ORIGINAL ARTICLE

Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction

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ABSTRACT

BACKGROUND

In patients with ST-segment elevation myocardial infarction (STEMI) with multivessel coronary artery disease, the time at which complete revascularization of nonculprit lesions should be performed remains unknown.

METHODS

We performed an international, open-label, randomized, noninferiority trial at 37 sites in Europe. Patients in a hemodynamically stable condition who had STEMI and multivessel coronary artery disease were randomly assigned to undergo immediate multivessel percutaneous coronary intervention (PCI; immediate group) or PCI of the culprit lesion followed by staged multivessel PCI of nonculprit lesions within 19 to 45 days after the index procedure (staged group). The primary end point was a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year after randomization. The percentages of patients with a primary or secondary end-point event are provided as Kaplan–Meier estimates at 6 months and at 1 year.

RESULTS

We assigned 418 patients to undergo immediate multivessel PCI and 422 to undergo staged multivessel PCI. A primary end-point event occurred in 35 patients (8.5%) in the immediate group as compared with 68 patients (16.3%) in the staged group (risk ratio, 0.52; 95% confidence interval, 0.38 to 0.72; P<0.001 for noninferiority and P<0.001 for superiority). Nonfatal myocardial infarction and unplanned ischemia-driven revascularization occurred in 8 patients (2.0%) and 17 patients (4.1%), respectively, in the immediate group and in 22 patients (5.3%) and 39 patients (9.3%), respectively, in the staged group. The risk of death from any cause, the risk of stroke, and the risk of hospitalization for heart failure appeared to be similar in the two groups. A total of 104 patients in the immediate group and 145 patients in the staged group had a serious adverse event.

CONCLUSIONS

Among patients in hemodynamically stable condition with STEMI and multivessel coronary artery disease, immediate multivessel PCI was noninferior to staged multivessel PCI with respect to the risk of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year. (Supported by Boston Scientific; MULTISTARS AMI ClinicalTrials.gov number, NCT03135275.)

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Primary percutaneous coronary intervention (PCI) is the strategy of choice to restore blood flow in the culprit artery of patients with acute ST-segment elevation myocardial infarction (STEMI).[1-4] In patients presenting with STEMI, multivessel coronary artery disease is common and is associated with an increased risk of recurrent myocardial infarction and death.[5-8] Evidence from randomized, controlled trials showed that complete revascularization with multivessel PCI was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death, myocardial infarction, and ischemia-driven revascularization at 1 year.[9-14] In particular, the COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) trial showed that among patients with STEMI and multivessel coronary artery disease, the risk of a composite of cardiovascular death or myocardial infarction and the risk of a composite of cardiovascular death, myocardial infarction, or ischemia-driven revascularization were lower in patients with complete revascularization than in patients with PCI of culprit lesions only.[13] Whereas current guidelines recommend complete revascularization in patients with STEMI and multivessel coronary artery disease, the time at which revascularization of nonculprit lesions should be performed — immediately, during the index procedure, or in a staged strategy, after the index procedure — remains unknown.[2-4,15]

The Multivessel Immediate versus Staged Revascularization in Acute Myocardial Infarction (MULTISTARS AMI) trial was designed to investigate whether immediate multivessel PCI at the time of primary PCI was noninferior to staged multivessel PCI in patients in hemodynamically stable condition with STEMI and multivessel coronary artery disease.

Methods

Trial Design and Oversight

The MULTISTARS AMI trial was an investigator-initiated, multinational, randomized, open-label trial that evaluated a strategy of immediate multivessel PCI (multivessel PCI during the index procedure) as compared with a strategy of staged multivessel PCI (PCI of the culprit lesion in the index procedure, followed by PCI of nonculprit lesions between 19 and 45 days after the index procedure) in patients in hemodynamically stable condition who had STEMI and multivessel coronary artery disease. The trial design has been published elsewhere.[16] The protocol (available with the full text of this article at NEJM.org) was designed by the principal investigators and the steering committee and was approved by the ethics committees at all the trial sites. The authors vouch for the integrity and completeness of the data and for the fidelity of the trial to the protocol, and the statisticians vouch for the accuracy of the data analysis. The first author wrote the first draft of the manuscript, and all the authors agreed to submit the manuscript for publication. The trial was supported by Boston Scientific, which had no role in the design of the trial; the collection, analysis, and interpretation of data; or the writing of the manuscript. A detailed list of the participating sites, trial investigators, and oversight committees is provided in the Supplementary Appendix (available at NEJM.org).

