



# Effects of deferred versus immediate stenting on left ventricular function in patients with ST elevation myocardial infarction

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## Abstract

**Background:** Previous studies have shown conflicting results on the benefits of deferred stenting (DS) in infarct size and the incidence of microvascular obstruction in patients with ST elevation myocardial infarction (STEMI). However, effect of DS on left ventricular (LV) function was not known. We aimed to evaluate whether DS improve LV function and relevant clinical outcomes after STEMI, using follow-up data from the INNOVATION study (NCT02324348).

**Methods:** In total, 114 patients were randomly assigned to DS group or immediate stenting (IS) group at a 1:1 ratio. LV functional remodeling indices and MACE (major adverse cardiac events: a composite of death, non-fatal MI, unplanned target vessel revascularization, or hospitalization due to heart failure) were compared between DS and IS groups.

**Results:** Serial echocardiographic analyses were completed in 89 subjects (78%). There were no significant changes in LV volume in either group. While LV ejection fraction and wall motion score index (WMSI) improved in both groups during follow-up, the increments were not statistically different between the 2 groups ( $4.3 \pm 8.2$  vs  $3.2 \pm 7.1$ ,  $P = .504$  for  $\Delta$ LV ejection fraction;  $-0.16 \pm 0.25$  vs  $-0.16 \pm 0.25$ ,  $P = .99$  for  $\Delta$ WMSI). However,  $E/e'$  was decreased and  $e'$  was increased only in the DS group ( $-3.31 \pm 5.60$  vs  $-0.46 \pm 3.10$ ,  $P = .005$  for  $\Delta E/e'$ ;  $0.77 \pm 1.71$  vs  $-0.22 \pm 1.64$ ,  $P = .009$  for  $\Delta e'$ ). The incidence of major adverse cardiac events was numerically lower in the DS group than in the IS group without a statistical significance at 1-year follow-up.

**Conclusions:** Routine DS improved LV diastolic function but not systolic function compared with IS in patients with STEMI.

**Abbreviations:** DS = deferred stenting, EF = ejection fraction, HoHF = hospitalization for congestive heart failure, IRA = infarct-related artery, IS = immediate stenting, LAD = left anterior descending, LV = left ventricular, LVEDV = left ventricular end-diastolic volume, LVEDVI = left ventricular end-diastolic volume index, LVESV = left ventricular end-systolic volume, LVESVI = left ventricular end-systolic volume index, MACE = major adverse cardiac events, MRI = magnetic resonance imaging, MVO = microvascular obstruction, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, STEMI = ST elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization, WMSI = wall motion score index.

**Keywords:** drug-eluting stents, left, percutaneous coronary intervention, ST elevation myocardial infarction, ventricular function

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

In approximately 30% to 65% of patients with ST elevation myocardial infarction (STEMI), optimal myocardial tissue perfusion cannot be achieved due to persistent microvascular obstruction (MVO), even after the successful restoration of epicardial coronary artery patency with primary percutaneous coronary intervention (PCI).<sup>[1–4]</sup> MVO is often caused by the distal embolization of clots and atheromatous plaque debris during stent implantation and by myocardial and endothelial inflammation in infarct-related arteries (IRA). Overwhelming evidences from various MVO phenotypes indicate that the presence of MVO is independently associated with poor clinical outcomes in patients with STEMI.<sup>[5–7]</sup> Deferred stenting (DS) is used to mitigate or prevent MVO by avoiding stent implantation in a highly inflammatory and thrombotic conditions. A proof-of-concept study suggested that DS with intention-to-stent after 4 to 16 hours reduced the angiographic no-reflow phenomenon.<sup>[8]</sup> However, 3 subsequent randomized controlled trials (RCTs) with longer deferral intervals, including the INNOVATION study, did not demonstrate substantial benefits of routine DS in terms of infarct size, the incidence of MVO, or clinical outcomes.<sup>[7,9,10]</sup> To date, one large RCT and a few small observational studies have reported conflicting long-term clinical outcomes after immediate stenting (IS) versus DS.<sup>[7,11,12]</sup> Overall, data on long-term prognosis after DS remain very limited. However, a recent patient-pooled analysis including data from 5 RCT (DEFER-STEMI, DANAMI 3-DEFER, INNOVATION, MIMI, and PRIMACY) showed better clinical outcomes in terms of cardiovascular death or hospitalization due to heart failure in the DS group than in the IS group during a median follow-up of 480 days, which were clarified with 99% of the Bayesian posterior probabilities (Jolicœur EM, MD, presented in late-breaking science ESC 2019, unpublished data, September 2019). These better clinical outcomes were mainly driven by reductions of hospitalization due to heart failure. Therefore, we aimed to evaluate the impact of DS on left ventricular (LV) function after STEMI using follow-up data from the INNOVATION study (NCT02324348).

