Journal of the American Heart Association

ORIGINAL RESEARCH

Quantitative Flow Ratio to Predict Non–Target-Vessel Events Before Planned Staged Percutaneous Coronary Intervention in Patients With Acute Coronary Syndrome

Sarah Bär, MD*; Raminta Kavaliauskaite, MD*; Tatsuhiko Otsuka, MD; Yasushi Ueki, MD, PhD; Jonas Häner, MD; Jonas Lanz, MD, MSc; Monika Fürholz, MD; Fabien Praz, MD; Lukas Hunziker, MD; George CM Siontis, MD, PhD; Thomas Pilgrim, MD, MSc; Stefan Stortecky, MD, MPH; Sylvain Losdat, PhD; Stephan Windecker, MD; Lorenz Räber, MD, PhD

BACKGROUND: The optimal time point of staged percutaneous coronary intervention (PCI) among patients with acute coronary syndrome (ACS) remains a matter of debate. Quantitative flow ratio (QFR) is a novel noninvasive method to assess the hemodynamic significance of coronary stenoses. We aimed to investigate whether QFR could refine the timing of staged PCI of non-target vessels (non-TVs) on top of clinical judgment for patients with ACS.

METHODS AND RESULTS: For this cohort study, patients with ACS from Bern University Hospital, Switzerland, scheduled to undergo out-of-hospital non-TV staged PCI were eligible. The primary end point was the composite of non-TV myocardial infarction and urgent unplanned non-TV PCI before planned staged PCI. The association between lowest QFR per patient measured in the non-TV (from index angiogram) and the primary end point was assessed using multivariable adjusted Cox proportional hazards regressions with QFR included as linear or penalized spline (nonlinear) term.

QFR was measured in 1093 of 1432 patients with ACS scheduled to undergo non-TV staged PCI. Median time to staged PCI was 28 days. The primary end point occurred in 5% of the patients. In multivariable analysis (1018 patients), there was no independent association between non-TV QFR and the primary end point (hazard ratio, 0.87 [95% CI, 0.69–1.05] per 0.1 increase; *P*=0.125; nonlinear *P*=0.648).

CONCLUSIONS: In selected patients with ACS scheduled to undergo staged PCI at a median of 4 weeks after index PCI, QFR did not emerge as an independent predictor of non-TV events before planned staged PCI. Thus, this study does not provide conceptual evidence that QFR is helpful to refine the timing of staged PCI on top of clinical judgment.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02241291.

Key Words: acute coronary syndrome ■ multivessel disease ■ quantitative flow ratio ■ staged percutaneous coronary intervention

Correspondence to: Lorenz Räber, MD, PhD, Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, 3010 Bern, Switzerland. Email: lorenz.raeber@insel.ch

*S. Bär and R. Kavaliauskaite contributed equally and are co-first authors.

This manuscript was sent to Saket Girotra, MD, SM, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Preprint posted on July 27, 2023. doi: https://doi.org/10.1101/2023.07.24.23292979.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.031847

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This was the first study to investigate the association between non–target-vessel (non-TV) quantitative flow ratio (QFR) and non-TV events occurring before planned staged percutaneous coronary intervention (PCI) among patients with acute coronary syndrome with multivessel disease to derive first conceptual knowledge whether QFR could be helpful to optimize the timing of staged PCI on top of clinical judgment.
- Among 1093 patients with acute coronary syndrome and 1262 non-TVs scheduled to undergo out-of-hospital staged PCI within a median of 28 days from index PCI, QFR did not emerge as an independent predictor of non-TV events occurring prior to the planned staged PCI.

What Are the Clinical Implications?

- Among patients with acute coronary syndrome in whom, according to the operator's judgment, it is feasible to perform out-of-hospital staged PCI within a median of 1 month from the index PCI, this study does not provide conceptual evidence that QFR could be helpful to optimize the timing of the staged PCI (ie, to schedule staged PCI earlier in case of lower QFR) on top of clinical judgment.

Nonstandard Abbreviations and Acronyms

COMPARE-ACUTE	Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD
COMPLETE	Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI
DS	diameter stenosis
FFR	fractional flow reserve
MVD	multivessel disease
non-TV	non–target-vessel
QCA	quantitative coronary angiography
QFR	quantitative flow ratio
RCT SMILE	Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention

Multivessel disease (MVD) among patients with acute coronary syndrome (ACS) is present in up to 50% of patients with both ST-segment–elevation myocardial infarction (STEMI) and non–ST-segment–elevation acute coronary syndrome (NSTE-ACS)[1] and is associated with impaired prognosis.[2] Complete revascularization results in improved clinical outcomes compared with culprit-lesion-only revascularization in STEMI,[3–7] and indirect evidence supports the same for NSTE-ACS.[8,9] Accordingly, complete revascularization obtains a class I (level of evidence A) recommendation for STEMI and a class IIa (level of evidence C) for NSTE-ACS in the current European Society of Cardiology guidelines.[1] However, the optimal time point of non–target-vessel (non-TV) staged percutaneous coronary intervention (PCI) remains a matter of ongoing debate.[1,10] Coronary hemodynamics as assessed by fractional flow reserve (FFR) of medically treated nonculprit lesions have been reported to be inversely related to an increased risk of subsequent events among patients presenting with ACS.[11,12] However, it remains unknown whether coronary hemodynamics are useful to determine the optimal time point of staged PCI in patients with ACS and MVD.

FFR represents the current gold standard for the hemodynamic assessment of coronary lesions.[13] Notwithstanding, FFR is infrequently used in patients with ACS owing to cost considerations, the invasive nature of the investigation, the need for vasodilator administration, additional time required to complete the study,[14] and concerns about its accuracy in the acute setting, especially in STEMI.[15] Quantitative flow ratio (QFR) is a novel, noninvasive, hyperemia-free method to calculate FFR derived from biplane coronary angiography using 3-dimensional quantitative coronary analysis (QCA) and Thrombolysis in Myocardial Infarction frame counting.[16–18] Among patients with chronic coronary syndrome, a QFR-based revascularization strategy using 0.80 as the cutoff for ischemia (and treatment), has shown to improve 1-year clinical outcomes as compared with an angiography-guided approach.[19] In ACS, good correlation with FFR,[20] predictive ability for clinical events,[20,21] as well as good agreement between acute QFR compared with staged QFR have been reported.[20,22,23]

To assess whether QFR is able to refine the timing of staged PCI on top of clinical judgment in patients with ACS and MVD, we investigated the association between QFR of non-target vessels (non-TV) planned for staged PCI and non-TV events before planned staged PCI within the large, prospective Cardiobase Bern PCI registry.

METHODS

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

Patient Population

The Cardiobase Bern PCI registry (NCT02241291) is a prospective, single-center, observational registry of all consecutive patients undergoing PCI at Bern University Hospital, Switzerland, established in 2009. There are no exclusion criteria other than inability or unwillingness to provide written informed consent. Baseline procedural and clinical outcomes are assessed at hospital discharge and 1 year after PCI by an independent clinical events committee. The registry complies with the Declaration of Helsinki and is approved by the institutional ethics committee.

