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Methods
- Retrospective observational cohort study
- 188 elective primary mitral and/or aortic valve surgery with comorbid coronary artery lesions (visually estimated stenosis ≥ 50%)
- QFR-guided group (n=69)
- CAG-guided group (n=119)
- Median follow-up 31.6 months
- MACE definition: all-cause death, MI, stroke, unplanned repeated revascularization, CV rehospitalization
- Statistical analysis: Propensity score weighting with overlap weighs

Results

A
- Cumulative Incidence of MACE (%)
- Years of follow-up
- HR (95% CI) P
- QFR vs. CAG
- CAG-guided
- QFR-guided
- 0.45 (0.24-0.84) .012

B
- Cumulative Incidence of Mortality (%)
- Years of follow-up
- HR (95% CI) P
- QFR vs. CAG
- CAG-guided
- QFR-guided
- 0.38 (0.16-0.93) .029

C
- Cumulative Incidence of MI (%)
- Years of follow-up
- HR (95% CI) P
- QFR vs. CAG
- CAG-guided
- QFR-guided
- 0.25 (0.06-1.07) .056

D
- Cumulative Incidence of Stroke (%)
- Years of follow-up
- HR (95% CI) P
- QFR vs. CAG
- CAG-guided
- QFR-guided
- 0.84 (0.29-2.39) .769

Procedural results
- Comorbid CABG:
  - 58.1% vs. 100%, p<0.001
- Number of grafts per patient:
  - 0.9±0.7 vs. 1.6±0.5; p<0.001

The PSW KM estimates of time to first MACE (A), mortality (B), MI (C) and stroke (D)

Conclusion:
Compared with CAG-guided CABG, QFR-guided CABG is associated with less grafting and better clinical outcome in primary valve surgery with comorbid coronary artery disease.
To confirm, the FAVOR IV-QVAS trial (NCT03977129) is on-going.
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Glossary of Abbreviations

ACC, American College of Cardiology
AHA, American Heart Association
APT, Antiplatelet therapy
CABG, Coronary artery bypass grafting
CAD, Coronary artery disease
CAG, Coronary angiography
CI, Confidence interval
CKD, Chronic kidney disease
COPD, Chronic obstructive pulmonary disease
CPB, Cardiopulmonary bypass
DAPT, Dual antiplatelet therapy
EACTS, European Association for Cardio-Thoracic Surgery
ECG, Electrocardiograph
ESC, European Society of Cardiology
FARGO, Fractional Flow Reserve vs. Angiography Randomization for Graft Optimization trial
FFR, Fractional flow reserve
GRAFFITI, Graft Patency After FFR-guided vs. Angio-guided CABG Trial
HR, Hazard ratio
ITA, Internal thoracic artery
LAD, Left anterior descending artery
LCX, Left circumflex artery
LDL-C, Low-density lipoprotein cholesterol
LVEDD, Left ventricular end diastolic diameter
LVEF, Left ventricular ejection fraction
MACE, Major adverse cardiovascular events
MI, Myocardial infarction
NYHA, New York Heart Association
OAC, Oral anticoagulant
PARTNER 3, Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis trial
PCI, Percutaneous coronary intervention
QFR, Quantitative flow ratio
FAVOR IV-QVAS, Quantitative Flow Ratio Guided Revascularization Strategy for patients undergoing Primary Valve Surgery with Comorbid Coronary Artery Disease
RCA, Right coronary artery
SAVE-IT, Strategies for Revascularization in Patients Undergoing Heart Valve Surgery With Concomitant Coronary Artery Disease
SD, Standard deviation
SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
97  VHD, Valvular heart disease

98  VHS, Valvular heart surgery

99
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.
The propensity score weighting analysis showed that for patients undergoing heart valve surgery and concomitant coronary artery bypass grafting (CABG), quantitative flow ratio (QFR) guidance was associated with less grafting and better clinical outcomes.
ABSTRACT

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

Methods: This observational study screened all 2,081 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 ≥ 50%) were included. Sixty-nine patients with QFR analysis received bypasses only for lesions with QFR ≤0.80 (QFR-guided group). The remaining 119 patients without QFR analysis received bypasses for all stenosis ≥ 50% (CAG-guided group). Propensity overlap weighting was used to neutralize the intergroup imbalance. The primary endpoint was MACE.

Results: After propensity score weighting, the baseline characteristics were comparable. Concomitant CABG was performed 58.1% vs 100% in QFR-guided and CAG-guided group, respectively. The mean number of grafts was significantly lower in QFR-guided group than in CAG-guided group (0.9±0.7 vs. 1.6±0.5; p<0.001). The weighted 30-day incidence of MACE was numerically lower in QFR-guided group than in CAG-guided group, but not statistically significant (6.3% vs 11.8%; p=0.429). After a median follow-up of 31.6 months, the weighted risk of MACE and mortality were significantly lower in QFR-guided group than in CAG-guided group (MACE: hazard ratio, 0.45; 95% CI, 0.24-0.84; p=0.012; mortality: hazard ratio, 0.38; 95% CI, 0.16-0.93; p=0.029).
Conclusions: Compared with CAG-guided CABG, 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 FAVOR IV-QVAS trial (NCT03977129) is ongoing.

