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Clinical prognostic value of a novel quantitative flow ratio from a single projection in patients with coronary bifurcation lesions treated with the provisional approach

Jing Kan[1], MPH; Zhen Ge[1], MD; Shaoping Nie[2], MD; Xiaofei Gao[1], MD; Xiaobo Li[1], MD; Imad Sheiban[3], MD; Jun-Jie Zhang[1], MD; Shao-Liang Chen[1]*, MD

1. Division of Cardiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, People's Republic of China; 2. Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China; 3. Division of Cardiology, Pederzoli Hospital-Peschiera del Garda, Verona, Italy

J. Kan and Z. Ge contributed equally to this work.

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KEYWORDS

- bifurcation
- drug-eluting stent
- other imaging modalities

Abstract

Background: A novel quantitative flow ratio (μQFR) for bifurcated coronary vessels, derived from a single projection, has been recently reported. Provisional stenting is effective for most bifurcation lesions. However, the clinical value of the side branch (SB) μQFR in patients with coronary bifurcation lesions undergoing provisional stenting remains unclear.

Aims: This study aims to determine the clinical predictive value of the SB μQFR after provisional stenting in patients with coronary bifurcation lesions.

Methods: Between June 2015 and May 2018, 288 patients with true coronary bifurcation lesions who underwent a provisional approach without SB treatment (including predilation, kissing balloon inflation or stenting) were classified by an SB μQFR <0.8 (n=65) and ≥0.8 (n=223) groups. The primary endpoint was the three-year composite of target vessel failure (TVF), including cardiac death, target vessel myocardial infarction (TVMI), and revascularisation (TVR).

Results: Three years after the procedures, there were 43 (14.9%) TVFs, with 19 (29.2%) in the SB μQFR <0.8 and 24 (10.8%) in the SB μQFR ≥0.8 groups (adjusted hazard ratio [HR] 2.45, 95% confidence interval [CI] 1.39-5.54; p=0.003), mainly driven by increased TVMI (16.9% vs 5.4%, adjusted HR 3.29, 95% CI: 1.15-6.09; p=0.030) and TVR (15.4% vs 2.2%, adjusted HR 6.39, 95% CI: 2.04-13.48; p=0.007). Baseline diameter stenosis at the ostial SB and SB lesion length were the two predictors of an SB μQFR <0.8 immediately after stenting the main vessel, whereas previous percutaneous coronary intervention and an SB μQFR <0.8 were the two independent factors of 3-year TVF.

Conclusions: An SB μQFR <0.8 immediately after the provisional approach is strongly associated with clinical events. Further randomised studies with large patient populations are warranted.

**Corresponding author: Nanjing First Hospital, Nanjing Medical University, 140 Hanzhong Rd, Gulou, Nanjing, Jiangsu, Nanjing 210029, People's Republic of China. E-mail: chmengx@hotmail.com*

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Abbreviations

KBI	kissing balloon inflation
LAD	left anterior descending coronary artery
LCx	left circumflex coronary artery
MI	myocardial infarction
MV	main vessel
PCI	percutaneous coronary intervention
µQFR	novel quantitative flow ratio
SB	side branch
ST	stent thrombosis
TVF	target vessel failure

Introduction

Coronary artery bifurcation is anatomically complicated; stenting coronary bifurcation lesions yields suboptimal clinical results, including frequent stent thrombosis (ST) and unplanned repeat revascularisations, compared to non-bifurcation lesions[1]. While the main vessel (MV) lesion is the primary determinant of clinical outcome, in this modern era of percutaneous coronary intervention (PCI) using drug-eluting stents (DES), when and how to treat side branch (SB) lesions are still key questions[2]. This is largely because of the dissociation between anatomical severity and functional significance[3,4]. The DKCRUSH VI study[5] is the only randomised study analysing the differences in clinical outcome between fractional flow reserve (FFR)-guided and angiography-guided stenting of bifurcation lesions. The study failed to show a clinical benefit of FFR guidance, except for a lower requirement for SB stenting. One reason for this may be the high rate (9%) of failure to access the SB using rigid pressure wires after stenting the MV. Thus, angiography-derived quantitative flow ratio (QFR), without the administration of adenosine or the use of costly and less manageable pressure wires, is becoming a point of interest[6].

Several studies have analysed the diagnostic performance of the QFR in comparison with pressure wire-measured FFR[6-13] and revealed that the QFR showed good agreement, diagnostic accuracy, and predictive value compared with FFR[8,10,12], except for borderline FFR zones with acute myocardial infarction (AMI)[11]. However, the first-generation software for calculating QFR requires two angiographic projections with angles 25° apart and does not apply to SB QFR measurements. The accuracy of an MV µQFR measurement from a single angiographic projection has recently been demonstrated to have as good a diagnostic performance as FFR[14] among patients in the FAVOR II China study[15]. In this study, however, the agreement between SB µQFR and FFR was not reported. Furthermore, the predictive value of SB µQFR immediately after provisional stenting (the predominant stenting technique for uncomplicated bifurcation lesions) for short- and long-term clinical outcomes is unclear. Accordingly, this study aims to identify the prevalence of SB µQFR <0.8 after stenting the MV without SB treatment (including predilation, kissing balloon inflation or SB stenting) and the association of SB µQFR with clinical events during 3 years of follow-up.

