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ORIGINAL STUDIES

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Influence of fractional flow reserve on grafts patency: Systematic review and patient-level meta-analysis

Gabor G. Toth PhD, MD[1] | Carlos Collet PhD, MD[2] | Anne Langhoff Thuesen MD[3,4] | Takuya Mizukami MD[2,5] | Filip Casselman PhD, MD[6] | Lars Peter Riber MD[3] | Frank Van Praet MD[6] | Anders Junker MD[4] | Sakura Nagumo MD[2,7] | Bernard De Bruyne PhD, MD[2,8] | Lisette Okkels Jensen PhD, MD[4] | Emanuele Barbato PhD, MD[2,9]

[1]Division of Cardiology, University Heart Center Graz, Medical University of Graz, Graz, Austria

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

[3]Department of Cardiothoracic Surgery, Odense University Hospital, Odense, Denmark

[4]Department of Cardiology, Odense University Hospital, Odense, Denmark

[5]Clinical Research Institute for Clinical Pharmacology and Therapeutics, Showa University, Tokyo, Japan

[6]Departement of Cardiovascular and Thoracic Surgery, OLV Hospital Aalst, Aalst, Belgium

[7]Division of Cardiology, Department of Internal medicine, Showa University Fujigaoka Hospital, Kanagawa, Japan

[8]Department of Cardiology, Universtiy Hospital Center Lausanne, Lausanne, Switzerland

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

Correspondence
Emanuele Barbato, Cardiovascular Research Center, OLV Hospital Aalst, Moorselbaan n. 164, B-9300, Aalst, Belgium.
Email: emanuele.barbato@olvz-aalst.be

Abstract

Objective: To investigate the impact of invasive functional guidance for coronary artery bypass graft surgery (CABG) on graft failure.

Background: Data on the impact of fractional flow reserve (FFR) in guiding CABG are still limited.

Methods: Systematic review and individual patient data meta-analysis were performed. Primary objective was the risk of graft failure, stratified by FFR. Risk estimates are reported as odds ratios (ORs) derived from the aggregated data using random-effects models. Individual patient data were analyzed using mixed effect model to assess relationship between FFR and graft failure. This meta-analysis is registered in PROSPERO (CRD42020180444).

Results: Four prospective studies comprising 503 patients referred for CABG, with 1471 coronaries, assessed by FFR were included. Graft status was available for 1039 conduits at median of 12.0 [IQR 6.6; 12.0] months. Risk of graft failure was higher in vessels with preserved FFR (OR 5.74, 95% CI 1.71–19.29). Every 0.10 FFR units decrease in the coronaries was associated with 56% risk reduction of graft failure (OR 0.44, 95% CI 0.34 to 0.59). FFR cut-off to predict graft failure was 0.79.

Conclusion: Surgical grafting of coronaries with functionally nonsignificant stenoses was associated with higher risk of graft failure.

KEYWORDS

coronary artery bypass surgery, fractional flow reserve, graft patency

Abbreviations: AUC, area under the curve; CABG, coronary artery bypass graft surgery; FFR, fractional flow reserve; MACCE, major adverse cerebro- and cardiovascular event; MACE, major adverse cardiovascular event.

Gabor G. Toth and Carlos Collet contributed equally to this study.

1 | INTRODUCTION

Percutaneous myocardial revascularization directed by the hemodynamic significance of coronary stenoses has been associated with reduced spontaneous myocardial infarction, recurrent revascularization rate.[1,2] Therefore, percutaneous coronary intervention guided by invasive functional testing is recommended by the European Society of Cardiology guidelines (Class I, LOE A).[3] Data are less convincing when functional guidance is applied to surgical revascularization. In observational studies, invasive physiological guidance has been associated with increased graft patency up to 6 years of follow-up.[4–7] Nonetheless, prospective clinical trials have shown conflicting results.[8,9] Differences in design and the limited sample size of the individual studies might have accounted for the lack of consistency in the association between functional parameters in native coronary vessels and graft patency. We conducted a systematic review and an individual patient-level data meta-analysis of prospective trials[4,7–9] to investigate the impact of invasive functional guidance for coronary artery bypass graft surgery (CABG) on graft failure. We hypothesized that bypass grafts anastomosed to coronary arteries with functionally significant stenoses have higher patency rates, as compared to bypass grafts on vessels with functionally nonsignificant stenoses.

