Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial


Summary

Background Despite successful treatment of the culprit artery lesion by primary percutaneous coronary intervention (PCI) with stent implantation, thrombotic embolisation occurs in some cases, which impairs the prognosis of patients with ST-segment elevation myocardial infarction (STEMI). We aimed to assess the clinical outcomes of deferred stent implantation versus standard PCI in patients with STEMI.

Methods We did this open-label, randomised controlled trial at four primary PCI centres in Denmark. Eligible patients (aged >18 years) had acute onset symptoms lasting 12 h or less, and ST-segment elevation of 0.1 mV or more in at least two or more contiguous electrocardiographic leads or newly developed left bundle branch block. Patients were randomly assigned (1:1), via an electronic web-based system with permuted block sizes of two to six, to receive either standard primary PCI with immediate stent implantation or deferred stent implantation 48 h after the index procedure if a stabilised flow could be obtained in the infarct-related artery. The primary endpoint was a composite of all-cause mortality, hospital admission for heart failure, recurrent infarction, and any unplanned revascularisation of the target vessel within 2 years’ follow-up. Patients, investigators, and treating clinicians were not masked to treatment allocation. We did analysis by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01435408.

Findings Between March 1, 2011, and Feb 28, 2014, we randomly assigned 1215 patients to receive either standard PCI (n=612) or deferred stent implantation (n=603). Median follow-up time was 42 months (IQR 33–49). Events comprising the primary endpoint occurred in 109 (18%) patients who had standard PCI and in 105 (17%) patients who had deferred stent implantation (hazard ratio 0.99, 95% CI 0.76–1.29; p=0.92). Procedure-related myocardial infarction, bleeding requiring transfusion or surgery, contrast-induced nephropathy, or stroke occurred in 28 (5%) patients in the conventional PCI group versus 27 (4%) patients in the deferred stent implantation group, with no significant differences between groups.

Interpretation In patients with STEMI, routine deferred stent implantation did not reduce the occurrence of death, heart failure, myocardial infarction, or repeat revascularisation compared with conventional PCI. Results from ongoing randomised trials might shed further light on the concept of deferred stenting in this patient population.

Funding Danish Agency for Science, Technology and Innovation, and Danish Council for Strategic Research.

Introduction Timely primary percutaneous coronary intervention (PCI) with balloon dilatation and stent implantation is the standard treatment for patients with ST-segment elevation myocardial infarction (STEMI). However, in some patients this procedure causes reduced coronary blood flow, despite a patent epicardial vessel, or distal embolisation—complications that are associated with impaired prognosis. Because most infarct-related lesions contain residual thrombus after wiring and balloon dilatation, removal of the thrombus has been regarded as an important part of primary PCI. However, randomised trials of mechanical and manual thrombectomy and distal protection did not give consistent results, whereas pharmacological treatment seemed more promising.

Registry data suggest that an alternative strategy of delaying or deferring stent implantation, after a stable blood flow has been secured in the infarct-related artery, could preserve coronary blood flow and reduce the risk of embolisation, and thereby potentially improve clinical outcome. Deferred stenting seems to both reduce thrombus burden and increase myocardial salvage in patients with STEMI, and stent implantation per se has never consistently been associated with improved outcome. On the other hand, there is a risk of reocclusion when the infarct-related artery is left unstented. Thus, it remains to be evaluated whether the risk of reocclusion of the infarct-related artery in the period between the index and deferred procedure, in addition to potential complications related to another invasive procedure, would be outweighed by a lower risk of embolisation and flow disturbances in the vascular bed distal to the infarct lesion. Also unknown is whether a possible...
Research in context

