The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Ischemic postconditioning or deferred stent implantation versus conventional primary angioplasty and complete revascularization versus treatment of culprit lesion only: Rationale and design of the DANAMI 3 trial program

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Background In patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, ischemic postconditioning has been shown to reduce infarct size, but the effect on clinical outcome has not been tested in a large randomized trial. In addition, deferring stent implantation in the infarct-related lesion 1 to 3 days after acute opening of the infarct-related artery could have protective effects, by reducing the risk of injury caused by distal embolization and microvascular obstruction. Finally, a considerable fraction of patients present with lesions in other coronary artery branches than the infarct-related artery. Whether a strategy of complete or partial revascularization of these patients should be preferred remains uncertain.

Study design The DANAMI 3 trial program was designed to investigate 3 different randomized treatment strategies in patients with ST-segment elevation myocardial infarction: (1) ischemic postconditioning versus conventional treatment with a primary end point of death and hospitalization for heart failure; (2) deferring stent implantation in the infarct-related lesion versus conventional treatment with a primary end point of death, hospitalization for heart failure, reinfarction, and repeat revascularization; and (3) treatment of the culprit lesion only versus fractional flow reserve–guided complete revascularization in patients with multivessel disease, with a primary end point of death, reinfarction, and repeat revascularization.

Summary The DANAMI 3 trial program will determine whether either of 2 approaches to reduce reperfusion injury and distal microvascular obstruction with postconditioning or deferred stent implantation will translate into improved clinical outcome and whether patients with multivessel disease undergoing primary percutaneous coronary intervention will benefit from a strategy of complete or partial revascularization. (Am Heart J 2015;0:1-9.)

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Reperfusion injury and distal embolization

Percutaneous coronary intervention (PCI) with stent implantation is the most efficacious treatment of patients with ST-segment elevation myocardial infarction (STEMI), by reducing the occurrence of reinfarction and improving prognosis in comparison with fibrinolytic therapy.[1-3] However, a postprocedural normal epicardial blood flow (thrombolysis in myocardial infarction [TIMI] flow grade 3) may be present despite an impaired microvascular perfusion and hence adverse outcome.[4,5] Reperfusion therapy with primary PCI can be considered a "double edged sword" because the ischemic injury may additionally

be worsened by what is known as reperfusion injury.[6] Ischemic postconditioning (iPOST), defined as repetitive interruptions of blood flow to the injured region applied after a prolonged period of ischemia and reperfusion, is suggested to limit the extent of reperfusion injury and has been shown to reduce infarct size in patients with STEMI.[7-11] The effect on the final infarct size has been evaluated with different surrogate markers such as biomarkers,[8,10,11] echocardiography,[9-11] single-photon emission computed tomography,[9-11] and cardiac magnetic resonance.[7,12] In addition, iPOST has been shown to increase the coronary flow reserve and improve ST-segment resolution.[13] Whether these improvements in surrogate markers translate into improved clinical outcome for patients undergoing primary PCI has not yet been investigated in a randomized trial.

Disturbances in the microcirculation caused by reperfusion injury cover a complex chain of events within this vascular territory. However, distal embolization of thrombotic material from the ruptured plaque may also be present, although attempts to improve outcome by avoiding embolization by means of distal protection devices have, in previous trials, been unsuccessful.[14,15]

Despite successful revascularization of the epicardial part of the occluded vessel, distal embolization occurs in 5% to 10% of the patients and impairs prognosis after primary PCI.[14,16-18] Because thrombus burden under the influence of antithrombotics is reduced considerably during the subsequent days, it is possible that postponement of the stent implantation (DEFER) may limit the risk of embolization and improve the prognosis of the patients.[19] Stent implantation per se does not seem to alter prognosis,[20-22] and thus, a strategy of DEFER may allow leaving the vessel unstented if no significant residual stenosis is present after the thrombus is resolved.