2 | METHODS

2.1 | Search strategy and data collection

Two independent reviewers (SN and CC) systematically searched Medline and Scopus applying a predefined search strategy (Table S1). Clinical studies were included with the following criteria: a) Prospective studies or randomized clinical trials of patients undergoing CABG with prior invasive functional assessment; b) Angiographic follow-up, either by invasive coronary angiography or coronary CT angiography. No restrictions were applied concerning to language. Studies of retrospective nature or with insufficient data for extraction were excluded. The search was conducted in March 2020. The results of the search strategy are provided in the Figure S1. Study designs, fractional flow reserve (FFR) cut-off and endpoint definitions are shown in Table S2. Principal investigators of all eligible trials were contacted to share individual patient data, which were obtained from Fractional Flow Reserve versus Angiography Randomization for Graft Optimization Trial (FARGO) and from Graft Patency After FFR-guided versus Angiography-guided CABG Trial (GRAFFITI). [8,9] For the other studies the investigators either declined data sharing[7] or database was no longer available.[4] Vessel-level data pertaining FFR value and graft patency were obtained by digital extraction of individual data from the original publications; this was possible for Impact of Preoperative FFR on Arterial Bypass Graft Functionality Trial (IMPAG).[7] All trials were approved by the local Ethics Committees. The protocol was developed according to the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis (Table S3).[10] Bias assessment was performed using the Cochrane Collaboration's ROBINS 1 tool. This systematic review and meta-analysis is registered in the International prospective register of systematic reviews (PROSPERO CRD42020180444).

2.2 | Outcomes of interest

The primary outcome of interest was to determine the risk of graft failure stratified by functional lesion severity of native coronary vessels in patients treated with CABG. Functional lesion severity was based on FFR cut-off adopted in each study and reported as abnormal FFR (values equal to or below the adopted cut-off) or preserved FFR (values above the adopted cut-off; Table S2). In cases of chronic total occlusions or lesions with diameter stenosis greater than 90% in which invasive FFR measurements are not indicated or not feasible, a FFR value of 0.50 was imputed as previously done.[1, 2] Imputed values were excluded for calculation of optimal cut-off value. Graft failure was defined in the presence of at least one of the following features: (1) TIMI flow grade <3; (2) native coronary not fully opacified by the graft (i.e., graft antegrade flow not dominant); (3) diameter stenosis at the anastomosis more than 50%. This definition incorporates the definitions adopted in each individual study.

The secondary objectives were: (1) To define the best FFR cut-off value in the native stenotic coronary artery prior to CABG predictive of graft failure, based on the individual vessel-level analysis; (2) to identify independent predictors of graft failure, based on the individual patient-level analysis; (3) to compare clinical outcomes after FFR- versus angiography-guided CABG.

Major adverse cardiovascular events (MACE) were defined as the composite of all-cause death, myocardial infarction, and target vessel revascularisation. Major adverse cardiovascular and cerebrovascular events (MACCE) were defined as the composite of all-cause death, myocardial infarction, target vessel revascularization, and stroke.

2.3 | Statistical methods

Categorical variables are reported as percentages, and continuous variables are reported as mean ± *SD* or median (interquartile range) as appropriate. Binary outcomes from aggregated data were combined with random-effects model using the DerSimonian and Laird method, which was used to compare the risk of graft failure in vessels with preserved and abnormal FFR. Risk estimates are reported as odds ratios (ORs) with 95% confidence intervals (CI) derived from the study-level data. Heterogeneity between the trials was assessed with the Cochran's Q test and I^2 statistics: I^2 values of 25%, 50%, and 75% represented mild, moderate, and important heterogeneity, respectively. Publication bias was explored with funnel plot. To investigate the best FFR cut-off value to predict graft failure, the area under the receiver operating characteristics curve (AUC) was used. For this analysis only measured FFR values were included. The relationship between FFR in the native coronary artery prior to CABG and the probability of graft failure was assessed by logistic regression analysis adjusted by study. To assess predictors of graft failure, multivariate models were cast using mixed effect models with study as grouping variables. Cox

regression analysis adjusted by trial was used to compare clinical outcomes between an FFR- and angiography-guided CABG. A probability value of $p < 0.05$ was considered as significant. All analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Risk of graft failure stratified by FFR values: study-level analysis