Evidence before this study
We searched PubMed, MEDLINE, and ClinicalTrials.gov from January, 2000, to February, 2016, for studies published in English or ongoing studies comparing standard or immediate versus deferred or delayed stent implantation of the culprit vessel in patients undergoing primary percutaneous coronary intervention (PCI). With the search terms “delayed stent implantation” and “deferred stent implantation”, together with “primary percutaneous coronary intervention”, and “ST-segment elevation myocardial infarction”, we identified five small registries at the time of search, whereas two studies (one registry and one randomised study) were published during our trial. In Cañés and colleagues’ 2004 study, deferred PCI after intensive pharmacological treatment resulted in a reduction in thrombus-related angiographic events. In a study by Isaaz and colleagues in 2006, ST-segment resolution and thrombolysis in myocardial infarction flow was improved when stent implantation was postponed for at least 24 h. In 2009, Meneveau and colleagues showed that in patients referred for primary or rescue PCI and matched for demographic and procedural characteristics, delaying of stent implantation for 24 h also reduced flow disturbances and distal embolisation. Similar findings were reported in 2011 by Tang and colleagues, who grouped their patients according to a residual thrombus burden score after thrombus aspiration into immediate stent implantation in patients with low score and delayed stent implantation in patients with a high score. These investigators reported an improved echocardiographic wall motion score in patients who had delayed stent implantation. Finally, in 2012, Ke and colleagues identified patients with a high thrombus burden after acute thrombectomy and, in addition to improvements in coronary blood flow parameters, reported both an increased left ventricular ejection fraction and a reduced occurrence of cardiac events when stent implantation was deferred for at least 7 days.

During the present trial, we published a registry of 124 consecutive patients with STEMI, in whom the blood flow through the infarct-related lesion could be stabilised in 90% without stent implantation. The myocardial salvage evaluated by magnetic resonance was high and the occurrence of subsequent cardiac events was low. Another magnetic resonance study by Carrick and colleagues showed an improvement in both myocardial salvage and in coronary blood flow in patients at high risk randomised to deferred stent implantation versus patients treated with standard PCI.

Added value of this study
In this open-label, randomised controlled DANAMI 3-DEFER trial—the largest of its kind so far—we investigated whether deferred stent implantation compared with standard PCI would improve the clinical outcomes of patients with STEMI. Our findings show that deferred stent implantation 48 h after the index primary PCI procedure did not reduce the risk of death, heart failure, or reinfarction compared with standard immediate stent implantation in patients with STEMI. Routine deferred stenting was associated with an increased rate of target vessel revascularisation.

Implications of all the available evidence
Whereas most previous studies have indicated an improvement in angiographic, electrocardiographic, or imaging parameters in patients treated with deferred stent implantation, none have addressed clinical endpoints in a randomised setting. So, the question has been whether the improvements in surrogate endpoints shown in these registries and small randomised studies translate into clinical endpoints. Our trial answers some of these questions, in that the results show no difference in any clinical endpoint, not even when they are combined. However, despite an increased risk of reocclusion during the waiting period for the second procedure, we recorded a small difference in left ventricular function at 18 months in favour of deferred stent implantation. Our study does not explain why deferred stent implantation does not improve outcome or whether there might still be a place for this treatment approach in high-risk patients. We eagerly await the results of ongoing randomised trials (MIMI, NCT01360242; INNOVATION, NCT02324348; and PRIMACY, NCT01542385), which might shed further light on the concept of deferred stenting in STEMI.

Methods

Study design and patients
We did this open-label, randomised controlled trial at four primary PCI centres in Denmark. We included patients (aged >18 years) presenting with chest pain of less than 12 h duration, and ST-segment elevation greater than 0.1 mV in at least two contiguous leads. Members of the invasive PCI team (HK, TE, SH, LH, EJ, FP, KS, PC, ODB, HEB, CJT, EHC, JR, H-HT, ABV, JA, SEJ, BR, LOJ) asked eligible patients to participate in the trial. Major exclusion criteria included intolerance of contrast media or of the relevant anticoagulant or antithrombotic medication, unconsciousness or cardiogenic shock, stent thrombosis, indication for acute coronary artery bypass surgery, or increased bleeding risk. Patients with stenosis of 50% or more in diameter (angiographically determined) in one or more non-infarct-related arteries were eligible to participate in the DANAMI-3-PRIMULTI trial.97

benefit of deferred stenting will reduce the risk of subsequent impairment of left ventricular function and ensuing development of heart failure.

