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Impact of direct stenting on myocardial injury assessed by cardiac magnetic resonance imaging and prognosis in ST-elevation myocardial infarction☆

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ABSTRACT

Background: The results of studies investigating the clinical benefit of a direct stenting (DS) strategy in ST-elevation myocardial infarction (STEMI) are inconsistent and data regarding cardiac magnetic resonance (CMR) parameters of myocardial injury are lacking. The aim of this study was to investigate the effect of DS on myocardial damage in comparison to a conventional stenting technique (CS) with predilation in patients with reperfused STEMI.

Methods: In a subanalysis of the randomized LIPSIA CONDITIONING trial (NCT02158468), STEMI patients were stratified according to the percutaneous coronary intervention technique into the DS (n = 171) or CS (n = 171) group after matching the patients for age (±5 years), gender, and TIMI flow before coronary intervention. Patients underwent CMR imaging within one week after infarction. Clinical outcome (death, reinfarction, hospitalization for heart failure) was assessed within 6 months after the index event.

Results: Patients in the DS group had significantly lower infarct size (16 vs. 19% of left ventricular mass; $p = 0.046$) and microvascular obstruction with significant improvement of left ventricular parameters, which was associated with favorable clinical outcome with a lower incidence of heart failure hospitalizations (4% vs. 11%, $p = 0.011$) and mortality (5% vs. 12%, $p = 0.034$) as compared to patients with CS. In multivariate Cox regression analysis, DS was identified as an independent predictor of reduced mortality (HR 0.30, 95% CI 0.11–0.87, $p = 0.026$).

Conclusion: In patients with acute reperfused STEMI, DS is safe and feasible with a significant reduction of infarct size compared to CS and subsequent lower incidence of heart failure hospitalizations and mortality.

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1. Introduction

Percutaneous coronary intervention (PCI) with stent implantation is the primary therapeutic strategy in patients with acute ST-elevation myocardial infarction (STEMI) [1,2]. Conventional stenting technique (CS) with balloon predilation of the lesion enables easy and uncomplicated passage of the stent across the culprit lesion with complete stent expansion after deployment. However, direct stenting (DS) without predilation has some advantages over CS including better angiographic outcomes, reduced no-reflow episodes, shorter procedural and fluoroscopy times, use of less contrast medium and lower cost of the procedure [3,4]. Moreover, DS presumably restores distal coronary flow promptly and prevents dissection, acute recoil, distal embolization, and endothelial damage.

In stable coronary artery disease, 2 meta-analyses of randomized controlled trials have shown that DS reduces the incidence of periprocedural myocardial infarction and consequently the risk of death at 6-month follow-up as compared to CS [5,6]. In acute coronary syndrome (ACS), which differs from stable coronary artery disease in having more thrombus burden and microvascular dysfunction, data regarding DS remain controversial. While DS was associated with

Abbreviations: ACS, Acute coronary syndrome; CMR, Cardiac magnetic resonance; CS, Conventional stenting technique; DS, Direct stenting technique; LV, Left ventricle; MACE, Major adverse cardiac events; PCI, Percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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lower mortality and a reduction in major adverse cardiac events (MACE) in some studies [7], other studies did not show any significant difference between DS and CS [8].

The potential beneficial effect of DS was suggested to be mediated by a lower incidence of congestive heart failure caused by a fewer occurrence of no-reflow/microvascular obstruction [9]. Cardiac magnetic resonance (CMR) is an established tool to assess all relevant pathophysiological consequences of myocardial ischemia and reperfusion after STEMI [10,11]. To the best of our knowledge, there are currently no CMR data evaluating the morphological, functional, and microvascular effect of DS in comparison to CS in STEMI patients undergoing primary PCI. The aim of this study was therefore to investigate the effect of DS on infarct size and microvascular obstruction assessed by CMR and its effect on 6-month clinical outcome in patients with STEMI treated by primary PCI.

