ORIGINAL ARTICLE

Complete Revascularization Guided by Functional Coronary Angiography in STEMI

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ABSTRACT

BACKGROUND

Complete coronary-artery revascularization is recommended in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease, but the preferred strategy for identifying nonculprit lesions that warrant treatment remains uncertain.

METHODS

In this international, randomized trial, we assigned patients with STEMI and multivessel disease in whom the culprit lesion had been successfully treated to undergo complete coronary-artery revascularization guided by functional coronary angiography (physiology-guided group) or by conventional angiography (angiography-guided group). The primary outcome was a composite of death from any cause, myocardial infarction, cerebrovascular accident (stroke or transient ischemic attack), or ischemia-driven revascularization, assessed in a time-to-event analysis. The primary safety outcome was a composite of contrast-associated acute kidney injury or major bleeding.

RESULTS

A total of 1823 patients underwent randomization; 913 were assigned to the physiology-guided group and 910 assigned to the angiography-guided group. The median age of the patients was 66 years (interquartile range, 58 to 76), and 24% were women. At a median follow-up of 17.9 months, a primary-outcome event had occurred in 81 patients (8.9%) in the physiology-guided group and in 125 patients (13.7%) in the angiography-guided group (hazard ratio, 0.62; 95% confidence interval [CI], 0.47 to 0.83; P<0.001). A primary-safety-outcome event occurred in 42 patients (4.6%) in the physiology-guided group and in 65 patients (7.1%) in the angiography-guided group (hazard ratio, 0.63; 95% CI, 0.43 to 0.93; P=0.02).

CONCLUSIONS

In patients with STEMI and multivessel coronary artery disease, a strategy of complete coronary-artery revascularization guided by functional coronary angiography resulted in a lower risk of a primary-outcome event (death, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization) than a strategy guided by conventional angiography. (Funded by the Italian Health Ministry and others; AIR-STEMI ClinicalTrials.gov number, NCT05818475.)

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Complete coronary-artery revascularization has become the standard of care for patients presenting with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease.[1] However, the appropriate strategy for identifying which nonculprit lesions warrant revascularization remains uncertain. In clinical practice, decisions regarding nonculprit lesions are still largely based on angiographic assessment despite its limited ability to define lesions that are functionally important and warrant revascularization. Functional coronary angiography is now available and enables an assessment of coronary physiology directly from angiographic images, including both fractional flow reserve (FFR) estimates and pullback analysis, without the need for pressure wires or hyperemic agents. In patients with chronic coronary syndromes and intermediate lesions, this approach has been shown to be noninferior to wire-based FFR and superior to angiography-guided decision making.[2-5] However, evidence regarding the role of functional coronary angiography in the treatment of patients with STEMI and multivessel coronary artery disease remains limited. We conducted the international, randomized Functional Coronary Angiography to Indicate and Guide Revascularization in STEMI Patients with Multivessel Disease (AIR-STEMI) trial to evaluate whether a strategy of complete coronary-artery revascularization guided by functional coronary angiography is superior to one guided by conventional angiography in patients with STEMI and multivessel disease.

Methods

Trial Design and Oversight

This trial was an investigator-initiated, international, prospective, randomized superiority trial. The design of the trial has been described previously.[6] The protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating center. The Italian Health Ministry was the primary sponsor of the trial, with funding administered through the University Hospital of Ferrara. The nonprofit organization Consorzio Futuro in Ricerca coordinated international centers and trial committees and received unrestricted funding from Sahajanand Medical Technologies and Siemens Healthineers and software licenses for angiography-derived FFR analyses from Pulse Medical Imaging Technology and Pie Medical Imaging. The sponsors had no role in the design or conduct of the trial; collection, management, analysis, or interpretation of the data; or preparation of the manuscript. An independent data and safety monitoring committee oversaw the trial and assessed the safety profile. Site monitoring and data collection were performed by the Ferrara University Hospital academic research organization (additional details are provided in the Supplementary Appendix, available at NEJM.org). The executive committee designed the trial and was responsible for its conduct. The first draft of the manuscript was written by the first and last authors. The authors had full access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients were eligible if they were hospitalized with a STEMI, had undergone successful percutaneous coronary intervention (PCI) of the culprit lesion, and had multivessel coronary artery disease with at least one lesion in a nonculprit coronary artery with a reference vessel diameter of at least 2.5 mm and an angiographically estimated diameter stenosis of 50 to 99%. Key exclusion criteria were the inability to identify a clear culprit lesion, presence of a nonculprit lesion in the left main coronary artery, planned or previous surgical revascularization, and life expectancy of less than 1 year. The full list of inclusion and exclusion criteria is provided in the Supplementary Appendix and has been reported previously.[6] All the patients provided written informed consent (additional details are available in the Supplementary Appendix).

