Received: 11 January 2021 | Revised: 15 February 2021 | Accepted: 14 March 2021

DOI: 10.1002/ccd.29694

ORIGINAL STUDIES

WILEY

Changes in surgical revascularization strategy after fractional flow reserve

Stephane Fournier MD[1,2,3] | Gabor G Toth MD/PhD[4] | Bernard De Bruyne MD/PhD[1,2] | Petr Kala MD[5] | Flavio L Ribichini MD[6] | Filip Casselman MD[2] | Ruben Ramos MD[7] | Zsolt Piroth MD[8] | Anna Piccoli MD[6] | Martin Penicka MD/PhD[2] | Martin Mates MD[9] | Petr Nemec MD[9] | Frank Van Praet MD[2] | Bernard Stockman MD[2] | Ivan Degriek MD[2] | Mariano Pellicano MD/PhD[2] | Emanuele Barbato MD/PhD[2,3]

[1]Department of Cardiology, Lausanne University Center Hospital, Lausanne, Switzerland

[2]Cardiovascular Research Center Aalst, OLV Clinic, Aalst, Belgium

[3]Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

[4]University Heart Center Graz, Department of Cardiology, Medical University Graz, Graz, Austria

[5]Department of Cardiology and Internal Medicine, University Hospital Brno and Medical Faculty of Masaryk University, Brno, Czech Republic

[6]Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy

[7]Department of Cardiology, Hospital Santa Marta—Centro Hospitalar Lisboa Central, Lisbon, Portugal

[8]Department of Cardiology, Hungarian Institute of Cardiology, Budapest, Hungary

[9]Cardiovascular Center, Na Homolce Hospital, Prague, Czech Republic

Correspondence
Emanuele Barbato, MD, PhD, Department of Advanced Biomedical Sciences, University Federico II, Via Pansini n. 5, 80131 Naples, Italy.
Email: emanuele.barbato@unina.it

Funding information
CardioPaTh; Fondation Vaudoise de Cardiologie; Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung

Abstract

Aims: In the randomized GRAFFITI trial, surgeons drew their strategy based on coronary angiography. When patients were randomized to fractional flow reserve (FFR)-guidance, surgeons were informed of the FFR values and asked to redraw their strategy. The aim of this study was to investigate the changes induced by FFR knowledge.

Methods and Results: The intended and performed strategy (before and after FFR) were compared. Among 172 patients, 84 with 300 lesions were randomized to the FFR-guided group. The intended strategy was to bypass 236 stenoses:108 with a venous and 128 with an arterial graft. After disclosing FFR, a change in strategy occurred in 64 lesions (21.3%) of 48 (55%) patients. Among 64 lesions for which the intended strategy was medical therapy, 16 (25%) were bypassed after disclosing FFR. The number of procedures with >1 venous graft planned was significantly reduced from 37 to 27 patients (p = .031). The proportion of on-pump surgery was significantly reduced from 71 to 61 patients (p = .006). The rates of clinical events at 1 year were similar between patients with or without at least one change in strategy.

Discussion: FFR-guided CABG is associated with a simplified surgical procedure in 55% of the patients, with similar clinical outcomes.

KEYWORDS
coronary artery disease, coronary bypass grafts, fractional flow reserve

1 | INTRODUCTION

In patients with stable coronary artery disease, an invasive haemodynamic evaluation such as fractional flow reserve (FFR) is

Abbreviations: CABG, coronary artery bypass graft; DS, diameter stenosis; FFR, fractional flow reserve; GRAFFITI trial, graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting trial; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

