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Circulation 2007;115;3181-3188; originally published online Jun 11, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.667592
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Long-Term Safety and Efficacy of Drug-Eluting Stents

Two-Year Results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) Multicenter Registry

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Background—The long-term safety and efficacy of drug-eluting stents (DES) have been questioned recently.

Methods and Results—Between July 2002 and June 2005, 10 629 patients undergoing elective percutaneous coronary intervention with either DES (n=3064) or bare-metal stents (BMS, n=7565) were enrolled in a prospective registry comprising 13 hospitals. We assessed the cumulative incidence of major adverse cardiac events (death, acute myocardial infarction, and target-vessel revascularization) and angiographic stent thrombosis during 2-year follow-up. A propensity score analysis to adjust for different baseline clinical, angiographic, and procedural characteristics was performed. The 2-year unadjusted cumulative incidence of major adverse cardiac events was 17.8% in the DES group and 21.0% in the BMS group (P=0.003 by log-rank test). Angiographic stent thrombosis was 1.0% in the DES group and 0.6% in the BMS group (P=0.09). After adjustment, the 2-year cumulative incidence of death was 6.8% in the DES group and 7.4% in the BMS group (P=0.35), whereas the rates were 5.3% in DES and 5.8% in BMS for acute myocardial infarction (P=0.46), 9.1% in DES and 12.9% in BMS for target-vessel revascularization (P<0.00001), and 16.9% in DES and 21.8% in BMS for major adverse cardiac events (P<0.0001). Independent predictors of target-vessel revascularization in the DES group were diabetes mellitus (hazard ratio 1.36, 95% confidence interval 1.06 to 1.76), renal failure (hazard ratio 1.69, 95% confidence interval 1.06 to 2.69), and reference vessel diameter (hazard ratio 0.64, 95% confidence interval 0.45 to 0.93).

Conclusions—In this large real-world population, the beneficial effect of DES in reducing the need for new revascularization compared with BMS extends to 2 years without evidence of a worse safety profile. **(*Circulation*. 2007;115:3181-3188.)**

Key Words: stents ■ drugs ■ revascularization ■ registries

Drug-eluting stent (DES) use in percutaneous coronary interventions (PCIs) has been increasing sharply since its introduction into the market, and millions of patients worldwide have received either a sirolimus-eluting stent or a paclitaxel-eluting stent to treat coronary artery narrowings.[1] The reason for this increase lies in the remarkable reduction in the rate of restenosis and need for new revascularization procedures associated with DES compared with conventional bare-metal stents (BMS).[2–6]

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Despite the encouraging results of many randomized trials, however, fears of untoward events ascribable to DES use over long-term follow-up have been posited by a number of studies.[7–9] In addition, previous experience with vascular brachytherapy suggests that neointimal proliferation could simply be delayed and not prevented by some antirestenotic treatments.[10] Indeed, data about the long-term clinical results of DES use in settings other than randomized controlled trials, although somewhat reassuring, are scarce and refer to limited numbers of patients.[11] In the present study, we analyzed a large, real-world multicenter registry to investigate the effects of DES beyond 1 year of follow-up.

Methods

Study Design and Patient Population

The REAL registry (REgistro regionale AngiopLastiche dell'Emilia-Romagna) has been described previously.[12] Briefly, REAL is a large,

Received September 29, 2006; accepted April 13, 2007.

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The online-only Data Supplement, consisting of figures, a table, and a list of investigators, is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.106.667592/DC1.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.667592**

prospective World Wide Web–based registry launched on July 2002 and designed to collect clinical and angiographic data on all consecutive PCIs performed in a 4-million-residents region of Italy. The registry is ongoing. Thirteen public and private centers of interventional cardiology participate in data collection. Procedural data are retrieved directly and continuously from the resident databases of each laboratory, which share a common prespecified data set. These data are open for evaluation, and periodic audits are performed by the Regional Health Care Administration.

Between July 2002 and June 2005, 15 027 patients resident in the region underwent PCI with stent implantation. A total of 1229 patients (8.2%) who had been treated with both DES and BMS have been excluded from the present study population, as well as 3169 (21.1%) patients admitted with a diagnosis of ST-elevation myocardial infarction (MI). The present study population therefore consists of 10 629 patients. Mean follow-up was 703 days (median 697 days, range 182 to 1279 days).

The REAL registry was based on current clinical practice; therefore, regulatory authorities required only an ordinary written informed consent to perform coronary intervention, which was obtained from all patients. The protocol of the study is in accordance with the Declaration of Helsinki.

