



HAL
open science

Compared Outcomes of ST-Elevation Myocardial Infarction Patients with Multivessel Disease Treated with Primary Percutaneous Coronary Intervention and Preserved Fractional Flow Reserve of Non-Culprit Lesions Treated Conservatively and of Those with Low Fractional Flow Reserve Managed Invasively: Insights from the FLOWER MI trial.

Pierre Denormandie, Tabassome Simon, Guillaume Cayla, Philippe Gabriel Steg, Gilles Montalescot, Isabelle Durand-Zaleski, Alicia Le Bras, Hervé Le Breton, Yann Valy, François Schiele, et al.

HAL Id: hal-03327827

<https://hal.science/hal-03327827>

Submitted on 29 Aug 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

► **To cite this version:**

Pierre Denormandie, Tabassome Simon, Guillaume Cayla, Philippe Gabriel Steg, Gilles Montalescot, et al.. Compared Outcomes of ST-Elevation Myocardial Infarction Patients with Multivessel Disease Treated with Primary Percutaneous Coronary Intervention and Preserved Fractional Flow Reserve of Non-Culprit Lesions Treated Conservatively and of Those with Low Fractional Flow Reserve Managed Invasively: Insights from the FLOWER MI trial.. *Circulation: Cardiovascular Interventions*, 2021, 14 (11), pp.e011314. 10.1161/CIRCINTERVENTIONS.121.011314 . hal-03327827

Compared Outcomes of ST-Elevation Myocardial Infarction Patients with Multivessel Disease Treated with Primary Percutaneous Coronary Intervention and Preserved Fractional Flow Reserve of Non-Culprit Lesions Treated Conservatively and of Those with Low Fractional Flow Reserve Managed Invasively: Insights from the FLOWER MI Trial

Running Title: *Denormandie et al.; Deferring PCI in STEMI patients with multivessel*

Pierre Denormandie, MD¹; Tabassome Simon, MD, PhD^{2,3}; Guillaume Cayla, MD, PhD⁴; Philippe Gabriel Steg, MD^{3,5}; Gilles Montalescot, MD, PhD⁶; Isabelle Durand-Zaleski, MD, PhD⁷; Alicia le Bras, MD⁷; Hervé le Breton, MD, PhD⁸; Yann Valy, MD⁹; François Schiele, MD, PhD^{3,10}; Thomas Cuisset, MD, PhD¹¹; Gérald Vanzetto, MD, PhD^{3,12}; Sébastien Levesque, MD, PhD¹³; Pascal Goube, MD¹⁴; Olivier Nallet, MD¹⁵; Denis Angoulvant, MD, PhD¹⁶; François Roubille, MD, PhD¹⁷; Anaïs Charles Nelson¹⁸; Gilles Chatellier, MD¹⁸; Nicolas Danchin, MD^{1,2}; Etienne Puymirat, MD, PhD^{1,2}; for the FLOWER-MI study investigators

¹Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Européen Georges Pompidou, Department of Cardiology, Université de Paris, Paris, France; ²AP-HP, Hôpital Saint Antoine, Department of Clinical Pharmacology and Unité de Recherche Clinique (URCEST), Université Pierre et Marie Curie (UPMC-Paris 06), INSERM U-698, Paris, France; ³French Alliance for Cardiovascular Trials (FACT); ⁴Cardiology Department, Nîmes University Hospital, Montpellier University, Nîmes, France; ⁵Université de Paris, INSERM Unité-1148, and Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, France; ⁶Sorbonne Université, ACTION Study group, Institut de Cardiologie (APHP), INSERM UMRS 1166, Hôpital Pitié-Salpêtrière, Paris, France; ⁷Clinical Research Unit Eco Ile de France, Hôpital Hôtel Dieu, AP-HP, Paris, France; ⁸Univ Rennes, CHU Rennes, Inserm, LTSI - UMR1099, F 35000 Rennes, France; ⁹Department of Cardiology, CH Saint-Louis, La Rochelle, France; ¹⁰Department of Cardiology, University Hospital Besançon, Besançon, France, EA 3920 University of Burgundy Franche-Comté, Besançon, France; ¹¹ACTION Study Group, Cardiology Department, INSERM UMR1062, INRA UMR1260, Centre Hospitalier Universitaire La Timone, Aix-Marseille University, Marseille, France; ¹²Department of Cardiology, University Hospital, 38000 Grenoble Alpes, France, INSERM, U1039, Radiopharmaceutiques Biocliniques, Grenoble Alpes University, 38000 Grenoble Alpes, France; ¹³Cardiovascular Interventional Unit, Division of Cardiology, Department of Medicine, Centre Cardio-Vasculaire, CHU de Poitiers, Poitiers, France; ¹⁴Department of Cardiology, Centre Hospitalier Sud Francilien, Corbeil Essonne, France; ¹⁵Cardiology Department, Groupe Hospitalier Intercommunal Le Raincy-Montfermeil, Montfermeil, France; ¹⁶Cardiology Department and EA4245 T2i, University Hospital of Tours and Tours University, 37000 Tours, France; ¹⁷Department of Cardiology, Regional University Hospital of Montpellier, Montpellier, France, PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier, France; ¹⁸Clinical Research Unit and CIC 1418 INSERM, George-Pompidou European Hospital, AP-HP, 75015 Paris, France

