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Microvascular dysfunction of the non-culprit circulation predicts poor prognosis in patients with ST-segment elevation myocardial infarction☆

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ABSTRACT

Background: Endothelial and microvascular dysfunction are frequently found in the non-culprit territory in patients with acute myocardial infarction (AMI). We aimed to determine whether an impaired coronary physiology of the non-culprit territory impacts long-term prognosis.

Methods: FISIOIAM was an observational single-center study which included patients with AMI and another coronary artery lesion in a different territory. Intracoronary physiology of the non-culprit artery was analyzed early after primary percutaneous coronary intervention of the culprit artery, using fractional flow reserve (FFR), index of microcirculatory resistance (IMR), coronary flow reserve (CFR), endothelium-dependent CFR (eCFR) and macrovascular endothelial function . Patients were followed for a composite outcome of cardiovascular death, non-fatal myocardial infarction, coronary revascularization, and hospitalization due to heart failure or unstable angina.

Results: A total of 84 patients (mean age: 62 ± 10 years) were included and functional abnormalities were detected in 93% of them. During follow-up (median of 1422 days; interquartile range, 1287–1634), 13.1% of the patients experienced at least one adverse cardiovascular event. Kaplan-Meier analysis revealed that patients with a CFR < 2 had a higher risk of events (Hazard Ratio, HR: 4.97, 95% Confidence Interval, CI, 1.32–18.75), whereas other parameters such as FFR, IMR, eCFR, and macrovascular endothelial function had no effect. A low CFR was an independent predictor of cardiovascular events, even after adjustment for age and traditional cardiovascular risk factors (adjusted HR: 6.62, 95% CI, 1.30–33.70).

Conclusions: The presence of abnormal coronary microvascular function as measured by a CFR < 2 in the non-culprit territory predicts future risk of adverse cardiovascular events.

1. Introduction

Prompt reperfusion of the occluded epicardial coronary artery by primary percutaneous coronary intervention (PCI) is the guideline-recommended treatment for ST-segment elevation myocardial infarction (STEMI) [1]. In the culprit territory, microvascular dysfunction is very prevalent and correlates with worse outcomes [2]. In the non-culprit artery, microvascular and endothelial dysfunction are also prevalent, [3–5] but the prognostic implications of these have not been reported to date. We aimed to evaluate the hypothesis that endothelial and microvascular dysfunction in the non-culprit coronary arteries may also predict long-term clinical outcomes after STEMI.

2. Methods

2.1. Study population and protocol

The study design and primary results of the FISIOAM study have

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been previously described [3]. Briefly, the FISIOIAM (FISIOlogía del Infarto Agudo de Miocardio) was an observational, prospective, single-center study which included patients who had had a STEMI with successful revascularization of the culprit artery and at least another lesion in a non-culprit territory with a stenosis severity between 40 and 90% by visual assessment. The physiological study of the non-culprit artery was performed in a second procedure soon after initial revascularization of the culprit artery in a three-phased protocol, which subsequently evaluated the macrovascular endothelial function and both the endothelium-dependent and independent microvascular function.

Macrovascular endothelial dysfunction was defined as any significant vasoconstriction (reduction $\geq$ 50% of the vessel diameter) in an epicardial coronary segment after acetylcholine infusion. Endothelium-independent microvascular dysfunction was defined as an index of microcirculatory resistance (IMR) higher than 25 or a CFR < 2, obtained after induction of hyperemia by means of an intravenous perfusion of adenosine (at a dose of 140 μg/kg per minute). Microvascular endothelial dysfunction was defined as an endothelial CFR (eCFR) < 1.5. Percutaneous coronary intervention of the non-culprit artery stenosis was performed as per usual clinical practice, usually when fractional flow reserve (FFR) was $\leq$0.8.

Local institutional review board approved the study, and all patients provided written informed consent to participate in the study.

2.2. Variables, definitions, and end points

All relevant clinical and procedural data, the physiological invasive parameters and long- term outcomes were systematically recorded in a database at the time of the study enrollment and the information was updated through electronic medical record review and, when necessary, by telephone follow-up.

