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Cardiac Risk of Noncardiac Surgery after Percutaneous Coronary Intervention with Drug-eluting Stents

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Background: **The American College of Cardiology released a scientific advisory that included a recommendation to delay elective of noncardiac surgery (NCS) for 1 yr after percutaneous coronary intervention (PCI) with a drug-eluting stent (DES).**

Methods: **This single-center, retrospective study examined the risk for complications of NCS performed within 2 yr after DES placement and examined whether this risk changed based on the time between procedures. The primary endpoint was major adverse cardiac events (MACEs) during the hospitalization for NCS. Bleeding events were analyzed as a secondary endpoint.**

Results: **From April 22, 2003, to December 31, 2006, a total of 520 patients underwent NCS within 2 yr after PCI with a DES at Mayo Clinic. The majority, 84%, of the DES placed were Cypher stents. The frequency of MACE was not found to be significantly associated with the time between PCI and NCS (rate of MACEs 6.4, 5.7, 5.9, and 3.3% at 0–90, 91–180, 181–365, and 366–730 days after PCI with DES, respectively; $P = 0.727$ for comparison across groups). Characteristics found to be associated with MACEs in univariate analysis were advanced age ($P = 0.031$), emergent NCS ($P = 0.006$), shock at time of PCI ($P = 0.035$), previous history of myocardial infarction ($P = 0.046$), and continuation of a thienopyridine (ticlopidine or clopidogrel) into the preoperative period ($P = 0.040$). The rate of transfusion did not seem to be associated with antiplatelet therapy use.**

Conclusions: **The risk of MACEs with NCS after DES placement was not significantly associated with time from stenting to surgery, but observed rates of MACEs were lowest after 1 yr.**

THE optimal time for NCS after stent placement has been the subject of much debate. Recently, the American Heart Association (AHA) and American College of Cardiology (ACC) released a scientific advisory on the prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents.[1] One of the recommendations of the scientific advisory is to delay elective noncardiac surgery (NCS) for 1 yr after drug-eluting stent (DES) placement, based on studies finding discontinuation of thienopyridine therapy to be the leading predictor for stent thrombosis in nonsurgical patients and case reports of stent thrombosis in patients undergoing NCS. To date, no large studies have addressed timing of NCS after percutaneous coronary intervention (PCI) with DES.

Data with respect to bare-metal stents (BMSs) has been conflicting. Our previous study in patients with BMSs showed that NCS should be delayed for at least 90 days after PCI with BMS.[2]

Drug-eluting stents reduce the rates of repeat target vessel revascularization or coronary artery bypass grafting surgery.[3,4] DESs effectively reduce neointimal proliferation and rates of angiographic restenosis; however, the same drugs delay stent endothelialization,[5,6] thus potentially prolonging the period where the DES is at higher risk for stent thrombosis.[6] Indeed, cases of late DES thrombosis have been reported up to 18 months after placement.[7–10] Interestingly, late DES thrombosis and maintained BMS patency have been reported in patients who had both BMSs and DESs.[9,10]

Dual antiplatelet therapy, aspirin and thienopyridine, is used to prevent stent thrombosis.[11] Discontinuation of antiplatelet therapy is a strong predictor of early and late thrombotic stent occlusion[12] and may increase the risk of cardiac events[13] in nonsurgical and surgical patients. Thienopyridine drugs increase the risk of intraoperative bleeding in patients undergoing cardiac surgery[14] and are almost always discontinued before both cardiac and noncardiac surgery.

To test the hypothesis that the rate of postoperative major adverse cardiac events (MACEs) is inversely related to time after PCI with DES, we performed a large-scale, retrospective analysis of all patients who underwent NCS after PCI with DES at Mayo Clinic. We also addressed whether an optimal delay after PCI with DES exists to minimize the perioperative risk of MACEs and bleeding events.

Materials and Methods

After institutional review board approval, we identified 520 patients who underwent NCS after PCI with DES at Mayo Clinic, Rochester, Minnesota. The DESs were

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placed between April 22, 2003, and July 21, 2006, and the surgeries were performed between June 16, 2003, and December 28, 2006. The patients were identified by cross matching the Mayo Clinic PCI registry with the Mayo surgical database. The complete medical records of the 520 patients identified were then reviewed individually by the same study physician.