Procedures and Postintervention Medications

Interventional strategy and device use, including type of DES, were left to the discretion of the attending physicians. Periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medications were used according to the operator's decision and current guidelines. Antiplatelet treatment was prescribed according to current standards of treatment, including lifelong aspirin for all patients, 1 month of ticlopidine (250 mg BID) or clopidogrel (75 mg/d) treatment for patients treated with BMS, and the same treatment for at least 2 months for patients treated with DES. The duration of dual-antiplatelet therapy has been gradually lengthened for patients treated with DES during the 3 years of the registry on the basis of new recommandations.[13]

Definitions and Follow-Up

The primary end point of the survey was the occurrence of major adverse cardiac events (MACE), defined as (1) death (cardiac and noncardiac), (2) nonfatal acute MI, and (3) target-vessel revascularization (TVR). MI during follow-up was diagnosed by local cardiologists at the hospital of admission according to standard criteria (rise in the creatine kinase level to more than twice the upper limit of normal with an increased creatine kinase-MB and newly developed Q waves). TVR was defined as any reintervention (surgical or percutaneous) to treat a luminal stenosis occurring in the same coronary vessel treated at the index procedure, within and beyond the target-lesion limits. The protocol of the REAL registry did not include routine angiography for any subgroup of patients; therefore, virtually all reinterventions can be considered clinically driven. Thrombotic stent occlusion was documented angiographically as a complete occlusion (Thrombolysis In Myocardial Infarction flow 0 or 1) or a flow-limiting thrombus (Thrombolysis in Myocardial Infarction flow 1 or 2) in a previously successfully treated artery. Lesion length and vessel reference diameter were estimated visually by the operators. Online quantitative coronary analysis was allowed if required by the attending physician. Follow-up was obtained directly and independently from the Emilia-Romagna Regional Health Agency through analysis of the hospital discharge records and the mortality registries. This ensures a complete follow-up for 100% of patients resident in the region, including all out-of-hospital deaths (this is the reason for the a priori exclusion of patients who live outside the region). All repeat interventions during follow-up (either surgical or percutaneous) were collected prospectively from the single institutions as well and matched with the administrative data to adjust for eventual inconsistency. Hospital records were reviewed for additional information whenever deemed necessary. Specific queries were sent to the single institution to justify or correct discrepancies between administrative data, largely provided by independent cardiologists, and data derived from the Web-based PCI database, compiled by the interventional cardiologists.

Statistical Analysis

Continuous variables were expressed as mean±SD and were compared with Student unpaired t test. Categorical variables were expressed as counts and percentages, and the χ^2 test was used for comparison. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method and compared by the log-rank test. Because of the observed differences in baseline characteristics between the treatment groups, a propensity score analysis was performed by use of a logistic regression model for treatment with DES versus BMS. This analysis included a number of clinical, angiographic, and procedural variables, such as age, sex, modified Charlson comorbidity index, diabetes mellitus, prior angioplasty, prior coronary artery bypass graft, prior MI, in-stent restenosis, target vessel, left main stenting, number of lesions treated, reference vessel diameter, lesion length, ostial lesion, chronic total occlusion, bifurcation, and year and hospital of treatment. The logistic model by which the propensity score was estimated showed good predictive value (C-statistic=0.823), and calibration characteristics by the Hosmer-Lemeshow test (P=0.32). The score was then incorporated into subsequent proportional-hazards models as a covariate. To avoid overadjustment, the multivariable Cox regression analysis was performed using only the 2 variables "propensity score" and "treatment." Cox proportional hazards models adjusted with the propensity score were also used to assess the effect of DES use in several subgroups of patients. The propensity score was then used to select 2 cohorts of patients for each treatment arm to perform a matched comparison. The main goal of the present analysis was to select 2 subgroups of patients with largely overlapping demographic and procedural characteristics for a thorough evaluation of stent thrombosis. In fact, for this population, we also assessed the incidence of probable stent thrombosis, defined as unexplained deaths within 30 days after the procedure or acute MI that involved the target-vessel territory without angiographic confirmation, and possible stent thrombosis, defined as unexplained deaths that occurred at least 30 days after the procedure. Multivariable analyses were performed to identify independent predictors of TVR using the following variables: age, sex, diabetes mellitus, prior PCI, prior coronary artery bypass graft, prior MI, renal failure, left main treatment, proximal left anterior descending coronary artery treatment, in-stent restenosis, number of lesions treated, chronic total occlusion, bifurcation, ostial lesion, reference vessel diameter, total lesion length, and use of DES. All analyses were performed with the SAS 8.2 system.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

In the first 3 years of activity of the REAL registry, 7565 patients were treated only with BMS, and 3064 patients were treated solely with DES (of whom 1939 were treated with only a sirolimus-eluting stent, 1032 with only a paclitaxel-eluting stent, and 93 with both stents). Use of DES was not uniform across the centers, with rates ranging from 19% to 65% of the procedures. A number of differences were observed in demographics (Table 1) and in angiographic and procedural characteristics (Table 2) between the 2 groups. Patients in the DES group were younger (65±11 versus 68±11 years, P<0.0001) and more frequently had diabetes mellitus (30.7% versus 22.4%, P<0.0001) and prior PCI (13.3% versus 10.4%, P<0.0001) than those in the BMS group. Diagnosis of acute coronary syndromes at admission was similar in the 2 groups. DES were more frequently implanted in the left anterior descending coronary artery

