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ORIGINAL RESEARCH

Quantitative Flow Ratio to Predict Nontarget Vessel–Related Events at 5 Years in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Angiography-Guided Revascularization

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BACKGROUND: In ST-segment–elevation myocardial infarction, angiography-based complete revascularization is superior to culprit-lesion-only percutaneous coronary intervention. Quantitative flow ratio (QFR) is a novel, noninvasive, vasodilator-free method used to assess the hemodynamic significance of coronary stenoses. We aimed to investigate the incremental value of QFR over angiography in nonculprit lesions in patients with ST-segment–elevation myocardial infarction undergoing angiography-guided complete revascularization.

METHODS AND RESULTS: This was a retrospective post hoc QFR analysis of untreated nontarget vessels (any degree of diameter stenosis [DS]) from the randomized multicenter COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial by assessors blinded for clinical outcomes. The primary end point was cardiac death, spontaneous nontarget vessel myocardial infarction, and clinically indicated nontarget vessel revascularization (ie, ≥70% DS by 2-dimensional quantitative coronary angiography or ≥50% DS and ischemia) at 5 years. Of 1161 patients with ST-segment–elevation myocardial infarction, 946 vessels in 617 patients were analyzable by QFR. At 5 years, the rate of the primary end point was significantly higher in patients with QFR ≤0.80 (n=35 patients, n=36 vessels) versus QFR >0.80 (n=582 patients, n=910 vessels) (62.9% versus 12.5%, respectively; hazard ratio [HR], 7.33 [95% CI, 4.54–11.83], *P*<0.001), driven by higher rates of nontarget vessel myocardial infarction (12.8% versus 3.1%, respectively; HR, 4.38 [95% CI, 1.47–13.02], *P*=0.008) and nontarget vessel revascularization (58.6% versus 7.7%, respectively; HR, 10.99 [95% CI, 6.39–18.91], *P*<0.001) with no significant differences for cardiac death. Multivariable analysis identified QFR ≤0.80 but not ≥50% DS by 3-dimensional quantitative coronary angiography as an independent predictor of the primary end point. Results were consistent, including only >30% DS by 3-dimensional quantitative coronary angiography.

CONCLUSIONS: Our study suggests incremental value of QFR over angiography-guided percutaneous coronary intervention for nonculprit lesions among patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Key Words: ST-segment–elevation myocardial infarction ■ coronary flow ■ fractional flow reserve ■ angiography

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CLINICAL PERSPECTIVE

What Is New?

- Quantitative flow ratio is a novel, noninvasive, vasodilator-free method to assess the hemodynamic significance of coronary stenoses.
- In patients with ST-segment–elevation myocardial infarction undergoing angiography-guided complete revascularization of all nonculprit lesions with ≥70% stenosis by visual estimate, quantitative flow ratio identified additional lesions at risk for future nontarget vessel–related events through 5 years of follow-up.

What Are the Clinical Implications?

- Quantitative flow ratio showed incremental value over angiography alone in nonculprit lesion assessment in patients with ST-segment–elevation myocardial infarction.
- Quantitative flow ratio may emerge as a convenient, noninvasive, vasodilator-free method to assess nonculprit lesion significance in patients with ST-segment–elevation myocardial infarction.

Nonstandard Abbreviations and Acronyms

2D	2-dimensional
3D	3-dimensional
%DS	percent diameter stenosis
DS	diameter stenosis
FFR	fractional flow reserve
NCL	nonculprit lesion
non–TV-MI	nontarget vessel myocardial infarction
non-TVR	nontarget vessel revascularization
MI SYNTAX	Myocardial Infarction TAXus and Cardiac Surgery
QFR	quantitative flow ratio
TV-MI	target vessel myocardial infarction

The prevalence of multivessel disease in patients with ST-segment–elevation myocardial infarction (STEMI) amounts to ≈50%.[1] These patients are at highest risk for future cardiac events[2,3] including an increased risk of mortality, and several trials have investigated the role of complete versus culprit-lesion-only revascularization to further improve outcomes.[4–11] Recently, outcome data of the COMPLETE (Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI) trial showed a reduction in cardiovascular death and myocardial infarction (MI) in favor of patients undergoing complete angiography-guided percutaneous coronary intervention (PCI).[12]

Hemodynamic lesion assessment with use of fractional flow reserve (FFR) assumes a class IA indication in guidelines on myocardial revascularization among patients with chronic coronary syndromes[13] considered for PCI.[14] Although 2 randomized clinical trials (RCTs) reported improved outcomes of FFR-guided complete revascularization versus culprit-lesion-only PCI in patients with acute MI,[7,8] the superiority of the FFR-guided strategy was driven by a reduction in repeat revascularization and a direct comparison of angiography-guided versus FFR-guided complete revascularization in this patient population is missing to date. The ongoing FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) trial is currently investigating the issue (NCT02943954).

From a practical standpoint, the use of invasive FFR in the acute setting of STEMI is inconvenient because of the need for additional nonculprit vessel wire manipulation, the administration of adenosine with potential adverse effects, lengthening of procedure time, and additional costs.[15,16]

Quantitative flow ratio (QFR) has emerged as a novel, noninvasive, vasodilator-free method to calculate FFR from biplane angiography using computational modeling of 3-dimensional (3D) quantitative coronary angiography (QCA) and TIMI (Thrombolysis in Myocardial Infarction) frame counts.[17–19] It has been broadly validated against FFR in chronic coronary syndromes[19] and more recently for the assessment of nonculprit lesion (NCL) in STEMI, showing areas under the curve (AUCs) of 0.89 to 0.97[20–23] with good agreement between QFR assessment at the time of the index and subsequent staged procedure.[20,22] QFR is time efficient and omits any additional invasive procedures, drug administration, or further costs[18]; therefore, it is potentially useful in patients with STEMI. In the COMFORTABLE AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trial, an international multicenter RCT of patients with STEMI to compare bare metal stents with biolimus-eluting stents, patients underwent angiography-guided complete revascularization for stenoses ≥70% by visual estimate.[24] We aimed to investigate the incremental value of nontarget vessel QFR over angiography-guided PCI to predict major adverse cardiac events during follow-up throughout 5 years.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

All untreated nontarget vessels from the COMFORORTABLE AMI cohort,[24] at any degree of stenosis, were eligible for QFR measurement after angiography-guided complete revascularization. The study design as well as 1-, 2-, and 5-year outcomes have been previously published.[24–27] Briefly, COMFORTABLE AMI was a single-blinded RCT of 1161 patients with STEMI undergoing primary PCI comparing bare metal stents and biolimus-eluting stents at 11 sites in Europe and Israel between 2009 and 2011. The main exclusion criteria were MI secondary to stent thrombosis; mechanical complications of acute MI; noncardiac comorbid conditions with life expectancy <1 year; planned surgery within 6 months of PCI (unless dual antiplatelet therapy was maintained throughout the perisurgical period); history of bleeding diathesis or known coagulopathy; use of vitamin K antagonists; known intolerance to aspirin, clopidogrel, heparin, stainless steel, biolimus, or contrast material; and (possible) pregnancy. Patients were 1:1 randomly assigned to receive either bare metal stents or biolimus-eluting stents. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent. Clinical end points were adjudicated by an independent clinical events committee.

Angiography

All patients underwent diagnostic angiography using standard angiographic projections with at least 2 orthogonal planes per region of interest at the time of PCI. Administration of nitroglycerin before angiography was performed whenever clinically feasible. Complete revascularization based on visual estimation from angiography (ie, stenosis ≥70% by visual estimate) was recommended with staged PCI to be performed within no longer than 3 months. Treatment of lesions between 50% and 70% were left to the discretion of the operators. All untreated vessels at any degree of stenosis underwent QFR if the quality was sufficient (see below). Untreated lesions were categorized in focal ≤20 mm versus diffuse >20 mm.[28]

QFR Analysis

QFR analysis was performed in the Bern University Hospital Corelab by certified analysts blinded for patient outcomes using dedicated software (QAngio XA 3D version 1.2, Medis Medical Imaging Systems) (Figure 1). If obtained, optimal angiographic projections for QFR computation as defined by the software manufacturers were used. Contrast QFR using frame counting[16] was measured from the ostium of the index vessel to a distal anatomic landmark visible on both projections at a vessel diameter of ≥2.0 mm. Distal end point selection at a minimum vessel diameter of ≥1.5

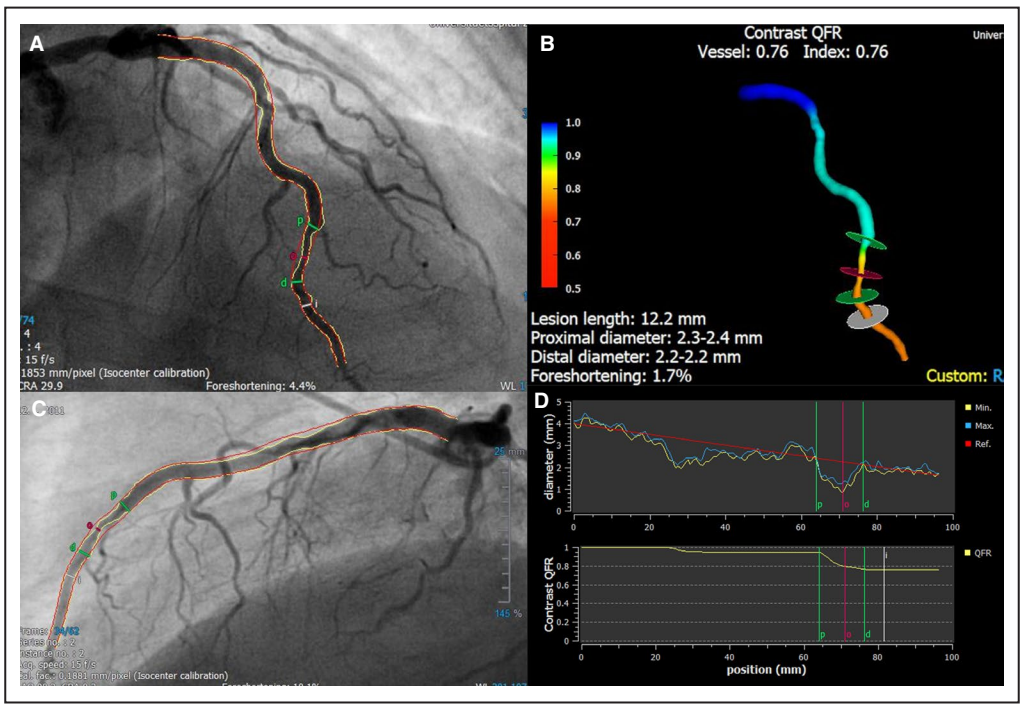


Figure 1. Quantitative flow ratio (QFR) analysis.
Example of a left anterior descending artery requiring revascularization according to a QFR value of 0.76 that was missed by angiography. **A** and **B**, Two angiographic projections ≥25° apart, (**C**) 3-dimensional vessel reconstruction, (**D**) vessel diameter, and QFR curves over the length of the vessel.

