MULTivessel Immediate versus STAged RevaScularization in Acute Myocardial Infarction (MULTISTARS AMI)

A randomized study of immediate versus staged revascularization after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

August 27, 2023

Background

- Patients with acute ST-segment elevation myocardial infarction (STEMI) frequently present with **multivessel coronary artery disease (MVD)**.[1]
- Previous studies support **complete revascularization** in patients with STEMI and MVD.[2]
- The **optimal timing** of revascularization of non-culprit lesions, i.e. immediate versus staged percutaneous coronary intervention (PCI), remains unknown.[3,4]
- The **MULTISTARS AMI** trial was designed to address this evidence gap in STEMI patients.[5]

Study Design

- The MULTISTARS AMI trial was an multinational, randomized, open-label trial that evaluated a strategy of multivessel PCI during the index procedureas 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 indexre) in patients in hemodynamically stable condition who had STEMI and multivessel coronary artery disease.

- 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 according to the Thrombolysis in Myocardial Infarction flow grading system and the patient was in a hemodynamically stable condition

- Eligible patients were randomized in a 1:1 open-label fashion to either immediate PCI or staged PCI. 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 within 19-45 days after revascularization of the infarct-related artery (median 37 days).

- A third-generation, biodegradable-polymer, everolimus-eluting Synergy stent (Boston Scientific Corporation, Marlborough, MA) was recommended for PCI. Fractional flow reserve (FFR) and intravascular ultrasound (IVUS) use was up to individual operators.

- Follow-up was performed at 30 days (±7 days), at 6 months (±14 days), and at 1 year (±14 days)

Inclusion criteria:

- Acute STEMI within 24 hours of symptom onset

Found to have multivessel CAD, defined as at least one additional angiographically relevant (≥70% diameter stenosis on coronary angiography based on visual estimation) stenosis in a nonculprit coronary artery that was ≥2.25-5.75 mm in diameter

- Successful PCI of the culprit artery
- Hemodynamically stable
- At least one additional angiographically relevant lesion in a non–infarct-related artery suitable for PCI

Key Exclusion Criteria

- Cardiogenic shock
- Need for emergency coronary artery bypass graft surgery
- Previous coronary artery bypass graft surgery
- Stent thrombosis
- In-stent restenosis
- Chronic total occlusion of a major coronary artery
- Left main disease or left main equivalent with ostial LAD or ostial LCX stenosis
- Any contraindications for dual antiplatelet therapy for at least 90 days (except for patients on oral anticoagulation)

Primary Objective

- Primary end point: A composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year.

- Secondary end points included a composite of death from any cause, nonfatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalizationfor heart failure at 6 months after randomization.

- 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.

Study Design

Patients with acute STEMI and MVD after successful PCI of the culprit artery

MVD was defined as at least one non-culprit coronary artery (2.25 ≤mm and 5.75 ≥mm) with 70% ≤diameter stenosis on coronary angiography

1:1 randomization

Immediate PCI xedni gnirud) tirpluc-non fo (erudecorp snoisel N=418

**everolimus-eluting stent was recommended*

Staged PCI (within 19 to 45 days) of non-culprit lesions

N=422

Primary end point: all-cause death, non-fatal myocardial infarction, stroke, ischemia-driven revascularization, or hospitalization for heart failure at 1 year

Study Power and Follow-up

- Based on an estimated rate of the primary end point of **18%** in both arms
  - a non-inferiority risk ratio of 1.46 and a one-sided significance level of 0.05,
  - a sample size of 800 patients was calculated to rule out the null hypothesis of the inferiority of immediate multivessel PCI compared to a staged procedure.
  - To allow for a 5% drop-out rate, a total of **840 patients** were recruited.
- **Recruitment:** October 2016 to June 2022, 37 sites in Europe.
- **Analysis:** Intention-to-treat, non-inferiority of the primary end point was analyzed using a one-sided Farrington-Manning score test and risk ratio and 95% confidence interval were calculated.
- **Follow-up (vital status):** 97.8% in the immediate PCI group and 97.4% in the staged PCI group.

