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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)

Javier Escaned, MD, PhD,*† Mauro Echavarría-Pinto, MD,*‡ Hector M. Garcia-Garcia, MD, PhD,‡ Tim P. van de Hoef, MD,§ Ton de Vries, MA,‖ Prashant Kaul, MD,¶ Ganesh Raveendran, MD,# John D. Altman, MD,** Howard I. Kurz, MD,†† Johannes Brechtken, MD,‡‡ Mark Tulli, MD,§§ Clemens Von Birgelen, MD, PhD,‖‖ Joel E. Schneider, MD,¶¶ Ahmed A. Khashaba, MD,## Allen Jeremias, MD,*** Jim Baucum, MD,††† Raul Moreno, MD,‡‡‡ Martijn Meuwissen, MD, PhD,§§§ Gregory Mishkel, MD,‖‖‖ Robert-Jan van Geuns, MD, PhD,‡ Howard Levite, MD,¶¶¶ Ramon Lopez-Palop, MD,### Marc Mayhew, MD,**** Patrick W. Serruys, MD, PhD,‡ Habib Samady, MD,†††† Jan J. Piek, MD, PhD,§ Amir Lerman, MD,‡‡‡‡ on behalf of the ADVISE II Study Group

ABSTRACT

OBJECTIVES The purpose of this study was to assess the diagnostic accuracy of the instantaneous wave-free ratio (iFR) to characterize, outside of a pre-specified range of values, stenosis severity, as defined by fractional flow reserve (FFR) ≤0.80, in a prospective, independent, controlled, core laboratory-based environment.

BACKGROUND Studies with methodological heterogeneity have reported some discrepancies in the classification agreement between iFR and FFR. The ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II) study was designed to overcome limitations of previous iFR versus FFR comparisons.

METHODS A total of 919 intermediate coronary stenoses were investigated during baseline and hyperemia. From these, 690 pressure recordings (n = 598 patients) met core laboratory physiology criteria and are included in this report.

RESULTS The pre-specified iFR cut-off of 0.89 was optimal for the study and correctly classified 82.5% of the stenoses, with a sensitivity of 73.0% and specificity of 87.8% (C statistic: 0.90 [95% confidence interval (CI): 0.88 to 0.92, $p < 0.001$]). The proportion of stenoses properly classified by iFR outside of the pre-specified treatment (≤0.85) and deferral (≥0.94) values was 91.6% (95% CI: 88.8% to 93.9%). When combined with FFR use within these cut-offs, the percent of stenoses properly classified by such a pre-specified hybrid iFR-FFR approach was 94.2% (95% CI: 92.2% to 95.8%). The hybrid iFR-FFR approach obviated vasodilators from 65.1% (95% CI: 61.1% to 68.9%) of patients and 69.1% (95% CI: 65.5% to 72.6%) of stenoses.

CONCLUSIONS The ADVISE II study supports, on the basis rigorous methodology, the diagnostic value of iFR in establishing the functional significance of coronary stenoses, and highlights its complementariness with FFR when used in a hybrid iFR-FFR approach. (ADenosine Vasodilator Independent Stenosis Evaluation II-ADVISE II; NCT01740895) (J Am Coll Cardiol Intv 2015;8:824–33) © 2015 by the American College of Cardiology Foundation.

From the *Cardiovascular Institute, Hospital Clinico San Carlos and Centro Nacional de Investigaciónes Cardiovasculares Carlos III (CNIC), Madrid, Spain; †Faculty of Medicine, Complutense University of Madrid, Spain; ‡Erasmus MC, Department of Cardiology, Rotterdam, the Netherlands; §AMC Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ‖Cardialysis BV, Rotterdam, the Netherlands; ¶University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; #Cardiovascular Division of the University of Minnesota, Minneapolis, Minnesota; **St. Anthony's Heart and Vascular Center and Colorado Heart and Vascular PC, Denver, Colorado; ††Division of Cardiology, Department of Medicine, Washington

The instantaneous wave-free ratio (iFR) is a recently-introduced pressure-derived, hyperemia-free index for the functional assessment of coronary stenoses (1). Previous studies have investigated the classification agreement between iFR and fractional flow reserve (FFR), used as a reference standard, which in general has been good (1–8). However, some discrepancies in their agreement have been observed, potentially related to methodological heterogeneity. Although the possible benefits and limitations of nonhyperemic indexes to guide coronary revascularization still need to be determined (9), a prospective study with rigorous methodology was deemed required to accurately establish the diagnostic value of iFR.

Since the introduction of iFR, a hybrid iFR-FFR diagnostic strategy has been proposed, where upper and lower iFR cut-offs are used to restrict decisions on the basis of iFR to those regions in which its agreement with FFR is very high, and FFR use is limited to the intermediate iFR range of values called the "adenosine zone" (3). Hence, the ADVISE II (ADenosine Vasodilator Independent Stenosis Evaluation II) study was designed to investigate, in a prospective, controlled, core laboratory-based environment, the diagnostic accuracy of iFR to characterize coronary stenosis severity as determined by FFR, exploring also the usefulness and convenience of the hybrid iFR-FFR approach.

