The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 11, 2017 VOL. 376 NO. 19

Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI

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ABSTRACT

BACKGROUND

The instantaneous wave-free ratio (iFR) is an index used to assess the severity of coronary-artery stenosis. The index has been tested against fractional flow reserve (FFR) in small trials, and the two measures have been found to have similar diagnostic accuracy. However, studies of clinical outcomes associated with the use of iFR are lacking. We aimed to evaluate whether iFR is noninferior to FFR with respect to the rate of subsequent major adverse cardiac events.

METHODS

We conducted a multicenter, randomized, controlled, open-label clinical trial using the Swedish Coronary Angiography and Angioplasty Registry for enrollment. A total of 2037 participants with stable angina or an acute coronary syndrome who had an indication for physiologically guided assessment of coronary-artery stenosis were randomly assigned to undergo revascularization guided by either iFR or FFR. The primary end point was the rate of a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months after the procedure.

RESULTS

A primary end-point event occurred in 68 of 1012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates, 0.7 percentage points; 95% confidence interval [CI], –1.5 to 2.8; P=0.007 for noninferiority; hazard ratio, 1.12; 95% CI, 0.79 to 1.58; P=0.53); the upper limit of the 95% confidence interval for the difference in event rates fell within the prespecified noninferiority margin of 3.2 percentage points. The results were similar among major subgroups. The rates of myocardial infarction, target-lesion revascularization, restenosis, and stent thrombosis did not differ significantly between the two groups. A significantly higher proportion of patients in the FFR group than in the iFR group reported chest discomfort during the procedure.

CONCLUSIONS

Among patients with stable angina or an acute coronary syndrome, an iFR-guided revascularization strategy was noninferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac events at 12 months. (Funded by Philips Volcano; iFR SWEDEHEART ClinicalTrials.gov number, NCT02166736.)

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*A complete list of participating centers and investigators in the Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDEHEART) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 18, 2017, at NEJM.org.

N Engl J Med 2017;376:1813-23.
DOI: 10.1056/NEJMoa1616540

A Quick Take is available at NEJM.org

Coronary revascularization is warranted only if a patient has one or more coronary-artery stenoses that are hemodynamically important. Large randomized studies have shown that fractional flow reserve (FFR) is superior to angiographic assessment for the detection of hemodynamically important coronary-artery stenoses and that use of FFR to guide coronary revascularization improves clinical outcomes.[1-3] FFR is measured by advancing a coronary-pressure guidewire distal to a stenotic lesion and then administering adenosine to assess the pressure gradient across the lesion during hyperemia.

Studies have shown that resting indexes (derived from the pressure measurement at rest, without the administration of adenosine) have diagnostic accuracy similar to that of FFR as independent measures of ischemia.[4-7] The instantaneous wave-free ratio (iFR) is a recently developed physiological index used to assess the severity of stenosis.The iFR is calculated by measuring the resting pressure gradient across a coronary lesion during the portion of diastole when microvascular resistance is low and stable.[8] Benefits of iFR include the ability to obtain an instantaneous lesion assessment without the need to administer a hyperemic agent, such as adenosine. Although there are some differences between FFR and iFR in diagnostic results, a large outcome-based clinical trial has yet to establish whether such differences are of clinical relevance.[8-10] The aim of this trial was to investigate whether iFR is noninferior to FFR with respect to subsequent clinical outcomes among patients who have an indication for physiologically guided assessment of coronary-artery stenosis.

Methods

Trial Design

The Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDEHEART) trial was a multicenter, randomized, controlled, open-label clinical trial in which comprehensive national registries were used for patient data collection, randomization, and follow-up. The trial design has been reported previously.[11] The trial was conducted in accordance with the Declaration of Helsinki and was approved by ethical review boards in Sweden, Denmark, and Iceland. The trial was funded by an unrestricted research grant from Philips Volcano, which had no role in the design of the trial or the collection, analysis, or reporting of the data.