TABLE 1. Baseline Clinical Characteristics of Patients According to Treatment With BMS or DES

Variable	BMS (n=7565)	DES (n=3064)	P
Age, y	68±11	65±11	<0.0001
Men	75.4	74.7	0.48
Diabetes mellitus	22.4	30.7	<0.0001
Hypertension	72.5	70.5	0.048
Hypercholesterolemia	54.0	58.7	<0.0001
Current smoker	24.4	24.7	0.74
Charlson comorbidity index	1.4±1.4	1.3±1.4	<0.0001
Prior MI	27.9	26.9	0.33
Prior coronary angioplasty	10.4	13.3	<0.0001
Prior coronary bypass surgery	9.6	9.8	0.71
Poor LVEF (<0.35)	7.8	7.9	0.94
High-risk patients	50.5	69.6	<0.0001
Renal failure	5.0	4.8	0.71
Clinical presentation			
Stable angina pectoris*	48.2	47.6	0.56
Unstable angina pectoris†	51.8	52.4	0.56

LVEF indicates left ventricular ejection fraction. Values are percent or mean±SD.

*Including silent ischemia.

†Including non–ST-elevation acute MI.

TABLE 2. Angiographic Lesion Characteristics and Procedural Details for Patients Treated With BMS or DES

Variable	BMS (n=11190)*	DES (n=4392)*	P
Treated coronary vessel			
LAD	35.7	55.6	<0.0001
Proximal LAD	14.9	26.1	<0.0001
Left circumflex	27.5	21.5	<0.0001
Right	33.3	19.0	<0.0001
Left main	1.1	2.5	<0.0001
Unprotected left main	0.7	1.9	<0.0001
Bypass graft	2.4	1.4	0.0002
Lesion type			
Type A/B1	41.5	31.9	<0.0001
Type B2/C	58.5	68.1	<0.0001
Bifurcation	13.3	20.3	<0.0001
Ostial lesion	6.3	11.8	<0.0001
Chronic total occlusion	6.8	7.2	0.39
In-stent restenosis	0.7	1.9	<0.0001
Average lesion length,† mm	15.3±6.8	18.6±8.6	<0.0001
Average stent length, mm	16.5±4.6	20.4±6.2	<0.0001
Reference vessel diameter,† mm	3.1±0.5	2.8±0.4	<0.0001
Lesion length >20 mm	22.5	40.6	<0.0001
Lesion length >30 mm	4.3	12.6	<0.0001
Reference vessel diameter <2.5 mm	19.7	31.2	<0.0001
Total lesion length,‡ mm	22.3±13.4	26.5±15.5	<0.0001
Multivessel intervention‡	20.7	21.6	0.31
No. of lesions treated	1.5±0.8	1.4±0.7	0.004
Total stent length,‡ mm	24.5±14.4	28.3±16.4	<0.0001
Gp IIb/IIIa inhibitors	23.0	25.9	0.41
Complete procedural success‡	98.1	98.1	0.89

LAD indicates left anterior descending coronary artery; GP, glycoprotein. Values are percent or mean±SD.

*Total number of lesions.

†Visual estimation.

‡Referred to 7565 patients in the BMS group and 3064 patients in the DES group.

(55.6% versus 35.7%, $P<0.0001$) and were used more frequently to treat an unprotected left main coronary artery (1.9% versus 0.7%, $P<0.0001$) and less frequently in bypass grafts (1.4% versus 2.4%, $P=0.0002$) than in the BMS group. Angiographic lesion profiles were generally less favorable in the DES group (American Heart Association/American College of Cardiology lesion type B2/C: 68.1% DES versus 58.5% BMS, $P<0.0001$). In fact, DES were used more often to manage bifurcations (20.3% versus 13.3%, $P<0.0001$), ostial lesions (11.8% versus 6.3%, $P<0.0001$), long lesions (lesion length >20 mm; 40.6% DES versus 22.5% BMS, $P<0.0001$), and small vessels (average reference vessel diameter 2.8±0.4 versus 3.1±0.5 mm, $P<0.0001$) than in the BMS group. Multivessel intervention was performed in 21% of the patients and was evenly distributed in the 2 groups. Complete procedural success was obtained in 98.1% of the procedures in both groups.

The 2-year unadjusted cumulative incidence of MACE is shown in Table 3. Notably, the incidence of angiographic stent thrombosis did not appear significantly different in the 2 groups (1.0% DES versus 0.6% BMS, $P=0.09$).

