in patients with an FFR_{CT}-guided evaluation was higher than in the usual care cohort (mean: 9.6 ± 10.6 mSv vs. 6.4 ± 7.6 mSv; $p < 0.001$) as many patients received a noninvasive test that did not require the use of radiation.

Resource utilization. Mean 1-year per-patient costs of medical care were similar in the FFR_{CT}-guided ($3,049) and usual care strategy groups ($2,579; $p = 0.82$ [95% CI on the $471 difference: -$2,129 to +$1,423]). Costs were relatively low overall in the noninvasive stratum, with median costs of $484 in the FFR_{CT} group and $507 in the usual care group; the small minority of patients who had invasive procedures drove higher mean costs in both groups (**Figure 1**). Findings were essentially unchanged in the propensity score-matched population.

Mean per-patient "downstream costs," excluding costs of the initial tests, were similar: $2,755 for the FFR_{CT} group and $2,260 in the usual care group ($p = 0.47$). In sensitivity analyses, a cost weight for FFR_{CT} equal to that of CTA led to higher mean per-patient costs in the FFR_{CT} group compared with the usual care group ($3,223 vs. $2,579; $p < 0.01$), as did a cost weight of 3 times that of CTA ($3,570 vs. $2,579; $p < 0.001$).

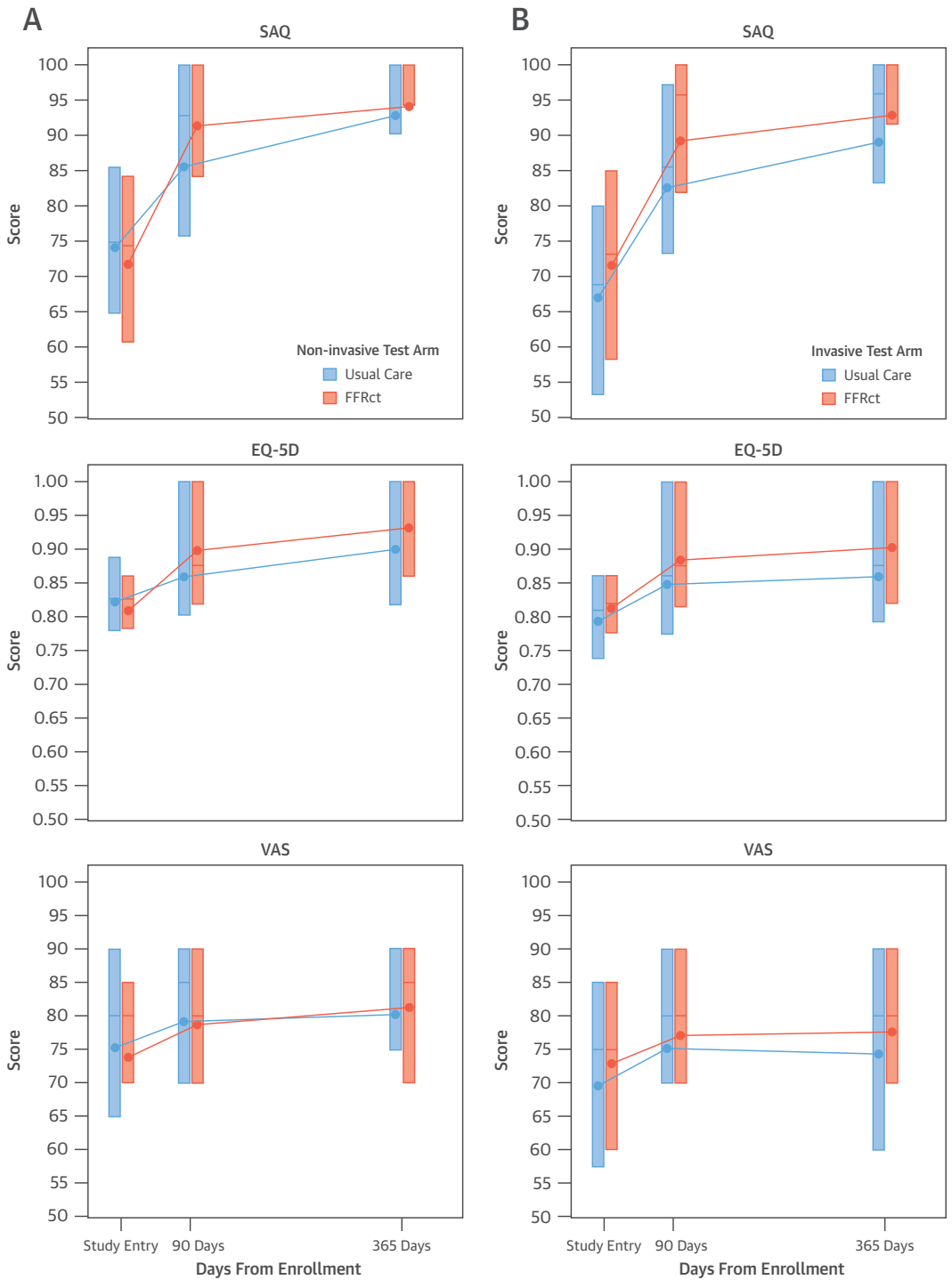
QOL. Functional status and QOL improved from baseline to 12 months of follow-up in the planned noninvasive group ($p < 0.001$ for all measures), with greater improvements in the FFR_{CT} strategy group on the EQ-5D (mean change: 0.12 vs. 0.07; $p = 0.02$) with similar improvements on the SAQ and VAS scales (**Figure 3**). Findings were essentially unchanged in the propensity score-matched population (data not shown).

