Rationale and design of the MULTISTARS AMI Trial: A randomized comparison of immediate versus staged complete revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease

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Background About half of patients with acute ST-segment elevation myocardial infarction (STEMI) present with multivessel coronary artery disease (MVD). Recent evidence supports complete revascularization in these patients. However, optimal timing of non-culprit lesion revascularization in STEMI patients is unknown because dedicated randomized trials on this topic are lacking.

Study design The MULTISTARS AMI trial is a prospective, international, multicenter, randomized, two-arm, open-label study planning to enroll at least 840 patients. It is designed to investigate whether immediate complete revascularization is non-inferior to staged (within 19-45 days) complete revascularization in patients in stable hemodynamic conditions presenting with STEMI and MVD and undergoing primary percutaneous coronary intervention (PCI). After successful primary PCI of the culprit artery, patients are randomized in a 1:1 ratio to immediate or staged complete revascularization. The primary endpoint is a composite of all-cause death, non-fatal myocardial infarction, ischemia-driven revascularization, hospitalization for heart failure, and stroke at 1 year.

Conclusions The MULTISTARS AMI trial tests the hypothesis that immediate complete revascularization is non-inferior to staged complete revascularization in stable patients with STEMI and MVD. (Am Heart J 2020;228:98-108.)

About half of patients presenting with ST-segment elevation myocardial infarction (STEMI) exhibit multivessel coronary artery disease (MVD).[1-3] These patients are at increased risk of adverse cardiovascular events.[2-5] Multivessel coronary artery disease in STEMI patients is associated with increased rates of death, recurrent myocardial infarction, repeat revascularization, and heart failure.[2-5]

Revascularization strategies in patients with STEMI and MVD have been investigated in several trials. PRAMI (Preventive Angioplasty in Acute Myocardial Infarction), enrolling a total of 465 patients, demonstrated superiority of immediate complete versus culprit lesion only

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Submitted May 2, 2020; accepted July 20, 2020.

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https://doi.org/10.1016/j.ahj.2020.07.016

Table I. Current evidence of complete versus culprit lesion only revascularization in patients with ST-segment elevation myocardial infarction and multivessel disease

Trial	Year	n	Primary endpoint	Follow-up	Primary endpoint in complete versus culprit-only revascularization groups	HR (95% CI)	Comment
PRAMI(1)	2013	465	Cardiac death, non-fatal myocardial infarction, or refractory angina	23 months (mean follow-up)	9.0% versus 23.0%	0.35 (0.21-0.58)	Complete revascularization during index procedure
CvLPRIT(2)	2015	296	All-cause death, recurrent myocardial infarction, ischemia-driven revascularization, and heart failure	12 months	10.0% versus 21.2%	0.45 (0.24-0.84)	2/3 of complete revascularization during index procedure
DANAMI-3-PRIMULTI(3)	2015	627	All-cause death, non-fatal reinfarction, and ischemia-driven revascularization of non-infarct related arteries	>12 months (median follow-up 27 months)	13.0% versus 22.0%	0.56 (0.38-0.83)	FFR-guided PCI of non-culprit arteries 2 days after index procedure
COMPARE-ACUTE(4)	2017	885	All-cause death, non-fatal myocardial infarction, revascularization, and cerebrovascular events	12 months	7.8% versus 20.5%	0.35 (0.22-0.35)	FFR-guided PCI of non-culprit arteries (84% during index procedure)
COMPLETE(5)	2019	4041	Cardiovascular death or myocardial infarction	3 years	7.8% versus 10.5%	0.74 (0.60-0.91)	Randomization stratified according to the intended timing of non-culprit lesion PCI

CI, confidence interval; *FFR*, fractional flow reserve; *HR*, hazard ratio; *PCI*, percutaneous coronary intervention.