Four prospective studies comprising 503 patients referred for CABG were included, with 1471 native coronary arteries assessed by FFR. Baseline clinical and procedural characteristics are shown in Tables S4 and S5. Median angiographic follow-up was performed mainly by invasive angiography at a median of 12.0 [IQR 6.6; 12.0] months. Graft patency status was available for 1039 conduits. Graft failure occurred in 185 cases (18%). There was higher risk of graft failure in bypasses anastomosed to native coronaries with preserved FFR (OR 5.74, 95% CI 1.71–19.29, $p = 0.02$; Figure 1). Graft patency rates and clinical events stratified by study are shown **in** Table S6. A significant statistical heterogeneity was observed between studies ($I^2 = 91\%$, $p < 0.001$). Concerning the risk of bias, three studies were found at moderate risk of bias, mainly driven by missing data on graft patency due to absence of angiographic follow-up (Figure S2). The funnel plot is shown in Figure S3.

3.2 | FFR cut-off to predict graft failure: vessel-level analysis

Individual vessel-level data was available for 484 conduits. The distribution of FFR values at baseline in the native coronary arteries is depicted in Figure S4. In cases of graft failure, FFR in the native coronary arteries was higher compared to those with patent grafts (0.80 ± 0.10 vs. 0.72 ± 0.11, respectively; $p = 0.001$; Figure S5). Adjusted logistic regression analysis revealed significant association between baseline FFR, as a continuous variable, and graft failure (OR 0.44, 95% CI 0.34 to 0.59) (Figure 2). There was a 56% reduction in the risk of graft failure for every 0.10 decrease in FFR units in the native coronary vessel. The optimal cut-off value of FFR to predict future graft failure was 0.79 with an AUC of 0.73 (95% CI 0.67 to 0.79; sensitivity 0.66 and specificity 0.83) (Figure S6). Considering the type of conduit, the optimal cut-off value was 0.79 (AUC 0.83, 95% CI 0.77 to 0.90; sensitivity 0.90 and specificity 0.76) for arterial grafts and 0.80 (AUC 0.54 95% CI 0.43 to 0.65; sensitivity 0.71 and specificity 0.46) for venous grafts.

3.3 | Independent predictors of graft failure: patient-level analysis

Individual patient-level analysis was available for 144 patients with 260 bypass anastomoses. A Sankey diagram with nodes of trial, target vessel, conduit type, FFR values, and graft failure is shown in Figure 3. By univariate analysis significant associations with graft failure were observed with target vessel, diabetes mellitus, conduit type, and FFR

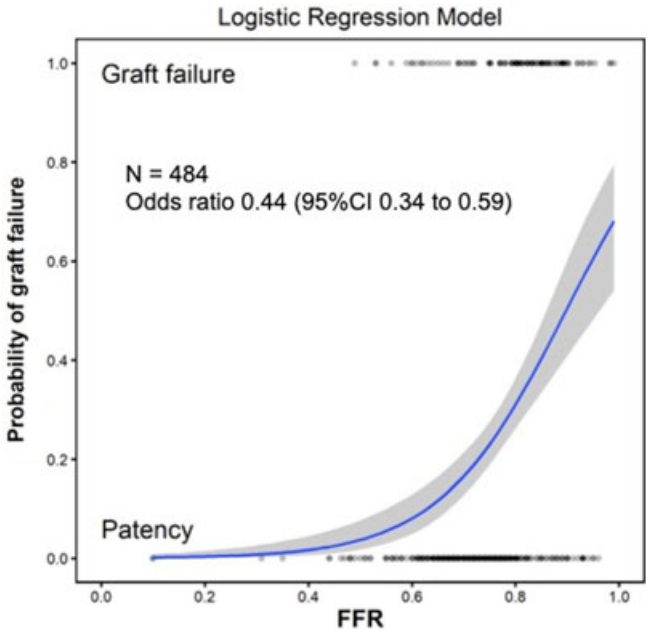

FIGURE 2 Probability of graft failure in function of FFR values. Adjusted logistic regression analysis showed significant association between FFR, as a continuous variable, and graft failure. There was a 56% reduction in the risk of graft failure for every 0.10 decrease in FFR units in the native coronary artery [Color figure can be viewed at wileyonlinelibrary.com]

