

Temporal Trends in the Use of Drug-eluting Stents for Approved and Off-label Indications: A Longitudinal Analysis of a Large Multicenter Percutaneous Coronary Intervention Registry

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ABSTRACT

Background: We sought to examine the temporal variations in the rate of both bare-metal stent (BMS) and drug-eluting stent (DES) use for off-label indications after the reports of an increased risk of very late stent thrombosis in patients with DES at the 2006 meeting of the European Society of Cardiology (ESC).

Hypothesis: To determine whether the decrease in use of DES has affected both on and off-label indications.

Methods: The study cohort included patients undergoing coronary intervention in a large regional registry, the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC₂). Patient demographic and clinical characteristics for patients with DES in the third quarter of 2006 (pre-ESC) were compared to those from the fourth quarter of 2008 (post-guideline changes). Use of DES for off-label indications, such as ST-segment elevation myocardial infarction (STEMI), in-stent restenosis (ISR), and saphenous vein graft (SVG) interventions, were evaluated.

Results: The overall deployment of DES fell sharply from 83% pre-ESC to a plateau of 58% in the first quarter of 2008. This corresponded to a rise in BMS use, while angioplasty procedures stayed the same. The STEMI subgroup showed the most dramatic change, from 78% to only 36%. Off-label use in SVGs showed a similar trend, from 74% to 43%. Drug-eluting stent deployment for ISR was less affected, though it also fell 25% (from 79%–56%).

Conclusions: The use of DES has fallen dramatically from June 2006 to December 2008, particularly for nonapproved indications. Our study provides a real-world assessment of contemporary change in DES use in response to the presentation of negative observational studies.

Introduction

After the first drug-eluting stent (DES) was approved by the Food and Drug Administration (FDA) for use in the United States in 2003, it quickly became the most commonly used stent type in percutaneous coronary intervention (PCI).¹ In September 2006, at the European Society of Cardiology (ESC) meeting, an observational study including patients who had received DES at a single institution, documented an increased risk of very late stent thrombosis compared to patients treated with bare-metal stents (BMS; 2.6% vs 1.3% over an 18 mo period).² Several other studies provided further evidence of an increased risk of very late stent thrombosis with DES vs BMS.^{3,4} Subsequent consensus

statements from the FDA and the Society of Coronary Angiography and Interventions (SCAI) in January 2007 recommended careful consideration of use of DES for off-label indications.⁵ Media reaction was swift, condemning DES technology as a potentially lethal heart device, and inciting a wave of panic for patients previously treated.

In light of these recent studies, there have been signs from industry data that the use of DES has dropped dramatically. However, there has been no attempt to quantify whether the decrease has occurred for approved or off-label indications. Furthermore, it is unclear whether more recent, less sensational trials demonstrating DES efficacy and safety have made an impact in DES use. In this study, we sought

to examine the temporal variations in the rates of both BMS and DES use for off-label indications in a statewide registry.

Methods

Subjects

The study cohort for our analysis included patients undergoing PCI in a large regional registry of contemporary PCI, the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). The details of the registry and of the data collection process have been described elsewhere.^{6–9} Briefly, procedural data on all patients undergoing elective and nonelective PCI at participating hospitals were collected using standardized data collection forms. Baseline data included clinical, demographic, procedural, and angiographic characteristics, as well as, medications used before, during, and after the procedure, and in-hospital outcome. All data elements were prospectively defined and the protocol was approved by the local institution review board at each institution. The data was collected by a dedicated staff member and forwarded to the coordinating center. Medical records of all patients undergoing coronary artery bypass grafting, or of patients who died in the hospital were reviewed to ensure data accuracy. A further 2% of cases were randomly selected for audit.

The BMC2 database was queried for the total use of DES, BMS, and angioplasty alone over the study period of January 2006 to December 2008. Patient demographic and clinical characteristics for patients given DES in the third quarter of 2006 (pre-ESC) were compared to those from the first quarter of 2008, when the nadir post-guideline changes were reached. Furthermore the median rate of DES use for all patients at each individual participating hospital was determined for the study period. Use of DES for off-label indications, such as ST-segment elevation myocardial infarction (STEMI), in-stent restenosis (ISR), and saphenous vein graft (SVG) interventions, were also reported. Finally, we evaluated the trends in use of DES in diabetic and elderly (≥ 80 yrs old) patients undergoing intervention.

