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Characterization of Post-Operative Risk Associated With Prior Drug-Eluting Stent Use

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Objectives The aim of this study was to assess risk of inpatient surgery at any time after percutaneous coronary intervention (PCI) with drug-eluting stents (DES).

Background Risk of adverse events, including stent thrombosis (ST), in patients undergoing surgical procedures with prior DES remains poorly defined.

Methods Outcomes of consecutive patients having inpatient surgical procedures after PCI with DES, placed from April 28, 2003 until December 31, 2006 at a tertiary-care medical center, were studied. Primary and secondary end points were 30-day post-operative risk of the Academic Research Consortium (ARC) definite and modified probable definitions of ST and combined 30-day post-operative risk of death, nonfatal myocardial infarction (MI), or ST, respectively. Multivariable logistic regression analyses were used to determine independent risk factors.

Results Six hundred six inpatient surgeries on 481 patients with a mean time from PCI to surgery of 1.07 $\pm$ 0.89 years were evaluated. The primary and secondary end points occurred after 11 (2.0%) and 56 (9%) surgeries, respectively. Risk of the combined end point and ST decreased significantly in the first 1 to 6 months after PCI ($p < 0.0001$ and $p < 0.014$, respectively); however, risk persisted when time between PCI and surgery was >12 months. Independent correlates of the combined end point include emergency surgery, antecedent MI, the pre-operative use of intravenous heparin, and atherosclerotic lesion length treated with DES. Oral antiplatelet status at time of surgery was not a correlate of events.

Conclusions Risk of 30-day post-operative adverse events, including ST, remains significantly higher when surgery is performed soon after PCI, while intermediate-term risk extending at least 2 to 3 years remains important. (J Am Coll Cardiol Intv 2009;2:542–9) © 2009 by the American College of Cardiology Foundation

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Coronary artery stenting has increased in the last several years with the advent of drug-eluting stents (DES) (1). The initial enthusiasm for DES due to reductions in restenosis has been tempered by concerns about stent thrombosis (ST), particularly late ST (2,3).

The risk of noncardiac surgery in weeks following percutaneous coronary intervention (PCI) with bare-metal stents (BMS) has been well-examined (4,5). The risk of DES thrombosis in the perioperative period is thought related to 3 main factors—cessation of dual antiplatelet therapy for surgery, a hypercoagulable state associated with surgery, and non-endothelialization of the stent (6). It is difficult, however, to judge actual risk associated with surgery after DES, because there have been no large-scale systematic reviews of the topic and existing reports to do not provide consistent findings (7–9). Given the currently limited data (10), we sought to better characterize perioperative risk associated with prior DES use.

Methods

Patient selection. This study protocol was approved by the Cleveland Clinic Institutional Review Board. All patients having undergone PCI at the Cleveland Clinic with DES from 2003 until the end of 2006 were identified by the Cleveland Clinic PCI database in which consecutive patients are enrolled. These patients were cross-matched with the Cleveland Clinic operating room database to identify those patients having undergone any inpatient surgical procedure at any time point after PCI. Patients were excluded if they had undergone percutaneous surgical procedures, experimental procedures, procedures performed outside the main campus, or heart transplantation (Fig. 1). Surgical risk was defined by a previously validated risk index (11).

Information regarding the resulting cohort of patients was obtained from an interrogation of the medical record. Information was gathered regarding baseline demographic data, past medical history, baseline laboratory values, and medications at time of surgery, including antiplatelet medication status before and at the time of surgery (Online Appendix 1: core variables). Creatinine clearance was calculated with the Cockroft-Gault equation.

Follow-up and clinical events. Follow-up was established by evidence of clinical visit at or after 30 days after the surgical procedure or by occurrence of a primary or secondary end point. A clinical visit to an affiliate hospital or satellite clinic was deemed acceptable for follow-up as electronic medical records were available for review. Death was established either by the Social Security Death Index (last updated on February 2, 2008) and/or by review of the paper and electronic medical record.

