JACC: CARDIOVASCULAR INTERVENTIONS VOL. 1, NO. 4, 2008

ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2008.06.005

Outcomes and Complications With Off-Label Use of Drug-Eluting Stents

Results From the STENT (Strategic Transcatheter Evaluation of New Therapies) Group

Bruce R. Brodie, MD,* Thomas Stuckey, MD,* William Downey, MD,* Angela Humphrey, MS,† Barbara Bradshaw, RN,* Chris Metzger, MD,‡ James Hermiller, MD,§ Fred Krainin, MD,‖ Stanley Juk, MD,¶ Barry Cheek, MD,# Peter Duffy, MD,** Henry Smith, MD,†† John Edmunds, MD,†† Jay Varanasi, MD,†† Charles A. Simonton, MD,‡‡ for the STENT (Strategic Transcatheter Evaluation of New Therapies) Group

Greensboro, Charlotte, High Point, and Pinehurst, North Carolina; Kingsport, Tennessee; Indianapolis, Indiana; and Florence and Columbia, South Carolina

Objectives This study evaluates outcomes and complications in patients treated with drug-eluting stents (DES) for "off-label" indications.

Background Drug-eluting stents have been effective in randomized trials, but their safety and efficacy for off-label indications has not been well studied.

Methods The STENT (Strategic Transcatheter Evaluation of New Therapies) Registry is the largest multicenter U.S. registry evaluating outcomes of DES. Off-label indications included ostial, left main, long, bifurcation, and in-stent restenotic lesions, saphenous vein grafts, chronic total occlusions, small or large vessels, multilesion or multivessel percutaneous coronary interventions, and ST-segment elevation myocardial infarction. Outcomes were adjusted using Cox proportional hazards regression and propensity analyses.

Results Drug-eluting stents were used in an off-label manner in 59% of patients. The patients who received off-label treatment were more often male, had a higher incidence of prior infarction and bypass surgery, and lower ejection fractions. Off-label versus "on-label" use of DES was associated with higher rates of death, myocardial infarction, target vessel revascularization, major adverse cardiac events, and stent thrombosis at 9 months and 2 years. Off-label use of DES compared with off-label use of bare-metal stents (BMS) had lower rates of death, myocardial infarction, target vessel revascularization, and major adverse cardiac events at 9 months and 2 years and lower rates of stent thrombosis at 9 months.

Conclusions Off-label use of DES is associated with higher event rates compared with on-label use of DES, which is consistent with a higher risk clinical and lesion profile. However, event rates with off-label use of DES are lower compared with off-label use of BMS. Pending results from randomized trials, our data support the use of DES for off-label indications in selected patients. (J Am Coll Cardiol Intv 2008;1:405–14) © 2008 by the American College of Cardiology Foundation

From the *LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; †R. Stuart Dickson Institute for Health Studies, Charlotte, North Carolina; ‡Holston Valley Medical Center, Kingsport, Tennessee; §Indiana Heart Institute, Indianapolis, Indiana; ‖McLeod Regional Medical Center, Florence, South Carolina; ¶Sisters of Charity Providence Hospitals, Columbia, South Carolina; #High Point Regional Health System, High Point, North Carolina; **Moore Regional Medical Center, Pinehurst, North Carolina; ††Eagle Cardiology, Greensboro, North Carolina; and the ‡‡Carolinas Medical Center, Charlotte, North Carolina. Supported by unrestricted research grants from Cordis Corporation, Boston Scientific Corporation, Possis Medical, and The Medicines Company. Dr. Downey was a consultant for Cordis Corporation, and Dr. Hermiller is a consultant for Boston Scientific Corporation. Dr. Simonton has become Medical Director for Abbott Vascular since these data were collected.

Manuscript received February 12, 2008; revised manuscript received May 22, 2008, accepted June 12, 2008.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 4, 2008
AUGUST 2008:405–14

Drug-eluting stents (DES) have been shown to be very effective in reducing target vessel revascularization (TVR) in multiple randomized trials (1,2). Drug-eluting stents have been used with increasing frequency for "off-label" indications, but there are limited data regarding the safety and efficacy of off-label use (3–5). Furthermore, there is growing concern regarding potential increased risk of late stent thrombosis, especially with off-label use (6).

The STENT (Strategic Transcatheter Evaluation of New Therapies) Group is the first and largest multicenter prospective registry to evaluate late outcomes with DES in the U.S. The purpose of this study is to evaluate outcomes with off-label use of DES from the STENT Registry and to compare outcomes of off-label use with on-label use of DES and with off-label use of bare-metal stents (BMS).

Abbreviations and Acronyms

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

Methods

The STENT Group. The STENT Group created a multicenter registry to evaluate coronary artery stent use and outcomes in real-world clinical settings beginning in May 2003. Patients undergoing percutaneous coronary intervention (PCI) at 8 coronary interventional centers consented to participate in this study, which included 9-month and 2-year follow-ups. This is the largest prospective registry for evaluating DES in the U.S. and is supported by unrestricted grants from the industry. Detailed methodology of this registry has been previously reported (7).

Definitions. Off-label use was defined as DES use in lesion or patient subsets that have not been extensively studied in randomized trials and for which DES does not have Food and Drug Administration approval (8,9). This group included patients with ST-segment elevation myocardial infarction (STEMI), chronic total occlusions, saphenous vein graft lesions, bifurcation lesions, ostial lesions, left main lesions, in-stent restenotic lesions, small or large vessels (<2.5 mm or >3.75 mm), long lesions (>28 mm), and multilesion or multivessel PCI. On-label use included all other patients.

