

ORIGINAL ARTICLE

Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI

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ABSTRACT

BACKGROUND

Coronary revascularization guided by fractional flow reserve (FFR) is associated with better patient outcomes after the procedure than revascularization guided by angiography alone. It is unknown whether the instantaneous wave-free ratio (iFR), an alternative measure that does not require the administration of adenosine, will offer benefits similar to those of FFR.

METHODS

We randomly assigned 2492 patients with coronary artery disease, in a 1:1 ratio, to undergo either iFR-guided or FFR-guided coronary revascularization. The primary end point was the 1-year risk of major adverse cardiac events, which were a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization. The trial was designed to show the noninferiority of iFR to FFR, with a margin of 3.4 percentage points for the difference in risk.

RESULTS

At 1 year, the primary end point had occurred in 78 of 1148 patients (6.8%) in the iFR group and in 83 of 1182 patients (7.0%) in the FFR group (difference in risk, -0.2 percentage points; 95% confidence interval [CI], -2.3 to 1.8 ; $P < 0.001$ for noninferiority; hazard ratio, 0.95 ; 95% CI, 0.68 to 1.33 ; $P = 0.78$). The risk of each component of the primary end point and of death from cardiovascular or noncardiovascular causes did not differ significantly between the groups. The number of patients who had adverse procedural symptoms and clinical signs was significantly lower in the iFR group than in the FFR group (39 patients [3.1%] vs. 385 patients [30.8%], $P < 0.001$), and the median procedural time was significantly shorter (40.5 minutes vs. 45.0 minutes, $P = 0.001$).

CONCLUSIONS

Coronary revascularization guided by iFR was noninferior to revascularization guided by FFR with respect to the risk of major adverse cardiac events at 1 year. The rate of adverse procedural signs and symptoms was lower and the procedural time was shorter with iFR than with FFR. (Funded by Philips Volcano; DEFINE-FLAIR ClinicalTrials.gov number, NCT02053038.)

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FOR THE PAST 20 YEARS, PHYSIOLOGICAL measurements obtained during invasive procedures have been used to guide coronary revascularization. Pioneering work supported the use of flow measurements to make safe decisions about revascularization,^{1,2} but this approach was soon superseded by the use of fractional flow reserve (FFR), which measures pressure as a surrogate of flow to estimate the severity of stenosis.³⁻⁵ FFR was successful largely because of its technical simplicity and because clinical trials showed that it was associated with improved clinical outcomes after percutaneous coronary intervention (PCI).^{6,7} Consequently, FFR is now included in the appropriate-use criteria for coronary angiography and in the American College of Cardiology–American Heart Association–European Society of Cardiology guidelines; despite these recommendations, its adoption remains limited.⁸⁻¹⁰

FFR must be measured during maximal hyperemia, which is typically induced with the administration of a potent intravenous or intracoronary vasodilator, such as adenosine.¹¹ Several studies have questioned the need for the administration of a vasodilator to assess stenosis severity.¹²⁻¹⁴ In these studies, investigators found that in determining stenosis severity, FFR was not superior to the instantaneous wave-free ratio (iFR), a pressure-derived index of stenosis severity that is not obtained with the administration of a vasodilator. We aimed to determine the efficacy and safety of an iFR-guided strategy versus an FFR-guided strategy for coronary revascularization.

METHODS

TRIAL DESIGN AND MANAGEMENT

DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) is a multicenter, international, randomized, blinded trial in which iFR is being compared with FFR for physiologically guided coronary revascularization. The trial, which is ongoing, is being performed at 49 interventional sites across 19 countries on 4 continents. The 1-year outcomes, on which the primary trial analysis is based, are reported here.

The trial was designed by the steering committee (for a list of committee members, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Central ethics

approval was granted by the National Research Ethics Service Committee London, and local ethics approval was granted at each participating site. The trial is funded by an unrestricted educational grant from Philips Volcano, which had no role in the design of the trial, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

Trial management and oversight were performed by personnel at the Imperial College Trials Unit, Imperial College London, who maintained the clinical database and conducted all the data analyses independent of the funder. A risk assessment established that the trial was of low risk to the patients; therefore, no data and safety monitoring board was established. The first draft of the manuscript was written by the first author, and all the authors participated in trial oversight, approved all subsequent drafts of the manuscript, and made the decision to submit the manuscript for publication. The steering committee and all the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the trial protocol and statistical analysis plan, which are available at NEJM.org.