Events such as myocardial infarction (MI) or ST were adjudicated (S.A.) on the basis of available clinical data. Diagnosis of perioperative MI was established with biomarkers, electrocardiographic evidence of ischemia or infarction, and clinical course as previously published (12). "Definite" ST events were classified on the basis of the Academic Research Consortium (ARC) definition (13). "Probable" ST was a modified version of the ARC definition. The modification involved excluding any unexplained death within 30 days of PCI as a probable ST and requiring evidence of an MI with evidence of ischemia in the territory of the prior stent without another obvious cause within the 30-day post-operative period. The rationale for modification of the definition was to avoid arbitrary assignment of ST as a cause of death in patients having undergone surgery within 30 days of PCI.

End points. The primary end point for this study was prospectively defined as the 30-day post-operative incidence of ST (as in the preceding), and the secondary end point was defined as the 30-day post-operative combined incidence of ST, nonfatal MI (non-stent thrombosis), or death.

Statistical methods. Continuous data are expressed as mean ± SD or with median and 15th and 85th percentile values (comparable to 1 SD) as appropriate. For continuous variables, Wilcoxon rank sum tests were used to analyze 2-level group differences and Kruskal-Wallis tests were used to analyze 3-level group differences. Categorical data are displayed as frequencies and percentages, and comparisons are made with chi-square tests (Fisher exact tests if appropriate).

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
ST = stent thrombosis

Multivariable logistic regression analyses were used to determine independent risk factors for the combined end point. A stepwise selection approach was used with criteria of $p \leq 0.05$ for retention of variables to form an initial model. Bootstrap bagging methods were then used to determine important reliable predictors with random resampling and automated analysis of 1,000 datasets for each end point. Covariates entered into ≥50% of the bootstrapping runs were retained in the final parsimonious model.

The unit of observation for this study is surgery following DES. To allow for at least a 15-day uninterrupted follow-up after index surgery, for patients with more than 1 temporally related surgery, the index surgery was taken as the last surgery in the sequence for the primary analysis. Generalized estimating equations (GEE) (14) were developed to account for within-patient correlation of repeated measurements (multiple surgeries/patient). Final parameter estimates are the results of GEE-adjusted models.

Transformations of scale for continuous variables were used to meet model assumptions and for proper calibration of predictive variables with outcome. Univariable trend plots

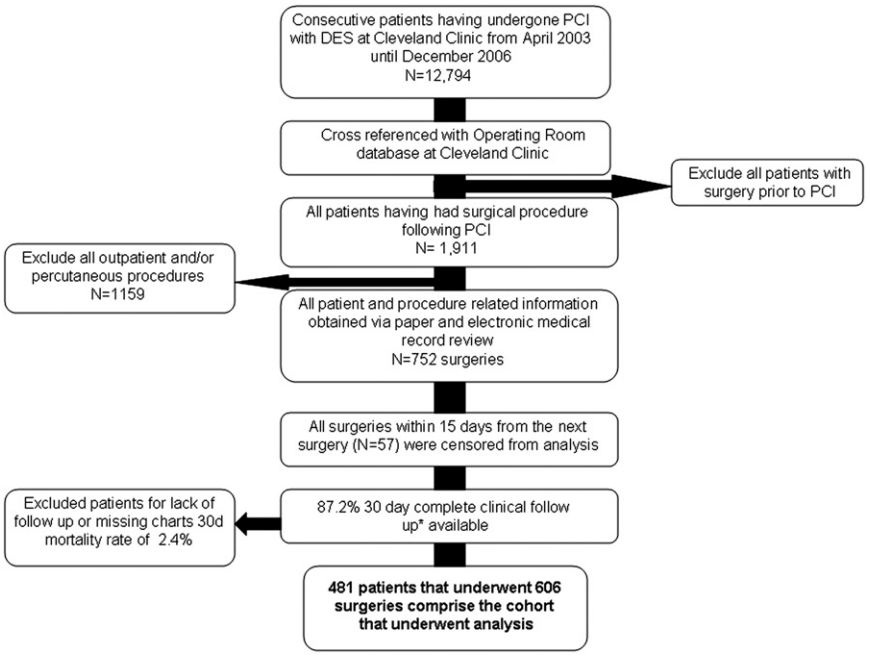

Figure 1. Patient Selection

All consecutive patients having undergone inpatient surgery at any time point after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) were initially identified. The final cohort was selected as shown in this flow diagram. *Complete clinical follow-up includes Social Security Death Index information and complete electronic and paper chart review.