was chosen in vessels with ≤2.5 to 2.0 mm proximal reference diameter, which is in line with a previous study.[20] All analyses were performed according to a previously suggested standard operating procedure.[18] The conventional cutoff of ≤0.80 for detection of significant ischemia was used.[16–18] All nontarget vessels including major side branches (obtuse marginal, intermediate branch, diagonal branch) without staged PCI and ≥2.0 mm proximal reference diameter were eligible for QFR analysis. The exclusion criteria for QFR analysis were absence of 2 projections with an angle ≥25° apart; lack of isocenter calibration; substantial vessel overlap or vessel foreshortening; severe tortuosity; poor contrast; TIMI flow ≤2; tachycardia >100 per minute; atrial or ventricular arrhythmia; ostial left main or ostial right coronary artery stenosis; bifurcation lesions with 1,1,1 Medina classification; vessels with retrograde fillings; grafted coronary arteries; and bypass grafts.

Intraobserver and Interobserver Reliability

For intraobserver and interobserver reliability testing, repeated QFR analyses by 3 independent Corelab analysts including 20 randomly assigned vessels were used.

Clinical End Points

The primary end point was the composite of cardiac death, spontaneous nontarget vessel MI (non–TV-MI), and clinically indicated nontarget vessel revascularization (non-TVR) throughout 5 years in patients with at least 1 vessel with QFR ≤0.80 versus patients with all vessels with QFR >0.80. Secondary end points included the individual components of the primary end point, any spontaneous MI, and any revascularization.

Detailed definitions of all clinical end points were previously reported.[24]

Cardiac death was defined as any death from immediate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment.

MI was defined according to the extended historical definition.[29] All MIs (TV-MI, non–TV-MI, Q-wave MI, non–Q-wave MI) were spontaneous MIs >48 hours after intervention. Periprocedural MIs ≤48 hours after intervention were excluded from the present analysis. TV-MI was defined as MI attributed to the vessel intervened at baseline and non–TV-MI as MI attributed to a vessel not intervened at baseline.

Non-TVR was clinically indicated using the same definition as for target vessel revascularization, ie, lesions with diameter stenosis (DS) ≥70% (by 2-dimensional [2D] QCA) or DS ≥50% (by 2D QCA) and 1 of the following: (1) a positive history of recurrent angina pectoris presumably related to the nontarget vessel; (2) objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent) presumably related to the nontarget vessel; and (3) abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve and FFR).[24]

We performed multivariable predictor analysis of the primary end point and determined the predictive power of QFR ≤0.80 (accuracy, sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) to detect the primary end point.

Statistical Analysis

Continuous variables are presented as mean±SD and categorical variables as counts with percentages. Baseline, procedural, and 3D QCA variables were compared using chi-square test, Fisher exact test, or *t* test, as appropriate. Cumulative incidences of the clinical end points through 5 years and from 1 to 5 years were compared using Cox proportional hazard models and are displayed via Kaplan-Meier curves. Hazard ratios (HRs) are provided with 95% confidence intervals (CIs). To identify predictors of the 5-year primary end point, we ran univariable Cox proportional hazards models for all patient baseline characteristics, QFR ≤0.80, and DS ≥50%, and we subsequently ran a multivariable Cox proportional hazards model including all variables that had a significant association with the primary end point in univariable analysis. We conducted receiver operating characteristic (ROC) analysis to assess the sensitivity, specificity, and PPV/NPV of QFR ≤0.80 for the 5-year primary end point. To account for changing event risk over time, we additionally performed cumulative case/dynamic control (ie, time-dependent) ROC analyses at 1, 2, 3, 4, and 5 years using the Kaplan-Meier estimator of the censoring distribution. All analyses were conducted in Stata 15 and RStudio 1.1.463. Significance tests were 2-tailed with a significance level set to 0.05.

RESULTS

Baseline Patient and Procedural Characteristics

A total of 1161 patients with STEMI were randomized and 1157 patients included in the present analysis. At 5 years, clinical follow-up information was available in 1100 patients, of whom 927 (84.3%) patients were eligible for QFR analysis. After exclusion attributable to clinical or technical exclusion criteria as shown in Figure 2, a total of 617 (56.1%) patients with 946 vessels were available for the final analysis. Baseline clinical and procedural characteristics were similar for the QFR ≤0.80 group and QFR >0.80 group, except for MI SYNTAX (Myocardial Infarction TAXus and Cardiac

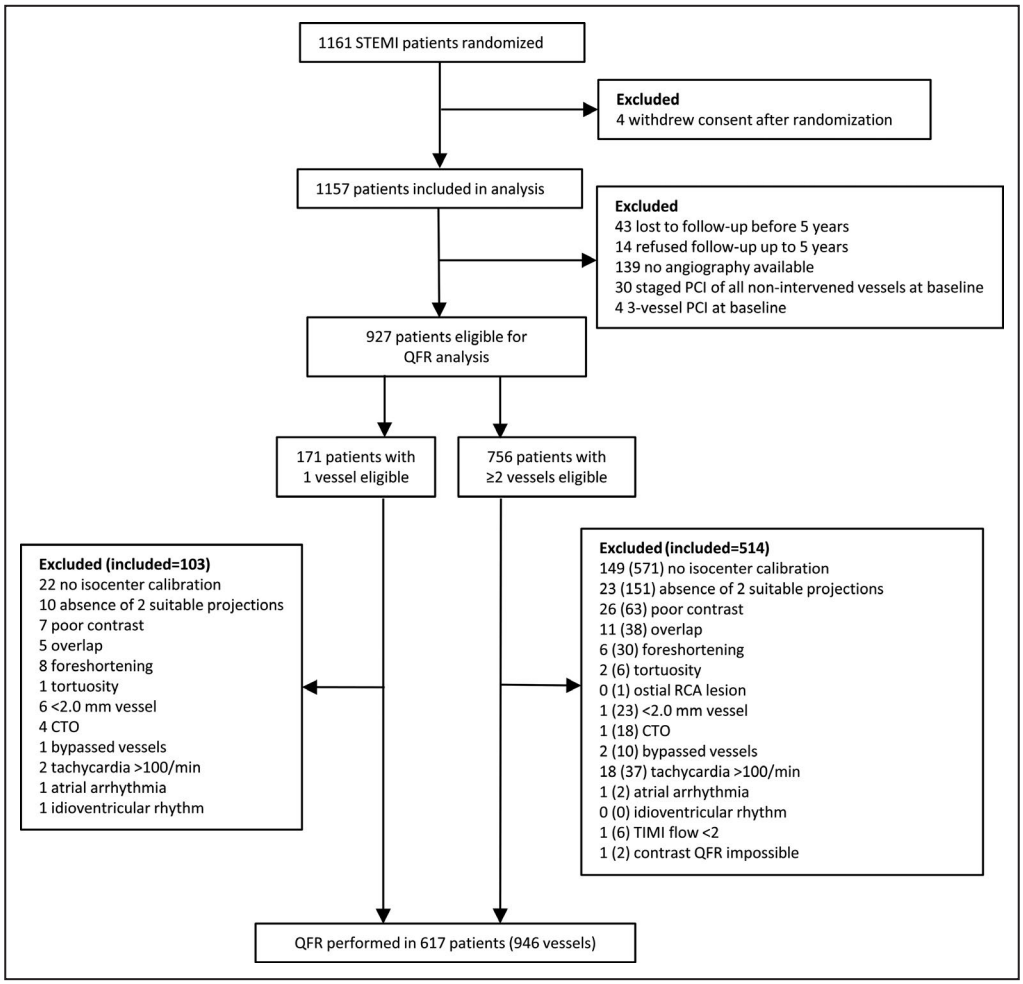


Figure 2. Patient flowchart.
Depicted are numbers of patients (vessels). CTO indicates chronic total occlusion; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

Surgery) score (ie, post–wire-crossing SYNTAX score),[30,31] which was significantly higher, and DS ≥50% by 3D QCA, which was significantly more frequent in the QFR ≤0.80 group (Table 1).

Three-Dimensional QCA and QFR Characteristics

Mean (percent DS [DS%]) of NCL was 36.5% (±10.5, range 9.5%–70.3%) (Figure S1). Only 1 of 946 (0.1%) vessels revealed DS% above the revascularization threshold of ≥70% (DS 70.3%). The mean QFR of NCL was 0.93 (±0.09, range 0.21–1.00) (Figure S2). In 36 of 946 (3.8%) vessels QFR was ≤0.80 and in 910 (96.2%) QFR was >0.80. In the QFR ≤0.80 group, left anterior descending artery was the most frequent vessel (77.8%) followed by the right coronary artery (19.4%) and the left circumflex artery (2.8%). The majority (66.7%, n=24) of vessels with QFR ≤0.80 exhibited diffuse disease (ie, lesion length >20 mm[28]). Most mismatches between angiographic and functional lesion severity (QFR ≤0.80 but DS <50%) were located in the left anterior descending (83.3%) artery, fewer in the right coronary artery (16.7%), and none in the left circumflex artery (Figure 3). QCA analyses indicated that DS% (P<0.001) and area stenosis (P<0.001) were higher, minimal lumen diameter (P<0.001) was lower, and lesion length (P<0.001) was longer in vessels with QFR ≤0.80 versus >0.80 (Table 2).

