

SUPPLEMENTAL MATERIAL

Table S1. Landmark Analysis of Clinical Endpoints from 1 to 5 Years.

	QFR≤0.80 (N=35)	QFR>0.80 (N=582)	HR (95% CI)	p-value
Cardiac death, non-TV-MI, non-TV TVR, n (%)	10 (43.5)	42 (7.8)	6.68 (3.35-13.33)	<0.001
Cardiac death, MI (any), revascularization (any)	10 (43.5)	63 (12.0)	4.16 (2.14-8.12)	<0.001
Cardiac death or MI (any)	4 (14.7)	33 (6.1)	2.53 (0.90-7.15)	0.079
Cardiac death, TV-MI, TVR, n (%)	4 (15.9)	42 (7.8)	2.00 (0.72-5.56)	0.187
Death, n (%)	1 (3.1)	38 (6.7)	0.46 (0.06-3.32)	0.439
Cardiac death, n (%)	0 (0.0)	13 (2.3)	-	-
Non-TV-MI, n (%)	3 (10.0)	14 (2.6)	4.06 (1.17-14.12)	0.028
Non-TV TVR, n (%)	10 (43.5)	29 (5.4)	9.75 (4.75-20.04)	<0.001
Revascularization (any), n (%)	10 (43.5)	50 (9.6)	5.25 (2.66-10.37)	<0.001
MI (any), n (%)	4 (14.7)	23 (4.3)	3.65 (1.26-10.54)	0.017
MI Q-wave, n (%)	2 (6.5)	6 (1.1)	6.02 (1.21-29.82)	0.028
MI non Q-wave, n (%)	3 (11.0)	19 (3.6)	3.18 (0.94-10.74)	0.063
Stroke (any), n (%)	1 (3.3)	9 (1.7)	1.96 (0.25-15.48)	0.523

Depicted are number of patients (%) and hazard ratios (HR) with 95% confidence intervals (CI) from univariable Cox proportional hazards regressions with p-values. MI = myocardial infarction, non-TV-MI = non-target vessel myocardial infarction, non-TV
TVR = non-target vessel revascularization, TV-MI = target vessel myocardial infarction, TVR = target vessel revascularization, QFR = Quantitative Flow Ratio.

Table S2. Patient and Procedural Characteristics for >30% DS.

	QFR≤0.80 (N=35)	QFR>0.80 (N=412)	p-value
Patient characteristics (patient-level)			
Sex (female), n (%)	10 (28.6)	96 (23.3)	0.534
Age, years	63.1 ±11.4	61.7 ±11.6	0.499
BMI, kg/m ²	27.3 ±3.5	27.1 ±4.0	0.764
Diabetes mellitus, n (%)	8 (22.9)	59 (14.3)	0.213
Hypertension, n (%)	22 (62.9)	203 (49.3)	0.159
Hypercholesterolemia, n (%)	25 (71.4)	224 (54.8)	0.075
Family history of CAD, n (%)	13 (38.2)	122 (30.0)	0.335
Killip I or II, n (%)	33 (94.3)	409 (99.3)	0.051
Killip IV, n (%)	1 (2.9)	2 (0.5)	0.217
Left ventricular function, %	49.1 ±10.4	48.7 ±10.5	0.853
MI SYNTAX Score	16.2 ±10.9	11.4 ±7.71	<0.001
Procedural characteristics (patient-level)			
Infarct vessel			0.010
Left main (LM), n (%)	0 (0.0)	1 (0.2)	
Left anterior descending (LAD), n (%)	5 (14.3)	165 (40.0)	
Left circumflex (LCX), n (%)	7 (20.0)	62 (15.0)	
Right coronary artery (RCA), n (%)	23 (65.7)	184 (44.7)	
Number of lesions in infarct vessel, n	1.03 ±0.17	1.12 ±0.37	0.141

Table S2. continued

Type of intervention			0.217
PCI - implantation of stent(s), n (%)	34 (97.1)	410 (99.5)	
PCI - only balloon dilatation, n (%)	1 (2.9)	2 (0.5)	
Number of stents per lesion, n	1.37 ±0.81	1.43 ±0.73	0.642
Total stent length per lesion, mm	28.4 ±15.5	27.1 ±13.4	0.578
Average stent diameter, mm	3.24 ±0.44	3.17 ±0.41	0.352
Direct stenting, n (%)	11 (32.4)	112 (27.3)	0.552
Maximal balloon pressure, atm	16.3 ±3.5	15.4 ±3.2	0.099
Thrombus aspiration, n (%)	23 (65.7)	244 (59.2)	0.479
Non-target vessel (patient-level)	N=35	N=412	<0.001
Left anterior descending (LAD), n (%)	27 (77.1)	133 (32.3)	
Left circumflex (LCX), n (%)	1 (2.9)	173 (42.0)	
Right circumflex (RCA), n (%)	7 (20.0)	106 (25.7)	
DS ≥50% by 3D-QCA, n (%)	23 (65.7)	38 (9.2)	<0.001
Non-target vessel (vessel-level)	N=36	N=542	<0.001
Left anterior descending (LAD), n (%)	28 (77.8)	153 (28.2)	
Left circumflex (LCX), n (%)	1 (2.8)	256 (47.2)	
Right circumflex (RCA), n (%)	7 (19.4)	133 (24.5)	
DS ≥50% by 3D-QCA, n (%)	24 (66.7)	43 (7.9)	<0.001

Values are mean±SD or n (%). BMI = body mass index, CAD = coronary artery disease, DS% = diameter stenosis, MI SYNTAX Score = Myocardial Infarction TAXus and Cardiac Surgery Score, PCI = percutaneous coronary intervention, 3D-QCA = 3D-Quantitative Coronary Angiography.

Table S3. 3D-QCA Analysis for >30% DS.