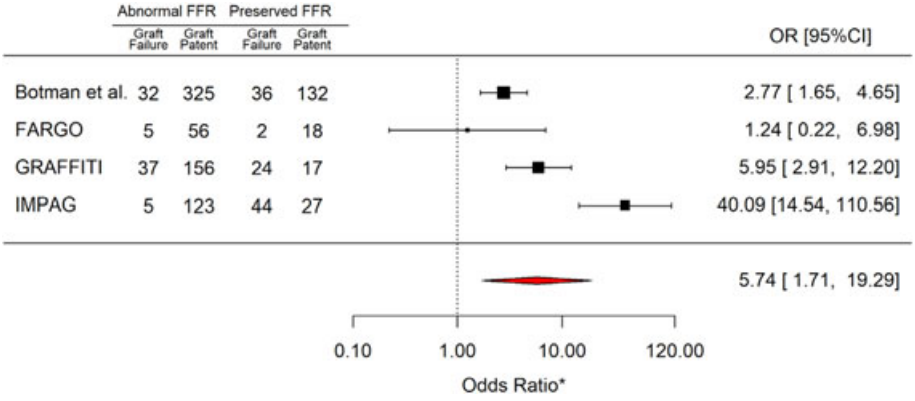

FIGURE 1 Risk of graft failure in vessels with preserved and abnormal FFR. Risk of graft failure according to functional status of the native coronary arteries prior coronary bypass surgery. Preserved and abnormal FFR were defined according to each study protocol. Odds ratio is presented on log scale [Color figure can be viewed at wileyonlinelibrary.com]

in the native vessel prior to CABG (Tables S7 and S8). After adjustment, the only type of conduit (OR 2.77 95%CI 1.52 to 5.06 for venous conduits) and FFR (OR 0.77 95% CI 0.62 to 0.95) remained significant predictors of graft failure.

3.4 | Surgical strategy and clinical outcome

In two studies (GRAFFITI and FARGO) comprising 268 patients, randomized to FFR-guided versus angiography-guided CABG, FFR-guidance was associated with fewer bypass graft anastomoses (2.51 ± 0.93 vs. 2.90 ± 0.84, respectively; $p < 0.001$). The number of arterial grafts was similar between strategies (1.29 ± 0.60 vs. 1.38 ± 0.69, respectively; $p = 0.244$). At a median follow-up of 14.0 [6.6 to 40.0] months there was no difference in the rate of MACE (HR 0.99, 95% CI 0.94 to 1.59; $p = 0.975$) or MACCE (HR 1.04, 95% CI 0.92 to 1.56; $p = 0.904$) between strategies. (Figure 4) No difference was observed in any of the individual components of MACCE (Table S9). The rate of persistent angina was low and similar between FFR-guided versus angiography-guided cohorts (CCS II-IV, 6 (4.6%) vs. 8 (5.9%); $p = 0.809$).

4 | DISCUSSION

The present systematic review and meta-analysis demonstrated lower risk of graft failure, when a bypass is anastomosed to stenotic coronaries with functionally significant disease. The best FFR value to predict graft failure was 0.79. Moreover, FFR is an independent predictor of graft failure. No difference was observed in clinical outcomes between the FFR-guided and angiography-guided CABG.

