Preliminary outcomes of quantitative flow ratio-guided coronary bypass grafting in primary valve surgery: A propensity score weighted analysis

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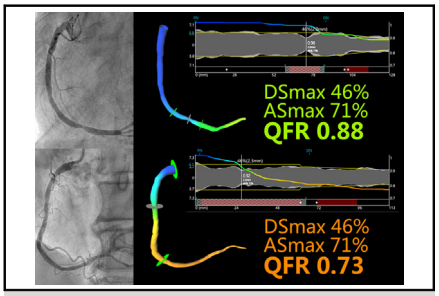
ABSTRACT

Objectives: The guidelines recommend fractional flow reserve-guided coronary artery bypass grafting (CABG) during primary valve surgery without evidence. Quantitative flow ratio (QFR) is a novel coronary angiography (CAG)-based fractional flow reserve measurement. We aimed to compare the early clinical outcomes between QFR-guided and CAG-guided CABG in these patients.

Methods: This observational study screened all 2081 patients admitted to our institution for elective primary mitral and/or aortic valve surgery from January 2017 to September 2020. Of them, all 188 patients with comorbid coronary artery lesions (visual estimated stenosis $\geq$50%) were included. Sixty-nine patients with QFR analysis received bypasses only for lesions with QFR $\leq$0.80 (QFR-guided group). The remaining 119 patients without QFR analysis received bypasses for all stenosis $\geq$50% (CAG-guided group). Propensity overlap weighting was used to neutralize the intergroup imbalance. The primary end point was major adverse cardiovascular events.

Results: After propensity score weighting, the baseline characteristics were comparable. Concomitant coronary artery bypass grafting was performed 58.1% versus 100% in the QFR-guided and CAG-guided groups, respectively. The mean number of grafts was significantly lower in QFR-guided group than in the CAG-guided group (0.9 $\pm$ 0.7 vs 1.6 $\pm$ 0.5 [$P < .001$]). The weighted 30-day incidence of major adverse cardiovascular events was numerically lower in the QFR-guided group than in the CAG-guided group, but not statistically significant (6.3% vs 11.8% [$P = .429$]). After a median follow-up of 31.6 months, the weighted risk of major adverse cardiovascular events and mortality were significantly lower in the QFR-guided group than in the CAG-guided group (major adverse cardiovascular events: hazard ratio, 0.45; 95% CI, 0.24-0.84; $P = .012$; mortality: hazard ratio, 0.38; 95% CI, 0.16-0.93; $P = .029$).

Conclusions: Compared with CAG-guided coronary artery bypass grafting, QFR-guided CABG is associated with less grafting and better clinical outcome in primary valve surgery with comorbid coronary artery disease. To confirm this finding, the Quantitative Flow Ratio Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease trial (NCT03977129) is ongoing. (JTCVS Open 2024;21:90-108)



Coronary stenoses of similar anatomical degree but different physiologically significance.

CENTRAL MESSAGE

Coronary functional assessment may benefit patients of primary valvular heart disease and comorbid coronary artery disease with less grafting and better clinical outcome.

PERSPECTIVE

The propensity score weighting analysis showed that for patients undergoing heart valve surgery and concomitant CABG, QFR guidance was associated with less grafting and better clinical outcomes.

See Discussion on page 109.

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Abbreviations and Acronyms

APT	= antiplatelet therapy
CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CAG	= coronary angiography
DAPT	= dual antiplatelet therapy
FAVOR IV-QVAS	= Quantitative Flow Ratio Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease
FFR	= fractional flow reserve
ITA	= internal thoracic artery
LAD	= left anterior descending artery
MACE	= major adverse cardiovascular events
OAC	= oral anticoagulant
PCI	= percutaneous coronary intervention
QFR	= quantitative flow ratio
SAPT	= single antiplatelet therapy
VHS	= valvular heart surgery

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It is reported that approximately 20% of patients undergoing valvular heart surgery (VHS) have comorbid coronary artery disease (CAD) at the preoperative coronary angiography (CAG) screen.[1,2] Reviews of the Society of Thoracic Surgeons Database indicate that the surgical mortality and morbidity of combined VHS and coronary artery bypass grafting (CABG) is 2 to 4 times that of VHS alone.[3]

Concomitant CABG and VHS is complex and challenging, but the indication is still controversial. According to American College of Cardiology/American Heart Association guidelines, CABG should be considered for coronary stenosis ≥70% (for left main stenosis ≥50%) (Class IIa), leaving stenoses between 50% and 70% unclarified.[4] Meanwhile, in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for valvular heart disease, CABG is recommended for coronary stenosis >70% (Class I) and should be considered if coronary stenosis is between 50% and 70% (Class IIa).[5] Of note, all these recommendations were based on limited evidence (level C).

The guidance on revascularization strategy is shifting from anatomic to physiologic. Percutaneous coronary intervention (PCI) guided with fractional flow reserve (FFR) reduces stenting with improved clinical outcomes.[6-9] Without functional assessment of the coronary artery to identify the ischemia, unnecessary CABG may result in flow competition and graft failure, prolonging cardiopulmonary bypass and aortic clamping time, thus increasing surgical risk. However, the effectiveness of FFR-guided CABG has yet to be proved.[10]

The quantitative flow ratio (QFR) is a novel, intelligent, noninvasive method that enables efficient computation of FFR from CAG in excellent concordance with catheter-based FFR (92.7% accuracy, 94.6% sensitivity, and 91.7% specificity from the Functional Assessment by Various Flow Reconstructions [FAVOR] II China study).[11-15] The optimal approach was validated in the FAVOR multicenter study, proving that QFR can be computed without pharmacology-induced hyperemia.[13] The FAVOR II China study and the parallel FAVOR II Europe-Japan study showed a high diagnostic accuracy of in-procedure QFR.[14,15] QFR-guided PCI showed improved clinical outcomes in the Comparison of Quantitative Flow Ratio-Guided and Angiography-Guided Percutaneous Intervention in Patients With Coronary Artery Disease, NCT03656848 trial (FAVOR III China trial).[16]

The aim of this observational cohort study was to compare the clinical outcomes of QFR-guided versus CAG-guided CABG for patients with CAD undergoing primary VHS and offer preliminary data for designing a future randomized trial.

METHODS

Ethical Statement

This study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine on July 9, 2021 (ID: 2021-No.93). This was a retrospective observational study without intervention. Patient written consent was waived by the ethics committee.

Patients

From January 2017 to September 2020 all patients admitted to our institution for elective mitral and/or aortic valve surgery due to primary VHD were screened. Patients with at least 1 coronary artery lesion (stenosis ≥50% by visual evaluation) diagnosed with preoperative CAG were included into the study.

The exclusion criteria included patients with a history of previous cardiac surgery, planned second-stage PCI, secondary valvular heart disease (eg, ischemia and cardiomyopathy), transcatheter valve intervention, cardiogenic shock or other critical conditions, and the target vessels being ungraftable.

When patients were sent for QFR analysis and received bypass only for QFR ≤ 0.80, they were assigned to the QFR-guided group. The remaining patients, who did not receive QFR analysis, among whom all stenosis ≥50% in major coronary arteries (diameter ≥1.5 mm) were bypassed according to the guidelines and surgeon's decision, were assigned to the CAG-guided group.[4,5] The preoperative, intraoperative, and postoperative data were collected and retrospectively reviewed from our hospital database and logged into a clinical study-specific medical record created for each patient.

QFR Analysis

The standard 7-position CAG was taken in the catheter lab preoperatively. The images were sent to the core lab (CardHemo; Med-X Research Institute) for computation of the QFR. Analysis was performed by experienced analysts using the AngioPlus system (Pulse Medical Imaging Technology) as previously described.[11-15] The value of QFR $\leq$ 0.80 was defined as QFR-positive. The demonstration of QFR analysis is shown in Figure E1.

Follow-up and Outcomes

Follow-up data were collected from our institutional database. All patients completed outpatient visit 30 days postsurgery then received an outpatient or telephone visit every half-year. The primary end point was major adverse cardiovascular events (MACEs), defined as all-cause death, myocardial infarction, stroke, unplanned repeated revascularization, and cardiovascular rehospitalization. Definitions for all end points are listed in Appendix E1.

Statistical Analysis

Continuous data were reported as the mean $\pm$ SD or median (P25-P75) and analyzed using the Student *t* test, whereas categorical data were presented as numbers (percentages) and compared by χ^2 test, Fisher exact test, or Cochran-Mantel-Haenszel χ^2 test. Primary data analysis was performed by propensity overlap weighting to adjust the differences in the baseline characteristics and to achieve more similar populations between the 2 groups. Propensity scores were first calculated using a logistic regression model with QFR-guided group as the response variable (CAG-guided group as control) and all characteristics in Table 1 except left ventricular ejection fraction classification as covariates. The balance was evaluated by standardized differences using a threshold of 0.1. The rate difference between the 2 groups and 95% CI were calculated using the Newcombe-Wilson method. The Kaplan-Meier method was used to draw survival curves of events and the confidence band of the curves was estimated by log-log transformation. The design-based sampling errors of hazard ratio (HR) for weighted extended outcomes were computed by the Taylor series method. To examine the robustness of extended follow-up outcomes as sensitivity analyses, 2 multivariate regression analyses were conducted. One included raw baseline characteristics with significance < 0.1. The other included the propensity score as the only covariate. All statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc).

