



ORIGINAL STUDIES

EDITORIAL COMMENT: Expert Article Analysis for:

[How strong is the warranty of a negative FFR? Comment on long-term outcome after deferred revascularization due to negative fractional flow reserve in intermediate coronary lesions by Weerts et al.](#)

Long-term outcome after deferred revascularization due to negative fractional flow reserve in intermediate coronary lesions

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Abstract

Objectives: The aim was to assess long-term outcome after deferring intervention of coronary lesions with a fractional flow reserve (FFR) value of >0.80 in a real-world patient population and then to identify factors associated with deferred target lesion failure (DTLF).

Background: Deferring coronary interventions of intermediate lesions based on FFR measurement is safe, irrespective of the extent of coronary artery disease. However, FFR values near the cut-off of >0.80 may have less favorable outcome.

Methods: A retrospective analysis was performed in patients with deferred coronary intervention based on FFR value >0.80 . The primary endpoint was DTLF, a composite of acute coronary syndrome (ACS) and any coronary revascularization, related to the initially deferred stenosis.

Results: A total of 600 patients, mean age of 66 ± 10 years, and 751 coronary lesions with negative FFR values (mean 0.88 ± 0.04) were included. The mean follow-up was 27 ± 15 months. DTLF occurred in 44 patients (7.3%), revascularization in 42 (7%), and ACS without revascularization in 2 patients (0.3%). Patients with DTLF more often had diabetes mellitus, previous coronary artery bypass grafting, multivessel disease (MVD), and lower FFR at inclusion. Multivariable regression analysis showed that lower deferred FFR values [FFR 0.81–0.85: hazard ratio (HR) 2.79 (95% CI [confidence interval]; 1.46–5.32), $p .002$], MVD [HR 1.98 (95% CI; 1.05–3.75), $p .036$], distal lesions [HR 2.43 (95% CI; 1.29–4.57), $p .006$], and lesions located in a saphenous vein graft (SVG) [HR 6.35 (95% CI; 1.81–22.28), $p .004$] were independent predictors for DTLF.

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Conclusions: The long-term rate of DTLF of initially deferred coronary lesions was 7.3%. Independent predictors for DTLF are lower deferred FFR value, the presence of MVD, distal lesions, and lesions in SVG.

KEYWORDS

ACS/NSTEMI, coronary angiography, coronary artery disease, coronary blood flow, fractional flow reserve, percutaneous coronary intervention

1 | INTRODUCTION

Visual and functional assessments of coronary artery stenosis severity may be discordant in intermediate coronary lesions.^{1,2} In such lesions, addition of fractional flow reserve (FFR) measurements has an extensive evidence base and it has proven to be more of a functional assessment for ischemia-inducing stenosis than coronary angiography alone.^{3–5} Hence, for intermediate lesions, FFR is the current standard of care to provide a better well-informed decision whether or not to perform coronary interventions.⁶ Early validation studies for FFR showed values of <0.75 to be correlated with reversible myocardial ischemia, with a specificity of 100%.^{4,7} Currently in the clinical field, deferring coronary interventions of intermediate lesions based on a negative FFR value with a threshold of >0.80 is widely accepted and proven to be safe in multiple randomized studies, irrespective of the extent of coronary artery disease (CAD) and clinical indication.^{3,8–12} The incidence of long-term ischemic events for deferred lesions based on negative FFR results in real-world patients is less well known and varies from 0.6% at 1 year to 23% at 3 years due to different normal values (FFR >0.75 or >0.80) and clinical indication such as stable CAD and acute coronary syndromes (ACSs).^{9–11,13–17}

Several studies have shown that FFR values from 0.81 to 0.85 show more recurrent ischemic events than those with a higher FFR value, especially in ACS patients,^{14,18–21} whereas a recent surgical study reported a preoperative FFR of 0.78 or lower to be positively associated with a higher graft patency.²² It is questionable whether these FFR values are a borderline range in which dichotomous use for recommending coronary intervention is appropriate.

Different independent risk factors for recurrent ischemic events for negative FFR results have been identified in previous studies, which differ from solely FFR values,²⁰ to also ACS indication,^{18,23,24} multivessel coronary artery disease (MVD),^{18,24} previous ischemic events,¹⁸ proximal lesion location,²¹ and diabetes mellitus (DM).^{25,26} However, the question remains which risk factors truly contribute to less favorable outcome in patients with deferred revascularization due to a negative FFR.

We sought to assess long-term outcome after deferring coronary intervention of coronary lesions with a value of FFR >0.80 in a real-world patient population. We aimed to identify to what extent the risk factors for occurrences of events identified in previous studies have an impact on outcome and to assess the independent predictive value of FFR values. We thereby strive to enhance the level of evidence for

therapeutic and follow-up decisions in FFR values that are considered being negative.