2. Methods

2.1. Study population and protocol

This study was performed as a predefined substudy of the *Cardioprotection by combined intrahospital remote ischemic perconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial* (NCT02158468) which evaluated the effect of co-application of intrahospital remote ischemic conditioning and postconditioning on myocardial salvage. Study design, and results have been reported previously [12].

In short, the LIPSIA CONDITIONING trial is a prospective, controlled, single-center study which randomized 696 STEMI patients with symptoms <12 h to either (i) combined intrahospital remote ischemic perconditioning plus postconditioning in addition to primary PCI, (ii) postconditioning in addition to PCI, or (iii) conventional PCI.

Exclusion criteria were prior fibrinolysis, cardiogenic shock, pregnancy, participation in another trial, age <18 years, co-morbidity with a limited life expectancy <6 months, and contraindications to CMR at study entry. Primary PCI was performed according to standard clinical practice. Stenting of the culprit lesion was recommended unless the vessel had a diameter of <2.0 mm. DS was recommended to avoid potential microembolization. CS was done in case of failure to clearly identify the infarct-related lesion or to cross the lesion. Thrombus aspiration or the use of glycoprotein IIb/IIIa inhibitors was left to the operators' discretion. The study was conducted according to the Declaration of Helsinki. National ethics committee approved the study and all patients provided written informed consent.

For the purpose of the current substudy, patients enrolled in the LIPSIA CONDITIONING trial were divided according to the PCI technique into a CS group with predilation before implantation of the stent and a DS group without predilation. Patients were matched for age (±5 years), gender and Thrombolysis In Myocardial Infarction (TIMI) flow before PCI. The extent of myocardial injury was assessed with CMR imaging parameters including infarct size, microvascular obstruction, myocardium at risk and myocardial salvage index. The primary clinical endpoint of the study was mortality within 6 months after the index event. Secondary efficacy endpoints were reinfarction and new congestive heart failure, which were analyzed individually as well as in combination with death as MACE. Safety endpoints were the occurrence of bleeding and stroke.

2.2. Cardiac magnetic resonance

By protocol, CMR was performed on days 2–5 after the index event for the assessment of myocardial salvage, infarct size, the presence and extent of microvascular obstruction, left ventricular (LV) ejection fraction, and end-systolic and end-diastolic volumes. The detailed scan protocol on a clinical 1.5 or 3.0 Tesla scanner has been described previously [11]. For all quantitative analyses, certified CMR evaluation software was used by blinded observers in the CMR core laboratory (cmr42, Circle Cardiovascular Imaging, Inc., Calgary, AB, Canada). Infarct size, myocardium at risk, and microvascular obstruction were expressed as percentage of LV mass (%LV). Myocardial salvage index was calculated as myocardial salvage divided by the myocardium at risk [11]. Microvascular obstruction – if present – was included into the overall infarct size analysis and was additionally quantified separately. The CMR core laboratory has excellent reproducibility and low inter- and intraobserver variability for infarct size and myocardial salvage assessment [13].

2.3. Statistical analysis

Continuous data were expressed as median with interquartile range. Categorical data were presented as frequency with percentage. Differences between groups were assessed by Fisher's exact or the X^2 test for categorical variables, and were evaluated using the non-parametric Mann-Whitney *U* test for continuous data. Kaplan-Meier graphs were used to illustrate the mortality rates in the two groups.

Predictors for mortality were identified by univariate and stepwise multivariate Cox regression analysis. Multivariate stepwise regression was performed using only variables with a *p*-value <0.05 in univariate regression analysis. To adjust for baseline differences between patients with DS versus CS patients were matched for TIMI flow pre-PCI, gender and age (±5 years). All tests were 2-tailed, and a *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics 17.0.0.0 (IBM, Armonk, New York).

3. Results

3.1. Patient characteristics

From April 2011 to May 2014, 696 patients with STEMI were randomized in the LIPSIA CONDITIONING trial. Of these, 525 patients (75%) underwent DS during primary PCI, whereas 171 patients underwent CS with predilation. After matching the patients for age (±5 years), gender and TIMI flow pre-PCI, 171 patients in DS group were compared to 171 patients in CS group.

