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Usefulness of assessment of fractional flow reserve and coronary flow velocity reserve in determination of the significance of borderline stenoses in the anterior descending artery in patients with multivessel disease

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ORIGINAL ARTICLE/PRACA ORYGINALNA

Usefulness of assessment of fractional flow reserve and coronary flow velocity reserve in determination of the significance of borderline stenoses in the anterior descending artery in patients with multivessel disease

Przydatność cząstkowej rezerwy wieńcowej i echokardiograficznego pomiaru rezerwy przepływu wieńcowego w ocenie istotności granicznych zwężeń w zakresie gałęzi przedniej zstępującej u pacjentów z chorobą wielonaczyniową

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Abstract

Introduction. Assessment of the significance of borderline stenosis in the area of the anterior descending artery in patients with multivessel coronary artery disease is a challenge. Currently, ractional flow reserve (FFR) and coronary flow reverse (CFR) methods are available.

Aim. The aim of the study was to compare the usefulness of fractional flow reverse (FFR) and CFR methods in the assessment of left anterior descending artery (LAD) borderline stenosis in patients with multivessel coronary disease (MVD) and isolated LAD stenosis.

Material and methods. We examined 100 patients with suspected ischemic heart disease. The examination revealed MVD disease with borderline stenosis of the LAD in 23 patients. Significant changes were confirmed with FFR and CFR.

Results. Abnormal FFR (82% vs. 22%; $p < 0.001$) and abnormal CFR (32% vs. 12%; $p = 0.029$) were significantly more commonly observed in patients with MVD. The mean FFR (0.76 vs. 0.84; $p < 0.001$), the mean CFR (2.13 vs. 2.31; $p = 0.075$). Positive CFR and FFR values were found in 7 MVD patients and in 3 patients with single-vessel lesions (32% vs. 4%; $p < 0.001$). Negative CFR and positive FFR values were noted in 11 patients with MVD and 14 with lesions only in LAD (50% vs. 18%; $p < 0.001$). Positive CFR and negative FFR 0 vs 6 patients (0% vs. 8%; $p < 0.001$). Negative CFR and negative FFR were obtained in 4 patients from the MVD group and in 55 patients from the group of borderline stenosis only in LAD (18% vs. 71%; $p < 0.001$). MACE was observed significantly more frequently in the MVD group than in the group of patients with borderline lesions only in LAD (47% vs. 6%; $p = 0.004$).
Conclusions. Positive FFR and CFR results correlate with more frequent MACE episodes.

Keywords: PCI, MACE, FFR, MVD, CFR

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Introduction

Multivessel coronary disease (MVD) is defined as the presence of stenosis ≥ 50% of the diameter of two or more coronary vessels. MVD indicates a worse prognosis and significantly higher mortality than a single-vessel disease. In MVD, revascularization can be performed with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) [1, 2].

An assessment of the necessity and method of myocardial revascularization should take into account the size of the vessel, angiographic and functional severity of the lesion, and viability of the ischemic myocardial area [3].

While managing patients with MVD, the attending physician should be extremely careful in choosing the appropriate revascularization method. He/she should make a multifactorial assessment of not only the anatomy of the coronary artery, ischemic load, myocardial

function, age and comorbidities, but also adequacy of myocardial revascularization, predicted perioperative mortality and the patient's preferences.

In order to assess the significance of the stenosis in borderline lesions, it is useful to measure the fractional flow reserve (FFR) [4]. Angiographically borderline coronary flow may be sufficient to maintain perfusion without inducing symptoms of ischemia, hereby not requiring an intervention. FFR is an invasive method for identifying lesions responsible for reversible ischemia.

FFR is the ratio of the mean pressure measured behind the stenosis (Pd, *distal pressure*) to the average pressure in the aorta (Pa, *aortic pressure*) under conditions of maximum hyperemia, i.e. congestion, which is obtained with the use of pharmacological agents, most often adenosine. When there is no stenosis, both pressures are equal and FFR is 1. A restriction reducing flow also reduces FFR. FFR ≤ 0.80 is identified as significant ischemia [5–8] (Figure 1).