2 | MATERIALS AND METHODS

2.1 | Study population

A retrospective analysis was performed of all patients with a negative FFR (value >0.80) and deferred revascularization at the Maastricht University Medical Center (MUMC+) and Zuyderland Medical Center, Heerlen, the Netherlands, between January 2012 and December 2014. This study was approved by the institutional review boards of both reference centers. It is performed and conforms to the principles of the Declaration of Helsinki. All patients provided informed consent for the procedure.

2.2 | Data collection

Data were collected retrospectively for this study. Baseline demographics and data related to the FFR measurement at index procedure were obtained using electronic medical records of both reference centers. Follow-up data and events were obtained from the electronic medical record and by telephone contact with either the treating cardiology hospital or the primary care physician between January 2017 and August 2018.

2.3 | Definitions

Deferred revascularization was defined as both no immediate and planned revascularization based on initial FFR measurement as per decision by the operator or the heart team. MVD was defined as 50% or more luminal diameter stenosis in ≥ 2 major epicardial stenosis. Based on the current ESC guidelines, ACS was defined as type 1 ischemia presented as ST-segment elevated myocardial infarction (STEMI), non-ST-segment elevated myocardial infarction (NSTEMI), or unstable angina.^{27,28}

2.4 | Angiographic analysis and FFR assessment

Coronary angiography and FFR measurement were performed in both reference centers according to standard clinical practice techniques, as described earlier.² Briefly, coronary angiogram was acquired via

either a radial (preferred) or femoral approach. FFR measurements were performed by using a 0.014-in. pressure sensor-tipped wire (PrimeWire Prestige, Volcano Corporation or PressureWire, St. Jude Medical) positioned distal to a lesion during adenosine-induced hyperemia. A lesion assessed with a hyperemic FFR value >0.80 was considered functionally nonsignificant for causing ischemia. FFR measurements in all clinical settings were included to identify all cases with negative FFR deferred lesions, and this included both planned FFR measurements and ad hoc decisions. In the event of multiple lesions being present in the same epicardial artery branch, the most severe stenosis was used for further follow-up and analysis.

2.5 | Endpoints

The primary outcome was deferred target lesion failure (DTLF), defined as any unplanned deferred target lesion-related revascularization or deferred target lesion-related ACS after dismissal from the initial FFR measurement. Target lesion was defined as the lesion in which the initial FFR measurement was performed. ACS related to the target lesion was based on ECG, echocardiography, or coronary angiography. Subjective unstable angina without objectified evidence of deferred lesion failure was not considered DTLF.

2.6 | Statistical analysis

All quantitative measurements are presented as mean \pm SD or median [interquartile range]. Categorical data are expressed as absolute frequencies with percentages. Nonparametric Mann-Whitney *U* test was used to test unpaired, not normally distributed data. Unpaired Student's *t* test was used to analyze unpaired normally distributed parameters. Chi-square test was used to test categorical, unpaired data. Fisher's exact test was used in case the Chi-square test showed observed count below 10 or expected count below 5.

In case multiple FFR values of >0.80 were present in different coronary vessels, the lowest value was used for patient-level analysis to best represent daily clinical practice. Side branches were included in the analyses of their main branch based on segment definitions by the synergy between percutaneous coronary intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) study.²⁹

The probability of DTLF was estimated using multivariable Cox proportional hazard model to estimate the differences in time to event expressed as hazard ratio (HR) with 95% confidence intervals (CIs). The model was built by manual stepwise forward variable selection employing a threshold from univariable analysis of $p < .25$ for inclusion. Candidate variables were graphically tested for proportional hazard assumption and included clinical characteristics (age, sex, cardiovascular risk factors, previous history of infarction or revascularization, and estimated glomerular filtration rate [eGFR]), indication for coronary angiography, categorized FFR values, MVD, lesion location, left ventricular ejection fraction (LVEF), amount of FFR negative deferred lesions, and