POPULATION

Patients who had undergone coronary angiography were assessed for trial eligibility. Patients were eligible for inclusion in the trial if they had coronary artery disease with at least one native artery in which the stenosis was of questionable physiological severity (typically, an artery with 40 to 70% stenosis of the diameter on visual assessment). Patients with tandem stenoses (i.e., stenoses separated by more than 10 mm within a single vessel) that would require independent evaluation and treatment were excluded. A full list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. No exclusions were made on the basis of heart rate or rhythm. Written informed consent was obtained from all the patients before their enrollment in the trial.

RANDOMIZATION

Eligible patients were randomly assigned to undergo revascularization guided by either FFR or iFR. Randomization was performed with the use of an automated and validated online randomization tool (SRUB, Imperial College London). During the trial procedures, investigators were allowed

to obtain FFR or iFR measurements only in accordance with group assignment. Verification of the data was performed in each patient with the use of the electronic physiology record, which was uploaded directly from the physiological console for each patient into the electronic clinical record (Fig. S1 in the Supplementary Appendix). During the procedure, patients were not told which technique was used for physiological assessment, and they remained unaware of their group assignment throughout the entire course of the trial. The research nurses and doctors who were responsible for the follow-up visits were also unaware of the group assignments.

PROCEDURE

Before the FFR or iFR measurement was obtained, intracoronary nitrates were administered to control vasomotor tone. The physiological measurements were obtained in the routine manner with the use of a coronary-pressure guidewire (Philips Volcano) (Figs. S1 and S2 in the Supplementary Appendix). Physiological assessment was performed in all vessels with questionable stenosis severity. In patients with an acute coronary syndrome, physiological assessment was performed in only non-culprit vessels, after the culprit vessel had been revascularized. Prespecified treatment thresholds were an FFR of 0.80 and an iFR of 0.89 (Fig. S3 in the Supplementary Appendix). When the FFR or iFR for a given stenosis was equal to or lower than the prespecified threshold, the stenosis was revascularized with a drug-eluting stent or a bioresorbable vascular scaffold or by coronary-artery bypass grafting (CABG). When the FFR or iFR was higher than the prespecified threshold, treatment was deferred. When multivessel revascularization was attempted, investigators could choose to prespecify a staged treatment plan, with the staged procedure performed within 60 days. Adverse procedural signs and symptoms were documented.

Routine clinical follow-up assessments were performed at 30 days and at 1 year, and follow-up by telephone was conducted at 6 months. Complete monitoring of every electronic clinical record was performed, and the data were confirmed by on-site source-document verification in a randomly selected 30% of patients.

END POINTS

The primary end point was the 1-year risk of major adverse cardiac events, which were a com-

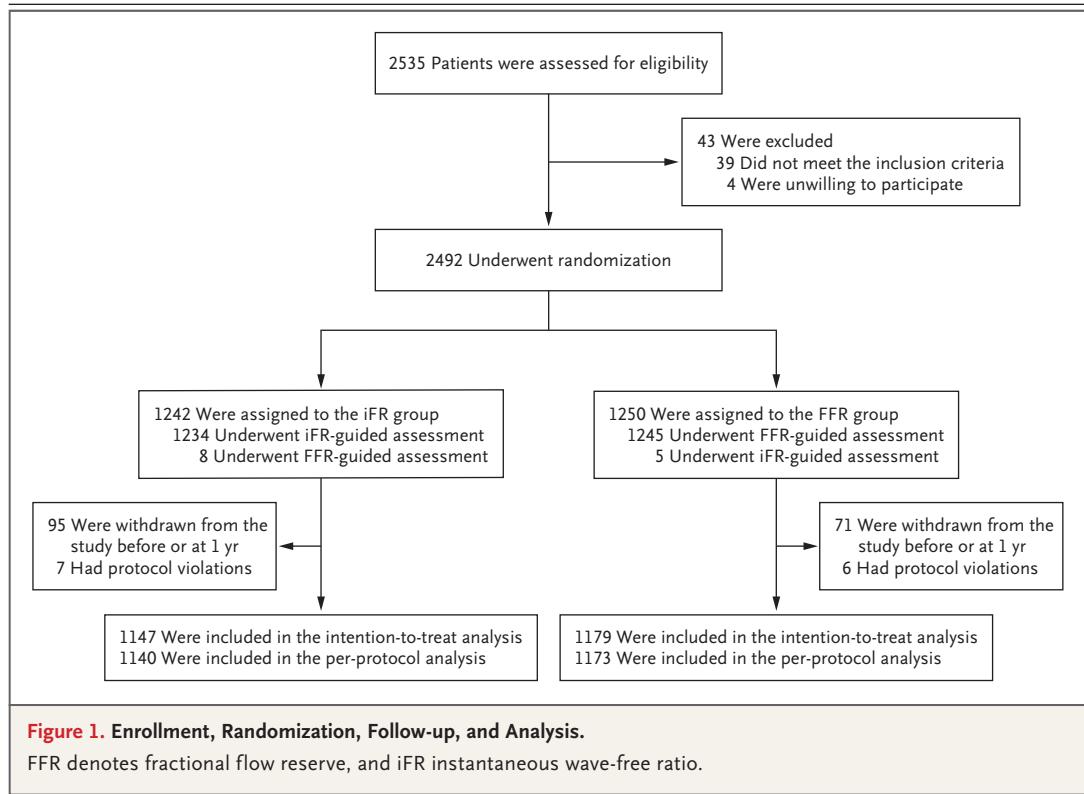
posite of death, nonfatal myocardial infarction, or unplanned revascularization. Death was considered to be from cardiovascular causes unless an unequivocal noncardiovascular cause was established. Myocardial infarction was classified as either spontaneous or periprocedural and as either ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI). Revascularization was considered to be unplanned when it was not the index procedure and was not identified at the time of the index procedure as a staged procedure to occur within 60 days. Detailed end-point definitions, which did not change after the commencement of the trial, are provided in the Supplementary Appendix.

