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Very Long-Term Clinical Outcomes After Direct Stenting in Patients Presenting With ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Background/Purpose: Direct Stenting (DS) could be associated with reduced distal embolization and improved reperfusion in patients with ST-segment elevation myocardial infarction (STEMI). However, the impact of DS on long-term outcomes remains unclear, therefore we evaluated the impact of DS on very long-term clinical outcome in STEMI.

Methods/Materials: Between April 2002 and December 2004, patients presenting with STEMI undergoing percutaneous coronary intervention were investigated. The study population was divided into two groups: DS and conventional stenting (CS) and stratified according to initial TIMI flow. Major adverse cardiac events (MACE) were assessed at 10 years and all-cause mortality at 15 years. Cox proportional hazards models were used. When the proportional hazards assumption was not satisfied, landmark analysis at mid-term (2 years) was performed.

Results: A total of 812 consecutive patients were evaluated, 6 patients were excluded due to inadequate angiographic images, 450 (55.8%) underwent DS and 356 (44.2%) CS.

At 15 years follow-up, DS was associated with a reduction in all-cause mortality (DS 35.0% vs. CS 45.3%, aHR 0.74, 95% CI 0.58–0.93, $p = 0.010$). The landmark analysis at 2 years identifies reduced 2-year MACE in DS compared with CS (6.8% vs.14%, aHR 0.67, 95% CI 0.49–0.93, $p = 0.015$) and beyond 2 years no significant differences were found between the groups (27.4% vs. 29.3%, aHR 1.00, 95% CI 0.74–1.36, $p = 0.999$). In patients with baseline TIMI 0–1, DS was associated with lower 10-year MACE and 15-year mortality compared with CS (aHR0.71, 95%CI 0.55–0.92, $p = 0.010$ and aHR0.65, 95%CI 0.50–0.84, $p = 0.001$, respectively).

Conclusions: DS was associated with reduced 15-year all-cause mortality and reduced mid-term MACE rate in patients with STEMI. Clinical events reduction associated with DS was particularly relevant in patients with initial TIMI flow 0–1.

1. Introduction

Primary percutaneous coronary intervention (PCI) with drug-eluting stent is the standard of care for treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI). However, optimal myocardial reperfusion remains challenging and the impact of direct stenting on long term clinical outcomes remains unclear.

Direct stenting (DS) without balloon predilation has the potential to mitigate distal embolization and no reflow by entrapping thrombotic material behind the stent struts. Conversely, balloon predilation may improve vessel visualization and optimize stent sizing, crossing, and expansion.

Direct stenting as opposed to routine predilation followed by stent implantation conventional stenting (CS) showed improved reperfusion parameters and a possible reduction in early all-cause mortality in the context of STEMI [1–8]. However, the majority of studies evaluated short-term outcomes in a limited number of patients and data on long term outcome are scarce [9].

The clinical benefit of DS might be particularly relevant, when this technique is adopted in infarct related artery with reduced TIMI flow

Abbreviations: CAD, Coronary Artery Disease; CI, Confidence Intervals; CS, Conventional Stenting; DES, Drug eluting stent; DS, Direct Stent; GPi, Glycoprotein IIb/IIIa inhibitors; aHR, Adjusted Hazard Ratio; LTB, Large thrombus burden; MACE, Major Adverse Cardiac Events; MI, myocardial infarction; PCI, Percutaneous Coronary Intervention; SD, Standard deviation; STB, Small thrombus burden; STEMI, ST segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; TVR, Target vessel revascularization.

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or large thrombus burden (LTB), given the possible higher risk of distal embolization and microvascular obstruction in this subpopulation.

Given this background, we evaluated the impact of direct stenting compared with conventional stenting on very long-term clinical outcomes also in relation to thrombus burden and baseline TIMI flow.

2. Material and methods

From April 2002 to December 2004, all consecutive patients diagnosed with STEMI undergoing PCI with drug eluting stent (DES), at the Erasmus University Medical Center (EMC), Rotterdam, the Netherlands were evaluated. Patients with non-quantifiable thrombus burden were excluded.

Demographic, clinical, and procedural data were collected from the hospital databases. Coronary angioplasty and intracoronary stent implantation were performed using standard clinical practice. All patients were pre-treated with a loading dose of aspirin and clopidogrel. All patients were discharged with the prescription for dual antiplatelet therapy. The decision whether to perform direct stenting, thrombectomy, and administration of glycoprotein IIb/IIIa inhibitors (GPi) was made by the operator. Direct stenting was defined as stent positioning and deployment without prior balloon pre-dilation of the stenosis, either before or after thrombus aspiration [10]. Conventional stenting was defined by stenting after balloon pre-dilation of the stenosis.