were used to display covariate relationships with outcomes. Statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Five hundred forty-one patients underwent 752 inpatient surgeries from April 28, 2003 to December 31, 2006 at the Cleveland Clinic at any time after PCI with DES. Eighty-nine surgeries from 60 patients were excluded due to missing core variables including perioperative medication/antiplatelet use at or before the time of surgery, and 57 surgeries were not used in the analysis, because they occurred in the 15 days before the index surgery. Results from these patients were analyzed separately. Therefore, 481 patients who underwent 606 surgeries comprise the principal study cohort. Types of surgery are shown in Table 1. Results of 57 surgeries not included in the analysis, due to temporal proximity to the index procedure, are shown in Table 2. Mean time from PCI to surgery was 1.07 ± 0.89 years with a median of 0.88 years (15th and 85th percentiles of 70 days and 2 years, respectively).

Patients who had surgery within 1 month of PCI were different in many ways compared with those who had surgery at a later time point. Patients were more frequently taking aspirin or clopidogrel within 24 h of surgery, less often taking statins, and less likely to be hypertensive. Furthermore, duration of time (days) not taking either aspirin or clopidogrel before surgery was significantly shorter when time from PCI to surgery was <1 month (Table 3).

There were 381 surgeries (63%) performed on patients taking neither aspirin or clopidogrel, 126 surgeries (21%) performed on patients taking both oral antiplatelet agents, 86 surgeries (15%) performed on patients taking only aspirin, and 6 (1%) surgeries performed on patients taking only clopidogrel.

Table 1. Frequencies of Types of Surgery

Type of Surgery	Frequency (%)
Cardiac	130 (22%)
Orthopedic	120 (20%)
Vascular	119 (20%)
Urologic	65 (11%)
Gastrointestinal	61 (10%)
Dermatologic	34 (5.6%)
Head/neck	32 (5.3%)
Thoracic	25 (4.1%)
Hepatobiliary	16 (2.6%)
Intracranial	4 (0.6%)

Table 2. Comparison Between Patients Included in the Analysis Versus Those Excluded Due to Timing of Index Surgery

Variable	Included Patients (n = 606)	Excluded Patients (n = 57)	p Value
Age	67 ± 11	65 ± 12	0.21
Creatinine clearance	83 ± 47	83 ± 55	0.68
Emergency surgery	5.8%	11%	0.16
Diabetes	43%	54%	0.09
Interval (yrs) from PCI to surgery	1.07 ± 0.89	0.78 ± 0.64	0.03
ASA, clopidogrel, or both at surgery	37%	56%	0.0042
Stent thrombosis	11	1	0.97

Mean ± SD are shown for continuous variables.
ASA = acetylsalicylic acid; PCI = percutaneous coronary intervention.

ST. There were 11 ST events (2.0%, 95% confidence limits: 0.8% to 3.3%; 4 definite, 7 probable) during the 30-day post-operative period. They occurred at a median of 2 days after surgery. One probable ST event occurred in the cohort of the 57 surgeries (1.8%) that was excluded from the primary analysis due to surgery within 15 days before the index surgery. Clinical descriptions of those patients having an ST event are shown in Table 4. There was a higher incidence of ST when surgery was performed within 1 month after PCI as compared with surgery performed after 30 days after PCI (p = 0.04) (Fig. 2). Over time, however, despite a reduction in the incidence of ST, risk seems to persist (Fig. 3A).

Univariate correlates for the 30-day risk of ST include: a lower pre-operative ejection fraction (p = 0.004), use of IV heparin in the pre-operative period (up until the time of surgery) (p = 0.006), absence of hypertension (p = 0.02), use of aspirin within 24 h of surgery (p = 0.03), and a lower mean creatinine clearance (p = 0.05). A multivariable model was not constructed for the end point of ST, due to the small absolute number of events.