Multivessel disease

Approximately 40% of patients with STEMI have multivessel disease, that is, a significant stenosis in at least 1 of the nonculprit epicardial coronary arteries or their major side branches in addition to that in the infarct-related artery (IRA).[23] Patients with multivessel disease have more comorbidity and a higher mortality after primary PCI than those with single-vessel disease.[24-26] A complete revascularization strategy, as compared to revascularization of the IRA only, could in these patients potentially improve prognosis but may, on the other hand, also be associated with potential disadvantages both in terms of early and late complications related to the additional PCI and stenting, that is, side branch closure, periprocedural infarction, in-stent restenosis, and stent thrombosis. Data from 3 registry analyses have given conflicting results of early, complete revascularization with regard to both mortality and need for repeat revascularization.[27-29] The results of a recent randomized controlled trial indicated a clinical benefit of acute complete revascularization compared with PCI of the IRA only.[30] However, in that trial, the rate of recruitment, premature cessation, differences in basic patient characteristics, and definition of the primary end point could be questioned with regard to the interpretation of data. Furthermore, revascularization in that study was not guided by fractional flow reserve (FFR).

Table I. DANAMI 3 inclusion and exclusion criteria

Inclusion criteria
1. Age ≥18 y
2. Acute onset of chest pain with <12 h duration
3. ST-segment elevation ≥0.1 mV in ≥2 contiguous leads or documented newly developed left bundle-branch block
Exclusion criteria
1. Potential pregnancy
2. Known intolerance of aspirin, $P2Y_{12}$ receptor antagonists, heparin, or contrast medium
3. Inability to understand information or to provide informed consent
4. Unconsciousness or cardiogenic shock
5. PCI not possible
6. Indication for acute coronary artery bypass grafting
7. Patient presenting with stent thrombosis
8. Hemorrhagic diathesis or known coagulopathy

This article describes the rationale and study design for the DANAMI 3 trial program, which tests 3 hypotheses: (1) does iPOST improve clinical outcome, (2) does a DEFER strategy improve clinical outcome, and (3) is FFR-guided complete revascularization clinically superior to IRA revascularization only.

Methods

Study objectives and design

The DANAMI 3 trial program comprises 3 different randomized multicenter trials evaluating whether the clinical outcome of patients with STEMI can be improved and myocardial damage reduced by either (1) iPOST (DANAMI 3-iPOST) or (2) by deferred stenting (DANAMI 3-DEFER) and, in addition, (3) the study evaluates whether complete FFR-guided revascularization versus IRA-only revascularization improve clinical outcome in patients with STEMI and multivessel disease (DANAMI 3-PRIMULTI).

The DANAMI 3 trial program is an investigator-initiated, multicenter trial with participation from all centers in Denmark performing primary PCI using a prospective randomized open blinded end points design.[31] Randomization was initiated in 2011 and recruitment terminated in 2014, when the planned number of included patients was reached. The inclusion and exclusion criteria are listed in Table I, and reasons for exclusion are shown in Table II. Patient flowchart is shown in Figure.

Study organization

Patients were included consecutively from the 4 primary PCI centers in Denmark, comprising a catchment

Table II. Screened patients not included in the study

Reason for exclusion	Patients (n = 2131)*
STEMI diagnosis rejected	516
Symptom duration >12 h	271
Unwillingness to participate	143
Inability to provide informed consent for mental or communicational reasons	225
Inability to provide consent due to unconsciousness or cardiogenic shock	283
Known intolerance of aspirin, $P2Y_{12}$ receptor antagonists, heparin, or contrast	4
Hemorrhagic diathesis or known coagulopathy	23
Severe comorbidity with short life expectancy	34
Known or suspected severe renal impairment	9
Stent thrombosis	177
PCI not possible	50
Indication for acute CABG	88
Culprit lesion is in bypass graft	7
Initial flow TIMI 2-3 and not eligible for deferred stenting	125
Procedure-related reasons	7
Logistic reasons or center not participating in DANAMI 3-DEFER at time of randomization	118
Logistic reasons	138
Other reasons	58
Excluded after randomization	
Unable to achieve TIMI 2-3 flow during index procedure	27

Abbreviation: *CABG*, Coronary artery bypass graft.
*Twenty patients had >1 exclusion criterion.