recommended in the absence of documented ischemia at non-invasive imaging testing in order to decide if a stenotic vessel needs to be revascularized or not.[1,2] In the field of percutaneous coronary intervention (PCI), randomized clinical trials demonstrated the benefit of FFR-guidance[3-9] but the level of evidence is not as high in the field of surgical revascularisation.[10] Retrospective data suggest that - as compared to angiography-guided coronary artery bypass graft (CABG) surgery - FFR-guided CABG surgery is associated with a simplified surgical intervention and with a higher graft patency rate at 6 years,[11] leading to a significantly lower rate of overall death and myocardial infarction.[12] More recently, in the single-blinded prospective multicenter randomized controlled trial for FFR-guided versus angiography-guided CABG (GRAFFITI) trial, FFR-guided CABG was also associated with a significantly simplified surgical procedure without impact on 1-year graft patency. Nevertheless, so far, the simplification of the surgical procedure has only been observed by comparing angiography-guided versus FFR-guided groups, in contrast to PCI studies where performing FFR during a diagnostic angiography was associated with reclassification of the revascularization decision in about half of the patients.[13] In the FFR-guided group of the GRAFFITI trial, surgeons were asked to draw their intended strategy before and after FFR measurement of every stenosis invasively assessed by FFR. The aim of the present predefined sub-study of the GRAFFITI trial was therefore to investigate the changes in surgical procedure induced by FFR knowledge.

2 | METHODS

2.1 | Patients and study design

The study design and the main results of the GRAFFITI trial have been previously published.[11,14] Briefly, GRAFFITI (NCT01810224) was a single-blinded, open-label, prospective, randomized controlled multicenter trial where patients scheduled for CABG surgery were prospectively included in 6 European centers. The main inclusion criteria were the presence of a significantly diseased left anterior descending or left main stem coronary artery by angiography or by FFR and at least one additional major coronary artery with an angiographically intermediate stenosis; while the main exclusion criteria were acute ST-elevation myocardial infarction, moderate to severe valve disease with indication for valve surgery and severe left ventricular dysfunction. During the diagnostic procedure, every intermediate coronary stenosis was measured by FFR, but the results were kept concealed. The surgeons in charge of performing CABG were asked to draw their intended revascularization strategy based on the plain coronary angiogram regarding the following aspects: (a) intended target vessels; (b) types and number of grafts; (c) need for heart-lung machine; (c) possibility of minimal-invasive approach. Then, patients were randomized to angiography-guided or to FFR-guided strategy. In the FFR-guided group, surgeons were disclosed the measured FFR values and had to readjust the initially intended surgical strategy according to the functional significance of each coronary stenosis by FFR using the traditional cut-off value of ≤0.80. "Intended" planned target vessels, types and number of grafts, need for heart-lung machine and possibility of minimal-invasive approach were compared to the final "performed" strategy after FFR disclosure. The study is aligned with the Helsinki Declaration's principles. Study approval was obtained from the local ethic committees of each participating centres.

2.2 | Statistics

This is a pre-defined sub-analysis of the GRAFFITI trial. Difference in survival was assessed by the Kaplan–Meier curves. The impact of FFR on the change in revascularization strategy was evaluated by the κ-statistics and the Bowker-McNemar test. Statistical analysis was carried out using the SPSS 24.0 software (SPSS Inc., Chicago, IL) and figures were created with Prism 7.0a (GraphPad Software, La Jolla, CA) and Stata 14.3.

3 | RESULTS

Among the 172 patients randomized in the GRAFFITI trial, 84 patients with 300 lesions were randomized to the FFR-guided group. Their baseline characteristics together with their angiography findings are

TABLE 1 Patients investigated (FFR-guided group only)

Variables	N (%) or median [IQR]
Male gender	73 (83%)
Age	67 [62; 72]
EuroScore I	2.64 [1.38; 5.12]
Hypertension	68 (77%)
Hyperlipidemia	70 (80%)
Previous myocardial infarction	15 (17%)
Previous PCI	19 (22%)
Diabetes mellitus	31 (35%)
Smoking	47 (53%)
Total number of lesions	300
Lesions per patient	3 [3; 4]
Diameter stenosis (%)	60 [50; 80]
Fractional flow reserve	0.73 [0.54; 0.83]
Total number of lesions with FFR ≤ 0.80	201 (70%)
Total number of lesions with DS ≥ 50%	270 (90%)
Lesion location	
-LAD	107 (37%)
-LCX	92 (32%)
-RCA	91 (31%)

Abbreviations: DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

summarized in Table 1. Among the 300 lesions, 201 (70%) were significant by FFR.