TABLE 1 Baseline characteristics per-patient level

	Total <i>n</i> = 600
Age, years	66 \pm 10
Male sex	381 (64%)
Body mass index	27 [24–30]
Diabetes mellitus	126 (21%)
Hypercholesterolemia	291 (51%)
Hypertension	365 (63%)
Prior MI	188 (32%)
Prior PCI	245 (41%)
Prior CABG	57 (10%)
Current smoker	132 (23%)
eGFR, MDRD	60 [59–60]
Impaired renal failure (eGFR <60)	152 (26%)
LVEF	55 \pm 11
Clinical presentation	
ACS indication	141 (24%)
Multivessel disease	222 (37%)
Left main disease	22 (4%)
Assessed lesion characteristics	
FFR lesions total, <i>n</i>	751
FFR value, ratio	0.88 \pm 0.04
≥ 2 FFR measurements	135 (23%)
RCA	188 (31%)
RCA dist	82 (14%)
Left main	50 (8%)
LAD	296 (49%)
LAD dist	72 (12%)
CX	203 (34%)
SVG	14 (2%)
Location of all epicardial vessels combined	
Proximal lesion	250 (37%)
Mid lesion	268 (40%)
Distal lesion	159 (23%)
Discharge medication	
Acetylsalicylic acid	309 (75%)
Statin	369 (89%)
Anti-diabetics	79 (19%)
P2Y12 inhibitor	292 (61%)
Follow-up	
Follow-up, months	27 \pm 15
All-cause mortality	59 (10%)

Note: Values are mean \pm SD, or median [interquartile range].

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CX, left circumflex artery; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SVG, saphenous vein graft.

discharge treatment (acetylsalicylic acid, P2Y12 inhibitor, statins, and antidiabetics). Age, sex, and prevalence of DM were regarded as clinically important confounders and kept in the model irrespective of *p* value. Survival curves were made based on Kaplan–Meier estimates and were compared using the log-rank test. A *p* value of $<.05$ was considered significant.

Statistical analysis was performed using SPSS (IBM Corp. Released 2015; IBS SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

3 | RESULTS

3.1 | Clinical characteristics

During the study period, a total of 607 patients had an FFR value of >0.80 for at least one vessel and did not undergo immediate or planned revascularization based on FFR measurement at inclusion date. Seven patients (1%) were excluded for analysis; 3 patients had died within the initial hospitalization period; and in 4 patients follow-up was unavailable.

Overall patient and lesion characteristics are summarized in Table 1. Mean age was 66 ± 10 years and one third were female. Nearly half of all patients had a history of previous revascularization: PCI (41%) and coronary artery bypass grafting (CABG) (10%). Mean LVEF was 55%. A total of 141 patients (24%) admitted with an ACS underwent FFR measurement of the nonculprit artery. A total of 751 coronary lesions with deferred revascularization based on negative FFR values were included. Mean FFR per-patient level was 0.88 ± 0.04 . In 23% of the patients, negative FFR measurements were performed in two or more coronary arteries. In 49% of the patients, FFR was performed in the left anterior descending artery (LAD). By combining the location of the FFR lesion measurement of all coronary vessels, it was possible to analyze proximal lesions 37% times and distal lesions 23% times, respectively.

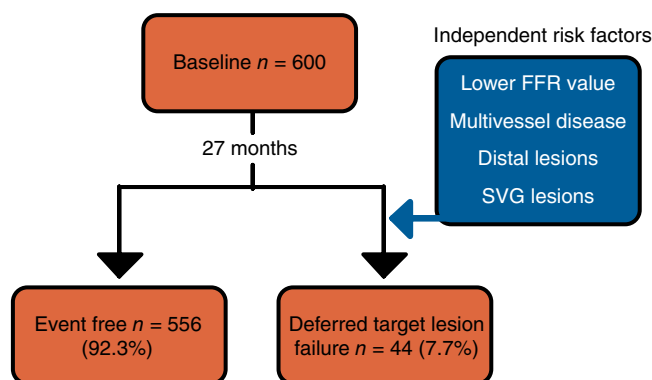


FIGURE 1 Long-term event rate of initially coronary intervention deferred FFR negative lesions. After mean follow-up of 27 ± 15 months, 44 patients (7.7%) presented with deferred target lesion failure related to an initially deferred lesion based on FFR value >0.80 . Lower FFR values, especially 0.81–0.85, multivessel disease, distal epicardial lesions, and SVG lesions all independently increase the likelihood of an event. FFR, fractional flow reserve; SVG, saphenous vein graft [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Clinical outcomes

Main clinical outcomes are displayed in Figure 1. After a mean follow-up of 27 ± 15 months, 44 patients (7.3%) had DTLF. This group comprised 11 patients with stable angina and 33 patients with ACS, of which 6 with STEMI, 15 with NSTEMI, and 12 with unstable angina. Patients generally incurred an event within the first 2 years of follow-up (Figure 2). In patients with DTLF, 42 underwent deferred target lesion-related revascularization: PCI and CABG in 38 patients and 4 patients, respectively. All but 2 patients with ACS had undergone revascularization. The indications for revascularization were a new ACS event (74%), significant ischemia identified by FFR <0.80 (11%), significant stenosis visually assessed by coronary angiography (11%), and impaired myocardial perfusion scintigraphy (2%). Patient and lesion characteristics based on outcome are listed in Table 2.

