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## Fractional Flow Reserve–Guided Versus Angiography–Guided Coronary Artery Bypass Graft Surgery

Gabor Toth, MD; Bernard De Bruyne, MD, PhD; Filip Casselman, MD, PhD; Frederic De Vroey, MD; Stylianos Pyxaras, MD; Luigi Di Serafino, MD, PhD; Frank Van Praet, MD; Carlos Van Mieghem, MD, PhD; Bernard Stockman, MD; William Wijns, MD, PhD; Ivan Degrieck, MD; Emanuele Barbato, MD, PhD

**Background**—Fractional flow reserve (FFR) is well established for patients undergoing percutaneous coronary intervention, yet little is known about candidates for coronary artery bypass graft surgery.

**Methods and Results**—From 2006 to 2010, we retrospectively included in this registry 627 consecutive patients treated by coronary artery bypass graft surgery having at least 1 angiographically intermediate stenosis. In 429 patients, coronary artery bypass graft surgery was based solely on angiography (angiography-guided group). In 198 patients, at least 1 intermediate stenosis was grafted with an FFR  $\leq 0.80$  or deferred with an FFR  $> 0.80$  (FFR-guided group). The end point was major adverse cardiovascular events at 3 years, defined as the composite of overall death, myocardial infarction, and target vessel revascularization. The rate of angiographic multivessel disease was similar in the angiography-guided and FFR-guided groups (404 [94.2%] versus 186 [93.9%];  $P=0.722$ ). In the FFR-guided group, this was significantly downgraded after FFR measurements to 86.4% ( $P<0.001$  versus before FFR) and was associated with a smaller number of anastomoses (3 [2–3] versus 3 [2–4];  $P<0.001$ ) and rate of on-pump surgery (49% versus 69%;  $P<0.001$ ). At 3 years, major adverse cardiovascular events were not different between the angiography-guided and FFR-guided groups (12% versus 11%; hazard ratio, 1.030; 95% confidence interval, 0.627–1.692;  $P=0.908$ ). However, the FFR-guided group compared with the angiography-guided group presented a significantly lower rate of angina (Canadian Cardiovascular Society class II–IV, 31% versus 47%;  $P<0.001$ ).

**Conclusions**—FFR-guided coronary artery bypass graft surgery was associated with a lower number of graft anastomoses and a lower rate of on-pump surgery compared with angiography-guided coronary artery bypass graft surgery. This did not result in a higher event rate during up to 36 months of follow-up and was associated with a lower rate of angina. (*Circulation*. 2013;128:1405-1411.)

**Key Words:** coronary angiography ■ coronary artery bypass ■ coronary artery disease ■ fractional flow reserve

Myocardial revascularization is recommended to improve symptoms and clinical outcome, following the latest joint guidelines of the European Society of Cardiology and the European Association of Cardio-thoracic Surgery.<sup>1</sup> Improvement in clinical outcome, in particular, has been associated with revascularization of the underlying ischemic burden.<sup>2</sup> The underlying ischemic burden, if not demonstrated by noninvasive functional testing, should be confirmed at the time of the diagnostic coronary angiography by the measurement of fractional flow reserve (FFR). FFR, in fact, allows this identification with unequal spatial resolution of the coronary stenosis responsible for reversible ischemia. In addition, percutaneous revascularization performed in the presence of an abnormal FFR (ie, FFR  $\leq 0.80$ ) results in an improved clinical outcome compared with a revascularization strategy guided solely by the angiographic severity of the coronary stenosis.<sup>3–9</sup>

### Editorial see p 1393 Clinical Perspective on p 1411

Nevertheless, only scarce data supporting the role of FFR in the guidance of surgical revascularization are available. Botman et al<sup>10</sup> showed a significant relationship between functionally significant coronary stenosis as demonstrated by FFR and graft patency at 1 year. The aim of our retrospective study was to investigate the impact of FFR measurement at the time of the preoperative diagnostic coronary angiography on surgical revascularization and its related clinical outcome compared with conventional angiographic guidance.