RESULTS

Study Flow

Overall, 2081 patients underwent primary VHS from January 2017 to September 2020 in our institution. Preoperative CAG was undertaken in 1320 patients, of whom 188 (14.2%) were diagnosed with at least 1 coronary artery stenosis $\geq$50%. Sixty-nine patients who were sent for QFR analysis and received bypasses only for lesions with QFR $\leq$ 0.80 were assigned to the QFR-guided group. The remaining 119 patients without QFR analysis who directly received bypasses for all stenosis $\geq$50% were assigned to the CAG-guided group (Figure 1).

Baseline Characteristics

Baseline patient demographics, coronary artery disease characteristics, risk variables, and comorbidity are summarized in Table 1. Before propensity score weighting, the QFR-guided group had a higher proportion of patients with coronary stenosis from 50% to 69%, and a lower proportion of patients with stenosis $\geq$90%, compared with the CAG-guided group. The number of diseased vessels per patient was similar between the 2 groups, which is the same as the proportions of 1-, 2- or 3-vessel disease and left main disease. All other baseline characteristics were originally comparable between the 2 groups (Table 1).

Weighting for propensity score yielded 2 groups with no significant difference in baseline characteristics with very low standardized mean differences showing excellent balance (Table 1). The distribution of propensity scores of the 2 groups is demonstrated in Figure E2. The changes in covariate balance before and after weighting is illustrated in Figure E3.

Before propensity score weighting, patients in the QFR-guided group underwent significantly more combined aortic surgeries, compared with those in the CAG-guided group. All other non-CABG procedure-related characteristics were comparable between the 2 groups (Table 1).

Weighting for propensity score yielded 2 groups with no significant difference in all non-CABG procedure-related characteristics, with very low standardized mean differences showing excellent balance (Table 1).

Procedure-Related Results

The 69 patients in the QFR-guided group had a total of 125 diseased major coronary arteries (visually estimated stenosis $\geq$50%, diameter $\geq$1.5 mm, suitable as bypass target), which were considered indicated to CABG. After QFR analyses, 70 out of 125 (56.0%) of the above vessels had a QFR > 0.8 and bypass were avoided. Specifically, of the 125 diseased coronary arteries, there were 66 vessels of 50% to 69% stenosis, among which 20 (30.3%) were QFR-positive and bypassed. The remaining 59 vessels were $\geq$70% stenosed, among which 24 (40.7%) were QFR-negative and bypass were avoided (Table 2). At the patient level, CABG was simplified or avoided in 47 out of 69 (68.1%) patients, among whom 14 patients had less bypass grafting and 33 patients completely avoided CABG. The type of conduits bypassed to different coronary targets is shown in Table E1. In the QFR-guided group, 88.0% of all grafted left anterior descending arteries (LADs) were bypassed with an internal thoracic artery (ITA). In the CAG-guided group, the proportion was 70.1%.

With weighting, all CAG-guided patients received concomitant CABG, whereas only 58.1% of the QFR-guided patients underwent concomitant CABG. The number of grafts per patient was significantly lower in the QFR-guided group than in the CAG-guided group (0.9 vs 1.6 [P < .001]). The crossclamp time in the QFR-guided group was significantly lower than that in the CAG-guided group (75.1 vs 84.1 minutes [P = .030]) (Table 3). The length of total hospital stay and postsurgery hospital

TABLE 1. Demographic, clinical, and procedure-related characteristics

Characteristics	Crude				Propensity score weighted			
	QFR-guided group (n = 69)	CAG-guided group (n = 119)	*P* value	SMD	QFR-guided group	CAG-guided group	*P* value	SMD
Female	26 (37.7)	44 (37.0)	.923	0.015	40.0	40.0	1.000	<0.001
Age (y)	66.9 ± 7.0	65.5 ± 7.7	.201	0.197	66.2 ± 7.1	66.2 ± 7.1	1.000	<0.001
Etiology of valve disease			.660	0.189			1.000	<0.001
Rheumatic	16 (23.2)	19 (16.0)			21.1	21.1		
Degenerative	45 (65.2)	83 (69.7)			65.9	65.9		
Infectious	1 (1.5)	2 (1.7)			2.1	2.1		
Congenital	7 (10.1)	15 (12.6)			10.9	10.9		
Medical history								
Hypertension	50 (72.5)	80 (67.2)	.454	0.114	72.4	72.4	1.000	<0.001
Diabetes mellitus	20 (29.0)	37 (31.1)	.762	0.046	30.4	30.4	1.000	<0.001
Hyperlipidemia*	34 (49.3)	53 (44.5)	.530	0.095	47.4	47.4	1.000	<0.001
Stroke	12 (17.4)	19 (16.0)	.800	0.038	20.4	20.4	1.000	<0.001
Myocardial infarction†	7 (10.1)	15 (12.6)	.613	0.078	11.9	11.9	1.000	<0.001
COPD	7 (10.1)	15 (12.6)	.613	0.078	10.6	10.6	1.000	<0.001
CKD‡	10 (14.5)	20 (16.8)	.676	0.064	17.1	17.1	1.000	<0.001
Atrial fibrillation	31 (44.9)	43 (36.1)	.234	0.180	40.5	40.5	1.000	<0.001
Peripheral vascular disease§	3 (4.4)	8 (6.7)	.504	0.104	5.6	5.6	1.000	<0.001
Patients with diseased vessel‖								
Left main disease	3 (4.4)	6 (5.0)	.830	0.033	4.9	4.9	1.000	<0.001
1-vessel disease	30 (43.5)	49 (41.2)	.803	0.101	43.2	43.2	1.000	<0.001
2-vessel disease	20 (29.0)	40 (33.6)			32.1	32.1		
3-vessel disease	19 (27.5)	30 (25.2)			24.7	24.7		
No. of diseased vessels per patient	1.8 ± 0.9	2.0 ± 1.0	.363	0.140	1.9 ± 0.9	1.9 ± 1.0	1.000	<0.001
Patients with diseased vessel¶								
50%-69%	50 (72.5)	67 (56.3)	.028	0.342	68.5	68.5	1.000	<0.001
70%-89%	33 (47.8)	67 (56.3)	.262	0.170	48.3	48.3	1.000	<0.001
≥90%	8 (11.6)	34 (28.6)	.007	0.434	18.3	18.3	1.000	<0.001
SYNTAX score#	7 (5-12)	8 (5-13)	.384	0.238	7 (5-13)	7 (5-12)	1.000	<0.001
Left ventricle								
LVEDD (mm)	55 (49-59)	55 (50-62)	.451	0.095	55 (48-59)	54 (49-61)	1.000	<0.001
LVEF (%)	63 (58-68)	62 (52-67)	.245	0.217	63 (57-68)	63 (55-67)	1.000	<0.001
Valvular procedures								
Isolated mitral valve	32 (46.4)	60 (50.4)	.593	0.081	48.4	48.4	1.000	<0.001
Isolated aortic valve	23 (33.3)	39 (32.8)	.937	0.012	32.3	32.3	1.000	<0.001
Mitral and aortic valves	13 (18.8)	18 (15.1)	.508	0.099	17.1	17.1	1.000	<0.001
Comorbid procedures								
Tricuspid valve	19 (27.5)	30 (25.2)	.726	0.053	27.3	27.3	1.000	<0.001
Atrial fibrillation ablation	11 (15.9)	18 (15.1)	.881	0.023	17.2	17.2	1.000	<0.001
Left atrial appendage occlusion	14 (20.3)	17 (14.3)	.285	0.159	18.5	18.5	1.000	<0.001
Aortic surgery	12 (17.4)	5 (4.2)	.002	0.435	10.5	10.5	1.000	<0.001

Frequency for categorical variables is not applicable after propensity score weighting. Values for categorical variables after propensity score weighting are presented as percentage only. Values for categorical variables with crude analysis are presented as n (%). Values for continuous variables are presented as mean ± SD or median (interquartile range). *QFR*, Quantitative flow ratio; *CAG*, coronary angiography; *CABG*, coronary artery bypass grafting; *SMD*, standardized mean difference; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; *LVEDD*, left ventricular end diastolic diameter; *LVEF*, left ventricular ejection fraction; *LDL-C*, low-density lipoprotein cholesterol. *Defined as baseline or historical low-density lipoprotein cholesterol ≥2.6 mmol/L. †Includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and silent/unrecognized myocardial infarction. Definition shown in Appendix E1. ‡Defined as stage 3 or higher chronic kidney disease (estimated glomerular filtratin rate <60 mL/min/1.73 m^2). §Defined as 1 or more of the following: claudication, carotid occlusion or ≥50% stenosis, amputation for arterial disease, previous or planned intervention on limb arteries or carotids. ‖Defined as stenosis of ≥50% by visual estimation. ¶Calculated at patient level according to the degree of the coronary artery stenosis by visual estimation. #A comprehensive angiographic assessment of the coronary vasculature. SYNTAX score: 0 to 22, low anatomical complexity; 23 to 32, intermediate anatomical complexity; and ≥33, high anatomical complexity.

