

Rationale and Design of the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial

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TITLE

Rationale and Design of the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial.

SHORT TITLE

FLOWER-MI study

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ABSTRACT

Background: In ST-elevation myocardial infarction (STEMI) patients presenting with multivessel disease (MVD), recent studies have demonstrated the superiority of fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) for non-culprit lesions compared to culprit lesion treatment-only therapy. FFR- and angio-guided PCI have however never been compared in STEMI patients.

Trial design: FLOWER MI is an open label multicenter national randomized clinical trial. The aim is to investigate FFR-guided complete revascularization in comparison to angio-guided complete revascularization in STEMI patients with successful PCI of the culprit lesion and $\geq 50\%$ stenosis in at least one additional non-culprit lesion requiring PCI. Eligible patients will be randomized after successful primary PCI in a 1:1 fashion to either FFR-guided or angio-guided complete revascularization during the index procedure or a staged procedure before discharge (≤ 5 -Day). Patients assigned to FFR guidance first have FFR measured in each non-culprit vessel and only undergo PCI if FFR is ≤ 0.80 . The primary end point of the study is a composite of major adverse cardiac events, including all-cause death, non-fatal MI, and unplanned hospitalization leading to urgent revascularization at 1 year. Secondary end points will include the individual adverse events, cost-effectiveness, quality of life, and 30-day, 6-month, and 3-year outcomes. Based on estimated event rates, a sample size of 1170 patients is needed to show superiority of the FFR-guided revascularization with 80% power.

Conclusion: The aim of FLOWER-MI trial is to assess whether FFR-guided complete revascularization in the acute setting is superior angio-guided complete revascularization.

ClinicalTrials.gov Identifier: NCT02943954

KEY-WORDS: Fractional flow reserve, Percutaneous coronary intervention, ST-elevation myocardial infarction

Introduction

The primary objective of percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is to restore epicardial flow in the culprit vessel and myocardial perfusion (1). However, the pathophysiological process of coronary artery disease in myocardial infarction (MI) is not limited to the culprit vessel. It is estimated that 40% to 65% of the patients presenting with STEMI have multivessel disease (MVD), which is associated with worse clinical outcome compared with single-vessel disease (1–4). Whether non-culprit lesions justify immediate or rapid intervention, however, is the subject of considerable debate.

The recent prospective randomized PReventive Angioplasty in AMI (PRAMI) or Complete versus Lesion-only PRimary PCI Trial (CvLPRIT) trials indicate that complete acute revascularization improves clinical outcomes compared with revascularization of the culprit lesion only (5-6). These studies showed a relative risk reduction of 65% and 55%, respectively, for the primary endpoint (all-cause mortality, non-fatal MI or any revascularization). In addition, MV-PCI may also be beneficial when ≥ 1 culprit lesion is suspected. Apart from a potential prognostic benefit, MV-PCI may also be more convenient for the patient, as it obviates subsequent procedures. Furthermore, there are logistic and economic reasons to perform MV-PCI as it may limit staged procedures and reduce length of hospital stays, and thereby medical costs.

Yet, in the setting of primary PCI, the first step is to identify which lesions should be considered for additional stent implantation. In fact, assessing the severity of non-culprit lesions, and whether they are likely to cause myocardial ischemia and might therefore warrant revascularization, is a true diagnostic challenge. In daily life, and particularly in the setting of emergency coronary angiography for acute MI, most interventional cardiologists assess the

severity of coronary artery stenoses by visual analysis of the coronary angiogram. As previously demonstrated, however, visual estimation of the degree of coronary stenosis is a poor indicator of the haemodynamic relevance of the lesions (7). Coronary angiography may both underestimate and overestimate the functional severity of a lesion and may lead to overtreatment, with additional costs and risks (7-10).

