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Myocardial Damage in Patients With Deferred Stenting After STEMI

A DANAMI-3–DEFER Substudy

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ABSTRACT

BACKGROUND Although some studies found improved coronary flow and myocardial salvage when stent implantation was deferred, the DANAMI-3–DEFER (Third DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction) did not show any improvement in clinical outcome in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) and deferred stenting.

OBJECTIVES This study sought to evaluate the effect of deferred stent implantation on infarct size, myocardial salvage, and microvascular obstruction (MVO) in patients with STEMI.

METHODS In the present DANAMI-3 substudy, a total of 510 patients with STEMI were randomized to PCI with deferred versus immediate stent implantation. The patients underwent a cardiac magnetic resonance examination before discharge after the index procedure and again 3 months later. The primary endpoint was final infarct size.

RESULTS Deferred stenting did not reduce final infarct size (9% left ventricle [LV]; interquartile range [IQR]: 3% to 18% vs. 10% LV; IQR: 3% to 18%; $p = 0.67$). Similarly, deferred stenting was not associated with myocardial salvage index (66%; IQR: 50% to 89% vs. 67%; IQR: 49% to 88%; $p = 0.80$) or presence of MVO (43% vs. 42%; $p = 0.78$). In a post hoc analysis, stent length was the only subgroup of 7 that had an effect on outcome. In patients with a stent length ≥24 mm, deferred stenting reduced the final infarct size (6% LV; IQR: 2% to 18% vs. 13% LV; IQR: 7% to 23%; $p = 0.006$; and p for interaction $= 0.005$).

CONCLUSIONS In the DANAMI-3–DEFER cardiac magnetic resonance substudy, routine deferred stenting did not reduce infarct size or MVO and did not increase myocardial salvage. These results do not support the use of routine deferred stenting in STEMI patients treated with primary PCI. (DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction [DANAMI-3]; NCT01435408) (J Am Coll Cardiol 2017;69:2794–804)

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In patients with ST-segment elevation myocardial infarction (STEMI), timely primary percutaneous coronary intervention (PCI), including stent implantation, is the recommended treatment (1,2). Primary PCI is performed to restore coronary blood flow, and thereby improve myocardial salvage and reduce myocardial infarct size, which results in improved prognosis (3). However, the PCI procedure may be complicated by coronary blood flow disturbances, leading to myocardial hypoperfusion, which is related to larger infarct size and impaired prognosis (4–10). Thus, every step should be taken to prevent such flow disturbances to improve the outcome in patients treated with primary PCI.

As implantation of a coronary stent can itself lead to impaired flow (11), it has been suggested that deferred or delayed stenting may prevent coronary flow disturbances, and thereby improve outcome (12). Accordingly, DEFER-STEMI (Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or slow-reflow in Acute ST-Segment Elevation Myocardial Infarction) showed that deferred stenting improved coronary flow and myocardial salvage index (13). In DANAMI-3-DEFER (Third DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction), we did not detect any clinical benefits of deferring stent implantation compared with conservative treatment on the combined endpoint of all-cause death, admission for heart failure, reinfarction, and unplanned target vessel revascularization (14). However, the study was not powered to detect differences in the individual hard endpoints, and any potential reduction in mortality or admission for heart failure following deferred stenting could have been counterbalanced by the significantly higher rate of unplanned target vessel revascularization in the deferred stenting group (14). Moreover, we observed a small improvement in left ventricular ejection fraction (LVEF) at 18 months following deferred stenting (14). Cardiac magnetic resonance imaging (CMR) allows for accurate assessment of infarct size, myocardial salvage, and microvascular obstruction (MVO). All of these variables are associated with increased mortality and development of heart failure (15,16), and consequently serve as surrogate endpoints in studies evaluating myocardial function after primary PCI.

In this paper, we present the results of the DANAMI-3-DEFER CMR substudy, describing the effect of a strategy of deferred stent implantation on infarct size, myocardial salvage index, and MVO.

METHODS

STUDY DESIGN AND POPULATION. This is a CMR substudy of the DANAMI-3-DEFER trial, of which the randomization and treatment allocation were described previously (14,17). In brief, patients with STEMI presenting within 12 h after symptom onset with ≥1 mV ST-segment elevation in at least 2 contiguous leads of the electrocardiogram were randomized 1:1 to either conventional PCI or PCI with deferred stent implantation. For the purpose of the present substudy, additional exclusion criteria were claustrophobia and/or other contraindications to CMR. A total of 1,215 patients were included in the main trial at 2 centers and were evaluated for the primary endpoint, which was a composite of all-cause mortality, reinfarction, admission for heart failure, and target vessel revascularization after a minimum 2 years of follow-up. Patients with multivessel disease were further randomized to staged fractional flow reserve (FFR)-guided complete revascularization or infarct-related artery-only PCI (18). All patients were included after written informed consent, and the national ethics committee approved the protocol. The trial was performed in accordance with the Helsinki declaration and registered with ClinicalTrials.gov (NTC01435408).