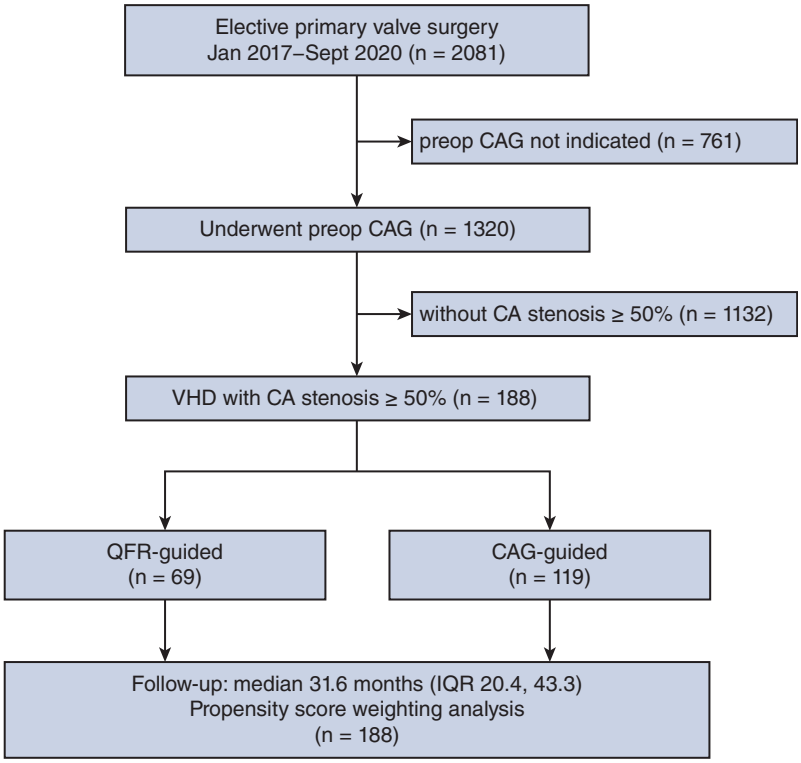

FIGURE 1. Study flow diagram. *CAG*, Coronary angiography; *CA*, coronary artery; *VHD*, valvular heart disease; *QFR*, quantitative flow ratio; *IQR*, interquartile range.

stay were both shorter in the QFR-guided group compared with the CAG-guided group (total: 18.5 vs 28.6 days [$P < .001$]; postsurgery: 11.7 vs 18.7 days [$P = .002$]) (Table 3).

30-Day Outcomes

MACE was reported in 8.7% (6 out of 69) and 11.8% (14 out of 119) of the patients in the QFR-guided and CAG-guided groups, respectively. Mortality was 7.3% (5 out of 69) and 7.6% (9 out of 119) in the QFR-guided and CAG-guided groups, respectively. Of note, none of the patients had ischemic events during weaning from cardiopulmonary bypass.

With propensity score weighting, the 30-day incidence of MACE was 6.3% in the QFR-guided group and 11.8% in the CAG-guided group (absolute difference, −5.5%;

TABLE 2. Quantitative flow reserve (QFR) positive proportion in different coronary artery territories, stratified by degree of coronary artery stenosis

	QFR ≤ 0.8			
Coronary artery stenosis	**Total**	**LAD**	**LCX**	**RCA**
Overall	55/125 (44.0)	37/60 (61.7)	11/32 (34.4)	7/33 (21.2)
Stenosis by visual estimation				
50%-69%	20/66 (30.3)	14/34 (41.2)	3/13 (23.1)	3/19 (15.8)
70%-89%	23/47 (48.9)	15/18 (83.3)	5/16 (31.3)	3/13 (23.1)
≥90%	12/12 (100)	8/8 (100)	3/3 (100)	1/1 (100)
Areal stenosis by QCA				
50%-69%	9/53 (17.0)	6/27 (22.2)	2/11 (18.2)	1/15 (6.7)
70%-89%	37/62 (59.7)	26/28 (92.9)	6/17 (35.3)	5/17 (29.4)
≥90%	9/10 (90.0)	5/5 (100)	3/4 (75.0)	1/1 (100)
Diameter stenosis by QCA				
40%-49%	7/54 (13.0)	5/27 (18.5)	2/12 (16.7)	0/15 (0)
50%-69%	37/60 (61.7)	26/27 (96.3)	6/17 (35.3)	5/16 (31.3)
70%-89%	11/11 (100)	6/6 (100)	3/3 (100)	2/2 (100)

Values are presented as n/N (%). *LAD*, Left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery; *QCA*, quantitative coronary angiography.

TABLE 3. Procedure-related results

Characteristics	Crude				Propensity score weighted			
	QFR-guided group (n = 69)	CAG-guided group (n = 119)	Difference (95% CI)	*P* value	QFR-guided group	CAG-guided group	Difference (95% CI)	*P* value
Concomitant CABG	36 (52.2)	119 (100.0)	−47.8 (−59.6 to −36.0)	<.001	58.1	100.0	−41.9 (−58.3 to −25.5)	<.001
No. of grafts per patient	0.8 ± 1.0	1.7 ± 0.9	−0.9 (−1.2 to −0.6)	<.001	0.9 ± 0.7	1.6 ± 0.5	−0.7 (−1.0 to −0.4)	<.001
CPB time (min)	118.9 ± 36.5	131.1 ± 49.3	−12.2 (−24.6 to 0.3)	.055	119.2 ± 26.5	130.3 ± 23.4	−11.1 (−22.6 to 0.6)	.063
Crossclamp time (min)	76.3 ± 26.2	85.3 ± 35.0	−9.0 (−17.9 to 0.2)	.046	75.1 ± 18.1	84.1 ± 16.5	−9.0 (−17.1 to 0.8)	.030
Hospital stay (d)	19.3 ± 6.3	26.7 ± 20.2	−7.3 (−11.2 to −3.4)	<.001	18.5 ± 4.1	28.6 ± 13.2	−10.1 (−15.2 to −5.0)	<.001
Post-surgery hospital stay (d)	12.5 ± 5.2	16.6 ± 18.9	−4.2 (−7.8 to −0.6)	.024	11.7 ± 3.4	18.7 ± 12.7	−7.0 (−11.4 to −2.6)	.002

Frequency for categorical variables is not applicable after propensity score weighting. Values for categorical variables after propensity score weighting are presented as percentage only. Values for categorical variables with crude analysis are presented as n (%). Values for continuous variables are presented as mean ± SD. *QFR*, Quantitative flow ratio; *CAG*, coronary angiography; *CABG*, coronary artery bypass grafting; *CPB*, cardiopulmonary bypass.

95% CI, −20.8% to 9.5%; $P = .429$) (Table 4). Specifically, the 30-day incidence of all-cause death with weighting was 4.8% in the QFR-guided group and 7.8% in the CAG-guided group (absolute difference, −3.0%; 95% CI, −17.1% to 10.7%; $P = .611$). The incidence of myocardial infarction with weighting was 1.5% in the QFR-guided group and 6.7% in the CAG-guided group, respectively (absolute difference, −5.2%; 95% CI, −18.5% to 6.8%; $P = .280$). The incidence of stroke with weighting was 2.0% in the QFR-guided group and 3.4% in the CAG-guided group, respectively ($P = .723$). There was no repeat revascularization or cardiovascular rehospitalization in either group (Table 4).

Extended Follow-up Outcomes

The median follow-up time was 31.6 months (interquartile range, 20.4-43.3 months). MACE was reported in 24.6% (17 out of 69) and 34.5% (41 out of 119) of the patients in QFR-guided and CAG-guided groups, respectively. Mortality was 13.0% (9 out of 69) and 21.8% (26 out of 119) in the QFR-guided and CAG-guided groups, respectively. Of note, there was no repeated revascularization in either group.

The propensity score weighted Kaplan-Meier estimates of time to first MACE, mortality, myocardial infarction, and stroke are shown as Figure 2. In the QFR-guided group, the risk of MACE was significantly lower than in the CAG-guided group (HR, 0.45; 95% CI, 0.24-0.84; $P = .012$) (Figure 2, *A*). Specifically, mortality in the QFR-guided group were significantly lower (HR, 0.38; 95% CI, 0.16-0.93; $P = .029$) (Figure 2, *B*), whereas the risk of myocardial infraction was numerically lower (HR, 0.25; 95% CI, 0.06-1.07; $P = .056$) (Figure 2, *C*), compared with that in CAG-guided group. For stroke, no significant difference

TABLE 4. Thirty-day clinical outcomes

Events	Crude				Propensity score weighting			
	QFR-guided group (n = 69)	CAG-guided group (n = 119)	Difference (95% CI)	*P* value	QFR-guided group	CAG-guided group	Difference (95% CI)	*P* value
MACE	6 (8.7)	14 (11.8)	−3.1 (−11.5 to 7.1)	.511	6.3	11.8	−5.5 (−20.8 to 9.5)	.429
All-cause death	5 (7.3)	9 (7.6)	−0.3 (−7.8 to 9.0)	.937	4.8	7.8	−3.0 (−17.1 to 10.7)	.611
Myocardial infarction*	1 (1.5)	7 (5.9)	−4.4 (−10.3 to 2.6)	.262	1.5	6.7	−5.2 (−18.5 to 6.8)	.280
Stroke	3 (4.4)	4 (3.4)	1.0 (−4.7 to 8.9)	.709	2.0	3.4	−1.4 (−13.5 to 10.2)	.723
Repeated revascularization	0	0	–	–	0	0	–	–
CV rehospitalization	0	0	–	–	0	0	–	–

Frequency for categorical variables is not applicable after propensity score weighting. Values for categorical variables after propensity score weighting are presented as percentage only. Values for categorical variables with crude analysis are presented as n (%). Same events were counted only once in the same patient. *QFR*, Quantitative flow reserve; *CAG*, coronary angiography; *CV rehospitalization*, cardiovascular rehospitalization; *MACE*, major adverse cardiovascular events. *Includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and silent/unrecognized MI. Definition shown in Appendix E1.