3D-QCA variable (patient-level)	QFR≤0.80 (N=35)	QFR>0.80 (N=412)	p-value
Diameter stenosis, %	54.2 ±8.1	40.1 ±7.1	<0.001
Area stenosis, %	69.9 ±8.3	52.6 ±11.4	<0.001
Lesion length, mm	31.0 ±16.9	22.3 ±13.8	<0.001
Proximal diameter, mm	2.77 ±0.61	2.93 ±0.64	0.155
Minimal lumen diameter, mm	1.33 ±0.37	1.77 ±0.45	<0.001
Distal diameter, mm	2.46 ±0.49	2.62 ±0.65	0.169
Reference diameter, mm	2.88 ±0.54	2.96 ±0.65	0.486
3D-QCA variable (vessel-level)	QFR≤0.80 (N=36)	QFR>0.80 (N=542)	p-value
Diameter stenosis, %	54.2 ±8.0	39.5 ±6.8	<0.001
Area stenosis, %	69.9 ±8.1	51.9 ±11.2	<0.001
Lesion length, mm	30.4 ±17.0	22.0 ±13.8	<0.001
Proximal diameter, mm	2.75 ±0.62	2.92 ±0.64	0.124
Minimal lumen diameter, mm	1.32 ±0.37	1.78 ±0.44	<0.001
Distal diameter, mm	2.45 ±0.49	2.60 ±0.65	0.162
Reference diameter, mm	2.86 ±0.55	2.94 ±0.65	0.453

Values are mean±SD. DS% = diameter stenosis, QFR = Quantitative Flow Ratio,

3D-QCA = 3D-Quantitative Coronary Angiography.

Table S4. Clinical Outcomes at 5 Years for >30% DS.

	QFR≤0.80 (N=35)	QFR>0.80 (N=412)	HR (95% CI)	p-value
Cardiac death, non-TV-MI, non-TVR, n (%)	22 (62.9)	57 (14.0)	6.61 (4.03-10.84)	<0.001
Cardiac death, MI (any), revascularization (any), n (%)	22 (62.9)	81 (19.9)	4.48 (2.80-7.19)	<0.001
Cardiac death or MI (any), n (%)	10 (29.6)	42 (10.4)	3.34 (1.67-6.65)	0.001
Cardiac death, TV-MI, TVR, n (%)	13 (37.5)	53 (13.0)	3.48 (1.90-6.38)	<0.001
Death, n (%)	4 (11.4)	41 (10.0)	1.20 (0.43-3.34)	0.733
Cardiac death, n (%)	3 (8.6)	21 (5.2)	1.75 (0.52-5.86)	0.366
Non-TV-MI, n (%)	4 (12.8)	15 (3.9)	3.52 (1.17-10.60)	0.025
Non-TVR, n (%)	19 (58.6)	35 (8.9)	9.58 (5.46-16.79)	<0.001
Revascularization (any), n (%)	19 (58.6)	63 (15.8)	4.99 (2.98-8.35)	<0.001
MI (any), n (%)	7 (22.4)	24 (6.2)	4.15 (1.79-9.64)	0.001
MI Q-wave, n (%)	3 (9.2)	4 (1.0)	9.54 (2.14-42.63)	0.003
MI non Q-wave, n (%)	5 (16.4)	21 (5.4)	3.24 (1.22-8.59)	0.018
Stroke (any), n (%)	3 (9.0)	7 (1.8)	5.27 (1.36-20.37)	0.016

Depicted are number of patients (%) with ≥ 1 DS >30% and hazard ratios (HR) with 95% confidence intervals (CI) from Cox regressions with p-values. MI = myocardial infarction, non-TV-MI = non-target vessel myocardial infarction, non-TVR = non-target vessel revascularization, TV-MI = target vessel myocardial infarction, TVR = target vessel revascularization, QFR = Quantitative Flow Ratio.

Table S5. Independent Predictor Analysis for >30% DS.

Primary endpoint (cardiac death, non-TV-MI, non-TVR)	Univariable analysis N=447 HR (95% CI)	p-value	Multivariable analysis N=447 HR (95% CI)	p-value
Sex (female)	1.36 (0.83-2.20)	0.219		
Age, years (per 1 year increase)	1.03 (1.01-1.05)	0.001	1.02 (1.00-1.04)	0.047
BMI, kg/m ² (per 1 kg/m ² increase)	1.02 (0.96-1.07)	0.570		
Diabetes mellitus	2.04 (1.23-3.39)	0.006	1.59 (0.89-2.86)	0.120
Hypertension	1.70 (1.08-2.69)	0.021	1.20 (0.71-2.04)	0.489
Hypercholesterolemia	1.33 (0.84-2.10)	0.228		
Family history of CAD	1.06 (0.66-1.71)	0.800		
Killip III or IV	7.38 (2.33-23.40)	0.001	2.39 (0.55-10.50)	0.247
Left ventricular function, % (per 5% decrease)	1.29 (1.16-1.43)	<0.001	1.28 (1.15-1.43)	<0.001
MI SYNTAX Score (per 5 points increase)	1.31 (1.17-1.47)	<0.001	1.10 (0.95-1.26)	0.198
QFR ≤0.80	6.61 (4.03-10.84)	<0.001	7.60 (3.85-15.04)	<0.001
DS ≥50% by 3D-QCA	2.27 (1.36-3.81)	0.002	0.64 (0.31-1.36)	0.247

Results from univariable and multivariable Cox proportional analyses for patients with ≥1 DS >30%. Depicted are estimated hazard ratios (HR) with 95% confidence intervals (CI) of the primary endpoint (cardiac death, non-TV-MI, non-TVR) for patient baseline characteristics, QFR ≤0.80, and DS ≥50% by 3D-QCA. Multivariable analysis was performed for variables with a significant association with the primary endpoint in univariable analysis. BMI = body mass index, CAD = coronary artery disease, DS% = diameter stenosis by 3D-QCA, MI SYNTAX Score = Myocardial Infarction TAXus and Cardiac Surgery Score, non-TV-MI = non-target vessel myocardial infarction, non-TVR = non-target vessel revascularization, QFR = Quantitative Flow Ratio, 3D-QCA = 3D-Quantitative Coronary Angiography.