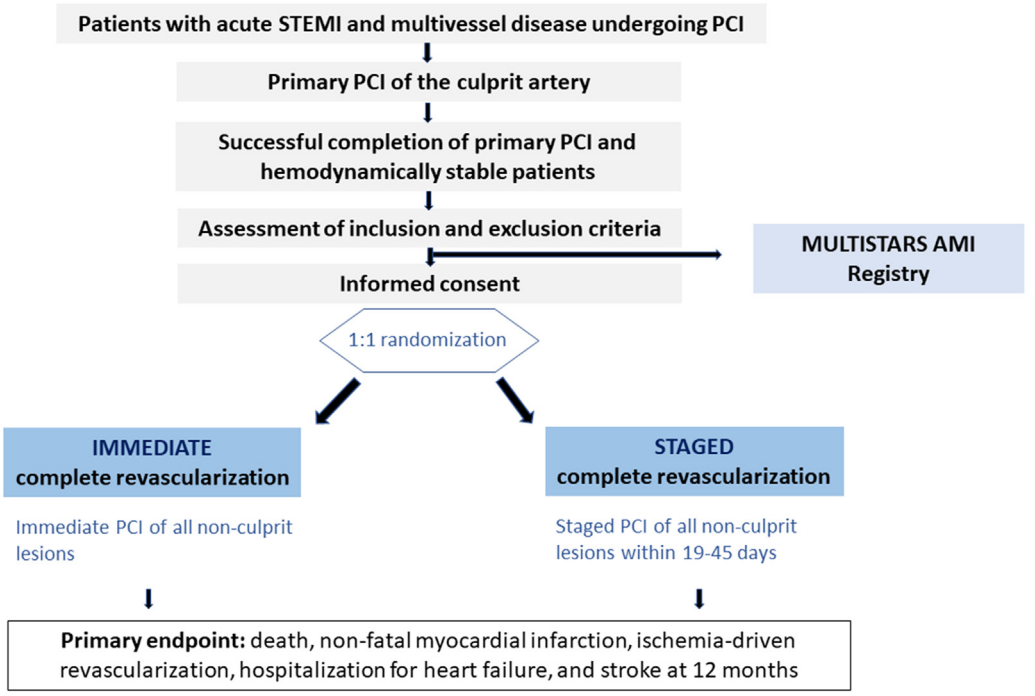
revascularization in terms of cardiac death, non-fatal myocardial infarction, or refractory angina at a mean follow-up of 23 months.[6] Similarly, CvLPRIT (Complete versus Lesion-Only Primary PCI) showed in a total of 296 patients that index admission complete revascularization as compared to culprit lesion only percutaneous coronary intervention (PCI) significantly reduced the primary endpoint, a composite of death, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization at 12 months.[7] These findings were supported by DANAMI-3-PRIMULTI (Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease). DANAMI-3-PRIMULTI included a total of 627 patients after successful primary PCI and provided evidence that fractional flow reserve (FFR)-guided complete revascularization as compared with no further invasive intervention was associated with a reduced risk of the composite endpoint of death, non-fatal myocardial infarction, and ischemia-driven revascularization, assessed when the last patient had been followed up for 1 year.[8] In line with these findings, COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) demonstrated in 885 patients that FFR-guided complete revascularization of non-infarct-related coronary arteries as compared to culprit lesion only PCI resulted in a lower risk of death, non-fatal myocardial infarction, revascularization, and cerebrovascular events at 12 months.[9] COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) then demonstrated that among patients with STEMI and MVD, complete revascularization was superior to culprit lesion only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization, and benefits of complete revascularization were observed regardless of whether complete revascularization was performed during or after the index hospitalization.[10,11] Hence, complete revascularization of hemodynamically stable STEMI patients is strongly supported by recent evidence (Table I).[12,13] However, the optimal timing of revascularization of non-culprit lesions in STEMI patients, i.e. immediate versus staged PCI, remains a matter of ongoing debate.

The prospective, international, multicenter, randomized, two-arm, open-label MULTISTARS AMI (MULTivessel Immediate versus STAged RevaScularization in Acute Myocardial Infarction) trial is designed to investigate whether immediate complete revascularization is non-inferior to staged (within 19-45 days) complete revascularization in stable patients with STEMI and MVD.

Study objectives

MULTISTARS AMI is an investigator-initiated, prospective, international, multicenter, randomized, two-arm,

Figure 1



Study flow chart. PCI, percutaneous coronary intervention, STEMI, ST-segment elevation myocardial infarction.

open-label study designed to establish whether immediate complete revascularization is non-inferior to staged (within 19 – 45 days) complete revascularization after successful primary PCI of the culprit coronary artery in hemodynamically stable patients presenting with STEMI and MVD. The trial is registered at www.clinicaltrials.gov under NCT03135275.

