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3-Year Comparison of Drug-Eluting Versus Bare-Metal Stents

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Objectives The aim of this study was to compare 3-year cumulative outcomes to landmark second- and third-year outcomes with the routine use of drug-eluting stents (DES) (>75% "off-label") with a comparable group treated with bare-metal stents (BMS).

Background Long-term safety concerns after "off-label" DES use persist, despite recent 2-year data showing comparable safety to BMS use.

Methods Clinical outcomes (nonfatal myocardial infarction, all-cause mortality) were assessed in 1,147 consecutive patients who received a BMS in the year before the introduction of DES at Wake Forest University Baptist Medical Center and 1,246 consecutive patients that received a DES after it became our routine choice with equivalent complete 3-year follow-up.

Results Stents were used for "off-label" indications in 80% of DES patients. At 3 years, the hazard ratio for DES compared with BMS for cumulative target vessel revascularization was 0.65 (95% confidence interval [CI]: 0.51 to 0.82), nonfatal myocardial infarction or death was 0.85 (95% CI: 0.71 to 1.03), and all-cause mortality 0.80 (95% CI: 0.64 to 1.01). The DES clinical benefits occurred entirely within the first year, with similar rates of these clinical end points in the second and third year. The cumulative hazard ratio of stent thrombosis DES compared with BMS was 1.07 (95% CI: 0.57 to 2.01), with similar rates of stent thrombosis in the third year ($p = 0.70$).

Conclusions The routine clinical use of DES for "off-label" indications was associated with lower clinical end points at 3 years than treatment with BMS in a comparable group of patients, with similar cumulative rates of stent thrombosis. There was no evidence of late "catch-up" of adverse DES events. (J Am Coll Cardiol Intv 2009;2:231–9) © 2009 by the American College of Cardiology Foundation

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Concerns of stent thrombosis (ST) more than 1 year after placement of drug-eluting stents (DES) (1–3) have fueled an extensive evaluation of the late safety of these devices (4,5), particularly in higher-risk patients receiving DES for "off-label" indications (6,7). Importantly, some studies have observed a rate of late ST of up to 0.6%/year for several years after DES, without evidence of reduction in the incidence of this low frequency event (8). Whereas attention has been focused on late ST, several recent single-center and registry studies have observed that hard cardiac end points including nonfatal myocardial infarction (MI) and death are lower after the use of DES compared with bare-metal stents (BMS) in routine practice at 1 to 2 years after stent treatment (9–11). Whether the beneficial outcomes observed with DES compared with BMS persist after 2 years remains uncertain. Accordingly, we compared clinical outcomes, including rates of ST, nonfatal MI, and death at 3 years, in well-matched groups of patients treated with DES and BMS in routine clinical practice, including a large majority of high-risk patients treated for "off-label" indications.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis
TVR = target vessel revascularization

Methods

Patients at our institution undergoing percutaneous coronary intervention (PCI) from April 2002 to April 2005 were included in the study. Consecutive patients (n = 1,164) representing all patients who underwent coronary artery stenting between April 2002 and April 2003, before the Food and Drug Administration approval of DES in the United States, received BMS and served as the control group. The study group consisted of 1,285 consecutive patients who received DES after these stents were fully available (February 2004) and had replaced BMS as our routine stents of choice (≥90% use). Any patient that had a BMS placed after the availability of DES was excluded from this study to minimize selection bias of stent type when both BMS and DES were available. Patients were also excluded if they received both BMS and DES (n = 8) or were unavailable for follow-up (BMS = 17; DES = 31). Patients were not excluded from the study for any other reason. Thus, 1,147 BMS and 1,246 DES patients comprised the control and study groups, respectively. The study was approved by the Institutional Review Board of Wake Forest University Baptist Medical Center. We have previously reported the 9-month (12) and 2-year (9) follow-up of most of these patients.

PCI was performed according to standard techniques. Because sirolimus-eluting stents were available much earlier than paclitaxel-eluting stents, they comprised most of the DES used in the study: sirolimus-eluting stents = 972; paclitaxel-eluting

Table 1. Baseline Clinical and Procedural Characteristics by Stent Type

Characteristic	BMS (n = 1,147)	DES (n = 1,246)	p Value
Male gender	66%	65%	0.600
Age, yrs	64 ± 12	63 ± 12	0.165
Heart failure class III or IV	15%	16%	0.533
Current smoker	31%	34%	0.149
Diabetes mellitus	32%	32%	0.638
Hypertension	76%	78%	0.309
Hypercholesterolemia	68%	65%	0.210
Vascular disease	20%	18%	0.224
History of renal failure	5%	6%	0.222
Previous PCI	29%	23%	0.003
Previous CABG	17%	16%	0.491
Left ventricular ejection fraction, %	48 ± 16	50 ± 11	0.247
Indications for procedure			
Myocardial infarction within 7 days	37%	41%	0.083
On-label	25%	20%	0.004
Off-label	75%	80%	0.004
Target lesion vessel			
Native coronary artery	93%	94%	0.304
Saphenous vein graft	7%	6%	0.341
Procedural			
Number of vessels stented	1.2 ± 0.4	1.2 ± 0.4	0.173
Number of lesions stented	1.5 ± 0.8	1.4 ± 0.7	0.629
Stented length per lesion, mm	20 ± 10	25 ± 8	<0.001