## 2. Methods

### 2.1. Study design, patient population, randomization, and study procedure

The INNOVATION study was a 2-center, prospective, randomized, controlled, open-label clinical trial for patients with STEMI. The design, methods, and main results of the INNOVATION study were previously published.<sup>[9]</sup> Patients were eligible for enrollment if the following criteria were met: age  $\geq 18$  years;  $> 30$  minutes of typical chest pain;  $\geq 1$  mm of ST elevation in  $\geq 2$  contiguous leads;  $< 12$  hours duration of ischemic symptoms; thrombolysis in myocardial infarction (TIMI) flow 0, 1, or 2 before the procedure; and achievement of TIMI 3 flow after balloon angioplasty or thrombus aspiration. The exclusion criteria were as follows: cardiogenic shock, history of myocardial infarction or coronary artery bypass surgery, rescue PCI after fibrinolysis,  $< 1$  year life expectancy, acute occlusion of the left main coronary artery, contraindication to cardiac magnetic resonance imaging (MRI), STEMI due to stent thrombosis, and major coronary dissection (type D–F) after procedures achieving TIMI 3 flow. Eligible patients were randomly assigned to the IS group or the DS group in a 1:1 ratio after achievement of TIMI 3

flow before stent implantation. Randomization was performed with a block size of 2 and stratified according to the site of the participating center and the location of the IRA (left anterior descending [LAD] vs non-LAD) using an interactive web-based system.

In the DS group, the second-stage stenting procedure was scheduled at 3 to 7 days after the primary reperfusion procedure. Withdrawal of stent implantation in case of minimal plaque burden on follow-up angiography was allowed in the DS group. If a patient with concurrent STEMI and multivessel disease underwent primary PCI, intervention for the non-IRA was deferred in both groups. Dual antiplatelet therapy was maintained for at least 12 months. This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No. 2013AN0120) and Sejong General Hospital (IRB No. 1220). The informed consent was obtained from all enrolled patients.

### 2.2. Echocardiographic analyses

All randomized patients were scheduled to receive comprehensive echocardiographic evaluations immediately and at 9 months after the primary PCI. Standard echocardiography was conducted according to the recommendations of the American Society of Echocardiography.<sup>[13]</sup> All images of interest were recorded for 3 cardiac cycles (or 10 in the presence of atrial fibrillation). Serial imaging with similar angles was highly recommended during follow-up. Quantitative core-laboratory measurements for LV dimension, volume, and systolic and diastolic functions were performed by an expert cardiologist dedicated to echocardiography in Korea University Anam Hospital who was blinded to the random assignments. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured by manual tracing of the blood–tissue interface in the apical 4- and 2-chamber views in end-diastole and end-systole. The LVEDV index (LVEDVI) and LVESV index (LVESVI) were each calculated by dividing the LVEDV and LVESV by the body surface area. Left atrial volume was measured using the biplane modified Simpson method, and the left atrial volume index was calculated by dividing the left atrial volume by the body surface area. The LV ejection fraction (LVEF) was estimated using the modified Simpson method. Mitral inflow velocity during early diastole (E) and late diastole (A) and deceleration time of early diastolic mitral inflow (DT) were measured on pulse-wave Doppler images acquired from an apical 4-chamber view, with the sample volume positioned at the tip of a mitral leaflet. Early diastolic tissue velocity ( $e'$ ) of the mitral annulus was obtained using tissue Doppler imaging, and  $E/e'$  was calculated. Systolic ejection velocity ( $s'$ ) was also obtained using tissue Doppler imaging.<sup>[14]</sup> The wall motion score was measured and summed in each ventricular segment from multiple short-axis, apical 2-chamber, 4-chamber, and long-axis views. The wall motion score index (WMSI) was derived by dividing the total wall motion score into 17 segments.

### 2.3. Assessment of clinical outcomes

The occurrence of major adverse cardiac events (MACE), defined as a composite of death, non-fatal myocardial infarction (MI), unplanned target vessel revascularization (uTVR), or hospitalization for congestive heart failure (HoHF), was evaluated in each patient during follow-up. An MI was defined as an elevation in