Study organization

The study organization of MULTISTARS AMI includes a steering committee, a data safety monitoring board (DSMB), and a clinical endpoints committee (CEC). The steering committee is responsible for the scientific content of the protocol, the management of the study, and the writing of the manuscript. The study is monitored by an independent DSMB and all clinical endpoints will be adjudicated by an independent CEC. All study-related measures follow standard operating procedures (SOPs) for study management, monitoring, and data management.

MULTISTARS AMI is funded by the Investigator-Sponsored Research Program of Boston Scientific Corporation (Marlborough, MA, USA; grant number ISROTH10277). Boston Scientific Corporation has no role in study design, data collection, analysis, monitoring, and interpretation as well as writing of the manuscripts. The authors are solely responsible for the design and conduct of the study, all study analysis, the drafting and editing of publications, and their final content.

The first patient was included in January 2017, and in June 2020, a total of 393 patients have been enrolled in the study. Patient inclusion is planned to continue until the end of 2021, and primary endpoints at 1 year should be available for analysis by the end of 2022.

Patient population

A total of 840 patients with acute STEMI and MVD will be enrolled at >30 sites in 4 countries (Switzerland, Germany, Austria, and Italy). Randomization takes place after successful primary PCI of the culprit artery to either immediate or staged (within 19-45 days) complete revascularization in a 1:1 ratio (Figure 1). Patients ≥18 years of age presenting with acute STEMI within 24 hours of symptom onset and with MVD, defined as at least one non-culprit coronary artery stenosis (≥70% luminal diameter narrowing by visual estimate in at least two projections) in a major epicardial coronary artery or major branch (with a visually estimated lumen diameter between 2.25 mm and 5.75 mm), are eligible for enrollment. Only hemodynamically stable patients after successful PCI of the culprit artery and with non-culprit lesions suitable for PCI are included. Patients with stable hemodynamics at the end of culprit artery PCI are eligible for enrolment into MULTISTARS AMI. The definition of

Table II. MULTISTARS AMI inclusion and exclusion criteria

Inclusion criteria
Age ≥18 years
Patients with acute STEMI presenting within 24 hours of symptom onset
Suitability for PCI by transfemoral or transradial access
Identifiable culprit lesion
Coronary anatomy suitable for complete percutaneous revascularization with the third-generation, biodegradable-polymer, everolimus-eluting Synergy® stent
TIMI flow grade 2 or 3 after PCI of the culprit artery
Stable hemodynamics after PCI of the culprit artery
Non-culprit artery lesion with ≥70% diameter stenosis by visual estimation in at least two projections in a vessel with a lumen diameter of 2.25 – 5.75 mm
Exclusion criteria
Inability to give informed consent
Pregnancy at time of inclusion
Prior CABG
Pre-existing severe kidney disease (eGFR <30 ml/min/1.73 m^2 or renal replacement therapy)*
Prior allergic reaction to everolimus or any stent material
Cardiogenic shock
Prolonged resuscitation (>10 minutes)
Need for emergency CABG
Planned hybrid revascularization
Chronic total occlusion
Left main disease (>50% diameter stenosis) or left main equivalent
Coronary artery dissection
Stent thrombosis
In-stent restenosis
Mechanical complication of acute myocardial infarction
Planned coronary, cerebrovascular, or peripheral arterial revascularization
Planned cardiac or major surgery
Any contraindications for dual antiplatelet therapy for at least 90 days (except for patients on oral anticoagulation)
Life expectancy <1 year

CABG, coronary artery bypass grafting; *eGFR*, estimated glomerular filtration rate; *PCI*, percutaneous coronary intervention; *STEMI*, ST-segment elevation myocardial infarction; *TIMI*, Thrombolysis In Myocardial Infarction. *when information on renal function is available at the time of primary PCI.

hemodynamic stability is in accordance with the inclusion criteria of the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial to clearly separate the patient populations.[14] Accordingly, hemodynamic stability is defined as absence of systolic blood pressure <90 mmHg, catecholamine therapy to maintain systolic blood pressure >90 mmHg, and/or clinical signs of hypoperfusion. Inclusion and exclusion criteria are summarized in Table II.

In accordance with Good Clinical Practice guidelines and as approved by the ethics committees, informed consent is obtained with the use of a prespecified process. As soon as coronary intervention is planned and the patient fulfills study entry criteria, the patient will be informed about the trial and asked for written informed consent by the admitting cardiologist. As patients are often not able to give written informed consent in the acute STEMI setting, a study-specific informed consent process was developed to avoid any treatment delay. According to this process, patients who are not able to provide written consent give oral informed consent after successful primary PCI. An independent physician not involved in the conduct of the study is witness to the oral informed consent, which will be documented on the informed consent form. When oral informed consent is not possible in the acute STEMI setting, eg, due to conscious sedation, the patient cannot be included in the study. After the procedure, the patient confirms the oral consent by signing the informed consent form.