Combined events. The 30-day post-operative combined end point occurred after 56 (9%, 95% confidence interval: 7% to 12%) surgeries in this cohort. There were 32 (5.0%) deaths and 23 (4.1%) nonfatal MIs (non-ST) within the 30-day post-operative period. Surgeries that were per-

Table 3. Baseline Characteristics

	Time From PCI to Surgery				
	<1 Month (n = 51)	1–6 Months (n = 147)	6–12 Months (n = 144)	>12 Months (n = 264)	p Value
Age, yrs*	66 (66.3 ± 12.1)	69 (67.5 ± 11.5)	68 (66.9 ± 10.9)	67 (67.4 ± 10)	0.81
Female	23 (45%)	47 (32%)	33 (23%)	69 (26%)	0.013
Hypertension	36 (71%)	120 (82%)	129 (90%)	231 (88%)	0.003
Diabetes	28 (55%)	69 (47%)	54 (38%)	108 (41%)	0.11
Dyslipidemia	43 (84%)	137 (93%)	126 (88%)	253 (96%)	0.003
Creatinine clearance*	71.3 (81.2 ± 53)	73.8 (80 ± 43)	89.7 (90 ± 45)	76 (83 ± 49)	0.087
Emergency surgery	8 (16%)	15 (10%)	3 (2.1%)	9 (3.4%)	0.0001
Surgery on aspirin	36 (71%)	58 (39%)	46 (32%)	76 (29%)	<0.0001
Surgery on clopidogrel	28 (56%)	38 (26%)	23 (16%)	43 (16%)	<0.0001
Beta-blockers within 24 h of surgery	41 (80%)	117 (80%)	129 (90%)	225 (86%)	0.12
Statin use within 24 h of surgery	37 (73%)	121 (83%)	129 (90%)	224 (85%)	0.03
Sirolimus eluting stent	35 (69%)	96 (65%)	104 (72%)	194 (73%)	0.23
Pre-operative IV heparin	11 (22%)	30 (21%)	28 (20%)	40 (15%)	0.44
Pre-operative EF	40 (41 ± 7)	55 (50 ± 13.2)	55 (49.8 ± 13.2)	55 (51 ± 13.1)	0.0021
Pre-operative Hgb	10.3 (11 ± 1.7)	12.3 (12 ± 2)	13 (13 ± 2.1)	12.5 (12.4 ± 2)	<0.0001
Pre-operative WBC	9 (11.6 ± 8)	7.2 (8.1 ± 3.6)	6.9 (7.9 ± 3.4)	7.5 (8.5 ± 5.3)	0.0004
Days before surgery ASA stopped	0 (1.27 ± 2.5)	2 (4.6 ± 6.44)	5 (5.8 ± 7.9)	5 (6.0 ± 8.8)	<0.0001
Days before surgery clopidogrel stopped	0 (1.8 ± 3.2)	5 (6.2 ± 10.4)	5.5 (7.1 ± 11)	5 (11.5 ± 54)	<0.0001

*Median (mean ± SD) shown for continuous variables.
ASA = acetylsalicylic acid; EF = ejection fraction; Hgb = hemoglobin; PCI = percutaneous coronary intervention; WBC = white blood cell count.

Table 4. Description of Stent Thrombosis Events

Patient #	Aspirin at Surgery	Clopidogrel at Surgery	Stent Type/Vessel	Stent Size (mm)	Time From PCI to Surgery (days)	Surgery	Definite vs. Probable Stent Thrombosis
1	Yes	Yes	Paclitaxel/LAD	3.5 × 20	5	Cardiac (noncoronary)	Probable
2	Yes	Yes	Sirolimus/LAD	2.5 × 23	11	Thoracic	Probable
3	Yes	No	Sirolimus/LCx	3.5 × 23	18	Cardiac (coronary + valve	Probable
4	Yes	Yes	Sirolimus/diagonal/LAD	2.5 × 13	33	Vascular	Probable
5	No	No	Sirolimus/RCA	3.0 × 18	50	Orthopedic	Probable
6	No	No	Sirolimus/ R PDA	2.5 × 8	150	Vascular	Probable
7	Yes	Yes	Paclitaxel/LCx	3.0 × 24	182	Vascular	Definite
8	Yes	No	Sirolimus/LAD/diagonal	2.5 × 23	235	Vascular	Probable
9	No	No	Sirolimus/LAD	3.5 × 13	351	GI	Definite
10	Yes	No	Sirolimus/R PDA	2.5 × 8	552	Thoracic	Definite
11	No	No	Sirolimus/obtuse marginal	2.5 × 13	1,103	GI	Definite