3.1 | Changes in procedural strategy

Among the 300 lesions, the intended strategy was to bypass 236 of them (79%): 108 with a venous (36%) and 128 with an arterial graft (43%) (Table 2). After disclosing FFR, a change in strategy occurred in 64 lesions (21.3%), and at least one change in bypass strategy occurred in 48 (55%) patients. Of interest, among the 64 lesions for which the intended strategy was medical therapy, 16 (25%) were finally bypassed (13 with a venous, 3 with an arterial graft). In addition, among the 108 lesions intended to be grafted with a venous conduit, 25 (23.1%) were eventually not bypassed; while among the 128 lesions intended to be grafted with an arterial conduit, the change in strategy occurred in 18 lesions (14.1%) eventually treated with medical therapy (n = 15), or with a saphenous venous graft (SVG) (n = 3). The details are presented in Table 2 and Figure 1. There was a trend toward higher rate of patients with single vessel bypass grafting after disclosing FFR (7 patients before vs. 14 patients after FFR, p = .092) and the number of procedures with >1 intended SVG was significantly reduced after FFR disclosure from 37 to 27 patients (p = .031).

The proportion of intended on-pump surgery was significantly reduced from 71 to 61 patients (p = .006), and a trend toward an increase in the rate of minimally invasive strategy was observed (from 4 patients to 9 patients, p = .125) after disclosing FFR.

TABLE 2 Intended strategy versus performed strategy after FFR

Strategy		Performed		
		No graft	Venous graft	Arterial graft
Intended	No graft	48	13	3
	Venous graft	25	78	5
	Arterial graft	15	3	110

TABLE 3 Clinical endpoints at 1 year

	No change in strategy	At least 1 change	p-value
Death	0 (0%)	3 (6%)	.124
Myocardial infarction	0 (0%)	0 (0%)	N.A.
Stroke	0 (0%)	2 (4%)	.212
Target vessel revascularization	2 (5,3%)	0 (0%)	.101
MACE	2 (5,3%)	3 (6%)	.882

Abbreviation: MACE, major adverse cardiovascular events.

