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CLINICAL RESEARCH

Long-Term Outcome After Drug-Eluting Versus Bare-Metal Stent Implantation in Patients With ST-Segment Elevation Myocardial Infarction

5 Years Follow-Up From the Randomized DEDICATION Trial (Drug Elution and Distal Protection in Acute Myocardial Infarction)

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Objectives This study sought to compare the long-term effects of drug-eluting stent (DES) compared with bare-metal stent (BMS) implantation in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention.

Background The randomized DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) trial evaluated the outcome after DES compared with BMS implantation in patients with STEMI undergoing primary percutaneous coronary intervention.

Methods Patients with a high-grade stenosis/occlusion of a native coronary artery presenting with symptoms <12 h and ST-segment elevation were enrolled after giving informed consent. Patients were randomly assigned to receive a DES or a BMS in the infarct-related lesion. Patients were followed for at least 5 years, and clinical endpoints were evaluated from population registries and hospital charts. The main endpoint was the occurrence of the first major adverse cardiac event (MACE), defined as cardiac death, nonfatal recurrent myocardial infarction, and target lesion revascularization.

Results Complete clinical status was available in 623 patients (99.5%) at 5 years follow-up. The combined MACE rate was insignificantly lower in the DES group (16.9% vs. 23%), mainly driven by a lower need of repeat revascularization ($p = 0.07$). Whereas the number of deaths from all causes tended to be higher in the DES group (16.3% vs. 12.1%, $p = 0.17$), cardiac mortality was significantly higher (7.7% vs. 3.2%, $p = 0.02$). The 5-year stent thrombosis rates were generally low and similar between the DES and the BMS groups. No cardiac deaths occurring within 1 month could be clearly ascribed to stent thrombosis, whereas stent thrombosis was involved in 78% of later-occurring deaths.

Conclusions The 5-year MACE rate was insignificantly different, but the cardiac mortality was higher after DES versus BMS implantation in patients with STEMI. Stent thrombosis was the main cause of late cardiac deaths. (J Am Coll Cardiol Intv 2013;6:548–553) © 2013 by the American College of Cardiology Foundation

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Primary percutaneous coronary intervention (PCI) reduces death and recurrent myocardial infarction compared with fibrinolysis in patients with ST-segment elevation myocardial infarction (STEMI) (1,2). Drug-eluting stents (DES) decrease the risk of restenosis and the need for target vessel revascularization (TVR) compared with bare-metal stents (BMS) (3,4) but at higher risk of late stent thrombosis (5–8), especially in patients with acute coronary syndromes (9,10). Two recent meta-analyses including data from 15 and 11 randomized controlled trials, respectively, have evaluated the safety and efficacy of early generation DES compared with bare-metal stents in patients undergoing primary PCI (11,12). Both analyses found an expected, significant reduction in TVR among patients treated with DES and a nonsignificant trend toward a reduced mortality even beyond 1 year of follow-up. Both analyses reported an increased rate of late (>1 year) stent thrombosis in the DES group. The DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) trial evaluated how implantation of DES compared with BMS affects the outcome in 626 patients with STEMI undergoing primary PCI. We have previously reported a reduced need for repeat revascularization at 8 months and 3 years in the DES group (13,14). The present study reports complete 5-year clinical follow-up data.

Methods

Study design and patient population. Patients with a high-grade stenosis/occlusion of a native coronary artery presenting with symptoms <12 h and ST-segment elevation ≥0.2 mV in ≥2 contiguous leads were enrolled after giving informed consent.

PCI procedure and medication. All patients were treated with aspirin, clopidogrel, unfractionated heparin, and if no contraindication, a glycoprotein IIb/IIIa receptor blocker. Patients were randomly assigned in a 2 × 2 design to treatment with or without distal protection and to receive a DES or a BMS in the infarct-related lesion. Lifelong aspirin, 75 mg daily, and 12 months of clopidogrel, 75 mg daily, were prescribed after initial treatment.

Clinical outcome follow-up. Patients were followed for at least 5 years, and clinical endpoints were evaluated from Danish population registries and hospital charts.

Study endpoints and definitions. The main endpoint was the occurrence of major adverse cardiac events (MACE), defined as cardiac death, nonfatal recurrent myocardial infarction, and target lesion revascularization (TLR). The endpoint adjudicators were blinded to the initial treatment strategy unless angiographic review of the index procedure was necessary to decide whether TVR or TLR was present.