BMS = bare-metal stent(s); CABG = coronary artery bypass grafting; DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

Table 2. Post-Index Procedure Medications Use by Stent Type

Medication	BMS	DES	p Value
Clopidogrel			
At 6 months	388/693 (56)	784/1,057 (74)	<0.001
At 1 yr	340/686 (50)	601/1,051 (57)	0.002
At 2 yrs	297/678 (44)	494/1,043 (47)	0.148
At 3 yrs	263/669 (39)	378/1,024 (37)	0.320
Aspirin			
At 6 months	625/647 (97)	980/1,004 (98)	0.224
At 1 yr	611/640 (95)	968/998 (97)	0.106
At 2 yrs	594/632 (94)	951/990 (96)	0.056
At 3 yrs	578/623 (93)	877/980 (90)	0.027
Statin			
At 6 months	594/687 (86)	931/1,053 (88)	0.227
At 1 yr	593/680 (87)	931/1,047 (89)	0.280
At 2 yrs	574/672 (85)	941/1,039 (91)	0.001
At 3 yrs	566/663 (85)	801/1,020 (79)	<0.001

Each time interval expressed as No. using / No. alive (%). Medications data were not available for all patients.
Abbreviations as in Table 1.

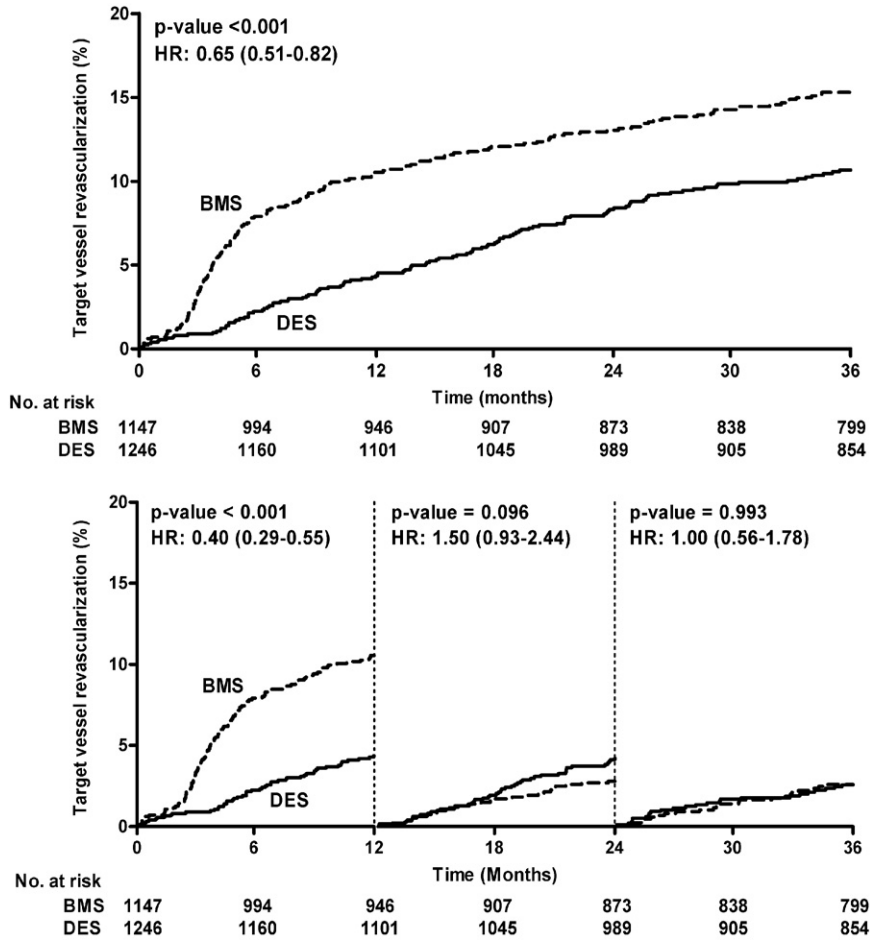

Figure 1. Kaplan-Meier Plots of Cumulative Incidence and Landmark Incidence of Target Vessel Revascularization