METHODS

ADVISE II was a prospective, international, multicenter (n = 45) study that aimed to assess the diagnostic value of iFR to characterize, without concomitant administration of hyperemic agents, coronary stenosis severity as determined by the FFR (NCT01740895). The Ethics Committees and Institutional Review Boards of each participating center approved the study, and all patients gave written informed consent.

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PATIENT SELECTION AND PRESSURE TRACES ACQUISITION. Patients eligible for enrollment were age 18 to 85 years, suitable for coronary angiography and percutaneous coronary intervention (PCI), and had coronary stenosis (>40% diameter stenosis by visual assessment) in 1 or more native major epicardial vessel or its branches. Stable angina or acute coronary syndromes (only nonculprit vessels and >48 h from symptoms onset in case of myocardial infarction) were allowed. Complete inclusion and exclusion criteria are provided in the Online Appendix. Data acquisition included electrocardiographic (ECG) signal recording (required by the iFR calculation algorithm) and setting the reading of mean aortic pressure (P_a) at 3 beats. After

ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

P_a = aortic pressure

PCI = percutaneous coronary intervention

P_d = distal pressure

P_d/P_a = baseline distal-to-aortic pressure ratio

ROC = receiver-operating characteristic

University School of Medicine, St. Louis, Missouri; ‡‡Regions Hospital, Saint Paul, Minnesota; §§Cardiovascular Research of North Florida, Gainesville Florida; ‖‖Thoraxcentrum Twente, Department of Cardiology, Medisch Spectrum Twente, and Health Technology and Services Research, MIRA, University of Twente, Enschede, the Netherlands; ¶¶Wake Heart and Vascular Institute, Raleigh, North Carolina; ##Al Dorrah Heart Care Hospital, Ain Shams University, Cairo, Egypt; ***Stony Brook University Medical Center, Stony Brook, New York; †††Greenville Memorial Hospital, Grenville, South Carolina; ‡‡‡Hospital Universitario la Paz, Madrid, Spain; §§§Department of Cardiology, Amphia Hospital, Breda, the Netherlands; ‖‖‖Prairie Heart Institute, St. John's Hospital, Springfield, Illinois; ¶¶¶AtlantiCare Regional Medical Center, Egg Harbor Township, New Jersey; ###Hospital Universitario de San Juan de Alicante, Alicante, Spain; ****Wellmont Holston Valley Medical Center, Kingsport, Tennessee; ††††Division of Cardiology, Department of Medicine, Andreas Gruentzig Cardiovascular Center, Emory University School of Medicine, Atlanta, Georgia; and the ‡‡‡‡Center for Coronary Physiology and Imaging, Division of Cardiovascular Diseases, and Department of Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This study was funded by Volcano Corporation. The sponsor of the study had no role in the study design, data acquisition, data analysis or writing of the manuscript. All analyses were independently performed by the core laboratory (Cardialysis). Dr. Escaned has had consultancies/been a speaker at educational events for Volcano Corporation and St. Jude Medical. Dr. Echavarría-Pinto has served as a speaker at educational events organized by Volcano Corporation and St. Jude Medical. Dr. van de Hoef has served as a speaker at educational events organized by Volcano Corporation, St. Jude Medical, and Boston Scientific. Dr. Kaul has served as a consultant to Cardiovascular Systems Inc. Dr. von Birgelen has served as a consultant to Abbott Vascular, Boston Scientific, and Medtronic (including lecture fees or travel expenses); has received travel expenses from Biotronik; has received lecture fees from Merck Sharp & Dohme; and his institution has received research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. Dr. Jeremias has served as a consultant to Volcano Corporation. Dr. Mishkel has served as a speaker/trainer for Volcano Therapeutics. Dr. Samady has received a research grant from Volcano Corporation and St. Jude Medical. Dr. Lerman has received an unrestricted grant from Volcano to support an NIH project. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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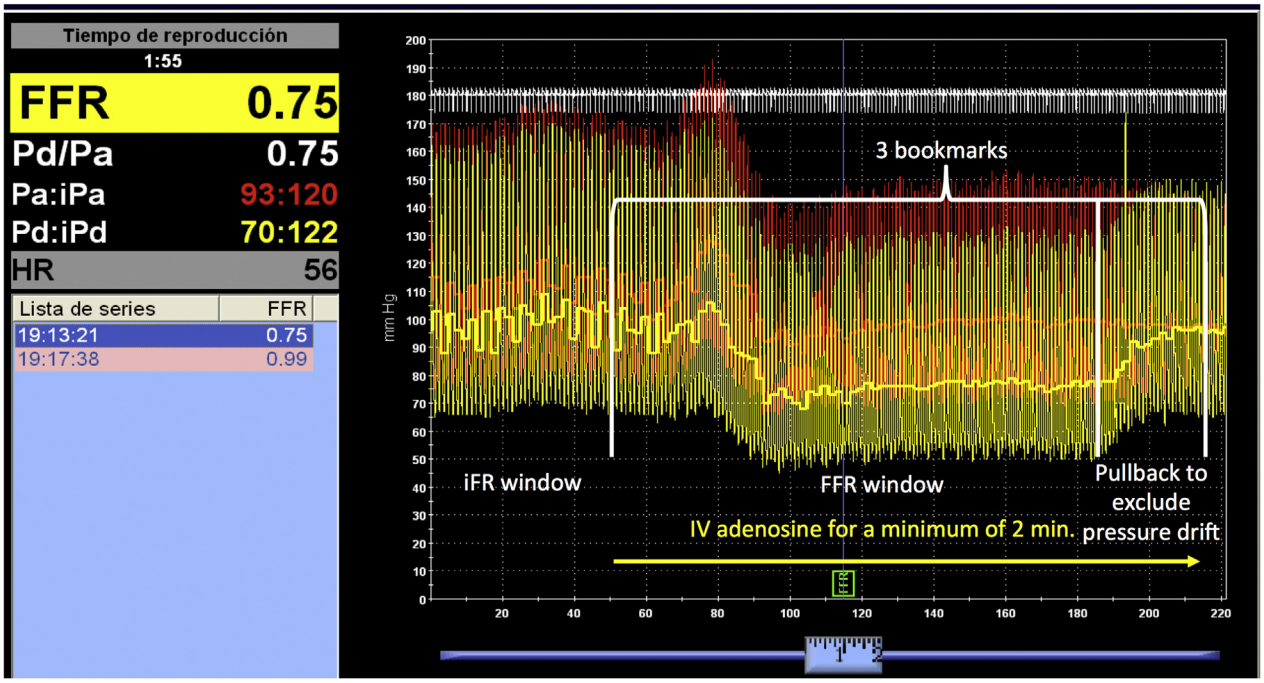
FIGURE 1 Example of the Methodology for Pressure and Electrocardiogram Acquisition