A Quick Take is available at NEJM.org

Eligibility

Patients were eligible for the trial if they presented with an acute STEMI within 24 hours after symptom onset and were found to have multivessel coronary artery disease, defined as the presence of angiographically relevant stenosis (stenosis of ≥70% of the artery diameter on coronary angiography, as estimated on the basis of a visual assessment) in at least one nonculprit coronary artery that was at least 2.25 to 5.75 mm in diameter. After undergoing successful PCI of the culprit artery, patients in hemodynamically stable condition who had at least one additional, angiographically relevant lesion in a non–infarct-related artery that was considered to be suitable for PCI were included. Detailed descriptions of stable hemodynamic condition and of the inclusion and exclusion criteria are provided in the Supplementary Appendix. As soon as the coronary intervention was planned and the trial-entry criteria were met, patients provided informed consent according to a trial-specific process to avoid a delay in treatment. The informed consent process is provided in the Supplementary Appendix.

Randomization and Treatment

Patients underwent randomization after successful primary PCI of the culprit artery. The primary PCI was considered to be successful if the culprit artery had a flow grade of 2 or 3 accord-

ing to the Thrombolysis in Myocardial Infarction flow grading system (grades range from 0 to 3, with higher grades indicating better flow) and the patient was in a hemodynamically stable condition. Randomization was performed with the use of a Web-based program (secuTrial; interActive Systems) and variable block sizes. Patients were randomly assigned, in a 1:1 ratio, to undergo immediate multivessel PCI (immediate group) or staged multivessel PCI (staged group). Each PCI was performed according to current guidelines and with the use of standard interventional techniques.[3,4,17] In the immediate group, PCI of nonculprit lesions was performed immediately after revascularization of the infarct-related artery, during the same procedure. In the staged group, PCI of nonculprit lesions was performed between 19 and 45 days after revascularization of the infarct-related artery. A third-generation, biodegradable-polymer, everolimus-eluting stent (Synergy; Boston Scientific) was recommended for PCI. The use of fractional flow reserve–guided PCI or intravascular imaging–guided PCI (including the use of intravascular ultrasonography or optical coherence tomography) was left to the operator's discretion. Thrombus aspiration was performed, and glycoprotein IIb/IIIa inhibitors and dual antiplatelet therapy were administered according to current guidelines.[3,18,19] All the patients received appropriate medical care and secondary preventive measures, including lifestyle recommendations, counseling for smoking cessation, high-intensity statin therapy, and heart-failure medication when indicated.[3,20]

Follow-up was performed at 30 days (±7 days), at 6 months (±14 days), and at 1 year (±14 days). Follow-up by means of a telemedicine visit was allowed during the coronavirus disease 2019 (Covid-19) pandemic. Adherence to the protocol and the completeness of trial-related data capture were monitored at all trial sites.

PRIMARY AND SECONDARY END POINTS

The primary end point was a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year after randomization.[12,14] Secondary end points included a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 6 months after randomization, as well as individual components of the primary end point at 6 months and at 1 year. Other secondary end points are described in the Supplementary Appendix.

The classification of both spontaneous and procedure-related myocardial infarction was based on the Third Universal Definition of Myocardial Infarction.[21] Unplanned ischemia-driven revascularization was defined as revascularization because of angina symptoms, new ischemic changes on electrocardiography (ECG), or signs of reversible myocardial ischemia on noninvasive imaging. Detailed definitions of the end points are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The initial trial design specified that 1200 patients would be required for the analysis of a composite primary end point of death from any cause, nonfatal myocardial infarction, or unplanned ischemia-driven revascularization at 1 year. In July 2019, after inclusion of 217 patients and because of slow enrollment, the steering committee approved the change of the primary end point to a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year.

On the basis of an estimated 18% incidence of a primary end-point event in each trial group,[11,12] a noninferiority risk ratio of 1.46, and a one-sided significance level of 0.05, we calculated that a sample size of 800 patients would be needed to rule out the null hypothesis of the inferiority of immediate multivessel PCI to staged multivessel PCI. The noninferiority margin is in line with that in previous studies in patients with multivessel coronary artery disease.[22-24] To allow for a 5% dropout rate, 840 patients were recruited. No interim analysis was performed.