Intraobserver and Interobserver Reliability

Intraobserver reliability analysis showed agreement on QFR classification (QFR ≤0.80 versus >0.80) in 100% of vessels. Intraclass correlation coefficient for continuous QFR was 0.67. Interobserver reliability analysis showed agreement on QFR classification in 90% of vessels, an intraclass correlation coefficient of 0.76, and a κ coefficient of 0.68.

Table 1. Patient and Procedural Characteristics

	QFR ≤0.80 (n=35)	QFR >0.80 (n=582)	*P* Value
Patient characteristics (patient-level)			
Women, n (%)	10 (28.6)	133 (22.9)	0.415
Age, y	63.1±11.4	60.7±11.6	0.232
BMI, kg/m^2	27.3±3.5	27.0±4.0	0.730
Diabetes mellitus, n (%)	8 (22.9)	78 (13.4)	0.130
Hypertension, n (%)	22 (62.9)	262 (45.0)	0.054
Hypercholesterolemia, n (%)	25 (71.4)	323 (55.8)	0.080
Family history of CAD, n (%)	13 (38.2)	185 (32.2)	0.457
Killip I or II, n (%)	33 (94.3)	577 (99.1)	0.055
Killip IV, n (%)	1 (2.9)	3 (0.5)	0.209
Left ventricular function, %	49.1±10.4	48.7±10.3	0.840
MI SYNTAX score	16.2±10.9	11.1±7.6	<0.001
Procedural characteristics (patient-level)			
Infarct vessel			0.003
LM artery, n (%)	0 (0.0)	1 (0.2)	
LAD artery, n (%)	5 (14.3)	251 (43.1)	
LCX artery, n (%)	7 (20.0)	80 (13.7)	
RCA, n (%)	23 (65.7)	250 (43.0)	
Lesions in infarct vessel, n	1.03 (0.17)	1.09 (0.33)	0.236
Type of intervention			0.209
PCI—implantation of stent(s), n (%)	34 (97.1)	579 (99.5)	
PCI—only balloon dilatation, n (%)	1 (2.9)	3 (0.5)	
Stents per lesion, n	1.37±0.81	1.41±0.72	0.766
Total stent length per lesion, mm	28.4±15.5	26.8±13.4	0.505
Average stent diameter, mm	3.24±0.49	3.20±0.41	0.569
Direct stenting, n (%)	11 (32.4)	175 (30.2)	0.848
Maximal balloon pressure, atm	16.3±3.5	15.3±3.2	0.073
Thrombus aspiration, n (%)	23 (65.7)	353 (60.7)	0.597
Nontarget vessel (patient-level)	n=35	n=582	<0.001
LAD artery, n (%)	27 (77.1)	183 (31.4)	
LCX artery, n (%)	1 (2.9)	255 (43.8)	
RCA, n (%)	7 (20.0)	144 (24.7)	
DS ≥50% by 3D QCA, n (%)	23 (65.7)	38 (6.5)	<0.001
Nontarget vessel (vessel-level)	n=36	n=910	<0.001
LAD artery, n (%)	28 (77.8)	226 (24.8)	
LCX artery, n (%)	1 (2.8)	463 (50.9)	
RCA, n (%)	7 (19.4)	221 (24.3)	
DS ≥50% by 3D QCA, n (%)	24 (66.7)	43 (4.7)	<0.001

Values are mean±SD or number (percentage). 3D indicates 3-dimensional; BMI, body mass index; CAD, coronary artery disease; DS, diameter stenosis; LAD, left anterior descending; LCX, left circumflex; LM, left main; MI SYNTAX, Myocardial Infarction TAXus and Cardiac Surgery; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; RCA, right coronary artery; and QFR, quantitative flow ratio.

Clinical Events

Cumulative event rates at 5 years are summarized in Table 3 and Figure 4. The proportional hazards assumption was met for all reported outcomes. At 5 years of follow-up, the rate of the primary end point was significantly higher in the QFR ≤0.80 group as compared with the QFR >0.80 group (62.9% versus 12.5%, respectively; HR, 7.33 [95% CI, 4.54–11.83], *P*<0.001).

This was driven by differences in spontaneous non–TV-MI (12.8% versus 3.1%, respectively; HR, 4.38 [95% CI, 1.47–13.02], *P*=0.008) and non-TVR (58.6% versus 7.7%, respectively; HR, 10.99 [95% CI, 6.39–18.91], *P*<0.001). The non–TV-MIs occurred after a

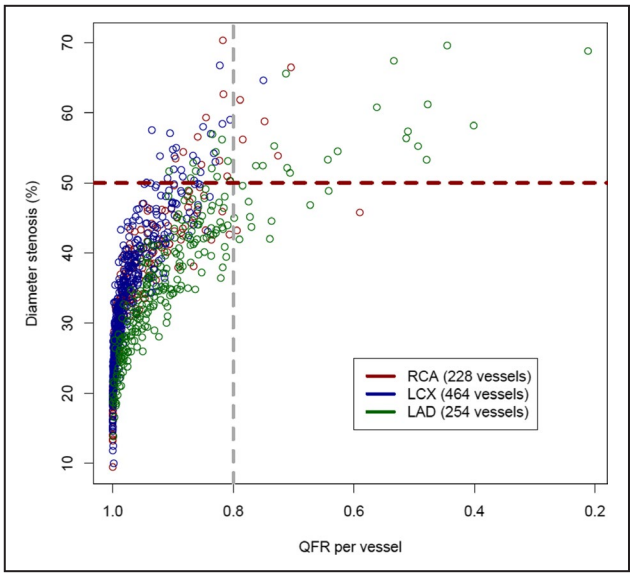


Figure 3. Scatterplot diameter stenosis vs quantitative flow ratio (QFR; vessel-level).
LAD indicates left anterior descending; LCX, left circumflex; and RCA, right coronary artery.

median follow-up of 2.5 years (interquartile range, 1.3–4.3 years). Cardiac death occurred numerically more frequently but CIs were wide and risk estimates were imprecise (8.6% versus 4.7%, respectively; HR, 1.92 [95% CI, 0.58–6.33], *P*=0.284). Rates of any spontaneous MI (22.4% versus 5.8%, respectively; HR, 4.38 [95% CI, 1.93–9.92], *P*<0.001) and any revascularization (58.6% versus 15.0%, respectively; HR, 5.17 [95% CI, 3.14–8.52], *P*<0.001) were significantly higher in the QFR ≤0.80 group. Consistently, exploratory end points of cardiac death, any spontaneous MI, and any revascularization (62.9% versus 18.8%, respectively; HR, 4.68 [95% CI, 2.96–7.41], *P*<0.001) as well as cardiac death and any spontaneous MI (29.6% versus 9.7%, respectively; HR, 3.58 [95% CI, 1.82–7.02], *P*<0.001) showed significantly higher rates in the QFR ≤0.80 group (Table 3).

When applying a landmark analysis at 1 year, results for the primary end point and its components remained fully consistent (Table S1).

We performed a sensitivity analysis considering only patients with at least one >30% stenosis (Tables S2 through S6 and Figures S2 through S4). Results for this population (QFR ≤0.80 n=35 versus QFR >0.80 n=412) were consistent with those of the overall study cohort.

Independent Predictor Analysis

In multivariable analysis there was a significant association between QFR ≤0.80 and the primary end point, with a 7.8 times higher expected hazard for patients with QFR ≤0.80 (*P*<0.001). Further independent predictors of the primary end point in multivariable analysis were MI SYNTAX score (per 5-point increase) and left ventricular ejection fraction but not DS ≥50% by 3D QCA (Table 4). Results for the population including only >30% stenosis were fully consistent (Table S5).

Diagnostic Performance of QFR

Using the conventional QFR cutoff point of ≤0.80 for the prediction of the primary end point (cardiac death, spontaneous non–TV-MI, non-TVR) at 5 years, accuracy was 86.2%, sensitivity was 23.4%, specificity was

Table 2. Three-Dimensional QCA Analysis

Three-Dimensional QCA Variable (Patient-Level)	QFR ≤0.80 (n=35)	QFR >0.80 (n=582)	*P* Value
Diameter stenosis, %	54.2±8.1	35.4±9.6	<0.001
Area stenosis, %	69.9±8.3	45.9±15.0	<0.001
Lesion length, mm	31.0±16.9	19.9±13.2	<0.001
Proximal diameter, mm	2.77±0.61	2.90±0.63	0.264
Minimal lumen diameter, mm	1.33±0.37	1.89±0.50	<0.001
Distal diameter, mm	2.46±0.49	2.62±0.65	0.170
Reference diameter, mm	2.88±0.54	2.92±0.66	0.702
Three-Dimensional QCA Variable (Vessel-Level)	**QFR ≤0.80 (n=36)**	**QFR >0.80 (n=910)**	***P* Value**
Diameter stenosis, %	54.2±8.1	33.3±9.6	<0.001
Area stenosis, %	69.9±8.1	42.5±15.6	<0.001
Lesion length, mm	30.4±17.0	18.6±13.1	<0.001
Proximal diameter, mm	2.75±0.62	2.86±0.64	0.333
Minimal lumen diameter, mm	1.32±0.37	1.92±0.51	<0.001
Distal diameter, mm	2.45±0.49	2.60±0.65	0.177
Reference diameter, mm	2.86±0.55	2.88±0.66	0.797

Values are mean±SD. QCA indicates quantitative coronary angiography; and QFR, quantitative flow ratio.