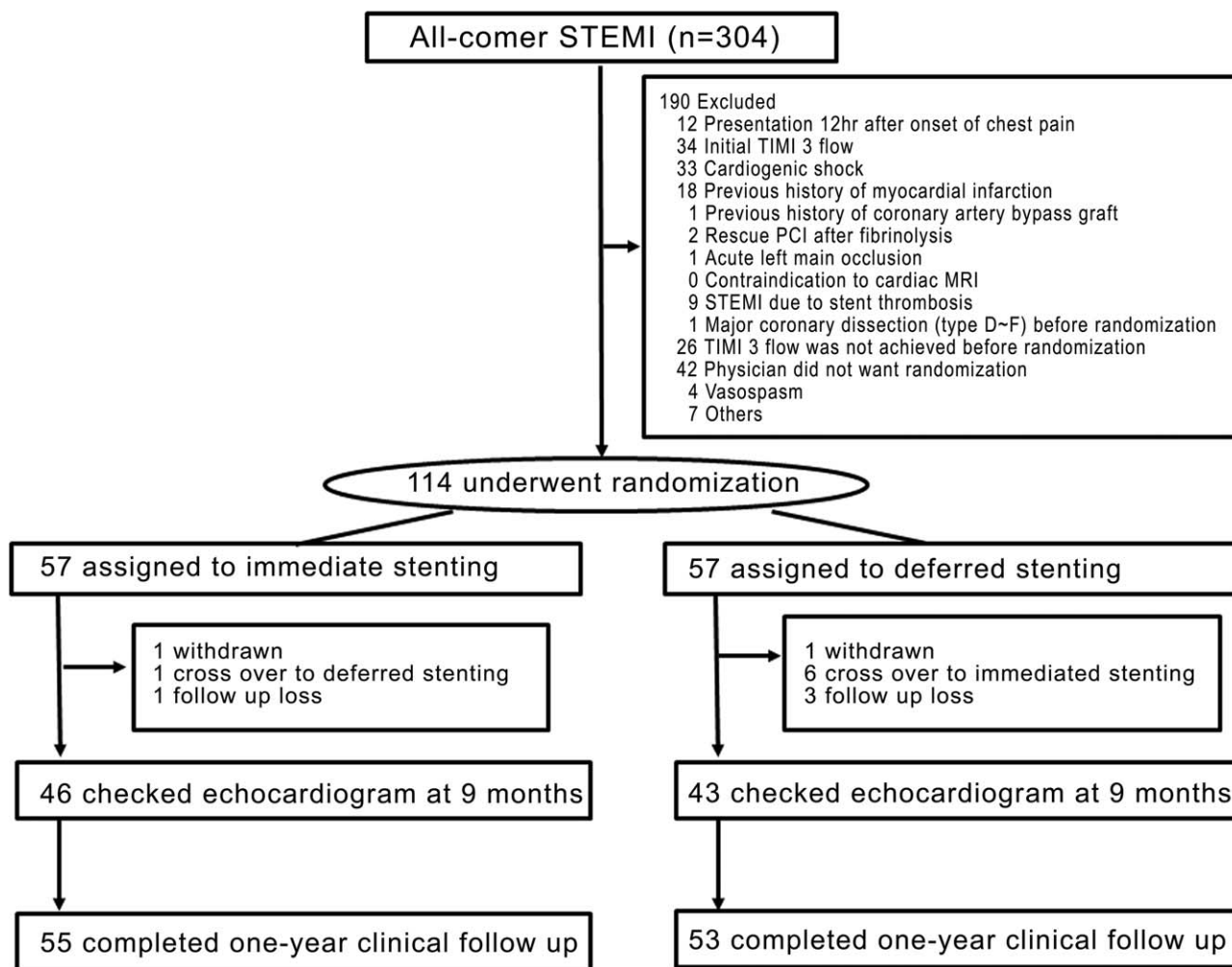
cardiac enzymes (troponin or myocardial band fraction of creatine kinase) greater than the upper limit of the normal value, with ischemic symptoms or electrocardiography findings indicative of ischemia unrelated to the index procedure.

TVR was defined as percutaneous or surgical revascularization of any segment of the treated target vessels including non-IRAs. Target lesion revascularization (TLR) was defined as any percutaneous or surgical revascularization of the segment from 5 mm proximal to the stent to 5 mm distal to the stent in the IRA or non-IRA. Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium.<sup>[15]</sup> TIMI major bleeding was defined as intracranial bleeding or clinically significant overt signs of hemorrhage plus a decrease in hemoglobin of >5.0g/dL and, if measured, a decrease in hematocrit of >15%.<sup>[16]</sup> All outcomes of interest were confirmed by a single cardiologist who was blinded to the study purpose.

**2.4. Statistical analysis**

Differences in baseline characteristics between the IS and DS groups were compared using Student *t* test or the Mann–Whitney

*U* test for continuous variables and Fisher exact test for categorical variables, as appropriate. We used the intention-to-treat principle to evaluate the primary and secondary endpoints, and we analyzed missing data with a multiple imputation procedure. This analysis was based on 10 data sets that were imputed using the Markov chain Monte Carlo method, and the comparison between 2 groups was analyzed using the average of the estimates from 10 imputed data sets. Differences in the serial changes of the echocardiographic parameters between the IS and DS groups were evaluated using a 2-way repeated-measures analysis of variance. Additional analysis of covariance (ANCOVA) was also performed to evaluate the effects of between-subjects with hypertension and indicators (*e'* and *E/e'*) indicating diastolic function. Comparison of the diastolic function grade change over time between the IS and DS groups was analyzed using a generalized estimating equation.<sup>[17]</sup> A survival curve for 1-year MACE was constructed with Kaplan–Meier estimates and compared with the log-rank test. A Cox proportional hazards model was used to compare the risk of MACE between the IS and DS groups. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS version 20; SPSS, Chicago, IL).