Specific clinical inclusion and exclusion criteria for this investigation have been reported previously.[24] In brief, all patients with ACS included in the Cardiobase Bern PCI registry scheduled to undergo single staged PCI between 2009 and 2017 were eligible for this analysis. According to the institutional protocol, patients were mostly scheduled between 2 and 8 weeks from index PCI; however, up to 6 months was allowed.[24] Patients with in-hospital staged PCI were excluded, as reported previously,[24] since they usually represent different subsets of patients with either critical lesions requiring urgent intervention or patients who are not willing to return for staged PCI procedures (ie, advanced age or living far away). Patients with cardiogenic shock, multiple staged PCIs, staged cardiac surgery, or missing information on staged PCI were also excluded.[24]

QFR and 3-Dimensional QCA Analysis

QFR was assessed post hoc and had no role in patient management. QFR was assessed using the index procedure angiogram in the non-TVs planned for staged PCI by experienced and certified analysts blinded for patient outcomes at the Corelab of Bern University Hospital, Switzerland, using a dedicated software (QAngio XA 3D version 1.2; Medis Medical Imaging Systems, Leiden, the Netherlands). QFR-specific exclusion criteria were absence of 2 projections with angle ≥25° apart, lack of isocenter calibration, substantial vessel overlap or vessel foreshortening, severe tortuosity, poor contrast, ostial left main or right coronary artery stenosis, slow flow, tachycardia >100/min, and arrhythmias (ie, atrial fibrillation, atrial flutter, idioventricular rhythm, [nonsustained] ventricular tachycardia). Contrast QFR using frame counting[25] was measured from the ostium to a distal landmark at a minimum of 1.5 mm distal vessel reference diameter, as reported previously.[21,22] The conventional QFR cutoff of ≤0.80 was used to detect significant ischemia.[16–18] Lesion complexity was assessed according to the American College of Cardiology/American Heart Association (ACC/AHA) criteria.[26] Two of the authors (S.B. and R.K.) had full access to all data and take responsibility for its integrity and the data analysis.

Treatment

PCI was performed according to the recommendations and guidelines[27–30] valid at the time of presentation. Briefly, unfractionated heparin (initial bolus of 70–100 IU/kg body weight) was administrated during the procedure. Dual antiplatelet therapy consisting of acetylsalicylic acid and a potent $P2Y_{12}$ inhibitor was initiated before or immediately after the index procedure. The recommended dual antiplatelet therapy duration was usually 12 months from the index treatment but modified among patients taking oral anticoagulants or at high bleeding risk. Drug-eluting stents were routinely used. From 2009 onward, angiography-guided complete revascularization was performed in non-TVs of patients with ACS with visual angiographic stenosis ≥50% if deemed technically feasible. Staged procedures were usually performed between 2 and 8 weeks following index PCI according to institutional practice, but the exact timing was left to the operators' discretion.[24] It cannot be excluded that patient- or lesion-related factors may have played a role in the scheduling. Therefore, this study aimed at investigating the potential value of QFR on top of clinical judgment.

Patient Follow-Up

Patients were systematically and prospectively followed throughout 1 year to assess clinical outcomes and status of medical treatment. A health questionnaire was sent to all living patients with questions on rehospitalization and adverse events, followed by telephone contact in case of missing response. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. For patients who underwent treatment for adverse events at other medical institutions, external medical records, discharge letters, and coronary angiography documentation were systematically collected and reviewed.

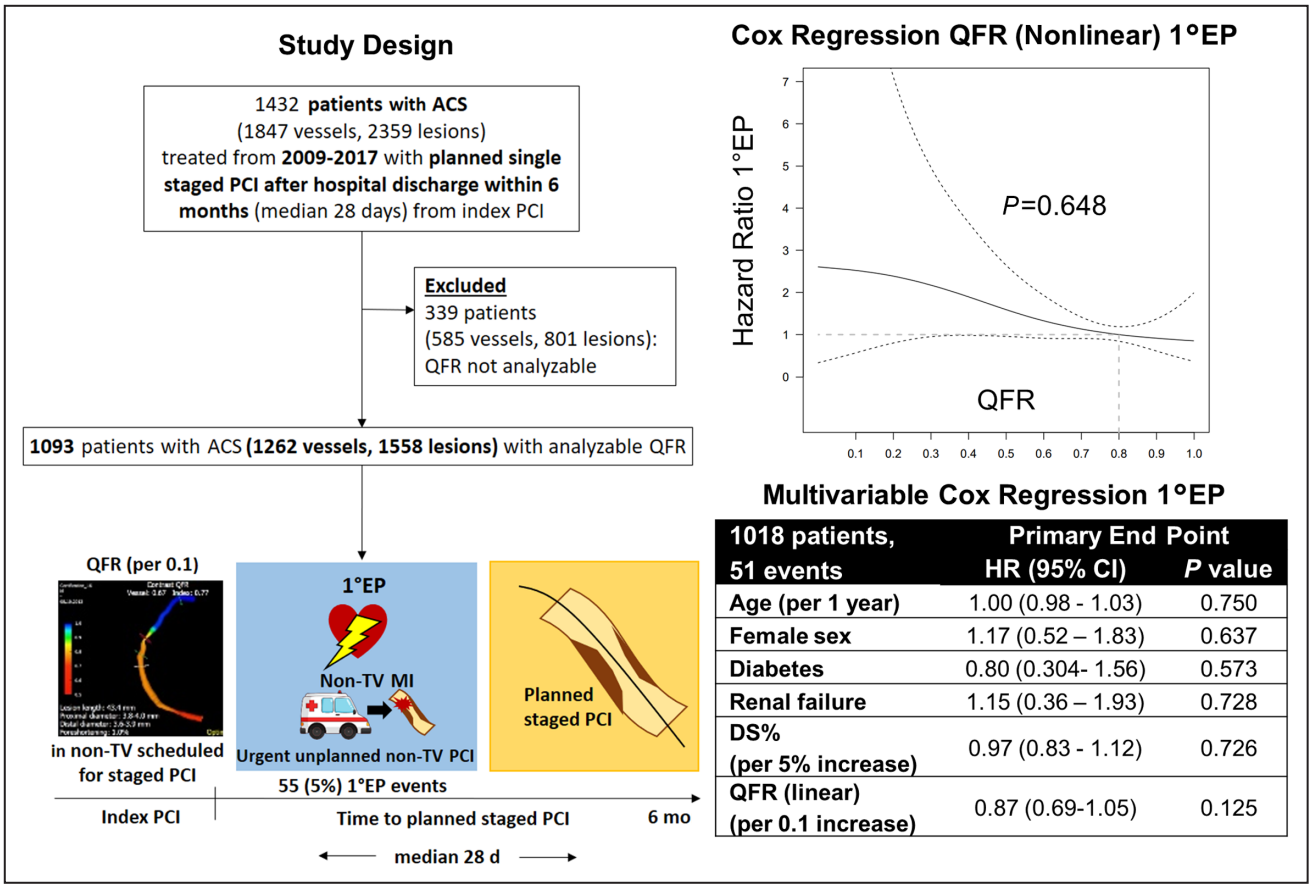

Figure 1. Study design and key findings.
Study design (left) and primary end point results (right). For nonlinear QFR, hazard ratios were calculated using the reference hazard corresponding to QFR=0.80 (gray dashed line) from a Cox proportional hazards model with penalized splines. 1°EP indicates primary end point; ACS, acute coronary syndrome; DS, diameter stenosis; HR, hazard ratio; non-TV MI, non–target-vessel myocardial infarction; non-TV PCI, non–target-vessel percutaneous coronary intervention; PCI, percutaneous coronary intervention; and QFR, quantitative flow ratio.

Primary Analysis and End Point Definition

The primary analysis was an independent predictor analysis of the association between the lowest QFR per patient (per 0.1 increase) and the composite of non-TV myocardial infarction (MI) and urgent unplanned non-TV PCI, occurring before the planned staged PCI (Figure 1). MI was defined according to a modified historical definition.[31] Non-TV MI was defined as MI attributed to nonculprit vessels at baseline. Urgent unplanned non-TV PCI was defined as urgent PCI in non-TVs performed earlier than planned due to ≥1 of the following: (1) recurrent MI,[31] (2) unstable angina,[28] (3) worsening congestive heart failure, (4) cardiogenic shock, or (5) symptomatic arrhythmia refractory to medication. This event had to be clearly distinguishable from the staged PCI procedure scheduled at index presentation.[24] Clinical events were adjudicated by a clinical event committee consisting of 2 cardiologists (and a third one in case of disagreement) with use of original source documents.