To adjust for differences in baseline clinical and angiographic characteristics, a propensity score analysis of the data was performed as described previously. As shown in Figure 1, the 2-year incidence of MACE was significantly reduced by DES compared with BMS (DES 16.9% versus BMS 21.8%, hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.65 to 0.85), and this was driven mainly by the reduction in TVR (DES 9.1% versus BMS 12.9%, HR 0.68, 95% CI 0.57 to 0.80). Conversely, rates of death and MI were similar in the 2 cohorts of patients (death: DES 6.8% versus BMS 7.4%, HR 0.90, 95% CI 0.72 to 1.13; MI: DES 5.3% versus BMS 5.8%, HR 0.91, 95% CI 0.72 to 1.16; and death and MI: DES 10.9% versus BMS 12.3%, HR 0.87, 95% CI 0.73 to 1.04). As shown in Figure 2, DES were associated with a similar reduction of risk of TVR and MACE across all subgroups tested.

In a further analysis, we used our propensity score model to perform a matched comparison. Thus, we obtained a population of 3354 patients (n=1677 for each treatment group) with very similar clinical, angiographic, and procedural characteristics (see Table and Figure, online-only Data Supplement). The clinical outcomes of these cohorts paralleled those observed in the entire population: MACE, BMS 21.5% versus DES 18.1% ($P=0.002$); death, BMS 6.8% versus DES 6.7% ($P=0.7$); acute MI, BMS 5.7% versus DES 5.6% ($P=0.9$); and TVR, BMS 13.9% versus DES 10.8% ($P=0.0008$). In this population, angiographic stent thrombosis was observed in 1.5% of BMS and 1.6% of DES patients

TABLE 3. Two-Year Unadjusted and Propensity Score–Adjusted Cumulative Incidence of MACE in Patients Treated With BMS or DES

	BMS (n=7565)	DES (n=3064)	*P*
Unadjusted			
All MACE	21.0	17.8	0.003
Death	8.0	5.7	0.0002
Cardiac	4.6	3.5	0.05
Noncardiac	3.3	2.1	0.001
Unknown	0.1	0.1	...
Acute MI	5.4	5.5	0.64
TVR	12.0	11.2	0.60
PCI	10.3	9.6	0.6
CABG	1.6	1.7	0.9
Target-lesion revascularization	9.2	7.3	0.009
Angiographic stent thrombosis	0.6	1.0	0.09
Acute (<24 h)	0.1	0.1	0.4
Subacute (24 h to 30 d)	0.3	0.3	0.8
Late (30 d to 6 mo)	0.1	0.2	0.7
Very late (>6 mo)	0.1	0.4	0.01
Propensity score–adjusted			
All MACE	21.8	16.9	<0.0001
Death	7.4	6.8	0.35
Cardiac	4.3	4.4	0.9
Noncardiac	3.0	2.4	0.2
Acute MI	5.8	5.3	0.46
TVR	12.9	9.1	<0.0001
PCI	11.2	7.8	<0.0001
CABG	1.7	1.4	0.2
Target-lesion revascularization	9.9	5.8	<0.0001

Values are percentages. *P* values are by log-rank test for unadjusted incidence and by Cox proportional hazards model for propensity score–adjusted incidence. CABG indicates coronary artery bypass grafting.