area of approximately 5.6 million citizens. All centers were performing primary PCI at 24 hours 7 days a week throughout the entire study period and had a minimum volume of 300 primary PCI procedures annually. A fifth center was initially part of the study, but due to regional organizational changes, they stopped performing primary PCI after inclusion of 9 patients. These patients were removed from all analyses, as centers were required to randomize at least 25 patients to participate in the study. The steering committee encompassed representatives from all participating centers. The data safety monitoring board (DSMB) consisted of 1 invasive and 2 noninvasive cardiologists. The DSMB regularly reviewed interim analyses for both safety and efficacy end points. The clinical events committee (CEC) is responsible for adjudicating all primary and major secondary end points and consists of 3 experienced cardiologists, 1 invasive and 2 noninvasive. No members of the CEC or DSMB participated in recruitment or data collection or had access to any information regarding treatment allocations. A list of all committee members is given in online Appendix.

Randomization was performed using a Web-based electronic case report form (eCRF) system, in which central baseline characteristics of patients were entered and clinical events registered during the follow-up period of the trial. Additional patient characteristics and procedure-related variables were collected from 2 national PCI registries (Eastern and Western Denmark Heart Registries), into which the results of all coronary angiograms and PCI procedures in Denmark are entered.

The DANAMI 3 trial program was registered on www.clinicaltrials.gov under NCT01435408 (DANAMI 3-iPOST and DANAMI 3-DEFER) and NCT01960933 (DANAMI 3-PRIMULTI).

