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Clinical Outcome of Patients Undergoing Non-Cardiac Surgery in the Two Months Following Coronary Stenting

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OBJECTIVES We sought to determine the frequency and timing of complications at our institution when surgery was performed within two months of coronary stent placement.

BACKGROUND The optimal delay following coronary stent placement prior to non-cardiac surgery is unknown.

METHODS We analyzed the Mayo Clinic Percutaneous Coronary Intervention and Surgical databases between 1990 and 2000 and identified 207 patients who underwent surgery in the two months following successful coronary stent placement.

RESULTS Eight patients (4.0%) died or suffered a myocardial infarction or stent thrombosis. All 8 patients were among the 168 patients (4.8%, 95% confidence interval [CI] 2.1 to 9.2) undergoing surgery six weeks after stent placement; the frequency of these events ranged from 3.8% to 7.1% per week during each of the six weeks. No events occurred in the 39 patients undergoing surgery seven to nine weeks after stent placement (0%, 95% CI 0.0 to 9.0).

CONCLUSIONS These data suggest that, whenever possible, non-cardiac surgery should be delayed six weeks after stent placement, by which time stents are generally endothelialized, and a course of antiplatelet therapy to prevent stent thrombosis has been completed. (J Am Coll Cardiol 2003;42:234–40) © 2003 by the American College of Cardiology Foundation

Stent thrombosis is a highly morbid complication of coronary stent placement. Most cases of stent thrombosis result in Q-wave myocardial infarction (MI) or death (1–7). With the use of combined antiplatelet therapy after stent placement (aspirin and thienopyridine) the frequency of stent thrombosis is extremely low, generally <1%, and it usually occurs in the first few days following stent placement (1,8,9). However, the impact of non-cardiac surgery on the frequency and timing of stent thrombosis is unclear. It follows, therefore, that the optimal delay following coronary stent placement prior to non-cardiac surgery is unknown. The only previous study addressing this issue reported a mortality rate of 32% among 40 patients when surgery was performed ≤2 weeks following stent placement; in that study, neither death, MI, nor stent thrombosis occurred when surgery was performed after a >2 week delay (10). We examined the frequency and timing of complications at our institution when non-cardiac surgery was performed within two months of coronary stent placement.

METHODS

We performed a retrospective analysis of the Percutaneous Coronary Intervention database and the General Surgery database at Mayo Clinic and identified 207 patients who underwent non-cardiac surgery within 60 days of coronary stent placement. Surgical procedures included in this analysis were those that required a significant incision and had the potential for perioperative bleeding. Procedures such as joint aspirations, endoscopy, and skin biopsies, among others, were not included in this analysis. All patients undergoing percutaneous coronary revascularization at the Mayo Clinic are followed up according to a protocol approved by the Mayo Clinic Institutional Review Board. The Percutaneous Coronary Intervention database includes baseline and in-hospital demographic, clinical, and angiographic data.

Definitions. Successful stent placement was defined as ≥20% reduction in the lumen diameter stenosis, resulting in a final residual stenosis within the stent of <50% by visual estimation, with achievement of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 and without the in-laboratory occurrence of death, Q-wave MI, or requirement of coronary artery bypass graft (CABG) surgery (11). A perioperative MI was considered to have occurred when at least two of the following three criteria were met: 1) chest pain >30 min; 2) persistent electrocardiographic (ECG) changes suggestive of ischemia; or 3) characteristic elevations in serum creatine kinase (CK) levels or CK-MB isoform (≥2 times normal). Q-wave MI was defined as two of the above criteria with new pathologic Q waves in the coronary distribution of the stented artery. Thrombus was considered to be present when one or more lumen-filling defects in a coronary artery were visualized with contrast

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CI = confidence interval
INR = International Normalized Ratio
MI = myocardial infarction
NHLBI = National Heart, Lung, and Blood Institute
TIMI = Thrombolysis In Myocardial Infarction

present on three sides. Dissections were diagnosed when contrast staining was apparent within the vessel wall, and they were classified according to the National Heart, Lung, and Blood Institute (NHLBI) classification system (12). Single-vessel disease was defined as the presence of a ≥70% lesion in one of the three major coronary arteries or their major branches. Multivessel disease was defined as the presence of a ≥70% lesion in a major coronary artery or its major branches and a ≥50% lesion in a second coronary artery or its major branches. The angiographic severity of coronary artery stenoses was assessed visually using two orthogonal views. Lesions were classified according to the modified American Heart Association/American College of Cardiology lesion classification scheme by the interventional cardiologist performing the angioplasty procedure, immediately before the procedure was performed (13). Using a modified Simpson's rule, left ventricular ejection fractions were calculated from ventriculography performed in a 30° right anterior oblique projection (14).

