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Fractional Flow Reserve Versus Angiographically-Guided Coronary Artery Bypass Grafting

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ABSTRACT

BACKGROUND The value of fractional flow reserve (FFR) evaluation of coronary artery stenosis in coronary artery bypass grafting (CABG) is uncertain, and stenosis assessments usually rely on visual estimates of lesion severity.

OBJECTIVES This randomized clinical trial evaluated graft patency and clinical outcome after FFR-guided CABG versus angiography-guided CABG.

METHODS A total of 100 patients referred for CABG were randomly assigned to FFR-guided or angiography-guided CABG. Based on the coronary angiogram, a heart team made a graft plan for all patients, and FFR evaluations were performed. In FFR-guided CABG, coronary lesions with FFR >0.80 were deferred, and a new graft plan was designed accordingly, whereas the surgeon was blinded to the FFR values in patients who underwent angiography-guided CABG. The primary endpoint was graft failure in the percentage of all grafts after 6 months.

RESULTS Angiographic follow-up at 6 months was available for 72 patients (39 vs. 33 in the FFR-guided and angiography-guided groups, respectively). Graft failures of all grafts were similar in both groups (16% vs. 12%; p = 0.97). Rates of death, myocardial infarction, and stroke were also similar in the study groups, and no difference was seen in revascularization before angiographic follow-up. After 6 months, deferred lesions (n = 24) showed a significant reduction in mean FFR from index to follow-up (0.89 ± 0.05 vs. 0.81 ± 0.11; p = 0.002). Index FFR did not influence graft patency.

CONCLUSIONS FFR-guided CABG had similar graft failure rates and clinical outcomes as angiography-guided CABG. However, FFR was reduced significantly after 6 months in deferred lesions. (Fractional Flow Reserve Versus Angiography Randomization for Graft Optimization [FARGO]; NCT02477371) (J Am Coll Cardiol 2018;72:2732–43)

In patients with coronary artery disease, coronary revascularization is performed to improve symptoms and clinical outcomes (1). Earlier treatment strategies were based on visual assessment of coronary stenosis severity by coronary angiography. Physiological evaluation, primarily fractional flow reserve (FFR) measurement, of coronary artery lesions has become a recommended method to assess the functional severity of coronary lesions (2–4). Physiological evaluation of coronary artery stenosis

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improves decision-making and improves clinical outcome for patients undergoing percutaneous coronary intervention (PCI) (3–5). Using FFR-guided PCI, nonsignificant coronary lesions will not be revascularized, thus avoiding unnecessary coronary interventions associated with a small but definite risk of short- and long-term cardiac events. In contrast, the value of FFR is inadequately investigated in coronary artery bypass grafting (CABG). In CABG, stenosis assessments, and consequently, grafting, almost always rely on visual estimates of lesion severity. A previous prospective nonrandomized trial indicated better graft patency of grafts to functionally significantly stenosed arteries when using FFR (6). A retrospective trial that compared FFR-guided with angiography-guided CABG showed fewer grafted lesions, a similar 3-year rate of major adverse cardiac events, and significantly less angina in the FFR-guided group versus the angiography-guided group (7). The long-term effect of leaving functionally insignificant stenoses ungrafted remains to be investigated. At present, no randomized clinical trials have assessed functional lesion testing in the context of CABG. Therefore, the present prospective randomized clinical trial evaluated graft patency and clinical outcomes after FFR-guided CABG versus angiography-guided CABG.

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METHODS

STUDY DESIGN AND PARTICIPATING CENTERS. The FARGO (Fractional Flow Reserve Versus Angiography Randomization for Graft Optimization) trial was a prospective, controlled, open-label, randomized (1:1) multicenter trial of patients referred for CABG. The study was performed at Odense, Aarhus, and Aalborg University Hospitals, Denmark. Study design is shown in **Figure 1**. The study protocol was approved by the Danish Research Ethics Committee (S-20130050) and The Danish Data Protection Agency (14/9063). All patients provided written informed consent to study participation.

PARTICIPANTS. Patients referred for CABG with stable angina or stabilized non-ST-segment elevation myocardial infarction and/or unstable angina were eligible if they had ≥1 study lesions planned for grafting by the heart team. The definition of the study lesion was a visually assessed ≥50% stenosis of a major epicardial artery with a proximal reference segment diameter >2.5 mm that was passable by an FFR wire. Study lesions could be located at all coronary arteries. Exclusion criteria were concomitant valve surgery, former heart surgery, left main lesion without intermediate severity lesions in the right coronary artery, treatment with dipyridamole, single-vessel disease, p-creatinine ≥150 μmol/l, and emergency surgery. A screening log was maintained in 1 center, which recruited 62 of the 100 patients.

RANDOMIZATION AND DATA COLLECTION. Patients were randomly allocated (1:1) to undergo either FFR-guided CABG or angiography-guided CABG, and data were collected using a dedicated electronic randomization system and case report form, TrialPartner (DEFACTUM, Olof Palmes Allé 15, DK-8200 Aarhus N). Randomization was performed in permutated blocks by center, and stratified by sex and the presence of diabetes.

GRAFT PLAN. Based on the coronary angiogram, the heart team made a plan for grafting in all patients. Subsequently, the patients were randomized to FFR-guided or angiography-guided grafting, and a new invasive evaluation with FFR measurements of index lesions was performed. Some patients had FFR evaluations at diagnostic angiography before the heart team conference; these FFR measurements were blinded to the heart team. A final graft plan was recorded in the case report form. In the FFR-guided group, coronary lesions with FFR ≤0.80 were planned for grafting, and lesions with FFR >0.80 were deferred. In the angiography-guided group, the surgeon was blinded to the FFR values, and the initial graft plan followed, if possible.