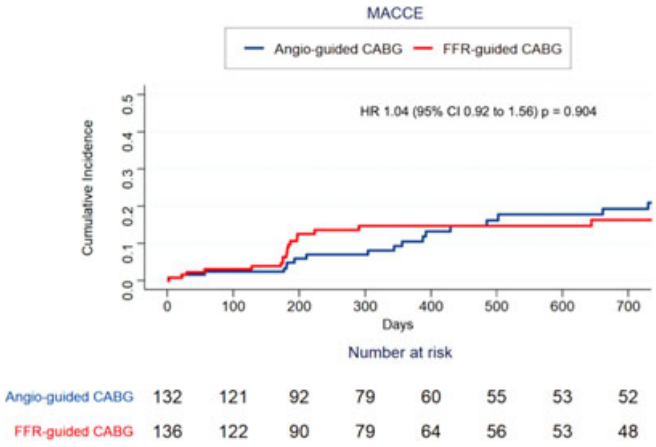

FIGURE 4 Kaplan Meier curves comparing FFR-guided versus angiography-guided CABG. There was no difference in the rate of major adverse cardiac and cerebral events between FFR-guided versus angiography-guided CABG [Color figure can be viewed at wileyonlinelibrary.com]

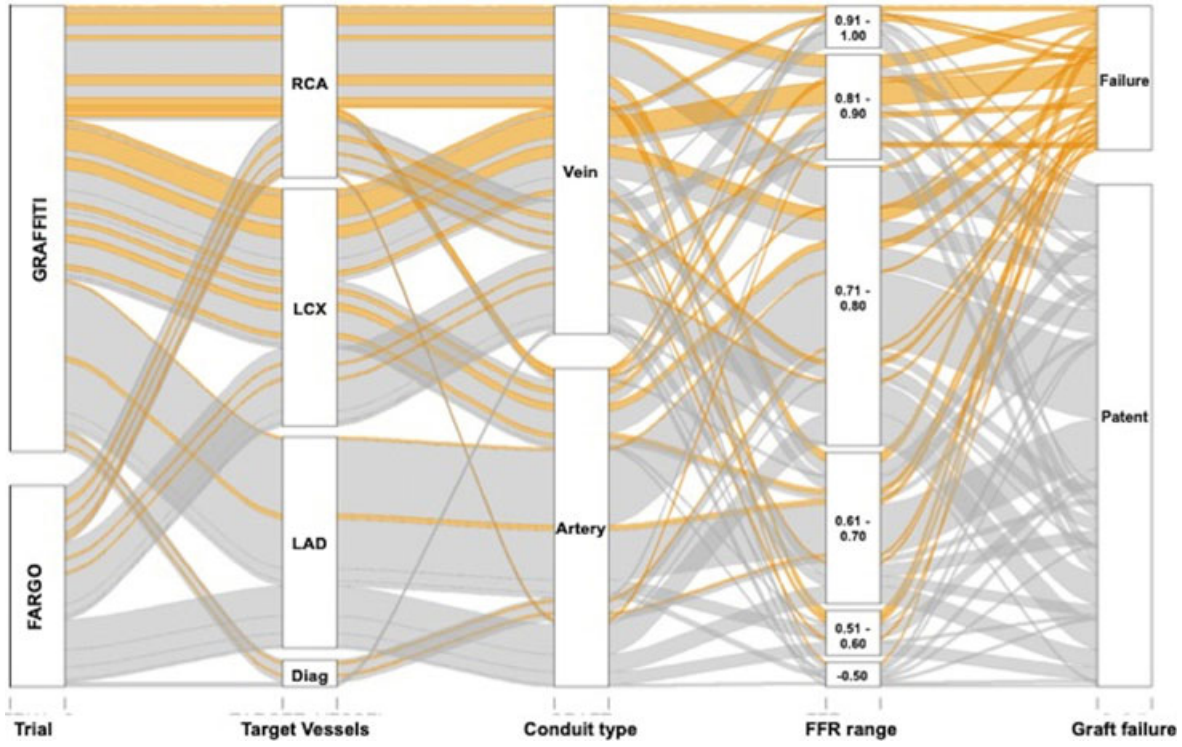

FIGURE 3 Sankey diagram with subsequent nodes of trial, target vessel, conduit type, FFR values and graft patency. Visualization of individual patient-level analysis with 260 bypass anastomoses showing the target vessel, conduit type, range of FFR and graft patency at follow-up. Diag, diagonal; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Impact of FFR on graft failure