We defined a composite primary end point of adverse cardiovascular events that included cardiovascular death, myocardial infarction, coronary revascularization, and hospitalization due to heart failure or unstable angina. The secondary endpoint was a composite of all-cause death, non-fatal myocardial infarction, coronary revascularization, non-fatal stroke, and hospitalization due to heart failure or unstable angina. Patients were followed for a median of 48 months.

2.3. Statistical analysis

Continuous variables are summarized as mean (SD) and were compared using Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables are presented as frequency (%) and were compared using the χ^2 test. Normalcy and homogeneity of the variances were tested using the Kolmogorov-Smirnov and Levene tests.

Kaplan-Meier event-free curves were drawn for patients with normal and abnormal coronary function and differences between the 2 curves were tested using the log-*rank* test. Multivariate Cox regression analysis was performed to assess the effect of all individual physiological defects on adverse events and adjust for age, sex, and traditional cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking). Missing data were imputed for the multivariate analysis with multiple imputation with chained equations (mice package, R v.4.0). Hazard ratios were calculated with 95% confidence interval. All p values were 2-tailed at a 0.05 significance level. Statistical analysis was performed with SPSS 26.0 (IBM Corp, Armonk, NY) and R v 4.0.

3. Results

A total of 84 patients with STEMI and multivessel disease were included from July 2016 to December 2017. No patients were lost to follow-up.

Mean age at enrollment was 62 $\pm$ 10 years and 87% of the patients were male. Baseline demographics, clinical and physiological characteristics of the patients, split by the presence of low CFR, high IMR and low eCFR, are summarized in Table 1.

Globally, most patients presented macrovascular or microvascular endothelial dysfunction, over one third presented a depressed CFR, and one quarter a high IMR. Only 6 patients (7.1%) had a completely normal study, defined as a nonpathological FFR, IMR, CFR, macrovascular response to acetylcholine and eCFR.

3.1. Prognostic impact of endothelial and microvascular dysfunction

Long term clinical events are shown in Table 2. At a median follow-up of 4 years, the primary endpoint occurred in 11 patients (13.1%)-an annual incidence of 3.3%. Median time to the first cardiovascular event was 895 days (IQR 518 – 1222). Ten patients (11.9%) died during follow up, eight of them from non-cardiovascular causes. Hospitalization for unstable angina was the most common cardiovascular event (9.5%; n = 8); of these, 6 patients required urgent percutaneous coronary intervention whereas the remaining two cases were discharged on optimal medical therapy.

Kaplan-Meier analysis showed that a CFR < 2 (Fig. 1) was significantly associated with a higher incidence of the primary endpoint (HR: 4.97, 95% confidence interval, CI: 1.32–18.75; log-rank $P = 0.009$) whereas the rest of parameters had no impact (Supplementary figure S1). A Cox proportional hazards regression model also confirmed that a CFR < 2 (HR, 6.62; 95 %CI, 1.30–33.74; $P = 0.023$) was the only variable independently associated with the primary endpoint, even after adjusting for age and all cardiovascular risk factors (Table 3).

The secondary endpoint occurred in 17 (20.2%) patients (Supplementary Table S1). A CFR < 2 was a predictor of the secondary endpoint in Kaplan-Meier analysis, and after adjusting for other physiological and clinical parameters in Cox regression (HR 3.29; 95% CI: 1.07– 10.16, p = 0.04) (Table S2). Supplementary Figs. S1 and S2 show the Kaplan-Meier curves for the secondary outcome. The rest of the physiological parameters had no bearing on the secondary outcome.

4. Discussion

In this contemporary real-world study of patients with STEMI and multivessel disease, we demonstrated that those with a low coronary flow reserve in the non-culprit coronary territories were at higher risk for cardiovascular complications at median follow-up of 4 years.