For outcomes at 9 months and 2 years, reinfarction was defined as a new elevation of the myocardial band fraction of creatine kinase >2 times the normal amount and includes both STEMI and non-STEMI. Target vessel revascularization was defined as a repeat procedure anywhere in the target vessel, including repeat PCI or coronary artery bypass graft surgery. The TVR procedure was used instead of target lesion revascularization (TLR), because determinations were assessed by the operators without a core angiographic laboratory to distinguish TLR from TVR occurring at sites other than the target lesion. Stent thrombosis was defined using a modified Academic Research Consortium definition of definite or probable stent thrombosis: angiographically documented stent thrombosis, a myocardial infarction in the distribution of the target vessel, or sudden cardiac death.

Study population. Our study population with 9-month follow-up is shown in Figure 1. Of 26,941 PCI procedures performed at 8 centers from May 2003 to June 2006, 24,713 patients consented to participate in the Registry (92%), 20,868 patients were unique (first procedure for a patient in the Registry), and 19,453 had 9-month follow-up (93%). Of these patients, 8,897 had DES-only stents implanted for off-label indications, and these patients form our study group. Outcomes in these patients were compared with 6,063 patients with on-label use of DES and with 2,131 patients with off-label use of BMS who had 9-month follow-up.

Our study population with 2-year follow-up is shown in Figure 2. This study population is a subgroup of the study population with 9-month follow-up. Of 11,705 PCI procedures performed from May 2003 through February 2005, 10,326 patients consented (88%), 8,942 patients were unique, and 8,532 patients had 2-year follow-up (95%). Of these patients, 3,603 had DES-only stents implanted for off-label indications, and these patients form our study

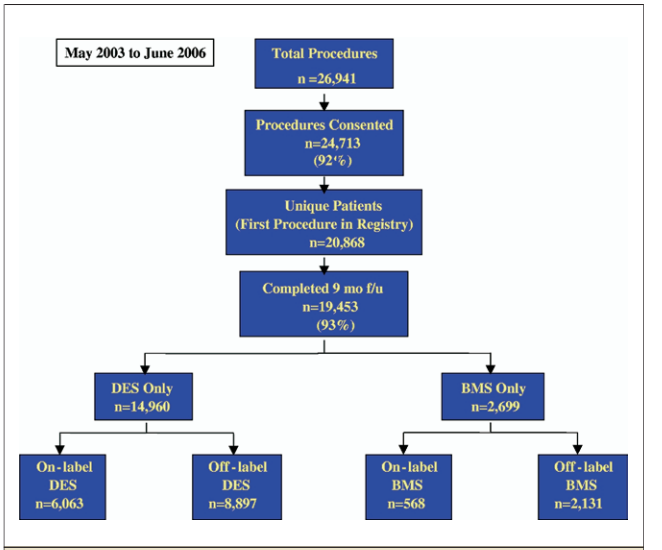

Figure 1. Study Population (9-Month Follow-Up)

Our study population (9-month follow-up) consists of all patients who had DES-only stents used for off-label indications and who had 9-month clinical follow-up. BMS = bare-metal stent(s); DES = drug-eluting stent(s); f/u = follow-up.

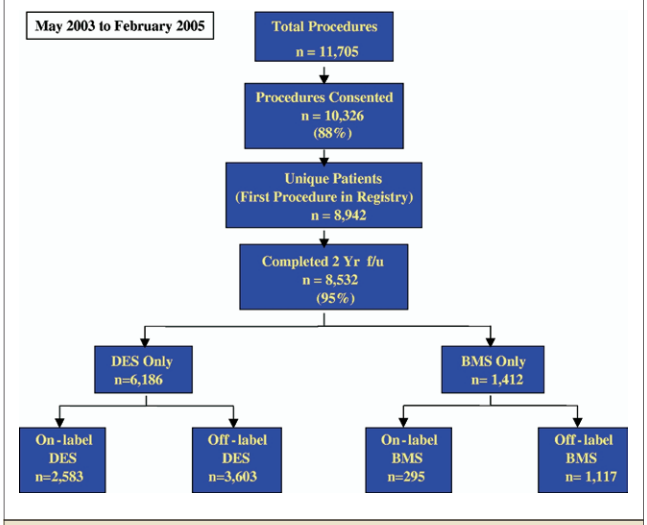

Figure 2. Study Population (2-Year Follow-Up)

Our study population (2-year follow-up) consists of all patients who had DES-only stents used for off-label indications and who had 2 year clinical follow-up. Abbreviations as in Figure 1.

group with 2-year follow-up. Outcomes in these patients were compared with 2,583 patients with on-label use of DES and with 1,117 patients with off-label use of BMS who had 2-year follow-up.

In patients with off-label use of DES and 9-month follow-up, sirolimus-eluting stents were used in 49% of patients, paclitaxel-eluting stents were used in 48% of patients, and both types were used in 3% of patients. In patients with on-label use of DES and 9-month follow-up, sirolimus-eluting stents were used in 49% of patients and paclitaxel-eluting stents were used in 51% of patients.

Data collection. All data were collected prospectively by study coordinators at participating hospitals. Procedural data, including adjunctive pharmacology, device utilization, reference vessel diameter, lesion length, and lesion characteristics (including off-label versus on-label indications) were assessed by the operating interventional cardiologist and were recorded at the conclusion of each procedure. Comprehensive chart reviews were performed for the index hospitalization for each patient shortly after discharge. Post-discharge clinical follow-up was conducted by telephone interview at 9 and 24 months after the procedure. Complete hospital records were reviewed for every patient reporting a cardiac event following the index hospitalization. All data were entered into a centralized database for quality control and statistical analysis (R. Stuart Dickson Institute for Health Studies, Charlotte, North Carolina). Physicians adjudicated all major events including death, TVR, and stent thrombosis, and audits were performed on 10% of the first 4,000 procedures and 5% thereafter.