CORONARY PHYSIOLOGY ASSESSMENT. The study lesions were visualized by coronary angiography, which was performed by standard techniques. Before invasive measurements, all patients received 5,000 IE of intravenous heparin and intracoronary nitroglycerin. A 0.014-inch coronary pressure wire (St. Jude Medical, St. Paul, Minnesota) was equalized with the guiding catheter pressure and advanced distal to the study lesion. Maximal hyperemia was induced by intravenous adenosine, which was administered at a rate of 140 μg/kg of body weight per min through a central or a cubital vein. FFR was calculated as the mean distal coronary pressure (measured with the pressure wire) divided by the mean aortic pressure (measured simultaneously with the guiding catheter) during maximal hyperemia (8).

CABG. CABG was performed according to the final graft plan, with intended grafting of all coronary arteries planned for grafting. The decision regarding on-pump and/or off-pump surgery was left to the

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

FFR = fractional flow reserve

MACCE = major adverse cardiac and cerebrovascular event

PCI = percutaneous coronary intervention

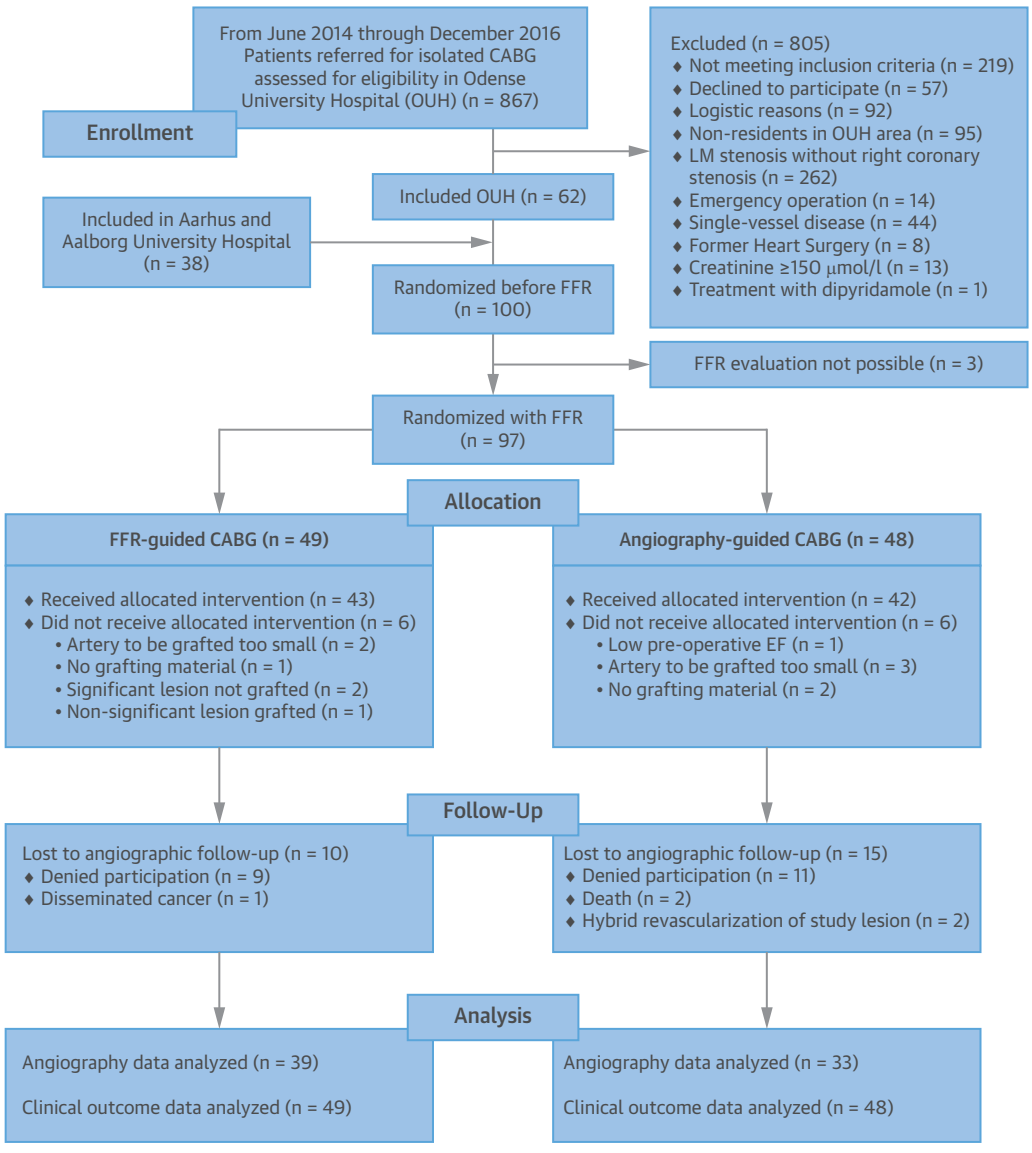
RIMA = right internal mammary artery

TIMI = Thrombolysis In Myocardial Infarction

TVMI = target vessel myocardial infarction

TVR = target vessel revascularization

FIGURE 1 CONSORT Flow Diagram



Consort flow diagram of patients included in the study from June 2014 to December 2016 showing the number of patients that were randomized, followed treatment allocation, completed follow-up, and included in data analysis, and reasons for exclusion. CABG = coronary artery bypass grafting; EF = ejection fraction; FFR = fractional flow reserve; LM = left main stenosis; OUH = Odense University Hospital.

discretion of the surgeon. The internal mammary arteries, radial arteries, and saphenous vein were used for bypass grafting. If possible, study vessels received single grafts, whereas the remaining grafts were performed according to the attending surgeon's choice. The saphenous vein and radial artery were harvested using conventional open techniques. The left internal mammary artery (LIMA) and right internal mammary artery (RIMA) were harvested as pedicles. Graft quality was evaluated by inspection of all grafts. Graft flow was assessed pre-operatively via a Transit Time Flow Meter (Medistim, Oslo, Norway), which recorded the transit time flow and pulsatility index by a probe size matching the conduit. Mean arterial pressure was recorded at the same time. Post-operatively, all patients received medical treatment according to current guidelines, with statins and aspirin given to all patients unless specifically contraindicated. Aspirin was substituted with clopidogrel, if not tolerated. Patients with non–ST-segment

elevation myocardial infarction were treated with aspirin lifelong and ticagrelor for 12 months. Patients were followed post-operatively and offered rehabilitation according to local practice.