Keywords: Fractional flow reserve; quantitative flow ratio; primary valve surgery; coronary artery bypass grafting
Central Picture Legend

Coronary stenoses of similar anatomical degree but different physiologically significance.


**Introductions**

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

The concomitant CABG with VHS is more complex and challenging, but the indication is still controversial. According to the ACC/AHA 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 ESC/EACTS guidelines for valvular heart disease (VHD), 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 of revascularization strategy is shifting anatomically to physiologically. Percutaneous coronary intervention (PCI) guided with fractional flow reserve (FFR) reduces the stenting with improved clinical outcomes [6-9]. Without functional assessment of coronary artery to identify the ischemia, unnecessary CABG may result in flow competition and graft failure, prolonging of 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 the FFR from coronary angiography in excellent concordance with catheter-based FFR (92.7% accuracy, 94.6% sensitivity and 91.7% specificity from FAVOR II China study) [11-15]. The optimal approach was validated in the FAVOR (Functional Assessment by Various Flow Reconstructions) 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 showed a high diagnostic accuracy of in-procedure QFR [14, 15]. QFR-guided PCI showed improved clinical outcomes in FAVOR III China trial (Comparison of Quantitative Flow Ratio-Guided and Angiography-Guided Percutaneous InterVention in Patients With cORonary Artery Disease, NCT03656848) [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 9th, 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 one 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 VHD (e.g. ischemia, cardiomyopathy, etc.), transcatheter valve intervention, cardiogenic shock or other critical conditions, and the target vessels ungraftable.

When patients were sent for QFR analysis and received bypass only for QFR ≤0.80, they were divided to QFR-guided group. The remaining patients, without receiving QFR analysis, of whom all stenosis ≥ 50% in major coronary arteries (diameter ≥1.5mm) were bypassed according to the guidelines and surgeon’s decision, were divided to CAG-guided group [4, 5].

The preoperative, intraoperative, and postoperative data were collected and retrospectively reviewed from our hospital database and logged in a clinical study-specific medical record created for each patient.

**QFR Analysis**

The standard 7-position CAG was taken in catheter lab preoperatively. The images were sent to the core lab (CardHemo, Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China) for computation of the QFR. Analysis was performed by the experienced analysts using the AngioPlus system (Pulse Medical Imaging Technology, Shanghai, China) as previously described [11-15]. The value of QFR ≤0.80 was defined as QFR-positive. The demonstration of QFR analysis is shown in Figure S1.
Follow-up and Outcomes

Follow-up data were collected from our institutional database. All patients completed outpatient visit 30 days post-surgery, then received an outpatient or telephone visit every half a year. The primary endpoint was major adverse cardiovascular events (MACE), defined as all-cause death, myocardial infarction, stroke, unplanned repeated revascularization, and cardiovascular rehospitalization. Definitions for all endpoints are listed in Supplementary appendix.

Statistical Analysis

Continuous data were reported as the mean ± standard deviation (SD) or median (P25, P75) and analyzed using student t-test, while categorical data were presented as numbers (percentages) and compared by chi-square test, Fisher exact test or Cochran-Mantel-Haenszel chi-square 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 two groups. To calculate the weights, propensity scores were first calculated using a logistic regression model with QFR-guided group as response variable (CAG-guided group as control) and all characteristics in table 1 except LVEF classification as covariates. The balance was evaluated by standardized differences using a threshold of 0.1. The rate difference between two groups and its 95% confidential interval (CI) were calculated using Newcombe-Wilson method. Kaplan-Meier method was used to draw survival curves of events, and confidence band of the curves was estimated by log-log transformation. The design-based sampling errors of hazard ratio for weighted extended outcomes were computed.
by the Taylor series method. To examine the robustness of extended follow-up outcomes as sensitivity analyses, two multivariate regression analyses were conducted. One included raw baseline characteristics with significance less than 0.1. The other included the propensity score as the only covariate. All statistical analyses were performed with SAS software (version 9.4), and tests were done at the both-sided 0.05 significance level unless otherwise noted.

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, in which 188 (14.2%) patients were diagnosed at least one coronary artery stenosis ≥50%. Sixty-nine patients who were sent for QFR analysis and received bypasses only for lesions with QFR ≤0.80 were divided to QFR-guided group. The remaining 119 patients without QFR analysis directly received bypasses for all stenosis ≥ 50% were divided to CAG-guided group. (Fig. 1).

Baseline characteristics

Baseline patient demographics, coronary artery disease characteristics, risk variables, and co-morbidity are summarized in Table 1.

Before propensity score weighting, QFR-guided group had a higher proportion of patients with coronary stenosis from 50-69%, and a lower proportion of patients with stenosis ≥90%, compared to CAG-guided group. The number of diseased vessels per patient was similar
between two groups, same as the proportions of one-, two- or three-vessel disease and left main disease. All other baseline characteristics were originally comparable between two groups (Table 1).

Weighting for propensity score yielded two groups with no significant difference in baseline characteristics, with very low SMDs showing excellent balance (Table 1). The distribution of propensity score of the two groups was demonstrated in Figure S2. The changes in covariate balance before and after weighting was illustrated in Figure S3 Non-CABG procedural characteristics

Before propensity score weighting, patients in QFR-guided group received significantly more combined aortic surgeries, compared to those in CAG-guided group. All other non-CABG procedural characteristics were comparable between two groups (Table 1).