We did the DANAMI 3-DEFER trial to assess whether deferred stent implantation compared with conventional primary PCI would reduce the risk of jeopardised myocardial vascular flow and improve the clinical course of patients with STEMI.
The study protocol for the present trial was approved by the ethics committee of the Capitol Region and has been previously published elsewhere.\(^a\) We did this study in accordance with the Declaration of Helsinki, and ethics committee approval was received, according to local regulations. Data were gathered electronically and stored at the clinical trials unit at Rigshospitalet, Copenhagen. All patients provided written informed consent.

Randomisation and masking
Patients were randomly assigned (1:1), via an electronic web-based system with permuted block sizes of two to six, to receive either deferred stent implantation or conventional PCI.\(^b\) Patients, investigators, and treating clinicians were not masked to treatment allocation. The invasive PCI team had no further involvement in subsequent treatment or assessment of the patients.

Procedures
In patients with an angiographic thrombolysis in myocardial infarction (TIMI) flow of 0–1 in the infarct-related artery on arrival at study centres, the lesion was wired, and thrombectomy and balloon dilatation were done if necessary (with a balloon diameter substantially smaller than the reference size of the vessel) to restore and stabilise TIMI 2–3 flow using as little manipulation of the lesion as possible.\(^c\) In patients with TIMI flow 2–3 at arrival, clinicians judged whether wiring, thrombectomy, and balloon dilatation of the lesion were needed to stabilise flow.

In patients assigned to receive deferred stent implantation, we recommended retraction of the coronary guidewire (if one was inserted in the artery) followed by 10 min of observation to assure stability of the lesion before removal of the sheath, and intravenous administration of either a glycoprotein IIb/IIIa antagonist or bivalirudin for at least 4 h after the index procedure. Repeat coronary angiography with the intention to implant a stent in the infarct-related artery was scheduled about 48 h (at least 24 h) after the index procedure. If the infarct-related lesion was deemed stable at the second examination (<30% residual stenosis, no significant thrombus burden, and no visible dissection) stent implantation could be waived. In that case, patients were offered an additional control angiography 3 months after the second examination.\(^d\)

In patients assigned to receive conventional treatment, PCI was done (preferably including immediate stent implantation with drug-eluting stents) according to local routines. A transthoracic echocardiography was scheduled at least 12 months after the index PCI, and the examination was done with use of a standardised protocol. Left ventricular ejection fraction was estimated with the biplane Simpson’s method and reported by the examining technician, and images were reviewed by an experienced cardiologist (KFK or LKø) who was masked to treatment allocation.

We followed up all patients at their local hospitals with a general policy of encouraging them to participate in rehabilitation programmes. All additional patient management during admission and follow-up, including anticoagulant and antithrombotic regimens, was done in accordance with contemporary guidelines and at the discretion of the treating clinicians.

Outcomes
The primary endpoint was a composite of all-cause mortality, hospital admission for heart failure, recurrent myocardial infarction, or unplanned revascularisation of the infarct-related artery. Key prespecified secondary endpoints were the components of the primary endpoint, cardiac mortality, TIMI flow after the procedure, and left ventricular function evaluated with echocardiography at

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\(^a\) We included 1223 patients, of whom eight patients (n=4 in each group) were excluded secondarily because TIMI flow 2–3 was never obtained.

\(^b\) 4370 patients screened for eligibility

\(^c\) 2639 excluded

\(^d\) 3854 had STEMI confirmed

\(^e\) 516 excluded

\(^f\) 516 did not have STEMI

\(^g\) 1215 randomly assigned†

\(^h\) 603 allocated to receive deferred stent implantation

\(^i\) 603 included in intention-to-treat analysis

\(^j\) 612 allocated to receive conventional PCI

\(^k\) 612 included in intention-to-treat analysis

\(^l\) 603 allocated to receive deferred stent implantation

\(^m\) 603 included in intention-to-treat analysis

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STEMI=ST-segment elevation myocardial infarction. CABG=coronary artery bypass graft operation. PCI=percutaneous coronary intervention. TIMI=thrombolysis in myocardial infarction. *20 patients met two criteria for exclusion. †We included 1223 patients, of whom eight patients (n=4 in each group) were excluded secondarily because TIMI flow 2–3 was never obtained.
least 1 year after the index PCI (at one centre). We identified data for study outcomes from the National Danish Heart Registry and from local registries of invasive data, and used hospital records for validation by the events committee.