Address for Correspondence:

Etienne Puymirat, MD, PhD
Hôpital Européen Georges Pompidou
Department of Cardiology
20 rue Leblanc, 75015 Paris, France
Tel: + 00 33 (0)1 56 09 28 51
Fax: + 00 33 (0)1 56 09 38 10
Email : etienne.puymirat@aphp.fr

Abstract

Background: In patients with ST-elevation myocardial infarction (STEMI) and multivessel disease, percutaneous coronary intervention (PCI) for non-culprit lesions guided by FFR is superior to treatment of the culprit lesion alone. Whether deferring non-culprit PCI is safe in this specific context is questionable. We aimed to assess clinical outcomes at one-year in STEMI patients with multivessel coronary artery disease and an FFR-guided strategy for non-culprit lesions, according to whether or not ≥ 1 PCI was performed.

Methods: Outcomes were analyzed in patients of the randomized FLOWER MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) trial in whom, after successful primary PCI, non-culprit lesions were assessed using FFR. The primary outcome was a composite of all-cause death, non-fatal MI, and unplanned hospitalization with urgent revascularization at one year.

Results: Among 1,171 patients enrolled in this study, 586 were assigned to the FFR-guided group: 388 (66%) of them had ≥ 1 PCI and 198 (34%) had no PCI. Mean FFR before decision (i.e., PCI or not) of non-culprit lesions were 0.75 ± 0.10 and 0.88 ± 0.06 , respectively. During follow-up, a primary outcome event occurred in 16 of 388 patients (4.1%) in patients with PCI and in 16 of 198 patients (8.1%) in patients without PCI (adjusted hazard ratio, 0.42; 95% confidence interval, 0.20 to 0.88; $P = 0.02$).

Conclusions: In patients with STEMI undergoing complete revascularization guided by FFR measurement, those with ≥ 1 PCI had lower event rates at 1 year, compared with patients with deferred PCI, suggesting that deferring lesions judged relevant by visual estimation but with FFR > 0.80 may not be optimal in this context. Future randomized studies are needed to confirm this data.

Registration: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02943954. Funded by a grant from the French Ministry of Health and an unrestricted grant provided by the Abbott Company.

Key words: Acute myocardial infarction; Fractional flow reserve; Multivessel disease; Revascularization; ST-elevation myocardial infarction

Non-standard Abbreviations and Acronyms

ACS, acute coronary syndrome

CCS, chronic coronary syndromes

COMPARE-ACUTE, Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD

DANAMI-3, DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction

EQ-5D, European Quality of Life–5 Dimensions

FFR, fractional flow reserve

FLOWER MI, Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction

MACE, major adverse cardiac event

MI, myocardial infarction

PCI, percutaneous coronary intervention

PROSPECT, Providing Regional Observations to Study Predictors of Events in the Coronary Tree

STEMI, ST-elevation myocardial infarction

Clinical Perspective

What is Known:

- The FLOWER MI trial showed that the FFR-guided strategy is not superior to an angiography-guided strategy in terms of death, re-infarction or urgent revascularization at one year in STEMI patients with multivessel disease.
- Our data show that in patients with STEMI undergoing complete revascularization guided by FFR measurement, those with ≥ 1 PCI have lower event rates at 1 year, compared with patients with deferred PCI, suggesting that deferring lesions judged relevant by visual estimation but with FFR >0.80 may not be optimal in this context.

What the Study Adds:

- For STEMI patients with multivessel disease, FFR-guided PCI for non-culprit lesions should not be the reference for guiding complete myocardial revascularization, as deferred lesions may lead to increased risk of subsequent clinical events at one year.

Circulation: Cardiovascular
Interventions



Introduction

The role of fractional flow reserve (FFR) in the assessment of coronary lesions of indeterminate severity is well-established in the setting of chronic coronary syndromes (CCS).¹⁻⁵ An FFR-guided strategy results in better clinical outcomes compared with angiography alone, while conservative management for non-functional lesions appears safe over the long term in this setting.^{1,6}

In patients with ST-elevation myocardial infarction (STEMI) who have multivessel disease, percutaneous coronary intervention (PCI) of non-culprit lesions has been shown to be superior to treatment of the culprit lesion alone, whether or not it is guided by FFR.^{7,8} In STEMI patients, however, little is known regarding outcomes of patients with FFR-guided multivessel PCI, comparing patients who actually undergo PCI with those who have deferred PCI (i.e., those with $\text{FFR} \geq 0.80$). Recently, the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER MI) trial has shown that an FFR-guided strategy did not achieve superiority over an angiography-guided strategy for treatment of non-culprit lesions with respect to the risk of death, myocardial infarction (MI), or urgent revascularization at 1-year.^{9,10}

The value of an FFR guided strategy is predicated on the ability of FFR measurements to identify lesions (and patients) with a low risk of subsequent ischemic outcomes that can be managed conservatively. While this has been clearly established in CCS, there is conflicting data regarding outcomes of patients with a preserved FFR value following acute coronary syndrome (ACS).¹¹

The aim of the present study was to assess clinical outcomes at one-year in STEMI patients with multivessel coronary artery disease in the FFR-guided arm of the FLOWER MI trial, according to whether or not non-culprit lesions PCI was performed following FFR measurement (≥ 1 PCI versus none).