Trial administration, data collection and management, statistical analyses, and central adjudication were conducted by personnel at the Uppsala Clinical Research Center, Uppsala, Sweden. The trial was designed by the authors, who wrote all drafts of the manuscript and made the decision to submit the manuscript for publication. The authors vouch for the integrity and completeness of the data and analyses and for the fidelity of the study to the trial protocol, which is available with the full text of this article at NEJM.org.

Registry-Based Enrollment

All patients who were enrolled in the trial were included in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR; for details, see the Supplementary Appendix, available at NEJM.org). The registry contains data on patients from all 30 coronary intervention centers in Sweden and 1 in Iceland; it is funded solely by national health authorities and provides immediate and continuous feedback on processes and quality-of-care measures. A center in Denmark also participated in the trial and entered all relevant data into the SCAAR. All baseline and procedural data were entered online directly into the registry, as described previously.[12]

Patient Population

Patients with stable angina pectoris, unstable angina pectoris, or non–ST-segment elevation myocardial infarction (NSTEMI) who had an indication for physiologically guided assessment of a coronary lesion (with 40 to 80% stenosis on visual examination) were eligible for inclusion. In patients with suspected stable angina, any lesion could be assessed; in patients with unstable angina or NSTEMI, only nonculprit lesions were evaluated and culprit lesions were managed as clinically indicated. All participants provided written informed consent. (Further details about the inclusion and exclusion criteria are provided in the Supplementary Appendix.)

RANDOMIZATION

Using a Web-based platform in the SCAAR, we randomly assigned patients to undergo revascularization guided by either iFR or FFR. If inclusion criteria were met after we had entered a patient's baseline information into the registry, a pop-up window indicated that the patient was potentially eligible for the trial. The treating physician was then asked to respond to questions in a randomization module in the registry to confirm the absence of exclusion criteria and to verify that the patient had provided written informed consent. If the patient was eligible, a randomization button appeared that allowed the patient to be assigned to either the iFR group or the FFR group.

INVASIVE PROCEDURES

In both trial groups, intracoronary nitroglycerin was administered before the lesion was assessed. Lesions with at least 80% stenosis on angiography were treated without the use of physiological indexes. For lesions with 40 to 80% stenosis on visual examination, physiologically guided assessment was performed.

The iFR and FFR measurements were obtained with the use of a coronary-pressure guidewire (Philips Volcano) (Fig. S1 in the Supplementary Appendix). For FFR, hyperemia was induced with the administration of intracoronary or intravenous adenosine, in accordance with the clinical practice at each participating center. Revascularization of the investigated vessel was mandated if the iFR was 0.89 or lower or the FFR was 0.80 or lower; these thresholds indicated the presence of hemodynamically important stenosis. When the iFR was higher than 0.89 or the FFR was higher than 0.80, revascularization of the vessel was deferred.

Revascularization was performed in accordance with standard clinical practice. Percutaneous coronary intervention (PCI) and coronary-artery bypass grafting (CABG) were considered to be revascularization procedures for the purposes of this trial. At the conclusion of the procedure, the treating physician asked the patients to assess their level of chest discomfort during the procedure on a four-point grading scale, ranging from none to severe. The type of $P2Y_{12}$ inhibitor that was administered during and after PCI was left to the discretion of the physician; however, lifelong treatment with acetylsalicylic acid was recommended.

DATA COLLECTION, END POINTS, AND FOLLOW-UP

Baseline patient demographic data were obtained from the SCAAR. Specific trial-related data that were not included in the registry were collected in a separate module embedded in the SCAAR. The data were obtained through an online questionnaire, which was completed by the treating physician, and included the results of the angiographic assessment of coronary-artery stenosis, an indication of whether the results of the physiologically guided assessment of coronary-artery stenosis influenced the treatment strategy, the patient report of chest discomfort during assessment, and any deviations from the protocol.