Weighting for propensity score yielded two groups with no significant difference in all non-CABG procedural characteristics, with very low SMDs showing excellent balance (Table 1).

Procedural results

The 69 patients in QFR-guided group had a total of 125 diseased major coronary arteries (visually estimated stenosis ≥50%, diameter ≥ 1.5mm, suitable as bypass target), which were considered indicated to CABG. After QFR analyses, 70 of 125 (56.0%) of the above vessels had a QFR>0.8 and bypass were avoided. Specifically, of all the 125 diseased coronary arteries, there were 66 vessels of 50-69% stenosis, among which 20 (30.3%) were QFR positive and bypassed. The rest 59 vessels were ≥70% stenosed, among which 24 (40.7%)
were QFR negative and bypass were avoided (Table 4). At patient level, CABG was
simplified or avoided in 47 of 69 (68.1%) patients, among which 14 patients had less bypass
grafting and 33 patients were completely avoided from CABG. The type of conduits bypassed
to different coronary targets was shown in Table S1. In QFR-guided group, 88.0% of all
grafted LADs were bypassed with internal thoracic artery (ITA). While in CAG-guided
group, the proportion was 70.1%.

With weighting, all CAG-guided patients received concomitant CABG, while only 58.1%
of the QFR-guided patients underwent concomitant CABG. The number of grafts per patient
was significantly lower in QFR-guided group than in CAG-guided group (0.9 vs. 1.6;
p<0.001). The cross-clamping time in QFR-guided group was significantly lower than that in
CAG-guided group (75.1 vs. 84.1min; p=0.030) (Table 2). The length of total hospital stay
and post-surgery hospital stay were both shorter in QFR-guided group compared to CAG-
guided group (Total: 18.5 vs. 28.6 days; p<0.001; post-surgery: 11.7 vs. 18.7 days; p=0.002)
(Table 2).

**30-day Outcomes**

MACE was reported in 8.7% (6/69) and 11.8% (14/119) of the patients in QFR-guided
and CAG-guided group, respectively. Mortality was 7.3% (5/69) and 7.6% (9/119) in QFR-
guided and CAG-guided group, 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 QFR-
guided group and 11.8% in CAG-guided group (absolute difference, -5.5%; 95% CI, -20.8%
Specifically, the 30-day incidence of all-cause death with weighting was 4.8% in QFR-guided group and 7.8% in CAG-guided group (absolute difference, -3.0%; 95% CI, -17.1% to 10.7%; p=0.611). The incidence of myocardial infarction with weighting was 1.5% in QFR-guided group and 6.7% in CAG-guided group, respectively (absolute difference, -5.2%; 95% CI, -18.5% to 6.8%; p=0.280). The incidence of stroke with weighting was 2.0% in QFR-guided group and 3.4% in CAG-guided group, respectively (p=0.723). There was no repeated revascularization or cardiovascular rehospitalization in either group (Table 3).

**Extended follow-up outcomes**

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

The propensity score weighted Kaplan–Meier estimates of time to first MACE, mortality, myocardial infarction and stroke are shown as Figure 2. In QFR-guided group, the risk of MACE was significantly lower than in CAG-guided group (hazard ratio, 0.45; 95% CI, 0.24-0.84; p=0.012; Fig. 2A). Specifically, mortality in QFR-guided group were significantly lower (hazard ratio, 0.38; 95% CI, 0.16-0.93; p=0.029; Fig. 2B), while the risk of myocardial infarction was numerically lower (hazard ratio, 0.25; 95% CI, 0.06-1.07; p=0.056; Fig 2C), compared to that in CAG-guided group. For stroke, no significant difference was observed
between the two groups (hazard ratio, 0.84; 95% CI, 0.29-2.39; p=0.769; Fig. 2D).

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 ≥90%; combined aortic surgery).

While there is still some evidence of association, QFR-guided strategy was not statistically significant as an independent risk factor associated to MACE (hazard ratio, 0.59; 95%CI, 0.33 to 1.08; p=0.088), mortality (hazard ratio, 0.47; 95%CI, 0.21 to 1.09; p=0.078), myocardial infarction (hazard ratio, 0.35; 95%CI, 0.09 to 1.34; p=0.126) and stroke (hazard ratio, 1.22; 95%CI, 0.44 to 3.43; p=0.702). Another multivariate regression analysis, including the propensity score as the only covariate, revealed congruent results with the main analysis (Table S2).

See Figure 4 for a graphical abstract of the study.

QFR results

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

Table 4 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% (37/60) of the left anterior descending artery (LAD) territory, 34.4% (11/32) in left circumflex artery (LCX) territory, and 21.2% (7/33) in right coronary artery
(RCA) territory. For lesions of similar degree, those in LAD territory tend to be the most physiologically significant, followed by those in LCX and RCA territory.

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

Figure S4 is a scatter plot demonstrating relations between QFR and different measures of stenosis, colored in the three coronary territories. Compared with visual estimation, diameter stenosis and areal stenosis from quantitative coronary analysis (QCA) showed better correlation with QFR.