CFR is a prognostic marker in a wide range of situations [6] including angina with non-obstructed coronary arteries [7], stable coronary artery disease [8] and the culprit territory in patients with STEMI [9,10]. However, to date there were no data on the prognostic implications of a depressed CFR in the non-culprit territory in patients with STEMI. Of note, the mechanisms responsible for a low CFR in the non-culprit artery are not clearly established. We previously described a higher prevalence of low CFR than that of high IMR in this context, which means that –at least in part– the depression of CFR may be explained by an increased flow at rest, rather than by a decreased hyperemic flow alone. Van der Hoeven et al. [4] measured CFR and microvascular resistance during the acute phase and at one month, and found similar results. Of note, at one month CFR increased by 30%, while IMR decreased and resting microcirculatory resistance increased. Thus, it seems there are transient changes in the non-culprit circulation that involve an increased flow at rest and a decreased hyperemic flow during the acute phase. Possible involved factors include increased left ventricular filling pressures, compensatory hyperkinesis of remote areas and neurohumoral activation causing global coronary arteriolar vasoconstriction [11].

Intriguingly, our findings showed that IMR of the non-culprit artery does not correlate with long-term prognosis. It has been previously reported that a higher IMR in the culprit artery is associated with worse outcomes after STEMI, including adverse left ventricular remodeling [12] and death [12,13]. However, this was not later replicated in other studies [14,15], suggesting that the prognostic impact of IMR is less consistent than that of CFR, and seems more important when both

Table 1
Baseline demographic, clinical, angiographic and physiologic characteristics.