DISCUSSION

In this multicenter, prospective study of stable, symptomatic patients with suspected CAD, an evaluation strategy based on use of CTA selectively augmented by FFR_{CT} was associated with a high rate of cancellation of planned invasive catheterization (**Central Illustration**); a significantly lower rate of ICA showing no obstructive CAD; improved information available to guide revascularization; and equivalent clinical outcomes, QOL, and radiation exposure as compared with a usual care strategy of ICA. Furthermore, the FFR_{CT}-guided strategy was associated with significantly lower resource utilization and cost in patients with planned invasive evaluation. These findings suggest that the combination of anatomic and functional data provided by the FFR_{CT}-guided testing strategy may safely reduce use of invasive catheterization and costs of care over 1 year in selected patients undergoing evaluation for suspected CAD.

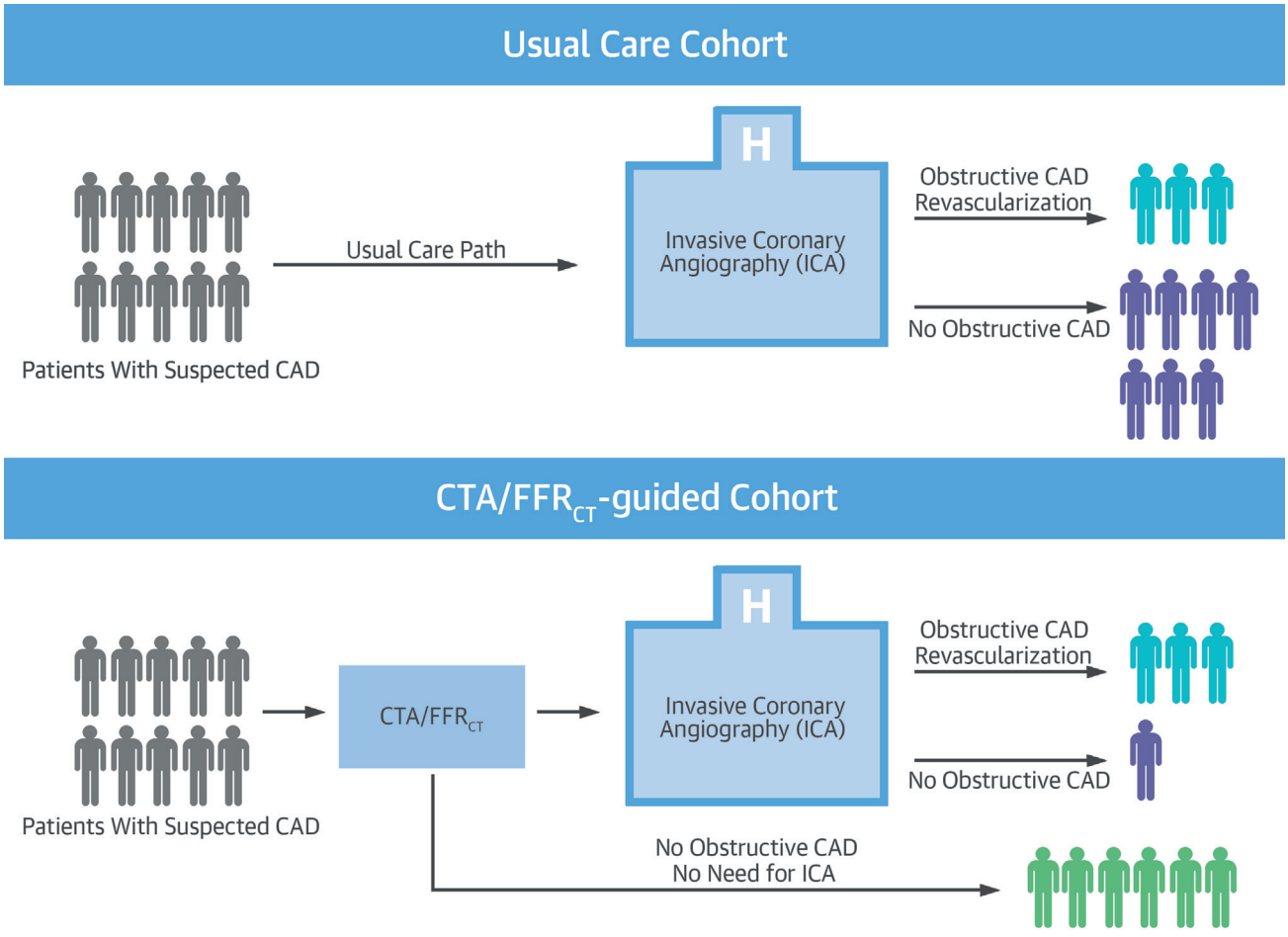
Few adverse clinical events occurred over the year of follow-up in the entire PLATFORM cohort. Indeed, the overall 0.9% MACE rate at 12 months was lower than the 1.7% MACE rate at 12 months in the PROMISE trial using similar MACE components (1). These results suggest that the safety of an FFR_{CT}-guided approach observed at 90 days (10) is durable over the longer term. These favorable clinical outcomes are further underscored by the absence of any late clinical events and only 1 late revascularization following an FFR_{CT}-guided decision to cancel a

FIGURE 3 QOL Scores