**Anti-thrombosis therapy and bleeding events**

Concomitant medications at discharge and last follow-up were shown as Table S3. 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=0.036; DAPT: 21.0% vs. 38.9%, p=0.022). There was no significant difference between the two groups in administration of isolated OAC, OAC with single antiplatelet therapy (SAPT) or isolated SAPT at discharge (OAC: 18.4% vs. 10.7%, p=0.220; OAC+SAPT: 54.1% vs. 43.2%, p=0.212; SAPT: 6.1% vs. 5.8%, p=0.945). At last follow-up, no significant difference was observed in different antithrombosis therapy between the two groups (OAC: 25.7% vs. 28.4%, p=0.729; OAC+SAPT: 26.2% vs. 22.6%, p=0.638; DAPT: 6.5% vs. 5.4%, p=0.779; SAPT: 36.8% vs. 36.9%, p=0.993).
During follow-up, the incidence of major bleeding was 2.9% (2/69) and 4.2% (5/119) in QFR-guided group and CAG-guided group. The incidence of fatal bleeding events was 2.9% (2/69) and 3.4% (4/119), respectively.

Discussion

From this observational study, we found that for patients with coronary artery disease undergoing primary valve surgery, QFR-guided CABG had better clinical outcomes, less grafting, 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 less graft numbers and better graft patency with FFR guidance were shown in most studies, significant improvement in clinical outcome was not observed, neither in a large registry study [17], nor in the Fractional Flow Reserve vs. Angiography Randomization for Graft Optimization (FARGO) trial [18] and the Graft Patency After FFR-guided vs. Angio-guided CABG Trial (GRAFFITI) [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 were performed. The STS 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 PARTNER 3 trial [20].

Based on the above phenomenon, we hypothesized that functional assessment may help guiding CABG during valve surgery to improve clinical outcome. Although CABG decision making is still upon the anatomical assessment, the ACC/AHA and the ESC/EACTS guidelines for VHD recommend physiological assessment for patients with comorbid CAD, but lack evidence [4, 5]. Randomized trial of FFR-guided CABG in valvular surgery is very few. We conducted this observational study to evaluate the efficacy of QFR-guided CABG in this situation. Based on this preliminary data, we designed the FAVOR IV-QVAS trial (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 SAVE-IT (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, reporting improved 1-year clinical outcomes with QFR-guided strategy, by reducing MACE by more than a half [21]. Our study showed very similar results and confirmed the advantage of this novel strategy at a longer follow-up period.

Del Forno and colleagues enrolled 77 VHS candidates with moderate coronary stenosis
All CABG was intentionally omitted without preoperative functional assessment. There were no in-hospital deaths with only 1 postoperative myocardial infarction. The 6-year overall survival was excellent with very few PCI. 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 three main factors, that competitive flow may affect the patency rate of the graft [23]; proximal lesion 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 50-69% stenosis in QFR-guided group, 39 patients had at least one 50-69% stenosis omitted to CABG due to negative QFR. During follow-up, only two patients were discovered with clinically silent MI around 2 years after surgery without repeated revascularization. Thereout, our result seemed to be generally consistent with the conclusion from Del Forno and his colleagues. However, in our study, positive QFR was detected in 30.3% of all moderate coronary lesions (50-69%, visually estimated). Similarly in the FAME trial, 35% of all 1,174 lesions between 50% and 70% were hemodynamically significant [8]. Grafting only those lesions ≥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 CAG-guided group more CABG were
performed, however, merely resulting in a difference of less than one graft and nine minutes of cross-clamping time averagely. It was challenging to explain how this modest difference in procedure could cause such significant difference in clinical outcome. In QFR-guided group, 88.0% of all grafted LADs were bypassed with ITA. While in CAG-guided group, the proportion was 70.1%. One hypothesis is that in CAG-guided group, when more bypass was performed, surgeons could have used less ITAs than in QFR-guided group. This phenomenon was possibly resulted from the two different CABG strategies. This could be a potential mechanism that QFR-guided strategy gained advantage over the CAG-guided strategy.

Another possible hypothesis is that this was related to the difference of anti-thrombotic therapy in the two groups. Concomitant CABG could have largely affected the post-operative anti-thrombotic therapy, and restrict the infusion of hemostatic, plasma and cryoprecipitate. In the long run, especially during the first year postoperatively, a complex anti-thrombotic strategy may continuously lead to mismanagement and clinical events as well. In Michigan Anticoagulation Quality Improvement Initiative (MAQI2) registry, patients with warfarin and aspirin had a higher rate of bleeding events (28.3 vs 13.3 per 100 patient-years, p<0.001) compared to those with isolated warfarin, without much difference in rates of ischemic stroke (0.56 vs 0.48 per 100 patient-years, p=0.89) [26]. In our study, from the K-M curves of MACE, mortality and MI, we found a persistently growing advantage of QFR-guided group over CAG-guided group during the first post-operative year. The difference seemed stabilized thereafter when anti-platelet therapies were mostly downgraded. In this study, higher proportion of isolated APT, mainly DAPT, was administered in CAG-guided group (Table
S3). During follow-up, the incidence of major bleeding was numerically lower in 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 benefits the elderly and fragile population that can go straight forward to transcatheter valve implantation if the revascularization is not needed [27].