Statistical Analysis

Patient characteristics, hospital data, and DES use were reported as frequencies for categorical data and means for continuous data. All comparisons were performed using SAS software, with a P value of <0.05 considered statistically significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

The study cohort included 79 388 patients undergoing PCI between January 2006 and September 2008. Patient demographic, clinical, and preprocedural data for patients in the pre-ESC era as compared to the last quarter of the

study period are listed in Table 1. Among patients treated with DES in the third quarter of 2006 vs the fourth quarter of 2008, there were fewer patients with a history of obesity ($\text{BMI} \geq 30$) and hypertension. Conversely, there were more DES patients in the third quarter of 2006 with significant valve disease and recent gastrointestinal bleeding (<30 d prior). Preprocedural clinical characteristics also differed between the third quarter of 2006 and the first quarter of 2008 as more emergency PCI, cardiogenic shock, and visible thrombus was found in the earlier period (Table 1).

The overall deployment of DES vs BMS heavily favored DES use initially, until it fell sharply after September 2006 (Figure 1). A plateau of 57% DES use was reached by December 2007. The fourth quarter of 2007 was a nadir for the usage of DES, with a gradual rise through 2008. The reduction in the use of DES corresponded to a rise in BMS use, while angioplasty procedures stayed the same. The median DES use at each participating hospital was also compared over time (Figure 2). Though DES use at each institution was at a relatively similar rate at the beginning of the study time period, by the beginning of 2007 there was a greater variation in the proportion of patients treated with DES at a given hospital.

Off-label Indications

The study cohort was then analyzed by 3 off-label indications, as well as 2 special clinical populations. The STEMI subgroup showed the most dramatic change, from 78% use pre-September 2006, to only 36% at the tail end of the study period (Figure 3). Off-label use in SVGs showed a similar trend, from 74% to 43% (Figure 4). Drug-eluting stent deployment for ISR was less affected, though it also fell more than 25% (from 79%–56%) through March 2008 (Figure 5). Simultaneously, use of angioplasty for patients with ISR increased from 3% at the beginning of the study period, to as high as 14% by March 2008.

Special populations: In diabetics, DES use dropped from 83% to 58%. Similarly, DES use fell from 78% in the first quarter of 2006 to 46% in the first quarter of 2008 in patients >80 years old.

Discussion

In April 2003, the FDA approved sirolimus-eluting stents (SES Cypher, Cordis Corporation, Bridgewater, NJ) for use in patients with coronary artery disease. Approval for paclitaxel-eluting stents quickly followed in March 2004. The use of DES expanded beyond FDA-approved indications, and off-label use, such as in acute coronary syndrome and SVG disease, grew at the same rapid pace despite the lack of clinical trials demonstrating safety and efficacy in these patient populations.

In September 2006, at the ESC meeting, an observational study was presented which revealed a 0.6% per year increased risk of very late stent thrombosis in patients

Table 1. For Patients Receiving Drug-Eluting Stents: Clinical and Procedural Characteristics in Baseline (Q3 2006) and Post Guideline Revision (Q4 2008)

	Jul–Sep 2006 N = 4849	Oct–Dec 2008 N = 4826	p value
Historical Variables			
Male	3165 (65.3%)	2786 (65.1%)	0.86
Age ≥ 80 years old	556 (11.5%)	491 (10.2%)	0.04
Current Smoking	1215 (25.1%)	1171 (24.3%)	0.37
Obese (BMI ≥ 30)	2125 (45.2%)	2293 (48.7%)	0.0006
Hypertension	3980 (82.1%)	4099 (84.9%)	0.0002
Previous MI	1674 (34.5%)	1656 (34.3%)	0.83
Diabetes	1673 (34.5%)	1787 (37.0%)	0.01
CHF	713 (14.7%)	670 (13.9%)	0.25
PVD/CVA	1269 (26.2%)	1201 (24.9%)	0.15
Dialysis dependent renal failure	81 (1.7%)	74 (1.5%)	0.59
Significant valve disease	219 (4.5%)	152 (3.2%)	0.0008
Recent GI bleed	107 (2.2%)	35 (1.1%)	<0.0001
Atrial fibrillation	400 (8.3%)	419 (8.7%)	0.44
Cardiac arrest	63 (1.3%)	53 (1.1%)	0.36
PCI	2093 (43.2%)	2275 (47.1%)	<0.0001
CABG	880 (18.2%)	921 (19.1%)	0.24
COPD	848 (17.5%)	856 (17.7%)	0.75
Presenting Variables			
Emergency PCI	605 (12.5%)	476 (9.9%)	<0.0001
Current MI (<7 days prior)	1309 (27.0%)	1317 (27.3%)	0.75
Cardiogenic shock	69 (1.4%)	44 (0.9%)	0.02
EF < 50%	1393 (28.7%)	1252 (25.9%)	0.002
CTO	92 (1.9%)	81 (1.7%)	0.42
Restenosis	393 (8.1%)	483 (10.0%)	0.001
Thrombus	582 (12.0%)	395 (8.2%)	<0.0001