Prospective registry

For patients who are pre-screened for the trial, but who do not meet the inclusion criteria and do not enter the trial, the reason for study exclusion is documented in a parallel registry. This registry then allows for an estimation of the proportion of screened patients enrolled in the randomized trial.

Randomization and invasive procedures

After successful primary PCI of the culprit artery according to current guidelines and using standard techniques, patients are randomly allocated in a 1:1 ratio to either immediate complete revascularization or staged (19-45 days) complete revascularization (Table III). Patient randomization is performed electronically via a secured web-based electronic case report form (eCRF) system and using block randomization to ensure equal numbers of patients in both arms (secuTrial, interactive Systems GmbH, Berlin, Germany). Variable block sizes are used to reduce the predictability of the sequences.

In the immediate complete revascularization group, PCI of all non-culprit lesions is performed immediately after culprit artery PCI. In the staged complete revascularization group, PCI of all non-culprit lesions is performed within 19-45 days during a second procedure. Percutaneous coronary revascularization is performed with standard techniques and according to current guidelines using the third-generation, biodegradable-polymer, everolimus-eluting Synergy stent.[15,16] The choice of the access site is left at the discretion of the operator. The use of FFR or intravascular imaging including intravascular ultrasound (IVUS) and optical coherence tomography (OCT) is left at the discretion of the operator.[15,16] Thrombus aspiration is performed and glycoprotein IIb/IIIa inhibitors are administered in accordance with contemporary guidelines and local standards.[17,18] Left ventricular function is assessed by echocardiography during the index hospitalization. Dual antiplatelet therapy is planned to be given for at least 90 days, preferably for 12 months following the index PCI, with the exception of patients with any indication for oral anticoagulation.[17-19] In these patients, either triple or dual antithrombotic therapy can be administered following PCI. All patients receive optimal medical management and secondary prevention according to current

Table III. MULTISTARS AMI data acquisition.

	Screening	*Randomization*	*Immediate PCI of non-culprit lesions (Group 1)*	*Hospitalization and discharge*	*Staged PCI of non-culprit lesions at 19-45 days (Group 2)*	*Staged hospitalization and discharge (Group 2)*	*FUP: 30-day* (Group 1, by visit or phone)*	*FUP: 6-month (by visit or phone)*	*FUP: 1-year (by visit)*
Group 1 ("immediate complete revascularization")	x	x	x	x			x	x	x
Group 2 ("staged complete revascularization")	x	x		x	x	x	x	x	x
Informed consent	x								
In-/exclusion criteria	x								
Medical history	x								
Physical examination	x			x	x				x
Blood analysis	x			x	x	x			
12 lead ECG	x			x	x	x			x
Medication regimen	x	x	x	x	x	x	x	x	x
Index procedure	x								
Randomization		x							
Transthoracic echocardiography				x		x			
Adverse events, primary and secondary endpoints			x	x	x	x	x	x	x
EQ-5D questionnaire							x	x	x
Final status									x

ECG, electrocardiogram; *EQ-5D*, EuroQol 5D; *FUP*, follow-up; *PCI*, percutaneous coronary intervention. *An additional follow-up 30 days after complete revascularization is performed by visit or phone in Group 2.

guidelines and recommendations irrespective of the randomly assigned study treatment.

Primary and secondary endpoints

Endpoint definitions are given in Table IV. The primary endpoint is a composite of all-cause death, non-fatal myocardial infarction, unplanned ischemia-driven revascularization, hospitalization for heart failure, and stroke at 1 year.