On the other hand, our results were in contrast with some studies. A subgroup analysis from Thalji et al. 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 [28]. 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 non-functional at early stage, but protective from atherosclerosis at long-run. For borderline lesions in critical vessels (e.g., 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 omitted to CABG. During follow-up, no repeated revascularization was observed in this study. Among all 14 MI events observed, four were perioperative, and the rest 10 MI were all clinically silent. In our study, most of the physiologically insignificant lesions (46 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 a longer 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 QFR-guided group of this study.

Despite weighting, confounding and selection bias were not eliminated. Secondly, the results of one 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 numerically lower risks of MACE, all-cause death, and MI associated with the QFR-guided strategy had still enhanced our confidence for conducting a larger sample-size, prospective trial. Thirdly, a fixed cut-off value for QFR was adopted in this study. Recently, studies have discovered specific FFR cut-offs for different type of conduits. The IMPAG trial from Glineur and his colleagues discovered a threshold of 0.78 for arterial grafts, especially ITA [29]. Concerning that radial artery are more sensitive to competitive flow than ITA and vein, 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. Fourthly, this is a single center study and the results may not extrapolate to the general population. Finally, the long-term follow-up is needed to identify the risks of myocardial infarction and repeated revascularization for the deferring concomitant CABG during VHS. Thus, this study should be considered speculative and hypothesis-generating. The conclusion needs to be confirmed by the FAVOR IV-QVAS randomized clinical trial (NCT03977129).
In summary, 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. Multicenter randomized clinical trial with large sample size is warranted.
Acknowledgments

None
REFERENCES


coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet. 2015 Nov 7;386(10006):1853-60


**Figure legends**

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

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

**Figure 3.** The crude Kaplan–Meier estimates reporting time to first MACE (A), mortality (B), myocardial infarction (C) and stroke (D). CAG: coronary angiography; CI: confidential interval; HR: hazard ratio; MACE: Major adverse cardiovascular events; MI: myocardial infarction; QFR: quantitative flow ratio.

**Figure 4.** Graphical abstract: Retrospective observational study showed that compared with CAG-guided CABG, 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 FAVOR IV-QVAS trial (NCT03977129) is on-going.

**Figure S1.** Quantitative analysis demonstrating diameter stenosis, areal stenosis and QFR results of two right coronary arteries. Coronary stenoses of similar anatomical degree but different physiologically significance. AS: Areal stenosis; DS: diameter stenosis; QFR: quantitative flow ratio.

**Figure S2.** Diagram demonstrating the distribution of propensity score of the two 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 non-outliers. Extra dots represent outliers. CAG: coronary angiography; QFR: quantitative flow ratio.

**Figure S3.** Standardized Mean Difference (SMD) distribution diagram illustrating the changes in covariate balance before and after weighting. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; LAAO: left atrial appendage occlusion; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MI: myocardial infarction; SMD: standardized mean difference; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