Patients with DTLF more often had DM (34 vs. 20%, *p* .03), as well as a history of CABG (21 vs. 9%, *p* .03) and MVD (66 vs. 35%, *p* $<.001$). Mean baseline FFR was significantly lower in patients with DTLF (0.85 vs. 0.88, *p* $<.001$). Right coronary artery (RCA) and LAD lesions were more often measured in patients with DTLF, in particular distal lesions (distal RCA 14 (32%) vs. 68 (12%), *p* $<.001$; distal LAD 11 (25%) vs. 61 (11%), *p* .006). Event rates in the left main and left circumflex artery were not statistically significant between the two groups. Saphenous vein graft (SVG) showed a trend toward more DTLF (3 (7%) vs. 11 (2%), *p* .08). Distal lesion location, based on combining all epicardial vessels together, was more often measured in patients with DTLF (23 (40%) vs. 136 (22%), *p* $<.001$). Per-lesion level comparisons showed numbers in line with those per-patient level analyses. Discharge medication did not differ between the two groups. Length of follow-up was longer in patients with DTLF (37 ± 11 vs. 27 ± 15 months, *p* $<.001$).

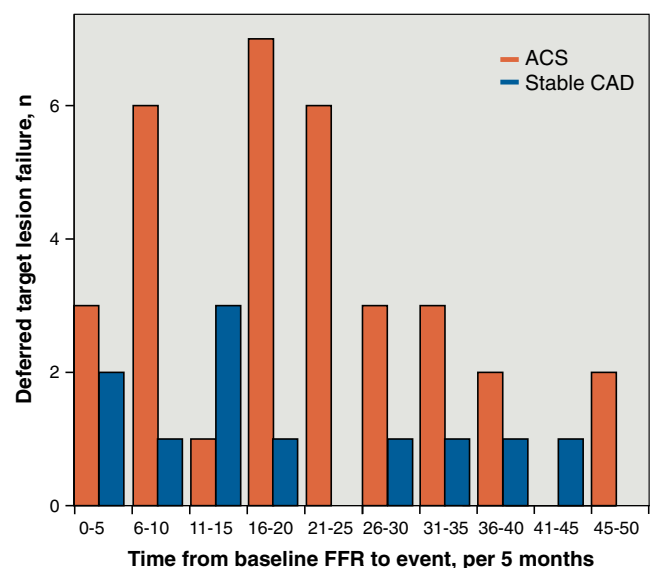


FIGURE 2 Time to deferred target lesion failure per 5 months. Combined histogram for deferred target lesion failure (DTLF). Indication for DTLF is marked as acute coronary syndrome (ACS) or stable coronary artery disease (CAD). Patients mainly incur an event within the first 2 years of follow-up [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Patient and lesion characteristics based on patient outcome

	DTLF <i>n</i> = 44	Event-free <i>n</i> = 556	<i>p</i> value
Age, years	65 ± 10	66 ± 10	.41
Male sex	33 (75%)	348 (63%)	.10
Body mass index	27 [25–30]	27 [24–30]	.69
Diabetes mellitus	15 (34%)	111 (20%)	.03
Hypercholesterolemia	27 (66%)	264 (50%)	.05
Hypertension	31 (72%)	334 (62%)	.18
Prior MI	16 (36%)	172 (32%)	.49
Prior PCI	21 (48%)	224 (41%)	.36
Prior CABG	9 (21%)	48 (9%)	.03
Current smoker	9 (21%)	122 (23%)	.81
eGFR, MDRD	60 [59–60]	60 [59–60]	.81
Impaired renal function (eGFR <60)	141 (26%)	11 (26%)	.94
LVEF	58 ± 8	55 ± 11	.11
Clinical presentation			
ACS indication	6 (14%)	135 (24%)	.11
Multivessel disease	29 (66%)	193 (35%)	<.001
Left main disease	3 (7%)	19 (3%)	.21
Assessed lesion characteristics			
FFR lesions total, <i>n</i>	61	690	-
FFR value, ratio	0.85 ± 0.04	0.88 ± 0.04	<.001
≥2 FFR measurements	17 (39%)	118 (21%)	.008
RCA	22 (50%)	166 (30%)	.006
RCAdist	14 (32%)	68 (12%)	<.001
Left main	1 (2%)	49 (9%)	.16
LAD	26 (59%)	270 (49%)	.18
LADdist	11 (25%)	61 (11%)	.006
CX	9 (21%)	194 (35%)	.05
SVG	3 (7%)	11 (2%)	.08
Location of all epicardial vessels combined			
Proximal lesion	13 (23%)	237 (38%)	.09
Mid lesion	21 (37%)	247 (40%)	.67
Distal lesion	23 (40%)	136 (22%)	<.001
Discharge medication			
Acetylsalicylic acid	26 (63%)	283 (76%)	.09
Statin	35 (85%)	334 (90%)	.43
Anti-diabetics	12 (29%)	67 (18%)	.08
P2Y12 inhibitor	23 (56%)	269 (62%)	.49
Follow-up			
Follow-up, months	37 ± 11	27 ± 15	<.001
All-cause mortality	7 (16%)	52 (9%)	.18

Note: Values are mean ± SD, or median [interquartile range]. Deferred target lesion failure (DTLF) is based on per-patient level analysis. A total of 30% of the patients had multiple FFR measurements in different epicardial vessels; hence, this analysis is not per-lesion level.