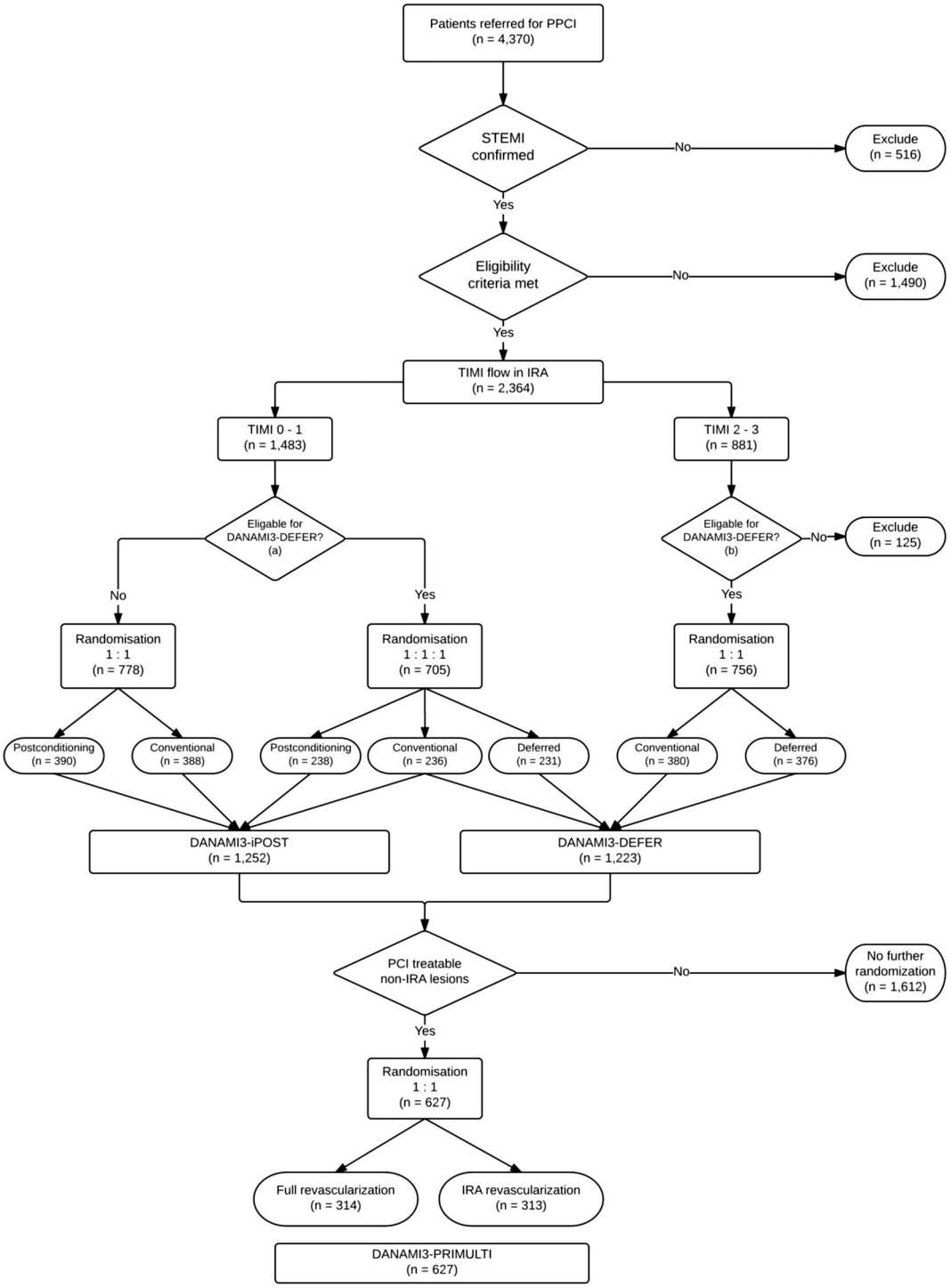
Randomization and invasive procedures

Patients were included in the trial after informed consent as described below. As soon as the assumed culprit lesion was identified, the physician reported TIMI flow in the IRA to an assistant, who performed the randomization using the eCRF. Because patients with TIMI flow grade 2 or 3 already had experienced reperfusion (and thus potential reperfusion injury) before admission to the catheterization laboratory, they were randomized 1:1 to either DEFER or conventional primary PCI and could not be randomized to iPOST. Patients with TIMI flow grade 0 or 1 were randomized 1:1:1 to iPOST, DEFER, or conventional PCI. If the interventionalist considered the patient unsuitable for DEFER (due to patient characteristics, coronary anatomy, or treatment logistics), this was reported in the eCRF before randomization. In these cases, patients with TIMI flow grade 0 or 1 were randomized 1:1 to conventional treatment or iPOST using a separate stratum, whereas patients with TIMI flow grade 2 to 3 were excluded. This ensures that the DANAMI 3-DEFER trial only includes patients from the control group who were considered eligible for DEFER, while keeping the ratio of controls 1:1 in both the DANAMI 3-DEFER and DANAMI 3-iPOST trials. By decision of the steering committee, from October 1, 2012, patients presenting with TIMI flow grade 0 or 1 were no longer randomized into the DANAMI 3-DEFER part of the trial program, as it was estimated that this would allow all 3 trials to reach the required number of patients simultaneously.

Primary PCI was performed preferably with floppy guide wires, predilatation using compliant balloons, and everolimus-eluting stents. Thrombectomy was performed at the discretion of the physician. In case a TIMI flow grade >1 could not be obtained after randomization, patients were excluded from further analyses. Randomization was performed using permuted-block randomization with block sizes varying from 2 to 6 patients (in cases of 1:1 randomization) or 3 to 9 patients (in cases of 1:1:1 randomization) and stratified by center. The randomization procedure is summarized in Figure.

Ischemic postconditioning. In patients randomized to iPOST, this was performed before stent implantation, within 60 seconds but at least 30 seconds after opening of the artery. After TIMI 2 to 3 flow in the IRA was secured by wire insertion alone, thrombectomy, dilatation with an undersized balloon, or a combination of these procedures, a compliant balloon with sufficient diameter to obstruct blood flow to the peripheral vascular bed was inflated at low pressure (4-8 atmosphere) and subsequently deflated

Figure



Randomization flow chart. (a) For procedural reasons: 11 patients; logistic reasons or center not participating in DANAMI 3-DEFER at time of randomization: 768 patients. (b) For procedural reasons: 7 patients; logistic reasons or center not participating in DANAMI 3-DEFER at time of randomization: 118. Abbreviations: *PPCI*, primary percutaneous coronary intervention.

after 30 seconds. The deflated balloon was left in situ for another 30 seconds before reinflation. Ischemic postconditioning was repeated for 4 cycles (30 seconds obstruction followed by 30 seconds perfusion each) and was followed by stent implantation.[7]

