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Angiography versus Hemodynamics to Predict the Natural History of Coronary Stenoses: A FAME 2-Substudy

Running Title: *Ciccarelli et al.; FFR vs Angiography Mismatch*

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Abstract

Background—Among patients with documented stable coronary artery disease (CAD) and in whom no revascularization was performed, we compared the respective values of angiographic diameter stenosis (DS) and of fractional flow reserve (FFR) in predicting natural history.
Methods—The present analysis included the 607 patients from the Fractional flow reserve versus angiography in multivessel evaluation 2 (FAME 2) trial in whom no revascularization was performed. FFR varied from 0.20 to 1.00 (average 0.74 ± 0.16) and DS (by QCA) varied from 8% to 98% (average 53 ± 15). The primary end point, defined as VOCE (Vessel oriented clinical endpoint) at 2 years, was a composite of prospectively adjudicated cardiac death, vessel-related myocardial infarction, vessel-related urgent and not urgent revascularization. The stenoses were divided into 4 groups according to FFR and %DS values: Positive Concordance (PC: FFR≤0.80; DS≥50%); Negative Concordance (NC: FFR>0.80; DS<50%); Positive Mismatch (PM: FFR≤0.80; DS<50%); Negative Mismatch (NM: FFR>0.80; DS≥50%).
Results—The rate of VOCE was highest in the PC group (Log Rank: X^2=80.96; p=0.001), and lowest in the NC group. The rate of VOCE was higher in the PM group than in the NM group (H.R. 0.38, 95% C.I. 0.21 – 0.67; p=0.001). There was no significant difference in VOCE between the PC and the PM (both groups with FFR≤0.80, H.R. 0.77, 95% C.I. 0.57 – 1.09; p=0.149) and no significant difference in rate of VOCE between the NM and NC (both groups with FFR>0.80, H.R. 1.89, 95% C.I. 0.96 – 3.74; p=0.067).
Conclusions—In patients with stable coronary disease, physiology (FFR) is a more important determinant of the natural history of coronary stenoses than anatomy (DS).
Clinical Trial Registration—URL: https://clinicaltrials.gov Unique Identifier: NCT01132495.

Key Words: fractional flow reserve; coronary angiography; coronary artery disease; coronary atherosclerosis; fractional flow reserve, stable coronary artery disease, Coronary physiology, Diameter stenosis, percutaneous coronary intervention

Clinical Perspective

What is new?

- The data were obtained in a unique population of patients in whom no mechanical revascularization was initially proposed whatever the severity of the stenoses.
- The results indicate, for the first time, that the spontaneous clinical evolution ("natural history") of coronary stenoses is better predicted by physiologic information than by angiography.

What are the clinical implications?

- Measurements of FFR should no longer be limited to angiographically intermediate stenosis, but should be contemplated in stenoses that are mild or severe by visual evaluation.
- Since clinical outcome is the ultimate validation test for any new diagnostic metrics or new treatment strategy the present findings suggest that FFR should replace – or be used in conjunction with - the 50% DS criteria for the definition of obstructive CAD.

Fractional flow reserve FFR [1-5] has become the standard of reference for the invasive evaluation of coronary stenosis.[1-4, 6] Patients with an FFR value >0.80 do not benefit from mechanical revascularization, while patients with an FFR ≤0.80 do benefit from revascularization.[7-9] FFR has now a class IA recommendation in the latest European Guidelines to guide myocardial revascularization in the absence of conclusive non-invasive diagnostic work-up.[10]

Nevertheless, interventional cardiologists still prefer angiography for guiding decision making about revascularization, even in the absence of any budget and logistic constraints.[11] The angiographic thresholds of 50% or 70% diameter stenosis (DS) are still used to define "obstructive" coronary artery disease to risk stratify patients,[12] to justify revascularization, to serve as endpoint in studies on revascularization strategies,[13, 14] and to validate other approaches[15, 16].

Accordingly, we investigated the spontaneous, vessel oriented clinical outcome of patients from the FAME 2 trial in whom no revascularization was performed but in whom both the angiographic (DS) and functional (FFR) severity was known.[8] The aim of the study was to compare the accuracy of both approaches in predicting the 'natural history' of coronary artery disease.

Methods

Anonymized patient level data will be made available by the corresponding author for reasonable requests. Consent was not obtained for data sharing but the presented data are anonymized and risk of identification is minimal.

Patients

The details of the FAME 2 trial have been previously reported.[8] In short, the FAME 2 trial randomized consecutive patients with stable angina and in whom 1, 2 or 3 vessel percutaneous revascularization was based on the visual estimate of the angiogram. FFR was measured in all stenoses that were considered potential targets for revascularization. Only if at least one lesion had an FFR≤0.80, the patient was randomized to percutaneous coronary intervention (PCI) with second generation drug eluting stent (DES) or medical therapy. When no stenosis had an FFR≤0.80, patients were enrolled in a registry and received the best medical therapy. A random sample of 50% of the registry patients underwent the same follow-up as the patients in the randomized trial. In the present analysis, we focused on patients who were treated only with best available MT alone and who had 2 years of clinical follow-up, namely patients randomized to best available MT (n=441) plus patients enrolled in the registry who underwent clinical follow-up (n=166). All patients provided written informed consent. The trial was approved by the institutional review board at the 23 participating center in Europe and North America.

Fractional flow reserve was measured in all the stenoses with the use of a pressure monitoring guide wire (PressureWire Certus or PressureWire Aeris, St. Jude Medical). Hyperemia was obtained with adenosine IV or IC according to the operator's preference.

Quantitative coronary angiography was performed in all stenosis by QCA was performed using the Medis software (the Netherlands). The operator was blinded to the FFR values and to patient's clinical outcome. Angiographic DS, minimal lumen diameter (MLD, mm), lesion length (LL, mm), and the reference lumen diameter (RLD, mm) of the proximal and distal reference segments were measured. A cut-off value of 50% was used for DS and of 1.4 for MLD.

Syntax Score[17] was calculated in all patients by 4 different investigators blinded to each other, unaware of the segment in which the FFR was measured. The mean values of the global SYNTAX score were taken for analysis.

Study endpoints

The primary endpoint of the present analysis trial was the rate of major adverse cardiovascular event (MACE) at 2 years, defined as the composite of cardiovascular (CV) death, target vessel–related myocardial infarction (MI), and ischemia driven target vessel revascularization (TVR) (both urgent and non-urgent). All outcomes were adjudicated by an independent clinical events committee whose members were unaware of the treatment assignments and of the FFR and angiographic details of the lesions. The present study specifically investigates the relationship between vessel-related events defined as "vessel oriented clinical endpoint" (VOCE) and lesion hemodynamics (FFR) or angiographic parameters (diameter stenosis and minimal luminal diameter). All the events at follow-up were blindly reviewed and were unequivocally assigned to the culprit vessel in case of MI and ischemia-driven TVR. When the identification of the culprit vessel was not possible/feasible (i.e., in case of CV death, no coronary angiography performed, or non–ST-segment elevation MI in patients with multivessel disease), the endpoint was assigned to all the stenotic vessels of those patients. According to their respective FFR and %DS values the lesions were divided in 4 groups, as follows: Positive Concordance (PC: FFR≤0.80; DS≥50%); Negative Concordance (NC: FFR >0.80; DS <50%); Positive Mismatch (PM: FFR ≤0.80; DS <50%); Negative Mismatch (NM: FFR >0.80; DS ≥50%) **(Figure 1).**

Statistical Analysis

All analyses were done on lesion level, using robust standard errors that accounted for the correlation of lesions within patients. Discrete variables are summarized as frequencies and

percentages. Continuous variables are presented as mean ± standard deviation (SD). Chi-square test was used for categorical variables. Time to event occurrence of clinical endpoints was analyzed by Kaplan Meier analysis with differences in survival curves assessed by log-rank test. Hazard ratios and 95% confidence intervals [CI] were analyzed using Cox regression analysis with robust standard errors as in a marginal model to account for clustering. Hazard ratios of continuous variables are expressed per one SD change. Multivariable adjustment was performed after forward selection of clinical and angiographic baseline characteristics associated with VOCE, with significance for addition to the model set at $p \leq 0.15$. Variables considered for forward selection were age, male gender, body mass index, smoker, hypertension, hypercholesterolemia, diabetes overall, insulin dependent diabetes, renal insufficiency, previous PCI, previous MI, silent ischemia, multivessel disease, ejection fraction, Canadian class score for angina, left circumflex / right coronary versus left anterior descending artery (LAD), DS≥50%, FFR ≤0.80 and SYNTAX score (in tertiles). As the proportional hazard assumption was not satisfied for the multivariable model, we included an interaction term between FFR (≤0.80 versus >0.80) and time (≤90 days versus >90 days). In a sensitivity analysis, we forced the SYNTAX score as ordered tertiles into the multivariable model. Finally, we determined the prognostic performance of DS≥50% and FFR≤0.80 using Harrell's c and estimated the integrated discrimination improvement [18] of adding FFR≤0.80 to DS≥50% in the model. Statistical analyses were performed using IBM SPSS 20.0 statistical package (IBM Inc., New York, USA), GraphPad 5.0 (GraphPad Software Inc., CA, USA) and Stata 14.2 (StataCorp, College Station, Texas, USA).

Results

Patients and Vessels

Out of the 607 patients, both FFR and angiographic assessment of DS by QCA was obtained in 567 (93%) patients (799 stenoses).

Forty patients were excluded due to lack of angiographies or to impossibility to calculate the DS related to one or more of the following factors: inadequate filling of the vessel by contrast medium, overlap of side branches, guiding catheter not well visible, foreshortening of the stenotic segment, and chronic total occlusion.