Statistical methods. Baseline and outcome variables were compared using *t* tests for continuous variables and the chi-square test or Fisher exact test for categorical variables. A p value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina).

Kaplan-Meier event curves were constructed for TVR, death or myocardial infarction, and stent thrombosis for each subgroup, and comparisons between subgroups were made with log-rank tests.

When adjusting for differences in baseline risk profile between off-label DES use versus on-label DES use, Cox proportional hazards regression models were used. Variables included in the model were site, age, gender, diabetes, hypertension, hyperlipidemia, smoking status, prior infarction, prior bypass surgery, and prior PCI. Clinical acuity (STEMI, non–ST-segment elevation acute coronary syndrome, or stable angina) and angiographic variables were not included, because these were used to define off-label use. When adjusting for differences in baseline risk between off-label DES use and off-label BMS use, propensity analysis was used. Propensity scores were calculated with a

Table 1. Baseline Characteristics

	On-Label DES (n = 6,063)	Off-Label DES (n = 8,897)	Off-Label BMS (n = 2,131)	p Value 1	p Value 2
Age, yrs (mean ± SD)	62.9 ± 11.5	63.1 ± 11.8	65.4 ± 12.3	0.24	<0.0001
Female	2,194 (36.2)	2,905 (32.7)	635 (29.8)	<0.0001	0.01
Diabetes	1,937 (32.0)	2,966 (33.3)	631 (29.6)	0.08	0.0001
Hypertension	4,542 (74.9)	6,622 (74.4)	1,529 (71.8)	0.52	0.01
Hyperlipidemia	3,763 (62.1)	5,350 (60.1)	1,036 (48.6)	0.02	<0.0001
Ever smoker	3,667 (60.5)	5,386 (60.5)	1,318 (61.9)	0.95	0.27
Prior infarction	1,277 (21.1)	2,105 (23.7)	527 (24.7)	0.0002	0.3
Prior bypass surgery	662 (10.9)	1,724 (19.4)	559 (26.2)	<0.0001	<0.0001
Prior PCI	1,491 (24.6)	2,453 (27.6)	572 (26.8)	<0.0001	0.52
STEMI	0 (0.0)	1,450 (16.3)	631 (29.6)	—	<0.0001

Values are n (%) unless otherwise noted. p Value 1: off-label DES versus on-label DES use. p Value 2: off-label DES versus off-label BMS use.
BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Angiographic and Procedural Characteristics

	On-Label DES (n = 6,063)	Off-Label DES (n = 8,897)	Off-Label BMS (n = 2,131)	p Value 1	p Value 2
Target lesion (n)	6,063	14,867	3,002		
Left main	0 (0.0)	223 (1.5)	28 (0.9)	<0.0001	<0.0001
Left anterior descending	2,421 (39.9)	5,337 (35.9)	676 (22.5)		
Circumflex	1630 (26.9)	3256 (21.9)	575 (19.2)		
Right coronary artery	2,012 (33.2)	5,047 (33.9)	1,267 (42.2)		
Saphenous vein graft	0 (0.0)	995 (6.7)	453 (15.1)		
Ejection fraction % (mean ± SD)	52.5 ± 11.3	50.3 ± 12.2	47.7 ± 13.2	<0.0001	<0.0001
Reference vessel diameter, mm (mean ± SD)	3.0 ± 0.4	3.0 ± 0.5	3.3 ± 0.8	0.3	<0.0001
Lesion length, mm (mean ± SD)	14.4 ± 5.8	17.0 ± 11.2	15.6 ± 9.6	<0.0001	<0.0001
Stent length, mm (mean ± SD)	20.1 ± 7.6	23.9 ± 13.2	21.0 ± 11.3	<0.0001	<0.0001
Number of stents/procedure	1.07 ± 0.29	1.74 ± 0.85	1.47 ± 0.74	<0.0001	<0.0001
Adjunctive pharmacology					
Glycoprotein IIb/IIIa platelet inhibitor	3,224 (53.2)	4,935 (55.5)	1,256 (58.9)	0.006	0.004
Bivalirudin	2,017 (33.3)	2,797 (31.4)	345 (16.2)	0.02	<0.0001
Enoxaparin	444 (7.3)	700 (7.9)	226 (10.6)	0.22	<0.0001
Multivessel PCI	0 (0.0)	1,801 (20.2)	207 (9.7)	—	<0.0001
Multilesion PCI	0 (0.0)	4,728 (53.1)	689 (32.3)	—	<0.0001
Angiographic success	6,020 (99.3)	14,464 (97.3)	2,924 (97.4)	<0.0001	0.8

Values are n (%) unless otherwise noted. Target lesion is expressed as the number of target lesions treated as a percentage of the total number of lesions treated in each subgroup. Angiographic success is expressed at the number of lesions treated successfully (final stenosis ≤ 50% and TIMI flow grade ≥ 2) as a percentage of total lesions treated in each subgroup. p Value 1: off-label DES versus on-label DES use. p Value 2: off-label DES versus off-label BMS use.

