

## ORIGINAL ARTICLE

# Clinical Outcome After Drug Eluting Stents Compared to Bare Metal Stents in Unselected Real-World Population with Acute Myocardial Infarction

Ahmed Elghanam<sup>1</sup>; Sherif Elzahwy<sup>2</sup>; Hanan Hafez<sup>2</sup>; Nabil Farag<sup>2</sup> and Mohamed Taher<sup>2</sup>

<sup>1</sup>Department of Cardiology, National Heart Institute, Egypt and <sup>2</sup>Department of Cardiology, Ain Shams University, Egypt

- Background** The results of the PASSION (1) and the TYPHOON (2) trials cannot be generalized to all patients with acute MI, since high-risk patients were excluded. This called us for a study to evaluate the safety and efficacy of DES when used in clinical practice in an unselected "real-world" population with acute MI.
- Methods** This prospective registry was conducted on 227 consecutive patients referred for PCI using either drug eluting stent (DES) (n= 94) or bare metal stent (BMS) (n= 133) after acute myocardial infarction (MI). Patients referred for PCI within the first 72 hours after acute MI with elevated CK-MB, or after that during their hospital stay in the presence of angiographically visible thrombus were considered for this study. All patients were enrolled regardless of the clinical or anatomical presentation. Myocardial perfusion imaging was done for all patients with symptoms of myocardial ischemia at follow up; 21.3% of the DES group and to 24.1% of the BMS groups (P >0.05). Angiographic follow-up was clinically driven, 12.8% of the DES and to 22.6% of the BMS (P <0.05).
- Results** Baseline clinical characteristics were comparable, except that LV EF <35% was more prevalent among BMS (20.3% vs. 12.7%; P <0.05). Mean time from symptom onset till PCI was significantly less among BMS (39 vs. 57 hrs; P <0.001). PCI within 12 hours was done more frequently among BMS (57.8% vs. 29.7%; P <0.001). Also the incidence of cardiogenic shock was significantly higher among BMS (15% vs. 5.3%; P <0.05). On the other hand, angiographic lesion profiles were less favourable in DES group (Type C: 75% DES vs. 57% BMS, P <0.01). In fact, DES were used more often to manage long lesions (57% vs. 32%; P <0.001), and small vessels (11% vs. 2%; P <0.01). The mean RVD was lower (2.84 vs. 3.1mm; P <0.05) and the mean lesion length was higher among DES group (22.9 vs. 19.1 mm; P <0.05). After a median follow-up of 12.6 months for the DES, and 11.9 months for the BMS group (P >0.05), the incidence of cardiac death (6.8% vs. 2.1%; P <0.05), TLR (9.8% vs. 3.2%; P <0.05), TVR (9.8% vs. 4.3%; P <0.05) and TVF (21.8% vs. 9.6%; P <0.01) were significantly higher among BMS. The primary end point of the study-cumulative MACE was also higher among BMS (23.3% vs. 10.6%; P <0.01). There was no significant difference between the two groups regarding stent thrombosis (ST) (4.2% in DES, vs. 4.5% in BMS; P >0.05) or non fatal MI (4.2% in DES, vs. 7.5% in BMS; P >0.05). A pattern of focal restenosis was found in 75% of restenotic patients treated with DES, conversely, a diffuse pattern of restenosis was found more often in restenotic patients treated with BMS (69%; P <0.05). After adjustment, use of BMS was not independently associated with a higher risk of death. Multivariable analysis showed that DM, RVD <2.5 mm, lesion length >30 mm, type C lesion, and use of BMS were significantly associated with TLR (P <0.05).
- Conclusions** In an unselected real-world population, no evidence exists of a decreasing efficacy of DES in patients with acute MI. Also by reducing the rates and improving the pattern of restenosis, DES may reduce subsequent occurrence of death.
- Keywords** Drug eluting vs bare metal stent.  
(Heart Mirror J 2010; 4(1): 80-85)

### Abbreviations and Acronyms

DES	: Drug eluting stent
BMS	: Bare metal stent
MACE	: Major adverse cardiac events
PCI	: Percutaneous coronary intervention
RVD	: Reference vessel diameter
TLR	: Target lesion revascularization
TVR	: Target vessel revascularization
TVF	: Target Vessel Failure
LV EF	: Left ventricular ejection fraction

## INTRODUCTION

The reduction of intimal hyperplasia by DES depends on appropriate drug dose distribution in the arterial wall. Even non-obstructing micro-thrombi can significantly alter the drug distribution in the arterial wall. Clot between artery and stent can reduce drug uptake 10-fold, whereas clot overlying the stent can shield drug from systemic washout, increasing arterial drug uptake 30-fold (3).

Sirolimus could decrease endothelial function (4), enhance platelet aggregation (5), and delay vascular healing (6) furthermore, rapamycin and paclitaxel potentiate expression of tissue factor (7). Altogether, these features can potentially increase the risk of thrombotic complications after DES implantation in very susceptible patients such as those treated during the acute phase of MI.

Most randomized trials evaluating DES have excluded patients with acute myocardial infarction, a setting in which the use of DES remains controversial and in which rapid treatment may limit a physician's ability to assess the patient's capacity to adhere to thienopyridine therapy.

Although the PREMIER study raised concerns about using DES in acute MI, it is not yet clear if adverse events in that study were related to DES used or other factors such as medical compliance (8).

In the STRATEGY trial involving 175 patients with acute MI, the rate of MACE was significantly reduced by the use of DES. However, a different GP IIb/IIIa inhibitor was used in the two study groups, which confounded the interpretation of the comparison between the two types of stents (9).

Although the results of the TYPHOON (2) and PASSION (1) studies represent considerable advances in our understanding of the role of DES in acute MI, with a significant reduction in TLR in the SES trial, and a trend in the PES trial that had a low BMS TLR, results of both trials cannot be generalized to all patients with AMI, since high-risk patients were excluded. This called us for a study to evaluate the safety and efficacy of DES when used in clinical practice in an unselected 'Real-world' population with acute MI.

## METHODS

### Patient Population

This prospective single centre study was conducted on 227 consecutive patients referred for PCI between September 2005 and May 2007 using either DES (n= 94) or BMS (n= 133) after acute MI.

Patients referred for PCI within the first 72 hours after either acute ST segment elevation or non ST segment elevation MI with elevated CK-MB, or after that during their hospital stay in the presence of angiographically visible thrombus were considered for this study. All patients were enrolled regardless of the clinical or anatomical presentation, including patients admitted with cardiogenic shock and patients with unprotected left main lesions.

### Follow Up

Clinical follow-up was scheduled for all living patients at 30 days and again at 12 to 18 month after the index procedure. Myocardial perfusion imaging was done for patients with symptoms of myocardial ischemia. Angiographic follow-up beyond the initial procedure was clinically driven, and was not routinely performed in all patients.

### The Primary End Point

The occurrence of major adverse cardiac events (MACE) defined as cardiac death, non-fatal MI, clinically driven target lesion revascularization or target vessel revascularization.

### Definitions

ST was classified according to Academic Research Consortium (ARC) classification (10).

### Statistical Analysis

Continuous variables were presented as mean±SD and were compared by means of the Student unpaired t test. Categorical variables were presented as counts and percentages and compared by means of the chi-square test. The hazard ratio was determined using Cox proportional hazards models. Multivariate analyses were done using logistic regression analysis to identify independent predictors of adverse events, using all clinical, angiographic, and procedural variables.

## RESULTS

### Baseline Clinical Characteristics

Baseline clinical characteristics were comparable, except that arterial hypertension was more common among DES group (56.4% vs. 39.8%;  $P < 0.01$ ), while LV EF  $< 35\%$  was more prevalent among BMS group (20.3% vs. 12.7%;  $P < 0.05$ ) (Table 1).

