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Interventional Cardiology

Two-Year Clinical Outcomes With Drug-Eluting Stents for Diabetic Patients With De Novo Coronary Lesions
Results From a Real-World Multicenter Registry

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Background—The long-term effectiveness of drug-eluting stents (DES) in unselected diabetics in routine practice is currently unclear.

Methods and Results—To evaluate the long-term effectiveness of bare metal stents and DES in a real-world setting of diabetic patients, we analyzed 2-year follow-up data from all diabetic patients with de novo lesions enrolled in a prospective Web-based multicenter registry (Registro Regionale Angioplastiche dell'Emilia-Romagna; study period, 2002 to 2004) comprising all 13 hospitals performing percutaneous coronary interventions in the Emilia-Romagna region of Italy. Among the 1648 eligible patients treated with either bare metal stents alone (n=1089) or DES alone (n=559), 27% were insulin dependent and 83% had multivessel coronary disease. At 2 years, use of DES was associated with lower crude incidence of major adverse cardiac advents (all-cause mortality, nonfatal myocardial infarction, and target vessel revascularization) compared with bare metal stents (22.5% versus 28.1%; *P*=0.01). After propensity score adjustment, only target vessel revascularization appeared significantly lower in the DES group (11.6% versus 15.0%; hazard ratio, 0.66; 95% confidence interval, 0.46 to 0.96; *P*=0.041). Two-year angiographic stent thrombosis occurred in 1.5% DES patients and 0.7% of the bare-metal-stents patients (*P*=0.18). At Cox regression analysis, predictors of 2-year major adverse cardiac advents were left ventricular ejection fraction <35%, Charlson comorbidity index, insulin-dependent diabetes, and total lesion length.

Conclusions—In this large, real-world, diabetic population, the use of DES was associated with a moderate reduction in the 2-year risk of target vessel revascularization, a benefit that was limited to non–insulin-dependent diabetic patients. Larger long-term studies are needed to clarify the long-term effectiveness and safety of such devices in diabetic patients. (***Circulation***. 2008;117:923-930.)

Key Words: diabetes mellitus ■ drugs ■ registries ■ restenosis ■ stents

Patients with diabetes mellitus account for >25% of all percutaneous coronary interventions (PCIs).[1,2] Diabetic patients are known to have poor long-term outcomes after PCIs or bare metal stent (BMS) implantation.[2,3] Randomized trials that recruited broad samples of patients both with and without diabetes mellitus showed that the use of drug-eluting stents (DES) for treatment of de novo coronary lesions can provide improved clinical/angiographic outcomes relative to BMS.[4,5] A randomized study comparing DES and BMS in diabetic patients[6] and a subgroup analysis focused on diabetic patients in randomized trials[7] have shown that the use of DES is associated with a reduced risk of restenosis and target lesion revascularization. However, a subgroup meta-analysis indicated that diabetes mellitus remains a significant risk factor for restenosis after both BMS and DES implantation.[8] To shed more light on the long-term relative benefits of using different types of stents for diabetic patients submitted to

PCI in a real-world setting, we investigated the 2-year clinical outcomes recorded in a large multicenter registry.

Methods

Setting and Eligibility Criteria

Launched in July 2002, Registro Regionale Angioplastiche dell'Emilia-Romagna (REAL) is a large, prospective, Web-based registry designed to collect clinical and angiographic data for all consecutive PCIs performed in the Emilia-Romagna region ($\approx$4 million inhabitants) of central-northern Italy.[9] All 13 public and private interventional cardiology centers in Emilia-Romagna participate in data collection. Because the REAL registry was designed to observe current clinical practice, the ethics committees of each participating hospital required only an ordinary written informed consent for coronary intervention (in line with national regulations) and anonymous publication of scientific data, which was obtained from all patients. In the present study (conceived in accordance with the principles of the most recent revision of the Declaration of Helsinki), we analyzed data from all enrolled diabetic patients resident in the Emilia-Romagna region who underwent PCI between July 2002 and December 2004 for treatment of de novo coronary lesions and were implanted solely with a single variety of stent, either BMS or just 1 of the 2 available types of DES (Cypher [Cordis, Johnson & Johnson, Miami Lake, Fla {SES}] or Taxus [Boston Scientific, Natick, Mass {PES}]). Diabetic patients with acute ST-elevation myocardial infarction treated with primary or rescue PCI were excluded from analysis, as were patients who received >1 variety of stent.