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Methods

PATIENT POPULATION

Patients presenting with *de novo* coronary bifurcation lesions intended for PCI at participating centres, between June 2015 and May 2018, were evaluated for an intention-to-treat analysis in the study. Patients were included if they had only one bifurcation lesion treated with provisional stenting (MV stenting with a jailed wire in the SB), were >18 years old, presented with silent ischaemia, stable or unstable angina, or myocardial infarction (MI) >24 hours prior to treatment. For study inclusion, all bifurcation lesions were Medina 1, 1, 1 or 0, 1, 1 with a reference vessel diameter (RVD) in the SB ≥2.5 mm by visual estimation. Patients who had participated in other clinical trials were excluded from this analysis.

PROVISIONAL STENTING PROCEDURE

The provisional stenting technique has been described previously[2,5,16,17]. The MV and SB were wired. Predilating the SB was not encouraged. A stent with a stent/artery ratio of 1.1:1 was implanted in the MV, then the proximal optimisation technique (POT) using non-compliant balloons (1:1 of balloon/stent ratio, >18 atm) was performed. After MV stenting, ballooning or stenting the SB was performed, if the SB Thrombolysis in Myocardial Infarction (TIMI) flow was <3. Patients who had undergone SB treatment (predilation, kissing balloon inflation or stenting) before SB µQFR measurement were excluded from this analysis.

MEASUREMENT OF µQFR

The measurements of µQFR for the MV and all SBs have been described elsewhere[14]. The µQFR was computed using a prototype software (AngioPlus Core, Pulse Medical Imaging Technology) by three experienced technicians who were blinded to the objectives of this study. The computation included 1) delineation of the interrogated epicardial coronary artery during contrast injection and calculation of contrast flow velocity based on the centreline length divided by the contrast dye filling time; 2) selection of the analysis frame with sharp lumen contour at the stenotic segment as the key frame; 3) delineation of the lumen contour of the interrogated vessel and its SBs with diameters of ≥1.0 mm on the key frame; 4) reconstruction of the reference diameter function with the step-down size across bifurcations; 5) modelling of hyperaemic flow velocity based on the contrast flow velocity and calculation of pressure drop based on fluid dynamics equations, assuming a blood density of 1,060 kg/m^3 and viscosity of 0.0035 kg/(m.s).

INTRA- AND INTEROBSERVER ANALYSIS

To analyse intraobserver variability in µQFR measurements, 30 randomly selected vessels were analysed simultaneously by three well-trained technicians who were blinded to the study objectives. For interobserver variability analysis, 20 vessels were randomly selected and reanalysed by the same technician and a second technician 1 week later. The µQFR of the MV and SB

were calculated at baseline and immediately after stenting the MV and POT.

MEDICATION AND FOLLOW-UP

Procedural anticoagulation was achieved with unfractionated heparin. All patients were treated with aspirin preprocedure and received a 300 mg loading dose of clopidogrel if not on chronic dual antiplatelet therapy. After the intervention, all patients received 100 mg/day of aspirin indefinitely and clopidogrel 75 mg/day for at least 12 months. Additional medications for secondary prevention, including statins, β-blockers and angiotensin-converting enzyme inhibitors, were prescribed according to current guidelines. Clinical follow-up was done through office visits or telephone interviews at 1, 6, 12, 24, and 36 months.

ENDPOINTS AND DEFINITIONS

The primary endpoint was target vessel failure (TVF) at 3-year follow-up, defined as the composite of cardiac death, target vessel MI (TVMI), or clinically driven target vessel revascularisation (TVR). Death from cardiac causes was defined as any death without a clear non-cardiac cause. Protocol-defined periprocedural MI (within 48 hours) was defined as a creatine kinase myocardial band (CK-MB) >10× the upper reference limit (URL) of the assay, or >5× URL plus either i) new pathological Q waves in ≥2 contiguous leads or new left bundle branch block (LBBB); ii) angiographically documented graft or coronary artery occlusion or new severe stenosis with thrombosis; iii) imaging evidence of new loss of viable myocardium; or iv) new regional wall motion abnormality. Spontaneous MI (after 48 hours) was defined as a clinical syndrome of MI with CK-MB or troponin >1× the URL and new ST-segment elevation or depression, or any of the findings described above. All MIs were considered TVMI unless there was clear evidence that they were attributable to a non-target vessel[16,17]. Clinically driven TVR was defined as angina or ischaemia attributable to the target vessel requiring repeat PCI or coronary artery bypass graft. Secondary endpoints included cardiac death, TVMI, clinically driven target lesion revascularisation (TLR), and all-cause death. Definite or probable ST, according to the Academic Research Consortium,[18] was the major safety endpoint. All events were adjudicated by a central committee using original source documents blinded to treatment. The functionally complete revascularisation was defined by a post-PCI μQFR >0.80 in all treated vessels.

STATISTICAL ANALYSIS

Patients were assigned to the SB μQFR <0.8 and SB μQFR ≥0.8 groups immediately after MV stenting with final POT.

Baseline characteristics are reported as counts and percentages or as mean±standard deviation (SD). The chi-squared or Fisher's exact tests were used to compare categorical variables. The Student's t-test or Wilcoxon rank-sum scores for non-normally distributed data were used to compare continuous variables. Time-to-first event curves were generated using Kaplan-Meier analysis and compared using the log-rank test. Landmark analysis was used to determine the difference in TVF within 30 days, from 31 days to 1 year, and from 1 to 3 years between the two groups. Cox regression analysis was used to compare the differences in the primary endpoints and to identify the predictors of 3-year TVF and SB μQFR <0.8 after stenting the MV with POT, with outputs of hazard ratios (HR), 95% confidence intervals (CI), and p-values. Baseline variables with a p-value <0.05 between the groups were used for an adjusted analysis of endpoints. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. All analyses were performed with Stata v12.0 (StataCorp).