Table S6. Landmark Analysis of Clinical Endpoints from 1 to 5 Years for >30% DS.

	QFR≤0.80 (N=35)	QFR>0.80 (N=412)	HR (95% CI)	p-value
Cardiac death, non-TV-MI, non-TV-R, n (%)	10 (43.5)	42 (7.8)	6.68 (3.35-13.33)	<0.001
Cardiac death, MI (any), revascularization (any)	10 (43.5)	63 (12.0)	4.16 (2.14-8.12)	<0.001
Cardiac death or MI (any)	4 (14.7)	33 (6.1)	2.53 (0.90-7.15)	0.079
Cardiac death, TV-MI, TVR, n (%)	4 (15.9)	42 (7.8)	2.00 (0.72-5.56)	0.187
Death, n (%)	1 (3.1)	38 (6.7)	0.46 (0.06-3.32)	0.439
Cardiac death, n (%)	0 (0.0)	13 (2.3)	-	-
Non-TV-MI, n (%)	3 (10.0)	14 (2.6)	4.06 (1.17-14.12)	0.028
Non-TV-R, n (%)	10 (43.5)	29 (5.4)	9.75 (4.75-20.04)	<0.001
Revascularization (any), n (%)	10 (43.5)	50 (9.6)	5.25 (2.66-10.37)	<0.001
MI (any), n (%)	4 (14.7)	23 (4.3)	3.65 (1.26-10.54)	0.017
MI Q-wave, n (%)	2 (6.5)	6 (1.1)	6.02 (1.21-29.82)	0.028
MI non Q-wave, n (%)	3 (11.0)	19 (3.6)	3.18 (0.94-10.74)	0.063
Stroke (any), n (%)	1 (3.3)	9 (1.7)	1.96 (0.25-15.48)	0.523

Depicted are number of patients (%) with ≥ 1 DS >30% and hazard ratios (HR) with 95% confidence intervals (CI) from Cox regressions with p-values. MI = myocardial infarction, non-TV-MI = non-target vessel myocardial infarction, non-TV-R = non-target vessel revascularization, TV-MI = target vessel myocardial infarction, TVR = target vessel revascularization, QFR = Quantitative Flow Ratio.

Table S7. Diagnostic Ability of QFR ≤ 0.80 for the Prediction of the Primary Endpoint for Different DS%.

	All DS% (N=617)	DS>25% (N=541)	DS>30% (N=447)	DS>40% (N=227)	DS>50% (N=64)
QFR (mean)	0.93 \pm 0.09	0.92 \pm 0.09	0.91 \pm 0.1	0.85 \pm 0.11	0.76 \pm 0.15
Diameter stenosis, %	36.5 \pm 10.5	38.7 \pm 9.1	41.1 \pm 8.2	47.4 \pm 6.6	55.8 \pm 5.8
Accuracy, %	86.2	86.0	84.3	79.7	78.1
Sensitivity, %	23.4	25.9	27.8	40.0	76.1
Specificity, %	97.5	97.1	96.5	92.4	79.1
Positive predictive value, %	62.9	62.9	62.9	62.9	64.0
Negative predictive value, %	87.6	87.5	86.2	82.8	87.2

Values are mean \pm SD. DS% = diameter stenosis, QFR = Quantitative Flow Ratio.

Table S8. 3D-QCA and QFR in Treated vs. Untreated Non-Target Vessels.

QFR and 3D-QCA variable (vessel-level)	Treated non-TV (N=89)	Untreated non-TV (N=946)	p-value
QFR	0.80 ±0.11	0.95 ±0.08	<0.001
Diameter stenosis, %	54.2 ±12.4	34.1 ±10.4	<0.001
Area stenosis, %	70.7 ±14.7	43.5 ±16.2	<0.001
Lesion length, mm	19.8 ±10.9	19.1 ±13.5	0.609
Proximal diameter, mm	2.74 ±0.63	2.85 ±0.63	0.122
Minimal lumen diameter, mm	1.23 ±0.42	1.90 ±0.52	<0.001
Distal diameter, mm	2.43 ±0.57	2.59 ±0.64	0.024
Reference diameter, mm	2.69 ±0.59	2.88 ±0.66	0.009

Values are mean±SD. DS% = diameter stenosis, non-TV = non-target vessel, QFR =

Quantitative Flow Ratio, 3D-QCA = 3D-Quantitative Coronary Angiography.

Table S9. Angiography-based Treatment Decision for Non-Target Vessels vs. QFR Measurement.

Angiography-based treatment decision	QFR ≤ 0.80	QFR > 0.80	Total
Treated non-TV, n (%)	44 (49.4)	45 (50.6)	89 (100)
Untreated non-TV, n (%)	36 (3.8)	910 (96.2)	946 (100)