Deferred stenting. In patients randomized to DEFER, the physicians were encouraged to secure stable TIMI 2 or 3 flow exercising as little manipulation of the lesion as possible, that is, thrombectomy and/or dilatation using an undersized balloon during the initial procedure. In cases of unstable flow and threatened vessel closure despite repeat balloon dilations, implantation of a stent was considered necessary. These patients were considered "cross-overs" to conventional treatment but analyzed with affinity to their allocated treatment group according to the intent-to-treat principle. In case a stable (at least 10 minutes) TIMI flow grade 2 or 3 was achieved, a repeat coronary angiography with intended stent implantation in the IRA lesion was scheduled to be performed preferably >48 hours after the index procedure but within the index admission. Stent implantation could be waived, in case the lesion in the IRA at the time of the secondary procedure was considered angiographically insignificant. In these cases, a 3-month follow-up angiogram was planned.

Multivessel revascularization. In patients with additional significant (>50% diameter) stenoses not related to the IRA lesion, in arteries >2.0 mm considered suitable for PCI, a secondary randomization was performed to either PCI of the IRA only (ie, no further treatment) or complete revascularization. In patients randomized to complete revascularization, this was performed >48 hours after the index procedure but before discharge according to local routines. All multivessel PCI procedures were performed guided by FFR. Only stenoses with an FFR value <0.80 or a visually estimated diameter stenosis >90% were considered significant and subsequently stented. In patients randomized to complete revascularization with lesions deemed unsuitable for treatment with PCI (proximal chronic total occlusions of long duration, heavy calcification, or extreme tortuosity), coronary artery bypass surgery was considered.

All additional patient management during hospitalization and follow-up, including anticoagulant and antithrombotic regimens, was in accordance with contemporary guidelines at the discretion of the treating physicians.

Follow-up

Clinical follow-up is currently ongoing. All patients will be followed up for at least 2 years.

Primary end points

DANAMI 3-iPOST. The primary objective of this part was to investigate the effect of iPOST to protect the myocardium and reduce subsequent development of congestive heart failure. Therefore, a composite of all-cause death and development of heart failure was chosen as the primary end point (Table III).

DANAMI 3-DEFER. The primary objective of this part of the trial was to protect the microvasculature against distal embolization and thus to investigate the influence of the treatment on the development of heart failure. However, because a DEFER strategy leaves the culprit vessel unstented until deferred stenting or, in cases without flow-limiting stenosis, even permanently unstented, reinfarction and repeat target vessel revascularization were included as components of the primary end point (Table III).

DANAMI 3-PRIMULTI. The primary end point was a composite of all-cause mortality, myocardial infarction, or ischemia (either subjective or objective)–driven revascularization of nonculprit coronary artery lesions eligible for and randomized to either of the 2 treatment arms at the time of the index procedure (Table III).

Secondary end points

A number of surrogate and imaging end points will be analyzed to assess clinical outcome and to provide further insight into the effect of the different treatment strategies on a number of physiological mechanisms. In DANAMI 3-iPOST and DANAMI 3-DEFER, we will specifically analyze whether these reperfusion strategies can reduce the extent of microvascular obstruction, as assessed by magnetic resonance imaging (MRI). Secondary end points are listed in Table III.

All end points related to mortality or hospitalizations will be identified using national registries, in which all deaths and hospital referrals in Denmark are reported. Events will subsequently be adjudicated by the CEC members, who will review all relevant medical records, angiograms, and other available material. Patients will be seen in an outpatient clinic at the randomizing center after a minimum of 12 month (12-18 months) where a physician will assess angina status (Canadian Cardiovascular Society Angina Grading Scale) and symptoms of heart failure (New York Heart Association Functional Classification) and perform an echocardiogram following a standardized protocol. Echocardiographic images are digitally stored and will be analyzed off-line by a core laboratory, blinded to allocated treatments. In patients without contraindications, a cardiac MRI is performed during index hospitalization and repeated after 3 months. All MRI analyses will be performed by a core laboratory, blinded to randomized treatment allocation. Quality of life will be measured using validated self-assessment forms (EQ-5D).