Randomization

Within 48 hours after successful treatment of the culprit lesion, eligible patients were randomly assigned in a 1:1 ratio to undergo complete revascularization guided by functional coronary angiography (physiology-guided group) or by conventional angiography (angiography-guided group). Randomization was performed centrally with the use of a secure Web-based system in accordance with a computer-generated allocation

sequence, with stratification according to center, sex, age (<75 or ≥75 years of age), and nonculprit-vessel location (left anterior descending artery or non–left anterior descending artery). Treatment assignments were concealed until the time of randomization.

TREATMENTS AND FOLLOW-UP

Patients in the physiology-guided group underwent functional coronary angiography assessment of all nonculprit lesions with an angiographically estimated diameter stenosis of 50% or greater. Functional coronary angiography consisted of an estimation of the distal FFR value in the nonculprit vessel; lesions with an FFR value of 0.80 or less were considered to be functionally important and were treated with PCI in accordance with a virtual-PCI plan that was based on the FFR pullback curve. Analyses were performed at a central core laboratory with the use of angiography-derived FFR software, including Murray law–based quantitative flow ratio (AngioPlus Core, Pulse Medical Imaging Technology) and vessel FFR (CAAS vFFR, Pie Medical Imaging). PCI of lesions with negative functional assessment (value, >0.80) was considered to be a protocol violation. Patients in the angiography-guided group underwent PCI of all nonculprit lesions with an angiographically estimated diameter stenosis of 50% or greater.

In both groups, the goal was for complete revascularization to be achieved during the initial hospitalization, either during the first (index) procedure or in a staged procedure at the discretion of the operator. Second-generation drug-eluting stents were used, with a recommendation for sirolimus-eluting, biodegradable-polymer, ultrathin strut stents (Supraflex Cruz, Sahajanand Medical Technologies). All the patients received guideline-directed medical therapy. Dual antiplatelet therapy was recommended for at least 12 months unless contraindicated owing to a high risk of bleeding. Follow-up assessments were performed at 1 month and every 6 months thereafter.

OUTCOMES

The primary outcome was a composite of death from any cause, myocardial infarction, cerebrovascular accident (stroke or transient ischemic attack), or ischemia-driven revascularization, assessed in a time-to-event analysis. The primary analysis was performed when the last enrolled patient reached 12 months of follow-up (prespecified data cutoff). Key secondary outcomes were the first occurrence of cardiovascular death or myocardial infarction (composite outcome), the individual components of the primary outcome, ischemic stroke, and stent thrombosis. The primary safety outcome was the first occurrence of contrast-associated acute kidney injury or major bleeding, defined as Bleeding Academic Research Consortium (BARC) type 3, 4, or 5. All clinical events were reported by investigators and were adjudicated by an independent clinical-events committee, the members of which were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

We estimated that 9% of the patients in the angiography group would have a primary-outcome event. Assuming a relative risk reduction of 35% with the physiology-guided strategy, we calculated that a sample of 1718 patients would provide the trial with 80% power at a two-sided alpha level of 0.05 to detect a significant between-group difference with respect to the primary outcome. To account for an anticipated 5% attrition rate, the target sample size was increased to at least 1800 patients.

All analyses were performed according to the intention-to-treat principle. Time-to-event curves were estimated with the use of the Kaplan–Meier method. The primary outcome was analyzed with a Cox proportional-hazards model, with treatment group as the sole covariate; results are reported as hazard ratios with corresponding 95% confidence intervals. Given the potential for competing events, complementary analyses based on cumulative-incidence functions and Fine–Gray subdistribution hazard models were performed for selected outcomes. For cardiovascular death, noncardiovascular death was considered to be a competing event; for nonfatal outcomes, death from any cause was treated as a competing event.