Complete CMR data were obtained in 279 patients and clinical follow-up at 6 months was completed in all 342 patients. Patients with predilation (CS group) had higher incidence of 3-vessel disease compared to patients underwent DS while patients in the DS group were treated more often with Bivalirudin during primary PCI. Moreover, in the DS group patients underwent significantly more often thrombus aspiration before stenting. Otherwise, there were no significant differences in patient characteristics between both groups (Table 1).

Table 1
Baseline characteristics.

Variable	Direct stenting (n = 171)	Predilation (n = 171)	*p*
Age (years)	66 (55–74)	67 (56–76)	0.689
Male sex	109/171 (64%)	109/171 (64%)	1.000
Cardiovascular risk factors			
Current smoking	61/171 (36%)	66/171 (39%)	0.654
Hypertension	132/171 (77%)	127/171 (74%)	0.614
Hypercholesterolemia	74/171 (43%)	72/171 (42%)	0.913
Diabetes mellitus	47/171 (28%)	33/171 (19%)	0.096
Body mass index (kg/m^2)	27 (25–31)	27 (25–30)	0.130
Previous myocardial infarction	16/171 (9%)	21/171 (12%)	0.416
Pain-to-balloon time (min)	194 (131–369)	222 (128–356)	0.542
Killip class on admission			0.691
1	148/171 (87%)	148/171 (87%)	
2	16/171 (9%)	12/171 (7%)	
3	2/171 (1%)	3/171 (2%)	
4	5/171 (3%)	8/171 (4%)	
Anterior infarction	73/171 (43%)	82/171 (48%)	0.385
GP IIb/IIIa antagonists	39/171 (23%)	45/171 (26%)	0.530
Anticoagulation			**0.045**
Bivalirudin	128/171 (75%)	110/171 (64%)	
Heparin	43/171 (25%)	61/171 (36%)	
3-vessel disease	28/171 (16%)	38/171 (22%)	**0.043**
TIMI flow grade before PCI			1.000
0	83/171 (49%)	83/171 (49%)	
1	24/171 (14%)	24/171 (14%)	
2	45/171 (26%)	45/171 (26%)	
3	19/171 (11%)	19/171 (11%)	
TIMI flow grade post-PCI			0.077
0	1/171 (1%)	6/171 (3%)	
1	2/171 (1%)	3/171 (2%)	
2	13/171 (8%)	22/171 (13%)	
3	155/171 (90%)	140/171 (82%)	
Conditioning	51/171 (30%)	63/171 (37%)	0.189
RIC + post-conditioning	55/171 (32%)	41/171 (24%)	
Post-conditioning	65/171 (38%)	67/171 (39%)	
Not done			
Thrombectomy	125/171 (73%)	85/171 (50%)	<0.001
Peak CK (μmol/L*s)	20 (8–32)	23 (11–35)	0.890
Peak CK-MB (μmol/L*s)	2.3 (1.3–4.2)	2.6 (1.3–4.0)	0.822
Peak Troponin (ng/L)	233 (75–751)	304 (65–663)	0.517
ST-segment resolution (%)	69 (53–90)	63 (37–84)	0.363

Continuous data are presented as median and interquartile range.
CK = creatine kinase, CMR = cardiac magnetic resonance, PCI = primary percutaneous coronary intervention, RIC = remote ischemic conditioning, TIMI = Thrombolysis in Myocardial Infarction.

Table 2
Cardiac magnetic resonance parameters and cardiac events.

