Impact of Routine Fractional Flow Reserve Evaluation During Coronary Angiography on Management Strategy and Clinical Outcome

One-Year Results of the POST-IT Multicenter Registry

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Background—Penetration of fractional flow reserve (FFR) in clinical practice varies extensively, and the applicability of results from randomized trials is understudied. We describe the extent to which the information gained from routine FFR affects patient management strategy and clinical outcome.

Methods and Results—Nonselected patients undergoing coronary angiography, in which at least 1 lesion was interrogated by FFR, were prospectively enrolled in a multicenter registry. FFR-driven change in management strategy (medical therapy, revascularization, or additional stress imaging) was assessed per-lesion and per-patient, and the agreement between final and initial strategies was recorded. Cardiovascular death, myocardial infarction, or unplanned revascularization (MACE) at 1 year was recorded. A total of 1293 lesions were evaluated in 918 patients (mean FFR, 0.81±0.1). Management plan changed in 406 patients (44.2%) and 584 lesions (45.2%). One-year MACE was 6.9%; patients in whom all lesions were deferred had a lower MACE rate (5.3%) than those with at least 1 lesion revascularized (7.3%) or left untreated despite FFR≤0.80 (13.6%; log-rank P=0.014). At the lesion level, deferral of those with an FFR≤0.80 was associated with a 3.1-fold increase in the hazard of cardiovascular death/myocardial infarction/target lesion revascularization (P=0.012). Independent predictors of target lesion revascularization in the deferred lesions were proximal location of the lesion, B2/C type and FFR.

Conclusions—Routine FFR assessment of coronary lesions safely changes management strategy in almost half of the cases. Also, it accurately identifies patients and lesions with a low likelihood of events, in which revascularization can be safely deferred, as opposed to those at high risk when ischemic lesions are left untreated, thus confirming results from randomized trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01835808.

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Key Words: coronary angiography ■ decision aids ■ fractional flow reserve ■ management strategy ■ outcome

Fractional flow reserve (FFR) has been validated as a reliable surrogate for inducible ischemia,[1] supporting its use during invasive procedures for functional assessment of coronary lesions. Landmark randomized trials have demonstrated that deferral of nonsignificant lesions based on FFR is not only safe[2] but also that FFR-guided

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WHAT IS KNOWN

- Fractional flow reserve–guided revascularization has been shown to improve clinical outcomes and reduce costs in patients involved in clinical trials.

WHAT THE STUDY ADDS

- Assessment of lesion severity using fractional flow reserve has the potential to safely change treatment strategy in a high proportion of cases.
- Routine use of fractional flow reserve may reduce downstream need for noninvasive stress testing and new procedures.
- Findings from randomized trials were reproduced in a real-world setting, further reinforcing the role of fractional flow reserve as a powerful tool for risk stratification and clinical decision making.

revascularization is associated with a better clinical outcome up to 2 years, when compared with standard angiography.[3] Results from the FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) study suggested that deferring the revascularization of epicardial stenosis with an FFR≤0.80 was associated with an 11.4% absolute increase in the risk of major cardiovascular events at 24 months (8.1% in revascularized patients versus 19.5% in medically treated), an hazard that was mainly driven by urgent revascularization.[4]

In spite of the overwhelming evidence of its potential clinical and economic benefits[5] and strong guideline recommendation,[6] the adoption of FFR in the real-world is perceived to vary significantly. Reasons for this disparity are several, but most operators still do rely the most on angiographic eyeballing to decide on the functional significance of coronary lesions and the need for revascularization.[7]

The Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease (POST-IT) was a prospective registry designed to describe the patterns of the use of FFR in an unselected real-world population, to assess its impact on clinical decision making—concerning both lesion and patient management—and the 1-year outcome of such a strategy.

Methods

Study Design and Patient Population

The POST-IT registry was an investigator-initiated observational study, designed to prospectively include all patients referred for coronary angiography in which at least 1 lesion was evaluated by FFR. All centers capable of performing FFR were invited to participate and there were no predefined exclusion criteria, other than the patient's unwillingness to provide written informed consent and life expectancy <1 year because of known noncardiovascular comorbidity. The decision to perform FFR was left to the operator in each case.

The study primary purpose was to evaluate the clinical outcome of a management strategy based on FFR evaluation of patients referred for angiography with suspected or confirmed obstructive coronary artery disease on routine daily practice. The impact of FFR on decision making (revascularization versus medical therapy versus further noninvasive stress test), both per-lesion and per-patient, was also assessed.

Data Collection and Monitoring

Patient baseline and procedural characteristics were prospectively collected at the time of inclusion and recorded in a dedicated electronic case report form. To ensure the quality and reliability of the data, external monitoring was undertaken.

FFR Cutoff and Management Strategy

As part of the inclusion algorithm, treating physicians were asked to establish a management plan for each lesion (revascularization, medical therapy or noninvasive stress test) based on all available information before and after FFR determination. Agreement between the final and initial strategies was recorded for each evaluated lesion and per-patient. There was no specific recommendation whether to use any of the cutoffs previously validated in randomized trials (0.75 or 0.80). Clinical decisions were entirely left at the operators' discretion. Please refer to the Data Supplement file for a detailed description.

Clinical Follow-Up and End Point Definition

Patients were followed for 12 months after the index procedure for the occurrence of the composite primary end point (MACE) of death from cardiovascular causes, myocardial infarction (MI) or new unplanned revascularization (please refer to the Data Supplement file for detailed definitions of all study end points). An independent committee reviewed each reported event for consistency before final adjudication. For the purpose of the outcome analysis, the population was divided into 3 groups according to the management of lesions and patients in a way that they would resemble relevant populations in randomized trials as much as possible: group 1 consisted of patients in whom all lesions evaluated were deferred based on an FFR>0.80 and no other lesions were revascularized; group 2 consisted of patients who underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) of at least 1 lesion either during the index procedure or subsequently; and finally, patients in group 3 were those in whom at least 1 lesion with an FFR≤0.80 was left untreated. A similar approach was chosen for the per-lesion analysis: group 1, deferred lesions with FFR>0.80; group 2, lesions revascularized, regardless of FFR value; and group 3, lesions with FFR≤0.80 who were not treated.

Statistical Analysis

Continuous variables with normal distribution were expressed as means and SD. Continuous variables with a non-normal distribution were expressed as median and interquartile range. Normality was tested with the Kolmogorov–Smirnov test and Q–Q Plot visual assessment. Discrete variables were expressed as percentages. Agreement between initial and post-FFR treatment strategy was assessed by the Cohen κ test. Whenever necessary, comparison of baseline characteristics or outcomes was performed using the χ^2 test, with Yates correction when appropriate, for categorical variables, the Student *t* test, the Satterthwaite test or 1-way ANOVA for continuous variables with normal distribution and the Kruskal–Wallis test for continuous variables with a non-normal distribution. Unadjusted event-free survival was evaluated by Kaplan–Meier estimates and statistical significance assessed by the log-rank test. Adjusted risk estimates were obtained using Cox proportional hazard models, including variables found to differ significantly between groups on univariate analysis or deemed to be clinically relevant. A detailed description of these variables is presented in the Methods section of the Data Supplement. For all comparisons, a *P* value of <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CIs) were calculated. Statistical analysis was performed with IBM SPSS Statistics version 19.0 (SPSS Inc, Chicago, IL).

Ethics and Regulation

The study was undertaken according to best clinical practices and all patients provided written informed consent. The protocol complies with the Declaration of Helsinki and was approved by institutional review boards at each participating site. A registration was made on the

Portuguese National Data Protection Commission and ClinicalTrials.gov (identifier: NCT01835808).

Results

Population Baseline Characteristics

From March 2012 to November 2013, 918 patients were enrolled in 19 hospitals. Inclusion rate per participating center is summarized in Table I in the Data Supplement. The flowchart of patient inclusion is shown in Figure 1, and population baseline characteristics are depicted in Table and in Table II in the Data Supplement. Despite the main indication for coronary angiography was suspected or known stable coronary artery disease, a significant proportion of patients (35.4%) were enrolled in the setting of an acute coronary syndrome (ACS), either recent or ongoing. Although some differences existed between the 3 study groups, there was no clear clustering of adverse characteristics known to decisively influence hard clinical outcomes.

Lesion Characteristics and FFR Procedure

A total of 1293 lesions were evaluated (1.4 per patient). The main characteristics of study lesions, according to the revascularization strategy, are detailed in the Table III in the Data Supplement. The overall success rate of the FFR procedure was 99.4% (1285/1293 lesions). Operator-reported reasons for unsuccessful FFR evaluation were the inability to cross the lesion with the pressure guidewire (n=4), acute target lesion occlusion after wiring (n=2), excessive bradycardia (n=1), and equipment malfunction (n=1). Average FFR was 0.81±0.10 and decreased significantly with increasing stenosis severity (Figure I in the Data Supplement). Overall, target lesions were treated according to FFR information in 93% of the cases (1195/1285; Figure 2) and 154 patients (16.8%) underwent PCI of at least 1 lesion not evaluated by FFR during the index procedure.

Management Strategy

Strategy Change: Per-Patient Analysis

In as many as 406 patients (44.2%), final treatment decision was not consistent with the baseline plan (Cohen κ, 0.33; Figure 3A). The proportion of patients ultimately undergoing revascularization after FFR was known was higher than planned at baseline: it increased from 34.8% to 44.0% for PCI and from 4.1% to 8.3% for CABG (Figure II in the Data Supplement). Even when patients initially considered for additional noninvasive stress testing were excluded, still the absolute number of patients finally undergoing PCI and CABG increased (from 319 to 321 and from 38 to 49, respectively).

Strategy Change: Per-Lesion Analysis

After FFR evaluation, management strategy changed in 45.2% of the lesions (584/1293). Globally (Figure 3B), the number of revascularized lesions (by PCI or CABG) increased from the initially planned 374 (28.9%) to a final 497 (38.4%).

