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CLINICAL RESEARCH

Acceptance, Panic, and Partial Recovery

The Pattern of Usage of Drug-Eluting Stents After Introduction in the U.S. (A Report From the American College of Cardiology/ National Cardiovascular Data Registry)

Ronald J. Krone, MD,* Sunil V. Rao, MD,† David Dai, PHD,† H. Vernon Anderson, MD,‡ Eric D. Peterson, MD, MPH,† Michael A. Brown, MD, MS,§ Ralph G. Brindis, MD, MPH,‖ Lloyd W. Klein, MD,¶ Richard E. Shaw, PHD,# William S. Weintraub, MD,** on behalf of the ACC/NCDR Investigators††

St. Louis, Missouri; Durham, North Carolina; Houston, Texas; Philadelphia, Pennsylvania; San Francisco, California; Wilmington, Delaware; and Washington, DC

Objectives Review the use of drug-eluting stents (DES) to evaluate changes in use.

Background The DES were approved after several small studies in carefully selected patients showed dramatic reduction in in-stent restenosis. The DES were then rapidly adopted into routine practice. In 2006, 3 years after introduction, serious concerns regarding long-term safety were raised.

Methods We queried the American College of Cardiology/National Cardiovascular Data Registry (ACC/NCDR) CathPCI Registry. The percentage of DES used through mid-2009 was reviewed overall and in subgroups of patients categorized by lesion type, clinical factors, insurance, and hospital characteristics. Multivariable logistic models relating these covariates to DES usage were constructed for 3 relevant time intervals.

Results A total of 2,247,647 coronary stent procedures were analyzed. By 2005 over 90% of first stents placed were DES. Safety concerns arising in 2006 reduced DES use to 64% of first stent placed. After publication of salutary outcomes data in 2008, usage increased to 76% by mid-2009. The logistic models demonstrated decreased likelihood of DES usage in patients with: 1) ST-segment elevation myocardial infarctions; and 2) no medical insurance. The DES usage increased for in-stent restenosis. Hospital characteristics were not associated with significant differences in DES usage.

Conclusions There was rapid adoption of DES into U.S. clinical practice. Concern for late stent thrombosis in 2006 significantly altered DES use with reductions seen in subgroups at risk for thrombosis and patients with no insurance. These rapid cyclic changes after DES introduction reinforce the need for continuous, timely reporting of outcomes data after the introduction of new technologies. (J Am Coll Cardiol Intv 2010;3:902–10) © 2010 by the American College of Cardiology Foundation

From the *Division of Cardiology, Washington University School of Medicine, St. Louis, Missouri; †Duke Clinical Research Institute, Durham, North Carolina; ‡Cardiology Division, University of Texas Health Science Center, Houston, Texas; §Cardiology Division, Temple University, Philadelphia, Pennsylvania; ‖Cardiology Division, Kaiser Permanente, San Francisco, California; ¶Cardiology Section, Rush Medical College, Chicago, Illinois; #Sutter Pacific Health Centers, San Francisco, California; **Division of Cardiology, Christiana Care Health Services, Wilmington, Delaware; and the ††American College of Cardiology, Washington, DC. This work was supported exclusively from fees generated by the ACC/NCDR. Dr. Brown is a member of the Speakers' Bureau for Eli Lilly/Daiichi-Sankyo and Abbott Vascular and has received modest compensation (<$10,000/year) from Eli Lilly/Daiichi-Sankyo and Abbott Vascular for speakers fees. Dr. Peterson has received research support from Bristol-Myers Squibb/Sanofi-Aventis, Merck/Schering-Plough, Eli Lilly, and Johnson & Johnson. Dr. Rao has received research funding from Cordis. All other authors report that they have no relationships to disclose.

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Polymer-coated stents eluting antiproliferative drugs (DES) were introduced to solve the problem of late restenosis of the bare-metal stents (BMS) used in percutaneous coronary interventions (PCIs). Several small studies with highly selected patients showed marked reduction in in-stent restenosis (1,2), and these led to approval for use in the U.S. Thereafter, DES were rapidly incorporated into clinical practice (3). However, concerns were raised early about the possible thrombogenicity of DES (4–6). In mid-2006, a series of studies reporting increased stent thrombosis or even death after stopping antiplatelet therapy were presented (7–9) and were highly publicized (10). A Food and Drug Administration (FDA) Advisory Panel on the Safety and Efficacy of Drug-Eluting Stents then released a statement recognizing a small but significant risk of late thrombosis with DES but endorsed them as safe and effective when used in the lesion subsets in which the original use was approved (i.e., "on label", simple straightforward lesions in otherwise healthy people) (11). However, over one-half of stent implantations at that time were "off label" for which there were no data (3). At the time of the FDA statement, more than 1,250,875 DES had been recorded in the American College of Cardiology National Cardiology Data Registry (ACC/NCDR). Since 2007, multiple reports have been published documenting the delayed endothelization of DES and the potential for late stent thrombosis (12), emphasizing the need for prolonged antiplatelet therapy with dual agents (DAPT) (9). More recently, a number of large studies have shown that the long-term risks are not greater for DES compared with BMS (13–16) and might be better (17).