Echocardiographic measurement of coronary flow velocity reserve (CFR) is a non-invasive alternative for assessing the severity of stenosis in the left anterior descending artery (LAD). A LAD analysis [16–18] consists in comparing the maximum flow velocity in the vessel before and during or immediately after adenosine administration. The test result < 2.0 is identified as ischemia [19–22] (Figure 2).

Objectives

The aim of the study was to compare the usefulness of the invasive (FFR) and non-invasive (CFR) methods in the assessment of LAD borderline stenosis in patients with multivessel disease and isolated LAD stenosis. Another goal of the project was to assess the prognostic value of FFR and CFR in end points major adverse cardiovascular events (MACE): death, rehospitalization for cardiovascular reasons, percutaneous coronary intervention (PCI) LAD, acute coronary syndromes (ACS) in LAD, as well as an assessment of patients after a 12-month observation period using a non-invasive exercise test.

Material and methods

The study group consisted of 100 patients who, based on the clinical picture and non-invasive tests — exertion test, single photon emission computed tomography (SPECT), angioCT — were qualified for invasive diagnosis of ischemic heart disease. A coronary angiography enabled to reveal multivessel coronary artery disease with borderline stenosis in LAD, defined as 30–70% stenosis — MVD (+) group in 22 patients and, isolated borderline stenosis LAD– MVD (–) group in 78 patients.

All patients underwent an FFR procedure for lesions located in LAD (Fig. 1), followed by a non-invasive echocardiographic assessment of CFR The values of FFR < 0.80 and CFR < 2.0 indicated significant severity of the stenosis. The patients were next consulted by the HeartTeam group and qualified for PCI or coronary artery bypass graft (CABG). The HeartTeam consisted of the leading cardiologist, an invasive cardiologist and a cardiac surgeon. In the case of discrepancies in the results of FFR and CFR examinations, the patient's clinical background and preferences were taken into account in order to select the optimal method of treatment.

The observation period was 12 months, after which the patients underwent a control exercise test. An occurrence of MACE was identified as the endpoint and it included: death, rehospitalization for cardiovascular reasons, PCI LAD, ACS in LAD, as well as a positive result of an exercise test in the 12-month follow-up period.

FFR was assessed with the Quantien (St. JudeMedical/Abbott) and WaveWireTM (Volcano Inc.) systems using 0.014 inch (0.35 mm) diameter angioplasty guidewires with a fixed piezoelectric pressure sensor.

FFR was measured under condition of maximum hyperemia after administration of adenosine. Adenosine was administered as intracoronary boluses, in increasing doses, starting with 120 mcg. Subsequent doses were increased by 120 µg until the maximum value of 600 µg in one bolus [9–13]. FFR < 0.80 indicated a functionally significant stenosis.

Non-invasive assessment of CFR in LAD was made with the use of Doppler echocardiography by an experienced echocardiographer on the GE Vivid E95 device. In order to obtain optimal imaging conditions for the assessment of CFR LAD, a high-frequency transducer (4–8 MHz) or a harmonic transducer (3.5–5 MHz) was used [14]. In order to visualize the distal LAD segment, the apical projection, being an intermediate projection

between 2 and 3-chamber projection, was used [14, 15]. A modified left parasternal view was used for the middle and sometimes also for the distal segment of LAD [23]. Adenosine was used to achieve a vasodilating effect. The drug was administered intravenously at a dose of 140 µg/kg/min over 2–3 minutes. CFR is calculated as the ratio of the maximum coronary blood flow achieved after administration of a coronary vasodilator to the value of the basal (resting) blood flow.

Results

Differences regarding demographic parameters and the frequency of comorbidities in patients from MVD (+) and MVD (–) groups were not statistically significant (Table 1). Abnormal LAD FFR (82% vs. 22%; $p < 0.001$) and abnormal CFR (32% vs. 12%; $p = 0.029$) were significantly more common in patients with MVD (+). The mean FFR values for MVD (+) patients and the MVD (–) group were 0.76 and 0.84, respectively ($p < 0.001$). The mean CFR values for the analyzed groups were 2.13 and 2.31, respectively ($p = 0.075$), respectively. Positive CFR and FFR results were observed in 7 MVD (+) patients and in 3 patients with single-vessel lesions (32% vs. 4%; $p < 0.001$) (Table 2).