ANGINA CLASSIFICATION. Before CABG and before the study-related angiography at 6 months, the severity of angina, graded according to the Canadian Cardiovascular Society classification system, was assessed in each patient by interviewing the patient about angina symptoms in daily activities and during physical exercise (9).

ANGIOGRAPHIC FOLLOW-UP. Angiographic and clinical follow-up were performed after 6 months to visualize all grafts and the genuine coronary arteries. All deferred lesions were re-evaluated by FFR, in the FFR-guided group. Patients in whom the FFR of the study lesion had dropped to <0.80 and who had symptoms of angina or a positive myocardial perfusion scintigraphy were treated by PCI of the deferred lesion. Patients with graft failure and symptoms of angina or a positive ischemic test were treated by PCI of the relevant vessel as well. An endpoint committee, which included a cardiologist and a cardiac surgeon blinded to group assignment and pre-operative FFR values, assessed the Thrombolysis In Myocardial Infarction (TIMI) flow grade of all grafts (10). Discrepancies were solved by consensus. All revascularizations after CABG, myocardial infarctions, and stroke were identified and adjudicated by the endpoint committee.

ENDPOINTS AND FOLLOW-UP. The primary endpoint was the percentage of graft failure of all grafts at 6 months. Graft failure was defined as less than TIMI flow grade 3 and/or anastomosis stenosis >50%. TIMI flow grades were based on the results of the TIMI trial (11).

Secondary endpoints included: 1) graft stenosis of shaft or anastomoses after 6 months; 2) rate of major adverse cardiac and cerebrovascular events (MACCEs) at 6 months, which was defined as a composite of all-cause mortality, nonprocedural myocardial infarction, any repeat revascularization, and stroke; 3) the individual components of MACCEs at 6 months; 4) change in functional angina class at 6 months assessed by the Canadian Cardiovascular Society classification system; 5) surgical procedure time, extra-corporal circulation time, and cross clamp-time; and 6) maximal levels of p-creatine kinase MB the first 24 h after the operation.

ENDPOINT DEFINITION. Mortality was defined as death from all causes. Myocardial infarction was the third definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation (12). Procedural-related myocardial infarction was the third definition used by the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation (12).

Stroke was defined as brain, spinal cord, or retinal cell death attributable to ischemia, based on: 1) imaging or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 h or until death, when other etiologies could be excluded (13).

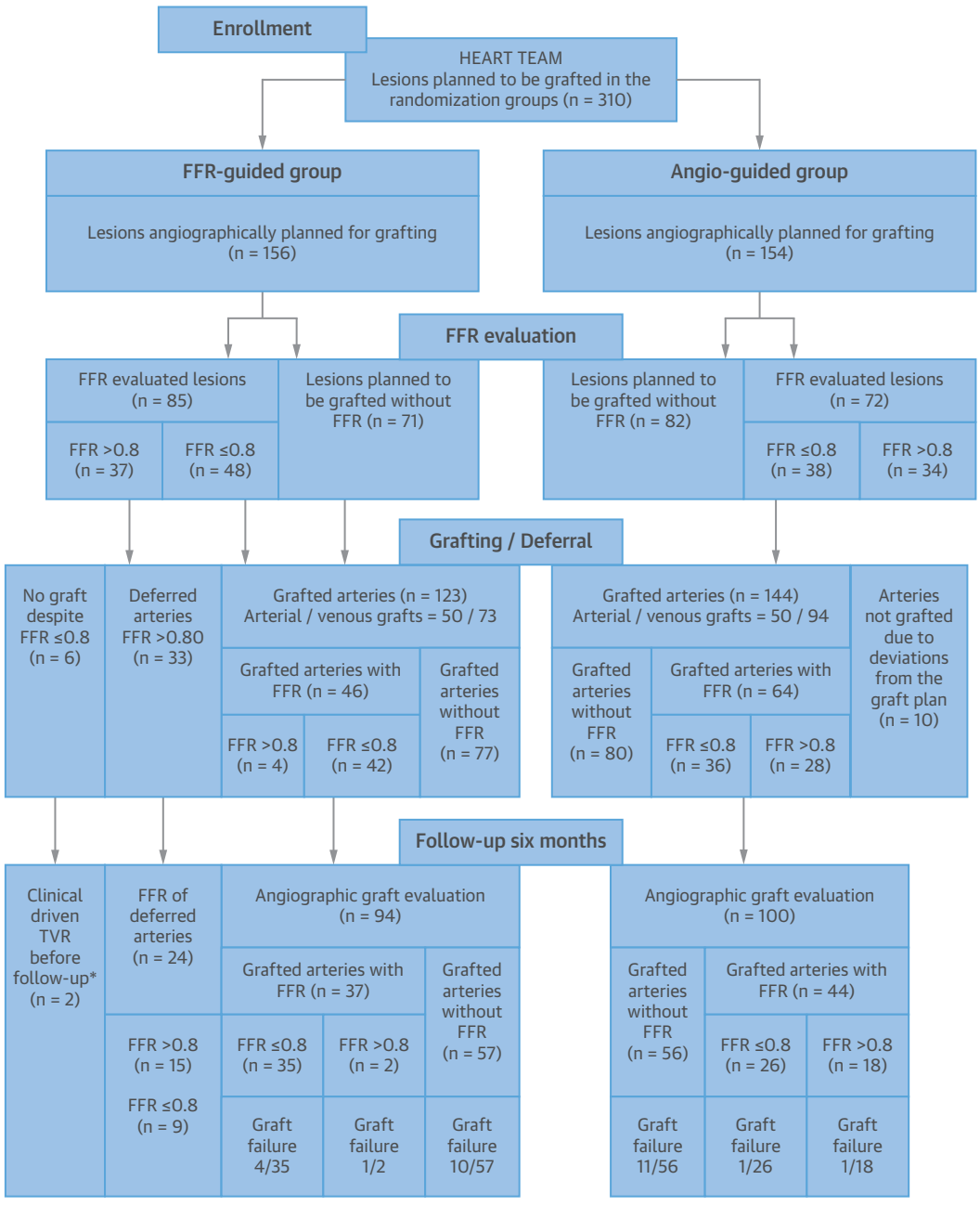
TABLE 1 Baseline Characteristics of Study Population