To investigate the impact of these issues on stent choice, we accessed data from the ACC-NCDR (18). We specifically looked at DES usage in complex, "off label" lesions as well as in clinical subgroups that had been systematically excluded from the approval studies. Because of the financial burden long-term DAPT might impose on patients and its importance in preventing late stent thrombosis, we also assessed the impact of medical insurance on DES placement.

Methods

The ACC/NCDR Cath/PCI registry is a voluntary registry whose purpose includes quality assessments of diagnostic coronary angiography and percutaneous coronary intervention procedures (18). Data were entered locally with ACC certified data entry software, into version 2.0 or 3.0, and transmitted to the database. Data were checked for consistency and completeness before incorporation into the database. The data elements are available on the ACC website.

Patient selection. Data from 945 hospitals participating in the NCDR Cath/PCI registry from April 1, 2003 to July 1, 2009, were analyzed. The type of stent used was evaluated. Only the first PCI/hospital admission was considered. If any DES were used in the index PCI lab visit, then that lab visit is considered "DES". Thus, a patient could have multiple PCIs/admission, but the DES designation refers only to the first PCI of that admission. In addition to analysis of the population as a whole, analyses of subgroups were performed.

Statistical analysis. The number of DES and BMS for the total group and selected subgroups were evaluated each quarter (Q) from 2003 until mid-2009, and the percentage of DES was calculated. The comparisons of baseline features (Table 1) were made with Pearson chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. For the determination of factors independently associated with DES use, a list of patient and hospital characteristics was entered into 3 multivariable models: "early-peak period" 2005 Q1 through 2006 Q2, "nadir" 2007 Q2 through 2008 Q2, and "late" 2008 Q4 through 2009 Q2. The variables were age, sex, diabetes, indications for the procedure (elective, non–ST-segment elevation acute coronary syndrome [unstable angina and non–ST-segment elevation myocardial infarction], or ST-segment elevation myocardial infarction [STEMI]), vein grafts, chronic total occlusions, de novo lesions or in-stent restenosis, bifurcation lesions, hospital size, annual PCI volume, teaching hospital, location/community type, and hospital owner. Type of medical insurance was also reviewed, and the no insurance group was compared with: 1) government insurance (Veterans Administration, Medicare, or Medicaid); and 2) private insurance or HMOs. In addition, because patients within a hospital are more likely to be treated in a similar way, generalized estimating equation models with exchangeable working correlation structure were used to adjust for correlations among clustered responses (e.g., within hospital correlations). The 95% confidence intervals and p values were calculated for all listed variables for each time period.

Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
FDA = Food and Drug Administration
OR = odds ratio
PCI = percutaneous coronary intervention
Q = calendar quarter
STEMI = ST-segment elevation myocardial infarction

Results

Between April 1, 2003 and July 1, 2009, a total of 2,247,647 coronary stent procedures were performed in participating hospitals. The DES usage rose from 0.1% of the total stent

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Table 1. Comparison of Features of Patients With DES vs. BMS

	Total (n = 2,446,402)	% Overall	n = 1,648,760	% DES	n = 797,642	% BMS	% DES Used
Demographic data							
Age (yrs)							
Mean		64.28		64.04		64.77	
Sex							
Male	1,628,498	66.57	1,091,257	66.19	537,241	67.35	67.01
Female	817,904	33.43	557,503	33.81	260,401	32.65	68.16
Insurance							
Missing	7,538	0.31	1,871	0.11	5,667	0.71	24.82
Government	1,270,835	51.95	843,111	51.14	427,724	53.62	66.34
Commercial	738,563	30.19	518,143	31.43	220,420	27.63	70.16
HMO	305,211	12.48	213,848	12.97	91,363	11.45	70.07
None	122,512	5.01	70,540	4.28	51,972	6.52	57.58
Non U.S. insurance	1,743	0.07	1,247	0.08	496	0.06	71.54
Diabetes							
Missing	277	0.01	141	0.01	136	0.02	50.90
No diabetes	1,656,412	67.71	1,098,603	66.63	557,809	69.93	66.32
Diabetes	697,056	31.98	478,099	33.05	218,357	29.87	68.59
Hypertension							
Missing	260	0.01	152	0.01	108	0.01	58.46
No	582,754	23.82	368,443	22.35	214,311	26.87	63.22
Yes	1,863,388	76.17	1,280,165	77.64	583,223	73.12	68.70
Tobacco history							
Missing	495	0.02	295	0.02	200	0.03	59.60
Never	961,261	39.29	659,638	40.01	301,623	37.81	68.62
Yes-former	845,097	34.54	579,006	35.12	266,091	33.36	68.51
Yes-current	639,549	26.14	409,821	24.86	229,728	28.80	64.08
Dyslipidemia							
Missing	444	0.02	234	0.01	210	0.03	52.70
No	631,656	25.82	383,204	23.24	248,452	31.15	60.67
Yes	1,814,302	74.16	1,265,322	76.74	548,980	68.83	69.74
Family history coronary artery disease: age <55 yrs							
Missing	503	0.02	305	0.02	198	0.02	60.64
No	1,758,318	71.87	1,199,866	72.77	558,452	70.01	68.24
Yes	687,581	28.11	448,589	27.21	238,992	29.96	65.24
NYHA functional class (heart failure patients)							
Missing	717	0.32	227	0.16	490	0.59	31.66
1	31,564	14.14	20,827	14.91	10,737	12.85	65.98
2	53,381	23.91	33,717	24.14	19,664	23.53	63.16
3	76,626	34.32	49,541	35.47	27,085	32.40	64.65
4	60,965	27.31	35,356	25.31	25,609	30.64	57.99
Admission symptoms							
Missing	364	0.01	210	0.01	154	0.02	57.69
Presentation							
No symptoms	302,434	12.36	212,149	12.87	90,285	11.32	70.15
Atypical pain	169,242	6.92	123,220	7.47	46,022	5.77	72.81
Stable angina	414,417	16.94	300,734	18.24	113,683	14.25	72.57
ACS: unstable angina	832,905	34.05	587,472	35.63	245,433	30.77	70.53
ACS: NSTEMI	384,942	15.74	244,197	14.81	140,745	17.65	63.44
ACS: STEMI	342,098	13.98	180,778	10.96	161,320	20.22	52.84

