Bare-Metal Stent Outcomes in an Unselected Patient Population

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Summary

Background: Randomized trials have shown that drug-eluting stents (DES) substantially reduce in-stent restenosis compared with bare-metal stents (BMS).

Hypothesis: Revascularization event rates related to BMS restenosis may be higher in the trials setting than in real-world experience, calling into question the extent of benefit possible with widespread DES use in regular practice.

Methods: Between December 1998 and March 2003, 17,102 patients with BMS registered in the Goodroe Healthcare Solutions Data Warehouse met the inclusion criteria for this retrospective study of catheterization laboratory data. We examined the database for evidence of diagnostic angiography or percutaneous coronary intervention (PCI) readmission within 1 year after stenting.

Results: Repeat PCI was documented for 2,070 patients, and 232 were referred for coronary artery bypass graft surgery (CABG)—in sum, 13.5% of the cohort. Stented region revascularization was observed in 8.4%: 1,350 patients underwent subsequent PCI, and 84 of the patients referred for CABG had in-stent lesion recurrence. Only 1,207 (7.1%) patients required stent-related PCI after 30 days, the time frame consistent with restenosis.

Conclusions: In this “real-world” series, reintervention of a stented region after the first follow-up month was documented in fewer than 8% of patients in a large cohort that had received BMS. The rate of clinical events potentially related to BMS in-stent restenosis in this large, unselected patient population is substantially lower than that in the control arms of some DES trials. The incremental benefit of widespread conversion from

BMS to DES may be smaller in some patient populations than is suggested by the results of those trials.

Key words: coronary stent, outcomes, coronary restenosis, angioplasty

Introduction

The major health and economic consequence of in-stent restenosis is symptom-driven revascularization, often with percutaneous coronary intervention (PCI).¹ Rapid acceptance of drug-eluting stents (DES) was based on evidence from randomized trials that they reduce in-stent restenosis. A meta-analysis of 11 such DES trials illustrates that stented-lesion revascularization declined by as much as 81% compared with bare-metal stent (BMS) control groups.² Whether the same dramatic reduction in repeat revascularization can be achieved outside the trials setting depends on the baseline incidence of revascularization for clinically evident BMS restenosis in the “real world.”

Because coronary artery disease is progressive in nature, many patients require additional revascularization for lesions in other coronary segments even when the initially stented segment remains fully patent. Cutlip *et al.* analyzed 5-year follow-up data for 1,288 randomized patients in stent trials and observed that after the first year the hazard rate for stented lesion events (including death, infarction, and revascularization) was 1.7% while that related to nonstented lesions was 6.3%.³ Accordingly, to quantify the need for revascularization related to in-stent restenosis, we examined the angiographic data from catheterization laboratory readmissions in patients who received BMS prior to the market release of DES.

Methods

The data analyses described herein were conducted with approval from the Stanford University Panel for Human Subjects in Medical Research.

We examined cardiac catheterization laboratory data from 17 hospitals that use CathSource™ Enterprise software (Goodroe Healthcare Solutions, Norcross, Ga., USA) to identify patients who received BMS between December 1, 1998, and March 31, 2003. Contributing hospitals are geographical-

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ly distributed throughout the United States and submit cardiac catheterization records to the Goodroe Data Warehouse every 3 months. An automated rules engine validated the clinical and device usage data for consistency within each patient record. Patients who suffered out-of-laboratory death, stroke, or recurrent cardiac symptoms may have returned to cardiologists or hospitals other than their original providers, and those events would not have been captured in the Goodroe Data Warehouse.

We excluded patients who also underwent atherectomy or brachytherapy, and patients whose PCI records did not include physician-entered data describing the location of the stented arterial segment, or lesion type and severity. We reviewed the data-harvesting pattern to ensure that the Warehouse received data from each hospital for at least 9 months subsequent to each index BMS procedure. Unique patient and site identifiers assigned during the data collection process were used to search the database for repeat PCI or diagnostic catheterization records up to 365 days following the index BMS admission. The angiographic data from subsequent catheterization laboratory procedures were examined to determine the anatomical targets of repeat PCI as well as diagnostic results that advised coronary artery bypass surgery (CABG) referral.