Negative CFR and positive FFR values were found in 11 patients with MVD (+) and 14 from the MVD (–) group (50% vs. 18%; $p < 0.001$). No MVD (+) patient demonstrated positive CFR and negative FFR values . In contrast, the above values were noted in 6 patients from the MVD (–) group (0% vs. 8%; $p < 0.001$). Negative CFR and negative FFR values were observed in 4 patients from the MVD (+) group and in 55 patients from the MVD (–) group (18% vs. 71%; $p < 0.001$).

In the 12-month follow-up period, MACE episodes (47% vs. 6%; $p = 0.004$) were observed significantly more frequently in patients with MVD (+), in particular rehospitalization for cardiovascular reasons (38% vs. 5%, $p = 0.008$). Besides, PCI in LAD was performed significantly more often in this group during clinical observation (55% vs. 22%; $p = 0.004$). Acute coronary syndrome in LAD occurred in 5% vs 1% ($p = 0.393$), deaths were noted in 5% vs. 0% ; ($p = 0.220$).

During the 12-month follow-up period, a positive ECG exercise test result was also significantly more frequently observed in the group of patients with MVD (+) (28% vs. 9%; $p = 0.035$).

According to the receiver operating characteristic (ROC) analysis, a MACE episode was predicted during the CFR procedure for: 92% sensitivity and 52% specificity, positive predictive value (PPV) — 21%, negative predictive value (NPV) — 98%, a cut-off point ≤ 2.3. For CFR < 2.0, sensitivity is 50%, specificity — 89%, PPV — 38%, NPV — 93% (Figure 4).

For FFR < 0.76 (Figure 3), the corresponding values were: 67% sensitivity, 72% specificity, PPV — 25%, NPV — 94%. For FFR < 0.8, the sensitivity was 67%, specificity — 69%, PPV — 23%, NPV — 94%. A ROC curve analysis revealed that the difference between FFR and CFR values was statistically insignificant and p = 0.341. Despite a larger area under the ROC curve (AUC) for CFR, FFR is equally reliable as the non-invasive CFR procedure (Figure 5).

In the constructed multivariate logistic regression model, in which the occurrence of the MACE composite endpoint in the long-term follow-up was taken as the dependent variable, the predictor of the occurrence of the event turned out to be only MVD (OR = 6.82; 95% CI: 1.90–24.39; p = 0.003).

In the group of patients with MACE in the long-term follow-up, statistically significantly lower solei CFR values (p = 0.045) were observed at baseline, with no statistically significant differences in FFR (p = 0.292).

Discussion

This study demonstrates that both non-invasive CFR and invasive FFR are useful tools in evaluation of patients with multivessel disease and isolated LAD stenosis. These tests help to select the appropriate treatment strategy. Besides, they have a prognostic value. This study showed a higher incidence of MACE in the group of patients with positive results.

Coronary frow velocity reserve (CFR)

A study conducted by Carlo Caiati in 1999 revealed that patients with significant LAD stenosis demonstrated the following values: CFR -2.79 (+/– 0.9), with 86% sensitivity and 90% specificity [19]. In a project by Yoshiki Matsumura, conducted in 2003, 138 patients underwent coronary angiography. It revealed a significant LAD stenosis in 30 patients. The patients were next administered the CFR procedure. A cut-off value of < 2.0 appeared to be extremely precise. CFR < 2.0 had 90% sensitivity, 93% specificity, PPV of 77% and NPV of

97% in a significant LAD stenosis [21]. Masaaki Takeuchi (2002) in his study compared wall motion score (WMI) with CFR diagnostics of patients with a significant LAD stenosis. For CFVR ≤ 2.0, the sensitivity was 75%, specificity — 81%, and diagnostic accuracy — 79% in detecting a significant LAD stenosis [20].

A ROC analysis conducted in our study group shows that MACE episodes are predicted while performing the CFR procedure. The values are the following: sensitivity — 92%, specificity 52%, PPV — 21%, NPV — 98% at the cut-off point for significance of the examined stenosis CFR ≤ 2.3. For the defined cut-off CFR < 2, the sensitivity was 50%, specificity — 89%, PPV — 38%, NPV — 93%. The difference in sensitivity and PPV in comparison to referral studies can be caused by relatively small group of MACE patients.