Continued on next page

Table 1. Continued

	Total (n = 2,446,402)	% Overall	n = 1,648,760	% DES	n = 797,642	% BMS	% DES Used
Lesion characteristics bypass grafts							
Missing	475	0.02	269	0.02	206	0.03	56.63
No graft	2,284,942	93.40	1,556,119	94.38	728,823	91.37	68.10
Yes-artery	11,012	0.45	7,505	0.46	3,507	0.44	68.15
Yes-vein	149,973	6.13	84,867	5.15	65,106	8.16	56.59
In-stent restenosis							
Missing	242	0.01	150	0.01	92	0.01	61.98
No	30,449	1.24	18,422	1.12	12,027	1.51	60.50
De novo	2,203,596	90.07	1,469,174	89.11	734,422	92.07	66.67
Restenosis	139,007	5.68	107,821	6.54	31,186	3.91	77.57
De novo/restenosis	63,720	2.60	48,006	2.91	15,714	1.97	75.34
Hospital features							
Number of CMS-certified beds							
Median	2,445,940	427.00	1,648,692	427.00	797,248	430.00	
Location/missing	461	0.02	68	0.00	393	0.05	14.75
Community type							
Rural	309,704	12.66	196,646	11.93	113,058	14.17	63.49
Suburban	665,571	27.21	436,680	26.49	228,891	28.70	65.61
Urban	1,470,666	60.12	1,015,366	61.58	455,300	57.08	69.04
Profit type							
Missing	461	0.02	68	0.00	393	0.05	14.75
Government	38,472	1.57	27,099	1.64	11,373	1.43	70.44
Private/community	2,182,199	89.20	1,465,249	88.87	716,950	89.88	67.15
University	225,270	9.21	156,344	9.48	68,926	8.64	69.40
Average annual PCI volume							
Median	2,446,402	886.61	1,648,760	901.03	797,642	872.45	
Hospital region							
Missing	607,790	24.84	235,559	14.29	372,231	46.67	38.76
West	298,135	12.19	237,752	14.42	60,383	7.57	79.75
Northeast	229,253	9.37	169,909	10.31	59,344	7.44	74.11
Midwest	590,850	24.15	452,876	27.47	137,974	17.30	76.65
South	720,374	29.45	552,664	33.52	167,710	21.03	76.72
Teaching hospital							
Missing	461	0.02	68	0.00	393	0.05	14.75
No	1,122,620	45.89	770,155	46.71	352,465	44.19	68.60
Yes	1,323,321	54.09	878,537	53.28	444,784	55.76	66.39

In all categories, bare-metal stent (BMS) versus drug-eluting stent (DES) and % DES used, $p < 0.0001$.

ACS = acute coronary syndrome; NSTEMI = non–ST-segment myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STEMI = ST-segment myocardial infarction.

insertions in 2003-Q1 to 86% by 2004-Q4 and remained ≥90% until 2006-Q3. Beginning in 2006-Q3, DES percentage fell dramatically, reaching its nadir of 64% in 2007-Q4. By 2009-Q2 usage had increased to 76% of all stents (Fig. 1). Patient demographic data are presented in Table 1.

Table 2 shows the multivariable logistic model for the insertion of a DES, and Figures 2 and 3 show usage patterns over time for selected variables. With the exception of patients with in-stent restenosis and bifurcation lesions, DES placement declined in all other off-label subgroups (Table 2, Figs. 2A to 2D).