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In the deferred stenting group, thrombectomy and balloon dilatation were performed at the operator's discretion to achieve a stable Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 or 3, but the operator was encouraged to use as little mechanical manipulation as possible, using small-sized balloons to establish flow. A 10-min period was recommended to ensure a stable TIMI flow grade 2 or 3 after guidewire removal. The use of a glycoprotein IIb/IIIa inhibitor for 12 to 18 h or bivalirudin intravenously for 4 h post-PCI was also encouraged. Stent implantation was postponed at least 24 h after the index procedure.

In the conventional group, PCI including stent implantation was performed and additional antithrombotic medication was administered according to current guidelines.

CMR SUBSTUDY. The present CMR substudy was undertaken at 1 of the participating centers (Rigshospitalet, Copenhagen University Hospital, Denmark). Patients underwent a CMR examination

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

FFR = fractional flow reserve

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

MVO = microvascular obstruction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

before discharge after the index procedure (acute CMR), and a second examination approximately 90 days later (follow-up) to assess acute and final infarct size, acute and final myocardial salvage index, MVO, LVEF, and left ventricular (LV) volumes. Both examinations were performed on a 1.5-T scanner (Siemens, Erlangen, Germany) using a 6-channel body-array coil. Scout images, as well as 2-, 3-, and 4-chamber images, were used to set up the short-axis image plane. The area at risk was assessed on the initial examination using a T_2-weighted short-tau inversion-recovery sequence (19,20). Infarct size and LVEF and LV volumes were assessed on both examinations using delayed, contrast-enhanced, electrocardiogram-triggered inversion-recovery images (21) and steady-state free precession cine images, respectively. Delayed contrast-enhanced images were obtained 10 min after intravenous injection of 0.1 mmol/kg body weight gadolinium-based contrast (Gadovist, Bayer Schering, Berlin, Germany). All images were obtained in the short-axis plane, with 8-mm slices without gaps covering the entire LV.

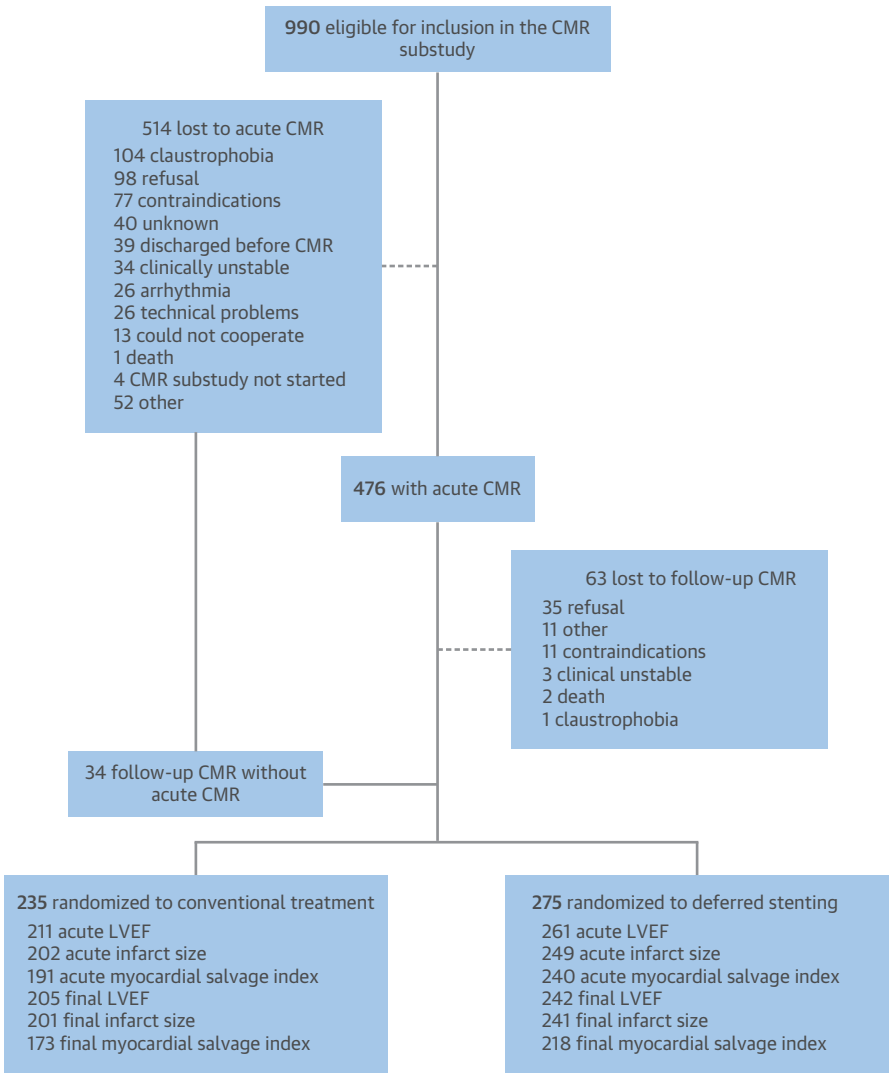
CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) was used for all quantitative CMR analyses. The analyses were performed by a reader blinded to all clinical data, including treatment allocation, and a second blinded reader approved the analyses. The area at risk was detected using the signal intensity in an area of normal myocardium + 2 SD, and infarct size by a 5 SD threshold (22,23). The normal myocardium was identified visually in each short-axis slide. Hyperintensive myocardial areas widespread in the nonculprit myocardial territory were excluded from the analysis of area at risk and infarct size. In the case of several distinct infarct territories, the culprit territory was defined on the basis of the location of edema and MVO on the CMR scan in the acute phase. In the few patients with only a follow-up scan and several distinct infarct territories, the culprit territory was defined on the basis of the initial coronary angiogram. MVO was defined as hypointense areas within the contrast-enhanced infarct region on the delayed enhanced images, and was measured manually (15). Acute and final myocardial salvage index was calculated as: area at risk (g) − acute or final infarct size (g)/area at risk (g). LVEF, LV mass, and LV volumes were measured including papillary muscles as part of the LV volume. Interobserver reproducibility was assessed in 20 randomly chosen patients, and expressed as mean difference: 0.2 ± 3.0 g for acute mass, 0.5 ± 2.0% for acute LVEF, 0.1 ± 1.0% LV for acute infarct size, and 1 ± 1% LV for area at risk.