Procedural and Postintervention Practices

Interventional strategy and choice of device were decided by the attending physician. Administration of periprocedural platelet glycoprotein IIb/IIIa inhibitors and antithrombotic medications was based on the operator's discretion and current guidelines. Lifelong aspirin was prescribed to all patients. One month of ticlopidine (250 mg twice a day) or clopidogrel (75 mg/d) was recommended to all patients treated with BMS. Taking one or the other of these medications for at least 2 months was recommended (during the study period) for patients treated with SES and for at least 6 months for recipients of PES.

Web-Based Registry

The REAL registry has been described in detail elsewhere.[9] In brief, lesion length and vessel reference diameter are visually estimated by the operators (Online quantitative coronary analysis is allowed if required by the attending physician). Procedural success is defined as residual stenosis <30% by visual estimate in the presence of a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. During follow-up, acute myocardial infarction (AMI) is diagnosed by local cardiologists at the hospital of admission according to standard criteria (increased levels of troponin or creatine kinase-MB, accompanied by chest pain and/or ischemic ECG changes). Target vessel revascularization (TVR) is defined as any surgical/percutaneous reintervention performed to treat a luminal stenosis occurring in the same coronary vessel as the index procedure (within/beyond the target lesion limits). Stent thrombosis is angiographically documented as complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) of a previously successfully treated artery. Data on all repeat surgical/percutaneous interventions during follow-up also are prospectively recorded. Comorbidities are recorded using the Charlson index.[10] To verify the registry data correctness, periodic audits are performed by the Regional Health Care Administration.

Follow-Up Data Collection

Follow-up was closed on October 31, 2006. For the present study, follow-up data at 30 days and 12 and 24 months were obtained by the Emilia-Romagna Regional Health Agency, which has direct access to municipal registries and hospital discharge records. This warranted complete follow-up for all patients resident in the region; patients who lived outside the region were excluded from the study (see above). The prospectively collected data from the Web-based registry related to all repeat surgical/percutaneous interventions performed during follow-up were matched with the administrative data to identify any inconsistencies. Specific queries were sent to the individual institutions to justify or correct discrepancies between the data recorded on the Web-based registry (compiled by interventional cardiologists) and the administrative data (provided largely by independent cardiologists). When deemed necessary, hospital records were reviewed for additional information.

Main Outcome Measures

The predefined primary outcome measure of this study was cumulative occurrence at 24 months of major adverse cardiac events (MACE), in terms of all-cause mortality, nonfatal AMI, or TVR. Predefined secondary outcome measures (at 24 months) were all-cause mortality, death resulting from any cause or nonfatal AMI, and occurrence of TVR. In the overall study population, we compared recipients of DES and BMS. Clinical effectiveness comparisons (in terms of all-cause mortality/AMI, TVR, and MACE) between DES and BMS were performed for several clinical, angiographic, and procedural patient characteristics.

Statistical Analysis

Continuous variables were expressed as mean±SD and compared through the use of the Student unpaired t test. Categorical variables were expressed as percentages, and the χ^2 test was used for comparison. We calculated unadjusted cumulative frequencies of the various adverse events (and of angiographically proven stent thrombosis) at 30 days, 12 months, and 24 months. Cumulative incidences of different adverse events were estimated by the Kaplan–Meier method and compared by use of the log-rank test. Risk reduction of the primary and secondary outcome measures (at 24 months) was evaluated with Cox's proportional-hazards models. To adjust for potential confounders, a propensity score analysis was performed by use of a logistic regression model, testing the propensity to receive a DES rather than a BMS. We tested all available variables that we thought could be of potential relevance: age, sex, Charlson index, insulin-dependent diabetes mellitus, poor (<35%) left ventricular ejection fraction, prior AMI, prior PCI, prior coronary artery bypass graft, clinical presentation, reference vessel diameter, total treated lesions length, lesion type, vessel treated, multivessel PCI, chronic total occlusion treatment, ostial lesion treatment, bifurcation treatment, glycoprotein IIb/IIIa agent administration, year of treatment, and treatment center. Multivariate Cox regression analysis was then performed using only 2 variables as covariates: propensity score and type of treatment (DES versus BMS). Cox's proportional-hazards models adjusted with the propensity score also were used to assess relative risks of all-cause mortality/AMI, TVR, and MACE in subgroups of patients. Finally, to identify independent predictors of death or AMI and MACE at 2 years, a further multivariate Cox regression analysis was performed in which stent type (DES versus BMS) and all the 20 variables listed above were entered into the model. All statistical tests were 2 sided; values of $P<0.05$ were considered significant. All analyses were performed with the SAS 8.2 system (SAS Institute, Cary, NC).