**Table 1:** Baseline Clinical Characteristics:

Characteristic	DES	BMS	P value
Number of patients, n (%)	94 (41.4%)	133 (58.6%)	
Age, years	55.8±10.5	52.8±9.2	>0.05
Male gender, n (%)	78 (83%)	117 (88%)	>0.05
<b>Cardiovascular risk factors:</b>			
Diabetes mellitus, n (%)	40 (42.6%)	47 (35.3%)	>0.05
Current cigarette smoking, n (%)	54 (57.4%)	74 (55.6%)	>0.05
Arterial hypertension, n (%)	53 (56.4%)	53 (39.8%)	<0.01
Dyslipidemia, n (%)	46 (48.9%)	53 (39.8%)	>0.05
Family history of CAD, n (%)	27 (28.7%)	27 (20.3%)	>0.05
<b>Medical history:</b>			
Previous stroke, n (%)	3 (3.2%)	1 (0.8%)	>0.05
Peripheral arterial disease, n (%)	5 (5.3%)	4 (3%)	>0.05
Previous MI, n (%)	5 (5.3%)	11 (8.3%)	>0.05
Previous CABG, n (%)	4 (4.3%)	8 (6%)	>0.05
Previous PCI, n (%)	5 (5.3%)	12 (9%)	>0.05
Renal impairment, n (%)	12 (12.9%)	14 (10.5%)	>0.05
LVEF, %	53.4±8.1	52.2±10.7	>0.05
LVEF <35 %, n (%)	12 (12.7%)	27 (20.3%)	<0.05

**Clinical Presentation**

There were substantial differences in clinical presentation between patients receiving BMS compared with those treated with DES, the mean time from symptom onset till PCI was significantly higher among the DES group (57.12±37.7 vs. 39.63±42.7 hrs; P <0.001). PCI within 12 hours was done more frequently among the BMS group (54.9% vs. 25.5%; P <0.001). Also the incidence of cardiogenic shock was significantly higher among the BMS group (15% vs. 5.3%; P <0.05) (Table 2).

**Table 2:** Clinical Presentation:

Presentation	DES	BMS	P value
Mean time from symptom onset to PCI, h	57.12±37.7	39.63±42.7	<0.001
PCI within 12 hrs, n (%)	24 (25.5%)	73 (54.9%)	<0.001
STEMI, n (%)	67 (72.8%)	119 (89.5%)	<0.001
Anterior MI, n (%)	45 (47.9%)	67 (50.4%)	>0.05
Non STEMI, n (%)	25 (27.2%)	14 (10.5%)	<0.001
Primary PCI, n (%)	23 (24.5%)	73 (54.9%)	<0.001
Rescue PCI, n (%)	5 (5.3%)	4 (3%)	>0.05
Post MI angina, n (%)	66 (70.2%)	55 (41.4%)	<0.01
Received thrombolytics, n (%)	45 (47.9%)	40 (30.1%)	>0.05
Cardiogenic shock, n (%)	5 (5.3%)	20 (15%)	<0.05
Heart failure, n (%)	7 (7.4%)	5 (5.3%)	>0.05
AF, n (%)	3 (3.2%)	7 (5.3%)	>0.05
Peak CK-MB (IU)	183.84±76.8	178±108.7	>0.05
Mechanical ventilation, n (%)	2 (2.1%)	6 (4.5%)	>0.05

**Baseline Angiographic Characteristics**

On the other hand, angiographic lesion profiles were less favourable in the DES group (AHA/ACC lesion type C: 75.5% DES vs. 57.1% BMS, P <0.01). In fact, DES were used more often to manage long lesions (57.4% vs. 32.3 %; P <0.001), and small vessels (11.7% vs. 2.3%; P <0.01). The mean RVD was significantly lower (2.84±0.27 vs. 3.1±0.35 mm; P <0.05), and the mean lesion length was significantly higher (22.9±11.5 vs. 19.1±8.23 mm; P <0.05) among the DES group (Table 3).

**Table 3:** Baseline Angiographic Characteristics:

Characteristic	DES	BMS	P value
<b>CAD:</b>			
1 vessel, n (%)	10 (10.6%)	14 (10.5%)	>0.05
2 vessels, n (%)	33 (35.1%)	60 (45.1%)	>0.05
3 vessels, n (%)	51 (54.5%)	59 (44.4%)	>0.05
<b>Infarct related artery:</b>			
LAD, n (%)	66 (70%)	73 (54.9%)	>0.05
Proximal LAD, n (%)	23 (24.5%)	32 (24.1%)	>0.05
SVG, n (%)	1 (1.1%)	2 (1.5%)	>0.05
LIMA, n (%)	1 (1.1%)	1 (0.8%)	>0.05
Complex (C) lesion, n (%)	71 (75.5%)	76 (57.1%)	<0.01
Calcified lesion, n (%)	18 (19.1%)	19 (14.3%)	>0.05
Visible thrombus, n (%)	32 (34%)	54 (40.6%)	>0.05
Bifurcation lesion, n (%)	16 (17%)	16 (12%)	>0.05
Both branches stented, n (%)	2 (2.2%)	0	--
PTCA side branch after stenting, n (%)	4 (4.3%)	3 (2.3%)	>0.05
Ostial lesion, n (%)	1 (1.1%)	4 (3%)	>0.05
RVD, mm	2.84±0.27	3.1±0.35	<0.05
Small vessel, n (%)	11(11.7%)	3 (2.3%)	<0.01
Lesion length, mm	22.9±11.5	19.1±8.23	>0.05
Long lesion, n (%)	54 (57.4%)	43 (32.3%)	<0.001
Initial diameter stenosis, %	92.7±8.3	93.8±7.6	>0.05
Total occlusion, n (%)	12 (12.8%)	10 (7.5%)	>0.05
TIMI flow baseline grade	1.95±1.2	1.8±1.35	>0.05
0-1, n (%)	27 (28.7%)	49 (36.8%)	<0.05
2, n (%)	22 (23.4%)	18 (13.5%)	<0.05
3, n (%)	45 (47.9%)	66 (49.6%)	>0.05

**Procedural Results**

The peri- and post-procedural antiplatelet therapeutic scheme differed between patients treated with either BMS or DES in our series. Patients in the DES group received fewer glycoprotein IIb/IIIa inhibitors (54% vs. 81%; P <0.001), but had a longer clopidogrel prescription time as defined by the study protocol (14 month vs. 5 month; P <0.001).

Among patients who received a DES, the average implanted stent length was greater (29.26±12. vs. 22.44±8.7mm; P <0.05), and more vessels per patient were

stented (1.4 vs. 1.1; P <0.05). There was no significant difference between the DES and BMS groups regarding the other procedural parameters (Table 4).

Among patients who received a DES, the average implanted stent length was greater (29.26±12. vs. 22.44±8.7mm; P <0.05), and more vessels per patient were stented (1.4 vs. 1.1; P <0.05). There was no significant difference between the DES and BMS groups regarding the other procedural parameters (Table 4).