Cardiac magnetic resonance	Direct stenting		Predilation		p
LV ejection fraction (%)	n = 137	50 (43–59)	n = 137	49 (40–57)	**0.046**
LV end diastolic volume (mL)	n = 138	131 (109–151)	n = 138	134 (113–155)	**0.022**
LV end systolic volume (mL)	n = 138	62 (51–82)	n = 137	69 (53–85)	**0.015**
Myocardium at risk (%LV)	n = 127	32 (25–40)	n = 126	36 (25–44)	0.072
Infarct size (%LV)	n = 133	16 (7–23)	n = 131	19 (9–29)	**0.046**
Myocardial salvage index	n = 125	49 (31–74)	n = 125	44 (24–68)	0.073
Microvascular obstruction (%LV)	n = 133	0 (0–1.3)	n = 131	0.4 (0–2.6)	**0.006**

Cardiac events in 6 months	Direct stenting	Predilation	p
Mortality – n (%)	9/171 (5)	21/171 (12)	**0.034**
Heart failure – n (%)	6/171 (4)	19/171 (11)	**0.011**
Re-infarction – n (%)	6/171 (4)	3/171 (2)	0.502
MACE – n (%)	18/171 (11)	29/171 (17)	0.116
Stroke – n (%)	1/171 (1)	1/171 (1)	1.000
Bleeding – n (%)	1/171 (1)	2/171 (1)	0.624

Continuous data are presented as median and interquartile range.
LV = left ventricle, n = number, MACE = major adverse cardiac events.

3.2. Cardiac magnetic resonance results

In the matched analysis, patients with DS had significantly smaller infarct size ($p = 0.021$) and lower extent of microvascular obstruction ($p = 0.006$) with improvement of LV parameters. In patients with CS, the extent of myocardium at risk was numerically larger and the myocardial salvage index was numerically smaller without reaching statistical significance (Table 2).

3.3. Clinical outcome

Compared to CS, patients undergoing DS had a significantly lower mortality and incidence of heart failure after 6 months (Table 2). Fig. 1 depicts Kaplan–Meier plots showing the risk of mortality stratified by the DS versus CS group. Moreover, a trend to a reduced MACE rate was observed without reaching statistical significance. The occurrence of stroke and bleeding was similar in both groups (Table 2). In univariate Cox regression analysis (Table 3), DS (hazard ratio 0.41, 95% confidence intervals 0.19–0.90, $p = 0.027$) was a significant predictor of reduced mortality. After multivariate adjustment for other established markers of patient risk, DS remained a significant and independent predictor of mortality (hazard ratio 0.30, 95% confidence interval 0.11–0.87, $p = 0.026$).

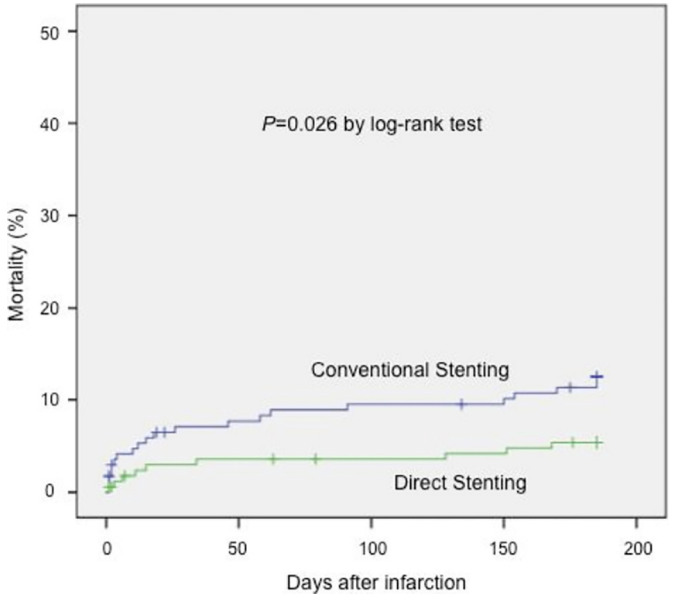

Fig. 1. Kaplan-Meier graph showing 6-month cumulative mortality rate according to direct stenting and predilation.