The proportional-hazards assumption was assessed for all models and subgroup analyses with the use of Schoenfeld residuals and graphical methods (Figs. S1, S2, and S3 in the Supplementary Appendix); no major protocol violations were observed. Prespecified subgroup analyses were performed, and results are presented in forest plots. Missing data were minimal and were handled with the use of available-case analyses, with

no imputation of missing values. There were no interim analyses. There was no adjustment for multiplicity, and the widths of the confidence intervals should not be used to infer treatment effects. Additional details regarding the statistical analysis are provided in the statistical analysis plan, available with the protocol. All analyses were performed by independent statisticians using R software (R Foundation for Statistical Computing).

RESULTS

PATIENTS

From May 8, 2023, to January 31, 2025, a total of 6131 patients at 21 sites in Italy and Pakistan were screened for eligibility (Fig. S4). Of these, 1823 patients underwent randomization, with 913 assigned to the physiology-guided group and 910 to the angiography group. Baseline demographic and clinical characteristics appeared to be balanced between the two groups (Table 1). Details regarding the representativeness of the patient sample are provided in Table S1. The median age of the patients was 66 years (interquartile range, 58 to 76), and 24% were women. The assigned treatment strategy was implemented in 886 patients (97.0%) in the physiology-guided group and in 871 patients (95.7%) in the angiography-guided group. In the physiology-guided group, a total of 1332 procedures were performed, and 1147 nonculprit vessels were assessed; functional coronary angiography was feasible in 1132 vessels (98.6%), with additional wire-based assessment in 15 vessels (1.3%) (Table 2). Overall, 590 nonculprit vessels (51.4%) were classified as functionally important, and PCI was performed on 596 vessels (51.9%) (Table 2). The virtual-PCI plan was implemented in 482 of 596 treated lesions (80.8%). In the angiography-guided group, 1590 procedures were performed, and PCI was performed on 1071 of 1128 nonculprit vessels (94.9%) (Table 2). Additional data regarding PCI procedures are available in Table S2. The median follow-up was 17.9 months (interquartile range, 12.0 to 24.0). Clinical follow-up was complete for 98.9% of the patients in the physiology-guided group and 99.2% of those in the angiography-guided group.

PRIMARY OUTCOME

At the time of the primary analysis, a primary-outcome event (the first occurrence of any component of the composite outcome of death from any cause, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization) had occurred in 81 patients (8.9%) in the physiology-guided group and in 125 patients (13.7%) in the angiography-guided group (hazard ratio, 0.62; 95% confidence interval [CI], 0.47 to 0.83; P<0.001) (Table 3 and Fig. 1). The number needed to treat to prevent one primary-outcome event was 21 (95% CI, 13 to 51). Subgroup analyses showed that the effect of physiology-guided complete revascularization on the primary outcome appeared to be consistent across prespecified subgroups (Fig. 2). Results for efficacy and safety outcomes, which were analyzed with Cox proportional-hazards models, are shown in Table S6. Post hoc sensitivity analyses to assess the cumulative incidence of primary-outcome events — excluding procedure-related myocardial infarction, the primary outcome according to analysis population, effects that are specific to high-enrollment centers, and center-level clustering — are shown in Figures S5 and S6 and Tables S7 and S8.

SECONDARY OUTCOMES

Cardiovascular death or myocardial infarction (composite outcome) occurred in 52 patients (5.7%) in the physiology-guided group and in 96 patients (10.5%) in the angiography-guided group (hazard ratio, 0.52; 95% CI, 0.37 to 0.73) (Fig. S7). The incidence of death, whether from any cause or from cardiovascular causes, did not appear to differ between the groups (Table 3 and Figs. S8 and S9). The causes of death are summarized in Table S3. Myocardial infarction occurred in 35 patients (3.8%) in the physiology-guided group and in 73 patients (8.0%) in the angiography-guided group (hazard ratio, 0.47; 95% CI, 0.31 to 0.70) (Fig. S10). Procedure-related myocardial infarction occurred in 15 patients (1.6%) in the physiology-guided group and in 33 patients (3.6%) in the angiography-guided group, whereas spontaneous myocardial infarction occurred in 21 patients (2.3%) and 45 patients (5.0%) in the respective groups (Table 3 and Table S4 and Figs. S10, S11, and S12).