There was no significant difference in percentage of DES usage for any of the hospital variables over the 3 time periods. The logistic model demonstrated 3 groups where the odds ratio (OR) of DES usage changed significantly after 2006 (Fig. 3, Table 2). The likelihood of usage in patients with in-stent restenosis was increased at the early "peak period" 2005 Q1 to 2006 Q2 (OR: 1.64), and the OR increased further over the last 2 periods (OR: 2.46 late period). The percentage use of DES in patients with in-stent restenosis remained the highest of all groups 88.5%% vs. 74.9% in Q2-2009, with DES insertion rates over 2.5 times more likely than BMS insertion (Table 2, Fig. 2A).

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Table 2. Multivariable Logistic Regression Models Relating Variables to Likelihood of DES Implantation for the 3 Periods Monitored

Level	OR	Lower CL	Upper CL	p Value
Early period January 1, 2005 to June 30, 2006				
Saphenous vein grafts	0.43	0.41	0.46	<0.0001
STEMI vs. elective PCI	0.55	0.53	0.58	<0.0001
In-stent restenosis	1.64	1.51	1.80	<0.0001
No insurance vs. HMO	0.67	0.63	0.72	<0.0001
No insurance vs. commercial insurance	0.68	0.64	0.72	<0.0001
Bifurcation lesion	1.44	1.38	1.50	<0.0001
Chronic total occlusions	0.74	0.71	0.77	<0.0001
No insurance vs. government insurance	0.84	0.79	0.88	<0.0001
Age/10-yr increase	0.91	0.90	0.93	<0.0001
Female	1.13	1.11	1.16	<0.0001
NSTEACS vs. elective PCI	0.95	0.92	0.98	0.0013
Diabetes	0.98	0.96	1.00	0.0574
Government vs. private/community hospital	1.48	0.88	2.46	0.1425
University vs. private/community hospital	1.20	0.83	1.74	0.3344
Rural vs. urban hospital	1.10	0.85	1.43	0.4674
Suburban vs. urban hospital	0.93	0.75	1.14	0.4765
Teaching hospital vs. other	0.95	0.77	1.18	0.6480
Certified hospital beds/100 increase	1.01	0.94	1.08	0.7759
Annual PCI volume/100 increase	1.00	0.98	1.02	0.9894
Nadir April 1, 2007 to March 31, 2008				
STEMI vs. elective PCI	0.39	0.37	0.40	<0.0001
No insurance vs. commercial insurance	0.50	0.48	0.52	<0.0001
In-stent restenosis	2.40	2.29	2.54	<0.0001
No insurance vs. HMO	0.51	0.49	0.53	<0.0001
Saphenous vein grafts	0.58	0.56	0.60	<0.0001
Chronic total occlusions	0.73	0.71	0.75	<0.0001
Bifurcation lesion	1.39	1.35	1.42	<0.0001
No insurance vs. government insurance	0.63	0.61	0.65	<0.0001
Age/10-yr increase	0.91	0.90	0.92	<0.0001
NSTEACS vs. elective PCI	0.86	0.84	0.87	<0.0001
Female	1.09	1.07	1.10	<0.0001
Diabetes	1.07	1.06	1.09	<0.0001
Teaching hospital	0.87	0.75	1.02	0.0911
Suburban vs. urban hospital	0.91	0.77	1.07	0.2398
Certified beds/100 increase	0.97	0.93	1.02	0.2847
University vs. private/community hospital	0.89	0.68	1.16	0.3986
Rural vs. urban hospital	1.07	0.87	1.31	0.5194
Government vs. private/community hospital	1.01	0.68	1.49	0.9557
Annual PCI volume/100 increase	1.00	0.98	1.01	0.9690

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Patients with STEMIs had a substantially lower percentage of DES implantation than patients with other indications throughout the entire period (Fig. 3A). The likelihood of DES usage in STEMI dropped significantly after the FDA advisory, with the OR of DES insertion dropping from 0.55 to 0.39 (Fig. 3C). Hospital insurance strongly influenced the likelihood of a DES insertion. During the peak usage period, patients with no insurance were two-thirds as likely to receive a DES as patients with insurance (OR: 0.67). This disparity increased after 2007, so that by the last period patients with no insurance were less than one-half as likely to get a DES as patients with insurance (OR: 0.41) (Fig. 3B). Figure 3C graphs ORs for each variable for each of the 3 periods. In-stent restenosis, no insurance, and STEMIs were dramatically affected in the decline period, out of proportion to the other variables. The ORs for the other variables did not change significantly over the 3 periods (except saphenous vein grafts, which moved toward parity with native vessels).