Methods

Patients

The authors declare that all supporting data are available within the article [and its online supplementary files]. The study design and results of the FLOWER MI trial have been published previously.^{9,10} In brief, the FLOWER-MI trial was an investigator-initiated, randomized, open, blinded end-points (PROBE design) multicenter trial in which FFR-guided complete revascularization was compared to angiography-guided complete revascularization in STEMI patients at the early stage.

All STEMI patients (≥ 18 years old) with successful culprit lesion PCI (primary, rescue or pharmaco-invasive; defined as TIMI flow ≥ 2 and residual stenosis $< 30\%$) were eligible for enrollment if the non-infarct-related coronary arteries (IRA) (i.e., major epicardial coronary artery or their major side branches ≥ 2.0 mm in diameter) showed ≥ 1 lesion with a stenosis $\geq 50\%$ in diameter by visual assessment, judged amenable to PCI by the interventional cardiologist performing the PCI. Non-IRA lesions were identified as not being responsible for the acute MI when confronted with the infarct territory determined by the diagnostic electrocardiogram (ECG). Inclusion and exclusion criteria are detailed elsewhere.^{9,10}

In both groups, complete revascularization during index procedure was encouraged. If not possible, however, complete revascularization could be performed during another, staged, procedure, as early as possible, before hospital discharge and ≤ 5 days of the initial procedure. The use of drug-eluting stents was encouraged.⁹ Patients of both groups received optimal medical therapy as per the guidelines.^{1,12}

The study protocol was approved by an ethics committee (Comité de Protection de Personnes (CPP) Ile de France XI, April 14, 2016). Before randomization, as required by Good Clinical Practice guidelines,⁹ informed consent was obtained after completion of the

culprit-artery procedure, either orally (with subsequent signature) in the case of immediate multivessel procedure, or in writing after the initial procedure had been completed and before the second procedure. A Data Monitoring Committee (DMC) provided trial oversight, and assessed the safety profile of the trial. Independent clinical research associates monitored the sites and gathered the data. All events were analyzed and adjudicated by an independent, three-person, clinical evaluation committee.

FFR measurement

FFR was measured in all target lesions using the Radi Medical Systems wire (Abbott). FFR measurement technique is detailed in the protocol.¹⁰ In the FFR group, an FFR value ≤ 0.80 was considered significant for ischemia with a recommendation that the corresponding PCI be performed. Repeating FFR measurement after completion of PCI was encouraged. An FFR > 0.80 was considered non-significant for ischemia and PCI on the corresponding lesion was not to be performed.

Endpoints

Our aim was to assess clinical outcomes at one-year in patients with multivessel coronary artery disease and an FFR-guided strategy for complete revascularization, according to whether or not PCI is performed (≥ 1 PCI versus none). The primary outcome of the present analysis was the composite of all-cause death, non-fatal MI, and unplanned hospitalization leading to urgent revascularization (major adverse cardiac event, MACE) at one year.

Secondary outcomes included the following: procedure time(s), total amount of contrast agent used during the initial hospital stay; and at 1, 6, 12, and 36 months: individual components of the primary outcome; any revascularization (urgent or elective); urgent revascularization for non-culprit artery target lesion; rehospitalization for angina or for acute heart failure; any rehospitalization in a cardiology department; functional class as assessed with the use of the Canadian Cardiovascular Society (CCS) classification of angina; health-

related quality of life (as measured by the score on the European Quality of Life–5 Dimensions [EQ-5D] scale);¹³ number of anti-anginal medications; and, cost-effectiveness and cost utility at one year.

Statistical analysis

All analyses were performed in the intention-to-treat population. Clinical event rates and other categorical data are summarized as percentages. Continuous data are presented as means (standard deviations) or as medians [interquartile range (IQR)].

Groups were compared using Student (or Wilcoxon tests) for continuous variables and χ^2 (or Fisher tests) for discrete variables. Survival curves for the primary outcome were estimated using the Kaplan-Meier. For time-to-event outcomes, treatment effect was estimated using a Cox model for primary outcome and secondary outcomes with more than 10 events per group and results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).¹⁴ Schoenfeld tests were used to check the proportional hazard assumption.

For count variable (number of anti-anginal medications at 12 months), a negative binomial model was performed to estimate the mean number of medications in each group. Treatment effect was estimated using the ratio of the two means. For CCS classification of angina (≥ 1 vs. asymptomatic), a logistic regression model was used to estimate the treatment effect.

All models were adjusted on the age, sex, hypertension, diabetes, dyslipidemia, location of MI and Killip class.