Fractional flow reserve (FFR)

Previous studies confirmed that FFR < 0.80 is an indication of a functionally significant stenosis. In the DEFER study, the incidence of major adverse cardiac events (MACE) was significantly higher in patients with FFR < 0.75 [4] in five- and fifteen-year follow-up. However, in FAME 1 and FAME 2 studies, FFR < 0.80 was considered functionally significant [5–6].

Our analysis showed that FFR < 0.76 indicates a significant borderline LAD stenosis, which allows to predict more frequent occurrence of MACE events. A ROC analysis shows the following values: sensitivity — 67%, specificity — 72%, PPV — 25% and NPV — 94%.

Our study with population of 100 patients similarly to DEFER study with 325 patients is relatively small comparing to FAME 1 and FAME 2 that scored populations respectively 1005 and 1220 patients. This makes the cut off < 0.80 more reliable as it comes from studies with higher statistical strength.

There was no statistically significant difference in the predictive value of both CFR and FFR procedures ($p = 0.341$). For the MACE assessment, in the studied group of patients, FFR turned out to as a reliable echocardiographic tool as CFR, despite a larger AUC area calculated in the ROC analysis.

The size of the study groups and the short observation period of 12 months are limitations of the study.

Conclusions

The above data show usefulness of non-invasive diagnostics, i.e. CFR and invasive diagnostics, i.e., FFR in assessing the significance of borderline stenosis and selecting the optimal method of treatment in patients with MVD. Positive FFR and CFR results correlate with more frequent MACE episodes in this group of patients, especially for FFR < 0.76 and CFR < 2.3. The invasive FFR procedure is “non-inferior” in comparison to the non-invasive CFR procedure in this group of patients.

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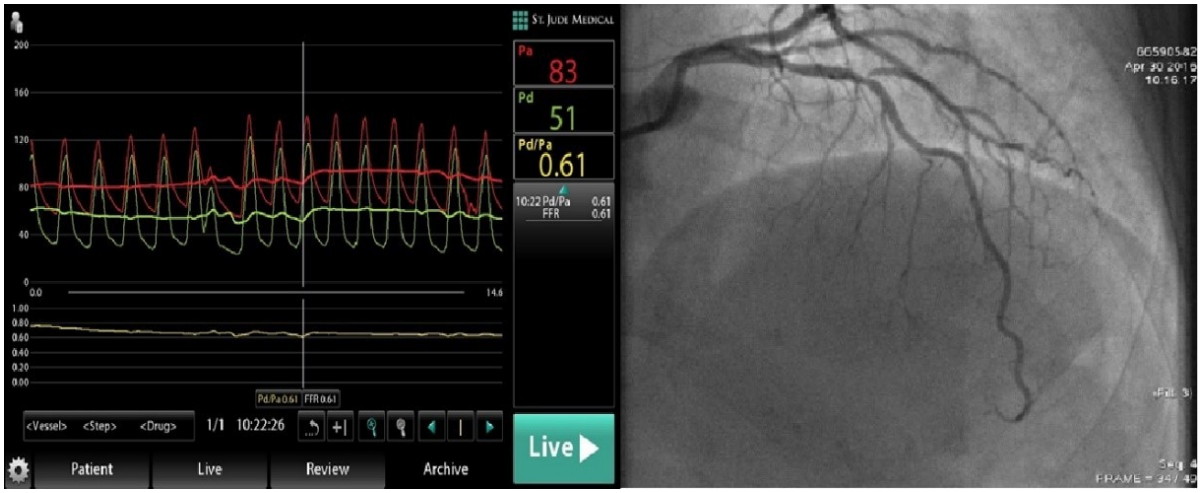