**Table 4:** Procedural Results:

Results	DES	BMS	P value
GP IIb/IIIa inhibitor use, n (%)	51 (54.3%)	108 (81.2%)	<0.001
IAB pump during PCI, n (%)	1 (1.1%)	5 (3.8%)	>0.05
Maximum inflation pressure, atm	14.65±1.56	13.9±2.04	>0.05
Mean number of vessels treated, n (%)	1.4±0.8	1.1±0.46	<0.05
Number of lesion treated, n (%)	1.3±0.64	1.1±0.36	>0.05
Number of stents at target lesion, n (%)	1.15±0.42	1.1±0.3	>0.05
Overlapping stents, n (%)	14 (14.9%)	11 (8.3%)	>0.05
Total stent length at target lesion, mm	29.26±12.73	22.44±8.7	<0.05
Stent length to lesion length ratio	1.3±0.4	1.2±0.3	>0.05
Mean nominal stent diameter, mm	3.12±0.29	3.3±0.35	>0.05
Attempted direct stenting, n (%)	49 (52.1%)	74 (55.6%)	>0.05
Successful direct stenting, n(%)	47 (50%)	74 (55.6%)	>0.05
Final TIMI flow grade	2.8±0.15	2.7±0.14	>0.05
0-1, n (%)	0	0	--
2, n (%)	2 (2.1%)	7 (6%)	>0.05
3, n (%)	92 (97.9%)	125 (94%)	>0.05
Angiographic success, n (%)	92 (97.9%)	125 (94%)	>0.05
Clopidogrel prescription, month	14.6±4.5	5.3±4.2	<0.001
No reflow, n (%)	3 (3.2%)	7 (5.3%)	>0.05
Side-branch occlusion, n (%)	4 (4.3%)	4 (3%)	>0.05
Intraprocedural ST, n (%)	0	0	--
Residual thrombus opposite stent, n (%)	1 (1.1%)	4 (3%)	>0.05
Residual edge dissection, n (%)	1 (1.1%)	2 (1.5%)	>0.05

**Events during the First 30 Days**

In-hospital and 30 days outcomes were similar between the 2 groups (P >0.05) (Table 5).

**Longer Term Outcome**

Complete follow-up information was available for all patients. Although in-hospital and 30 days events were similar in both groups, after a median follow-up of 12.6 months for the DES, and 11.9 months for the BMS group (P >0.05), the primary end point of the study-cumulative

MACE was significantly higher among the BMS group (23.3% vs. 10.6%; P <0.05) (Table 6).

**Table 5:** In Hospital and 30 days Clinical Outcomes

	DES	BMS	P value
All death, n (%)	1 (1.1%)	4 (3%)	>0.05
Cardiac death, n (%)	1 (1.1%)	4 (3%)	>0.05
Non fatal MI, n (%)	3 (3.2%)	4 (3%)	>0.05
STEMI, n (%)	2 (2.2%)	4 (3%)	>0.05
NSTEMI, n (%)	1 (1.1%)	0	--
Target lesion related MI, n (%)	3 (3.2%)	4 (3%)	>0.05
Clinically driven TLR, n (%)	0	0	--
TVF, n (%)	4 (4.3%)	8 (6%)	>0.05
MACE, n (%)	4 (4.3%)	8 (6%)	>0.05
UA, n (%)	3 (3.2%)	0	--
Early stent thrombosis, n (%)	3 (3.2%)	3 (2.3%)	>0.05
Definite early ST, n (%)	1 (1.1%)	0	--
Probable early ST, n (%)	2 (2.2%)	3 (2.3%)	>0.05
Early ST not on ASA, n (%)	1 (1.1%)	0	--
<b>Other events:</b>			
ICD implantation, n (%)	0	2 (1.5%)	--
Femoral pseudoaneurysm, n (%)	0	1 (0.8%)	--
LV pseudoaneurysm, n (%)	1 (1.1%)	1 (0.8%)	>0.05
Retroperitoneal haematoma, n (%)	0	1 (0.8%)	--
Haemodialysis, n (%)	0	4 (3%)	--

**Table 6:** Cumulative Clinical Outcomes:

	DES	BMS	P value
Mean clinical follow up duration ,m	12.6±7.0	11.9±7.3	>0.05
All death, n (%)	2 (2.1%)	9 (6.8%)	<0.05
Cardiac death, n (%)	2 (2.1%)	9 (6.8%)	<0.05
Time of death, d	240.3±339.1	124.3±217	<0.001
Non fatal MI, n (%)	4 (4.3%)	10 (7.5%)	>0.05
STEMI, n (%)	2 (2.1%)	8 (6%)	>0.05
NSTEMI, n (%)	2 (2.1%)	2 (1.5%)	>0.05
Target Lesion related MI, n (%)	3 (3.2%)	7 (5.3%)	>0.05
Time of MI, day	106±209.6	249.6±305.8	<0.05
Clinically driven TLR, n (%)	3 (3.2%)	13 (9.8%)	<0.05
PCI, n (%)	3 (3.2%)	12 (9%)	<0.05
PTCA, n (%)	1 (1.1%)	5 (3.8%)	>0.05
CABG, n (%)	0	1 (0.8%)	--
Clinically driven TVR, n (%)	4 (4.3%)	13 (9.8%)	<0.05
Non TVR, n (%)	6 (6.4%)	22 (16.5%)	<0.05
TVF, n (%)	9 (9.6%)	29 (21.8%)	<0.01
Cumulative MACE, n (%)	10 (10.6%)	31 (23.3%)	<0.01
UA, n (%)	7 (7.4%)	5 (3.8%)	>0.05
Stent thrombosis, n (%)	4 (4.2%)	6 (4.5%)	>0.05
Premature clopidogrel discontinuation	1 (1.1%)	3 (2.3%)	>0.05

**Efficacy of DES**

Clinically driven TLR (9.8% vs. 3.1%; P <0.05), TVR (9.8% vs. 4.3%; P <0.05) and TVF (21.8% vs. 9.6%; P <0.01) were significantly higher among BMS group (Table 6).

**Stent Thrombosis**

At the time of ST, 4 of the 10 patients (40%) were not on dual antiplatelet therapy because of drug intolerance, or completing the prescribed duration of dual antiplatelet therapy (Table 7).

**Table 7: Stent Thrombosis:**

Stent thrombosis	DES n 4 (4.2%)	BMS n 6 (4.5%)	P value
On dual antiplatelet therapy, n (%)	2 (1.1%)	4 (3 %)	>0.05
Not on dual antiplatelet therapy, n (%)	2 (2.1%)	2 (1.5%)	>0.05
Acute ST, n (%)	2 (2.1%)	2 (1.5%)	>0.05
Subacute ST, n (%)	1 (1.1%)	1 (0.8%)	>0.05
Late ST, n (%)	1 (1.1%)	3 (2.3%)	>0.05
Definite ST, n (%)	1 (1.1%)	1 (0.8%)	>0.05
Probable ST, n (%)	2 (2.1%)	3 (2.3%)	>0.05
Possible ST, n (%)	1 (1.1%)	2 (1.5%)	>0.05
ST related death, n (%)	2 (2.1%)	3 (2.3%)	>0.05
ST related nonfatal MI, n (%)	2 (2.1%)	2 (1.5%)	>0.05

**Follow up Myocardial Perfusion Imaging**

MPI was done to 20 patients (21.3%) of the DES group and to 32 (24.1%) patients of the BMS groups (P >0.05).

**Follow up Angiographic Outcome**

Follow up angiography was done to 12 patients (12.8%) of the DES and to 30 patients (22.6%) of the BMS (P <0.05). Patients without follow-up angiography were free of symptoms, and no adverse events were observed among those patients.

The antiproliferative properties of DES are demonstrated by a significant lower late loss (1.1 vs. 0.6 mm; P <0.05). This was accompanied by a significant reduction in ISR (4.3% vs. 12.1%; P <0.05).

Different patterns of lumen re-narrowing were found in patients who developed restenosis after treatment with DES (n= 4) compared with those treated with BMS (n= 16). A pattern of focal restenosis was found in 75% of restenotic patients treated with DES, conversely a diffuse pattern of restenosis was found more often in restenotic patients treated with BMS (69 %; P <0.05). The ISR length was also significantly shorter in patients treated with DES (9 mm vs. 15 mm; P <0.05) (Table 8).

