

3-Year Clinical Outcome of Patients With Chronic Total Occlusion Treated With Drug-Eluting Stents

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Objectives The aim of this study was to evaluate whether percutaneous coronary intervention (PCI) with drug-eluting stent (DES) reduces major adverse cardiac events (MACE) in patients with chronic coronary total occlusions (CTO) compared with bare-metal stent (BMS) during 3-year follow-up.

Background The long-term prognosis of patients with CTO treated with PCI and DES implantation is poorly investigated.

Methods We compared the 3-year clinical outcome of 124 patients with CTO after successful PCI with DES implantation with that of 159 patients with CTO previously treated with BMS. MACE were defined as death, myocardial infarction, and target lesion revascularization (repeat PCI or coronary artery bypass surgery) and were considered as combined primary end point.

Results After 3 years, the composite end point was significantly lower in the DES than in the BMS group: 18% versus 28%, respectively, ($p < 0.05$). The difference was due to the reduction of target lesion revascularization with DES compared with BMS—8% versus 21%, respectively, ($p < 0.004$). The Cox proportional hazards model identified: DES versus BMS (adjusted hazard ratio [HR]: 0.338, 95% confidence interval [CI]: 0.19 to 0.60, $p = 0.0001$), lesion length (HR: 1.033, 95% CI: 1.008 to 1.058, $p = 0.012$), and final minimal lumen diameter (HR: 0.456, 95% CI: 0.232 to 0.898, $p = 0.023$) as independent predictors of MACE at 3-year follow-up.

Conclusions After 3 years, DES were superior to BMS in reducing MACE in patients with CTO and should be considered the preferred treatment strategy. (*J Am Coll Cardiol Intv* 2009;2:1260–5)
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During the past 25 years the use of percutaneous coronary intervention (PCI) has become common in the management strategy of patients with chronic coronary total occlusion (CTO) (1). Patients with successful recanalization of CTO with PCI have better clinical outcome and improved left ventricular function compared with patients in whom the attempt to re-canalize CTO has failed (2-5). Moreover, in patients with left anterior descending CTO, successful PCI is associated with improved long-term survival (6). The

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high restenosis rate has limited the benefits of plain old balloon angioplasty; the implantation of bare-metal stents (BMS) has lowered the rate of repeat target lesion revascularization (TLR). The introduction of sirolimus- (SES) and paclitaxel-eluting stents (PES) has resulted in a further important reduction of restenosis in patients with CTO (7-10) with apparently durable benefits (11). However, data on long-term follow-up have shown conflicting results (12,13). An increased rate of target vessel revascularization (TVR) in patients with CTO treated with SES has been recently reported (12). Conversely, a recent randomized study has shown that the documented superior short-term clinical and angiographic results of SES over BMS are maintained during 3-year follow-up (13).

The present study aimed to evaluate the 3-year clinical outcome of successful recanalization with DES implantation compared with BMS in patients with CTO.

Methods

Study population. The study population consisted of 283 consecutive patients with CTO of native coronary vessels and evidence of related myocardial ischemia or viability who underwent successful revascularization with implantation of DES or BMS in our institution. A CTO was defined as a complete obstruction of the vessel with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 and an estimated duration of >3 months. Age of the occlusion was determined by the interval from the last episode of acute coronary syndrome or myocardial infarction consistent with the location of the occlusion. A successful PCI was defined as final TIMI flow grade ≥ 2 and a residual stenosis <30% after stent implantation. Patients with CTO of the left main coronary artery or of a previously stented coronary artery were not included. The DES group included 124 consecutive patients with CTO, who received SES or PES between January 2003 and February 2006. The BMS group included 159 consecutive patients with CTO who had received BMS in the 4 years preceding the introduction of DES at our hospital. There was no temporal overlap in the 2 groups with regard to stent placement. Only 1 type of stent was used in each CTO. The study was conducted in a large-

volume laboratory with more than 1,000 PCIs/year, during both BMS and DES time frames. All CTO interventions were performed by standard antegrade approach.