FFR values ranged from 0.20 to 1.00 (0.74 ± 0.16), and of DS from 8% to 98% (53 ± 15%). There was a modest correlation between FFR and %DS (-0.55, 95% CI -0.61 to -0.49, p<0.001, **Figure 1**) and between FFR and MLD (0.38, 95% CI 0.10 to 0.66, p=0.009, **Figure 2**). FFR and %DS values were concordant (both positive or both negative) in 533 stenoses (66.7%) and were discordant in (one criteria positive, the other negative) in 266 lesions (33.3%). A positive concordance (PC: FFR≤0.80; DS≥50%) was present in 317 lesions (39.8%), a negative concordance (NC: FFR>0.80; DS<50%) was present in 216 lesions (27%), a positive mismatch (PM: FFR≤0.80; DS<50%) was present in 153 lesions (19.1%), and a negative mismatch (NM: FFR>0.80; DS≥50%) was present in 113 lesions (14.1%).

Patients and lesions characteristics

Table 1 shows the baseline clinical characteristics, the angiographic and hemodynamic details of the whole population and of the four subgroups populations. Overall, the four groups were comparable except for peripheral vascular disease (highest rate in NM group vs lowest rate in PC group), the history of a previous PCI (highest rate in NM group vs lowest rate in PC group), the inter-tertile repartition of the Syntax Score, the diameter stenosis percentage (highest value in PC

group vs lowest value NC group), the minimal lumen diameter (highest value in NC group vs lowest value in PC group), the lesion length (highest value in PC group vs lowest value in NC group), the stenosis localizations, and the FFR distribution as well. A pairwise testing among the groups for the characteristics that had significant overall p-values is available in the supplemental data (**Table S1**).

Clinical correlates

Clinical 2-year follow-up was available in all patients. The total number of VOCE and their individual components are shown in **Figure 3**. Overall, VOCE's occurred in 26% of cases. The rate of VOCE was highest in the group of stenoses with positive concordance (PC: FFR≤0.80; DS≥50%; 125/317 lesions [39.4%]) and lowest in stenoses with a negative concordance (NC: FFR>0.80; DS<50%; 17/216 lesions [7.9%]). The rate of VOCE's was similar in stenoses with a positive mismatch (PM: FFR≤0.80; DS<50%) and with a positive concordance (50/153 lesions [32.7%] vs 125/317 lesions [39.4%], respectively, p =0.139. In contrast, the rate of VOCE's of stenoses with negative mismatch (NM: FFR>0.80; DS≥50%) was lower as compared with stenoses with a positive mismatch (16/113 lesions [14.2%] 50/153 lesions [32.7%], respectively, p=0.001) but was not significantly different as compared with stenoses with a negative concordance (17/216 [7.9%], p =0.099).

Figure 4 shows the time to event curves for VOCE and for their respective components in the 4 groups of patients. The color code is the same than in **Figure 1.** There was no significant difference in term of lesion related outcome between the negative mismatch (NM: FFR>0.80; DS≥50%) and the negative concordance (NC: FFR>0.80; DS<50%), even though there was a trend (p=0.099). When the angiographic cut-off was set at 70% DS, the outcome results did not change (**Figure S1A and S1B**). **Figure 5**, **S2, S3, S4 and S5** show the time to event curves for

the individual components of VOCE and illustrate that the differences in VOCE is driven by the rate of revascularizations.

Figure 6 shows that the rate of VOCE over time is significantly larger when lesions have a DS ≥ 50% or when lesions have an FFR≤0.80, but the difference between the event curves is markedly larger for FFR than for DS.

Table 2 shows the univariable analysis of predictors of VOCE. The global SYNTAX score was not found a significant predictor for vessel related outcome (**Table 2**).

Table 3 shows the multivariable analysis of predictors of VOCE after forward selection of predictors. Only FFR, DS and silent ischemia were selected for the model. On average, FFR≤0.80 was associated with 4.16-fold increase in the hazard of VOCE and DS≥50% with a 1.36-fold increase. After introduction of an interaction term, FFR ≤0.80 was associated with a 7.28-fold increase in the hazard of VOCE during the first 90 days, and with a 3.29-fold increase in the hazard of VOCE occurring later than 90 days. **Table S2** presents results of multivariable analyses after tertiles of the SYNTAX score were forced into the model; results for FFR≤0.80 and DS≥50% were similar. Harrell's c was 0.61 (95% CI 0.58 to 0.65) for the prognostic performance of DS≥50% and 0.65 (95% CI 0.63 to 0.68) for the performance of FFR≤0.80. The integrated discrimination improvement of adding FFR≤0.80 to DS≥50% in the model was 1.44 (95% CI 1.12 to 1.77, p<0.001).

Discussion

Summary of Findings

The present analysis describes the 2-year outcome of a unique patient population, namely patients with angiographically and physiologically fully characterized coronary artery disease

and in whom no revascularization was proposed initially. Events were adjudicated by an independent clinical event committee, unaware of the angiogram and the FFR values. DS and FFR were compared side-by-side to clinical outcome data. The data indicate that the FFR value predicts the natural history significantly better than DS, suggesting that "physiology trumps anatomy"[19]. In addition, among the stenoses with mismatch between DS and FFR, more than half had a low FFR in the presence of an angiographically mild stenosis.

Rate and reasons for 'mismatch'

In the present study, an approximately 33% rate of mismatch between DS and FFR was found. This is similar that what we found in previous work by Toth at al. [15] (36%) as well as by Park et al.[20] in non-left main stenoses (39%) and in left main stenoses (40%). This relatively high rate of apparent discordance ('mismatch') between anatomy and physiology is actually not surprising as it relates to many different factors. First there are a number of specific reasons like inaccuracy of border detection, foreshortening of the stenotic segment, superimposition of side branches, asymmetry of the stenotic segment, as well as inaccuracies of the pressure measurements. Second, like every metrics in medicine, cut-off values of both DS and FFR are surrounded by a grey zone. However, the most important reason for the disconnect between anatomy and physiology relates to the myocardial mass that depends on the stenosis and to the vasodilatory capacity of the vascular bed. The reference diameter partially accounts for the myocardial mass. This is the reason why the optimal cut-off value for DS decreases when the diameter of the vessel increases, typically in LM and proximal LAD.[15, 20] Also in the present data, LAD stenoses are under-represented in the group of 'negative mismatch' and over-represented in the group with a 'positive mismatch'. Stated another way, any stenosis in the LAD is more likely to be hemodynamically significant than in other arteries, even when its angiographic appearance is

only mild. In contrast, the angiogram does not provide any clue about the vasodilatory capabilities of the microvasculature in the downstream territory. This is illustrated by the finding that for a similar degree of angiographic severity, FFR is higher in older patients and in diabetic patients.[20-22] Moreover, FFR takes into account the entire epicardial resistance between the guiding and the pressure sensor while DS provides more focal information. Finally, it is likely that discrete morphologic lesion characteristics not captured by the angiogram like lesion eccentricity, surface roughness and the presence of plaque rupture influence lesion hemodynamics.[20]

Outcome according to physiology versus anatomy

There is a general believe that stenosis severity on angiography is related to worse outcome. Many previous studies reported only a very elusive link between angiographic severity of the lesions and patients outcome.[23, 24] The present data indicate that, indeed, lesion-related outcome is better when DS is low **(Figure 6)**. In contrast, very robust data support a strong negative relationship between outcome and non-invasive signs of reversible myocardial ischemia.[25] A meta-analysis by Johnson and al[26] indicates that the higher the FFR the better the outcome. Yet, in many of these patients revascularization was performed based on the FFR values, which inevitably influences the relationship between the index value of FFR and the natural history of the patients. Recent data by Barbato et al[27] confirmed this 'dose-response' relationship between the actual value of FFR and clinical outcome. There are, however, very little data comparing side-by-side the prognostic value of anatomic and functional data in the same patients.[28] In addition, in none of these studies the patients had been followed during a long period of time without mechanical intervention, and the events adjudicated by an independent event committee. The present study is unique by the fact that, regardless of the severity of the stenoses, the patients

were not treated by revascularization, so that the outcome data of the present study can be regarded as the 'natural history' of the stenoses in stable patients, without interference of PCI or CABG on the fate of these lesions.

In the present study, FFR predicted outcome markedly better than DS. In addition, the present data show that when a lesion is angiographically mild but hemodynamically significant, the event rate is as high than when both angiography and hemodynamics indicate a significant lesion. Conversely, in case of angiographically significant stenoses but hemodynamic non-significant stenosis the clinical outcome is as favorable than when both angiography and hemodynamics indicate a non-significant stenoses. In other words, what determines lesions-related outcome is less its angiographic appearance than its hemodynamic significance.

The SYNTAX SCORE was developed in angiographic 3-vessel disease patients to characterize the complexity of the stenoses and the extent of the atherosclerotic burden [17]. The SYNTAX score has proven very useful in clinical decision-making between CABG and PCI in these 3-vessel disease patient mainly because CABG is largely 'immune' to the anatomic complexity of the disease while the technical aspects of the PCI procedures are heavily influenced by these anatomic characteristics [29]. It might sound intuitively logical to find some relationship between the SYNTAX score and the 'natural history' of the stenosis. This was not found in the present dataset. Yet, one have to realize that the SYNTAX score have been developed for 3 vessel disease patients while in the FAME 2 the majority of patients had 1 or 2-vessel disease. Accordingly, the global SYNTAX score was markedly lower in FAME 2 than in most studies focusing on 3 vessel-disease patients. In addition the present analysis focused on the lesion level outcome while the SYNTAX score is a global estimates of atherosclerotic burden and complexity. Data derived from coronary CT angiography very convincingly indicate that a high

atherosclerotic burden is an independent predictor of 'hard' events even in patients with angiographically non-obstructive coronary artery disease [30]. Therefore, the absence of relationship found between the SYNTAX score and the rate of VOCE seen in the present study should be interpreted with prudence. This total atherosclerotic burden is reflected by a lower FFR and is probably one of the mechanistic links to explain why FFR predicts events better that angiographic diameter stenosis.