Table 2. Continued

Level	OR	Lower CL	Upper CL	p Value
Late period October 1, 2008 to June 30, 2009				
STEMI vs. elective PCI	0.39	0.37	0.41	<0.0001
No insurance vs. commercial insurance	0.41	0.39	0.43	<0.0001
In-stent restenosis	2.46	2.33	2.59	<0.0001
No insurance vs. HMO	0.41	0.39	0.43	<0.0001
No insurance vs. government insurance	0.53	0.51	0.56	<0.0001
Chronic total occlusions	0.75	0.73	0.77	<0.0001
Saphenous vein grafts	0.65	0.62	0.67	<0.0001
Per 10-yr increase	0.90	0.89	0.90	<0.0001
Bifurcation lesion	1.34	1.31	1.39	<0.0001
NSTEACS vs. elective PCI	0.87	0.85	0.90	<0.0001
Diabetes	1.07	1.05	1.08	<0.0001
Female	1.04	1.02	1.06	<0.0001
Teaching hospital	0.87	0.76	1.01	0.0653
University vs. private/community hospital	0.79	0.62	1.02	0.0695
Rural vs. urban hospital	1.13	0.93	1.39	0.2198
Government vs. private/community hospital	1.15	0.74	1.79	0.5314
Suburban vs. urban hospital	0.96	0.83	1.11	0.5643
Certified beds/100 increase	0.99	0.95	1.03	0.6842
Annual PCI volume/100 increase	1.00	0.98	1.01	0.7504

The variables are listed in the order of decreasing discrimination (odds ratio [OR]). The increased usage of DES in patients with in-stent restenosis and lower usage in patients with STEMIs and no insurance is noticed in the nadir period and continuing into the late period. None of the variables related to type of hospital were significant in any period.

CL = 95% confidence level; HMO = health maintenance organization; NSTEACS = non–ST-segment elevation acute coronary syndrome (unstable angina and non–ST-segment elevation myocardial infarction); other abbreviations as in Table 1.

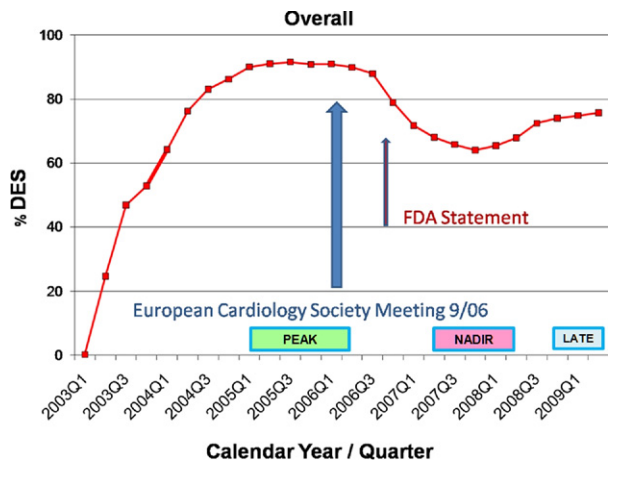

Figure 1. DES as a Percentage of Total Stents Inserted

The results of the BASKET-LATE study (Basel Stent Cost-effectiveness trial-Late Thrombotic Events) (7) and a meta-analysis by E. Camenzind were presented at the European Society of Cardiology Meeting in September 2006 **(blue arrow)**. The Food and Drug Administration (FDA) statement was published 2006-calendar quarter (Q)4 **(red arrow)**. The 3 periods used for calculation of the multivariable logistic models are indicated by the colored bars. The time periods used for the calculation of the multivariable logistic regression models are indicated on the figure. DES = drug-eluting stent(s).

Discussion

These data document wide alterations in DES usage after their introduction in 2003. Initial rapid acceptance resulted in peak usage in 2005 with DES accounting for 90% of all stent implantations. A dramatic fall off in DES usage in late 2006 coincided with increasing concern for late stent thrombosis. Ultimately, DES usage increased in response to reassuring safety data but failed to achieve peak usage rates during the height of enthusiasm in early 2006. This pattern has also been shown in patients with non-STEMI from the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry (19). From multivariable logistic models used here, ORs for DES usage decreased over the 3 specified time periods for STEMI patients and for patients with no insurance but increased in patients with in-stent restenosis. This suggests a more discriminating approach to DES placement (Fig. 3C) in response to changing safety data and an awareness of the importance of prolonged DAPT.