The Medical Ethics Committee of the EMC reviewed the study protocol and waived the need for additional informed consent because of the non-interventional character of this retrospective study using anonymous data collection. The investigation conforms to the principles outlined in the Declaration of Helsinki.

2.1. Angiographic analysis

The angiographic data were revised by two experienced interventional cardiologists as described previously [11]. Thrombolysis In Myocardial Infarction (TIMI) flow was assessed, no-reflow considered as decreased antegrade flow (TIMI flow <2) in absence of occlusion at treatment site or distal embolization. Distal embolization was defined as migration of filling defect distally in the infarct related vessel or one of its branches, or a new abrupt cut-off of the distal vessel or one of its branches [12]. Thrombus burden was graded in accordance with TIMI thrombus grade classification [13]: grade 0 (G0), no angiographic characteristics of thrombus; grade 1 (G1), suggestive but not diagnostic angiographic characteristics of thrombus, such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex meniscus; grade 2 (G2), defined thrombus with greatest dimensions ≤1/2 the vessel diameter; grade 3 (G3), defined thrombus with greatest linear dimension >1/2 but <2 vessel diameters; grade 4 (G4), defined thrombus with largest dimensions ≥2 vessel diameters; grade 5 (G5), occluded vessel.

Patients with an occluded infarct related artery (G5) were reclassified, before thrombectomy, after obtaining a minimal antegrade flow by guide-wire crossing or small (1.5 mm diameter) deflated balloon passage or dilation, as proposed by Sianos et al. [11]. After G5 reclassification, thrombus burden was stratified in two groups, defined as small thrombus burden (STB) for thrombus less than G4 and large thrombus burden (LTB) for thrombus equal or greater than G4.

2.2. Clinical follow-up

Survival data were obtained from the municipal civil registry in the Netherlands. Health questionnaires were sent to all the living patients with specific questions on adverse cardiac events. If needed, referring cardiologists and general practitioners were contacted for additional information. Follow-up was performed at 10 years and survival data were collected at 15 years.

Major adverse cardiac event (MACE) was defined as all-cause death, repeat myocardial infarction (MI), and target vessel revascularization (TVR). TVR was defined as any repeat percutaneous intervention or coronary artery bypass grafting of any segment of the infarct related artery.

2.3. Statistical analysis

Categorical variables expressed as counts and percentages were tested for statistical significance using the Pearson chi-square test or Fisher's exact test as appropriate. Continuous variables reported as mean ± standard deviation (SD) were compared using the Student *t*-test.

Logistic regression analysis was performed to examine the predictors of direct stenting.

The univariate analysis was performed using the Cox proportional hazards regression, with all the following variables: age, gender, diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking, family history of coronary artery disease, previous MI, previous PCI, primary PCI, stent thrombosis at the index procedure, cardiogenic shock, multivessel disease, infarct related artery, multivessel PCI, glycoprotein IIb/IIIa inhibitors, bifurcation stenting, direct stenting, thrombectomy, baseline TIMI flow 0–1, final TIMI flow 3, no reflow, and LTB. Subsequently, variables with p values ≤0.10 were entered into the multivariate Cox model, direct stenting was forced into the model to estimate its effect on clinical outcomes.

Proportional hazards assumptions were tested by adding interaction terms between direct stenting and time to the Cox model. The assumption was deemed to be violated in case of significant interaction ($p < 0.05$). In case of violation of the assumption, landmark analysis was performed.

Long term follow-up analysis was performed and for this reason a mid-term (2 years) landmark point was chosen. Statistical significance was set at the 2-tailed p value <0.05 and 95% confidence intervals (CI) were presented for all adjusted hazard ratio (aHR) and unadjusted hazard ratio (HR). All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, New York).

3. Results

Between April 2002 and December 2004, 812 consecutive STEMI patients were treated with PCI and DES at our institution, 806 patients (99.3%) were included in the analysis and 6 were excluded due to the inadequate angiographic images that made baseline thrombus burden or TIMI flow non-quantifiable. Baseline clinical characteristics of the patient population are reported in Table 1. Direct stenting was performed in 450 patients (55.8%) and CS in 356 (44.2%).

TIMI flow grade 0–1 at baseline was observed in 73% of the total patients and in 63.6% of those treated with direct stenting.

Glycoprotein IIb/IIIa inhibitors were administered more often in the CS than in the DS group (55.6% vs 46.2%, $p = 0.009$). Postdilation was performed in 262 (32.5%) patients without difference between the two groups (DS 33.8% vs CS 30.9%, $p = 0.405$).

Thrombectomy was performed more frequently in the DS compared with the CS group (10.0% vs. 5.1%, $p = 0.012$). In our study, only 45 patients underwent thrombectomy and direct stent. In this subgroup, 10-year TVR occurred in 6 (13.3%) patients, 10-year MI in 6 (13.3%) patients, 10-year mortality in 10 (22.2%) patients and overall 10-year MACE occurred in 16 (35.6%) patients. Mortality at 15 years occurred in 12 (26.7%) patients.