The largest dataset reporting in 727 patients the impact of FFR-guidance of CABG on graft patency and on clinical outcome is derived from a retrospective registry. Here, higher graft patency rate was reported in conduits anastomosed to vessels with abnormal FFR as compared to purely angiography-guided grafts with uncertain functional severity (95% vs. 79%, respectively; $p = 0.03$). While clinical follow-up did not show any difference in MACE between the two groups up to 3-years, longer term follow-up suggested clinical benefit in terms of myocardial infarction and all-cause death at 6 years, favoring the FFR-guided group (16% vs. 25%; hazard ratio 0.59 [95% CI, 0.38–0.93]; $p = 0.020$).[5,6] Two prospective registries showed higher failure rate of bypasses, placed on native vessels with functionally nonsignificant stenoses. Botman et al. reported a 2.4 fold increase in the risk of graft failure in conduits anastomosed to vessels with non-significant stenoses compared to vessels with functionally significant disease based on an FFR cut-off of 0.75.[4] Similarly, the IMPAG registry showed a 62% versus 4% ($p < 0.01$) graft failure rate at 6-months respectively, based on an FFR cut-off value of 0.78.[7] In contrast, the superior graft patency rate following FFR-guidance was not confirmed in the two available randomized clinical trials (both using a FFR cut-off value of 0.80). In FARGO trial a 12% versus 16% ($p = 0.97$) graft failure rate at 6 months was observed in the angiography-guided versus FFR-guided groups, respectively.[8] In the GRAFFITI trial, almost identical graft failure rates (20% vs. 19%; $p = 0.885$) were observed in the angiography-guided versus FFR-guided groups at 12 months.[9] In these two trials, no differences were observed regarding clinical outcomes, although none of them was powered for clinical endpoints. Reassuringly no signal of hazard was reported either.

Significant differences in study designs and sample sizes might explain the difference in results between registries and trials. In fact, in registries the objective was to compare patency rate of grafts and/or anastomoses implanted on functionally significant versus functionally not-significant stenotic vessels; while in randomized clinical trials the objective was to compare the impact of angiographic- versus functional-guided CABG on graft failure at the patient level. The latter study design has therefore the intrinsic limitation of diluting the statistical power owing to the proportion of otherwise functionally significant stenotic vessels bypassed even in the angiographic-guided group. The present analysis has an increased statistical power to establish the impact of invasive functional guidance of CABG on graft failure.

While all native coronary stenoses included in the analysis were deemed angiographically significant and therefore target for grafting, the patency rate was higher when also functional severity of disease was confirmed by FFR, confirming previous retrospective findings.[11] A risk continuum was observed between FFR values in the native coronary arteries prior to surgery and graft failure, where every 0.10 increase in FFR value increased the risk of graft failure by almost 50%. Importantly, the best cut-off value predictive of graft failure was 0.79, allowing from the practical point of view the adoption of the same established 0.80 FFR cut-off value for both percutaneous and surgical revascularization.

4.2 | FFR and CABG: clinical implications

Indication for CABG mainly follows the angiographic finding of complex multivessel disease, where noninvasive functional testing is of limited spatial resolution.[12] Discordance between angiographic appearance and functional relevance of coronary stenoses increases with the number of diseased vessels, which is typically high in the surgical population.,[13] The rate of inappropriate functional revascularization decisions (i.e., functional overtreatment, functional undertreatment, or both) is expectedly higher. Retrospective data suggested that implementation of FFR assessment in the decision-making process results in marked simplification of the surgical strategy, as compared to purely angiography-guided approach.[5,6] The same findings were confirmed in the present meta-analysis, where FFR guidance resulted in fewer anastomoses compared to angiography-guided CABG. Even though severity of coronary artery disease was comparable, fewer anastomoses were not associated with the signal of cardiovascular hazard during the follow-up.