Intracoronary stent implantation technique. Coronary angioplasty and intracoronary stent implantation were performed using standard percutaneous techniques via the femoral, brachial, or radial artery. In the earlier time period, 8F guide catheters and over-the-wire systems were utilized. In the more recent study period, rapid-exchange systems and 6F and 7F guide catheters were more commonly used. Intravascular ultrasound was used infrequently (<10%), at the discretion of the operator.

Medical therapy. All patients received pre-procedural oral aspirin (325 mg) and intravenous heparin to achieve an activated clotting time of approximately 300 s, or approximately 250 s if a platelet glycoprotein IIb/IIIa inhibitor was used. In patients receiving a combination of warfarin and aspirin, warfarin was initiated the evening of the procedure and intravenous heparin was continued until the International Normalized Ratio (INR) was ≥2.0. In patients receiving ticlopidine (which became routine in early 1995), the first dose was administered before the procedure (generally within 1 h), with an initial loading dose of 500 mg, and a 250-mg dose was administered later that evening followed by 250 mg twice a day for two to four weeks, in addition to aspirin 81 to 325 mg daily. After March 1998, clopidogrel was substituted for ticlopidine and was given as a loading dose of 300 mg either immediately before or during the procedure, followed by 75 mg daily for two to four weeks.

Bleeding complications. The hospital charts of all patients included in the study were reviewed; only bleeding data from three charts (1.4%) were unavailable for review. The following data were collected from the surgical, anesthesia, nursing, and physician's notes and reports: date of percutaneous coronary intervention and surgery, type of surgery, interval between last dose of antiplatelet agent (aspirin and thienopyridine) and warfarin (and INR level), surgical procedure, estimated blood loss, presence of excessive surgical bleeding (defined as persistent bleeding despite adequate use of electrocautery and suture, or decreased clotting time within the surgical field), and perioperative transfusion requirements.

End points. The frequency of death, Q-wave MI, non–Q-wave MI, stent thrombosis, surgical bleeding complications, and repeat revascularization with either CABG or repeat angioplasty of the target vessel were analyzed. The earliest and latest dates that patients in this study received stents were July 31, 1990, and June 23, 2000.

Statistical analyses. Data are presented as the mean ± 1 SD, or percentages. Comparisons between groups were made using one-way analysis of variance, the Pearson chi-square test, or the Wilcoxon rank-sum test, as appro-

Table 1. Baseline Clinical Characteristics of Patients in the Entire Study Group, and Those With and Without an Adverse Event Analyzed Separately

	All Patients (n = 207)	Patients With an Event (n = 8)	Patients Without an Event (n = 199)	p Value†
Age (yrs)*	66.9 ± 9.8	67.1 ± 12.0	66.9 ± 9.8	0.95
Male patients (%)	65.2	75.0	64.8	0.55
Prior myocardial infarction (%)	51.7	50.0	51.8	0.92
Prior CABG (%)	20.8	25.0	20.6	0.76
History of smoking	65.5	50.0	66.2	0.35
History of hypercholesterolemia (%)	64.4	62.5	64.5	0.91
History of hypertension (%)	69.3	71.4	69.2	0.90
History of diabetes (%)	27.5	25.0	27.6	0.87
Pre-procedural shock (%)	5.5	12.5	5.2	0.38

*Continuous variables are presented as mean values ± SD. †The p values relate to comparisons between patients with and without an event.
CABG = coronary artery bypass graft surgery.