Example of the methodology for pressure traces acquisition in the ADVISE II study. First, correct normalization was recorded (in this case, in the label fractional flow reserve [FFR] = 0.99). Then, a single electrocardiogram and pressure recording included baseline pressures for a minimum of 20 s, adenosine infusion for a minimum of 2 min, and pressure wire pullback maneuver. Three bookmarks for core laboratory analyses were placed: 1) when adenosine infusion started; 2) when the pullback maneuver started; and 3) when the pressure sensor reached the tip of the guiding catheter. The operator was blinded to instantaneous wave-free ratio (iFR), which was calculated off-line at the core laboratory. IV = intravenous; P_a = aortic pressure; P_d = distal pressure; P_d/P_a = baseline distal-to-aortic pressure ratio.

intracoronary nitrates (300 μg) and acquisition of coronary angiograms, P_a and intracoronary distal pressure (P_d) were recorded as follows (Figure 1). First, the pressure wire was zeroed and equalized, and its correct equalization (P_d/P_a ratio of 1.0 ± 0.02) confirmed during a 10 s acquisition. Afterward, the pressure sensor was positioned distal to the index stenosis and the guiding catheter was flushed with saline. Baseline pressures were recorded for at least 20 s before inducing hyperemia. Adenosine administration through a large vein at a rate of 140 μg/kg/min for a minimum of 2 min and pressure wire pullback maneuver to check for pressure drift were both mandatory. In the same pressure recording, 3 bookmarks for core laboratory analyses were placed: 1) when adenosine infusion started; 2) when the pullback maneuver started; and 3) when the pressure sensor reached the tip of the guiding catheter. If a P_d/P_a ratio <0.98 or >1.02 at the catheter tip was documented, the protocol mandated repeat assessment. The s5/s5i console and PrimeWire Prestige PLUS coronary pressure wire (Volcano Corporation, San Diego, California) were used in all cases.

iFR AND FFR CALCULATION. All pressure recordings were analyzed by an independent Core Laboratory (Cardialysis, Rotterdam, the Netherlands) using iFR calculation software (HARVEST, Volcano Corporation) fully consistent with online commercial systems. This computational algorithm performs automated analyses on the basis of a synchronized ECG signal and determines the appropriate diastolic intervals for pressure measurements. By automatic identification of fiducial time points in the cardiac cycle, the diastolic window for pressure measurement is calculated beginning 25% into diastole and ending 5 ms before end diastole. iFR is then calculated as P_d/P_a ratio during this pre-specified period of time, within mid to late diastole under nonhyperemic conditions—the wave-free period—when it has been shown that intrabeat microvascular resistance is stable and minimized (1,6,10).

FFR was experimentally and clinically validated under conditions of maximum and stable hyperemia (11) and is automatically calculated by current computational software as the minimum P_d/P_a ratio found in the pressure recording. However, during

intravenous adenosine infusion, the minimum hyperemic P_d/P_a ratio might develop before stabilization of hyperemia, a situation that flaws the theoretical framework of FFR, as neither driving nor distal pressures are stable (12). Hence, conforming to its original validation (11,13), core laboratory analyses included a thorough review of pressure recordings to corroborate that FFR was calculated: 1) after initiation of adenosine infusion; 2) within stable hyperemia; and 3) before the pullback maneuver. Stable hyperemia was defined as the plateau in mean P_a after stabilization of changing hemodynamics following the initiation of adenosine infusion and before the pullback maneuver (12). If a plateau was not clearly observed, stable hyperemia was then defined as the period of pressure recording in which no further systematic fall in P_a was observed, following the initiation of adenosine infusion but before the initiation of the pullback (12). Within stable hyperemia, the minimum P_d/P_a ratio was then labeled as FFR.