Results

PATIENT POPULATION

Between June 2015 and May 2018, 1,113 patients with true bifurcation lesions were screened **(Figure 1)**. Of them, 825 patients were excluded: chronic total occlusions (CTOs) in 89 patients (60 CTOs in the MV, 16 in the SB, and 12 in both the MV and the SB); a two-stent approach in 9 patients; poor imaging quality in 192 patients; and 535 undergoing SB treatment (including predilation or kissing balloon inflation or stenting). Finally, 288 patients were included in this study. Immediately after the PCI procedures, 65 (22.6%) patients had an SB μQFR <0.8 and 223 (77.4%) patients had an SB μQFR ≥0.8.

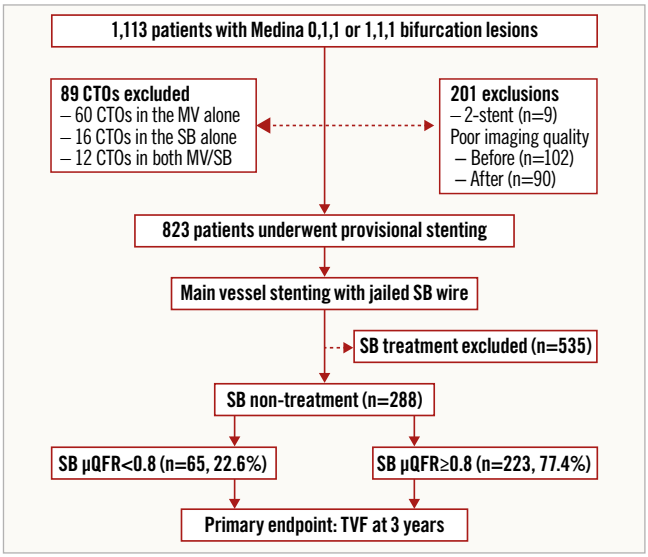

Figure 1. *Study flowchart. Of 288 patients with true coronary bifurcation lesions after stenting the main vessel (MV) without side branch (SB) treatment (including predilation, or kissing balloon inflation or stenting), 65 patients had an SB quantitative flow ratio (μQFR) of <0.8 and 223 patients had an SB μQFR ≥0.8.*
CTO: chronic total occlusion; TVF: target vessel failure

BASELINE CLINICAL CHARACTERISTICS

Patients in the SB μQFR <0.8 group were older (66.4±10.0 years vs 64.4±9.9 years; p=0.017) and had more frequent previous PCI

(32.3% vs 13.0%; p=0.001), compared to patients in the SB μQFR ≥0.8 group **(Table 1)**.

LESION AND PROCEDURAL CHARACTERISTICS

The lesion length in the MV was 37.5±12.4 mm in the SB μQFR <0.8 group **(Table 2)**, significantly longer than the 34.9±17.4 mm in the SB μQFR ≥0.8 group (p=0.022). Baseline diameter stenosis at the ostial SB (59.9% vs 52.0%; p=0.072) and SB lesion length (14.5±7.1 vs 13.4±9.2; p=0.382) were comparable between the two groups. More lesions needed to be treated (2.23±0.86 vs 1.92±0.82; p<0.001) in the SB μQFR <0.8 group, resulting in a higher rate of staged procedures (40.0% vs 26.0%; p=0.043) and fewer complete revascularisations (40.0% vs 63.7%; p=0.001). Most procedures were performed using the transradial approach. Intravscular ultrasound guidance was used in fewer than 30% of patients.

Table 1. Baseline characteristics of patients.

		SB μQFR <0.8 (n=65)	SB μQFR ≥0.8 (n=223)	*p*-value
Age, years		66.4±10.0	64.4±9.9	0.017
Male, n (%)		51 (78.5)	165 (74.0)	0.518
Body mass index, kg/m^2		24.6±3.1	24.6±2.9	0.629
Body surface area, m^2		1.86±0.16	1.86±0.17	0.888
Hypertension, n (%)		44 (67.7)	144 (64.6)	0.767
Diabetes, n (%)		23 (35.4)	69 (30.9)	0.546
Hyperlipidaemia, n (%)		34 (52.3)	107 (48.0)	0.575
Previous MI, n (%)		10 (15.4)	30 (13.5)	0.686
Previous PCI, n (%)		21 (32.3)	29 (13.0)	0.001
Previous CABG, n (%)		0	2 (0.9)	1.000
Renal dysfunction, n (%)		4 (6.2)	8 (3.6)	0.478
Current smoker, n (%)		14 (21.5)	41 (18.4)	0.592
Family history, n (%)		2 (3.1)	11 (4.9)	0.739
GI bleeding, n (%)		2 (3.1)	5 (2.2)	0.658
Stroke, n (%)		7 (10.8)	24 (10.8)	1.000
Peripheral artery disease, n (%)		1 (1.5)	17 (7.6)	0.085
Heart failure, n (%)		8 (12.3)	18 (12.6)	1.000
LVEF, %		59.4±8.4	60.8±7.5	0.583
Heart rate, bpm		72.7±10.9	74.1±11.1	0.695
Systolic blood pressure, mmHg		135.9±17.9	131.8±17.3	0.300
Diastolic blood pressure, mmHg		77.9±10.2	78.6±10.5	0.909
Clinical presentation, n (%)	Silent ischaemia	3 (4.6)	11 (4.9)	1.000
	Stable angina	13 (20.0)	42 (18.8)	0.858
	Unstable angina	34 (52.3)	122 (54.7)	0.778
	AMI >24 h	15 (23.1)	48 (21.5)	0.865
	STEMI	6 (9.2)	25 (11.2)	0.821
	NSTEMI	9 (13.8)	23 (10.3)	0.500