Table 2. Post-Discharge Medication Use in the Study Group

	All Patients (n = 207)	Patients With an Event (n = 8)	Patients Without an Event (n = 199)	p Value
Abciximab*	22.3	12.5	21.6	0.54
Aspirin	95.2	100.0	95.0	0.52
Ticlopidine	37.7	25.0	38.2	0.45
Clopidogrel	40.1	50.0	39.7	0.56
Beta-blocker	62.8	50.0	63.3	0.44
ACE inhibitor	28.5	37.5	28.1	0.57
Calcium channel blocker	33.3	25.0	33.7	0.61

*Used during the percutaneous coronary intervention.
ACE = angiotensin-converting enzyme.

priate. All analyses were performed using SAS software (SAS Inc., Cary, North Carolina). One-way analysis of variance was employed for the variables that are summarized using mean ± SD. The Pearson chi-squared test was used for binary response variables, summarized with percentages. The Wilcoxon rank-test was used for the discrete ordinal variables, summarized with percentages for each level.

RESULTS

Baseline characteristics. The 207 patients included in this study underwent surgery 1 to 60 days following stent implantation. The baseline clinical and postprocedural angiographic characteristics of all 207 patients in the study population, and of patients grouped into those who did (n = 8) and did not (n = 199) suffer a major adverse event, are summarized in Table 1.

Adjunctive medical therapy. The medical therapies received at discharge (Table 2) did not differ between patients who did and did not suffer an adverse event after non-cardiac surgery. Only 21% of patients (n = 43) were discharged while receiving warfarin; 75% of patients (n = 155) were discharged while receiving aspirin and a thienopyridine.

Procedural characteristics. The procedural characteristics of the revascularization procedure are displayed in Tables 3 and 4. Patients who suffered a major adverse event had a significantly more severe residual stenosis (17 ± 17% vs. 9 ± 17%, p = 0.04) than those who did not have an event.

Surgical procedures. Types of surgical procedures are listed in Table 5. Most patients in the study underwent vascular surgery. None of the patients who underwent genitourinary, head and neck, or breast surgery in this study suffered a major adverse event, although the number of such patients was relatively small.

Adverse events. Eight of 207 patients had major adverse cardiac events. Of these, six patients died, two of whom suffered or were suffering an MI before dying (Table 6). One patient had a non-fatal MI. The percentage of patients suffering a major adverse event and the number of weeks that surgery was performed after stent placement are displayed in Figure 1.

Bleeding complications from surgery. At the time of surgery, 54 patients (26%) received both aspirin and thienopyridine, 29 patients (14%) received aspirin and had received the last dose of thienopyridine within the previous 10 days, 104 patients (51%) received aspirin only, 13

Table 3. Baseline Angiographic Characteristics of the Study Group

	All Patients (n = 207)	Patients With an Event (n = 8)	Patients Without an Event (n = 199)	p Value
Vessel treated				
Left anterior descending	44.0	50.0	43.7	0.73
Left circumflex	30.0	50.0	29.1	0.21
Right coronary artery	30.9	37.5	30.7	0.68
Saphenous vein graft	10.1	0.0	10.6	0.33
Number of vessels dilated				0.06
1	84.5	62.5	85.4	
2	14.5	25.0	14.1	
3	1.0	12.5	0.5	
Initial luminal diameter stenosis (%)*	83.8 ± 13.8	80.8 ± 17.1	84.0 ± 13.5	0.35
Initial TIMI flow*				0.37
0	8.2	7.7	8.3	
1	3.9	0.0	4.1	
2	14.7	7.7	15.1	
3	73.2	84.6	72.5	
Reference diameter (mm)*	3.3 ± 0.7	3.2 ± 0.4	3.4 ± 0.7	0.44

*Denominator is number of treated lesions.
TIMI = Thrombolysis In Myocardial Infarction.