A myocardial infarction occurring during follow-up was defined as an increase above the upper normal limit of creatine kinase-myocardial band or troponins in the presence of relevant symptoms of an acute coronary syndrome (15). Stroke was defined as the development of disabling neurological symptoms and objective findings lasting at least 24 h. TLR was defined as revascularization of the target lesion in the presence of recurrent angina, and TVR was defined as revascularization anywhere in the index vessel. Stent thromboses were categorized according to the Academic Research Consortium definitions (16).

Statistical analysis. In order to detect a 50% reduction in MACE (power 80%, type 1 error 5%), 600 patients had to be included in the trial. Categorical variables were compared using the chi-square or Fisher exact test, and continuous variables were compared using the Mann-Whitney *U* test and the Student *t* test. The Kaplan-Meier method was used to create survival estimates, and the log-rank test was used for their comparison. Patients were censored at the time of last follow-up. The comparisons were unadjusted for other covariates except for randomization to distal protection. Interaction analyses were performed by Cox proportional hazards models. All p values were 2-sided.

Results

Baseline demographics and procedural results. Of the included 626 patients, 313 received a DES (46% sirolimus-eluting stents, 41% paclitaxel-eluting stents, and 13% zotarolimus-eluting stents), and 313 received a BMS (38% cobalt alloy, 62% stainless steel). Baseline characteristics of patients and lesion are described in Table 1.

Clinical events. Patients were followed up for a median of 2,095 days (maximum 2,493 days). Complete clinical events data were available in 623 patients. Three patients were lost to follow-up between 3- and 5-year follow-up due to emigration.

The 5-year clinical outcomes are depicted in Figure 1, and the clinical events in Table 2. The primary study reported endpoints at 8 months follow-up, and these data are repeated in the table. At 5 years, the combined MACE rate tended to be lower in the DES group (p = 0.07), mainly driven by a higher need for repeat revascularization in the BMS group. Death rates were numerically higher in the DES group (51 vs. 38 events, p = 0.17), with a significant difference in cardiac deaths (24 vs. 10 events, p = 0.02) (Fig. 2). As previously reported, 13 patients in the DES group versus 5 patients in the BMS group suffered a cardiac death within 8 months after the index procedure, mainly due to progressive heart failure or malignant arrhythmias.

Stroke rates were low at 5 years (4.2% vs. 3.2%, p = 0.67, data not shown). Times to events are illustrated by the

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TLR = target lesion revascularization
TVR = target vessel revascularization

Table 1. Baseline Characteristics of Patients and Lesions

	DES (n = 313)	BMS (n = 313)	p Value
Age, yrs	62 ± 12	63 ± 12	0.41
Men	73	74	0.93
Diabetes mellitus	9.3	11.5	0.43
Hypertension	32	34	0.67
Hyperlipidemia	19	21	0.54
Smoker	53	55	0.88
Previous myocardial infarction	6.1	7.0	0.20
Symptom onset to balloon, min (median)	222	225	0.66
Multivessel disease	35	40	0.44
Infarct-related artery LAD/CX/RCA	40/13/47	43/12/45	0.59
Baseline TIMI flow grade 0–1	65	70	0.27

Values are mean ±SD or %, except as noted.
BMS = bare-metal stent; CX = circumflex artery; DES = drug-eluting stent; LAD = left anterior descending coronary artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Kaplan-Meier method and were compared by the log-rank test, unadjusted for other covariates except for distal protection (cardiac mortality, p = 0.77 for interaction). No interaction was found between the use of distal protection and the type of stent implanted.

Stent thrombosis. The occurrence of stent thrombosis is reported in Table 3. In general, 5-year stent thrombosis rates were low and similar in the DES and the BMS groups (5.4%). Numerically, more definite stent thromboses were seen in the BMS group (3.8% vs. 1.6%, p = 0.14), and very late stent thrombosis occurred in 3.2% of the DES group and in 2.9% of the BMS group (p = NS). Three patients with a DES died of progressive heart failure, one after admittance for late definite stent thrombosis, whereas 7 patients survived a definite stent thrombosis in a BMS. None of the early cardiac deaths were clearly related to a stent thrombosis, whereas 14 of 18 (78%) occurring after 1 month could be ascribed to a stent thrombosis.