Limitations

A number of limitations should be taken into account. First, like in the original FAME 2 trial, neither the patients nor the physicians were blinded to the FFR values.[31] Second, this analysis was not pre-specified in the initial protocol. Therefore, reliable QCA analysis was not possible for technical reasons in a sizable proportion of stenoses (23%). It cannot be excluded that this has contributed to an enrichment of the trial population in mild to moderate stenoses. For the same reasons, the numbers in each subgroup of patients are relatively small. Even with these relatively small subgroups one can distinguish statistical trends toward differences in the rate of VOCE between the groups with a negative concordance (FFR >0.8, DS<50%) and the group with a negative mismatch (FFR >0.80, DS>50%). It can therefore not be excluded that with larger numbers the difference in outcome between the PM and PC groups as well as between the NM and NC groups would have become significant. However, this would not have changed the main conclusion of the study. Third, left main stenoses were not included in FAME 2. Therefore the conclusions of the present analysis should be restricted to non-LM stenoses. Yet, Park et al[20] showed that LM stenoses - more than non-LM stenosis - have a high proportion of positive mismatch, precisely these lesions that are underestimated by angiography and in which FFR is important because revascularization of these lesions have important prognostic implications.

Fourth, the angiograms were not performed with the intention to perform QCA nor to calculate the SYNTAX score. This might have contributed to a lower accuracy of these angiographic approaches.

Conclusion

From this side-by-side comparison of DS and FFR to lesion-related outcome, it appears that the main determinant of the 'natural history' of a lesion is its hemodynamic significance rather than its angiographic appearance. Nowadays, DS is the cornerstone of the definition of CAD.[32] Since clinical outcome is the ultimate validation test for any new treatment or metrics the present findings suggest that FFR should replace the 50% DS criteria for the definition of obstructive CAD.

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Table 1. Baseline Clinical, Angiographic, and Fractional Flow Reserve (FFR) Characteristics

	PC (n=317)	NC (n=216)	PM (n=153)	NM (n=113)	p
Patients characteristics					
Age	64.0±10.1	63.8±10.0	64.7±9.9	64.9±10.0	0.70
Male (%)	250 (79)	250 (116)	250 (163)	250 (221)	0.076
Body Mass Index	28.8±4.4	27.9±4.2	28.2±5.0	28.1±4.5	0.16
Smoker (%)	70 (22)	70 (32)	70 (46)	70 (62)	0.78
Hypertension (%)	247 (78)	247 (114)	247 (161)	247 (219)	0.072
Dyslipidemia (%)	249 (79)	249 (115)	249 (163)	249 (220)	0.80
Diabetes Overall (%)	83 (26)	83 (38)	83 (54)	83 (73)	0.36
Diabetes ID (%)	32 (10)	32 (15)	32 (21)	32 (28)	0.20
Renal Failure (%)	8 (3)	8 (4)	8 (5)	8 (7)	0.40
Peripheral Vascular Disease (%)	31 (10)	31 (14)	31 (20)	31 (27)	0.003
Cerebro-Vascular Accident (%)	11 (3)	11 (5)	11 (7)	11 (10)	0.094
Previous Myocardial Infarction (%)	114 (36)	114 (53)	114 (75)	114 (101)	0.70
Previous PCI (%)	39 (12)	39 (18)	39 (25)	39 (35)	0.010
Silent Ischemia (%)	53 (17)	53 (25)	53 (35)	53 (47)	0.91
Left Ventricular Ejection Fraction <50% (%)	40 (13)	40 (19)	40 (26)	40 (35)	0.78
Multi Vessel Disease (%)	221 (70)	221 (102)	221 (144)	221 (196)	0.24
Syntax					<0.001
Tertile 1	136 (45)	91 (46)	50 (35)	57 (53)	
Tertile 2	83 (27)	55 (28)	45 (31)	23 (21)	
Tertile 3	85 (28)	52 (26)	48 (34)	28 (26)	
Angina					0.96
Asymptomatic	31 (10)	17 (8)	18 (12)	12 (11)	
CCS class 1	67 (21)	49 (23)	35 (23)	32 (28)	
CCS class 2	145 (46)	107 (50)	68 (44)	50 (44)	
CCS class 3	48 (15)	24 (11)	23 (15)	13 (12)	
CCS class 4	26 (8)	19 (9)	9 (6)	6 (5)	
Angiographic characteristics					
Diameter Stenosis Percentage	66.2±10.7	39.9±7.7	40.4±7.1	58.2±6.9	<0.001
8-49 (%)	-	216 (100)	153 (100)	-	-
50-69 (%)	203 (64)	-	-	104 (92)	-
70-98 (%)	114 (36)	-	-	7 (8)	-
Minimal Lumen Diameter	0.9±0.8	1.6±0.3	1.5±0.4	1.2±0.4	<0.001
Reference Lumen Diameter	3.2±9.6	2.8±0.6	2.6±0.5	2.8±0.8	0.71

Lesion Length	16.7±37.8	10.6±6.8	11.9±8.1	15.1±9.4	<0.001
Left Anterior Descending Artery (%)	142 (45)	99 (46)	98 (64)	43 (38)	<0.001
Left Circumflex Artery (%)	71 (22)	64 (30)	27 (18)	27 (24)	0.001
Right Coronary Artery (%)	104 (33)	53 (25)	28 (18)	43 (38)	<0.001
Fractional Flow Reserve	0.62±0.13	0.87±0.05	0.71±0.09	0.87±0.05	<0.001
≤0.8 (%)	317 (100)	-	153 (100)	-	-
>0.8 (%)	-	216 (100)	-	113 (100)	-

BMI, Body mass index; Diabetes ID, insulin dependent; PCI, percutaneous coronary intervention; MI, Myocardial Infarction; MVD, Multivessel disease; EF, Ejection fraction; CCS, Canadian class score; LCx/RCA, Left circumflex artery/ right coronary artery; FFR, Fractional flow reserve. All P-values account for the correlation of lesions within patients. Note that p-values are global p-values for equality across all 4 groups. A pairwise testing among the groups for the characteristics that had significant overall p-values is available in the supplemental data (**Table S1**).

Table 2. Univariable predictors of vessel oriented clinical endpoint (VOCE)

	VOCE			
	yes (n=208)	no (n=591)	HR	p
Patients characteristics				
Age	64.4 (SD 10.9)	64.1 (SD 9.7)	1.01 (0.85 to 1.21)	0.88
Male	158 (76)	440 (74)	1.04 (0.72 to 1.50)	0.85
BMI	28.4 (SD 4.2)	28.3 (SD 4.6)	1.02 (0.88 to 1.18)	0.78
Risk factors				
Smoker	42 (20)	123 (21)	0.95 (0.66 to 1.38)	0.81
Hypertension	163 (78)	452 (76)	1.07 (0.73 to 1.57)	0.72
Hypercholerolemia	161 (77)	471 (80)	0.90 (0.64 to 1.28)	0.57
Diabetes overall	58 (28)	146 (25)	1.11 (0.79 to 1.56)	0.54
Diabetes ID	25 (12)	45 (8)	1.47 (0.90 to 2.39)	0.12
Renal insufficiency	6 (3)	18 (3)	1.06 (0.37 to 3.00)	0.92
History				
Previous PCI	40 (19)	105 (18)	1.09 (0.72 to 1.64)	0.69
Previous MI	73 (35)	233 (39)	0.82 (0.59 to 1.13)	0.21
Silent Ischemia	25 (12)	103 (17)	0.69 (0.42 to 1.14)	0.15
Presentation				
MVD	143 (69)	440 (74)	0.79 (0.58 to 1.08)	0.15
EF<50%	26 (13)	88 (15)	0.78 (0.50 to 1.22)	0.28
Syntax				0.15
Tertile 1	76 (37)	258 (44)	Ref.	
Tertile 2	60 (29)	146 (25)	1.74 (0.95 to 3.17)	
Tertile 3	60 (29)	153 (26)	1.37 (0.73 to 2.57)	
Angina				
Asymptomatic	17 (8)	61 (10)	Ref.	0.28
CCS class 1	44 (21)	139 (24)	1.09 (0.58 to 2.06)	
CCS class 2	98 (47)	272 (46)	1.26 (0.70 to 2.26)	
CCS class 3	37 (18)	71 (12)	1.80 (0.93 to 3.48)	
CCS class 4	12 (6)	48 (8)	0.93 (0.40 to 2.17)	
Angiographic characteristics				
LCx/RCA	108 (52)	274 (46)	1.23 (0.94 to 1.61)	0.13
DS≥50%	141 (68)	289 (49)	2.01 (1.50 to 2.70)	0.00
FFR≤0.80	175 (84)	294 (50)	4.55 (3.06 to 6.77)	0.00

Numbers of events id followed by percentage in brackets. VOCE, Vessel oriented clinical endpoint; C.I., Confidence interval; BMI, Body mass index; Diabetes ID, insulin dependent; PCI, percutaneous coronary intervention; MI, Myocardial Infarction; MVD, multivessel diseas); EF, Ejection fraction; CCS, Canadian class score; LCx/RCA, Left circumflex artery/ right coronary artery; DS, Diameter stenosis; FFR, Fractional flow reserve.

Table 3. Multivariable predictors of vessel oriented clinical endpoint (VOCE)

	HR (95% CI)	p
Model 1: Average estimates		
FFR ≤0.80	4.16 (2.74 to 6.31)	<0.001
DS ≥50%	1.36 (1.00 to 1.85)	0.050
Silent Ischemia	0.65 (0.40 to 1.07)	0.092
Model 2: Accounting for interaction of FFR with time		
FFR ≤0.80		
up to 90 days	7.28 (2.92 to 18.2)	<0.001
above 90 days	3.29 (1.79 to 4.78)	<0.001
DS ≥50%	1.36 (1.00 to 1.85)	0.049
Silent Ischemia	0.65 (0.40 to 1.07)	0.092

Multivariable model after forward selection of clinical and angiographic baseline characteristics associated with VOCE reported in Table 2, with significance for addition to the model set at p ≤0.15. Proportional hazards test based on Schoenfeld residuals positive for Model 1 (p=0.013), negative for Model 2 (p=0.32) after introduction of an interaction term between FFR (≤0.80 vs >0.80) and time (≤90 days vs >90 days). CI, confidence interval; VOCE, Vessel oriented clinical endpoint; DS, diameter stenosis; FFR, fractional flow reserve.