Thrombectomy was an independent predictor of direct stenting; on the other hand patients with previous MI, cardiogenic shock, primary PCI, stent thrombosis at the presentation, LAD infarct related artery, and initial TIMI flow 0–1 were less likely to be treated direct stenting (Supplemental Table S1).

Table 1
Baseline clinical and angiographic characteristics.

	Total ($n = 806$)[a]	Direct Stenting ($n = 450$)	Conventional Stenting ($n = 356$)	p value
Age, years	59.1 ± 11.5	58.6 ± 11.4	59.9 ± 11.7	0.126
Female	171 (21.2%)	89 (19.8%)	82 (23.0%)	0.298
Diabetes mellitus	80 (9.9%)	46 (10.2%)	34 (9.6%)	0.813
Hypertension	218 (27.0%)	122 (27.1%)	96 (27.0%)	1.000
Hypercholesterolemia[a]	240 (29.9%)	142 (31.6%)	98 (27.7%)	0.245
Smoking	305 (37.8%)	188 (41.8%)	117 (32.9%)	0.010
Family history of CAD	213 (26.4%)	136 (30.2%)	77 (21.6%)	0.006
Previous MI	81 (10.0%)	33 (7.3%)	48 (13.5%)	0.005
Previous PCI	46 (5.7%)	18 (4.0%)	28 (7.9%)	0.022
MI presentation				
Primary PCI	725 (90.0%)	393 (87.3%)	332 (93.3%)	0.006
Cardiogenic shock	77 (9.6%)	32 (7.1%)	45 (12.6%)	0.011
Stent thrombosis	22 (2.7%)	6 (1.3%)	16 (4.5%)	0.008
Multivessel disease	313 (38.8%)	166 (36.9%)	147 (41.3%)	0.216
Infarct-related artery				
Left main stem	12 (1.5%)	3 (0.7%)	9 (2.5%)	0.039
Left anterior descending	410 (50.9%)	213 (47.3%)	197 (55.3%)	0.028
Right coronary artery	300 (37.2%)	185 (41.1%)	115 (32.3%)	0.010
Circumflex coronary artery	79 (9.8%)	46 (10.2%)	33 (9.3%)	0.721
Vein or IMA graft	5 (0.6%)	3 (0.7%)	2 (0.6%)	1.000
Multivessel PCI	86 (10.7%)	48 (10.7%)	38 (10.7%)	1.000
Glycoprotein IIb/IIIa inhibitors	406 (50.4%)	208 (46.2%)	198 (55.6%)	0.009
Bifurcation stenting	52 (6.5%)	24 (5.3%)	28 (7.9%)	0.152
Thrombectomy	63 (7.8%)	45 (10.0%)	18 (5.1%)	0.012
TIMI flow at baseline				
0	464 (57.6%)	206 (45.8%)	258 (72.5%)	<0.001
1	124 (15.4%)	80 (17.8%)	44 (12.4%)	0.039
2	112 (13.9%)	81 (18.0%)	31 (8.7%)	<0.001
3	106 (13.2%)	83 (18.4%)	23 (6.5%)	<0.001
Final TIMI flow 3	643 (78.9%)	343 (76.2%)	291 (82.2%)	0.045
No reflow	12 (1.5%)	4 (0.9%)	8 (2.2%)	0.145
Dissection	25 (3.1%)	11 (2.4%)	14 (3.9%)	0.306
Distal embolization	59 (7.3%)	30 (6.7%)	29 (8.1%)	0.496
Large thrombus burden	226 (28.0%)	121 (26.9%)	105 (29.5%)	0.430

CAD, coronary artery disease; IMA, internal mammary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.
[a] Data available for hypercholesterolemia: 804/806.

Table 2
Predictors of 15-year all-cause mortality.