**Figure 1.** Flowchart of enrolled patients. MRI=magnetic resonance imaging, PCI=percutaneous coronary intervention, STEMI=ST elevation myocardial infarction, TIMI=thrombolysis in myocardial infarction.

**Table 1**  
Baseline clinical characteristics of the study subjects.

	IS group (n=57)	DS group (n=57)	P value
Age, y	59.2±10.3	59.9±13.2	.77
Male sex	47 (82.5)	48 (84.2)	>.99
Diabetes mellitus	17 (29.8)	18 (31.6)	>.99
Hypertension	21 (36.8)	36 (63.2)	.008
Current smoker	28 (49.1)	32 (56.1)	.57
Dyslipidemia	17 (29.8)	23 (40.4)	.33
Family history of CAD	2 (3.5)	4 (7.0)	.68
PAOD	1 (1.8)	0	>.99
Previous PCI	0	2 (3.5)	.50
Previous CVA	3 (5.3)	3 (5.3)	>.99
Chronic renal failure	0	1 (1.8)	>.99
Killip class on admission			.99
1	55 (96.4)	54 (94.7)	
2 or 3	2 (3.6)	3 (4.3)	
Anterior wall MI	37 (64.9)	32 (56.1)	.34
Systolic blood pressure	131±25	128±20	.53
Diastolic blood pressure	79±20	79±12	.97
Heart rate	75±18	79±15	.15
Prior statin therapy	20 (35.1)	22 (38.6)	.70
Medication at discharge			
Aspirin	57 (100)	56 (98.2)	>.99
Thienopyridine	57 (100)	56 (98.2)	>.99
Statin	57 (100)	54 (94.7)	.24
ACEI or ARB	38 (66.7)	42 (73.7)	.54
Beta-blocker	48 (84.2)	48 (84.2)	>.99
Other parameters			
Hospital stay, h	98 [29–146]	121 [97–151]	.01
ICU stay, h	29 [22–45]	33 [24–63]	.17

Data are presented as n (%), mean±standard deviation, or median [interquartile range]. ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CAD=coronary artery disease, CVA=cerebrovascular accident, DS=deferred stenting, ICU=intensive care unit, IS=immediate stenting, MI=myocardial infarction, PAOD=peripheral arterial occlusive disease, PCI=percutaneous coronary intervention.

### 3. Results

#### 3.1. Study population and treatment

From February 2013 through March 2015, a total of 304 patients were screened for enrollment in this study. Among them, 114 (37.5%) were enrolled and randomly assigned to either the DS group (n=57) or the IS group (n=57). Six patients in the DS group were moved into the IS group due to progression of dissection or fear of progression after randomization. One patient in the IS group was moved into the DS group following the operator's discretion. Two patients withdrew informed consent during follow-up. All enrolled patients underwent a baseline echocardiographic study on the same day or the day after the primary reperfusion procedure. Among them, 89 patients (78%) completed scheduled follow-up echocardiography 9 months after the primary reperfusion procedure. Four patients in the 2 groups (3.5%) were lost to follow-up. Finally, 55 patients (96%) in the IS group and 53 patients (93%) in the DS group were included in an analysis of clinical outcomes (Fig. 1). The baseline demographic and clinical characteristics were well-balanced between the 2 groups, except for hypertension (36.8% vs 63.2% in the IS vs DS groups;  $P=.008$ ). The patients in both groups took similar medications at discharge (Table 1). The baseline angiographic and procedural characteristics are shown in Table 2. The LAD was the most frequently involved IRA in both groups, and the proportion of patients with high thrombus burden was relatively