	CFR ≥ 2 N = 52	CFR < 2 N = 31	*P*	IMR ≤ 25 N = 60	IMR > 25 N = 23	*P*	eCFR ≥ 1.5 N = 41	eCFR < 1.5 N = 32	*P*
Age, years	60.31 (10.30)	64.90 (9.7)	0.046	61.59 (9.42)	62.19 (10.7)	0.816	61.57 (11.3)	62.38 (9.4)	0.745
Male, n (%)	46 (88.5)	26 (83.9)	0.793	50 (83.3)	22 (95.7)	0.263	34 (82.9)	29 (90.6)	0.544
BMI, kg/m^2	28.77 (4.5)	27.01 (3.54)	0.068	26.37 (3.45)	28.78 (4.4)	0.020	28.52 (4.8)	27.82 (3.54)	0.494
Hypertension, n (%)	26 (50.0)	16 (51.6)	1	29 (48.3)	13 (56.5)	0.673	25 (61.0)	11 (34.4)	0.43
Dyslipidemia, n (%)	17 (32.7)	15 (48.4)	0.235	23 (38.3)	9 (39.1)	1	17 (41.5)	11 (34.4)	0.707
Diabetes, n (%)	4 (7.7)	7 (22.6)	0.109	8 (13.3)	3 (13.0)	1	6 (14.6)	3 (9.4)	0.749
Smoking status, n (%)			0.553			0.157			0.104
Never smoked, n (%)	15 (28.8)	12 (38.7)		23 (38.3)	4 (17.4)		12 (29.3)	13 (40.6)	
Former smoker, n (%)	28 (53.8)	13 (41.9)		28 (46.7)	13 (56.5)		24 (58.5)	11 (34.4)	
Current smoker, (%)	9 (17.3)	6 (19.4)		9 (15.0)	6 (26.1)		5 (12.2)	8 (25.0)	
Killip class at admission			0.802			0.667			0.656
I, n (%)	49 (94.2)	28 (90.3)		55 (91.7)	22 (95.7)		38 (92.7)	30 (93.8)	
II, n (%)	2 (3.8)	2 (6.5)		3 (5.0)	1 (4.3)		2 (4.9)	2 (6.2)	
III-IV, n (%)	1 (1.9)	1 (3.2)		2 (3.3)	0 (0.0)		1 (2.4)	0 (0.0)	
GRACE score on admission	108.19 (24.74)	116.58 (25.01)	0.141	111.23 (27.07)	111.57 (19.18)	0.957	108.98 (24.70)	114.41 (27.12)	0.375
Systolic blood pressure, mmHg	135.12 (25.26)	132.81 (26.46)	0.693	134.48 (25.71)	133.65 (25.79)	0.896	135.54 (23.56)	129.50 (28.27)	0.323
Diastolic blood pressure, mmHg	78.77 (16.87)	75.42 (11.85)	0.335	77.70 (15.93)	77.04 (13.45)	0.861	78.20 (14.86)	75.31 (15.34)	0.42
Heart rate, bpm	72.92 (17.95)	76.48 (13.43)	0.342	73.18 (16.45)	77.04 (16.33)	0.341	75.66 (14.98)	74.75 (19.06)	0.82
Peak High- sensitivity cardiac Troponin T, ng/dL	2034.00 [IQR, 1017.50, 3482.50]	2658.00 [IQR, 1177.50, 5336.00]	0.23	1966.00 [IQR, 996.50, 3496.50]	2744.00 [IQR, 1525.00, 4439.50]	0.193	1814.00 [IQR, 920.25, 3487.75]	2639.00 [IQR, 1153.50, 3726.25]	0.357
Creatinine, mg/dL	0.90 (0.20)	0.93 (0.24)	0.511	0.90 (0.22)	0.96 (0.19)	0.23	0.88 (0.19)	0.93 (0.23)	0.301
Culprit artery			0.834			0.78			0.245
LAD, n (%)	15 (28.8)	8 (25.8)		14 (23.3)	9 (39.1)		8 (19.5)	10 (31.2)	
Diagonal branch, n (%)	1 (1.9)	0 (0.0)		0 (0.0)	1 (4.3)		1 (2.4)	0 (0.0)	
Circumflex, n (%)	4 (7.7)	3 (9.7)		3 (5.0)	4 (17.4)		4 (9.8)	3 (9.4)	
Left marginal branch, n (%)	3 (5.8)	2 (6.5)		5 (8.3)	0 (0.0)		2 (4.9)	3 (9.4)	
RCA, n (%)	26 (50.0)	18 (58.1)		35 (58.3)	9 (39.1)		26 (63.4)	13 (40.6)	