Ischemic stroke occurred in 3 patients (0.3%) in the physiology-guided group and in 4 patients (0.4%) in the angiography-guided group (Fig. S13). Ischemia-driven coronary revascularization occurred in 29 patients (3.2%) and 47 patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)
Median age (IQR) — yr	67 (58–76)	66 (57–75)
Female sex — no. (%)	223 (24.4)	208 (22.9)
Coexisting conditions — no. (%)		
Hypertension	638 (69.9)	614 (67.5)
Dyslipidemia	482 (52.8)	504 (55.4)
Diabetes	195 (21.4)	205 (22.5)
Current smoker — no. (%)	292 (32.0)	278 (30.5)
Previous myocardial infarction — no. (%)	87 (9.5)	98 (10.8)
Previous PCI — no. (%)	96 (10.5)	105 (11.5)
Previous cerebrovascular accident — no. (%)†	33 (3.6)	38 (4.2)
Chronic kidney disease — no. (%)	116 (12.7)	127 (14.0)
Peripheral artery disease — no. (%)	100 (11.0)	106 (11.6)
Clinical presentation — no. (%)		
Cardiac arrest	34 (3.7)	32 (3.5)
Killip class ≥2‡	192 (21.0)	171 (18.8)
Laboratory data		
Median hemoglobin (IQR) — g/dl	13.7 (12.5–14.9)	13.9 (12.8–15.0)
Median creatinine clearance (IQR) — ml/min	85.2 (69.5–100.4)	83.0 (67.2–98.8)
Median left ventricular ejection fraction (IQR) — %	50.0 (45.0–55.0)	50.0 (44.0–56.0)
Length of hospital stay (IQR) — days	5.0 (3.5–6.5)	5.5 (4.0–6.0)
Medication at discharge — no. (%)		
Aspirin	890 (97.5)	874 (96.0)
Clopidogrel	201 (22.0)	195 (21.4)
Ticagrelor	623 (68.2)	609 (66.9)
Prasugrel	82 (9.0)	94 (10.3)
Oral anticoagulation	86 (9.4)	85 (9.3)
ACE inhibitor or ARB	790 (86.5)	772 (84.8)
Beta-blocker	698 (76.5)	685 (75.3)
Statin	882 (96.6)	878 (96.5)
Ezetimibe	522 (57.2)	525 (57.7)
Bempedoic acid	12 (1.3)	18 (2.0)
PCSK9 inhibitor	17 (1.9)	14 (1.5)

* ACE denotes angiotensin-converting enzyme, ARB angiotensin II receptor blocker, IQR interquartile range, PCI percutaneous coronary intervention, and PCSK9 proprotein convertase subtilisin–kexin type 9.
† Cerebrovascular accident was defined as a stroke or transient ischemic attack.
‡ According to the four-class Killip classification of heart failure, class I indicates no clinical signs of heart failure, class II indicates findings consistent with mild-to-moderate heart failure, class III indicates overt pulmonary edema, and class IV indicates cardiogenic shock.

(5.2%), respectively (Fig. S14). Stent thrombosis occurred in 6 patients (0.7%) and 11 patients (1.2%), respectively (Table 3 and Table S5 and Fig. S15).

SAFETY OUTCOMES

A primary-safety-outcome event (contrast-associated acute kidney injury or major bleeding) occurred in 42 patients (4.6%) in the physiology-guided group