**Table 2**  
Angiographic and procedural characteristics of the study subjects.

	IS group (n=57)	DS group (n=57)	P value
Infarct-related artery			.20
Left anterior descending artery	37 (64.9)	32 (56.1)	.58
Left circumflex artery	4 (7.0)	1 (1.8)	>.99
Right coronary artery	16 (28.1)	24 (42.1)	.18
Number of diseased vessels			.28
1	17 (29.8)	24 (42.1)	
2	25 (43.9)	20 (35.1)	
3	15 (26.3)	13 (22.8)	
TIMI flow before PCI			.91
0	36 (63.2)	37 (64.9)	
1	11 (19.3)	8 (14.0)	
2	10 (17.5)	12 (21.1)	
Presence of collateral flow	16 (28.1)	16 (28.1)	>.99
Final TIMI flow after primary reperfusion			.56
0–1	0	0	
2	1 (1.8)	2 (3.5)	
3	56 (98.2)	55 (96.5)	
TIMI thrombus grade			.68
1	1 (1.8)	2 (3.5)	
2	1 (1.8)	0	
3	5 (8.8)	5 (8.8)	
4	6 (10.5)	9 (15.8)	
5	44 (77.2)	41 (71.9)	
Door to TIMI 3 flow time, min	56 [42–84]	58 [44–70]	.99
TIMI 3 flow to stenting time, min	8 [5–12]	4358 [3118–5816]	<.001
Abciximab use	40 (70.2)	44 (77.2)	.52
Stenting of culprit lesion	57 (100)	53 (92.9)	.12
Stent diameter in IRA	3.1±0.4	3.4±0.4	.01
Stent length in IRA	24±7	24±7	.72
Total stent number	1.2±0.4	1.1±0.6	.20
Total stent length	27±13	25±13	.31
Transradial approach	23 (40.3%)	17 (29.8)	.24
Complete revascularization	47 (82.5)	45 (78.9)	.81

Data are presented as n (%), mean±standard deviation, or median [interquartile range]. DS=deferred stenting, IRA=infarct-related artery, IS=immediate stenting, PCI=percutaneous coronary intervention, TIMI=thrombolysis in myocardial infarction.

similar between the 2 groups (87.7% of total). The deferral interval was 72.8 hours on average in the DS group. Four patients (7%) in the DS group did not undergo stent implantation according to the operator's discretion. The stent diameter was significantly larger in the DS group than in the IS group ( $3.4±0.4$  vs  $3.1±0.4$  mm;  $P=.01$ ). The length of hospital stay was longer in the DS group than in the IS group (median, 98 hours vs 121 hours;  $P=.01$ ); however, the length of intensive care unit stay did not significantly differ between the 2 groups (median, 29 hours vs 33 hours;  $P=.17$ ) (Table 1).

#### 3.2. LV functional remodeling

Follow-up echocardiograms were obtained at a mean of 9.5 and 8.4 months after the primary reperfusion in the IS and DS groups, respectively ( $P=.07$ ). The changes in LVEDVI and LVESDVI during the follow-up were not different between the IS and DS groups. While the LVEF and WMSI were improved in both groups during follow-up, the increments were not different between the 2 groups (Table 3). The  $e'$  increased in the DS group (baseline  $5.11±1.9$  vs follow-up  $5.81±1.7$ ;  $P=.006$ ), whereas it was not changed in the IS group.  $E/e'$  also significantly decreased

**Table 3**  
Serial echocardiographic analysis in the immediate stenting and deferred stenting groups.

	IS group (n=46)		DS group (n=43)		P value*
	Baseline	Follow-up	Baseline	Follow-up	
LVEDD, mm	48.3±3.6	49.7±5.2	49.2±4.7	50.1±5.3	.61
LVESD, mm	33.6±5.8	32.5±7.5	32.7±5.4	32.6±6.4	.91
LVEDVI, mL/m <sup>2</sup>	49.3±16.3	51.1±16.7	46.8±15.1	48.6±15.7	.98
LVESVI, mL/m <sup>2</sup>	25.8±13.9	25.2±11.5	24.2±11.5	23.8±13.5	.87
LVMI, g/m <sup>2</sup>	97.8±19.8	98.4±26.3	102.3±19.7	102.0±28.4	.99
LVEF, %	48.5±10.7	52.1±8.6	49.1±10.2	53.5±9.7	.65
WMSI	1.44±0.30	1.28±0.28	1.44±0.29	1.27±0.23	.91
LAVI	30.1±10.1	31.8±9.8	28.3±9.8	30.1±8.8	.99
E velocity, m/s	59.8±16.4	54.4±13.2	62.1±17.6	57.2±14.9	.89
E/A	0.93±0.39	0.89±0.49	0.95±0.46	0.90±0.41	.88
DT, ms	183.5±36.6	204.6±46.4	218.0±39.3 <sup>†</sup>	225.5±59.8	.23
e', cm/s	5.85±1.9	5.76±1.8	5.11±1.9	5.81±1.7	.03
s', cm/s	6.77±8.2	5.89±1.4	5.21±1.6	5.89±1.3	.24
E/e'	10.7±3.1	10.1±3.0	13.1±5.5 <sup>‡</sup>	10.0±3.5	.02
Classification of diastolic function <sup>‡</sup>					
Normal	9 (19.6)	15 (32.6)	4 (9.3)	10 (23.3)	
Mild	15 (32.6)	22 (47.8)	18 (41.9)	19 (44.2)	
Moderate	10 (21.7)	6 (13.0)	14 (32.6)	9 (20.9)	
Severe	12 (26.1)	3 (6.5)	7 (16.3)	5 (11.6)	

Data are presented as n (%) or mean ± standard deviation.