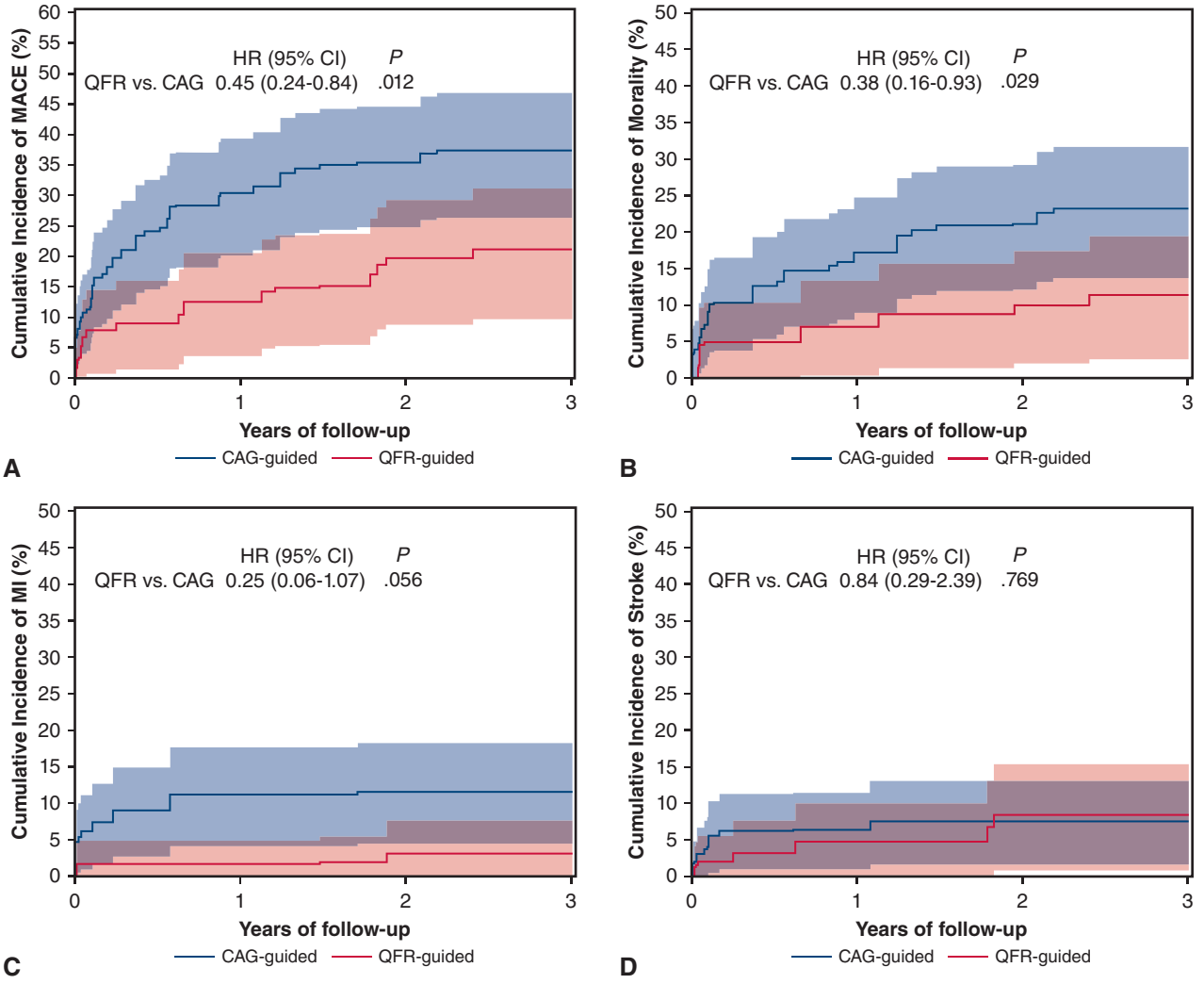

FIGURE 2. The propensity score weighted Kaplan-Meier estimates of time to first major adverse cardiovascular events (*MACE*) (A), mortality (B), myocardial infarction (C), and stroke (D). Number of patients at risk was not applicable for weighted results. *CAG*, Coronary angiography; *HR*, hazard ratio; *QFR*, quantitative flow ratio; *MI*, myocardial infarction.

was observed between the 2 groups (HR, 0.84; 95% CI, 0.29-2.39; $P = .769$) (Figure 2, *D*). The crude Kaplan-Meier graphs estimates of time to first MACE, mortality, myocardial infarction, and stroke is shown as Figure 3.

Multivariate regression analysis was conducted for sensitivity analysis. Results were attenuated after adjustment for potential confounding factors (patients with coronary artery stenosis of 50%-69%, patients with coronary artery stenosis $\geq$90%, or combined aortic surgery). Although there is still some evidence of association, the QFR-guided strategy was not statistically significant as an independent risk factor associated to MACE (HR, 0.59; 95% CI, 0.33-1.08; $P = .088$), mortality (HR, 0.47; 95% CI, 0.21-1.09; $P = .078$), myocardial infarction (HR, 0.35; 95% CI, 0.09-1.34; $P = .126$), or stroke (HR, 1.22; 95% CI, 0.44-3.43; $P = .702$). Another multivariate regression analysis, including the propensity score as the only covariate, revealed congruent results with the main analysis (Table E2). See Figure 4 for a graphical abstract of the study.

QFR Results

All QFR results were obtained from the QFR-guided group. Patients in the CAG-guided group were not sent for QFR analysis.

Table 2 demonstrated QFR positive proportion in different coronary artery territories, stratified by degree of coronary artery stenosis. Regarding coronary territories, QFR-positive was found in 61.7% (37 out of 60) of the LAD territory, 34.4% (11 out of 32) in left circumflex artery territory, and 21.2% (7 out of 33) in right coronary artery territory. For lesions of similar degree, those in LAD territory tend to be the most physiologically significant, followed by those in left circumflex artery and right coronary artery territory.

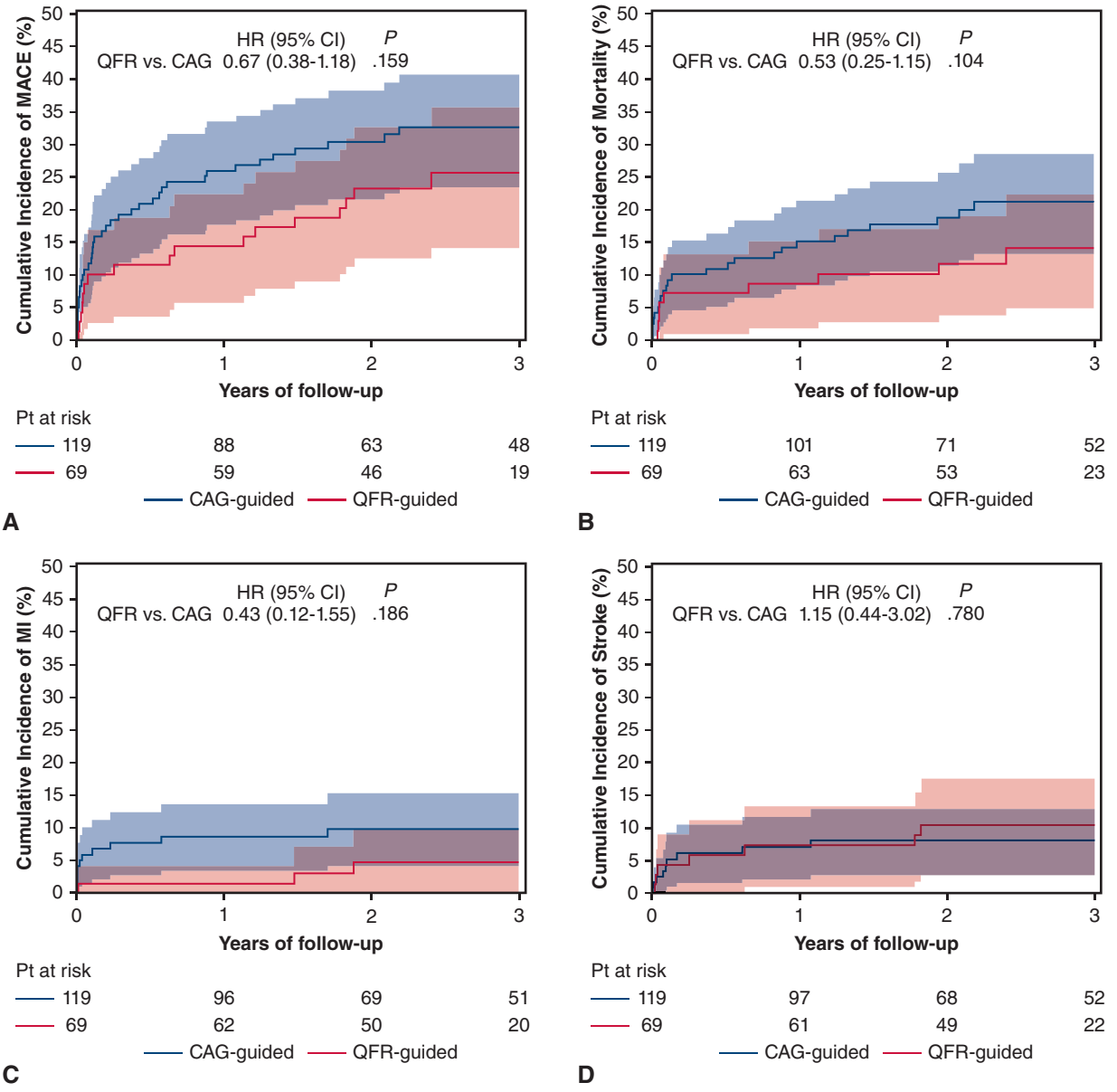

FIGURE 3. The crude Kaplan-Meier estimates reporting time to first major adverse cardiovascular event (*MACE*) (A), mortality (B), myocardial infarction (C), and stroke (D). *CAG*, Coronary angiography; *HR*, hazard ratio; *QFR*, quantitative flow ratio; *MI*, myocardial infarction.