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CX, left circumflex artery; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MDRD, modification of diet in renal disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; SVG, saphenous vein graft.

TABLE 3 Multivariable analysis for predictors of deferred target lesion failure

	HR	95% CI	<i>p</i> value
Age (per year increase)	1.00	0.97–1.03	.836
Male sex	0.64	0.32–1.27	.200
Diabetes mellitus	1.27	0.67–2.43	.463
FFR value (0.81–0.85) ^a	2.79	1.46–5.32	.002
Multivessel disease	1.98	1.05–3.75	.036
Any deferred distal lesion	2.43	1.29–4.57	.006
Deferred saphenous vein graft	6.36	1.81–22.28	.004

^aFractional flow reserve (FFR) value of 0.81–0.85 compared to FFR value >0.85.

3.3 | Risk prediction

A multivariable Cox regression hazard model showed DTLF to be more often present in patients with lower FFR values [FFR 0.81–0.85: HR 2.79 (95% CI; 1.46–5.32), *p* .002], the presence of MVD [HR 1.98 (95% CI; 1.05–3.75), *p* .036], distal lesions [HR 2.43 (95% CI; 1.29–4.57), *p* .006], and lesions located in an SVG [HR 6.35 (95% CI; 1.81–22.28), *p* .004] (Table 3). Survival curves of these variables are shown in Figure 3. Of patients with DM, the rate of DTLF was higher, but the prevalence of DM did not reach statistical significance in risk prediction analyses. Sensitivity analyses of the adjusted multivariable analysis model, corrected for follow-up periods of 27 and 30 months (mean and median follow-up of the entire cohort), showed similar results (Tables S1 and S2).

4 | DISCUSSION

We investigated here the long-term outcome after deferring coronary interventions of coronary lesions with a value of FFR >0.80 in an unselected real-world patient population. Our results show that DTLF occurred in 7.3% after a mean follow-up of 27 ± 15 months. Independent risk factors for DTLF were lower FFR values, MVD, and lesions located distally. Lesions with DTLF more often originated from either RCA, LAD, or SVG.

4.1 | Lesion-related events

Landmark trials FAME, FAME 2, and DEFER, as well as recent large cohort analyses from PRIME-FFR that addressed outcome of deferred lesions based on negative FFR results had clinical outcomes based on per-patient level decision for revascularization.^{3,9,11,24,30} Hence, risk for an event during follow-up based on a single lesion FFR assessment is difficult to correlate in patients with multiple lesions. Since many patients have MVD, which is correlated with worse outcome,³¹ we focused instead on outcome per-lesion level by using DTLF as primary endpoint.

Other studies with comparable follow-up periods have reported similar DTLF event rates to those presented here (Table 4 and Figure 4). For example, Masrani et al reported a DTLF event rate of 18% after 4.5 years follow-up.¹⁹ Likewise, Hakeem et al reported a DTLF event