The primary analysis was performed according to the intention-to-treat principle. Sensitivity analyses were performed in the per-protocol population to evaluate the robustness of the results of the primary analysis. Protocol violations were assessed by the steering committee, and the per-protocol population was defined on the basis of the committee's recommendations. We used a one-sided Farrington–Manning score test to analyze the noninferiority of immediate multi-

vessel PCI to staged multivessel PCI with respect to the primary end point and calculated the risk ratio and 95% confidence interval. If immediate multivessel PCI was found to be noninferior to staged multivessel PCI, a prespecified superiority analysis would be performed with the use of a log-rank test. Primary and secondary time-to-event end points were analyzed on a time-to-first-event basis. The percentages of patients with a primary or secondary end-point event at 6 months and at 1 year are provided as Kaplan–Meier estimates. Cumulative incidence curves were calculated to visualize events in both groups during the follow-up period. End points that did not include death from any cause were adjusted for the competing risk of death. Survival analyses of the primary end point were performed as landmark analyses, with assessment of events occurring before day 45 and those occurring on or after day 45 and assessment of events occurring through month 6 and those occurring after month 6, to permit the assessment of time-dependent differences between the two trial groups.

Results of prespecified subgroup analyses of the primary end point are presented as forest plots of the risk ratios and 95% confidence intervals for comparisons between the two trial groups. Effect sizes for secondary end points are presented as hazard ratios, risk ratios, or Wilcoxon–Mann–Whitney odds ratios (quality-of-life data) with corresponding 95% confidence intervals. Results are reported as point estimates and 95% confidence intervals; adjustment for multiplicity was not performed, and the 95% confidence intervals should not be used to infer definitive treatment effects for secondary end points.

No imputation of missing data was performed, with the exception of the analysis of the quality-of-life data. For the time-to-event analyses, data from patients were censored on the date of the last known contact with the patient. Sample size calculation and all statistical analyses were performed with the use of SAS software, version 9.4, for Windows (SAS Institute).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Immediate Group (N=418)	Staged Group (N=422)
Median age (IQR) — yr	66 (58–74)	64 (55–73)
Male sex — no. (%)	321 (76.8)	341 (80.8)
Race — no. (%)†		
White	409 (97.8)	416 (98.6)
Black	1 (0.2)	2 (0.5)
Asian	8 (1.9)	4 (0.9)
Medical history — no./total no. (%)		
Hypertension	228/418 (54.5)	212/422 (50.2)
Diabetes	66/418 (15.8)	65/422 (15.4)
Dyslipidemia	112/418 (26.8)	114/420 (27.1)
Previous PCI	33/417 (7.9)	23/422 (5.5)
Previous myocardial infarction	28/417 (6.7)	20/421 (4.8)
Previous stroke	7/418 (1.7)	11/422 (2.6)
Peripheral artery disease	11/417 (2.6)	8/422 (1.9)
Family history of CAD	108/415 (26.0)	114/421 (27.1)
Smoking history — no./total no. (%)		
Former	78/414 (18.8)	57/421 (13.5)
Current	140/413 (33.9)	149/421 (35.4)
Presentation — no./total no. (%)		
Resuscitation before hospital arrival	14/418 (3.3)	18/422 (4.3)
Left bundle-branch block	5/411 (1.2)	6/414 (1.4)
Location of myocardial infarction — no./total no. (%)		
Anterior	162/409 (39.6)	167/405 (41.2)
Inferior	55/409 (13.4)	46/405 (11.4)
Lateral	172/409 (42.1)	169/405 (41.7)
Posterior	91/409 (22.2)	80/405 (19.8)

* The immediate group underwent immediate multivessel PCI; the staged group underwent PCI of the culprit lesion followed by staged multivessel PCI of nonculprit lesions within 19 to 45 days after the index procedure. CAD denotes coronary artery disease, IQR interquartile range, and PCI percutaneous coronary intervention.
† Race was reported by the investigator.

RESULTS

PATIENTS

From October 2016 through June 2022, a total of 2907 patients with STEMI were screened at 37 sites in Europe. We randomly assigned 418 of these patients to the immediate group and 422 to the staged group (Fig. S1 in the Supplementary Appendix). Follow-up was complete in 409 patients (97.8%) in the immediate group and in 411 patients (97.4%) in the staged group. Baseline characteristics are reported in Table 1. The per-protocol population consisted of 375 patients in the immediate group and 346 patients in the staged group (Fig. S2). The

Table 2. Procedural Characteristics.