**Table 8: Follow up Angiographic Outcome:**

	DES	BMS	P value
Cases with angiographic follow up, n (%)	12 (12.8%)	30 (22.6%)	<0.05
Mean angiographic follow up duration, m	12.3±5.4	12.6±7.4	>0.05
<b>Indications for angiography:</b>			
Positive TC 99m perfusion SPECT	4 (3.3%)	16 (12%)	<0.05
MI, n (%)	1 (1.1%)	5 (3.8%)	>0.05
UA, n (%)	4 (4.3%)	3 (2.3%)	>0.05
Effort angina, n (%)	1 (1.1%)	3 (2.3%)	>0.05
Preoperative CA, n (%)	1 (1.1%)	0	--
Planned PCI to non culprit vessel, n (%)	0	1 (0.8%)	--
Percent diameter stenosis	23.75±36.6	40±36.9	<0.05
ISR length, mm	9.2±2.6	14.9±7.1	<0.05
Binary ISR, n (%)	4 (4.3%)	16 (12.1%)	<0.05
<b>Mehran class:</b>			
Focal restenosis, n (%)	3 (75%)	5 (31%)	<0.05
Focal instent, n (%)	1 (25%)	4 (25%)	>0.05
Focal edge ISR, n (%)	2 (50%)	1 (6%)	<0.05
Diffuse restenosis, n (%)	1 (25%)	11 (69%)	<0.05
Diffuse intrastent, n (%)	1 (25%)	8 (50%)	<0.05
Diffuse proliferative, n (%)	0	2 (12.5%)	--
Diffuse occlusive, n (%)	0	3 (18.75%)	--
Instent Late loss, mm	0.68±0.82	1.16±0.9	<0.05
Aneurysm formation, n (%)	0	0	--

**Characteristics of Patients with ST**

ST developed in 10 patients (4.4% of the overall sample). ST was significantly associated with the total stent length, lower LV EF%, presence of visualized thrombus within the lesion, calcified lesion, type C lesion, and residual edge dissection (P <0.05) (Table 9).

**Pattern of Restenosis**

Stent type was the only factor significantly associated with the pattern of restenosis, with a positive association between BMS and diffuse restenosis (P <0.05) (Table 10).

**Predictors of Death**

To determine whether the difference between groups in terms of death is affected by the difference in baseline characteristics we performed multivariable analysis. After adjustment, the use of BMS was not independently associated with a higher risk of death. Multivariable analysis showed that cardiogenic shock, intra-aortic balloon pump use, left ventricular EF <35% and DM were independent significant predictors of death (Table 11).

**Table 9:** Characteristics of Patients with ST:

	ST (n=10)	Control (n= 218)	P value
Duration of MI, h	60.8±44.9	49.8±38.5	>0.05
DM, n (%)	4 (44.4%)	84 (38.5%)	>0.05
Renal impairment, n (%)	1 (11.1%)	25 (11.5%)	>0.05
GP IIb/IIIa use, n (%)	6 (66.7%)	153 (70.2%)	>0.05
Stent length, mm	32.1±12.8	24.3±10.5	<0.05
Overlapping stents, n (%)	1 (11.1%)	24 (11.0%)	>0.05
Maximal balloon pressure (atm)	13.75±2.3	14.1±3.3	>0.05
RVD, mm	3.2±0.3	2.95 ± 0.2	>0.05
Cardiogenic shock, n (%)	1 (11.1%)	24 (11%)	>0.05
LVEF, %	47.8±7.6	55.4±5.9	<0.05
Bifurcating stenting, n (%)	3 (33.3%)	24 (11%)	>0.05
LMCA, n (%)	1 (11.1%)	0	--
Thrombus in lesion, n (%)	5 (55.6%)	81 (37.2%)	<0.05
Calcified lesion, n (%)	6 (66.7%)	31 (14.2%)	<0.05
Type C lesion, n (%)	8 (88.9%)	139 (63.8%)	<0.05
TIMI flow at baseline	2.2±1.0	1.9±1.1	>0.05
Residual edge dissection, n (%)	1 (11.1%)	2 (1%)	<0.05
Residual thrombus near to stent, n (%)	1 (11.1%)	0	--
Prescribed duration of anti-platelet therapy, m	9.9±8.1	10.5±7.8	>0.05
Premature discontinuation of Clopidogrel, n (%)	0	4 (1.8%)	--
Number of lesions treated, n (%)	1	1.5±0.7	>0.05

**Table 10:** Factors Associated with Focal and Diffuse Patterns of Restenosis:

Variables	Focal ISR (n= 8)	Defuse ISR (n= 12)	P value
BMS, n (%)	3 (37.5%)	1 (83.3%)	<0.05
DES, n (%)	5 (50%)	11 (91.7%)	<0.05
DM, n (%)	3 (37.5%)	4 (33.3%)	>0.05
Type C lesion, n (%)	4 (50%)	5 (41.7%)	>0.05
Lesion length, mm	26.7±7.6	27.3±9.2	>0.05
Stent length, mm	31.8±10.4	32.4±9.7	>0.05
RVD, mm	2.9±0.18	3.1±0.2	>0.05
Stent diameter, mm	3.1±0.2	3.2±0.18	>0.05
Maximal inflation pressure (atm)	13.9±2.5	14.3±1.9	>0.05

**Table 11:** Predictors of Death during follow up:

	HR	95% CI	P value
Duration of MI	1.2	0.7 – 1.9	>0.05
Cardiogenic shock	6.9	4.3 – 11.7	<0.001
Intra-aortic balloon pump use	5.9	3.8 – 10.5	<0.001
LVEF <35%	2.3	1.7 – 5.1	<0.05
Diabetes mellitus	2.6	1.9 – 6.3	<0.05
Culprit vessel LMCA	1.4	0.8 – 1.9	>0.05
Culprit vessel LAD	1.3	0.8 – 2.0	>0.05
Stent type	1.1	0.6 – 1.7	>0.05
Post procedure TIMI flow	0.9	0.4 – 1.8	>0.05
Prescribed duration of Clopi-dogrel	1.1	0.7 – 1.8	>0.05

**Predictors of TLR**

Multivariable analysis identified several factors associated with a higher risk of TLR. Among clinical factors, DM significantly correlated with the likelihood of reintervention. With respect to baseline angiographic lesion characteristics, RVD <2.5mm, lesion length >30mm, ostial lesion, type C lesion, and calcified lesion were significantly associated with TLR. With respect to procedural characteristics, only use of BMS was significant independent predictor of TLR (P <005) (Table 12).

**Predictors of MACE**

Among clinical factors that independently predicted MACE were age (10 years increment), DM, and LVEF <35% (P <005). Among baseline angiographic parameters, RVD <2.5 and type C lesion were significant independent predictors of MACE (P <005). Among procedural characteristics only the use of BMS was a significant independent predictor of MACE (P <005) (Table 13).

**The interaction of restenosis risk factors with DES effect on ISR**

The interaction of known restenosis risk factors (DM, RVD, and lesion length) with the DES treatment effect on ISR was evaluated. The use of DES among diabetic patients was associated with 29% relative risk reduction, also the use of DES among patients with lesion length >25mm was associated with 26% relative risk reduction. The use of DES among patients with RVD 2.5 – 3 mm was associated with 16% relative risk reduction, while the use of DES among patients with RVD <2.5 mm was associated with only 13% relative risk reduction (Table 14).