Finally, we performed a sensitivity analysis that examines only patients who got an FFR and in whom FFR was positive in the FFR with ≥ 1 PCI group (n=293) and who got an FFR which was negative in the FFR without PCI group (n=193) for the primary outcome. A two-sided P value of ≤ 0.05 was considered significant. Analyses were performed using SAS

software, version 9.2 (SAS Institute, North Carolina, US) and R statistical software version 4.0.2 (R Core Team, Vienna, Austria).

Results

Patients

Among 1,171 patients enrolled in the FLOWER MI trial, 586 were assigned to the FFR-guided group: 388 (66%) of them had ≥ 1 PCI and 198 (34%) had no PCI on non-culprit lesions. Baseline patient characteristics were similar between groups, with a mean age of 62.5 ± 11.0 years (Table 1). Infarct location determined by ECG was mostly inferior. Baseline angiographic characteristics are detailed in (Table 2). Syntax score at baseline including culprit lesions was well balanced in both groups, and the average number of culprit lesions was: 1.23 ± 0.51 (median 1 [IQR: 1-1]). Medications administered during the procedure, at discharge and at one year are described in Table I in the online-only Data Supplement.

Non-culprit lesion intervention

Staged intervention for non-culprit lesions was used in $\geq 96\%$ of the patients in both groups. Mean time delay between interventions was 2.5 ± 1.3 days (median: 2 days [IQR: 2;3]) in the FFR without PCI and 2.8 ± 3.9 days (median: 2 days [IQR: 2;3]) in the FFR with ≥ 1 PCI groups.

In the FFR with ≥ 1 PCI group, FFR measurement was attempted in 568/695 (81.7%), versus 261/285 lesions (91.6%) in the FFR without PCI group. No severe adverse event was reported. Mean FFR values were 0.75 ± 0.10 versus 0.88 ± 0.06 respectively in both groups. The mean number of stents used per patient (i.e., in the FFR with ≥ 1 PCI) was 1.52 ± 0.85 . Drug-eluting stents were used in 99% of cases.

Clinical outcomes

Clinical outcomes are summarized in Table 3. At one year, the primary outcome occurred in 16 patients (4.1%) in the FFR with ≥ 1 PCI group and in 16 (8.1%) in the group without PCI (Adjusted HR, 0.42; 95% CI, 0.20 to 0.88; P=0.02) (Figure 1).

Death from any cause occurred in 3 and 6 patients for the FFR without PCI and FFR with ≥ 1 PCI groups; nonfatal re-infarction in 11 and 7 patients, and unplanned hospitalization leading to urgent revascularization in 8 and 7 patients, respectively.

The rate of any revascularization was higher in patients without PCI (10.1% vs. 4.6%; adjusted HR, 0.45; 95% CI, 0.23 to 0.88). Both urgent and non-urgent revascularizations in non-culprit arteries were higher in the FFR without PCI group (urgent revascularizations: 8/198 vs. 7/388; non-urgent revascularizations: 13/198 vs. 12/388). A detailed list of all revascularization procedures is presented in supplementary File (Table II in the online-only Data Supplement).

Similar trends were found in the sensibility analysis which examined only patients that got an FFR and in whom FFR was positive in the FFR with ≥ 1 PCI group and that got an FFR in whom FFR was negative in the FFR without PCI group (Table III in the online-only Data Supplement).

Discussion

The FLOWER-MI trial is the first study which compared FFR- versus Angiography-guided complete revascularization in STEMI patients with multivessel disease. The present analysis shows that in patients undergoing complete revascularization guided by FFR measurement, those with ≥ 1 PCI had lower event rates at 1 year, compared with patients with deferred PCI. This may explain why an FFR-guided strategy was not superior to an angio-guided strategy in the whole trial population.

Coronary pressure-derived FFR is the current standard of care for the functional assessment of lesion severity in patients with intermediate-grade stenosis without evidence of ischaemia in non-invasive testing, or in those with multivessel disease.¹ In the setting of CCS, the DEFER randomized controlled trial has demonstrated over the long term (i.e. 15 years of follow-up) that the prognosis of functionally non-significant deferred lesions is excellent, and that PCI of such stenoses has no advantage and even results in more MI when compared with medical therapy.⁶ In a recent meta-analysis and systematic review, Liou KP *et al* have shown that the event rate in patients with ACS is much higher than in patients with CCS despite following an FFR-guided revascularization strategy.¹¹ Deferring revascularization does not appear to be as safe for ACS as it for CCS, when using contemporary FFR cut-offs validated in CCS. Several studies have demonstrated that ulcerated plaques and the underlying inflammatory processes are often present in territories other than that of the culprit lesions, suggesting that a general inflammatory process is present in the weeks/months following an ACS.^{15,16} In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial, however, the incidence of cardiovascular events at 3 years did not differ between patients with or without plaque rupture of non-culprit lesions.¹⁵ Also, patients with ACS have a higher cardiovascular risk profile at baseline. These differences may explain the higher recurrent MI and all-cause mortality rates reported in this population. Indeed, studies have reported a higher rate of clinical events for each given range of FFR in those with ACS compared with CCS,^{17,18} even when the FFR value was above the threshold for revascularization. This could partly explain that the FFR could be faulted in ACS patients. In the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME) trial, the benefit of using FFR to guide PCI in multivessel disease did not differ between patients with unstable angina or Non ST-elevation myocardial infarction (NSTEMI), compared with CCS. Patients with STEMI at the acute stage were however excluded.¹⁹