BMS = bare-metal stent(s); DES = drug-eluting stent(s); HR = hazard ratio.

stents = 262; both = 12. Anticoagulation during PCI was accomplished with unfractionated heparin or bivalirudin per standard protocol. Patients received glycoprotein IIb/IIIa receptor inhibition according to usual protocol with abciximab or eptifibatide at the discretion of the interventionalist (12). All patients were treated with aspirin (81 to 325 mg/day) before PCI and indefinitely thereafter. Patients also received clopidogrel (300 to 600 mg as a loading dose, given before or immediately after the procedure, followed by 75 mg/day). Clopidogrel was given for a minimum of 1 month in BMS-treated patients, for a minimum of 3 months for sirolimus-eluting stent-treated patients, and for a minimum of 6 months for paclitaxel-eluting stent-treated patients. Additional clopidogrel use was at the discretion of the physician responsible for clinical care of the patient.

Before hospital discharge, patient and procedural data and hospital outcomes were entered into the Wake Forest University Baptist Medical Center Cardiovascular Information Services Database. Collection of data and outcomes measures conformed to the American College of Cardiology National Cardiovascular Database Registry definitions for cardiovascular data (13). Clinical follow-up was obtained as follows: independent chart review, including a follow-up visit with a cardiologist at 3 years, was available for 80% of patients; and review of the Social Security Death Index for which the death records were the only available follow-up in 2% of patients. Scripted phone interviews at 3 years were obtained in 18% of patients who did not have follow-up with either chart or Social Security Death Index review. Events occurring at outside institutions were reviewed and confirmed. Follow-up was censored at 3 years ± 30 days, with complete 3-year follow-up available in 96% of BMS and 91% of DES patients. All patients reported in the study had clinical follow-up. In the patients in whom complete 3-year follow-up was not available, outcomes were included in all Kaplan-Meier and Cox proportional hazards analysis until the point they were lost to follow-up.

Stent thrombosis was defined following the recommendations of the Academic Research Consortium (ARC) for

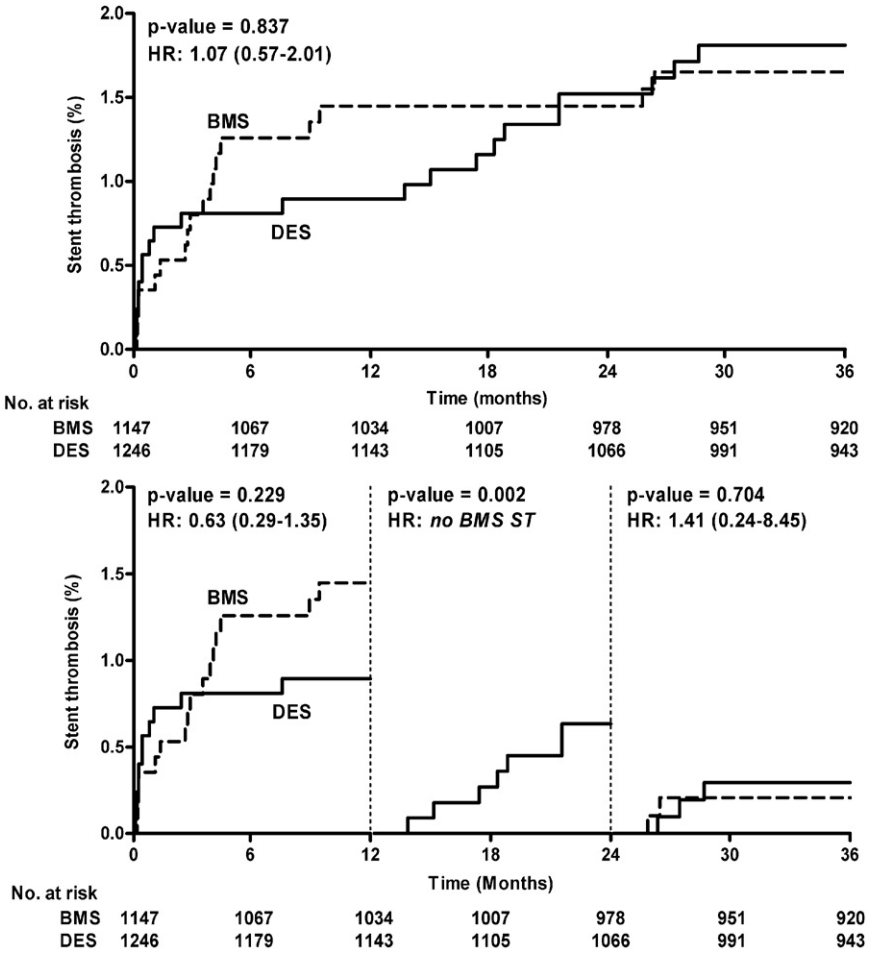

Figure 2. Kaplan-Meier Plots of Cumulative Incidence and Landmark Incidence of Stent Thrombosis