Posterolateral branch, n (%)	2 (3.8)	0 (0.0)		2 (3.3)	0 (0.0)		0 (0.0)	2 (6.2)	
PDA, n (%)	1 (1.9)	0 (0.0)		1 (1.7)	0 (0.0)		0 (0.0)	1 (3.1)	
Final TIMI flow 3, n (%)	52 (100.0)	30 (96.8)	0.792	59 (98.3)	23 (100.0)	1	40 (97.6)	32 (100.0)	1
LVEF, %	55.00 [IQR, 50.00, 60.00]	55.00 [IQR, 45.00, 60.00]	0.338	55.00 [IQR, 50.00, 60.00]	52.00 [IQR, 43.00, 58.00]	0.44	55.00 [IQR, 50.00, 60.00]	55.00 [IQR, 49.50, 61.00]	0.46
Non-culprit artery			0.597			0.36			0.217
LAD, n (%)	19 (36.5)	15 (48.4)		28 (46.7)	6 (26.1)		16 (39.0)	15 (46.9)	
Diagonal branch, n (%)	3 (5.8)	0 (0.0)		3 (5.0)	0 (0.0)		1 (2.4)	2 (6.2)	
Circumflex, n (%)	9 (17.3)	6 (19.4)		13 (21.7)	2 (8.7)		7 (17.1)	6 (18.8)	
Left marginal branch, n (%)	6 (11.5)	4 (12.9)		6 (10.0)	4 (17.4)		8 (19.5)	1 (3.1)	
Intermediate artery, (%)	3 (5.8)	1 (3.2)		3 (5.0)	1 (4.3)		2 (4.9)	2 (6.2)	
RCA, n (%)	9 (17.3)	5 (16.1)		6 (10.0)	8 (34.8)		4 (9.8)	6 (18.8)	
PDA, n (%)	3 (5.8)	0 (0.0)		1 (1.7)	2 (8.7)		3 (7.3)	0 (0.0)	
Lesion length, mm.	13.29 (8.60)	15.64 (9.51)	0.249	14.71 (9.06)	12.76 (8.76)	0.379	13.31 (8.60)	13.09 (6.57)	0.904
Type of vasoconstriction in response to Ach, n (%)			0.137			0.476			0.749
None	20 (38.5)	16 (51.6)		24 (40.0)	12 (52.2)		19 (46.3)	12 (37.5)	
Diffuse	23 (44.2)	7 (22.6)		24 (40.0)	6 (26.1)		13 (31.7)	12 (37.5)	
Focal	9 (17.3)	8 (25.8)		12 (20.0)	5 (21.7)		9 (22.0)	8 (25.0)	
Baseline *Tmn*, sec	0.88 (0.45)	0.80 (0.54)	0.459	0.67 (0.35)	1.30 (0.50)	<0.001	0.84 (0.38)	0.75 (0.50)	0.402
Hyperemia *Tmn*, sec	0.29 (0.17)	0.55 (0.36)	<0.001	0.26 (0.12)	0.72 (0.31)	<0.001	0.34 (0.24)	0.38 (0.29)	0.496
Baseline Pd/Pa	0.94 (0.06)	0.90 (0.07)	0.009	0.94 (0.06)	0.92 (0.07)	0.366	0.94 (0.05)	0.91 (0.07)	0.03
FFR	0.84 (0.09)	0.80 (0.11)	0.76	0.82 (0.10)	0.85 (0.09)	0.163	0.83 (0.09)	0.83 (0.09)	0.757
FFR < 0.8, n (%)	17 (32.7)	11 (35.5)	0.984	22 (36.7)	6 (26.1)	0.514	15 (36.6)	9 (28.1)	0.608
CFR	3.25 (1.23)	1.46 (0.32)	<0.001	2.83 (1.42)	1.92 (0.66)	0.4	2.89 (1.39)	2.22 (1.23)	0.34
CFR < 2, n (%)	0 (0.0)	31 (100.0)	<0.001	18 (30.0)	13 (56.5)	0.47	10 (24.4)	17 (53.1)	0.23
IMR	19.49 (11.22)	32.66 (25.29)	0.2	15.45 (4.49)	47.78 (21.77)	<0.001	22.36 (15.04)	24.29 (19.26)	0.631
IMR < 25n (%)	10 (19.2)	13 (41.9)	0.47	0 (0.0)	23 (100.0)	<0.001	10 (24.4)	9 (28.1)	0.927
eCFR	1.94 (1.05)	1.41 (0.61)	0.21	1.77 (1.01)	1.67 (0.72)	0.702	2.25 (0.97)	1.09 (0.25)	<0.001
eCFR < 1.5, n (%)	15 (32.6)	17 (63.0)	0.23	23 (42.6)	9 (47.4)	0.927	0 (0.0)	32 (100.0)	<0.001