Circulation: Cardiovascular
Interventions

Among patients with STEMI and multivessel disease, the DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction (DANAMI-3) and Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD (COMPARE-ACUTE) trials previously demonstrated that FFR-guided revascularization of non-infarct related arteries compared with culprit-lesion-only revascularization was associated with a reduction in MACE, driven by a reduction in the number of subsequent PCI procedures.^{7,8} An FFR sub study of the COMPARE ACUTE trial, has shown that lower non-infarct-related arteries FFR measured at the time of the primary PCI during STEMI predicted a higher risk of cardiovascular mortality, nonfatal MI, or revascularization of the given non-infarct-related arteries when treated with medical therapy only.²⁰



To our knowledge, contrary to CCS, there are no data on clinical outcomes in multivessel STEMI patients with an FFR-guided strategy, according to whether or not PCI was actually performed. Our results show that the number of revascularization procedures for non-culprit arteries is higher in patients without PCI compared to patients with ≥ 1 PCI, and that this finding holds true for both urgent and non-urgent revascularizations. Deferring PCI in non-culprit lesions in STEMI patients with multivessel disease is therefore questionable, especially since the complications related to stenting have considerably decreased over the past 10 years with newer antithrombotic treatments and new generations of drug-eluting stents.^{1,2} Multivessel disease being a marker of severity in ACS patients, one may hypothesize that physician should combine both anatomic and functional aspect of coronary artery disease to optimize the revascularization strategy.

The limitations of the present analysis are the same as those of the FLOWER MI trial. In addition, the main limitation of the current analysis is that the study was carried out as an open-label trial and we cannot exclude that unjustified revascularizations were performed on

deferred lesions during follow-up, particularly non-urgent procedures. Although the number of urgent and non-urgent revascularizations was too low to be interpreted, and both were lower in the ≥ 1 PCI group, unjustified revascularizations on deferred lesions might have biased our findings against FFR. However, the rates of non-fatal MI and unplanned revascularization were also higher in patients without PCI. The comparison is non-randomized and the present analysis is underpowered due to low number of events. Therefore, its results can only be considered hypothesis-generating and future randomized studies are needed to confirm this data. Finally, for logistical reasons, the evaluation of completeness of revascularization, and FFR measurements were not assessed by a core-lab and relied on the investigators' evaluations. Pressure pull back recordings to assess for drift were not recommended for the study.



In conclusion, in patients with STEMI undergoing complete revascularization guided by FFR measurement, those who underwent a PCI had lower event rates at 1 year, compared with patients with in whom PCI was not performed, based upon the results of FFR measurements. This may explain why an FFR-guided strategy was not superior to an angio-guided strategy in the whole trial population compared to CCS population. Because of the non-randomized nature of the present analysis and of the low number of events observed, however, our results can only be considered hypothesis-generating and will need confirmation with a longer follow-up or with future randomized studies.

Acknowledgments

The authors are deeply indebted to all patients who accepted to participate in the surveys, and to the physicians who took care of the patients at the participating institutions. The authors

would like to thank Dr. Juliette DJADI-PRAT and all personal involved in this study for their help in managing the FLOWER-MI study.

Sources of Funding

FLOWER-MI is an academic study, funded by a grant from the "Programme Hospitalier de Recherche Clinique» (PHRC) issued by the French Ministry of Health. The study was sponsored by Assistance Publique-Hôpitaux de Paris, with an unrestricted grant from Abbott which provided the coronary pressure guidewire (Radi Medical Systems). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. None of the funders had a role in the design and conduct of the study, data collection and management.



Disclosures

None.

Supplemental Materials

Supplemental Tables I-III

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165. doi: 10.1093/eurheartj/ehy394.
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407-477. doi: 10.1093/eurheartj/ehz425.
3. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J, Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-8. doi: 10.1056/NEJM199606273342604.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, Klauss V, Manoharan G, Engström T, Oldroyd KG, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-224. doi: 10.1056/NEJMoa0807611.
5. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001. doi: 10.1056/NEJMoa1205361.
6. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J*. 2015;36:3182-3188. doi: 10.1093/eurheartj/ehv452.
7. Engström T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, et al; DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665-71. doi: 10.1016/s0140-6736(15)60648-1.
8. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, et al; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376:1234-1244. doi: 10.1056/NEJMoa1701067.
9. Puymirat E, Simon T, de Bruyne B, Montalescot G, Steg G, Cayla G, Durand-Zaleski I, Blanchard D, Danchin N, Chatellier G; FLOWER-MI study investigators. Rationale and design of the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial. *Am Heart J*. 2020;222:1-7. doi: 10.1016/j.ahj.2019.12.015.
10. Puymirat E, Cayla G, Simon T, Steg PG, Montalescot G, Durand-Zaleski I, le Bras A, Gallet R, Khalife K, Morelle JF, et al; FLOWER-MI Study Investigators. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. *N Engl J Med*. 2021. doi: 10.1056/NEJMoa2104650.