All patients were pre-treated with aspirin and either ticlopidine (500 mg/day at least 3 days before the procedure) or clopidogrel (a loading dose of 300 mg at least 6 h before the procedure). After the procedure, all patients were given aspirin indefinitely and either ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for at least 4 weeks after implantation of BMS and for at least 3 or 6 months after implantation of SES or PES, respectively. Glycoprotein IIb/IIIa inhibitors were given at the discretion of the operator.

Angiographic analysis. Angiographic analysis was done on end-diastolic frames demonstrating the stenosis on its more severe view. The view with the least foreshortening was selected for the analysis. A computer-assisted automated algorithm (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands) and standard morphologic criteria were used for the analysis of the entire treated segment. Reference vessel diameter, minimal lumen diameter, and residual stenosis percentage were measured. Lesion length was measured after vessel recanalization.

End points. Major adverse cardiac events (MACE) were defined as death, myocardial infarction, and TLR and were considered the combined primary end point of the study. The secondary end point was TLR. Myocardial infarction was diagnosed in the presence of new pathological Q waves on electrocardiogram or a rise in creatine kinase (or myocardial band fraction) of more than twice the upper limit of normal. Target lesion revascularization (TLR) consisted of repeat PCI or coronary artery bypass surgery due to restenosis or re-occlusion of the target lesion in the presence of objective evidence of ischemia. According to the definitions of the Academic Research Consortium, stent thrombosis (acute: <1 day; subacute: 1 to 30 days; late: >30 days; very late: >1 year) was categorized as follows: 1) "definite" as an acute coronary syndrome with angiographic documentation of either occlusion of the target lesion or thrombus within or adjacent to a previously stented segment; 2) "probable" in case of any unexplained death within 30 days or if a target vessel myocardial infarction occurred without angiographic documentation; and 3) "possible" in case of any unexplained death after 30 days that could not be attributed to another cause (14,15).

Abbreviations and Acronyms

BMS = bare-metal stent(s)

CTO = chronic coronary total occlusion(s)

DES = drug-eluting stent(s)

MACE = major adverse cardiac events

PCI = percutaneous coronary intervention

PES = paclitaxel-eluting stent(s)

SES = sirolimus-eluting stent(s)

TIMI = Thrombolysis In Myocardial Infarction

TLR = target lesion revascularization

TVR = target vessel revascularization

Table 1. Baseline Clinical Characteristics

Variable	DES (n = 124)	BES (n = 159)	p Value
Age (yrs)	63 ± 10	61 ± 10	NS
Women	31 (25)	33 (21)	NS
Previous myocardial infarction	76 (61)	117 (73)	<0.03
Previous coronary artery bypass surgery	4 (3)	3 (2)	NS
Previous percutaneous coronary intervention	9 (7)	8 (5)	NS
Diabetes			NS
Not insulin-requiring	35 (28)	36 (22)	
Insulin-requiring	7 (6)	6 (4)	
Hypertension	89 (72)	107 (67)	NS
Hypercholesterolemia	76 (61)	110 (69)	NS
Current smoker	48 (39)	72 (48)	NS
Ejection fraction (%)	52 ± 9	52 ± 11	NS

Data are reported as mean ± SD or n (%). Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of blood pressure-lowering agents. Hypercholesterolemia was defined as total cholesterol >230 mg/dl or use of a lipid-lowering agent.
BMS = bare-metal stent(s); DES = drug-eluting stent(s).

Follow-up protocol included evaluation at hospital discharge and a clinical visit or telephone interview after discharge and at 6, 12, 24, and 36 months.

Statistical analysis. We performed a retrospective analysis of data that were prospectively collected according to the protocol of our institution. Data are presented as mean ± SD or percentages. Comparisons between groups were performed with *t* test for continuous data and the chi-square test or Fisher exact test for categorical data when appropriate. Statistical significance was accepted at $p \leq 0.05$.