Studies performed for new device approvals (or a new pharmaceutical) are designed to demonstrate efficacy and safety, usually in the short term. In the case of DES, approval studies focused on the patients with lesions most likely to demonstrate clearly and cleanly a reduction in

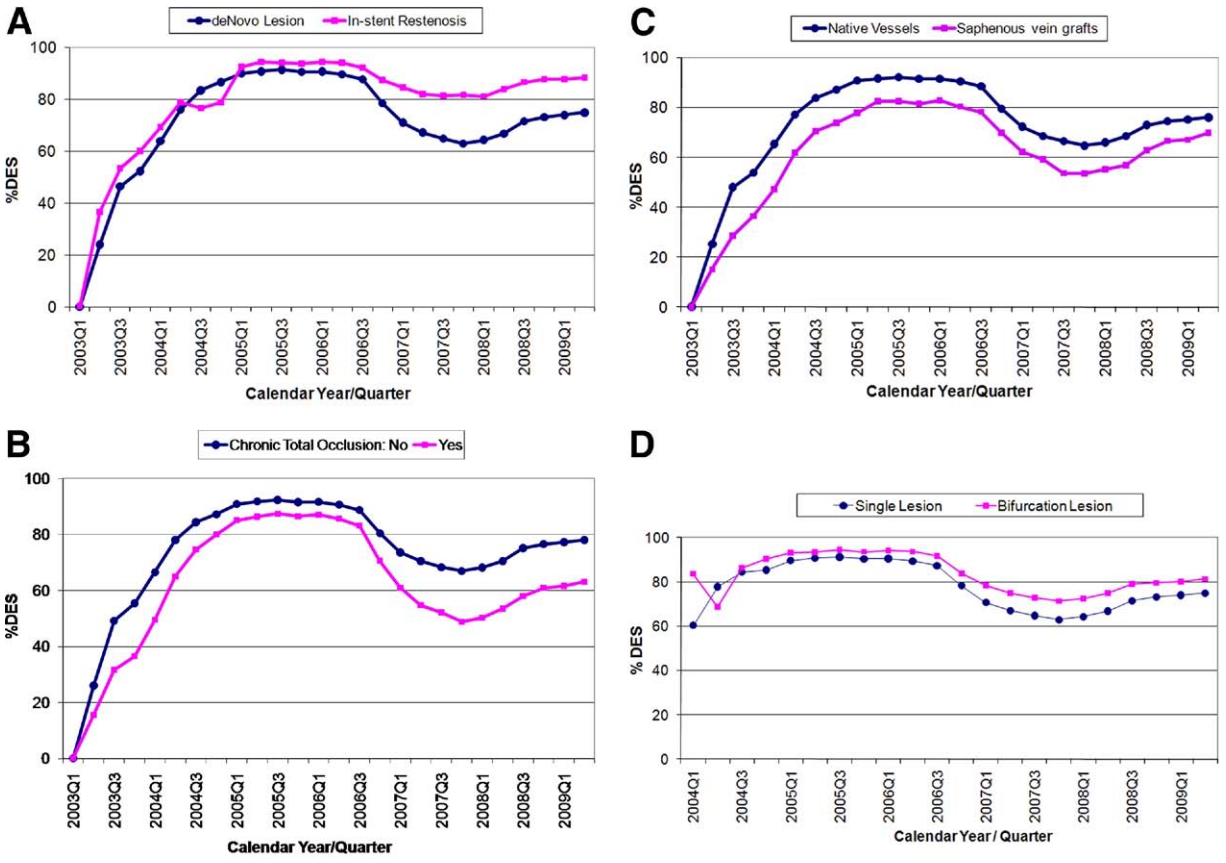

Figure 2. DES Usage by Off-Label Indications

(A) Drug-eluting stent (DES) usage for in-stent restenosis. **(B)** DES usage for chronic total occlusion lesions. **(C)** DES usage for saphenous vein grafts. **(D)** DES usage for bifurcation lesions. Data only available from database version 3, starting in 2004.

restenosis: simple, straightforward lesions in patent native vessels—excluding bifurcations, ostial lesions, calcified lesions, left main lesions, vessels <2.5 mm, or patients with in-stent stenosis; all of this in patients free of higher risk comorbidities, such as acute myocardial infarction or shock (1,2). The initial approval studies were not designed to evaluate long-term safety. Because DES prolong the period of vulnerability to thrombosis by delaying stent endothelization (20), the importance of prolonged DAPT shown to reduce stent thrombosis during the vulnerable period became apparent in 2004 with the publication of 4 case reports of stent thrombosis within a few days of stopping DAPT and much later than would be expected—nearly 1 year after DES implantation (6) . These initial concerns were heightened by the landmark BASKET-LATE study (Basel Stent Cost-effectiveness trial-Late Thrombotic Events) presented at the European Cardiology Society meeting in 2006 (7). In this study, patients were followed after the thienopyridine component of DAPT, clopidogrel, was stopped at 6 months. Increased rates of late stent thrombosis were reported, and DES usage dropped precipitously after this report. Then, beginning in 2007, studies showing a very low incidence of late stent thrombosis and infarction with DES usage in a wide variety of patients while maintaining superiority over BMS in terms of target lesion revascularization were published (16,21–23). Some studies, however, continued to show a slight increased risk of thrombosis but no increased mortality in patients receiving DES (24,25). Coinciding with recognition of the critical importance of DAPT with DES usage, Spertus et al. (26) documented that nearly 14% of patients had stopped taking clopidogrel within 30 days of receiving a DES for STEMI, with a subsequent 10-fold increase in mortality. These concerns were addressed in updated guidelines for PCI emphasizing that DAPT be continued for at least 1 year after DES implantation and that patients be screened "for the ability to comply with the recommended . . . [DAPT] therapy" (27). This update, offered in 2008—5 years after the introduction of DES into the general U.S. market—coincided with the publication of a well-conceived FDA-mandated follow-up study emphasizing real world (i.e., off label) activity 2008 (28).