For stenosis of 50% to 69% by visual estimation, 30.3% were physiologically significant. For those of 70% to 89%, 48.9% were physiologically significant. For those ≥90%, 100% were physiologically significant.

Figure E4 is a scatter plot demonstrating relations between QFR and different measures of stenosis, colored in the 3 coronary territories. Compared with visual estimation, diameter stenosis, and areal stenosis from quantitative coronary analysis showed better correlation with QFR.

Antithrombosis Therapy and Bleeding Events

Concomitant medications at discharge and last follow-up were shown as Table E3. With weighting, at discharge, lower proportion of isolated antiplatelet therapy (APT), especially dual antiplatelet therapy (DAPT), was administered in QFR-guided group than in CAG-guided group with weighting (isolated APT: 27.1% vs 44.7% [$P = .036$]; DAPT: 21.0% vs 38.9% [$P = .022$]). There was no significant difference between the 2 groups in administration of isolated oral anticoagulant (OAC), OAC with single antiplatelet therapy (SAPT) or isolated SAPT at discharge (OAC: 18.4% vs 10.7% [$P = .220$]; OAC + SAPT: 54.1% vs 43.2% [$P = .212$]; SAPT: 6.1% vs 5.8% [$P = .945$]). At last follow-up, no significant difference was observed in different antithrombosis therapy between the 2 groups (OAC: 25.7% vs 28.4% [$P = .729$];

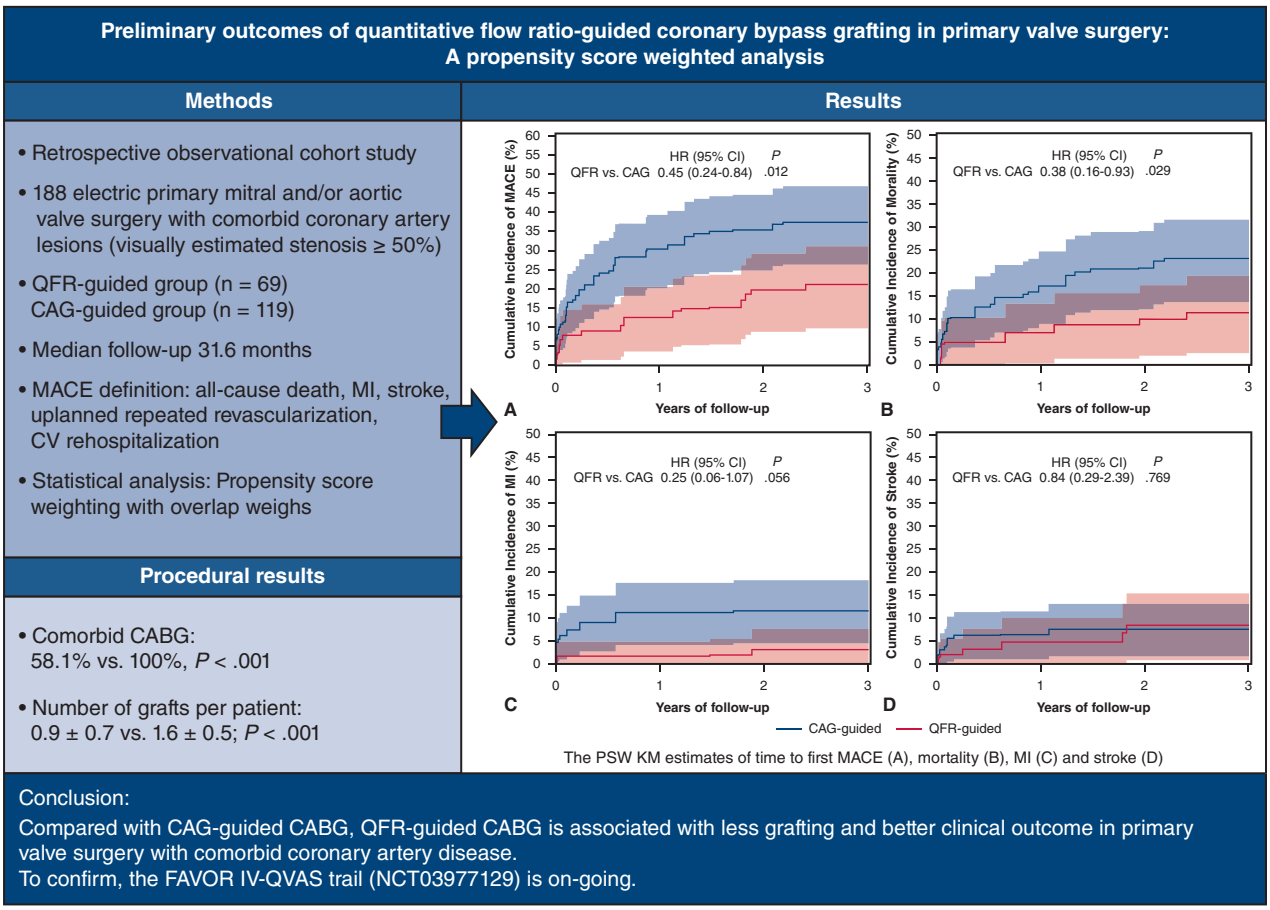

FIGURE 4. Graphical abstract: Retrospective observational study showed that compared with coronary angiography-guided coronary artery bypass grafting (*CABG*), quantitative flow ratio (*QFR*)-guided CABG is associated with less grafting and better clinical outcome in primary valve surgery with comorbid coronary artery disease. To confirm this finding, the Quantitative Flow Ratio Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease trial (NCT03977129) is ongoing. *CAG*, Coronary angiography; *MACE*, major adverse cardiovascular event; *MI*, myocardial infarction; *CV*, cardiovascular; *HR*, hazard ratio; *PSW KM*, propensity score weighted Kaplan-Meier; *FAVOR IV-QVAS*, Quantitative Flow Ratio Guided Revascularization Strategy for Patients Undergoing Primary Valve Surgery With Comorbid Coronary Artery Disease.

OAC + SAPT: 26.2% vs 22.6% [$P = .638$]; DAPT: 6.5% vs 5.4% [$P = .779$]; SAPT: 36.8% vs 36.9% [$P = .993$]).

During follow-up, the incidence of major bleeding was 2.9% (2 out of 69) and 4.2% (5 out of 119) in the QFR-guided group and the CAG-guided groups, respectively. The incidence of fatal bleeding events was 2.9% (2 out of 69) and 3.4% (4 out of 119), respectively.

DISCUSSION

From this observational study, we found that for patients with CAD undergoing primary valve surgery, QFR-guided CABG had better clinical outcomes, less grafting, and shorter operative time and hospital stay, with no additional risk of repeated revascularization.

In recent decades, many efforts have been made to apply FFR in CABG to guide the surgical revascularization strategies. Although fewer grafts and better graft patency with FFR guidance are shown in most studies, significant improvement in clinical outcome has not been observed, including in a large registry study[17] and the Fractional Flow Reserve versus Angiography Randomization for Graft Optimization trial[18] and the Graft Patency After FFR-guided versus Angio-guided CABG Trial.[19] Moreover, less grafting, due to FFR-guided CABG not to bypass the arteries without ischemia, challenges the traditional concept of surgical complete revascularization.

However, the clinical scenario of dealing VHD with CAD is very different from CAD alone, in terms of

pathophysiology and surgical complexity. From our data, we have observed a significantly higher operative risk when more CABG procedures were performed. The Society of Thoracic Surgeons Database also indicated a significantly higher operative mortality for valvular surgeries with concomitant CABG, compared with isolated valvular surgeries.[3] It has also been noticed that in the current clinical practice, without FFR guidance, concomitant CABG was conducted up to twice as much as PCI for patients with undergoing surgical or transcatheter valve intervention, as reported by the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients With Aortic Stenosis trial.[20]

Based on the above phenomenon, we hypothesized that functional assessment may help guiding CABG during valve surgery to improve clinical outcomes. Although CABG decision making is still based on the anatomical assessment, the American College of Cardiology/American Heart Association and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for valvular heart disease recommend physiological assessment for patients with comorbid CAD, but lack evidence.[4,5] Randomized trials of FFR-guided CABG in valvular surgery are very few. We conducted this observational study to evaluate the efficacy of QFR-guided CABG in this situation. Based on these preliminary data, we designed the Quantitative Flow Ratio Guided Revascularization Strategy for patients undergoing Primary Valve Surgery with Comorbid Coronary Artery Disease, NCT03977129. Another ongoing randomized controlled trial is the Strategies for Revascularization in Patients Undergoing Heart Valve Surgery with Concomitant Coronary Artery Disease, NCT02173860 trial, in which catheter-based FFR was adopted.