MI = myocardial infarction, CHF = congestive heart failure, PVD = peripheral vascular disease, CVA = cerebral vascular accident, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, EF = ejection fraction, CTO = chronic total occlusion. Dialysis-dependent renal failure was defined as those patients requiring peritoneal or hemodialysis. Thrombus was defined as visible thrombus at the time of initial angiography.

receiving DES. Very late stent thrombosis is a serious complication of DES use, with 60% of patients presenting with either STEMI or death.¹⁰ In light of these findings, revised guidelines from the SCAI and the FDA advised caution in the use of DES and in assessing

appropriateness of patients for prolonged dual antiplatelet therapy.⁴

In the present study, we sought to evaluate the impact these presentations and publications had on the use of DES through a statewide registry. A sharp decline in

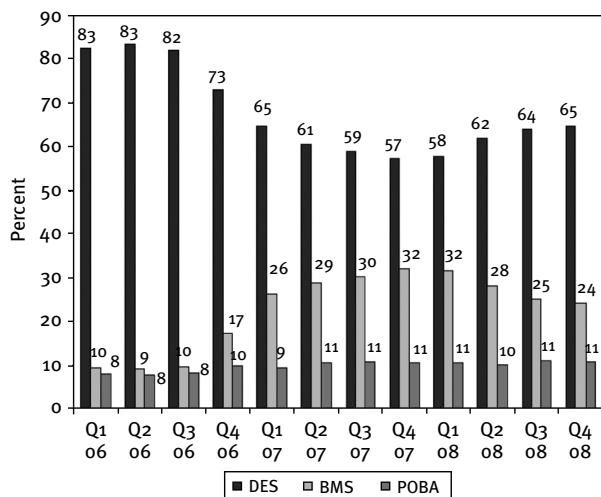


Figure 1. Stent use among all patients undergoing PCI from January 2006 to March 2008. Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent, PCI, percutaneous coronary intervention; POBA, balloon angioplasty alone, Q1 06, January to March 2006; Q2 06, April to June 2006; Q3 06, July to September 2006; Q4 06, October to December 2006; Q1 07, January to March 2007; Q2 07, April to June 2007; Q3 07, July to September 2007; Q4 07, October to December 2007; Q1 08, January to March 2008; Q2 08, April to June 2008; Q3 08, July to September 2008; Q4 08, October to December 2008.

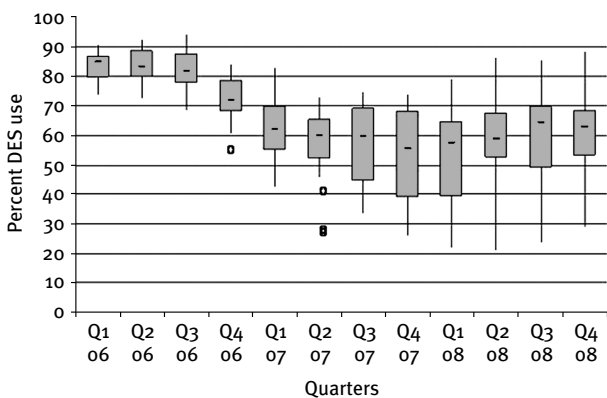


Figure 2. Median rate of DES use across all participating hospitals for any patient undergoing PCI. Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent, PCI, percutaneous coronary intervention; POBA, balloon angioplasty alone, Q1 06, January to March 2006; Q2 06, April to June 2006; Q3 06, July to September 2006; Q4 06, October to December 2006; Q1 07, January to March 2007; Q2 07, April to June 2007; Q3 07, July to September 2007; Q4 07, October to December 2007; Q1 08, January to March 2008; Q2 08, April to June 2008; Q3 08, July to September 2008; Q4 08, October to December 2008.