The primary end point was the rate of a composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months after the procedure. Unplanned revascularization was defined as revascularization that was not the index procedure and was not identified at the time of the index procedure as a staged procedure to be performed within 60 days. Key secondary end points were the rate of each component of the primary end point within 12 months after the procedure, chest discomfort during the procedure, target-lesion revascularization, stent thrombosis, and restenosis. (For further details on primary and secondary end points, see the Supplementary Appendix.)

Information on death from any cause was obtained from national population registries. In Sweden, data on myocardial infarction and unplanned revascularization were obtained from the Swedish Web-Based System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry (for details, see the Supplementary Appendix). In Denmark, data on myocardial infarction and revascularization were obtained from the Danish National Patient Registry and the Western Denmark Heart Registry, in accordance with previous studies.[13,14] In Iceland, a research nurse conducted clinical follow-up.

If a suspected end-point event was detected,

current health care records and angiographic results were obtained. Death and myocardial infarction events were adjudicated by an independent clinical event adjudication committee whose members were unaware of the group assignments. Unplanned revascularization events and secondary angiographic outcomes were assessed by an independent experienced observer who was unaware of the group assignments.

STATISTICAL ANALYSIS

We calculated that a sample size of 2000 patients would provide the trial with 85% power to test the hypothesis that iFR would be noninferior to FFR with respect to the primary end point. We anticipated a primary end-point event rate in the FFR group of 8%, which was based on historical data from the SWEDEHEART registry in a population that includes a mix of patients with either stable angina or acute coronary syndromes. The selected noninferiority margin for the difference in event rates was 3.2 percentage points, which corresponded to a noninferiority margin for the hazard ratio of 1.40 that was based on the anticipated event rate in the FFR group.

All end-point analyses were performed on a per-protocol basis. Differences between groups in time-to-event end points were assessed with the use of a log-rank test. Kaplan–Meier estimates of the rate of primary end-point events were compared between the two groups with the use of the approach suggested by Machin and Gardner.[15] If the upper limit of the two-sided 95% confidence interval for the difference in event rates was less than the prespecified delta value (3.2 percentage points), iFR would be considered to be noninferior to FFR. Hazard ratios were calculated with the use of Cox proportional-hazards models. Differences between group means were assessed with the use of a two-tailed Student's t-test. Chi-square tests or Fisher's exact tests were used to test differences between proportions. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Subgroup analyses were carried out for the primary end point and its components with the use of a proportional-hazards model that included the trial group, subgroup, and interaction between trial group and subgroup as variables; analyses within groups are presented as hazard ratios and 95% confidence intervals, and analyses of interactions as P values.

RESULTS

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC DATA

The trial was conducted at 13 hospitals in Sweden, 1 hospital in Denmark, and 1 hospital in Iceland. During the trial period (May 2014 to October 2015), 20.3% of patients who presented to the trial hospitals with stable angina, unstable angina, or NSTEMI were included in the trial. A total of 2037 participants were enrolled in the trial; 1019 were assigned to the iFR group, and 1018 to the FFR group. Data for 18 patients were excluded from the analyses because these patients received an incorrect group assignment or had unacceptable side effects associated with adenosine or because of technical issues or other reasons; data for the remaining 2019 patients were included in the analyses (Fig. 1). The two groups were similar in terms of risk factors, indication for angiography, extent of coronary artery disease, and clinical and demographic characteristics (Table 1). The mean age was 68 years, and 21.8% of the patients had diabetes mellitus, 62.0% had stable angina, and 33.0% had had a previous myocardial infarction.

Procedural characteristics for the two trial groups are shown in Table 2. A total of 1568 lesions (1.55 lesions per patient) were assessed in the iFR group, and 1436 (1.43 lesions per patient) were assessed in the FFR group (P=0.002). The mean (±SD) iFR was 0.91±0.10, and the mean FFR was 0.82±0.10. In the iFR group, 29.1% of the lesions were hemodynamically important, as compared with 36.8% of the lesions in the FFR group (P<0.001). Revascularization was performed in 536 patients in the iFR group and in 569 patients in the FFR group (P=0.11). PCI was the primary revascularization procedure in 81.4% of the patients who underwent revascularization.