Baseline Characteristics

	Immediate PCI (n=418)	Staged PCI (n=422)
Age, years – median (IQR)	66 (58-74)	64 (55-73)
Male sex – no. (%)	321 (76.8)	341 (80.8)
Medical history		
Hypertension – no. (%)	228 (54.5)	212 (50.2)
Diabetes – no. (%)	66 (15.8)	65 (15.4)
Dyslipidemia – no. (%)	112 (26.8)	114/420 (27.1)
Previous PCI – no. (%)	33/417 (7.9)	23 (5.5)
Previous myocardial infarction – no. (%)	28 /417 (6.7)	20/421 (4.8)
Previous stroke – no. (%)	7 (1.7)	11 (2.6)
Family history of CAD – no. (%)	108/415 (26.0)	114/421 (27.1)
Smoking history		
Former – no. (%)	78/414 (18.8)	57/421 (13.5)
Current – no. (%)	140/413 (33.9)	149/421 (35.4)
Presentation		
Resuscitation prior to hospital arrival – no. (%)	14 (3.3)	18 (4.3)
Left bundle branch block – no. (%)	5/411 (1.2)	6/414 (1.4)

Procedural Characteristics

	Immediate PCI (n=418)	Staged PCI (n=422)
Location of culprit lesions – no. (%)		
Left main	-	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)
Number of vessels with significant non-culprit lesions – 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. (%)		
Radial	301/418 (72.0)	311/422 (73.7)
Femoral	117/418 (28.0)	111/422 (26.3)
Access site for staged procedure – no. (%)		
Radial	-	296/386 (76.7)
Femoral	-	90/386 (23.3)
Hospital stay, days – median (IQR)		
Index procedure	4 (3-6), n=410	4 (3-6), n=408
Index plus staged procedures	-	5 (4-7), n=370
Time to staged procedure, days – median (IQR)	-	37 (30-43), n=386

Procedural Characteristics

	Immediate PCI (n=418)	Staged PCI (n=422)
Peri-procedural antiplatelet drugs – no. (%)		
Clopidogrel	41/417 (9.8)	25/422 (5.9)
Ticagrelor	150/418 (35.9)	167/422 (39.6)
Prasugrel	169/418 (40.4)	178/422 (42.2)
GP IIb/IIIa inhibitor	42/418 (10.0)	39/422 (9.2)
Fractional flow reserve – no. (%)	12/418 (2.9)	36/386 (9.3)
Intravascular ultrasound – no. (%)	8/418 (1.9)	8/386 (2.1)
Optical coherence tomography – no. (%)	2/418 (0.5)	7/386 (1.8)
Contrast use, ml – median (IQR)		
Index procedure	250 (199-320), n=415	170 (130-220), n=419
Index plus staged procedures	-	333 (258-411), n=380
Fluoroscopy time, min – median (IQR)		
Index procedure	18 (13-25), n=410	10 (7-16), n=415
Index plus staged procedures	-	24 (16-34), n=372
Procedure duration, min – median (IQR)		
Index procedure	73 (58-93), n=416	52 (40-69), n=421
Index plus staged procedures	-	105 (80-138), n=380