ENDPOINTS. The primary endpoint in the present study was final infarct size, and secondary endpoints were salvage index, the occurrence and severity of MVO determined by CMR, LVEF, and LV volumes. Unpaired CMR data were included in the analyses on equal terms as paired CMR data, but these could not be included in the calculation of salvage and change from baseline to follow-up. Major adverse cardiac events (MACE) were defined as all-cause mortality, admission for heart failure, recurrent infarction, and any unplanned revascularization of the target vessel (14).

SUBGROUPS. We evaluated the outcome in the following subgroups known to be associated with increased risk of no-/slow-reflow: age (≥65 and <65 years), TIMI flow grade before PCI (0/1, 2, and 3), symptom onset to intervention (<3, 3 to 6, and >6 h), and stent length in the culprit lesion (≥24 and <24 mm) (13). Additional subgroups were sex, infarct location (anterior and nonanterior), and the use of thrombectomy. Stent length was used as an indicator of lesion length, and a 24-mm cutoff was used because the upper interquartile range (IQR) for patients without no-/slow-reflow during PCI in a large cohort was 23 mm (24). Also, long lesions result in more complex PCI (with, for example, occlusion of side branches) and may have heavier thrombus burden, which per se increases the risk of flow disturbances. Only 8 patients in the present study had vessel size ≤2.5 mm, making analysis of this particular subgroup invalid (13).

STATISTICAL ANALYSIS. Proportions were compared using chi-square or Fisher exact tests, and were presented as frequencies and percentages. Continuous variables were tested for normality, and the Student *t* test or Mann-Whitney *U* test was used to evaluate differences in mean ± SD or median (IQR) values, respectively. We also evaluated the effect of deferred stenting on infarct size in a linear regression model, adjusting for area at risk. Interaction between subgroups and treatment allocation was evaluated in an analysis of covariance. To interrogate a potential selection bias from the eligible patients who were not participating in the study (CMR nonparticipants), the effect of deferred stenting on duration to first MACE during a minimum of 2 years of follow-up was assessed in patients participating in the present CMR substudy using a Cox regression analysis. In addition, we evaluated interaction between deferred stenting and CMR participants/nonparticipants in a Cox regression model, with the time to first MACE as the dependent variable. Baseline characteristics were also compared between the patients included in

FIGURE 1 **Trial Profile**



CMR = cardiac magnetic resonance; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

the CMR substudy (participants) and CMR nonparticipants. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Figure 1 shows the trial profile. A total of 990 STEMI patients in the DANAMI-3-DEFER trial were included at the center performing CMR, and were thus considered for the CMR substudy. Of these, 510 (52%) underwent at least 1 CMR examination and were therefore included in the present study. Baseline characteristics of the patients are shown in Table 1, and PCI procedural data and discharge medication are shown in Table 2. In general, the treatment groups were well balanced, except that there were fewer stents, more treatment with glycoprotein IIb/IIIa inhibitors, and less treatment with bivalirudin in the deferred stenting group. The patients included in the present study (CMR participants) were younger, had more diabetes and hypertension, less frequently had previous myocardial infarction, had shorter time from symptoms to intervention, and were less often Killip class II to IV compared with CMR nonparticipants

TABLE 1 Baseline Characteristics of the Patients

	Conventional PCI (n = 235)	Deferred Stenting (n = 275)
Age, yrs	59.4 ± 11.5	58.4 ± 11.0
Male	179 (76.2)	217 (78.9)
Diabetes	23 (9.8)	19 (6.9)
Hypertension	85 (36.3)	99 (36.0)
Current smoking	124 (52.8)	164 (59.6)
Hyperlipidemia	88 (37.4)	95 (34.3)
Previous myocardial infarction	11 (4.7)	12 (4.4)
Infarct location		
Anterior	114 (48.5)	112 (40.7)
Inferior	112 (47.7)	150 (54.5)
Posterior	8 (3.4)	8 (2.9)
Left bundle branch block	1 (0.4)	5 (1.8)
Symptoms to intervention, h	2.6 (1.9–4.2)	2.7 (1.9–4.4)

Values are mean ± SD, n (%), or median (interquartile range). All parameters are $p > 0.05$.