defects are combined [8]. Also, different thresholds have been used for IMR, and Fearon et al. [13] used a cutoff of 40 in the culprit artery, which is quite higher than the standard of 25, and probably more specific for microvascular obstruction.

Endothelial dysfunction was also not a predictor of adverse cardiovascular events. Previous reports have shown that endothelial dysfunction is associated with an increased cardiovascular risk both in patients with and without obstructive coronary lesions [16]. However, contradictory results have been published regarding the prognostic role of endothelial dysfunction after STEMI [17,18]. Endothelial function testing is particularly challenging in the setting of an acute coronary syndrome ACS [19] and consequently, most of the studies have explored the endothelium-dependent vasoreactivity weeks after the index event, as opposed to our study where the measurements took place a median of 2 days after primary PCI. It is possible that the high prevalence of endothelial dysfunction we observed is a transient phenomenon, as has been previously suggested [5], particularly if optimal medical therapy including high-dose statins and angiotensin converting enzyme

Table 2
Composite primary endpoint and its components during follow-up.

	All patients (n = 84)	CFR < 2 (n = 31)	CFR ≥ 2 (n = 52)	Abnormal MEF (n = 48)	Normal MEF (n = 32)	IMR > 25 (n = 23)	IMR ≤ 25 (n = 60)	eCFR < 1.5 (n = 32)	eCFR ≥ 1.5 (n = 41)	FFR ≤ 0.8 (n = 28)	FFR > 0.8 (n = 55)
Composite endpoint, n (%)	11 (13.1)	8 (25.8)	3 (5.8)	5 (10.4)	6 (18.8)	4 (17.4)	7 (11.7)	5 (18.8)	6 (14.6)	4 (14.3)	7 (12.7)
Cardiovascular death, n (%)	2 (2.4)	1 (3.2)	1 (1.9)	2 (4.2)	0 (0)	1 (4.3)	1 (1.7)	0 (0)	2 (4.9)	1 (3.6)	1 (1.8)
Myocardial infarction, n (%)	1 (1.2)	0 (0)	1 (1.9)	0 (0)	1 (3.1)	0 (0)	1 (1.7)	0 (0)	1 (2.4)	1 (3.6)	0 (0)
Unstable angina or need for urgent coronary revascularization, n (%)	8 (9.5)	6 (18.8)	2 (3.8)	3 (6.3)	5 (15.6)	3 (13.0)	5 (8.3)	4 (12.5)	4 (9.8)	3 (10.7)	5 (9.1)
Heart failure, n (%)	1 (1.2)	1 (3.2)	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (1.7)	1 (3.1)	0 (0)	0 (0)	1 (1.8)