RESULTS

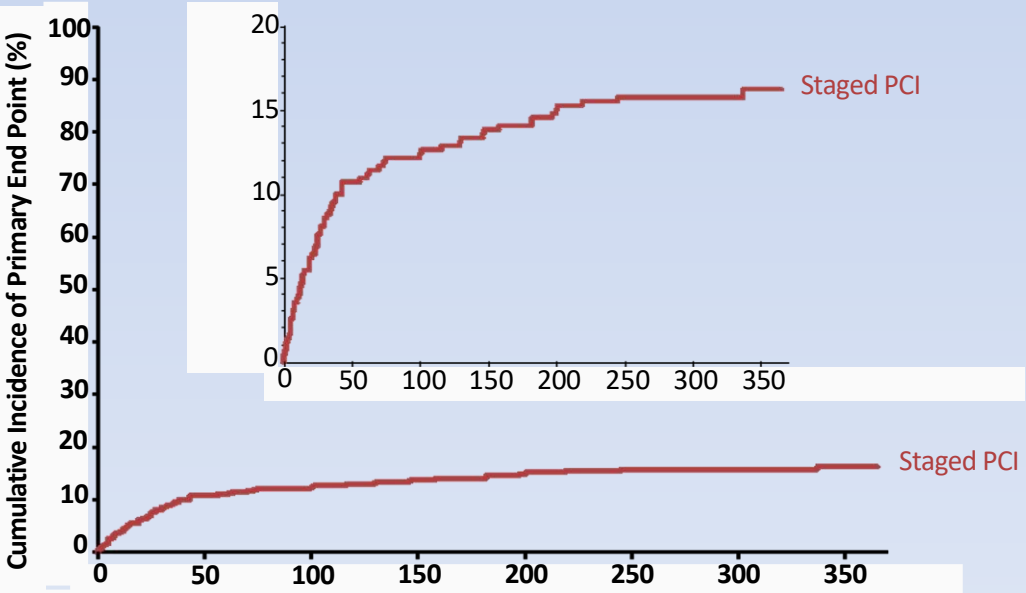
- The primary endpoint, (all-cause death, nonfatal MI, stroke, unplanned ischemia-driven target lesion revascularization [ID-TLR], hospitalization for heart failure) at 1 year, for immediate vs. staged PCI, was: 8.5% vs. 16.3% (relative risk 0.52, 95% confidence interval 0.38-0.72; p for non inferiority < 0.001; p for superiority < 0.001).

Primary and Secondary Outcomes

	Immediate PCI (n=418) no. (%)	Staged PCI (n=422) no. (%)	Treatment effect
Primary end point			
Death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure	35 (8.5)	68 (16.3)	0.52 (0.38 to 0.72)
Secondary end points at 1 year			
Death	12 (2.9)	11 (2.6)	1.10 (0.48 to 2.48)
Non-fatal myocardial infarction	8 (2.0)	22 (5.3)	0.36 (0.16 to 0.80)
Stroke	5 (1.2)	7 (1.7)	0.72 (0.23 to 2.26)
Unplanned ischemia-driven revascularization	17 (4.1)	39 (9.3)	0.42 (0.24 to 0.74)
Hospitalization for heart failure	5 (1.2)	6 (1.4)	0.84 (0.26 to 2.74)
Death or non-fatal myocardial infarction	19 (4.6)	32 (7.7)	0.58 (0.33 to 1.03)
Cardiac death	5 (1.2)	6 (1.4)	0.84 (0.26 to 2.74)
Target vessel revascularization	10 (2.4)	12 (2.9)	0.83 (0.36 to 1.93)
Target lesion revascularization	9 (2.2)	12 (2.9)	0.75 (0.32 to 1.78)
Stent thrombosis	5 (1.2)	6 (1.4)	0.84 (0.26 to 2.75)
Acute kidney failure	15 (3.6)	13 (2.9)	1.26 (0.59 to 2.70)
Major bleeding (BARC 3 or 5)	13 (3.1)	21 (4.8)	0.65 (0.32 to 1.31)
Procedural success	347/383 (90.6)	308/338 (91.1)	0.94 (0.56 to 1.56)
Quality of life (EQ-5D-5L index)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.02 (0.91 to 1.12)