One-Year Clinical Outcome

Per-Patient Analysis

Complete 12-month follow-up was available for 912 of 918 patients (99.3%) and vital status was known for 916 (99.8%; Figure 1). Total MACE was 6.9% at 12 months in the entire cohort and was the lowest in group 1 patients (5.3%). The stepwise increase in total MACE across groups was statistically significant in an unadjusted analysis of the crude incidence (P=0.043, Figure 4A; Table IV in the Data Supplement), but not after correction for relevant differences in baseline characteristics (Figure 5A). The pattern was similar when only ischemia-driven events were considered. Freedom from the primary end point at 12 months was 94.6% in patients in whom management decisions changed based on FFR versus 91.9% in those with concordant decisions between baseline and post-FFR (log-rank P=0.12; Figure III in the Data Supplement). The incidence of both cardiovascular death and acute MI was numerically lower in group 1, although the difference was not statistically significant. Importantly, all the end points related to repeat revascularization were consistently lower in group 1, when compared with groups 2 and 3 (Table IV in the Data Supplement). However, patients in group 3 had the highest event rate for all end points considered, with the exception of total mortality. The adjusted hazard of target lesion revascularization (TLR) at 12 months in group 3,

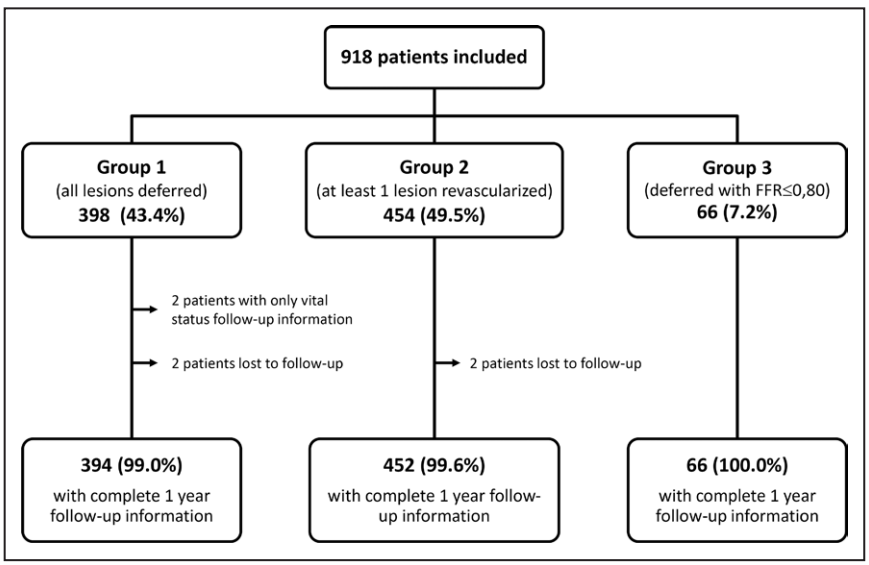

Figure 1. Study flowchart. FFR indicates fractional flow reserve.

Table. Population Baseline Characteristics According to Management Strategy: Group 1 (All Lesions Deferred), Group 2 (At Least 1 Lesion Revascularized), and Group 3 (At Least 1 Lesion With an FFR≤0.80 Not Treated)

Variable (%)	Total (n=918)	Group 1 (n=398)	Group 2 (n=454)	Group 3 (n=66)	*P* Value*
Demographics					
Age, y, mean±SD	65.1±10.2	66.7±10.0	63.8±10.3	64.9±9.4	<0.001
Male sex, n (%)	700 (76.3)	283 (71.1)	367 (80.8)	50 (75.8)	0.004
Cardiovascular risk factors, n (%)					
Diabetes mellitus	321 (35.0)	125 (31.4)	164 (36.1)	32 (48.5)	0.020
Hypertension	741 (80.7)	333 (83.7)	361 (79.5)	47 (71.2)	0.039
Smoking (current/former <1 y)	221 (24.1)	77 (19.3)	126 (27.8)	18 (27.3)	0.070
High cholesterol	691 (75.8)	299 (75.5)	339 (75.3)	53 (80.3)	0.670
Previous clinical history, n (%)					
Myocardial infarction	280 (31.5)	125 (31.5)	135 (29.8)	20 (30.8)	0.843
PCI	323 (35.2)	148 (37.2)	145 (31.9)	30 (45.5)	0.054
CABG	29 (3.2)	13 (3.3)	12 (2.6)	4 (6.1)	0.329
Other CVD†	75 (9.5)	30 (8.7)	39 (10.0)	6 (10.3)	0.812
Left ventricular EF					0.170
≤50%	155 (16.9)	63 (15.8)	85 (18.7)	7 (10.6)	
>50%	515 (56.1)	236 (59.1)	236 (52.1)	43 (65.2)	
Unknown	248 (27.0)	99 (24.9)	133 (29.3)	16 (24.2)	
Indication for angiography and clinical setting, n (%)					
Known/suspected stable CAD	556 (60.6)	238 (59.9)	268 (59.0)	50 (75.8)	0.202
Valvular heart disease/Other	37 (4.0)	19 (4.8)	16 (3.5)	2 (3.0)	0.202
On-going ACS	230 (25.1)	98 (24.6)	123 (27.1)	9 (13.6)	0.202
Recent ACS	95 (10.3)	43 (10.8)	47 (10.4)	5 (7.6)	0.202
STEMI†	55 (6.0)	29 (7.3)	25 (5.5)	1 (1.5)	0.402
NSTEMI/UA†	40 (4.4)	14 (3.5)	22 (4.9)	4 (6.1)	0.402
Procedural and angiographic characteristics, n (%)					
No. of diseased vessels (>50%)					<0.001
1 vessel	380 (41.1)	173 (43.5)	187 (41.2)	20 (30.3)	
2 vessels	242 (26.4)	52 (13.1)	166 (36.6)	24 (36.4)	
3 vessels	102 (11.1)	14 (3.5)	73 (16.1)	15 (22.7)	
Revascularization at the index procedure					<0.001
No. of lesions evaluated‡	1.4±0.7	1.3±0.5	1.5±0.8	1.8±0.9	
No. of deferred lesions‡	0.9±0.8	1.3±0.5	0.4±0.7	1.6±0.8	
Any PCI	408 (44.4)	…	387 (85.2)§	21 (31.8)	

See Table II in the Data Supplement file for complete information on baseline patient characteristics. ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, symptomatic cardiovascular disease other than CAD; EF, ejection fraction; FFR, fractional flow reserve; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

**P* values are for the comparison between management groups.

†Proportions refer to patients with evaluation of nonculprit lesions in the setting of a recent ACS (n=95).

‡Average±SD per-patient.

§The remaining patients were referred for CABG.

taking revascularized patients as the reference category, was 2.38 (95% CI, 1.05–5.43; *P*=0.039). The corresponding hazard ratio (HR) for group 1 was 0.98 (95% CI, 0.48–1.99; *P*=0.945.). The observed differences between groups both in total MACE and in target lesion failure were mainly driven by a large increase in the hazard of revascularization events in group 3 (Table IV in the Data Supplement).

For the 201 patients in whom an additional stress test would have been undertaken (based on angiography alone), complete follow-up information was available for all but two, who were

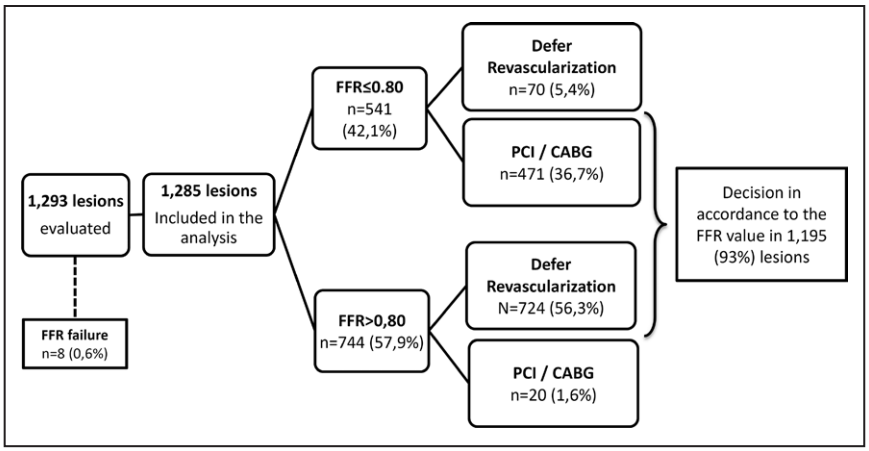

Figure 2. Management of study lesions according to fractional flow reserve (FFR) values. CABG indicates coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

alive at 1 year. A management decision that did not include additional testing was made based on FFR in all cases (Figure 3). The 1-year MACE rate in this group was 6.5%, which compares favorably to the reminder of the reclassified population (4.6%; *P*=0.9). In the subgroup of patients in whom all lesions were deferred based on FFR (n=86), 3 events occurred at 12 months (3.5%): 2 were ad hoc revascularizations based on physician's decision (no further evidence of ischemia or angina), and 1 non–ST-segment–elevation ACS with no evidence of disease progression and no subsequent intervention performed.

Per-Lesion Analysis

For the purpose of the per-lesion analysis, all fatal events of unknown cause were adjudicated as cardiovascular deaths and any ischemic events (including death) for which a detailed or unequivocal description was not available were considered possibly related to a study lesion. Results are summarized in Figure 4B; Table V in the Data Supplement. Taken together, the combined 1-year rate of cardiovascular death or MI definitely or possibly related to a study lesion was significantly lower in group 1 than in groups 2 and 3 (0.7% versus 2.2% versus 2.9%; *P*=0.047).