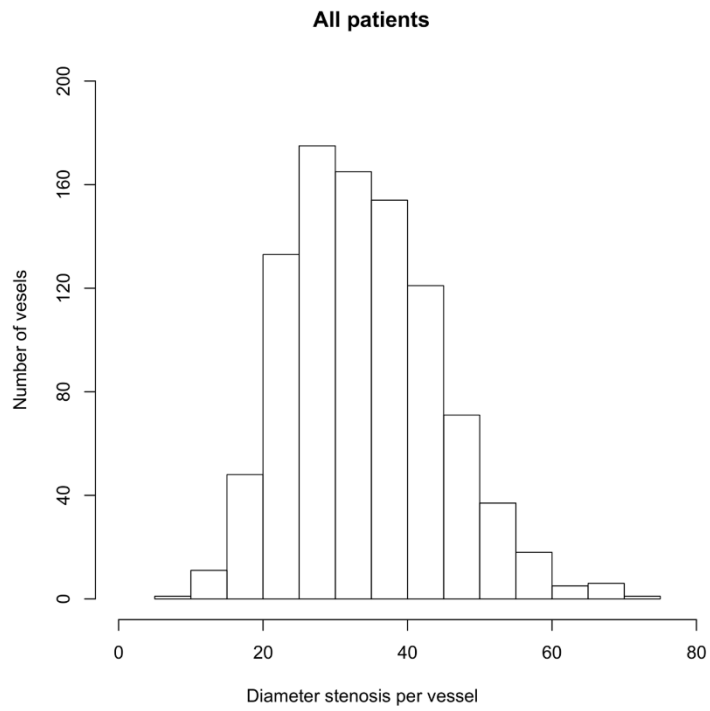
Values are n (%) vessels. Non-TV = non-target vessel, QFR = Quantitative Flow Ratio.

Table S10. Baseline QFR and 3D-QCA Values of Vessels with a Non-TVR Event.

QFR and 3D-QCA variable (vessel-level)	DS% \geq50% by 2D- QCA with ischemia (N= 36)	DS% \geq70% by 2D- QCA (N=15)	p-value
QFR	0.84 \pm 0.13	0.86 \pm 0.14	0.678
Diameter stenosis, %	42.0 \pm 9.1	41.7 \pm 11.6	0.918
Area stenosis, %	57.5 \pm 11.9	58.6 \pm 14.1	0.757
Lesion length, mm	22.5 \pm 15.3	28.1 \pm 17.4	0.260
Proximal diameter, mm	2.70 \pm 0.55	2.82 \pm 0.71	0.496
Minimal lumen diameter, mm	1.66 \pm 0.37	1.86 \pm 0.38	0.086
Distal diameter, mm	2.49 \pm 0.49	2.60 \pm 0.50	0.486
Reference diameter, mm	2.87 \pm 0.54	3.21 \pm 0.47	0.036

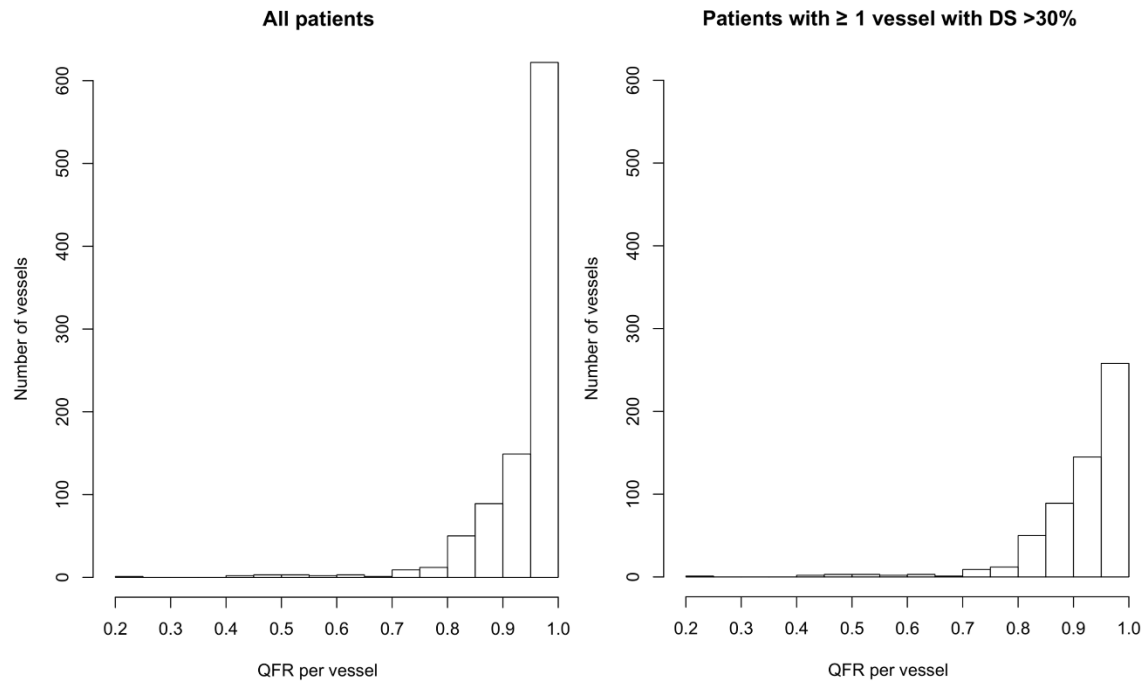
Values are mean \pm SD. Shown are QFR and 3D-QCA values calculated from the baseline angiography according to DS% \geq 50% by 2D-QCA with ischemia or DS% \geq 70% by 2D-QCA at the timepoint of the non-TVR event. DS% = diameter stenosis, non-TV = non-target vessel, QFR = Quantitative Flow Ratio, 3D-QCA = 3D-Quantitative Coronary Angiography.

Figure S1. Distribution of DS% (vessel-level).