To date, retrospective evidence on this topic is also very scarce. The only other study was a propensity-score matching analysis from Yang and colleagues,[21] reporting improved 1-year clinical outcomes with QFR-guided strategy, by reducing MACE by more than a half. Our study showed very similar results and confirmed the advantage of this novel strategy at a longer follow-up period.

Del Forno and colleagues[22] enrolled 77 VHS candidates with moderate coronary stenosis (50%-70%). The CABG was intentionally not to perform without preoperative coronary functional assessment in 77 patients reported by Del Forno. There were no in-hospital deaths with only 1 postoperative myocardial infarction. The 6-year overall survival was excellent with very few PCIs. The authors concluded that moderate coronary stenosis at the time of VHS can be safely overlooked and mostly does not need any further treatment. The benefit of CABG for moderate stenosis may be restricted by 3 main factors, that competitive flow may influence the patency rate of the graft[23]; proximal lesions will be accelerated after CABG[24]; and atherosclerosis may be stabilized even healed with modern secondary prevention therapies.[25] In our study, among the 50 patients with 50% to 69% stenosis in the QFR-guided group, 39 patients who had at least 1 50% to 69% stenosis were excluded from CABG due to negative QFR. During follow-up, only 2 patients were discovered to have clinically silent myocardial infarction around 2 years after surgery without repeated revascularization. Therefore, our result seems to be generally consistent with the conclusions from Del Forno and colleagues.[22]

However, in our study, positive QFR was detected in 30.3% of all moderate coronary lesions (50%-69%, visually estimated). Similarly, in the Fractional Flow Reserve versus Angiography for Guidance of PCI in Patients With Multivessel Coronary Artery Disease trial, 35% of all 1174 lesions between 50% and 70% were hemodynamically significant.[8] Grafting only those lesions $\geq$70% and overlooking those between 50% and 70% could left many physiologically significant lesions untreated. Moreover, our data showed that about half of coronary lesions between 70% and 90% (visually estimated) were QFR-negative. Therefore, functional assessment could be a more precise measure to guide CABG during valve surgery.

Another interesting phenomenon was observed. In the CAG-guided group more CABG were performed; however, merely resulting in a difference of < 1 graft and 9 minutes of crossclamp time (average). It was challenging to explain how this modest difference in procedure could cause such significant difference in clinical outcome. In the QFR-guided group, 88.0% of all grafted LADs were bypassed with ITA. Although in the CAG-guided group, the proportion was 70.1%. One hypothesis is that in the CAG-guided group, when more bypasses were performed, surgeons could have used fewer ITAs than in the QFR-guided group. This phenomenon possibly resulted from the 2 different CABG strategies. This could be a potential mechanism by which QFR-guided strategy gained an advantage over the CAG-guided strategy. Another possible hypothesis is that this was related to the difference in antithrombosis therapy in the 2 groups. Concomitant CABG could have largely influenced the postoperative antithrombosis therapy, and restricted the infusion of hemostasis medications, plasma, and cryoprecipitate. In the long run, especially during the first year postoperatively, a complex antithrombotic strategy may continuously lead to mismanagement and clinical events. In the Michigan Anticoagulation Quality Improvement Initiative Registry, patients taking warfarin and aspirin had a higher rate of bleeding events (28.3 vs 13.3 per 100 patient-years [$P < .001$]) compared with those receiving isolated warfarin, without much difference in rates of ischemic stroke (0.56 vs 0.48 per 100 patient-years [$P = .89$]).[26] In our study, from the Kaplan-Meier curves of MACE, mortality, and myocardial infarction, we found a persistently growing advantage in the

QFR-guided group over the CAG-guided group during the first postoperative year. The difference seemed to stabilize thereafter when antiplatelet therapies were mostly downgraded. In this study, a higher proportion of isolated APT, mainly DAPT, was administered in the CAG-guided group (Table E3). During follow-up, the incidence of major bleeding was numerically lower in the QFR-guided group. However, how the difference in antithrombotic therapy was related to bleeding or ischemic events needs further research, due to limited number of events.

Furthermore, in the era of minimally invasive technology, the functional-guided revascularization strategy may change the treatment paradigm for patients with VHD and moderate coronary disease, especially elderly and fragile populations that can go straight to transcatheter valve implantation if revascularization is not needed.[27]

On the other hand, our results are in contrast with some studies. A subgroup analysis from Thalji and colleagues[28] reported that in patients with ≥50%, but <70% coronary stenosis undergoing aortic valve replacement, concomitant CABG reduced risk of late death by more than one-third. The advantage was even more significant in patients with single-vessel LAD disease, mostly grafted with ITA. This well-conducted study has reminded us, that arterial grafts over borderline lesions could be nonfunctional at early stage, but protective from atherosclerosis in the long run. For borderline lesions in critical vessels (eg, LAD), when arterial graft is available, a more positive strategy may bring long-term benefit.

Another major concern is the long-term outcome of those hemodynamically insignificant lesions that did not undergo CABG. During follow-up, no repeat revascularization was observed. Among all 14 myocardial infarction events observed, 4 were perioperative, and the rest were clinically silent. In our study, most of the physiologically insignificant lesions (46 out of 70) were moderate lesions (50%-70%). We suppose that these hemodynamically insignificant moderate lesions, under modern secondary prevention, may not be likely to progress and lead to ischemic event in a 3- to 5-year period. In the long-term, regular monitoring and an elective second-stage PCI—when necessary—could be a preferable approach to ensure future safety.

This study had some limitations. First, this was a retrospective and observational study. Patients with marginal coronary lesions and complicated comorbid procedures were more likely to be sent for QFR analysis and then divided to the QFR-guided group of this study. Despite weighting, confounding and selection bias were not eliminated. Second, the results of 1 sensitivity analysis did not align statistically with those of the main analysis due to the constraints imposed by the limited sample size and events. However, the observed lower risks of MACE, all-cause death, and myocardial infarction associated with the QFR-guided strategy enhanced our confidence for conducting a larger sample-size, prospective trial. Third, a fixed cutoff value for QFR was adopted in this study. Recently, studies have discovered specific FFR cutoffs for different type of conduits. The Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function (IMPAG) trial from Glineur and colleagues[29] discovered a threshold of 0.78 for arterial grafts, especially ITA. Because radial arteries are more sensitive to competitive flow than ITAs and veins, a recent observational study proposed a lower threshold of 0.71 for radial artery graft.[30] Thus, a more precise QFR-guided strategy may further improve the outcome. Fourth, this is a single-center study and the results may not extrapolate to the general population. Finally, long-term follow-up is needed to identify the risks of myocardial infarction and repeated revascularization that accompany deferring concomitant CABG during VHS. Thus, this study should be considered speculative and hypothesis-generating. The conclusion needs to be confirmed by the Quantitative Flow Ratio Guided Revascularization Strategy for patients undergoing Primary Valve Surgery with Comorbid Coronary Artery Disease, NCT03977129.

CONCLUSIONS

Compared with CAG-guided CABG, QFR-guided CABG is associated with less grafting, shorter hospital stay, and better clinical outcome in patients with comorbid coronary artery disease undergoing primary valve surgery. A multicenter randomized clinical trial with a large sample is warranted.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/three-year-outcomes-of-quantit-7048.

Conflict of Interest Statement

Dr Zhu has received research grants for being an investigator on clinical trials sponsored by and receiving grant funding from Novartis, Sanofi, AstraZeneca, and Bayer. Dr Tu is the cofounder of Pulse Medical and reports consultancy and grants from Pulse Medical. Dr Zhao has received research grants from Medtronic, Johnson & Johnson, Novartis, and Astra Zeneca; for being an investigator on clinical trials sponsored by Novartis, Sanofi, Bayer, and Astra Zeneca; and has received nonfinancial support from

Medtronic and Johnson & Johnson. All other authors reported no conflicts of interest.

The *Journal* policy requires that editors and reviewers disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: fractional flow reserve, quantitative flow ratio, primary valve surgery, coronary artery bypass grafting

APPENDIX E1. OUTCOME DEFINITIONS

All-Cause Death

Any death, resulting from cardiovascular, noncardiovascular or undetermined cause.

Myocardian Infarction (MI)

Evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and silent/unrecognized MI. In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

MI may be adjudicated for an event that has characteristics of a MI, but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

Perioperative MI (CABG-Related; Type 5 MI)

Elevation of cardiac troponin (cTn) values >10 times the 99th percentile upper reference limit in patients with normal baseline cTn values.[E1] In patients with elevated preprocedural cTn in whom cTn levels are stable (≤20% variation) or falling, the postprocedural cTn must rise by >20%. However, the absolute postprocedural value still must be >10 times the 99th percentile upper reference limit. In addition, 1 of the following elements is required:

- Development of new pathological Q waves;
- Angiographic-documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Spontaneous MI (Type 1/Type 2 MI)

Acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper reference limit, and with at least one of the following[E1]:

- Symptoms of acute myocardial ischemia;
- New ischemic electrocardiograph changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy (type 1).

Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for type 2 MI.

Silent MI

New pathological Q-wave criteria for MI in asymptomatic patient detected during routine electrocardiograph follow-up or compared with a prior visit, or cardiac imaging evidence of MI, such as new reduced ventricular wall motion detected during routine ultrasound echocardiography follow-up that cannot be directly attributed to an interim acute coronary syndrome event or coronary revascularization procedure.[E2] The date of a silent MI was defined as the midpoint between the date when the electrocardiograph or the echocardiography findings were abnormal and the last known date when electrocardiograph or echocardiography findings were normal.