Abbreviations as in Table 1.

logistical regression model that included all demographic, clinical, and angiographic variables, including variables used to define off-label use. The ability of the propensity score to effectively balance off-label DES use and off-label BMS use at baseline is shown in the Online Appendix Table. The predictive ability of the propensity score was assessed by the C-statistic. Propensity scores were entered into the Cox proportional hazards regression model as a covariate along

Table 3. Outcomes

				Unadjusted		Adjusted	
	On-Label DES	Off-Label DES	Off-Label BMS	p Value 1	p Value 2	Hazard Ratio 1 (95% CI)	Hazard Ratio 2 (95% CI)
Outcomes at 9 months	(n = 6,063)	(n = 8,897)	(n = 2,131)				
Death	118 (2.0)	304 (3.4)	146 (6.9)	<0.0001	<0.0001	1.75 (1.41–2.16)	0.55 (0.43–0.70)
Myocardial infarction	124 (2.1)	270 (3.0)	106 (5.0)	<0.0001	<0.0001	1.45 (1.17–1.80)	0.50 (0.38–0.65)
Death/myocardial infarction	228 (3.8)	538 (6.1)	233 (10.9)	<0.0001	<0.0001	1.60 (1.37–1.67)	0.53 (0.44–0.64)
TVR	189(3.1)	498 (5.6)	162 (7.6)	<0.0001	0.0006	1.79 (1.51–2.12)	0.48 (0.39–0.60)
MACE	391(6.5)	929 (10.4)	351 (16.5)	<0.0001	<0.0001	1.62 (1.43–1.82)	0.51 (0.44–0.59)
Stent thrombosis	37 (0.6)	88 (1.0)	33 (1.6)	0.01	0.04	1.62 (1.10–2.39)	0.51 (0.31–0.82)
Outcomes at 2 years	(n = 2,583)	(n = 3,603)	(n = 1,117)				
Death	130 (5.0)	243 (6.7)	148 (13.3)	0.006	<0.0001	1.29 (1.04–1.60)	0.54 (0.42–0.70)
Myocardial infarction	87 (3.4)	177 (4.9)	81 (7.3)	0.003	0.004	1.37 (1.05–1.77)	0.62 (0.45–0.86)
Death/myocardial infarction	202 (7.8)	392 (10.9)	208 (18.6)	<0.0001	<0.0001	1.34 (1.13–1.60)	0.57 (0.46–0.70)
TVR	163 (6.3)	415 (11.5)	140 (12.5)	<0.0001	0.37	1.87 (1.55–2.24)	0.61 (0.48–0.77)
MACE	333 (12.9)	717 (19.9)	308 (27.6)	<0.0001	<0.0001	1.55 (1.36–1.77)	0.57 (0.49–0.68)
Stent thrombosis	23 (0.9)	54 (1.5)	22 (2.0)	0.04	0.28	1.59 (0.97–2.61)	0.65 (0.36–1.18)

Values are n (%) unless otherwise noted. p Value 1 and Hazard Ratio 1 compare off-label DES with on-label DES use. Hazard ratios are assessed directly with Cox proportional hazards regression models. p Value 2 and Hazard Ratio 2 compare off-label DES with off-label BMS use. Hazard ratios are assessed with propensity scores entered into Cox proportional hazards regression models.

MACE = major adverse cardiac events include death, myocardial infarction, or target revascularization; TVR = target lesion revascularization; other abbreviations as in Table 1.

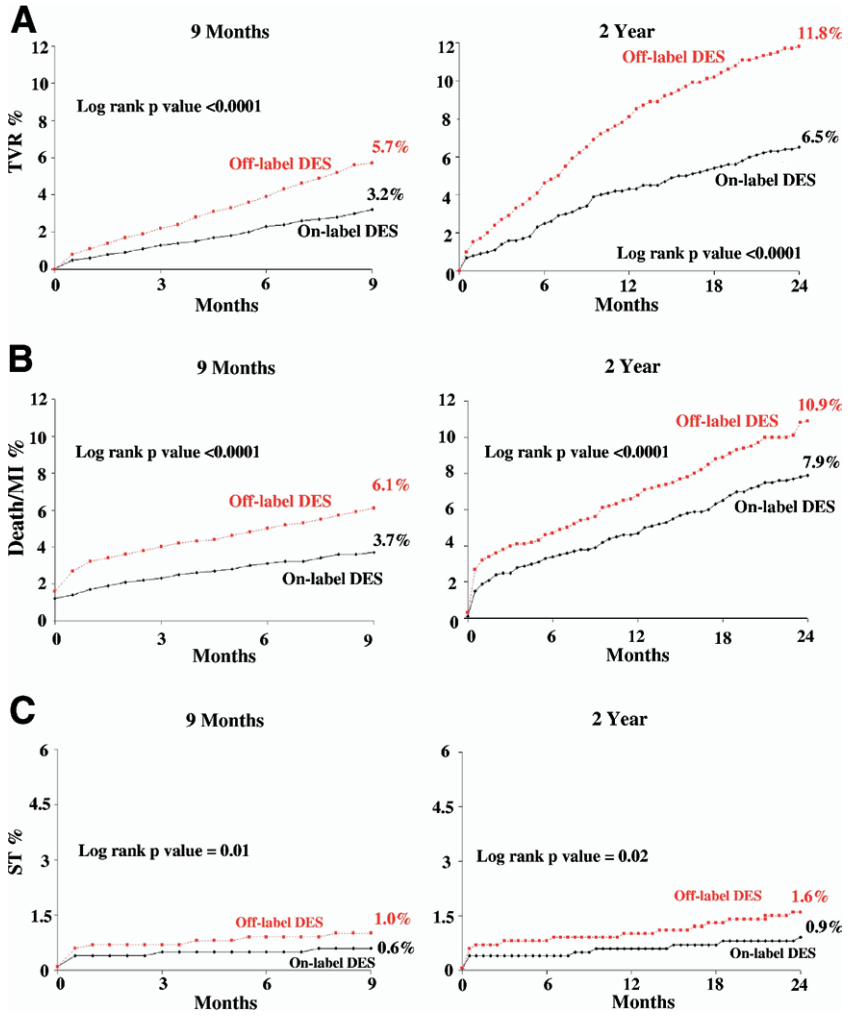

Figure 3. Comparison of Event Rates Between Off-Label and On-Label Use of DES

Kaplan-Meier estimates comparing event rates at 9 months and 2 years between off-label and on-label use of DES: **(A)** target vessel revascularization (TVR), **(B)** death or myocardial infarction (Death/MI), and **(C)** stent thrombosis (ST). Abbreviations as in Figure 1.

with variables that were not balanced in the propensity models.