PCI = percutaneous coronary intervention.

TABLE 2 Procedural Data and Medication at Discharge

	Conventional PCI (n = 235)	Deferred Stenting (n = 275)
Radial access	6 (2.6)	13 (5.3)
Total arteries treated/patient		
0	0 (0)	1 (0)
1	210 (89)	240 (87)
2	22 (9)	29 (11)
3	3 (1)	5 (2)
Total implanted stents	1 (1–2)	1 (1–2)*
Maximum stent diameter, mm	3.5 (3.0–4.0)	3.5 (3.0–3.5)
Stent length in culprit territory, mm	18 (15–23)	18 (15–24)
Total stent length, mm	22 (18–31)	18 (12–30)*
No stenting	4 (1.7)	31 (11.7)*
Pre-treatment with heparin	222 (95.3)	234 (96.7)*
Use of glycoprotein IIb/IIIa inhibitor	36 (15.5)	108 (44.6)*
Use of bivalirudin	171 (73.4)	137 (55.6)*
Thrombus aspiration	140 (59.6)	171 (62.2)
Killip class II–IV at any time	12 (5.1)	10 (3.6)
Multivessel disease	100 (42.6)	112 (40.7)
Operator-reported TIMI flow before primary PCI		
0	82 (34.9)	87 (31.6)
1	6 (2.6)	11 (4.0)
2	64 (27.2)	64 (23.3)
3	83 (35.3)	113 (41.1)
Operator-reported TIMI flow after primary PCI		
0	0 (0.0)	1 (0.4)
1	0 (0.0)	3 (1.1)
2	6 (2.6)	4 (1.5)
3	229 (97.4)	267 (97.1)
Medical therapy at discharge		
Antiplatelet therapy		
Aspirin	231 (98.3)	273 (99.3)
Clopidogrel	14 (6.0)	16 (5.8)
Prasugrel	182 (77.4)	217 (78.9)
Ticagrelor	38 (16.2)	39 (14.2)
Statin	234 (99.6)	273 (99.3)
Beta-blocker	212 (90.2)	257 (93.5)
ACE inhibitor or angiotensin-II receptor blocker	93 (39.7)	106 (38.5)
Calcium-channel blocker	24 (10.2)	16 (5.8)

Values are n (%) or median (interquartile range). *$p < 0.05$ for difference between the treatment groups.

ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

(Online Tables 1 and 2). CMR participants and non-participants also differed in their use of clopidogrel, ticagrelor, prasugrel, and statins (Online Table 2).

CMR IMAGING FINDINGS. The median time from the index PCI to the acute CMR and follow-up examinations was similar in the 2 treatment groups (time to acute CMR: 1 day; IQR: 1 to 1 day vs. 1 day; IQR: 1 to 1 day; $p = 0.12$; time to follow-up: 91 days; IQR: 88 to 94 days vs. 92 days; IQR: 89 to 97 days; $p = 0.39$, respectively).

Area at risk, acute infarct size, MVO expressed as frequency or as a percentage of LV mass, and acute myocardial salvage index did not differ between the patients treated with deferred stenting or conventional PCI (**Table 3, Central Illustration**). Accordingly, final infarct size and myocardial salvage index were also similar in the 2 treatment groups (**Table 3, Central Illustration**). Acute LVEF was slightly higher in the deferred stenting group, but the difference became insignificant at follow-up (**Table 3**). None of the LV volumes were different in the treatment groups, and no change was observed from baseline to follow-up in any CMR parameter (**Table 3**). The infarct size increased from baseline to follow-up in 69 (18%) patients, with no statistically significant difference between the groups (16% and 19%; $p = 0.52$). There was also no statistically significant difference in the incidence of patients with increased infarct size over time among patients randomized to FFR-guided complete revascularization compared with culprit-only (21% vs. 16%; $p = 0.47$). There was no statistically significant association between deferred stenting and acute ($p = 0.52$) or final infarct size ($p = 0.98$) when adjusting for area at risk in linear regression models, and there was no interaction between deferred stenting and area at risk ($p = 0.63$ and $p = 0.92$).