Table 2. Procedural Data.*

Variable	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)
Procedures		
Total — no.	1332	1590
Index procedures — no.	913	910
With PCI of nonculprit vessels — no./total no. (%)	115/913 (12.6)	197/910 (21.6)
Staged procedures — no.	419	680
With PCI of nonculprit vessels — no./total no. (%)	397/419 (94.7)	674/680 (99.1)
Median no. of days from index procedure to staged procedure (IQR)	3.0 (2.0–4.0)	2.0 (0–4.0)
Radial-artery access — no./total no. (%)	1291/1332 (96.9)	1539/1590 (96.8)
Median volume of contrast medium used (IQR) — ml	180.0 (117.5–242.5)	223.0 (158.0–288.0)
Culprit vessel — no. (%)		
Left main coronary artery	29 (3.2)	22 (2.4)
Left anterior descending artery	341 (37.3)	351 (38.6)
Circumflex artery	219 (24.0)	206 (22.6)
Right coronary artery	324 (35.5)	331 (36.4)
Nonculprit vessel		
Total no.	1147	1128
Location — no./total no. (%)		
Left anterior descending artery	479/1147 (41.8)	473/1128 (41.9)
Circumflex artery	352/1147 (30.7)	342/1128 (30.3)
Right coronary artery	316/1147 (27.6)	313/1128 (27.7)
Reference-vessel diameter (IQR) — mm	3.0 (2.7–3.3)	3.0 (2.7–3.3)
Median percent diameter stenosis (IQR)	80.0 (72.5–87.5)	79.0 (72.0–86.0)
Percent diameter stenosis — no./total no. of vessels (%)		
50–69%	266/1147 (23.2)	224/1128 (19.9)
70–89%	675/1147 (58.8)	711/1128 (63.0)
90–99%	206/1147 (18.0)	182/1128 (16.1)
Median lesion length (IQR) — mm	23.0 (15.0)	23.0 (16.0)
Physiological assessment — no./total of nonculprit vessels		
Angiography-derived fractional flow reserve	1132/1147	NA
Wire-based fractional flow reserve	15/1147	NA
Fractional flow reserve (IQR)	0.80 (0.70–0.90)	NA
Functionally important nonculprit vessel — no./total no. (%)	590/1147 (51.4)	NA
Nonculprit vessel treated with PCI — no./total no. (%)	596/1147 (52.0)	1071/1128 (94.9)

* Data regarding quantitative coronary angiography were assessed at a central core laboratory. NA denotes not applicable.

and in 65 patients (7.1%) in the angiography-guided group (hazard ratio, 0.63; 95% CI, 0.43 to 0.93; P=0.02) (Fig. S16). Contrast-associated acute kidney injury occurred in 20 patients (2.2%) in the physiology-guided group and 36 (4.0%) in the angiography-guided group, and bleeding of BARC type 3, 4, or 5 occurred in 23 patients (2.5%) in the physiology-guided group and 33 (3.6%) in the angiography-guided group (Table 3 and Figs. S17 and S18).

Table 3. Efficacy and Safety Outcomes.

Outcome	Physiology-Guided Revascularization (N=913)	Angiography-Guided Revascularization (N=910)	Hazard Ratio (95% CI)*	P Value
	no. of patients (%)			
Primary outcome†	81 (8.9)	125 (13.7)	0.62 (0.47–0.83)	<0.001
Secondary outcomes				
Cardiovascular death or myocardial infarction	52 (5.7)	96 (10.5)	0.52 (0.37–0.73)	
Death	36 (3.9)	46 (5.1)	0.77 (0.50–1.20)	
Cardiovascular death	20 (2.2)	31 (3.4)	0.64 (0.36–1.12)	
Noncardiovascular death	16 (1.8)	15 (1.6)	1.07 (0.53–2.17)	
Myocardial infarction	35 (3.8)	73 (8.0)	0.47 (0.31–0.70)	
Procedure-related	15 (1.6)	33 (3.6)	0.45 (0.24–0.83)	
Spontaneous	21 (2.3)	45 (4.9)	0.46 (0.27–0.77)	
Ischemic stroke	3 (0.3)	4 (0.4)	0.75 (0.17–3.35)	
Ischemia-driven coronary revascularization	29 (3.2)	47 (5.2)	0.61 (0.38–0.97)	
Other outcomes				
Stent thrombosis	6 (0.7)	11 (1.2)	0.54 (0.20–1.47)	
Definite	6 (0.7)	10 (1.1)	0.60 (0.22–1.65)	
Probable	0	1 (0.1)	—	
Safety outcomes				
Composite of contrast-associated acute kidney injury or BARC stage 3, 4, or 5‡	42 (4.6)	65 (7.1)	0.63 (0.43–0.93)	0.02
Contrast-associated acute kidney injury	20 (2.2)	36 (4.0)	0.55 (0.32–0.94)	
BARC stage 3, 4, or 5	23 (2.5)	33 (3.6)	0.69 (0.41–1.18)	

* Hazard ratios for the primary outcome were estimated with Cox proportional-hazards models. For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used to evaluate treatment effects. For outcomes for which death was a competing event, hazard ratios were estimated with Fine–Gray subdistribution hazard models.