Discussion

The higher rate of MACE in patients treated with BMS compared with those treated with DES during primary PCI described in earlier reports seems to vanish with time. In this randomized study, overall MACE rates after 5 years were insignificantly higher among patients who had received BMS, and the tendency towards a difference was mainly driven by an increased revascularization rate in the BMS group during the early months after inclusion in the trial. According to its primary endpoint, the DEDICATION trial included a per-protocol angiographic follow-up at 8 months that could have influenced the decision to perform revascularization at that time (17–19). This could at least partly explain the finding that the 8 months TVR rates in the present study were higher than the 1-year TVR rates reported in a recent meta-analysis to which the DEDICATION trial also provided data (11). By contrast, revascularization rates beyond 8 months and up to 5 years of follow-up were low and not statistically significant between the 2 groups. There were no study-related angiographic controls during that time, so repeat revascularizations were entirely driven by clinical symptoms. Mortality, and in particular cardiac mortality, was significantly higher in the

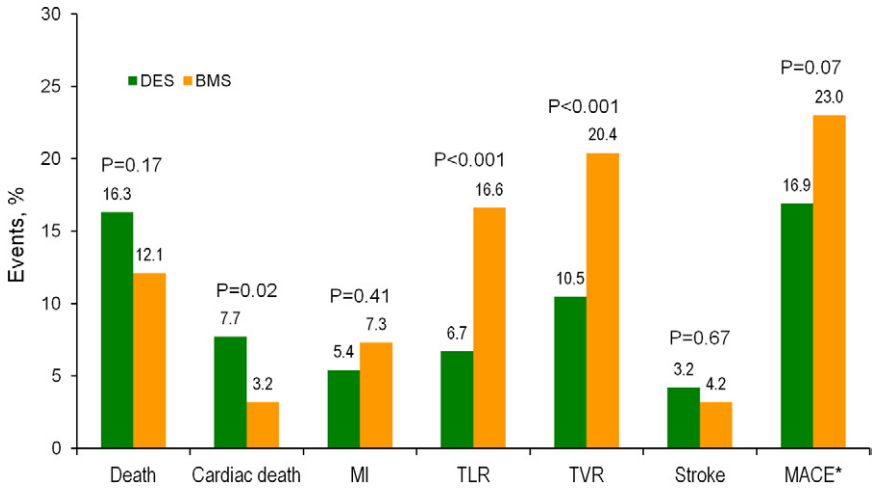

Figure 1. MACE During 5 Years of Follow-Up

The primary endpoints of major adverse cardiac events (MACE) during 5 years of follow-up among patients with drug-eluting stents (DES) **(green bars)** or bare-metal stents (BMS) **(orange bars)**. *MACE = cardiac death, MI and TRL; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

Table 2. Clinical Outcomes

	DES (n = 313)	BMS (n = 313)	p Value
Events from 0 to 8 months			
MACE*	28 (8.9)	45 (14.4)	0.05
Death	16 (5.1)	8 (2.6)	0.14
Cardiac death	13 (4.2)	5 (1.6)	0.09
MI	5 (1.6)	8 (2.6)	0.42
MI in infarct related artery	3 (1.0)	6 (1.9)	0.51
Target vessel revascularization	20 (6.4)	50 (16.0)	<0.001
Target lesion revascularization	16 (5.1)	41 (13.1)	<0.001
Events from 8 months to 5 years			
MACE	24 (7.7)	25 (8.0)	1.00
Death	35 (11.2)	30 (9.6)	0.60
Cardiac death	11 (3.5)	5 (1.6)	0.20
MI	12 (3.8)	15 (4.8)	0.70
Target vessel revascularization	13 (4.2)	16 (5.1)	0.70
Target lesion revascularization	5 (1.6)	11 (3.5)	0.20
Events from 0 months to 5 years			
MACE	53 (16.9)	72 (23.0)	0.07
Death	51 (16.3)	38 (12.1)	0.17
Cardiac death	24 (7.7)	10 (3.2)	0.02
MI	17 (5.4)	23 (7.3)	0.41
Target vessel revascularization	33 (10.5)	64 (20.4)	0.001
Target lesion revascularization	21 (6.7)	52 (16.6)	<0.001

Values are n (%). *MACE at 8 months was originally reported as the composite of cardiac death, MI in the infarction-related artery, and target lesion revascularization (13). At 5 years, all MIs were included as MACE.