Characteristic	Immediate Group (N=418)	Staged Group (N=422)
Location of culprit lesion — no. (%)		
Left main coronary artery	—	1 (0.2)
Left anterior descending coronary artery	163 (39.0)	176 (41.7)
Left circumflex coronary artery	67 (16.0)	77 (18.2)
Right coronary artery	188 (45.0)	169 (40.0)
Location of nonculprit lesions undergoing PCI — no./total no. (%)		
Left main coronary artery	1/402 (0.2)	4/362 (1.1)
Left anterior descending coronary artery	205/402 (51.0)	180/362 (49.7)
Left circumflex coronary artery	196/402 (48.8)	152/362 (42.0)
Right coronary artery	134/402 (33.3)	124/363 (34.2)
No. of vessels with relevant nonculprit lesions — no./total no. (%)		
1	316/380 (83.2)	275/342 (80.4)
≥2	64/380 (16.8)	67/342 (19.6)
Access site for index procedure — no./total no. (%)		
Radial artery	301/418 (72.0)	311/422 (73.7)
Femoral artery	117/418 (28.0)	111/422 (26.3)
Access site for staged procedure — no./total no. (%)		
Radial	—	296/386 (76.7)
Femoral	—	90/386 (23.3)
Method of PCI guidance — no./total no. (%)		
Fractional flow reserve	12/418 (2.9)	36/386 (9.3)
Intravascular ultrasonography	8/418 (1.9)	8/386 (2.1)
Optical coherence tomography	2/418 (0.5)	7/386 (1.8)
Stents used per patient		
Index procedure		
Median (IQR) — no.	3 (2–4)	1 (1–2)
No. of patients with data	417	421
Index plus staged procedures		
Median (IQR) — no.	—	3 (2–4)
No. of patients with data	—	357
Total stent length		
Index procedure		
Median (IQR) — mm	64 (44–90)	32 (24–48)
Patients with data	417	421
Index plus staged procedures		
Median (IQR) — mm	—	72 (52–102)
No. of patients with data	—	357
Volume of contrast material		
Index procedure		
Median (IQR) — ml	250 (199–320)	170 (130–220)

Table 2. (Continued.)

Characteristic	Immediate Group (N=418)	Staged Group (N=422)
No. of patients with data	415	419
Index plus staged procedures		
Median (IQR) — ml	—	333 (258–411)
No. of patients with data	—	380
Duration of fluoroscopy		
Index procedure		
Median (IQR) — min	18 (13–25)	10 (7–16)
No. of patients with data	410	415
Index plus staged procedures		
Median (IQR) — min	—	24 (16–34)
No. of patients with data	—	372
Duration of procedure		
Index procedure		
Median (IQR) — min	73 (58–93)	52 (40–69)
No. of patients with data	416	421
Index plus staged procedures		
Median (IQR) — min	—	105 (80–138)
No. of patients with data	—	380
Time from index procedure to staged procedure		
Median (IQR) — days	—	37 (30–43)
No. of patients with data	—	386
Hospital stay		
Index procedure		
Median (IQR) — days	4 (3–6)	4 (3–6)
Patients with data	410	408
Index plus staged procedures		
Median (IQR) — days	—	5 (4–7)
Patients with data	—	370

representativeness of the trial population is shown in Table S1.

TREATMENT

Procedural characteristics are shown in Table 2 and Table S2. Crossover from the immediate group to the staged group occurred in 12 patients (2.9%), whereas crossover from the staged group to the immediate group was not observed. Reasons for crossover are provided in Table S3. In patients who underwent staged multivessel PCI, the median time from randomization to the staged intervention was 37 days (interquartile range, 30 to 43). In the staged group, the intervention was performed as an outpatient procedure in 10 patients (2.6%).

PRIMARY AND SECONDARY END POINTS

At 1 year, a primary end-point event — a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure — occurred in 35 patients (8.5%) in the immediate group as compared with 68 patients (16.3%) in the staged group (risk ratio, 0.52; 95% confidence interval [CI], 0.38 to 0.72; P<0.001 for noninferiority and P<0.001 for superiority) (Table 3 and Fig. 1).