Table 4. Final Angiographic Characteristics of the Study Group

	All Patients (n = 207)	Patients With an Event (n = 8)	Patients Without an Event (n = 199)	p Value
Number of stents placed				0.48
1	58.5	50.0	58.8	
2	30.4	25.0	30.7	
3	8.2	25.0	7.5	
4+	2.9	0.0	3.0	
Residual dissection	44.4	37.5	44.7	0.69
Residual stenosis (%)*	9 ± 17	17 ± 17	8 ± 17	0.04
TIMI flow post procedure*				0.73
0	0.3	0.0	0.4	
1	0.3	0.0	0.4	
2	0.0	0.0	0.0	
3	99.3	100.0	99.3	

*Denominator is number of treated lesions.
TIMI = Thrombolysis In Myocardial Infarction.

patients (6.3%) received no antiplatelet agents, and 4 patients (2.0%) received aspirin and warfarin, all of whom had an INR ≥1.7 (Table 7). Only two patients were described by either the surgeon or the anesthesiologist as having excessive bleeding during surgery; one patient received both aspirin and ticlopidine, and the second patient received aspirin alone. None of the four patients with an elevated INR due to warfarin at the time of surgery had clinically significant bleeding. No major clinical events were attributed to bleeding complications. A total of 67 patients (33%) received a red blood cell transfusion during or immediately after the surgical procedure; platelet transfusions were administered to six patients. The transfusion requirements in relation to the anticoagulation/antiplatelet regimen are enumerated in Table 7. There was no apparent association between transfusion requirements and time of discontinuation of antiplatelet and anticoagulant therapy. The majority of transfusions in patients receiving the dual antiplatelet regiment (aspirin and thienopyridine) were performed for blood loss that had occurred before surgery secondary to vascular complications related to the percutaneous coronary intervention, such as hematoma or pseudoaneurysm.

DISCUSSION

The most important finding of this study is that the risk of stent thrombosis and other major complications after non-cardiac surgery is greatest in the first six weeks after stent placement and less thereafter, although due to the small number of events and the wide confidence intervals around these point estimates, the findings of this study should be regarded as suggestive and not definitive. The overall rate of complications was lower than in an earlier study of this issue (10).

Stent thrombosis. Stent thrombosis has been occurring less frequently in recent years than ever before, in part because of the combination therapy with both aspirin and a thienopyridine, and because of better understanding about how stents should be deployed (15–18). However, when stent thrombosis occurs, it usually results in either Q-wave MI or death (1,8,9). Therefore, risk factors associated with stent thrombosis should be identified and steps taken to avoid this highly morbid complication.

Effect of surgery on hemostasis. Surgery promotes thrombosis, and by its very nature requires thrombosis; all patients

Table 5. Type of Surgical Procedure

		Antithrombotic Regimen				
Type of Surgery	All Groups (n = 204) n (%)	Aspirin and a Thienopyridine (n = 54)	Aspirin and Last Thienopyridine ≤10 Days Before Surgery (n = 29)	Aspirin and Warfarin (n = 4)	Aspirin Alone (n = 104)	No Antiplatelet or Anticoagulant Therapy for >10 Days (n = 13)
Vascular repair (PCI complication)	68 (33.3%)	31 (57.4%)	5 (17.2%)	3 (75.0%)	27 (25.9%)	2 (15.3%)
Vascular surgery	50 (24.5%)	8 (14.8%)	5 (17.2%)	1 (25.0%)	33 (31.7%)	3 (23.0%)
Orthopedic	16 (7.8%)	2 (3.7%)	3 (10.3%)	—	9 (8.6%)	2 (15.3%)
Genitourinary	12 (5.8%)	—	1 (3.4%)	—	9 (8.6%)	2 (15.3%)
GI—abdominal	17 (8.3%)	5 (9.2%)	3 (10.3%)	—	8 (7.6%)	1 (7.6%)
Thoracic	15 (7.3%)	—	5 (17.2%)	—	9 (8.6%)	1 (7.6%)
Head and neck	9 (4.4%)	3 (5.5%)	3 (10.4%)	—	2 (1.9%)	1 (7.6%)
Breast	5 (2.4%)	—	1 (3.4%)	—	3 (2.8%)	1 (7.6%)
Other	12 (5.8%)	5 (9.2%)	3 (10.3%)	—	4 (3.8%)	

GI = gastrointestinal; PCI = percutaneous coronary intervention.