PRIMARY END POINT

No patients were lost to follow-up. A primary end-point event occurred in 68 of 1012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates, 0.7 percentage points; 95% confidence interval [CI], –1.5 to 2.8; P=0.007 for noninferiority) (Fig. 2). The upper limit of the two-sided 95% confidence interval for the difference in event rates fell within the prespecified noninferiority margin of 3.2 percentage points. The hazard ratio, estimat-

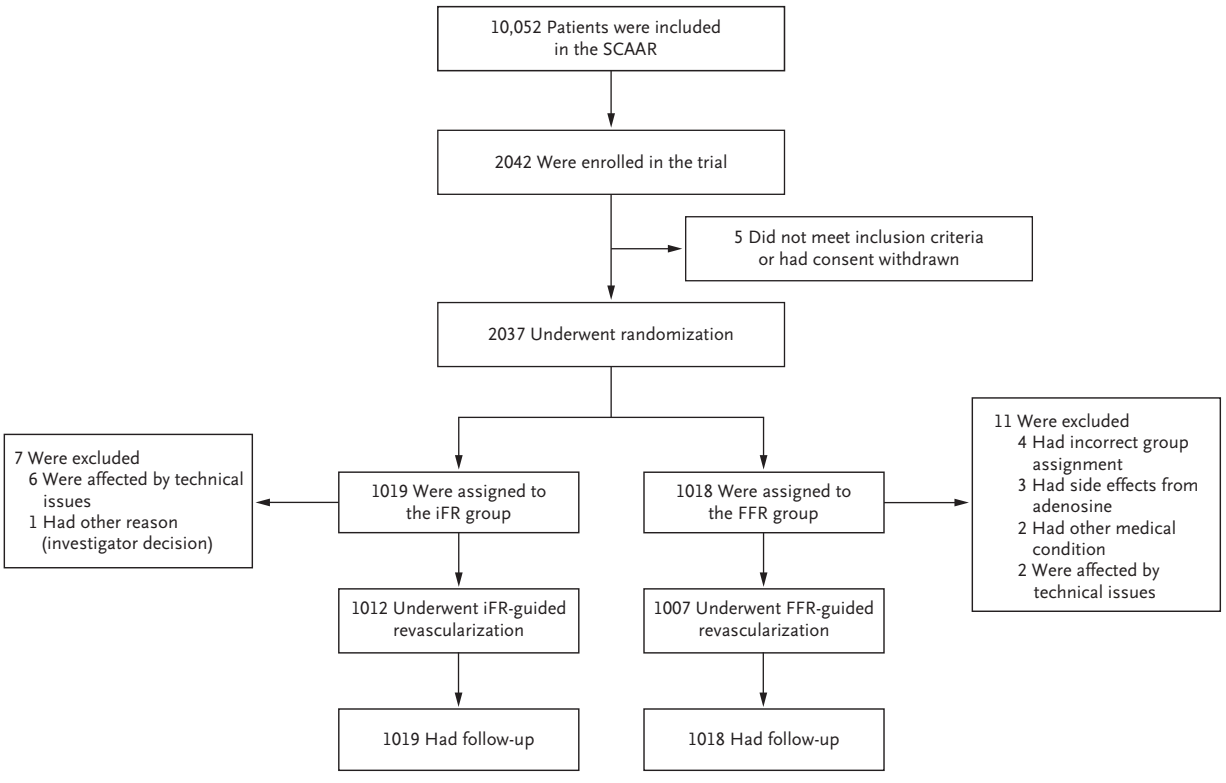

Figure 1. Enrollment, Randomization, and Follow-up.
FFR denotes fractional flow reserve, iFR instantaneous wave-free ratio, and SCAAR Swedish Coronary Angiography and Angioplasty Registry.

ed with the use of an unadjusted Cox regression model, was 1.12 (95% CI, 0.79 to 1.58; P=0.53) (Table 3). No significant heterogeneity of treatment effect was detected in subgroup analyses (Fig. S2 in the Supplementary Appendix).