Statistical analyses

For the DANAMI 3-iPOST study, we estimated that the annual rate of the primary end point would be 11% in the control group. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction in the primary end point of 25%, with a 2-sided α level of .05 and a power of 80% by enrolling 1,100 patients.

Table III. DANAMI 3 end points

DANAMI 3-iPOST	iPOST vs conventional PCI	Timeframe
Primary end point (composite)	All-cause mortality or hospitalization for heart failure	2 y
Secondary end points	1. All of the above components	1. 2 y
	2. TIMI flow	2. Postprocedure
	3. ST-segment resolution	3. 90 min postprocedure
	4. Wall motion index (echo)	4. 1 y
	5. Salvage index (MRI)	5. 90 d
	6. Infarct size (MRI)	6. 90 d
	7. LVEF (MRI/echo)	7. 90 d/1 y
	8. Microvascular obstruction	8. 48 h
	9. Quality of life	9. 1 y
DANAMI 3-DEFER	**DEFER vs conventional PCI**	**Timeframe**
Primary end point (composite)	All-cause mortality, hospitalization for heart failure, myocardial infarction, or unplanned target vessel revascularization	2 y
Secondary end points	1. All of the above components	1. 2 y
	2. TIMI flow	2. Postprocedure
	3. ST-segment resolution	3. 90 min postprocedure
	4. Wall motion index (echo)	4. 1 y
	5. Salvage index (MRI)	5. 90 d
	6. Infarct size (MRI)	6. 90 d
	7. LVEF (MRI/echo)	7. 90 d/1 y
	8. Microvascular obstruction	8. 48 h
	9. Quality of life	9. 1 y
DANAMI 3-PRIMULTI	**Culprit only vs complete revascularization**	**Timeframe**
Primary end point (composite)	All-cause mortality, myocardial infarction, or ischemia (either subjective or objective)–driven revascularization of nonculprit coronary lesions.	1 y
Secondary end points	1. All of the above components	1. 1 y
	2. Cardiac death or myocardial infarction	2. 1 y
	3. Hospitalization for ACS or acute heart failure	3. 1 y
	4. Angina status	4. 1 y
	5. Quality of life	5. 1 y
	6. Myocardial salvage (MRI)	6. 90 d
	7. LVEF (echo)	7. 1 y
	8. Cardiac death, myocardial infarction, repeat revascularization, or occurrence of definite stent thrombosis (according to ARC definition) of nonculprit lesions	8. 1 y

Abbreviations: *echo*, Echocardiography; *LVEF*, left ventricular ejection fraction; *ACS*, acute coronary syndrome; *ARC*, Academic Research Consortium.

In the DANAMI 3-DEFER study, we expected event rates to differ substantially between patients with TIMI flow grade 0 to 1 and TIMI flow grade 2 to 3 at randomization. For this reason, we decided to analyze in 2 strata depending on prerandomization TIMI flow grade and report these results separately as prespecified hypothesis-generating analyses. A combined analysis of both 2 strata was planned as the primary analyses. For the primary end point, we estimated an annual event rate of 13% in the 2 strata combined, as we also included repeated urgent and nonurgent target vessel revascularization and myocardial infarction in the end point. With an inclusion period of 2½ years and a minimum follow-up of 2 years, we will be able to detect a relative reduction of 25% in the primary end point, with a 2-sided α level of .05 and a power of 80% by enrolling 920 patients.

For the DANAMI 3-PRIMULTI study, we estimated the primary end point to occur with an annual rate of 18% in the group treated for the infarct lesion only. With an inclusion period of 2½ years and a minimum follow-up of 1 year, we were able to detect a relative reduction of 30% in the primary end point, with a 2-sided α level of .05 and a power of 80% by enrolling 618 patients. This study was stopped after inclusion of 627 patients.

Table IV. Randomized treatment allocation—postconditioning versus conventional treatment (DANAMI 3-iPOST)

Treatment	Conventional	iPOST	All patients
Randomized	624	628	1252
Unable to achieve TIMI 2-3	7	11	18
In analyses	617	617	1234

Table V. Randomized treatment allocation—deferred stenting versus conventional treatment (DANAMI 3-DEFER)

Treatment	Conventional	DEFER	All patients
Randomized	616	607	1223
Unable to achieve TIMI 2-3	4	4	8
In analyses	612	602	1215

The end points will be analyzed using the log-rank test and Cox regression as the secondary analysis. An additional follow-up after 4 years is planned in all studies, focusing on the combined end point of all-cause mortality and hospitalization for heart failure. Although patients who did not achieve TIMI 2 or 3 flow during the index procedure are excluded from primary analyses, additional sensitivity analyses including these patients will be performed.