11. Liou KP, Ooi SM, Hoole SP, West NEJ. Fractional flow reserve in acute coronary syndrome: a meta-analysis and systematic review. *Open Heart*. 2019;6:e000934. doi: 10.1136/openhrt-2018-000934.
12. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177. doi: 10.1093/eurheartj/ehx393.
13. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208. doi: 10.1016/0168-8510(90)90421-9.
14. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.
15. Xie Y, Mintz GS, Yang J, Doi H, Iñiguez A, Dangas GD, Serruys PW, McPherson JA, Wennerblom B, Xu K, et al. Clinical outcome of nonculprit plaque ruptures in patients with acute coronary syndrome in the PROSPECT study. *JACC Cardiovasc Imaging*. 2014;7:397-405. doi: 10.1016/j.jcmg.2013.10.010.
16. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med*. 2002;347:5-12. doi: 10.1056/NEJMoa012295.
17. Masrani Mehta S, Depta JP, Novak E, Patel JS, Patel Y, Raymer D, Facey G, Zajarias A, Lasala JM, Singh J, et al. Association of Lower Fractional Flow Reserve Values With Higher Risk of Adverse Cardiac Events for Lesions Deferred Revascularization Among Patients With Acute Coronary Syndrome. *J Am Heart Assoc*. 2015;4:e002172. doi: 10.1161/JAHA.115.002172.
18. Lee JM, Choi KH, Koo BK, Shin ES, Nam CW, Doh JH, Hwang D, Park J, Zhang J, Lim HS, et al. Prognosis of deferred non-culprit lesions according to fractional flow reserve in patients with acute coronary syndrome. *EuroIntervention*. 2017;13:e1112-e1119. doi: 10.4244/EIJ-D-17-00110.
19. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, Pijls NH. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv*. 2011;4:1183-1189. doi: 10.1016/j.jcin.2011.08.008. PMID: 22115657.
20. Piróth Z, Boxma-de Klerk BM, Omerovic E, Andréka P, Fontos G, Fülöp G, Abdel-Wahab M, Neumann FJ, Richardt G, Abdelghani M, et al. The Natural History of Nonculprit Lesions in STEMI: An FFR Substudy of the Compare-Acute Trial. *JACC Cardiovasc Interv*. 2020;13:954-961. doi: 10.1016/j.jcin.2020.02.015.

Table 1. Baseline Characteristics of the Patients

	Patients without PCI (n=198)	Patients with PCI (≥1) (n=388)	P Value
Characteristic			
Age – yr	61.2±11.5	62.8±10.7	0.36
Median	61.0	62.0	
IQR	54.0-71.0	55.0-70.0	
BMI *	26.9±4.3	27.0±4.2	0.82
Median	26.5	26.8	
IQR	23.9-29.1	24.2-29.1	
Missing	4	2	
Male sex – no. (%)	162 (81.8)	336 (86.6)	0.13
Medical history			
Hypertension – no. (%)	87 (43.9)	166 (42.8)	0.79
Diabetes mellitus – no. (%)	35 (17.7)	72 (18.6)	0.79
Hypercholesterolemia – no. (%)†	80 (40.4)	152 (39.2)	0.77
Current smoker – no. (%)	93 (47.0)	142 (36.6)	0.09
Family history of coronary artery disease – no. (%)	62 (32.0)	111 (28.8)	0.44
Previous myocardial infarction – no. (%)	16 (8.1)	29 (7.5)	0.79
Previous PCI – no. (%)	17 (8.6)	42 (10.8)	0.39
Previous stroke – no. (%)	5 (2.5)	11 (2.8)	0.83
Peripheral-vessel disease – no. (%)	5 (2.5)	11 (2.8)	0.83
Chronic renal insufficiency – no. (%)‡	3 (1.5)	8 (2.1)	0.76
Cancer – no. (%)§	14 (7.1)	29 (7.5)	0.64
Location of infarct – no. (%) 			<0.001
Anterior	84 (42.6)	89 (23.2)	
Inferior	100 (50.8)	259 (67.6)	