Abbreviations as in Figure 1.

definite and probable ST as presentation with acute coronary syndrome (ACS) and definite angiographic or pathologic evidence of ST, unexplained death within 30 days of stent placement, or target vessel infarction in the absence of angiography (14). "On-label" stent use was patterned after the study criteria used in the initial randomized DES studies (15,16), as follows: >18 years old; single de-novo native coronary artery lesions <30 mm in length without thrombus; left ventricular ejection fraction ≥25%; no MI within 7 days of the procedure; and no evidence of renal failure (serum creatinine ≤2.0 mg/dl). Stent use in all other patients was defined as "off-label." This definition of "on-label" use is similar to the information for use guidelines for both Cypher (Cordis Corporation, Miami, Florida) and TAXUS (Boston Scientific, Inc., Billerica, Massachusetts) with the exception that renal failure was not specifically listed as a contraindication for DES use in the instructions for use. Nonfatal MI was defined as ischemic symptoms and an elevation of creatine kinase-myocardial band >2 × the upper limit of normal, with or without ST-segment elevation or development of Q waves. Periprocedural MIs arising at the time of the index procedure were not included in the outcomes.

Statistical methods. Descriptive statistics (means and SD of continuous factors, frequency counts and relative frequencies of categorical factors) were calculated and compared with the Wilcoxon rank sum test for continuous factors and chi-square testing for categorical factors. Hazard ratios (HRs) are presented along with their 95% confidence intervals (CIs). Kaplan-Meier plots of cumulative incidence were constructed from index procedure to 3 years of follow-up. The log-rank test was used to test for differences between DES and BMS incidence curves. Cox proportional hazards modeling was used to assess independent predictors of outcomes at 3 years to account for follow-up data censored before 3 years. All measured baseline patient and procedural variables were included in the model regardless of clinical significance and removed in a

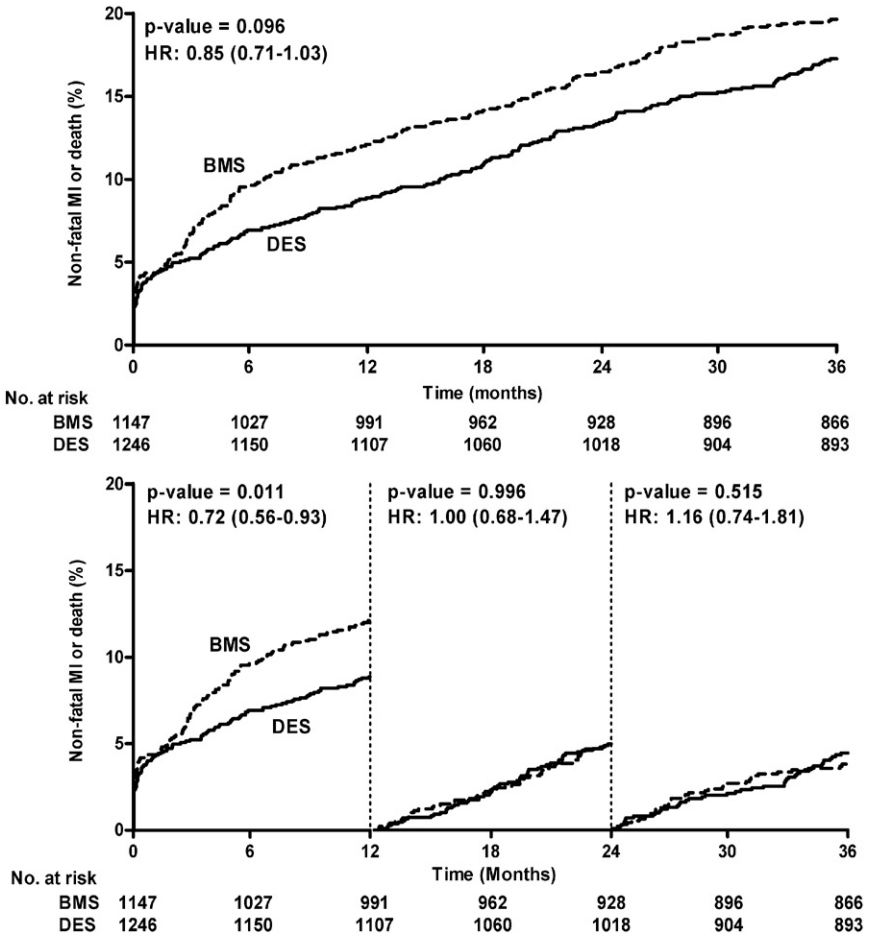

Figure 3. Kaplan-Meier Plots of Cumulative Incidence and Landmark Incidence of Nonfatal MI or Death