Clinical and angiographic data were collected in accordance with the guidelines of the American College of Cardiology National Cardiovascular Data Registry.⁴ Interventional cardiologists coded the location and severity of diseased and treated arterial segments according to the specifications contained in Appendix A of those guidelines. Cardiologists typically used visual estimates to assess reference vessel diameter, lesion length, and diameter stenoses, and these measurements were recorded in the interventional procedure record. Recurrent coronary artery lesions were defined as those with $\geq 50\%$ diameter stenosis at the time of subsequent diagnostic catheterization, or those in which repeat PCI was performed regardless of lesion severity. To accommodate the possibility of inconsistency in arterial segment coding that could result in underestimation of stented-segment reintervention (i.e., stent-related restenosis that was later coded as an adjacent segment), we expanded our definition of the “stented region” to include the stented segment together with proximal and distal arterial segments, or the ostium of an adjacent arterial branch. Coronary anatomy outside the stent region was termed “remote” anatomy. Independent core laboratory review of angiographic data is not part of the Warehouse quality control process. The methodology for assessing angiographic results in this setting is different from that in the trials setting, where angiographic core laboratory analysis is the standard and routine follow-up angiography is often performed.

Results

Patient and Procedural Characteristics

Catheterization laboratory records were found for 27,452 patients who received BMS between December 1, 1998, and

March 31, 2003. We excluded 8,774 patients who also underwent atherectomy or brachytherapy, or whose catheterization laboratory records did not include complete details for the stented lesion. Another 1,576 patients were excluded because the hospital did not submit data for 9 follow-up months. Hospitals that submitted data for 12 months or more after all index procedure dates contributed more than 95% of the qualifying 17,102 patients. The average patient age was 64.3 ± 12.2 years, 63.5% were male, and approximately 25% were diabetic (Table I). The proportion of the study population (41%) receiving lipid-reduction therapy at the time of the index stent procedure was substantially lower than anticipated, causing us to consider the possibility of underreporting in this data field. Approximately half of the patients had unstable angina and 9% were admitted with acute myocardial infarction.

Previously untreated (de novo) lesions were the sole therapeutic target of the index stent procedure in 94% of the patients. One stent was placed in 68.7% of the index procedures and two stents were used in 23.8%; fewer than 8% of the patients received more than two stents. While 76.5% of the patients underwent stenting in a single arterial segment, 51% had

TABLE I Patient, anatomical, and procedural traits

Patient traits	
Age (years)	64.2 $\pm$ 12.2
Male (%)	63.5
Prior PCI (%)	25.7
Prior CABG (%)	17.7
Diabetic (%)	24.7
Hypercholesterolemia with statin therapy (%)	41.0
Hypertension (%)	63.7
Myocardial infarction at admission (%)	8.7
Current smoker (%)	23.6
Unstable angina (%)	52.3
Multivessel disease (%) ^a	32.4
Anatomical and procedural traits	
Single-vessel revascularization (%)	89.3
Single-segment stent (%)	76.5
Reference vessel diameter (mm)	3.14 $\pm$ 0.5
Stent size > 3.0 mm (%)	67.3
Stent length (mm)	15.8 $\pm$ 5.6
Stents used in study vessel	1.4
Target lesion location	
Left main	1.0
Left anterior descending	38.2
Left circumflex	23.5
Right	37.4
Procedural outcomes	
Death during stent admission (%)	0.008
Urgent CABG during stent admission (%)	0.05

^a Lesions $\geq 70\%$ diameter reduction in more than one major epicardial artery.

$\pm$ One standard deviation.

Abbreviations: PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft surgery.

multisegment disease (defined as two or more lesions $\geq 70\%$ diameter stenosis). Single-vessel stenting was performed in 89.3%; however, 32% of the patients had multivessel disease.

Diagnostic catheterization within the first year was documented in 3,623 (21.4%) patients. One-third of those angiograms resulted in recommendation for medical management without further revascularization. Without access to the details of noninvasive tests for myocardial ischemia or the patient's symptomatic status we cannot comment on the choice between medical management and reintervention. Subsequent PCI was performed in 2,070 (12.1%) and CABG was recommended for another 232 (1.4%) of the study patients, for a total of 2,302 patients who underwent repeat revascularization (13.5% of the cohort).

Diagnostic Catheterization Findings in Patients Referred for Bypass Surgery

Coronary artery bypass grafting was recommended for 232 of the patients who had undergone diagnostic catheterization but not additional PCI. Of these, 148 had lesions with $\geq 50\%$ diameter stenosis in unstented arterial segments. Recurrent lesions within the stented segment were documented in 84 of the patients referred for CABG (0.5% of the cohort) (Table II).