Table 3. Primary and Secondary End Points.*

End Point	Immediate Group (N=418)	Staged Group (N=422)	Treatment Effect (95% CI)
Primary end point at 1 yr			
Death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure — no. (%)	35 (8.5)	68 (16.3)	0.52 (0.38–0.72)†
Secondary end points at 1 yr‡			
Death from any cause — no. (%)	12 (2.9)	11 (2.6)	1.10 (0.48–2.48)§
Nonfatal myocardial infarction — no. (%)	8 (2.0)	22 (5.3)	0.36 (0.16–0.80)§
Stroke — no. (%)	5 (1.2)	7 (1.7)	0.72 (0.23–2.26)§
Unplanned ischemia-driven revascularization — no. (%)	17 (4.1)	39 (9.3)	0.42 (0.24–0.74)§
Hospitalization for heart failure — no. (%)	5 (1.2)	6 (1.4)	0.84 (0.26–2.74)§
Death from any cause or nonfatal myocardial infarction — no. (%)	19 (4.6)	32 (7.7)	0.58 (0.33–1.03)§
Cardiac death — no. (%)	5 (1.2)	6 (1.4)	0.84 (0.26–2.74)§
Vascular death — no. (%)	1 (0.2)	0 (0.0)	—
Noncardiovascular death — no. (%)	6 (1.4)	5 (1.2)	1.21 (0.37–3.95)§
Cardiac death or nonfatal myocardial infarction — no. (%)	12 (2.9)	27 (6.5)	0.44 (0.22–0.87)§
Target-vessel revascularization — no. (%)	10 (2.4)	12 (2.9)	0.83 (0.36–1.93)§
Target-lesion revascularization — no. (%)	9 (2.2)	12 (2.9)	0.75 (0.32–1.78)§
Stent thrombosis — no. (%)	5 (1.2)	6 (1.4)	0.84 (0.26–2.75)§
Acute renal insufficiency or renal-replacement therapy — no. (%)	15 (3.6)	13 (2.9)	1.26 (0.59–2.70)§
Major bleeding — no. (%)¶	13 (3.1)	21 (4.8)	0.65 (0.32–1.31)§
Procedural success — no./total no. (%)	347/383 (90.6)	308/338 (91.1)	0.94 (0.56–1.56)‖
Median EQ-5D-5L index score (IQR)**	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.02 (0.91–1.12)††

* The percentages of patients with a primary or secondary end-point event are provided as Kaplan–Meier estimates.
† The treatment effect is the risk ratio with 95% confidence interval for a primary end-point event in the immediate group as compared with the staged group. Values were calculated with the Farrington–Manning score test. P<0.001 for noninferiority of immediate multivessel PCI to staged multivessel PCI, and P<0.001 for superiority.
‡ Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects.
§ The treatment effect is the hazard ratio with 95% confidence interval for the event in the immediate group as compared with the staged group. Values were calculated with the Fine and Gray model considering competing risk all-cause death.
¶ Major bleeding was assessed by the investigator as a type 3 or 5 event on the Bleeding Academic Research Consortium scale, with a type 3 event defined as any clinical, laboratory, or imaging evidence of bleeding and a type 5 event as fatal bleeding.
‖ The treatment effect is the odds ratio with 95% confidence interval for the response in the immediate group as compared with the staged group. Values were calculated with the asymptotic Wald method.
** The European Quality of Life–5-Dimension–5-Level (EQ-5D-5L) questionnaire was used to assess quality of life. The EQ-5D-5L index score ranges from –0.661 to 1.0, with higher scores indicating better quality of life. Data are for 402 patients in the immediate group and 405 patients in the staged group. Values of zero were imputed for patients who died during follow-up (13 patients in the immediate group and 10 patients in the staged group), and data were imputed for one dimension for 1 patient in the immediate group at 6 months.
†† The treatment effect is the odds ratio with 95% confidence interval for the response in the immediate group as compared with the staged group. Values were calculated according to the Mann–Whitney measure of superiority.

The percentage of patients who died from any cause did not appear to differ between the two groups (hazard ratio, 1.10; 95% CI, 0.48 to 2.48) (Table 3 and Fig. S3 and Table S4). Nonfatal myocardial infarction occurred in 8 patients (2.0%) in the immediate group and in 22 pa-

tients (5.3%) in the staged group (hazard ratio, 0.36; 95% CI, 0.16 to 0.80) (Table 3). In the staged group, 7 of the 22 nonfatal myocardial infarctions occurred before the staged intervention. Procedure-related myocardial infarctions were observed in 3 patients in the immediate group and in 14 patients in the staged group (Table S5). No apparent differences in the percentage of patients with spontaneous myocardial infarction were observed in the trial groups. In an exploratory analysis in which procedure-related myocardial infarctions were excluded, a primary end-point event occurred in 34 patients (8.2%) in the immediate group and in 59 patients (14.1%) in the staged group (hazard ratio, 0.55; 95% CI, 0.36 to 0.84) and nonfatal myocardial infarctions occurred in 5 patients (1.2%) in the immediate group and in 8 patients (1.9%) in the staged group (hazard ratio, 0.62; 95% CI, 0.20 to 1.89).