MI = myocardial infarction; other abbreviations as in Figure 1.

backward stepwise fashion until all remaining covariates were statistically significant predictors of outcome ($p < 0.05$). Known clinical predictors of outcome (i.e., MI indication for PCI, heart failure, age) were retained in the models regardless of statistical significance. Because of the low rates of stent thromboses, we dropped all nonstatistically significant variables including clinical predictors from the multivariate model. The proportional hazards assumption was tested for all variables by examining log-log survival curves. No variables in the final models violated the proportional hazards assumption. The SAS, Version 9.1 Statistical Software Package (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

Results

The baseline clinical characteristics of the BMS and DES groups were similar (Table 1). By study criteria 75% of BMS and 80% of DES ($p = 0.004$), were "off-label" patients and/or procedures, including treatment for MI within 7 days in 37% of BMS and 41% of DES patients ($p = 0.08$). Medication use during the follow-up period was available for most of the patients in the study (Table 2). Aspirin use remained >90% in both groups at 3 years. Clopidogrel use was higher at 6 months in the DES group (74%) versus the BMS group (56%) ($p < 0.002$). Thereafter, clopidogrel use declined and was essentially the same. At 3 years, clopidogrel use was 39% BMS and 37% DES ($p = 0.29$). At 3 years, any antiplatelet therapy was in use in 95% of BMS and 91% of DES ($p = 0.006$).

Kaplan-Meier plots of the cumulative incidence of selected outcomes at 3 years as well as for each year during the follow-up period are shown for the entire BMS and DES groups in Figures 1 to 4. The clinical and procedural covariates for each of the stent types were similar for each time period analyzed ($p > 0.05$). The cumulative hazard of target vessel revascularization (TVR) was lower with DES compared with BMS (HR: 0.65, 95% CI: 0.51 to 0.82). The DES TVR

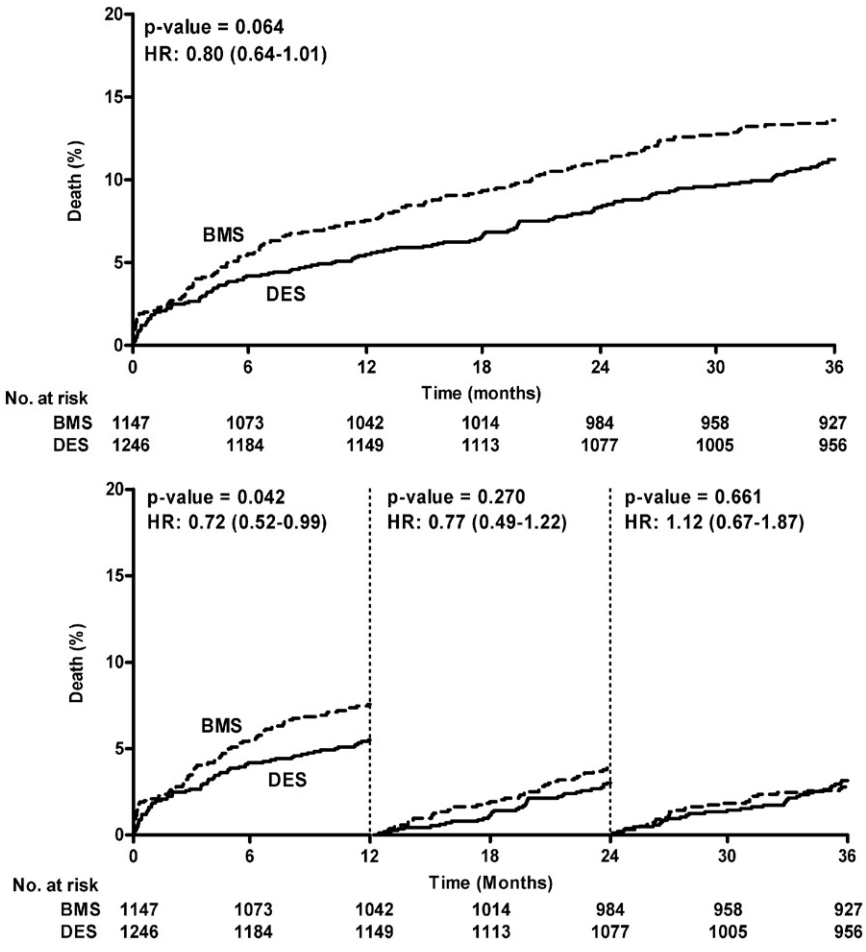

Figure 4. Kaplan-Meier Plots of Cumulative Incidence and Landmark Incidence of Death