GI = gastrointestinal; LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery; R PDA = right posterior descending artery.

formed within 1 month of PCI were associated with a much higher risk ($p = 0.0001$) (Fig. 2). As with ST, despite a reduction in risk over time, risk persisted even when surgery was performed as far out as 2 to 3 years after PCI (Fig. 3B).

Emergency surgery and high-risk surgeries were significant univariate predictors of the combined end point ($p < 0.001$), as was use of clopidogrel ($p = 0.002$) or aspirin ($p = 0.008$) in the 24 h before surgery. These variables were often interrelated. Other univariate correlates of the combined end point included lower pre-operative creatinine clearance ($p = 0.01$), lower pre-operative ejection fraction ($p = 0.001$), lower pre-operative hemoglobin ($p = 0.001$), and elevated pre-operative white blood cell count ($p = 0.0002$). Furthermore, a shorter interval (days) of not taking aspirin before surgery was also noted to be a significant univariate correlate ($p = 0.043$).

Independent correlates for the 30-day post-operative combined end point include MI in the 30 days before surgery ($p = 0.0004$), use of pre-operative IV heparin ($p = 0.0004$), emergency surgery ($p = 0.004$), and length of the atherosclerotic lesion where DES was placed ($p = 0.02$) (Table 5). Once these variables were considered, use of aspirin or clopidogrel in the 24 h before surgery was not a significant predictor of the combined end point ($p = 0.4$).

A separate analysis of the 30-day post-operative combined end point was performed, having excluded coronary artery bypass grafting surgeries ($n = 483$). The incidences of ST and the combined primary end point were 2.1% and 9.3%, respectively, and were not significantly different from the overall population ($p > 0.4$). Independent correlates for the 30-day post-operative combined end point included MI in the 30 days before surgery ($p < 0.0001$), use of pre-operative IV heparin ($p = 0.0004$), and higher surgical risk ($p = 0.003$) (Table 6). Again, use of aspirin or clopidogrel in the 24 h before surgery was not a significant correlate of the combined end point ($p = 0.8$).

Discussion

This study reports upon the heretofore incompletely described 30-day post-operative risk associated with prior

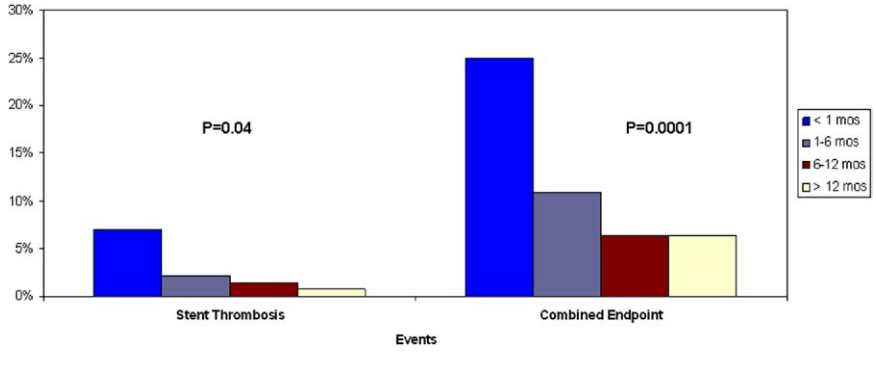

Figure 2. Events as Stratified by Time From PCI to Surgery

Stent thrombosis and the combined end point were significantly higher when time from percutaneous coronary intervention (PCI) to surgery was <1 month. Despite a reduction in events over time, events seem to persist over time.