DS=deferred stenting, DT=deceleration time, IS=immediate stenting, LAVI=left atrial volume index, LVEDD=left ventricular end-diastolic diameter, LVEDVI=left ventricular end-diastolic volume index, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic diameter, LVESVI=left ventricular end-systolic volume index, LVMI=left ventricular mass index, WMSI=wall motion score index.

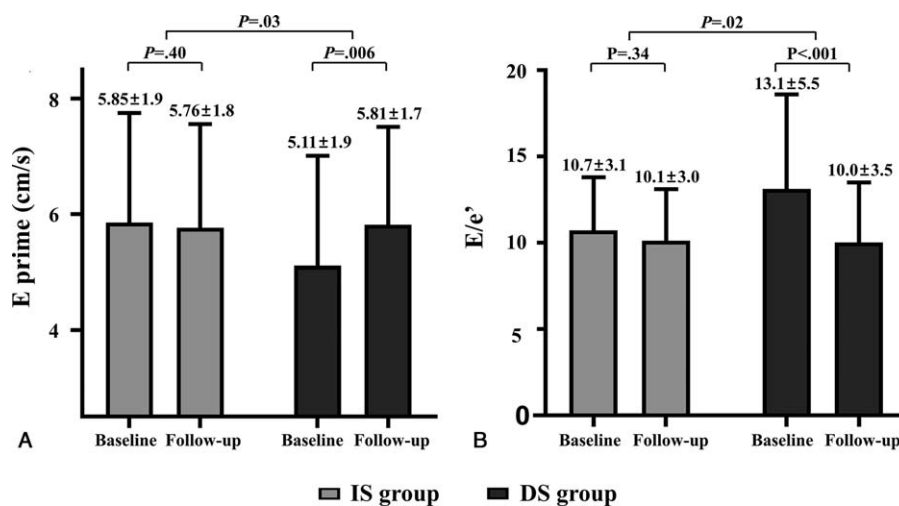
\* P value between the IS and DS groups by repeated-measures analysis of variance.

<sup>†</sup> P<.05, comparison of baseline values between the IS and DS groups.

<sup>‡</sup> P=.31, comparison of the diastolic function grade change over time between the IS and DS groups using a generalized estimating equation.

only in the DS group during follow-up (baseline 13.1±5.5 vs follow-up 10.0±3.5; P<.001) but not in the IS group (Fig. 2). Neither e' nor E/e' was related to hypertension in ANCOVA analysis (P=.84; P=.69, respectively). In addition, s' decreased in the IS group but increased in the DS group during follow-up. There was no significant difference in the diastolic function grade change over time between the IS and DS groups (P=.31).

In the subgroup analysis of patients with anterior wall MI, serial improvements in e' and E/e' were observed only in the DS group. Furthermore, the change in s' between the IS and DS groups showed a statistical trend toward significance (P=.06). The s' was increased in the DS group but was unchanged in the IS group during follow-up (see Table S1, Supplemental Digital Content, which demonstrates differences in serial echocardi-



**Figure 2.** Changes of left ventricular diastolic function during follow-up in deferred stenting group and immediate stenting group. Panel A shows the baseline and the follow-up of the E wave within each group. Panel B shows the baseline and the follow-up of the E/e' within each group. DS=deferred stenting, IS=immediate stenting.

**Table 4**  
One-year clinical outcomes in the immediate stenting and deferred stenting groups.

	IS group (n = 55)	DS group (n = 53)	P value*
MACE	5 (9.1%)	2 (3.8%)	.32
Death	1 (1.8%)	0	>.99
Nonfatal MI	0	1 (1.9%)	.49
Unplanned TVR	2 (3.6%)	1 (1.9%)	>.99
Unplanned TLR	1 (1.8%)	1 (1.9%)	>.99
Stent thrombosis	0	1 (1.9%)	.49
Hospitalization due to heart failure	2 (3.6%)	1 (1.9%)	>.99
TIMI major bleeding	0	1 (1.9%)	>.99

Data are presented as n (%).

DS=deferred stenting, IS=immediate stenting, MACE=major adverse cardiac events, MI=myocardial infarction, TIMI=thrombolysis in myocardial infarction, TLR=target lesion revascularization, TVR=target vessel revascularization.

\*Based on the Cox proportional hazards model.

graphic changes between IS and DS groups among patients with anterior wall MI, <http://links.lww.com/MD2/A272>).