Abbreviations as in Figure 1.

benefit occurred entirely within the first year, with similar rates of TVR in the second and third year. The 3-year cumulative hazard of ST was 1.07 (95% CI: 0.57 to 2.01). There was no BMS ST during the second year, but there were 7 DES stent thromboses. There were 2 stent thromboses during the third year in the BMS group and 3 in the DES groups ($p = 0.99$). There was a lower cumulative hazard of death in the DES group compared with the BMS group that persisted out to 3 years (HR: 0.80, 95% CI: 0.64 to 1.01). The cumulative hazard of nonfatal MI or death was also lower in the DES patients compared with the BMS patients (HR: 0.85, 95% CI: 0.71 to 1.03). The DES benefit seemed to occur entirely within the first year, with similar rates of nonfatal MI or death in the second and third years.

We examined the relation between clopidogrel use and outcomes in the first year. The overall HR for nonfatal MI or death was 0.62 (95% CI: 0.43 to 0.88) for those taking clopidogrel versus those not taking clopidogrel at 6 months. In those taking clopidogrel at the time of an event or at 6 months, the HR for nonfatal MI or death for DES versus BMS was 0.58 (95% CI: 0.34 to 0.99). For those not taking clopidogrel at the time of an event or at 6 months, the HR for nonfatal MI or death for DES versus BMS was 0.76 (95% CI: 0.46 to 1.25).

Multivariate analysis of ST and nonfatal MI or death for the entire study population over the 3-year study period is shown in Table 3. History of renal failure (HR: 2.49, 95% CI: 1.88 to 3.30), and diabetes mellitus (HR: 1.65, 95% CI: 1.35 to 2.02), were 2 of the strongest independent predictors of increased nonfatal MI or death, whereas DES use (HR: 0.81, 95% CI: 0.67 to 0.99), was the strongest independent predictor of lower nonfatal MI or death. The HRs of nonfatal MI or death for DES versus BMS were also compared across covariate strata (Fig. 5). For almost all of the clinical and lesion variables assessed, the point estimate of the HR for nonfatal MI or death favored DES, although the upper boundaries of the 95% CIs crossed the line of equivalency.

Table 3. Cox Proportional Hazards Multivariate Analysis of Nonfatal MI or Death, and Stent Thrombosis to 3 Years

	Nonfatal MI or Death		Stent Thrombosis	
Multivariate Model	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Clinical variables				
History of renal failure	2.49 (1.88–3.30)	<0.001		
Vascular disease	1.69 (1.37–2.09)	<0.001		
Diabetes mellitus	1.65 (1.35–2.02)	<0.001	2.05 (1.09–3.85)	0.026
MI indication for index PCI	1.59 (1.30–1.94)	<0.001	1.89 (1.01–3.54)	0.048
Hypertension	1.56 (1.17–2.10)	0.003		
Heart failure class III or IV	1.47 (1.17–1.85)	0.001		
Current smoker	1.34 (1.07–1.68)	0.011		
Age, per 10 yrs	1.32 (1.19–1.45)	<0.001		
Procedural variables				
DES use	0.81 (0.67–0.99)	0.040	1.12 (0.60–2.12)	0.721
No. of lesions stented	1.32 (1.17–1.48)	<0.001	1.87 (1.40–2.50)	<0.001

Only drug-eluting stent (DES) use, number of lesions stented, myocardial infarction (MI), indication for index percutaneous coronary intervention (PCI), and diabetes mellitus were included in stent thrombosis model due to the low number of overall events.

CI = confidence interval; HR = hazard ratio.

Discussion

In this large, contemporary experience comprising mainly coronary stent procedures classified as "off-label" (4,5), we observed comparable clinical outcomes in the third year after stent therapy, including ST, nonfatal MI or death, and all-cause mortality. As a consequence, at 3 years "off-label" DES use was associated with significantly lower cumulative clinical event rates of TVR and favorable trends in nonfatal MI or death compared with BMS use. Thus, the substantial benefit of DES use compared with BMS use in the first year after stent placement was preserved, without evidence of significant "catch-up" of late adverse clinical events after DES use.