Stroke

An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Includes ischemic, hemorrhagic and undetermined type.

Ischemic stroke. An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic stroke. An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined stroke. An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, but with insufficient information to allow categorization as either ischemic or hemorrhagic stroke.

Unplanned Repeated Revascularization

Any repeated coronary artery bypass graft surgery or percutaneous coronary intervention, whether ischemic-driven or not.

Cardiovascular Rehospitalization

Combination of rehospitalization for angina and rehospitalization for heart failure.

Rehospitalization for Angina

Ischemic discomfort (angina or symptoms believed to be equivalent) ≥10 minutes in duration, occurring:

- At rest, or
- In an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity and prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in a stay ≥24 hours (or a change in calendar date if the hospital admission or discharge times are not available). And at least 1 of the following:

a) New or worsening ST or T wave changes on resting electrocardiogram (in the absence of confounders, such as left bundle branch block or left ventricular hypertrophy):
   - Transient ST elevation (duration <20 minutes), and
   - ST depression and T-wave changes.

b) Definite evidence of inducible myocardial ischemia as demonstrated by:
   - An early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression before 5 METS or
   - Stress echocardiography (reversible wall motion abnormality) or
   - Myocardial scintigraphy (reversible perfusion defect), or
   - Magnetic resonance imaging (myocardial perfusion deficit under pharmacologic stress), and
   - Believed to be responsible for the myocardial ischemic symptoms/signs.

c) Angiographic evidence of new or worse by ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d) Need for coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass grafting) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization or subsequent to transfer to another institution without interceding home discharge. And:
   - Negative cardiac biomarkers and no evidence of acute MI,
   - Rehospitalization for heart failure, and
   - An admission to the hospital where patient length of stay extends for at least 24 hours or as measured by a change in calendar date.

And

Typical signs, symptoms, and diagnostic testing results consistent with the diagnosis of heart failure. Laboratory findings consistent with heart failure include elevated natriuretic peptides, radiological evidence of congestion, and either echocardiographic or invasive evidence of elevated filling pressures.

And

Receive treatment specifically directed at heart failure, including at least 1 of the following:

- Significant augmentation in oral diuretic therapy,
- Initiation of intravenous diuretic (even a single dose) or vasoactive agent (eg, vasodilator, vasopressor, or inotropic therapy), and
- Mechanical circulatory support or fluid removal.

Significant augmentation of oral diuretic therapy is defined; for example, as the doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, or initiation of combination diuretic therapy to relieve congestion. Combination diuretic therapy could include a thiazide-type diuretic (eg, hydrochlorothiazide, metolazone, or chlorothiazide) plus a loop diuretic or a mineralocorticoid receptor antagonist (eg, spironolactone or eplerenone) plus a loop diuretic. Mechanical fluid removal includes ultrafiltration, hemofiltration, and dialysis as well as thoracentesis or paracentesis for heart failure management.

E-References

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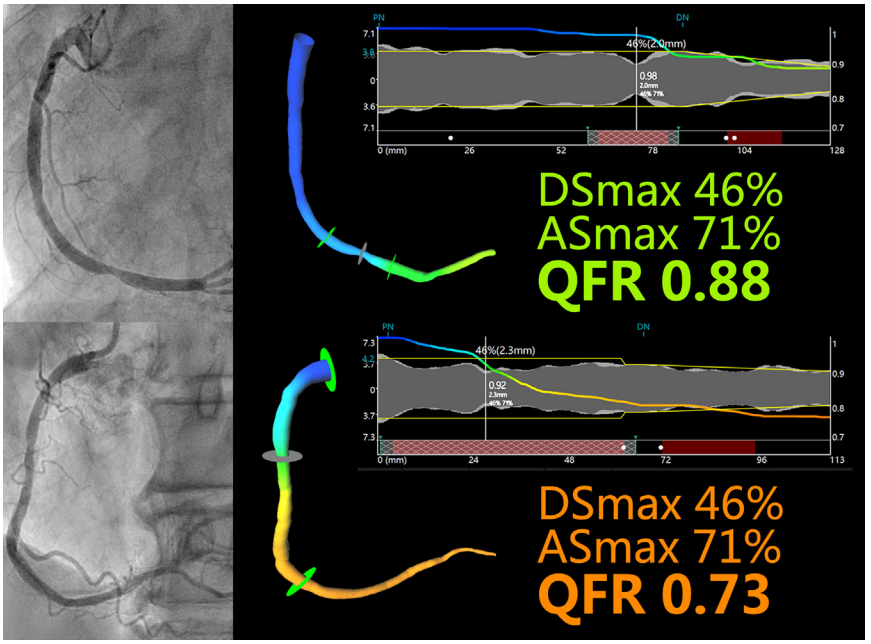

FIGURE E1. Quantitative analysis demonstrating diameter stenosis, areal stenosis and quantitative flow ratio (*QFR*) results of 2 right coronary arteries. Coronary stenoses of similar anatomical degree but different physiologically significance. *DS*, Diameter stenosis; *AS*, areal stenosis.

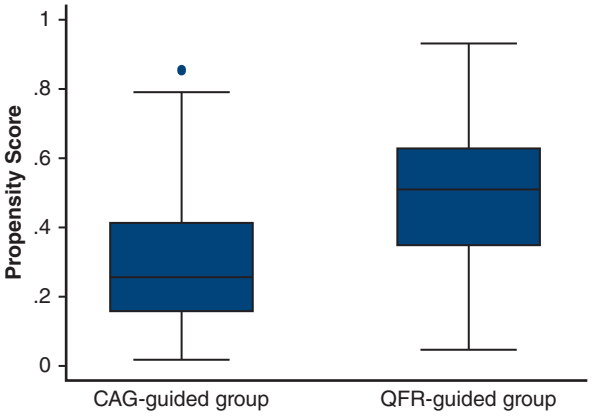

FIGURE E2. Diagram demonstrating the distribution of propensity score of the 2 groups. The lower and upper borders of the box represent the lower and upper quartiles (25th percentile and 75th percentile). The middle horizontal line represents the median. The lower and upper whiskers represent the minimum and maximum values of nonoutliers. Extra dots represent outliers. *CAG*, Coronary angiography; *QFR*, quantitative flow ratio.

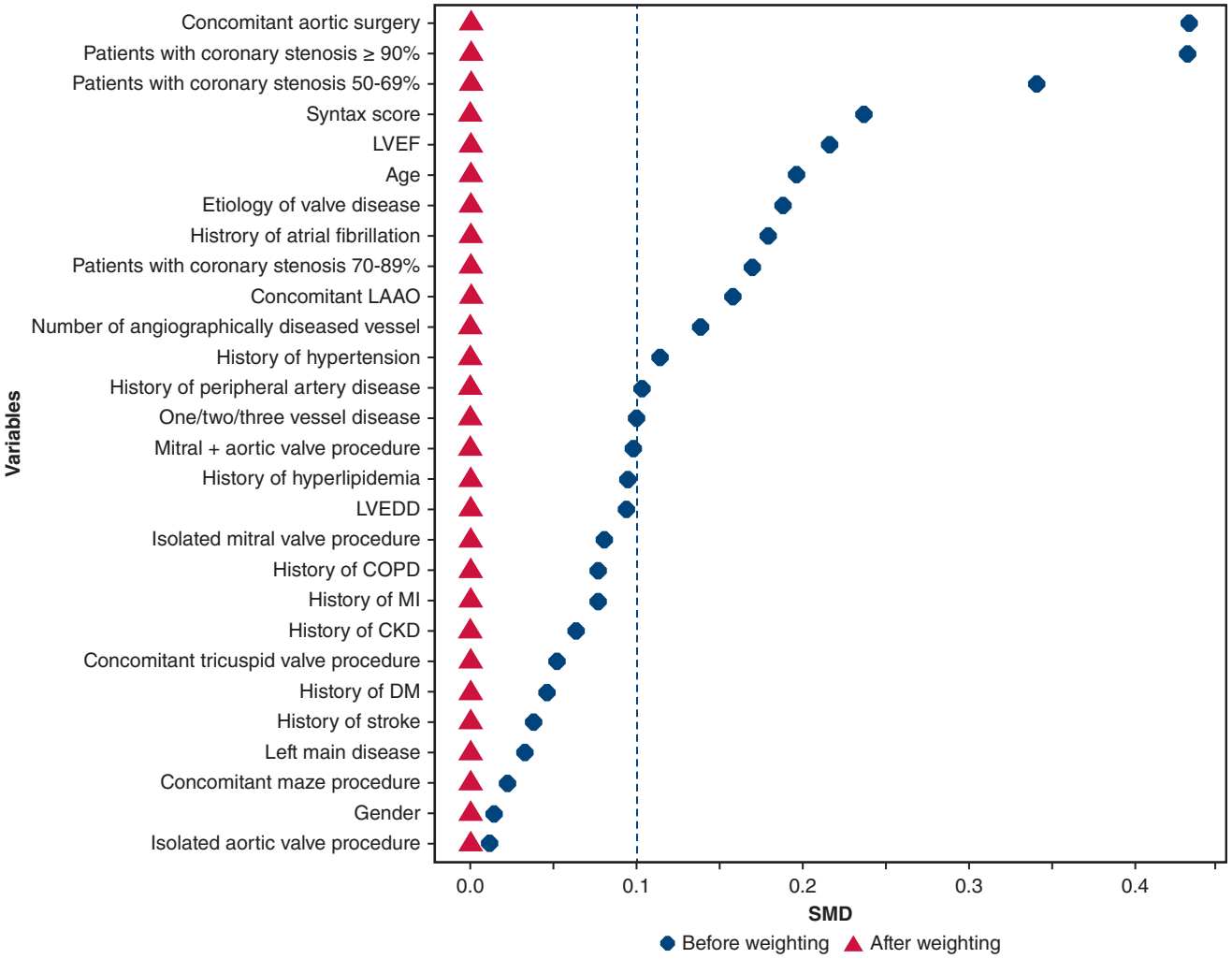

FIGURE E3. Standardized mean difference (*SMD*) distribution diagram illustrating the changes in covariate balance before and after weighting. *SYNTAX*, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; *LVEF*, left ventricular ejection fraction; *LAAO*, left atrial appendage occlusion; *LVEDD*, left ventricular end-diastolic diameter; *COPD*, chronic obstructive pulmonary disease; *MI*, myocardial infarction; *CKD*, chronic kidney disease; *DM*, diabetes mellitus.