Fractional flow reserve (FFR) is designed for the functional assessment of lesion severity during coronary angiography and has become the standard of reference for decision making about revascularization. (1,11). Several studies have demonstrated that an FFR-guided strategy reduced the rate of major cardiovascular events in stable patients and non-ST-elevation acute coronary syndrome (NSTEMI-ACS) compared to with angiography-guided PCI or conservative treatment (10,12-14). In the context of STEMI, the feasibility and safety of using FFR in patients without hemodynamic instability has been demonstrated (15). Two recent randomized trials, 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) have recently evaluated an FFR-guided approach to justify the use of PCI for non-infarct-related coronary artery lesions among patients presenting with STEMI and MVD (16,17). The results showed that patients who had complete (FFR-guided) revascularization during the same (or a staged) procedure had fewer repeat revascularizations than those who received treatment for the infarct-related coronary artery only. In the above-mentioned studies, MVD in the control group was treated conservatively with standard guideline-based medical therapy. To date, the FFR-strategy has never been compared to angiography-guided PCI in STEMI patients with MVD.

The Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER MI) trial was designed to address the following question:

does FFR-guided complete revascularization translate into better clinical outcomes and lower costs compared to angio-guided complete revascularization in STEMI patients with MVD?

Methods

Study design

FLOWER-MI is an investigator-initiated, multicenter randomized controlled trial in which 1,170 STEMI patients with MVD will be randomized between December 2016 and June 2019. All 42 participating centers are located in metropolitan France and listed in **Supplementary File 1**. Our primary objective is to determine whether, in STEMI patients with MVD amenable to PCI, the use of FFR in addition to angiography will improve one-year cardiovascular outcomes, compared with the current practice of angiography-guided PCI, by improving the appropriateness of revascularizations.

A flowchart of the trial is shown in **[Figure 1]**.

All STEMI patients (≥ 18 years old) with successful culprit lesion PCI (primary, rescue or pharmaco-invasive; defined as TIMI flow ≥ 2 and residual stenosis $< 30\%$) and $\geq 50\%$ diameter stenosis by visual estimate in at least one additional non-culprit lesion in a major epicardial coronary artery (i.e., non-infarct related lesion(s)), in which revascularization is contemplated and judged amenable to PCI will be randomized into two groups: angiography-guided PCI or FFR-guided PCI. Only hemodynamically stable patients with non-culprit lesions judged feasible for both FFR and PCI are eligible to be randomized. The complete inclusion and exclusion criteria are listed in **Table 1**.

Informed consent will be obtained before randomization, as required by Good Clinical Practice guidelines. Oral approval in the presence of a third person (who is not involved in the

study) before or during the primary PCI procedure, followed by a signature after the procedure, will also be accepted to avoid further treatment delay.

After successful and uncomplicated primary PCI treatment of the culprit lesion, eligible patients will be randomized 1:1, with the recommendation to randomize the patient as close to the procedure as possible. The randomization will be stratified by center, and type of procedure (immediate or staged). The list will be balanced by different sized and randomly alternated blocks. The data coordination center will prepare the randomization list before enrolment begins. The randomization of patients will be done through a web-based centralized randomization system (Cleanweb software, Telemedicine technologies SAS, Boulogne-Billancourt, France). Neither members of study committees nor investigators will have access to any information regarding treatment allocation.

In the FFR-guided PCI group, fractional flow reserve will be measured in all lesions judged $\geq 50\%$ reduction of diameter by visual estimate and amenable to PCI, with a standard coronary pressure wire and after complete hyperemia has been achieved with intracoronary adenosine (bolus of 100 μg in the RCA and 200 μg in the LCA), or intravenous adenosine (Krenosin® administered at 140 $\mu\text{g}/\text{kg}/\text{min}$ preferably via a central vein) as in usual care and trials (18). In addition, an intracoronary bolus of $\geq 200\text{mg}$ isosorbide dinitrate (or any other form of intracoronary nitrates) is recommended at least 30 seconds before the first measurements (18). FFR is 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 (18). The Radi Medical Systems (Abbott) will be used for FFR measurements in all centers. We recommended several measurements to the investigators (i.e., ≥ 2), and averaging the results. If the patient is assigned to the FFR guided strategy, then FFR is first measured:

- An FFR value of ≤ 0.80 will be considered significant for ischemia with a recommendation that non-culprit PCI is performed. It is encouraged (but not mandatory) that FFR after completion of PCI is also performed and the value registered in the database.
- An FFR of >0.80 will be considered non-significant for ischemia with a recommendation that medical management is pursued.