The percentage of patients with stroke did not appear to differ between the immediate group and the staged group (Table 3). A total of 17 patients (4.1%) in the immediate group and 39 patients (9.3%) in the staged group underwent unplanned ischemia-driven revascularization (hazard ratio, 0.42; 95% CI, 0.24 to 0.74) (Table 3 and Fig. S3). In 1 patient in the immediate group and in 7 patients in the staged group, unplanned ischemia-driven revascularization was performed during the index hospitalization. In the staged group, 23 of the 39 patients underwent unplanned ischemia-driven revascularization before the staged intervention. Of these 23 patients, 2 patients had cardiac arrest prompting unplanned revascularization; 1 patient had cardiogenic shock due to severe mitral regurgitation and underwent emergency coronary-artery bypass grafting and mitral-valve surgery; 1 patient had angina symptoms, an elevated cardiac troponin level, and dynamic ECG changes; 2 patients had angina symptoms and an elevated cardiac troponin level; 3 patients had angina symptoms and dynamic ECG changes; 1 patient had an elevated cardiac troponin level and dynamic ECG changes; and 13 patients had isolated angina. Rates of hospitalization for heart failure did not appear to differ between the groups (Table 3). Major bleeding (type 3 or 5 event on the Bleeding Academic Research Consortium scale, with a type 3 event defined as any clinical, laboratory, or imaging evidence of bleeding and a type 5 event as fatal bleeding) was reported in 13 patients (3.1%) in the immediate group and in 21 patients (4.8%) in the staged group (hazard ratio, 0.65; 95% CI, 0.32 to 1.31) (Table 3 and Fig. S4).

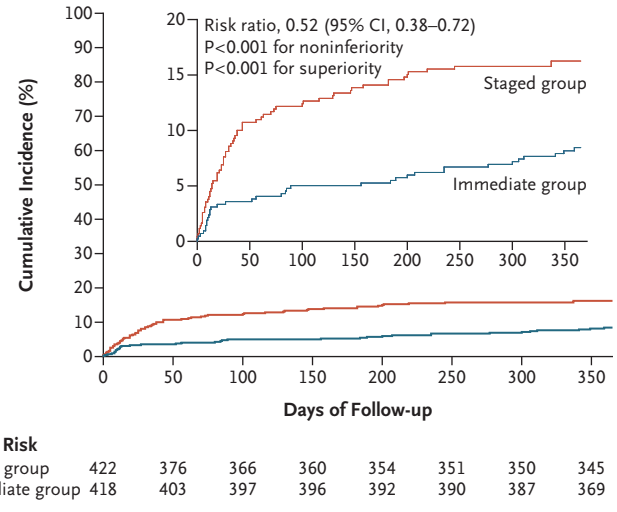

Figure 1. Cumulative Incidence of the Primary End Point.

The primary end point was a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year. The immediate group underwent immediate multivessel PCI; the staged group underwent PCI of the culprit lesion followed by staged multivessel PCI of nonculprit lesions within 19 to 45 days after the index procedure. The inset shows the same data on an enlarged y-axis.

In the per-protocol population, a primary end-point event occurred in 31 of 375 patients (8.3%) in the immediate group and in 58 of 346 patients (16.5%) in the staged group (risk ratio, 0.50; 95% CI, 0.36 to 0.71). For the primary end point, there was no apparent differential treatment effect in the prespecified subgroups (Fig. 2).

During the 45 days after randomization, a primary end-point event occurred in 15 patients (3.6%) in the immediate group and in 45 patients (10.7%) in the staged group (hazard ratio, 0.33; 95% CI, 0.18 to 0.59) (Fig. S5). Between day 45 and 1 year, the incidence of a primary end-point event did not appear to differ between the two groups (hazard ratio, 0.86; 95% CI, 0.47 to 1.57). During the first 6 months after randomization, a primary end-point event occurred in 22 patients (5.3%) in the immediate group and in 59 patients (14.1%) in the staged group (hazard ratio, 0.36; 95% CI, 0.22 to 0.59) (Table S6).