Core laboratory analyses included an exhaustive evaluation of pressure waveforms to confirm that none of the following exclusion criteria were present: inappropriate normalization of the pressure wire (P_d/P_a ratio <0.98 or >1.02), ECG artifacts or significant arrhythmias in the first 20 s of the recording ("iFR calculation window"), loss of P_a or P_d signals at any point during the recording, automatic calculation pitfalls (identification of FFR during ectopic beats, P_a or P_d noise, wire whipping artifacts, and so on), dampening of P_a or P_d waveforms, pressure drift higher than <0.98 or >1.02, and absence of ECG or pressure-pullback recording.

HYBRID iFR-FFR APPROACH. This hybrid iFR-FFR diagnostic strategy was designed to increase adoption of physiology-guided PCI by decreasing the need for vasodilators whereas maintaining a very high classification agreement with a lone-FFR strategy (3). Two independent iFR values with very high negative and positive predictive values to exclude (defer-iFR value) and identify (treatment-iFR value) FFR-significant stenoses were investigated, assuming thus that only those stenoses with iFR values in-between would require vasodilator drugs for standard FFR classification. On the grounds of retrospectively-acquired data, it was found that a treatment iFR value ≤0.85, a deferral iFR value ≥0.94, and the use of FFR within the 0.86 and 0.93 iFR values ("adenosine zone") resulted in an overall 95% classification agreement with a lone-FFR strategy and obviated the need for vasodilators in 57% of patients.

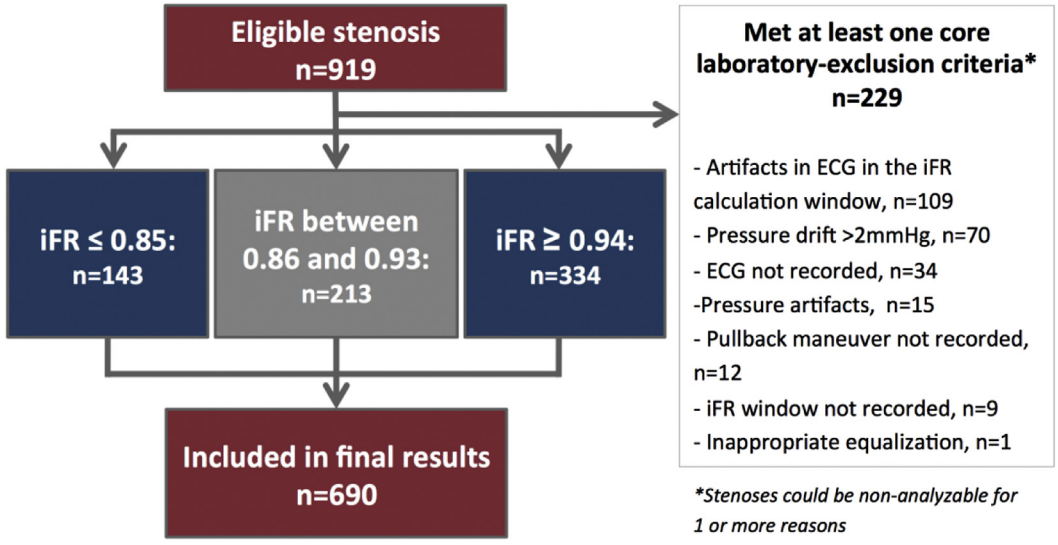
ENDPOINTS. The primary endpoint of the study was the percentage of stenoses properly classified by the iFR values ≤0.85 and ≥0.94, as proposed by the hybrid iFR-FFR approach. Hemodynamic severity was defined as FFR ≤0.80. Pre-specified secondary endpoints were: 1) the diagnostic performance of the iFR 0.89 cut-off; 2) the optimal iFR cut-off against FFR ≤0.80 derived from receiver-operating characteristic (ROC) curve analyses; 3) the minimum iFR exclusion ranges around the iFR 0.89 cut-off in which the iFR and FFR agreement was ≥80%, ≥90%, and ≥95%; 4) the correlation coefficient between iFR and FFR; and 5) the proportion of stenosis and patients free from vasodilator drugs expected from the previously-mentioned pre-specified hybrid iFR-FFR approach.

STATISTICAL ANALYSIS. For quantitative variables, data are expressed as mean ± SD. Non-normal data are reported as the median with first and third quartiles (Q1, Q3). For categorical data, counts and percentages are provided. The 95% confidence intervals (CIs) of the means of continuous variables and percentages of categorical variables were calculated with *t* tests and Clopper-Pearson (Exact) approaches, respectively. ROC curve analyses were performed to determine the optimal iFR cut-off against FFR ≤0.80, defined as the value that maximized correct classification. Pearson's correlation coefficient (r) between iFR and FFR was computed, and the Fisher Z transformation was used to provide its 95% CIs. Linear regression was used to further characterize the iFR and FFR relationship, and being as this was a multicenter study, between-center variability was assessed by adding participating center as random effect. However, a significant effect parameter was not found for any of the centers, and the total effect of adding such a center effect to the analysis was nonsignificant ($p = 0.165$). We, therefore, concluded that the center effect could be ignored. The SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and STATA 12.1 (StataCorp, College Station, Texas) statistical software packages were used. Applicable tests were 2-tailed, and differences were considered significant at $p < 0.05$.