	FFR-Guided CABG (n = 49)	Angio-Guided CABG (n = 48)	p Value
Demographic characteristics			
Male	44 (88)	44 (89)	0.77
Age, yrs	66.4 ± 6.4	65.3 ± 8.8	0.51
Body mass index, kg/m^2	27.7 ± 3.7	27.4 ± 3.8	0.72
Systolic blood pressure, mm Hg	137 ± 19	147 ± 23	0.31
Diastolic blood pressure, mm Hg	76 ± 11	78 ± 13	0.31
Clinical characteristics			
Hypertension	33 (67)	33 (67)	0.94
Hypercholesterolemia	42 (86)	36 (75)	0.18
Diabetes mellitus	11 (22)	11 (23)	0.87
Family history of CVD	26 (53)	27 (56)	0.59
Current smoker	13 (27)	8 (17)	0.34
Creatinine, ml/min	80 ± 15	86 ± 18	0.07
Diagnosis			
Stable angina	42 (86)	32 (67)	0.16
Unstable angina	1 (2)	5 (10)	
NSTEMI/STEMI	6 (12)	10 (21)	
Heart failure	0 (0)	1 (1)	
Ejection fraction			
EF ≥55%	35 (71)	33 (68)	0.55
EF 30%–54%	14 (29)	15 (32)	
CCS classification			
I	2 (4)	2 (4)	0.55
II	37 (76)	35 (73)	
III	10 (20)	9 (19)	
IV	0 (0)	2 (4)	
Previous MI	14 (29)	10 (21)	0.38
Previous PCI	10 (20)	10 (21)	0.95
Angiographic vessel disease			0.74
2-vessel disease	10 (20)	14 (27)	0.32
3-vessel disease	39 (78)	34 (71)	
Left main stenosis	8 (16)	9 (18)	0.82
EuroSCORE I	2.5 ± 1.9	2.9 ± 2.8	0.95
EuroSCORE II	1.1 ± 0.6	1.2 ± 1.1	1.00

Values are n (%) or mean ± SD. Total p value for distribution of the different variables between the randomization groups.

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; CVD = cardiovascular disease; EF = ejection fraction; FFR = fractional flow reserve; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

FIGURE 2 Flow Diagram of Coronary Lesions



Flow diagram of coronary lesions included in the study showing the number of lesions planned to be grafted, the lesions evaluated by FFR, the lesions actually grafted and the patients who followed treatment allocation, lesions evaluated after 6 months with angiographic follow-up, and FFR of deferred lesions. *2 FFR-positive lesions in the FFR-guided group needed TVR before follow-up, because the lesions were not completely revascularized during surgery (protocol deviation). TVR = target vessel revascularization; other abbreviation as in Figure 1.

Levels of creatine kinase-MB were measured at least twice in all patients between 12 and 24 h after CABG. After discharge, a follow-up assessment was performed at 6 months. Before CABG and at 6 months, the severity of angina, graded according to the Canadian Cardiovascular Society classification system, was assessed. An electrocardiogram was obtained before CABG, at discharge, and at 6 months.

SAMPLE SIZE AND POWER CALCULATION. The primary purpose of the data analysis was to assess graft patency after 6 months in patients who underwent FFR-guided CABG versus angiography-guided CABG. We estimated minimum sample size to be 84 patients in each group, based on a 2-sided chi-square test with an alpha level of 0.05 and a statistical power of 0.80. We estimated a graft occlusion rate of 20% after 6 months in the grafts to arteries with FFR >0.8, as well as a graft occlusion rate of 5% in grafts to arteries with FFR ≤0.80 and a dropout rate of 15%. These graft patency rates were based on data from the study by Botman et al. (6) from 2007; these were the only available rates when the study was designed.

STATISTICAL METHODS. The primary endpoint is described as a percentage. Depending on whether data conformed to a normal distribution, continuous variables were compared using the Student's *t*-test or the Mann-Whitney U test. Categorical variables were compared using the chi-square test or Fisher exact test. Continuous variables were described as mean ± SD. A 2-sided value of $p < 0.05$ was considered significant. Analyses of the primary and secondary endpoints were performed according to the intention-to-treat principle. The subanalysis of graft occlusion for arterial grafts versus venous grafts and for grafts to significant lesions versus nonsignificant lesions was analyzed according to subgroups. All statistical analyses were performed using SPSS software version 24 (IBM, Armonk, New York).