Primary Outcome

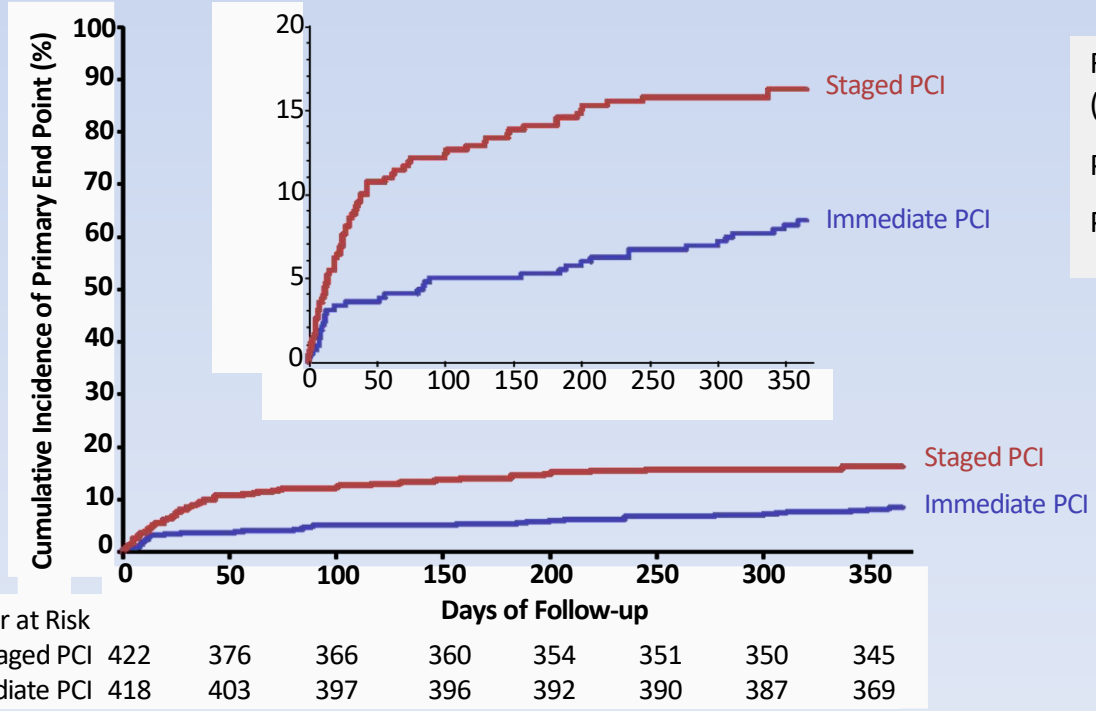
Composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year



Number at Risk								
Staged PCI	422	376	366	360	354	351	350	345
Immediate PCI	418	403	397	396	392	390	387	369

Primary Outcome

Composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure at 1 year



Number at Risk								
Staged PCI	422	376	366	360	354	351	350	345
Immediate PCI	418	403	397	396	392	390	387	369

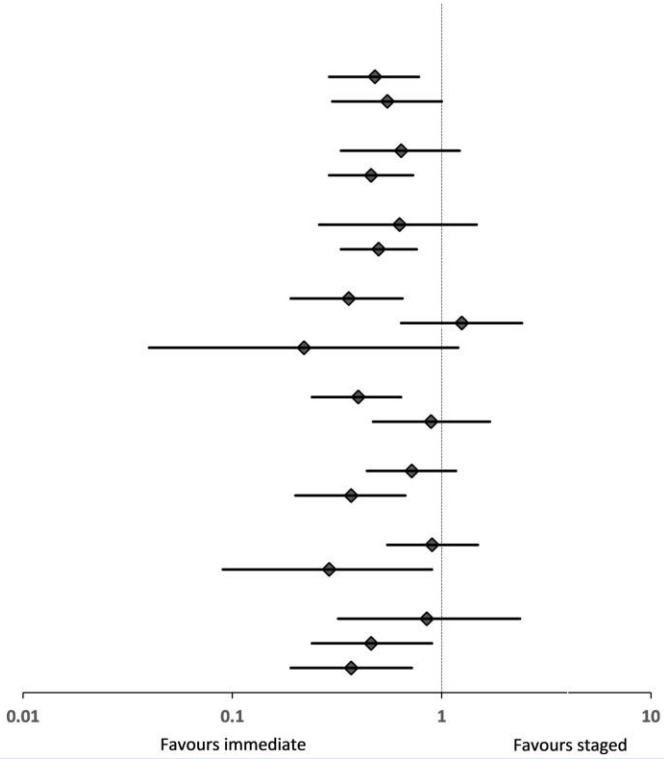
Risk ratio 0.52
(95% CI 0.38 to 0.72)