MACE = major adverse cardiac event(s); MI = myocardial infarction; other abbreviations as in Table 1.

DES group at 5 years follow-up, a trend that was already present when the 8 months and 3 years results were reported (13,14). The occurrence of very late stent thrombosis was low and similar in the 2 groups, but stent thrombosis, especially definite stent thrombosis, was more often associated with cardiac death in the DES group.

All-cause and cardiac mortality among our patients who had a DES implanted were similar to those reported in the recent meta-analysis, whereas the cardiac mortality among the BMS patients in the present study was considerably lower (11). Another recent meta-analysis by De Luca et al. (12) describes a similar pattern of reduced long-term rates of TVR and MACE in the DES group. However, patients who have a DES implanted have a higher risk of both reinfarction and very late stent thrombosis. Small differences in the demographic patient data could be responsible for these observed discrepancies. Patients enrolled in the DEDICATION trial were on average 2 years older; the presence of diabetes, hypertension, and hypercholesterolemia was lower compared with the patients in the meta-analysis; and the symptom onset-to-balloon duration was 30 min shorter in the DEDICATION trial. The 3-year cardiac mortality rate was 6.8% in patients who had a BMS implanted in the meta-analysis, a level that is considerably higher than in the

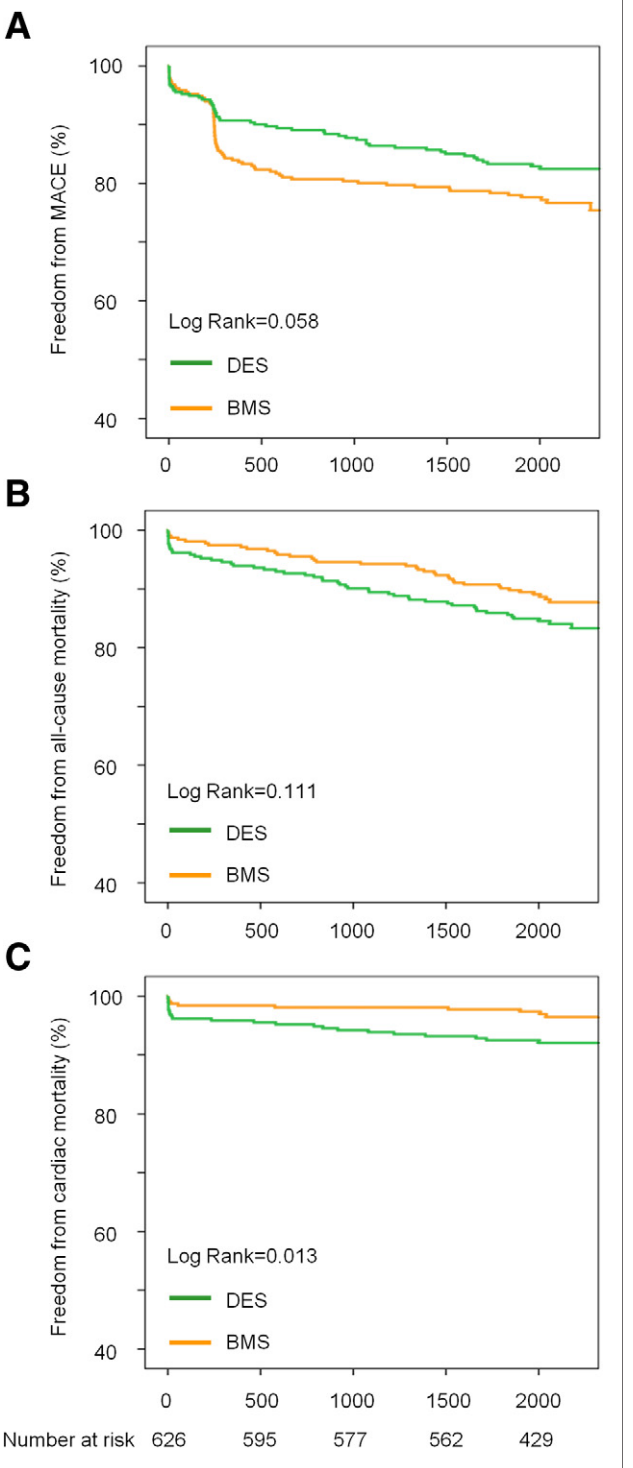

Figure 2. Kaplan-Meier Estimates of Survival and Freedom From MACE

Kaplan-Meier estimates of survival free of **(A)** MACE, **(B)** total mortality, and **(C)** cardiac mortality among patients with DES or BMS. Green lines = DES, Orange lines = BMS. Abbreviations as in Figure 1.