### 3.3. Clinical outcomes

During a median duration of 11.8 months, a composite of death, non-fatal MI, uTVR, or HoHF occurred in 5 patients (9.1%) in the IS group and 2 patients (3.8%) in the DS group (hazard ratio 0.43, 95% confidence interval 0.08–2.23;  $P=.32$ ) (Table 4 and Fig. 3). The incidences of death, non-fatal MI, uTVR, unplanned TLR (uTLR), stent thrombosis, HoHF, and major bleeding were very low, and there were no differences between the 2 groups, respectively. In the as-treated analysis, a composite of death, non-fatal MI, uTVR, or HoHF occurred in 5 patients (8.3%) in the IS

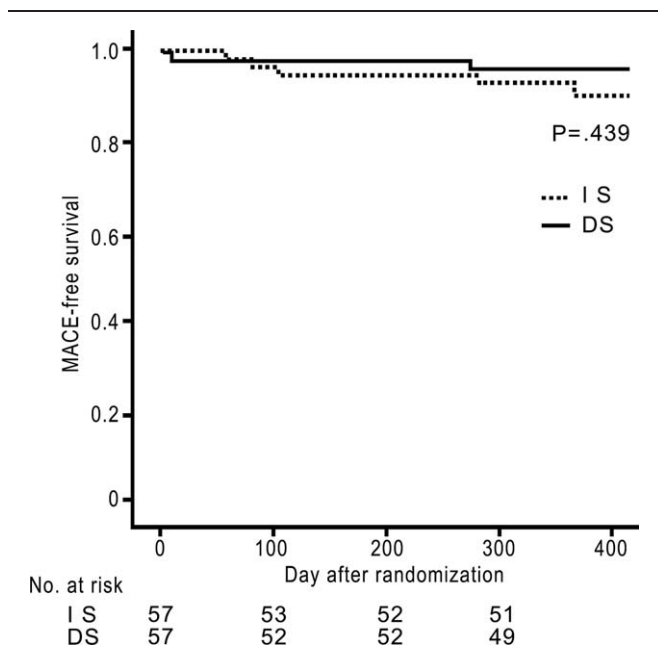
group and 2 patients (4.1%) in the DS group (hazard ratio 0.53, 95% confidence interval 0.10–2.72;  $P=.44$ ). The incidences of death, non-fatal MI, uTVR, uTLR, stent thrombosis, HoHF, and major bleeding were not significantly different between the 2 groups, and the differences were similar to those in the intention-to-treat analysis (see Table S2, Supplemental Digital Content, which demonstrates 1-year clinical outcomes in the IS and DS groups in as-treated analysis, <http://links.lww.com/MD2/A273>).

## 4. Discussion

We conducted a post hoc analysis of prospective randomized data comparing DS versus IS during primary percutaneous reperfusion for STEMI. Our primary finding was that diastolic function was improved in the DS group during follow-up, but not in the IS group. However changes in LV volume did not differ between the IS and DS groups, nor did they between baseline and follow-up within the same group. LVEF and LV WMSI improved in both groups during follow-up, but did not differ between groups. Notably, these findings persisted in patients with anterior wall MI, in whom the tissue markers for systolic function showed an increasing trend in the DS group. The occurrence of MACE was less frequent in the DS group than in the IS group, but the difference between the 2 groups was not statistically significant.

MVO is an important predictor of mortality and adverse clinical outcomes, and its presence is associated with LV systolic dysfunction.<sup>[3,18,19]</sup> In the INNOVATION study, DS did not reduce the incidence or size of MVO and did not influence LVEF or LV size.<sup>[9]</sup> Since baseline LVEF and LV volumes were preserved, and the mass and percentage of MVO were smaller than previously reported values, the ischemic insults in this study population might have been localized rather than affecting the entire myocardium.<sup>[20,21]</sup> Therefore, the LVEF and LV volume indices, which are representative measures of LV global systolic function, were not adequate to evaluate the effect of DS on LV function in our sample. However, fine parameters such as LV systolic tissue function, including strain of myocardial deformation, may be helpful for assessing differences in functional improvement caused by DS versus IS.

The benefits of primary PCI in relation to the echocardiographic parameters reflecting LV systolic and diastolic function were reported repeatedly in previous reports.<sup>[22,23]</sup> However, there are very few studies comparing the difference in LV function recovery according to the stenting strategy. In our study,  $E/e'$ , which is closely related to LV end-diastolic filling pressure, significantly decreased during follow-up in the DS group compared to the IS group. This difference may be attributable to improvements in LV tissue mechanics in diastole, as LV volume and EF remained within the normal range and were not significantly changed in the DS group. LV diastolic dysfunction occurs before LV systolic dysfunction in myocardial ischemia. Moreover, coronary microvascular dysfunction is closely associated with LV diastolic dysfunction.<sup>[24]</sup> We inferred that DS improves microvascular functional impairment and consequently ameliorates LV diastolic function. MVO on cardiac MRI implies not only an anatomical deterioration without consideration of coronary microvascular function, but also serious and irreversible myocardial injury.<sup>[25]</sup> In our study population, because cardiac MRI cannot detect coronary microvascular impairment without MVO, we were unable to determine whether DS prevented this functional damage. Therefore, further studies evaluating microvascular dysfunction parameters, such as the