Results

Baseline clinical variables and angiographic and procedural characteristics. Patients with off-label compared with on-label use of DES had a higher incidence of prior infarction, prior bypass surgery, and prior PCI, but were less often female (Table 1). Patients with off-label use of DES also had lower ejection fraction, longer lesions, longer stent length, more stents/procedure, more glycoprotein IIb/IIIa platelet inhibitor use, and lower angiographic success rates (Table 2).

Patients with off-label use of DES compared with off-label use of BMS were younger, more often female, and had higher rates of diabetes, hypertension, and hyperlipidemia, but a lower incidence of prior bypass surgery and STEMI (Table 1). Patients with off-label DES use have a higher frequency of left anterior descending artery PCI, lower frequency of saphenous vein graft PCI, higher ejection fraction, longer lesion length, longer stent length, more stents/procedure, less glycoprotein IIb/IIIa platelet inhibitor use, and more multivessel and multilesion PCI (Table 2).

Outcomes of off-label DES use versus on-label DES use. Off-label use of DES compared with on-label use of DES had higher rates of death, myocardial infarction, TVR, major adverse cardiac events (MACE: such as death, myocardial infarction, or TVR) and stent thrombosis at the 9-month and 2-year follow-ups (Table 3, Fig. 3). After adjustments with Cox proportional hazards regression models, all event

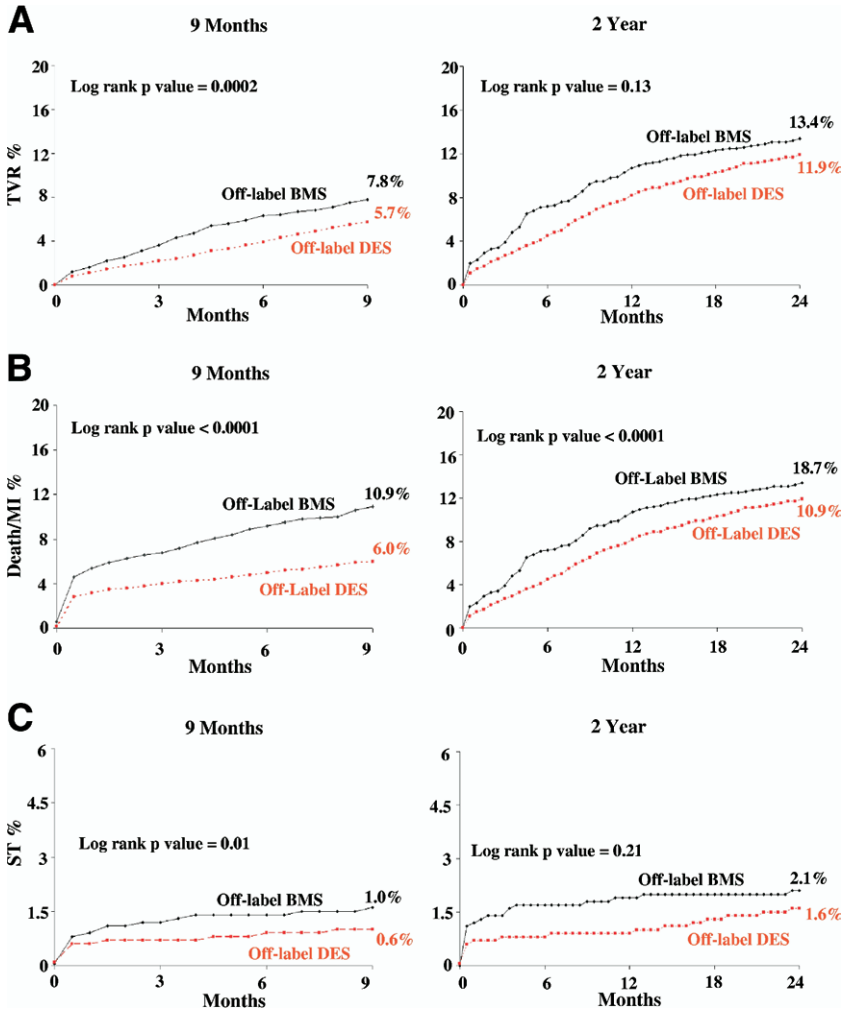

Figure 4. Comparison of Event Rates Between Off-Label Use of DES and BMS

Kaplan-Meier estimates comparing event rates at 9 months and 2 years between off-label use of DES and off-label use of BMS: **(A)** TVR, **(B)** death/MI, and **(C)** ST. Abbreviations as in Figures 1 and 3.

rates were significantly higher with off-label use at 9 months and 2 years, with the exception of stent thrombosis at 2 years.

When patients with STEMI were excluded from the off-label DES use group, all adjusted event rates were still significantly higher with off-label DES use at 9 months and 2 years.