RESULTS

STUDY POPULATION. Between January 9, 2013, and June 28, 2013, 919 stenoses from 797 patients were investigated and included in the study. Of these stenoses, 229 (24.9%) met at least 1 of the pre-defined core laboratory exclusion criteria, leaving 690 stenoses from 598 patients for final analyses. A STARD-type (STAndards for the Reporting of Diagnostic Accuracy Studies) (14) flow chart depicting this process is provided in **Figure 2**. Clinical and angiographic

FIGURE 2 Process Followed by Eligible Stenosis



A STARD-type flow diagram showing the process followed by eligible stenosis from inclusion to final results. ECG = electrocardiogram; other abbreviations as in Figure 1.

characteristics of the study population are shown in Tables 1 and 2. Overall, mean age was 63.6 ± 10.8 years, and 68.9% were male patients. The most common clinical presentation was chronic stable angina (53.5%), followed by unstable angina (25.3%), and the left anterior descending artery was the most commonly interrogated vessel (54.5%). Figure 3 shows the distribution of the FFR values in the

TABLE 1 General Characteristics of the Study Population (n = 598)

	Mean ± SD or %	95% CI*
Baseline demographics		
Age (yrs)	63.6 ± 10.8	62.7–64.5
Male	68.9	65.0–72.6
Medical history		
Prior myocardial infarction	35.2	31.3–39.2
Prior PCI	49.1	45.0–53.2
Prior CABG	4.7	3.2–6.7
Congestive heart failure	8.4	6.3–11.0
Hypertension	78.8	75.3–82.1
Diabetes mellitus	35.0	31.1–39.0
Current smoker (≤6 months)	22.6	19.3–26.3
History of other vascular disease	17.4	14.4–20.8
Renal dysfunction (serum creatinine >2.0)	2.9	1.7–4.6
Pulmonary disease	12.0	9.5–14.9
Clinical presentation		
Stable angina	53.5	49.4–57.6
Unstable angina	25.3	21.8–28.9
Silent ischemia	13.1	10.5–16.1
NSTEMI (>48 h before enrollment)	5.6	3.9–7.7
STEMI (>48 h before enrollment)	2.5	1.4–4.1

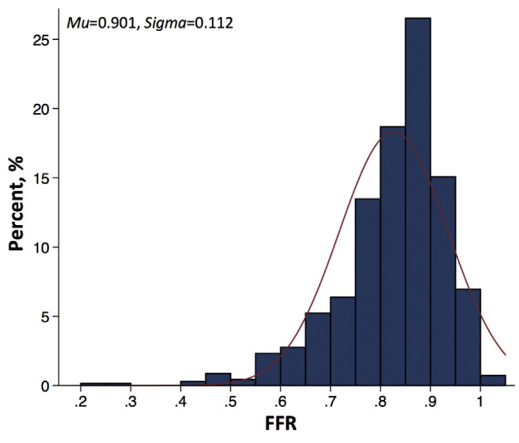
*95% confidence intervals (CIs) of the mean.
CABG = coronary artery bypass graft; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 General Characteristics of Epicardial Stenosis Included in Study (n = 690)

	% or Mean ± SD	95% CI*
Vessel		
Left anterior descending artery	54.5	50.7–58.3
Left circumflex	25.7	22.4–29.1
Right coronary artery	19.9	16.9–23.0
Stenosis characteristics†		
Lesion length (mm)	14.0 ± 7.9	13.40–14.59
Reference vessel diameter (mm)	3.0 ± 0.50	2.93–3.01
Percentage of diameter stenosis	60.0 ± 13.0	58.7–60.7
Lesion type (AHA)		
A	34.9	31.3–38.6
B1/B2	52.2	48.4–56.0
C	12.9	10.4–15.6
Current in-stent restenosis	7.1	5.3–9.3

*95% confidence intervals (CIs) of the mean. †Visual assessment.
AHA = American Heart Association.

FIGURE 3 Distribution of the FFR Values Observed in the Study



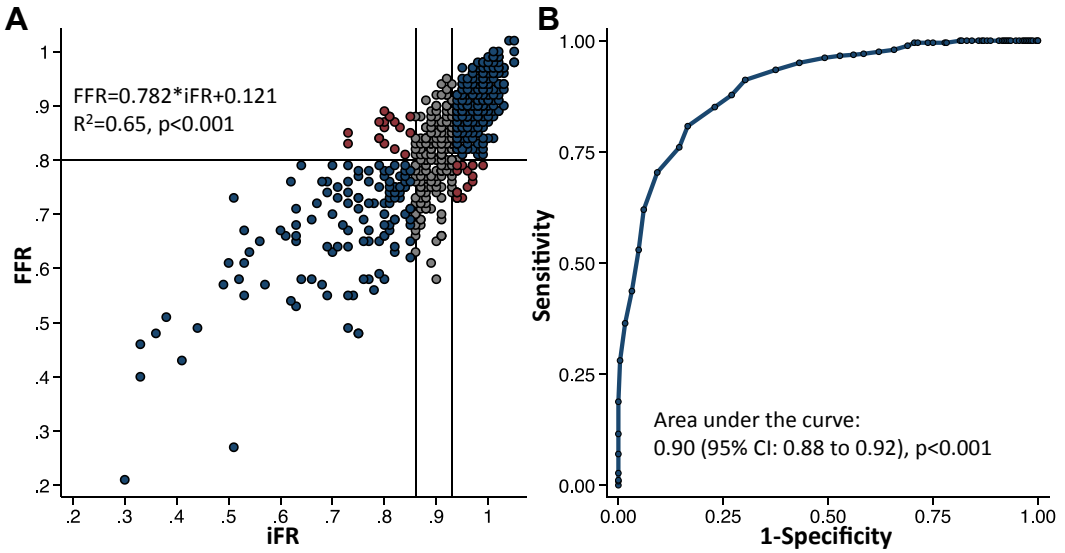
Frequency histogram with superimposed normal distribution of the fractional flow reserve (FFR) values in study population. Please note the unimodal FFR distribution as well as data clustering around the FFR 0.80 cut-off point.