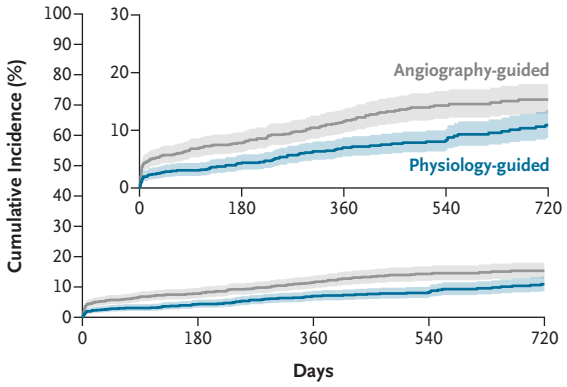
† The primary outcome was a composite of death, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization.

‡ Bleeding was staged according to the Bleeding Academic Research Consortium (BARC) scale, which ranges from 0 (no bleeding) to 5 (fatal bleeding).

DISCUSSION

In this multicenter, randomized trial, a strategy of complete coronary-artery revascularization guided by functional coronary angiography, with central core-laboratory support, resulted in a significantly lower incidence of a composite primary-outcome event than a strategy guided by conventional angiography. This benefit was accompanied by a significantly lower incidence of a composite of contrast-associated acute kidney injury or bleeding of BARC type 3, 4, or 5.

The benefit of complete coronary-artery revascularization, as compared with a culprit-lesion–only strategy, in patients with STEMI and multivessel disease is well established.[1] In most randomized trials, however, revascularization was guided predominantly by angiographic assessment, and this approach remains widely adopted in clinical practice. Two randomized trials have directly compared angiography-guided and physiology-guided strategies in patients with myocardial infarction, with differing results.[7,8] In the FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel



No. at Risk					
Angiography-guided	910	838	801	339	234
Physiology-guided	913	874	849	358	212
No. of Events					
Angiography-guided	1	71	105	121	125
Physiology-guided	1	40	64	71	81

Figure 1. Primary-Outcome Events after Revascularization.

Patients were randomly assigned to undergo physiology-guided revascularization or angiography-guided revascularization. The primary outcome was a composite of death, myocardial infarction, cerebrovascular accident (stroke or transient ischemic attack), or ischemia-driven coronary revascularization. The shading indicates 95% confidence intervals. The inset shows the same data on an expanded y axis.

ST-Elevation Myocardial Infarction) trial, FFR was assessed predominantly during staged procedures (in 96% of cases) and used primarily as a binary tool for lesion selection without a corresponding improvement in clinical outcomes.[8] In the FRAME-AMI (Fractional Flow Reserve versus Angiography-Guided Strategy for Management of Non-Infarction–Related Artery Stenosis in Patients with Acute Myocardial Infarction) trial, physiological assessment was most frequently integrated into the index procedure (in 60% of cases) and was associated with improved outcomes, driven mainly by a reduction in procedure-related myocardial infarction.[7] These differences in timing and implementation may explain, at least in part, the divergent findings of the two trials. In the present trial, functional coronary angiography of the nonculprit lesions was systematically applied during the index procedure and extended beyond lesion selection to include procedural planning through a predefined physiological treatment strategy.[9,10] This integrated use of physiological assessment was associated with a lower incidence of myocardial infarction, including both procedure-related and spontaneous events, as well as ischemia-driven coronary revascularization. Taken together, these findings across randomized trials suggest that the clinical benefit of physiological assessment depends not only on its use, but also on how it is integrated into the revascularization workflow.

Functional coronary angiography may provide a practical means of achieving such integration in the context of STEMI. Although evidence on functional coronary angiography has largely been generated in cases involving patients with chronic coronary syndrome, STEMI in acute-care settings may represent a particularly suitable context for its application.[11,12] By enabling incorporation of physiological assessment directly into the index procedure, this approach may overcome key limitations of wire-based physiological assessment, including the need for staged procedures and the separation between diagnostic assessment and procedural decision making.