Secondary endpoints (assessed at 6 months and 1 year) include:

- Primary endpoint at 6 months
- Single components of the primary endpoint
- All-cause death or non-fatal myocardial infarction
- Procedural success
- Target vessel revascularization
- Target lesion revascularization
- Cardiac death
- Cardiovascular death
- Cardiac death or non-fatal myocardial infarction
- Stent thrombosis
- Acute renal insufficiency or renal replacement therapy
- Bleeding events (categorized according to Bleeding Academic Research Consortium [BARC] grades)
- Quality of life as assessed by the EuroQol 5D (EQ-5D) questionnaire

Follow-up

Follow-up is performed at 30 days (corresponding to the second hospitalization in the staged complete revascularization group), 6 months, and 12 months after randomization. According to the protocol, the 30-day follow-up in the immediate complete revascularization group is performed either by phone or visit at 30 days (+/- 1 week), resulting in follow-up performed between 23-37 days after randomization. The 30-day follow-up in the staged complete revascularization group is performed for practical reasons during the hospitalization for the staged procedure (after the intervention), regardless of the timing within this window, resulting in follow-up performed between 19-45 days after randomization. An additional follow-up at 30 days after the staged procedure was incorporated into the visit schedule of the staged complete revascularization group to assure equal capturing of events up to 30 days after complete revascularization in both groups. Both groups must have a visit or telephone contact at 6 months (+/- 2 weeks) and one visit in person at 1 year (+/- 2 weeks) after randomization.

Table IV. Outcome definitions.

Endpoint	Definition
All-cause death	All deaths due to cardiovascular and non-cardiovascular causes. All deaths with a clear cardiac or unknown cause will be classified as *cardiac*. All deaths caused by non-coronary vascular causes will be classified as *vascular*. Only deaths due to a documented non-cardiovascular cause (e.g. trauma, cancer, suicide) will be classified as *non-cardiovascular*.
Myocardial infarction	Myocardial infarction is defined based on the Third Universal Definition of Myocardial Infarction. The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction: 1. Detection of a rise and/or fall of cardiac biomarkers (preferably cTn) with at least one value above the 99th percentile of the URL and with at least one of the following: a. Symptoms of ischemia b. New significant ST segment alterations, T-wave changes, or new LBBB in the ECG c. Development of pathological Q waves in the ECG d. Imaging evidence of new loss of viable myocardium e. Identification of an intracoronary thrombus by angiography 2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3. PCI-related myocardial infarction (MI type 4a): Elevation of cTn values >5 x 99th percentile occurring within 48 hours of the procedure in patients with normal baseline values (≤99th percentile), or a rise of cTn values >20 percent if baseline values are elevated or are stable or falling. In addition, either new or aggravating prolonged (>20 min) symptoms suggestive of myocardial ischemia, or new persistent ischemic ST segment changes or new pathological Q waves, or angiographic evidence of a flow-limiting complication such as persistent occlusion or persistent slow-flow, no-reflow, or embolization, and/or angiographic evidence of persistent loss of patency of a major (≥ 2.0 mm) side branch, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality are required. 4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. 5. For CABG, in patients with normal baseline cTn values (≤99th percentile URL), myocardial infarction is arbitrarily defined by elevations of >10 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographic documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium. 6. Pathological findings of an acute or a recent myocardial infarction. A rise of cardiac enzymes post procedure represents an inherent condition in the course of a myocardial infarction treated with primary PCI. Therefore, in case of new persistent ischemic ST segment changes or new/aggravating prolonged (>20 min) symptoms suggestive of myocardial ischemia, within 48 hours of the procedure, a coronary angiogram is recommended to confirm or exclude periprocedural myocardial infarction.
Ischemia-driven revascularization	Ischemia-driven revascularization is defined as unplanned revascularization due to angina symptoms, new ischemic ECG changes, or signs of reversible myocardial ischemia on non-invasive imaging. It includes: 1. TLR or TVR. 2. PCI performed in the staged complete revascularization group between randomization and the planned staged procedure for significant coronary lesions that were scheduled to be treated as staged, but which instead were treated earlier due to symptoms or evidence of ischemia. 3. PCI of lesions not identified previously as significant. 4. CABG for new symptoms or complications of PCI.
Hospitalization for heart failure	Hospitalization for heart failure is defined as hospital admission due to any of the following symptoms and signs of heart failure: Dyspnea, fatigue, fluid overload, pulmonary edema, elevated venous pressure, and elevated BNP or NT-pro BNP levels. Confirmation of heart failure according to local expert judgment will be required for the event to be classified as heart failure.
Stroke	The definition of stroke includes ischemic and hemorrhagic strokes. An ischemic stroke is defined as new focal neurologic deficit that either results in clinical symptoms lasting for at least 24 hours or that is associated with evidence of relevant infarction on CT scan or MRI of the brain. A hemorrhagic stroke is defined as an acute focal neurologic deficit that is associated with the evidence of intracranial bleeding on CT or MRI of the brain.