Table 6. Procedural Information About the Eight Patients Who Suffered Adverse Ischemic Events

Patient	Stent Placement Date	Pre-Procedural Shock	Vessel Stented	Thienopyridines	Type of Surgery
1	1993	No	LCX	none	femoral artery repair
2	1996	No	LAD, LCX	ticlopidine	femoral artery repair
3	1996	No	LM	ticlopidine	colonic resection
4	1997	Yes	LCX	ticlopidine	radial artery repair
5	1998	No	LAD, RCA	clopidogrel	hand surgery
6	1999	No	SVG to RCA	clopidogrel	esophagogastrectomy
7	1999	No	LAD	clopidogrel	cystoprostatectomy
8	1999	No	LAD	clopidogrel	left lung lobectomy

LAD = left anterior descending; LCX = left circumflex; LM = left main; RCA = right coronary artery; SVG = saphenous vein graft.

would bleed to death after surgery if thrombosis did not occur. However, surgical stress activates the sympathetic nervous system and causes release of neuroendocrine hormones (epinephrine, norepinephrine, cortisol, renin) and may indirectly trigger adverse cardiac, vascular, and pulmonary outcomes. Plasma procoagulant clotting factors increase, while fibrinolysis is decreased, resulting in a hypercoaguable state (19–21). These physiologic alterations that occur in the perioperative period may increase the risk of thrombosis of recently placed stents that might not have had the opportunity to re-endothelialize.

Placement of a coronary stent results in complete denudation of the endothelial surface; re-endothelialization is believed to take place within approximately eight weeks (22,23). It is interesting to note that among patients who receive stents and who do not undergo surgery, the highest risk of stent thrombosis is within the first few hours and days after stent placement, and that even just two weeks of therapy with a thienopyridine is associated with a very low rate of stent thrombosis after the thienopyridine is discontinued (24). Therefore, it is likely that partial endothelialization reduces the risk of stent thrombosis.

Earlier studies. Current recommendations are that revascularization be reserved for patients in whom an indication for revascularization otherwise exists; it is unusual that revascularization needs to be performed to "get a patient through" his or her surgical procedure (25). However, there are few data about the most appropriate duration that should elapse after percutaneous revascularization prior to surgery. In the only study of the issue that has been reported, Kaluza et al. (10) studied 40 patients and found that among those who underwent surgery within two weeks of stent placement the mortality rate was 32%. In contrast, there were no deaths, MIs, or episodes of stent thrombosis among the patients in whom >2 weeks elapsed before surgery.

The current study. The current study is much larger and confirms an increased risk of major adverse events among patients in whom surgery is performed early after stent placement. However, we found that the increased risk persists for six weeks; there were no major adverse events among the patients in our study who underwent surgery >6 weeks after stent placement (0%, 95% confidence interval [CI] 0.0 to 9.0). We believe that our results are consistent with the time course of re-endothelialization of coronary arteries after stent placement. It should also be noted that the increased risk of adverse events following surgery was much lower than the 32% mortality in the previously published study (10). In situations where non-cardiac surgery is fairly urgent, our study would suggest that the risk of major adverse cardiac events is fairly low even when surgery occurs prior to six weeks post stent placement (4.8%, 95%

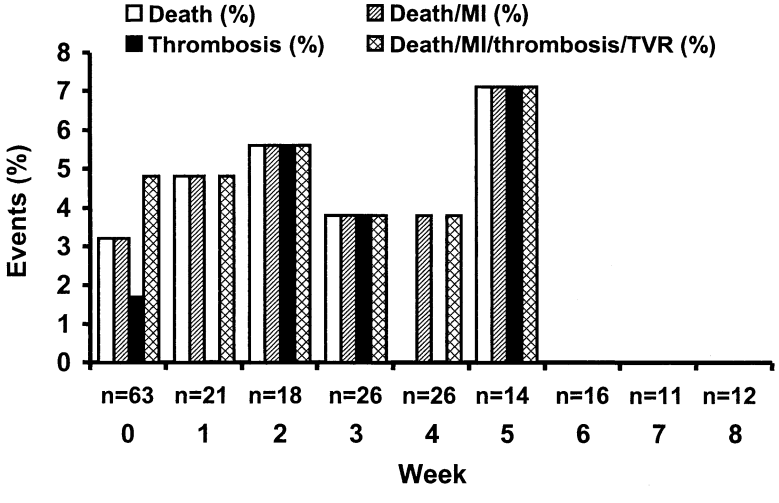

Figure 1. Adverse events within two months of coronary stent placement. MI = myocardial infarction; TVR = target vessel revascularization.