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

Study Population

Eligibility is reported in Figure 1. The 1648 patients who fully satisfied the eligibility criteria represented 88.8% of the 1855 diabetic patients enrolled in the REAL registry who received stents to treat de novo lesions in the absence of
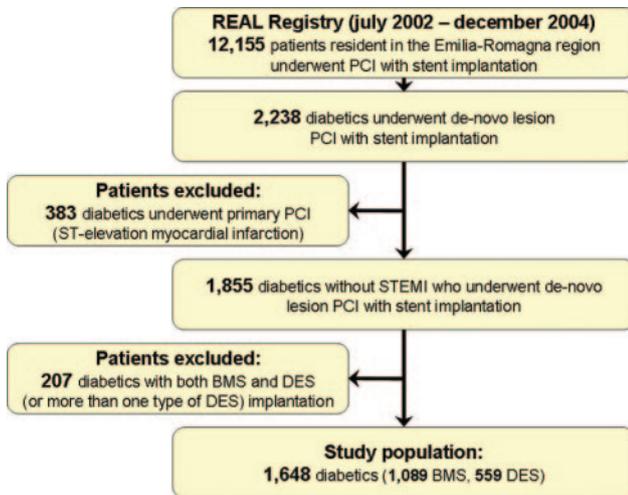
Figure 1. Study flowchart.

ST-elevation myocardial infarction during the study period. With regard to variety of stents, 1089 (66.1%) received only BMS, 396 (24%) received only SES, and 163 (9.9%) received only PES. Frequency of DES use in the 13 participating centers ranged from 16% to 48%. Overall, 27% (445 patients) were insulin dependent, 83% (1368) had multivessel coronary disease, 27% (445) had prior myocardial infarction, 11% (181) had poor left ventricular function, 31% (511) were admitted with a diagnosis of stable angina, and 27% (439) received platelet glycoprotein IIb/IIIa inhibitors. Tables 1 and 2 report baseline clinical, angiographic, and procedural characteristics according to type of stent (BMS versus DES) exclusively used. Compared with patients who received DES, those who received BMS had a somewhat more severe clinical profile; they were slightly older, had a higher Charlson comorbidity index, and more often exhibited subacute AMI, although they were less often insulin dependent. However, the overall angiographic picture of patients who received BMS was less severe. In both treatment groups, procedural success was achieved in >98% of the procedures performed.

Clinical Outcome

Complete 30-day and 12- and 24-month clinical outcome information was obtained for all patients. Median follow-up was 896 days (interquartile range, 646 to 1154 days). Table 3 reports unadjusted cumulative frequencies of different clinical events at 30 days and 12 and 24 months. Figure 2 shows comparisons of propensity score–adjusted 24-month cumulative incidence curves for the various adverse events. The logistic model by which the propensity score was calculated presented good predictive value (C statistic=0.829) and calibration characteristics (Hosmer-Lemeshow test, P=0.269). Comparisons between the DES and BMS groups showed that patients treated with DES had a nonsignificant lower risk of MACE (23.0% versus 28.8%; hazard ratio, 0.77; 95% confidence interval [CI], 0.59 to 1.01; P=0.09; Figure 2D) and a lower risk of TVR (11.6% versus 15.0%; hazard ratio, 0.66; 95% CI, 0.46 to 0.96; P=0.041; Figure 2C). No difference was apparent in terms of all-cause mortality (Figure 2A) or

Table 1.   Baseline Clinical Characteristics of Patients According to Treatment Group: BMS Versus DES

Characteristic	BMS (n=1089)	DES (n=559)	*P*
Age, y	69.3±9.6	66.3±9.9	0.001
Male, %	69.3	71.2	0.43
Insulin-dependent diabetes mellitus, %	25.4	30.9	0.02
Hypertension, %	67.9	66.1	0.46
Hypercholesterolemia, %	39.5	43.4	0.13
Smoking history, %	51.5	49.2	0.38
Charlson comorbidity index	1.7±1.7	1.5±1.6	0.02
Prior myocardial infarction, %	26.7	26.5	0.94
Prior coronary angioplasty, %	9.4	10.4	0.56
Prior coronary bypass surgery, %	11.6	11.2	0.86
Poor (<35%) LVEF, %	11.2	10.8	0.85
Multivessel coronary artery disease, %	83.1	83.4	0.89
Glycoprotein IIb/IIIa inhibitors use, %	25.4	29.1	0.17
Clinical presentation			
Stable angina pectoris,* %	29.8	33.5	0.13
Unstable angina pectoris or non–ST-elevation myocardial infarction, %	52.2	54.7	0.32
Subacute ST-elevation myocardial infarction,† %	18.0	11.8	0.001

Values are presented as percentages for categorical variables and as mean±SD for continuous variables.

*Includes silent ischemia. LVEF indicates left ventricular ejection fraction.