Among those randomized to immediate stenting, 2 (1%) patients did not have a stent implanted for clinical reasons, and 49 (18%) patients randomized to deferred stenting were immediately stented, because the interventionalist either felt unsure of the stability of the vessel flow or TIMI flow grade 2/3 could not otherwise be obtained. In a modified as-treated

analysis (excluding crossover patients), the final infarct size (as a percentage of the LV) was 10% (IQR: 3% to 18%) in those who were immediately stented and 8% (IQR: 3% to 16%) in the deferred stenting group (p = 0.19).

Final infarct size was similar across the majority of subgroups (Figure 2), although a significantly smaller final infarct size was observed in patients with stent lengths ≥24 mm in the culprit lesion compared with that of patients who received conventional treatment (Figure 2).

As in the main study, we found no reduction in the occurrence of cardiac events after deferred stent implantation in patients participating in the present study (hazard ratio: 0.97; 95% confidence interval: 0.60 to 1.56; p = 0.89). There was no interaction between deferred stenting and CMR participants/nonparticipants in a Cox regression analysis with MACE as the dependent variable (p = 0.53).

A total of 187 patients (37%) were also randomized to infarct-related artery PCI only or FFR-guided complete revascularization. Among these 187 patients, the number of patients treated with FFR-guided complete revascularization was equally divided between the immediate and deferred stenting groups (49% vs. 51%; p = 0.83), with no interaction in terms of final infarct size (p = 0.52).

TABLE 3 Outcome Evaluated by CMR

Endpoint	n*	Conventional PCI	n*	Deferred Stenting	p Value
Acute CMR median 1 day (IQR: 1 to 1 day) after PCI					
Area at risk, % LV	202	33 ± 12	229	32 ± 12	0.33
Acute infarct size, % LV	202	13 (6-24)	249	13 (6-21)	0.39
Acute myocardial salvage index, %	191	52 (35-74)	240	55 (37-75)	0.45
Presence of MVO	202	88 (43.6%)	249	105 (42.2%)	0.78
Median MVO, % LV	202	0.0 (0.0-2.0)	249	0.0 (0.0-2.3)	0.95
Median MVO for patients with MVO, % LV	87	2.6 (1.2-5.7)	104	2.7 (1.5-4.9)	0.71
Acute LVEF, %	211	50 ± 10	261	52 ± 10	0.026
Acute LV end-diastolic volume, ml	211	164 ± 37	261	162 ± 36	0.57
Acute LV end-systolic volume, ml	211	83 ± 30	261	78 ± 29	0.10
Follow-up CMR median 91 days (IQR: 88 to 96 days) after PCI					
Final infarct size, % LV	201	10 (3-18)	241	9 (3-18)	0.67
Myocardial salvage index, %	173	67 (50-89)	218	67 (49-88)	0.80
LVEF, %	205	59 ± 10	242	60 ± 9	0.25
LV end-diastolic volume, ml	205	166 ± 41	242	168 ± 39	0.67
LV end-systolic volume, ml	205	71 ± 32	242	70 ± 28	0.59
Change over time (follow-up acute)					
Infarct size, % LV	171	−4 ± 5	217	−3 ± 5	0.62
Myocardial salvage index, %	164	13 ± 16	211	12 ± 15	0.61
LVEF, %	181	8 ± 9	228	7 ± 7	0.20
LV end-diastolic volume, ml	181	1 ± 29	228	4 ± 24	0.22
LV end-systolic volume, ml	181	−12 ± 24	228	−9 ± 20	0.21

Values are mean ± SD, median (interquartile range), or n (%). *Not all patients had a full CMR examination conducted due to poor image quality or premature termination of the scan due to claustrophobia or inability to cooperate. Thus, some images are missing for area at risk and infarct size, resulting in a reduced number of patients with available salvage index.