Patient demographic data included risk factors for coronary artery disease, presenting condition at time of PCI (PCI performed on an elective basis or urgently for acute coronary syndrome, as well as pre-PCI cardiogenic shock), angiographic data (including number of stents placed, percent residual stenosis, postprocedural TIMI [Thrombolysis in Myocardial Infarction trial] flow, and successful PCI in all lesions stented), maintenance antiplatelet therapy (none, aspirin, ticlopidine or clopidogrel, or dual antiplatelet therapy), antiplatelet therapy before NCS (categorized as continued until $<$ 7 days before NCS, discontinued 7–30 days before NCS, and not used during the month before NCS), type of NCS (categorized according to ACC–AHA classification),[15] urgency of NCS (nonemergent or emergent), and use of general anesthesia.

Coronary angiography and intracoronary stent implantation was performed using standard percutaneous techniques.[16] Patients were usually prescribed long-term aspirin therapy in addition to ticlopidine or clopidogrel. All patients undergoing PCI at the Mayo Clinic have been prospectively followed up in a registry. It is routine practice for all patients at Mayo Clinic to have creatine kinase-MB and troponin levels measured every 8 h for 24 h after PCI. Demographic, clinical, and angiographic data are recorded by trained data technicians, and 10% of records are audited by the supervisor for quality control. Patients are prospectively contacted at 6 and 12 months and annually thereafter, and follow-up events are recorded.

Definitions

Perioperative complications associated with NCS were classified as MACEs (death, ST-elevation myocardial infarction [MI], non–ST-elevation MI, stent thrombosis, and repeat revascularization with either coronary artery bypass grafting or repeat angioplasty of the target vessel) and surgical bleeding complications that occurred in the hospital (during the surgical hospitalization or on readmission within 24 h of discharge).

A perioperative MI was diagnosed according to the criteria of the ACC,[17] by an increase and decrease of troponin or creatine kinase MB with at least one of the following four criteria: (1) ischemic symptoms, (2) development of pathologic Q waves on an electrocardiograph, (3) electrocardiographic changes indicative of ischemia, or (4) diagnosis made on coronary angiography. If ST elevation was present, this was classified as an ST-segment elevation MI, and if ST elevation was not present, this was classified as a non–ST-segment elevation MI.

Successful PCI was defined for each patient as final residual stenosis within all stents less than 50% by visual estimation.

Stent thrombosis was defined as the angiographic appearance of one or more luminal filling defects in a stented coronary artery, or presence of diagnostic electrocardiographic changes in the coronary distribution of the stented artery along with criteria for diagnosis of MI.

A surgical bleeding event was defined as the surgeon noting excessive blood loss due to diffuse microvascular bleeding or oozing in the operative note. Blood product transfusion requirements included intraoperative transfusion and transfusion during the first 24 postoperative hours. Antiplatelet therapy use in the month before NCS was recorded, and anticoagulants were said to have been discontinued if they were held less than 7 days before NCS.

Statistical Analysis

All analyses were performed using SAS version 8 (SAS Institute Inc., Cary, NC). To assess whether the risk for complications after NCS is associated with the duration of time from PCI to NCS, the time from PCI to NCS was assessed as a continuous variable as well as categorically ($\leq$ 90, 91–180, 181–365, and $>$ 365 days). These time categories were chosen as follows: less than 90 days because of the significantly increased rate of MACEs during this time period in our study on BMSs; 91–180 days because our preliminary data suggested a drop-off in MACEs after 6 months and because this would be in keeping with the pharmacokinetics of drug elution; and greater than 1 yr because of the recent advisory released by the AHA–ACC, recommending that NCS be delayed at least 1 yr after DES placement.

Patient and procedural characteristics were summarized and compared across timing groups using the chi-square test for discrete variables and the Kruskal–Wallis test for continuous and ordinal variables. Logistic regression analyses were performed to assess characteristics potentially associated with the development of MACEs. Given the duration of the study period, initial logistic regression analyses were performed to verify that the frequency of these events did not change significantly over calendar time. Because the time from PCI to NCS was not randomly assigned, any observed relation between the timing of procedures and the frequency of complications could be due to imbalances in other prognostic factors. However, given the limited number of events observed in the current sample, a multivariable analysis adjusting for all possible covariates was not feasible. Therefore, a single balancing variable was calculated and included as an adjustor variable in a multivariable analysis. To calculate the balancing score, the time from PCI to surgery ($\leq$ 90, 91–180, 181–365, and $>$ 365 days)