### Methods

#### Study Population

In this study, we retrospectively investigated patients who underwent coronary artery bypass graft surgery (CABG) in our

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institution between January 2006 and December 2010. The inclusion criterion was the presence of at least 1 intermediate stenosis at the time of coronary angiography, defined as diameter stenosis between 50% and 70% by visual estimation. Patients with a recent myocardial infarction (<30 days) or needing associated valve surgery were excluded.

Patients were divided into 2 groups: the angiography-guided group and the FFR-guided group. The angiography-guided group consisted of patients in whom no FFR was measured at the time of the preoperative coronary angiography and CABG was indicated solely on the basis of the angiographic severity of the coronary stenosis. The FFR-guided group consisted of patients in whom at least 1 intermediate stenosis was measured by FFR and grafted in the presence of FFR  $\leq 0.80$  or deferred with FFR  $> 0.80$ .

### Coronary Angiography and FFR Measurement

Coronary angiography was performed by a standard percutaneous femoral or radial approach with 6F or 7F diagnostic or guiding catheters. After the administration of 200 to 300  $\mu\text{g}$  intracoronary isosorbide dinitrate, the angiogram was repeated in the projection allowing the best possible visualization of the stenosis. Experienced operators not involved in the analysis of the data assessed stenosis severity. Multivessel disease was defined as the presence of stenosis in  $\geq 2$  major coronary arteries.

Performance of FFR measurement was left to the operator's discretion. FFR was measured as previously described.<sup>11,12</sup> Briefly, a pressure-monitoring guidewire (Certus PressureWire; St. Jude Medical Inc, St. Paul, MN) was advanced distal to the coronary artery stenosis. After the administration of intracoronary isosorbide dinitrate (200  $\mu\text{g}$ ), hyperemia was obtained with either intravenous infusion (140  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) or an intracoronary bolus of adenosine (70–100  $\mu\text{g}$ ). An FFR value  $\leq 0.80$  indicated an ischemia-producing coronary stenosis.

### Coronary Artery Bypass Surgery

The type of surgery, namely on-pump or off-pump, and the number and type of grafts were left to the surgeon's discretion.

### Study End Points

Primary end point of the study was the rate of major adverse cardiac events, defined as overall death, myocardial infarction, and target vessel revascularization occurring during up to 3 years of clinical follow-up. Secondary end points were all the individual end points included in major adverse cardiovascular events plus the number of graft anastomoses and symptoms at the last clinical follow-up available. Myocardial infarction was defined as previously described.<sup>13,14</sup> Target vessel revascularization was defined as any percutaneous or surgical revascularization performed at the follow-up either to the index study vessel or to the related vascular graft conduit.

In a group of patients undergoing a clinically indicated coronary angiography during the follow-up, the graft patency rate was evaluated. Here, a subanalysis was performed on a graft level. In particular, in the angiography-guided graft group, we included all the grafts implanted on coronary arteries with intermediate stenosis and no FFR available at the time of the baseline angiogram. In the FFR-guided graft group, we included all grafts implanted on coronary arteries with intermediate stenosis and FFR  $\leq 0.80$ , measured at the time of the baseline angiogram.

The Institutional Medical Ethics Committee approved the use of clinical data for this study, and patients provided their informed consent.

### Statistical Analysis

All analyses were performed with Prism GraphPad 5.0 (GraphPad Software Inc, La Jolla, CA) and SPSS 20.0 (IBM Inc, New York, NY). Continuous variables are expressed as mean  $\pm$  SD or as median (interquartile range) as appropriate. Categorical variables are reported as frequencies and percentages. Normal distribution was tested with the D'Agostino-Pearson omnibus K2 test. Comparisons between continuous variables were performed with the Student *t* test

or Mann-Whitney test. Comparisons between categorical variables were evaluated with the Fisher exact test or the Pearson  $\chi^2$  test as appropriate. The presence of multivessel disease before and after FFR measurement was compared by use of McNemar test. Linear regression analysis was performed to assess the relationship between FFR guidance and the number of anastomoses performed. Clinical variables (male sex, previous percutaneous coronary intervention) that showed a significant univariable association with the number of anastomoses entered the multivariable linear regression model. Logistic regression analysis was performed to assess the relationship between arterial or venous anastomoses and the presence/absence of Canadian Cardiovascular Society (CCS) class II to IV angina. Difference in survival was calculated by applying Kaplan-Meier curves. Cox proportional hazard analysis was performed to analyze clinical end points at the follow-up. In the subgroup of patients undergoing the angiographic follow-up, clinical variables like age and diabetes mellitus entered the multivariable model. A value of  $P < 0.05$  (2 tailed) was considered statistically significant.