At 1 year, functional status and quality of life (QOL) improved significantly in the noninvasive group **(A)**, with the fractional flow reserve using computed tomography (FFR_{CT}) group demonstrating significantly greater improvement on the 5-item EuroQOL scale (EQ-5D). Such improvement was also experienced in the invasive cohort **(B)**, with a similar level of improvement seen with both strategies with each scale. The **top of each box** indicates the 75th percentile, the **middle line** the 50th percentile, and the **bottom** the 25th percentile. Mean costs are indicated by the **point**, with changes over time indicated by the **lines**. SAQ = Seattle Angina Questionnaire; VAS = visual analog scale.

CENTRAL ILLUSTRATION **FFR_{CT}-Guided Care in Patients With Suspected CAD**



Douglas, P.S. et al. J Am Coll Cardiol. 2016;68(5):435–45.

In the planned invasive arm, all patients in the usual care cohort proceeded to catheterization, whereas 60% of patients in the computed tomography angiography (CTA)/fractional flow reserve using computed tomography (FFR_{CT})-guided cohort had their invasive procedure cancelled **(green figures)**. There was a marked reduction in the finding of no obstructive coronary artery disease (CAD) at catheterization **(purple figures)**. Similar numbers underwent revascularization **(blue figures)**. Each figure represents approximately 20 patients. ICA = invasive coronary angiography.

planned invasive catheterization, comparing favorably to the 2 events and 3 late revascularizations seen in the usual care group. Of note, our finding that the vast majority of procedures and events were clustered in the first 90 days has not previously been documented using adjudicated events and has implications for trial design and reimbursement policy.