In both groups, complete revascularization during the index procedure is encouraged. If it is not possible, however, complete revascularization can be performed during another procedure, as soon as possible, before discharge from the hospital and within 5 days of the initial procedure (staged procedure). The use of drug-eluting stents is encouraged in both strategies

Patients of both groups will receive an optimal medical therapy (including dual antiplatelet therapy, beta-blockers, statins, angiotensin-converting-enzyme inhibitor or Angiotensin II receptor blockers) as recommended in international contemporary guidelines in both strategies (1).

Follow-up will begin after the primary PCI, with visits scheduled at 1, 6, 12 and 36 months.

All medications, biology markers, PCI results, and major adverse cardiac events will be collected during the hospitalization and at discharge, as summarized in the **Supplementary File 2**. We will also assess the patient's quality of life with the European Quality of Life–5 Dimensions [EQ-5D] instrument (19)

Costs of the 2 strategies will also be prospectively recorded.

Primary and secondary end Points

The primary end-point of the study is the composite of all-cause death, non-fatal MI, and unplanned hospitalization leading to urgent revascularization (major adverse cardiac event, MACE), at 1 year between the FFR-guided strategy and the angio-guided strategy (**Table 2**).

Secondary endpoints include the following:

1. Individual components of the primary end-point at 1 year;
2. Rates of MACE including all-cause death, non-fatal MI, and unplanned hospitalization leading to urgent revascularization at 30 days, 6 months and 3 years;
3. Any revascularization (urgent or elective) at 1 year;
4. Urgent revascularization for non-culprit artery target lesion;
5. Rehospitalization for angina at 1 year;
6. Rehospitalization for acute heart failure at 1 year;
7. Any rehospitalization in cardiology at 1 year;
8. Procedure time(s), total amount of contrast agent used;
9. Functional class at 1 year as assessed with the use of the Canadian Cardiovascular Society classification of angina;
10. Health-related quality of life (as measured by the score on the European Quality of Life–5 Dimensions [EQ-5D] scale) at one year (19);
11. Number of anti-anginal medications used at discharge, 1, 6 and 12 months;
12. Cost-effectiveness and cost utility at one year between the FFR-guided and angio-guided strategies.

Data management and statistics

Forty-two centers eventually participated in the FLOWER-MI trial. All sites underwent training to the procedure before study initiation. Enrollment began in December 2016. Data will be collected in specifically-designed electronic case report form (eCRF). The data

management will be carried out by the URC (Unité de Recherche Clinique) of HEGP (Hôpital Européen Georges Pompidou), independently from the study sponsors.

Sample size

Using a .05 level of significance, a power of 0.80, a 1-year risk of MACE in the FFR-guided strategy of 9.5%, and a 1-year risk of MACE in the angio-guided strategy of 15%, at least 557 patients per group should be enrolled in the trial. Considering that 5% of patients will be lost to follow-up, a total of 1170 patients need to be randomized (585 patients per group). These estimates are based on the results of the PRAMI study and on previous studies involving FFR in patients with MV-CAD (5). No interim analysis has been planned.