End-point events were adjudicated with the use of anonymized source documentation by a committee of international experts who were not part of the steering committee. A consensus decision was made on the basis of prespecified end-point definitions. Members of the events committee remain unaware of the identities of the patients and their group assignments.

STATISTICAL ANALYSIS

The prespecified trial hypothesis was that iFR would be noninferior to FFR with respect to the risk of major adverse cardiac events at 1 year among patients undergoing physiologically guided revascularization. We based the sample size on an assumed annual rate of primary end-point events of 8.5% in a population that includes a mix of patients with either stable coronary disease or acute coronary syndromes¹⁵; given this rate, we calculated that a sample size of 2305 patients would provide the trial with 90% power to detect the noninferiority of iFR to FFR, with the use of a noninferiority margin of 3.4 percentage points for the difference in risk, at a type I error rate of 5%. To allow for attrition, the target sample size was set at 2500 patients.

Both a risk-difference analysis and a time-to-event analysis were performed. The time-to-event analysis was conducted with the use of the Kaplan–Meier method. A Cox survival model was used to derive hazard ratios. For the results of both analyses, two-sided 95% confidence intervals (whose upper limits correspond to the upper limits of one-sided 97.5% confidence intervals) and two-sided 99% confidence intervals (whose upper limits correspond to the upper limits of one-sided 99.5% confidence intervals) are reported. The va-



lidity of the proportional-hazards assumption was tested with Schoenfeld residuals. There were no signs of violation of the proportional-hazards assumption.

Patients who withdrew from the study before they reached 1 year of follow-up and who were event-free at their last visit were excluded from the risk-difference analysis for the primary end point and its components. Data for these patients were censored at the time of withdrawal for the time-to-event analysis. Patients who had a myocardial infarction or an unplanned revascularization before withdrawing from the study were included in the risk-difference analysis.

RESULTS

PATIENTS AND PROCEDURES

During the recruitment period (January 2014 to December 2015), a total of 2535 patients who underwent coronary angiography were assessed for trial eligibility. Of the 2492 patients who met the enrollment criteria, 1242 were assigned to the iFR group and 1250 to the FFR group (Fig. 1). The baseline demographic characteristics of the patients are shown in Table 1. The mean age of

the patients was 65 years, 76% were men, and 80% had stable coronary artery disease.

Procedural characteristics for the two trial groups are shown in Figure 1 and Table 2. A total of 99.4% of the patients assigned to the iFR group and 99.6% of those assigned to the FFR group underwent the assigned procedure. Crossover, which represented a deviation from the protocol, occurred in 13 cases and was due to profound early adenosine-induced bradycardia and hypotension in 1 case and to site errors in the remaining 12 cases. There were no cases in which heart-rhythm disturbances or lack of electrocardiographic assessment prevented FFR or iFR measurements from being obtained.