DES use, in both the total population, which included stable and ACS patients, as well as a decline in the use in key subgroups, was seen. The rapid fall in average

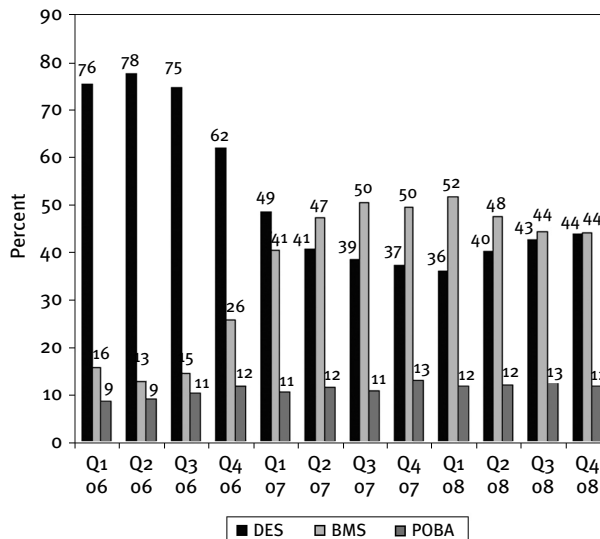


Figure 3. Stent use among patients presenting with STEMI. Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent, PCI, percutaneous coronary intervention; POBA, balloon angioplasty alone, Q1 06, January to March 2006; Q2 06, April to June 2006; Q3 06, July to September 2006; Q4 06, October to December 2006; Q1 07, January to March 2007; Q2 07, April to June 2007; Q3 07, July to September 2007; Q4 07, October to December 2007; Q1 08, January to March 2008; Q2 08, April to June 2008; Q3 08, July to September 2008; Q4 08, October to December 2008; STEMI, ST-segment elevation myocardial infarction.

DES use across all patients included in our analysis may be related to fear of the catastrophic outcomes of patients who suffer stent thrombosis, including STEMI and death. Additionally, increased media coverage and public awareness of side effects of prescription drugs and complications with medical devices may have fueled a more precipitous drop in the use of DES. However, the decline in DES use was not uniform, with marked variability in DES use between hospitals by the end of the first quarter of 2008. More recently, usage of DES in PCI appears to be leveling off, perhaps in part to recent reports which demonstrated no significant increase in stent thrombosis with DES when compared to BMS.¹¹⁻¹³

Off-label use of DES came under particular scrutiny following clinical statements made by professional societies. We chose patients with STEMI, SVG disease, and ISR as representative subgroups of off-label indications to further evaluate the impact of the landmark trials on DES use. Though a decline after the third quarter of 2006 was seen among all the subgroups, the most pronounced decline was seen in patients with STEMI. This most likely represents a higher level of concern regarding thrombus burden and general proinflammatory state at the time of intervention. This is further supported by the changing patient clinical characteristics pre-ESC and post-ESC, with a

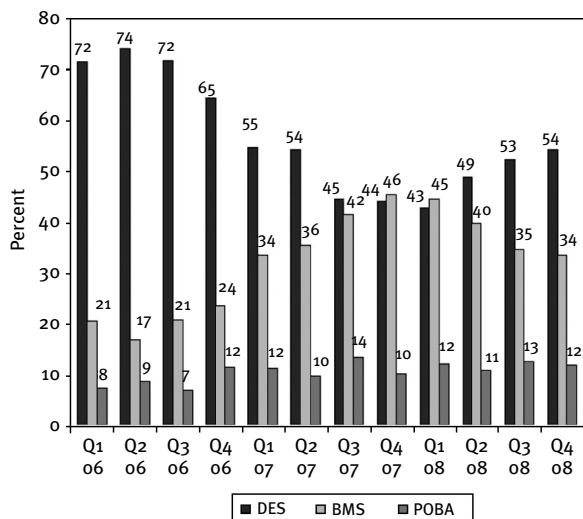


Figure 4. Stent use in patients undergoing vein graft intervention. Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent, PCI, percutaneous coronary intervention; POBA, balloon angioplasty alone, Q1 06, January to March 2006; Q2 06, April to June 2006; Q3 06, July to September 2006; Q4 06, October to December 2006; Q1 07, January to March 2007; Q2 07, April to June 2007; Q3 07, July to September 2007; Q4 07, October to December 2007; Q1 08, January to March 2008; Q2 08, April to June 2008; Q3 08, July to September 2008; Q4 08, October to December 2008.

statistically significant drop in the percentage of patients with visible thrombus on angiography who received a drug-eluting stent. The emergent pace of primary PCI in STEMI may also limit the physicians' ability to identify patient comorbidities or financial difficulties which could make compliance with long-term dual antiplatelet therapy difficult.