Statistics

The strategy of the design and analysis will be made in compliance with the CONSORT statement (<http://www.consort-statement.org>). An Intention-to-Treat (ITT) analysis will be performed, keeping patients in their randomization group and including protocol deviations. A 'Per-Protocol' (PP) sensitivity analysis will also be performed. Finally, a secondary Bayesian analysis will be used. The statistical analysis will be carried out with SAS software version 9.4 (SAS Institute, Cary, NC, USA) and the statistical significance level will be $p < 0.05$ (two-sided).

- Analysis of the primary endpoint

The primary objective of this study is to demonstrate the superiority of the FFR-guided strategy over the angio-guided strategy, in terms of risk reduction of the primary composite endpoint at one year.

The null hypothesis is that the proportions for primary efficacy variable are two groups are equal, versus the alternative hypothesis that the proportions in the two groups are not equal to 1: $H_0: p_2 = p_1 = 1$ vs. $H_1: p_2 \neq p_1$, where p_1 and p_2 are the proportions of the primary efficacy event in angiography-guided strategy and the FFR-guided PCI strategy respectively. This hypothesis will be tested using a 2-sided X^2 test. A mixed logistic-regression model will be performed adjusted on type of procedure (immediate or staged) and the trial site will be used as a random effect. Results will be presented as OR and their 95% confidence intervals.

- Analyses of secondary endpoints

All models will include the trial sites as random parameter and will be adjusted on type of procedure (immediate or staged).

For the time-to-event variables, survival curves will be estimated using the Kaplan-Meier method and compared using the Log-rank test. A Cox proportional hazards model with mixed effect will be used to estimate the hazard ratio and to obtain the 95% confidence limits.

For the time-to-event variables in presence of competing risks, cumulative incidence curve will be compared using the Gray test. Treatment effect will be estimated using the Fine and Gray model with mixed effect. Results will be presented as sub-distributed hazard ratio (SHR) with their 95% confidence interval.

For count variables, Poisson model with mixed effect will be performed to assess treatment effect or negative binomial model with mixed effect in case of overdispersion. In case of excess of zero, a zero inflated Poisson model with mixed effect or a zero inflated negative binomial model with mixed effect will be performed.

For ordinal data, polytomous logistic regression with mixed effect will be used.

- Safety analyses

The assessment of safety will be based on the frequency of adverse events (AE) and serious adverse events (SAE) occurring during follow-up. Occurrence and frequency of AE/SAE(s) will be summarised by group. Other safety data will be summarised if appropriate.

- Subgroup analyses

Pre-planned subgroups analyses will concern age, sex, procedure time, presence of risk factors, cardiovascular history and characteristics of the procedure.

General aspects of trial organization and ethical concerns

The study protocol has been approved by an ethics committee (CPP Ile de France XI, April 14, 2016). It is registered in the Clinicaltrials.gov registry (NCT02943954). The trial will be carried out under the authority of the steering committee which consists of 8 physicians (5 cardiologists and 2 methodologists). A Data Monitoring Committee (DMC) will regularly review the data to assess the safety profile of the trial (including serious adverse events and mortality). No interim analysis has been planned.

An endpoint adjudication committee composed of three cardiologists will be appointed.

Definitions of study outcomes are reported in **Supplementary File 3**. All severe adverse events collected with a specific focus on potentially procedure-related events (death, myocardial infarction, and any repeat revascularization) will be reviewed and adjudicated by this committee, which will be provided with all relevant clinical and biochemical information (including, if appropriate ECGs, biochemistry, imaging, pathology, etc...) and which will be blinded to the randomization assignment. Causes of death will be specifically categorized into cardiovascular and non-cardiovascular.

FLOWER-MI is an academic study. Its funding source is a 2015 grant from the "Programme Hospitalier de Recherche Clinique» (PHRC) issued by the French Ministry of Health. The study is sponsored by Assistance Publique-Hôpitaux de Paris, with financial assistance provided by the Saint-Jude Medical Company, which will provide 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.