TLR occurred in 2.7% of the deferred lesions from group 1, a rate that was similar to revascularized lesions (adjusted HR, 1.23; 95% CI, 0.61–2.76; *P*=0.496). Overall, the main reason reported by investigators for performing TLR was chest pain interpreted as angina (52.6%), either accompanied by a positive noninvasive stress test or invasive evidence of disease

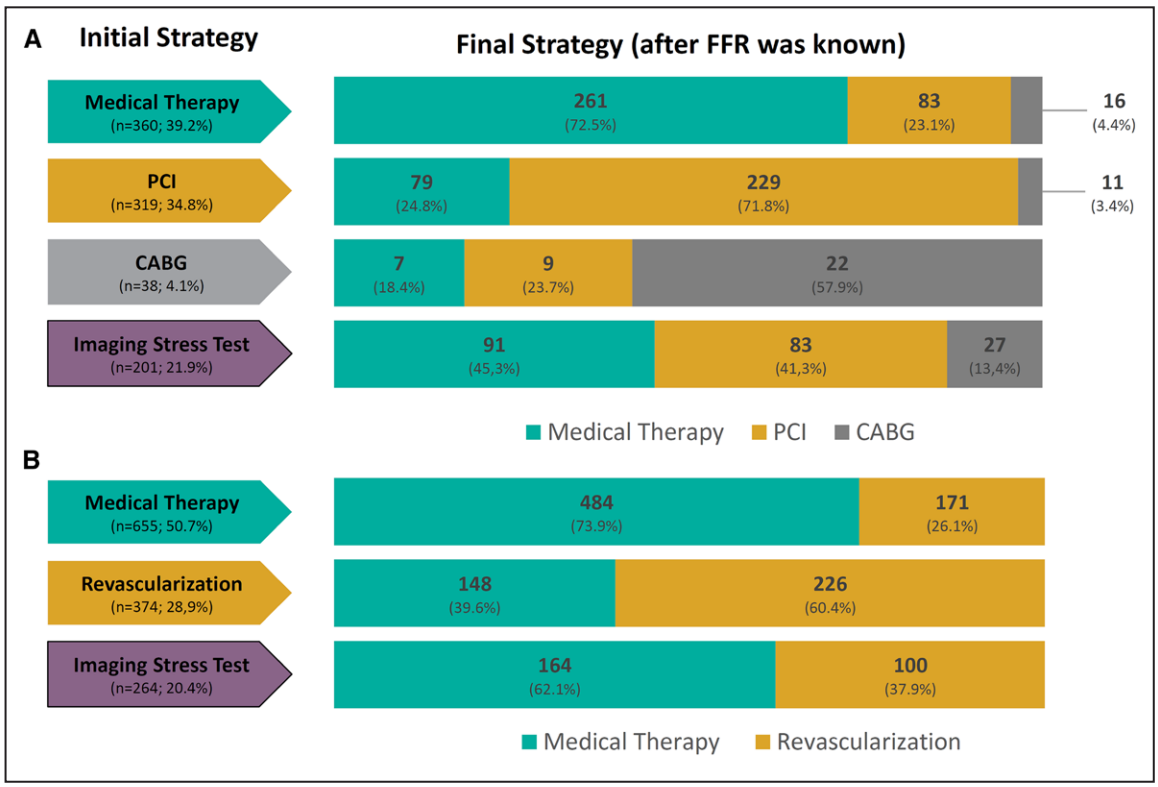

Figure 3. Strategy change per-patient (**A**) and per-lesion (**B**). CABG indicates coronary artery bypass grafting; FFR, fractional flow reserve; and PCI, percutaneous coronary intervention.

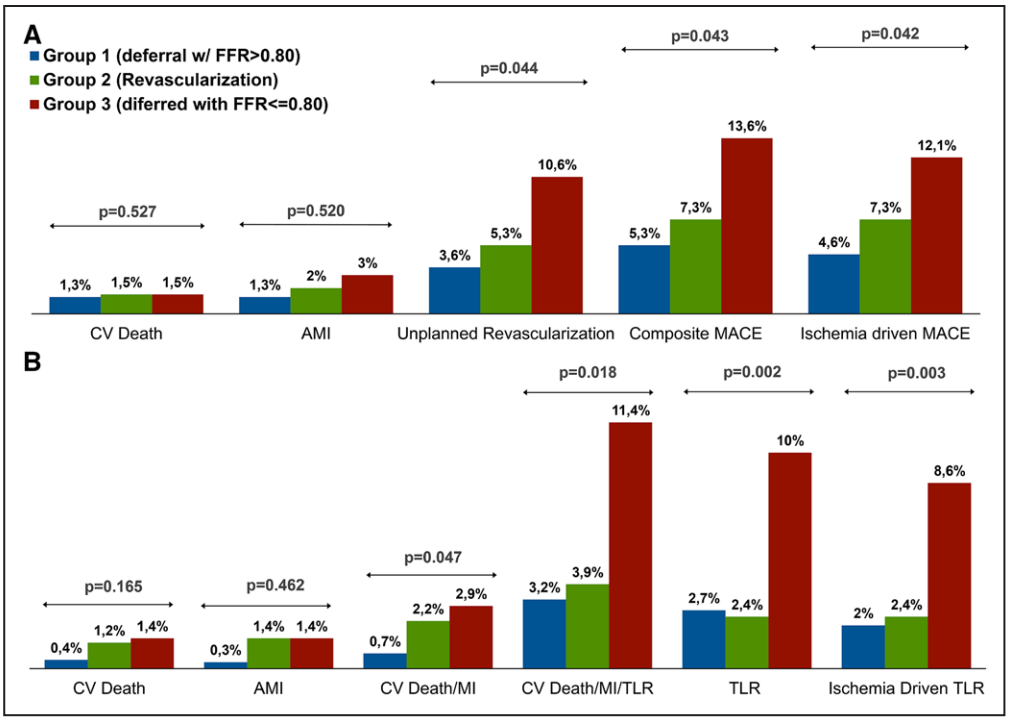

Figure 4. Crude incidence of 12-month outcomes per-patient (**A**) and per-lesion (**B**), according to management strategy. AMI indicates acute MI; CV, cardiovascular; FFR, fractional flow reserve; MACE, cardiovascular death, myocardial infarction or unplanned revascularization; MI, myocardial infarction; and TLR, target lesion revascularization.

progression, or MI. Importantly, in group 1, a significant proportion of events was driven by chest pain with no other evidence of ischemia (21%) or simply by ad hoc operator decision (without associated symptoms or evidence of ischemia; Table VI in the Data Supplement). Both the composite of death/MI in relation to study lesion or TLR (adjusted HR, 3.1; 95% CI, 1.28–7.54; *P*=0.012) and isolated TLR (adjusted HR, 4.7; 95% CI, 1.8–12.3; *P*=0.001) were significantly higher in group 3 than in group 2 lesions (Figures 4B and 5C and 5D).

Predictors of TLR in All Deferred Lesions

From the 1285 lesions evaluated at baseline, 794 (61.8%) were deferred by operator decision: 724 (56.4%) had an FFR>0.80 (group 1) and in the remaining 70, FFR measured ≤0.80 (group 3). Complete follow-up information was available for 786 (99.0%) of the lesions deferred in the index procedure, which were finally included in this subgroup analysis; 26 events occurred in this subset, yielding a rate of TLR of 3.1% at 1 year. The independent predictors of TLR were proximal location of the lesion (HR, 5.43; 95% CI, 2.16–13.65; *P*<0.001), lesion complexity defined as American College of Cardiology/American Heart Association B2/C type (HR, 2.45; 95% CI, 1.08–5.58; *P*=0.039), and a lower FFR value (HR [per unit increase], 0.003; 95% CI, 0.0–0.55; *P*=0.029).

Discussion

The present registry is one of the largest prospective studies ever performed to specifically address the impact of FFR on the management strategy and outcome of patients with known or suspected coronary artery disease undergoing coronary angiography.[8,9] Our main findings were that (1) routinely using FFR during invasive procedures to guide management was associated with a high proportion of change in treatment decisions, concerning both lesions and patients, (2) patients whose lesions were deferred based on an FFR>0.80 had an outcome that was at least as good as those for which revascularization was deemed necessary, and (3) lesions not revascularized despite an FFR≤0.80 are associated with a dire prognosis. In addition, we have shown that FFR was an independent predictor of TLR in deferred lesions, regardless of stenosis severity, lesion complexity, and classic clinical risk factors such as age, diabetes mellitus, and presentation as ACS.

Management Strategy

The adequacy of angiography to guide decisions on the best management of coronary lesions has been questioned.[7,10–12] Several studies have highlighted the disagreement between eyeballing and surrogates of functional significance of lesions (such as FFR) in several subsets of patients,[12] and the use of FFR has been shown to refine risk stratification and patient allocation to available treatment strategies, therefore optimizing clinical outcomes.[13–15] Accordingly, our data have shown that a change in management strategy occurred in a large proportion of patients (44.2%) and lesions (45.2%) as a direct consequence of FFR evaluation, without reducing the overall number of patients undergoing revascularization (namely by PCI). Three other studies reported on management strategy change based on FFR. In the RIPCORD (Does Routine Pressure Wire Assessment Influence Management Strategy at Coronary Angiography for Diagnosis of Chest Pain?) study[8] and in the FAMOUS NSTEMI (Fractional Flow Reserve Versus Angiographically Guided Management to Optimise Outcomes in Unstable Coronary Syndromes) trial,[16] the extent of change