Calculation: Cardiovascular
Interventions

Posterior	4 (2.0)	5 (1.3)	
Posterolateral	8 (4.1)	28 (7.3)	
Left bundle branch block	1 (0.5)	2 (0.5)	
Impossible to determine	1	5	
Arteries with stenosis – no. () per patients			<0.001
1	9 (4.6)	2 (0.5)	
2	151 (76.3)	273 (70.4)	
3	38 (19.2)	113 (29.1)	
Killip class ≥ 2 – no./total no. ()	13 (6.6)	24 (6.2)	0.70
Glycated hemoglobin –	6.0 \pm 1.1	6.2 \pm 1.3	0.14
Median	5.7	5.8	
IQR	5.5-6.0	5.5-6.3	
Missing	32	78	
Low-density lipoprotein cholesterol — mmol/liter	1.3 \pm 0.6	3.5 \pm 32.4	0.20
Median	1.2	1.2	
IQR	1.0-1.5	0.9-1.5	
Missing	15	28	
Peak creatinine — μ mol/liter	89.7 \pm 25.5	94.2 \pm 34.2	0.07
Median	87	88	
IQR	75-99	79-100	
Missing	1	1	
Left ventricular ejection fraction —	51.1 \pm 9.7	50.9 \pm 9.4	0.83
Median	50	50	
IQR	45-60	45-57.5	
Missing	9	17	

Data are presented as n (%) or means \pm SD or (IQR). FFR indicates fractional flow reserve; IQR, interquartile range; and PCI, percutaneous coronary intervention.

* Measurements for BMI (body-mass index; the weight in kilograms divided by the square of the height in meters).

† Patients described as having hypercholesterolemia were either receiving treatment with cholesterol-lowering medications or were known to have elevated levels of cholesterol (>200 mg per deciliter [5.2 mmol per liter]).

‡ Patients reported as having a clinical history of chronic kidney disease.



Circulation: Cardiovascular
Interventions

§ Only cancers with a life expectancy likely to be <2 years were excluded, so that non-melanoma skin cancers were not among exclusion criteria.

||The location of the infarct was determined on the diagnostic electrocardiogram.



Circulation: Cardiovascular Interventions

Table 2. Procedural Data

	Patients without PCI (n=198)	Patients with PCI (≥1) (n=388)	P Value
Type of Data			
SYNTAX score *† Baseline score, including culprit lesion	14.4±8.6	15.5±8.6	0.14
Location of culprit lesion — no./total no. of patients (%)			
Left main coronary artery	1/198 (0.5)	2/388 (0.5)	1
Left anterior descending artery	86/198 (43.4)	98/388 (25.3)	<0.001
Circumflex artery	36/198 (18.2)	88/388 (22.7)	0.21
Right coronary artery	76/198 (38.4)	205/388 (52.8)	0.001
Location of culprit lesion — no./total no. of lesions (%)*			<0.001
Left main coronary artery	1/237 (0.4)	2/481 (0.4)	
Left anterior descending artery	100/237 (42.2)	122/481 (25.4)	
Circumflex artery	41/237 (17.3)	94/481 (19.5)	
Right coronary artery	95/237 (40.1)	263/481 (54.7)	
Location of non-culprit — no./total no. of patients (%)			
Left main coronary artery	1/198 (0.5)	6/388 (1.6)	0.43
Left anterior descending artery	87/198 (43.9)	264/388 (68.0)	<0.001
Circumflex artery	85/198 (42.9)	154/388 (39.7)	0.45
Right coronary artery	67/198 (33.8)	112/388 (28.9)	0.22
Location of non-culprit lesions — no./total no. of lesions (%)*			0.005
Left main coronary artery	1/285 (0.4)	6/695 (0.9)	
Left anterior descending artery	110/285 (38.6)	348/695 (50.1)	
Circumflex artery	99/285 (34.7)	204/695 (29.4)	
Right coronary artery	75/285 (26.3)	137/695 (19.7)	
Non-culprit lesion stenosis on visual estimation – no. (%)			<0.001
<50%	8/285 (2.8)	21/695 (3.0)	

50–69%	171/285 (60.0)	243/695 (35.0)	
70–90%	96/285 (33.7)	370/695 (53.3)	
> 90%	6/285 (2.1)	46/695 (6.6)	
Missing	4/285 (1.4)	15/695 (2.2)	
Diameter of vessel with non-culprit lesion — mm*‡	-	2.9±0.5	-
Median	-	2.8	
IQR	-	2.5-3.0	
Missing	-	171	
Staged intervention of non-culprit lesion — no./total no. (%)	190/198 (96)	376/388 (97)	0,55
PCI of non-culprit lesion*			
FFR procedures attempted — no of lesions (%)	261/285 (91.6)	568/695 (81.7)	< 0.001
Mean FFR value			
FFR before PCI of non-culprit lesion	0.88±0.06	0.75±0.1	<0.001
Median	0.88	0.76	
IQR	0.85-0.92	0.70-0.79	
Missing	24/285	130/695	
FFR post PCI of non-culprit lesion	-	0.90±0.06	-
Median	-	0.90	
IQR	-	0.86-0.95	
Missing	-	522/695	
Lesions with FFR ≤0.80 — no. (%)	6/261 (2.3)	454/565 (80.4)	<0.001
Lesions with FFR >0.80 — no. (%)	255/261 (97.7)	111/565 (19.6)	
Missing	24	130	
Number of lesions with PCI	0/285 (0)	542/695 (78.2)	<0.001
Type of stent used (non-culprit lesions) — no. (%)			-
Zotarolimus eluting	-	95/695 (18.2)	
Sirolimus eluting	-	106/695(20.3)	
Paclitaxel eluting	-	0/695 (0)	
Everolimus eluting	-	306/695 (58.5)	
Others drug-eluting	-	22/695 (4.1)	