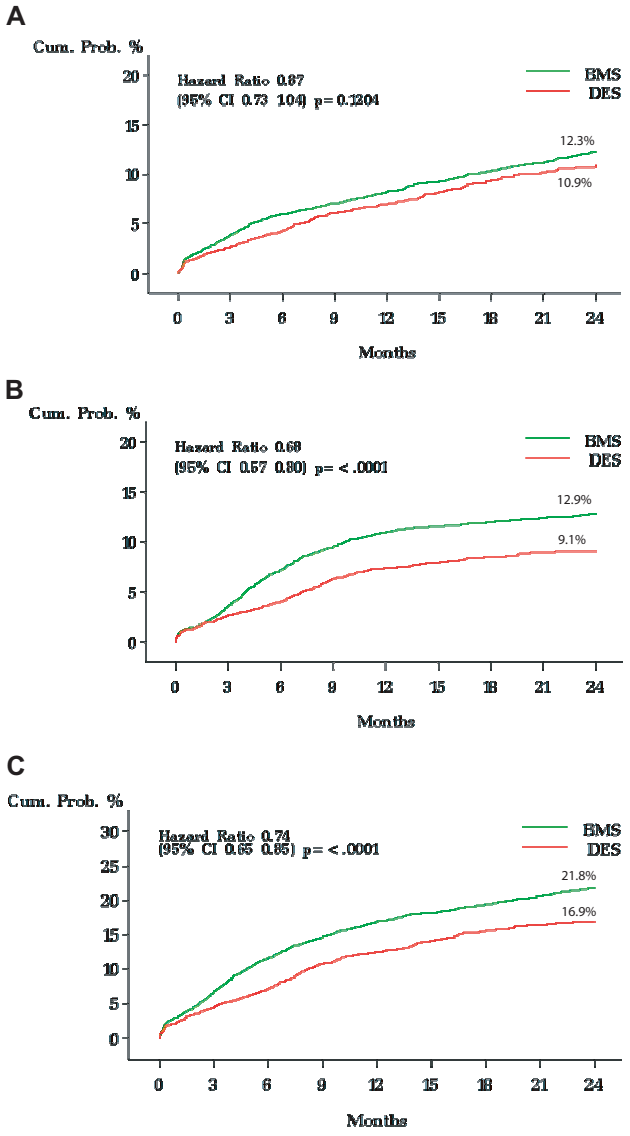

Figure 1. Propensity score–adjusted cumulative incidence (Cum. Prob.) of (A) death and acute MI, (B) TVR, and (C) MACE in the DES and the BMS groups.

(*P*=1.0), probable stent thrombosis in 0.6% of BMS and 0.2% of DES patients (*P*=0.15), possible stent thrombosis in 0.6% of BMS and 1.2% of DES patients (*P*=0.38), and overall stent thrombosis in 2.7% of BMS and 3.0% of DES patients (*P*=0.87; Figure 3).

Predictors of TVR

Table 4 lists the multivariate predictors of long-term TVR. In the overall population, the factors associated with 2-year TVR were diabetes mellitus, prior MI, prior PCI, prior coronary artery bypass graft surgery, proximal left anterior descending coronary artery treatment, in-stent restenosis, ostial lesion, reference vessel diameter, total lesion length, and use of DES. Within the DES group, the only predictors of TVR were diabetes mellitus, reference vessel diameter, and renal failure.

Discussion

This study confirms in a large, real-world population, which included patients with several high-risk indications, that no evidence exists of a decreasing efficacy of DES over time, and the safety profile of DES, at least with the current antiplatelet therapy regimen, does not differ significantly from that of BMS. Encouraging long-term results with DES have been reported previously.[14–16] Importantly, however, these results refer principally to selected patients and lesion types. The first report on the long-term efficacy and safety of DES in the treatment of unselected "all-comers" patients with complex disease came from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry,[11] which demonstrated that the use of a sirolimus-eluting stent is associated with a significantly lower incidence of MACE and TVR than BMS up to 2 years of follow-up in patients with de novo coronary artery lesions. Remarkably, however, as also acknowledged by the authors, only 508 DES patients were included in that report, and observation of rare and unexpected late complications requires a much larger sample size.[11]