The mechanisms underlying this benefit can be summarized as follows. First, physiological assessment during the index procedure allowed identification of nonculprit lesions without additional invasive diagnostic procedures, thereby reducing the need for staged interventions. Second, by restricting PCI to functionally important lesions, the physiology-guided strategy substantially reduced the number of nonculprit vessels treated, with a consequent decrease in procedure- and stent-related events. Third, physiological assessment was used not only for lesion selection but also to guide PCI. Pullback-based analysis enables discrimination between focal and diffuse disease, identification of the segment responsible for the greatest pressure loss, and refinement of the stent length and landing zones. This approach may enable more-targeted treatment of focal pressure drops and may reduce the risk of leaving functionally important segments untreated. In contrast, angiography-guided PCI relies primarily on visual assessment of the lesion severity by the operator and may fail to identify the segment responsible for the greatest physiological impairment. This concept is consistent with previous observations that linked focal disease to vulnerable plaque features and an increased risk of myocardial infarction.[13,14] Fourth, the physiology-guided approach was associated with a lower incidence of composite safety outcome events and fewer contrast-associated acute kidney injuries than the angiography-guided approach. This finding is biologically plausible, when we consider the

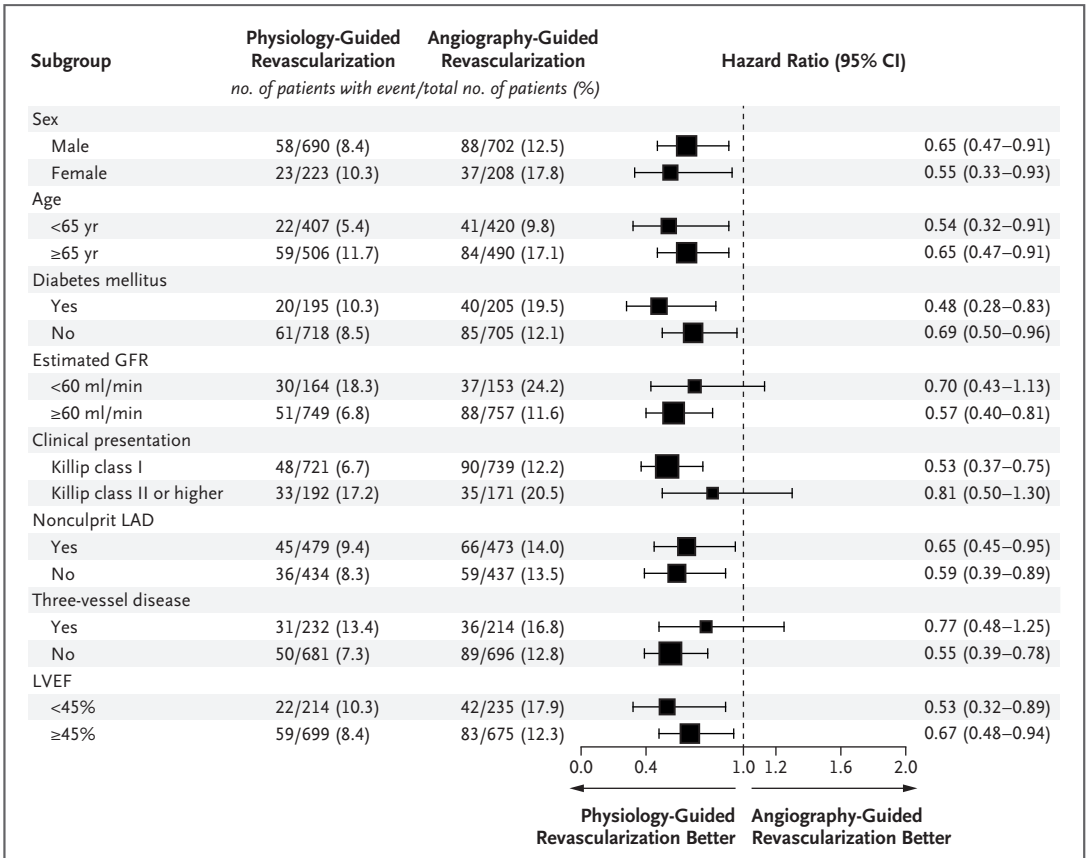


Figure 2. Subgroup Analysis of the Primary Outcome.