Table 1. Univariate Analysis of Characteristics Associated with MACEs*

Characteristic	Total n	MACEs		
		n	%	*P* Value*
Overall	520	28	5.4	
Age group				0.031
≤ 55 yr	77	1	1.3	
56–65 yr	113	6	5.3	
66–75 yr	180	8	4.4	
≥ 76 yr	150	13	8.7	
Sex				0.070
Male	360	15	4.2	
Female	160	13	8.1	
Current/former smoker				0.490
Yes	311	15	4.8	
No	209	13	6.2	
History of cholesterol ≥ 240 mg/dl				0.672
Yes	389	20	5.1	
No	131	8	6.1	
Diabetes				0.713
Yes	184	9	4.9	
No	336	19	5.7	
Hypertension				0.133
Yes	402	25	6.2	
No	118	3	2.5	
Previous MI				0.046
Yes	255	19	7.5	
No	265	9	3.4	
Previous CABG				0.479
Yes	120	8	6.7	
No	400	20	5.0	
Shock before PCI procedure				0.035
Yes	17	3	17.6	
No	503	25	5.0	
Indication for PCI				0.440
Elective	184	8	4.3	
Acute coronary syndrome	336	20	6.0	
Emergent surgery				0.006
Yes	28	5	17.9	
No	492	23	4.7	
Residual stenosis				0.463
≤ 5%	416	23	5.5	
6–49%	91	4	4.4	
≥ 50%	13	1	7.7	
Maintenance antiplatelet after PCI				0.512
None	4	1	25.0	
Aspirin	6	0	0.0	
Thienopyridine	18	0	0.0	
Aspirin and thienopyridine	488	26	5.3	
Time for PCI to surgery				0.337
≤ 90 days	125	8	6.4	
91–180 days	105	6	5.7	
181–365 days	170	10	5.9	
366–730 days	120	4	3.3	
Aspirin use before surgery				0.341
Used within 7 days before surgery	365	22	6.0	
Used within 30 days, but stopped > 7 days before surgery	60	1	1.7	
No use within 30 days before surgery	80	3	3.8	
Thienopyridine use before surgery				0.040
Used within 7 days before surgery	175	16	9.1	
Used within 30 days, but stopped > 7 days before surgery	70	3	4.3	
No use within 30 days before surgery	264	9	3.4	
Surgical risk group				0.476
Low	96	3	3.1	
Intermediate	293	16	5.5	
High	131	9	6.9	

(*continued*)

Table 1. Continued

Characteristic	Total n	MACEs		
		n	%	*P* Value*
General anesthesia				0.126
Yes	298	20	6.7	
No	222	8	3.6	
Number of stents placed				0.461
1	330	17	5.2	
2	126	7	5.6	
3	51	2	3.9	
4+	13	2	15.4	
Postprocedure TIMI flow grade classification				0.507
0	6	1	16.7	
1	1	0	0.0	
2	12	0	0.0	
3	497	27	5.4	
Successful PCI in all lesions				0.711
No	13	1	7.7	
Yes	507	27	5.3	

* *P* values are from analysis using logistic regression. Age, residual percent stenosis, and days from stent to surgery are analyzed as continuous variables. Because of missing data, columns do not always sum to overall n.

CABG = coronary artery bypass grafting; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction trial.

was treated as an ordinal variable, and an ordinal logistic regression model was constructed with univariate variables included as explanatory variables.[18] In all cases, two-tailed tests were performed, and statistical significance was inferred at $P \leq 0.05$.

Results

Clinical Characteristics

A total of 520 patients (160 female, 360 male) were identified who underwent NCS after PCI with DES during the study period. Patient characteristics were reflective of a high-risk population (table 1). The majority of NCSs were intermediate and high risk (table 2).[19] Twenty-eight of the 520 patients underwent emergent surgery. DESs were placed electively in 184 patients (35.4%), and 336 patients (64.6%) had DESs placed for acute coronary syndrome. One stent was placed in 63% of the patients, two stents were placed in 24%, and three or more stents were placed in 13%. The left anterior descending artery was stented in 46% of the cases, the right coronary artery was stented in 34%, and the left circumflex was stented in 29%. The majority, 84%, of the DESs placed were Cypher, sirolimus-eluting stents (Cordis, Johnson & Johnson, Miami Lakes, FL), whereas 16% received Taxus, paclitaxel-eluting stents (Boston Scientific, Natick, MA).