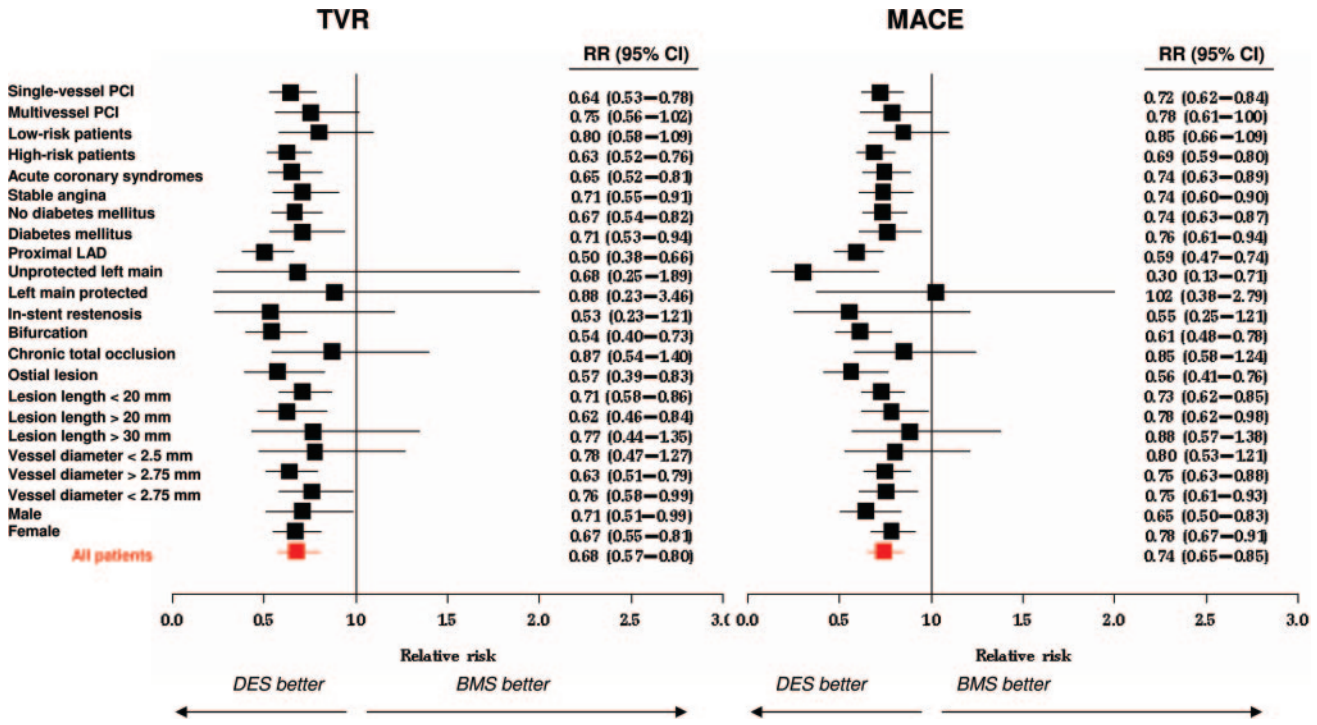

Figure 2. Propensity score–adjusted HRs of incidence of 2-year TVR and MACE associated with DES use in different subgroups of patients according to clinical and angiographic characteristics, by Cox proportional hazards model. High-risk patients were defined on the basis of the following criteria[12]: diabetes mellitus, left ventricular ejection fraction <0.35, lesion in the last remaining vessel, lesion in a main vessel providing collateral flow to another occluded main vessel, ostial lesion, lesion of the proximal left anterior descending coronary artery (LAD), lesion of the left main stem, bifurcation, vein graft, or chronic total occlusion.

Despite this paucity of data, millions of patients have already received a DES since these devices first appeared on the market in April 2002, and the rate of use has been increasing progressively over the years.[1] In addition, ≈25% of the patients are currently treated with DES in "off-label" situations.[17] In this context, results of large "real-life" multicenter registries may provide important information complementary to that provided by randomized clinical trials and single-center experiences. With >3000 patients treated solely with DES in a multicenter setting, the present analysis from the REAL registry represents the largest report of long-term follow-up of DES in daily practice.

To the best of our knowledge, the use of DES for the treatment of coronary artery disease does not reduce mortality compared with BMS, and therefore, the improvement in quality of life due to reduced restenosis and need for new revascularizations obtained with DES should be carefully weighed against possible negative effects on the safety profile. Preliminary long-term data from randomized trials have been reported recently, and these have fueled fears of increased rates of noncardiac death and acute MI with DES. The REAL registry does not provide evidence of an increased risk of angiographically documented stent thrombosis with DES up to 2 years. In addition, in the matched cohorts of patients, the incidence of definite, probable, and possible stent thrombosis did not appear significantly different between the 2 groups (Figure 3). Remarkably, as outlined in Table 3 and Figure 1, both rough and propensity score–adjusted mortality and MI rates were not significantly higher in patients treated with DES than in those treated with BMS. Thus, in our experience, the safety profile of DES was similar to that of BMS up to 2 years. A possible explanation of this result may be the selective use of DES in REAL, with a case-to-case careful evaluation of possible advantages and risks of DES implantation. Nevertheless, we acknowledge that for a safety evaluation, a 2-year follow-up may be inadequate. Therefore, longer follow-up, a larger number of patients, and, possibly, non–company-sponsored large randomized clinical trials are mandatory to definitively determine the safety of patients receiving these devices. In addition, although overall angiographic stent thrombosis rates were low and not significantly different between the 2 groups, after 6 months, significantly more new episodes occurred in the DES group. This reconciles well with the observation that DES may result in delayed arterial healing compared with BMS of similar implant duration,[7] and it provides evidence for the need for prolonged dual-antiplatelet treatment in DES-treated patients. Information about the actual antiplatelet regimen is not available in our registry; however, at least in the first year, dual-antiplatelet treatment was prescribed only for a few months and was likely interrupted after 6 months in the vast majority of the DES patients. Thus, new recommendations for prolonged antiplatelet treatment could result in a leveling of the incidence of stent thrombosis between the 2 groups even after 6 months.

The second important finding of the present study is that the beneficial effect of DES over BMS extends beyond 1 year without any evidence of a late "catch-up" phenomenon. This contrasts with observations in porcine models, in which the initial benefits of DES are reported to disappear with time,[18]