Figure Legends

Figure 1. Scatter plot of the angiographic diameter stenosis (DS) versus the fractional flow reserve values (FFR). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥50%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<50%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<50%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥50%).

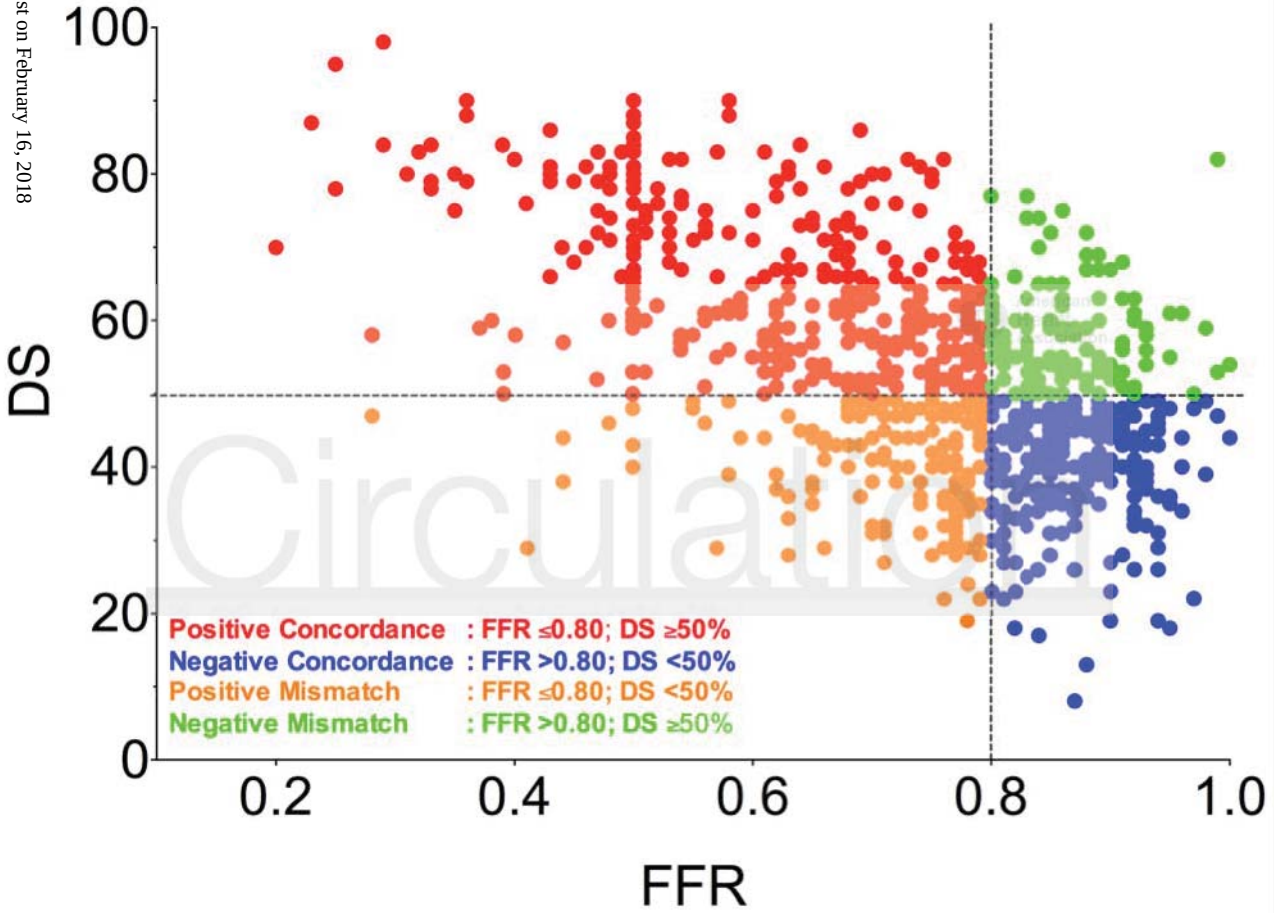
Figure 2. Scatter plot of the minimal lumen diameter (MLD) versus the fractional flow reserve values (FFR).

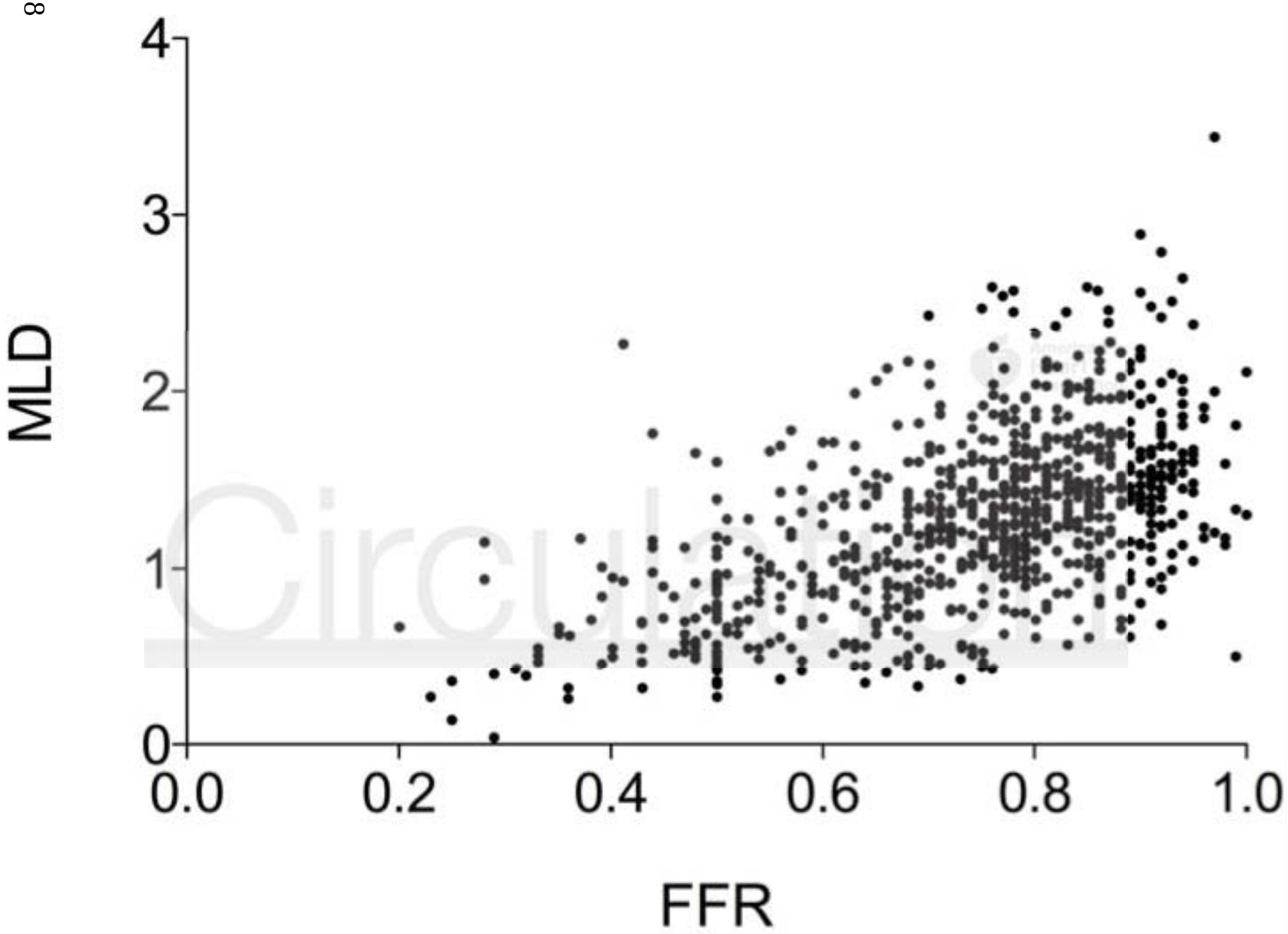
Figure 3. Rate (%) of Vessel Oriented Clinical Endpoint (VOCE) and their individual components according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). The color code is the same as in Figure 1. N. events: Number of events; HR:Hazard ratio; 95% CI: 95% Confidence Interval.