Limitations

The hypothesis of superiority of FFR-guided PCI over angio-guided PCI might be challenged, particularly in view of the results of the COMPARE ACUTE and COMPLETE trials (17, 20). The design of FLOWER MI was elaborated before the results from these trials were known. Previously, the FFR-guided PCI strategy had proved its superiority compared to angio-guided PCI in stable patients (10).

We finally chose a superiority design for the following reasons:

- in terms of clinical events, a non-inferiority design for testing an additional procedure is highly debatable;
- it would have made more sense to define the primary end-point as cost-effectiveness, with a superiority design (the co-primary end-point proposed by the reviewer), but this would have required to have the certainty that there was no deleterious effect on clinical events;
- because of the rules of the public tender to which we applied, we had to choose a clinical end-point as first end-point, and the non-inferiority hypothesis would have required a much larger sample size, which seemed unrealistic in the setting of emergency revascularization for STEMI;

- the expected MACE rate was determined using data from the FAST-MI registries and rendered the superiority hypothesis realistic within the sample size of the trial.

In this trial, there is no upper stenosis limit for the use of FFR. Previous studies have demonstrated that lesions with high degree of stenosis have a positive functional assessment in the great majority of cases. However, and particularly in an acute setting, the degree of stenosis would have to be appreciated by eye-ball measurement in most instances (i.e. highly operator-dependent), and that seemed inappropriate in the frame of a clinical trial. In addition, at the acute stage of MI, some degree of vasoconstriction is often present which may lead to over-estimation of degree of stenosis.

Although we used the ESC definition of periprocedural MI, those are difficult to define in STEMI patients (1). This can lead to a risk of underdiagnosing periprocedural MIs in patients with non-culprit artery PCI. If real, this risk would lead to potential bias against (rather than in favor of) the trial hypothesis.

Finally, for logistical reasons, the evaluation of completeness of revascularization was not done by a core-lab and relied on the investigator's evaluation in both arms.

Summary

The FLOWER-MI study is prospective, multicenter randomized controlled trial based in France in which 1,170 patients are included. This is the first trial to assess whether FFR-guided complete revascularization of STEMI patients with MVD gives better clinical outcomes and lower costs than angio-guided complete revascularization. To our knowledge, there are no randomized trials in progress comparing these two strategies. A multicenter observational registry in Italy will evaluate long-term clinical outcomes with an instantaneous

wave-free ratio (iFR) assessment of the non-culprit lesions during primary PCI for STEMI patients with multivessel coronary artery disease (NCT03561389): after revascularization procedure of the culprit lesion, non-culprit lesion(s) with an iFR ≤ 0.89 will undergo PCI while those with an iFR >0.89 will be managed conservatively. The study is not randomized and will be purely descriptive.

Journal Pre-proof

References

1. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541-619.
2. Meliga E, Fiorina C, Valgimigli M, et al. Early angio-guided complete revascularization versus culprit vessel PCI followed by ischemia-guided staged PCI in STEMI patients with multivessel disease. *J Intervent Cardiol* 2011;24:535-41.
3. Widimsky P, Holmes DR. How to treat patients with ST-elevation acute myocardial infarction and multi-vessel disease? *Eur Heart J* 2011;32:396-403.
4. Jaski BE, Cohen JD, Trausch J, et al. Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: comparison of single-vessel versus multivessel coronary artery disease. *Am Heart J* 1992;124:1427-33.
5. Wald DS, Morris JK, Wald NJ, et al; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115-23.
6. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963-72.
7. Tonino PAL, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010;55:2816-21.

8. Fischer JJ, Samady H, McPherson JA, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 2002; 90:210-5.
9. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995; 92:2333-42.
10. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
11. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;334:1703-8.
12. Pijls NHJ, 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;49:2105-11.
13. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
14. Layland J, Oldroyd KG, Curzen N, et al. Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS-NSTEMI randomized trial. *Eur Heart J* 2015;36:100-11.
15. Ntalianis A, Sels J-W, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;3:1274-81.
16. Engstrøm T, Kelbæk H, Helqvist S, et al. 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.