The Cox proportional hazards model was used to determine the independent correlates of the composite primary end point of MACE. Logistic regression was performed to determine the independent correlates of TLR and TVR. Event-free survival curves, from MACE and TLR and TVR, were constructed with the Kaplan-Meier method and compared with the log-rank test. Analyses were performed with the BMDP 2L software package (BMDP Statistical Software, Inc., Los Angeles, California).

Results

Study population. Baseline characteristics are shown in Table 1. Mean age was 62 ± 10 years (range 32 to 85 years); 219 patients were men. Diagnosis of previous myocardial infarction had been made in 193 patients, whereas 24 patients had undergone previous revascularization. Among 71 patients with diabetes mellitus, 13 had insulin-requiring diabetes. The DES group had a statistically significant lower prevalence of previous myocardial infarction in comparison with the BMS group.

Angiographic and procedural variables. Angiographic and procedural variables are shown in Table 2. Target vessel was

left anterior descending coronary artery in 156 patients, circumflex artery in 53 patients, and right coronary artery in 74 patients. Patients with single-vessel disease numbered 159, whereas 124 had multivessel disease. One vessel was treated in 187 patients, whereas 85 and 11 patients received treatment of 2 and 3 vessels, respectively. Glycoprotein IIb/IIIa inhibitors were used in 53 cases. All patients had final TIMI flow grade 3, apart from 2 patients in the BMS group that had TIMI flow grade 2. Patients treated with DES (83 patients with SES and 41 patients with PES) had statistically significantly longer lesion length and stented segment length and higher number of stents/lesion than patients treated with BMS. The BMS group had a larger baseline reference vessel diameter and a higher final minimal lumen diameter than the DES group.

Clinical follow-up. With the exception of 17 patients (6 treated with DES, and 11 treated with BMS) who were lost after hospital discharge, 266 patients were evaluated after a follow-up of 36 months. Clinical events are described in

Table 2. Angiographic Characteristics and Procedural Variables

Variable	DES (n = 124)	BES (n = 159)	p Value
Target vessel			NS
Left anterior descending	67 (54)	89 (56)	
Circumflex	18 (14)	35 (22)	
Right	39 (31)	35 (22)	
Treated coronary segment			NS
Proximal	43 (35)	54 (34)	
Middle	70 (36)	86 (54)	
Distal	11 (9)	19 (12)	
Number of diseased vessels			NS
1	61 (49)	98 (61)	
2	51 (41)	52 (33)	
3	12 (10)	9 (6)	
Number of treated vessels			NS
1	74 (60)	113 (71)	
2	44 (35)	41 (26)	
3	6 (5)	5 (3)	
Ostial lesion	2 (1)	2 (1)	NS
Bifurcation lesion	6 (5)	6 (4)	NS
Glycoprotein IIb/IIIa inhibitor therapy	25 (20)	28 (15)	NS
Lesion length (mm)	23 ± 10	16 ± 7	<0.0001
Stented segment length (mm)	37 ± 15	21 ± 8	<0.0001
Number of stent/lesion	1.6 ± 0.7	1.3 ± 0.6	<0.0003
Stent overlapping	62 (50)	45 (39)	<0.005
Reference vessel diameter (mm)	2.8 ± 0.3	3.0 ± 0.5	<0.001
Final minimal lumen diameter (mm)	2.4 ± 0.3	2.5 ± 0.3	<0.0004
Residual stenosis (%)	12 ± 6	11 ± 7	NS
Final TIMI flow grade 3	124 (100)	157 (99)	NS
Intravascular ultrasound examination	6 (5)	5 (3)	NS

Data are reported as n (%) or mean ± SD.
TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

Table 3. Clinical Events During 3-Year Follow-Up

Variable	DES (n = 118)	BES (n = 148)	p Value
Long-term events (all)	21 (18)	42 (28)	<0.05
Death	7 (6)	7 (5)	NS
Cardiac	2	4	
Noncardiac	5	3	
Myocardial infarction	4 (3)	3 (2)	NS
Q-wave	2	2	
Non-Q-wave	2	1	
TLR	10 (8)	32 (21)	<0.004
PCI	8	23	
CABG	2	9	
TVR (no TLR)	2 (2)	3 (2)	NS
PCI	2	3	
CABG	0	0	