Bare-metal stent	-	5/695 (1)	
Unknown	-	57/695 (8.2)	
Mean no. of stents used per patient			
Total	1.35±0.73	2.95±1.18	<0.001
Culprit lesion	1.35±0.73	1.43±0.81	
Non-culprit lesions	-	1.52±0.85	
Dimensions of stents (non-culprit lesions) — mm			
Mean length	-	25.4±12.4	-
Median	-	23.0	
IQR	-	16.0-32.0	
Mean diameter	-	2.9±0.5	-
Median	-	2.8	
IQR	-	2.5-3	
Characteristics of the procedure			
Procedure duration - min			
Culprit lesion			
Median	33	31	0.11
IQR	22-50	20-45	
Missing	18/198	27/388	
Non-culprit lesion			
Median	26	40	<0.001
IQR	18-36	20-44	
Missing	36/198	38/388	
Volume of contrast agent used – ml			
Culprit lesion			
Median	140	150	0.10
IQR	100-170	110-180	
Missing	30/198	52/388	
Non-culprit lesion			
Median	66	140	<0.001

IQR	45-100	100-190	
Missing	27/198	51/398	
Length of hospital stay — days			0.72
Median	5	5	
IQR	4-6	4-6	

Data are presented as n (%) or means \pm SD or median (IQR). FFR indicates fractional flow reserve; IQR, interquartile range; NA, not applicable; and PCI, percutaneous coronary intervention.

* Data were obtained at the angiographic core laboratory.

† The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score is used to describe the degree of angiographic complexity; a score of 0 indicates no angiographically significant disease, and higher scores indicate more extensive and complex coronary artery disease.

‡ Diameter of vessel with non-culprit lesion was defined using the stent size



Circulation: Cardiovascular Interventions

Table 3. Prespecified Clinical Outcomes at 1 Year

Outcomes	Patients without PCI (n=198)	Patients with PCI (≥1) (n=388)	Hazard Ratio (95% CI)	P value
	Primary outcome at 1 year*†	16 (8.1)	16 (4.1)	0.42 (0.20–0.88)
Death from any cause — no. (%)	3 (1.5)	6 (1.6)		
Myocardial infarction — no. (%)	11 (5.6)	7 (1.8)		
Unplanned hospitalization leading to urgent revascularization — no. (%)	8 (4.0)	7 (1.8)		
Secondary outcome at 1 year*				
Stent thrombosis — no. (%)	2 (1.0)	2 (0.5)		
Any revascularization— no. (%)‡	20 (10.1)	18 (4.6)	0.45 (0.23- 0.88)	
Hospitalization for heart failure — no. (%)	4 (2.0)	5 (1.3)		
Hospitalization for recurrent ischemia — no. (%)	19 (9.6)	13 (3.4)	0.37 (0.18- 0.76)	
Any hospitalization in Cardiology — no. (%)	34 (17.2)	34 (8.8)	0.50 (0.30- 0.81)	
Functional status at 1 year*				
Mean number of anti-anginal medications used per patient— no. §	0.98±0.46	0.96±0.44	0.02 (0- 0.04)	
EQ-5D score	0.86±0.19	0.86±0.19	0.00 (-0.01- 0.01)	
Recurrent ischemia — no. (%)#	19 (9.6)	13 (3.4)	0.37 (0.18- 0.76)	
CCS class ≥2**	12 (63.2)	8 (66.7)	-	

FFR indicates fractional flow reserve; and PCI, percutaneous coronary intervention.

* All models were adjusted on the age, sex, risk-factors, location of MI and Killip class excepted for stent thrombosis (number of events too low).

† Major Adverse Cardiac Events (MACE) denotes the composite of all-cause mortality, nonfatal myocardial infarction, and unplanned hospitalization leading to urgent revascularization, at one year.

‡ Any revascularization includes all first revascularizations that were elective or urgent and that were clinically indicated or not between the time of the index procedure and follow-up at 1 year.

§ Antianginal medications included beta-blockers, calcium antagonists, and nitrates. Rate of means estimated by a negative binomial model.

||The European Quality of Life–5 Dimensions (EQ-5D) scale is a visual-analogue scale that measures health-related quality of life. Scores range from 0 to 100, with higher scores indicating higher health-related quality of life.

Odds ratio estimated by logistic model.

** Angina was assessed according to the Canadian Cardiovascular Society (CCS) Functional Classification of Angina Pectoris.



Circulation: Cardiovascular Interventions

Figure Legends

Figure 1. Kaplan-Meier Event Curves of the Combined Primary Outcome.

Major Adverse Cardiac Events (MACE) denotes the composite of all-cause mortality, nonfatal myocardial infarction (MI), and unplanned hospitalization leading to urgent revascularization, at one year. PCI indicates percutaneous coronary intervention



Circulation: Cardiovascular
Interventions