17. Smits PC, Abdel-Wahab M, Neumann FJ, et al; Compare-Acute Investigators. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med 2017;376:1234-44.

18. Puymirat É, Muller O, Sharif F, et al. Fractional flow reserve: concepts, applications and use in France in 2010. Arch Cardiovasc Dis 2010;103:615-22.

19. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy Amst Neth 1990;16:199-208.

20. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med 2019;381:1411-21

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Competing interests

EP has received fees for lectures and/or consulting: Amgen, Astra-Zeneca, BMS, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, MSD, Novartis, Pfizer, The Medicine Company, Sanofi, Saint Jude Medical, Servier, Siemens.

Authors' contributions

EP is Coordinating Investigator for the FLOWER-MI trial, made substantial contributions to the conception and design of the FLOWER-MI trial, drafted the manuscript, and revised the manuscript critically for important intellectual content.

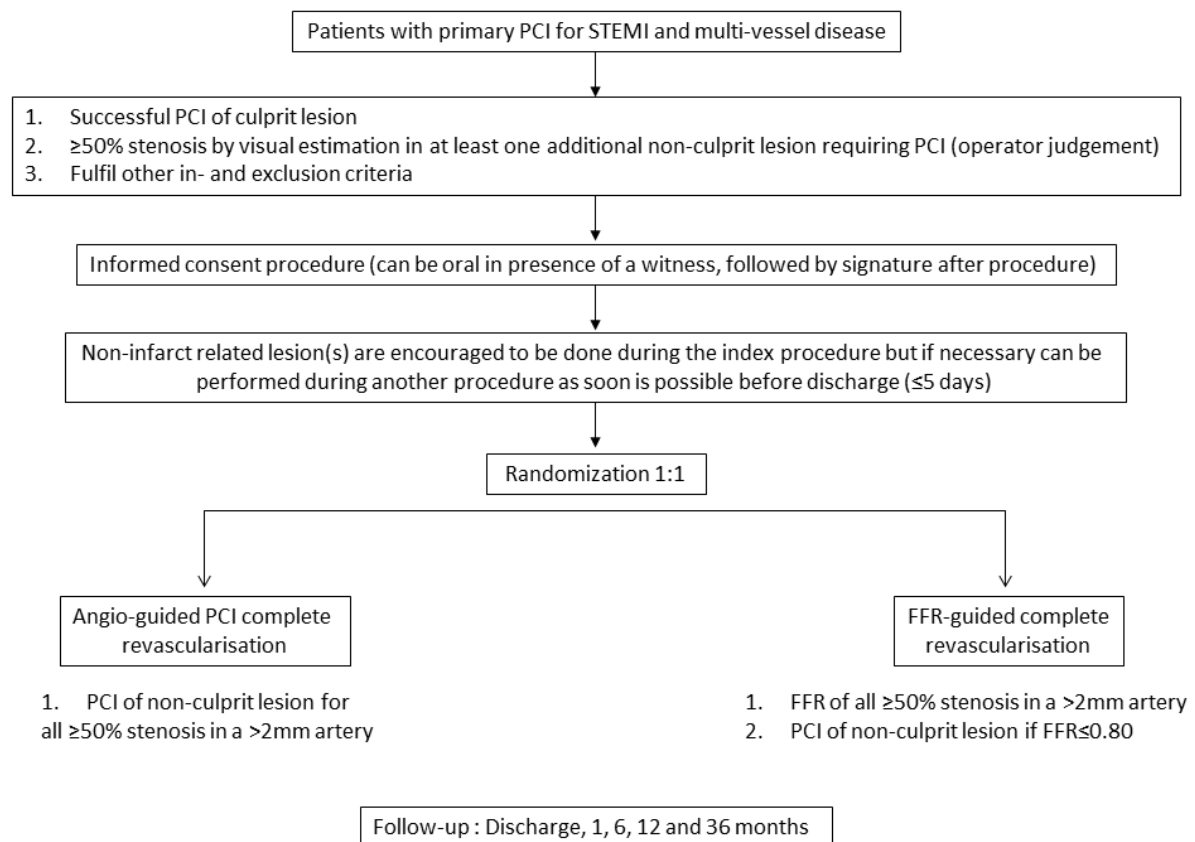
ND, BDB made substantial contributions to the conception and design of the FLOWER-MI trial, drafted the manuscript, and revised the manuscript critically for important intellectual content.