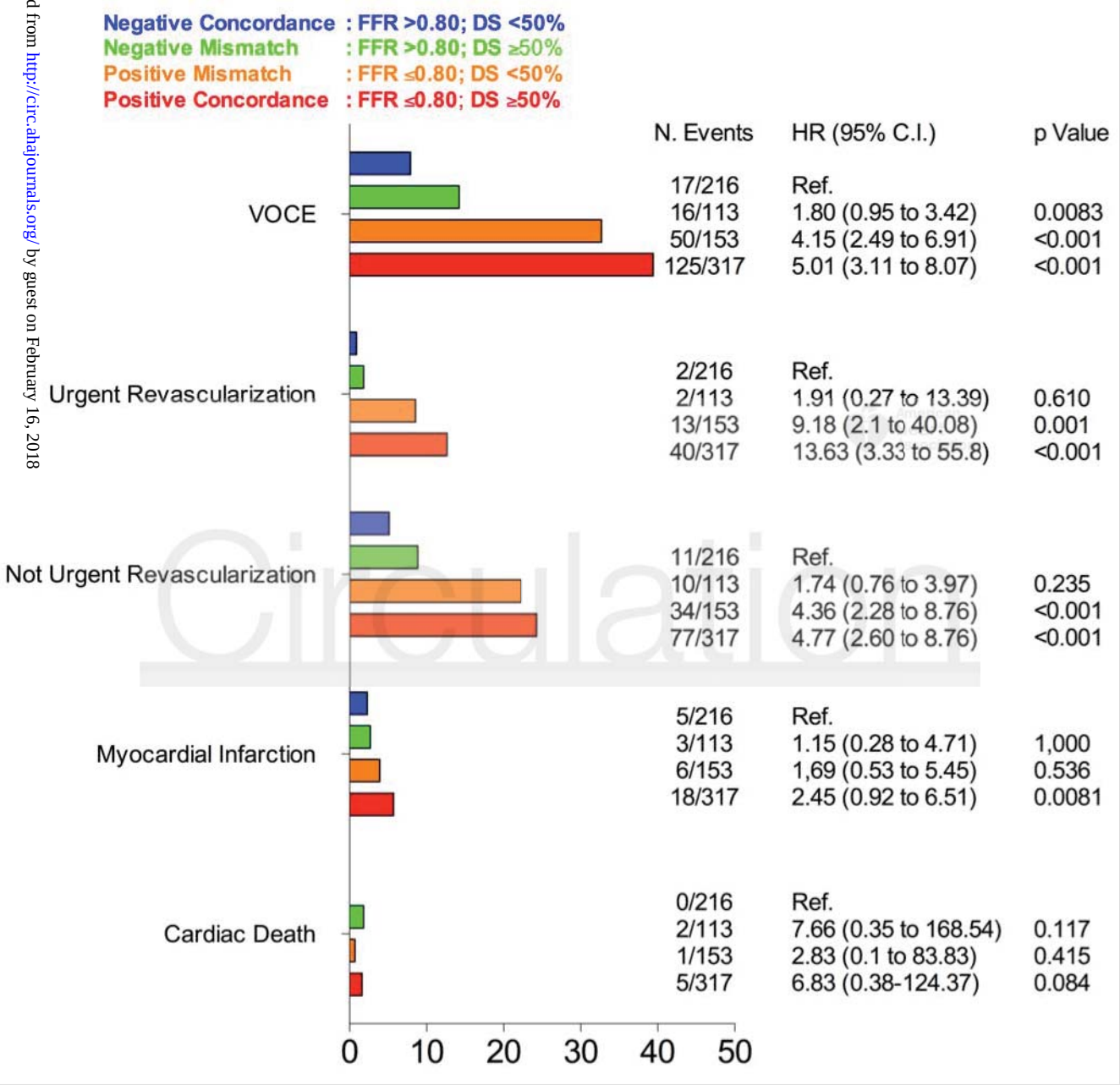
Figure 4. Kaplan Meier survival curve of 4 Groups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). The color code is the same as in Figure 1.

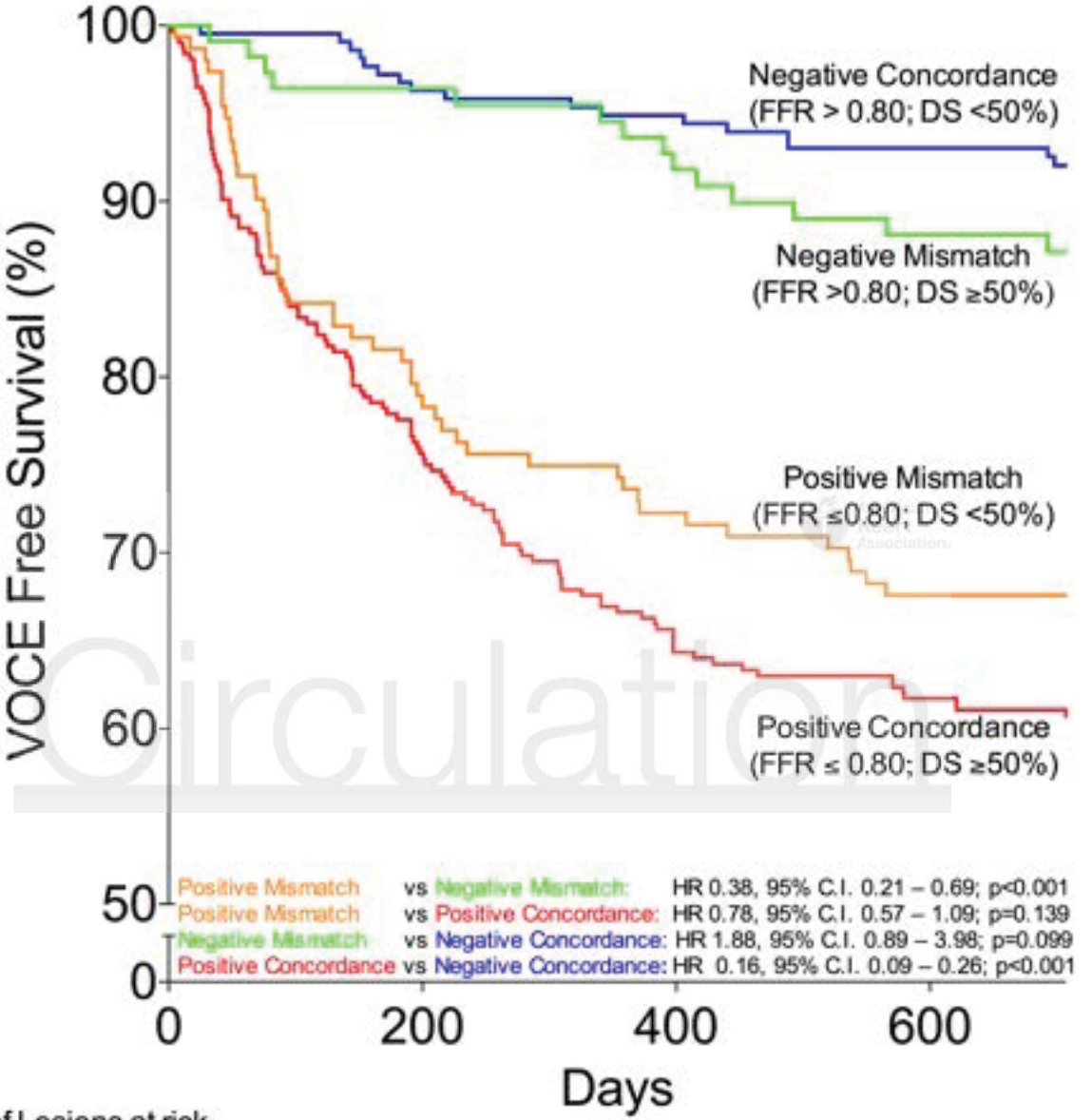
Figure 5. Kaplan Meier survival curve of 4 Groups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS) for the cumulative incidence of vessel related urgent and not urgent revascularization (A) and for the cumulative incidence of vessel related myocardial infarction and cardiovascular death (B). The color code is the same as in Figure 1.

Figure 6. Kaplan Meier survival according to the values of Percent Diameter Stenosis (DS) and Fractional Flow Reserve (FFR).

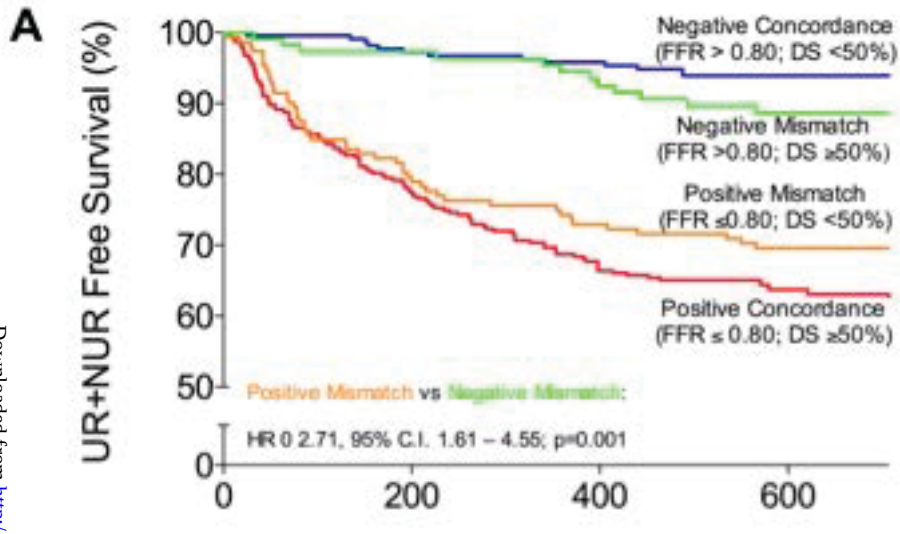






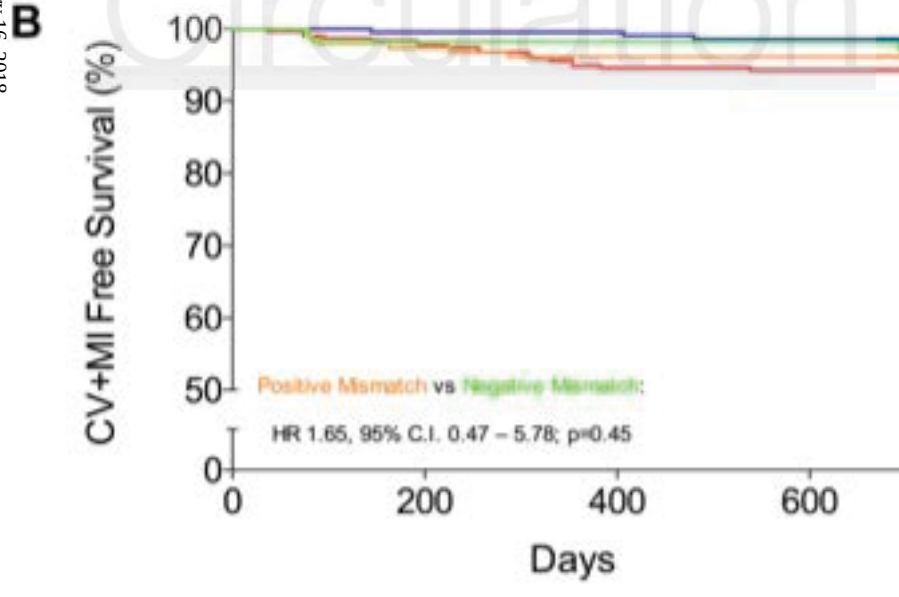


Number of Lesions at risk					
N. Concordance	: 216	208	204	201	160
N. Mismatch	: 111	106	100	96	82
P. Mismatch	: 152	123	109	102	84
P. Concordance	: 313	236	201	190	189