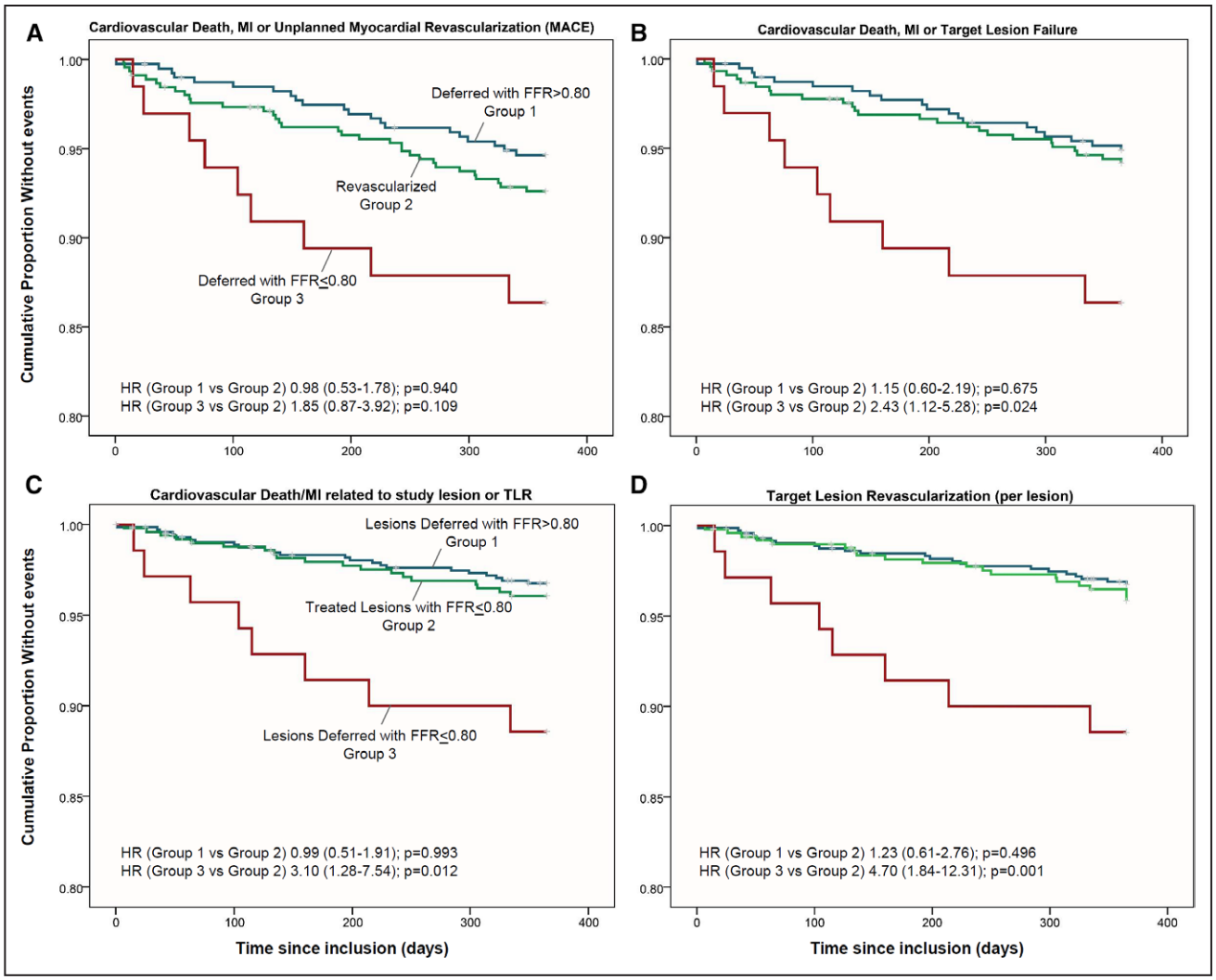

Figure 5. Kaplan–Meier estimates and adjusted hazard ratios for 12-month outcomes per-patient and per-lesion according to management strategy. **A**, Cardiovascular death, myocardial infarction, or unplanned revascularization (MACE), per-patient; (**B**) cardiovascular death, myocardial infarction, or target vessel failure, per-patient; (**C**) cardiovascular death or myocardial infarction related to study lesion or target lesion revascularization (TLR), per-lesion; (**D**) TLR, per-lesion. FFR indicates fractional flow reserve; HR, hazard ratio; and MI, myocardial infarction.

was 26% and 21%, respectively, far below the one we found. However, in both studies, all lesions ≥30% had to be interrogated and a significant proportion were either <50% or >70%; truly intermediate lesions (50% to 70%), for which a treatment strategy change was more likely to occur, were less frequent, potentially rendering the impact of FFR less pronounced. However, strategy change in our cohort was similar to the 43% recently reported by Van Belle et al[9] in a large multicenter prospective registry of 1075 patients whose design was closer to POST-IT in that only those lesions in which operators had doubts were included. However, there is a relevant difference in our study because additional imaging stress tests were allowed as a strategy before FFR was performed. Importantly, a final treatment decision was made during the index procedure in all the 22% of patients who would have undergone further stress testing. Not only these patients had a favorable outcome, particularly when all lesions were deferred based on FFR, but also a potential reduction in downstream costs, due to the avoidance of additional testing, new procedures and hospitalizations.

Importantly, as opposed to common belief, the use of FFR did not reduce the proportion of patients undergoing revascularization, either by PCI or CABG, even when those initially allocated to subsequent stress tests were not considered in the analysis.

Patient and Lesion Study Groups

Considering the study design, with broad acceptance and few exclusion criteria, a significant heterogeneity in the final patient sample was to be expected, thus making it necessarily difficult to obtain homogenous groups for evaluating the outcome only as a function of FFR-derived management. The rationale underlying our approach was to define study groups in a way that they would resemble relevant populations in randomized trials as much as possible. As such, the deferred arm of the DEFER[17] trial and the registry group of the FAME-2[4] trial (lesions with FFR above the ischemic threshold) are represented in group 1 (comprising patients in whom all study lesions were deferred, despite the fact other lesions could be

present but were not evaluated or treated), and the medical therapy arm of the FAME-2 trial[4] is represented by group 3 patients (in whom at least 1 lesion with an FFR≤0.80 was left untreated). One could argue that this division is arbitrary and that there were relevant disparities between groups that could justify differences on clinical outcome on their own, which in fact could be true. To adjust for these differences, adjusted HRs were calculated including relevant variables in the regression models. In addition, in the per-lesion analyses, not only were the study groups completely homogeneous about the management of study lesions based on FFR values but also the outcome measures mirrored those from the per-patient analyses.

Outcome of Deferred Lesions With FFR>0.80

Our results clearly indicate that deferring lesions with an FFR value above the established cutoff of 0.80 is associated with a low event rate at 1 year. The crude incidence of all predefined end points was the lowest in this group, both per-patient and per-lesion, with the exception of TLR in the per-lesion analysis. However, when only those revascularization events for which there was a clear indication were considered (excluding, for instance, ad hoc PCI of a study lesion in the absence of ischemia, ACS or angina), the TLR rate was actually lower than in groups 2 and 3. The incidence of cardiac death and TLR were comparable to the annualized incidence of the same end points reported in the deferral arm of the DEFER trial,[17] and the rates of new unplanned revascularization and MI were roughly the same as those in the registry arm of the FAME-2 trial.[4] Importantly, the absolute incidence of hard clinical end points not related to revascularization (cardiac death or acute MI) that could be definitely or possibly attributed to a study lesion was <1%. Overall, when differences in baseline characteristics were taken into account, the cumulative hazard of MACE for both lesions and patients not revascularized based on an FFR>0.80 was similar to the hazard of those deemed to need PCI or CABG.

Outcomes of Deferred Lesions With an FFR≤0.80

A small subgroup of lesions (n=70) and patients (n=66) were not revascularized because of operators' decision, despite functional evaluation revealing an FFR≤0.80. The reasons for deferring these lesions were not clear. The fact that patients in this group presented less often with severe symptoms and had a higher prevalence of multivessel and complex disease may have been a justification for operators to avoid revascularization.

In the per-patient analysis, MACE rate was higher in this group, a difference that was essentially driven by the need for new unplanned revascularization, as the incidence of cardiovascular death or MI did not differ significantly. The main reasons reported by investigators for unplanned revascularization procedures in this group were mostly related to documented ischemia, MI (that could not be attributed to other lesions), and disease progression (Table VI in the Data Supplement). The FAME-2 investigators have reported similar findings, and in fact, urgent revascularization drove the study primary end point in favor of the upfront PCI strategy in lesions with an FFR≤0.80.[4] Notably, event rates in group 3 were similar to those reported in medical therapy patients of the FAME-2 trial (total death: 1.5% versus 0.7%, MI: 3.0% versus 3.2%; and any revascularization: 19.7% versus 19.5%, respectively).

The best interaction between the primary end point of death/MI or urgent revascularization and FFR in deferred lesions in FAME-2 was 0.65, far below the mean 0.75±0.07 of group 3 lesions in our cohort. However (as shown in Figure IV in the Data Supplement), there is a clear association between the FFR value and the adjusted hazard of hard clinical events at 1 year, because the risk sharply increased below 0.70.

It cannot be excluded that the high rate of unplanned revascularization in group 3 could be a reflection of the nonblinded nature of treatment, possibly rendering treating physicians prone to interpret symptoms as being ischemia related and to perform revascularization. In the 70 lesions with an FFR≤0.80 that were left untreated, the crude incidence of death from cardiovascular cause or MI that could be definitely or possibly related to a study lesion was the highest among the 3 groups (2.9%), as opposed to lesions in group 1, which had the lowest event rate (0.7%).

The link between coronary flow impairment due to any given fixed stenosis and the risk of plaque instability leading to clinically meaningful acute thrombotic events is a matter of debate.[18] Despite the evidence that local flow conditions in the neighborhood of more complex and stenotic lesions may facilitate plaque erosion and that plaque morphological features known to be associated with future ACS are more frequently associated with surrogates of inducible ischemia,[19,20] trials performed in the setting of stable coronary artery disease have failed to demonstrate that revascularization significantly reduces the risk of hard clinical events, such as cardiac death or acute MI.[4,21–23] However, in many of these trials the ischemic burden was unknown or was only mild.[21,24] In a recently published meta-analysis of 3 randomized trials (SWISSI [Swiss Interventional Study on Silent Ischemia], FAME-2, and the nuclear substudy of the COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation] trial) of medical therapy versus PCI including 1557 patients with documented ischemia or an FFR≤0.80, PCI was associated with a significant 48% mortality reduction (95% CI, 0.30–0.92; P=0.02) at 3 years of follow-up.[25]

Strengths and Limitations

Considering that barely any exclusion criteria existed and that there were no specific recommendations as to which patients to include or how to guide treatment according to FFR, our results truly reflect current clinical practice.

The limitations of our registry are related to its observational design. Despite adequate statistical corrections, it cannot be definitely ruled out that differences in clinical outcome are not a consequence of baseline patient profile, rather than the adequacy of treatment based on FFR value. Only a matched analysis of patients and lesions with comparable risk could further clarify these findings; however, the small sample size of group 3 patients and lesions would necessary render it underpowered to allow meaningful conclusions.

Also, the per-lesion analysis of clinical events (namely cardiovascular death and MI) is limited by the fact that there is no way to definitively confirm that any given event is related with a specific lesion. However, by applying a worst-case-scenario approach (meaning that whenever in doubt, events were attributed to the study lesion), event rates would be, at the most, overestimated, but by the same extent in all 3 groups.

As stated above, the fact that FFR value was known may have influenced revascularization decisions in lesions not treated with an FFR≤0.80. Finally, a longer follow-up duration would be needed to further confirm our observations.

Conclusions

The results from our registry show that routine assessment of coronary lesions using FFR changes management strategy in a high proportion of cases. Also, they are largely confirmatory of seminal randomized trials and highlight the applicability of FFR to guide treatment of real-world patients with broad indications for coronary angiography. FFR accurately identified patients (and lesions) with a low likelihood of events, in which revascularization could be safely deferred, as opposed to those at high risk when ischemic lesions are left untreated.