Data are mean±standard deviation or n (%). AMI: acute myocardial infarction; CABG: coronary artery bypass graft; GI: gastrointestinal; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; μQFR: novel quantitative flow ratio; SB: side branch; STEMI: ST-segment elevation myocardial infarction

DYNAMIC CHANGE OF μQFR

The inter- and intraobserver variances were less than 5%.

At baseline, the absolute value of μQFR in the SB μQFR <0.8 group was lower than that in the SB μQFR ≥0.8 group (0.61±0.19 vs 0.71±0.22; p=0.001) **(Table 3)**, and the percentage of patients with an SB μQFR <0.8 was 90.8% (n=59), significantly different from the 59.2% (n=132) in the SB μQFR ≥0.8 group (p<0.001). However, the percentage of patients with a baseline MV μQFR <0.8 did not differ significantly between the two groups.

After stenting the MV and POT, the μQFR in the MV increased to 0.93±0.07 in the SB μQFR ≥0.8 group, compared to 0.91±0.09 (p=0.008) in the SB μQFR <0.8 group, resulting in a higher rate of μQFR <0.89 in the SB μQFR <0.8 group (23.1% vs 12.6%; p=0.047).

For the SB, immediately after stenting the MV and POT, a more profound increase of μQFR in the SB was measured in the SB μQFR ≥0.8 group (0.20±0.22), compared to 0.03±0.21 in the SB μQFR <0.8 group (p<0.001). Baseline diameter stenosis at the ostial SB (odds ratio [OR] 9.55, 95% CI: 1.51-15.92; p=0.023) and SB lesion length (OR 5.433, 95% CI: 1.201-10.93; p<0.001) were the two predictors of a μQFR <0.8 in the SB immediately after stenting the MV.

PRIMARY AND SECONDARY ENDPOINTS

At 30 days, the rate of endpoints was comparable between the two groups after adjusted analysis **(Table 4)**. Within one-year after stenting, the incidence of TVMI and TVR in the SB μQFR <0.8 group were 15.4% and 12.3%, respectively, significantly different to the 4.9% and 1.3% in the SB μQFR ≥0.8 group, by either unadjusted or adjusted analyses.

At 3-year follow-up, TVF was reported in 43 (20.0%) patients overall, with 29.2% of patients in the SB μQFR <0.8 group and 10.8% in the SB μQFR ≥0.8 group (adjusted HR 2.45, 95% CI: 1.30-5.53; p=0.003) experiencing TVF, largely driven by increased rates of TVMI (16.9% vs 5.4%, adjusted HR 3.29, 95% CI: 1.15-6.09; p=0.030) and TVR (15.4% vs 2.2%, adjusted HR 6.39, 95% CI: 2.04-13.48; p=0.007) **(Table 4, Figure 2)**. Landmark analysis between the two groups **(Figure 3)** showed a significant difference in TVF within 30 days and at one year but not between one and three years.

By multivariate analysis, previous PCI (OR 4.81, 95% CI: 1.07-21.69; p=0.041) and an SB μQFR <0.8 (OR 6.88, 95% CI: 2.09-22.64; p=0.002) were the two independent factors of 3-year TVF.

CORRELATION OF SB μQFR <0.8 WITH SB TIMI FLOW AND TVF

Immediately after the procedures, SB TIMI flow grade <3 was seen in 18 (6.3%) patients, with 15 (23.1%) in the SB μQFR <0.8 group and 3 (1.3%) in the SB μQFR ≥0.8 group (p<0.001)

Table 2. Lesions and procedural characteristics.

		SB μQFR <0.8 (n=65)	SB μQFR ≥0.8 (n=223)	*p*-value
No. of diseased vessels	Single-vessel disease, n (%)	12 (18.5)	61 (27.4)	0.194
	Two-vessel disease, n (%)	29 (44.6)	103 (46.2)	0.888
	Three-vessel disease, n (%)	24 (36.9)	59 (26.5)	0.120
	LM bifurcation lesions, n (%)	20 (30.8)	79 (35.4)	0.554
Moderate-severe calcification	Main vessel, n (%)	20 (30.8)	68 (30.5)	1.000
	Side branch, n (%)	9 (13.8)	19 (8.5)	0.234
Thrombus-containing lesion	Main vessel, n (%)	2 (3.1)	8 (3.6)	1.000
	Side branch, n (%)	1 (1.5)	0	0.226
TIMI flow grade 3 prior to procedure	Main vessel, n (%)	59 (90.8)	200 (89.7)	0.823
	Side branch, n (%)	62 (95.4)	213 (95.5)	0.334
Lesion length	Main vessel, mm	37.5±12.4	34.9±17.4	0.022
	Side branch, mm	14.5±7.1	13.4±9.2	0.382
Diameter stenosis	Main vessel, %	54.3±14.0	52.2±17.8	0.243
	Side branch, %	59.9±13.9	52.0±19.2	0.072
No. of lesions, n		2.34±0.87	2.14±0.91	<0.001
No. of treated lesions, n		2.23±0.86	1.92±0.82	<0.001
Transradial access, n (%)		50 (76.9)	187 (83.9)	0.201
IVUS guidance, n (%)		18 (27.7)	66 (29.6)	0.877
IABP, n (%)		0	1 (0.4)	1.000
MV TIMI flow grade 3 post-procedure, n (%)		64 (98.5)	222 (99.6)	0.862
SB TIMI flow grade 3 post-procedure, n (%)		50 (76.9)	220 (98.7)	<0.001
Staged PCI, n (%)		26 (40.0)	58 (26.0)	0.043
Complete revascularisation, n (%)		26 (40.0)	142 (63.7)	0.001