The number of vessels evaluated did not differ significantly between the iFR group and the FFR group (total number assessed, 1575 and 1608, respectively; mean $[\pm$ SD] number evaluated per patient, 1.27 ± 0.61 and 1.29 ± 0.63 ; $P=0.58$). The mean iFR and FFR measurements were close to their respective thresholds (mean iFR, 0.91 ± 0.09 ; mean FFR, 0.83 ± 0.09); these findings suggest that most of the assessed vessels had stenosis of intermediate severity (Figs. S4 and S5 in the Supplementary Appendix). The number of function-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	iFR Group (N = 1242)	FFR Group (N = 1250)
Age — yr	65.5±10.8	65.2±10.6
Sex — no. (%)		
Female	280 (22.5)	321 (25.7)
Male	962 (77.5)	929 (74.3)
Disease type — no. (%)†		
STEMI	49 (3.9)	42 (3.4)
Acute coronary syndrome	186 (15.0)	184 (14.7)
Stable disease	986 (79.4)	1012 (81.0)
Diabetes — no. (%)		
Non-insulin dependent	288 (23.2)	282 (22.6)
Insulin dependent	94 (7.6)	94 (7.5)
Smoking status — no. (%)		
Former smoker	461 (37.1)	443 (35.4)
Current smoker	243 (19.6)	262 (21.0)
Hypertension — no. (%)	873 (70.3)	884 (70.7)
Hypercholesterolemia — no. (%)	794 (63.9)	792 (63.4)
Previous myocardial infarction — no. (%)	358 (28.8)	376 (30.1)
Previous percutaneous coronary intervention — no. (%)	489 (39.4)	527 (42.2)
Previous heart condition — no. (%)	489 (39.4)	530 (42.4)
Congestive heart failure — no. (%)	77 (6.2)	67 (5.4)
NYHA class — no. (%)‡		
I	21 (1.7)	13 (1.0)
II	28 (2.3)	32 (2.6)
III	16 (1.3)	14 (1.1)
IV	1 (0.1)	3 (0.2)
Impairment of left ventricular function — no. (%)		
Mild	147 (11.8)	150 (12.0)
Moderate	65 (5.2)	58 (4.6)
Severe	23 (1.9)	27 (2.2)
CCS angina class — no. (%)§		
I	347 (27.9)	305 (24.4)
II	374 (30.1)	370 (29.6)
III	127 (10.2)	154 (12.3)
IV	81 (6.5)	72 (5.8)
Systolic blood pressure — mm Hg	133.9±20.3	134.3±20.1
Diastolic blood pressure — mm Hg	74.9±11.9	75.0±11.8
Heart rate — beats/min	68.9±12.6	69.1±12.8
Body-mass index¶	27.8±5.0	27.5±5.0
Total cholesterol — mmol/liter	4.1±1.0	4.1±0.9
Hemoglobin — mg/dl	13.9±1.6	13.8±1.6
Creatinine — mmol/liter	90.2±62.0	93.2±81.1

* Plus-minus values are means ±SD. There were no significant differences between the two groups in baseline characteristics. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. FFR denotes fractional flow reserve, iFR instantaneous wave-free ratio, and STEMI ST-segment elevation myocardial infarction.

† In patients with STEMI or an acute coronary syndrome, only nonculprit lesions were evaluated. Patients with STEMI were evaluated more than 48 hours after the event occurred.

‡ In the New York Heart Association (NYHA) functional classification system, classes range from I to IV, with higher classes indicating greater limitations of physical activity owing to heart disease.

§ In the Canadian Cardiovascular Society (CCS) functional classification system, classes range from I to IV, with higher classes indicating greater limitations of physical activity owing to angina.

¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Procedural Characteristics.*			
Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†
Radial-artery approach — no. of patients (%)	896 (72.1)	888 (71.0)	0.54
Procedure time — min			
Median	40.5	45.0	0.001
Interquartile range	27.0–60.0	30.0–66.0	
Hyperemic agent administered — no. of patients (% of total no. who received a hyperemic agent)			
Total	NA	1608 (100)	
Intracoronary adenosine	NA	455 (28.3)	
Intravenous adenosine	NA	950 (59.1)	
Other agent	NA	203 (12.6)	
Multivessel disease — no. of patients (%)	505 (40.7)	519 (41.5)	0.66
Type of vessel evaluated — no. (% of total vessels evaluated)‡			
Total	1575 (100)	1608 (100)	0.58
Left anterior descending artery	844 (53.6)	845 (52.5)	0.56
Left circumflex artery	323 (20.5)	333 (20.7)	0.89
Right coronary artery	374 (23.7)	393 (24.4)	0.65
Other	33 (2.1)	31 (1.9)	0.74
Unknown	1 (0.1)	6 (0.4)	0.06
Total no. of vessels evaluated or treated‡	1879	1940	0.42
No. of vessels evaluated or treated per patient‡	1.51±0.76	1.55±0.80	0.42
Functionally significant lesions — no. (% of total vessels evaluated)§	451 (28.6)	557 (34.6)	0.004
≥1 Functionally significant lesions present — no. of patients (%)§	426 (34.3)	486 (38.9)	0.02
Mean iFR	0.91±0.09	NA	
Mean FFR	NA	0.83±0.09	
Percent of lesions within the FFR range			
<0.60	NA	1.96	
0.60–0.90	NA	75.08	
>0.90	NA	22.96	
Revascularization performed — no. of patients (%)			
Total	590 (47.5)	667 (53.4)	0.003
CABG	25 (2.0)	42 (3.4)	0.04
PCI	565 (45.5)	625 (50.0)	0.02
Stents placed — no. (% of total stents placed)			
Total	822 (100)	906 (100)	0.86
Drug-eluting stent	811 (98.7)	893 (98.6)	
Bioresorbable vascular scaffold	11 (1.3)	13 (1.4)	
No. of stents placed per patient	0.66±0.92	0.72±0.96	0.09
Stent length per patient — mm			
Median	28.0	28.0	0.74
Interquartile range	18.0–42.0	18.0–44.0	

Table 2. (Continued.)

Variable	iFR Group (N=1242)	FFR Group (N=1250)	P Value†‡
Stent diameter — mm			
Median	3.00	3.00	0.44
Interquartile range	2.67–3.25	2.75–3.25	
Stents placed with postdilatation — no. (% of total stents placed)	407 (49.5)	425 (46.9)	0.28
PCI procedures performed with pressure wire — no. (% of total stents placed)	261 (31.8)	278 (30.7)	0.63
Patient-reported adverse procedural symptoms or signs — no. of patients (%)	39 (3.1)	385 (30.8)	<0.001
Patient-reported dyspnea — no. of patients (%)	13 (1.0)	250 (20.0)	
Patient-reported chest pain — no. of patients (%)	19 (1.5)	90 (7.2)	
Physician-reported adverse procedural signs — no. of patients (%)			
Heart-rhythm disturbance	2 (0.2)	60 (4.8)	
Significant hypotension	4 (0.3)	13 (1.0)	
Vomiting or nausea	1 (0.1)	11 (0.9)	
Ventricular arrhythmia or bronchospasm¶	1 (0.1)	8 (0.6)	
Other	4 (0.3)	38 (3.0)	

* Plus–minus values are means \pm SD. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, NA not applicable, and PCI percutaneous coronary intervention.

† P values that compare distributions were calculated by means of the Wilcoxon rank-sum test. P values that compare percentages were calculated by means of a test for proportions.

‡ Evaluated vessels are vessels that underwent physiological assessment. Treated vessels are vessels that underwent PCI.

§ Functionally significant lesions are lesions with an iFR or FFR equal to or lower than the treatment threshold (0.89 and 0.80, respectively).

¶ Serious adverse events included ventricular arrhythmias and bronchospasm; one case of ventricular arrhythmia occurred in the iFR group, and one case of ventricular arrhythmia and seven cases of bronchospasm occurred in the FFR group.

ally significant stenoses (i.e., stenoses with an iFR or FFR below the treatment threshold) was significantly lower in the iFR group than in the FFR group (451 vs. 557 [28.6% vs. 34.6% of total vessels evaluated], $P=0.004$).

In both the iFR group and the FFR group, the number of patients who underwent PCI (565 and 625, respectively) was greater than the number who had functionally significant stenoses (426 and 486, respectively). This is because PCI procedures that were performed in culprit vessels of patients with an acute coronary syndrome and in angiographically significant stenoses (neither of which required physiological assessment) were included in the totals. The median procedure time was significantly shorter in the iFR group than in the FFR group (40.5 minutes [interquartile range, 27.0 to 60.0] vs. 45.0 minutes [interquartile range, 30.0 to 66.0], $P=0.001$).