study. In general, the study population was composed of stenoses of intermediate angiographic (diameter stenosis: 60 ± 13% by visual assessment) and physiological severity (FFR: mean 0.83 ± 0.11; median 0.84 [Q1 0.77, Q3 0.90]). Finally, 248 (35.9%) vessels had FFR ≤0.80.

DIAGNOSTIC ACCURACY OF iFR AGAINST FFR. Figure 4A shows the scatterplot of the relationship between iFR and FFR. There was a strong linear correlation between both indexes (r = 0.81, 95% CI: 0.78 to 0.83, p < 0.001). ROC analyses identified 0.89 as the optimal iFR cut-off, with an area under the ROC curve (C statistic) of 0.90 (95% CI: 0.88 to 0.92, p < 0.001) (Figure 4B). Notably, the optimal iFR cut-off observed in the study matched the pre-specified one. This 0.89 iFR cut-off correctly classified 82.5% of total stenoses, with a sensitivity of 73.0% and specificity of 87.8%. For the study prevalence (FFR ≤0.80, 35.9%), the positive predictive and negative predictive values of this cut-off were 77.0% and 85.3%, respectively.

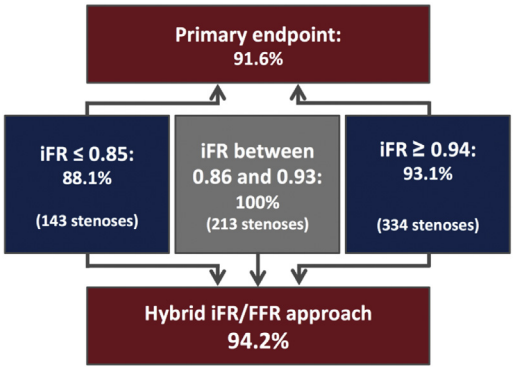
STUDY ENDPOINTS. The iFR treatment (≤0.85) and deferral (≥0.94) values correctly classified 88.1% (95% CI: 81.6% to 92.9%) and 93.1% (95% CI: 89.8% to 95.6%) of the stenoses, respectively. Thus, the overall proportion of stenoses properly classified by iFR outside such pre-specified iFR treatment (≤0.85) and deferral (≥0.94) values was 91.6% (95% CI: 88.8% to 93.9%) (Figure 5). The best iFR exclusion range around the pre-specified 0.89 cut-off to achieve ≥80% diagnostic accuracy was this cut-off

FIGURE 4 iFR Versus FFR Relationship



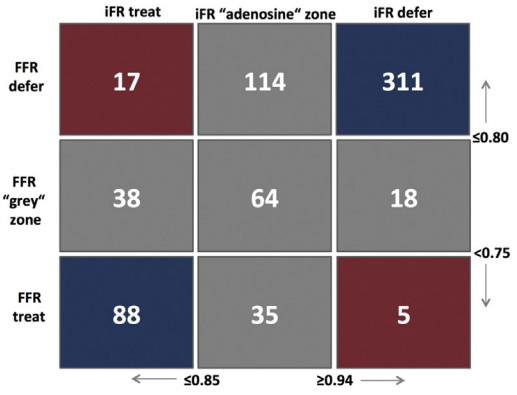
(A) The scatterplot of the relationship between iFR and FFR. **Vertical lines** are placed at the boundaries of the "adenosine zone" (iFR values of 0.86 and 0.93). The **horizontal line** is placed at the clinically-adopted 0.80 FFR cut-off value. **(B)** The receiver-operating characteristic curve of iFR against FFR ≤0.80. The optimal iFR cut-off identified in the ADVISE II study was 0.89. CI = confidence interval; other abbreviations as in Figure 1.

FIGURE 5 Primary Endpoint of the Study and Hybrid iFR-FFR Approach



The iFR treatment (≤0.85) and deferral (≥0.94) values correctly classified 88.1% and 93.1% of investigated stenoses, respectively. The overall proportion of stenoses properly classified by iFR outside of the pre-specified iFR values was 91.6%. This value increased to 94.2% after including standard classification with FFR in-between (hybrid iFR-FFR approach). Abbreviations as in Figure 1.