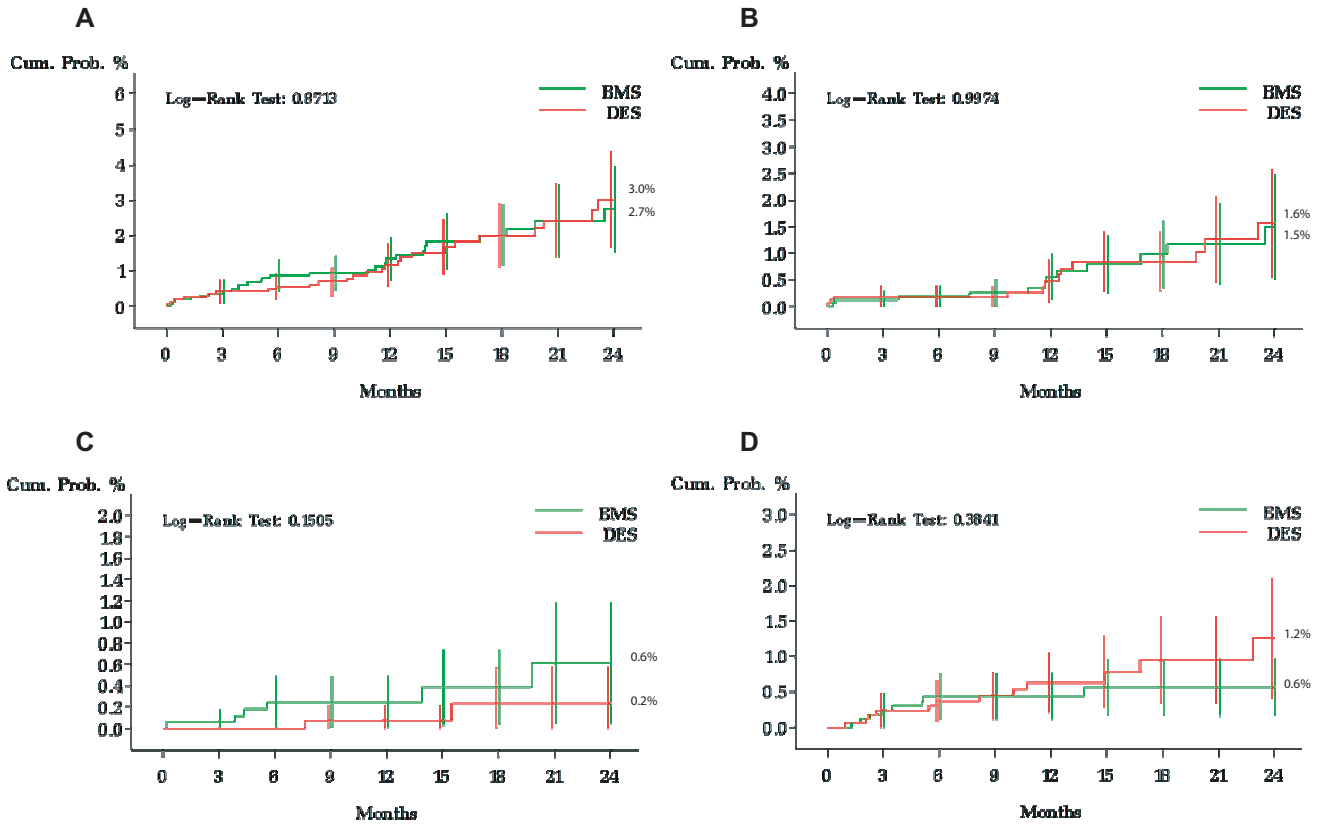

Figure 3. Cumulative incidence (Cum. Prob.) of overall stent thrombosis (A), angiographic stent thrombosis (B), probable stent thrombosis (C), and possible stent thrombosis (D) in the propensity score–matched population of patients treated with DES (n=1677) and BMS (n=1677). Bars represent CIs.

but mirrors long-term findings of the first DES trials[15,16,19] and the 2-year results of the RESEARCH registry.[11] As evident in Figure 1, the advantage of DES over BMS is largely obtained during the first year and then maintained without apparent loss of efficacy over time; however, the 46% reduction of target-lesion revascularization and the 32% reduction of TVR does not appear as striking as reported in clinical trials. This could be explained in part by the clinically driven nature of new revascularizations in our registry, whereas it has been demonstrated that mandatory angiographic follow-up as prescribed in randomized clinical trials can overestimate the absolute clinical benefits of DES.[20] Nevertheless, because TVR/target-lesion revascularization rates in each group were virtually in the single digits, the cost-effectiveness of DES requires further evaluation, and a strategy of selective use targeted to specific subgroups of patients and lesions could be hypothesized for future studies.

TABLE 4. Clinical, Procedural and Angiographic Multivariable Predictors of 2-Year TVR

	HR	95% CI	*P*
All patients			
DES	0.75	0.64–0.88	0.0004
Diabetes mellitus	1.26	1.09–1.46	0.002
Prior MI	0.81	0.69–0.96	0.01
Prior PCI	1.36	1.09–1.70	0.008
Prior CABG	1.32	1.05–1.67	0.02
Proximal LAD treatment	1.25	1.08–1.45	0.003
In-stent restenosis	1.89	1.24–2.89	0.003
Ostial lesion	1.34	1.11–1.62	0.002
Reference vessel diameter*	0.71	0.61–0.82	<0.0001
Total lesion length	1.007	1.00–1.01	0.02
DES group			
Diabetes mellitus	1.36	1.06–1.76	0.02
Reference vessel diameter*	0.64	0.45–0.93	0.02
Renal failure	1.69	1.06–2.68	0.03

LAD indicates left anterior descending coronary artery; CABG, coronary artery bypass grafting.