Table 3. Clinical Outcomes at 5 Years

	QFR ≤0.80 (n=35)	QFR >0.80 (n=582)	HR (95% CI)	*P* Value
Cardiac death, non–TV-MI, non-TVR, n (%)	22 (62.9)	72 (12.5)	7.33 (4.54–11.83)	<0.001
Cardiac death, MI (any), revascularization (any), n (%)	22 (62.9)	108 (18.8)	4.68 (2.96–7.41)	<0.001
Cardiac death or MI (any), n (%)	10 (29.6)	55 (9.7)	3.58 (1.82–7.02)	<0.001
Cardiac death, TV-MI, TVR, n (%)	13 (37.5)	74 (12.9)	3.50 (1.94–6.30)	<0.001
Death, n (%)	4 (11.4)	54 (9.3)	1.28 (0.46–3.54)	0.631
Cardiac death, n (%)	3 (8.6)	27 (4.7)	1.92 (0.58–6.33)	0.284
Non–TV-MI, n (%)	4 (12.8)	17 (3.1)	4.38 (1.47–13.02)	0.008
Non-TVR, n (%)	19 (58.6)	43 (7.7)	10.99 (6.39–18.91)	<0.001
Revascularization (any), n (%)	19 (58.6)	85 (15.0)	5.17 (3.14–8.52)	<0.001
MI (any), n (%)	7 (22.4)	32 (5.8)	4.38 (1.93–9.92)	<0.001
MI Q wave, n (%)	3 (9.2)	9 (1.6)	5.96 (1.61–22.03)	0.007
MI non–Q wave, n (%)	5 (16.4)	25 (4.6)	3.88 (1.49–10.15)	0.006
Stroke (any), n (%)	3 (9.0)	12 (2.2)	4.37 (1.23–15.50)	0.022

Depicted are number of patients (percentage) and hazard ratios (HRs) with 95% CI from univariable Cox proportional hazards regressions with *P* values. MI indicates myocardial infarction; non–TV-MI, nontarget vessel myocardial infarction; non-TVR, nontarget vessel revascularization; QFR, quantitative flow ratio; TV-MI, target vessel myocardial infarction; and TVR, target vessel revascularization.

97.5%, PPV was 62.9%, and NPV was 87.6%. ROC analysis yielded an AUC of 0.64 (95% CI, 0.58–0.70) (Figure 5). Expressed in absolute patient numbers, in 532 of 617 (86.2%) patients, QFR ≤0.80 versus QFR >0.80 correctly identified patients with versus those without a subsequent event (ie, occurrence of the

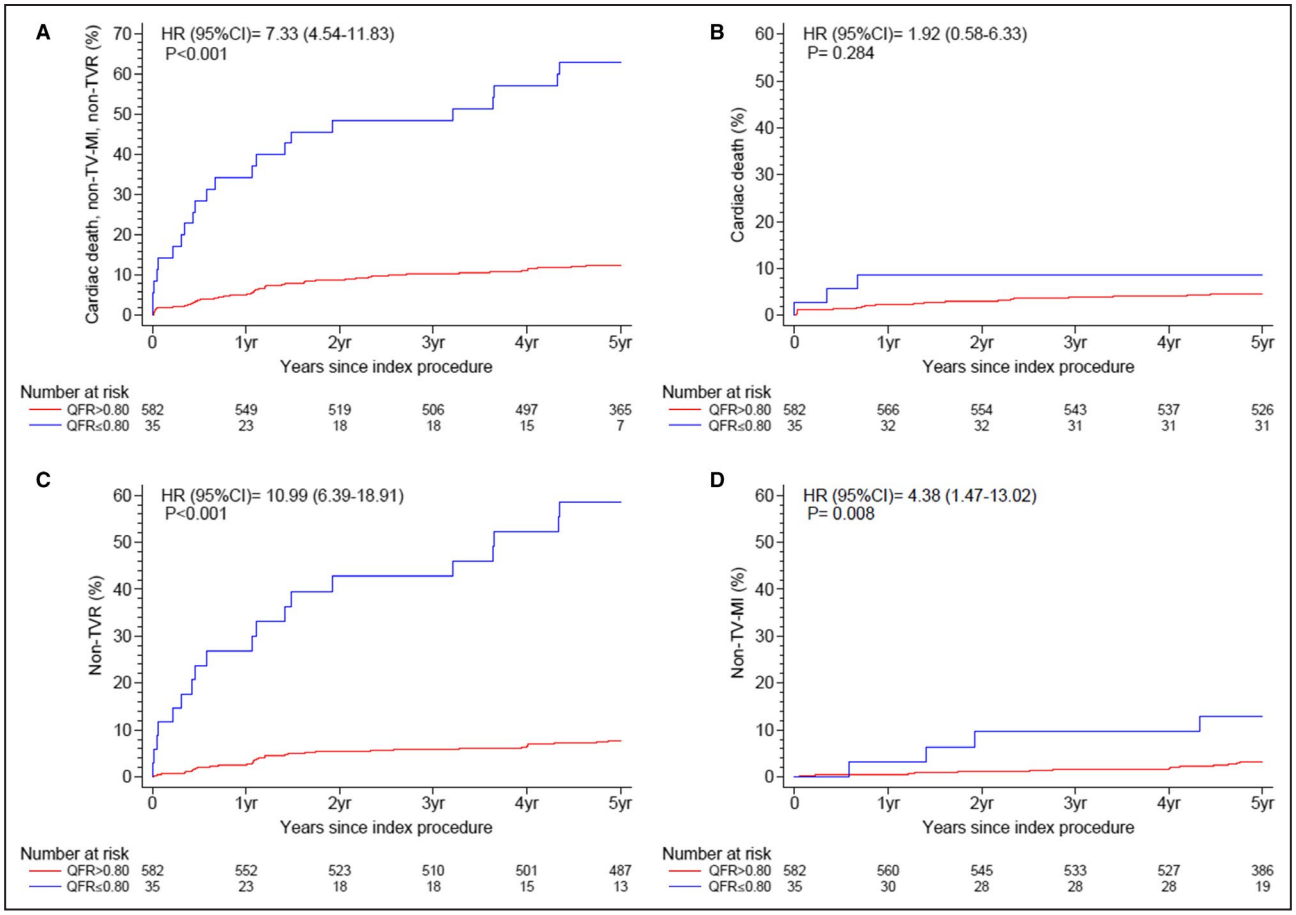


Figure 4. Kaplan-Meier curves of the primary end point.
Cumulative incidence curves from Cox proportional hazards models through 5 years for (**A**) primary end point: cardiac death, spontaneous nontarget vessel myocardial infarction (non–TV-MI), and nontarget vessel revascularization (non-TVR); (**B**) cardiac death, (**C**) non-TVR, and (**D**) spontaneous non–TV-MI. HR indicates hazard ratio; and QFR, quantitative flow ratio.

Table 4. Independent Predictor Analysis

Primary End Point (Cardiac Death, Non–TV-MI, Non-TVR)	Univariable Analysis n=617 HR (95% CI)	*P* Value	Multivariable Analysis n=571 HR (95% CI)	*P* Value
Female sex	1.23 (0.78–1.94)	0.374		
Age, y (per 1-y increase)	1.03 (1.02–1.05)	<0.001	1.02 (1.00–1.04)	0.061
BMI, kg/m^2 (per 1-kg/m^2 increase)	1.02 (0.97–1.07)	0.515		
Diabetes mellitus	2.15 (1.34–3.43)	0.001	1.63 (0.95–2.83)	0.079
Hypertension	1.66 (1.11–2.50)	0.015	1.14 (0.71–1.84)	0.588
Hypercholesterolemia	1.26 (0.83–1.92)	0.277		
Family history of CAD	0.83 (0.53–1.29)	0.402		
Killip III or IV	7.71 (2.83–20.99)	<0.001	3.03 (0.89–10.33)	0.077
Left ventricular function, % (per 5% decrease)	1.29 (1.17–1.43)	<0.001	1.25 (1.13–1.39)	<0.001
MI SYNTAX score (per 5 points increase)	1.39 (1.25–1.54)	<0.001	1.19 (1.05–1.34)	0.007
QFR ≤0.80	7.33 (4.54–11.83)	<0.001	7.75 (3.89–15.42)	<0.001
DS ≥50% by 3D QCA	2.63 (1.59–4.35)	<0.001	0.60 (0.28–1.28)	0.187

Results from univariable and multivariable Cox proportional hazard analyses. Depicted are estimated hazard ratios (HRs) with 95% CI of the primary end point (cardiac death, spontaneous nontarget vessel myocardial infarction [non–TV-MI], nontarget vessel revascularization [non-TVR]) for patient baseline characteristics, quantitative flow ratio (QFR) ≤0.80, and diameter stenosis (DS) ≥50% by 3-dimensional (3D) quantitative coronary angiography (QCA). Multivariable analysis was performed for variables with a significant association with the primary end point in univariable analysis. BMI indicates body mass index; CAD, coronary artery disease; and MI SYNTAX, Myocardial Infarction TAXus and Cardiac Surgery.

primary end point), whereas in 72 of 617 (11.7%) patients, QFR was >0.80 despite a subsequent event (false-negatives), and in 13 of 617 (2.1%) patients, QFR was ≤0.80 although no event occurred (false-positives). The best QFR cutoff to predict the primary end point was 0.93 with accuracy of 64.2%, sensitivity of 55.3%, specificity of 65.8%, PPV of 22.5%, and NPV of 89.1%. Results for the population including only >30% stenosis were comparable with slightly higher sensitivity (27.8%) at the cost of marginally lower specificity (96.5%) (Table S7 and Figure S3).

To account for changing event risk over time, we additionally performed time-dependent ROC analysis at 1, 2, 3, 4, and 5 years, which showed similar results (AUC range, 0.61–0.64) (Figure S5). As a comparator to QFR ≤0.80, we added the diagnostic ability of DS ≥50% by 3D QCA (Figure S6), which yielded markedly lower PPV (32.8%) for DS ≥50% as compared with QFR ≤0.80 (62.9%) but similar AUC (DS ≥50% 0.65 [0.59–0.72] and QFR ≤0.80 0.64 [0.58–0.70]).