Safety measurements were monitored by an independent data safety monitoring board, and all events were adjudicated by an independent clinical events committee, which justifies the open-label design of the trial. Deaths were classified as cardiac related unless they could be clearly attributed to another cause, as determined by the clinical events committee. A recurrent myocardial infarction was defined as typical chest pain accompanied by a rise of more than two times the upper reference limit of troponin, development of new Q waves on the electrocardiogram, or both. Stroke was defined as neurological deficiencies that developed within 24 h of the procedure and that lasted for at least 12 h. Contrast-induced nephropathy was defined as an increase of more than 50% in plasma creatinine.

Statistical analysis
For the primary endpoint, we estimated a 13% annual event rate in a combined analysis of the two strata. With an inclusion period of 2–5 years and a minimum follow-up of 2 years, 920 patients would need to be enrolled to detect a relative 25% reduction in the primary endpoint, with a two-sided α of 0.05 and 80% power. We assessed differences between groups in time-to-event endpoints with the log-rank test, and used the Kaplan–Meier method to present survival probabilities. We calculated hazard ratios (HRs) between groups using a Cox proportional hazards model. The assumption of the proportional hazard, linearity of continuous variables, and absence of interaction were deemed valid unless otherwise indicated. We assessed differences between group means and medians with the Student’s t test for unpaired samples or Mann–Whitney’s tests, and used χ² or Fisher’s exact tests to test differences between proportions. Because patients could also be included in the DANAMI-3-PRIMULTI trial, we tested for interaction with this treatment. We did post-hoc subgroup analyses for exploratory purposes. We did analyses by intention to treat. Statistical analyses were done with Stata (version 13.1). This trial is registered with ClinicalTrials.gov, number NCT01435408.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the trial profile. Between March 1, 2011, and Feb 28, 2014, we randomly assigned 1215 patients to receive conventional primary PCI (n=612) or deferred stent implantation (n=603). Baseline characteristic data were well balanced between groups (table 1). Median follow-up of all participants was 42 months (IQR 33–49), with the exception of eight patients (n=3 in the conventional PCI group and n=5 in the deferred stent implantation group) who emigrated after 8 months (5–13). All patients received optimum medical treatment, clinical assessment including echocardiographic control, implantation of intracardiac defibrillator whenever indicated, and rehabilitation according to national guidelines. Use of stents was lower in patients allocated to receive deferred stent implantation, and the antithrombotic regimen slightly different, than in those allocated to receive conventional PCI; otherwise, procedural characteristics and patient management at discharge did not differ between the groups (table 2). One (<1%) patient in each group had acute coronary artery bypass surgery, because of unstable flow and difficulties implanting a stent in the culprit lesion.

In patients in the deferred stent implantation group, reangiography was done a median of 3 days (IQR 1–4) after the index procedure, and in 85 (14%) patients the infarct-related lesion was deemed stable enough to waive stent implantation. 131 (22%) patients had a stent implanted during the PCI (crossovers), because the lesion or the coronary blood flow was deemed too unstable by the invasive cardiologist to allow deferral of the stent implantation. 11 (2%) patients planned to undergo deferred stenting had a stent implanted before the scheduled deferred procedure because of recurrent symptoms or ST-segment elevation. In eight of these

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Conventional PCI group (n=612)</th>
<th>Deferred stent implantation group (n=603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male</td>
<td>454 (74%)</td>
<td>457 (76%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>158 (26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146 (24%)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (9%)</td>
<td>56 (9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>249 (41%)</td>
<td>245 (41%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>308 (51%)</td>
<td>328 (54%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>45 (7%)</td>
<td>35 (6%)</td>
</tr>
<tr>
<td>Infarct location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>287 (47%)</td>
<td>252 (42%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>296 (48%)</td>
<td>322 (51%)</td>
</tr>
<tr>
<td>Posterior</td>
<td>26 (4%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>3 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Symptom onset to intervention (min)</td>
<td>168 (120–264)</td>
<td>168 (126–270)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>241 (39%)</td>
<td>248 (41%)</td>
</tr>
</tbody>
</table>

Data are median (range), median (IQR), or n (%). PCI=percutaneous coronary intervention.
patients the infarct-related artery was reoccluded or stenosis had worsened compared with that seen at the end of the index procedure. Reocclusion causing reinfarction occurred in one (<1%) patient during the last half of the study period.