OUTCOMES

At 1 year, the primary end point (a composite of major adverse cardiac events) had occurred in 78 of 1148 patients (6.8%) in the iFR group and in 83 of 1182 patients (7.0%) in the FFR group (Fig. 2). The hazard ratio was 0.95 (95% confidence interval [CI], 0.68 to 1.33; $P=0.78$), and the difference in risk was -0.2 percentage points (95% CI, -2.3 to 1.8 ; 99% CI, -2.9 to 2.5 ; $P=0.83$) (Table 3, and Table S2 in the Supplementary Appendix). The upper limits of the two-sided 95% and 99% confidence intervals were within the prespecified noninferiority margin of 3.4 percentage points ($P<0.001$ for noninferiority). The risks of each individual component of the primary end point and of death from cardiovascular or noncardiovascular causes did not differ significantly between the two groups.

The noninferiority of iFR to FFR was also

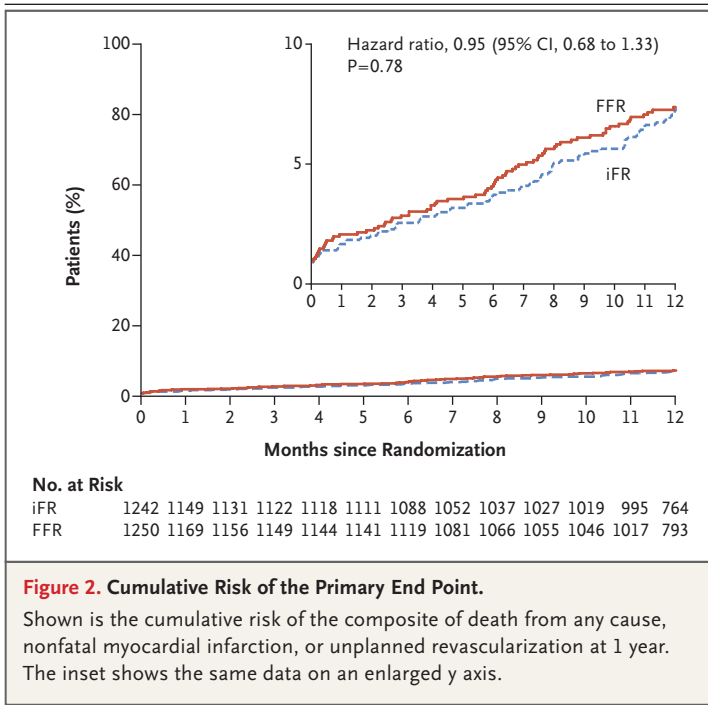


Figure 2. Cumulative Risk of the Primary End Point.

Shown is the cumulative risk of the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization at 1 year. The inset shows the same data on an enlarged y axis.

confirmed in the per-protocol analysis (Tables S4 and S5 in the Supplementary Appendix). In the per-protocol analysis, the hazard ratio for major adverse cardiac events was 0.94 (95% CI, 0.67 to 1.31; $P=0.72$), and the difference in risk was -0.3 percentage points (95% CI, -2.4 to 1.8 ; 99% CI, -3.0 to 2.4 ; $P=0.77$). The risk of each individual component of the composite end point did not differ significantly between the two groups in the per-protocol analyses.

PROCEDURAL SIGNS AND SYMPTOMS

In the iFR group, 39 patients (3.1%) reported adverse procedural symptoms or signs, including 19 who reported chest pain and 13 who reported dyspnea (Table 2). In the FFR group, 385 patients (30.8%) reported adverse procedural symptoms or signs, including 250 who reported dyspnea and 90 who reported chest pain. The difference between the two groups in the number of patients with adverse procedural symptoms or signs was significant ($P<0.001$) (Fig. S9 in the Supplementary Appendix). Serious adverse events (bronchospasm and ventricular arrhythmias) were reported in 8 patients in the FFR group (after hyperemia) and in 1 patient in the iFR group.

DISCUSSION

In the DEFINE-FLAIR trial, we found that iFR-guided coronary revascularization was noninferior to FFR-guided revascularization with respect to the risk of major adverse cardiac events. The use of iFR was also associated with a lower rate of procedural signs and symptoms and with a shorter procedural time than the use of FFR. There were no significant differences between the trial groups in the rates of death from any cause, death from cardiovascular causes, nonfatal myocardial infarction, and unplanned revascularization. These results suggest that the benefits of physiologically guided coronary revascularization with FFR can also be achieved with iFR. Our principal findings are similar to those now reported in the *Journal* by Götberg et al.¹⁶