**Figure 3.** Kaplan–Meier curve of MACE between deferred stenting and immediate stenting groups during a median follow-up of 11.8 months. DS=deferred stenting, IS=immediate stenting, MACE=major adverse cardiac events.

index of microcirculatory resistance, could further elucidate the effect of DS in patients with STEMI.

In patients with anterior MI, systolic tissue function showed an improving trend with marginal significance, and diastolic function improved significantly in DS group than in IS group. At baseline, the LV size was larger, the LVEF was lower, and the prevalence and extent of MVO was greater in patients with anterior MI. As ischemic insult and microvascular dysfunction are likely to be greater in patients with anterior MI, the effect of DS on the improvement in LV function may be enhanced. In this study, the incidences of 1-year adverse events were low in both the IS and DS groups. Although the 1-year MACE rate was 2.4 times higher in the IS group than in the DS group, it did not reach statistical significance owing to the small sample size and the inability to compare the 2 groups because of inadequate statistical power. However, good results were achieved with the interventional and medical treatments in patients with STEMI. In our study, uTVR occurred in only 1 patient (1.9%) in the DS group, in contrast to the DANAMI 3-DEFER study, which reported a higher uTVR rate in the DS group. The non-significant numerical differences in mortality and heart failure in favor of DS were offset by the high TVR rate. This was attributed to re-occlusion or worsening of the culprit lesion before the scheduled stent implantation. Our results do not support the use of routine DS to mitigate or prevent adverse clinical outcomes in patients with STEMI. However, DS improves LV diastolic function, which is one of the most important prognostic factors for myocardial ischemia and is related to better clinical outcomes.<sup>[26,27]</sup>

To date, 4 RCTs (DEFER-STEMI, DANAMI 3-DEFER, INNOVATION, MIMI) related to DS strategy in patients with STEMI have been published. Among them, 3 RCTs investigated surrogate endpoints regarding myocardial tissue perfusion and MVO. In DEFER-STEMI trial, DS strategy reduced no-reflow and increased myocardial salvage. In INNOVATION and MIMI trials, DS showed no benefit of reducing MVO. However, in the subgroup analysis of INNOVATION trial, DS reduced MVO in anterior wall STEMI patients.

Only DANAMI 3-DEFER investigated clinical outcome, however, DS failed to meet the primary endpoint of composite adverse clinical events (hazard ratio 0.99, 95% confidence interval 0.76–1.29;  $P = .92$ ). And one Bayesian randomized trial, PRIMACY trial, is currently in progress. In this trial, data from previous RCTs will be combined with PRIMACY to evaluate a posterior probability of efficacy.

Therefore, further large randomized studies with adequate statistical power and lower crossover rates are warranted to determine which patients would benefit from DS. Our group is currently performing a randomized trial to evaluate long-term clinical outcomes after IS versus DS in patients with anterior wall STEMI who are at high risk of MVO (INNOVATION-CORE trial, NCT03744000).

#### 4.1. Study limitations

Our study has several limitations. First, this study was a post-hoc analysis of the INNOVATION study, which compared infarct size and microvascular obstruction on cardiac MRI. Therefore, the sample size lacked enough power to clearly demonstrate the impact of DS on LV remodeling and clinical outcomes. However, encouraging results of this study may be useful to initiate a broader study. Second, in 22% of our study sample, serial

quantitative echocardiographic analyses were not completed, mostly owing to compliance issues. This may have caused selection bias in a fair comparison of the incidence of LV remodeling between the 2 groups. Selection bias could not be completely eliminated, although we attempted to control for missing values with the multiple imputation method. Third, the investigators and patients were not blinded to the study strategy. Fourth, as shown in the patient flowchart, many interventional cardiologists preferred not to enroll some patients because of concerns about the risk of acute re-occlusion or urgent revascularization in the DS group. This may represent a potential source of selection bias in patient enrollment. Thus, when interpreting the results, readers should take into consideration that our study was performed at 2 centers, enrolled more male patients and patients with anterior MI than did previous studies, and assessed major endpoints in a survivor population.

## 5. Conclusion

Routine deferral of stent implantation to prevent distal embolization of thrombi and atherosclerotic debris led to improvement of LV diastolic function but did not improve 1-year clinical outcomes in patients with STEMI. Further, larger studies are required to elucidate the impact of DS on clinical outcomes, as well as on LV structure and function.

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