†More than 24 hours after onset of symptoms.

all-cause mortality/AMI (Figure 2B). Of note, as reported in Figure 3, 2-year angiographic stent thrombosis occurred in 1.5% of the DES patients and 0.7% of the BMS patients (P=0.18). Unlike in the BMS group in which no case of angiographic stent thrombosis occurred after the first 12 months of follow-up, in the DES group, episodes continued to be recorded after the first year (2 versus 0 episodes; Figure 3). Tables 4 and 5 report results of Cox proportional-hazards analysis for prediction of all-cause mortality/AMI and MACE at 2 years. Of note, DES implantation almost reached borderline significance for prediction of MACE (P=0.054) but was not even a marginally significant predictor of all-cause mortality/AMI (P=0.49).

Subgroup Analysis

Figure 4 reports results of subgroup analysis of associations between DES implantation and risk of all-cause mortality/ AMI, TVR, or MACE at 2 years. Significant reductions in risk of MACE (Figure 4C) were recorded for non–insulin-dependent diabetics (but not for insulin-dependent diabetics), diabetics with acute coronary syndrome, and interventions involving vessels with a reference diameter of 2.5 to 3.0 mm. Notably, in focal lesions (≤10 mm), DES implantation was associated with increased risk of MACE and all-cause mortality/AMI. Other associations that reached statistical signif-

Table 2.   Angiographic Lesion and Procedural Characteristics According to Treatment Group: BMS Versus DES

Variable	BMS (n=1655)*	DES (n=802)*	P
Treated vessel, %			
Left anterior descending artery	32.6	52.5	<0.0001
Left circumflex artery	28.7	22.8	0.001
Right coronary artery	34.3	20.2	<0.0001
Unprotected left main coronary artery	1.6	2.6	0.97
Bypass graft	2.8	1.9	0.17
Lesion type (ACC/AHA classification)			
B₂ to C, %	59.3	68.9	<0.001
Bifurcation, %	12.7	18.0	0.0006
Ostial lesion, %	5.4	11.5	<0.0001
Chronic total occlusion, %	6.4	7.0	0.64
Lesions treated per patient,† n	1.5±0.8	1.4±0.7	0.012
Multivessel interventions, † %	22.6	21.1	0.49
Reference diameter of treated vessel, mm	3.0±0.5	2.8±0.4	<0.0001
Lesion length,‡ mm	15.2±6.4	17.9±7.5	<0.0001
Overall length of lesions (in individual patients),† mm	23.2±13.3	25.9±13.9	<0.0001
Overall length of stents (in individual patients),† mm	25.5±14.1	28.2±15.1	<0.0001
Maximal stent length, mm	16.2±5.1	19.6±6.6	<0.0001
Stent diameter, mm	3.1±0.5	2.8±0.3	<0.0001
Stents implanted per patient,† n	1.6±1.2	1.4±0.8	<0.0001
Direct stenting, %	48.6	31.2	<0.0001
Patients with complete procedural success,† %	98.4	98.1	0.76

ACC/AHA indicates American College of Cardiology/American Heart Association. Values are presented as percentages for categorical variables and as mean±SD for continuous variables.

*Total number of lesions treated (reported values refer to lesions unless otherwise specified).

†Values referring to 1089 patients in the BMS group and 559 in the DES group.

‡Visual estimation.

Table 3.   Unadjusted Cumulative Frequencies of Clinical Events at 30 Days and 1 and 2 Years According to Treatment Group: BMS Versus DES

	BMS (n=1089)	DES (n=559)	P
At 30 d, %			
All-cause mortality	1.7	1.6	0.955
Nonfatal AMI	0.7	0.9	0.568
Death or AMI	2.3	2.1	0.855
TVR	1.5	2.0	0.452
MACE	3.4	3.2	0.855
Angiographically proven stent thrombosis	0.3	0.5	0.62
At 1 y, %			
All-cause mortality	8	7.2	0.550
Nonfatal AMI	7	6.6	0.799
Death or AMI	14	11.6	0.190
TVR	12.4	9.9	0.128
MACE	22.2	17.4	0.019
Angiographically proven stent thrombosis	0.7	1.1	0.482
At 2 y, %			
All-cause mortality	12.3	10.2	0.218
Nonfatal AMI	8.9	9.1	0.894
Death or AMI	19.3	16.3	0.144
TVR	14.4	12.8	0.314
MACE	28.1	22.5	0.014
Angiographically proven stent thrombosis	0.7	1.5	0.176

icance regarded reductions in risk of TVR among non–insulin-dependent diabetics, women, left anterior descending coronary artery, and single-vessel treatments.