Table 3. Stent Thrombosis

	DES (n = 313)	BMS (n = 313)	p Value
Any stent thrombosis	17 (5.4)	17 (5.4)	1.0
Acute (<24 h)	1	1	
Subacute (1–30 days)	4	4	
Late (30 days to 1 year)	2	3	
Very late (>1 year)	10	9	
Definite stent thrombosis	5 (1.6)	12 (3.8)	0.14
Acute (<24 h)	1	1	
Subacute (1–30 days)	0	4	
Late (30 days to 1 year)	2	2	
Very late (>1 year)	2	5	
Probable stent thrombosis	4	0	
Possible stent thrombosis	8	5	

Values are n (%).
Abbreviations as in Table 2.

DEDICATION population (1.9% at 3 years, 3.2% at 5 years). The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial is the largest randomized trial to date investigating BMS versus DES in STEMI, comparing paclitaxel-eluting stents with BMS in 3,006 patients undergoing primary PCI for STEMI (20). The combined MACE rate was reduced in the paclitaxel group, entirely driven by a lower rate of both TLR and TVR, whereas there were no differences in mortality or reinfarctions in the 2 groups. Mortality in the HORIZONS-AMI trial is generally considered very low, with a 3.8% cardiac mortality in the BMS group. For comparison, the cardiac mortality in patients treated with BMS in the present study was 1.9% at 3 years and 3.2% at 5-year follow-up. Differences in outcome among the trials can probably be explained in part by a different patient selection. Compared with the HORIZONS-AMI population, the DEDICATION patients were 3 years older and had a higher frequency of Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 and 1 in the infarct-related artery at presentation. By contrast, the DEDICATION population had less diabetes, hypertension, and hyperlipidemia. Symptom onset-to-balloon durations were identical in the 2 studies. In HORIZONS-AMI, only 64% of the BMS patients were on thienopyridine treatment at 1-year follow-up, whereas clopidogrel was prescribed for 12 months in both stent groups in the DEDICATION trial. However, we did not record the medical compliance data of our patients. Thus, the lower mortality in the BMS group is difficult to explain by differences in baseline and procedure-related data, but prolonged thienopyridine treatment could play a role. GRACE (Global Registry of Acute Coronary Events) reported registry data on 5,093 patients treated with either DES or BMS after STEMI (21). Unadjusted 2-year mortality was similar among the 2 groups, with a trend toward a higher late mortality in the DES group. It should be stressed that comparisons generated from this registry report necessitated propensity analyses to adjust for differences in baseline characteristics among patients receiving DES and BMS. Still, a higher post-discharge mortality rate was seen in the DES group compared with the BMS group after these adjustments, which is in accordance with the findings of our randomized study, although it was not powered to detect differences in mortality.

Study limitations. Stent thrombosis occurring in the early phase of an acute coronary syndrome unrelated to mechanical problems during stent implantation is closely related to increased platelet activation. Patients undergoing PCI due to acute coronary syndromes are thus at higher risk for stent thrombosis when compared with patients undergoing PCI for stable coronary artery disease. Therefore, late and very late stent thrombosis have been a matter of concern in both randomized trials and registries of patients with STEMI treated with primary PCI (12,22–24), even though the risk seems to be lower with the newer-generation DES (7,25). In the present study, we did not find an increased risk of late stent thrombosis in the DES group, and only 2 patients had a very late (>1 year) definite stent thrombosis compared with 5 patients treated with BMS. Overall, the definite stent thrombosis rates at 5 years were lower in the DES group compared with previous reported data (11).

Conclusions

Implantation of a DES in patients undergoing primary PCI for STEMI was associated with a higher 5-year cardiac mortality that can only partially be explained by an increased occurrence of very late stent thrombosis. In the present study, cardiac mortality among patients treated with BMS was considerably lower than previously reported. Stent thrombosis was the main cause of late cardiac deaths.

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Key Words: bare-metal stent(s) ■ drug-eluting stent(s) ■ myocardial infarction ■ paclitaxel ■ percutaneous coronary intervention ■ sirolimus ■ stent thrombosis ■ zotarolimus.