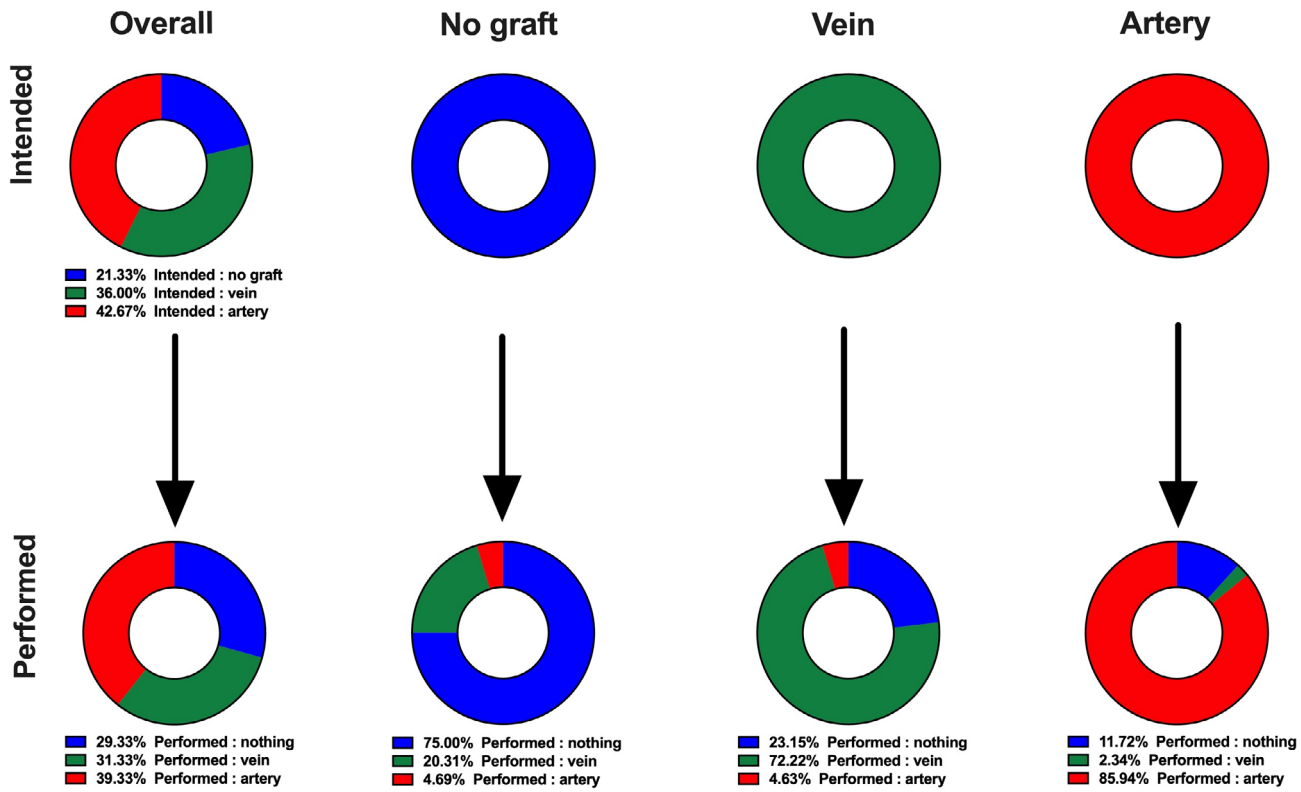

FIGURE 1 Intended versus performed strategy after disclosing fractional flow reserve, classified by intended strategy

3.2 | Overall changes and related clinical endpoints

By taking into account the cumulative changes in (a) bypass strategy, (b) pump strategy and (c) minimally invasive approach, 50 patients (57%) had at least one change, and 13 patients (15%) had ≥2 changes after disclosing FFR. The rates of death, myocardial infarction, stroke, target vessel revascularization, or major adverse cardiovascular events were similar between the 2 groups (Table 3).

4 | DISCUSSION

This sub-analysis of the GRAFFITI trial confirms that FFR-guidance is associated with a simplification of the surgical procedure with no detrimental impact on clinical outcomes up to 1-year follow-up. Previously, this finding had only been suggested in between-groups comparison, that is, in FFR-guided versus angiography-guided groups, either in retrospectives studies[12] or in randomized trials.[11] The present study proved these findings by comparing the same patients before and after disclosing FFR. In addition, the lack of clinical benefit observed with FFR-guidance at 1-year is not surprising. Firstly, in a retrospective study based on 627 patients, clinical endpoints did not differ at 3-year follow-up between the FFR-guided group and the angiography-guided group, and 6 years were necessary to observe a clinical benefit, with a reduction of death and myocardial infarction in the FFR-guided group.[12] Secondly, the GRAFFITI trial was powered to assess patency rate of bypass grafts, and the number of patients is therefore too small to observe any significant difference in terms of clinical endpoints, especially in this sub-study focusing on the FFR-guided group only. Of interest, it appears that a longer follow-up was also necessary in the field of PCI to observe a benefit of hard clinical endpoints, as it was the case for the FAME II trial where a benefit in terms of myocardial infarction reduction was observed only after 5-years.[9]

Interestingly, the recently published FARGO trial showed that in patients with multivessel disease, FFR before CABG surgery did not improve outcomes compared with angiography-guided surgery, in terms of graft failure and clinical outcomes.[15] Some interesting limitations have been suggested, such as, an early termination because of slower-than-expected enrolment or an important loss of follow-up. In addition, it also appears, that the follow-up (6 months) is probably too short in order to observe a clinical benefit or even a difference in the patency rate. At variance, the IMPAG trial observed in 199 coronary stenoses of 67 patients a positive correlation between the pre-operative FFR of the target vessel and the patency rate of the bypass anastomosis at 6 months.[16] This apparent discrepancy might be explained by the higher rate of arterial grafts implanted in the IMPAG study as compared with both FARGO and GRAFFITI trials. Indeed, the impact of FFR-guidance seems to be higher in arterial as compared with venous grafts.[17]

5 | LIMITATIONS

The GRAFFITI trial has some limitations. Firstly, due to slow recruitment, enrolment was stopped prematurely. Secondly, there are no data on the availabilities of radial grafts in the patients and in some cases, veins could have been chosen due to the lack of arterial alternatives. Thirdly, as the aim was to assess graft patency, 1 year of follow-up seems to be appropriate but might be too short to assess clinical outcomes and the interpretation of the present paper therefore needs to be confirmed in larger trials with longer follow-up.