Discussion

Whereas collaborative meta-analysis of randomized trials[5] and large registry studies[11,12] indicate that use of DES generally leads to lower rates of repeat revascularizations without relevant effects on mortality, little is known about the troublesome subset of diabetic patients. To the best of our knowledge, this is the largest available study from a real-world setting that addresses the issue of how use of DES affects the long-term outcome of diabetic patients. Relatively few data are available on the use of DES in diabetics, who remain a high-risk subpopulation.[13] Diabetic patients are known to be at high risk of restenosis after BMS implantation,[14] which, when occlusive, is associated with a worse prognosis.[15] At the same time, use of DES generally is associated with reduced rates of restenosis,[4,16] especially in the small vessels[17] typical of diabetics. Therefore, it is reasonable to suppose that the potential clinical impact in this difficult setting could be extremely relevant. However, in the present study, use of DES appeared to be associated with only a 23% reduction in the relative risk of MACE at 2 years, a difference largely attributable to lower risk of TVR.

The diabetic patients in this high-risk study population often had multivessel disease and acute coronary syndromes. In both the DES and BMS groups, more than one fifth of the patients experienced MACE during the first 2 years of follow-up, further confirming the detrimental effect of diabetes on clinical outcome after PCI, regardless of the type of stent implanted.[1] Use of DES was associated with a 34% reduction in TVR at 2 years but no apparent benefit in terms of risk of death or AMI. Although the crude incidence of MACE was lower in the DES group, after use of propensity score analysis to adjust for confounders, this difference did not remain significant. The entity of this nonsignificant reduction (23%) in relative risk of MACE at 2 years was itself unexpectedly low in view of the 40% to 60% reductions
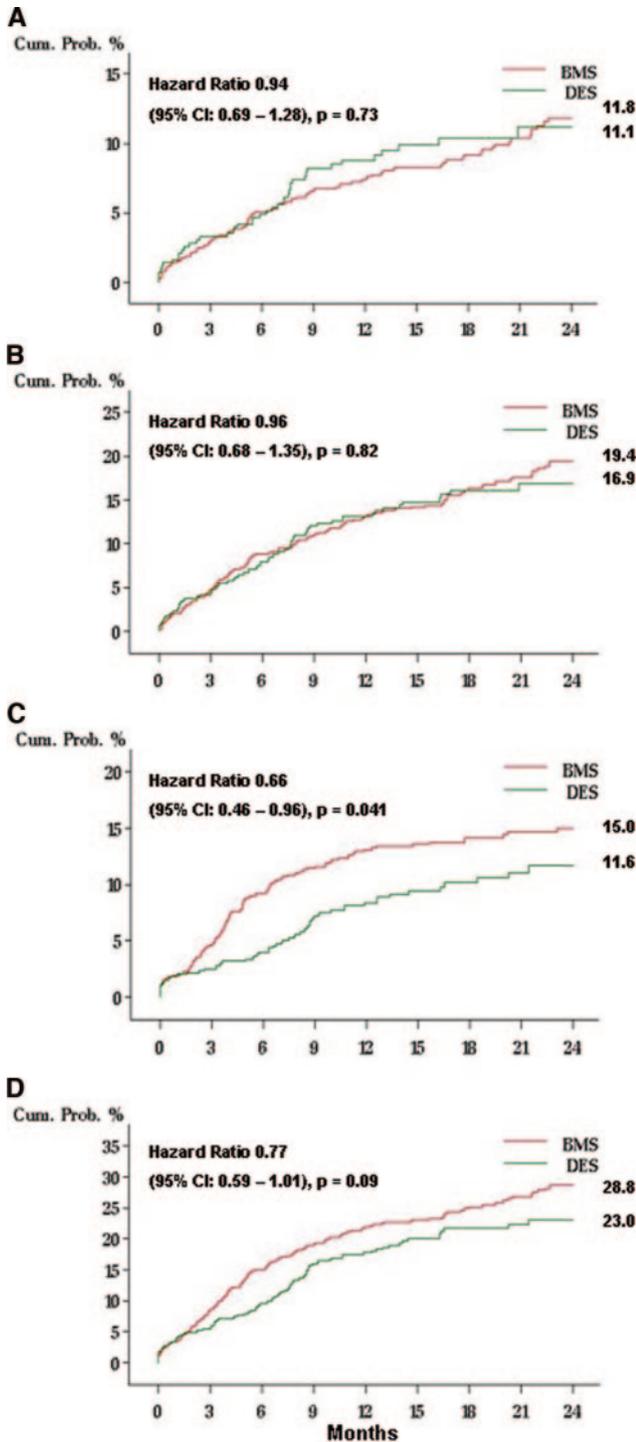
Figure 2. Two-year propensity score adjusted cumulative incidence in patients implanted with DES or BMS of all-cause mortality (A), all-cause mortality or nonfatal myocardial infarction (B), TVR (C), and any of these major adverse events (D). Cum. Prob. indicates cumulative probability.