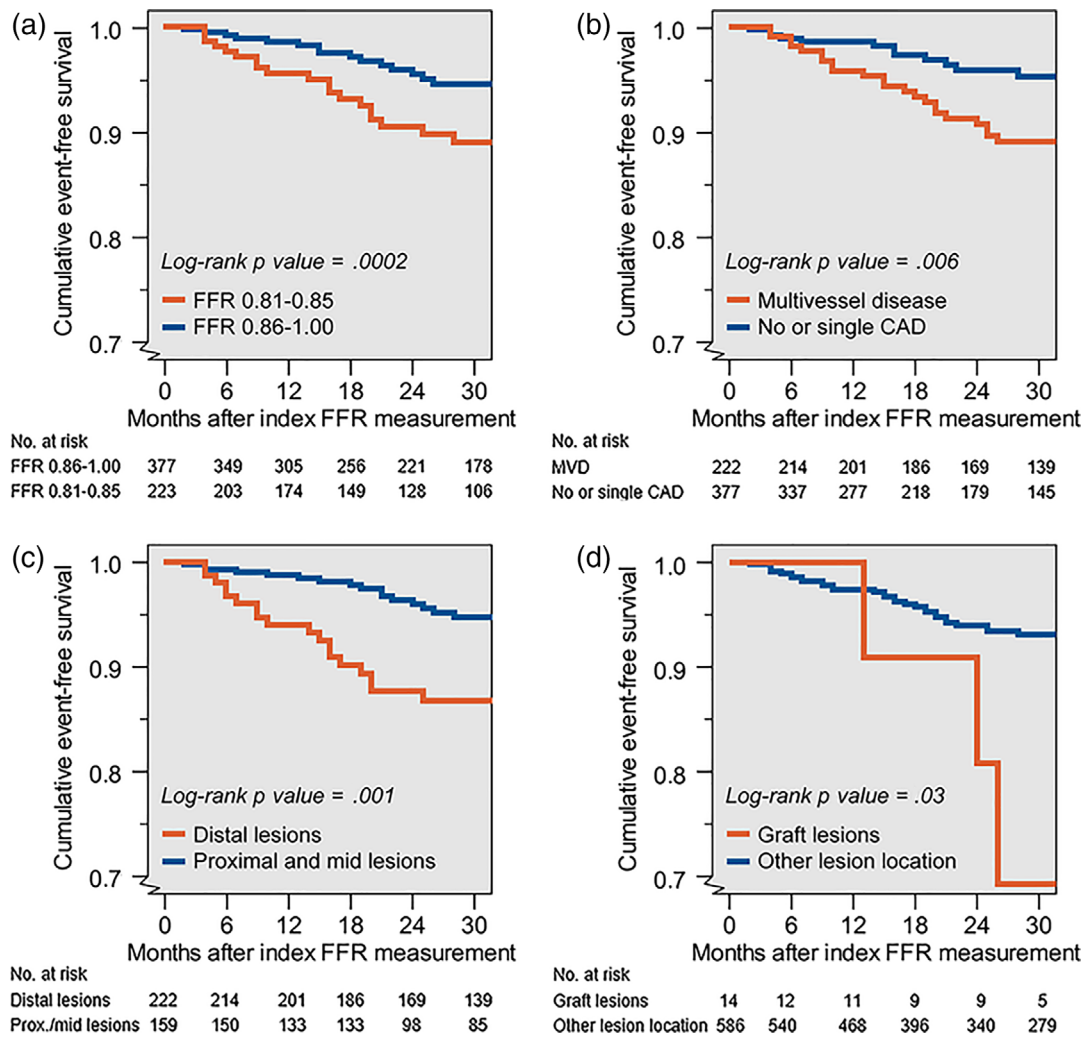


FIGURE 3 Survival curves for the different independent predictors of DTLF. Kaplan–Meier curves for patient-level outcome compared for (a) fractional flow reserve (FFR) values, (b) multivessel disease, (c) distal lesions, and (d) saphenous vein graft lesions. CAD, coronary artery disease; DTLF, deferred target lesion failure [Color figure can be viewed at wileyonlinelibrary.com]

rate of 18 and 9.5%, respectively, in patients initially presenting with ACS or stable CAD after 3.4 years follow-up.¹⁸ In stable CAD patients, Nakamura et al reported a DTLF rate of 7.8% at 2.8 years follow-up.³⁴ In ACS patients, Picchi et al reported a DTLF event rate of 9% at 2 years follow-up. Based on target lesion revascularization, Depta et al reported an event rate of 18% at 4 years with a 1-year incidence of 5.3% in a population regardless of indication.³² Time-to-event bias can be an important factor for these differences, as event rates will likely be higher during longer follow-up due to the progressive nature of CAD. In contrast, Lee et al recently reported a lower DTLF of 1.5 and 3.4% in respective non-culprit lesions of ACS patients and stable CAD patients after a follow-up period of 2 years.²⁴

The event rate we report is notably higher than Lee et al reported, even though the same definitions for DTLF were used.²⁴ The baseline clinical characteristics of both studies are comparable. However, our study population had more history of previous myocardial infarction (32% vs. 8%) and previous revascularization (46% vs. 27%). The higher burden of CAD history

may explain the higher DTLF rate in our real-world patient population. Similarly, Depta et al reported a history of CAD with an HR of 1.62 for DTLF.³² We, conversely, did not see this predictive relation for DTLF with a history of CAD, but found an association between DTLF and history of CABG in univariable analysis with an HR of 2.16.