Data are mean±standard deviation or n (%). IABP: intra-aortic balloon pumping; IVUS: intravascular ultrasound; LM: left main; MV: main vessel; PCI: percutaneous coronary intervention; μQFR: novel quantitative flow ratio; SB: side branch; TIMI: Thrombolysis in Myocardial Infarction

Table 3. Dynamic change of quantitative flow ratio.

		SB μQFR <0.8 (n=65)	SB μQFR ≥0.8 (n=223)	*p*-value
Target vessel, n (%)	LAD-LCx	16 (24.6)	65 (29.1)	0.386
	LAD-diagonal	36 (55.4)	128 (57.4)	
	LCx-obtuse marginal	11 (16.9)	21 (9.4)	
	Distal RCA	2 (3.1)	9 (4.0)	
Main vessel μQFR	Baseline	0.61±0.22	0.61±0.24	0.046
	<0.8, n (%)	46 (70.8)	167 (74.9)	0.523
	Post-procedure	0.91±0.09	0.93±0.07	0.008
	<0.89, n (%)	15 (23.1)	28 (12.6)	0.047
Side branch μQFR	Baseline	0.61±0.19	0.71±0.22	0.001
	<0.8, n (%)	59 (90.8)	132 (59.2)	<0.001
	Post-procedure	0.64±0.14	0.91±0.06	<0.001
	ΔμQFR	0.03±0.21	0.20±0.22	<0.001

Data are mean±standard deviation or n (%). LAD: left anterior descending artery; LCx: left circumflex; MV: main vessel; μQFR: novel quantitative flow ratio; RCA: right coronary artery; SB: side branch

(Table 2). Of patients with SB TIMI flow grade <3, >33.0% of patients suffered 3-year TVF **(Figure 4)**, with no significant difference between the SB μQFR <0.8 and ≥0.8 groups. Notably, of 270 patients with TIMI flow grade 3, the rate of 3-year TVF was 28.0% (14/50) in patients with an SB μQFR <0.8 and 10.5% (23/220) in patients with an SB μQFR ≥0.8 (p=0.003) **(Figure 3)**.

Discussion

To the best of our knowledge, this is the first study to report the clinical predictive value of the μQFR from a single projection in patients with true coronary artery bifurcation lesions treated with the provisional approach. We successfully measured the μQFR in the MV and SB in 82.7% of patients and found that 1) baseline diameter stenosis at the ostial SB and SB lesion length are predictors of an SB μQFR <0.8 immediately after stenting the MV; 2) a post-procedural SB μQFR <0.8 is strongly associated with TVMI, TVR, and subsequent TVF, within one year of the procedure; 3) previous PCI and an SB μQFR <0.8 predict the occurrence of three-year TVF.

Table 4. Primary and secondary endpoints.

	SB µQFR <0.8	SB µQFR ≥0.8	Unadjusted analysis		Adjusted analysis	
	(n=65)	(n=223)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
At 30 days						
TVF	9 (13.8)	13 (5.8)	2.59 (1.06-6.38)	0.038	2.44 (0.67-5.25)	0.162
Cardiac death	0	3 (1.3)	–	0.997	–	0.944
TVMI	8 (12.3)	11 (4.9)	2.71 (1.04-7.04)	0.041	2.57 (0.56-6.89)	0.227
PMI	8 (12.3)	10 (4.5)	2.99 (1.13-7.92)	0.028	2.73 (0.79-6.61)	0.091
TVR	1 (1.5)	0	–	0.995	–	0.994
ST	0	2 (0.9)	–	0.997	–	0.994
At 1 year						
TVF	16 (24.6)	15 (6.7)	4.53 (2.09-9.78)	<0.001	4.02 (1.77-6.83)	0.004
Cardiac death	1 (1.5)	3 (1.3)	1.15 (0.12-11.21)	0.907	1.02 (0.10-1.12)	0.638
TVMI	10 (15.4)	11 (4.9)	3.50 (1.42-8.67)	0.007	3.35 (1.03-7.33)	0.045
TVR	8 (12.3)	3 (1.3)	10.29 (2.65-40.04)	0.001	7.95 (1.13-35.98)	0.037
ST	0	3 (1.3)	–	0.997	–	0.995
Any death	2 (3.1)	5 (2.2)	1.38 (0.26-7.31)	0.702	1.26 (0.21-5.45)	0.608
At 3 years						
TVF	19 (29.2)	24 (10.8)	3.43 (1.73-6.77)	<0.001	2.45 (1.39-5.54)	0.003
Cardiac death	4 (6.2)	4 (1.8)	3.59 (0.87-14.77)	0.077	1.02 (0.09-3.20)	0.987
TVMI	11 (16.9)	12 (5.4)	3.58 (1.49-8.56)	0.004	3.29 (1.15-6.09)	0.030
TVR	10 (15.4)	5 (2.2)	7.93 (2.60-24.14)	<0.001	6.39 (2.04-13.48)	0.007
ST	2 (3.1)	4 (1.8)	1.74 (0.31-9.71)	0.529	1.48 (0.26-4.23)	0.390
Any death	6 (9.2)	13 (5.8)	1.64 (0.59-4.51)	0.335	1.58 (0.46-4.01)	0.995