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Disclosures

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Impact of Routine Fractional Flow Reserve Evaluation During Coronary Angiography on Management Strategy and Clinical Outcome: One-Year Results of the POST-IT Multicenter Registry

Sergio Bravo Baptista, Luís Raposo, Lino Santos, Ruben Ramos, Rita Calé, Elisabete Jorge, Carina Machado, Marco Costa, Eduardo Infante de Oliveira, João Costa, João Pipa, Nuno Fonseca, Jorge Guardado, Bruno Silva, Maria-João Sousa, João Carlos Silva, Alberto Rodrigues, Luís Seca and Renato Fernandes

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Correction

In the article by Baptista et al (Baptista SB, Raposo L, Santos L, Ramos R, Calé R, Jorge E, Machado C, Costa M, Infante de Oliveira E, Costa J, Pipa J, Fonseca N, Guardado J, Silva B, Sousa M-J, Silva JC, Rodrigues A, Seca L, Fernandes R. Impact of routine fractional flow reserve evaluation during coronary angiography on management strategy and clinical outcome: one-year results of the POST-IT multicenter registry. *Circ Cardiovasc Interv*. 2016;9:e003288. DOI: 10.1161/CIRCINTERVENTIONS.115.003288.), which published online on July 12, 2016, and appeared in the July 2016 issue of the journal, a correction was needed.

On page 1, in the subtitle, "One-Year Results of the POST-IT," has been changed to read "One-Year Results of the POST-IT Multicenter Registry."

This correction has been made to the article, which is available at http://circinterventions.ahajournals.org/content/9/7/e003288.

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Supplemental Material

Impact of routine Fractional Flow Reserve evaluation during coronary angiography on management strategy and clinical outcome: one-year results of the prospective POST-IT multicenter registry

Sergio Bravo Baptista, Luís Raposo, Lino Santos, Ruben Ramos, Rita Calé, Elisabete Jorge, Carina Machado, Marco Costa, Eduardo Oliveira, João Costa, João Pipa, Nuno Fonseca, Jorge Guardado, Bruno Silva, Maria João Sousa, João Carlos Silva, Alberto Rodrigues, Luís Seca, Renato Fernandes, on behalf of the POST-IT investigators.

Contents (links)

Supplemental Methods

- ### FFR cut-off and Management Strategy

The analysis of treatment strategy change was one of the endpoints of the study. Operators were asked to established and register their initial treatment strategy for each lesion and patient, based on all available information (including clinical setting, angiography, non-invasive tests….), before even performing FFR. It was stressed in the protocol that this decision should be announced before measuring FFR, in order to avoid bias. The available management alternatives were as follows:

1) *medical therapy*: meaning that patients/lesion would not warrant any further testing or revascularization procedures as a direct consequence of the index angiography, unless clinically indicated downstream during the follow up;

2) *revascularization*: either PCI or CABG, as a direct consequence of the qualifying procedure;

3) *Non-invasive functional testing*: meaning that patients would undergo subsequent non-invasive stress testing in order to better clarify management.

The three alternatives were available for both baseline and final decisions and had to be recorded for each evaluated lesion and for the patient, as a whole.

After FFR was evaluated in all lesions/vessels felt to be appropriate, investigators were asked to outline the final strategy. There was no specific recommendation on FFR cut-offs or on how FFR information should be incorporated and influence decisions. Information on whether or not both initial and final plans were the result of the decision from a single physician or a widened clinical discussion with other interventional cardiologists or cardiac surgeons was not captured.

- ### Clinical Follow-up and Endpoint definition

Sudden death and death from an unknown cause were considered cardiovascular for the purpose of the primary endpoint. Myocardial infarction was defined according to the third 2012 ESC/ACCF/AHA/WHF universal definition of MI[1]. Target lesion failure (TLF) was defined as any ischemic event or new revascularization procedure, which was not planned at the time of the index procedure, in a lesion that was evaluated by FFR at baseline, regardless of final treatment decision (deferral or revascularization). Thus, both elective staged PCI and elective CABG were not considered as events. Target lesion revascularization was defined as the need for new unplanned

revascularization in a lesion evaluated by FFR during the index procedure.

Ischemia driven revascularization was considered as those revascularization events that were undertaken under non-invasive evidence of ischemia with a localizing imaging test, a new FFR <0.80 or an acute coronary syndrome for which the lesion was considered culprit, according to the operators best judgment. Ischemia driven composite endpoints included ischemia driven revascularization.

For each adjudicated MACE, an attempt was made to identify causality between the event and the lesions evaluated at the index procedure, regardless of the intervention performed, if any. The association was considered to be "definitive" - if proven by autopsy or clinical means – or "possible" – if not proven, but plausible, in the opinion of the investigator. All sudden deaths or deaths from an unknown cause were ultimately considered to be related to the study lesions, unless proven otherwise.

- ## External Monitoring

For data monitoring purposes, an independent Clinical Research Associate was hired. In each center, a sample of at least 20% of all cases was reviewed. In centers with <20 patients, all files were reviewed. Monitoring included protocol compliance, as well as quality and accuracy of eCRF completion. Informed consent was checked in all patients.

- ## Statistical Analysis - Cox proportional hazard models

Variables were included in the regression models if they were found to differ significantly between groups in the univariate analysis (at a *p* value <0.05) or if they were deemed by the investigators to be clinically relevant for the interpretation of the outcomes in question, despite no difference at baseline.

In the **per-patient analysis** both the primary endpoint of one-year MACE and the composite of cardiovascular death/myocardial infarction/target lesion failure (reported in Figure 5, panels A and B, respectively), were adjusted for age, gender, hypertension, diabetes, acute coronary syndromes and number of vessels with stenosis>50%.

In the **per-lesion analysis** the hazard ratios for both the composite of cardiovascular death/myocardial infarction/target lesion revascularization and target lesion revascularization (reported in Figure 5, panels C and D, respectively) were adjusted for age, gender, hypertension, diabetes, acute coronary syndromes, number of vessels with stenosis>50%, location of the lesion in a proximal segment, B2/C type, vessel diameter and stent restenosis. In addition, FFR value was included as a covariate for the analysis of independent predictors of TLR.

Supplemental Table 1. Inclusion rate per center

Centre	City	Nº Patients Included	Nº Weeks including patients	Inclusion Rate/ week	Nº PCIs*	Ratio PCI/FFR†
Centro Hospitalar de Vila Nova de Gaia	Vila Nova de Gaia	169	88	1.9	1190	14%
Hospital de Santa Cruz - CHLO	Carnaxide	104	83	1.3	1190	9%
Hospital de Garcia de Orta	Almada	87	82	1.1	648	13%
Hospital de Santa Marta - Centro Hospitalar de Lisboa Central	Lisboa	86	62	1.4	1199	7%
Hospital Fernando da Fonseca	Amadora	85	87	1.0	577	15%
Centro Hospitalar Universitário de Coimbra	Coimbra	81	78	1.0	589	14%
Hospital do Divino Espirito Santo	Ponta Delgada	70	85	0,8	415	17%
Hospital Geral dos Covões - Centro Hospitalar de Coimbra	Coimbra	57	73	0.8	1084	5%
Hospital de Santa Maria – Centro Hospitalar de Lisboa Norte	Lisboa	42	33	1.3	728	9%
Hospital de Braga	Braga	31	76	0.4	542	6%
Hospital de São Teotónio	Viseu	21	68	0.3	372	6%
Centro Hospitalar de Setúbal	Setúbal	20	54	0.4	430	5%
Hospital de Santo André - Centro Hospitalar de Leiria-Pombal	Leiria	18	43	0.4	331	5%
Hospital Dr. Nélio Mendonça	Funchal	15	33	0.5	121	12%
Hospital Geral de Santo António - Centro Hospitalar do Porto	Porto	14	54	0.3	409	3%
Centro Hospitalar de São João	Porto	12	22	0.6	347	3%
Centro Hospitalar do Tâmega e Sousa	Penafiel	3	6	0.5	28	11%
Centro Hospitalar de Trás-os-Montes e Alto Douro - Unidade Hospitalar de Vila Real	Vila Real	2	11	0.2	52	4%
Hospital do Espírito Santo	Évora	1	1	1.0	4	25%
					918	9.2%

* Number of PCIs performed in each center during the inclusion period, excluding procedures performed in acute STEMI (P-PCI).

† This ratio is only intended to allow a quick view of the magnitude of FFR use in a given center. Although this percentage is commonly used to report FFR use, it should be noted that it may not reflect the actual use of fractional flow reserve.

Supplemental Table 2. Population baseline characteristics according to management strategy: Deferral Group (all lesions deferred), Revascularization Group (at least one lesion revascularized) and Not treated with FFR ≤0.80 (at least one lesion with an FFR≤0.80 left untreated) Group.