BNP, brain natriuretic peptide; *CABG*, coronary artery bypass grafting; *CT*, computed tomography; *cTn*, cardiac troponin; *ECG*, electrocardiogram; *LBBB*, left bundle branch block; *MRI*, magnetic resonance imaging; *NT-pro BNP*, N-terminal pro brain natriuretic peptide; *PCI*, percutaneous coronary intervention; *TLR*, target lesion revascularization; *TVR*, target vessel revascularization; *URL*, upper reference limit.

Substudies

The following substudies will yield mechanistic insights into effects of non-culprit artery PCI during the acute phase of STEMI, although the study is not adequately powered to draw firm conclusions in subgroups.

Coronary artery disease severity. The impact of immediate versus staged complete revascularization may vary according to coronary artery disease severity and extent.[20] Both the anatomical and functional SYNTAX scores will be calculated by blinded observers. The functional SYNTAX score will be calculated based on angiography-derived quantitative flow reserve (QFR) measurements of non-culprit lesions. Patients will then be divided according to the SYNTAX scores and the effect of immediate versus staged complete revascularization compared across SYNTAX score groups. Further, the impact of the residual SYNTAX scores on outcomes will be investigated.

Left ventricular systolic dysfunction. Differential effects of immediate versus staged complete revascularization will be investigated based on left ventricular systolic function at baseline. In patients with available follow-up echocardiography, the impact of immediate complete revascularization on left ventricular recovery will be assessed.

Access site. This subproject allows for a comparison of the safety and efficacy of immediate versus staged complete revascularization in relation to radial versus femoral access.

Kidney disease. Patients will be divided according to baseline estimated glomerular filtration rate and the impact of immediate versus staged complete revascularization on post-procedural kidney function and outcomes will be compared among groups.

Cost-effectiveness analysis. MULTISTARS AMI will allow for a cost-effectiveness analysis according to current standards. In this subproject, cost-effectiveness of immediate versus staged complete coronary revascularization will be assessed stratified to the different health care systems in the participating nations.

Sample size calculation

Sample size calculation was based on the primary endpoint and the available evidence published to date. Given the event rates reported in the most recent trials with similar trial designs as MULTISTARS AMI (immediate randomization at the time of primary PCI, similar in-/exclusion criteria),[8,9] sample sizes of 400 in each group achieve 80% power to exclude a non-inferiority ratio of 1.46 (R_0).[21-24] The margin was based on the expected rate of events in the staged complete revascularization group and a prespecified judgment about clinically meaningful difference. The power was computed for the case where both the staged and the immediate treatment group proportions are 18%, using the one-sided Farrington-Manning score test with the significance level targeted at 5%. Assuming a proportion of 5% dropping out in both groups, a total of 420 patients are needed in each group. Altogether, a total of 840 patients will be sufficient.

Data analysis

Intention-to-treat analyses will represent the primary analyses, with patients analyzed according to the randomized treatment allocation. As-treated analyses will be performed as sensitivity analyses. Given the randomization into either an immediate complete or a staged complete revascularization group, crossovers may occur when the randomized treatment allocation is not followed by the operator, which is expected to occur infrequently.

Endpoints will be analyzed by calculating event rates for the two groups counting the first occurrence of any component of the composite outcome. Event rates will be compared among groups using the one-sided Farrington-Manning score test. In addition, endpoints will be analyzed using a time-to-event approach. Kaplan-Meier curves will be plotted for the time from randomization to the occurrence of the clinical outcomes and comparisons between treatment arms performed by the log-rank test. Cox proportional hazard models will be fitted to estimate hazard ratios and 95% confidence intervals for treatment comparisons. All testing will be conducted at the 0.05 significance level. Non-inferiority of immediate to staged complete revascularization will be claimed if the upper limit of the one-sided 95% confidence interval of the risk ratio will not cross the prespecified non-inferiority margin. If non-inferiority can be claimed, an additional superiority analysis on a two-sided alpha of 0.05 will be performed.

Subgroup analyses of the primary endpoint will be performed with pre-specified covariates including age, sex, smoking status, history of myocardial infarction, infarct location, number of coronary arteries with stenosis, non-culprit artery stenosis severity, symptom duration, ECG characteristics, concomitant medication, type and duration of dual antiplatelet therapy, access site (radial versus femoral), lab values (including estimated glomerular filtration rate), and presence of co-morbidities such as diabetes, peripheral artery disease, left ventricular ejection fraction, prior myocardial infarction, and angina.