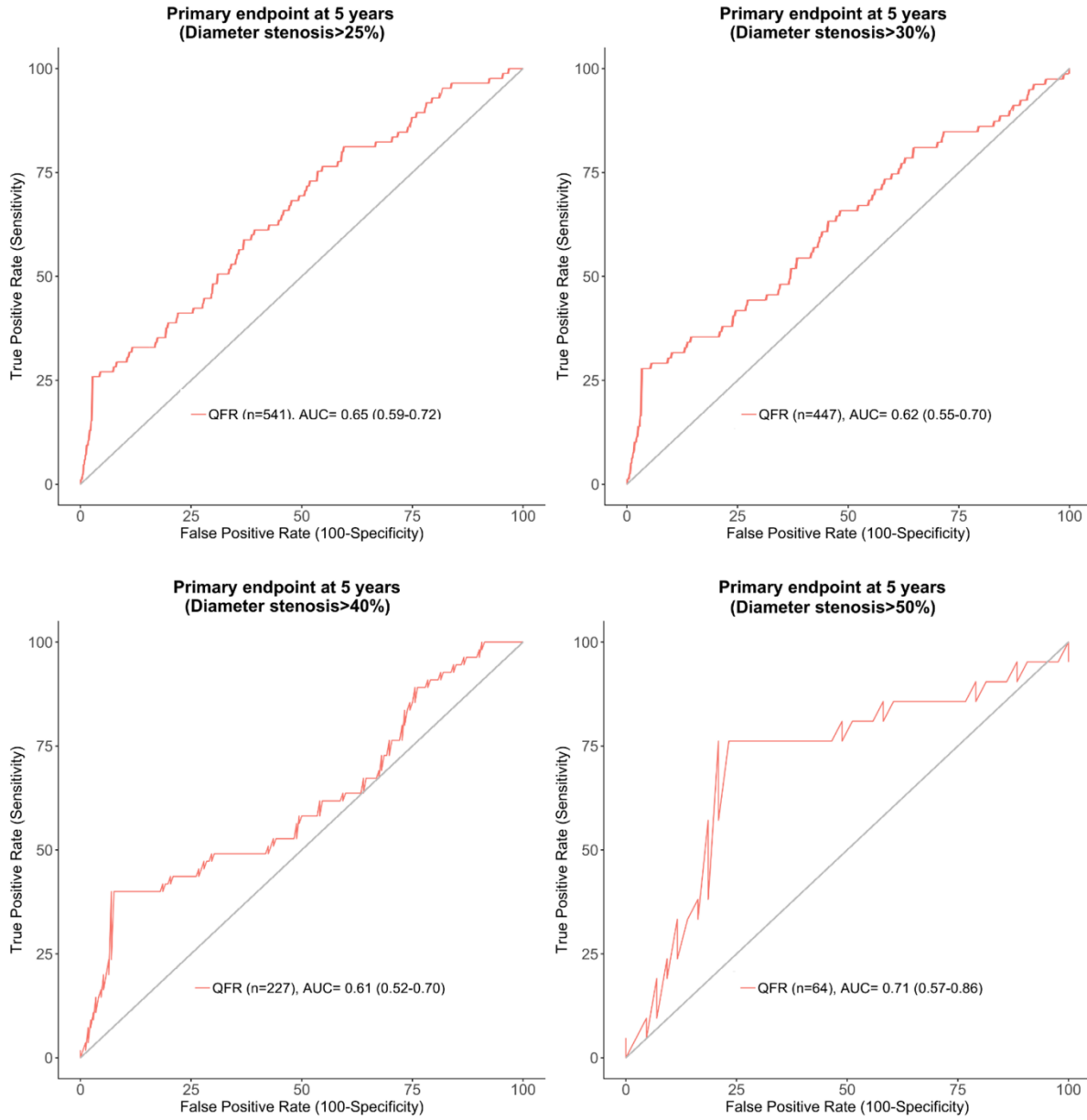
Distribution of DS% on vessel-level (n=946). DS% = diameter stenosis.

Figure S2. Distribution of QFR Values (vessel-level).



Distribution of QFR values on vessel-level for whole study cohort (n=946) (left) and $>30\%$ stenosis (n=578) (right). DS% = diameter stenosis, QFR = Quantitative Flow Ratio.

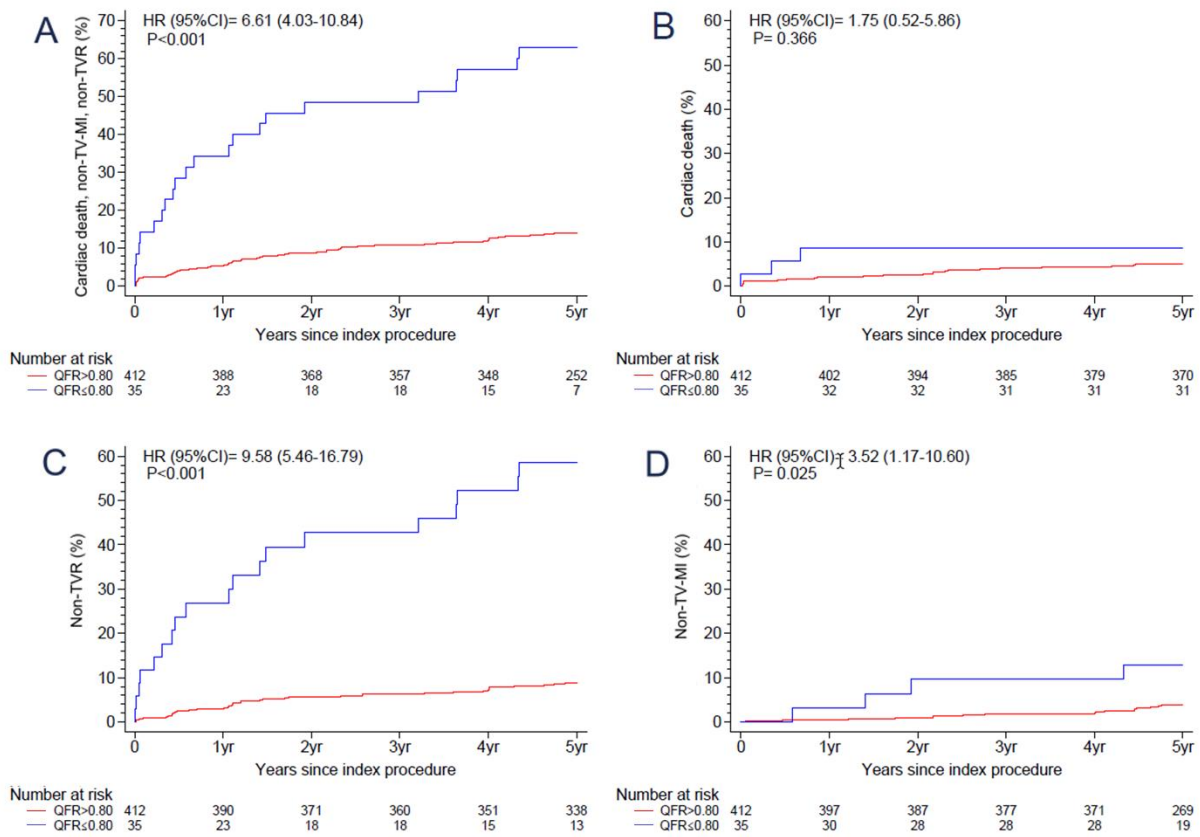
Figure S3. ROC Analyses for the Prediction of the Primary Endpoint for Different DS%.