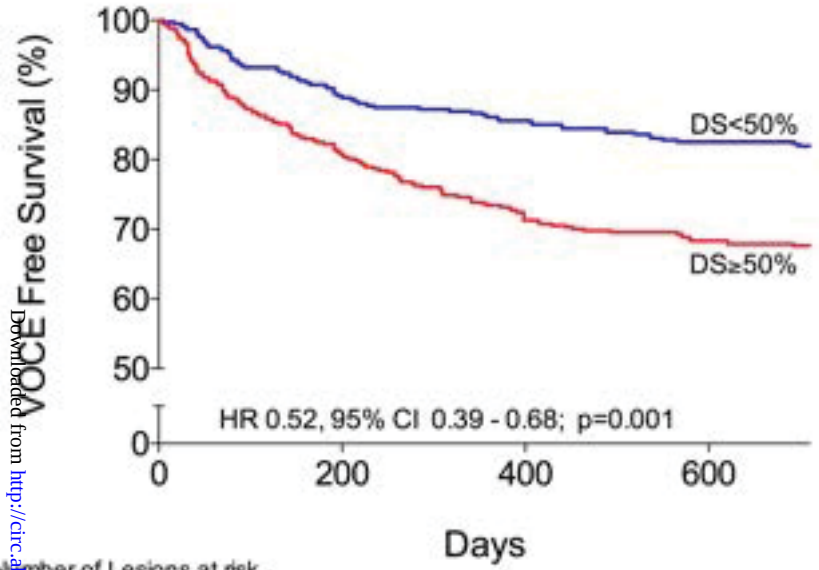
Number of Lesions at risk

N. Concordance	: 216	209	205	202	171
N. Mismatch	: 111	104	97	93	78
P. Mismatch	: 152	122	110	104	86
P. Concordance	: 313	240	204	193	161



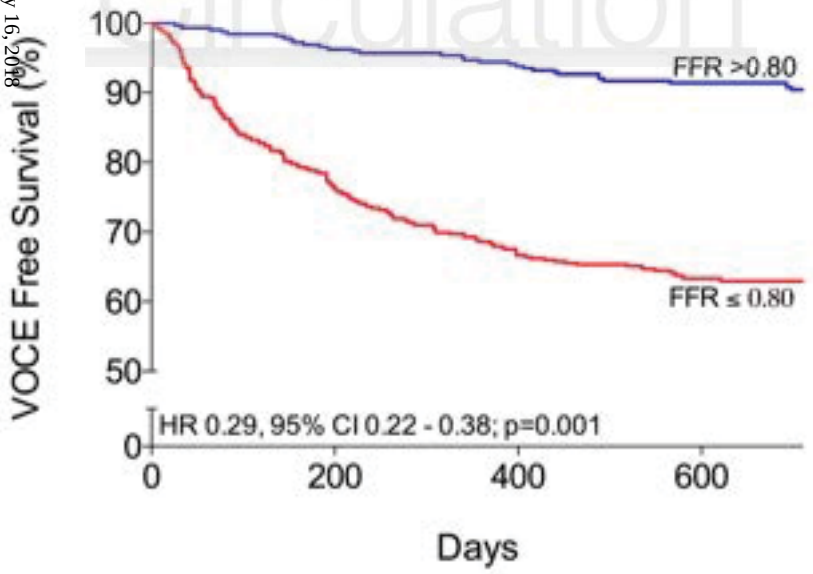
Number of Lesions at risk

N. Concordance	: 216	215	213	210	167
N. Mismatch	: 111	107	106	106	89
P. Mismatch	: 153	150	146	146	120
P. Concordance	: 314	307	293	291	253



Number of Lesions at risk

DS<50%	368	327	312	301	244
DS≥50%	424	340	300	284	250



Number of Lesions at risk

FFR>0.80	328	327	304	296	243
FFR≤0.80	464	340	307	293	251

Angiography versus Hemodynamics to Predict the Natural History of Coronary Stenoses: A FAME 2-Substudy

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SUPPLEMENTAL MATERIAL

Supplementary material to the manuscript entitled:

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Giovanni Ciccarelli, MD, Emanuele Barbato, MD, PhD, Gabor Toth, MD, PhD, Brigitta Gahl MSc, Panagiotis Xaplanteris, MD, PhD, Stephane Fournier, MD, Anastasios Milkas, MD, Jozef Bartunek, MD, PhD, Marc Vanderheyden, MD, PhD, Nico Pijls, MD, PhD, Pim Tonino, MD, PhD, William F Fearon, MD, Peter Jüni, MD, Bernard De Bruyne, MD, PhD

Figure legends

Figure S1A : Rate (%) of Vessel Oriented Clinical Endpoint (VOCE) and their individual components according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥70%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<70%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<70%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥70%).

Figure S1B : Scatter plot of the angiographic diameter stenosis (DS) versus the fractional flow reserve values (FFR). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥70%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<70%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<70%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥70%).

Figure S2 : Rate (%) of Urgent Revascularizations (UR) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥50%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<50%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<50%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥50%).

Figure S3 : Rate (%) of Non Urgent Revascularizations (NUR) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Figure S4 : Rate (%) of Myocardial Infarction (MI) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Figure S5 : Rate (%) of CV Death according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Figure S1A

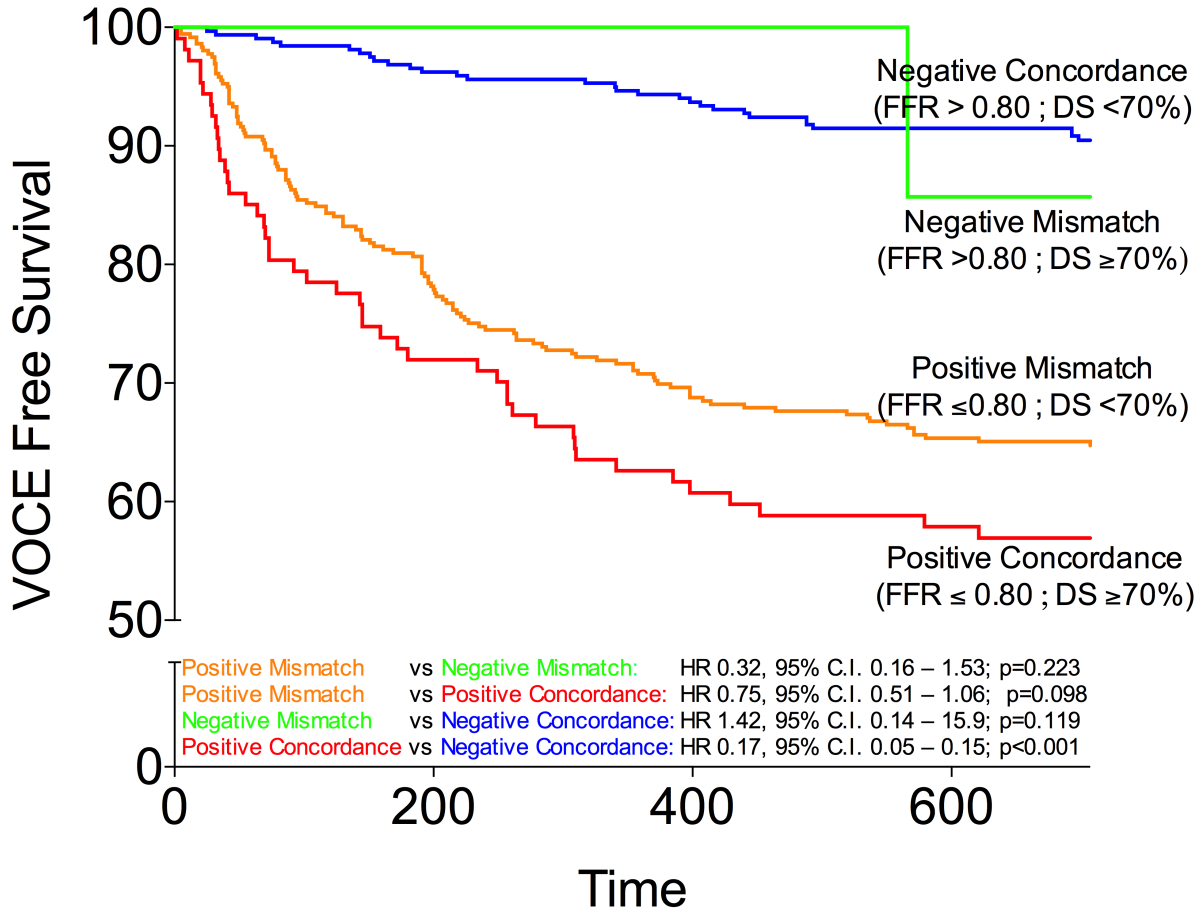


Figure S1A : Rate (%) of Vessel Oriented Clinical Endpoint (VOCE) and their individual components according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥70%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<70%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<70%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥70%).