**Figure S4.** Scatterplot showing relation between QFR and stenosis by visual evaluation (A), or diametrical stenosis by QCA (B), or areal stenosis by QCA (C). LAD: left anterior descending artery; LCX: left circumflex artery; QFR: quantitative flow ratio; RCA: right coronary artery; QCA: quantitative coronary angiography.
Table 1: Demographic, clinical and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Crude QFR-guided group (n=69)</th>
<th>Crude CAG-guided group (n=119)</th>
<th>P value</th>
<th>SMD</th>
<th>PSW QFR-guided group</th>
<th>PSW CAG-guided group</th>
<th>P value</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>26(37.7)</td>
<td>44(37.0)</td>
<td>0.923</td>
<td>0.015</td>
<td>40.0%</td>
<td>40.0%</td>
<td>1.000</td>
<td>&lt;0.001</td>
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<tr>
<td>Age (year)</td>
<td>66.9±7.0</td>
<td>65.5±7.7</td>
<td>0.201</td>
<td>0.197</td>
<td>66.2±7.1</td>
<td>66.2±7.1</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etiology of valve disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic</td>
<td>16(23.2)</td>
<td>19(16.0)</td>
<td>0.660</td>
<td>0.189</td>
<td>21.1%</td>
<td>21.1%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Degenerative</td>
<td>45(65.2)</td>
<td>83(69.7)</td>
<td></td>
<td></td>
<td>65.9%</td>
<td>65.9%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infectious</td>
<td>1(1.5)</td>
<td>2(1.7)</td>
<td></td>
<td></td>
<td>2.1%</td>
<td>2.1%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congenital</td>
<td>7(10.1)</td>
<td>15(12.6)</td>
<td></td>
<td></td>
<td>10.9%</td>
<td>10.9%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>50(72.5)</td>
<td>80(67.2)</td>
<td>0.454</td>
<td>0.114</td>
<td>72.4%</td>
<td>72.4%</td>
<td>1.000</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>20(29.0)</td>
<td>37(31.1)</td>
<td>0.762</td>
<td>0.046</td>
<td>30.4%</td>
<td>30.4%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperlipidemia\textsuperscript{a}</td>
<td>34(49.3)</td>
<td>53(44.5)</td>
<td>0.530</td>
<td>0.095</td>
<td>47.4%</td>
<td>47.4%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>12(17.4)</td>
<td>19(16.0)</td>
<td>0.800</td>
<td>0.038</td>
<td>20.4%</td>
<td>20.4%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction\textsuperscript{b}</td>
<td>7(10.1)</td>
<td>15(12.6)</td>
<td>0.613</td>
<td>0.078</td>
<td>11.9%</td>
<td>11.9%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>7(10.1)</td>
<td>15(12.6)</td>
<td>0.613</td>
<td>0.078</td>
<td>10.6%</td>
<td>10.6%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD\textsuperscript{c}</td>
<td>10(14.5)</td>
<td>20(16.8)</td>
<td>0.676</td>
<td>0.064</td>
<td>17.1%</td>
<td>17.1%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>31(44.9)</td>
<td>43(36.1)</td>
<td>0.234</td>
<td>0.180</td>
<td>40.5%</td>
<td>40.5%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease\textsuperscript{d}</td>
<td>3(4.4)</td>
<td>8(6.7)</td>
<td>0.504</td>
<td>0.104</td>
<td>5.6%</td>
<td>5.6%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with diseased vessel\textsuperscript{e}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main disease</td>
<td>3(4.4)</td>
<td>6(5.0)</td>
<td>0.830</td>
<td>0.033</td>
<td>4.9%</td>
<td>4.9%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>30(43.5)</td>
<td>49(41.2)</td>
<td></td>
<td></td>
<td>43.2%</td>
<td>43.2%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>20(29.0)</td>
<td>40(33.6)</td>
<td></td>
<td></td>
<td>32.1%</td>
<td>32.1%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>19(27.5)</td>
<td>30(25.2)</td>
<td>0.803</td>
<td>0.101</td>
<td>24.7%</td>
<td>24.7%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of diseased vessels per patient</td>
<td>1.8±0.9</td>
<td>2.0±1.0</td>
<td>0.363</td>
<td>0.140</td>
<td>1.9±0.9</td>
<td>1.9±1.0</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with diseased vessel&lt;sup&gt;f&lt;/sup&gt;</td>
<td>50-69%</td>
<td>70-89%</td>
<td>≥90%</td>
<td>SYNTAX score&lt;sup&gt;g&lt;/sup&gt;</td>
<td>50(72.5)</td>
<td>67(56.3)</td>
<td>0.028</td>
<td>0.342</td>
</tr>
<tr>
<td>--------------------------------------</td>
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<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>55(49-59)</td>
<td>55(50-62)</td>
<td>0.451</td>
<td>0.095</td>
<td>55(48-59)</td>
<td>54(49-61)</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63(58-68)</td>
<td>62(52-67)</td>
<td>0.245</td>
<td>0.217</td>
<td>63(57-68)</td>
<td>63(55-67)</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated mitral valve</td>
<td>32(46.4)</td>
<td>60(50.4)</td>
<td>0.593</td>
<td>0.081</td>
<td>48.4%</td>
<td>48.4%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isolated aortic valve</td>
<td>23(33.3)</td>
<td>39(32.8)</td>
<td>0.937</td>
<td>0.012</td>
<td>32.3%</td>
<td>32.3%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral and aortic valves</td>
<td>13(18.8)</td>
<td>18(15.1)</td>
<td>0.508</td>
<td>0.099</td>
<td>17.1%</td>
<td>17.1%</td>
<td>1.000</td>
<td>&lt;0.001</td>
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<tr>
<td>Comorbid procedures</td>
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<td></td>
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<td></td>
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<tr>
<td>Tricuspid valve</td>
<td>19(27.5)</td>
<td>30(25.2)</td>
<td>0.726</td>
<td>0.053</td>
<td>27.3%</td>
<td>27.3%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation ablation</td>
<td>11(15.9)</td>
<td>18(15.1)</td>
<td>0.881</td>
<td>0.023</td>
<td>17.2%</td>
<td>17.2%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial appendage occlusion</td>
<td>14(20.3)</td>
<td>17(14.3)</td>
<td>0.285</td>
<td>0.159</td>
<td>18.5%</td>
<td>18.5%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>12(17.4)</td>
<td>5(4.2)</td>
<td>0.002</td>
<td>0.435</td>
<td>10.5%</td>
<td>10.5%</td>
<td>1.000</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as baseline or historical LDL-C ≥2.6 mmol/L.

<sup>b</sup> Includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and silent/unrecognized MI.

Definition shown in supplementary appendix.

<sup>c</sup> Defined as stage 3 or higher chronic kidney disease (eGFR<60mL/min/1.73m2)

<sup>d</sup> Defined as one or more of the following: claudication; carotid occlusion or ≥50% stenosis; amputation for arterial disease; previous or planned intervention on limb arteries or carotids.

<sup>e</sup> Defined as stenosis of ≥50% by visual estimation.

<sup>f</sup> Calculated at patient level according to the degree of the coronary artery stenosis by visual estimation.

<sup>g</sup> A comprehensive angiographic assessment of the coronary vasculature. SYNTAX score: 0-22, low anatomical complexity; 23-32, intermediate anatomical complexity; and ≥33, high anatomical complexity.
Frequency for categorical variables is not applicable after PSW. Values for categorical variables after PSW are presented as percentage only. Values for categorical variables with crude analysis are presented as \( n \) (%). Values for continuous variables are presented as mean ± standard deviation or median values with interquartile ranges.