**Table 12:** Predictors of TLR during follow up:

	HR	95% CI	P value
DM	2.2	1.1 – 4.8	>0.05
RVD <2.5 mm	2.0	1.3 – 3.1	>0.05
Lesion length >30 mm	1.8	1.2 – 3.9	>0.05
Proximal LAD treatment	1.4	1.0 – 2.8	>0.05
Ostial lesion	1.3	0.9 – 1.7	>0.05
Type C lesion	1.9	1.4 – 3.6	>0.05
Calcified lesion	1.9	1.3 – 3.4	>0.05
Use of BMS	2.7	1.6 – 3.5	>0.05
Total stent length	1.5	1.0 – 2.3	>0.05
Predilatation	1.3	0.8 – 1.9	>0.05
Maximal balloon pressure	1.4	0.9 – 2.2	>0.05

**Table 13:** Predictors of MACE during follow up:

	HR	95% CI	P value
Age (10 year increment)	2.1	1.4 – 3.9	< 0.05
DM	2.4	1.3 – 4.4	< 0.05
LV EF < 35%	3.2	1.7 – 5.2	< 0.05
BMS utilization	2.6	1.7 – 4.9	< 0.05
Culprit LAD	1.4	0.9 – 1.7	> 0.05
RVD <2.5	2.8	1.5 – 4.2	< 0.05
Lesion length (1 mm decrease)	0.76	0.4 – 0.98	< 0.05
Type C lesion	2.9	1.6 – 4.7	< 0.05
More than one lesions treated	1.3	0.8 – 1.8	> 0.05

**Table 14:** Subgroup Analysis for the Rate of ISR among Patients who received either DES or BMS:

Group	DES, n (%)	BMS, n (%)	Relative Risk (95% CI)	P value
All	4/94 (4.3%)	16/133 (12%)	0.76 (0.55 – 0.94)	<0.01
<b>Diabetes</b>				
Diabetics	3/40 (7.5%)	12/47 (26%)	0.81 (0.66 – 1.1)	<0.01
Non Diabetics	1/54 (1.9)	4/86 (4.7%)	Reference group	--
<b>Reference vessel diameter, mm</b>				
RVD >3 mm	0/29	2/35 (5.7%)	Reference group	--
RVD 2.5-3 mm	1/42 (2.4%)	5/46 (10.9%)	0.84 (0.71- 1.2)	<0.05
RVD <2.5 mm	3/23 (13%)	9/52 (17.3%)	0.87 (0.76 – 1.4)	<0.05
<b>Lesion length, mm</b>				
<10 mm	0/25	1/31 (3.2%)	Reference group	--
10 to 25 mm	1/39 (2.6%)	3/48 (6.25%)	0.92 (0.84 – 1.7)	>0.05
>25 mm	3/30 (10%)	12/54 (26.7%)	0.79 (0.61 – 0.9)	<0.01

**DISCUSSION**

**Baseline clinical, angiographic and procedural characteristics:**

In the pivotal ENDEAVOR II trial, major exclusion criteria included MI within the preceding 72 hours (11). While the National Health Service NICE Recommendations for DES use excluded patients with angiographic evidence of thrombus in the target artery. Also the ESC recommends the use of DES strictly based on inclusion and exclusion criteria of the SIRIUS, TAXUS-IV, and TAXUS-VI studies, Main common exclusion criteria according to the ESC included elevated CK-MB, or visible thrombus (12). These exclusion criteria were the inclusion criteria in our study.

In the TYPHOON (2) and PASSION (1) trial patients were excluded if they have certain high-risk clinical or anatomical characteristics, however our patient population presented many of these characteristics: previous MI in 6.8%, LVEF <35% in 16.5%, rescue PCI in 4%, the infarction was caused by ST in 1%, cardiogenic shock

before PCI in 10%, 3.3% undergone MV, LM disease in 1%, ostial lesion in 2%, lesion length more than 30 mm in 13.6%, and bifurcation lesion in 14.5%. Given the unrestricted inclusion criteria in our study, this cohort of patients accurately reflects the daily practice in the “real world” of interventional cardiology, and therefore the results are extended to virtually all patients with AMI.

Unlike our study, both SIRIUS (13) and TAXUS IV (14) only recruited selected patients treated with single-lesion elective stenting with no ostial or bifurcation lesions. Despite the complexity and unselected nature of the treated population, our results are absolutely consistent with the data reported in both trials (TLR 3.2% in our DES group vs. 4.1% in SIRIUS and 4.4% in TAXUS IV).

Patients who received a DES for acute MI were less likely to undergo primary PCI (24.5% vs. 55%; P<0.001). This may reflect the paucity of data available at the time of the report, supporting DES use in this setting, as well as the concern of the occurrences of ST with DES (15,

6). Similarly in the DEScover Registry which aimed to characterize patients selected for DES in routine clinical practice in the USA, physicians favored BMS for patients with acute MI because of concerns of ST or potential lack of effectiveness (16).

In our study, patients who received DES had lower acute risk, but they had more DM (42.6% vs. 35.3%;  $P > 0.05$ ), longer lesion length (23 vs. 19 mm;  $P < 0.05$ ), smaller vessel diameter (3.12 vs. 3.3 mm;  $P < 0.05$ ) and type C lesions (75.5% vs. 57%;  $P < 0.01$ ) with the potential for increased late risk.

Despite the already favorable angiographic result with the control BMS, there was an additional reduction in TVR from 9.8% to 3.2% in the DES group compared with control ( $P < 0.05$ ). Equally important is the observation that this reduced need for repeat revascularization was not mitigated by an increased risk of short- or long-term fatal or nonfatal cardiovascular events

Before the advent of DES, operators used the shortest possible stents to treat the lesion (So called "Spot" stenting) because of awareness that the likelihood of restenosis was related to the implanted stent length. This study confirms the applicability of "Stenting long" with a lesion-to-stent ratio of 1:1.3, thus stenting back to angiographically "Normal" vessel on either side of the lesion without the penalty of ISR. Furthermore stent length was not a predictor of TLR in our multivariable analysis ( $P > 0.05$ ).

In the RESEARCH registry, similar to our study patients who received DES were more likely to have type C lesions (75% vs. 57%;  $P < 0.01$ ) (17). The greater average length of DES compared with BMS implanted (29 vs. 22 mm;  $P < 0.05$ ) is in accordance with the RESEARCH and T-SEARCH (17, 18). This change in practice probably reflects a goal of more complete lesion coverage, as stent discontinuity and edge injury have been shown to be associated with post-DES restenosis (19). It may also reflect the early portion of a clinical practice shift to PCI in more complex lesion subsets. The smaller diameter of stents used in the DES group (3.1 vs. 3.3 mm;  $P < 0.05$ ) is also in accordance with findings from the RESEARCH and T-SEARCH registries (17, 18) and probably reflects the reports of relatively low restenosis rates in small vessels treated with DES (17).

### Angiographic Outcome

The most important angiographic finding of this report is that a pattern of focal restenosis was found in 75% of restenotic patients treated with the DES, but was found in only 31% of restenotic patients treated with the BMS ( $P < 0.05$ ). Current perceptions based on a limited number of restenotic lesions in SES and PES have led to the concept that when restenosis occurs it is likely to be focal that carries a more benign prognosis and could easily be treated with repeated PCI (14, 19-21). The relatively "Benign"

features of the restenotic process occurring with DES may have somehow contributed to the lower death (2.1% vs. 6.8%;  $P < 0.05$ ) and MI (4.3% vs. 6.8%;  $P < 0.05$ ) rates seen at follow-up as compared with BMS.