Data are reported as n (%).
 CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

Table 3. At 3-year follow-up, the primary end point of the study occurred in 21 (18%) patients treated with DES and in 42 (28%) patients treated with BMS ($p < 0.05$). During the follow-up period, 2 patients in the DES group and 4 patients in the BMS group died from a cardiac etiology, whereas 4 patients in the DES group and 3 patients in the BMS group suffered myocardial infarction. Patients treated with DES underwent a TLR procedure less frequently compared with patients treated with BMS—10 (8%) versus 32 (21%), respectively ($p < 0.004$). TVR was performed in 2 patients in the DES group and in 3 patients in the BMS group.

In the DES group 2 patients had myocardial infarction and then underwent TLR with PCI. In the BMS group 2 patients had myocardial infarction and then underwent TLR (1 with PCI, and 1 with coronary artery bypass graft). During the first year, 4 patients in the DES group and 28 patients in the BMS group had MACE ($p < 0.0001$).

The following variables were entered into the Cox proportional hazards model to determine the independent predictors of the composite primary end point: type of stent (DES vs. BMS), previous myocardial infarction, diabetes, target vessel, treated vessel segment, lesion length, stent length, number of stents/lesion, reference vessel diameter, final minimal lumen diameter, and residual stenosis percentage. The Cox proportional hazards model identified: type of stent (DES vs. BMS) (adjusted hazard ratio [HR]: 0.338, 95% confidence interval [CI]: 0.19 to 0.60, $p = 0.0001$), lesion length (HR: 1.033, 95% CI: 1.008 to 1.058, $p = 0.012$), final minimal lumen diameter (HR: 0.456, 95% CI: 0.232 to 0.898, $p = 0.023$), and residual stenosis percentage (HR: 1.031, 95% CI: 0.996 to 1.068, $p = 0.089$) as independent predictors of MACE at 3-year follow-up. To determine the influence of time on the composite end

point, the year of PCI was introduced into the Cox proportional hazards model but was not a predictor of events.

To determine the independent predictors of TLR and TVR, the same aforementioned variables entered into the logistic regression model. Stepwise logistic regression analysis identified: the type of stent (DES vs. BMS) (odds ratio [OR]: 0.29, 95% CI: 0.137 to 0.613, $p = 0.0011$), diabetes (OR: 1.99, 95% CI: 0.992 to 3.98, $p = 0.0496$), and residual stenosis percentage (OR: 1.08, 95% CI: 0.98 to 1.13, $p = 0.0014$) as independent predictors of TLR and TVR at 3-year follow-up.

The 3-year survival rates free from MACE were 80% in the DES group and 69.4% in the BMS group (log rank $p = 0.025$) (Fig. 1). The 3-year survival rates free from TLR and TVR were 88.4% in the DES group and 74.4% in the BMS group (log rank $p = 0.044$) (Fig. 2). A DES implantation resulted in a reduction of 36% in MACE and of 62% in TLR compared with BMS.

Stent thrombosis. Definite very late thrombosis occurred in 4 patients in the DES group at 27, 31, and 33 (2 cases) months, respectively. Definite late thrombosis occurred in 3 patients in the BMS group at 1, 6, and 8 months, respectively. Definite sub-acute thrombosis occurred in 1 patient in the BMS group. Probable late thrombosis occurred in 1 patient in the DES group and in 1 patient in the BMS group ($p = NS$).

Discussion

The present study demonstrates that in patients with CTO: 1) the benefits of DES compared with BMS with regard to MACE, demonstrated at 1 year, are maintained up to 3-year follow-up; and 2) type of stent, stenosis length, and final minimal luminal diameter are predictors of MACE after 3 years of follow-up.