## Results

### Clinical Characteristics

We included 627 patients: 429 in the angiography-guided group and 198 in the FFR-guided group. Clinical characteristics are summarized in Table 1. There were no significant differences in baseline characteristics between the 2 groups except that angiography-guided patients were older and more frequently were female and diabetic. FFR-guided patients more frequently had percutaneous coronary intervention in the past.

### Angiographic and Surgical Characteristics

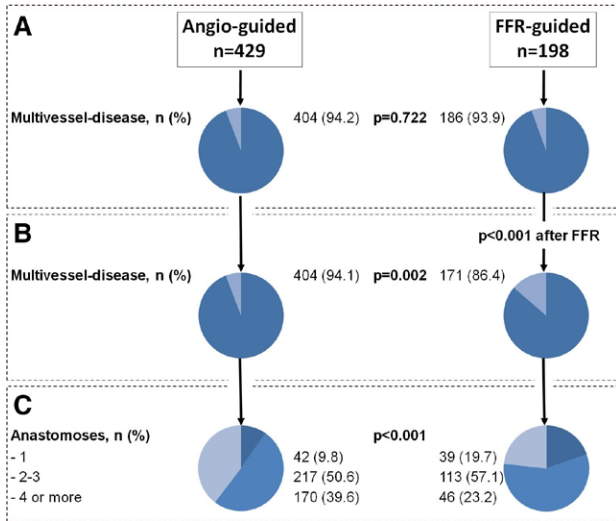
The rate of multivessel disease at coronary angiography was similar between the 2 groups (404 [94.2%] in the angiography-guided group versus 186 [93.9%] in the FFR-guided group;  $P = 0.722$ ; Figure 1A). After FFR measurement, the rate of multivessel disease was significantly downgraded in the FFR-guided group (171 [86.4%];  $P < 0.001$  versus before FFR measurement,  $P = 0.002$  versus angiography-guided group; Figure 1B).

After CABG, total anastomoses per patient (3 [interquartile range (IQR), 2–3] versus 3 [IQR, 2–4];  $P < 0.001$ ) and venous anastomoses per patient (1 [IQR, 0–1] versus 1 [IQR, 1–2];

**Table 1. Clinical Characteristics**

	Angiography-Guided Group (n=429)	FFR-Guided Group (n=198)	P Value
Age, y	69 (63–76)	65 (56–72)	<0.001
Male sex, n (%)	309 (72)	162 (82)	0.010
BMI, kg/m <sup>2</sup>	27 (24–30)	28 (25–30)	0.066
Hypertension, n (%)	338 (79)	155 (78)	0.917
Hypercholesterolemia, n (%)	287 (67)	128 (65)	0.587
Diabetes mellitus, n (%)	128 (30)	43 (22)	0.034
Previous MI, n (%)	62 (14)	40 (20)	0.081
Previous PCI, n (%)	102 (24)	97 (49)	<0.001
Smoking habit, n (%)	177 (41)	84 (42)	0.794
Family history, n (%)	103 (24)	48 (24)	1.000
PVD, n (%)	73 (17)	27 (14)	0.293
LVEF, %	71 (60–80)	71 (61–79)	0.931

BMI indicates body mass index; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.



**Figure 1.** Rate of patients with multivessel disease before (A) and after (B) fractional flow reserve (FFR) measurement. Rate of patients with 1, 2 to 3, and ≥4 anastomoses (C). Angio indicates angiography.