Outcomes of off-label DES use versus off-label BMS use. Off-label use of DES compared with off-label use of BMS had significantly lower rates of death, myocardial infarction, TVR, and MACE at the 9-month and 2-year follow-ups (Table 3, Fig. 3). After adjustments with propensity analyses, each of these event rates remained significantly lower with DES versus BMS (Table 3). The predictive ability of the propensity score model was very good with a C-statistic of 0.80.

Stent thrombosis was significantly less frequent with off-label DES use versus off-label BMS use at 9 months, both before and after adjustments, but was not significantly different at 2 years (Table 3, Fig. 4). There was a mild trend for higher rates of stent thrombosis from 1 to 2 years with DES versus BMS (20 of 3,569 or 0.6% vs. 2 of 1,095 or 0.2%, p = 0.13).

Unadjusted outcomes with DES in the 12 subgroups of off-label use are shown in Table 4. Comparison of outcomes between DES and BMS in the 12 subgroups showed consistently lower event rates and lower propensity adjusted hazard ratios for TVR and death or myocardial infarction with DES use (Fig. 5).

Discussion

Our study found that off-label use of DES comprises about 59% of all DES use. Patients with off-label DES use had a

Table 4. Unadjusted Outcomes in Subgroups of Off-Label Use of DES

	STEMI	CTO	SVG	Bifurcation Lesions	Ostial Lesions	Left Main Lesions	In-Stent Restenosis	Small Vessels	Large Vessels	Long Lesions	Multivessel PCI	Multilesion PCI
Outcomes at 9 months	(n = 1,450)	(n = 288)	(n = 825)	(n = 1,650)	(n = 1,871)	(n = 223)	(n = 657)	(n = 858)	(n = 1,196)	(n = 1,771)	(n = 1,801)	(n = 4,728)
Death	91 (6.3)	9 (3.1)	39 (4.7)	43 (2.6)	61 (3.3)	15 (6.7)	28 (4.3)	17 (2.0)	35 (2.9)	68 (3.8)	64 (3.6)	166 (3.5)
Myocardial infarction	41 (2.8)	7 (2.4)	44 (5.3)	55 (3.3)	66 (3.5)	12 (5.4)	20 (3.0)	31 (3.6)	32 (2.7)	69 (3.9)	62 (3.4)	152 (3.2)
Death/myocardial infarction	125 (8.6)	16 (5.6)	73 (8.9)	94 (5.7)	119 (6.4)	25 (11.2)	45 (6.9)	46 (5.4)	60 (5.0)	132 (7.5)	123 (6.8)	298 (6.3)
TVR	67 (4.6)	14 (4.9)	62 (7.5)	113 (6.9)	112 (6.0)	13 (5.8)	46 (7.0)	74 (8.6)	44 (3.7)	118 (6.7)	112 (6.2)	296 (6.3)
MACE	174 (12.0)	28 (9.7)	119 (14.4)	180 (10.9)	207 (11.1)	34 (15.3)	82 (12.5)	105 (12.2)	95 (7.9)	229 (12.9)	206 (11.4)	529 (11.2)
Stent thrombosis	18 (1.2)	4 (1.4)	9 (1.1)	24 (1.5)	17 (0.9)	2 (0.9)	6 (0.9)	8 (0.9)	9 (0.8)	24 (1.4)	17 (0.9)	50 (1.1)
Outcomes at 2 years	(n = 548)	(n = 124)	(n = 329)	(n = 697)	(n = 796)	(n = 82)	(n = 272)	(n = 317)	(n = 365)	(n = 627)	(n = 764)	(n = 2,011)
Death	41 (7.5)	5 (4.0)	29 (8.8)	43 (6.2)	55 (6.9)	10 (12.2)	22 (8.1)	15 (4.7)	28 (7.7)	44 (7.0)	52 (6.8)	142 (7.1)
Myocardial infarction	28 (5.1)	5 (4.0)	32 (9.7)	34 (4.9)	45 (5.7)	7 (8.5)	17 (6.3)	23 (7.3)	16 (4.4)	39 (6.2)	40 (5.2)	103 (5.1)
Death/myocardial infarction	64 (11.7)	9 (7.3)	51 (15.5)	75 (10.8)	91 (11.4)	15 (18.3)	37 (13.6)	36 (11.4)	40 (11.0)	79 (12.6)	89 (11.7)	229 (11.4)
TVR	49 (8.9)	15 (12.1)	60 (18.2)	78 (11.2)	88 (11.1)	6 (7.3)	42 (15.4)	47 (14.8)	30 (8.2)	88 (14.0)	108 (14.1)	255 (12.7)
MACE	99 (18.1)	22 (17.7)	99 (30.1)	132 (18.9)	160 (20.1)	19 (23.2)	71 (26.1)	69 (21.8)	64 (17.5)	154 (24.6)	173 (22.6)	428 (21.3)
Stent thrombosis	7 (1.3)	3 (2.4)	9 (2.7)	13 (1.9)	5 (0.6)	1 (1.2)	4 (1.5)	4 (1.3)	2 (0.6)	13 (2.1)	14 (1.8)	30 (1.5)

Values are n (%) unless otherwise noted.
CTO = chronic total occlusion; SVG = saphenous vein graft; other abbreviations as in Tables 1 and 3.

higher risk clinical profile and higher risk lesion profile compared with patients with on-label DES use. Off-label use of DES was associated with significantly higher rates of death, myocardial infarction, TVR, and MACE at 9 months and 2 years and significantly higher rates of stent thrombosis at 9 months. After adjusting for differences in clinical variables, event rates were still significantly higher with off-label use, reflecting the higher risk clinical profile (STEMI patients) and higher risk lesion profile that could not be adjusted with the multivariable analyses. Although event rates were higher with off-label use of DES compared with on-label use, outcomes were still very good with low rates of TVR and stent thrombosis at 9 months and 2 years.