Widespread "off-label" DES use has been criticized, because of fear of a higher incidence of late adverse events including ST than would be observed with "on-label" DES use (17). However, several recent single-center and registry studies of "off-label" procedures and patients have observed similar (18) and, in several instances, better cumulative clinical outcomes with DES use than with BMS at 2 years (9–11). Unfortunately, given the substantial benefit observed in the first year after DES use compared with BMS use and the low rate of late DES thrombosis, the effect of late catch-up with DES might not be discernible at 2 years. Only limited data are available for "off-label" DES use after 3 years. Daemen et al. (8,19) have evaluated clinical event rates at 3 and 4 years in consecutive patients treated with DES. They found comparable cumulative rates of nonfatal MI and death with DES and BMS but measurable rates of ST with DES and not BMS. These observations represent the earliest experience of DES use outside of randomized clinical trials and, as such, might not represent the fullest application of DES that has been observed with maturation of the stent therapy, including more prolonged antiplatelet therapy.

The evaluation of late events after DES use in patients with an initial uncomplicated post-stent therapy course provided the first clinical evidence of a possible "catch-up" with DES that was not thought to occur with BMS, due almost exclusively to ST (1–3). Closer evaluation of 2 of the principal studies that brought these observations to attention, BASKET-LATE (Basel Stent Cost-Effectiveness Trial: Late thrombotic. events) and SCAARS (Swedish Coronary Angiography and Angioplasty Registry) (1,2), revealed that cumulative event rates of DES and BMS were actually similar, despite the occurrence of late DES thrombosis. The use of these landmark analyses provides evidence of low-frequency signals that might be obscured by evaluation of cumulative outcomes only. However, emphasis on these low-frequency events without understanding their impact on cumulative end points might lead to an inappropriate assessment of the potential benefit of stent therapy. Moreover, as our observations suggest, rates of late adverse clinical events due to underlying atherosclerotic coronary artery disease occurs at a much greater frequency (i.e., 5%/year) than the rates due to ST (i.e., 0.5%/year).

The importance of antiplatelet therapy after stent therapy, particularly DES use, has received increasing recognition (1,17,20,21). Although current guidelines recommend at least 1 year of dual antiplatelet therapy after DES (17), the optimal duration of dual antiplatelet therapy remains uncertain. Moreover, eliminating or significantly reducing rates of late DES thrombosis with prolonged (>1 year) dual antiplatelet therapy remains untested (20). In this study, close to one-half of the patients were taking clopidogrel at 2 years in addition to aspirin (approximately 95% use). Whether the use of dual antiplatelet therapy at 3 years in this study was responsible for the apparent lower rates of ST observed in this study compared with BASKET-LATE (1), where clopidogrel was stopped at 6 months by protocol, remains uncertain. Interestingly, we observed a small but significant decrease in the use of aspirin and clopidogrel in DES patients between the second and third years after stent placement but with identical rates of late ST, 0.5%/year. Defining the optimal duration of dual antiplatelet after DES use awaits the results of adequately powered randomized clinical trials.

The potential mechanisms responsible for the lower event rates in the DES patients were not specifically addressed in this study. Greater use of clopidogrel in the DES patients compared with the BMS patients at 6 months might have contributed to this apparent benefit of DES. Our findings suggest that clopidogrel use likely contributed to a lower rate of nonfatal MI or death in DES patients at 6 months, because clopidogrel use was associated with lower event rates at 6