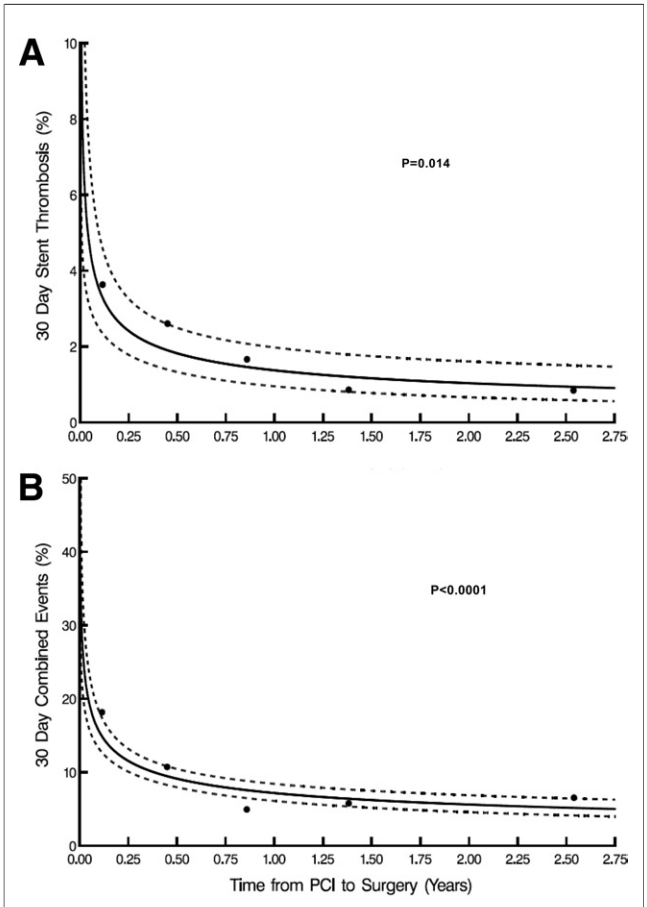

Figure 3. Stent Thrombosis and Combined End Point Events as Function of Time From PCI

Surgeries were divided into quintiles on the basis of time. The mean number of events in each quintile is plotted at the average time. **Error bands** represent 68% confidence intervals, similar to 1 SD. **(A)** Stent thrombosis events as a function of time from percutaneous coronary intervention (PCI). **(B)** Combined end point events as a function of time from PCI.

DES use. Overall risk of ST in this cohort was 2.0%, with 4 definite and 7 probable adjudicated events. A similar risk of ST was noted when coronary artery bypass grafting surgeries were excluded from the analysis. Overall risk of the combined end point of death, nonfatal MI, or ST was 9.0%. For ST, risk seemed to be significantly higher when the time interval between PCI and surgery was shorter. Furthermore, although the risk of both the primary and secondary end points decreased for the increasing interval between PCI and surgery, the risk of an event seems to persist—with an approximately 1% risk of thrombosis occurring when the time interval between PCI and surgery was between 2 to 3 years.

Emergency surgery and MI in the 30 days before surgery were independent correlates of the 30-day post-operative combined end point. They serve to validate the model for the combined end point, because they have been shown to predict complications in noncardiac surgery (11,15,16). Longer atherosclerotic target lesion length was also an independent correlate of the 30-day post-operative combined end point. Longer atherosclerotic coronary lesions might be a surrogate for more extensive coronary artery disease burden as well as use of longer stents and/or overlapping/bifurcating stents, all of which might impact endothelialization of the DES. In this cohort, however, direct PCI-related characteristics such as stent length or diameter were not independent predictors of the combined end point.

The use of IV heparin in the pre-operative period also seems to be a robust independent predictor of the 30-day combined end point. A possible explanation for this is the well-described heparin rebound phenomenon (17). Intravenous unfractionated heparin also might cause platelet activation (18,19). The combination of these effects, in conjunction with the hypercoagulable state known to occur after surgery, could serve to explain the apparent correlation between heparin use and risk (20).