SECONDARY END POINTS

The number of deaths from any cause at 12 months did not differ significantly between the iFR group (15 deaths, including 8 from cardiovascular causes) and the FFR group (12 deaths, including 6 from cardiovascular causes) (P=0.57) (Table 3). The rates of nonfatal myocardial infarction, unplanned revascularization, and target-lesion revascularization also did not differ significantly between the two groups. One confirmed case of stent thrombosis occurred in the iFR group, and two confirmed cases occurred in the FFR group. Restenosis was observed in 1.9% of the patients in the iFR group and in 1.8% in the FFR group (P=0.87). Chest discomfort during the procedure was reported by 3.0% of the patients in the iFR group and by 68.3% of the patients in the FFR group (P<0.001).

DISCUSSION

In patients with stable angina, unstable angina, or NSTEMI who had an indication for physiologically guided assessment of coronary-artery stenosis, an iFR-guided revascularization strategy was noninferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac outcomes and was associated with less chest discomfort. Our principal findings are similar to those reported now in the *Journal* by Davies et al.[16]

Significantly more lesions were assessed in the iFR group than in the FFR group. It is possible that the adenosine-related chest discomfort that occurred when FFR measurements were obtained made the treating physicians less inclined to investigate additional lesions in patients with multivessel disease. This suggests that adherence

Table 1. Baseline Characteristics of the Patients.*

Characteristic	iFR Group (N=1019)	FFR Group (N=1018)
Age — yr	67.6±9.6	67.4±9.2
Male sex — no. (%)	756 (74.2)	766 (75.2)
Body-mass index†	27.6±4.3	27.6±4.3
Indication for angiography — no. (%)		
Stable angina	632 (62.0)	632 (62.1)
Unstable angina	211 (20.7)	208 (20.4)
NSTEMI	176 (17.3)	178 (17.5)
Angina class — no./total no. with stable angina (%)‡		
I	153/632 (24.2)	121/632 (19.1)
II	355/632 (56.2)	343/632 (54.3)
III	49/632 (7.8)	74/632 (11.7)
IV	0	3/632 (0.5)
Missing data	75/632 (11.9)	91/632 (14.4)
Diabetes mellitus — no. (%)	232 (22.8)	213 (20.9)
Hypertension — no. (%)	730 (71.6)	710 (69.7)
Hyperlipidemia — no. (%)	733 (71.9)	704 (69.2)
Smoking status — no. (%)		
Never smoked	351 (34.4)	368 (36.1)
Former smoker	501 (49.2)	467 (45.9)
Current smoker	159 (15.6)	167 (16.3)
Missing data	8 (0.8)	16 (1.6)
Previous myocardial infarction — no. (%)	337 (33.1)	335 (32.9)
Previous percutaneous coronary intervention — no. (%)	429 (42.1)	425 (41.7)
Previous coronary-artery bypass grafting — no. (%)	49 (4.8)	43 (4.2)
Angiographic findings — no. (%)§		
Nonsignificant coronary artery disease	203 (20.0)	198 (19.4)
One-vessel disease	452 (44.3)	453 (44.5)
Two-vessel disease	256 (25.1)	267 (26.2)
Three-vessel disease	108 (10.6)	101 (9.9)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in baseline characteristics. FFR denotes fractional flow reserve, iFR instantaneous wave-free ratio, and NSTEMI non–ST-segment elevation myocardial infarction.

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

‡ Angina was classified among the patients with stable angina according to the Canadian Cardiovascular Society functional classification; classes range from I to IV, with higher classes indicating greater limitations of physical activity owing to angina.

§ Significant coronary artery disease was defined as the presence of at least 50% stenosis. Classification of one-vessel, two-vessel, or three-vessel disease was based on visual estimation.

to the protocol in the FFR group was suboptimal owing to the expected side effects of adenosine.