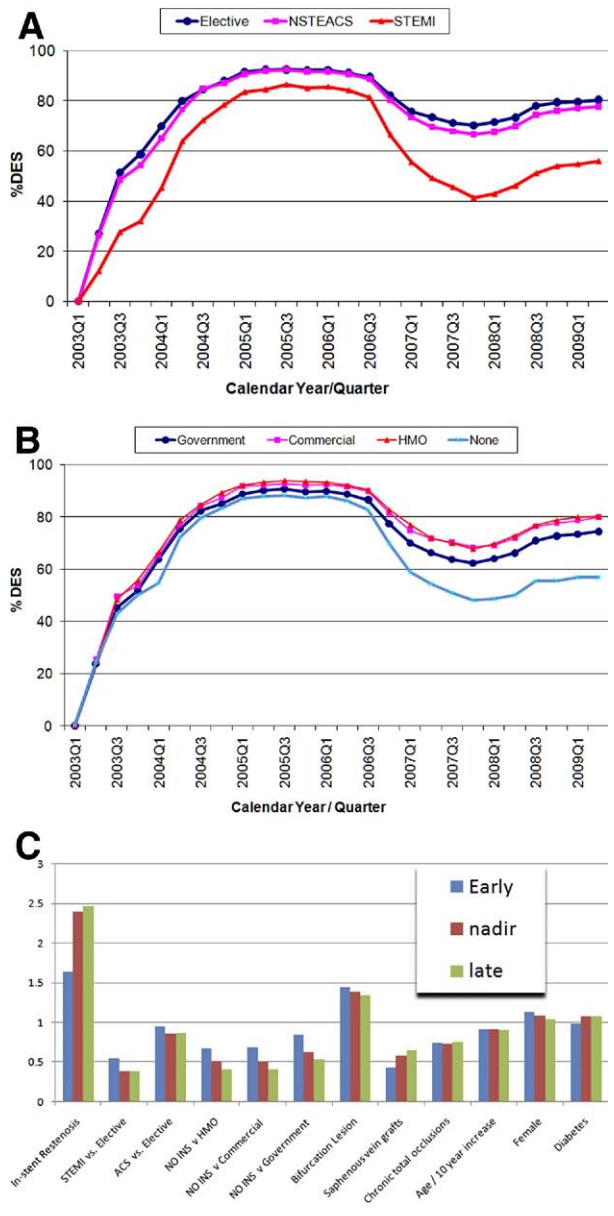

Figure 3. DES Usage by Indications, Medical Insurance, and Odds Ratios From the Multivariable Logistic Analyses

(A) Drug-eluting stent (DES) usage by indications for the procedure. **(B)** DES usage by medical insurance. **(C)** Odds ratios from the multivariable logistic analyses (Table 2) for the 3 time periods. Note that the likelihood of inserting a DES increased after 2007 for patients with in-stent restenosis and decreased at that time for patients with ST-segment elevation myocardial infarctions (STEMIs) and no insurance (NO INS). The likelihood of using a DES in patients with saphenous veins also increased (but still less than in the native vessel) after 2007. ACS = acute coronary syndrome; HMO = health maintenance organization; Government = Veterans Administration, Medicare, or Medicaid; None = no medical insurance; NSTEACS= unstable angina and non-STEMI.

We have documented that, after the FDA advisory in 2006, DES usage became more selective and use increased for in-stent restenosis and became less frequent in STEMI and in patients without medical insurance. The reasons driving increased DES usage rates in 2009 are not clear from this analysis but might be related to the introduction of second-generation drug-eluting stents and the awareness of the value of prolonged DAPT.

The experiences described here emphasize the inherent uncertainty when new technologies are introduced to clinical practice, especially when use is clearly going to go outside of the patient populations included within the initial approval studies (11,29). Most approval studies are adequately powered to prove efficacy but underpowered to evaluate safety (30). There is a clear need for aggressive post-market surveillance of new technologies with rapid evaluation and presentation of long-term results in real world populations and not just the patients similar to those in the original approval studies that might only account for a fraction of patients actually receiving these technologies. This might speed identification of concerns soon after widespread adoption so that corrective actions can be taken, or, as with DES, earlier recognition of the importance of long-term DAPT can be recommended before too many patients are placed at risk.

Study limitations. The ACC/NCDR is a voluntary national registry. Although not all interventional catheterization laboratories in the U.S. participate, it is estimated that approximately 75% of coronary interventions are captured.