In patients assigned to conventional primary PCI, nine (1%) patients did not have a stent implanted because of technical problems or risk of distal embolisation in connection with immediate stent implantation (crossovers). Four (<1%) patients in this group underwent an urgent PCI procedure during the index hospital admission, three of whom had supplementary stent implantation in the infarct-related artery (one patient had acute stent thrombosis).

The composite primary endpoint of all-cause mortality, hospital admission for heart failure, recurrent infarction, and any unplanned revascularisation of the target vessel occurred in 109 (18%) patients in the conventional primary PCI group and 105 (17%) patients in the deferred stent implantation group (figure 2). HRs for the individual components of the composite endpoint were 0·83 (95% CI 0·56–1·20; p=0·37) for all-cause mortality, 0·82 (0·47–1·40; p=0·49) for hospital admission for heart failure, 1·10 (0·69–1·60; p=0·49) for non-fatal recurrent myocardial infarction, and 1·70 (1·04–2·92; p=0·0342) for unplanned target vessel revascularisation. There were no significant differences in the occurrence of cardiac-related deaths between groups (table 3). A per-protocol and an as-treated analysis did not change these findings substantially (appendix).

Echocardiography was done in 775 (64%) patients a median of 18 months (IQR 17–19) after the index PCI. Left ventricular ejection fraction was slightly higher in patients who received deferred stent implantation than in those who received conventional PCI (54·8% vs 53·5%; p=0·0431; table 4).

Serious events related to the additional revascularisation procedures occurred in a few patients, with no significant differences between groups (table 5). Three of the complications in the deferred stenting group were associated with the second procedure.

The primary outcome was consistent across subgroups (appendix), and flow disturbances and distal embolisation were reported in less than 10% of patients (data not shown). Subgroup analyses did not show any significant differences in the primary endpoint between groups. No significant interaction was shown between complete revascularisation and deferred stenting (appendix).

See Online for appendix
Table 3: Clinical outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional PCI group (n=612)</th>
<th>Deferred stent implantation group (n=603)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite primary endpoint</td>
<td>109 (18%)</td>
<td>105 (17%)</td>
<td>0.99 (0.75–1.30)</td>
<td>0.92</td>
</tr>
<tr>
<td>All-cause death</td>
<td>53 (9%)</td>
<td>44 (7%)</td>
<td>0.83 (0.56–1.20)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hospital admission for heart failure</td>
<td>28 (5%)</td>
<td>23 (4%)</td>
<td>0.82 (0.47–1.40)</td>
<td>0.49</td>
</tr>
<tr>
<td>Non-fatal myocardial reinfarction</td>
<td>40 (7%)</td>
<td>42 (7%)</td>
<td>1.10 (0.69–1.60)</td>
<td>0.49</td>
</tr>
<tr>
<td>Any unplanned target vessel revascularisation</td>
<td>23 (4%)</td>
<td>39 (7%)</td>
<td>1.70 (1.04–2.92)</td>
<td>0.0345</td>
</tr>
</tbody>
</table>

Secondary endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional PCI group (n=612)</th>
<th>Deferred stent implantation group (n=603)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td>26 (4%)</td>
<td>22 (4%)</td>
<td>0.85 (0.48–1.50)</td>
<td>0.58</td>
</tr>
<tr>
<td>Target vessel revascularisation by PCI</td>
<td>21 (3%)</td>
<td>32 (5%)</td>
<td>1.50 (0.90–2.70)</td>
<td>0.11</td>
</tr>
<tr>
<td>Target vessel revascularisation by coronary artery bypass graft surgery</td>
<td>3 (&lt;1%)</td>
<td>8 (1%)</td>
<td>2.70 (0.71–10.1)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise specified. PCI=percutaneous coronary intervention.