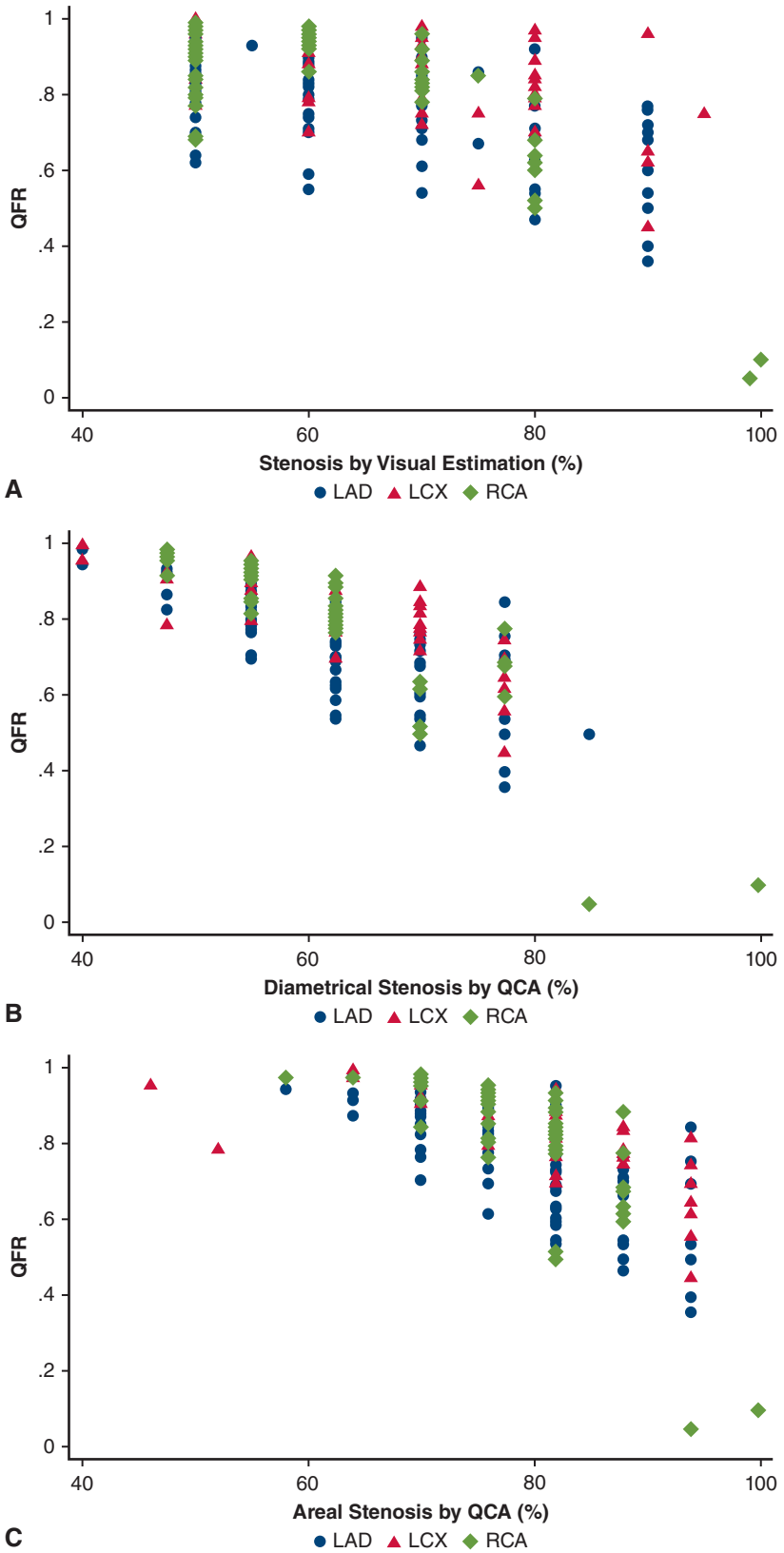

FIGURE E4. Scatterplot showing relation between quantitative flow ratio (*QFR*) and stenosis by visual evaluation (A), or diametrical stenosis by quantitative coronary angiography (*QCA*) (B), or areal stenosis by QCA (C). *LAD*, Left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery.

TABLE E1. Type of conduits bypassed to different coronary targets

	QFR-guided group					CAG-guided group				
		LAD territory (n = 31)		LCX	RCA		LAD territory (n = 113)		LCX	RCA
Type of conduits	Total (N = 55)	LAD (n = 25)	DIA (n = 6)	territory (n = 12)	territory (n = 12)	Total (n = 202)	LAD (n = 97)	DIA (n = 16)	territory (n = 48)	territory (n = 41)
ITA	22 (40.0)	22 (88.0)	0	0	0	69 (34.2)	68 (70.1)	1 (6.3)	0	0
RA	0	0	0	0	0	2 (1.0)	0	0	0	2 (4.9)
SV	33 (60.0)	3 (12.0)	6 (100)	12 (100)	12 (100)	131 (64.9)	29 (29.9)	15 (93.8)	48 (100)	39 (95.1)

Values are presented as n (%). *QFR*, Quantitative flow reserve; *CAG*, coronary angiography; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *RCA*, right coronary artery; *ITA*, internal thoracic artery; *RA*, radial artery; *SV*, saphenous vein.

TABLE E2. Effect of quantitative flow ratio (QFR)-guidance on extended follow-up outcomes adjusted by the propensity score

Events	Adjusted hazard ratio (95% CI)	Adjusted *P* value
MACE	0.46 (0.25-0.86)	.016
All-cause death	0.41 (0.18-0.93)	.032
Myocardial infarction*	0.28 (0.07-1.09)	.067
Stroke	0.86 (0.29-2.51)	.778

MACE, Major adverse cardiovascular event. *Includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and silent/unrecognized myocardial infarction. Definition shown in Appendix E1.

TABLE E3. Concomitant medications at discharge and last follow-up

	Crude						Propensity score weighting					
	At discharge			At last follow-up			At discharge			At last follow-up		
Medication	QFR-guided group (n = 69)	CAG-guided group (n = 119)	*P* value	QFR-guided group (n = 69)	CAG-guided group (n = 119)	*P* value	QFR-guided group (%)	CAG-guided group (%)	*P* value	QFR-guided group (%)	CAG-guided group (%)	*P* value
Antithrombotic therapy												
Isolated APT	19 (29.2)	51 (47.2)	.020	26 (40.0)	47 (46.1)	.440	27.1	44.7	.036	43.3	42.3	.912
SAPT	3 (4.3)	6 (4.7)	.787	21 (30.4)	39 (32.8)	.436	6.1	5.8	.945	36.8	36.9	.993
DAPT	16 (23.2)	45 (37.8)	.023	5 (7.2)	8 (6.7)	.972	21.0	38.9	.022	6.5	5.4	.779
Isolated OAC	12 (17.4)	8 (6.7)	.028	17 (24.6)	23 (19.3)	.595	18.4	10.7	.220	25.7	28.4	.729
OAC + APT	33 (47.8)	48 (40.3)	.419	18 (26.1)	22 (18.5)	.366	54.1	43.2	.212	26.2	22.6	.638
Statin	64 (92.8)	110 (92.4)	.574	63 (91.3)	108 (90.8)	.619						
RAASi	33 (47.8)	43 (36.1)	.332	35 (50.7)	56 (47.1)	.257						
β receptor blocker	58 (84.1)	96 (80.7)	.734	54 (78.3)	86 (72.3)	.439						
Diuretic	64 (92.8)	100 (84.0)	.084	17 (24.6)	28 (25.5)	.902						
Spirolactone	60 (87.0)	98 (82.4)	.406	13 (18.8)	25 (22.7)	.536						

Frequency for categorical variables is not applicable after propensity score weighting. Values for categorical variables after propensity score weighting are presented as percentage only. *QFR*, Quantitative flow reserve; *CAG*, coronary angiography; *APT*, antiplatelet therapy; *SAPT*, single antiplatelet therapy; *DAPT*, dual antiplatelet therapy; *OAC*, oral anticoagulant; *RAASi*, renin-angiotensin-aldosterone system inhibitors.