QFR was assessed linearly, and, based on previous evidence of an inverse, nonlinear relationship between FFR and non-TV events plateauing at FFR 0.60,[12] an additional analysis with a nonlinear term for QFR was performed. Other covariates were added on the basis of clinical reasoning and consisted of age (per 1-year increase), female sex, renal failure (ie, glomerular filtration rate <60 mL/min), diabetes, and 3-dimensional QCA diameter stenosis (DS%) (per 5% increase). We also assessed these associations separately for the primary end point components, except for nonlinear QFR, owing to the limited number of events. In addition, we planned 2 sensitivity analyses: (1) patient level, using the same model as described, but with DS% replaced by ACC/AHA lesion complexity, and (2) vessel level, using the following QFR and angiographic/3-dimensional QCA characteristics: QFR per vessel (per 0.1 increase), 3-dimensional QCA DS% (per 5% increase), minimum lumen diameter (per 1-mm increase), residual QFR (per 0.1 increase) (ie, the residual QFR

after virtual PCI predicted by an inherent algorithm in the QAngio XA 1.2 software), and ACC/AHA lesion complexity. As exploratory analyses, we assessed the primary analysis model with 25% increments of DS% (more aligned with clinical practice) and QFR using the common ischemic threshold 0.80[16–18] as well as 0.60 on the basis of previous evidence on FFR.[12]

Statistical Analysis

All analyses were performed using Stata 16 (StataCorp, College Station, TX) and R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean±SD, and categorical variables are expressed as counts with percentages. For the primary end point, we fitted univariable and multivariable Cox proportional hazards regressions including the variables as indicated above. We also fitted lowest QFR per patient as nonlinear using penalized smoothing splines with 2 degrees of freedom. The models were run using the survival R package. For the vessel-level analysis we used mixed-effects Cox proportional hazards models including patient identity as a random factor to correct for multiple vessels per patient using the coxme R package.[32,33] Owing to the model's higher complexity, we did not use a nonlinear term for QFR. For all multivariable models, we checked for the presence of multicollinearity by calculating the variance inflation factors of all independent variables and confirmed that all variance inflation factors were <2. For all Cox models, we also checked the proportional hazard assumption and can confirm that it was met for all reported end points.

Patients were censored at the time of the primary end point event, or at the time of the planned staged PCI, whichever occurred first. For vessel-level analysis, the culprit vessel of a non-TV MI was attributed a non-TV MI event and an urgent unplanned non-TV PCI. If other vessels were treated during this same procedure, these were not adjudicated to have an event, since this treatment is likely to have been driven by logistical reasons; that is, if a patient presents for another urgent invasive procedure, all remaining vessels are usually treated, even though they may not be responsible for the acute presentation. For urgent unplanned PCI, if no clear culprit vessel could be identified from source data, all vessels treated during this procedure were adjudicated as an urgent unplanned PCI event. Significance tests were 2-tailed, with a significance level set to 0.05.

RESULTS

Patient Population

Between January 2009 and December 2017, 8657 patients with ACS (STEMI and NSTE-ACS) were consecutively enrolled in the Cardiobase Bern PCI Registry. Staged PCI was scheduled for 1764 patients, of whom 1432 patients (1702 vessels, 2197 lesions) fulfilled the clinical eligibility criteria[24] and were evaluated for QFR measurements. None were lost to follow-up, and only 1 death occurred during a planned staged PCI. A total of 1262 vessels with 1558 lesions from 1093 patients were analyzable by QFR. The most frequent exclusion criteria were absence of 2 appropriate projections, missing angiographic data, or missing isocenter calibration (Figure 2).

Baseline clinical characteristics and medical treatment at hospital discharge are summarized in Table 1. There were no significant differences in clinical characteristics between patients with QFR analysis available (N=1093) and those fulfilling the clinical eligibility criteria (N=1432)[24] (Table S1). Mean patient age was 65 years, 78% were male, 17% had diabetes, 56% of patients presented with STEMI, and 44% presented with NSTE-ACS. The median duration to planned staged PCI was 28 (interquartile range [IQR], 28–42) days, similar as for the total cohort.[24] Procedural characteristics of planned staged PCI and urgent unplanned non-TV PCI are provided in Table S2. Baseline characteristics of patients with versus without a primary end point event were comparable (Table S3). The indication for urgent premature non-TV PCI was most frequently unstable angina (n=31, 60%), followed by MI (n=9, 17%). In 13 (n=7) it was related to congestive heart failure, and only in a minority to refractory arrhythmia (n=3 [6%]) or cardiogenic shock (n=2 [4%]). Total clinical events throughout 1 year, premature events occurring before planned staged PCI for patients scheduled <4 weeks versus ≥4 weeks from index PCI, and treatment adherence at 1 year of this cohort have been reported previously.[24]

QFR and 3-Dimensional QCA Characteristics

Of 1262 vessels analyzed by QFR, 41.1% were left anterior descending (n=519), 30.6% left circumflex (n=386), 27.1% right coronary artery (n=342), and 1.2% (n=15) left main vessels. Mean QFR per patient was QFR 0.73±0.17, mean DS% 54.8±11.2%, and ACC/AHA angiographic lesion complexity (lesion level) was most frequently C, followed by B1 (Table 2; Figure 3).

Primary and Secondary Analyses

A total of 55 (5.0%) primary end point events had occurred within a median of 11 (IQR, 5–16) days before planned staged PCI. In multivariable analysis (1018 patients, 51 events), there was no independent association between linear or nonlinear QFR and the primary end point (multivariable HR, 0.87 [95% CI, 0.69–1.05]; *P*=0.125; QFR nonlinear *P*=0.648) (Figure 1; Table 3).