RESULTS

Inclusion in the randomized study was ended because of a much slower inclusion rate than expected. Many patients referred for CABG were excluded from the study, either because of severe atherosclerotic disease, or left main disease and no intermediate lesions. In patients eligible for the study, the visual estimation of coronary artery stenosis often harmonized with the FFR value. Therefore, few eligible patients had visually evaluated significant stenoses that were functionally nonsignificant.

BASELINE CHARACTERISTICS AND ANGIOGRAPHIC DATA. From June 2014 to December 2016, 100 patients were enrolled at 3 university hospitals in Denmark and randomly assigned to FFR-guided CABG or angiography-guided CABG (Figure 1). Index FFR measurements were obtained in 97 (97%) patients, leaving 49 patients in the FFR-guided group and 48 patients in the angiography-guided group. Baseline characteristics of the 2 study groups were similar with regard to age, sex, pre-operative morbidity, and diseased coronary vessels (Table 1).

TABLE 2 Baseline Characteristics of Invasive and Surgical Procedures

	FFR-Guided CABG (n = 49)	Angio-Guided CABG (n = 48)	p Value
FFR procedure characteristics			
No. of coronary arteries evaluated with FFR	85	72	
LAD	20 (24)	15 (21)	0.54
Diagonals	7 (8)	3 (4)	
CX	28 (33)	29 (40)	
RCA	30 (35)	25 (35)	
FFR evaluated arteries/patient	1.7 ± 0.9	1.5 ± 0.7	0.23
Mean FFR at index	0.78 ± 0.12	0.77 ± 0.13	0.54
Graft plan characteristics			
Angiographic graft plan	3.2 ± 0.7	3.2 ± 0.8	0.87
Final graft plan, n	2.5 ± 0.9	3.2 ± 0.8	<0.001
Anastomosis per patient	2.6 ± 0.9	3.0 ± 0.9	0.005
Grafted according to randomization	43 (88)	42 (88)	0.97
Grafted coronary arteries			
All grafts	123	144	
LAD grafted	47 (38)	48 (33)	0.84
Diagonals grafted	10 (8)	11 (8)	
CX grafted	38 (31)	50 (35)	
RCA grafted	28 (23)	35 (24)	
Graft characteristics			
Arterial grafts	50 (41)	50 (35)	0.32
Venous grafts	73 (59)	94 (65)	
CABG procedure characteristics			
Patients operated	49	48	
Rate of on-pump procedure	44 (90)	46 (96)	0.25
ECC time, min	77 ± 26	88 ± 31	0.075
Clamp time, min	43 ± 16	49 ± 22	0.12
Maximal CK-MB value, μg/l	39.1 ± 32.3	35.5 ± 39.4	0.62
Hospitalization, days	5.9 ± 1.9	6.3 ± 2.5	0.44
Reoperation or PCI first 7 days post-CABG			
Acute graft failure	1 (2)	0 (0)	–
Bleeding	2 (4)	2 (4)	–
Hybrid revascularization	1 (2)	3 (6)	–
PCI of deferred coronary artery	0 (0)	0 (0)	–

Values are n, n (%), or mean ± SD.

CK-MB = creatine kinase MB; CX = circumflex coronary artery; ECC = extra corporal circulation; LAD = left anterior descending coronary artery; RCA = right coronary artery; other abbreviations as in Table 1.

HEART TEAM GRAFT PLAN AND PRE-OPERATIVE FRACTIONAL FLOW RESERVE. The heart team decision, based on angiography, was to graft 310 coronary lesions (including 42 chronic total occlusions)—156 lesions in the FFR-guided group and 154 in the angiography-guided group (Figure 2). Of the lesions planned for grafting, FFR was measured pre-operatively in 85 (54%) lesions in the FFR-guided group and in 72 (47%) lesions in the angiography-guided group (Table 2). Mean FFR before grafting was similar in the 2 groups (Table 2). The rate of planned anastomoses per patient according to the

TABLE 3 Primary and Secondary Endpoints in Patients at 6 Months

	FFR-Guided CABG (n = 49)	Angio-Guided CABG (n = 48)	p Value
Patients with invasive follow-up at 6 months	39	33	
Graft failures			
Graft failures/all grafts per patient	16 ± 29	12 ± 17	0.97
Patients with graft failure	11 (28)	11 (33)	0.64
Patients with graft occlusion	6 (15)	5(15)	0.90
6-month clinical endpoints (all patients)			
Death	0 (0)	2 (4)	0.24
Myocardial infarction	1 (2)	0 (0)	0.50
Stroke	2 (4)	1 (2)	0.51
All revascularizations before follow-up	3 (6)	3 (6)	1.00
Hybrid revascularization decided at CABG	1 (2)	3 (6)	
Other revascularizations	2 (4)	0 (0)	
MACCE	6 (12)	6 (12)	0.97
CCS II–IV	5 (10)	2 (4)	0.29

Values are n, mean ± SD, or n (%).
MACCE = major adverse cardiac and cerebral event(s); other abbreviations as in Table 1.

angiography-based graft plan was similar in the 2 groups. Using FFR guidance, the number of planned anastomoses per patient decreased, resulting in a final graft plan with fewer planned anastomoses per patient in the FFR-guided group (2.5 ± 0.9 vs. 3.2 ± 0.8; p < 0.001) (Table 2).