AUC = area under the curve, DS% = diameter stenosis, QFR = Quantitative Flow

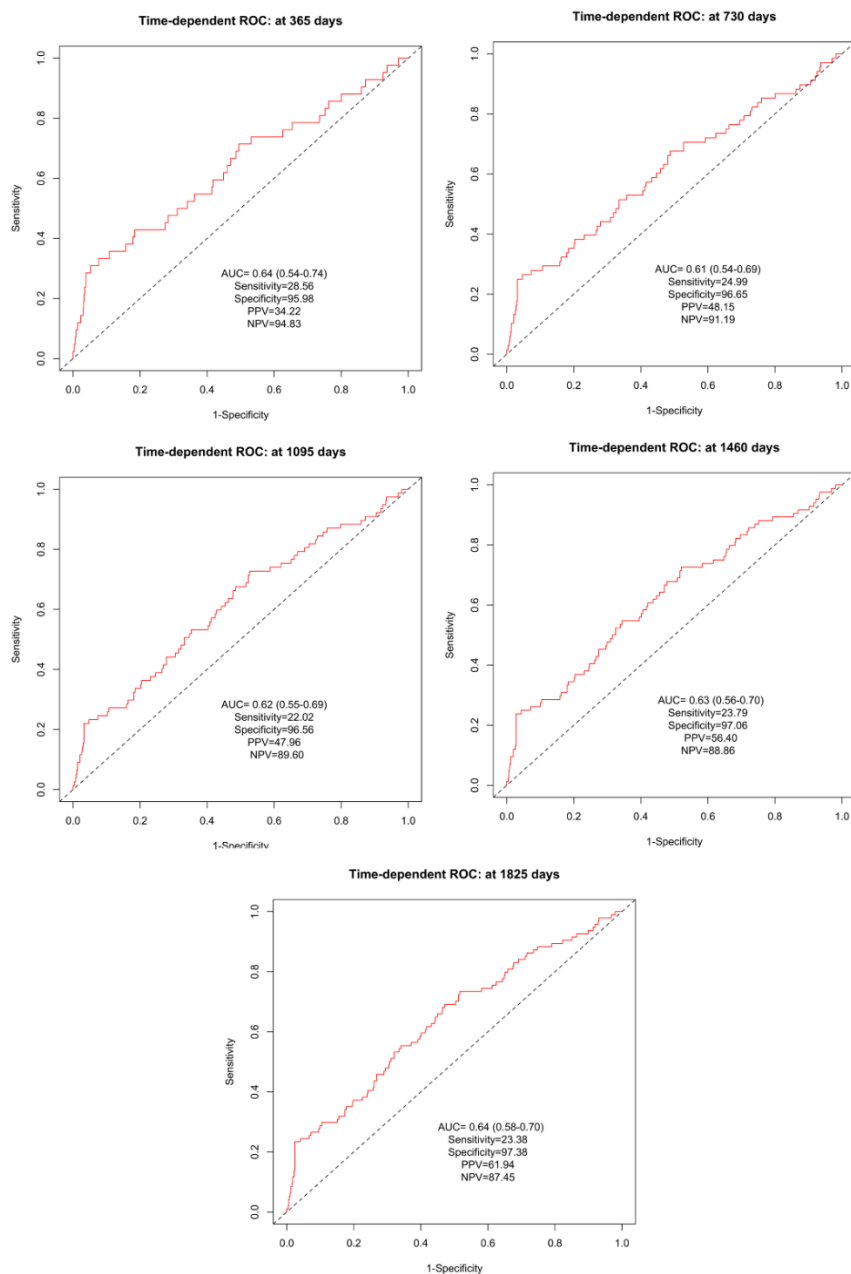
Ratio.

Figure S4. Kaplan Meier Curves of the Primary Endpoint for DS >30%.



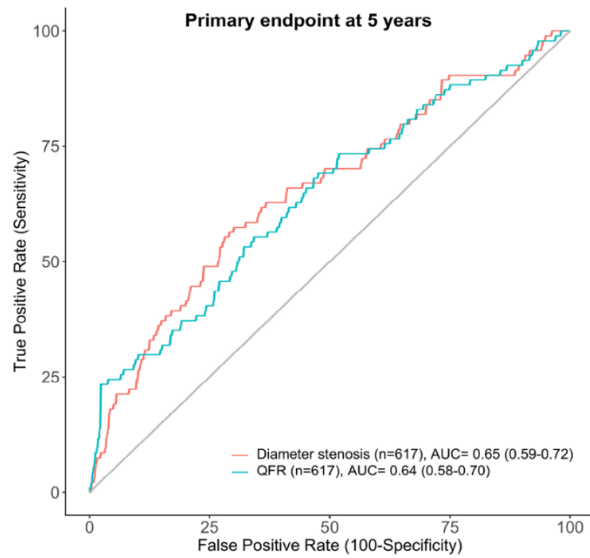
Cumulative incidence curves from Cox proportional hazards models through 5 years for patients with ≥ 1 DS >30% (n=447). A) primary endpoint: cardiac death, spontaneous non-TV-MI and non-TVR, B) cardiac death, C) non-TVR, D) spontaneous non-TV-MI. CI = confidence interval, HR = hazard ratio, non-TV-MI = non-target-vessel myocardial infarction, non-TVR = non-target vessel revascularization, QFR = Quantitative Flow Ratio.