Post-DES restenosis were located at the edge in 50% of the cases ( $P < 0.05$ ). Local injury outside the stent was observed in both cases of edge restenosis, as evidenced by predilation using a balloon longer than the stent. As such, it is possible that avoidance of injury at the edges of the stent by using shorter balloons, and by perhaps less predilation, may reduce restenosis rate.

Another interesting observation from our study is that post-DES edge restenosis occurred in the proximal stent border in both cases. Lemos et al. had previously reported the same observation (19). One would expect that edge restenosis should occur more frequently distally, where the vessel is likely to be both smaller in diameter and also subjected to greater injury from the balloon. It is tempting to speculate that elution of drug into the bloodstream may be producing higher drug concentrations at the distal edge with consequently lower rates of restenosis.

### Efficacy of DES

As far as long-term efficacy is concerned, our data seem to confirm that DES, consistently with the RESEARCH registry (17) provides a substantial TVR reduction as compared with BMS even in more complex patients than those enrolled in randomized controlled trials.

In our series, patients treated with DES clearly had a reduced risk of TLR (3.2% vs. 9.8%;  $P < 0.05$ ). The higher prevalence of DM, type C lesions, long lesions and small vessel in the DES group makes the observed benefit even more convincing.

Our results are in accordance with the SESAMI trial. In this trial, 320 patients who underwent coronary angiography for an acute MI were randomized to be treated with a SES or a BMS. Angiography at 1 year revealed that the incidence of restenosis was significantly lower in SES recipients than in the BMS recipients (9.3% vs. 21.3%). Overall, significant decreases in risk favoring SES over BMS were also observed in TLR (4.3% vs. 11.2%), and TVF (8.7% vs. 18.7%) (22).

In the PASSION trial (1), two specific uncoated stents were used making the polymer and paclitaxel the only difference between the two groups, whereas in our study, any uncoated stent was allowed. This discrepancy may explain why the rates of TLR in the BMS group were higher in our study than in the PASSION trial (9.8% vs. 7.8%).

Protocol-mandated angiography in DES trials may have overestimated (Usually double) the rates of TLR (23). Thus, protocol-mandated angiography may have biased revascularization against the BMS group through the well-described "Oculostenotic" reflex, thereby contributing

to an overestimation of benefit with DES. In our study angiographic follow-up beyond the initial procedure was obtained only if clinically indicated and was not routinely performed in all patients. In this way, non-clinically driven revascularizations are restricted and the rates of repeat intervention are more likely to reflect real-life practice (24). Moreover, we relied on clinical rather than angiographic follow-up data for clinical decision-making (Non-invasive stress testing was done in 23% of our patients), in an attempt to avoid unnecessary interventions in asymptomatic patients.

Also, data deriving from previous randomized trials that scheduled an angiographic follow-up indicate that clinical outcomes are strictly related to the angiographic ones; consequently, it could be argued that the encouraging clinical outcome in this series of patients may correspond to an effective control of angiographic restenosis.

### Safety of DES

Our data about the DES safety indicate that DES significantly reduces mortality (2.1% vs. 6.8%;  $P < 0.05$ ) and MI (4.3% vs. 6.8%;  $P < 0.05$ ) as compared with BMS. Also the incidence of ST is similar between the 2 groups. These data do not appear to justify the current DES late safety alert.

Inconsistent findings have been reported thus far with regard to the effect of DES on incidence of MI. In the first randomized clinical trials comparing DES with BMS, no difference in the incidence of MI was observed (14, 25). Second-generation randomized trials assessing the benefit of DES in patients at intermediate risk for ISR or all-inclusive registries reported trends toward MI reduction in the DES group, but none of them reached statistical significance (17, 26). More recently, a clear reduction in the cumulative incidence of MI in the DES group was reported in the SES-SMART trial, in which a selected group of high-risk patients has been evaluated (27). Similarly, in our patient population, a reduced incidence of MI was observed in the DES group.

Moreno, et al. conducted a meta-analysis of 25 randomized trials in which patients were allocated to receive a DES or a BMS. Acute MI occurred at a significantly lower rate in DES recipients (3.3% vs 4.2%) (28). Similarly Stettler, et al. conducted a meta-analysis of 38 randomized controlled trials that either compared DES with BMS or SES [Cypher] with PES [Taxus]. SES were associated with the lowest incidence of MI (29).

DES may possess attributes that would otherwise reduce the rates of death and MI compared with BMS. In this regard, recent reports have demonstrated that ISR is not as benign a process as previously thought, with a significant number of patients presenting with MI, and even death (30, 31).

### DES Thrombosis

The most important risk factors for acute and subacute DES thrombosis are primary stenting in STEMI and ACS (7).

Previous concerns relating to the possible association between thrombosis and DES have not been realized, with only 4 ST in the DES group (4.2%) and 6 ST in the control group (4.5%) ( $P > 0.05$ ).

Importantly, 2 of patients (50%) in the DES who developed ST were not on dual antiplatelet therapy at that time. This crystallizes the idea that patients need to have a firm understanding of the importance of long-term and uninterrupted dual antiplatelet therapy before DES implantation. This may be difficult to do during the urgent nature of an acute MI, where early termination of clopidogrel and increased mortality has been observed (8).

In the PASSION (1) trial the definition of ST was conservative, since angiographic documentation was required, which might have led to underestimation of the incidence of stent thrombosis (1%). However in the present study an alternative and more liberal definition of ST was used in order to establish the true incidence of ST. On the other hand, our definition of ST which included sudden death might overestimate the occurrence of ST, since sudden death after MI may be caused by arrhythmias that are not related to abrupt stent occlusion, also coronary patients may experience new occlusions at sites distant from the implanted stent (32).

A very important finding stressing the relevance of procedural variables was that 75% of the thrombotic events occurred in the first 30 days after DES implantation. Since the BMS era, we have known that early ST is largely related to stent under-expansion (33). While we focus on understanding the late safety issues of DES, we should continue to optimize stent deployment regardless of the stent type in an effort to prevent early thrombotic events. Unfortunately, in the present study we do not have data regarding suboptimal stent implantation in patients who developed ST, however ST may be related to stent under-expansion due to severely calcified lesions.

Acute or subacute ST occurred in 3 patients (3.1%) in the DES group and 3 patients (2.3%) in the BMS group. This incidence is not high, given the thrombotic environment at the time of stent placement, the potential for suboptimal stent deployment in the setting of PCI for acute MI, and decreased blood flow in a vessel that supplies infarcted myocardium. Also undersizing may be more frequent in AMI patients than in those without AMI because of low flow, reduced output, and vasoconstriction. In a study from the Thoraxcenter, the incidence of ST at 1 month after primary PCI with the use of PES was 2.9% although the definition of stent thrombosis was conservative since

angiographic documentation was required (34). We also found no evidence of an increase in the rate of late DES thrombosis, a topic that has recently caused concern (35).

Rates of ST in our study (4.2% in the DES vs. 4.5% BMS groups;  $P > 0.05$ ) were close to the TYPHOON (2) study (3.4% in the SES and 3.6% BMS groups;  $P = 1.00$ ) in which, the definition of late thrombosis in contrast to our study required angiographic proof.

When analyzing the occurrence of ST in our study, it is fair to say that our patients with ST developed it with "off-label" DES use. For on-label use, pooled analyses of eight randomized Cypher and TAXUS trials by Mauri, et al. (36) demonstrated identical ST rates of 3.5% in both selected BMS and DES patients using the new ARC definitions (10) that take not only angiographically proven ST but also MI in the target region and sudden unexplained death into consideration.