Ethical considerations

The protocol of the trial has been approved by our regional ethics committee, the collection of data complies with the regulatory rules of the Danish Data Protection Agency (2007-41-1667), and the study is being conducted in compliance with the Helsinki II Declaration. Particular care was taken to ensure that the primary PCI procedure was not delayed due to the information procedure. During preparation for the invasive procedure, the patient was briefly informed of the rationale for the study and main consequences of participation, including a potential need for an additional procedure and additional PCI, and provided written consent. After completion of the procedure and clinical stabilization if needed, the patients were informed in full detail and were given the opportunity to withdraw consent if wished. The institutional ethics committee in Denmark approved this procedure.

Based on previous experiences, iPOST can be performed without additional procedure-related risk.[7,10] We have previously published data from a series of STEMI patients treated with DEFER, suggesting that this can be performed with little or no additional risk to the patient.[19] The need for an additional procedure in patients randomized to DEFER may be associated with an increased risk of reocclusion of the IRA and procedure-related complications, such as bleeding. Given the potential benefit induced by a reduction in microvascular injury, we consider this risk counterbalanced. Similar considerations were made in the PRIMULTI part of the trial regarding a potential clinical benefit from treatment of all coronary lesions (vs IRA only) in connection with the repeat procedure performed in patients with multivessel disease randomized to complete revascularization.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

During the inclusion period, 4,370 patients referred from emergency medical services or local hospitals for primary PCI were screened. Of these, 516 were excluded as the diagnosis of STEMI was waived upon arrival at the catheterization laboratory, based on reevaluation of electrocardiogram, physical examination, or angiographic findings. Patients in whom the STEMI diagnosis was excluded were treated at the discretion of the attending physicians. In addition, 1,615 patients with STEMI were excluded for reasons summarized in Table II. The remaining 2,239 patients were randomized in the program with 1,252 patients randomized in the DANAMI 3-iPOST trial (Table IV) and 1,223 in the DANAMI 3-DEFER trial (Table V). Patients randomized to conventional treatment, who had TIMI flow grade 0 or 1 at the time of catheterization and in whom a potential allocation to DEFER had not been considered inappropriate by the treating physician (for either procedure-related or logistical reasons), served as controls in both DANAMI 3-iPOST and DANAMI 3-DEFER (n = 236) (Figure). At the end of the index procedure, the physician had been unable to achieve a stable TIMI flow grade 2 or 3 in 22 patients (1.0%), who were secondarily excluded, because neither iPOST nor a DEFER strategy would be clinically meaningful in this setting. Of the remaining 2,215 patients, 627 (28.3%) had non-IRA stenoses, potentially suitable for PCI, and were randomized in the DANAMI 3-PRIMULTI trial (Table VI).

Summary

The DANAMI 3 trial program encompasses 3 randomized trials nested in a Danish multicenter setup, in which 2,239 STEMI patients undergoing primary PCI were enrolled, to test 3 hypotheses: (1) will iPOST reduce reperfusion injury and subsequently improve outcome, (2) will DEFER reduce distal embolization and subsequently reduce myocardial damage and improve clinical outcome, and (3) will FFR-guided full revascularization of nonculprit lesions in STEMI patients be superior to culprit revascularization only.

Inclusion has been finalized by February 2014, and the primary end point of DANAMI 3-iPOST and DANAMI 3-DEFER will be concluded on February 2016 and DANAMI 3-PRIMULTI on February 2015.

Table VI. Randomized treatment allocation—infarct-related lesion versus complete revascularization (DANAMI 3-PRIMULTI)

Treatment	Patients
Infarct-related lesion only	313
Complete revascularization	314
	627

Appendix. DANAMI 3 committee members and investigators

DANAMI 3 steering committee

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