Three-Dimensional QCA and QFR of Treated Nontarget Vessels

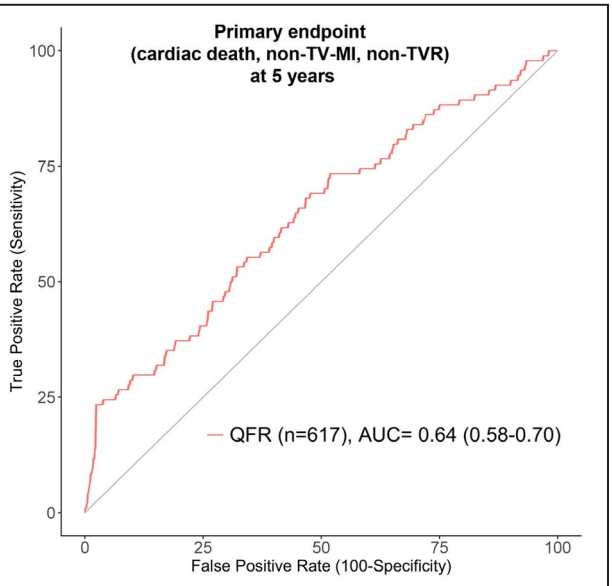
As a comparison, 3D QCA and QFR were also assessed in the nontarget vessels that were treated either during the index procedure or as a planned staged procedure. Of 128 vessels of 105 patients, 89 vessels of 79 patients were eligible for QFR measurement (Figure S7). Mean DS% was 54.2% (±12.4, range 26.2%–92.0%) and mean QFR was 0.80 (±11, range 0.40–0.99) (Figures S8 and S9). Compared with the nontarget vessels that were left untreated, QFR was significantly lower (*P*<0.001) and DS% was significantly higher (*P*<0.001) (Table S8). A total of 49.4% (n=44) of vessels had QFR ≤0.80 (Table S9).

QFR Distribution in Untreated Nontarget Vessels With a Non-TVR Event

Of 109 vessels of 62 patients with non-TVR during 5 years of follow-up, matched 2D QCA from the non-TVR angiographies and QFR values from the baseline angiographies were available in 51 (46.8%) vessels of 33 (53.2%) patients (Figure S10). A total of 36 (70.6%) vessels had DS% ≥50% with ischemia and 15 (29.4%) had DS% ≥70%. In vessels with 2D QCA, DS% ≥50%, and ischemia at the timepoint of the non-TVR event, mean QFR calculated from baseline angiography was 0.84 (±0.13, range 0.49–1.00). In vessels with 2D QCA DS% ≥70% at the timepoint of the non-TVR event, mean QFR calculated from baseline angiography was 0.86 (±0.14, range 0.48–1.00) (Table S10).

DISCUSSION

The salient findings of our study can be summarized as follows: In patients with STEMI undergoing primary PCI and angiography-guided complete revascularization, QFR ≤0.80 in nontarget vessels was associated with a 7 times higher rate of the primary end point of cardiac death, spontaneous non–TV-MI, and non-TVR at 5 years. Differences were driven by a 4-fold increased rate of spontaneous non–TV-MI and an 11-fold increased rate of non-TVR. Multivariable analysis identified QFR ≤0.80 but not DS ≥50% by 3D QCA,



QFR cut-off	0.80
Accuracy, %	86.2
Sensitivity, %	23.4
Specificity, %	97.5
Positive predictive value, %	62.9
Negative predictive value, %	87.6

Figure 5. Receiver operating curve (ROC) analysis for the primary end point.
Results of ROC analysis for the prediction of the primary end point at 5 years (cardiac death, spontaneous nontarget vessel myocardial infarction [non–TV-MI], nontarget vessel revascularization [non-TVR]). AUC indicates area under the curve; and QFR, quantitative flow ratio.

as an independent predictor for the occurrence of the primary end point. The conventional QFR cutoff ≤0.80 showed high specificity (97.5%) and good NPV (87.6%) but low sensitivity (23.4%) and moderate PPV (62.9%) in the prediction of the primary end point. The present study including 617 patients and 946 vessels is the largest data set published on QFR in patients with STEMI.

QFR Versus Angiography

Angiography-guided complete revascularization in patients with STEMI with multivessel disease has been shown to significantly reduce the composite end point of cardiovascular death and MI throughout 3 years median follow-up (HR, 0.74; 95% CI, 0.60–0.91 [*P*=0.004]) in the COMPLETE trial. In this study, revascularization was performed if nontarget vessel stenosis exceeded 70% by visual estimate or was ≥50% to 69% if additionally performed FFR amounted to ≤0.80.[12] The latter occurred in <1% of enrolled patients, and, therefore, identification of NCL requiring revascularization in the COMPLETE trial may be regarded as angiography-guided. Two RCTs investigating FFR-guided complete revascularization versus culprit-only PCI among patients with acute MI and multivessel disease, the DANAMI-3-PRIMULTI (Complete Revascularisation Versus Treatment of the Culprit Lesion Only in Patients With ST-Segment Elevation Myocardial Infarction and Multivessel Disease)[7] and COMPARE ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) trials,[8] showed better outcomes with FFR-guided complete revascularization (treatment if FFR ≤0.80). Of note, results were driven by a reduction in repeat revascularization with no differences for hard outcomes (MI or death) alone. Furthermore, patient selection in both trials used angiography guidance in a first step, as eligibility for randomization was based on ≥50% stenosis by visual estimate.

Our study analysis suggests that QFR in addition to angiographic assessment identifies patients at risk for future nontarget vessel–related adverse events including spontaneous MI and revascularization in a patient population of patients with STEMI undergoing angiography-guided complete revascularization. The lowest DS% in the group of patients with QFR ≤0.80 was 42%, suggesting that patients with STEMI may possibly not only benefit from treatment of stenoses ≥70% or ≥50% and positive FFR ≤0.80 but also of lower grade stenoses in the range of ≥40% to 70% in the presence of a positive QFR ≤0.80. Interestingly, among the nontarget vessels that were treated either during the index or as a planned staged procedure, 49.4% exhibited QFR ≤0.80.

However, it is currently unknown whether the pathophysiology of recurrent NCL events in acute coronary syndrome (ACS) is related to the degree of stenosis, its functional significance, or the plaque composition itself.[32] Thus, the definite role of any physiologic assessment in NCL among patients with acute coronary syndrome remains to be established with appropriate large-scale RCT data. For FFR, a respective trial (FLOWER-MI) comparing an angiography-guided versus FFR-guided NCL revascularization strategy in patients with STEMI is ongoing. For QFR, 2 RCTs (FAVOR III China [NCT03656848] and FAVOR III Europe Japan [NCT03729739]) are investigating angiography-guided versus QFR-guided PCI in stable patients, but, to our knowledge, there are no ongoing RCTs in patients with acute coronary syndrome.

In our study, 33% (n=12) of vessels in the QFR ≤0.80 group exhibited <50% stenosis, 67% (n=24) exhibited ≥50% to 70% stenosis, and the majority of vessels (67%)

exhibited diffuse disease (ie, lesion length >20 mm), which may explain why the significance was underestimated based on angiographic criteria alone. Of note, diffuse disease may be less amenable to revascularization and thus limit realizable treatment options. Mismatch between angiographic and functional lesion severity (ie, QFR ≤0.80 but DS <50%) occurred most frequently (83%) in the left anterior descending artery, which is in line with previous FFR investigations.[33]

Previous studies have shown that QFR outperforms 2D QCA[17,18] and 3D QCA outperforms 2D QCA[34] in the prediction of FFR ≤0.80. In our study, as QFR ≤0.80 and DS ≥50% by 3D QCA had similar sensitivity and specificity for the detection of the primary clinical end point, ROC analysis also yielded similar AUCs for QFR and DS%. However, QFR ≤0.80 proved to be the better predictive variable, as shown by the markedly higher PPV for QFR ≤0.80 than for DS ≥50% (62.9% versus 32.8%, respectively). This was also confirmed in multivariable analysis, where only QFR ≤0.80 but not DS ≥50% was independently associated with the primary end point.

Clinical Events

The results for the present study are in line with 2 previous QFR studies, which showed a 2- to 3-fold increase in the rate of patient-oriented major adverse cardiac events at 2 and 5 years[20,35] in patients with functionally incomplete revascularization based on QFR ≤0.80. At variance to these studies, the end point selection in our study focused on nontarget vessel–related events, allowing for a more direct mechanistic assessment of the association between the QFR value and the adverse events. Indeed, our results revealed that in the QFR ≤0.80 group, 71.4% (n=5) of MIs were related to the vessel with QFR ≤0.80. Furthermore, we extended QFR calculation to all eligible nontarget vessels, whereas in previous studies, QFR was calculated for stenoses ≥50% by visual estimate.[20,35] This might be laborious, but in view of new methods like artificial intelligence, routine implementation of this approach might be possible. Alternatively, our data also support a less extreme approach using >30% stenosis as a cutoff for QFR analysis, as results for this subpopulation were similar compared with the overall study results.

Application of QFR

Collectively, the current evidence on QFR in NCLs of patients with STEMI suggests a diagnostic and prognostic incremental benefit over angiography alone. It is noteworthy that the safe and noninvasive QFR procedure is able to predict future adverse events including spontaneous MI and revascularization related to NCLs without the need of additional measures beyond diagnostic angiography and dedicated software, which may be of particular importance to streamline the effective workflow for patients with STEMI. As an important limitation to the widespread use of QFR, it has to be acknowledged that QFR calculation in our retrospective data set was possible in only 56% of patients. However, in previous targeted prospective studies, QFR calculation was possible in 96% to 99% of cases.[17,18]

In this STEMI population, the NPV of QFR >0.80 to preclude the primary end point was high (87.6%), but further prospective research is warranted to investigate whether revascularization of lesions with QFR >0.80 in this setting can safely be deferred. The moderate PPV of QFR ≤0.80 to predict primary end point events may be at least in part related to the low number of lesions with QFR ≤0.80 (n=36, 5.7%). Furthermore, the low sensitivity to detect the primary end point may reflect the low prevalence of higher grade stenoses (mean DS 36.5% [±10.5]). When conducting ROC analysis including only patients with higher degrees of stenosis (>25%, >30%, >40%, >50%), sensitivity incrementally increased, reaching a maximum of 76.2% in stenoses >50% (Table S7, Figure S3). The best QFR cutoff to detect the primary end point was 0.93, which may warrant further investigation in future studies.