There was 1 case of late DES thrombosis (>30 days after the procedure), which raised some concern that delayed endothelialization within a DES might lead to ST outside the usual time period for BMS. Late DES thrombosis occurred four month after discontinuation of clopidogrel, thus, the excess risk of LST may not be confined to the days after clopidogrel discontinuation. This suggests that mechanisms in addition to antiplatelet therapy are responsible for this phenomenon. One proposed mechanism could be hypersensitivity to the polymer coating of the stent. If so, bioabsorbable polymers or a DES without polymer may have an advantage (6).

Although no case of late ST has been observed in patients on dual antiplatelet therapy, this regimen cannot be recommended indefinitely and sometimes needs to be interrupted because of bleeding complications or need for surgery.

Finally, given the high rates of stent thrombosis in both groups (4.2 % in the DES group and 4.5% in the uncoated-stent group), a further emphasis on the potential benefit of more aggressive or prolonged antithrombotic strategies in this challenging setting appear warranted.

### Factors That Contribute to DES Thrombosis

Numerous studies have tried to determine the incidence and predictors for stent thrombosis. Such data might be used to determine who would be a good candidate for a DES, or alternatively who would be better served by a BMS or by CABG. Moreover, these data could potentially be used to identify patients who would need adjunctive treatment upon termination of antiplatelet therapy, such as during the perioperative period (37).

Among the procedure-related factors stent underexpansion, long or multiple stents, and residual dissections appear to be most important for the development of in-stent thrombosis (38, 39). Several patient related factors have been reported to be associated with an increased risk of stent thrombosis, including low ejection

fraction (40) and stenting in the setting of ACS (23, 41). Certain lesion characteristics are reported to be associated with an increased risk of stent thrombosis. In DES, this pertains in particular to long lesions (40). Similarly in our study stent thrombosis was significantly associated with the duration of MI, lower LV EF%, presence of visualized thrombus within the lesion, calcified lesion, type C lesion, total stent length, and residual edge dissection ( $P < 0.05$ ).

At the time of stent thrombosis, 50% of the DES group and 33% of the BMS group were not on dual antiplatelet therapy because of drug intolerance, or completing the prescribed duration of dual antiplatelet therapy. On the basis of the current report, it can be speculated that factors that affect the rate of stent thrombosis may include failure to achieve adequate stent apposition in the presence of heavily calcified lesion or suboptimal use of antiplatelet medication.

### Optimal Duration of Antiplatelet Therapy in Recipients of DES

Dual antiplatelet treatment (Aspirin and clopidogrel) was prescribed for at least 1 year in the DES groups. In addition, the use of glycoprotein IIb/IIIa inhibitors during the procedure was ultimately accomplished in 54.3% of patients. Under this antiplatelet regimen there was no increase in the rate of stent thrombosis in the DES group.

The 2005 European Society of Cardiology and the 2005 ACC/AHA/Society for Cardiovascular Angiography and Interventions recommendations suggest maintaining dual antiplatelet therapy for 12 months, at least "In patients who are not at high risk of bleeding" (42). Knowing that at the time of DES thrombosis, 2 of the 4 patients (50%) were not on dual antiplatelet therapy, some may be tempted to continue such therapy even longer. However, such therapy was shown to portend genuine bleeding risks, as demonstrated in the MATCH and CHARISMA trials (43, 44). It must also be acknowledged that it is not entirely clear that being on dual antiplatelet therapy is completely protective against late stent thrombosis. For instance two of our patients (50%) had DES thrombosis while on dual antiplatelet therapy.

There is a paucity of data concerning when the re-endothelialization of DES is completed; therefore, it is impossible to give any relevant advice about when dual antiplatelet treatment can be/should be interrupted. As the majority (75%) of the DES thrombosis cases, however, occurred within 12 months in our study, the prolongation of the dual antiplatelet treatment for 12 months seems to be sufficient. Information to support this approach is, however, lacking. Moreover, this not only increases the cost of DES implantation, but also the risk for bleeding.

### Predictors of TLR

In our study ostial lesions were independently associated with TLR ( $P < 0.05$ ). Similarly in the RESEARCH study,

lesions involving ostial sites had a higher risk of restenosis, which may be related, at least in part, to technical difficulties in stent positioning and vessel scaffolding at the ostium (17).

In the present study, a higher incidence of TLR was observed in patients with type C lesions, as Lansky, et al. previously reported (45).

In the SIRIUS trial, small vessel size, long lesion length, and diabetes were shown to significantly increase the incidence of restenosis after SES (13). These characteristics were confirmed as independent predictors of clinical restenosis in our study ( $P < 0.05$ ).

### **Predictors of Restenosis**

In the SIRIUS trial, TLR were 6.3% in the subgroup with vessel size  $< 2.75$  mm compared with 1.9% in the subgroup with vessels size  $\geq 2.75$  mm (13). Similarly, in TAXUS V trial, the subgroup with small vessels had a TLR of 10.4%, and the subgroup with large vessels had a TLR of 0% (46). In our study, RVD  $< 2.5$  mm was significantly associated with TLR ( $P < 0.05$ ). These results provide strong support for the role of vessel size as an important predictor of restenosis in the DES era.

In the SIRIUS trial, angiographic restenosis rates were 17.6% among patients with DM and 6% among patients without DM (47). In contrast, comparable rates of angiographic restenosis rates also were found among patients with (6.4%) and without (8.4%) DM in the TAXUS IV trial (48). In our study, the presence of DM was associated with an increased risk for clinical restenosis ( $P < 0.05$ ). Thus, although use of a DES consistently reduces the risk of restenosis in diabetic patients (49), it appears unlikely that such a local treatment can reduce the overall clinical risk of patients with DM, given the systemic nature of the disease and its close link to atherosclerotic disease progression.

Finally, Park, et al. evaluated ISR as a function of lesion length and found that angiographic restenosis in vessels  $< 33$  mm was 4%, 33–51 mm was 7.1% and  $> 51$  mm was 15.4% (50). Thus, despite a significant reduction in ISR with DES, lesion length does still appear to be an independent predictor of restenosis. Similarly in our study lesion length  $> 30$  mm was a significant predictor of TLR ( $P < 0.05$ ).

Interaction of Restenosis Risk Factors with DES Effect on ISR.

The Achilles heel of bare-metal stent implantation has been the development of angiographic in-stent restenosis. After implantation of a BMS, there are a number of established predictors of restenosis, particularly lesion length, RVD, and the presence of DM (51). This study provides the evidence base for the treatment of patients with these risk factors.

The population evaluated in this study is representative of patients presenting in current clinical practice, with lesion lengths  $> 20$  mm in 57.4%, small-vessel ( $< 2.5$ -mm diameter) disease in 11.7%, and medically treated diabetes in 42.6%. The interaction of known restenosis risk factors (DM, RVD, and lesion length) with the DES treatment effect on ISR was evaluated. There were no detectable significant treatment interactions that would suggest a lack of clinical anti-restenosis benefit for DES in subset patients including DM or variations in vessel diameter or lesion length.

The use of DES among diabetic patients was associated with 29% relative risk reduction. Similarly in the SIRIUS trial, the angiographic restenosis was significantly decreased in diabetic patients receiving SES versus BMS (17.6% v 50.5%) (47). Similar results were also seen in the TAXUS-IV study, in which binary restenosis in diabetic patients was decreased by 81% (48).

In our study, the use of DES among patients with lesion length  $> 25$  mm was associated with 26% relative risk reduction. In the RESEARCH registry of patients receiving SESs, 96 patients with an average stent length of 61.2 mm had a binary restenosis rate of 11.9% (52).

Also the use of DES among patients with RVD  $< 2.5$  mm was associated with 13% relative risk reduction. Data from the E-SIRIUS and C-SIRIUS trials have shown significantly reduced ISR in small vessels measuring 2.5–3.0 mm (26, 53). Leon, et al. evaluated the angiographic and clinical outcome in patients from six multicenter trials receiving SES in vessels  $\leq 2.7$  mm in diameter. The rate of ISR was 3.2% vs. 38.5% for patients receiving BMS (54).