Figure S5. Time-dependent ROC analyses.



Displayed are time-dependent ROC (i.e. cumulative case/dynamic control) analyses at 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days), and 5 years (1825 days) for QFR ≤ 0.80 predicting the primary endpoint (cardiac death, spontaneous non-TV-MI, non-TVR). AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value, QFR = Quantitative Flow Ratio, ROC = receiver operating curve.

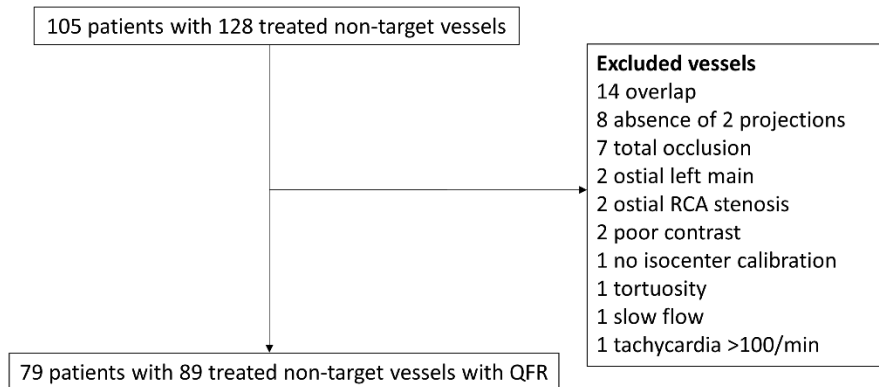
Figure S6. ROC analyses for QFR ≤ 0.80 and DS $\geq 50\%$.



	QFR	DS
Cut-off	0.80	50%
Accuracy, %	86.2	81.2
Sensitivity, %	23.4	22.3
Specificity, %	97.5	91.8
PPV, %	62.9	32.8
NPV, %	87.6	86.8

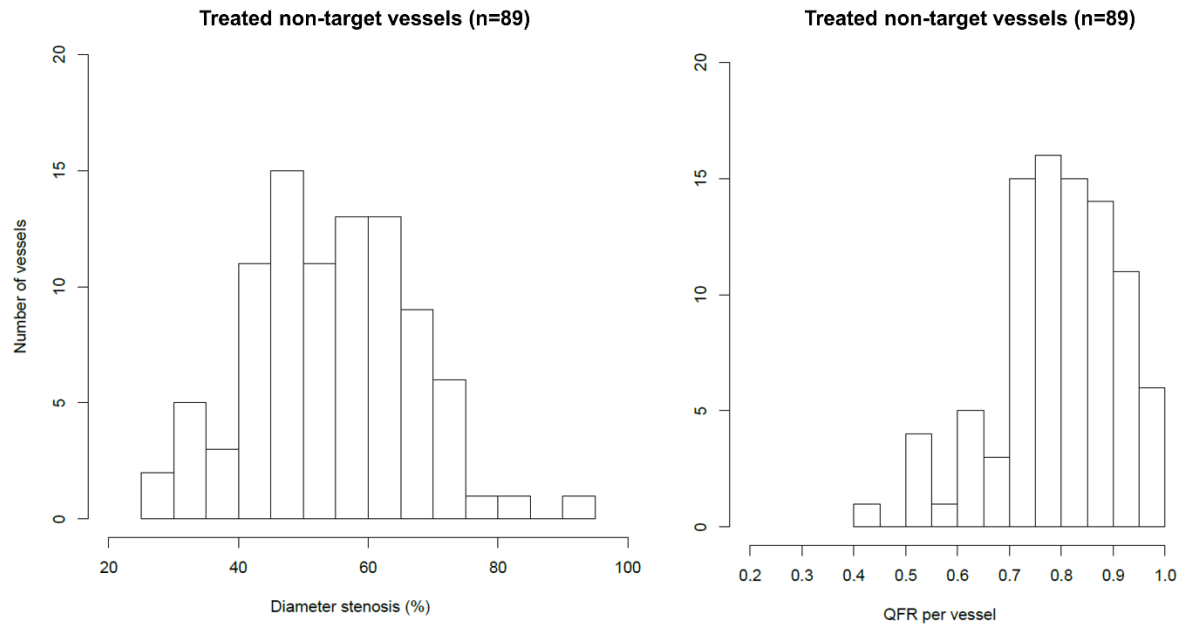
ROC analyses for QFR ≤ 0.80 vs. DS $\geq 50\%$ by 3D-QCA predicting the primary endpoint (cardiac death, spontaneous, non-TV-MI, non-TVR) at 5 years. AUC = area under the curve, DS% = diameter stenosis, NPV = negative predictive value, PPV = positive predictive value, QFR = Quantitative Flow Ratio, ROC = receiver operating curve. 3D-QCA = 3D-Quantitative Coronary Angiography.

Figure S7. Flowchart of Treated Non-Target-Vessels.