	Unajusted HR(CI 95%)	p value	Adjusted HR(CI 95%)	p value
Age (yrs)	1.07 (1.06–1.08)	<0.001	1.06 (1.05–1.08)	<0.001
Female	1.46 (1.13–1.88)	0.003	1.29 (0.99–1.67)	0.060
Diabetes mellitus	1.33 (0.94–1.86)	0.104		
Arterial hypertension	1.10 (0.87–1.41)	0.428		
Hypercholesterolemia	0.77 (0.60–0.99)	0.039	0.92 (0.71–1.19)	0.512
Smoking	0.74 (0.58–0.93)	0.011	1.43 (1.11–1.85)	0.006
Family history of CAD	0.38 (0.27–0.52)	<0.001	0.57 (0.41–0.79)	0.001
Previous MI	1.86 (1.37–2.54)	<0.001	1.12 (0.78–1.60)	0.551
Previous PCI	1.75 (1.18–2.60)	0.005	1.04 (0.56–1.91)	0.911
Primary PCI	0.73 (0.53–1.02)	0.067	1.16 (0.81–1.66)	0.415
Stent thrombosis at index procedure	1.84 (1.05–3.20)	0.032	2.39 (1.08–5.28)	0.032
Cardiogenic shock	4.30 (3.23–5.72)	<0.001	3.44 (2.53–4.67)	<0.001
Multivessel disease	1.91 (1.53–2.38)	<0.001	1.47 (1.14–1.88)	0.003
Infarct-related artery (LAD)	0.90 (0.72–1.12)	0.327		
Multivessel PCI	1.59 (1.15–2.19)	0.005	1.03 (0.71–1.48)	0.885
Glycoprotein IIb/IIIa inhibitors	0.64 (0.51–0.80)	<0.001	0.70 (0.55–0.88)	0.003
Bifurcation stenting	0.95 (0.60–1.51)	0.824		
Direct stenting	0.69 (0.55–0.86)	0.001	0.74 (0.58–0.93)	0.010
Thrombectomy	0.89 (0.58–1.35)	0.573		
Final TIMI flow 3	0.75 (0.58–0.97)	0.026	0.78 (0.59–1.04)	0.088
No reflow	1.94 (0.92–4.10)	0.084	0.70 (0.31–1.57)	0.386
LTB	0.86 (0.67–1.11)	0.253		
Baseline TIMI flow 0–1	1.05 (0.82–1.35)	0.712		

HR, hazard ratio; CI confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LTB, large thrombus burden; TIMI, Thrombolysis In Myocardial Infarction.
Results of the univariate Cox proportional hazards model investigating 23 variables as potential predictors of all-cause mortality and of the multivariate analysis using the 16 variables significant at $p \leq 0.10$ in the univariate analysis.

3.1. Clinical follow-up

Completeness of clinical follow-up at 10 years was obtained in 797 (98.9%) patients, in addition mortality data were collected up to 15 years in 797 (98.9%) patients. At 10-year follow-up, overall MACE rate was 42.4% ($N = 338$), MI rate 14.5% ($N = 112$), TVR rate 14.1% ($N = 109$) and mortality rate 26.6% ($N = 212$). At 15 years, overall mortality rate was 39.5% ($N = 315$).

Cox proportional hazards regression in the total population with 10 years follow-up for MACE showed that the proportional hazards assumption was violated (the interaction between direct stenting and time was statistically significant). Therefore, a landmark analysis at the 2 year landmark point was added. Before and after the two-year landmark point, the interaction between direct stenting and time was not statistically significant.

At 15 years follow-up for all-cause mortality, the assumption of proportionality was met in the total population. In the subgroups of patients with initial TIMI flow 0–1 and LTB the test for proportionality was also satisfied.

At 15 years follow-up, DS was associated with a reduction in all-cause mortality (DS 35.0% vs. CS 45.3%, aHR 0.74, 95% CI 0.58–0.93, $p = 0.010$) (Table 2) (Fig. 1) (Supplemental Fig. S1).

DS was associated with reduced 2-year MACE compared with CS (6.8% vs.14%, aHR 0.67, 95% CI 0.49–0.93, $p = 0.015$) and beyond 2 years no significant differences were found between the two groups (27.4% vs. 29.3%, aHR 1.00, 95% CI 0.74–1.36, $p = 0.999$) (Fig. 2) (Tables 3 and 4).

At 10 years follow-up, MI and TVR events rates were similar between the two groups (DS 13.4% vs. CS 16.1%, aHR 0.86, 95% CI 0.59–1.25, $p = 0.425$; and DS 12.7% vs. CS 16.1%, aHR 0.83, 95% CI 0.56–1.22, $p = 0.339$, respectively).

Patients with baseline TIMI flow grade 0–1 treated with DS experienced lower 15-year all-cause mortality (34.4% vs. 45.1%, aHR 0.65, 95% CI 0.50–0.84, $p = 0.001$) and 10-year MACE (36.1% vs. 47.8%, aHR 0.71, 95% CI 0.55–0.92, $p = 0.010$) and compared with CS (Tables 5 and 6). At 10 years follow-up, MI and TVR events rates were similar between the two groups (DS 15.8% vs. CS 16.8%, aHR 0.94 95% CI 0.62–1.42, $p = 0.759$; and DS 14.4% vs. CS 17.2%, aHR 1.73, 95%CI 0.88–3.38, $p = 0.111$, respectively) in patients with baseline TIMI 0–1 (Supplemental Table S2 and Supplemental Table S3).

In the subgroup of patients with LTB direct stenting had no impact on 15-year mortality and on 10-year MACE (mortality: aHR 0.62, 95% CI 0.39–1.01, $p = 0.050$, MACE: aHR 0.77, 95% CI 0.50–1.18, $p = 0.224$,) (Supplemental Table S4 and Supplemental Table S5).