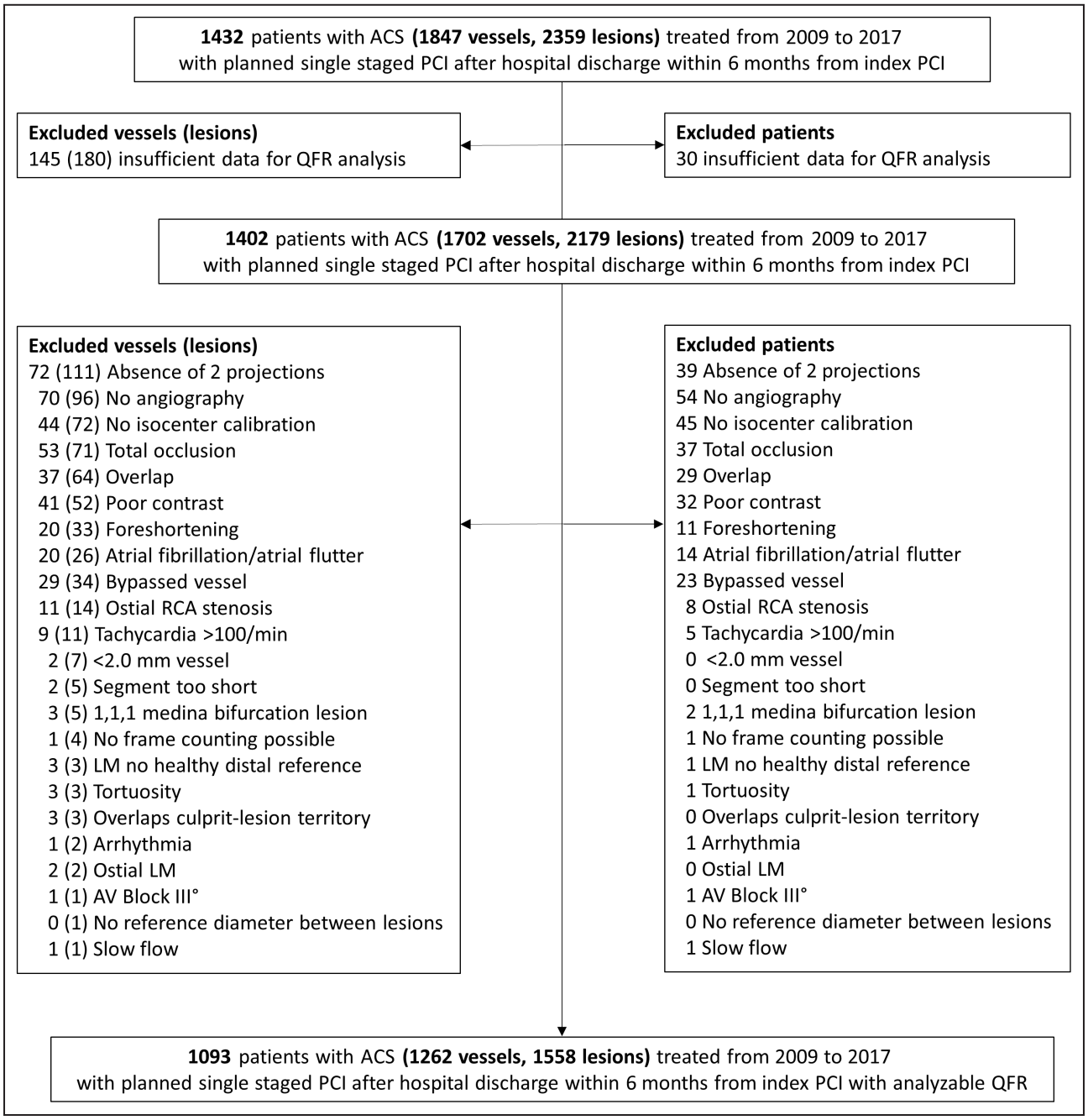

Figure 2. Flowchart.
ACS indicates acute coronary syndrome; LM, left main; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; and RCA, right coronary artery.

Overall, none of the variables in the model showed a significant association with the primary end point composite (Table 3). The sensitivity analysis on patient level using ACC/AHA lesion complexity instead of DS% showed consistent results (multivariable HR, 0.90 [95% CI, 0.74–1.05]; *P*=0.173; QFR nonlinear *P*=0.603) (Table 3). Also, in the sensitivity analysis on vessel level, there was no independent association between QFR and the primary end point (multivariable HR, 0.84 [95% CI, 0.65–1.04]; *P*=0.083) (Table 3). Cumulative event curves of the primary end point components and planned staged PCI are shown in Figure 4.

With respect to the individual primary end point components, there was a significant univariable association between linear QFR (per 0.1) and non-TV MI (HR, 0.69 [95% CI, 0.52–0.91]; *P*=0.008), but not with

Table 1. Patient Characteristics

	Patients (N=1093)
Age, y	65±11
Female sex	238 (22)
BMI, kg/m^2	27.3±4.2
Smoker	403 (37)
Hypercholesterolemia	564 (52)
Hypertension	633 (58)
Diabetes	188 (17)
Family history of CAD	267 (24)
Previous MI	62 (5.7)
Previous PCI	92 (8.4)
Previous CABG	12 (1.1)
Left ventricular function, %	51±11
Indication	
Unstable angina	45 (4.1)
NSTEMI	440 (40)
STEMI	608 (56)
Congestive heart failure	
Killip I	948 (87)
Killip II	113 (10)
Killip III	32 (2.9)
Renal failure (GFR <60 mL/min)	172 (16)
Renal failure requiring dialysis	15 (1.4)
Peripheral arterial disease	42 (3.8)
History of stroke or TIA	46 (4.2)
History of gastrointestinal bleeding	13 (1.2)
History of malignancy	93 (8.5)
COPD	57 (5.2)
Anemia*	155 (14)
Days from index to planned staged PCI	28 (28–42)
Medication at hospital discharge	
Aspirin	1082 (99)
Potent P2Y$_{12}$ inhibitor (prasugrel or ticagrelor)	851 (78)
Clopidogrel	240 (22)
Any dual antiplatelet therapy	1081 (99)
Oral anticoagulation (vitamin K antagonists or NOAC)	60 (5.5)
Statin	1043 (95)

Values are n (%), mean±SD, or median (interquartile range). ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MI, myocardial infarction; NOAC, novel oral anticoagulant; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIA, transitory ischemic attack.

*Anemia was defined as hemoglobin <130 g/L in men and <120 g/L in women.

urgent premature non-TV PCI (HR, 0.92 [95% CI, 0.79–1.07]; *P*=0.299) (Table 4). Owing to the limited sample size, nonlinear QFR terms and multivariable associations were not assessed.

Table 2. QFR and 3-Dimensional QCA

	Patients (N=1093)	Vessels (N=1262)
Diameter stenosis, %	54.8±11.2	53.6±11.5
Area stenosis, %	70.4±12.6	69.0±13.4
Lesion length, mm	26.1±12.1	25.0±12.0
Proximal diameter, mm	2.86±0.59	2.82±0.59
Distal diameter, mm	2.45±0.57	2.47±0.57
Minimum lumen diameter, mm	1.36±0.57	1.34±0.56
QFR	0.73±0.17	0.75±0.17

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

Exploratory Analyses

As exploratory analyses, we assessed univariable associations for DS% in more clinically applicable increments, that is, 25% and binary QFR, using the common ischemic threshold of 0.80 and 0.60 as derived from an FFR study on the topic.[12] These results are consistent with the main analysis and are shown in Table S4 and Figure S1.

DISCUSSION

In this cohort study of patients with ACS and MVD scheduled to undergo out-of-hospital staged PCI within a median of 28 (IQR, 28–42) days from the index presentation, non-TV QFR of vessels scheduled for staged PCI using the index procedure angiogram did not show an independent association with non-TV events occurring before the planned staged PCI. Therefore, this study does not provide conceptual evidence for QFR being able to optimize the timing of staged PCI (ie, to plan earlier in case of lower QFR) on top of clinical judgment. These results apply to patients scheduled on average 4 weeks after the index procedure and mean QFR value of 0.73 in the untreated nonculprit vessel.