Table 7. Bleeding Complications and Transfusion Requirements

	Antithrombotic Regimen					
	Aspirin and a Thienopyridine (n = 54)	Aspirin and Last Thienopyridine ≤10 Days Before Surgery (n = 29)	Aspirin and Warfarin (n = 4)	Aspirin Alone (n = 104)	No Therapy for >10 Days (n = 13)	p Value
Excessive surgical bleeding, n	1	0	0	1	0	
Number of patients transfused, n (%)	23 (42.6%)	5 (17.2%)	1 (25%)	33 (31.7%)	5 (38.5%)	0.54

CI 2.1 to 9.2). This is similar to the low perioperative event rate previously reported from our institution following balloon angioplasty (26).

The risk of increased surgical bleeding is an important issue in patients undergoing non-cardiac surgery after coronary stent placement because of the potent antiplatelet agents administered to such patients, including aspirin and a thienopyridine (generally clopidogrel). These agents exert their antiplatelet effects via different mechanisms, but both aspirin and thienopyridines result in irreversible inhibition of platelet function and prolongation of the bleeding time. The recovery of platelet function occurs from 7 to 10 days after the discontinuation of treatment (27). We were not able to identify a relationship between the incidences of surgical bleeding in patients receiving a single antiplatelet agent, dual antiplatelet therapy, and no antiplatelet regiment; furthermore, transfusion requirements were similar in these groups. This was probably due to the relatively small number of patients in our study, the many different kinds of surgical procedures performed with greatly varying risks of bleeding, and the inescapable bias that patients undergoing surgical procedures associated with a greater risk of bleeding more frequently discontinued antiplatelet therapy prior to the surgical procedure, a bias that could not be eliminated in this study. However, a large prospective study confirmed the results of smaller retrospective studies indicating that there is a clear relationship between perioperative bleeding and administration of a thienopyridine shortly before or at the time of surgery (28–31). Our data clearly indicate that the risk of stent thrombosis and other complications is increased when surgery is performed within six weeks after stent placement and that, when possible, surgical procedures ought be delayed for at least six weeks following stent placement. Delaying surgery will not only allow completion of a full course of thienopyridine after stent placement, which has been shown to reduce the frequency of stent thrombosis, but will also allow for the subsequent recovery of platelet function, which probably does reduce the risk of perioperative bleeding even though it could not be demonstrated in this study (28–31). It should be noted that the frequency of stent thrombosis following surgery may be different following coronary brachytherapy, because the time course of endothelialization of the stent is delayed in this setting (32).

Finally, we should also mention that some investigators have proposed the use of heparin-coated stents for the prevention of early thrombotic occlusion. The results of the Aspirin Alone Antiplatelet Regimen After Intracoronary Placement of the Carbostent (ANTARES) study suggest low rates of stent thrombosis (33). These results are supported by the findings of Vrolix et al. but do not differ significantly from recent data suggesting that stent thrombosis rates continue to decline (34,35). No randomized controlled data support the use of heparin-coated stents for the prevention of stent thrombosis in general, or for preoperative coronary stenting in particular (36).

Study limitations. This retrospective study is subject to the limitations of all such studies. However, two limitations deserve special emphasis. Our ability to determine a relationship between time to surgery and bleeding, and the impact of adjunctive antiplatelet and anticoagulant therapy, are severely limited in this study, as previously described. Therefore, analysis of the relationship between bleeding and transfusion requirements on the one hand and antiplatelet and anticoagulant therapy on the other should be interpreted with great caution. Similarly, identification of additional covariates of stent thrombosis and clinical outcomes is limited because there were few clinical events. Specifically, there is a risk of "overfitting" (modeling idiosyncracies in the sample that may not generalize to other populations) if there are fewer than 10 events per covariate (37). The second important limitation relates to the possibility that "sicker" patients had to proceed to surgery more rapidly and that delaying surgery could not be expected to eliminate all adverse events.

Conclusions. Nonetheless, we conclude that delaying surgery for up to six weeks after completing a course of therapy with a thienopyridine is associated with a lower frequency of stent thrombosis and other adverse events.

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