Table 2. Surgical Procedures* (n = 520)

Surgical Group	n (%)
High risk	
Vascular	103 (20)
Any emergency	28 (5)
Intermediate risk	
Nose, mouth, and pharynx	13 (3)
Digestive system	118 (23)
Musculoskeletal system	103 (20)
Respiratory system	29 (6)
Nervous system	21 (4)
Endocrine system	9 (2)
Low risk	
Ear	3 (1)
Hemi and lymphatic system	9 (2)
Urinary system	51 (10)
Male genital	7 (1)
Female genital	7 (1)
Integumentary system	9 (2)
Miscellaneous	10 (2)

* Categorized according to American College of Cardiology–American Heart Association classification.[19]

The median time from PCI to NCS was 203.5 days (interquartile range, 94.5–349.5 days). One hundred twenty-five patients had NCS within 90 days of PCI with DES, 105 patients had NCS 91–180 days after PCI with DES, 170 patients had NCS 181–365 days after PCI with DES, and 120 patients had NCS 366–730 days after PCI with DES. We analyzed the association between patient characteristics and the time from DES placement to surgery (table 3).

Risk of Perioperative MACEs

Of the 520 patients, 28 (5.4%) experienced one or more in-hospital MACEs (4 ST-elevation MIs, 10 non–ST-elevation MIs, 4 stent thromboses, 6 repeat revascularizations, and 14 deaths). The rate of MACEs did not change significantly with time after placement (6.4, 5.7, 5.9, and 3.3% for patients undergoing NCS 0–90, 91–180, 181–365, and > 365 days, respectively, after PCI; $P = 0.337$; odds ratio [OR] = 0.97; 95% confidence

Table 3. Univariate Analysis of Patient Characteristics Associated with the Time from Drug-eluting Stent Placement to Surgery

		Time from PCI to Noncardiac Surgery								
		0–90 Days		91–180 Days		181–365 Days		> 1 yr		
Variable	Total n	n	%	n	%	n	%	n	%	*P* Value*
Overall	520	125	100	105	100	170	100	120	100	
Age group										0.665
≤ 55 yr	77	20	16.0	21	20.0	22	12.9	14	11.7	
56–65 yr	113	26	20.8	20	19.0	37	21.8	30	25.0	
66–75 yr	180	43	34.4	34	32.4	59	34.7	44	36.7	
≥ 76 yr	150	36	28.8	30	28.6	52	30.6	32	26.7	
Sex										0.540
Male	360	93	74.4	72	68.6	115	67.6	80	66.7	
Female	160	32	25.6	33	31.4	55	32.4	40	33.3	
Current/former smoker										0.572
Yes	311	80	64.0	61	58.1	96	56.5	74	61.7	
No	209	45	36.0	44	41.9	74	43.5	46	38.3	
History of cholesterol ≥ 240 mg/dl										0.005
Yes	389	80	64.0	79	75.2	140	82.4	90	75.0	
No	131	45	36.0	26	24.8	30	17.6	30	25.0	
Diabetes										0.500
Yes	184	39	31.2	42	40.0	63	37.1	40	33.3	
No	336	86	68.8	63	60.0	107	62.9	80	66.7	
Hypertension										0.676
Yes	402	99	79.2	83	79.0	132	77.6	88	73.3	
No	118	26	20.8	22	21.0	38	22.4	32	26.7	
Previous MI										0.014
Yes	255	76	60.8	51	48.6	71	41.8	57	47.5	
No	265	49	39.2	54	51.4	99	58.2	63	52.5	
Previous CABG										0.683
Yes	120	24	19.2	26	24.8	40	23.5	30	25.0	
No	400	101	80.8	79	75.2	130	76.5	90	75.0	
Preprocedural shock										< 0.001
Yes	17	13	10.4	0	0.0	2	1.2	2	1.7	
No	503	112	89.6	105	100	168	98.8	118	98.3	
Indication for PCI										0.394
Elective	184	40	32.0	43	41.0	63	37.1	38	31.7	
Acute coronary artery	336	85	68.0	62	59.0	107	62.9	82	68.3	
Residual stenosis										0.142
≤ 5%	416	97	77.6	82	78.1	132	77.6	105	87.5	
6–49%	91	22	17.6	22	21.0	33	19.4	14	11.7	
≥ 50%	13	6	4.8	1	1.0	5	2.9	1	0.8	
Maintenance antiplatelet after PCI										0.149
None	4	3	2.4	0	0.0	1	0.6	0	0.0	
Aspirin	6	3	2.4	2	1.9	0	0.0	1	0.8	
Thienopyridine	18	3	2.4	3	2.9	5	2.9	7	5.9	
Aspirin and thienopyridine	488	114	92.7	100	95.2	164	96.5	110	93.2	
Aspirin use before surgery										0.362
Used within 7 days before surgery	365	87	70.2	74	72.5	124	76.5	80	68.4	
Used within 30 days, but stopped > 7 days before surgery	60	12	9.7	11	10.8	21	13.0	16	13.7	
No use within 30 days before surgery	80	25	20.2	17	16.7	17	10.5	21	17.9	
Thienopyridine use before surgery										< 0.001
Used within 7 days before surgery	175	80	64.5	42	41.2	34	20.6	19	16.1	
Used within 30 days, but stopped > 7 days before surgery	70	8	6.5	28	27.5	25	15.2	9	7.6	
No use within 30 days before surgery	264	36	29.0	32	31.4	106	64.2	90	76.3	
Surgical risk group										0.326
Low	96	20	16.0	22	21.0	29	17.1	25	20.8	
Intermediate	293	64	51.2	63	60.0	100	58.8	66	55.0	
High	131	41	32.8	20	19.0	41	24.1	29	24.2	
General anesthesia										0.023
Yes	298	57	45.6	62	59.0	106	62.4	73	60.8	
No	222	68	54.4	43	41.0	64	37.6	47	39.2	
Number of stents placed										0.749
1	330	82	65.6	64	61.0	108	63.5	76	63.3	
2	126	33	26.4	24	22.9	39	22.9	30	25.0	
3	51	9	7.2	14	13.3	17	10.0	11	9.2	
4+	13	1	0.8	3	2.9	6	3.5	3	2.5	