It has previously been proposed that a hybrid iFR-FFR approach might be advantageous for the detection of functionally significant stenoses, with iFR used as the initial measure and FFR used only to evaluate stenoses that were of intermediate severity on iFR-guided assessment.^{17,18} However, the results of our trial suggest that iFR alone can effectively identify stenoses that require intervention. Our trial also provides clinical evidence that there is no significant advantage to the administration of a hyperemic agent — a finding consistent with results of studies in which iFR and FFR were compared with other reference standards.^{13,14,19,20}

Although evidence supporting the benefits of physiologically guided revascularization has accumulated over the past decade, adoption of this approach in clinical practice has lagged. There are many reasons for this, including equipment and drug costs, inadequate reimbursement, physician preferences, patient symptoms, and additional procedural burden. Although adenosine is a generally safe drug that is used in millions of diagnostic procedures annually, its risks are well documented^{21,22} and it is not suitable for every patient; therefore, avoiding the use of adenosine is preferable.^{11,23,24} In addition, adenosine contributes substantially to the cost of physiological stenosis assessment, and its use is hampered in many countries because it is unavailable or not indicated for this purpose. Thus, the ability to perform physiological assessments of coronary-

Table 3. Outcomes for Difference in Risk at 1 Year.*

Outcome	iFR Group no./total no. (%)	FFR Group no./total no. (%)	Difference in Risk		P Value
			percentage points (95% CI)	percentage points (99% CI)	
Primary end point: death from any cause, nonfatal myocardial infarction, or unplanned revascularization	78/1148 (6.8)	83/1182 (7.0)	-0.2 (-2.3 to 1.8)†	-0.2 (-2.9 to 2.5)	0.83
Unplanned revascularization	46/1147 (4.0)	63/1181 (5.3)	-1.3 (-3.0 to 0.4)	-1.3 (-3.1 to 1.9)	0.13
Nonfatal myocardial infarction	31/1148 (2.7)	28/1180 (2.4)	0.3 (-1.0 to 1.6)	0.3 (-1.4 to 2.0)	0.62
Death from cardiovascular causes	7/1147 (0.6)	4/1179 (0.3)	0.3 (-0.3 to 0.8)	0.3 (-0.5 to 1.0)	0.34
Death from noncardiovascular causes	15/1147 (1.3)	9/1179 (0.8)	0.5 (-0.3 to 1.4)	0.5 (-0.5 to 1.6)	0.19
Death from any cause	22/1147 (1.9)	13/1179 (1.1)	0.8 (-0.2 to 1.8)	0.8 (-0.5 to 2.1)	0.11

* Patients who had a myocardial infarction or an unplanned revascularization before withdrawing from the study were included in the analyses.

† For the primary end point, the upper limit of the 95% confidence interval was 1.8 percentage points, which was within the prespecified non-inferiority margin of 3.4 percentage points.

artery stenoses without the use of adenosine may increase the use of such assessments in clinical practice.

Although the patients were not informed of their group assignments, adverse procedural symptoms or signs occurred in 30.8% of the patients in the FFR group, as compared with 3.1% of the patients in the iFR group. This difference is most likely due to the side effects of adenosine. It is therefore possible that at least some patients in the FFR group became aware of their group assignment. Such unblinding could have led to bias in the rates of unplanned revascularization, especially if patients discussed these symptoms with their physicians.

The number of functionally significant stenoses was lower in the iFR group than in the FFR group. This difference could be a consequence of dissimilar thresholds for the two measures. In addition, iFR has been shown to be more closely linked to coronary flow reserve than FFR, and a previous study has shown higher revascularization rates associated with assessment guided by FFR than with assessment guided by coronary flow reserve.²⁵ Regardless of the explanation, the results of our trial suggest that the use of iFR can lead to outcomes similar to those associated with FFR and to the placement of fewer (potentially unnecessary) stents.

The clinical population in our trial differed from the population in the FAME trial (Fractional Flow Reserve Versus Angiography for Multivessel

Evaluation), in which all the patients had multivessel disease and were scheduled for revascularization.⁶ In DEFINE-FLAIR, only 41% had multivessel disease. Although the benefit of coronary revascularization in patients with single-vessel disease is likely to be more uncertain, our trial population is probably similar to the population that would be seen in current clinical practice. Given the clinical evidence in support of physiologically guided revascularization, it was considered unethical to repeat a study similar to FAME, in which iFR-guided revascularization was compared with angiography-guided revascularization.