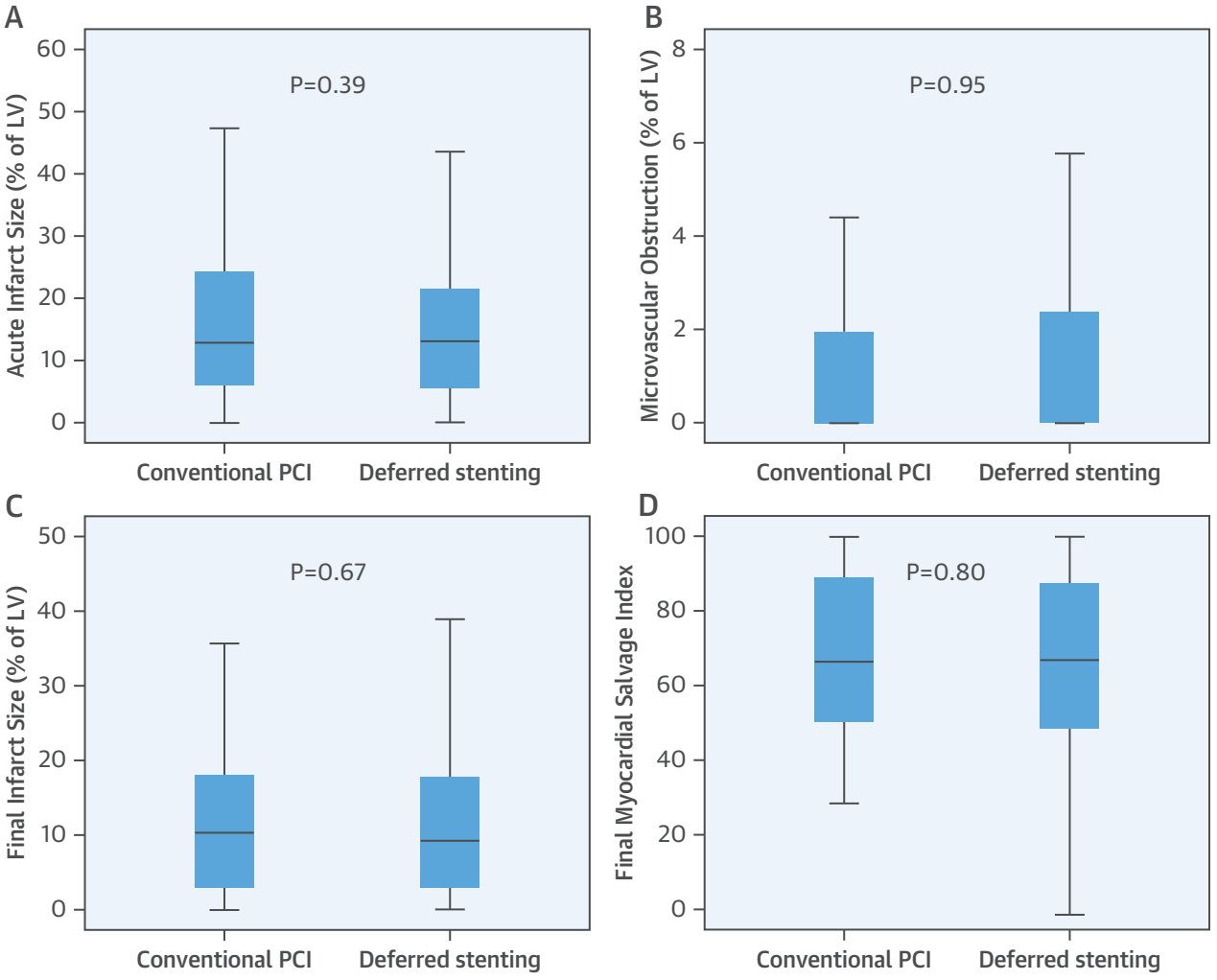
CMR = cardiac magnetic resonance; LV = left ventricle; LVEF = left ventricular ejection fraction; MVO = microvascular obstruction; PCI = percutaneous coronary intervention.

DISCUSSION

We used CMR to evaluate 510 STEMI patients, and found that a strategy of routine deferred stenting had no effect on infarct size, myocardial salvage index, or MVO compared with a strategy of immediate stenting in this relatively large, randomized study. As MVO and acute and final infarct size assessed by CMR are important predictors for mortality and development of congestive heart failure (15,16), it is doubtful whether the slight improvement in LVEF detected by echocardiography at 18 months will translate into improved long-term outcome of our patients (14). Thus, the present CMR results confirm the findings of our main study, and the DANAMI-3-DEFER studies therefore do not support the use of routine deferred stent implantation in patients with STEMI except, perhaps, for patients with long culprit lesions.

Stent implantation during primary PCI is usually preferred to avoid early reocclusion, although improvement in hard endpoints has not been documented (11). PCI without stenting could potentially result in a better final TIMI flow compared with routine stent implantation, and several small previous studies showed favorable angiographic results after deferred compared with immediate stent implantation in patients with myocardial infarction (25). It has therefore been hypothesized that immediate stenting during primary PCI increases the risk of no-/slow-reflow and other intraprocedural thrombotic events observed in approximately 12% of STEMI patients (10). Deferred stent implantation could thus improve intraprocedural and post-procedural flow and microvascular function, and subsequently improve myocardial salvage, thereby improving outcomes. In the DEFER-STEMI study, stent implantation 4 to 16 h after the index PCI resulted in a reduced incidence of both no-/slow-reflow (5.9% vs. 28.6%) and intraprocedural thrombotic events, and an improved final TIMI flow compared with immediate stenting (13). These favorable angiographic outcomes were accompanied by a 12% absolute increase in myocardial salvage index determined by CMR (13).