CABG PROCEDURE. A total of 267 coronary arteries were grafted, of which 100 (37%) were arterial grafts. In the FFR-guided group, 33 coronary arteries were deferred. Of the randomized patients, 43 (88%) patients in the FFR-guided group and 42 (88%) patients in the angiography-guided group were grafted according to randomization (Figure 1). Because of deferred grafting of FFR insignificant stenoses in the FFR-guided group, the number of anastomoses was significantly lower per patient than those in the angiography-guided group (2.6 ± 0.9 vs. 3.0 ± 0.9; p = 0.005) (Table 2). No difference was seen in the rate of on-pump surgery between the FFR-guided group versus the angiography-guided group (90% vs. 96%; p = 0.25). Length of hospital stay was the same in the 2 groups, as was the rate of complications (Table 3). Because of poor target vessels, 4 patients (1 in the FFR-guided group and 3 in the angiography-guided group) were changed to hybrid revascularization and received PCI during hospitalization after CABG. None of the deferred coronary arteries in the FFR-guided group needed revascularization after CABG during the index hospitalization.

ANGIOGRAPHIC FOLLOW-UP AT 6 MONTHS. Angiographic follow-up after 6 months was available in 72 (74%) patients (39 patients in the FFR-guided group and 33 patients in the angiography-guided group) (Figure 1). Reasons for not undergoing angiography included death before follow-up in 2 patients, hybrid procedure (PCI) of study vessel in 2 patients, disseminated cancer in 1 patient, and late withdrawal of consent to control angiography in 20 patients (Figure 1).

GRAFT FAILURES. The primary endpoint, graft failures of all grafts occurred in 16% versus 12% (p = 0.97) of the grafts and in 28% versus 33% (p = 0.64) of the patients in the FFR-guided and angiography-guided groups, respectively. Graft occlusion occurred in 6 (15%) patients versus 5 (15%) patients of the FFR-guided group versus the angiography-guided group (p = 0.90) (Table 3). The study vessels with a FFR >0.80 were deferred in the FFR-guided group and grafted in the angiography-guided group. Graft failure rates were similar in subgroups of grafted arteries with nonsignificant stenosis (FFR >0.80) versus grafted arteries with significant stenosis (FFR ≤0.80) (8.1% vs. 10%; p = 0.80) (Table 4). Arterial grafts and venous grafts had similar graft failure rates in both groups and overall (14.5% vs. 14.3%; p = 0.97) (Table 4).

FFR IN DEFERRED LESIONS. After 6 months, deferred lesions were evaluated with FFR (n = 24) and showed a significant reduction in mean FFR from the index procedure to follow-up (0.89 ± 0.05 vs. 0.81 ± 0.11; p = 0.002) (Central Illustration). In coronary arteries with pre-operative FFR >0.80, deferred lesions with decreased FFR values of ≤0.80 were compared with graft failure. Among all lesions with pre-operative FFR >0.80, 9 (37.5%) deferred lesions had a significant FFR value of ≤0.80 and 2 (10%) graft failures occurred (p = 0.044).

CLINICAL OUTCOMES. Clinical follow-up was available in all patients (Table 4). Rates of death, myocardial infarction, and stroke were similar in the study groups. All-cause mortality at 6 months was 0% in the FFR-guided group and 4.1% in the angiography-guided group; 1 patient died because of pulmonary embolism, and 1 died because of mediastinitis (p = 0.24). At 6 months, 88.8% of the patients in the FFR-guided group were free from angina compared with 95.8% in the angiography-guided group (p = 0.29). Angina was significantly reduced from baseline to 6 months after CABG in all patients, with no difference between the randomization groups. Angina was only reported in patients with graft failure or low FFR (23.3% vs. 0%; p = 0.001).

There was no difference in re-intervention, including hybrid procedure, before study-related angiographic follow-up. Excluding the hybrid procedure, 2 revascularizations occurred in FFR-positive

lesions in the FFR-guided group because the lesions were not completely revascularized during surgery despite a FFR <0.80 (protocol deviation).

In FFR-negative lesions, in the angiography-guided group, there were 2 asymptomatic graft failures with no target vessel revascularization (TVR) or target vessel myocardial infarction (TVMI) at the angiographic follow-up. In the FFR-guided group, there was no TVR and/or TVMI in deferred lesions before the angiographic follow-up (Table 4).

TABLE 4 Primary and Secondary Endpoints in Coronary Lesions at 6 Months

	FFR-Guided CABG (n = 94)	Angio-Guided CABG (n = 100)	p Value
Graft failures at 6 months			
All graft failures	15 (16)	13 (13)	0.56
Occluded grafts/ TIMI flow grade 0	7 (7)	6 (6)	0.89
Graft stenosis/TIMI flow grade 1–2	6 (6)	6 (6)	
Planned coronary artery not grafted	2 (2)	1 (1)	
Arterial graft failures at 6 months			
Arterial grafts at 6 months	38	32	
Arterial graft failures	5 (13)	5 (16)	0.76
Venous graft failures at 6 months			
Venous grafts at 6 months	56	68	
Venous graft failures	10 (18)	8 (12)	0.33
FFR-guided group			
Difference in mean FFR (index to follow-up)			
Mean FFR at index procedure	0.89 ± 0.05		
Mean FFR at follow-up	0.81 ± 0.11		
Mean FFR difference from index to follow-up	−0.08 ± 0.11		0.002
	Arterial Grafts (n = 70)	**Venous Grafts (n = 124)**	
Graft failure in all patients according to graft type			
Graft failures at 6 months	10 (14.3)	18 (14.5)	0.97
	FFR ≤0.80 (n = 61)	**FFR >0.80 (n = 20)**	
Graft failure in all patients according to FFR value			
Graft failures at follow-up	5 (8)	2 (10)	0.80
	Deferred Lesions (n = 24)	**Grafts to FFR >0.80 (n = 20)**	
Events in coronary arteries with index FFR >0.80			
Lesions with FFR ≤0.80 or graft failure at follow-up	9 (37.5) Lesions with FFR ≤0.80	2 (10) Graft failures	0.044
TVR/TVMI until follow-up	0	0	

Values are n (%), n, or mean ± SD.

TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; TVMI = target vessel myocardial infarction; other abbreviations as in Table 1.