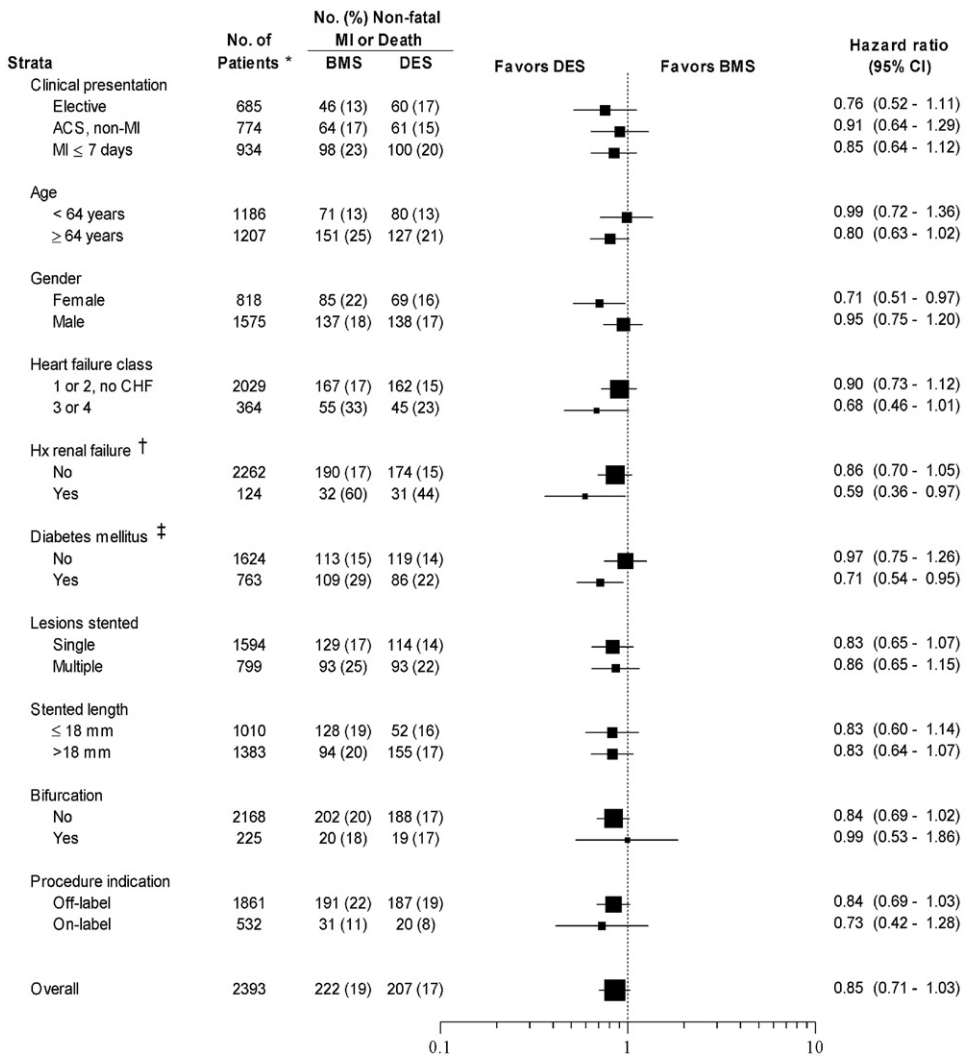

Figure 5. Hazard Ratio Plot of Nonfatal MI or Death up to 3 Years Comparing DES With BMS, Stratified by Covariate

The **size of each box** is proportional to the relative sample size of each strata. *Number of patients that did not have censored follow-up data prior to 3 years; †8 patients did not have history of renal failure data available; ‡7 patients did not have diabetes mellitus data available. ACS = acute coronary syndrome; BMS = bare-metal stent(s); CHF = congestive heart failure; CI = confidence interval; DES = drug-eluting stent(s); MI = myocardial infarction.

months and was more commonly used in DES than BMS patients during the first year. However, our data also suggest that there were additional factors contributing to the lower rate of nonfatal MI or death in DES patients at 6 months, independent of clopidogrel use, because event rates were lower in the first year for DES than BMS in those taking clopidogrel. Further evaluation of potential mechanisms of DES benefit, such as lowering the rate of MIs associated with BMS restenosis (22,23), needs to be performed to determine a better understanding of DES effects.

Observational studies such as ours might be subject to ascertainment bias due to unequal follow-up. However, we obtained nearly complete follow-up in both groups, so that ≥90% of the patients had follow-up available at 3 years. The landmark analysis used in this study might result in imbalances in baseline covariates in subsequent time periods. We evaluated the baseline covariates of the 2 stent types for each landmark period and did not observe any statistically significant differences between the 2 groups. Our study might also be confounded by selection bias. However, our DES and BMS patients had very similar baseline clinical and lesion characteristics. Moreover, use of a recent historical control group avoids the potential selection bias of stent therapies when both BMS and DES are available. Randomized clinical trials would provide the fairest evaluation of DES efficacy and safety, but randomized clinical trials usually exclude the very type of high-risk patients that are of interest (24). Although there were more than 1,000 patients in each treatment group, the study

was underpowered to evaluate differences in the incidence of ST. Finally, our study did not examine outcomes beyond 3 years. Hopefully, longer-term follow-up of cohorts such as this will provide valuable information concerning the relative incidence of late adverse events after DES treatment.

Conclusions

We observed lower cumulative rates of nonfatal MI and all-cause mortality at 3 years in mainly "off-label" DES-treated patients compared with comparable BMS-treated patients. The clinical benefits of lower rates of TVR, all-cause death, and nonfatal MI or all-cause death with DES compared with BMS arose entirely within the first year after stent placement. Rates of these clinical events were similar between the 2 stent groups in the second and third year after stent placement. Left truncation in landmark survival analysis can result in covariate imbalances in subsequent landmark cohorts that can lead to bias in cumulative incidence measurements of 2 separate treatment groups, and thus landmark results should be interpreted within the context of overall cumulative incidence rates. Late ST (>1 year) occurred more frequently with DES than BMS in the second and third year after stent placement, but the 3-year cumulative rates of ST were almost identical. Thus, at 3 years, DES use in "off-label" patients seemed to retain better efficacy and comparable safety to that of BMS use, without evidence of significant late "catch-up" due to adverse DES events.

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