### **CONCLUSIONS AND RECOMMENDATIONS**

This study confirms that in an unselected real-world population, no evidence exists of a decreasing efficacy of DES in patients with acute MI. Also by reducing the rates and improving the pattern of restenosis, DES may directly reduce the subsequent occurrence of nonfatal MI. Unless the patient with acute MI has a contraindication to prolonged antiplatelet therapy, a DES should be implanted. Finally, given the high rates of ST in both groups, a further emphasis on the potential benefit of more aggressive or prolonged dual antiplatelet therapy in the setting of acute MI appears warranted.

---

#### **Corresponding Author**

Sherif Samir Elzahwy MD,  
Cardiology Departement, Ain Shams University Hospital  
E-mail: sherifsm@hotmail.com

---

#### **REFERENCES**

1. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med* 2006; 355(11):1105-13.

2. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med* 2006; 355(11):1093-104.
3. Welt FG, Edelman ER, Vukmirovic N, et al. Stent release of a rapamycin analogue: Tissue pharmacokinetics of rapid versus delayed release. *J Am Coll Cardiol* 2003; 41:74A.
4. Jeanmart H, Malo O, Carrier M, et al. Comparative study of cyclosporine and tacrolimus vs newer immunosuppressants mycophenolate mofetil and rapamycin on coronary endothelial function. *J Heart Lung Transplant* 2002; 21(9):990-8.
5. Babinska A, Markell MS, Salifu MO, et al. Enhancement of human platelet aggregation and secretion induced by rapamycin. *Nephrol Dial Transplant* 1998; 13(12):3153-9.
6. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? *Circulation* 2004; 109(6):701-5.
7. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol* 2006; 98(3):352-6.
8. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: Results from the PREMIER registry. *Circulation* 2006; 113(24):2803-9.
9. Valgimigli M, Percoco G, Malagutti P, et al. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: A randomized trial. *JAMA* 2005; 293(17):2109-17.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; 115(17):2344-51.
11. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: Clinical and angiographic results of the ENDEAVOR II trial. *Circulation* 2006; 114(8):798-806.
12. Silber S, Albertsson P, Aviles FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; 26(8):804-47.
13. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; 349(14):1315-23.
14. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS-IV trial. *Circulation* 2004; 109(16):1942-7.
15. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; 364(9444):1519-21.
16. Williams DO, Abbott JD, Kip KE. Outcomes of 6906 patients undergoing percutaneous coronary intervention in the era of drug-eluting stents: Report of the DEScover Registry. *Circulation* 2006; 114(20):2154-62.
17. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004; 109(2):190-5.
18. Ong AT, Serruys PW, Aoki J, et al. The unrestricted use of paclitaxel-versus sirolimus-eluting stents for coronary artery disease in an unselected population: One-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. *J Am Coll Cardiol* 2005; 45(7):1135-41.
19. Lemos PA, Saia F, Ligthart JM, et al. Coronary restenosis after sirolimus-eluting stent implantation: Morphological description and mechanistic analysis from a consecutive series of cases. *Circulation* 2003; 108(3):257-60.
20. Colombo A, Orlic D, Stankovic G, et al. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. *Circulation* 2003; 107(17):2178-80.
21. Popma JJ, Leon MB, Moses JW, et al. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation* 2004; 110(25):3773-80.
22. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent versus bare-metal stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol* 2007; 49(19):1924-30.
23. Urban P, Gershlick AH, Guagliumi G, et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: One-year follow-up of the e-Cypher registry. *Circulation* 2006; 113(11):1434-41.
24. Ruygrok PN, Melkert R, Morel MA, et al. Does angiography six months after coronary intervention influence management and outcome? Benestent II Investigators. *J Am Coll Cardiol* 1999; 34(5):1507-11.
25. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; 346:1773-80.
26. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004; 43(6):1110-5.
27. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: A randomized trial. *J Am Med Assoc* 2004; 292(22):2727-34.
28. Moreno R, Fernández C, Calvo L, et al. Meta-analysis comparing the effect of drug-eluting versus bare metal stents on risk of acute myocardial infarction during follow-up. *Am J Cardiol* 2007; 99(5):621-5.
29. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: A collaborative network meta-analysis. *Lancet* 2007; 370(9591):937-48.
30. Chen MS, John JM, Chew DP, et al. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006; 151(6):1260-4.

31. Nayak AK, Kawamura A, Nesto RW, et al. Myocardial infarction as a presentation of clinical in-stent restenosis. *Circ J* 2006; 70(8):1026-9.
32. Cutlip DE, Chhabra AG, Baim DS, et al. Beyond restenosis: Five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 2004; 110(10):1226-30.
33. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: A pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001; 103(15):1967-71.
34. Hofma SH, Ong AT, Aoki J, et al. One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; 91(9):1176-80.
35. Pfisterer M, Brunner La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: An observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* 2006; 48(12):2584-91.
36. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med* 2007; 356(10):1020-9.
37. Rabbat MG, Bavry AA, Bhatt DL, et al. Understanding and minimizing late thrombosis of drug-eluting stents. *Cleve Clin J Med* 2007; 74(2):129-36.
38. Chieffo A, Bonizzoni E, Orlic D, et al. Intraprocedural stent thrombosis during implantation of sirolimus-eluting stents. *Circulation* 2004; 109(22):2732-6.
39. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: An intravascular ultrasound study. *J Am Coll Cardiol* 2005; 45(7):995-8.
40. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293(17):2126-30.
41. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: Data from a large two-institution cohort study. *Lancet* 2007; 369(9562):667-78.
42. Smith SC, Jr, Feldman TE, Hirshfeld JW, Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI writing committee to update the 2001 guidelines for percutaneous coronary intervention). *Circulation* 2006; 113(1):156-75.
43. Diener PHC, Bogousslavsky PJ, Brass PLM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364(9431):331-7.
44. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354(16):1706-17.
45. Lansky AJ, Costa RA, Mintz GS, et al. Non-polymer-based paclitaxel-coated coronary stents for the treatment of patients with de novo coronary lesions: Angiographic follow-up of the DELIVER clinical trial. *Circulation* 2004; 109(16):1948-54.
46. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: A randomized controlled trial. *JAMA* 2005; 294(10):1215-23.
47. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients: A SIRIUS (SIRRollmUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004; 109(19):2273-8.
48. Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: The TAXUS-IV trial. *J Am Coll Cardiol* 2005; 45(8):1172-9.
49. Sabate M, Jimenez Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: The diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation* 2005; 112(14):2175-83.
50. Park SJ, Kim YH, Lee CW, et al. Stent length as a predictor of restenosis after long sirolimus-eluting stent implantation. *J Am Coll Cardiol* 2005; 45(3):64A.
51. Ho KL, Senerchia C, Rodriguez O, et al. Predictors of angiographic restenosis after stenting: Pooled analysis of 1197 patients with protocol-mandated angiographic follow-up from 5 randomized stent trials. *Circulation* 1998; 98:1362.
52. Degertekin M, Arampatzis CA, Lemos PA, et al. Very long sirolimus-eluting stent implantation for de novo coronary lesions. *Am J Cardiol* 2004; 93(7):826-9.
53. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: Double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003; 362(9390):1093-9.
54. Leon MB, Mehran R, Popma J, et al. Long-term results after sirolimus-eluting stent in small vessel lesions: An integrated analysis of six multicenter trials. *J Am Coll Cardiol* 2005; 45(Suppl A):64A.