4. Discussion

The major findings of our study on long-term clinical impact of stent implantation strategy in STEMI are: 1) at very long-term follow-up, mortality rate was lower in patients treated with DS compared with those undergoing CS. 2) The clinical benefit of DS was mainly driven by a reduction in mortality in patients with baseline TIMI 0-I, in whom DS was also associated with a lower long term MACE rate. 3) Stenting technique had no relevant impact on clinical outcomes in patients with large thrombus burden.

Several studies suggested direct stenting as a feasible and safe technique [1–5,7,8,14–26], especially in patients with acute myocardial infarction, often associated with a soft plaque rupture [27], not

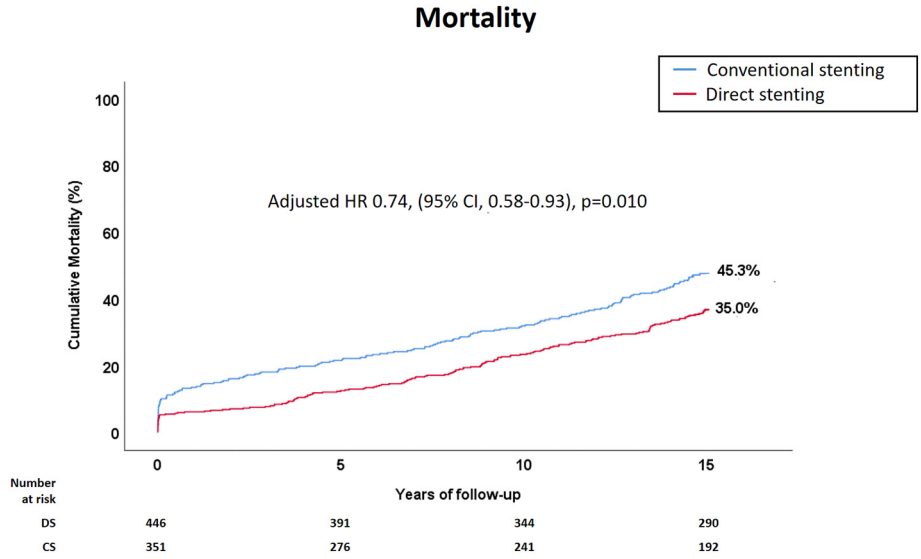

Fig. 1. All-cause mortality according to direct stenting and conventional stenting
HR hazard ratio; MACE major adverse cardiac events.
Kaplan–Meier estimates of the rate of mortality from any cause according to direct stenting and conventional stenting.

demanding aggressive lesion predilation to facilitate stent expansion. DS compared with CS was reported to improve myocardial perfusion with a concomitant reduction in procedural costs, contrast used, radiation exposure time, and procedural duration [20,23–25,28].

In addition, DS has been associated with a reduction of in-hospital and 1-year all-cause mortality in small randomized studies and in sub-analysis of a large randomized trail [1,3,7,8].

On the other hand, the long-term clinical benefit of this strategy is still unclear and despite being DS widely adopted [29], there is a lack of recommendations in current guidelines for the management of STEMI patients with regard of stent placement strategy [30].

In our study, DS was associated with a reduction in overall long-term all-cause mortality compared with CS. The benefit of the DS might be the clinical translation of a reduction in procedural thrombus dislodgment enhancing material entrapping behind the stent struts, reducing distal embolization, and the no-reflow phenomenon [1–4,8,16,17]. In addition, has been previously hypothesized that DS in absence of balloon predilation could also limit the arterial barotrauma and the consequent neointimal hyperplasia [4,31–34].

Our finding showed that in patients with TIMI 0–1 flow at baseline, a known predictor of impaired reperfusion and reduced survival [35–39], DS was associated with reduced long-term all-cause death and MACE. The impact on MACE was driven by all-cause mortality, in contrast with a negligible difference in MI and TVR.

A similar role of DS in the reduction of distal embolization might be hypothesized in patients presenting with LTB.

However, in our study the use of DS in angiographic highly thrombotic lesion was not associated with a relevant clinical benefit.