Conclusions

DES were rapidly adopted into clinical practice in the U.S. on the basis of studies showing efficacy against restenosis but that were underpowered to demonstrate long-term complications. Reports of late stent thrombosis surfacing 3 years after introduction led to a dramatic reduction in usage, and DES placement became more selective after this point. In addition to clinical criteria, the absence of health insurance greatly influenced the likelihood that a DES would be placed, no doubt related to the demonstration of the importance of continuous DAPT therapy and the consequences of early discontinuation. The patterns of DES usage described here strongly reinforce the need for continuous timely reporting of outcomes data after the introduction of new technologies to allow better understanding of the indications and precautions needed to assure optimal use and safety as soon as possible after introduction.

Reprint requests and correspondence: Dr. Ronald J. Krone, Washington University School of Medicine, 660 South Euclid, Campus Box 8086, St. Louis, Missouri 63110. E-mail: rkrone@wustl.edu.

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REFERENCES

1. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–31.
3. Rao SV, Shaw RE, Brindis RG, Klein LW, Weintraub WS, Peterson ED. On- versus off-label use of drug-eluting coronary stents in clinical practice (report from the American College of Cardiology National Cardiovascular Data Registry [NCDR]). Am J Cardiol 2006;97:1478–81.
4. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA Perspective. N Engl J Med 2004;351:1593–5.
5. Virmani R, Kolodgie FD, Farb A. Drug-eluting stents: are they really safe? Am Heart Hosp J 2004;2:85–8.
6. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
7. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. J Am Coll Cardiol 2006;48:2584–91.
8. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med 2007;356:1009–19.
9. Camenzind E, Steg PG, Wijns W. A cause for concern. Circulation 2007;115:1440–55.
10. Westphal SP. Concerns prompt some hospitals to pare use of drug-coated stents. Wall Street Journal. Washington D.C., June 22, 2006.
11. Popma JJ, Weiner B, Cowley MJ, Simonton D, McKormack D, Feldman T. FDA advisory panel on the safety and efficacy of drug-eluting stents: summary of findings and recommendations. J Interv Card 2007;20:425–46.
12. Daemen J, Tanimoto S, García-García HM, et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction Am J Card 2007;99:1027–32.
13. Anderson HV. Drug-eluting stents: life insurance with a better death benefit. J Am Coll Cardiol 2008;51:2025–7.
14. Applegate RJ, Sacrinty MT, Kutcher MA, et al. "Off-label" stent therapy: 2-year comparison of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2008;51:607–14.
15. Hannan EL, Racz M, Walford G, et al. Drug-eluting versus bare-metal stents in the treatment of patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol Intv 2008;1:129–35.
16. Malenka DJ, Kaplan AV, Lucas FL, Sharp SM, Skinner JS. Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. JAMA 2008;299:2868–76.
17. Douglas PS, Brennan JM, Anstrom KJ, et al. Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the ACC/NCDR. J Am Coll Cardiol 2009;53:1629–41.
18. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS, Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. J Am Coll Cardiol 2001;37:2240–5.
19. Roe MT, Chen AY, Cannon CP, et al. Temporal changes in the use of drug-eluting stents for patients with non-ST-segment-elevation myocardial infarction undergoing percutaneous coronary intervention from 2006 to 2008: results from CRUSADE and ACTION-GWTG registries. Circ Cardiovasc Qual Outcomes 2009;2:414–20.
20. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation 2007;115:2435–41.
21. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
22. Shishehbor MH, Goel SS, Kapadia SR, et al. Long-term impact of drug-eluting stents versus bare-metal stents on all-cause mortality. J Am Coll Cardiol 2008;52:1041–8.
23. Groeneveld PW, Matta MA, Greenhut AP, Yang F. Drug-eluting compared with bare-metal coronary stents among elderly patients. J Am Coll Cardiol 2008;51:2017–24.
24. Park D-W, Yun S-C, Lee S-W, et al. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug-eluting stent: data from an observational cohort study of drug-eluting versus bare-metal stents. J Am Coll Cardiol Intv 2008;1:494–503.
25. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50:463–70.
26. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803–9.
27. King SB III, Smith SC Jr., Hirshfeld JW Jr., Jacobs AK, Morrison DA, Williams DO. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. J Am Coll Cardiol 2008;51:172–209.
28. Lasala JM, Cox DA, Dobies D, et al. Usage patterns and 2-year outcomes with the TAXUS express stent: (ARRIVE-1 Registry). Catheter Cardiovasc Interv 2008;72:433–45.
29. Strom BL. How the US drug safety system should be changed. JAMA 2006;295:2072–5.
30. Slottow P, Tina L, Waksman R. Overview of the 2007 Food and Drug Administration Circulatory System Devices Panel Meeting on the Endeavor zotarolimus-eluting coronary stent. Circulation 2008;117:1603–8.

Key Words: coronary artery stents ■ drug-eluting stents ■ outcomes assessment ■ percutaneous coronary intervention ■ stent thrombosis.