CABG: coronary artery bypass grafting; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; PSW: propensity score weighting; SMD: standardized mean difference; SYNTAX: Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.
Table 2: Procedural results

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>PSW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QFR-guided group (N=69)</td>
<td>CAG-guided group (N=119)</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of grafts per patient</td>
<td>36(52.2)</td>
<td>119(100.0)</td>
</tr>
<tr>
<td>Number of grafts per patient</td>
<td>0.8±1.0</td>
<td>1.7±0.9</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>118.9±36.5</td>
<td>131.1±49.3</td>
</tr>
<tr>
<td>Cross clamping time (min)</td>
<td>76.3±26.2</td>
<td>85.3±35.0</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>19.3±6.3</td>
<td>26.7±20.2</td>
</tr>
<tr>
<td>Post-surgery hospital stay (day)</td>
<td>12.5±5.2</td>
<td>16.6±18.9</td>
</tr>
</tbody>
</table>

Frequency for categorical variables is not applicable after PSW. Values for categorical variables after PSW are presented as percentage only. Values for categorical variables with crude analysis are presented as n (%). Values for continuous variables are presented as mean ± standard deviation. CABG: coronary artery bypass grafting; CAG: coronary angiography; CI: confident interval; CPB: cardiopulmonary bypass; PSW: propensity score weighting; QFR: quantitative flow reserve.
Table 3: 30-day clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
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</tr>
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<tr>
<td></td>
<td>QFR-guided group</td>
<td>CAG-guided group</td>
</tr>
<tr>
<td></td>
<td>(N=69)</td>
<td>(N=119)</td>
</tr>
<tr>
<td></td>
<td>Difference (95% CI)</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>6(8.7%)</td>
<td>14(11.8%)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>5(7.3%)</td>
<td>9(7.6%)</td>
</tr>
<tr>
<td>Myocardial infarction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1(1.5%)</td>
<td>7(5.9%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3(4.4%)</td>
<td>4(3.4%)</td>
</tr>
<tr>
<td>Repeated revascularization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CV rehospitalization</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and silent/unrecognized MI. Definition shown in supplementary appendix.

Frequency for categorical variables is not applicable after PSW. Values for categorical variables after PSW 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.

CAG: coronary angiography; CI: confident interval; CV rehospitalization: Cardiovascular rehospitalization; MACE: Major adverse cardiovascular events; PSW: propensity score weighting; QFR: quantitative flow reserve.
Table 4. QFR positive proportion in different coronary artery territories, stratified by degree of coronary artery stenosis.

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

Data are presented as n/N(%).
LAD: left anterior descending artery; LCX: left circumflex artery; QCA: quantitative coronary angiography; QFR: quantitative flow ratio; RCA: right coronary artery.
Elective primary valve surgery
Jan 2017– Sept 2020 (n=2081)

- preop CAG not indicated (n=761)

Underwent preop CAG (n=1320)

- without CA stenosis ≥ 50% (n=1132)

VHD with CA stenosis ≥ 50% (n=188)

QFR-guided
(n=69)

CAG-guided
(n=119)

Follow-up: median 31.6 months (IQR 20.4, 43.3)
Propensity score weighting analysis
(n=188)
Preliminary outcomes of quantitative flow ratio-guided coronary bypass grafting in primary valve surgery: A propensity score weighted analysis

Methods
- Retrospective observational cohort study
- 188 elective primary mitral and/or aortic valve surgery with comorbid coronary artery lesions (visually estimated stenosis ≥ 50%)
- QFR-guided group (n=69)
- CAG-guided group (n=119)
- Median follow-up 31.6 months
- MACE definition: all-cause death, MI, stroke, unplanned repeated revascularization, CV rehospitalization
- Statistical analysis: Propensity score weighting with overlap weighs

Results

The PSW KM estimates of time to first MACE (A), mortality (B), MI (C) and stroke (D)

Procedural results
- Comorbid CABG:
  58.1% vs. 100%, p < 0.001
- Number of grafts per patient:
  0.9±0.7 vs. 1.6±0.5; p < 0.001

Conclusion:
Compared with CAG-guided CABG, QFR-guided CABG is associated with less grafting and better clinical outcome in primary valve surgery with comorbid coronary artery disease.
To confirm, the FAVOR IV-QVAS trial (NCT03977129) is on-going.
Preliminary outcomes of quantitative flow ratio-guided coronary bypass grafting in primary valve surgery: A propensity score weighted analysis

Qiang Zhao, Jiaxi Zhu, Yunpeng Zhu, Wei Zhang, Shengxian Tu
Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China
Outcome Definitions

All-cause death
Any death, resulting from cardiovascular, non-cardiovascular or undetermined cause.

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$^1$)
Elevation of cardiac troponin (cTn) values $>$10 times the 99th percentile upper reference limit in patients with normal baseline cTn values. In patients with elevated preprocedural cTn in whom cTn levels are stable ($\leq$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, one 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$^1$)
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:

- symptoms of acute myocardial ischemia;
- new ischemic ECG 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;
- 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 ECG 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 cardiography follow-up that cannot be directly attributed to an interim acute coronary syndrome event or coronary revascularization procedure. The date of a silent MI was defined as the midpoint between the date when the ECG or the echocardiography findings were abnormal and the last known date when ECG 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 (CABG) 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 thought 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 of ≥24 hours (or a change in calendar date if the hospital admission or discharge times are not available).