4. Discussion

In this first study investigating the effect of DS versus CS on myocardial damage assessed by CMR in patients with STEMI undergoing primary PCI, DS was associated with significantly smaller infarct size with subsequent lower mortality rates at 6-month follow-up.

4.1. Effect of DS on myocardial damage

In our study, patients with CS had significantly larger infarct size and more microvascular obstruction, which was also reflected by relatively lower rates of TIMI flow grade 3 after PCI. This may be explained by an increased likelihood of thrombus fragmentation and plaque dislodgement resulting in distal embolization associated with balloon inflation in CS [3,14]. Our findings are consistent with previous observational studies and a recent meta-analysis of 12 studies including 8998 patients with ACS, which observed better angiographic outcomes and less no-reflow following DS as compared to CS [3,7,14–17]. In a

Table 3
Predictors of 6-month mortality in Cox regression analysis.

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Direct stenting	0.41 (0.19–0.90)	**0.027**	0.30 (0.11–0.87)	**0.026**
Age (years)	1.13 (1.08–1.19)	**<0.001**	1.13 (1.06–1.20)	**0.001**
Male sex	2.43 (1.18–5.01)	**0.016**	–	n.s.
Body mass index (kg/m^2)	0.99 (0.92–1.07)	0.861		
Hypertension	2.12 (0.74–6.08)	0.162		
Diabetes mellitus	2.34 (1.12–4.85)	**0.023**	–	n.s.
Hypercholesterolemia	0.75 (0.36–1.58)	0.451		
Current smoking	0.18 (0.05–0.59)	**0.005**	–	n.s.
Previous infarction	1.00 (1.00–1.00)	**0.011**	–	n.s.
Killip-class	2.19 (1.62–2.96)	**<0.001**	1.79 (1.13–2.83)	**0.013**
TIMI flow pre-PCI	1.05 (0.76–1.45)	0.778		
TIMI flow post-PCI	0.63 (0.41–0.99)	**0.046**	–	n.s.
Pain-to-balloon time (min)	1.00 (1.00–1.00)	0.284		
Anterior infarction	1.21 (0.59–2.48)	0.595		
3-vessel disease	1.89 (1.20–2.99)	**0.006**	–	n.s.
Peak CK (μmol/L*s)	1.01 (1.00–1.02)	**0.031**	–	n.s.
Peak CK-MB (μmol/L*s)	1.14 (1.00–1.31)	0.056		
Peak troponin (ng/L)	1.00 (1.00–1.00)	**0.008**	1.00 (1.00–1.00)	**0.047**
ST-segment resolution (%)	0.99 (0.98–1.00)	**0.023**	0.98 (0.97–1.00)	**0.010**

CI, confidence interval, CK = creatine kinase, HR = hazard ratio, PCI = primary percutaneous coronary intervention, TIMI = Thrombolysis In Myocardial Infarction.

prospective descriptive study by Cuellas et al., the percentages of patients with TIMI myocardial perfusion grade 2–3 and with >70% ST-segment resolution was significantly higher in the DS group, indicating better tissue reperfusion [14]. In a randomized trial published by Loubeyre et al., a significant effect of DS on early ST-segment elevation resolution after PCI was reported [18]. Importantly, both TIMI myocardial perfusion grade and ST-segment resolution are known to be strong predictors of infarct size and patient prognosis including mortality [19].

On the other hand, the major limitation of DS in primary angioplasty appears to be the presence of thrombus, which prevents adequate stent selection, rather than anatomical factors [14]. A patent infarct-related artery (TIMI flow grade 2 to 3) at baseline is the most important factor favoring DS, allowing to clearly identify the infarct-related lesion [20]. Potential drawbacks of DS include underestimation of true vessel size, failure to cross the lesion, inadequate stent expansion, geographic miss, and late stent malapposition, which can lead to stent thrombosis, or restenosis. Gasior et al., for instance, demonstrated in a randomized trial that DS did not improve epicardial and myocardial reperfusion indexes and was associated with a higher incidence of in-stent restenosis at 1 year [8].