In the planned invasive stratum, FFR_{CT}-guided management was associated with significantly lower costs over 1 year of follow-up. The absolute difference in mean per-patient costs at 1 year was numerically greater than at 90 days ($4,047 vs. $3,391), and similar in percentage (33% vs. 32%), consistent with the low use of cardiac testing and the low rate of costly clinical events after 90 days. With no Medicare reimbursement rates yet established for FFR_{CT}, the base case analysis set the cost weight for FFR_{CT} to zero, but our results were unchanged when this cost weight was varied systematically in sensitivity analyses. In particular, when the cost weight for FFR_{CT} was set at 3 times that of CTA, consistent with early reimbursement decisions by some private payers, the FFR_{CT} strategy still had significantly lower costs in the invasive stratum. Furthermore, the "downstream cost" comparison, which excluded the costs of all initial tests, also showed a significantly lower cost for

FFR_{CT}-guided care in the invasive stratum, largely because this strategy led to lower use of invasive angiography. By contrast, in the planned noninvasive stratum, the cost of FFR_{CT}-guided management was similar to the cost of usual testing in both the base case and "downstream analysis" that excluded the costs of all initial tests. However, 1-year costs of FFR_{CT}-guided management in the noninvasive stratum became significantly higher in sensitivity analyses when the cost weight of FFR_{CT} was set equal to or above the CTA cost weight. In the noninvasive stratum, overall 1-year costs were lower than in the invasive stratum (**Figure 2**) and the costs of the initial noninvasive tests were a large proportion of total costs because of the infrequent use of subsequent invasive testing and revascularization.

QOL improved overall from baseline to 1 year of follow-up in the entire PLATFORM study population. After 1 year, the degree of improvement was generally not significantly different between the FFR_{CT}-guided and usual care groups. The significantly greater degree of improvement found in the noninvasive group at 90 days disappeared at 1 year, apart from a persistent difference in EQ-5D scores (**Figure 3**). Symptoms and QOL generally tend to equalize over time in actively managed patient populations as clinicians respond to patient-reported outcomes and seek to control their symptoms. In most coronary revascularization studies, the initial differences in QOL scores early after randomization have also tended to equalize over longer-term follow-up (16,17).

The "value proposition" of an FFR_{CT}-guided strategy is perhaps more nuanced in the noninvasive cohort, as QOL outcomes were improved as measured by the EQ-5D, but the rate of finding no obstructive disease was uniform and costs were similar-to-higher using a cost weight equal to CTA. Thus, as with all diagnostic tests, careful patient selection is paramount to realizing the potential value for clinical care.

STUDY LIMITATIONS. Although the PLATFORM study has many strengths, including the simultaneous reporting of clinical, economic, and patient-reported outcomes, it is important to acknowledge its limitations, including a small sample size and relatively brief follow-up duration that may be insufficient to detect an impact on clinical outcomes in this low- to intermediate-risk population. Although patients were treated and analyzed as prospectively allocated using a carefully controlled "experimental" intervention in the FFR_{CT} groups, this study was not randomized. However, propensity-matching analyses of all endpoints yielded similar results, suggesting that our findings were robust and not due to between-group baseline differences. Patient selection, enrollment in Europe, and use of Medicare cost weights might have had an impact on our findings, but the overall conclusions are unlikely to be sensitive to variations in practice pattern or cost weights. Because patients were enrolled in the planned invasive strategy group on the basis of a pre-existing physician order for cardiac catheterization, we could not address the efficacy or costs of prior noninvasive testing, or the direct-to-catheterization strategy chosen by local physicians in approximately one-half of patients. However, outcomes were similar regardless of prior noninvasive testing performance or type. Additionally, because the study's intervention was CTA followed by selective FFR_{CT}, we did not evaluate the performance of CTA alone.

CONCLUSIONS

When used as an alternative diagnostic strategy to guide care in patients with planned invasive catheterization, CTA plus selective FFR_{CT} was associated with a significantly lower rate of angiography showing no obstructive CAD, low rates of clinical outcomes, similar QOL, and significant cost savings. When used in those with planned noninvasive testing, clinical events were rare, and there were few differences in resource use or QOL, although the small sample size in this group precluded firm conclusions. 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.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: In stable patients with suspected coronary disease, measurement of FFR_{CT} provides functional and anatomical information comparable to that obtained by invasive testing but at lower cost.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to compare the clinical utility of FFR_{CT} with invasive strategies for evaluation of patients with suspected coronary disease.

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KEY WORDS economic outcomes, fractional flow reserve using computed tomography, major adverse cardiac events, quality of life

APPENDIX For expanded Methods and References sections as well as supplemental tables and a figure, please see the online version of this article.