recorded in the first year in meta-analyses of randomized trials not restricted to diabetic patients.[4,16] Clinical trials may have led to overestimates of the benefits (in terms of TVR and MACE) that DES can offer in routine clinical practice for several reasons: (1) protocol-driven angiography that enhances restenosis and revascularization rates compared with real-world (symptoms-driven) monitoring; (2) frequent use in
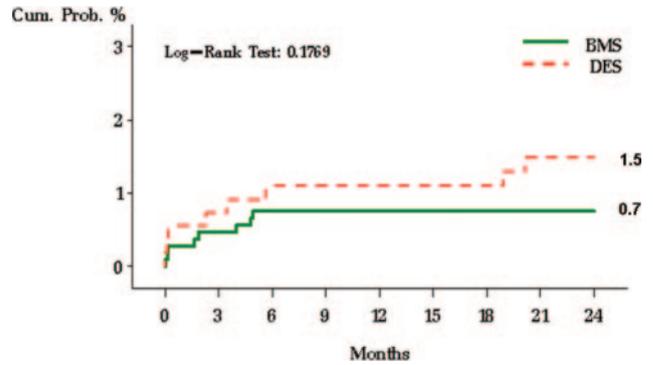
Figure 3. Kaplan–Meier curves representing the estimated 2-year incidence of angiographically proven stent thrombosis in patients implanted with DES or BMS.

control groups of thick-strut BMS[18]; and (3) less clinical benefit of DES in the high-risk patients (eg, diabetics) and complex lesions ("off-Label" use) that often are excluded from randomized trials but are common in clinical practice.[19] At the same time, it also is reasonable to suppose that the present observational study based on clinically driven monitoring may have underestimated the benefits of DES implantation (especially in view of the increased likelihood of clinically silent restenosis in diabetic patients).

Subgroup analyses of randomized trials[8,20] and registry studies[21,22] have generated suggestive evidence that the benefits of DES in diabetic patients may be somewhat limited. In the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry,[21] Diabetic patients constituted one of the few subgroups in which evidence of benefit did not reach statistical significance (and diabetes mellitus remained an independent predictor of adverse events and clinically driven TVR). In another observational subanalysis of diabetic patients (n=708) (RESEARCH and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries [T-SEARCH] registries),[22] neither SES nor PES appeared superior to BMS in reducing TVR and MACE at 2 years. Furthermore, in a meta-analysis of 4 trials specifically addressing the effects on restenosis of implanting BMS or DES in diabetic and nondiabetic patients, diabetes mellitus remained an independent risk factor for restenosis,[8] again suggesting that the use of DES does not completely bridge the gap between diabetic and nondiabetic patients. Finally, in a

Table 4. Multivariate Predictors of All-Cause Death/AMI at 2 Years (Cox Proportional-Hazards Model Analysis)

Variables	HR	95% CI	P
DES implantation (vs BMS)	0.89	0.66–1.22	0.49
Age (each incremental year)	1.03	1.01–1.04	0.001
LVEF <35%	1.82	1.29–2.56	0.0006
Charlson comorbidity index (each incremental unit)	1.42	1.32–1.52	<0.0001
Insulin-dependent diabetes mellitus	1.47	1.13–1.90	0.003
Overall length of lesions (each incremental millimeter)	1.02	1.01–1.04	0.04

HR indicates hazard ratio; LVEF, left ventricular ejection fraction. Only types of stent and variables reaching $P<0.05$ are listed.

Table 5. Multivariate Predictors of MACE at 2 years (Cox Proportional-Hazards Model Analysis)

| Variables	HR	95% CI	P
DES implantation (vs BMS)	0.78	0.60–1.004	0.054
LVEF <35%	1.44	1.05–1.96	0.02
Charlson Comorbidity Index (each incremental unit)	1.29	1.21–1.38	<0.0001
Insulin-dependent diabetes mellitus	1.32	1.05–1.64	0.02
Overall length of lesions (each incremental millimeter)	1.02	1.01–1.03	0.03

HR indicates hazard ratio; LVEF, left ventricular ejection fraction. Only types of stent and variables reaching $P<0.05$ are listed.

recently reported pooled analysis of 4 randomized trials evaluating the safety of SES compared with BMS, a lower survival rate was found among diabetic patients treated with SES.[20] Thus, the findings of the present study may not be considered altogether surprising.