Limitations and Strengths

This study trial is a retrospective post hoc analysis and therefore optimal angiographic projections for QFR calculation were not always available. QFR was computable in only 56.1% of patients mostly because of missing isocenter calibration or inadequate angiographic quality, aspects that can be addressed, as shown in previous prospective studies (successful QFR calculation in 96% to 99% of vessels).[17,18] The study population consisted of unbalanced comparator groups, which may weaken the reliability of the statistical analyses, led to wide CIs, and, owing to the low event number in the large QFR >0.80 group, might have biased the overall study results away from the null hypothesis. However, we addressed this by performing all analyses including only patients with >30% stenosis, and results for this lesser skewed were consistent with the overall study results. Furthermore, the study design of a QFR investigation regardless of DS was chosen to investigate the benefit of a truly physiologic assessment without an angiographic/QCA stenosis preselection, which is, to our knowledge, unique in the field of QFR. Lesions left untreated according to an angiographic assessment could consist of more complex lesions less/not amenable to revascularization, which would affect the practical implications of QFR detecting these lesions. As the original study design included no FFR analyses, comparison between QFR and FFR was

not possible and therefore no statement regarding the accuracy of QFR as compared with FFR in the setting of STEMI can be made. However, previous studies addressed this question sufficiently.[20–23] The strengths of our study are the randomized controlled multicenter design, independent event adjudication, QFR analysis blinded for patient outcomes, follow-up duration of 5 years, and the sample size of 617 patients and 946 vessels, representing, to our knowledge, the largest data set published on QFR in patients with STEMI.

CONCLUSIONS

The findings of the present study suggest an incremental diagnostic and prognostic value of QFR for NCL assessment in patients with STEMI undergoing angiography-guided complete revascularization.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S10
Figures S1–S10

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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-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-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-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-Quantiative 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-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-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 (%) 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 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 ±0.09	0.92 ±0.09	0.91 ±0.1	0.85 ±0.11	0.76± 0.15
Diameter stenosis, %	36.5 ±10.5	38.7±9.1	41.1±8.2	47.4±6.6	55.8±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±SD. DS% = diameter stenosis, QFR = Quantitiative 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)

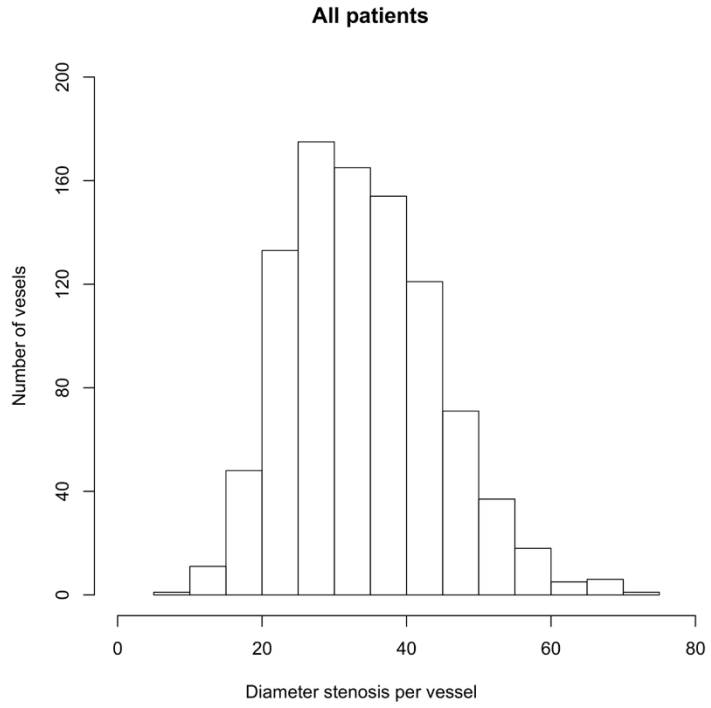
Values are n (%) vessels. Non-TV = non-target vessel, QFR = Quantitative Flow Ratio.

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

QFR and 3D-QCA variable (vessel-level)	DS% ≥50% by 2D-QCA with ischemia (N= 36)	DS% ≥70% by 2D-QCA (N=15)	p-value
QFR	0.84 ±0.13	0.86 ±0.14	0.678
Diameter stenosis, %	42.0 ±9.1	41.7 ±11.6	0.918
Area stenosis, %	57.5 ±11.9	58.6 ±14.1	0.757
Lesion length, mm	22.5 ±15.3	28.1 ±17.4	0.260
Proximal diameter, mm	2.70 ±0.55	2.82 ±0.71	0.496
Minimal lumen diameter, mm	1.66 ±0.37	1.86 ±0.38	0.086
Distal diameter, mm	2.49 ±0.49	2.60 ±0.50	0.486
Reference diameter, mm	2.87 ±0.54	3.21 ±0.47	0.036

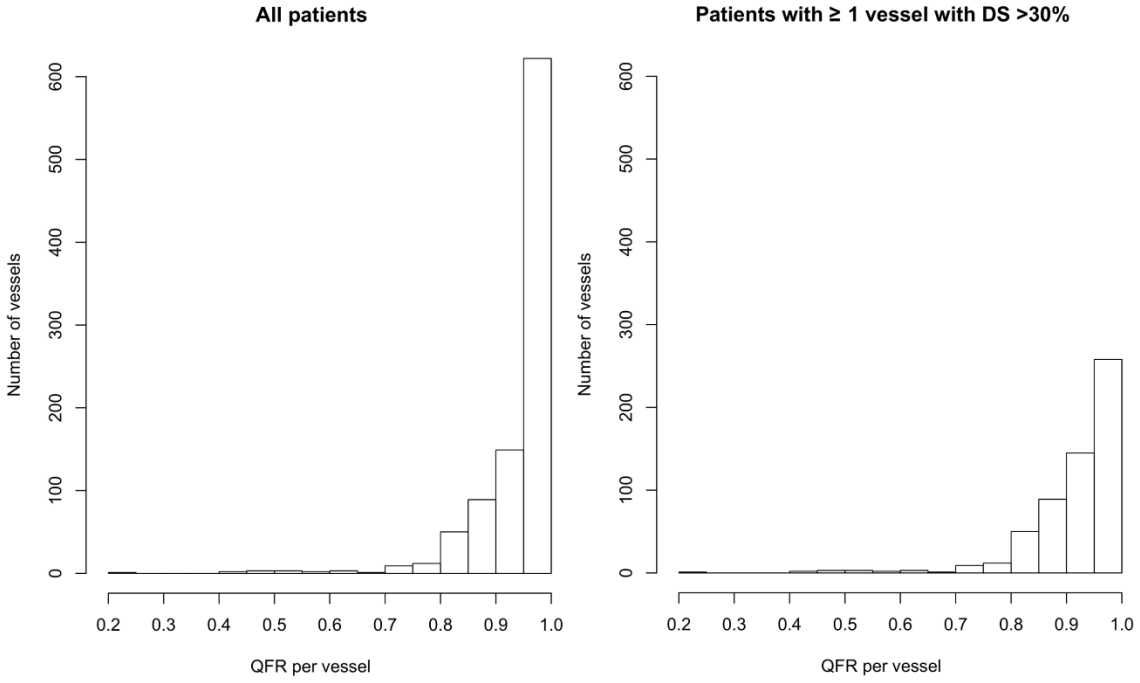
Values are mean±SD. Shown are QFR and 3D-QCA values calculated from the baseline angiography according to DS% ≥50% by 2D-QCA with ischemia or DS% ≥70% by 2D-QCA at the timepoint of the non-TVR event. DS% = diameter stenosis, non-TV = non-target vessel, QFR = Quantitative Flow Ratio, 3D-QCA = 3D-Quantitative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

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



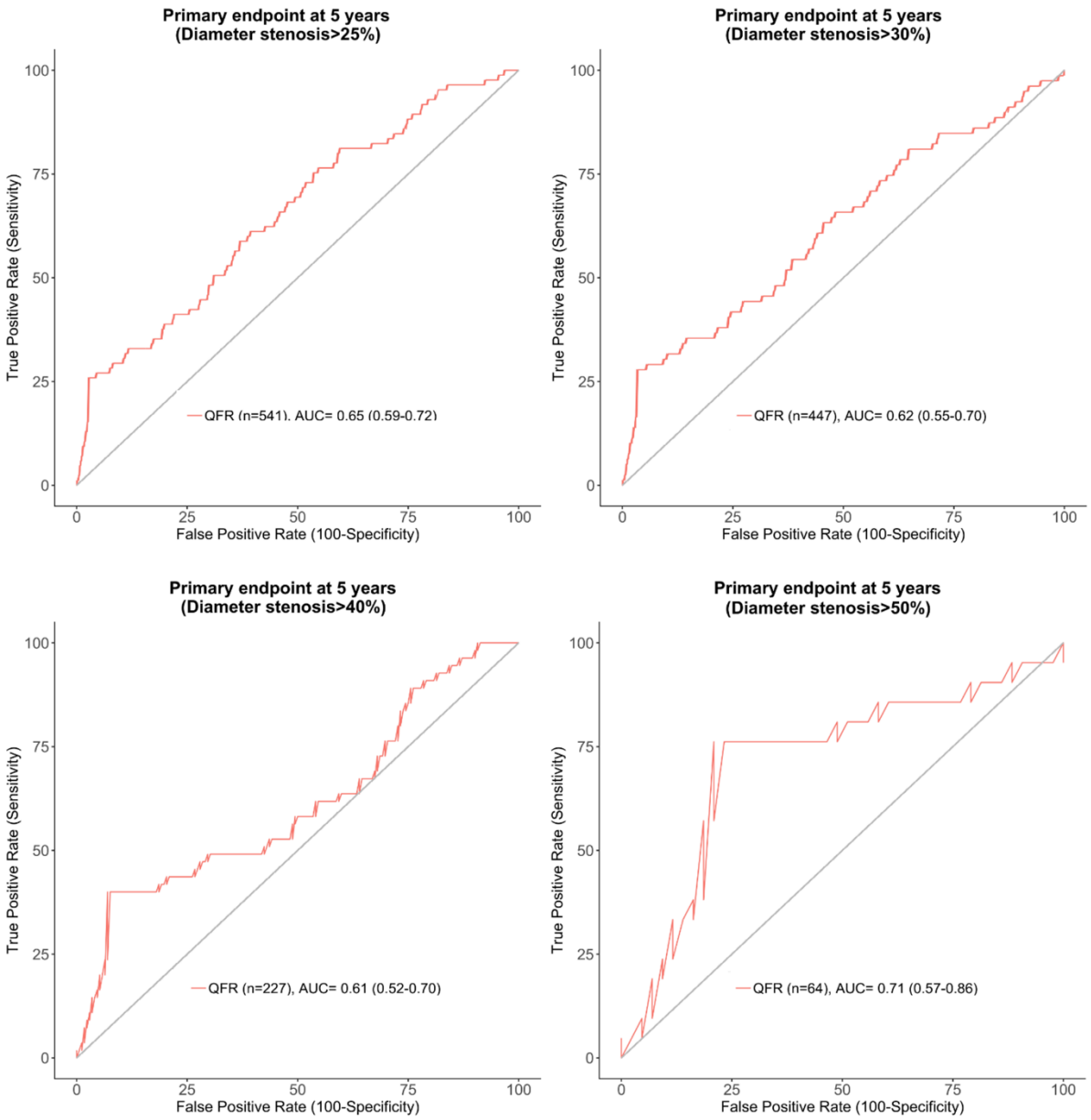
Distribution of DS% on vessel-level (n=946). DS% = diameter stenosis.