Current Recommendations on Nonculprit Lesion Revascularization in ACS

Current European Society of Cardiology guidelines on the management of STEMI[1] provide a class I (level of evidence A) recommendation for nonculprit-lesion revascularization during the index procedure or within 45 days from the index PCI, based on the treatment strategies in the randomized controlled trials (RCTs) that compared culprit-lesion-only versus complete revascularization.[3–7] In a pivotal subanalysis of one of these trials, that is, the COMPLETE (Complete Versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease After Early PCI for STEMI) trial,[7] the benefit of complete revascularization over culprit-lesion-only PCI was independent of whether staged PCI was

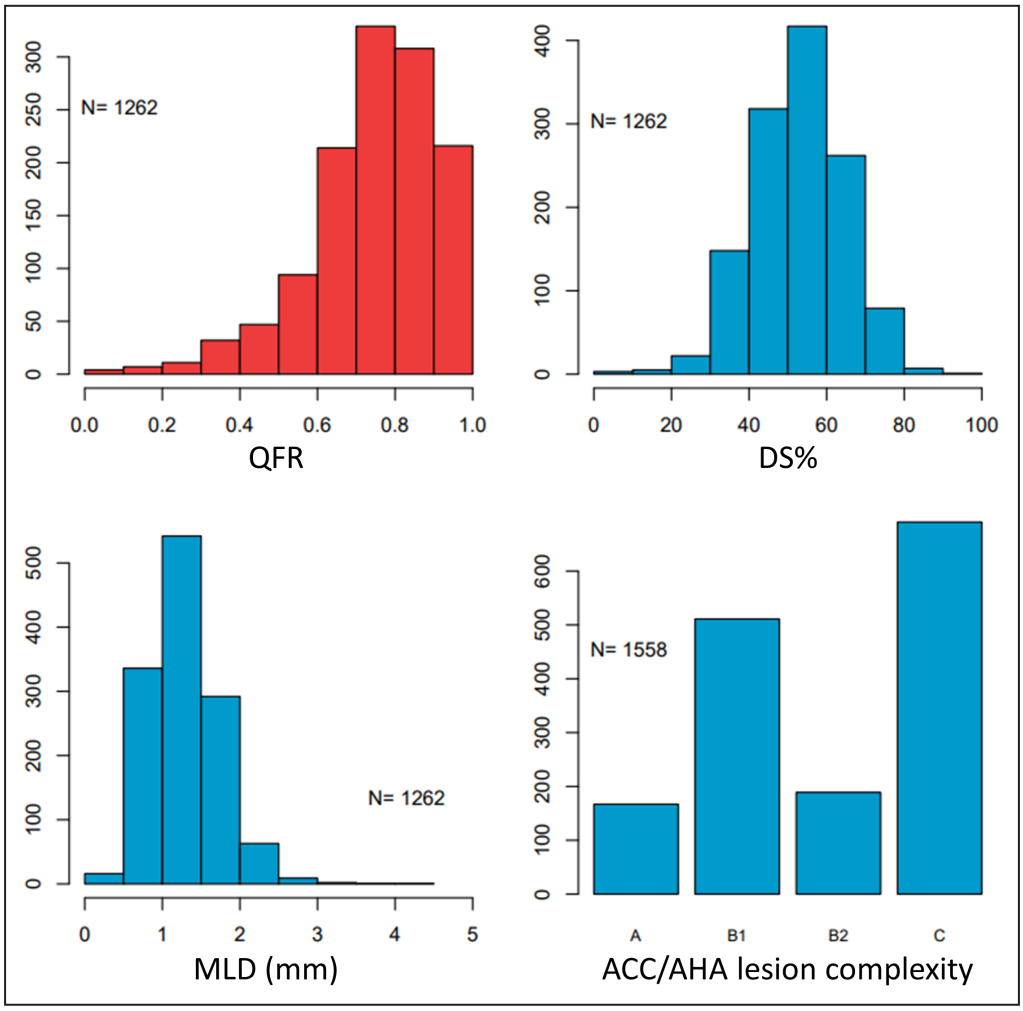

Figure 3. QFR and 3-dimensional QCA characteristics.
ACC/AHA indicates American College of Cardiology/American Heart Association; DS, diameter stenosis; MLD, minimum lumen diameter; QCA, quantitative coronary angiography; and QFR, quantitative flow ratio.

performed during the index hospitalization (median, 1 [IQR, 1–3] days) or after hospital discharge within maximum 45 days (median, 23 [IQR, 12.5–33.5] days).[10] In line, with this investigation, we had observed similar outcomes with early (ie, <4 weeks from index PCI) versus late (≥4 weeks from index PCI) staged PCI[24] in the same study population as reported here.[24]

For NSTE-ACS, a class IIa (level of evidence C) recommendation is given for immediate complete revascularization[1] based on the RCT SMILE[34] (Impact of Different Treatment in Multivessel Non ST Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention) and a meta-analysis,[9] where immediate complete revascularization was superior as compared with staged PCI.[28] Further, functional evaluation of the non-TV may be considered according to a IIb (level of evidence B) recommendation, even though the hemodynamic significance is not mentioned to be directly considered in the timing of staged PCI. Of note, in NSTE-ACS the superiority of complete revascularization versus culprit-lesion-only PCI is less established as compared with STEMI, and the evidence consists of meta-analyses of post hoc randomized or observational studies[8,9] as well as 1 prospective RCT on an elderly population with a median age of 80 years including 65% patients with NSTEMI.[35]

In the total cohort of our current study,[24] subgroup analysis on STEMI versus NSTE-ACS had not indicated a differential effect of staged PCI within ≤4 versus >4 weeks from the index PCI in terms of premature events before staged PCI.[24] Accordingly, and owing to the limited sample size, we had not assessed the association between QFR and premature non-TV events for STEMI versus NSTE-ACS.

Two recent RCTs on ACS patients with MVD showed noninferiority of immediate complete revascularization as compared with staged PCI (within 19–45 days[36] or in-hospital up to 42 days from index PCI[37]) including

Table 3. Cox Regressions Primary End Point

Primary analysis	N patients (N events)	Univariable		N patients (N events)	Multivariable	
		HR (95% CI)	*P* value		HR (95% CI)	*P* value
Age (per 1-y increase)	1093 (55)	1.01 (0.99–1.03)	0.419	1018 (51)	1.00 (0.98–1.03)	0.750
Female sex	1093 (55)	1.12 (0.60–2.08)	0.723	1018 (51)	1.17 (0.52–1.83)	0.637
Diabetes	1092 (55)	0.79 (0.37–1.67)	0.536	1018 (51)	0.80 (0.04–1.56)	0.573
Renal failure	1018 (51)	1.35 (0.69–2.64)	0.373	1018 (51)	1.15 (0.36–1.94)	0.728
DS% (per 5% increase)	1093 (55)	1.01 (0.90–1.13)	0.925	1018 (51)	0.97 (0.83–1.12)	0.726
QFR (per 0.1 increase)	1093 (55)	0.90 (0.78–1.04)	0.141	1018 (51)	0.87 (0.69–1.05)	0.125
Sensitivity analysis 1	**N Patients (N Events)**	**Univariable**		**N Patients (N Events)**	**Multivariable**	
		HR (95% CI)	*P* value		HR (95% CI)	*P* value
Age (per 1-y increase)	1093 (55)	1.01 (0.99–1.03)	0.419	1018 (51)	1.00 (0.98–1.03)	0.774
Female sex	1093 (55)	1.12 (0.60–2.08)	0.723	1018 (51)	1.17 (0.51–1.82)	0.642
Diabetes	1092 (55)	0.79 (0.37–1.67)	0.536	1018 (51)	0.81 (0.05–1.57)	0.588
Renal failure	1018 (51)	1.35 (0.69–2.64)	0.373	1018 (51)	1.16 (0.37–1.95)	0.710
Lesion complexity (B2 or C vs A or B1)	1093 (55)	1.17 (0.68–2.01)	0.577	1018 (51)	1.10 (0.48–1.73)	0.764
QFR (per 0.1 increase)	1093 (55)	0.90 (0.78–1.04)	0.141	1018 (51)	0.90 (0.74–1.05)	0.173
Sensitivity analysis 2	**N vessels (N events)**	**Univariable**		**N vessels (N events)**	**Multivariable**	
		HR (95% CI)	*P* value		HR (95% CI)	*P* value
QFR (per 0.1 increase)	1262 (59)	0.84 (0.61–1.14)	0.265	1262 (59)	0.83 (0.52–1.32)	0.422
DS% (per 5% increase)	1262 (59)	1.01 (0.84–1.22)	0.885	1262 (59)	0.82 (0.58–1.16)	0.257
MLD (per 1-mm increase)	1262 (59)	0.54 (0.15–1.96)	0.351	1262 (59)	0.31 (0.06–1.72)	0.181
Residual QFR (per 0.1 increase)	1177 (54)	0.83 (0.53–1.28)	0.392	1262 (59)	1.05 (0.56–1.96)	0.883
Lesion complexity (B2 or C vs A or B1)	1262 (59)	1.09 (0.47–2.52)	0.839	1262 (59)	0.89 (0.37–2.16)	0.801

Values are HR and associated 95% CI, extracted from Cox models. Main analysis and sensitivity analysis 1 correspond to Cox proportional hazards regressions. Sensitivity analysis 2 corresponds to a mixed-effects Cox model including patient identity as random factor to correct for multiple vessels per patient. Sample size for the multivariable model corresponds to the lowest sample size in the univariable models (ie, renal failure). DS indicates diameter stenosis; HR, hazard ratio; MLD, minimum lumen diameter; and QFR, quantitative flow ratio.