*P*<0.001) were significantly lower in the FFR-guided compared with the angiography-guided group, whereas only a trend was observed for arterial anastomoses (2 [IQR, 1–2] versus 2 [IQR, 1–2]; *P*=0.068; Table 2). This resulted in a higher arterial-venous anastomosis ratio in the FFR-guided compared with the angiography-guided group (71 [29%] versus 55 [45%], respectively; *P*<0.001). In addition, a significant overall difference was observed in the rate of single, 2 to 3, and ≥4 anastomoses per patient between the angiography-guided and the FFR-guided group (Figure 1C). In multivariable linear regression analysis, FFR guidance was significantly

**Table 2. Procedural Characteristics of Coronary Artery Bypass Graft Surgery**

	Angiography-Guided Group	FFR-Guided Group	<i>P</i> Value
Anastomosis per patient, median (IQR), n			
Arterial	2 (1–2)	2 (1–2)	0.068
Venous	1 (1–2)	1 (0–1)	<0.001
Anastomosis per group, n (%)			
Arterial	751/1373 (55)	367/518 (71)	<0.001
Venous	622/1373 (45)	151/518 (29)	
Grafted coronary arteries, n (%)			
LAD	425 (99)	196 (99)	1.000
LCx	380 (89)	170 (86)	0.575
RCA	346 (81)	130 (66)	<0.001
Rate of on-pump surgery, n (%)	269 (69)	97 (49)	<0.001
Pump time, median (IQR), min	95 (89–112)	89 (73–106)	0.067

FFR indicates fractional flow reserve; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex artery; and RCA, right coronary artery.

associated with the number of anastomoses performed ( $\beta$ , -0.20 [95% confidence interval (95% CI), -0.74 to -0.33]; *P*<0.001). Grafted coronary arteries were equally distributed between the 2 groups except for a lower rate of right coronary artery grafting in the FFR-guided group (Table 2). In addition, a lower rate of on-pump surgery was observed in the FFR-guided compared with the angiography-guided group (49% versus 69%; *P*<0.001), whereas only a trend toward lower pump time in the FFR-guided group was found.

**Clinical Follow-Up**

Clinical follow-up was available in 419 patients (98%) in the angiography-guided group and in 193 patients (97%) in the FFR-guided group at a median of 33.1 months (IQR, 21.7–36.0 months). Kaplan-Meier (Figure 2) and Cox regression (Table 3) analyses did not show any significant difference between the FFR-guided and angiography-guided groups with respect to overall death, myocardial infarction, target vessel revascularization, and major adverse cardiovascular events at 36 months.

At baseline, no significant difference was observed between the angiography-guided and FFR-guided groups in the rate of CCS class II to IV. At follow-up, the rate of CCS class II to IV was significantly lower in the FFR-guided compared with the angiography-guided group (Figure 3). A trend toward an association between arterial anastomoses and CCS class II to IV (odds ratio, 0.836; 95% CI, 0.689–1.014; *P*=0.069) was found, whereas no significant association was observed between venous anastomoses and CCS class II to IV (odds ratio, 1.063; 95% CI, 0.917–1.232; *P*=0.418).