DISCUSSION

In this randomized study, FFR-guided and angiography-guided CABG resulted in similar graft failure rates and clinical outcomes at 6 months. FFR-guidance significantly reduced the number of grafts. However, in the FFR-guided group, FFR values in deferred lesions were significantly reduced at 6-month follow-up (Central Illustration).

IMPACT OF FFR ON SURGICAL REVASCULARIZATION. Patients undergoing CABG usually have complex multivessel coronary artery disease or left main stenosis. When coronary arteries are evaluated with FFR, some of the angiographically significant lesions are found not to be functionally flow-limiting. Consequently, multivessel disease may be downgraded to 1- or 2-vessel disease (14). This downgrading was also found in our study, when the angiographically estimated presence of multivessel disease and the number of planned grafts was reduced after the FFR evaluation, which resulted in fewer grafts in FFR-guided CABG. The reduced clamp-time was suggestive of a more simple surgical protocol in the FFR-guided group. The findings of fewer grafts in FFR-guided patients and reduced clamp-time are in concordance with an earlier retrospective study (7).

GRAFT FAILURE. The primary endpoint of graft failure as a percentage of all grafts was similar in the FFR-guided group compared with the angiography-guided group. This endpoint included graft failures to both FFR-positive and FFR-negative lesions in the angiography-guided group and graft failures to only FFR-positive lesions in the FFR-guided group. The FFR-negative lesions that were grafted in the angiography-guided group and not grafted in the FFR-guided group were expected to produce the difference in outcome. However, graft failure rates in FFR-positive lesions versus FFR-negative lesions were also similar. This finding was contradictory to a prospective study that evaluated FFR in 164 patients before CABG and showed that the occlusion rate of bypass grafts implanted in functionally nonsignificant lesions was doubled compared with that of bypass grafts implanted in functionally significant lesions (6). Our results may be explained by our strict definition of graft failure (TIMI flow grade 3 and/or anastomotic stenosis >50%, or that the planned artery was not grafted).

A recent meta-analysis of graft patency rates after CABG showed patency rates from 1 week to 1 year of approximately 85% to 90%, which implied a 10% to 15% graft failure rate (15). The observed graft failure rates of 12% to 15% in the present study were within this range. Graft patency is a multifactorial parameter, including lesion severity, vessel diameter, surgical technique, and patient-related factors (16,17).

TABLE 5 Reasons for Graft Plan Deviations During CABG

	FFR-Guided Group (n = 49)	Angio-Guided Group (n = 48)
Graft plan not implemented for FFR-evaluated vessels	6	6
Low EF; short clamp-time preferred and randomization overruled		1
Artery planned for grafting visually too small (≥hybrid 2 patients)	2	2
Insufficient graft material (≥hybrid 2 patients)	1	2
Anatomic deviation		1
Significantly stenosed artery not grafted	2	
Non-significantly stenosed artery grafted	1	
Graft plan implemented for FFR-evaluated vessels – fewer or more grafts than planned	7	3
Artery planned for grafting visually too small	1	
Artery planned for grafting not found	1	2
1 or 2 more grafts than planned	5	1

The reasons for different graft plan deviations from the final graft plan according to randomization groups.
EF = ejection fraction; other abbreviations as in Figure 1.

When changing only 1 factor, such as lesion severity in our study, even a marked change in graft patency might be difficult to detect, because both significant and nonsignificant stenoses were treated in the angiography-guided group.

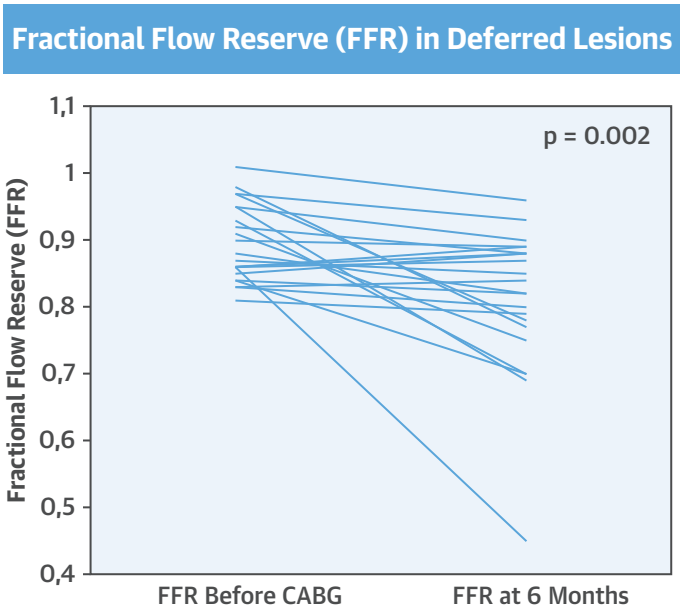
It is a matter of debate if grafting of moderately diseased and functionally insignificant coronary lesions is harmful. Accelerated atherosclerosis after grafting was described, particularly in arteries grafted by venous grafts (18). In contrast, arterial grafts were shown to protect the native coronary vessels from atherosclerotic disease (19). At least in theory, a combination of progressive coronary atherosclerosis and graft occlusion might constitute a clinical problem. However, in a prospective study of pre-operative FFR and 1-year graft patency, the high rate of occluded bypass grafts to functionally insignificant lesions did not lead to myocardial infarction or increased angina (6). In our study, graft occlusion alone was not related to angina; however, 1 patient experienced myocardial infarction due to graft occlusion.