100%[36] or 40%[37] patients with STEMI. While indicating that immediate complete revascularization is safe (in hemodynamically stable patients) and, according to the secondary superiority analyses of these trials, immediate complete revascularization may even be protective with respect to early events before planned staged PCI, no evidence on the optimal duration to staged PCI can be derived from these trials. Additional RCTs are currently investigating the issue (instantaneous wave-free ratio (iFR) Guided Multi-vessel Revascularisation During Percutaneous Coronary Intervention for Acute Myocardial Infarction (iMODERN),[38] STaged Interventional Strategies for Acute ST-seGment Elevation Myocardial Infarction Patient With Multi-vessel Disease (STAGED) (NCT04918030), Timing of FFR-guided PCI for Non-IRA in NSTEMI and MVD (OPTION-NSTEMI) (NCT04968808)).

Link Between Coronary Physiology and Non-TV Events

In a subanalysis of the COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) trial,[12] an inverse nonlinear relationship between deferred lesions among patients with STEMI investigated by FFR and non-TV events was observed, which plateaued at FFR 0.60. Additional evidence exists from retrospective analyses from mixed populations including 29% ACS, where FFR was shown to be continuously and inversely related to ischemic event risk.[11] These analyses support the concept that the functional significance of nonculprit lesions may represent an ischemic continuum with increasing inverse event risk, rather than a dichotomous state dividing at FFR 0.80. With respect to QFR, among patients with chronic coronary syndrome, QFR-guided revascularization has been reported to improve 1-year outcomes as compared with angiography-guided revascularization.[19] Further, in patients with STEMI, acute QFR shows even better agreement with 30-day FFR as acute FFR itself,[39] which in addition to its noninvasive and hyperemia-free nature makes it an interesting diagnostic tool for the ACS population.

However, in our investigation, we did not observe any independent association between QFR and

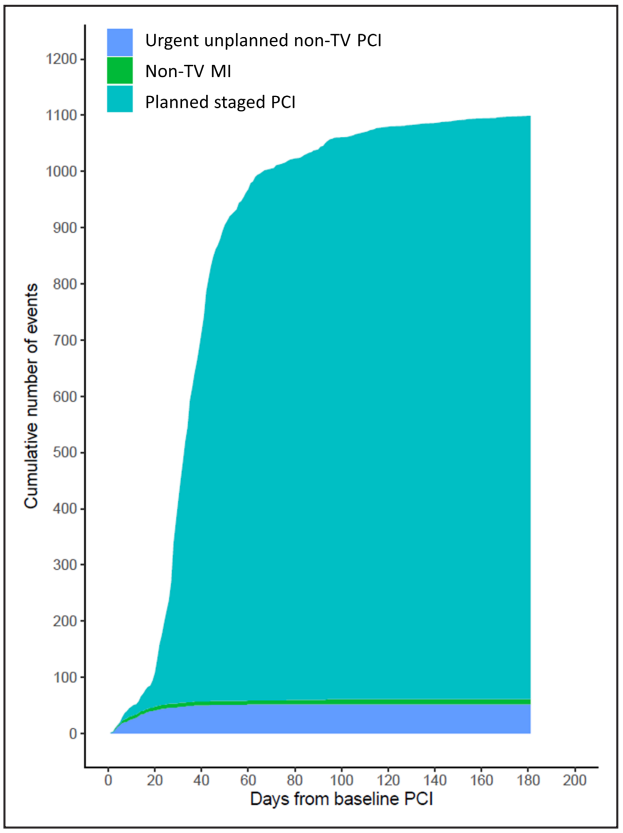

Figure 4. Cumulative event curves.
Cumulative event curves of urgent unplanned non-TV staged PCI, non-TV MI, and planned staged PCI. MI indicates myocardial infarction; non-TV, non–target-vessel; and PCI, percutaneous coronary intervention.

non-TV events occurring before staged PCI. These findings suggest that non-TV QFR may not be able to refine the timing of staged PCI, among patients undergoing operators' scheduled out-of-hospital staged PCI within a median of 28 days from index PCI. The overall event rate was 5%, the number of low QFR values (ie, <0.60) small, and the time frame for the events to occur short with a median of 28 days. Therefore, we cannot definitely exclude a potential association between QFR and non-TV events before staged PCI in a larger patient population with more pronounced ischemia and longer duration to staged PCI. Along these lines, we observed a significant univariable association between linear QFR and non-TV MI, as well as a trend toward higher clinical events with lower QFR (Figure S2), but these investigations are limited by low sample size. Further, there was a small trend, also impacted by the sample size, that patients with lower QFR seemed to be scheduled slightly earlier for staged PCI (Figure S3). This may have diluted outcomes, and further studies are required.

Finally, none of the other classical covariates in the prediction models showed an independent association with the primary end point, and also patient characteristics of patients with versus without a primary end point event were similar, implying that, taking into account all limitations of the current study, other factors may drive this type of event.

Table 4. Univariable Cox Regressions Primary End Point Components

Non-TV MI	N patients (N events)	Univariable HR (95% CI)	*P* value
Age (per 1-y increase)	1093 (9)	1.03 (0.97–1.09)	0.377
Female sex	1093 (9)	1.88 (0.47–7.52)	0.374
Diabetes	1093 (9)	…	…
Renal failure	1093 (9)	2.41 (0.60–9.64)	0.214
DS% (per 5% increase)	1093 (9)	1.07 (0.80–1.42)	0.650
QFR (per 0.1 increase)	1093 (9)	0.69 (0.52–0.91)	0.008
Urgent premature non-TV PCI	**N patients (N events)**	**HR (95% CI)**	***P* value**
Age (per 1-y increase)	1093 (52)	1.01 (0.98–1.03)	0.480
Female sex	1093 (52)	1.20 (0.64–2.24)	0.576
Diabetes	1093 (52)	0.84 (0.40–1.78)	0.649
Renal failure	1093 (48)	1.30 (0.65–2.61)	0.458
DS% (per 5% increase)	1093 (52)	1.02 (0.91–1.15)	0.758
QFR (per 0.1 increase)	1093 (52)	0.92 (0.79–1.07)	0.299

Values are HR and associated 95% CI, extracted from Cox models. DS indicates diameter stenosis; HR, hazard ratio; non-TV MI, non–target-vessel myocardial infarction; non-TV PCI, non–target-vessel percutaneous coronary intervention; and QFR, quantitative flow ratio.