We also compared outcomes in patients treated with off-label use of DES with outcomes in patients treated with off-label use of BMS. Off-label DES use compared with off-label BMS use was associated with lower adjusted rates for death, myocardial infarction, TVR, and MACE. The frequency of stent thrombosis was lower with off-label DES use versus off-label BMS use at both the 9-month and 2-year follow-ups, but the differences were statistically significant only at 9 months. Although the 12 subcategories of off-label use are very diverse, the reduction in the frequency of TVR and death or myocardial infarction was very similar across all subgroups.

Our findings are similar to results from previous registries comparing off-label with on-label use of DES (3,4). The D.E.S. Cover Registry evaluated 2,588 patients treated with DES for off-label or untested indications (3). After adjusting for differences in baseline variables, TVR was significantly higher and there were trends for higher rates of death, myocardial infarction, and stent thrombosis with off-label versus on-label use. Despite this, absolute event rates with off-label use were quite low (TVR 7.6% and stent thrombosis 0.7% at 1 year), which is similar to our study. The EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry compared outcomes with off-label versus on-label DES use and found higher rates of TLR (6.3% vs. 2.4%), MACE (17.5% vs. 8.9%), and stent thrombosis (1.6% vs. 0.9%) at 1 year with off-label use (4). These differences were significant after adjustments for differences in baseline variables.

Several registries have evaluated the unrestricted use of DES, and these registries have included large numbers of patients with off-label use (10–12). Iakovou et al. (10) evaluated 2,229 patients treated with DES in a real-world setting in Germany and Italy and found a frequency of stent thrombosis of 1.3%, which is somewhat higher than that seen with on-label use in randomized clinical trials. The e-Cypher Registry evaluated 15,157 patients treated with unrestricted utilization of sirolimus-eluting stents and found relatively low frequencies of TLR (3.1%) and stent thrombosis (0.9%) at 1 year (11). The ARRIVE I and II Registries

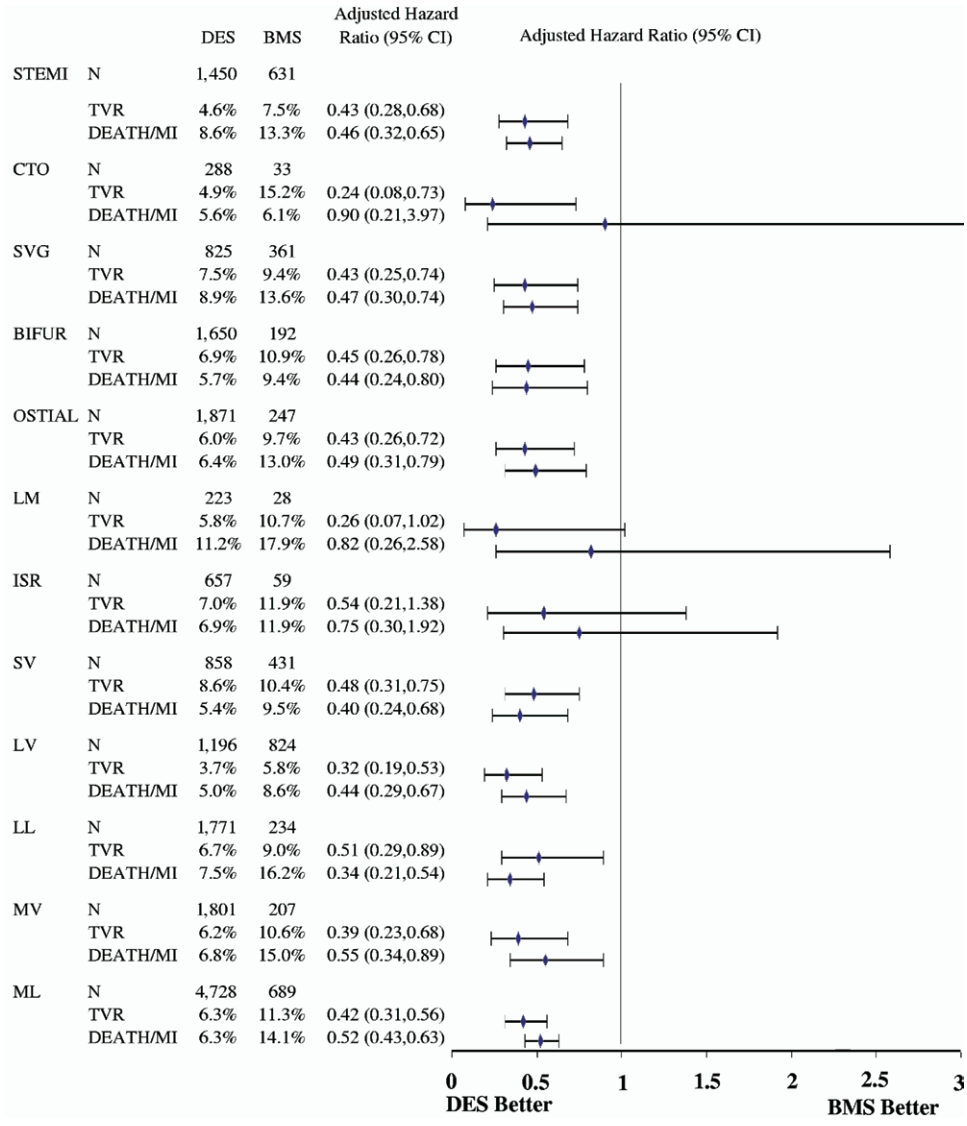

Figure 5. Comparison of Event Rates Between DES and BMS in Subgroups of Off-Label Use

Adjusted 9-month outcomes in subgroups of off-label use comparing rates of TVR and death/MI between DES and BMS. BIFUR = bifurcation lesion; CTO = chronic total occlusion; ISR = in-stent restenosis; LL = long lesion; LM = left main artery; LV = large vessel; ML = multilesion percutaneous coronary intervention; MV = multivessel percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SV = small vessel; SVG = saphenous vein graft; other abbreviations as in Figures 1 and 3.