6 | CONCLUSION

In conclusion, this sub-analysis of the GRAFFITI trial indicates that FFR-guided CABG is associated with a simplified surgical procedure in 55% of the patients, with similar clinical outcomes up to 1-year follow-up. Larger studies with longer follow-up are warranted to confirm this hypothesis-generating observation.

ACKNOWLEDGMENT

Stephane Fournier was supported by a research grant from the CardioPaTh PhD program, the Swiss National Science Foundation and the Fondation Vaudoise de cardiologie.

CONFLICT OF INTEREST

Dr Fournier reports consultancy fees from Cathworks serves as member of the advisory board of Bayer; Dr. De Bruyne reports grants from Abbott, grants from Boston Scientifoc, grants from Biotronic AG, personal fees from Abbott, personal fees from Opsens, personal fees from Boston Scientific, other from Siemens, other from GE, other from Bayer, other from Philips, other from Heartflow, other from Edwards Life Sciences, other from Ceyliad, during the conduct of the study; Dr Barbato. reports speaker's fees from Abbotth Vascular, Boston Scientitic and GE.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Stephane Fournier https://orcid.org/0000-0002-9422-9521
Gabor G Toth https://orcid.org/0000-0002-0283-9091

REFERENCES

1. Task Force M, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34:2949-3003.
2. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2017;69:2212-2241.

3. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol. 2007;49:2105-2111.
4. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371:1208-1217.
5. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991-1001.
6. Puymirat E, Peace A, Mangiacapra F, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. Circ Cardiovasc Interv. 2012;5:62-68.
7. Muller O, Mangiacapra F, Ntalianis A, et al. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. JACC Cardiovasc Interv. 2011;4:1175-1182.
8. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation. 2009;120:1505-1512.
9. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med. 2018;379:250-259.
10. Ahmadi A, Stanger D, Puskas J, Taggart D, Chandrashekhar Y, Narula J. Is there a role for fractional flow reserve in coronary artery bypass graft (CABG) planning? Ann Cardiothorac Surg. 2018;7:546-551.
11. Toth GG, De Bruyne B, Kala P, et al. Graft patency after FFR-guided versus angiography-guided coronary artery bypass grafting. The GRAFFITI trial. EuroIntervention. 2019;15:00463.
12. Fournier S, Toth GG, De Bruyne B, et al. Six-year follow-up of fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. Circ Cardiovasc Interv. 2018;11:e006368.
13. Van Belle E, Rioufol G, Pouillot C, et al. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. Circulation. 2014;129:173-185.
14. Toth GG, De Bruyne B, Kala P, et al. Study design of the graft Patency after FFR-guided versus angiography-guided CABG trial (GRAFFITI). J Cardiovasc Transl Res. 2018;11:269-273.
15. Thuesen AL, Riber LP, Veien KT, et al. Fractional flow reserve versus angiographically-guided coronary artery bypass grafting. J Am Coll Cardiol. 2018;72:2732-2743.
16. Glineur D, Grau JB, Etienne PY, et al. Impact of preoperative fractional flow reserve on arterial bypass graft anastomotic function: the IMPAG trial. Eur Heart J. 2019;40:2421-2428.
17. Fournier S, Toth GG, Colaiori I, De Bruyne B, Barbato E. Long-term patency of coronary artery bypass grafts after fractional flow reserve-guided implantation. Circ Cardiovasc Interv. 2019;12:e007712.

How to cite this article: Fournier S, Toth GG, De Bruyne B, et al. Changes in surgical revascularization strategy after fractional flow reserve. *Catheter Cardiovasc Interv*. 2021;98:E351–E355. https://doi.org/10.1002/ccd.29694