Variable (%)	Total Population (n=918)	Group 1 Deferral group w/ FFR>0.80 (n=398)	Group 2 Revascularization Group (n=454)	Group 3 Not treated with FFR≤0.80 (n=66)	*p value**
Demographics					
Age (years) [mean±SD]	65.1±10.2	66.7±10.0	63.8±10.3	64.9±9,4	<0.001
Male Gender [n(%)]	700 (76.3)	283 (71.1)	367 (80.8)	50 (75.8)	0.004
BMI (Kg/m^2) [mean±SD]	27.8±4.2	27.8±4.2	27.9±4.1	27.3±4.2	0.505
Cardiovascular risk factors [n(%)]					
Diabetes mellitus	321 (35.0)	125 (31.4)	164 (36.1)	32 (48.5)	0.020
Hypertension	741 (80.7)	333 (83.7)	361 (79.5)	47 (71.2)	0.039
Smoking (current/former<1year)	221 (24.1)	77 (19.3)	126 (27.8)	18 (27.3)	0.070
High Cholesterol	691 (75.8)	299 (75.5)	339 (75.3)	53 (80.3)	0.670
Prior clinical history [n(%)]					
Myocardial infarction	280 (31.5)	125 (31.5)	135 (29.8)	20 (30.8)	0.843
PCI	323 (35.2)	148 (37.2)	145 (31.9)	30 (45.5)	0.054
CABG	29 (3.2)	13 (3.3)	12 (2.6)	4 (6.1)	0.329
Other CVD	75 (9.5)	30 (8.7)	39 (10.0)	6 (10.3)	0.812
Left Ventricular EF					
<=50%	155 (16.9)	63 (15.8)	85 (18.7)	7 (10.6)	
>50%	515 (56.1)	236 (59.1)	236 (52.1)	43 (65.2)	0.170
Unknown	248 (27.0)	99 (24.9)	133 (29.3)	16 (24.2)	
Chronic Renal Failure	33 (3.6)	12 (3.0)	17 (3.7)	4 (6.1)	0.458
COPD	39 (4.3)	18 (4.5)	19 (4.2)	2 (3.0)	0.850
Cardiovascular Medication [n(%)]					
Any anti-platelet	727 (81.2)	310 (79.9)	362 (81.9)	55 (84.6)	0.585
Dual anti-platelet therapy	362 (40.5)	148 (38.1)	186 (42.2)	30 (46.2)	0.325
Oral anticoagulation	43 (4.8)	24 (6.2)	16 (3.6)	3 (4.7)	0.222
Lipid Lowering	711 (79.8)	307 (79.3)	351 (80.0)	53 (81.5)	0.913
Statin	699 (78.5)	303 (78.3)	345 (78.6)	51 (78.5)	0.995
ACEI/ARB	632 (72.5)	292 (76.4)	296 (69.3)	44 (69.8)	0.069
Beta-Blockers	534 (60.8)	238 (61.8)	254 (59.1)	42 (65.6)	0.514
Calcium Chanel Blockers	167 (19.1)	71 (18.4)	80 (18.7)	16 (25.0)	0.452
Nitrates	221 (25.2)	95 (24.7)	107 (24.9)	19 (29.7)	0.690
Other anti-ischemic drugs	60 (6.8)	28 (7.3)	27 (6.3)	5 (7.9)	0.801
Number of anti-anginal drugs**	1.13±0.90	1.13±0.89	1.10±0.89	1.29±1,0	0.313
Symptom status and Non-invasive testing [n(%)]					
Typical angina	494 (53.8)	191 (48.0)	270 (59.5)	33 (50.0)	
Atypical/non-anginal chest pain	184 (20.0)	105 (26.3)	67 (14.8)	12 (18.2)	0.002
Other symptoms/asymptomatic	240 (26.1)	102 (25.6)	117 (25.8)	21 (31.8)	
CCS Angina Class (n=494)					
I	18 (3.6)	9 (4.7)	8 (3.0)	1 (3.0)	
II	293 (59.7)	123 (64.7)	147 (54.6)	24 (72.7)	0.157
III	110 (22.3)	36 (18.8)	69 (25.6)	5 (15.2)	
IV	70 (14.2)	22 (11.5)	45 (16.7)	3 (9.1)	
Non invasive functional test	392 (42.7)	159 (39.9)	200 (44.1)	33 (50.0)	0.222
Positive functional test	330 (35.9)	130 (32.7)	175 (38.5)	25 (37.9)	0.192
ECG-stress test	250 (27.2)	97 (24.4)	132 (29.1)	21 (31.8)	0.210
Imaging functional test					
None performed	751 (81.8)	323 (81.2)	376 (82.8)	52 (78.8)	
SPECT	132 (14.4)	58 (14.6)	63 (13.9)	11 (16.7)	0.952
Dobutamine Stress Echo	31 (3.4)	15 (3.8)	13 (2.9)	3 (4.5)	
Perfusion MRI	4 (0.4)	2 (0.5)	2 (0.4)	0 (0.0)	
MSCT	59 (6.4)	26 (6.5)	26 (5.8)	7 (10.6)	0.320

Supplemental Table 2 (Cont). Population baseline characteristics according to management strategy: Deferral Group (all lesions deferred), Revascularization Group (at least one lesion revascularized) and Not treated with FFR ≤0.80 (at least one lesion with an FFR≤0.80 left untreated) Group.

Variable (%)	Total Population (n=918)	Group 1 Deferral group w/ FFR>0.80 (n=398)	Group 2 Revascularization Group (n=454)	Group 3 Not treated w/ FFR≤0.80 (n=66)	*p value**
Indication for angiography and Clinical setting [n(%)]					
Known/suspected stable CAD	556 (60.6)	238 (59.9)	268 (59.0)	50 (75.8)	0.202
Valvular Heart Disease/Other	37 (4.0)	19 (4.8)	16 (3.5)	2 (3.0)	
On-going ACS	230 (25.1)	98 (24.6)	123 (27.1)	9 (13.6)	
Recent ACS	95 (10.3)	43 (10.8)	47 (10.4)	5 (7.6)	
STEMI§	55 (6.0)	29 (7.3)	25 (5.5)	1 (1.5)	0.402
NSTEMI/UA§	40 (4.4)	14 (3.5)	22 (4.9)	4 (6.1)	
Procedural and Angiographic Characteristics [n(%)]					
Rhythm					
Sinus Rhythm	846 (92.0)	356 (89.4)	427 (94.1)	63 (95.5)	
Atrial Fibrillation/flutter	52 (5.7)	33 (8.3)	17 (3.8)	2 (3.0)	0.053
Pacemaker	20 (2.2)	9 (2.3)	10 (2.2)	1 (1.5)	
Heart Rate (bpm)	68±12	68±13	69±14	67±11	0.544
Transradial access	548 (59.7)	248 (62.3)	249 (54.8)	51 (77.3)	0.001
Procedure duration (min) [IQR]	45 [30-60]	38 [28-47]	51 [33-70]	50 [32-69]	<0.001
Fluoroscopy Time (min) [IQR]	9.5 [5.0-14.0]	7.0 [4.5-9.5]	12.0 [7.0-17.0]	10.1 [4.6-15.6]	<0.001
Number of diseased vessels (>50%)					
1 vessel	380 (41.1)	173 (43.5)	187 (41.2)	20 (30.3)	
2 vessels	242 (26.4)	52 (13.1)	166 (36.6)	24 (36.4)	<0.001
3 vessels	102 (11.1)	14 (3.5)	73 (16.1)	15 (22.7)	
Stenosis Severity†					
30-49%	148 (11.4)	91 (18.2)	44 (6.5)	13 (10.8)	
50-69%	738 (57.1)	343 (68.7)	332 (49.3)	63 (52.5)	<0.001
70-89%	356 (27.5)	64 (12.8)	256 (38.0)	36 (30.0)	
≥90%	51 (3.9)	1 (0.2)	42 (6.2)	8 (6.7)	
ACC/AHA Classification B2/C†	596 (46.2)	168 (33.8)	368 (54.6)	60 (50.4)	<0.001
Lesion location†					
Left Main	59 (4.6)	21 (4.2)	30 (4.5)	8 (6.7)	0.001
Proximal LAD	242 (18.7)	89 (17.8)	131 (19.4)	22 (18.3)	0.781
Any proximal lesion	430 (33.3)	172 (34.5)	223 (33.1)	35 (29.2)	0.537
Revascularization at the index procedure					
Number of lesions evaluated**	1.4±0.7	1.3±0.5	1.5±0.8	1.8±0.9	<0.001
Number of deferred lesions**	0.9±0.8	1.3±0.5	0.4±0.7	1.6±0.8	<0.001
Any PCI	408 (44.4)	-	387 (85.2)£	21 (31.8)	<0.001

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graf; MI: Myocardial infarction; CVD: Symptomatic vascular disease other than CAD; PCI: Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction; IQR: Interquartile Range (P25-P75).

**p* values are for the comparison between management groups.

** average±SD per patient.

§ Proportions refer to patients with evaluation of non-culprit lesions in the setting of a recent ACS (n=95)

† Proportions refer only to the characteristics of the lesions evaluated by FFR in the index procedure in each group.

^ Ivabradine, Nicorandil and/or Trimetazidine

£ The remaining patients were referred for CABG

Supplemental Table 3. Baseline characteristics of study lesions according to FFR and management strategy (Analysis refers only to lesions for which crossing with the pressure guide-wire was possible and Pd/Pa or FFR values were successfully obtained).

Variable (%)	Total Lesions (n=1.285)	Group 1 Deferred lesions w/ FFR>0.80 (n=724)	Group 2 Revascularized Lesions (n=491)	Group 3 Not treated lesions w/ FFR≤0.80 (n=70)	*p value**
Non-invasive testing†					
Documented Ischemia					
Yes	140 (10.9)	77 (10.6)	49 (10.0)	14 (20.0)	
No	106 (8.2)	58 (8.0)	46 (9.4)	2 (2.9)	0.057
Unknown	1039 (80.9)	589 (81.4)	396 (80.7)	54 (771.1)	
Known Necrosis	350 (30.9)	198 (31.0)	137 (31.8)	15 (23.4)	0.607¥
Indication for angiography and Clinical setting					
Stable angina	787 (61.2)	432 (59.7)	301 (61.3)	54 (77.1)	0.016
On-going ACS	300 (23.3)	181 (25.0)	110 (22.4)	9 (12.9)	0.058
Recent ACS (non-culprit lesion)					
STEMI	83 (6.5)	55 (7.6)	27 (5.5)	1 (1.4)	0.138¥
NSTEMI/UA	70 (5.4)	32 (4.4)	34 (6.9)	4 (5.7)	
Other indications	45 (3.5)	24 (3.3)	19 (3.9)	2 (2.9)	0.836
Angiographic Characteristics					
Lesion location					
Left Main	59 (4.6)	35 (4.8)	22 (4.5)	2 (2.9)	
Left Anterior Descending	705 (54.9)	313 (43.2)	335 (68.2)	57 (81.4)	
Circumflex	256 (19.9)	196 (27.1)	56 (11.4)	4 (5.7)	<0.001
Right Coronary Artery	263 (20.5)	179 (24.7)	77 (15.7)	7 (10.0)	
Bypass	2 (0.2)	1 (0.1)	1 (0.2)	0 (0)	
Proximal LAD	240 (18.7)	124 (17.1)	99 (20.2)	17 (24.3)	0.191
Any proximal lesion	427 (33.2)	261 (36.0)	147 (29.9)	19 (27.1)	0.046
Nº of diseased vessels (>50%)					
1 vessel	466 (36.3)	265 (36.6)	181 (36.9)	20 (28.6)	
2 vessels	392 (30.5)	183 (25.3)	182 (37.1)	27 (38.6)	<0.001
3 vessels	180 (14.0)	70 (9.7)	95 (19.3)	15 (21.4)	
Stenosis Severity					
30-49%	146 (11.4)	124 (17.1)	15 (3.1)	7 (10.0)	
50-69%	735 (57.2)	499 (68.9)	196 (39.9)	40 (57.1)	<0.001
70-89%	353 (27.5)	99 (13.7)	234 (47.7)	20 (28.6)	
≥90%	51 (4.0)	2 (0.3)	46 (9.4)	3 (4.3)	
ACC/AHA Classification B2/C†	593 (46.2)	256 (35.4)	304 (61.9)	33 (47.8)	<0.001
Vessel Reference Diameter (mm) [mean±SD]	2.98±0.46	3.02±0.47	2.95±0.45	2.82±0.42	<0.001
Small Vessel (≤2.5 mm)	417 (32.6)	214 (29.6)	173 (35.3)	30 (44.1)	0.013
Lesion Length					
<10 mm	232 (18.1)	180 (25.0)	44 (9.0)	8 (11.6)	
10-20 mm	849 (66.4)	487 (67.6)	318 (64.9)	44 (63.8)	<0.001
>20 mm	198 (15.5)	53 (7.4)	128 (26.1)	17 (24.6)	
Diffuse disease	186 (14.6)	55 (7.6)	109 (22.3)	22 (31.4)	<0.001
In-Stent restenosis	72 (5.6)	44 (6.1)	25 (5.1)	3 (4.3)	0.677
FFR value [average±SD]	0.81±0.10	0.88±0.10	0.71±0.08	0.75±0.07	<0.001