Such apparent paradox may be explained by the fact that the angiographic assessment of the coronary thrombus might be inaccurate in the quantification of the real amount of thrombotic material

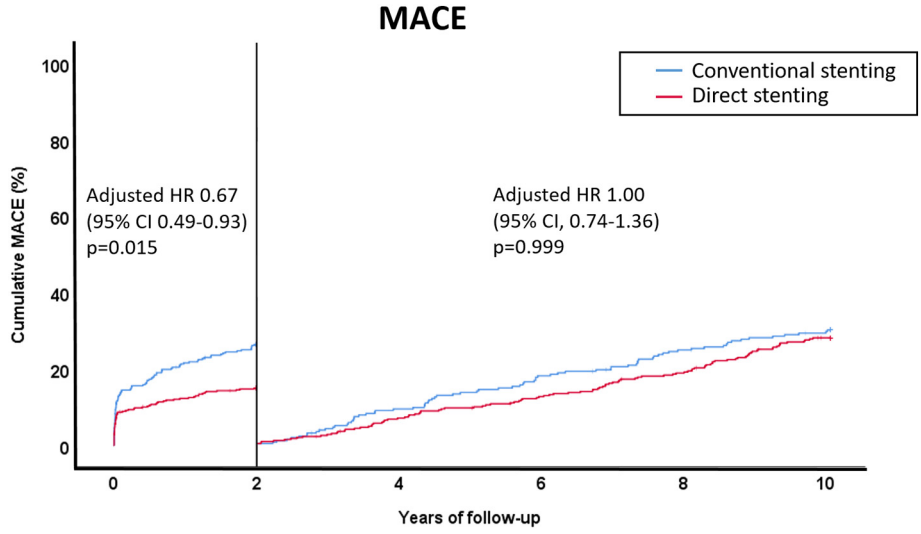

Fig. 2. Landmark analysis at 2-year for MACE according to direct stenting and conventional stenting
HR hazard ratio; MACE major adverse cardiac events.
Landmark analysis for cumulative MACE with a 2-year landmark time point, according to direct stenting and conventional stenting.

Table 3
Predictors of 2-year MACE.

	Unadjusted HR (CI 95%)	p value	Adjusted HR (CI 95%)	p value
Age (yrs)	1.02 (1.01–1.03)	0.001	0.01 (0.99–1.03)	0.111
Female	1.35 (0.95–1.93)	0.094	1.50 (1.03–2.17)	0.032
Diabetes mellitus	1.34 (0.84–2.14)	0.222		
Arterial hypertension	1.11 (0.79–1.56)	0.536		
Hypercholesterolemia	0.83 (0.59–1.18)	0.298		
Smoking	0.79 (0.57–1.10)	0.164		
Family history of CAD	0.67 (0.45–0.98)	0.039	0.86 (0.57–1.29)	0.461
Previous MI	1.85 (1.22–2.82)	0.004	1.03 (0.65–1.64)	0.907
Previous PCI	2.46 (1.50–4.01)	<0.001	1.64 (0.74–3.66)	0.227
Primary PCI	0.88 (0.54–1.44)	0.607		
Stent thrombosis at index procedure	3.35 (1.82–6.18)	<0.001	2.23 (0.84–5.97)	0.109
Cardiogenic shock	5.17 (3.65–7.33)	<0.001	4.38 (2.99–6.41)	<0.001
Multivessel disease	2.15 (1.57–2.94)	<0.001	1.81 (1.28–2.57)	0.001
Infarct-related artery (LAD)	1.12 (0.82–1.53)	0.472		
Multivessel PCI	1.73 (1.14–2.63)	0.011	0.81 (0.51–1.30)	0.385
Glycoprotein IIb/IIIa inhibitors	0.91 (0.66–1.23)	0.523		
Bifurcation stenting	1.81 (1.08–3.03)	0.025	1.37 (0.80–2.33)	0.251
Direct stenting	0.54 (0.39–0.74)	<0.001	0.67 (0.49–0.93)	0.015
Thrombectomy	0.85 (0.46–1.56)	0.597		
Final TIMI flow 3	0.78 (0.54–1.11)	0.167		
No reflow	2.91 (1.19–7.09)	0.019	0.87 (0.34–2.21)	0.762
LTB	1.53 (1.11–2.12)	0.009	1.39 (0.99–1.95)	0.053
Baseline TIMI flow 0–1	1.45 (0.80–1.64)	0.449		

HR, hazard ratio; CI confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LTB, large thrombus burden; TIMI, Thrombolysis In Myocardial Infarction.
Results of the univariate Cox proportional hazards model investigating 23 variables as potential predictors of MACE at 2 years follow-up and of the multivariate analysis using the 13 variables significant at p ≤ 0.10 in the univariate analysis.

Table 4
Predictors of MACE from 2 year to 10 years follow-up.