Plaque Morphology as a Potential Driver of Events

At variance to the clinical setting of chronic coronary syndrome demonstrating improved short- and middle-term outcomes with physiology-guided compared with angiography-guided revascularization using FFR[40] and QFR,[19] no superiority of FFR-guided versus angiography-guided complete nonculprit lesion revascularization has been observed in the STEMI population.[41] Vulnerable nonculprit plaque features such as high plaque burden, thin fibrous cap, and low minimal lumen area are highly prevalent in patients with ACS[42] and have been shown to be associated with subsequent events.[42] Therefore, and based on the findings of this study, it may be hypothesized, that plaque morphology may play a more important role as compared with physiology in driving early non-TV events occurring before planned staged PCI. This should be investigated in future intracoronary imaging studies.

Limitations

The study results need to be considered in light of several limitations:

1. It is an observational, nonrandomized, post hoc, single-center study.

2. Although statistical significance was not met for the primary end point, we observed a 13% risk reduction in the primary end point per 0.1 units of QFR that could be impacted by limited power.
3. The time point of staged PCI (and thus time to event) was defined by operators' judgment; however, the aim of the study was to investigate potential add-on value of QFR for the timing of staged PCI on top of clinical judgment and not QFR alone. A small trend toward staged PCIs scheduled later in case of higher QFR was observed, which may have diluted QFR-related outcomes, highlighting the need for further studies.
4. The number of vessels with low QFR was limited, and we observed a significant univariable association between linear QFR and non-TV MI as well as a trend toward a higher percentage of events with lower QFR, so that we cannot exclude a potential association between QFR and non-TV events occurring before staged PCI in larger patient populations with more pronounced ischemia and longer duration to staged PCI.
5. Highest-risk patients, that is, those undergoing in-hospital staged PCI (n=139) or those with cardiogenic shock at index presentation (n=70), were excluded from this study,[24] and thus, the results do not pertain to this higher risk population.
6. FFR and intracoronary imaging were used clinically at the discretion of the operators and could not be collected systematically.
7. Twenty-four percent of the patients had to be excluded due to unanalyzable QFR, most frequently angiographic quality related (absence of 2 suitable projections, overlap, poor contrast, foreshortening) (148 patients [10%]). Further issues were incomplete patient-related or angiographic data (84 patients [6%]) or missing isocenter calibration, which was sometimes not available in the angiograms from 2009 to 2011 (45 patients [3%]). However, the proportion of excluded patients is even smaller as compared with previous post hoc QFR analyses,[21–23] and we have compared the characteristics of included versus excluded patients from this cohort study with no relevant differences. Importantly, these technical issues do not represent a limitation to the QFR technique per se, since in prospective QFR studies, analyzability of the angiograms is usually 96% to 99%.[17,18]
8. The percentage of female patients was lower than in unselected cohorts of patients with ACS.[43]

CONCLUSIONS

In this cohort study of 1093 patients with ACS and MVD scheduled to undergo out-of-hospital staged PCI within 28 to 42 days from the index presentation, non-TV QFR derived from vessels planned for staged PCI using the baseline angiogram was not independently associated with non-TV events before staged PCI. Therefore, this study does not provide conceptual evidence that QFR may be able to help refine the timing of staged PCI on top of clinical judgment. The concept may warrant further investigation among larger populations with more pronounced ischemia and longer duration to staged PCI.

ARTICLE INFORMATION

Received July 19, 2023; accepted December 1, 2023.

Affiliations

Department of Cardiology, Bern University Hospital, Inselspital, University of Bern, Switzerland (S.B., R.K., T.O., Y.U., J.H., J.L., M.F., F.P., L.H., G.C.M.S., T.P., S.S., S.W., L.R.); Department of Cardiology, Itabashi Chuo Medical Center, Tokyo, Japan (T.O.); Department of Cardiovascular Medicine, Shinshu University School of Medicine, Nagano, Japan (Y.U.); and CTU Bern, University of Bern, Switzerland (S.L.).

Sources of Funding

None.

Disclosures

Dr Bär reports research grants to the institution from Medis Medical Imaging Systems, Abbott, and Bangerter-Rhyner Stiftung, and a personal research grant from the Swiss National Science Foundation, outside the submitted work. Dr Ueki reports personal fees from Infraredex, outside the submitted work. Dr Losdat is employed by CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. An up-to-date list of CTU Bern's conflicts of interest can be found at http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. Dr Praz has received travel expenses from Abbott Vascular, Edwards Lifesciences, and Polares Medical. Dr Häner has received a travel grant from Bayer. Dr Stortecky reports research grants to the institution from Edwards Lifesciences, Medtronic, Abbott Vascular, and Boston Scientific; speaker fees from Boston Scientific; and consulting fees from BTG and Teleflex, outside the submitted work. Dr Pilgrim reports research grants to the institution from Boston Scientific, Biotronik, and Edwards Lifesciences; speaker fees from Boston Scientific and Biotronik; consultancy for HighLife SAS; and proctoring for Boston Scientific and Medtronic. Dr Windecker reports research, travel, or educational grants to the institution without personal remuneration from Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Braun, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Cordis Medical, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Farapulse Inc., Fumedica, Guerbet, Idorsia, Inari Medical, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medalliance, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pharming Tech. Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, and V-Wave. Dr Windecker served as advisory board member or member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, AstraZeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, and V-Wave with payments to the institution but no personal payments. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. Dr Räber reports research grants to the institution from Abbott Vascular, Biotronik, Boston Scientific, Heartflow, Sanofi, Regeneron, Medis Medical Imaging Systems, and Bangerter-Rhyner Stiftung; speaker or consultation fees by Abbott Vascular, Amgen, AstraZeneca, Canon, Novo Nordisk, Medtronic, Occlutech, and Sanofi, outside the submitted work. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figures S1–S3