**AND**

At least one of the following:

a) New or worsening ST or T wave changes on resting electrocardiogram (ECG) (in the absence of confounders, such as left bundle branch block or left ventricular hypertrophy):
   - transient ST elevation (duration <20 minutes)
   - 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 prior to 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 CABG) 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**

An admission to the hospital where patient length of stay extends for at least 24 h or as measured by a change in calendar date.

**AND**

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

**AND**

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

1) significant augmentation in oral diuretic therapy;

2) initiation of intravenous diuretic (even a single dose) or vasoactive agent (eg, vasodilator, vasopressor, or inotropic therapy);

3) 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 main- tenance loop diuretic therapy; or initiation of combination diuretic therapy to relieve congestion. Combination diuretic therapy could include: 1) a
thiazide-type diuretic (eg, hydrochlorothiazide, metolazone, or chlorothiazide) plus a loop diuretic; or 2) 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 HF management.

References

Table S1. Type of conduits bypassed to different coronary targets.

<table>
<thead>
<tr>
<th></th>
<th>QFR-guided group</th>
<th></th>
<th>CAG-guided group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=55)</td>
<td>LAD territory (n=31)</td>
<td></td>
<td>LAD territory (n=113)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LAD (n=25)</td>
<td>DIA (n=6)</td>
<td></td>
</tr>
<tr>
<td>ITA</td>
<td>22(40.0)</td>
<td>22(88.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(1.0)</td>
</tr>
<tr>
<td>SV</td>
<td>33(60.0)</td>
<td>3(12.0)</td>
<td>6(100)</td>
<td>12(100)</td>
</tr>
<tr>
<td></td>
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<td>12(100)</td>
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</table>

Data are presented as n(%).
DIA: diagonal branch; ITA: internal thoracic artery; LAD: left anterior descending artery; LCX: left circumflex artery; RA: radial artery; RCA: right coronary artery; SV: saphenous vein.
Table S2. Effect of QFR-guidance on extended follow-up outcomes adjusted by the propensity score.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95%CI)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.46 (0.25-0.86)</td>
<td>0.016</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.41 (0.18-0.93)</td>
<td>0.032</td>
</tr>
<tr>
<td>Myocardial infarction(^a)</td>
<td>0.28 (0.07-1.09)</td>
<td>0.067</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86 (0.29-2.51)</td>
<td>0.778</td>
</tr>
</tbody>
</table>

\(^a\)Includes ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and silent/unrecognized MI. Definition shown in supplementary appendix.

CI: confident interval; HR: hazard ratio; MACE: Major adverse cardiovascular events; QFR: quantitative flow reserve.
Table S3. Concomitant medications at discharge and last follow-up.

<table>
<thead>
<tr>
<th>Antithrombotic therapy</th>
<th>Crude</th>
<th>At discharge</th>
<th>At last follow-up</th>
<th>PSW</th>
<th>At discharge</th>
<th>At last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>QFR-guided group (n=69)</td>
<td>CAG-guided group (n=119)</td>
<td>P value</td>
<td>QFR-guided group (n=69)</td>
<td>CAG-guided group (n=119)</td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated APT</td>
<td></td>
<td>19(29.2)</td>
<td>51(47.2)</td>
<td>0.020</td>
<td>26(40.0)</td>
<td>47(46.1)</td>
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<td>SAPT</td>
<td></td>
<td>3(4.3)</td>
<td>6(4.7)</td>
<td>0.787</td>
<td>21(30.4)</td>
<td>39(32.8)</td>
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<tr>
<td>DAPT</td>
<td></td>
<td>16(23.2)</td>
<td>45(37.8)</td>
<td>0.023</td>
<td>5(7.2)</td>
<td>8(6.7)</td>
</tr>
<tr>
<td>Isolated OAC</td>
<td></td>
<td>12(17.4)</td>
<td>8(6.7)</td>
<td>0.028</td>
<td>17(24.6)</td>
<td>23(19.3)</td>
</tr>
<tr>
<td>OAC+APT</td>
<td></td>
<td>33(47.8)</td>
<td>48(40.3)</td>
<td>0.419</td>
<td>18(26.1)</td>
<td>22(18.5)</td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td>64(92.8)</td>
<td>110(92.4)</td>
<td>0.574</td>
<td>63(91.3)</td>
<td>108(90.8)</td>
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<td>RAASI</td>
<td></td>
<td>33(47.8)</td>
<td>43(36.1)</td>
<td>0.332</td>
<td>35(50.7)</td>
<td>56(47.1)</td>
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<tr>
<td>β receptor blocker</td>
<td></td>
<td>58(84.1)</td>
<td>96(80.7)</td>
<td>0.734</td>
<td>54(78.3)</td>
<td>86(72.3)</td>
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<tr>
<td>Diuretic</td>
<td></td>
<td>64(92.8)</td>
<td>100(84.0)</td>
<td>0.084</td>
<td>17(24.6)</td>
<td>28(25.5)</td>
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<tr>
<td>Spirolactone</td>
<td></td>
<td>60(87.0)</td>
<td>98(82.4)</td>
<td>0.406</td>
<td>13(18.8)</td>
<td>25(22.7)</td>
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</tbody>
</table>

Frequency for categorical variables is not applicable after PSW. Values for categorical variables after PSW are presented as percentage only.