Patients with CTO represent a very high risk group for PCI. Balloon angioplasty of CTO is limited by frequent acute vessel

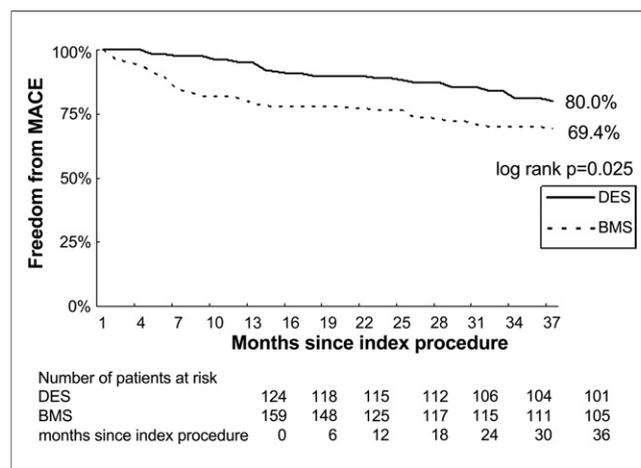
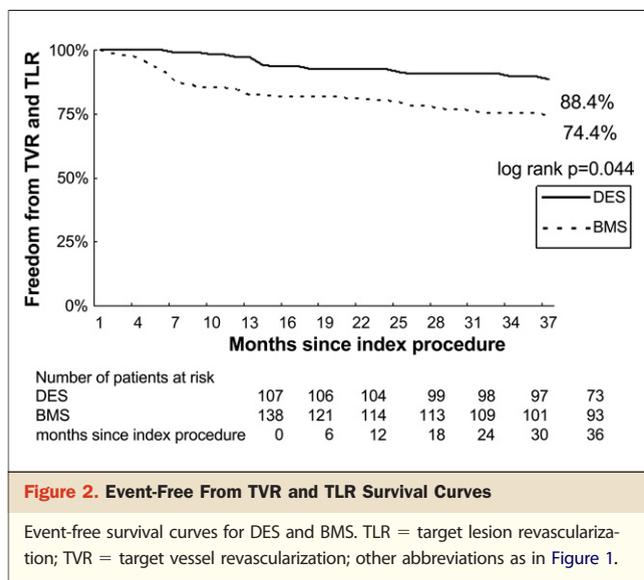


Figure 1. Event-Free From MACE Survival Curves

Event-free survival curves for drug-eluting stents (DES) and bare-metal stents (BMS). MACE = major adverse cardiac events.



re-occlusion and high rates of restenosis. Stent implantation has almost abolished the occurrence of abrupt vessel closure, but its impact on restenosis reduction has been less pronounced (4,5). Recently, both SES and PES have been shown to be safe and effective, and they have markedly reduced the incidence of restenosis and need for TLR in patients with CTO (6–10). However, poor, incomplete, and conflicting data are available about long-term follow-up in patients with CTO treated with DES (12,13).

We compared the long-term clinical outcome of 124 patients with CTO after successful PCI with DES implantation (both SES and PES) with that of 159 patients with CTO previously treated with BMS. We found that the incidence of MACE was markedly reduced among patients with CTO treated with DES as compared with BMS after 3-year follow-up. The benefit was due to the reduction of TLR. This finding confirms that the beneficial effect of DES in CTO is achieved through a reduction of restenosis and TVR (5–9) and is maintained for the long term.

Our data are not in line with Garcia-Garcia et al. (12). They showed that, despite clinical and angiographic benefits at 1 year, the use of SES was no longer associated with significantly lower rates of TLR and MACE in patients with CTO in comparison with BMS. Different factors might have influenced the high number of MACE in the DES group of the study by Garcia-Garcia et al. (12): 1) because mean stent diameter was lower in the DES group and reference vessel diameter was not provided, it is not possible to exclude that DES had been undersized; and 2) because lesion length was not available and stent length was not different between the groups, we cannot exclude that the length of implanted DES had been under-evaluated. Generally, 2 factors might hypothetically explain the absence of prolonged benefits of DES: a late catch-up phenomenon, and/or late stent thrombosis. The first is a significant luminal deterioration during late follow-up