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



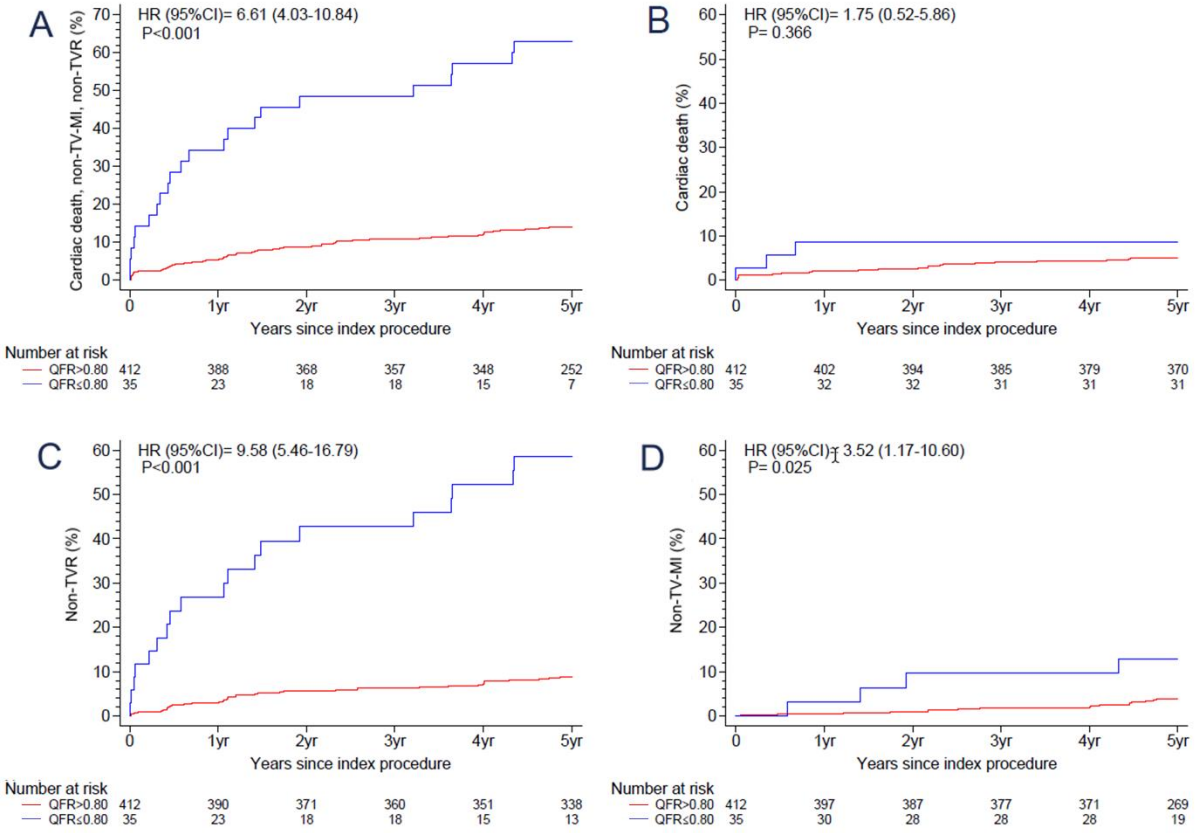
Distribution of QFR values on vessel-level for whole study cohort (n=946) (left) and >30% stenosis (n=578) (right). DS% = diameter stenosis, QFR = Quantitative Flow Ratio.

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



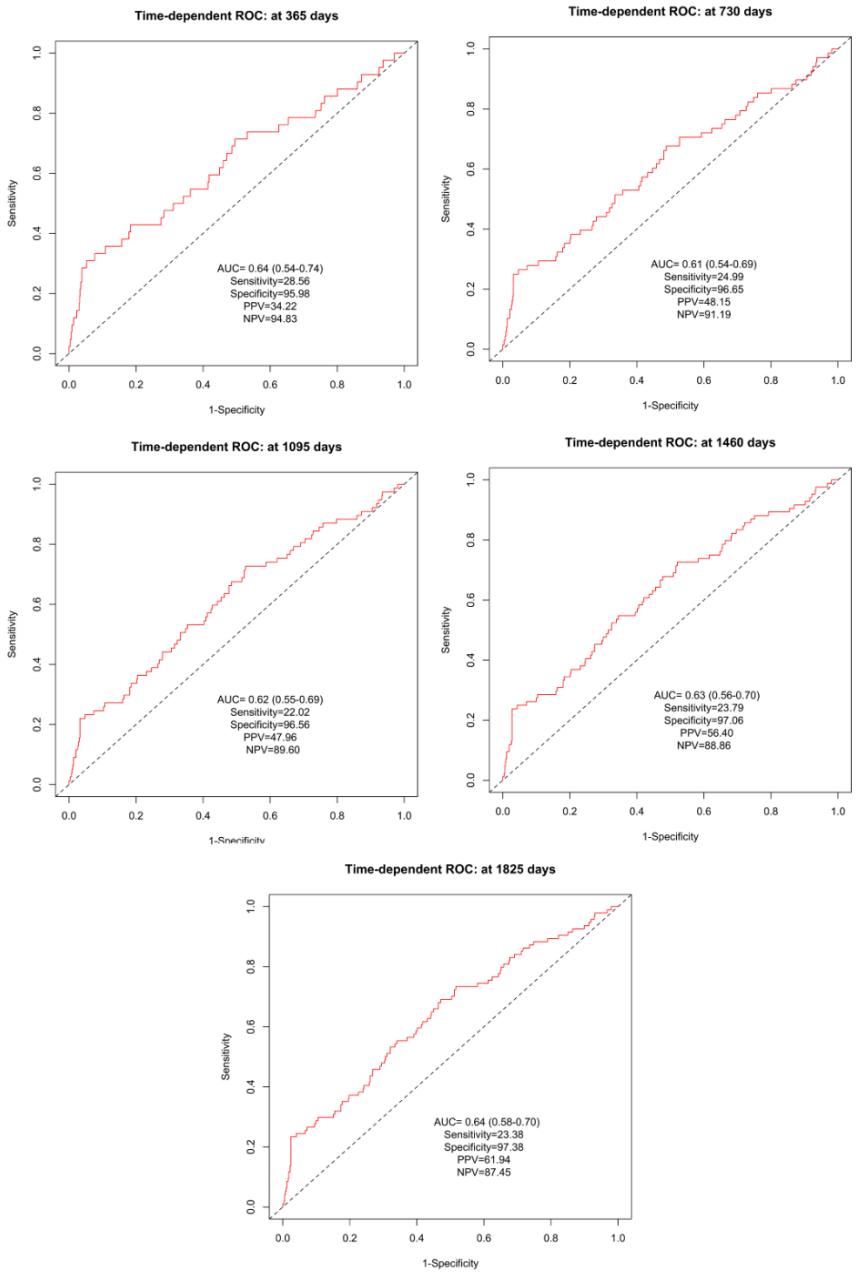
AUC = area under the curve, DS% = diameter stenosis, QFR = Quantitative Flow Ratio.

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



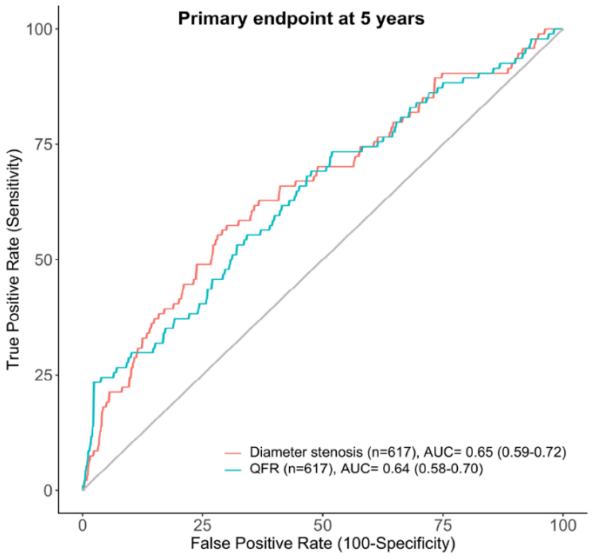
Cumulative incidence curves from Cox proportional hazards models through 5 years for patients with ≥1 DS >30% (n=447). A) primary endpoint: cardiac death, spontaneous non-TV-MI and non-TVR, B) cardiac death, C) non-TVR, D) spontaneous non-TV-MI. CI = confidence interval, HR = hazard ratio, non-TV-MI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

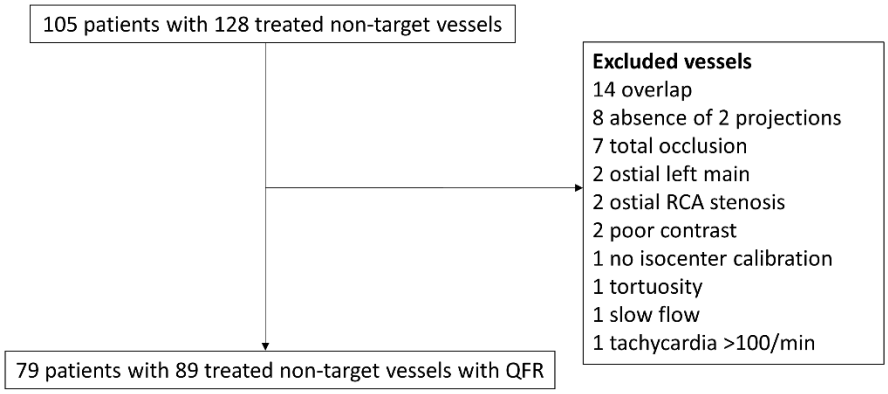
Figure S6. ROC analyses for QFR ≤0.80 and DS ≥50%.