Ethical considerations

The protocol has been approved by the ethics committees and the study is conducted according to local laws and regulations and in compliance with the Declaration of Helsinki. All sites receive extensive training before study initiation. All safety aspects will be monitored by an international DSMB (consisting of 3

cardiologists and 1 statistician). Based on documentation provided by the clinical trial sites, events will be adjudicated by a CEC (consisting of 3 cardiologists blinded to the patients' assigned treatment).

Discussion

Multivessel coronary artery disease is observed in about half of STEMI patients and is associated with worse outcomes compared with single vessel disease.[1-4] Recent randomized trials demonstrated superiority of complete over culprit lesion only revascularization in hemodynamically stable STEMI patients with MVD and resulted in a class IIa recommendation for non-culprit lesion PCI in this setting.[6-10,17] Further, in two large meta-analyses, a strategy of complete revascularization was associated with an over 30% relative risk reduction in cardiovascular mortality as compared with a strategy of culprit lesion only PCI in patients with STEMI and multivessel disease without cardiogenic shock at presentation.[25,26]

Optimal timing of non-culprit lesion PCI in STEMI patients with MVD is not yet established, and whether benefits of immediate complete revascularization outweigh related risks remains to be determined.[13,27,28] On the one hand, immediate complete revascularization may limit infarct size due to increased collateral flow, and may beneficially affect left ventricular remodeling by decreasing recurrent myocardial ischemia due to obstructive coronary artery lesions. Indeed, the observational Cardiovascular Magnetic Resonance (CMR) substudy of CvLPRIT suggested that immediate complete as compared with staged complete revascularization was related with smaller infarct size and improved left ventricular systolic function.[29] Given the diffuse inflammatory nature of acute coronary syndromes, immediate complete revascularization may further reduce rates of future adverse events related to complex and vulnerable non-culprit lesions.[30-32] Complete revascularization at the time of primary PCI has the advantage of exposing the patient to a single arterial puncture and coronary procedure and may be associated with lower health care costs as prolonged hospital stay or second hospitalization can be avoided. On the other hand, immediate complete revascularization of non-culprit lesions usually requires longer procedural duration and a higher amount of contrast agent, and may therefore entail an increased risk of acute kidney injury and acute left ventricular volume overload. Prolonged interventions during the acute phase of STEMI, when both inflammation and coagulation are activated to a maximal extent, may further carry an increased risk of periprocedural complications. In CULRPIT-SHOCK, which enrolled a total of 706 acute myocardial infarction patients with MVD and cardiogenic shock, the hazards of a prolonged procedure and a higher amount of contrast agent in the complete revascularization group seemed to outweigh the risks of repeat revascularization in the culprit-only revascularization group.[14,33]

Data on the optimal timing of complete revascularization in STEMI patients (during the same sitting or as a staged procedure) remain conflicting. Real-world registry data and *post hoc* analyses mostly reported a lower mortality with staged complete revascularization in STEMI patients.[28,34-36] While a large network analysis including over 40'000 patients from 4 prospective and 14 retrospective studies suggested superiority of staged over immediate complete revascularization in patients with STEMI and MVD,[37] consistent benefits of complete revascularization regardless of whether non-culprit lesion PCI was performed in the same sitting or as a staged procedure were demonstrated in a recent large meta-analysis including 10 randomized controlled trials.[25] The meta-analysis of Pascerini et al showed that complete revascularization performed during primary PCI was associated with reduced rates of mortality and myocardial infarction, whereas staged revascularization did not improve these outcomes.[13] In the only randomized trial investigating the timing of complete revascularization in STEMI patients published to date, similar rates of cardiovascular events were observed in the immediate and staged groups, although only limited conclusions can be drawn from this study given the small sample size of 65 patients per group.[38] In the randomized trials of complete versus culprit lesion only revascularization in STEMI, complete revascularization was either performed exclusively during the same sitting,[6] both during the same sitting or as a staged procedure,[7,9] or solely as staged procedure,[8,10,39] but comparisons among groups were lacking. In COMPLETE, randomization was stratified according to the intended timing of non-culprit lesion PCI (as a staged procedure either during or after the index hospitalization), and benefits of complete revascularization were observed irrespective of the investigator-determined timing of staged non-culprit lesion PCI.[10,11] Randomized data on the timing of complete revascularization in STEMI without cardiogenic shock at presentation are therefore warranted to determine whether immediate non-culprit lesion PCI in the acute setting of STEMI is non-inferior to a staged approach.