Premature cessation of oral antiplatelet therapy, particularly within 1 year after PCI with DES, has been identified as a factor associated with increased risk of ST (21). In the perioperative setting, however, continuation of oral antiplatelet therapy might not be considered feasible, due to increased risk of significant bleeding (22). In this analysis,

Table 5. Multivariable Predictors for the 30-Day Combined End Point

Risk Factors	Odds Ratio	95% CI	p Value
MI within 30 days of surgery	6.05	2.19–16.7	0.0004
Pre-operative IV heparin use	3.22	1.68–6.16	0.0004
Emergency surgery	4.26	1.56–11.6	0.004
Longer lesion length (mm)*	1.09	1.01–1.17	0.02
Lower pre-operative EF†	1.54	0.97–2.45	0.07
Shorter time from PCI to surgery‡	0.87	0.69–1.1	0.2
Aspirin and/or clopidogrel use 24 h before surgery	1.32	0.7–2.46	0.4

*Squared transformation. †Inverse transformation. ‡Natural log transformation.
CI = confidence interval; EF = ejection fraction; IV = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 6. Multivariable Predictors for the 30-Day Combined End Point (Excluding CABG)

Risk Factors	Odds Ratio	95% CI	p Value
MI within 30 days of surgery	14.42	3.84–54.2	<0.0001
Pre-operative IV heparin use	4.08	1.87–8.88	0.0004
Higher surgical risk	3.51	1.53–8.03	0.003
Shorter time from PCI to surgery*	0.94	0.69–1.26	0.7
Aspirin and/or clopidogrel use 24 h before surgery	1.09	0.52–2.3	0.8

*Natural log transformation.
CABG = coronary artery bypass grafting; other abbreviations as in Table 5.

surgery within 1 month of PCI was more likely to have been performed on patients taking aspirin or clopidogrel. Aspirin use in the perioperative period was also identified as a univariate predictor of both end points. Although this is likely due to timing of surgery after PCI, it might also reflect a potentially sicker patient population needing more urgent or emergent surgery shortly after PCI.

Attempting to dissect out the interplay and importance of these variables, the multivariable model for the 30-day post-operative combined end point demonstrates that taking aspirin and/or clopidogrel in the 24 h before surgery was not protective ($p = 0.3$), irrespective of interval between PCI and surgery. Although the reason for this remains uncertain, it suggests oral antiplatelet therapy in the perioperative period might not protect against adverse events, including ST. In this cohort, there were 3 ST events (Patients #7, #8, and #10 in Table 4) observed in surgeries performed on patients taking dual antiplatelet therapy (2 taking aspirin, 1 taking aspirin and clopidogrel) at an average of 323 days after PCI.

That IV heparin was a correlate of adverse outcomes and oral antiplatelet therapy was not apparently protective of such events suggests that these agents might be surrogates for clinical instability, surgical risk, or perceived risk of ST. For example, heparin was more often used before higher-risk surgeries (vascular, cardiovascular), and oral antiplatelet therapy was more likely to be continued when time from PCI to surgery was <1 month. Furthermore, emergent surgery often precluded any planned discontinuation of oral antiplatelet therapy. However, within the multivariable model, effects of IV heparin seemed to be independent of surgical risk and timing of surgery—even when higher-risk surgeries were removed from the analysis (data not shown). It might be that unmeasured variables, such as non-endothelialization of the stent, might be vitally important in determining risk—particularly in those undergoing surgery soon after PCI and while taking oral antiplatelet therapy.

The implications of these findings are important and widely applicable, particularly because surgery after PCI can be unpredictable. The incidence of a surgical procedure within 1 year after PCI with DES is approximately 4.4% (P. Berger, personal communications, May 2008).

Given widespread use of DES in PCI, the role of proper pre-operative risk stratification remains crucial in those with previous DES placement. The primary objective should be to delay elective surgery as far from the time of PCI as possible for risk reduction. In this cohort, the rate of ST was 7% when surgery was within 1 month of PCI, 2.9% when performed between 1 and 6 months after PCI, 1.4% between 6 and 12 months, and 0.78% when surgery was >12 months from PCI. One caveat is that delaying surgery does not eliminate the risk of adverse post-operative events, including ST. Furthermore, performing surgery with patients taking dual antiplatelet therapy might not confer protection from adverse post-operative events, including ST.