4.2 | Risk factors for worse prognosis

Previous studies did not report significant event rate differences in patients who presented at baseline with ACS or stable CAD and who had deferred lesions based on FFR.^{19,32} This is in line with our finding, whereas several other recent studies report a higher DTLF rate for patients presenting with ACS.^{18,24,33}

Our second finding, which included only lower FFR values, the presence of MVD, distal lesions, and SVG lesions independently correlated with DTLF, is supported by the adjusted multivariable

TABLE 4 Overview of studies reporting deferred target lesion failure based on negative FFR values

Author	Year	Definition of DTLF	Study population	Length of follow-up (years)	DTLF incidence (%)	Independent factors for DTLF
Deferred based on FFR >0.75						
Potvin et al ¹⁷	2006	ACS or intervention to lesion	Unselected group (n = 201)	1	8	No independent factor identified
Fischer et al ¹⁶	2006	Intervention to vessel	Unselected group (n = 111)	1	12	Not reported
Deferred based on FFR >0.80						
Sels et al ¹⁵	2011	Intervention to vessel	MVD and ACS (n = 328) MVD and stable CAD (n = 677)	2	13.7 10.6	Not reported
Masrani et al ¹⁹	2015	ACS or intervention to lesion	Unselected cohort (n = 674) ACS (n = 344) Stable CAD (n = 340)	4.5	182017	Lower FFR value in ACS patients
Depta et al ³²	2015	Intervention to lesion	Unselected cohort (n = 721)	4 1	18 5.3	Age, smoking, history of CAD or PCI, increased creatinine, MVD, lower FFR
Kennedy et al ²⁵	2016	ACS or intervention to lesion	DM (n = 122) Non-DM (n = 128)	3.3	18.1 7.5	DM
Hakeem et al ¹⁸	2016	ACS or intervention to lesion	ACS (n = 206) Stable CAD (n = 370)	3.4	25 12	Presentation with ACS, MVD
Adjedj et al ²¹	2016	Intervention to vessel	Unselected cohort (n = 691)	4	9.1	Proximal lesions
Picchi et al ³³	2017	Nonspecific cardiac death or ACS, or intervention to lesion	ACS (n = 319)	3 2 1	12 9 6	Peripheral vascular disease
Lee et al ²⁴	2017	ACS or intervention to vessel	ACS (n = 301) Stable CAD (n = 1,596)	2	3.4 1.5	ACS, diameter stenosis \leq 50%, MVD, previous revascularization, DM, lower FFR
Kennedy et al ²⁶	2017	ACS or intervention to lesion	DM (n = 252)	3.1	14.1	Insulin requiring DM, prior revascularization
Nakamura et al ³⁴	2019	ACS or intervention to lesion	Stable CAD (n = 192)	2.8	7.8	LDL-C at index FFR assessment
This study	2020	ACS or intervention to lesion	Unselected group (n = 600)	2.3	7.3	Lower FFR value, MVD, distal lesion, FFR in graft

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; DTLF, deferred target lesion failure; FFR, fractional flow reserve; DM, diabetes mellitus; FFR, fractional flow reserve; LDL-C, low-density lipoprotein cholesterol; MVD, multivessel disease; PCI, percutaneous coronary intervention.

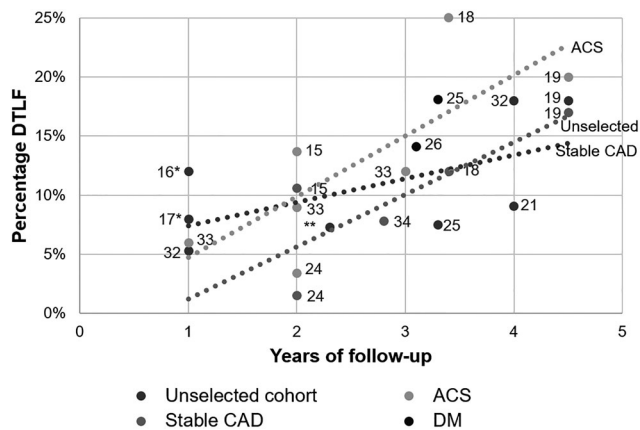


FIGURE 4 Visual summary of reported DTLF in the current literature. Scatterplot with linear plotted trend based on available published results in unselected cohorts, ACS patients, stable CAD patients, and patients with DM. Numbers indicate reference to the study. * indicates the marked studies using an FFR cut-off of >0.75 instead of >0.80 for deferral.^{16,17} ** indicates the current study. ACS, acute coronary syndrome; CAD, coronary artery disease; DM, diabetes mellitus; DTLF, deferred target lesion failure; FFR, fractional flow reserve

analysis (Table 3). It is also supported by sensitivity analyses of the adjusted multivariable analysis model corrected for follow-up periods of 27 and 30 months (mean and median follow-up of the entire cohort) (Tables S1 and S2).