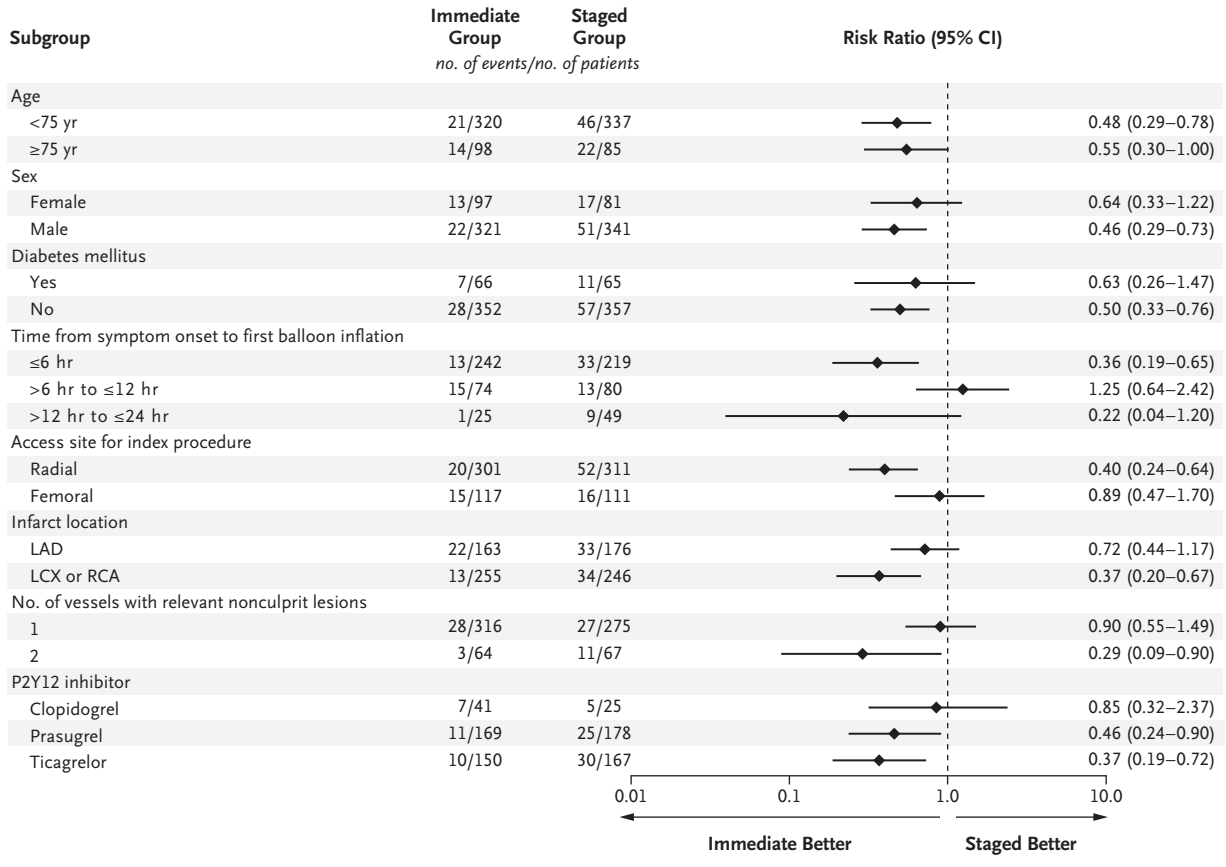

Figure 2. Subgroup Analyses of the Primary End Point.

The primary end point was a composite of all-cause death, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year. The risk ratios and associated 95% confidence intervals were calculated with the Farrington–Manning score test. LAD denotes left anterior descending coronary artery, LCX left circumflex coronary artery, and RCA right coronary artery.

During the interval from 7 months to 1 year, the percentage of patients with a primary endpoint event did not differ significantly between the two groups (hazard ratio, 1.46; 95% CI, 0.62 to 3.40).

SAFETY

A total of 104 patients in the immediate group and 145 patients in the staged group had a serious adverse event (Table S7).

DISCUSSION

The results of the MULTISTARS AMI trial showed that, in patients with STEMI and multivessel coronary artery disease, immediate multivessel PCI was noninferior to staged multivessel PCI with respect to the risk of a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year. Several randomized, controlled trials have shown that complete revascularization is safe and reduces the risk of recurrent myocardial infarction and future revascularization in patients in hemodynamically stable condition who have STEMI and multivessel coronary artery disease.[9-13] A prespecified analysis in the COMPLETE trial suggested that the benefit of complete revascularization as compared with culprit-lesion-only PCI was consistent irrespective of the timing (determined by the investigator) of the nonculprit-lesion PCI and that the benefit emerged mainly over the long term.[25] In the COMPLETE

trial, however, complete revascularization was performed as a staged procedure in all patients, and immediate PCI of nonculprit lesions during the index STEMI procedure was not a comparator.[13] The results of the MULTISTARS AMI trial support and extend the findings of the COMPLETE trial by showing that immediate multivessel PCI during the procedure for the index STEMI is noninferior to staged multivessel PCI. Of note, whereas the COMPLETE trial and the MULTISTARS AMI trial enrolled only patients with STEMI, the recently published BIOVASC trial, which showed that a strategy of immediate complete revascularization was noninferior to a strategy of staged complete revascularization, enrolled patients across the spectrum of acute coronary syndromes, including unstable angina, non–ST-segment elevation myocardial infarction, and STEMI.[14]