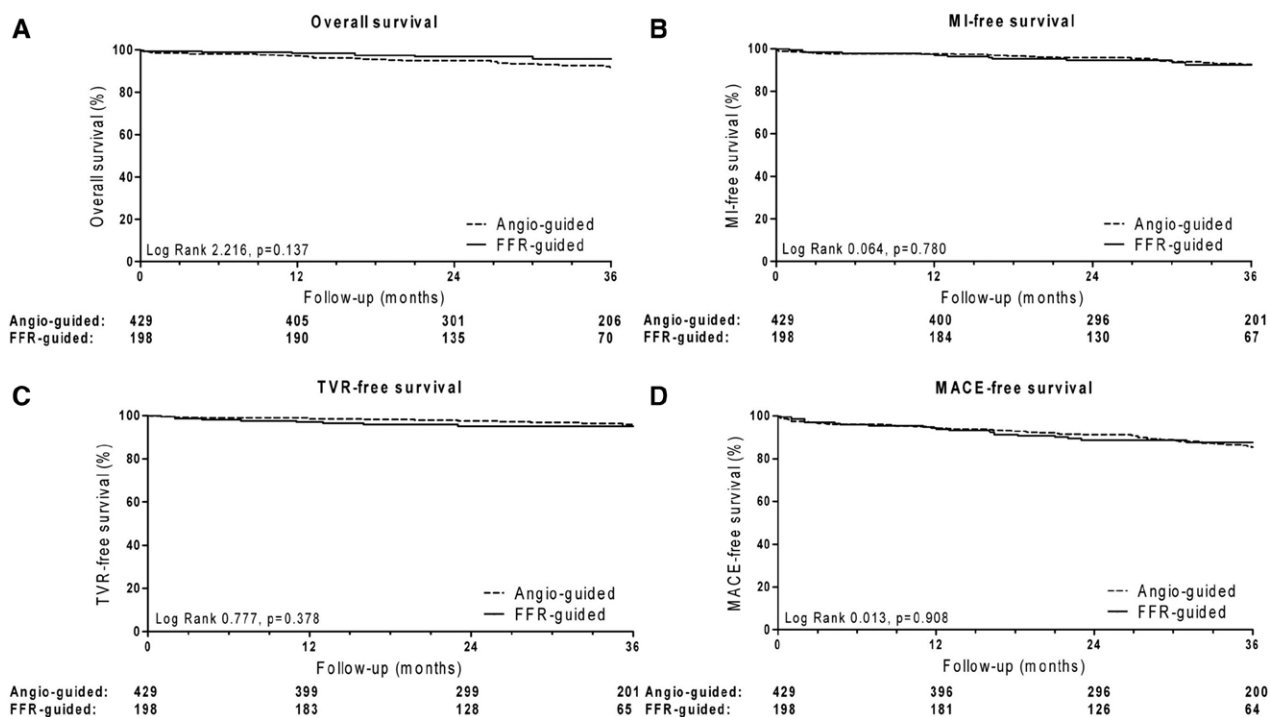
**Angiographic Follow-Up**

A subgroup of 155 patients (25%) underwent a clinically indicated coronary angiography during the follow-up. Clinical characteristics of these patients did not significantly differ from those of the overall group (data not shown). Of 234 grafts implanted on coronaries with intermediate stenosis, 174 were included in the angiography-guided graft group, and 60 were included in the FFR-guided graft group. Median time to angiographic follow-up was similar between these 2 groups: 22 months (IQR, 9–36 months) versus 21 months (IQR, 12–36 months), respectively (*P*=0.790). Compared with the angiography-guided graft group, higher overall graft occlusion-free survival (Figure 4A) and significantly fewer grafts (36 [21%] versus 3 [5%], respectively; adjusted hazard ratio, 0.523; 95% CI, 0.290–0.944; *P*=0.031) were found occluded in the FFR-guided graft group. Only a trend toward higher arterial graft occlusion-free survival was observed in the FFR-guided group (Figure 4B), with similar rates between the 2 groups in terms of occluded arterial grafts (15 [14%] versus 2 [4%]; unadjusted hazard ratio, 0.522; 95% CI, 0.249–1.091; *P*=0.101).

**Discussion**

In the present study, patients undergoing FFR measurement at the time of the diagnostic preoperative coronary angiogram (FFR-guided CABG) received fewer grafts, had fewer anastomoses, and had a lower rate of on-pump surgery compared with patients with no FFR measurement (angiography-guided CABG). Importantly, this lower number of grafts did not





**Figure 2.** Clinical events in the angiography (Angio)-guided and fractional flow reserve (FFR)-guided group during the 36-month follow-up. **A**, Overall survival (log rank, 2.216;  $P=0.137$ ). **B**, Myocardial infarction (MI)-free survival (log rank, 0.064;  $P=0.780$ ). **C**, Target vessel revascularization (TVR)-free survival (log rank, 0.777;  $P=0.378$ ). **D**, Major adverse cardiac event (MACE)-free survival (log rank, 0.013;  $P=0.908$ ).

result in an excess hazard during up to 36 months of follow-up and was associated with a lower rate of angina.