	Unadjusted HR (CI 95%)	p value	Adjusted HR (CI 95%)	p value
Age (yrs)	1.03 (1.02–1.05)	<0.001	1.02 (1.01–1.04)	0.001
Female	1.09 (0.76–1.56)	0.660		
Diabetes mellitus	1.09 (0.67–1.77)	0.734		
Arterial hypertension	1.17 (0.84–1.61)	0.355		
Hypercholesterolemia	0.79 (0.57–1.10)	0.165		
Smoking	0.88 (0.65–1.19)	0.397		
Family history of CAD	0.46 (0.31–0.69)	<0.001	0.55 (0.37–0.83)	0.004
Previous MI	2.41 (1.62–3.59)	<0.001	1.78 (1.13–2.79)	0.012
Previous PCI	2.12 (1.20–3.72)	0.009	1.03 (0.45–2.34)	0.947
Primary PCI	0.88 (0.55–1.42)	0.598		
Stent thrombosis at index procedure	2.70 (1.20–6.09)	0.017	2.31 (0.75–7.12)	0.143
Cardiogenic shock	1.12 (0.59–2.12)	0.725		
Multivessel disease	1.48 (1.10–1.99)	0.010	1.24 (0.91–1.70)	0.168
Infarct-related artery (LAD)	0.80 (0.60–1.08)	0.143		
Multivessel PCI	1.18 (0.73–1.90)	0.492		
Glycoprotein IIb/IIIa inhibitors	0.96 (0.72–1.29)	0.801		
Bifurcation stenting	0.83 (0.41–1.68)	0.601		
Direct stenting	0.89 (0.66–1.20)	0.455	1.00 (0.74–1.36)	0.999
Thrombectomy	0.68 (0.37–1.25)	0.213		
Final TIMI flow 3	0.71 (0.50–0.99)	0.043	0.72 (0.51–1.02)	0.061
No reflow	0.47 (0.07–3.37)	0.454		
LTB	0.73 (0.52–1.04)	0.085	0.74 (0.51–1.06)	0.104
Baseline TIMI flow 0–1	0.88 (0.64–1.22)	0.440		

HR, hazard ratio; CI confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LTB, large thrombus burden; TIMI, Thrombolysis In Myocardial Infarction.
Results of the univariate Cox proportional hazards model investigating 23 variables as potential predictors of MACE after 2 years follow-up and of the multivariate analysis using the 8 variables significant at p ≤ 0.10 in the univariate analysis and Direct stenting. Direct stenting was forced into the model to estimate its independent effect along with the other predictors of clinical outcomes.

Table 5
Predictors of 15 years all-cause mortality in patient with baseline TIMI flow 0–1.

	Unadjusted HR (CI 95%)	p value	Adjusted HR (CI 95%)	p value
Age (yrs)	1.08 (1.06–1.09)	<0.001	1.07 (1.05–1.08)	<0.001
Female	1.60 (1.20–2.13)	0.001	1.27 (0.94–1.72)	0.119
Diabetes mellitus	1.39 (0.94–2.05)	0.096	1.35 (0.90–2.02)	0.147
Arterial hypertension	1.17 (0.88–1.55)	0.286		
Hypercholesterolemia	0.82 (0.62–1.09)	0.167		
Smoking	0.72 (0.55–0.96)	0.023	1.47 (1.90–1.99)	0.011
Family history of CAD	0.37 (0.25–0.55)	<0.001	0.55 (0.37–0.82)	0.004
Previous MI	1.71 (1.19–2.46)	0.004	0.94 (0.62–1.43)	0.786
Previous PCI	1.55 (0.99–2.42)	0.057	1.81 91.08–3.04)	0.025
Primary PCI	0.71 (0.45–1.12)	0.137		
Stent thrombosis at index procedure	1.55 (0.82–2.92)	0.177		
Cardiogenic shock	3.84 (2.78–5.32)	<0.001	3.36 (2.38–4.76)	<0.001
Multivessel disease	1.69 (1.031–2.19)	<0.001	1.26 (0.94–1.69)	0.118
Infarct-related artery (LAD)	0.84 (0.65–1.09)	0.182		
Multivessel PCI	0.145 (0.97–2.17)	0.070	1.02 (0.65–1.62)	0.924
Glycoprotein IIb/IIIa inhibitors	0.66 (0.51–0.85)	0.002	0.70 (0.53–0.93)	0.013
Bifurcation stenting	0.68 (0.37–1.25)	0.214		
Direct stenting	0.69 (0.53–0.89)	0.004	0.65 (0.50–0.84)	0.001
Thrombectomy	0.87 (0.55–1.36)	0.537		
Final TIMI flow 3	0.63 (0.43–0.92)	0.017	0.73 (0.46–1.15)	0.175
No reflow	1.93 (0.91–4.10)	0.086	0.68 (0.28–1.64)	0.389
LTB	0.81 (0.61–1.08)	0.147		

HR, hazard ratio; CI confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LTB, large thrombus burden; TIMI, Thrombolysis In Myocardial Infarction.
Results of the univariate Cox proportional hazards model investigating 23 variables as potential predictors of all-cause mortality and of the multivariate analysis using the 14 variables significant at p ≤ 0.10 in the univariate analysis.

[40]. Moreover, angiography alone is not providing reliable information on thrombus organization, stability, extension and on its

Table 6
Predictors of 10 years MACE in patient with baseline TIMI flow 0–1.