In a finding consistent with that in recent randomized trials,[14] the MULTISTARS AMI trial showed that nonfatal myocardial infarction and unplanned ischemia-driven revascularization occurred in a higher percentage of patients in the staged multivessel PCI group than in the immediate multivessel PCI group, particularly during the first 45 days after randomization. Although procedure-related myocardial infarctions secondary to nonculprit-lesion PCI in the immediate group might have gone undetected because of the increased levels of biomarkers and the presence of clinical symptoms of STEMI, an analysis that excluded procedure-related myocardial infarctions (type 4) was supportive of the main results. Unstable plaque features in nonculprit lesions that have been described in patients with STEMI may confer a predisposition to plaque rupture and subsequent coronary events when PCI of nonculprit lesions is performed as a staged intervention.[26-28] Improved coronary blood flow in nonculprit vessels after immediate multivessel PCI may reduce the ischemic burden during the early phase of a STEMI event.

Between-group differences in the primary end point in our trial were driven by a lower risk of nonfatal myocardial infarction and of early unplanned ischemia-driven revascularization in the immediate group than in the staged group. Revascularization of nonculprit lesions performed between the initial procedure and the planned date of the staged intervention was defined as unplanned ischemia-driven revascularization when the procedure was performed because of angina symptoms, ischemic changes on ECG, or signs of reversible myocardial ischemia on noninvasive imaging.[14] This definition was used to distinguish planned staged procedures (which were performed according to the preference of the operator or the patient) from unplanned ischemia-driven procedures, a distinction that reduced the risk of overestimating the event rates. However, given the open-label trial design, we cannot exclude the possibility that patients in the staged group might have been more likely to be referred for earlier ischemia-driven intervention when the coronary anatomy was known.

An immediate multivessel PCI approach may also reduce the amount of total contrast volume and radiation exposure and may avoid the need for an additional arterial puncture, later revascularization procedures, or a second hospitalization, thereby potentially shortening the overall length of hospital stay.[15,29] In addition, immediate multivessel PCI may be preferred by some patients because delaying the treatment of nonculprit lesions may be worrisome to them.[15]

Our trial has limitations that should be considered. The primary end point was expanded during the course of the trial because of slow enrollment, and the addition of stroke and hospitalization for heart failure to the composite primary end point may have introduced a bias toward noninferiority, although rates of stroke and hospitalization for heart failure were relatively low and did not appear to differ between the trial groups. The trial was performed during the Covid-19 pandemic, which affected patient recruitment and may have delayed the procedures in some patients.[30] The small percentage of women included in the trial represents a limitation, as in recent cardiovascular trials. Our findings do not apply to patients who present with cardiogenic shock, left main coronary-artery disease, a chronic total occlusion, or previous coronary-artery bypass graft surgery, since these patients were excluded from our trial. The window of 19 to 45 days for staged multivessel PCI, along with the exclusion of patients with stent thrombosis, in-stent restenosis, and chronic total occlusion, may also have introduced a bias toward noninferiority. The complexity of the nonculprit lesions may have influenced whether the operators included or excluded

patients. In line with previous trials and reflecting contemporary clinical practice,[13,14,31] the indication for nonculprit-lesion PCI in patients with STEMI was based primarily on a visual assessment of the coronary angiogram, and no conclusions about the role of functional lesion assessment (fractional flow reserve or resting indexes) in this setting can be drawn. The use of intravascular imaging in our trial was also rather low. We also acknowledge the challenge that the diagnosis of procedure-related myocardial infarction in patients with STEMI may pose in the immediate and staged groups, and an increased risk of ascertainment bias for procedure-related myocardial infarction in the context of primary PCI as compared with staged elective PCI may have favored the immediate group. However, there did not appear to be a substantial difference in the risk of a primary end-point event in the trial groups after exclusion of procedure-related myocardial infarctions from the analysis.

Among patients in hemodynamically stable condition with STEMI and multivessel coronary artery disease, immediate multivessel PCI was noninferior to staged multivessel PCI with respect to the risk of a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year.

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APPENDIX

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