The sizes of the squares are proportional to the number of patients in each subgroup. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to evaluate treatment effects. The estimated glomerular filtration rate (GFR) was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula. LAD denotes left anterior descending coronary artery, and LVEF left ventricular ejection fraction.

lower number of vessels treated, fewer PCI procedures performed, and reduced exposure to contrast medium with the physiology-guided approach. Given the relatively small number of safety events, longer follow-up will be needed to define the clinical relevance of this finding.

Our trial has several limitations. The open-label design and the inclusion of revascularization in the primary outcome may have introduced ascertainment bias. The consistency of the findings for the prespecified composite outcome of cardiovascular death or myocardial infarction supports the biologic plausibility of the treatment effect. Because the experimental strategy incorporated both lesion selection and PCI planning, the relative contribution of each component to the observed benefit cannot be determined. Generalizability of the trial findings may be limited to patients with suitable coronary anatomy and angiographic image quality for functional coronary angiography. Functional coronary angiography was analyzed in a central core laboratory; although operator-performed analyses have been shown to be feasible and reproducible, further data will help to confirm the generalizability of these findings in routine clinical practice. The low overall use of intracoronary imaging may be relevant to the interpretation of stent-related outcomes, although its use was numerically greater in the angiography-guided group than in the physiology-guided group. Finally, because the present trial evaluated an integrated strategy based on functional coronary angiography, including lesion selection from angiographic images acquired during the index procedure and PCI planning based on physiological pullback, it remains uncertain

whether similar results would be achieved with other physiological methods if applied in a different workflow.

Among patients with STEMI and multivessel coronary artery disease, a strategy of complete coronary-artery revascularization guided by functional coronary angiography resulted in a lower risk of a primary-outcome event (death, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization) than a strategy guided by conventional angiography at a median of 17.9 months.

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REFERENCES

1. Mehta SR, Tiong DTW, Böhm F, et al. Complete versus culprit lesion-only revascularisation for acute myocardial infarction (Complete Revascularisation Trialists' Collaboration): an individual patient data meta-analysis of randomised trials. Lancet 2025;406:2772-81.
2. Daemen J, van der Eijk JA, Barbierato M, et al. Angiography-based physiology to guide coronary revascularization. N Engl J Med 2026;395:20-31.
3. Fearon WF, Jeremias A, Witberg G, et al. Angiography-derived fractional flow reserve to guide PCI. N Engl J Med 2026; 395:9-19.
4. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. Lancet 2021;398:2149-59.
5. Zhang R, Wang H-Y, Song L, et al. Rationales behind physiology-guided revascularization: diagnostic impact of quantitative flow ratio in the FAVOR III China trial. JACC Cardiovasc Interv 2026; 19:422-34.
6. Erriquez A, Colaiori I, Hakeem A, et al. Functional coronary angiography to indicate and guide revascularization in STEMI patients with multivessel disease: rationale and design of the AIR-STEMI trial. Am Heart J 2025;284:71-80.
7. Lee JM, Kim HK, Park KH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: a randomized trial. Eur Heart J 2023;44:473-84.
8. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. N Engl J Med 2021;385:297-308.
9. Escaned J, Berry C, De Bruyne B, et al. Applied coronary physiology for planning and guidance of percutaneous coronary interventions: a clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the European Society of Cardiology. EuroIntervention 2023; 19:464-81.
10. Faria D, Hennessey B, Shabbir A, et al. Functional coronary angiography for the assessment of the epicardial vessels and the microcirculation. EuroIntervention 2023; 19:203-21.
11. Spitaleri G, Tebaldi M, Biscaglia S, et al. Quantitative flow ratio identifies nonculprit coronary lesions requiring revascularization in patients with ST-segment-elevation myocardial infarction and multivessel disease. Circ Cardiovasc Interv 2018;11:e006023.
12. Erriquez A, Campo G, Guiducci V, et al. QFR for the revascularization of nonculprit vessels in MI patients: insights from the FIRE trial. JACC Cardiovasc Interv 2024;17:1425-36.
13. Yang S, Hwang D, Sakai K, et al. Predictors for vulnerable plaque in functionally significant lesions. JACC Cardiovasc Imaging 2025;18:195-206.
14. Scala A, Erriquez A, Cocco M, et al. Coronary atherosclerosis phenotypes in non-flow-limiting nonculprit lesions of older patients with mi stratified by focal and diffuse disease patterns. Circ Cardiovasc Interv 2025;18(7):e015281.