Figure 1. FFR assessment for LAD

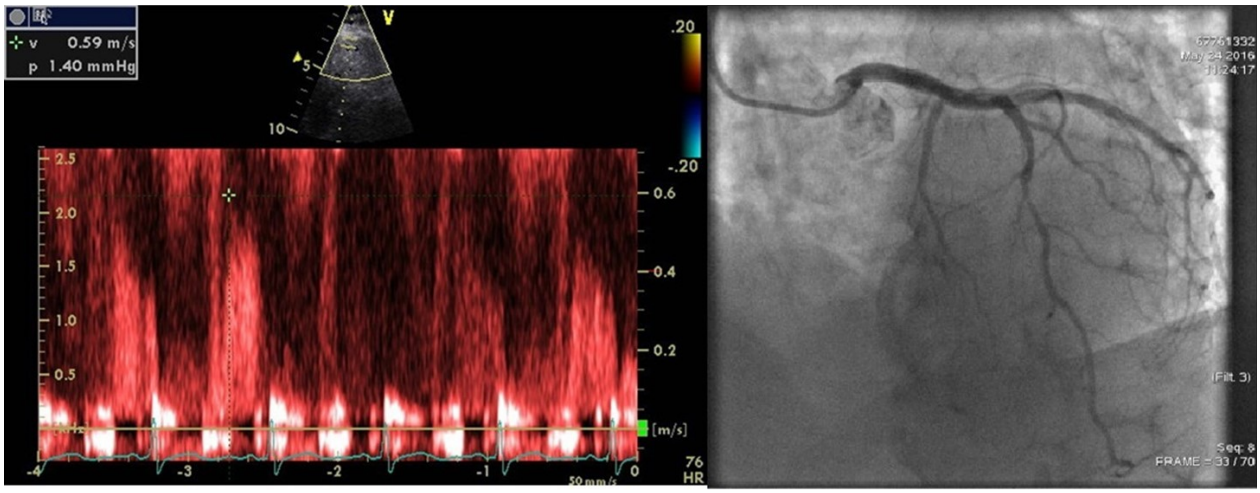


Figure 2. CFR assessment for LAD

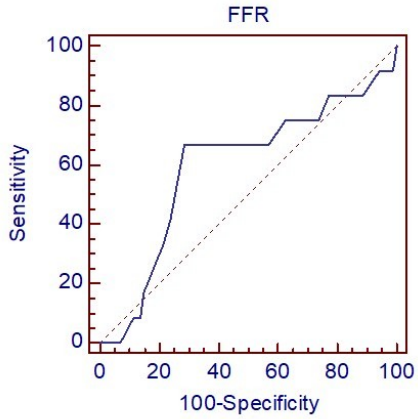


Figure 3. ROC analysis for FFR. FFR — fractional flow reserve; MACE — major adverse cardiac event; LAD — left anterior descending artery; ROC — Receiver Operating Characteristic; AUC — area under the ROC curve

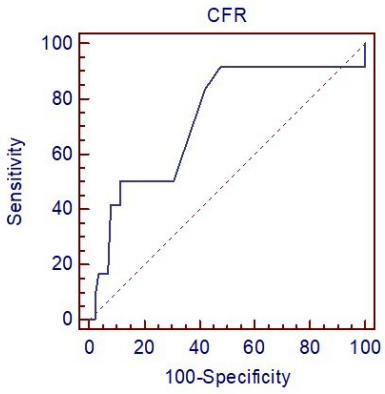
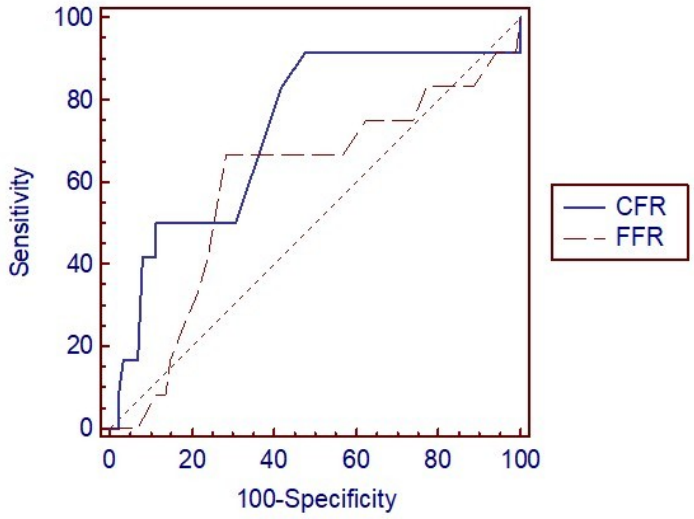


Figure 4. ROC analysis for CFR. FFR — fractional flow reserve; CFR — coronary flow velocity reserve; MACE — major adverse cardiovascular event; LAD — left anterior descending artery; ROC — Receiver Operating Characteristic; AUC — area under the ROC curve; CI — confidence interval; SE — sensitivity