Significantly more lesions were assessed as hemodynamically important in the FFR group than in the iFR group. As a result, there was a slight difference between the two groups in the number of stents implanted. The difference in the number of lesions assessed as hemodynamically important is likely to be related to differences between iFR and FFR in terms of lesion

Table 2. Procedural Characteristics in the Per-Protocol Population.*

Characteristic	iFR Group (N=1012)	FFR Group (N=1007)	P Value
Radial-artery approach — no. of patients (%)	841 (83.1)	811 (80.5)	0.13
Contrast material used per patient — ml			0.10
Median	110	115	
Interquartile range	80–155	80–160	
Procedure time — min†			0.09
Median	50.8	53.1	
Interquartile range	13.8–87.8	18.1–88.1	
Fluoroscopy time — min			0.57
Median	10.5	10.2	
Interquartile range	6.3–16.8	6.5–16.0	
Intravenous adenosine administered — no. of patients (%)	NA	695 (69.0)	
Total no. of lesions evaluated	1568	1436	
No. of lesions evaluated per patient	1.55±0.86	1.43±0.70	0.002
Hemodynamically important lesions — no. (% of total lesions evaluated)‡	457 (29.1)	528 (36.8)	<0.001
No. of hemodynamically important lesions per patient‡	0.45±0.71	0.52±0.68	0.05
Mean iFR	0.91±0.10	NA	
Mean iFR in hemodynamically important lesions‡	0.80±0.13	NA	
Mean FFR	NA	0.82±0.10	
Mean FFR in hemodynamically important lesions‡	NA	0.72±0.08	
Lesion complexity according to the ACC–AHA class — no./total no. of treated lesions (%)§¶			0.73
A	61/915 (6.7)	73/980 (7.4)	
B1	304/915 (33.2)	320/980 (32.7)	
B2	284/915 (31.0)	300/980 (30.6)	
C	139/915 (15.2)	165/980 (16.8)	
Missing data	127/915 (13.9)	122/980 (12.4)	
Lesions treated in the vessel — no./total no. of treated lesions (%)¶			0.68
Left main coronary artery	14/915 (1.5)	16/980 (1.6)	
Left anterior descending artery	434/915 (47.4)	469/980 (47.9)	
Left circumflex artery	176/915 (19.2)	179/980 (18.3)	
Right coronary artery	164/915 (17.9)	196/980 (20.0)	
Missing data	127/915 (13.9)	120/980 (12.2)	
Total no. of stents placed	698	787	
No. of stents placed per patient undergoing PCI	1.58±1.08	1.73±1.19	0.05
Stent length per patient — mm	34.2±21.9	36.8±24.5	0.10
Stent diameter — mm	2.97±0.47	3.01±0.49	0.27
Drug-eluting stents placed — no. (% of total stents placed)‖	696 (99.7)	770 (97.8)	0.50
PCI as primary revascularization procedure — no. of patients (%)	443 (43.8)	456 (45.3)	0.50
CABG as primary revascularization procedure — no. of patients (%)	93 (9.2)	113 (11.2)	0.13
Revascularization performed — no. of patients (%)	536 (53.0)	569 (56.5)	0.11

* Plus–minus values are means ±SD. The per-protocol population included all patients who underwent assessment for coronary-artery stenosis. CABG denotes coronary-artery bypass grafting, NA not applicable, and PCI percutaneous coronary intervention.
† Data on procedure time were available for only 904 patients.
‡ An iFR of 0.89 or lower and an FFR of 0.80 or lower indicated hemodynamically important stenosis.
§ Lesion complexity was classified according to the American College of Cardiology (ACC)–American Heart Association (AHA) classification; class A indicates a simple lesion, B1 and B2 a moderately complex lesion, and C a complex lesion.
¶ Treated lesions were lesions for which PCI was performed, including those that did not undergo physiologically guided assessment.
‖ Only second-generation drug-eluting stents were used.

Table 3. End Points at 12 Months in the Per-Protocol Population.