Patient-Level Analysis of Follow-Up Percutaneous Coronary Interventions

Of the 17,102 patients, 2,070 had additional PCI procedure records in the Goodroe system within 1 year (12.1% of the cohort). Any PCI within the stented region was observed in 1,350 patients (7.9% of the cohort) and 62 of these also underwent PCI to remote anatomy. Of the stented region reintervention subset, 1,207 (7.1% of the cohort) were readmitted more than 30 days after index stenting, the time frame most likely related to restenosis. Conversely, 723 patients (4.2% of the cohort) had additional PCI solely for lesions remote to the stent-

ed region, and 178 of these were readmitted within 30 days of the index stent procedure. To allow comparison of the stented region results with analyses conducted at the segment level, we report both in Table II.

Patients with multisegment disease had the highest rate for repeat PCI: 15.3% for patients who underwent multisegment stenting and 14.4% for those who had single-segment index stenting. Patients with single-segment stenting of single-segment disease had the lowest rate for subsequent PCI (8.2%). However, patients who had single-segment disease but received multisegment stenting underwent repeat procedures at a rate closer to the subset with multi-segment disease (13.9%).

In sum, the follow-up catheterization laboratory records of 1,434 patients (8.4% of the cohort) indicated either PCI to the stented region or CABG referral with lesions of $\geq 50\%$ diameter reduction in a stented region.

Angiographic Analysis of Follow-Up Percutaneous Coronary Interventions

We observed 2,494 readmissions for PCI in 2,070 patients within 1 year. The average time between the index stent procedure and subsequent PCI was 137 ± 99 days and the interval was 161 ± 90 days excluding procedures performed within the first follow-up month. One additional PCI was observed in 1,741 (84%) of the 2,070 patients, while 329 patients returned for reintervention more than once (255 patients 2 $\times$; 58 patients 3 $\times$; 11 patients 4 $\times$; 5 patients 5 $\times$).

Of the 2,494 follow-up PCIs, 1,627 (65.2%) involved the stented region (Fig. 1). Conversely, 867 (34.8%) of the reinterventions were limited to arterial segments remote from the stented region, namely, segments that were neither previously stented nor adjacent to a previously stented segment. Of the documented readmissions, 388 (15.6%) were for PCI within the first month. Of those 30-day events, 165 (42.5%) procedures were performed in the stented region, including 102 to treat segments adjacent to the stent. Just more than half

TABLE II Anatomical site of subsequent revascularization, patient level

	N	% of cohort
Diagnostic findings leading to CABG referral	232	1.4
Stented segment $\geq 50\%$ diameter reduction $\pm$ other lesions	84	0.5
Lesions $\geq 50\%$ only in nonstented segments	148	0.9
Patients with documented repeat PCI	2,070	12.1
Subsequent PCI(s) limited to the stented segment	592	3.5
Both stented and nonstented segment reintervention	435	2.5
Subsequent PCI(s) limited to any nonstented segment	1,043	6.1
Subsequent PCI(s) limited to the stented region ^a	1,245	7.3
Both stent region and remote reintervention	105	0.6
Subsequent PCI(s) limited to remote anatomy ^b	719	4.2
Patients with stented region CABG or repeat PCI	1,434	8.4

^a Stented region includes the stented segment and all adjoining arterial segments.

^b Remote anatomy is any arterial segment neither stented nor adjacent to the initially stented segment.

Abbreviations as in Table I.

FIG. 1 Anatomical target of follow-up percutaneous coronary interventions. Adjacent arterial segments are included with the stented segment to define a broader stented region. Percutaneous coronary intervention (PCI) limited to the stented region accounted for 1,500 (60.1%) of the reinterventions, while 127 (5.1%) procedures targeted both remote anatomy and the stented region. Remote coronary anatomy is defined as any arterial segment that was neither stented at the index procedure nor lies adjacent to the stented segment(s). Additional PCI limited solely to remote anatomy accounted for 867 (34.8%) of the PCI readmissions.

(1,454—58.3%) of the documented follow-up PCIs involved any stented region reintervention beyond the first follow-up month. Thirty-day PCI in remote lesions accounted for 215 (8.6%) of the PCI readmissions.