GC made substantial contributions to the conception and design of the FLOWER-MI trial, drafted the manuscript, and revised the manuscript critically for important intellectual content.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Figures

FIGURE I. Design of FLOWER-MI study.



FFR, Fractional flow reserve,

PCI, Percutaneous coronary intervention

STEMI, ST-elevation myocardial infarction

Tables

TABLE I. Inclusion and exclusion criteria

Inclusion criteria

-
1. STEMI patients
 2. Age ≥ 18 y
 3. Successful culprit lesion PCI (primary, rescue or pharmaco-invasive) and $\geq 50\%$ stenosis judged amenable to PCI in at least one additional non-culprit lesion
 4. Willing and able to provide informed, written consent
-

Exclusion criteria

-
1. Cardiogenic shock
 2. Previous coronary bypass surgery
 3. Extremely tortuous, calcified coronary vessels or chronic total occlusion
 4. Patients with multivessel disease to be referred to surgery
 5. Hypersensitivity to adenosine
 6. Life expectancy < 2 years
 7. Pregnancy
 8. Participation in another interventional therapeutic study at the same time or within 3 months prior to the beginning of the present study
 9. Participant not affiliated to the French social security
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TABLE II. Primary and Secondary Endpoints.**Primary and Secondary Endpoints**

Primary	The rate of death, myocardial infarction, and urgent myocardial revascularization (MACE) at one year.
Secondary	Cost-effectiveness Health-related quality of life (EQ-5D) MACE at 30 days, 6 months and 3 years Individual components of MACE at all times points Functional class Number of antianginal medications prescribed Procedure time Contrast use

Supplementary file 1. Trial sites.

Ville	Hôpital
Antibes	CH d'Antibes Juan-Les-Pins
Bayonne	Clinique Lafourcade
Besançon	CHU Besançon
Boulogne-Billancourt	Ambroise Paré
Brest	CHU Morvan
Bron	Louis Pradel
Caen	CHU Caen - Hôpital Côte de nacre
Caen	Institut Cardiovasculaire De Caen
Chambray-les-Tours	Hôpital Trousseau
Chartres	Résidence de l'hôtel-dieu
Clermont-Ferrand	CHRU Clermont-Ferrand Gabriel-Montpied
Corbeil-Essonnes	CH Sud-Francilien
Créteil	Henri Mondor, A.Chenevier
Dijon	Hôpital Du Bocage - CHU
La Rochelle	CH Saint-Louis
La Tronche	Hôpital A. Michallon
Le Chesnay	Hôpital Versailles
Libourne	CH Libourne
Lille	CHRU de Lille Hôpital Cardiologique
Lomme	Hôpital Saint Philibert
Lyon	Hôpital de la Croix Rousse
Lyon	CH St-Joseph et St-Luc

Marseille	Hôpital de la Timone
Marseille	CHU Marseille Nord
Metz	Hôpital de Mercy
Montfermeil	GHI Le Raincy-Montfermeil
Montpellier	Arnaud de Villeneuve
Nîmes	CHRU Nîmes
Paris	Bichat
Paris	Hôpital Européen Georges Pompidou
Paris	Pitié Salpêtrière
Paris	Cochin
Paris	Lariboisière
Pau	CH de Pau
Pessac	Haut-Lévêque Bordeaux
Poitiers	CHU poitiers
Rennes	CHU de Rennes Pontchaillou
Rouen	CHU de Rouen
Saint Herblain	CH René Gauducheau
Toulouse	CHU Rangueil
Tours	Clinique Saint Gatien
Valenciennes	Hôpital de Valenciennes

CH, Centre hospitalier; CHU, Centre hospitalier universitaire, CHRU, Centre hospitalier regional universitaire

Supplementary file 2. Summary table of visits schedule.