Variable	FFR
Classification variable	MACE LAD
Sample size	100
Positive group: MACR LAD = 1	12
Negative group: MACE LAD = 0	88
Disease prevalence (%)	Unknown
Area under the ROC curve (AUC)	
Area under the ROC curve (AUC)	0.594
Standard Error[a]	0.0973
95% Confidence interval[b]	0.491 to 0.691
z statistic	0.969
Significance level P (Area = 0.5)	0.3327
[a]DeLong et al., 1988 [b]Binomial exact	
Youden index	
Youden index J	0.3826
Associated criterion	≤ 0.76

Figure 5. Comparison of the ROC curve for FFR and CFR. FFR — fractional flow reserve; CFR — coronary flow velocity reserve; MACE — major adverse cardiac event; LAD — left anterior descending artery; ROC — Receiver Operating

Characteristic; AUC — area under the ROC curve; CI — confidence interval; SE — sensitivity

Table 1. Comparative characteristics of patients with multivessel disease with borderline LAD stenosis (MVD +) and patients with isolated borderline LAD lesions (MVD –)

Variable	MVD – (n = 78)	MVD + (n = 22)	p
Age, years	65.7 ± 9.6	66.2 ± 7.8	0.826
Women, n (%)	15 (19%)	2 (9%)	0.218
HA, n (%)	69 (88%)	22 (100%)	0.096
DM2, n (%)	32 (41%)	12 (55%)	0.259
Dyslipidemia, n (%)	75 (96%)	22 (100%)	0.470
Nicotinism, n (%)	23 (29%)	7 (31%)	0.833
AF, n (%)	16 (21%)	3 (14%)	0.554
GFR (ml/min/1.73 m²)	78 (64–95)	87 (70–110)	0.226
BMI > 30 kg/m^2	22 (28%)	11 (50%)	0.055
EF, %	53 (40–58)	46 (38–54)	0.061
LDL (mg/dL)	78 (58–98)	86 (60–112)	0.524

HA — hypertonia arterialis; DM2 — diabetes mellitus type 2; AF — atrial fibrillation; GFR — glomerular filtration rate; BMI — body mass index; EF — ejection fraction; LDL — low-density lipoprotein

Table 2. Comparison of CFR and FFR values and endpoints in MVD (+) and MVD (–) patients

Variable	MVD – (n = 78)	MVD + (n = 22)	p
MACE, n (%)	5 (6%)	7 (47%)	0.004
Death, n (%)	0 (0%)	1 (5%)	0.220
Rehospitalization, n (%)	4 (5%)	6 (38%)	0.008
ACS in LAD, n (%)	1 (1%)	1 (5%)	0.393
Positive stress test after 12 months, n (%)	7 (9%)	6 (28%)	0.035
PCI in LAD, n (%)	17 (22%)	12 (55%)	0.004
FFR < 0.8	17 (22%)	18 (82%)	< 0.001
CFR < 2.0	9 (12%)	7 (32%)	0.029
FFR	0.84 ± 0.09 0.86 (0.81–0.90)	0.76 ± 0.06 0.76 (0.71–	< 0.001

		0.77)	
CFR	2.31 ± 0.41 2.35 (2.10–2.50)	2.13 ± 0.38 2.20 (1.80–2.40)	0.075
CFR + and FFR +, n (%)	3 (4%)	7 (32%)	< 0.001
CFR – , and FFR +, n (%)	14 (18%)	11 (50%)	
CFR + and FFR –, n (%)	6 (8%)	0 (0%)	
CFR – and FFR –, n (%)	55 (71%)	4 (18%)	

MVD — multivessel disease; MACE — major adverse cardiac event; ACS — acute coronary syndrome; LAD — left anterior descending artery; PCI — percutaneous coronary intervention; FFR — fractional flow reserve; CFR — coronary flow velocity reserve

Table 3. Independent predictors of MACE occurrence in long-term follow-up

Variable	OR	95% CI	p
MVD	6.82	1.90–24.39	0.003

Table 4. Comparison of FFR and CFR depending on the occurrence of MACE in the long-term follow-up

Variable	MACE + n = 12	MACE – n = 88	p
FFR	0.80 ± 0.09	0.82 ± 0.09	0.292
CFR	2.05 ± 0.58	2.31 ± 0.37	0.045