We found that patients treated with DES persistently had lower incidence of TVR compared with those who received BMS. The adjusted TVR curves remained roughly parallel between 1 and 2 years, confirming lasting benefits of DES and excluding a brachytherapy-like catchup phenomenon.[23] Nevertheless, the extent of the 2-year reduction in need for TVR (34%) may appear rather low, especially in light of the 66% decrease in need for target lesion revascularization reported in a meta-analysis of data on diabetic patients enrolled in randomized trials.[7] Here again, however, regular angiographic monitoring could have greatly accentuated the recorded benefits.

In some high-risk subgroups of our study population (women, patients with acute coronary syndrome, those with left anterior descending artery, and patients with small-vessel disease), use of DES was associated with statistically significant reductions in MACE and/or TVR, broadly in line with similar findings from studies not specifically devoted to those with diabetes.[11,17,21,24] Subgroup analysis of non–insulin-dependent diabetics also suggested substantial improvements in the 2-year relative risk of MACE and TVR, whereas no benefit could be appreciated among insulin-dependent diabetics (for whom very high rates of in-lesion restenosis have been reported[13,25]). Furthermore, in agreement with previous reports of diabetic patients treated by elective BMS implantation,[2] in our overall study population, insulin-dependent diabetes emerged as an independent predictor of unfavorable long-term outcome. Of note, DES was associated with poor clinical outcome in only the focal lesion subgroup. Apart from the play of chance (within a restricted number of observations: 123 events in 378 patients), a plausible explanation for this unexpected subgroup finding could be an unfavorable risk-to-benefit ratio when treating lesions with a low a priori likelihood of restenosis.

Diabetes mellitus has been shown to be an independent predictor of stent thrombosis in patients treated with DES.[26,27] Our crude thrombosis rates were somewhat low in both groups, especially considering the high-risk study population. (Higher rates of angiographically proven stent thrombosis have been reported with both SES and PES.[22]) Remarkably,
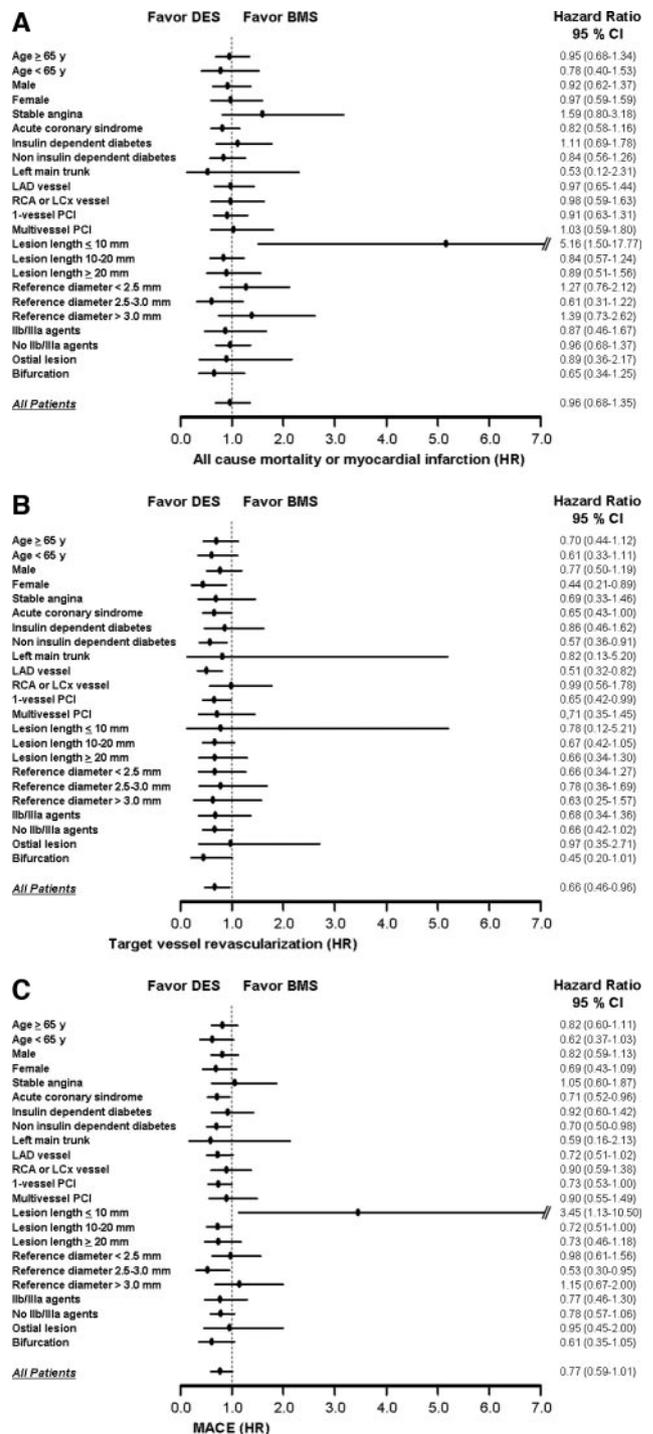
Figure 4. Propensity score–adjusted hazard ratios for 2-year incidence of all-cause mortality/AMI (A), TVR (B), or MACE (C) associated with DES use in various subgroups of patients according to clinical, angiographic, and procedural characteristics. LAD indicates left anterior descending coronary artery; RCA, right coronary artery; and LCx, left circumflex artery.