In line with previously published trials in this field and current guidelines not recommending *ad hoc* PCI of chronic total occlusions,[6-8] the presence of a chronic total occlusion was defined as exclusion criterion. While some studies on complete coronary revascularization in STEMI were based on angiography guidance,[6,7,10] others used functional lesion assessment for non-culprit lesion revascularization.[8,9] In accordance with COMPLETE,[10] fractional flow reserve measurements for non-culprit lesions with at least 70% diameter stenosis on visual estimation are not mandatory according to the MULTISTARS AMI protocol, but left at the discretion of the operator, thus reflecting clinical practice according to

current guideline recommendations. In a recent meta-analysis including randomized trials comparing complete versus culprit lesion only revascularization in patients with STEMI and MVD, no differential association with treatment between angiography- and fractional flow reserve-guided strategies on major cardiovascular outcomes was observed.[25] The time interval of 19 to 45 days for staged PCI is in line with previous studies and allows for a comparison of complete coronary revascularization performed in an activated, inflammatory acute coronary syndrome milieu with complete coronary revascularization performed under stable conditions when the patient has recovered from the acute phase of myocardial infarction.[38,40] Hence, the two selected time points of complete revascularization represent distinct conditions in the pathophysiological spectrum of coronary artery disease, which may affect outcomes. The fact that the 30-day follow-up in the immediate complete revascularization group is performed either by phone or visit, while for practical reasons it is performed during the second hospitalization in the staged group, followed by a phone call or visit at 30 days after the staged procedure, allows for equal capturing of events up to 30 days after completion of revascularization in any group. The two 30-day follow-ups in the staged group reflect the two separate procedures, and any event occurring more than 30 days after complete revascularization in both groups will be covered by the 6- and 12-month follow-up.

The definition of the primary endpoint, a composite of all-cause death, non-fatal myocardial infarction, unplanned ischemia-driven revascularization, hospitalization for heart failure, and stroke at 1 year, is in line with prior trials in patients with STEMI and MVD.(6-9) Non-fatal myocardial infarction, ischemia-driven revascularization, and hospitalization for heart failure are directly related to the study intervention and represent clinically meaningful adverse cardiac events.[4,6-9] Stroke represents a devastating cardiovascular complication following PCI, with event rates being potentially affected by the treatment allocation.[9] The definition of myocardial infarction includes both spontaneous and periprocedural myocardial infarction and is classified based on the Third Universal Definition of Myocardial Infarction.[41] Although the identification of periprocedural myocardial infarction following primary PCI remains challenging, definitions based on both elevated cardiac biomarkers and new clinical signs and symptoms of myocardial ischemia should allow for the detection of clinically-relevant events.

Among the ongoing studies comparing different revascularization strategies in acute coronary syndrome patients with MVD, only BioVasc (Direct Complete Versus Staged Complete Revascularization in Patients Presenting With Acute Coronary Syndromes and Multivessel Disease) – similarly to MULTISTARS AMI – aims to investigate the optimal timing of complete revascularization, i.e. immediate versus staged PCI of non-culprit lesions, but enrolls not only STEMI but also non–ST-segment elevation myocardial infarction (NSTEMI) patients. MULTISTARS AMI is, to the best of our knowledge, the only ongoing trial testing the hypothesis that in patients with STEMI and MVD, immediate complete revascularization is non-inferior to staged complete revascularization. MULTISTARS AMI will answer an unresolved issue in coronary revascularization and further define the optimal revascularization strategy in patients with STEMI and MVD.

Summary

Despite the high prevalence and the worse outcomes of patients with STEMI and MVD, the optimal timing of complete revascularization has not yet been investigated in a large-scale randomized study. The prospective, international, multicenter, randomized, two-arm, open-label MULTISTARS AMI trial is therefore designed to test the hypothesis that in stable patients presenting with STEMI and MVD, immediate complete revascularization is non-inferior to staged complete revascularization.

Acknowledgement

MULTISTARS AMI is funded by the Investigator-Sponsored Research Program of Boston Scientific Corporation (Marlborough, MA, USA; grant number ISROTH10277).

Appendix A

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