Table 4: Left ventricular ejection fraction at 18 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional PCI group (n=392)</th>
<th>Deferred stent implantation group (n=383)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>57 (50–60)</td>
<td>60 (50–60)</td>
<td>0.0420</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction ≤45%</td>
<td>70 (18%)</td>
<td>49 (13%)</td>
<td>0.0506</td>
<td></td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%), unless otherwise specified. PCI=percutaneous coronary intervention.

Table 5: Procedure-related complications

<table>
<thead>
<tr>
<th>Event</th>
<th>Conventional PCI group (n=612)</th>
<th>Deferred stent implantation group (n=603)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any procedure-related complication</td>
<td>28 (5%)</td>
<td>27 (4%)*</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Penprocedural myocardial infarction</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)*</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring transfusion or surgery</td>
<td>7 (1%)</td>
<td>11 (2%)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Contrast-induced nephropathy†</td>
<td>15 (2%)</td>
<td>11 (2%)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%). PCI=percutaneous coronary intervention. *Two patients had two complications. †50% rise in plasma creatinine.

Discussion

Our findings show that routine deferred stent implantation 48 h after the index primary angiography and PCI procedure did not improve the composite primary endpoint of all-cause death, development of heart failure, reinfarction or repeat revascularisation compared with conventional primary PCI. This finding differs from previous reports of smaller registries, which all showed an improvement in angiographic, electrocardiographic, and even clinical outcomes.9–11

Distal embolisation occurs in 5–10% of patients with STEMI treated with primary PCI and contemporary medication, and is associated with an increased risk of reinfarction and development of heart failure.20,21 The risk is particularly high in selected patients with a high thrombus burden,22 therefore, removal of the thrombus formation or part of it by mechanical or manual thrombectomy has been considered a potential solution. In a previous single-centre study, thrombectomy reduced cardiac mortality,23 a finding that could not be confirmed in subsequent larger multicentre trials.23,24

Intraprocedural flow reduction (slow or no flow) in connection with primary PCI was reported in many patients in previous studies, and has been regarded a strong predictor of long-term mortality.23,24 Thus, residual thrombus might best be left to dissolve during subsequent intensive antiplatelet therapy before stent implantation takes place. We have tested this concept in patients with STEMI, with results showing that deferred stent implantation can be done safely, that thrombus burden decreases considerably after 48 h, and that stent implantation can be avoided in some patients.24 In a meta-analysis,25 Freixa and colleagues concluded that the improved angiographic outcome in patients treated with deferred or delayed stent implantation seemed promising, but that randomised trials were needed to evaluate clinical outcomes. In another trial,26 which included patients at high risk of flow disturbances in connection with primary PCI, and selected by use of both clinical and angiographic criteria, Carrick and colleagues reported improved outcome in patients who had their stent implantation deferred for 4–16 h. Occurrence of flow abnormalities was higher and myocardial salvage lower in patients who had stents implanted immediately than in those who had deferred implantation.26

The primary outcome of our trial was consistent in subgroups of patients who might be expected to have an increased risk of flow reduction during stent implantation. Additionally, the investigator-reported occurrence of flow disturbance and embolisation was lower than expected. The non-significant numerical differences in mortality and heart failure in favour of deferred stent implantation were less pronounced and the frequency of target vessel revascularisation higher than expected, meaning the resultant primary endpoint was statistically neutral. The main cause of the significantly higher target vessel revascularisation rate in the deferred versus the conventional stenting group is the nearly 2% occurrence of reocclusion or worsening of the culprit lesion before the scheduled PCI, which provokes concern because it can lead to a potentially devastating clinical condition of the patients. Thus, deferred stenting can only be recommended in cases in which these complications are counterbalanced by a preponderance of clinical benefits, such as long-term...
improvement in the left ventricular function in this group by comparison with patients who were stented immediately. Whether the small difference in left ventricular ejection fraction at 1-5 years in favour of deferred stent implantation will translate into improved survival in the long-term remains to be determined. However, that the reocclusion rate seemed to diminish during the course of the trial is reassuring, and probably represents a learning curve of the ability to predict whether a reopened infarct-related lesion is stable enough to allow deferral of stent implantation. In a similar trial, reocclusion before the planned stent implantation occurred in 4% of patients. Another point to consider is that some patients in the conventional group of our trial also had serious events in the early phase of their disease after immediate stent implantation.