Data are n(%). Parameters for adjusted analysis included age, history of percutaneous coronary intervention, peripheral artery disease, renal dysfunction, heart failure, triple-vessel disease, lesion length in the main vessel and side branch, baseline diameter stenosis at the ostial side branch, number of lesions, number of treated lesions, staged percutaneous coronary intervention, final two-stent techniques, and complete revascularisation.
CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; PMI: periprocedural myocardial infarction; µQFR: novel quantitative flow ratio; SB: side branch; ST: stent thrombosis; TVF: target vessel failure; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation

The measurement of the µQFR has the advantage of not requiring the administration of adenosine (which may induce some side effects, i.e., dyspnoea and bradyarrhythmia) or the use of a costly pressure wire, and subsequently shortens the measuring time (usually 1-2 min)[6]. Since µQFR measurements rely largely on the identification of arterial boundaries from angiography, the reproducibility of µQFR is a major issue. Kornowski et al[7] reported that a high degree of concordance was found between two measurements of QFR performed by two different operators (interclass correlation coefficient of 0.97; p<0.001), which is consistent with our results. Since angiographic quality is the determinant of a successfully measured QFR[7-18], the failure of measurements varied from 5.9%[10] to 16%[9], similar to our findings. The common feature of these lesions is slow flow, with a QFR >0.80 due to no significant stenosis, but a TIMI flow grade <3. It is important to note that the µQFR only assesses the presence of ischaemia caused by lesions in the epicardial coronary vessels, so coronary microvascular lesions may present with a normal QFR but slow blood flow. Recently, a meta-analysis[19] of 16 studies demonstrated that 18% of evaluated vessels could not be analysed. Obviously, prospective analysis will promote the successful measurement of QFR given that the quality of angiography meets the requirements[19]. Diagnostic performance of the QFR is another concern. Results from the WIFI II Study[10] showed that the overall sensitivity, specificity, and positive and negative predictive values of the QFR in a single vessel were 77%, 86%, 75%, and 87%, respectively. The sensitivity and specificity of the QFR increased to 86.5% and 88.9%, respectively, in the FAVOR II China study[12], in line with a recent pooled analysis[19]. However, the accuracy of the SB µQFR was not analysed because of a lack of wire-based FFR in the SB.

Coronary bifurcation lesions account for 20-25% of treated lesions[1,2]. Although a 3D model of a bifurcated vessel for QFR measurement was introduced in 2015[20], successful measurement of the µQFR in both the MV and SB using a single projection was only reported more recently[14] in 330 vessels in the FAVOR II China study[15]. The vessel-based analysis demonstrated that not only had the sensitivity remained stable, but the specificity had increased from 89%[19] to 96.2%[14]. Contrary to the FAVOR II China study[15], our study included all bifurcation lesions needing treatment and reported a much lower baseline µQFR for both the MV and SB. Another