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graf; MI: Myocardial infarction; PCI: Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction; IQR: Interquartile Range (P25-P75).
**p* values are for the comparison between groups.
§ Proportions refer to lesions for which a revascularization decision was made.
† Evidence of ischemia or known necrosis on non-invasive tests that it attributable to the vessel were target lesion is located.
¥ Yates correction

Supplemental Table 4. Clinical outcome at 12 months according to management strategy: Deferral Group (all lesions deferred), Revascularization Group (at least one lesion revascularized) and Not treated with FFR ≤0.80 (at least one lesion with an FFR≤0.80 left untreated) Group. Per-patient analysis

Variable (%)	Total Population (n=912)	Group 1	Group 2	Group 3	*p value**
		Deferral group w/ FFR>0.80 (n=394)	Revasc Group (n=452)	Not treated with FFR≤0.80 (n=66)	
Primary Composite Outcome					
MACE	63(6.9)	21(5.3)	33(7.3)	9(13.6)	0.043
Cardiovascular Death†	13(1.4)	5(1.3)	7(1.5)	1(1.5)	0.941
Acute Myocardial Infarction	16(1.8)	5(1.3)	9(2.0)	2(3.0)	0.520
New unplanned Revascularization	45(4.9)	14(3.6)	24(5.3)	7(10.6)	0.044
MACE (ischemia driven)	59(6.5)	18(4.6)	33(7.3)	8(12.1)	0.042
Secondary Clinical Outcomes					
Cardiovascular Death, AMI or TLF	55(6.0)	20(5.1)	26(5.8)	9(13.6)	0.024
Cardiovascular Death or AMI	26(2.8)	9(2.3)	14(3.1)	3(4.5)	0.537
Total Death†	26(2.8)	10(2.5)	15(3.3)	1(1.5)	0.632
Death from Coronary Causes†	11(1.2)	4(1.0)	6(1.3)	1(1.5)	0.939§
Hospitalization for Coronary Causes	36(3.9)	14(3.6)	19(4.2)	3(4.5)	0.860
TLF (all events)	46(5.0)	15(3.8)	23(5.1)	8(12.1)	0.016
TLF(ischemia driven)	42(4.6)	12(3.0)	23(5.1)	7(10.6)	0.020
TLR (all events)	33(3.6)	11(2.8)	15(3.3)	7(10.6)	0.006
TLR (ischemia driven)	29(3.2)	8(2.0)	15(3.3)	6(9.1)	0.010

MACE: Major Adverse Cardiovascular Events (Death from cardiovascular causes, acute myocardial infarction or TLF); TLF: Target Lesion Failure; TLR: Target Lesion Revascularization. AMI: Acute Myocardial Infarction

* *p* values are for the comparison of crude incidences between management groups.

§ Yates Correction.

† Vital status and cause of death was known for N=916 patients (for 2 patients there was no follow-up information)

Supplemental Table 5. Clinical outcome at 12 months according to management strategy: Deferral Group (lesions deferred with a FFR>0.80), Revascularization Group and Not treated with FFR ≤0.80 (at least one lesion with an FFR≤0.80 left untreated) Group. Per-lesion analysis.

Variable (n;%)	Total Population (n=1,276)	Group 1 Deferred lesions w/ FFR>0.80 (n=716)	Group 2 Revasc. Lesions (n=490)	Group 3 Not treated lesions w/ FFR≤0.80 (n=70)	*p value**
Clinical events with definite/possible relation to a study lesion					
Death from Cardiovascular Cause	10(0.8)	3(0.4)	6(1.2)	1(1.4)	0.465§
Myocardial Infarction (AMI)	10(0.8)	2(0.3)	7(1.4)	1(1.4)	0.165§
Death from cardiovascular cause or AMI†	18(1.4)	5(0.7)	11(2.2)	2(2.9)	0.047§
Revascularization Related Events					
TLR (total events)	38(3.0)	19(2.7)	12(2.4)	7(10.0)	0.002
TLR (ischemia driven)	32(2.5)	14(2.0)	12(2.4)	6(8.6)	0.003
Combined clinical and Revascularization Related Events with definite/possible relation to a study lesion					
CV Death or AMI or TLR (total events)	50(3.9)	23(3.2)	19(3.9)	8(11.4)	0.003
CV Death or AMI or TLR (ischemia driven)	44(3.4)	18(2.5)	19(3.9)	7(10.0)	0.004

TLF: Target Lesion Failure. TLR: Target Lesion Revascularization. Ischemia driven events represent those for which there was a plausible evidence to justify revascularization or to adjudicate the event to the study lesion. For patients with more than one lesion included in the study, potential relationship to ischaemic events was assumed for only one of the lesions.

* *p* values are for the comparison of crude incidences between management groups.

§ Yates Correction.

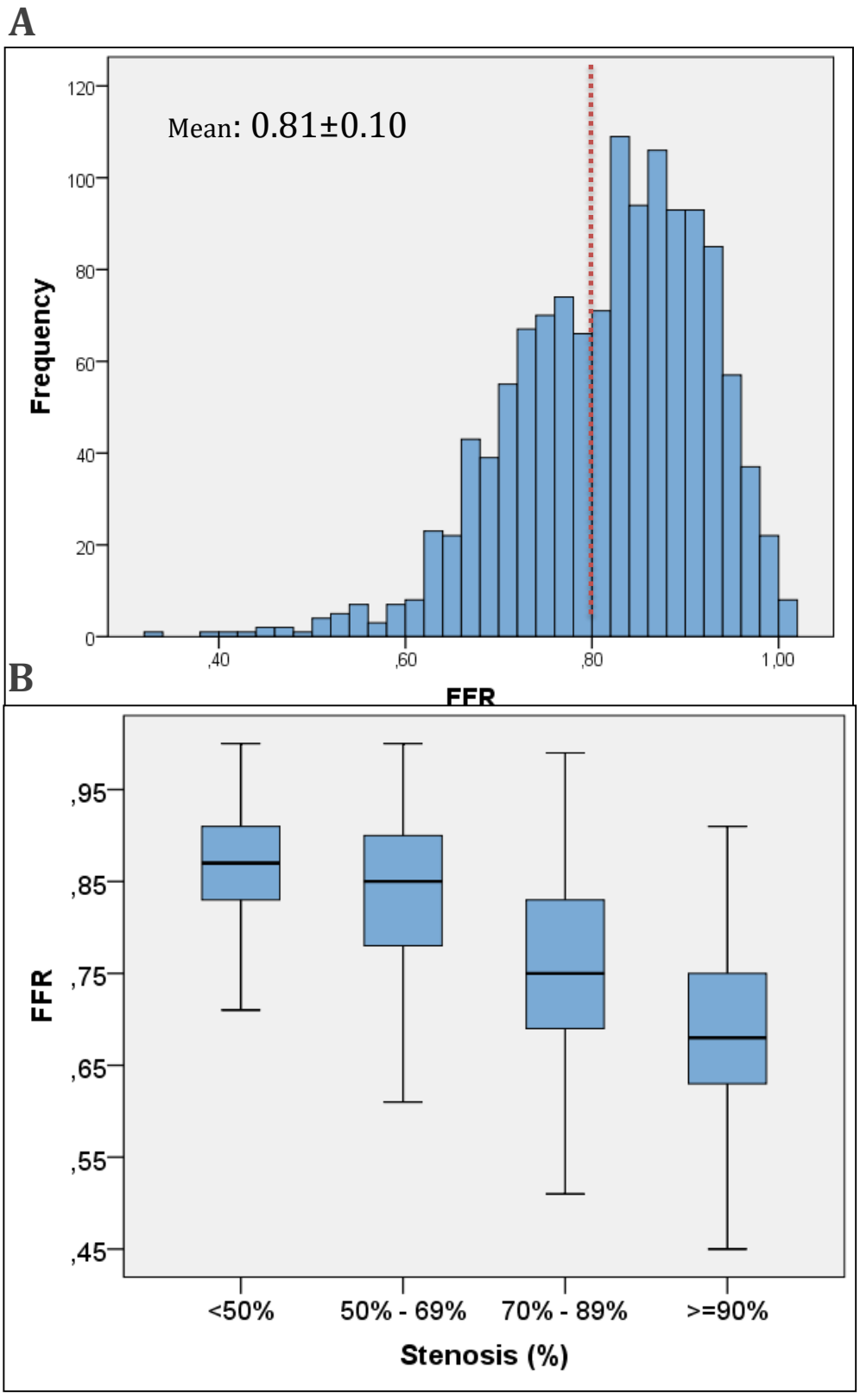
† *p*=0.04 for the comparison of deferral vs. revascularization groups; p>0.05 for all other comparisons between groups.

Supplemental Table 6. Operator reported reasons for target lesion revascularization according to management strategy: Deferral Group (lesions deferred with an FFR>0.80), Revascularization Group and Not treated with an FFR≤0.80 Group.