FIGURE 6 Absolute Counts of Stenoses Across Categories of iFR and FFR



Please note how most of the between-indexes disagreement was located within the FFR "gray zone" (FFR values between 0.75 and 0.80), where the ischemic potential of the interrogated stenosis is known to be less certain. Abbreviations as in Figure 1.

itself, because it correctly classified 82.5% of total stenoses. To achieve 90% and 95% classification agreement with FFR, the minimum iFR exclusion ranges below and above the optimal 0.89 cut-off were ≤0.86 (to predict FFR ≤0.80) and ≥0.94 (to predict FFR >0.80), which provided a percentage agreement of 91.0%, and ≤0.78 (to predict FFR ≤0.80) and ≥0.95 (to predict FFR >0.80), which provided a percent agreement of 95.3%. Finally, Figure 6 demonstrates how most of the classification disagreement between iFR and FFR was located within the FFR "gray zone" (FFR values between 0.75 and 0.80), where the ischemic potential of the stenosis is known to be less certain (15).

HYBRID iFR-FFR APPROACH. The percentage of stenoses properly classified by the pre-specified hybrid iFR-FFR approach was 94.2% (95% CI: 92.2% to 95.8%), and it had associated sensitivity, specificity, and positive and negative predictive values of 90.7%, 96.2%, 93.0%, and 94.9%, respectively (Figure 5). The estimated proportion of patients and stenoses free from vasodilator agents by such a pre-specified hybrid iFR-FFR approach amounted to 65.1% (95% CI: 61.1% to 68.9%) and 69.1% (95% CI: 65.5% to 72.6%), respectively.

DISCUSSION

The results of the ADVISE II study support the diagnostic value of iFR in establishing the hemodynamic severity of coronary stenoses and highlight its complementariness with FFR when used in a hybrid iFR-FFR approach.

iFR AS AN ALTERNATIVE FOR PHYSIOLOGICAL ASSESSMENT OF CORONARY STENOSIS. Although decision-making on the basis of intracoronary physiology was initiated 20 years ago with Doppler-tipped guide wires (15), the demonstration that intracoronary physiology is not only safe, but also results in better patient outcomes, came from studies comparing FFR with coronary angiography (16,17). This clinical evidence has made FFR the technique of choice for physiological assessment of coronary stenoses (18). Hence, the introduction of iFR took place at a time in which FFR constituted the paradigm (and for many the synonym) of intracoronary physiology, which was concomitantly facilitated by many common aspects between the 2 techniques. iFR is derived from the same theoretical framework as FFR (i.e., the relationship between the translesional pressure ratio and the impairment in myocardial blood supply caused by the interrogated stenosis) and is obtained with conventional pressure wires and appropriate software (1,11). Without a doubt, the main attractiveness of iFR is the avoidance of vasodilator drugs, identified as a cumbersome requirement for FFR interrogation (19). Thus, iFR appeared to many to be a potential step ahead toward the simplification of physiological stenosis assessment introduced by FFR many years ago.

The publication of the first study on iFR generated significant interest among interventional cardiologists (1–8). The RESOLVE (Multicenter Core Laboratory Comparison of the Instantaneous Wave-free Ratio and Resting Pd/Pa with Fractional Flow Reserve) study (8), a recent pooled-retrospective analysis, provides an excellent perspective of published and unpublished iFR versus FFR comparisons performed within the first year after the publication of the ADVISE study (1). In RESOLVE, data from individual studies was reanalyzed after standardization and application of inclusion and exclusion criteria, and iFR was recalculated using the original iFR calculation algorithm. There was relatively little variation in the diagnostic accuracy of iFR among the 6 independent research groups (n = 1,593), and it was proposed that these differences probably resulted from inconsistencies in data collection and analysis inherently linked to the retrospective design—including nonuniform patient and lesions characteristics, varying acquisition equipment and protocols, absence of ECG and final pressure wire pullback to exclude pressure drift, among others—as highlighted by the investigators.

The ADVISE II study was designed to address the limitations of retrospective studies like RESOLVE through a prospective, multicenter design, with rigorous, standardized methodology and independent analysis at a core laboratory. Key differential aspects included FFR technique standardization, corroboration of appropriate pre-measurement equalization, the acquisition of a single ECG and pressure recording encompassing baseline, induction and achievement of hyperemia, pressure wire pullback, and persistence of calibration at the catheter tip. This rigorous methodology becomes highlighted by the high exclusion rate (nearly 25% of tracings) in ADVISE II, superior to that reported in RESOLVE (17%), which is probably explained by the fact that in RESOLVE, exclusions due to ECG were not considered. In our study, nearly one-half (48%) of the excluded traces resulted from ECG pitfalls, probably mirroring a lack of awareness by catheterization laboratory personnel on the relevance of ECG for accurate iFR calculation and indicating an important methodological difference with RESOLVE. Importantly, in consonance with FFR theoretical framework (11), ADVISE II mandated FFR calculation as the minimal P_d/P_a ratio during the steady-state hyperemic plateau. Finally, a higher C statistic (0.90) in ADVISE II than in RESOLVE (0.81) was documented, and a very similar optimal iFR cut-off value was found (0.89 in ADVISE II, 0.90 in RESOLVE). This provides further evidence on the appropriateness of the use of this cut-off value in future studies.

Finally, RESOLVE also reported a good diagnostic performance of the largely neglected baseline P_d/P_a ratio. As the interest in the diagnostic performance of baseline P_d/P_a emerged when ADVISE II was already initiated, baseline P_d/P_a analyses were not included as pre-specified endpoints of the study. Yet, to investigate the value of this nonhyperemic index, a post-hoc analysis of ADVISE II data with the same methodology applied to the iFR versus FFR comparison reported in this paper has been performed, and is discussed in detail elsewhere (20).