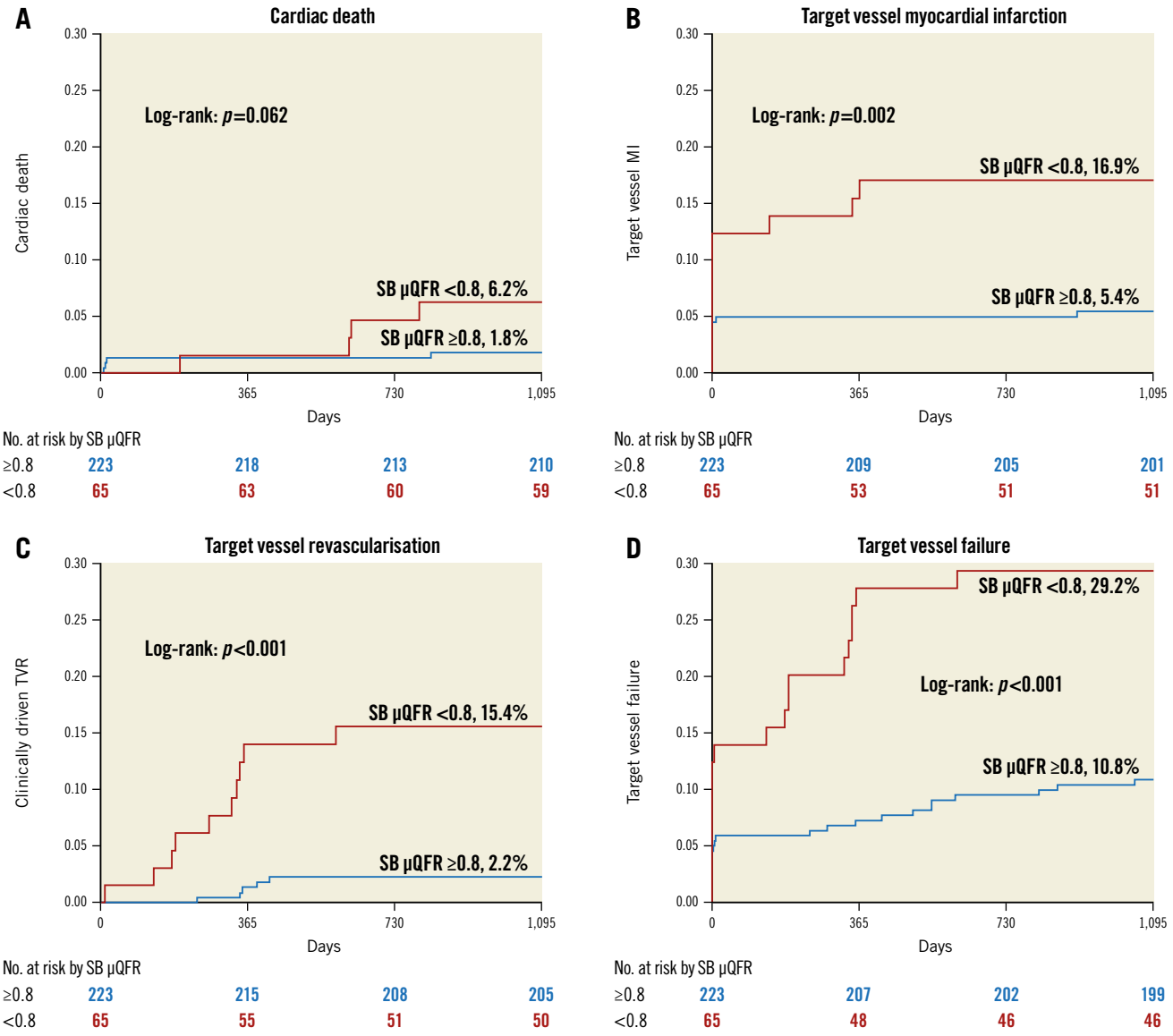

Figure 2. *Comparison of primary and secondary endpoints. Comparison of A) cardiac death, B) target vessel myocardial infarction, C) target vessel revascularisation, and D) target vessel failure between patients with a quantitative flow ratio in the SB (SB µQFR) <0.8 and ≥0.8. µQFR: novel quantitative flow ratio; SB: side branch*

important finding was the MV µQFR <0.89 after the stenting procedure, which was found in 124 (15.1%) patients, similar to the 13% of 123 vessels with suboptimal results from the HAWKEYE study[9]. Using wire-based FFR after stenting the MV, an SB FFR <0.75 was seen in 26% of 110 patients with bifurcation lesions[21], similar to the 22.6% in our study, using a cut-off of 0.8 for the µQFR.

Post-stenting wire-based FFR was the major predictor of clinical events after bifurcation stenting[4,21-24]. Unfortunately, while QFR has generally been accepted to be an alternative to functional parameters for ischaemia, there is no study systematically analysing the association of SB µQFR after the provisional approach with clinical outcomes. At 30 days after the procedure in our study, the differences in TVF and TVMI (driven by periprocedural MI) between the SB µQFR <0.8 and ≥0.8 groups by unadjusted analysis became non-significant after the adjusted analysis. However, the significant differences in TVMI, TVR, and TVF were sustained through three years of follow-up by either unadjusted or adjusted analyses **(Table 4)**. Furthermore, landmark analysis failed to show the difference in TVF from one year to three years between the two groups. Consequently, the more solid correlation of an SB µQFR <0.8 with the occurrence of TVMI, TVR, and TVF within one year has emerged, as most TVFs took place within one year.

The next concern is how to predict QFR in SBs after stenting the MV. The reasons for a reduced FFR post-stenting are multifactorial and include the presence of a muscle bridge, distal lesions, spasm, and microcirculatory dysfunction. In this study, age and SB lesion length were predictors of an SB µQFR <0.8 after the MV intervention. As a result, measurement of the µQFR in the SB after stenting the MV should be recommended, particularly

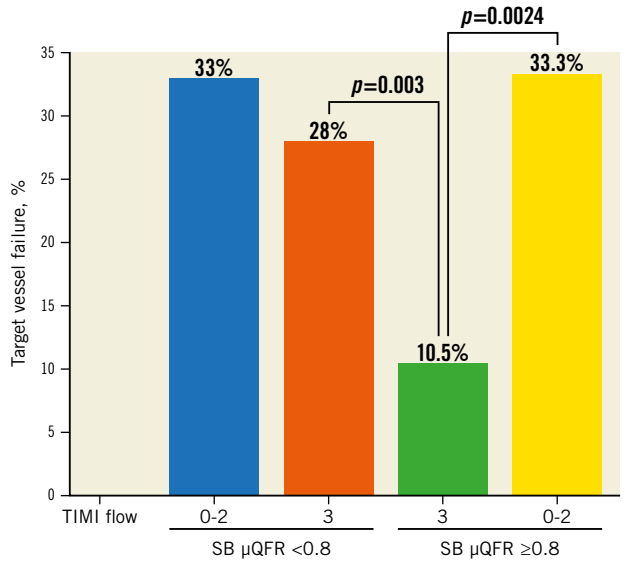

Figure 3. *Correlation of SB μQFR with TIMI flow and TVF. SB: side branch; TIMI: Thrombolysis in Myocardial Infarction; TVF: target vessel failure; μQFR: novel quantitative flow ratio*