Figure S1B

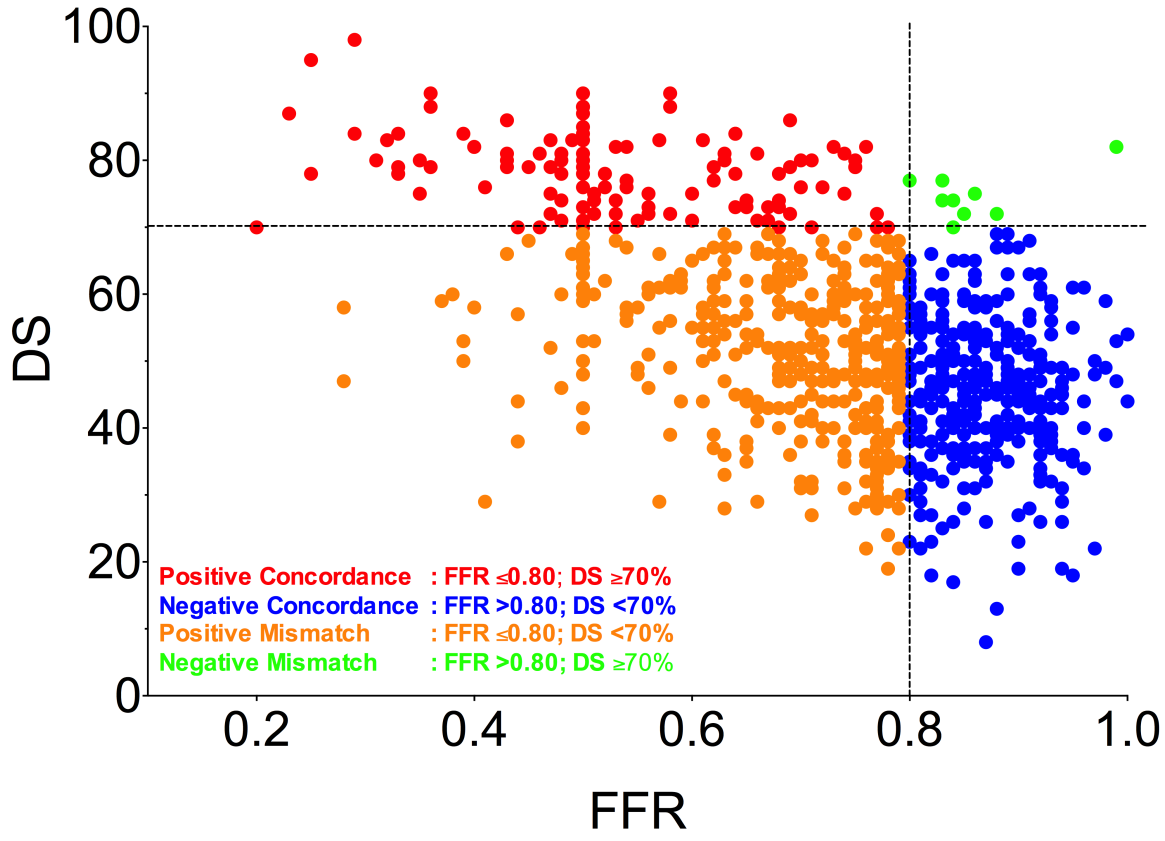
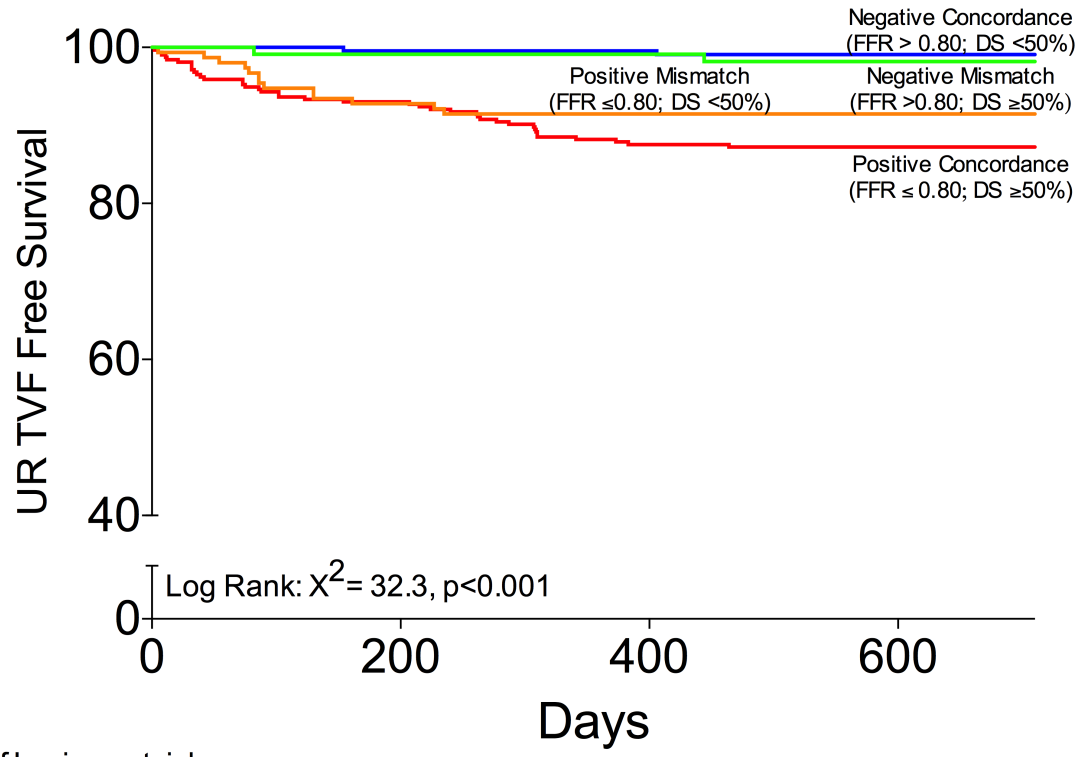


Figure S1B : Scatter plot of the angiographic diameter stenosis (DS) versus the fractional flow reserve values (FFR). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥70%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<70%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<70%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥70%).

Figure S2



Number of Lesions at risk					
N. Concordance	: 216	215	213	212	168
N. Mismatch	: 113	110	109	108	92
P. Mismatch	: 153	143	139	138	113
P. Concordance	: 316	293	272	270	236

Figure S2 : Rate (%) of Urgent Revascularizations (UR) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Red dots: Positive Concordance (PC: FFR≤0.80; DS≥50%); Blue dots: Negative Concordance (NC: FFR>0.80; DS<50%); Orange dots: Positive Mismatch (PM: FFR≤0.80; DS<50%); Green dots: Negative Mismatch (NM: FFR>0.80; DS≥50%).

Figure S3

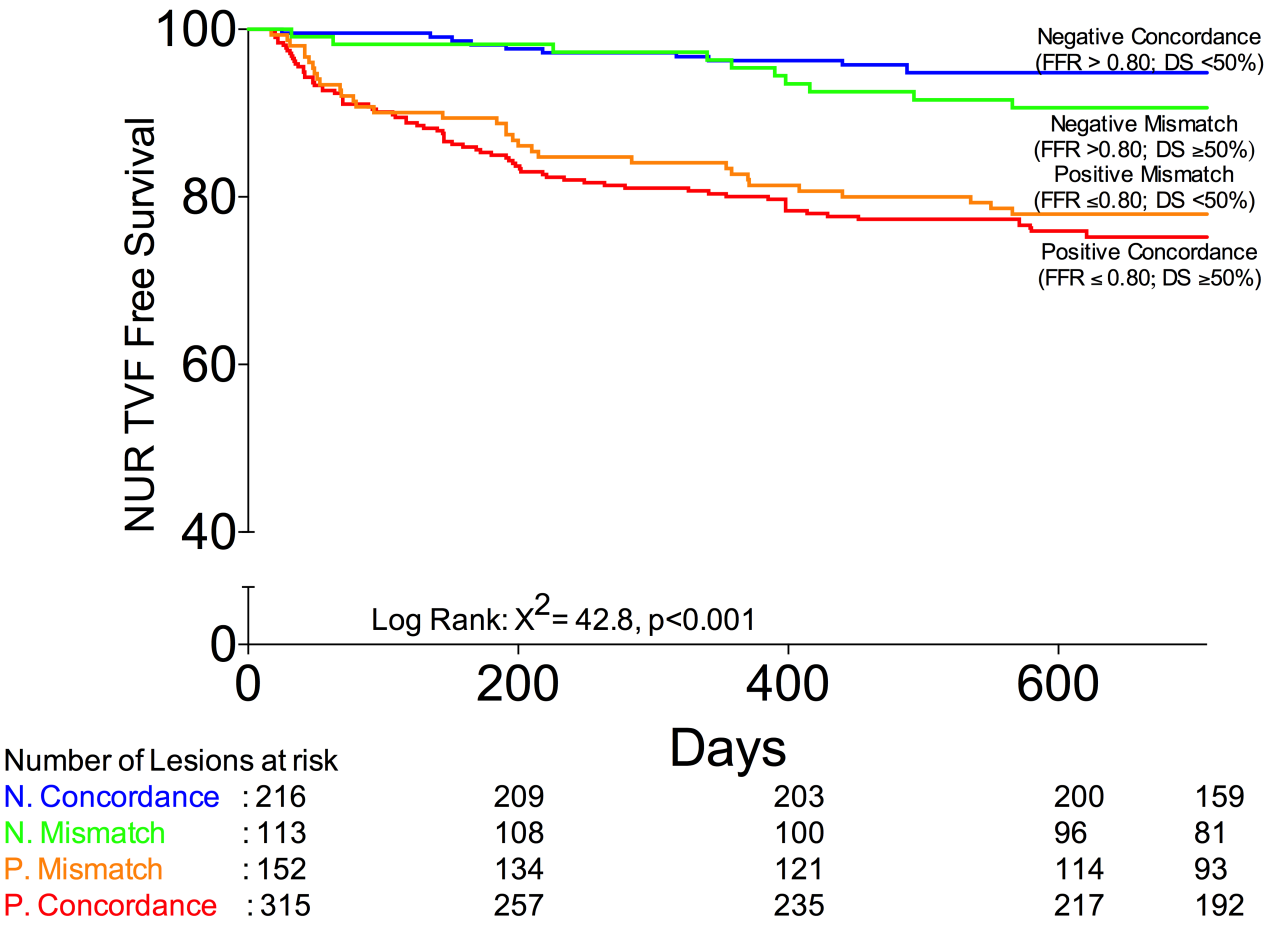
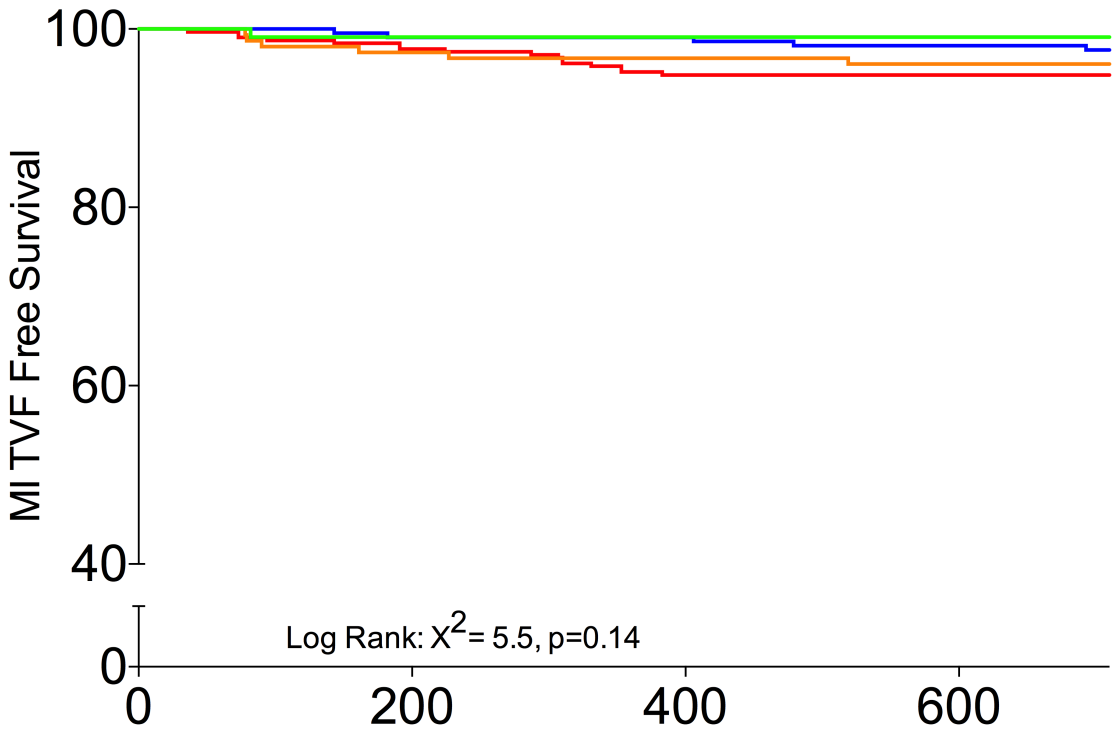