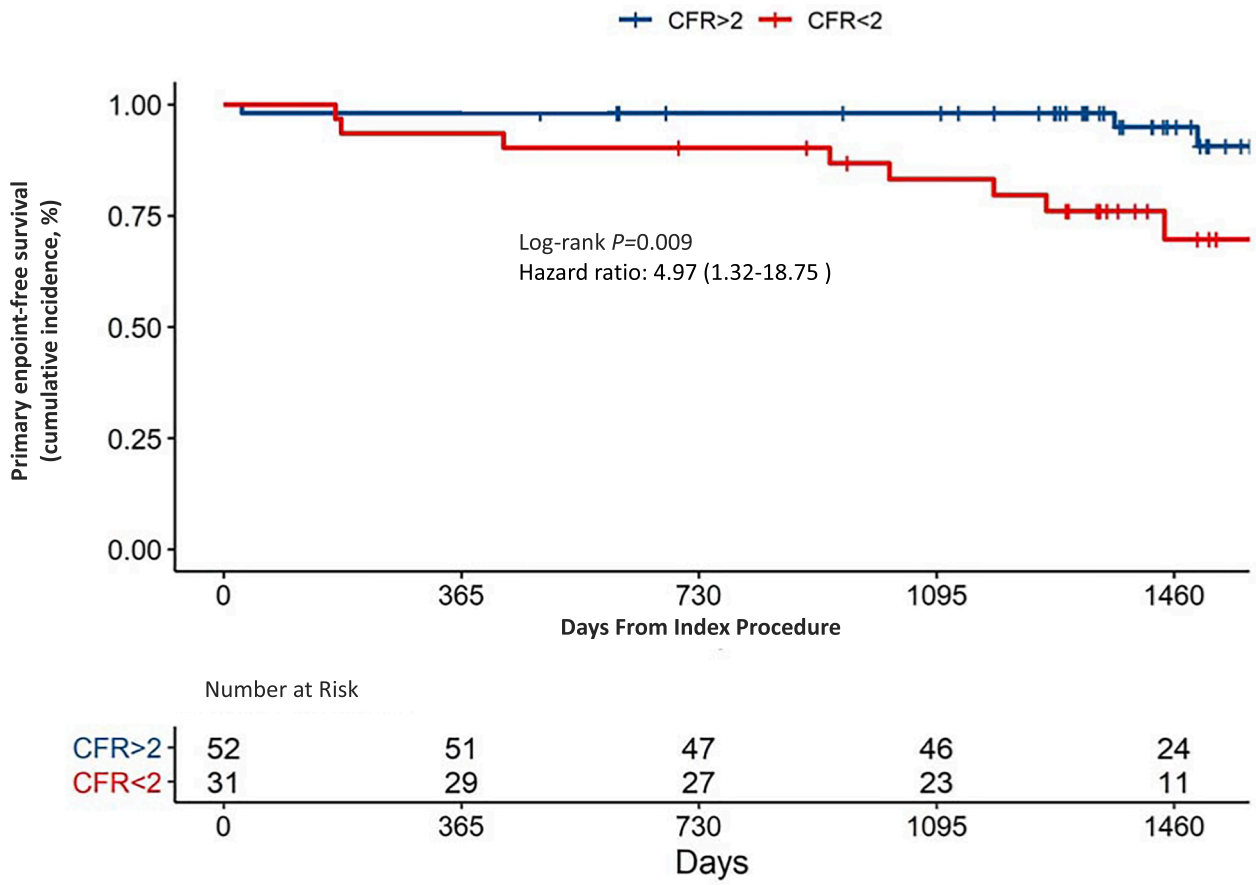

Fig. 1. Kaplan–Meier curves evaluating the incidence of the primary endpoint between patients with and without a coronary flow reserve (CFR) < 2.

Table 3
Prognostic factors for occurrence of the primary endpoint at 4 years (multivariate Cox proportional hazards regression analysis).

Variable	Hazard ratio (95% CI)	*p*
CFR < 2	6.62 (1.30–33.74)	0.02
IMR > 25	1.04 (0.23–4.70)	0.96
eCFR < 1.5	0.51 (0.11–2.33)	0.39
Macrovascular endothelial dysfunction	1.23 (0.25–6.19)	0.80
FFR ≤ 0.8	1.37 (0.35–5.42)	0.65
Age	0.98 (0.90–1.06)	0.572
Hypertension	1.19 (0.36–3.90)	0.77
Dyslipidemia	1.60 (0.44–5.81)	0.47
Diabetes	0.93 (0.16–5.52)	0.94
Smoking (past or present)	0.43 (0.08–2.29)	0.323

CFR, coronary flow reserve; eCFR, endothelium-dependent CFR; FFR, fractional flow reserve; CI: confidence interval; IMR, index of microcirculatory resistance.

inhibitors is duly prescribed after STEMI. These may be reasons why endothelial dysfunction did not increase the risk of adverse clinical events.

Revascularization trials [20–22] have shown that the non-culprit territory is not stable, in the sense that it has poor results with optimal medical therapy. Although physiology-guided PCI of the non-culprit artery is superior to medical therapy [23,24], a recent trial shows that the benefit of FFR-guided revascularization over angiography-guided revascularization observed in stable patients is not maintained here [25]. This may be due to inaccuracy of FFR in the setting of STEMI, plaque vulnerability of the non-culprit territory, or to other more complex physiological differences. There is some evidence that supports a link between microvascular dysfunction and vulnerable plaques, as it is associated with increased prevalence of thin-cap fibroatheroma and plaque rupture on optical coherence tomography [26,27]. Thus, CFR may be capturing here the combined effect of hemodynamic instability, plaque vulnerability and plaque burden.

Importantly, CFR can be measured using non-invasive tests,

including echocardiography, positron emission tomography, and cardiac magnetic resonance as well as by means of intracoronary Doppler or thermodilution wires. This could facilitate a comprehensive evaluation of patients with STEMI and may be important for evaluating future treatment strategies. Randomized controlled trials are needed to clarify this issue.

4.1. Limitations

Our study has several potential limitations. FISIOIAM was an observational, single-center study with no comparison group, and the results may be influenced by local peculiarities in patient management. Second, there was a relatively small number of major cardiovascular events during the follow-up period, which may affect the statistical power of the study and may limit conclusions, especially regarding subgroup analysis. In particular, women were underrepresented in our cohort, although we did not find differences in physiology between women and men, but the small sample does not allow for subgroup analysis of events. Additionally, we did not perform follow-up physiology after the acute phase of STEMI. Finally, we did not perform systematic intracoronary imaging, which may have provided additional information about plaque instability and vulnerability.

5. Conclusions

Microvascular dysfunction as measured by an CFR < 2 in the non-culprit artery is found in over one third of the patients after myocardial infarction. A low coronary flow reserve in the non-culprit artery independently predicts adverse clinical outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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