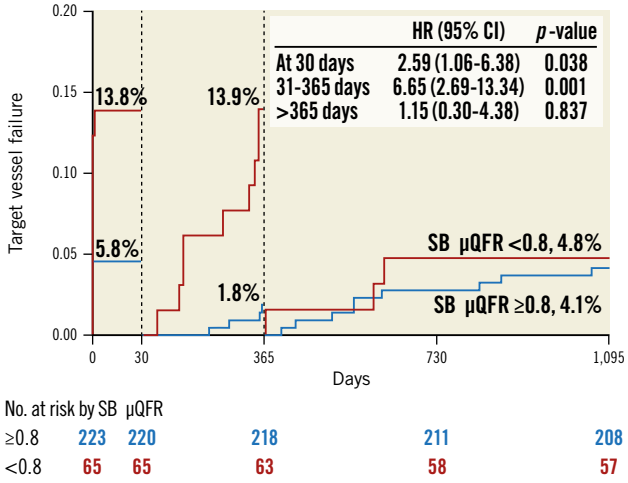

Figure 4. *Landmark analysis of target vessel failure. Landmark analysis showed a significant difference in target vessel failure at 30 days and between 31 and 365 days, but not between 366 days and 3 years, for patients with an SB μQFR <0.8 and an SB μQFR ≥0.8. CI: confidence interval; HR: hazard ratio; SB: side branch; μQFR: novel quantitative flow ratio*

for bifurcation lesions with long lesion lengths in the SB. We also found that previous PCI and an SB μQFR <0.8 were the two independent factors for TVF at three-year follow-up. The important role of SB lesion length has been clearly studied in the DEFINITION study[25], in which a lesion length ≥10 mm in the SB was the major criterion for defining complex bifurcation lesions. The recently published DEFINITION II trial[2] further confirmed the superiority of the systematic two-stent approach to the provisional approach for bifurcation lesions with complex coronary bifurcation lesions. Another striking finding was that an SB μQFR <0.8 was not rare (6.3%) among patients with SB TIMI flow grade 3; however, the underlying mechanisms may be correlated with microcirculatory dysfunction. Altogether, routine measurement of the μQFR in the SB after stenting the MV should be performed, particularly for lesions with a long lesion length in the SB.

Limitations

This study has several limitations. First, the coronary angiographies in the study were obtained without adherence to a dedicated QFR acquisition protocol; therefore, the QFR could not be analysed in 17.3% of the lesions, which hampered a per-patient and intention-to-treat analysis. The relatively high exclusion rate shows, in our opinion, that the quality of the image matters and supports the theory that there are optimal postures to expose lesions and improve measurement accuracy. Second, only patients with bifurcation lesions treated with the provisional approach were selected, which constituted a selection bias and did not allow for calculation of the real rate of SB μQFR <0.8 after both two- and one-stent techniques; however, this study aimed to analyse the impact of the SB μQFR on clinical outcomes for bifurcation lesions treated with provisional stenting only. Third, intravascular imaging was used in fewer than 35% of lesions. This may have increased the number of μQFR <0.89 in the MV and the likelihood of μQFR <0.8 in the SB. Therefore, translating our data into clinical practice should be done very cautiously. Fourth, as a *post hoc* analysis of μQFR measurements, patients with a reduced SB μQFR could not be randomly studied. Finally, the SB μQFR was not compared with pressure wire-based FFR. It is known that not only SB stenosis but also bifurcation angles and the amount of myocardium subtended contribute to FFR values in the SB. Therefore, further elaboration on the potential impact of these factors on the SB μQFR would be of interest. But our finding has linked the SB μQFR to clinical outcomes, which means the SB μQFR is clinically relevant. Altogether, further study is required to analyse the accuracy of the SB μQFR and to compare the treatment effects of two-stent vs one-stent techniques for an SB μQFR <0.8 after stenting the MV.

Conclusions

The μQFR can be reliably measured in most patients with coronary bifurcation lesions. An SB μQFR <0.8 is strongly correlated with clinical events.

Impact on daily practice

In coronary bifurcations, the novel μQFR derived from a single angiographic projection has an acceptable performance as compared to wire-based FFR. However, the relationship between the side branch (SB) μQFR and clinical outcomes after provisional stenting is unclear. In this study, we found a strong correlation between an SB μQFR <0.8 and target vessel failure within one year of MV stenting procedures. SB lesion length plays an important role in predicting the SB μQFR and clinical events after stenting the MV. The μQFR should be routinely measured and used to guide the necessity of SB treatment.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Excluded cases.

The supplementary data are published online at: https://www.asiaintervention.org/doi/10.4244/AIJ-D-22-00045

Supplementary data

Supplementary Table 1. Excluded cases.

Reasons	**Number**
Reference luminal diameter <2.5 mm by visual assessment	11
TIMI flow grade 0 or 1	23
No auto-calibration data in DICOM file	19
Severe vessel overlap at the stenotic segments	31
Poor angiographic image quality precluding precise contour delineation	101
Angiograms with frame rate <12.5 frames per second	7