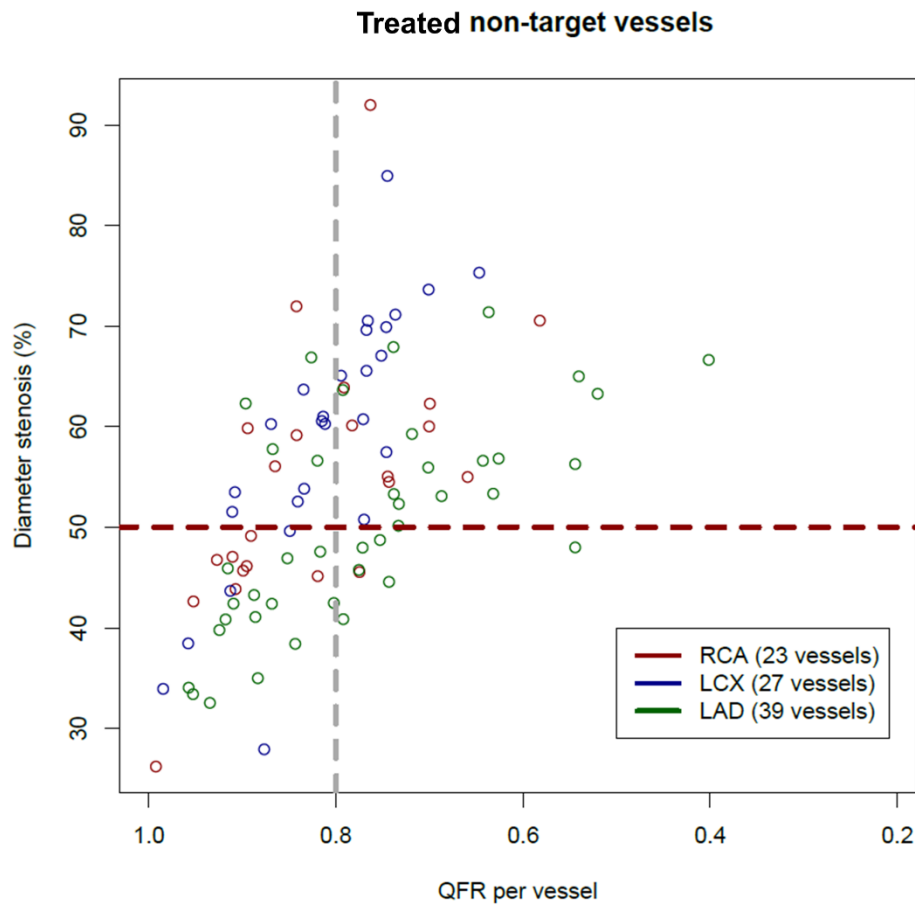
QFR = Quantitative Flow Ratio, RCA = right coronary artery.

Figure S8. Distribution of DS% and QFR of Treated Non-Target-Vessels.



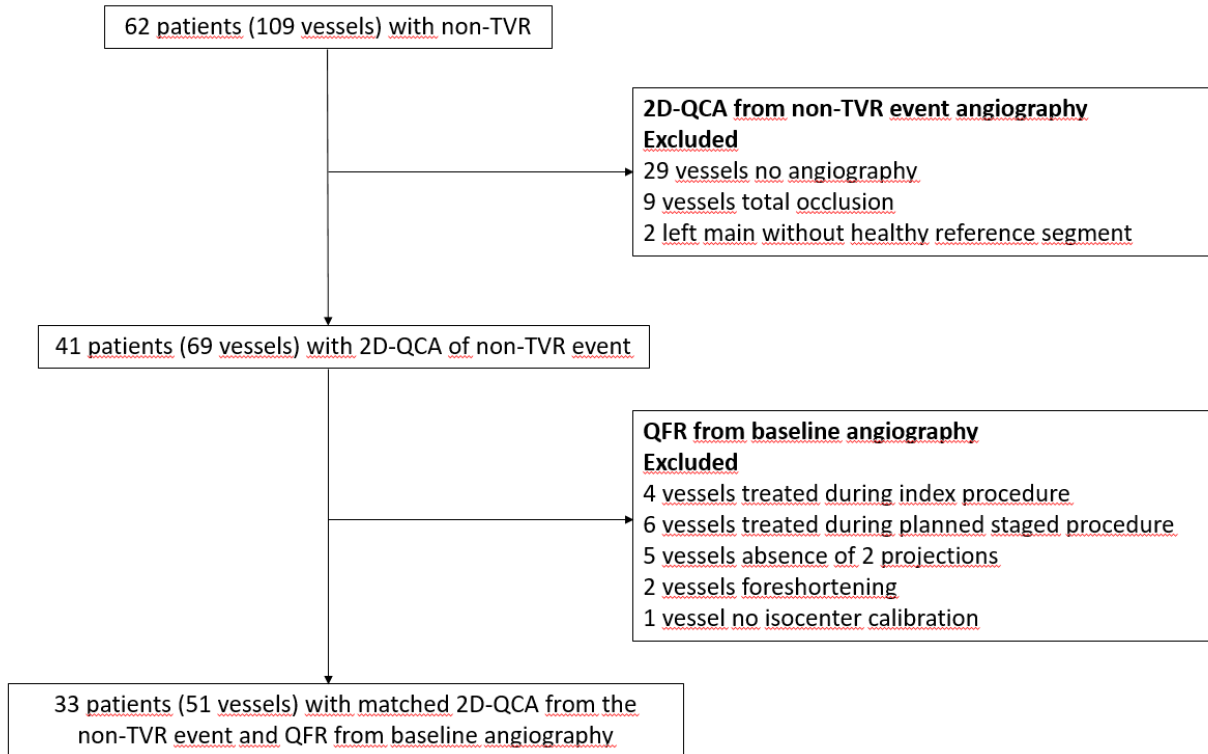
DS% = diameter stenosis. QFR = Quantitative Flow Ratio.

Figure S9. Scatterplot DS% vs. QFR of Treated Non-Target-Vessels.



DS% = diameter stenosis, LAD = left anterior descending artery, LCX = left circumflex artery, QFR = Quantitative Flow Ratio, RCA = right coronary artery.

Figure S10. Flowchart of Matched 2D-QCA and QFR of Vessels with a Non-TVR Event.



Non-TVR = non-target vessel revascularization, 2D-QCA = 2D-Quantitative Coronary Angiography, QFR = Quantitative Flow Ratio.