$P_{non\text{-}inferiority} < 0.0001$

$P_{superiority} = 0.0004$

Subgroup Analyses

Subgroup	Immediate Group events/patients	Staged Group events/patients	Risk Ratio (95% CI)
Age			
<75 yr	21/320	46/337	0.48 (0.29 - 0.78)
≥75 yr	14/98	22/85	0.55 (0.30 - 1.00)
Sex			
Female	13/97	17/81	0.64 (0.33 - 1.22)
Male	22/321	51/341	0.46 (0.29 - 0.73)
Diabetes			
Yes	7/66	11/65	0.63 (0.26 - 1.47)
No	28/352	57/357	0.50 (0.33 - 0.76)
Time from symptom onset to first balloon inflation			
<6 hr	13/242	33/219	0.36 (0.19 - 0.65)
≥6 hr to ≤12 hr	15/74	13/80	1.25 (0.64 - 2.42)
>12 hr to ≤24 hr	1/25	9/49	0.22 (0.04 - 1.20)
Access site for index procedure			
Radial	20/301	52/311	0.40 (0.24 - 0.64)
Femoral	15/117	16/111	0.89 (0.47 - 1.70)
Infarct location			
LAD	22/163	33/176	0.72 (0.44 - 1.17)
LCX or RCA	13/255	34/246	0.37 (0.20 - 0.67)
Number of vessels with relevant nonculprit lesions			
1	28/316	27/275	0.90 (0.55 - 1.49)
≥2	3/64	11/67	0.29 (0.09 - 0.90)
P_2Y_{12} inhibitor			
Clopidogrel	7/41	5/25	0.85 (0.32 - 2.37)
Prasugrel	11/169	25/178	0.46 (0.24 - 0.90)
Ticagrelor	10/150	30/167	0.37 (0.19 - 0.72)



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.Several randomized, controlled trials have shown that complete revascularization is safe.

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.

In a finding consistent with that in recent randomized trials,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 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.In addition, immediate multivessel PCI may be preferred by some patients because delaying the treatment of nonculprit lesions may be worrisome to them.

LIMITATION

- The small percentage of women included in the trial
- 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 multi-vessel PCI, along with the exclusion of patients with stent thrombosis, in-stent restenosis, and chronic total occlusion, may also have introduced a bias toward non-inferiority.
- The complexity of the non-culprit lesions may have influenced whether the operators included or excluded patients.
- the indication for non-culprit-lesion PCI in patients with STEMI was based primarily on a visual assessment of the coronary angiogram and The use of IVUS and FFR in our trial was also low.

Conclusions

The MULTISTARS AMI trial demonstrates that in patients with STEMI and MVD immediate multivessel PCI is non-inferior to staged multivessel PCI based on the 1-year risk for the composite of all-cause death, non-fatal myocardial infarction, stroke, unplanned ischemia-driven revascularization, or hospitalization for heart failure.

- این مقاله روی ۲۹۰۷ بیمار انفارکتوس حاد قلبی در ۳۷ مرکز در اروپا از اکتبر ۲۰۱۶ تا ژوئن ۲۰۲۲ انجام شد. بیماران بطور تصادفی ۱ به ۱ به دو گروه "درمان فوری چند رگ بعد از انفارکتوس حاد قلبی = Immediate group، ۴۱۸نفر و PCI مرحله ای Staged group=، ۴۲۲ نفر۴۵-۱۹ روزبعد از انفارکتوس حاد (میانه ۳۷ روز)" تقسیم شدند وتا یکسال فالوآپ انجام شد.
- البته بیماران شوک کاردیوژنیک وارد مطالعه نشدند. نتایج نشان داد که مرگ و میر کلی، انفارکتوس قلبی غیرکشنده، استروک و بستری به علت نارسایی قلبی یکسال بعد در گروه "درمان فوری" نسبت به "گروه درمان مرحله ای" نه تنها بدتر نبود (non-inferiority) حتی بهتر بود(superiority).

Immediate group: PCI اولیه بر روی رگ مسئول و PCI همزمان در سایر عروق درگیر
Staged group: PCI اولیه بر روی رگ مسئول و PCI در سایر عروق درگیر ۴۵-۱۹ روز بعد