There are limited data evaluating use of DES in vein grafts and concerns have been raised regarding the interaction of the drug-eluting stent with the aggressive atherosclerosis typical of vein graft disease. This concern may have played a part in the corresponding drop in DES use among the subset of patients undergoing PCIs in the BMC2 registry. Though also an off-label indication, a less well understood decline in DES in patients with restenosis was also seen, as well as an increase in angioplasty alone, from 4% to 14% by the first quarter of 2008. Patients with restenosis are at the greatest risk of subsequent restenosis and DESs have demonstrated marked benefits in this population.¹⁴ A decline in DES use may seem a bit counterintuitive in this subset.

The 2 patient populations that are more likely to benefit from DES use also demonstrated a puzzling decline in DES use. The dramatic efficacy of DES in the presence of diabetes has been well established.^{15,16} However, there was a similar decline in the use of DES in diabetic patients in the present

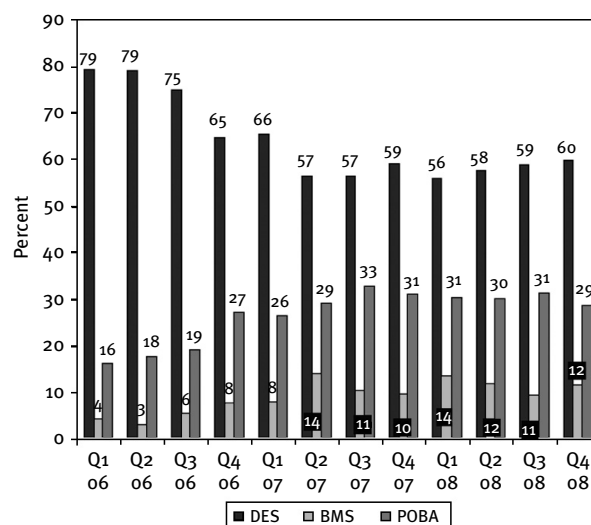


Figure 5. Stent use in restenotic lesions. Abbreviations: DES, drug-eluting stent; BMS, bare-metal stent, PCI, percutaneous coronary intervention; POBA, balloon angioplasty alone, Q1 06, January to March 2006; Q2 06, April to June 2006; Q3 06, July to September 2006; Q4 06, October to December 2006; Q1 07, January to March 2007; Q2 07, April to June 2007; Q3 07, July to September 2007; Q4 07, October to December 2007; Q1 08, January to March 2008; Q2 08, April to June 2008; Q3 08, July to September 2008; Q4 08, October to December 2008.

study. Finally, DES use in patients over 80 years old fell by almost half, which could be in part due to concern over long-term dual antiplatelet and thus increased bleeding risk in these patients.

Our study provides an example of a possible disconnect between emerging clinical evidence and clinical practice. In the past, appropriate clinical use of proven therapies has been observed in response to widely published, compelling clinical evidence, albeit the pace of adoption of such advances in care historically has been very slow.¹⁷ Our data would suggest that new device use may demonstrate a different pattern, with rapid changes in practice patterns in response to partial information demonstrating newly identified risks driving broad changes in device use, only some of which are based on newly reported evidence. This theory is further supported by data from the CRUSADE and ACTION-GWTG registries, which found a similar decline in DES use, though data was limited to patients presenting with non-ST-segment elevation myocardial infarction.¹⁸

When DESs were introduced, they were hailed as one of the greatest breakthroughs in cardiovascular medicine by both the medical press and the lay press. Physicians initially overwhelmingly adopted DES with limited data to support use in off-label patient populations. Subsequently and likely based primarily on the report from small observational studies, we observed a dramatic decline in use of DES

even in patient populations where the stents have been demonstrated to be particularly efficacious. This decline preceded the publication of the negative data in peer-reviewed literature and seems to have been fuelled by the negative publicity in the lay press. Despite a multitude of more recent data, DES use has yet to reach 2006 rates. Our study thus provides a glimpse into the changing patterns of uptake of a therapy that is widely covered by the lay press.

Study Limitations

This study was limited to an assessment of pre-PCI and procedural characteristics, and did not include an assessment of long-term outcomes such as late stent thrombosis. Our data suggest, but do not prove, a relationship between DES use and media reporting.

Conclusion

In this large multicenter registry, overall DES use has fallen dramatically from June 2006 to December 2008, though with marked variability in utilization rates between hospitals. The most pronounced decreased use of DES has occurred for nonapproved indications, including STEMI and SVG disease, but also seems to have occurred in populations where DES may be particularly efficacious. Our study provides a real-world assessment of contemporary change in DES use in response to the presentation of negative observational studies.

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