described in porcine models after DES implantation (16). However, observations 5 years after SES implantation (17) and after 2 years with PES in complex lesions (18) seem to indicate the absence of late catch-up phenomenon of DES. In our study, patients with CTO treated with DES had no statistically significant difference in repeat TLR after 1 year with respect to the BMS group. Given these data the presence of a late catch-up phenomenon with DES seems to be unlikely even in patients with very complex lesions as CTO. Late thrombosis is currently under evaluation as a potential factor affecting the long-term safety of DES. Although the possibility of an augmented stent thrombosis after DES implantation has been reported, a recent and large meta-analysis did not show an increased risk of definite stent thrombosis after SES as compared with BMS (19). We did not find statistically significant differences in stent thrombosis between the groups of patients with CTO treated with or without DES. Moreover, the superiority of DES over BMS in reducing MACE was obtained without an increase of death or myocardial infarction attributable to stent thrombosis. Unfortunately the safety of DES in the setting of CTOs has not yet been resolved. The number of patients included in the present study was not large enough to extrapolate definite conclusions about this issue. Although the low rate of stent thrombosis in the present study might seem reassuring, larger dedicated studies are needed to answer this question definitively. Furthermore, the role of long-term dual antiplatelet therapy in patients with CTO treated with DES remains to be defined.

Our results are in agreement with the data of a recent randomized trial (PRISON II [Primary Stenting of Totally Occluded Native Coronary Arteries II]), which shows the superiority of DES over BMS in patients with CTO (13). However, some main differences between the studies should be remarked upon. The present study is not randomized—differing from the PRISON II study—but reflects the outcomes of a real-world population: our patients treated with DES had less-favorable characteristics, including longer occlusions and stented lengths, traditionally recognized as predictors of an increased risk of restenosis. Despite these unfavorable patterns, the use of DES was associated with significantly better clinical outcomes (12). All patients included in the present study had a CTO lasting >3 months, whereas only 45% of the patients had a true CTO (>3 months) in the PRISON II study. If we reconsider the PRISON II results by including only patients with true CTO, the superiority of DES over BMS would not reach the statistical significance at 3-year follow-up.

At multivariate analysis we found that DES, stenosis length, and final minimal luminal diameter were independent predictors of freedom from MACE at 3-year follow-up. Prior studies showed lesion length and final minimal luminal diameter as independent predictors of MACE during the short-term period in CTO treated with DES (7,20), but an extended follow-up has never been previously evaluated. Our results are

not surprising if we think that the benefits of DES are obtained by reducing restenosis and consequent TLR. Long stenoses represent complex lesions and involve high-risk procedures. The extension of the disease increases the possibility of sites of incomplete stent expansion, increasing the risk for restenosis and re-intervention. Final minimal lumen diameter and residual stenosis are influenced by many factors that might provoke inadequate stent expansion (21): vessel resistance, stent dimensions, delivery pressure inflations, stent recoil, and use of noncompliant balloons. Small final minimal lumen diameters and high residual stenosis percentage might contribute to restenosis and consequent TLR. The finding that BMS had an increased frequency of events for all lesion lengths, final minimal luminal diameters, and residual stenosis percentage suggests that DES should always be preferred when lesion length is long, final minimal lumen diameter is expected to be small, or residual stenosis percentage is supposed to be high.

Study limitations. Our report presents some limitations. First, the study was not randomized: operator selection and inclusion criteria might have influenced the final results. Second, follow-up coronary angiography was not routinely performed but only in patients with evidence of spontaneous or inducible ischemia. Third, the sample size was relatively small, and although we found no differences in the rates of death, myocardial infarction, or stent thrombosis, the study did not have sufficient power to show a difference in these clinical events. Fourth, data about adjunctive medical therapy were not collected. Finally, the analysis of only successful cases could bias results. Despite these limitations, our study describes a real-world cohort of patients that had never been analyzed before. However, a randomized study with a larger cohort of patients is required.

Conclusions

The implantation of DES should be considered the preferred treatment strategy for patients with CTO undergoing PCI, because their benefits with regard to MACE are maintained during 3-year follow-up through a reduction of TLR.

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Key Words: bare-metal stent ■ chronic total occlusion ■ drug-eluting stent.