In our trial, the noninferiority margin for the difference in risk was set at 3.4 percentage points, which meant that the upper limit of the hazard ratio could have been as high as 1.40 while still allowing a claim of noninferiority. Although this noninferiority margin is wide, it is similar to margins used in other major clinical trials in cardiology.²⁶⁻³² The event rates were lower than had been expected, because the number of patients with an acute coronary syndrome who were enrolled in the trial was lower than had been anticipated. However, when we used the prespecified noninferiority margin to test the actual event rate among the prespecified number of patients, we found that iFR was noninferior to FFR even when the upper limit of a one-sided 99.5% confidence interval was used.

In conclusion, we found that coronary revas-

cularization guided by iFR was noninferior to revascularization guided by FFR with respect to major adverse cardiac events at 1 year. The rate of adverse procedural signs or symptoms was lower and the procedure time was shorter in the iFR group than in the FFR group.

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APPENDIX

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REFERENCES

- Di Mario C, Moses JW, Anderson TJ, et al. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. *Circulation* 2000;102:2938-44.
- Kern MJ, Donohue TJ, Aguirre FV, et al. Clinical outcome of deferring angioplasty in patients with normal transluminal pressure-flow velocity measurements. *J Am Coll Cardiol* 1995;25:178-87.
- Serruys PW, Di Mario C, Meneveau N, et al. Intracoronary pressure and flow velocity with sensor-tip guidewires: a new methodologic approach for assessment of coronary hemodynamics before and after coronary interventions. *Am J Cardiol* 1993;71:41D-53D.
- Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993;87:1354-67.
- Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol* 1990;15:459-74.
- Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
- Fearon WF, Shilane D, Pijls NHJ, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation* 2013;128:1335-40.
- Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused

- update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Thorac Cardiovasc Surg* 2012;143:780-803.
9. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Sertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012;59:857-81.
 10. Windecker S, Kohl P, Alfonso S, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2014; 35:2541-619.
 11. Pijls NHJ, Tonino PAL. The crux of maximum hyperemia: the last remaining barrier for routine use of fractional flow reserve. *JACC Cardiovasc Interv* 2011;4: 1093-5.
 12. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 2012;59: 1392-402.
 13. Sen S, Asrress KN, Nijjer S, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration: results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol* 2013;61: 1409-20.
 14. Petraco R, van de Hoef TP, Nijjer S, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv* 2014;7:492-502.
 15. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015;36:100-11.
 16. Göteborg M, Christiansen EH, Gudmundsdottir JJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med*. DOI: 10.1056/NEJMoa1616540.
 17. Petraco R, Park JJ, Sen S, et al. Hybrid iFR-FFR decision-making strategy: implications for enhancing universal adoption of physiology-guided coronary revascularization. *EuroIntervention* 2013;8:1157-65.
 18. Escaned J, Echavarría-Pinto M, García-García HM, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE II international, multicenter study (Adenosine Vasodilator Independent Stenosis Evaluation II). *JACC Cardiovasc Interv* 2015;8:824-33.
 19. Sen S, Nijjer S, Petraco R, Malik IS, Francis DP, Davies J. Instantaneous wave-free ratio: numerically different, but diagnostically superior to FFR? Is lower always better? *J Am Coll Cardiol* 2013;62:566.
 20. van de Hoef TP, Meuwissen M, Escaned J, et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. *EuroIntervention* 2015;11:914-25.
 21. Dilsizian V, Gewirtz H, Paivanas N, et al. Serious and potentially life threatening complications of cardiac stress testing: physiological mechanisms and management strategies. *J Nucl Cardiol* 2015; 22:1198-213.
 22. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. *J Am Coll Cardiol* 1994;23: 384-9.
 23. Kern MJ, Seto AH. On the search for an "easy" FFR: submaximal hyperemia and NTG-induced translesional pressure drop (Pd/Pa-NTG). *Catheter Cardiovasc Interv* 2016;87:270-2.
 24. Mallet ML. Proarrhythmic effects of adenosine: a review of the literature. *Emerg Med J* 2004;21:408-10.
 25. van de Hoef TP, van Lavieren MA, Damman P, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv* 2014;7:301-11.
 26. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016;375:2223-35.
 27. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;381:629-38.
 28. Mäkitallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016;388:2743-52.
 29. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883-91.
 30. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
 31. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;64: 1-12.
 32. von Birgelen C, Basalus MWZ, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. *J Am Coll Cardiol* 2012;59:1350-61.

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