### Role of FFR in Patients Selected for CABG

Myocardial revascularization is recommended when a large territory of reversible myocardial ischemia is present.<sup>1,2</sup> Of note, patients undergoing surgical revascularization usually present with complex coronary artery disease such as left main stenosis or multivessel disease. In these conditions, non-invasive functional testing has demonstrated limited accuracy and poor spatial resolution in detecting reversible ischemia.<sup>15</sup> On the contrary, FFR has high spatial resolution because it allows interrogation of each stenotic coronary artery and the unmasking of possible ischemia-producing stenoses.<sup>16</sup> This was particularly evident in our study. The rate of multivessel disease, in fact, was not significantly different between the 2 groups at baseline angiography. However, after FFR measurement, the rate of multivessel disease was significantly downgraded in patients in the FFR-guided group, suggesting that

several coronary stenoses deemed angiographically significant turned out to be not ischemia producing at the invasive functional evaluation.<sup>17</sup> A significant independent interaction was found between FFR measurement at the time of the diagnostic coronary angiography and surgical revascularization eventually adopted as confirmed by the inverse relationship found between FFR guidance and the number of anastomoses. As a consequence, the number of grafts and the total number of anastomoses, in particular the venous anastomoses, were significantly reduced in the FFR-guided group. The number of arterial anastomoses was similar between the 2 groups, with a higher arterial-venous anastomosis ratio in the FFR-guided group. In addition, the rate of  $\geq 4$  anastomoses and on-pump surgery were significantly reduced, with a trend toward a reduced pump time, suggesting overall a less complex surgical protocol performed in the FFR-guided group.

Grafted coronary arteries were equally distributed between the 2 groups except for a lower rate of right coronary artery grafting in the FFR-guided group. This is of no surprise considering that intermediate stenosis of the right coronary artery can be found more frequently with a nonsignificant FFR value<sup>18</sup> and can be attributed to the more limited subtended myocardial territory of the right coronary artery compared with the left coronary artery.

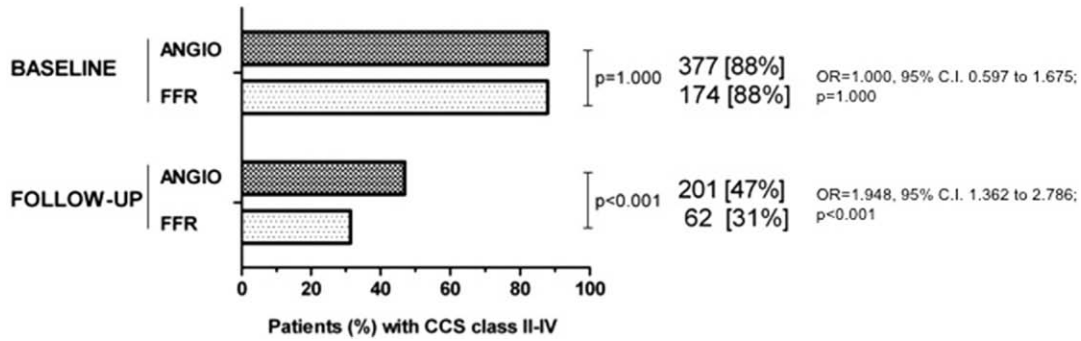
### FFR-Guided CABG and Clinical Outcome

An FFR-guided percutaneous revascularization has been associated with significant clinical benefit in different clinical and anatomic settings compared with a percutaneous revascularization strategy guided solely by the angiographic severity of the coronary stenosis.<sup>3-9</sup> In addition, deferral of coronary stenosis with nonsignificant FFR to optimal medical therapy

**Table 3. Clinical End Points at the 36-Month Follow-Up**

	Angiography-Guided Group (n=429), n (%)	FFR-Guided Group (n=198), n (%)	HR (95% CI)	P Value
Death	31 (7)	7 (4)	1.712 (0.843–3.475)	0.137
MI	25 (6)	12 (6)	0.913 (0.453–1.841)	0.780
TVR	14 (3)	9 (5)	0.671 (0.276–1.630)	0.378
MACEs	52 (12)	22 (11)	1.030 (0.627–1.692)	0.908

CI indicates confidence interval; FFR, fractional flow reserve; HR, hazard ratio; MACEs, major adverse cardiovascular event; MI, myocardial infarction; and TVR, target vessel revascularization.