DEFERRAL OF NONSIGNIFICANT CORONARY LESIONS. The significant decrease of mean FFR at follow-up was an important finding of this study. Accelerating atherosclerosis of the deferred coronary lesion is a likely explanation, and might suggest that functionally guided surgical revascularization could be associated with more repeat revascularization at longer term follow-up. This finding was in contrast to the DEFER (Deferral or Performance of Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis) study and to the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation I) study, in which deferral of functionally insignificant lesions in PCI-treated patients was safe (4,20). The DEFER study investigated patients with 1-vessel disease with intermediate stenosis and found FFR-guided PCI with deferral of nonsignificant stenoses to be safe, and provided similar clinical outcome compared with angiography-guided PCI (4,21). The FAME study investigated patients with multivessel disease and found that FFR-guided PCI significantly reduced the rate of MACCEs at 1 year compared with angiography-guided PCI (3,20). Both studies primarily looked at clinical endpoints. There was no angiographic follow-up, and deferred lesions were not evaluated with FFR after the index procedure.

Two studies evaluated serial FFR measurements over time in deferred coronary artery lesions (22,23). The YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial investigated FFR changes after 7 weeks of high-dose statin therapy compared with standard statin therapy in 2-vessel and 3-vessel disease, and found an increase in FFR in the high-dose group and a stable FFR in the standard therapy group (23). The Serial Morphological and Functional Assessment of Drug-Eluting Balloon for In-Stent Restenotic Lesions study examined serial morphological and functional assessment of drug-eluting balloon treatment for in-stent restenosis, and found that the in-stent FFR gradient remained stable or tended to further decrease from post-procedure to 6-month follow-up (22). These studies contradicted our findings because we found a reduction in the FFR value in the serial FFR assessment. One study found higher clinical event rates after deferral of nonsignificant, nonculprit lesions in patients with acute coronary syndrome compared with patients with stable angina (24). Patients referred for CABG might have accelerating atherosclerotic disease, and therefore, deferred coronary lesions might evolve differently in this group of patients.

CLINICAL OUTCOME. In the present study, the rate of death, myocardial infarction, stroke, and re-intervention at follow-up were similar in the FFR-guided CABG group compared with the angiography-guided CABG group. These findings were in line with the retrospective study by Toth et al. (7), which reported similar rates of MACCEs and significantly reduced rates of Canadian Cardiovascular Society classes II to IV in FFR-guided CABG compared with angiography-guided CABG (7). FFR-guided patients in our study did not experience more angina pectoris. Angina was only reported in

CENTRAL ILLUSTRATION **Change in Fractional Flow Reserve Before Coronary Artery Bypass Grafting and After 6 Months in Deferred Coronary Lesions**



Thuesen, A.L. et al. J Am Coll Cardiol. 2018;72(22):2732–43.

A significant reduction was found in mean fractional flow reserve (FFR) from the index procedure to follow-up. CABG = coronary artery bypass grafting.

patients with low FFR or graft failure, which indicated that graft failure and low FFR caused myocardial ischemia and not was due to day-to-day variance.

By comparing FFR-guided CABG with angiography-guided CABG, similar rates of graft failure and clinical outcomes, together with a significant decrease in FFR of deferred lesions after 6 months, did not advocate for an FFR-guided surgical revascularization strategy.

STUDY LIMITATIONS. This was the first randomized, controlled, multicenter trial that compared an FFR-guided revascularization strategy with an angiography-guided revascularization strategy. Different centers, surgeons, and cardiologists conducted the trial. Both patients and health professionals were blinded to the FFR results. These study characteristics increased the generalizability of our study.

The main limitation of the trial was the number of investigated patients. Retrospectively, the sample size calculation was optimistic. A recent meta-analysis described graft patency rates from 1 week to 1 year after CABG of 85% to 90% (14). When the study was designed, the available literature reported graft failure rates of 5% versus 20% in significant lesions versus nonsignificant lesions, respectively, which were the basis of the sample size calculation. Ideally, this type of study should either compare clinical outcomes in CABG populations randomized to angiography-guided or FFR-guided surgery, which would require a large sample size, or compare graft failure in FFR-negative lesions in the angiography-guided group versus TVR and/or TVMI for FFR-negative lesions in the FFR-guided group. Our study was not powered to give an answer for these 2 questions. However, the present study was the first randomized study in CABG patients to assess the outcomes in angiography-guided–treated, FFR-negative lesions and to show disease progression in deferred lesions. With this limitation, our study might be seen as a feasibility study and as hypothesis-generating for a larger study.

Second, the study was limited because of the 20 patients who did not return for follow-up angiography. This group could lead to a potential bias in the study, because it could be assumed that patients with symptoms of angina pectoris more likely would return

for invasive follow-up. To avoid difficulties in patients who did not return for invasive control angiography, we could have used noninvasive computed tomography angiography. Invasive coronary angiographic follow-up was chosen to visualize the grafts instead of computed tomography angiography to re-evaluate deferred lesions with FFR after 6 months.

Third, the follow-up period might have been too short. We chose this follow-up period because most graft failures take place within the first 6 months after CABG (16,25). Longer follow-up is needed to describe clinical outcomes.

Fourth, the operating surgeon could not comply with the graft plan in 12% of the patients, mostly due to the small caliber of the coronary arteries or lack of grafting material, which resulted in deviations from the planned grafting (**Table 5**). These intraoperative changes complicated a study of different grafting strategies, although it reflected reality in surgical revascularization.

CONCLUSIONS

FFR-guided CABG had similar graft failure rate and clinical outcomes as angiography-guided CABG. However, in FFR-guided patients, FFR was significantly reduced in deferred lesions after 6 months.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with conventional angiographic assessment, measurement of FFR to guide surgical revascularization does not improve short-term graft patency or clinical outcomes.

TRANSLATIONAL OUTLOOK: Larger randomized studies with longer follow-up are necessary to determine whether FFR-guided or angiographically-guided revascularization differentially influence rates of graft failure or the need for later revascularization.

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