*Per mm increase.

We analyzed the predictors of clinical restenosis in all patients and subsequently in patients treated with DES only. These analyses confirmed that DES use is independently associated with a reduction in TVR in the general population. We showed once again the predictive value of diabetes mellitus, prior MI, prior revascularization procedures, and a number of angiographic features, such as proximal left anterior descending coronary artery treatment, ostial lesion, reference vessel diameter, total lesion length, and in-stent restenosis, with regard to new revascularizations. Interestingly, however, within the DES-treated population, most of these factors lost their predictive value (Table 4), and only diabetes mellitus (HR 1.26), renal failure (HR=1.69), and reference vessel diameter (HR=0.64) were statistically significant. Small reference vessel diameter has consistently

been shown to increase the risk of repeat revascularizations in patients treated with DES,[3,21,22] and the REAL registry confirms this observation. Diabetes mellitus has traditionally been considered a major risk factor for the development of restenosis after PCI.[23] Although implantation of DES reduces MACE in patients with and without diabetes mellitus alike, there remains a trend toward a higher frequency of restenosis and repeat intervention in diabetic patients than in nondiabetic patients,[24,25] particularly in insulin-dependent patients.[26] Conflicting results emerged from other studies, in which diabetes did not affect the risk of angiographic and clinical restenosis.[22,27,28] These different results might have been driven by different study designs, different populations enrolled, different profile of DES use, or different rates of angiographic follow-up. The results of the present registry study support a persistent clinical impact of diabetes mellitus in patients undergoing PCI (26% increase in TVR risk) and in DES-treated patients alike (36% increase in TVR risk). Thus, although use of a DES consistently reduces the risk of restenosis in diabetic patients,[29] it appears unlikely that such a local treatment can reduce the overall clinical risk of patients with diabetes mellitus, given the systemic nature of the disease and its close link to atherosclerotic disease progression. The same probably holds true for patients with renal disease. In the present registry, renal failure was a significant predictor of repeat TVR in DES patients. End-stage renal failure has been shown to be a risk factor for repeat revascularizations in patients treated with BMS.[30] Although the efficacy of DES in reducing restenosis in patients with mid-to-moderate renal failure has been shown previously,[31,32] as well as in dialysis patients,[33] renal failure has consistently been associated with an increased incidence of stent thrombosis[34,35] and mortality[31] in DES-treated patients. Accelerated atherosclerosis with lipid abnormalities, hypercoagulation, and extensive coronary calcification may explain the higher cardiovascular risk within this population. Taken together, these observations highlight once again the importance of secondary prevention strategies to decrease the negative effect of known risk factors on outcomes of patients undergoing PCI with DES implantation, as well as for every other patient with coronary artery disease.

Conclusions

The REAL registry demonstrates that in a real-world, high-risk setting, DES reduce the incidence of repeat revascularization of the target vessel and MACE compared with BMS at 2 years of follow-up. The extent of this reduction was, however, lower than expected on the basis of the results of randomized trials. This beneficial effect was obtained without evidence of an overall worse safety profile, although further evaluation is needed to clarify the possible long-term thrombotic risk associated with DES implantation.

Source of Funding

This study was supported by the Regional Health Care Agency of Emilia-Romagna, Bologna, Italy.

Disclosures

None.

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CLINICAL PERSPECTIVE

Potential safety issues of drug-eluting stents (DES) over long-term follow-up has evoked considerable concern from cardiologists, healthcare providers, regulatory bodies, the media, and patients. Given this perspective, a new clinical trial designed to detect small differences in mortality and that includes strict postmarketing surveillance with large registries could be helpful. This article reports the 2-year results of a large, real-world multicenter registry, including 10 629 patients undergoing elective percutaneous coronary intervention with either DES (n=3064) or bare-metal stents (n=7565). Selection of patients for use of DES was left entirely to the physicians' discretion. Use of DES reduced the need for new revascularizations and overall major adverse cardiac events without any evidence of a late "catch-up" phenomenon beyond 1 year. Importantly, no significant difference in stent thrombosis was observed between DES and bare-metal stents up to 2 years, although after 6 months, more new episodes were observed in the DES group. Similarly, both rough and propensity score–adjusted mortality and myocardial infarction rates were not significantly higher in patients treated with DES. Thus, this study confirms that no evidence exists of decreasing efficacy of DES over time. Although further evaluation is needed to clarify the possible long-term thrombotic risk associated with DES implantation and the potential benefit of prolonged dual-antiplatelet treatment, the safety profile of DES does not appear to be dramatically different from that of bare-metal stents.