(Taxus Peri-Approval Registry, A U.S. Multi-Center Safety Surveillance Program) evaluated the expanded use of paclitaxel-eluting stents in 7,307 patients, 64% of whom had off-label use, and found a relatively low frequency of TVR (5.1%) and MACE (cardiac death, myocardial infarction, or TVR) (6.5%) at 1 year (12). Stent thrombosis occurred in 1.8% of patients at 1 year and 0.7% of patients from 1 to 2 years, which is somewhat higher than the frequency seen with on-label use in randomized trials.

Recently, Maroquin et al. (5) reported the results from the National Heart, Lung, and Blood Institute Dynamic Registry comparing outcomes in patients treated with DES versus BMS for off-label indications. Drug-eluting stents were associated with lower rates of TVR and similar rates of death or myocardial infarction. Several registries have compared outcomes with DES versus BMS in unrestricted populations that contain large percentages of patients with off-label use (13–15). The RESEARCH (Rapomycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) Registry and the National Heart, Lung, and Blood Institute Dynamic Registry compared outcomes in patients treated with DES with outcomes in patients who had BMS

implanted before the availability of DES (13,14). Both registries found less TVR with DES but no differences in death or myocardial infarction. The large SCAAR (Swedish Coronary Angiography and Angioplasty Registry) registry initially reported a higher incidence of death and death or myocardial infarction at 3 years with DES compared with BMS (15). However, further analysis with additional patients (>35,000) showed no differences in death or death or myocardial infarction at late follow-up (1 to 4 years) between DES and BMS (16). Tu et al. (17) reported data from the Ontario Registry showing lower rates of TVR and death at 2 and 3 years with DES compared with BMS in groups that were matched with propensity scoring. Some of the differences in event rates between the various registries may be explained by differences in definitions of myocardial infarction as well as differences in patient populations.

There are limited data from randomized trials comparing DES with BMS in subgroups of off-label use. Although there have been several randomized trials evaluating DES versus BMS in STEMI patients, the number of patients has been relatively small, the follow-up has been relatively short, and TVR has been influenced by mandated follow-up angiography in most trials (18–21). Randomized trials have been performed in only a few of the remaining subgroups, and the number of patients has been small and the follow-up has been generally short (22–27).

Study limitations. Although our study provides an opportunity to look at real-world outcomes with off-label use of DES, it has the limitations of an observational database. There may be hidden biases to choose BMS for sicker patients who may have multiple comorbidities, bleeding risk, or who may be noncompliant with dual antiplatelet therapy as well as other therapies. It is unlikely that these biases can be accounted for by statistical adjustments. It is also difficult to adjust for differences in risk profile in comparing outcomes between off-label and on-label DES use, because criteria used to define off-label use by definition cannot be included in the statistical model.

Our registry also does not have data regarding compliance with dual antiplatelet therapy. This is an important limitation, because compliance with clopidogrel and aspirin is a major determinant of stent thrombosis and adverse events (28,29).

Conclusions

This is the largest U.S. registry to evaluate outcomes with off-label use of DES. Our study shows that off-label use compared with on-label use of DES is associated with higher event rates at the 9-month and 2-year follow-ups, which is consistent with the higher risk clinical and lesion profile of patients with off-label use. In contrast, off-label use of DES is associated with lower rates of death, myocardial infarction, TVR, and MACE at 9 months and 2 years compared with off-label use of BMS. Stent thrombosis was significantly lower at 9 months but not at 2 years.

Therefore, although event rates with off-label use of DES are higher than with on-label use, outcomes are still remarkably good and are better than with off-label use of BMS. Adequately powered randomized trials with long-term follow-up will be needed to determine the safety and efficacy of DES versus BMS in the numerous diverse subgroups of off-label use. Until the results of large randomized trials are available, our data support the use of DES in selected patients in most subgroups of off-label use.

Acknowledgments

The authors extend special appreciation to the STENT registry central coordinator, Susan Christopher, and the executive assistant, Connie Poole, for their tremendous commitment to this study. In addition, each of the individual site data coordinators, nurse coordinators, and physician operators are thanked for their diligence and success with patient consents, data collection and follow-up. A complete list of the STENT Registry study centers is noted in the Appendix.

Reprint requests and correspondence: Dr. Bruce R. Brodie, 1126 North Church Street, Suite 300, Greensboro, North Carolina 27401. E-mail: bbrodie@triad.rr.com.

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Key Words: drug-eluting stents ■ off-label indications ■ percutaneous coronary intervention (PCI).

APPENDIX

STENT Registry Study Centers: Carolinas Medical Center, Charlotte, North Carolina; High Point Regional Hospital, High Point, North Carolina; Indiana Heart Institute, Indianapolis, Indiana; Moore Regional Medical Center, Pinehurst, North Carolina; Moses H. Cone Heart and Vascular Center/LeBauer Cardiovascular Research, Greensboro, North Carolina; McLeod Regional Medical Center, Florence, South Carolina; Sisters of Charity Providence Hospitals, Columbia, South Carolina; Wellmont Holston Valley Medical Center, Kingsport, Tennessee.

For a table on propensity adjustments, please see the online version of this article.