REFERENCES

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan G-A, Dweck MR, Galbraith M, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: developed by the Task Force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2023;44:3720–3826. doi: 10.1093/eurheartj/ehad191
2. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2015;36:1163–1170. doi: 10.1093/eurheartj/ehu505
3. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115–1123. doi: 10.1056/NEJMoa1305520
4. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665–671. doi: 10.1016/S0140-6736(15)60648-1
5. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015;65:963–972. doi: 10.1016/j.jacc.2014.12.038
6. Smits PC, Abdel-Wahab M, Neumann F-J, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, et al. Fractional flow reserve–guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;376:1234–1244. doi: 10.1056/NEJMoa1701067
7. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, López-Sendón J, Faxon DP, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381:1411–1421. doi: 10.1056/NEJMoa1907775
8. Rathod KS, Koganti S, Jain AK, Astroulakis Z, Lim P, Rakhit R, Kalra SS, Dalby MC, O'Mahony C, Malik IS, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2018;72:1989–1999. doi: 10.1016/j.jacc.2018.07.089
9. Siebert VR, Borgaonkar S, Jia X, Nguyen HL, Birnbaum Y, Lakkis NM, Alam M. Meta-analysis comparing multivessel versus culprit coronary arterial revascularization for patients with non-ST-segment elevation acute coronary syndromes. *Am J Cardiol*. 2019;124:1501–1511. doi: 10.1016/j.amjcard.2019.07.071
10. Wood DA, Cairns JA, Wang J, Mehran R, Storey RF, Nguyen H, Meeks B, Kunadian V, Tanguay J-F, Kim H-H, et al. Timing of staged nonculprit artery revascularization in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2019;74:2713–2723. doi: 10.1016/j.jacc.2019.09.051
11. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen S-L, et al. Prognostic value of fractional flow reserve. *J Am Coll Cardiol*. 2014;64:1641–1654. doi: 10.1016/j.jacc.2014.07.973
12. Piróth Z, Boxma-de Klerk BM, Omerovic E, Andréka P, Fontos G, Fülöp G, Abdel-Wahab M, Neumann F-J, Richardt G, Abdelghani M, et al. The natural history of nonculprit lesions in STEMI. *JACC Cardiovasc Interv*. 2020;13:954–961. doi: 10.1016/j.jcin.2020.02.015
13. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477. doi: 10.1093/eurheartj/ehz425
14. Pijls NHJ, Tonino PAL. The crux of maximum hyperemia: the last remaining barrier for routine use of fractional flow reserve. *JACC Cardiovasc Interv*. 2011;4:1093–1095. doi: 10.1016/j.jcin.2011.08.007
15. van der Hoeven NW, Janssens GN, de Waard GA, Everaars H, Broyd CJ, Beijnink CWH, van de Ven PM, Nijveldt R, Cook CM, Petraco R, et al. Temporal changes in coronary hyperemic and resting hemodynamic indices in nonculprit vessels of patients with ST-segment elevation myocardial infarction. *JAMA Cardiol*. 2019;4:736–744. doi: 10.1001/jamacardio.2019.2138
16. Collet C, Onuma Y, Sonck J, Asano T, Vandeloo B, Kornowski R, Tu S, Westra J, Holm NR, Xu B, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. *Eur Heart J*. 2018;39:3314–3321. doi: 10.1093/eurheartj/ehy445
17. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. *JACC Cardiovasc Interv*. 2016;9:2024–2035. doi: 10.1016/j.jcin.2016.07.013
18. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077–3087. doi: 10.1016/j.jacc.2017.10.035
19. Xu B, Tu S, Song L, Jin Z, Yu B, Fu G, Zhou Y, Wang J, Chen Y, Pu J, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398:2149–2159. doi: 10.1016/S0140-6736(21)02248-0
20. Chu J, Lin H, Yan W, Yuan D, Lai Y, Liu X. Angiographic quantitative flow ratio in acute coronary syndrome: beyond a tool to define ischemia-causing stenosis-a literature review. *Cardiovasc Diagn Ther*. 2022;12:892–907. doi: 10.21037/cdt-22-334
21. Bär S, Kavaliauskaite R, Ueki Y, Otsuka T, Kelbæk H, Engstrøm T, Baumbach A, Roffi M, von Birgelen C, Ostojic M, et al. Quantitative flow ratio to predict nontarget vessel-related events at 5 years in patients with ST-segment-elevation myocardial infarction undergoing angiography-guided revascularization. *J Am Heart Assoc*. 2021;10:e019052. doi: 10.1161/JAHA.120.019052
22. Spitaleri G, Tebaldi M, Biscaglia S, Westra J, Brugaletta S, Erriquez A, Passarini G, Brieda A, Leone AM, Picchi A, et al. Quantitative flow ratio identifies nonculprit coronary lesions requiring revascularization in patients with ST-segment–elevation myocardial infarction and multivessel disease. *Circ Cardiovasc Interv*. 2018;11:e006023. doi: 10.1161/CIRCINTERVENTIONS.117.006023
23. Lauri F, Macaya F, Mejía-Rentería H, Goto S, Yeoh J, Nakayama M, Quirós A, Liontou C, Pareek N, Fernández-Ortíz A, et al. Angiography-derived functional assessment of non-culprit coronary stenoses during primary percutaneous coronary intervention for ST-elevation myocardial infarction. *EuroIntervention*. 2020;15:e1594–e1601. doi: 10.4244/EIJ-D-18-01165
24. Otsuka T, Bär S, Losdat S, Kavaliauskaite R, Ueki Y, Zanchin C, Lanz J, Praz F, Häner J, Siontis GCM, et al. Effect of timing of staged percutaneous coronary intervention on clinical outcomes in patients with acute coronary syndromes. *J Am Heart Assoc*. 2021;10:e023129. doi: 10.1161/JAHA.121.023129
25. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. *J Am Heart Assoc*. 2018;7:e009603. doi: 10.1161/JAHA.118.009603
26. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation*. 1988;78:486–502. doi: 10.1161/01.CIR.78.2.486
27. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
28. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289–1367. doi: 10.1093/eurheartj/ehaa575

29. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315. doi: 10.1093/eurheartj/ehv320
30. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619. doi: 10.1093/eurheartj/ehs215
31. Vranckx P, Cutlip DE, Mehran R, Kint P-P, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention*. 2010;5:871–874. doi: 10.4244/EIJV5I7A146
32. Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. *Biometrics*. 2000;56:1016–1022. doi: 10.1111/j.0006-341X.2000.01016.x
33. Therneau TM, Grambsch PM, Pankratz VS. Penalized survival models and frailty. *J Comput Graph Stat*. 2003;12:156–175. doi: 10.1198/106186003 1365
34. Sardella G, Lucisano L, Garbo R, Pennacchi M, Cavallo E, Stio RE, Calcagno S, Ugo F, Boccuzzi G, Fedele F, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. *J Am Coll Cardiol*. 2016;67:264–272. doi: 10.1016/j.jacc.2015.10.082
35. Biscaglia S, Guiducci V, Escaned J, Moreno R, Lanzilotti V, Santarelli A, Cerrato E, Sacchetta G, Jurado-Roman A, Menozzi A, et al. Complete or culprit-only PCI in older patients with myocardial infarction. *N Engl J Med*. 2023;389:889–898. doi: 10.1056/NEJMoa2300468
36. Stähli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M, Kesterke R, Nordbeck P, Witzenbichler B, Lang IM, et al. Timing of complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2023;389:1368-1379. doi: 10.1056/NEJMoa2307823
37. Diletti R, den Dekker WK, Bennett J, Schotborgh CE, van der Schaaf R, Sabaté M, Moreno R, Ameloot K, van Bommel R, Forlani D, et al. Immediate versus staged complete revascularisation in patients presenting with acute coronary syndrome and multivessel coronary disease (BIOVASC): a prospective, open-label, non-inferiority, randomised trial. *Lancet*. 2023;401:1172–1182. doi: 10.1016/S0140-6736(23)00351-3
38. Beijnink CWH, Thim T, van der Heijden DJ, Klem I, Al-Lamee R, Vos JL, Koop Y, Dijkgraaf MGW, Beijk MAM, Kim RJ, et al. Instantaneous wave-free ratio guided multivessel revascularisation during percutaneous coronary intervention for acute myocardial infarction: study protocol of the randomised controlled iMODERN trial. *BMJ Open*. 2021;11:e044035. doi: 10.1136/bmjopen-2020-044035
39. Wang L, Travieso A, van der Hoeven N, van Leeuwen MAH, Janssens G, Mejía-Rentería H, Jerónimo A, Gonzalo N, Nijveldt R, van Royen N, et al. Improved nonculprit stenosis assessment in patients with ST-segment elevation myocardial infarction using quantitative flow ratio. *JACC Cardiovasc Interv*. 2023;16:1828–2830. doi: 10.1016/j.jcin.2023.04.045
40. Pijls NHJ, Fearon WF, Tonino PAL, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrøm T, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56:177–184. doi: 10.1016/j.jacc.2010.04.012
41. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, le Bras A, Gallet R, Khalife K, Morelle J-F, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med*. 2021;385:297–308. doi: 10.1056/NEJMoa2104650
42. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358
43. Fokkema ML, James SK, Albertsson P, Aasa M, Åkerblom A, Calais F, Eriksson P, Jensen J, Schersten F, de Smet BJ, et al. Outcome after percutaneous coronary intervention for different indications: long-term results from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *EuroIntervention*. 2016;12:303–311. doi: 10.4244/EIJY15M10_07