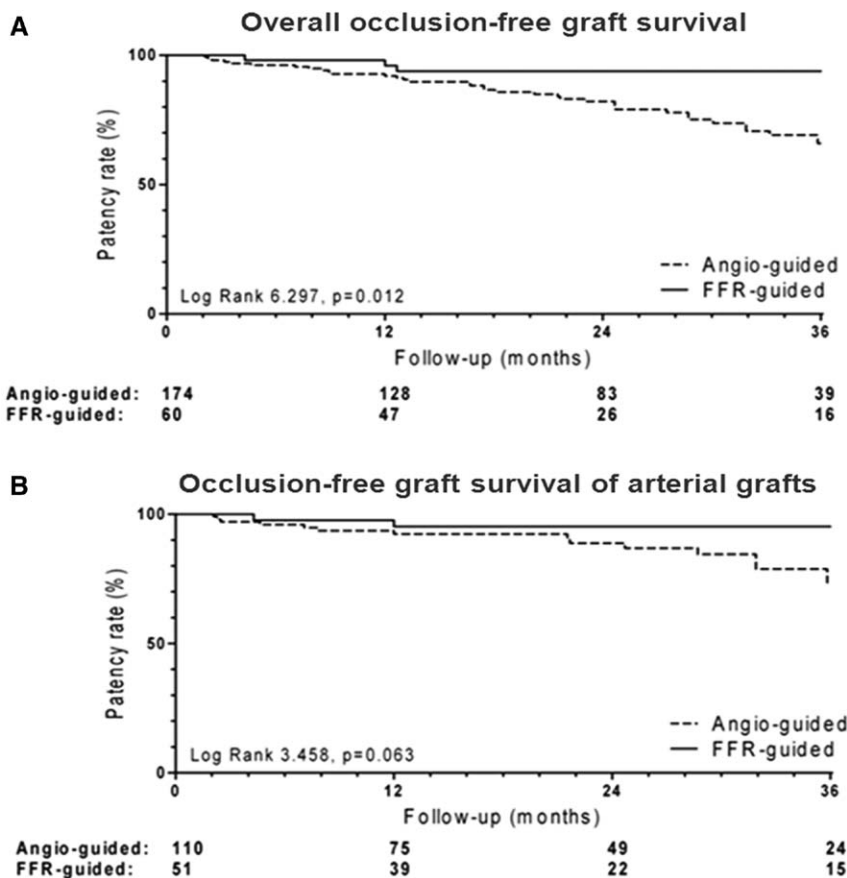
**Figure 3.** Rate of patients with symptoms (Canadian Cardiovascular Society [CCS] class II–IV) at baseline and at the last clinical follow-up. Angio indicates angiography; CI, confidence interval; FFR, fractional flow reserve; and OR, odds ratio.

has shown a favorable outcome.<sup>3,5</sup> In our patients in the FFR-guided group, we did not observe any signal of excess hazard during follow-up. In addition, patients in the FFR-guided group presented improved symptoms, considering that the rate of CCS class II to IV was significantly reduced compared with patients in the angiography-guided group. This is particularly remarkable considering that patients in the FFR-guided group underwent a more limited revascularization in terms of anastomoses and grafts implanted. We do not have a definitive explanation for the lower rate of angina in patients in the FFR-guided group. We can only speculate that, on one hand, the lack of FFR guidance might have left some of the functionally significant stenoses ungrafted in patients in the angiography-guided group but, on the other hand, in patients in the FFR-guided group, the higher arterial-venous anastomosis

ratio might have either limited the clinical impact of potential venous graft failure or warranted longer graft patency rate as a result of the predominance of the arterial bypasses. The latter is also suggested by the trend toward an association between arterial anastomoses and CCS class II to IV.

**FFR-Guided CABG and Graft Patency**

In a prospective registry, Botman et al<sup>10</sup> showed a significant relationship between functionally significant coronary stenosis as demonstrated by FFR and graft patency at 1 year. In particular, compared with grafts implanted on stenotic vessels with pathological FFR, the occlusion rate was nearly 3 times higher in those grafts implanted in stenotic vessels with nonsignificant FFR at the preoperative coronary angiography. Our findings in the subgroup of patients with angiographic follow-up confirm



**Figure 4.** Occlusion-free survival of grafts with angiographic follow-up. **A**, Occlusion-free survival of all grafts (log rank, 6.297; P=0.012). **B**, Occlusion-free survival of arterial grafts only (log rank, 3.45; P=0.063). Angio indicates angiography; and FFR, fractional flow reserve.

and extend to a longer time period these previous observations. In fact, we found that rate of graft occlusion was 4 times lower in the FFR-guided group during up to 3 years of follow-up compared with the angiography-guided group.