Discussion

The rate of documented repeat PCI in this study was 12.1% and the follow-up CABG rate was 1.4%, comparing favorably with other longitudinal studies. Aegma *et al.* reported a 10.3% target-vessel revascularization rate in a series of 3,146 patients followed for 9 months,⁵ and Ellis *et al.* reported an overall repeat revascularization rate of 13.4%.⁶ In contrast, some randomized DES trials report BMS reintervention rates as high as 22.9%.²

We used an expanded definition of “target lesion” to include anatomy adjacent to the stented segment because adjacent segment treatment may have been recorded due to inconsistent coding of arterial segments or lesions that straddle two or more segments. This anatomically generous definition reduced our risk of underestimating stent-related restenosis due to segment coding inconsistencies. With follow-up PCI and CABG combined, we observed revascularization of a stented region in 8.4% of the patients studied. From the DES trials, Babapulle *et al.*² reported a pooled target-lesion revascularization rate of 13.2% for patients with bare metal stents. Many trials included in that analysis used routine angiographic follow-up, which is widely known to have an inflationary effect on reintervention rates.⁶ The reintervention rate in this study may differ from the trials because of other factors that we did not examine in detail, including likely differ-

ences of patient and lesion traits and the methods for angiographic measurements and data collection.

Slightly more than 4% of the cohort returned for PCI to remote arterial segments without any further intervention in the stented region, and almost 1% were referred for CABG with documented lesions only in anatomy remote from the stented segment. Consequently, approximately 5% of this cohort required revascularization for symptomatic lesions remote from the previously stented anatomy within 1 follow-up year, with no reintervention of the stented region. Percutaneous coronary intervention to remote segments within the first month accounted for almost 9% of the documented readmissions. A substantial component of this early reintervention may be intentionally staged treatment of multisegment coronary disease, but we cannot speculate about the effect that DES use might have on this practice.

According to meta-analyses of DES trials, there are no significant differences in terms of mortality and post-stent acute myocardial infarction between DES and BMS² or between different types of DES.⁷ However, the randomized trials cannot be used to infer differential rates of very serious yet infrequent events beyond the first 9 months after stenting. McFadden *et al.* reported four cases of DES thrombosis between 343 and 442 days post stenting following interruption of antiplatelet therapy.⁸ These authors raise questions about the extended time period for risk of thrombotic stent closure as a result of suppressed endothelial regrowth over a DES, which may make itself apparent only upon discontinuation of antiplatelet medications. Careful longitudinal study of patients with DES is needed to observe not only in-stent restenosis rates in the real world, but also rates of infrequent but potentially life-threatening complications, such as stent thrombosis, beyond the first follow-up year.

The trade-off between restenosis and thrombosis becomes especially important when the risk of BMS in-stent restenosis is low and the added outcomes benefit of DES use is undefined. In attempting to identify risk factors for BMS in-stent restenosis, Ellis *et al.* found that 19 of 20 patient subgroups had repeat revascularization rates ranging between 4 and 10%.⁶ Accurate prospective identification of patients who have increased risk for restenosis remains an elusive goal, but the results of our study support the observation by Ellis *et al.* that subsets of the patient population with BMS have < 10% risk for restenosis-related revascularization. A similar study of large populations with DES is needed to quantify the overall reduction in repeat revascularization now that widespread DES use is well established.

Study Limitations

The results of this study are affected by several limitations. Due to the nature of the data collection process, we are unable to report serious events such as death and stroke: in a longitudinal study of patients with BMS, Aegma *et al.*⁵ reported that 2.1% suffered such events. The exclusion criteria were largely based on completeness of the angiographic data in the index stent procedure record and resulted in exclusion of ap-

proximately 32% of the patients with stents. We were unable to compare the traits of included and excluded patients; however, a few hospitals were the source of most of the exclusions and therefore the possibility of site bias exists. Other exclusions resulted from site failure to submit data to the warehouse consistently for 9 months after each enrolled index procedure. We did not survey the contributing hospitals to see how their interventional case complexity and volume compares with other centers.

Conclusions

Focused use of DES for patients at the highest risk of in-stent restenosis would not only improve the cost effectiveness of stenting, but would also protect patients with lower restenosis risk from potential stent-related complications associated with discontinuation of antiplatelet therapy long after stenting. While more than 90% of all patients with stents now receive DES, a growing body of evidence suggests that in subsets of the patient population with BMS fewer than 10% would require repeat revascularization to treat symptoms related to restenosis.

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