the nonsignificant difference in stent thrombosis rate between the 2 groups (DES versus BMS, 1.5% versus 0.7%) was attributable mainly to late and very late thrombosis episodes, a risk that has emerged in previous studies.[27–29] Autopsy findings[30] have raised concerns about the long-term safety of DES. Furthermore, clinical studies[19,31,32] indicate rising risks of death or death/AMI after the first 6 months of DES

implantation, plausibly linked to the discontinuation of thienopyridine therapy. Although no details on the long-term use of clopidogrel (or ticlopidine) are available in our registry, in patients implanted with DES, dual antiplatelet therapy was prescribed for only a few months (and was discontinued at 6 months in the vast majority). Of note, the higher absolute number of stent thrombosis episodes in the DES group was not matched by any difference in death or AMI at 2 years. This apparent paradox may be explained by a small increase of a quite uncommon but highly clinically relevant event like stent thrombosis (plausibly driven by DES use) being counterbalanced by a larger reduction of a more frequent but less relevant adverse event like in-stent restenosis, which, however, can sometimes be a cause of subsequent AMI.[33,34]

Study Strengths and Limitations

Although not immune from hidden confounding and other sources of bias typical of observational studies, this large subanalysis of a multicenter registry helps complete the picture gained from randomized trials (where highly selected patients are treated in a nonroutine setting). Selection bias should not be a major internal study limitation because the REAL registry enrolls all patients receiving PCI in the Emilia-Romagna region, because the present analysis regarded 89% of the patient population of interest (diabetic patients treated with stents for de novo lesions not associated with AMI), and because it was possible to obtain complete clinical outcome information in all cases. With respect to the possible role of unknown confounders, it is noteworthy that the DES and BMS groups appeared to be fairly balanced at baseline in terms of overall risk of major events after PCI; patients treated with BMS had a slightly worse clinical picture, whereas those treated with DES had slightly worse angiographic characteristics. This factor (in conjunction with the use of propensity score analysis to adjust for known confounders) supports the credibility of the primary analysis. Nevertheless, considering that no type of statistical adjustment (including inability to fully adjust for known and unknown confounders) can completely overcome the pitfalls of nonrandomized comparisons, our results should be interpreted with caution. Finally, in our study, stent thrombosis related only to angiographically documented stent thrombosis, and this may have led to an underestimation of the true incidence of stent thrombosis.

Conclusions

In this large, real-world, diabetic population, use of DES was associated with a modest reduction in the 2-year risk of TVR, a benefit that was limited to non–insulin-dependent diabetic patients. Larger, long-term studies are needed to clarify the long-term effectiveness and safety of DES in diabetic patients.

Acknowledgment

Source of Funding

Disclosures

None.

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CLINICAL PERSPECTIVE

In most centers, treatment with drug-eluting stents (DES) provides the current standard of care for diabetic patients undergoing percutaneous coronary interventions. The rationale for this choice is derived more from knowledge that diabetic patients are at high risk of restenosis after bare metal stent implantation than robust clinical evidence; indeed, diabetes mellitus is currently an "off-label" indication for DES. This article reports the 2-year results of a prospective multicenter registry subanalysis of 1648 diabetic patients treated by bare metal stent (n=1089) or DES (n=559) implantation. Selection of patients for treatment with DES was left to the physician's discretion. After adjustment for known confounders, use of DES was associated with a moderate reduction (11.6% versus 15%; *P*=0.04) in the need for new revascularizations (no benefit was detected in insulin-dependent diabetics). No difference was detected in adjusted 2-year rates of mortality, mortality or reinfarction, or major adverse events. Although no statistically significant difference could be observed in 2-year rates of angiographic stent thrombosis (1.5% for DES versus 0.7% for bare metal stents; *P*=0.17), it is noteworthy that very late stent thrombosis episodes occurred only in the DES group. In this large real-world diabetic population, use of DES was associated with a modest reduction in the 2-year risk of target vessel revascularization, a benefit that was limited to non–insulin-dependent diabetic patients. Larger long-term studies are needed to clarify the long-term effectiveness and safety of DES in diabetic patients.