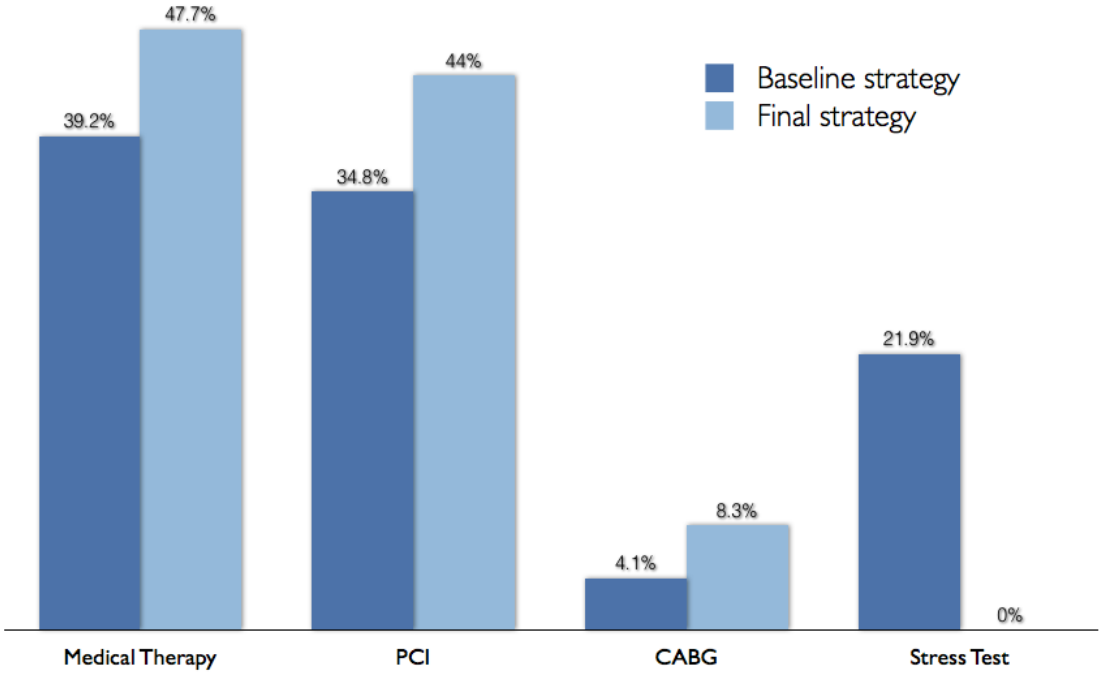
Reason (n;%)	Total Population (n=38/1,276)	Group 1	Group 2	Group 3
		Deferred lesions w/ FFR>0.80 (n=19/716)	Revasc. Lesions (n=12/490)	Not treated lesions w/ FFR≤0.80 (n=7/70)
Isolated symptoms (stable/unstable) *	9 (23.7)	4 (21.1)	4 (33.6)	1 (14.3)
Symptoms and positive NIST or disease progression or MI	20 (52.6)	8 (42.0)	8 (66.7)	4 (57.1)
Positive NIST (no symptoms)	4 (10.5)	3 (15.8)	-	1 (14.3)
Operator's decision (no symptoms, no documented ischemia)	5 (13.2)	4 (21.1)	-	1 (14.3)

ACS: acute coronary syndromes; NIST: non-invasive stress test;
* without reference to ischemia documentation or evidence of disease progression

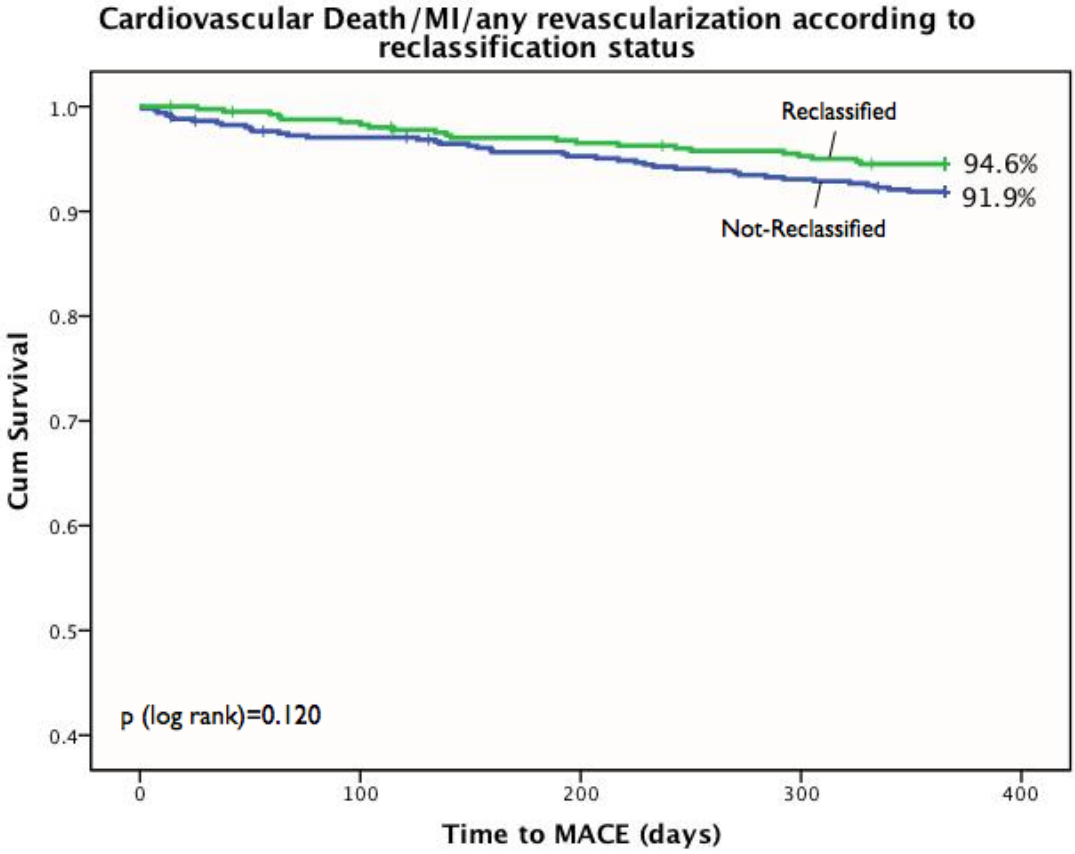
Supplemental Figure 1. Distribution of FFR values per-lesion (A) and according to angiographic stenosis severity (B)



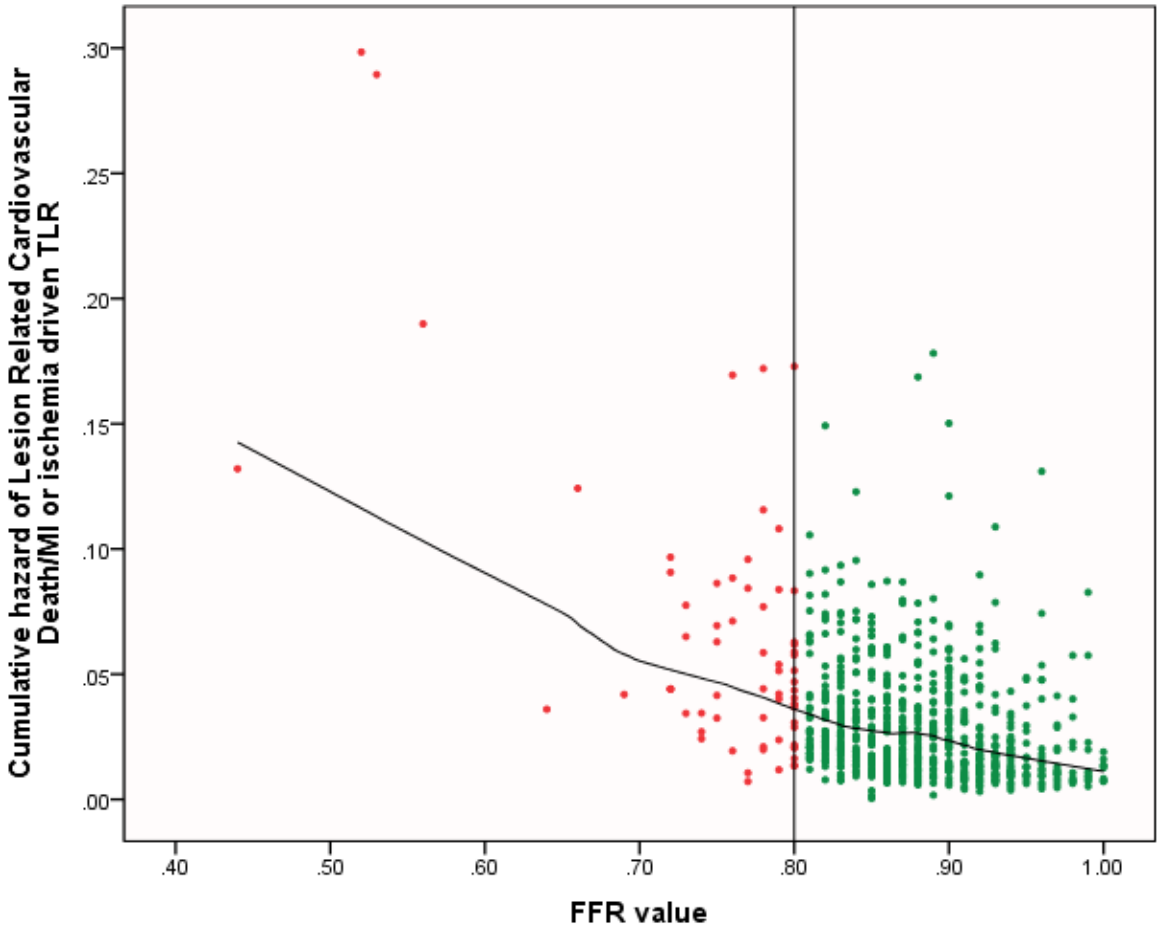
Supplemental Figure 2. Overall baseline and final treatment strategy



Supplemental Figure 3. Clinical outcomes (cardiovascular death/myocardial infarction/any revascularization) according to reclassification status



Supplemental Figure 4. Clinical outcomes according to FFR value in deferred lesions. Deferral of lesions with an FFR>0.80 (green dots, Group 1) was associated with the lowest event rate as opposed to those left untreated with an FFR<0.80 (red dots, Group 3) which were associated with the highest cumulative hazard of clinical events



Supplemental References

1. Kristian Thygesen JSA, Allan S. Jaffe, Maarten L. Simoons, Bernard R. Chaitman, and Harvey D. White: the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-2035