Previous studies that have investigated factors associated with events after deferred lesions based on negative FFR results have often reported lower FFR values and MVD as strongest predictors for later events (Table 4).^{18,20,21,24} Other factors identified in those studies, which would be associated with DTLF or higher rates of more general cardiovascular events, however, cannot be confirmed here. A reason for this could be that factors such as LDL-C values after baseline FFR have a stronger predictive value than statin use alone, and, thus, could be of additive value to risk factors identified in this study.³⁴

Distal lesions have not been reported to be associated with DTLF in previous studies. Based on previous literature, we would expect proximal segments to be more associated with DTLF because of more severe atherosclerosis and inflammation involvement compared with distal segments.^{21,35} In contrast, our results show that deferred distal lesions based on negative FFR values have a higher risk for DTLF than other locations (HR 2.43). Possibly, on the one hand, distal lesions more often show false-negative FFR results due to too proximal placement of the pressure-wire tip.³⁶ On the other hand, factors such as less myocardial supply for distal lesions would lead to physiologically true-negative FFR results.

Because previous studies often did not have the same clinical characteristics and DTLF definition, one can question which risk factors truly contribute to worse outcome. Taking this into account and considering the variety of risk factors found in multiple studies together with the possibility of multiple testing errors, one could assume that risk factors, besides lower FFR values and MVD, may not greatly influence outcome after all. Further

assessments for vulnerability of these lesions such as thin-capped fibroatheromas assessed by intravascular ultrasound (IVUS) or optical coherence tomography (OCT) could potentially clarify the reason for more events.³⁷

4.3 | Practical implications

FFR values near the cut-off of >0.80 may have less favorable outcome. FFR values represent a continuum in which patients with lower values show a disease state that has further progressed and, hence, likely present earlier with events during follow-up. This study shows that mainly FFR values range between 0.81 and 0.85, MVD and distal lesions are independent factors for events of initially deferred coronary lesions based on negative FFR. Based on our findings and the diversity of risk factors mentioned in earlier studies in different study populations, we share the opinion that more physiological and anatomical parameters should be taken into account rather than only borderline FFR values. New diagnostic modalities such as IVUS, OCT, and instantaneous wave-free ratio (iFR) as well as older methods such as coronary flow reserve (CFR) and intracoronary acetylcholine make it possible to identify patients at risk for clinical events based on other lesion characteristics such as plaque burden and thin-capped fibroatheromas,³⁸⁻⁴¹ and to evaluate more detailed aspects of prognostic importance like microvascular function.^{39,42} It will be useful to combine more characteristics with FFR values to further optimize risk stratification and to determine if patients would benefit from revascularization or other therapeutic strategies even with a negative FFR. Eventually, these additional assessments have the potential to change selection criteria for coronary interventions in intermediate lesions and could also lead to identification of new targets for novel therapies to decrease future events. In light of this, results of ongoing studies such as PECTUS and COMBINE (OCT-FFR) could give us more insight.

4.4 | Study limitations

This study has several limitations, primarily related to its observational and retrospective nature. A small number of patients were excluded due to loss to follow-up ($n = 7$); however, follow-up was completed in 99% of all cases. Key differences between different patient groups were minimized using multivariable analysis. Subjects were predominantly male. Although multivariable analysis showed no differences in sex, application of the results to women should still be done with caution. Selection bias could have contributed to differences.

Time to follow-up bias in this study could largely be explained by how healthcare is organized in the Netherlands, as patients who incur an event are followed up for a longer period by cardiologists, whereas patients who remain event-free are referred back to their general practitioner generally after 1-year postindex procedure. Nonetheless, our sensitivity analyses corrected for events up until 27 or 30 months showed similar results to the primary analysis.

Patients with multiple FFR negative deferred lesions were analyzed at patient level based on the lowest FFR value, instead of using generalized estimation equation to create FFR values per patient. We chose this method because it is rather practical than theoretical, and we believe that this better represents how data are interpreted and used in daily clinical work.

FFR was mainly performed in stable CAD patients and only 24% of the patients had ACS. Therefore, this study may be underpowered to detect differences in patients with ACS. The more significant DTLF occurrence in SVG lesions was only measured in 14 cases and thus should be interpreted with caution, although similar results were recently reported.⁴³ Finally, determination of whether a patient had MVD was based on the operator's judgment and was therefore subjective, similar to common practice.

5 | CONCLUSIONS

This study shows that the rate of target lesion failure of initially deferred coronary stenosis based on negative FFR values was 7.3% at ample 2-year follow-up in an unselected real-world population. These events were significantly more often present in patients with MVD, lower deferred FFR values, especially values between 0.81 and 0.85, distal epicardial lesions, and lesions located in an SVG. Further large-scale prospective studies are needed to better identify patient's characteristics, physiological, and anatomical parameters associated with DTLF, and also to investigate best treatment options to prevent future events in this subset of patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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