### Study Limitations

Several limitations of our study should be acknowledged. First, this is an observational study limited by its retrospective design. Second, we must acknowledge the wide CIs observed for major adverse cardiovascular events, reflecting the limited sample size of our study. The sample size that would be needed to limit the 95% CI to  $\approx 15\%$  corresponds to 3800 patients per group. Although on the basis of this number a clinically driven prospective randomized study would be difficult to perform, we believe our study is valuable in that it provides other surrogate end points for designing prospective studies (pump time, number of anastomosis, patency rate of grafts, etc). Third, coronary stenosis severity was not assessed by an independent angiographic core laboratory. Likewise, some disease of secondary coronary branches might not have been captured in our analysis. Although this limitation affected both groups equally, we cannot exclude an unbalance in favor of the FFR-guided group, that is, less severe disease overall. Fourth, the subanalysis performed in the group of patients with angiographic follow-up, although in line with previous findings,<sup>10,19</sup> should be considered speculative and only hypothesis generating. Here, we acknowledge a possible selection bias derived by the fact that only patients with a clinically indicated coronary angiography were analyzed.

In 29 patients in the FFR-guided group, an additional stenosis in another vessel was measured with FFR and not intervened accordingly, that is, grafted in the presence of FFR  $>0.80$  ( $n=19$ ) or deferred despite an FFR  $\leq 0.80$  ( $n=11$ ). Because these patients had at least 1 stenosis treated according to the FFR value, they were kept in the FFR-guided group. We believe that they had only limited impact (this impact, if any, was not favorable to the FFR-guided group) on our analysis and the interpretation of our results for the following reasons: baseline clinical characteristics of these patients were not significantly different from those of the overall population of the FFR-guided group (data not shown); and among these 29 patients, only 2 presented with target vessel revascularization at the clinical follow-up, both in nonindex vessels. In 1 patient, the left internal mammary artery was implanted on the left anterior descending artery despite the FFR value of the native stenotic vessel being 0.84 at the pre-CABG coronary angiography. Percutaneous coronary intervention of the left internal mammary artery was performed at follow-up. In the other patient, a stenotic left circumflex artery was not grafted despite the FFR value being 0.54 at the pre-CABG diagnostic angiogram. Percutaneous coronary intervention of the left circumflex artery was performed at follow-up.

### Conclusions

An FFR-guided CABG was associated with a lower number of graft anastomoses and with a lower rate of on-pump surgery compared with angiography-guided CABG. This did not result in a higher event rate during up to 36 months of follow-up and was associated with a lower rate of angina.

### Disclosures

Drs Wijns and De Bruyne are consultants for St. Jude Medical Inc. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

The data presented here might be clinically relevant in many respects. Although observational and limited in sample size, our study confirms that deferring revascularization on the basis of nonsignificant fractional flow reserve values even with bypass surgery is safe. This is particularly important if one considers that coronary artery bypass graft surgery is generally a once-in-a-lifetime operation. Therefore, surgeons are aiming at offering a complete revascularization with the best available vascular conduits. Leaving some of the stenoses with nonsignificant fractional flow reserve ungrafted did not show any excess hazard, whereas patients received mostly arterial grafts. This finding might contribute to the ongoing debate on less invasive or hybrid procedures; that is, once the left anterior descending coronary artery and other functionally significant stenoses are grafted with good arterial bypasses, remaining lesions, if they progress, could always be treated later with a good drug-eluting stent or vascular scaffold. Of course, this intriguing hypothesis needs to be tested prospectively in a randomized study. In this regard, our data provide a useful reference for sample size calculation and for the choice of the primary end point (clinical versus surrogate end point) for future trials.

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