CENTRAL ILLUSTRATION **Deferred Stenting, Infarct Size, and Microvascular Obstruction: Boxplots Illustrating Cardiac Magnetic Resonance Outcomes**



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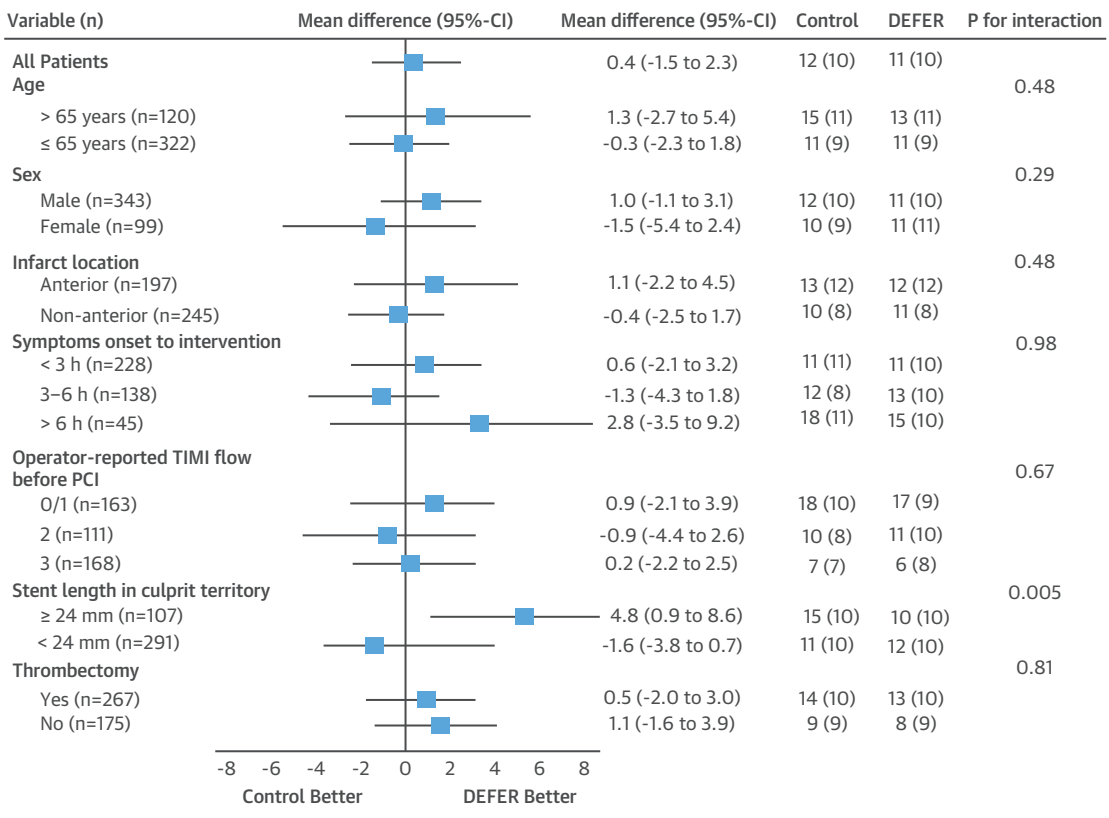
Boxplots illustrating the difference in median acute infarct size **(A)**, microvascular obstruction **(B)**, final infarct size **(C)**, and final myocardial salvage index **(D)** between the deferred stenting groups and the conventional PCI group. LV = left ventricle; PCI = percutaneous coronary intervention.

In the DANAMI-3-DEFER main study and the present substudy, deferred stenting did not improve clinical outcome, nor did it improve myocardial salvage, infarct size, or MVO. These findings corroborate those of the MIMI (Comparison of Immediate With Delayed Stenting Using the Minimalist Immediate Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction) study (26). The results of the MIMI study even suggested that deferred stenting could enhance MVO.

The designs of the trials evaluating deferred stent implantation may explain their different results. The DEFER-STEMI trial only included patients who were at high risk of developing no-reflow (13), and the MIMI study excluded patients with large thrombus due to high risk of no-/slow-reflow (26); the DANAMI-3-DEFER trial, however, focused on a routine strategy for all-comer STEMI patients (14). We subsequently evaluated the association between deferred stent implantation and some of the known risk factors for no-/slow-reflow, and found that patients with presumably long lesions ended up with smaller infarcts if implantation of their long stents (>24 mm in length) was postponed or deferred for >24 h. This was

FIGURE 2 **Forest Plot for the Mean Difference for the Primary Endpoint of Final Infarct Size and Subgroups**



Mean difference and 95% confidence interval (CI) for final infarct size between patients randomized to deferred stenting and conventional PCI. PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