End Point	iFR Group (N=1012)	FFR Group (N=1007)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary end point: death from any cause, nonfatal myocardial infarction, or unplanned revascularization	68 (6.7)	61 (6.1)	1.12 (0.79–1.58)	0.53
Death from any cause	15 (1.5)	12 (1.2)	1.25 (0.58–2.66)	0.57
Nonfatal myocardial infarction	22 (2.2)	17 (1.7)	1.29 (0.68–2.44)	0.42
Unplanned revascularization	47 (4.6)	46 (4.6)	1.04 (0.69–1.57)	0.84
Target-lesion revascularization	29 (2.9)	27 (2.7)	1.21 (0.70–2.07)	0.49
Restenosis	19 (1.9)	18 (1.8)	1.05 (0.55–2.01)	0.87
Stent thrombosis*	1 (0.1)	2 (0.2)		
Chest discomfort during procedure				<0.001†
None	982 (97.0)	319 (31.7)		
Mild	26 (2.6)	316 (31.4)		
Moderate	2 (0.2)	285 (28.3)		
Severe	2 (0.2)	87 (8.6)		

* Stent thrombosis was defined as the presence of stent occlusion on angiography and an acute clinical presentation.
† P value was calculated by means of the Wilcoxon rank-sum test.

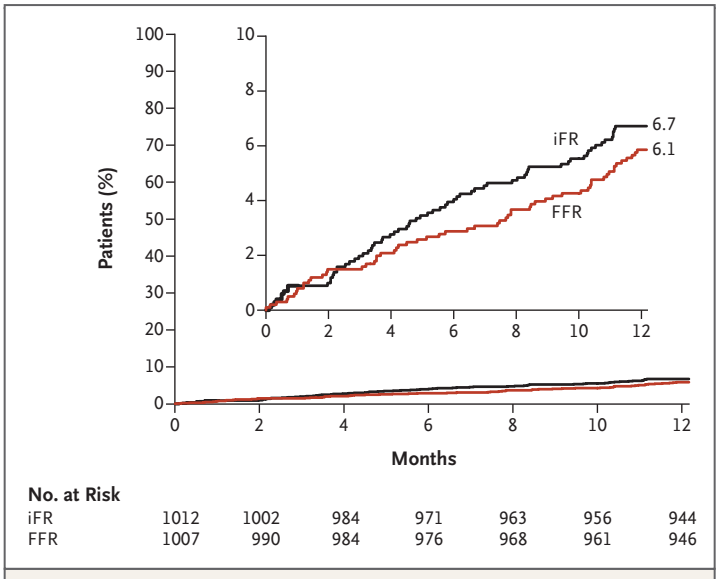

Figure 2. Kaplan–Meier Curves for the Primary End Point.
Shown are Kaplan–Meier curves for the cumulative risk of the composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization within 12 months after the index procedure. The inset shows the same data on an enlarged y axis.

classification. Previous trials have shown 80 to 85% agreement between iFR and FFR in the classification of lesions as hemodynamically important when the iFR threshold is 0.89.[8-10] Disagreement between the methods has usually been found to occur when the stenosis severity is in the intermediate range, close to the threshold.[8-10] This variation is unlikely to have an important effect on clinical outcomes, since observed rates of death and myocardial infarction are low in patient populations with FFR values close to the threshold of 0.80.[1-3,17]

Data suggest that in cases in which iFR and FFR classify lesions differently, iFR is the more accurate measure. In 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), iFR had better agreement with coronary flow reserve than did FFR.[5] Also, FFR was found to be more likely to overestimate lesion severity than iFR, most likely because hyperemia causes a pressure drop below the FFR threshold of 0.80 in lesions of interme-

diate severity despite normal coronary flow. Previous validation studies of iFR, in which other indexes of ischemia have been used as references, have shown that the diagnostic accuracy of iFR is similar to or better than that of FFR.[4-7] Validation studies of FFR have shown that FFR may correlate better with other indexes of ischemia when the threshold is 0.75, rather than 0.80.[18,19] Thus, the FFR threshold that was used in our trial may not have been optimal, although it was the threshold used in the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and FAME 2 trials.[2,3]