Figure S3 : Rate (%) of Non Urgent Revascularizations (NUR) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Figure S4



Number of Lesions at risk					
N. Concordance	: 216	214	212	210	167
N. Mismatch	: 111	108	107	106	91
P. Mismatch	: 153	150	147	145	119
P. Concordance	: 314	307	293	293	254

Figure S4 : Rate (%) of Myocardial Infarction (MI) according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Figure S5

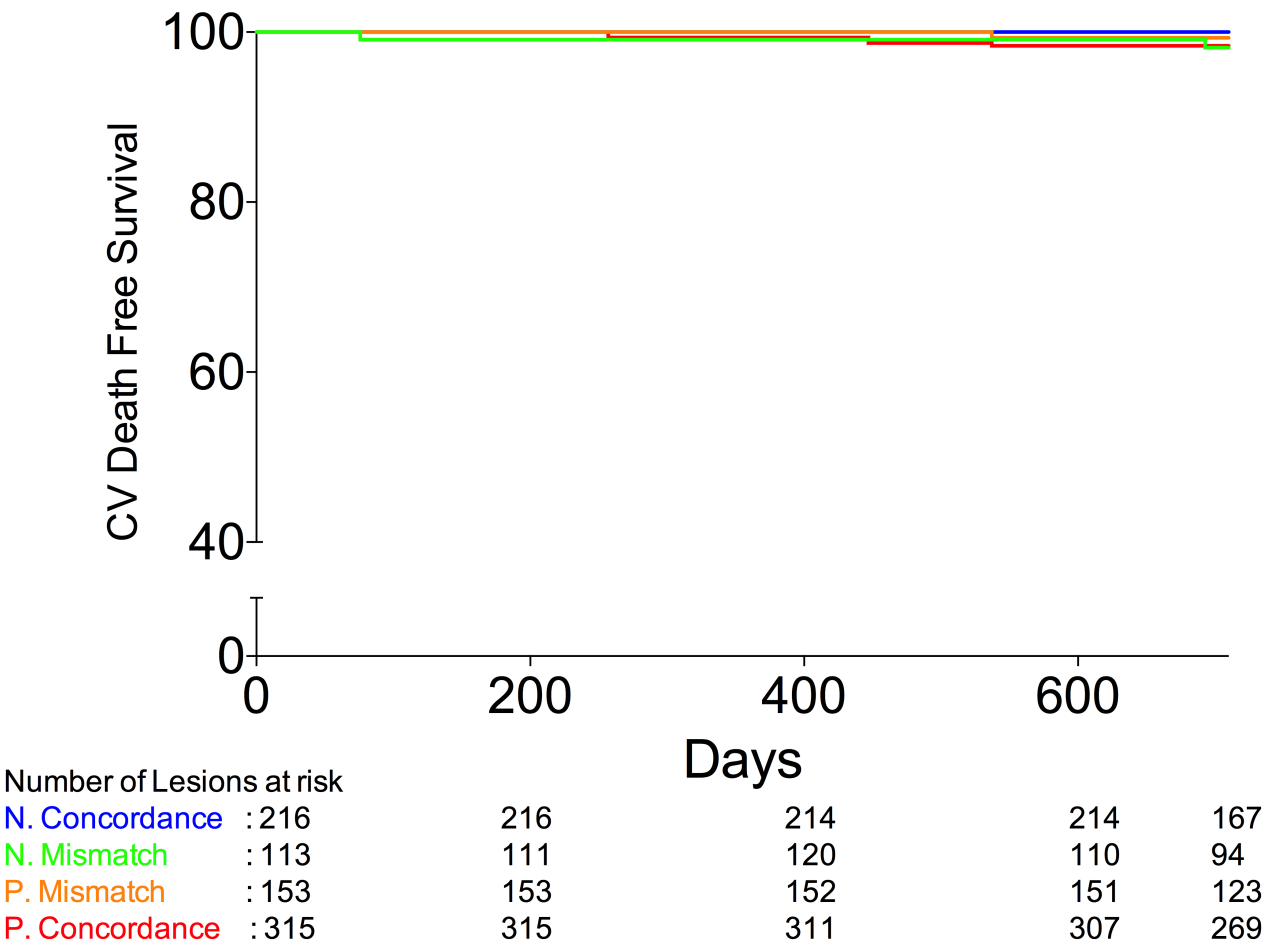


Figure S5 : Rate (%) of CV Death according to the 4 different subgroups according to the values of Fractional Flow Reserve (FFR) and Percent Diameter Stenosis (DS). Color code: Same as Figure S2.

Table S1 : P-values for pairwise analyses of the variables from table 1 with p<0.05.

	PC	NC	PM	NM
Male	Ref.	0.035	0.55	0.039
	-	Ref.	0.21	0.75
	-	-	Ref.	0.19
Peripheral Vascular Disease	Ref.	0.37	0.042	0.14
	-	Ref.	0.005	0.37
	-	-	Ref.	0.010
Previous PCI	Ref.	0.011	0.003	0.020
	-	Ref.	0.80	0.92
	-	-	Ref.	0.75
Diameter Stenosis	Ref.	<0.001	<0.001	<0.001
	-	Ref.	0.54	<0.001
	-	-	Ref.	<0.001
Minimal Lumen Diameter	Ref.	<0.001	<0.001	<0.001
	-	Ref.	0.001	<0.001
	-	-	Ref.	<0.001
Lesion Lenght	Ref.	0.005	0.030	0.48
	-	Ref.	0.14	<0.001
	-	-	Ref.	0.003
Left Anterior Descending	Ref.	0.100	<0.001	0.001
	-	Ref.	<0.001	0.039
	-	-	Ref.	<0.001
Left Circumflex Artery	Ref.	0.062	0.12	0.009
	-	Ref.	0.003	0.31
	-	-	Ref.	<0.001
Right Coronary Artery	Ref.	0.98	<0.001	0.22
	-	Ref.	<0.001	0.26
	-	-	Ref.	<0.001
Fractional Flow Reserve	Ref.	<0.001	<0.001	<0.001
	-	Ref.	<0.001	0.22
	-	-	Ref.	<0.001

Legend: P-values for pairwise analyses of the variables from table 1 with p<0.05.

Table S2: Multivariable predictors of vessel oriented clinical endpoint (VOCE) including SYNTAX

	HR (95% CI)	p
Model 1: Average estimates		
FFR<0.8	4.01 (2.60 to 6.20)	<0.001
DS ≥50%	1.34 (0.97 to 1.84)	0.074
SYNTAX	1.12 (0.93 to 1.36)	0.240
Model 2: Accounting for interaction of FFR with time		
FFR<0.80		
up to 90 days	6.65 (2.65 to 16.7)	<0.001
above 90 days	3.22 (1.69 to 4.76)	<0.001
DS ≥50%	1.34 (0.97 to 1.84)	0.073
SYNTAX	1.12 (0.93 to 1.36)	0.241

HR, Hazard ratio; CI, confidence interval; VOCE, Vessel oriented clinical endpoint; DS, diameter stenosis; FFR, fractional flow reserve.