an inclusion criterion in the DEFER-STEMI trial, and our results confirm that acute stent implantation of long lesions holds a higher risk for complications including flow disturbances, as also indicated by others (24). In this context, it is likely that the choice of treatment should probably be evaluated as a continuum, with increasing risk connected with longer lesions/stents. This finding must, however, be taken with caution, and confirmation in a prospective study is desirable. In the DEFER-STEMI trial, heavy TIMI thrombus burden was also an inclusion criterion, but information regarding thrombus burden is not presently available in this study. In contrast to the DEFER-STEMI and MIMI studies, patients in the DANAMI-3-DEFER study were randomized immediately after the diagnostic angiography and before PCI to prevent selection bias, leading to a relatively high crossover rate in the deferred stenting group. There was, however, no significant difference in the as-treated analysis. Patients with unstable flow or persistent ST-segment elevation were excluded from DEFER-STEMI. In the DANAMI-3-DEFER and DEFER-STEMI trials, balloon dilatation and thrombectomy were allowed to generate stable coronary blood flow, whereas only wire insertion and thrombectomy were allowed in the MIMI study. Timing of the deferred stenting procedure was also different: 4 to 16 h after the index procedure in DEFER-STEMI, and 24 to 48 h after the index procedure in DANAMI-3-DEFER and MIMI. Theoretically, reducing the deferred stenting delay would reduce the risk of bleeding and reocclusion, but might also increase the risk of no-/slow-flow, because a large thrombus may take at least 7 days to dissolve (27). In the DEFER-STEMI and MIMI trials, almost all patients in both treated groups were treated with glycoprotein IIb/IIIa inhibitors, with no difference between the groups. In DANAMI-3-DEFER, glycoprotein IIb/IIIa inhibitors were administered less frequently in the 2 groups (in 16% and 45%, respectively), which also could have affected the outcome. This approach was chosen because we wanted to compare a deferred stenting strategy including more

aggressive use of glycoprotein IIb/IIIa inhibitors to conventional treatment. The more frequent use of glycoprotein IIb/IIIa inhibitors with deferred stenting results in higher risk of bleeding, which is a potential caveat of a deferred stenting strategy.

In the present study, the acute CMR examination was performed before deferred stenting in the majority of patients, and therefore provides pathophysiological insight into the effect of stenting on MVO and infarct size. The results of a recent study suggest that stenting per se may increase the microvascular resistance in patients with a high thrombus burden (TIMI flow grade 0/1) and a high stent volume (diameter and length), and, to a lesser extent, in patients with a longer duration from symptom onset to treatment (28). In our study, we did not find any association between immediate stenting and MVO, even though increased microvascular resistance has been associated with MVO (29). MVO represents myocardial hemorrhage, intravascular obstruction, or extravascular compression of the microvasculature. T_2* can depict infarct hemorrhage and thus differentiate between the pathophysiological reasons for MVO, but was not available in the present study. However, it is questionable whether data from T_2* would have changed the overall result, because the MVO was similar between the treatment groups, and the majority (around 75%) of STEMI patients with MVO also have hemorrhage visualized by T_2* core (30).

Several attempts to prevent or reduce microvascular damage and improve myocardial salvage, targeting each of the potential mechanisms, in patients with STEMI treated with primary PCI have been evaluated. Interrogated methods include thrombectomy, proximal and distal protection, implantation of mesh-covered stents, intra-aortic balloon pumping, cooling, and ischemic and pharmacological conditioning, but none have been consistently shown to improve clinical outcome (31,32). Thrombectomy and distal protection reduced the incidence of distal embolization (33,34), but this did not translate into improved clinical outcome (35,36).

STUDY LIMITATIONS. More patients could be included in our study's deferred stenting group because they were admitted for a longer time at the CMR center while awaiting the second procedure. However, the groups were still comparable regarding baseline characteristics. Another limitation of the present study is the restricted number of patients included in the CMR part of the main trial, with only 413 patients undergoing both scans, which introduces selection bias because patients at higher risk are more likely not to undergo CMR for logistical reasons. However, there was no interaction between CMR participants/nonparticipants, and the treatment effect of deferred stenting on MACE was of the same magnitude as in the main trial (14). By the nature of the study, it was not possible to blind patients and investigators to the treatment allocation. However, blinded observers performed analyses of the CMR parameters. The present subgroup analyses were not pre-specified, and the finding of a significant difference may thus represent a chance finding. However, the subgroups were chosen to focus on patients with especially high risk of flow disturbance. The infrequent use of radial access in the present study is also a limitation, resulting in more usage of glycoprotein IIb/IIIa inhibitors and several procedures with deferred stenting. The interventionalist performing the PCI made the decision of immediate stenting in the deferred stenting group, and thus a certain crossover bias cannot be ruled out. Finally, patients who did not receive a stent were obviously not included in the analysis of patients who received different stent lengths.

CONCLUSIONS

In the present DANAMI-3-DEFER CMR substudy, deferred stenting did not reduce infarct size or the occurrence of MVO and did not improve myocardial salvage index in the entire group. Thus, we do not recommend routine deferred stenting in STEMI patients treated by primary PCI. However, whether deferred stenting is indicated in selected patients remains to be examined, and we did find a reduced infarct size among patients with stent length in the culprit territory ≥24 mm.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with STEMI, deferred coronary stenting does not reduce infarct size or MVO, increase myocardial salvage, or improve clinical outcomes compared with immediate stenting.

TRANSLATIONAL OUTLOOK: Future studies should assess the utility of deferred stenting in patients with STEMI who have long coronary lesions or large thrombus burden.

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KEY WORDS deferred stent implantation, infarct size, microvascular obstruction, percutaneous coronary intervention

APPENDIX For supplemental tables, please see the online version of this article.