	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

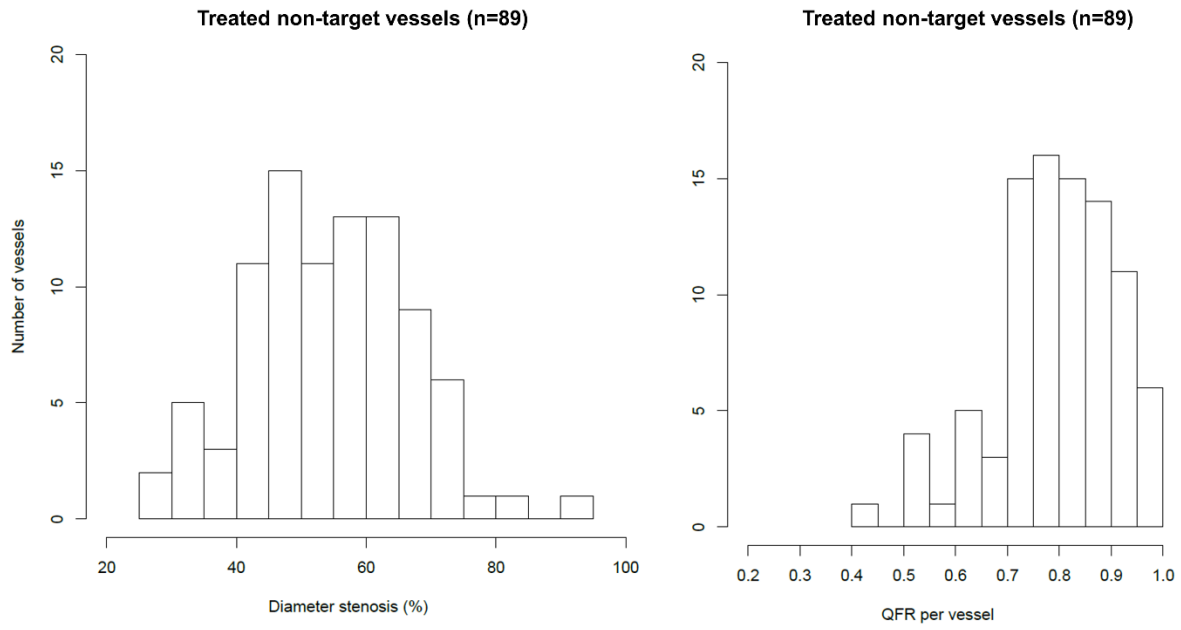
ROC analyses for QFR ≤0.80 vs. DS ≥50% by 3D-QCA predicting the primary endpoint (cardiac death, spontaneous, non-TV-MI, non-TVR) at 5 years. AUC = area under the curve, DS% = diameter stenosis, NPV = negative predictive value, PPV = positive predictive value, QFR = Quantitative Flow Ratio, ROC = receiver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

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



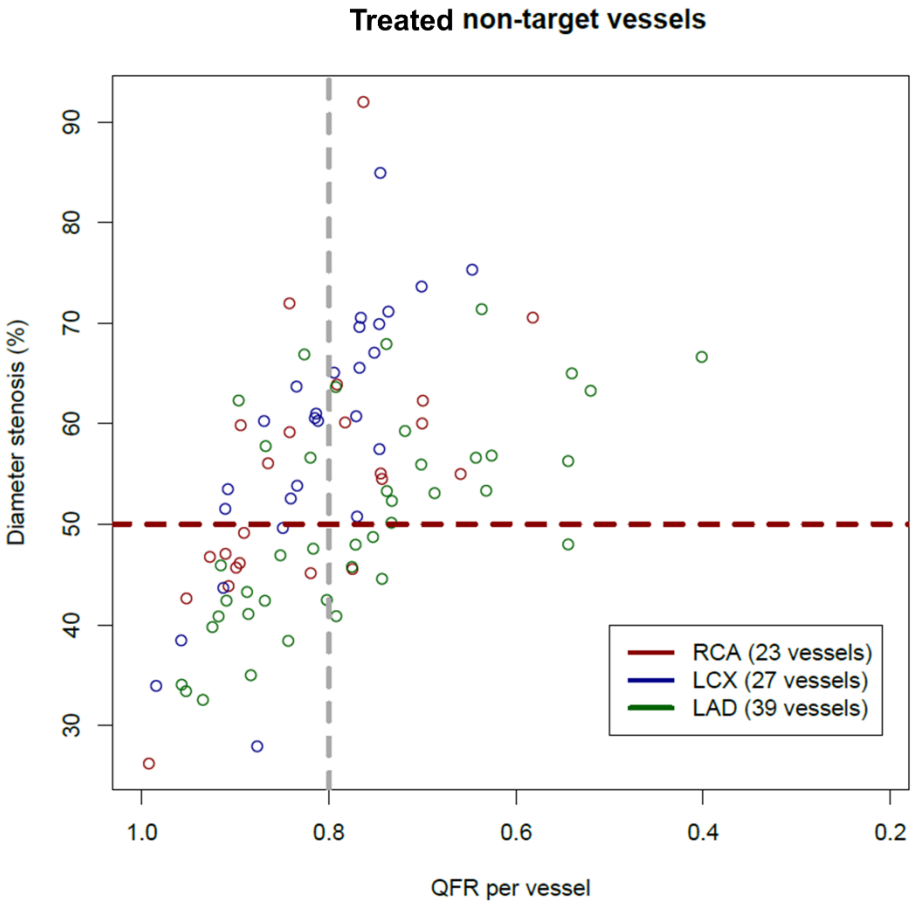
QFR = Quantitative Flow Ratio, RCA = right coronary artery.

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



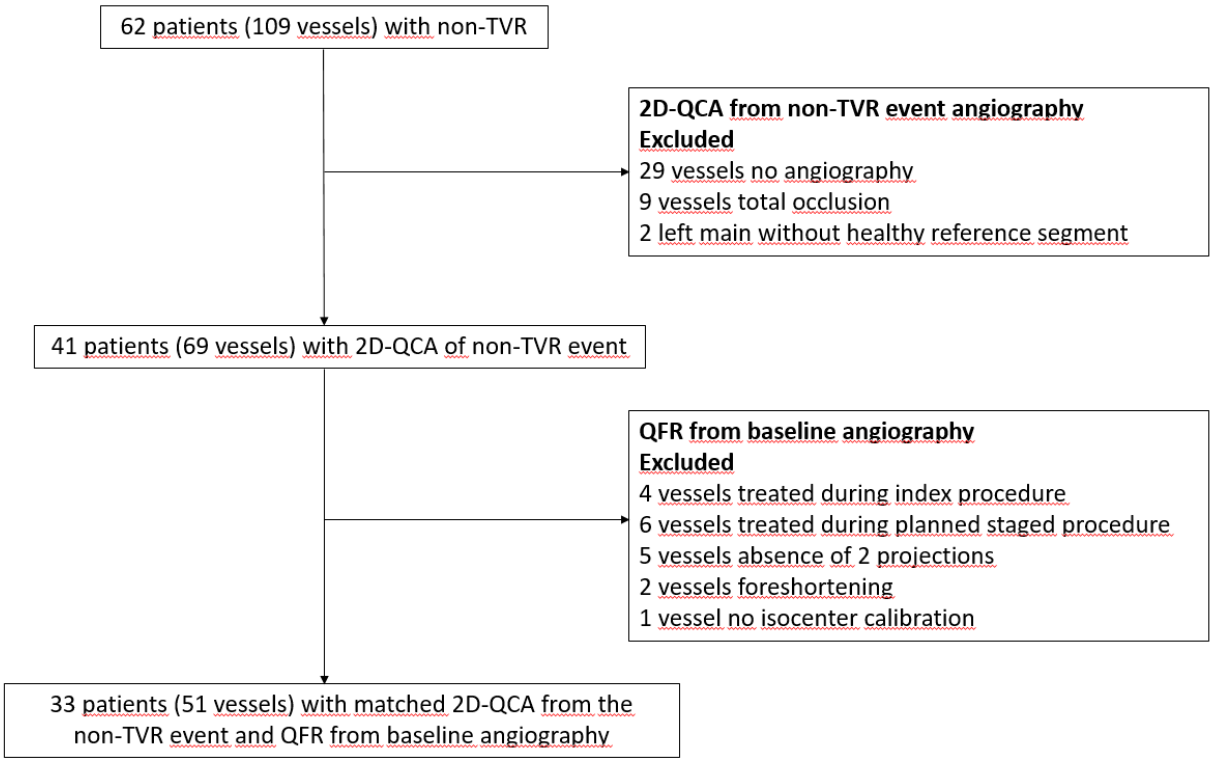
DS% = diameter stenosis. QFR = Quantitative Flow Ratio.

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.