Our study is unique in being the first study that comprehensively assesses all relevant pathophysiological consequences of myocardial ischemia and reperfusion in patients undergoing DS including infarct size, myocardial salvage, and microvascular obstruction using CMR in a large number of reperfused STEMI patients [21,22]. In addition to its important prognostic implications, evaluation of myocardial infarct architecture especially infarct size and microvascular obstruction using CMR may help to understand the pathophysiological background of both DS and CS especially in the presence of the inconsistent available data. Infarct size and microvascular obstruction are directly related to the occurrence of future cardiovascular events in reperfused STEMI patients and therefore our data provide a potential pathophysiological explanation for the reported improved clinical outcome of patients undergoing DS as reported in previous studies and our analysis [11].

4.2. DS and clinical outcome

The results of randomized studies investigating the clinical benefit of a DS strategy have been contradictory. Some studies suggested that DS reduces MACE and mortality, while others showed no difference [8,18,23,24]. These studies had relatively small sample sizes and were therefore underpowered to detect significant differences. Moreover, most of the studies did not reflect contemporary STEMI care, such as use of drug-eluting stents or newer antiplatelet therapies. However, the feasibility of performing a large randomized controlled trial of DS is hampered by certain lesion characteristics being unsuitable for DS, e.g. calcified, tortuous, or totally occluded vessels, as well as major bifurcations. A recent meta-analysis demonstrated reduced mortality rates following DS as compared with CS in short-term and 1-year follow-up [7]. In another meta-analysis including only non-randomized studies, DS was strongly associated with better short- and long-term mortality [9].

In our relatively large study, DS was associated with lower rates of mortality and congestive heart failure. Additionally, DS was identified as an independent predictor of reduced mortality in multivariate analysis. The observed improvement in survival in patients treated with DS was possibly related to enhanced epicardial and myocardial reperfusion in such patients resulting in reduced infarct size and less microvascular obstruction/no-reflow. Moreover, patients who underwent CS had a significantly higher incidence of heart failure, which may be explained with the deterioration of the LV ejection fraction as a consequence of larger infarcts in comparison to patients undergoing DS [20,25]. To avoid differences in baseline characteristics and to make both groups better comparable, we performed matching for TIMI flow pre-PCI, age, and gender. Our findings confirm even after thorough matching for baseline differences an independent predictive value of DS on clinical outcome and provide a potential pathophysiologic explanation by showing reduced myocardial damage in CMR imaging. Nevertheless, confirmation of these results and further evaluation of the protective effect of DS in the setting of STEMI in well-designed, adequately powered prospective randomized trials is definitely required.

4.3. Limitations

The main limitation of the study was the potential selection bias due to lack of randomization since selection of stenting technique with or without predilation was under the discretion of the operators. Predilation may be done due to large thrombus of more complex lesions, which may have affected the overall outcomes. A greater percentage of patients with three-vessel disease in the conventional stenting group may have also affected our results as well as the fact that thrombectomy was more frequently used in the DS group. However, as recently two large randomized trials have showed no benefit on clinical outcomes of routine thrombus aspiration strategy overall, a potential bias is limited. Moreover, we performed a matching for age, gender, and TIMI flow for the 2 groups as well as a multivariate adjustment in statistical analysis to minimize these potential biases.

Furthermore, missing of CMR data in about 94 patients may have affected our results. Ischemic conditioning may has also affected our results in general or in favor of one arm but the different treatment groups were equally distributed in the DS and CS groups. Other limitations are the lack of assessment of LV-function on 6-month follow-up and missing long-term clinical results.

In conclusion, in patients with acute reperfused STEMI, DS is safe and feasible with significant reduction of infarct size compared to CS, which resulted in a lower incidence of heart failure hospitalizations and lower mortality. Furthermore, DS was identified as an independent predictor of reduced 6-month mortality over and above other established prognostic factors.

Conflict of interest

There are no potential conflicts of interest, including related consultancies, shareholdings and funding grants regarding this manuscript.

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