USE OF THE HYBRID iFR-FFR APPROACH. The simplest way of assessing the diagnostic accuracy of iFR is to use FFR dichotomized at 0.80 as the reference standard. However, this approach is fraught by the limitations of dichotomizations in biological continuous systems (2,3,21). This makes comparisons sensitive to the characteristics of coronary stenosis populations, where lower intertechnique and intratechnique agreements are, by definition, expected when used in unimodal distributions peaking around cut-offs, as compared with broader distributions where more very severe and minimal stenoses are present (21). In this regard, it is important to acknowledge that the distribution of FFR values in ADVISE II was intermediate (diameter stenosis: 60 ± 13%; FFR: 0.83 ± 0.1) (**Figure 3**), which is the most challenging for the purpose of establishing the diagnostic accuracy of iFR, as data clustering near the FFR cut-off helps small differences lead to classification disagreement (2,3,21).

To overcome these limitations, a hybrid iFR-FFR approach has been proposed as a way to translate into practice the potential value of iFR as a diagnostic tool. The ADVISE II study supports the diagnostic value of this hybrid iFR-FFR diagnostic approach, as it properly classified 94.2% of total stenosis, with values of specificity, sensitivity, and positive and negative predictive values >90%. With this strategy, adenosine would not be required in 69% of the stenoses, and in 65% of patients, adenosine would not be needed at all. These figures support the potential of iFR to ease catheterization laboratory workflow and to reduce costs associated with ischemia-driven revascularization.

IMPLICATIONS OF ADVISE II RESULTS FOR CLINICAL PRACTICE. The ADVISE II study probably constitutes the definitive direct comparison between iFR and FFR. Because the low adoption of FFR (22) is clearly the first obstacle for translating the benefits of ischemia-driven revascularization to patients, the results of ADVISE II may contribute to increase its implementation, particularly when used synergistically with FFR. This is an

urgent task, because recent studies like RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) have demonstrated that revascularization decisions on the basis of angiography and available clinical information are modified in >30% of cases when physiological interrogation is performed (23). At a time that FFR is used in a minority of cases and, therefore, similar rates of misdiagnosis should be expected in non-FFR practices, a huge net benefit would be expected if a hybrid iFR-FFR approach is adopted, even if 5.8% stenoses would not be properly classified according to FFR (24).

A second obstacle to translate available evidence on the benefit of FFR to patients is the restriction of physiological interrogation to intermediate stenosis, and not to all potential revascularization targets, irrespective of their angiographic appearance. It is important to note that, in randomized studies, FFR has been measured in all stenoses regardless of their angiographic severity (16,17,25). However, as highlighted by observational studies including ADVISE II, most interventional cardiologists do not measure FFR in stenoses judged as clearly severe or nonsevere on the grounds that it interferes with catheterization laboratory workflow and increases costs. Although the cost-effectiveness analysis of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study has clearly demonstrated that the latter perception is wrong (25), the sharp decrease in the need for adenosine found in ADVISE II constitutes a potential solution for the former obstacle. Indeed, the forthcoming multicenter SYNTAX II trial (NCT02015832) that applies ischemia-driven revascularization to patients with triple-vessel disease treated with PCI has opted for a hybrid iFR-FFR approach to reduce procedural time in this type of complex procedure.

STUDY LIMITATIONS. The ADVISE II study is the first prospective, core laboratory-based intracoronary physiology study. Therefore, being a validation analysis, stringent core-laboratory criteria were applied. Although this approach reduces the potential for bias and threats to statistical internal validity, it might also limit the generalization of the findings to different populations. However, the fact that the diagnostic accuracy of iFR observed in clinical retrospective registries shows very little variations from that observed in this meticulous prospective study is reassuring.

CONCLUSIONS

The ADVISE II study observed a high diagnostic accuracy of iFR as compared to FFR and, therefore, supports the diagnostic value of this nonhyperemic index in establishing the hemodynamic severity of coronary stenoses and highlight its complementariness with FFR when used in a hybrid iFR-FFR approach.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Javier Escaned, Hospital Clinico San Carlos, 28040 Madrid, Spain. E-mail: escaned@secardiologia.es.

PERSPECTIVES

WHAT IS KNOWN? iFR is a novel adenosine-free index developed to simplify stenosis severity assessment and to expand the use of physiology in the catheterization laboratory. Although previous studies suggested a good overall classification agreement between iFR and FFR in terms of functional stenosis severity, a marked variability was noted between individual studies. ADVISE II was designed to validate the accuracy of iFR by applying a rigorous methodology that addressed methodological limitations of previous studies.

WHAT IS NEW? The study identified that the prespecified hybrid iFR-FFR approach properly classified 94.2% of the stenoses and obviated vasodilator need in 69.1% (95% CI: 65.5% to 72.6%) stenoses.

WHAT IS NEXT? Further to using FFR as a reference technique to assess iFR, as in ADVISE II, future studies must focus on demonstrating noninferiority of iFR with respect to FFR in terms of clinical outcomes when it is used as a decision-making tool.

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KEY WORDS adenosine, coronary artery disease, fractional flow reserve, instantaneous wave-free ratio, physiology, vasodilation

APPENDIX For inclusion/exclusion criteria and a list of participating centers, please see the online version of this article.