Actions	Inclusion visit	Discharge	30- Day ($\pm$ 5 days)	6- Month ($\pm$ 15 days)	12- Month ($\pm$ 30 days)	30- Month ($\pm$ 30 days)
Eligibility	X					
Informed consent	X					
Inclusion	X					
Randomization	X					
Medical history	X					
Quality-of-life questionnaire: EQ-5D		X	X	X	X	
Clinical assessment (face to face or by phone)	X	X	X	X	X	
Medical procedures						
- ECG	X					
- Coronary angiogram	X					
- PCI	X					
Biology tests:						
- Troponin	X					
- Hematology	X					
- Biochemistry	X	X	X	X	X	X

Actions	Inclusion visit	Discharge	30- Day ($\pm$ 5 days)	6- Month ($\pm$ 15 days)	12- Month ($\pm$ 30 days)	30- Month ($\pm$ 30 days)
Dispensation of treatments (including number and doses of cardiac medications)	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Major adverse cardiac events		X	X	X	X	X
Vital Status		X	X	X	X	X

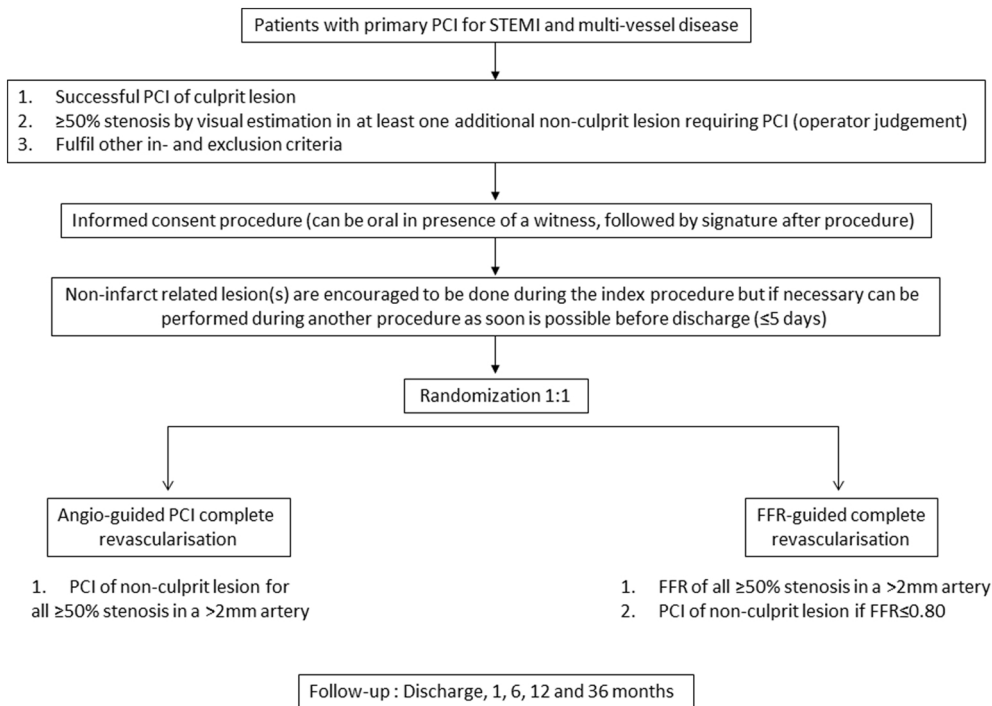


Figure 1