There are several possible reasons for the discrepancy between previous studies and the results of the present trial. First, our study is a multicentre trial, is comparatively large, and focuses mainly on clinical endpoints. Second, our participants were unselected patients with STEMI rather than high-risk patients, and we cannot rule out that deferred stent implantation might be more effective in selected patients. Third and probably most important, our trial is randomised, emphasising the limitations often encountered when findings from preliminary single-centre registries or efficacy trials do not translate into real-life practice because of a change in directed attention and assessments applied during the non-randomised trials.

Three randomised trials are underway. In the first two trials, the magnitude of microvascular obstruction and infarct size in patients treated with standard primary PCI will be compared with that of patients having their stent implanted 24-48 h (the MIMI trial, NCT01360242) or 5-7 days (the INNOVATION trial, NCT02324348) after the index procedure. In a third ongoing randomised trial, clinical endpoints similar to those assessed in our trial will be compared in patients treated with either immediate or stent implantation 4-7 days after the index procedure (the PRIMACY trial, NCT01542385).

In the present trial we focused on an endpoint combined of so-called hard clinical events and the somewhat softer event of target vessel revascularisation, which might be regarded as of less clinical importance, except in the case of potential life-threatening early reocclusion before scheduled deferred stent implantation. Although our study is the largest of its kind so far, it is restricted in size, which, taken together with the lower than expected event rate, weakened the likelihood of a significant result. Furthermore, the small numerical differences in mortality and heart failure hospital admission in favour of deferred stent implantation were outweighed by a significantly higher rate of unplanned repeat PCI or coronary artery bypass surgery in this group than in the conventional PCI group. Another limitation was that according to the trial protocol, randomisation had to be done before PCI. Had randomisation taken place after a stable flow in the infarct-related artery was obtained, we could have limited the number of patient crossovers to immediate stent implantation. However, this design allows for interpretation of the results in the context of an intention-to-treat approach, and thus for future unselected STEMI patients. Additionally, the analysis done in the as-treated population did not show any substantial differences in the endpoints. With the exception of situations when patients had to be transferred to their local hospitals because of insufficient ward capacity at the PCI centre, we enrolled unselected patients with STEMI, including those with low risk of flow disturbances and distal embolisation, a group that is probably less responsive to deferred stenting than a selected population. Detailed selection of patients with increased risk of slow or no flow might have given a different result. Different timing of deferred stent implantation (both earlier and later than the stipulated 48 h in our trial) might have also changed the outcome.

In conclusion, deferred stent implantation in patients with STEMI did not reduce the risk of death, heart failure, or reinfarction compared with standard immediate stent implantation. Routine deferred stenting was associated with an increased rate of target vessel revascularisation. We look forward to the results of the ongoing randomised trials, which might shed further light on the concept of deferred stenting in STEMI.

Contributors
The steering committee (TE, SH, LKs, DEH, LKL, H-HT, LOJ, HEB, and HK) designed the trial. The writing committee (HK, TE, SH, LKL, DEH, and LKs) gathered data, did statistical analyses, and wrote the report. All authors contributed to implementation of the study and data interpretation, and approved the report for publication. Other contributors are listed in the appendix. Clinical events committee—Kristian Thygesen (Chairman; Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark), Anders Galle (Department of Cardiology, Roskilde Hospital, Roskilde, Denmark), and Jørgen Jeppesen (Department of Medicine, Copenhagen University Hospital Glostrup, Glostrup, Denmark). Data safety monitoring board—Gorm Boje Jensen (Chairman; Department of Cardiology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark), Gunnar Gislasson (Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark), and David Erlinge (Department of Cardiology, Lund University, Lund, Sweden).

Declaration of interests
We declare no competing interests.

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