The proportion of evaluated lesions that were hemodynamically important was low in both groups. In the FAME trial, only patients with evidence of multivessel disease on angiographic assessment were enrolled, and 63% of the lesions were hemodynamically important.[2] In our trial, we intended to include any patient with an indication for physiologically guided lesion assessment, and the majority of the patients presented with single-vessel coronary artery disease. The low rates of hemodynamically important lesions that we observed most likely reflect the use of physiologically guided assessment in current clinical practice, predominantly for coronary lesions of intermediate severity.

FFR-guided PCI has been shown to be superior to angiography-guided PCI with respect to clinical outcomes.[2,3,20] Despite evidence supporting the use of FFR and despite the class Ia recommendation from the guideline of the American College of Cardiology Foundation–American Heart Association–Society for Cardiovascular Angiography and Interventions for the evaluation of stenoses of intermediate severity,[21,22] the clinical adoption of FFR is low.[23] This may be in part because the use of adenosine in the catheterization laboratory has infrequently been associated with complications.[24-26] On the basis of the findings observed in our study, iFR, which allows for lesion assessment without the use of adenosine, has the potential to increase the use of physiologically guided assessment among patients with coronary artery disease, the majority of whom still undergo angiographic assessment of lesion severity.

A noninferiority limit of 3.2 percentage points for the difference in event rates was chosen on the basis of the expected event rate of 8% in the FFR group. This cutoff corresponds to a noninferiority limit of 1.40 for the hazard ratio, which is consistent with the limit used in other large cardiovascular-outcomes trials with a noninferiority design.[27-29] In our trial, the overall event rates were lower than expected. Although the trial results showed that iFR was noninferior to FFR, the lower event rates meant that the fixed noninferiority limit of 3.2 percentage points allowed for a more generous confidence interval for the hazard ratio, a factor that constitutes a limitation of the trial.

Other trial limitations should also be noted. First, CABG was permitted as a revascularization procedure if it was clinically indicated. Since evidence confirming the clinical benefit of using FFR guidance in CABG is limited, the inclusion of patients treated with CABG in the trial may be considered a limitation. Second, reporting a continuous biologic variable, such as iFR or FFR, in a dichotomous manner (i.e., above vs. below a threshold) may omit clinical information from the decision-making process and represents a limitation to the clinical applicability of the trial. Finally, the treating physicians and the patients were aware of the group assignments, which could potentially have led to bias in the decision to perform unplanned revascularization.

In conclusion, among patients with an indication for physiologically guided assessment of coronary-artery stenosis, an iFR-guided revascularization strategy was found to be noninferior to an FFR-guided revascularization strategy with respect to the rate of major adverse cardiac events within 12 months after the procedure.

Supported by an unrestricted research grant from Philips Volcano to the Uppsala Clinical Research Center.

Dr. Götberg reports receiving lecture fees from Volcano, consulting fees and lecture fees from Boston Scientific, and fees for serving on an advisory board from Medtronic; Dr. Sandhall, receiving lecture fees from Philips Volcano and consulting fees and lecture fees from Boston Scientific; and Dr. Omerovic, receiving grant support and fees for serving on an advisory board from AstraZeneca and grant support from Abbott. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the staff at all centers participating in the Swedish Coronary Angiography and Angioplasty Registry collaboration for their professionalism and commitment to the trial; Dr. Hans Wedel (Nordic School of Public Health, Gothenburg, Sweden) for his initial statistical assistance; project manager Eva Jacobsson; the staff and the members of the clinical event adjudication committee led by cochairs Dr. Christoph Varenhorst and Dr. Claes Held (Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden); and Dr. Thomas Engstrøm (Rigshospitalet, Copenhagen) for his invaluable assistance with angiographic review.

APPENDIX

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