	Unadjusted HR (CI 95%)	p value	Adjusted HR (CI 95%)	p value
Age (yrs)	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	0.001
Female	1.36 (1.02–1.81)	0.035	1.25 (0.93–1.69)	0.143
Diabetes mellitus	1.40 (0.96–2.04)	0.082	1.34 (0.90–1.98)	0.146
Arterial hypertension	1.13 (0.86–1.50)	0.378		
Hypercholesterolemia	0.78 (0.59–1.04)	0.089	0.78 (0.58–1.05)	0.098
Smoking	0.83 (0.63–1.08)	0.157		
Family history of CAD	0.55 (0.39–0.78)	0.001	0.71 (0.50–1.01)	0.057
Previous MI	1.88 (1.33–2.65)	<0.001	1.19 (0.80–1.78)	0.388
Previous PCI	2.27 (1.51–3.42)	<0.001	2.08 (1.12–3.87)	0.021
Primary PCI	1.09 (0.66–1.78)	0.740		
Stent thrombosis at index procedure	2.62 (1.50–4.59)	0.001	1.22 (0.55–2.70)	0.628
Cardiogenic shock	2.79 (2.00–3.89)	<0.001	2.73 (1.92–3.87)	<0.001
Multivessel disease	1.49 (1.16–1.91)	0.002	1.24 (0.95–1.62)	0.112
Infarct-related artery (LAD)	1.01 (0.79–1.30)	0.942		
Multivessel PCI	1.18 (0.79–1.77)	0.424		
Glycoprotein IIb/IIIa inhibitors	1.01 (0.79–1.30)	0.913		
Bifurcation stenting	0.95 (0.55–1.63)	0.846		
Direct stenting	0.67 (0.52–0.87)	0.002	0.71 (0.55–0.92)	0.010
Thrombectomy	0.77 (0.49–1.22)	0.264		
Final TIMI flow 3	0.81 (0.54–1.21)	0.299		
No reflow	1.58 (0.70–3.56)	0.266		
LTB	1.08 (0.83–1.40)	0.580		

HR, hazard ratio; CI confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LTB, large thrombus burden; TIMI, Thrombolysis In Myocardial Infarction.
Results of the univariate Cox proportional hazards model investigating 22 variables as potential predictors of MACE and of the multivariate analysis using the 11 variables significant at p ≤ 0.10 in the univariate analysis.

tendency to migrate distally while, the assessment of TIMI flow grade might better reflect those characteristics [40–45].

A common criticism to a direct stenting approach is the fact that in STEMI patients and in particular in those with TIMI flow 0–1 or large thrombus burden, the optimal vessel visualization and sizing could be impaired. In those specific cases, thrombus aspiration, although having limited benefit in terms of clinical outcomes in unselected STEMI patients, might improve vessel visualization and sizing prior to DS avoiding predilation.

In our analysis we observed that patients treated with thrombectomy were more likely to undergo DS, as showed in previous studies and in line with a recent patient-level analysis from three randomized trials [46,47].

Our data suggest that DS might have a relevant clinical benefit extended to long-term clinical outcomes, in particular in patients with baseline TIMI flow 0–1 at high risk of distal embolization or no-reflow. Further large randomized trials are needed to fully elucidate the role of DS in acute patients.

4.1. Limitations

This is a single center observational study with its inherent limitations of selection bias. Treatment strategy including the decision to proceed with thrombus aspiration was per individual operator's discretion. Rheolytic thrombectomy (Possis Medical, Inc., Minneapolis, Minnesota) was the only thrombus aspiration system used. Only first generation DES were implanted, that permitted to analyze a homogeneous population of STEMI patients. Left anterior descending infarct related artery was more common in the conventional stenting strategy and might have had an impact on clinical outcomes. Variables as left ventricular ejection fraction, lesion characteristics, stent length and diameter were not analyzed, as these data were not available. Rescue PCI occurred in 10% of the population thus potential thrombus burden modification cannot be assessed.

5. Conclusions

Direct stenting might reduce long term all-cause mortality. The impact of direct stenting is particularly pronounced in patients with TIMI flow 0–1.

CRediT authorship contribution statement

Paola Scarparo: Data curation, Methodology, Formal analysis, Writing- Original draft preparation, **Riccardo Improta:** Data curation, Investigation, **Jeroen Wilschut:** Supervision, **Isabella Kardys:** Writing-Reviewing and Editing, **Wijnand K Den Dekker:** Supervision, **Joost Daemen:** Supervision, **Felix Zijlstra,** Supervision, **Nicolas M. Van Mieghem:** Supervision, **Roberto Diletti:** Supervision, Writing- Reviewing and Editing.

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Declaration of competing interest

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Appendix A. Supplementary data

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