The impact of graft failure on clinical outcomes remains to be proven. As demonstrated in the present meta-analysis, graft patency is lower in vessels without functionally significant lesions. On one hand, graft failure of a native vessel with functionally not significant stenosis might occur subclinically, because the native vessel has preserved function and therefore the bypass conduit was redundant in the first place. On the other hand, accelerated atherosclerosis progression has been reported in bypassed vessels, therefore the long-term risk of an occluded bypass can be anticipated.[14] Halabi et al. reported an association between venous graft stenosis or occlusion and death, myocardial infarction, or revascularization in 1243 patients after CABG.[15] Moreover, the Prevention of Autogenous Vein Graft Failure in Coronary Artery Bypass Procedures (PREVENT IV) trial that included 3014 patients undergoing CABG showed an increased risk of death and myocardial infarction in patients with venous graft failure.[16] Thus, graft failure appears to be a clinically relevant entity and efforts to avoid graft occlusion may translate in superior clinical outcomes.

The individual patient data meta-analysis from the two available RCTs comparing FFR versus angiographic guidance for CABG (i.e., FARGO and GRAFFITI) showed no differences in the occurrence of clinical events between strategies. Nonetheless, we must recognize that even when all data were combined, the sample size was underpowered to investigate differences in clinical outcomes. A large randomized clinical trial comparing FFR-guided versus angiography-guided CABG adequately powered for clinical events is still required. Based on the experience with the aforementioned trials where patient's recruitment was challenging, novel strategies should be considered that might facilitate patient inclusion. Recently, angiography-derived FFR at the time of the diagnostic coronary angiogram was shown to be predictive of graft occlusion after CABG.[17] This novel tool based on conventional coronary angiography may prove to be useful for CABG guidance and facilitate trial execution.

4.3 | Limitations

This systematic review and meta-analysis have some limitations to be acknowledged: (1) We were unable to address the impact of FFR-

guided CABG on hard clinical endpoints. Nonetheless, the increased risk of graft failure observed in vessels with preserved FFR portrays relevant clinical information. (2) Complete patient-level data were not available for all studies included. Moreover, angiographic follow-up was missing in 20% of the patients. (3) Follow-up period might be too short to capture all graft failures and clinical events.[5] (4) Data about other known factors associated with graft failure (e.g., target vessel caliber, target vessel pathology, pharmacologic preparation, graft storage, etc.) were not collected and therefore this could not be incorporated. Similarly, sequential grafts and supplied native coronary artery branches can show extreme variability. For the present analysis, it was necessary to simplify target vessels to main branches (i.e., LAD, LCx, RCA, Diagonal) and possible combinations and order of sequential anastomoses were not accounted for. Similarly, presence or absence of left main disease was not evaluated separately. (5) Quantitative angiographic data were not available for the total investigated population and therefore we were not able to compare the functional information with the angiographic data to estimate the added value of FFR as compared to quantified angiographic severity. (6) There was a significant statistical heterogeneity at the study-level meta-analysis. Also, the designs of these studies were different potentially leading to bias due to heterogeneity in treatment effects. Similarly, definition of graft failure was interpreted per protocol for study level analysis, as well as for patient-level analysis and not reassessed individually by a core lab.

5 | CONCLUSION

The surgical grafting of coronary vessels with functionally nonsignificant stenoses based on FFR translated into a higher risk of graft failure. The cut-off for predicting graft failure was similar to the one described for lesion significance to guide PCI. FFR in the native coronary vessels was an independent predictor of graft failure.

CONFLICT OF INTEREST

GT reports receiving research grants from Boston Scientific, Terumo and Abbott Vascular; and consultancy fees from Abbott Vascular, Biotronik and Medtronic. CC reports receiving research grants from Biosensor, Heart Flow Inc. and Abbott Vascular; and consultancy fees from Heart Flow Inc. and Philips Volcano. BDB reports receiving consultancy fees on his behalf from Boston Scientific, Abbott, and Opsens. EB receives speaker's fees from Abbott Vascular, Boston Scientific, General Electrics, and Opsens outside the present work. Other authors report no conflicts of interest.

ORCID

Gabor G. Toth https://orcid.org/0000-0002-0283-9091
Carlos Collet https://orcid.org/0000-0003-0227-0082

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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