Study limitations. This study remains limited in that it is derived from a single-center, retrospective cohort. The retrospective nature of the study combined with the need to combine DES and surgical databases to derive the patient cohort might have resulted in an underestimation of true incidence of perioperative ST, because events occurring during the period of antiplatelet therapy withdrawal before surgery would have been missed. Furthermore, although the incidence of ST in this cohort was high, the absolute number of events remains low. This precluded any robust statistical analysis to further define the relationships among variables.

For purposes of the principal statistical analysis and to allow at least a 15-day follow-up without another surgery, we excluded all surgeries performed within 15 days of a subsequent "index" surgery. After the 57 surgeries that were excluded due to this logic employed to allow for a 30-day follow-up after any surgery, one probable ST (1.7%) occurred before the index surgery and was therefore censored from the principal analysis. This incidence is similar to that observed for ST events in those surgeries that were included in the analysis ($p = 0.97$). Furthermore, there were only a few differences in baseline characteristics between included surgeries and excluded surgeries (Table 2). Given the reason for exclusion of these patient surgeries, these differences are expected. As such, we do not believe that selective exclusion of these surgeries would have significantly altered the interpretation of patient outcomes.

We also acknowledge the limitations of our definition of ST and its application in the perioperative period. A modified version of the ARC definitions was used to exclude perioperative events unrelated to ST. Because the perioperative setting can complicate the adjudication of an accurate diagnosis, the secondary combined end point was also evaluated, but it is possible that the relationship between death or MI and ST was misclassified in some patients

Finally, we acknowledge the possibility that not all follow-up events were captured. Routine follow-up was not protocolized. However, given the large catchment area of the hospital and affiliate hospitals linked by electronic medical records, 87.2% of patients had documented follow-up within 30 days, and 85% had a post-procedural electrocardiogram. All patients had known vital status at 30 days. Furthermore, those patients who received both cardiac and noncardiac care at this institution were more likely to return for follow-up or complications related to either issue.

Conclusions

We present the experience from a retrospective cohort having undergone inpatient surgical procedures after prior PCI with DES. The 30-day post-operative risk of ST was

2.0%, and that of ST, nonfatal MI, or death was 9.0%. Risk seems to be highest when the interval from PCI to surgery is <1 to 2 months, but some appreciable risk endures over at least 2 to 3 years. Use of perioperative oral antiplatelet agents might not protect against and use of pre-operative IV heparin might increase the risk of events in the post-operative period. Risk seems to be higher with antecedent MI, longer atherosclerotic lesion length, or emergency surgery. These findings need to be validated in a large prospective data set but, pending this, assist the clinician in making decisions about surgeries in patients with DES.

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REFERENCES

1. 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.
2. 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.
3. Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005;45:2088–92.
4. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234–40.
5. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94.
6. Riddell JW, Chiche L, Plaud B, Hamon M. Coronary stents and noncardiac surgery. Circulation 2007;116:e378–82.
7. Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. Catheter Cardiovasc Interv 2005;65:516–9.
8. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac surgery after coronary drug-eluting stent implantation. Am J Cardiol 2006;98:1212–3.
9. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122–4.
10. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. Anesthesiology 2008;109:596–604.
11. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9.
12. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
14. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003;157:364–75.
15. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977;297:845–50.
16. Goldman L, Caldera DL, Southwick FS, et al. Cardiac risk factors and complications in non-cardiac surgery. Medicine (Baltimore) 1978;57:357–70.
17. Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 1992;327:141–5.
18. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. Circulation 1998;97:251–6.
19. Anand SX, Kim MC, Kamran M, et al. Comparison of platelet function and morphology in patients undergoing percutaneous coronary intervention receiving bivalirudin versus unfractionated heparin versus clopidogrel pretreatment and bivalirudin. Am J Cardiol 2007;100:417–24.
20. Dahl OE. Mechanisms of hypercoagulability. Thromb Haemost 1999;82:902–6.
21. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–30.
22. Hodgson JM, Stone GW, Lincoff AM, et al. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. Catheter Cardiovasc Interv 2007;69:327–33.

Key Words: drug-eluting stents ■ perioperative risk ■ stent thrombosis.

APPENDIX

For a supplementary Methods section, please see the online version of this article.