(*continued*)

Table 3. Continued

Variable	Total n	Time from PCI to Noncardiac Surgery								*P* Value*
		0–90 Days		91–180 Days		181–365 Days		> 1 yr		
		n	%	n	%	n	%	n	%	
Postprocedure TIMI flow grade										0.488
0	6	3	2.4	1	1.0	2	1.2	0	0.0	
1	1	0	0.0	0	0.0	1	0.6	0	0.0	
2	12	3	2.4	1	1.0	5	3.0	3	2.5	
3	497	118	95.2	102	98.1	160	95.2	117	97.5	
Successful PCI in all lesions										0.155
No	13	6	4.8	1	1.0	5	2.9	1	0.8	
Yes	507	119	95.2	104	99.0	165	97.1	119	99.2	

* *P* values are from chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. Age, residual percent stenosis, number of stents and postprocedure TIMI (Thrombolysis in Myocardial Infarction trial) flow were analyzed as continuous variables.

CABG = coronary artery bypass grafting; MI = myocardial infarction; PCI = percutaneous coronary intervention.

interval [CI], 0.91–1.03 per 30 days with time treated as a continuous variable; $P = 0.727$ comparing across timing groups) (fig. 1 and table 4).

Because the time between DES placement and NCS was not controlled, a difference in the rate of MACEs between time categories can be caused by or masked by differences in other patient risk factors between these categories. We also performed a multivariate analysis using a balancing score to adjust for other patient risk factors and still found no relation between time from DES placement to NCS and MACEs ($P = 0.643$; OR = 1.02; 95% CI, 0.95–1.09 per 30 days) (table 4).

As an additional *post hoc* analysis, we compared the rate of MACEs in patients who had NCS performed less than 1 yr after DES placement with patients who had NCS performed greater than 1 yr after DES placement. There was no statistically significant difference (6.0% *vs.* 3.3%, respectively; $P = 0.255$).

Characteristics found to be associated with MACEs in univariate analysis were advanced age ($P = 0.031$; OR = 1.52; 95% CI, 1.04–2.21 per decade), emergent NCS ($P = 0.006$; OR = 4.4; 95% CI, 1.55–12.72), shock at time of PCI ($P = 0.035$; OR = 4.1; 95% CI, 1.11–15.19) and previous history of MI ($P = 0.046$; OR = 2.29; 95% CI, 1.02–5.16).

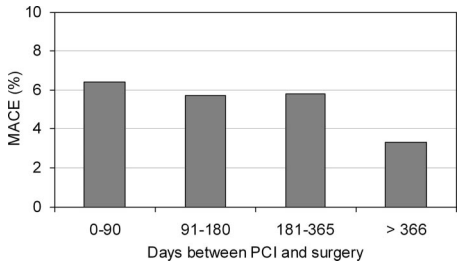

Fig. 1. Major adverse cardiac events (MACEs) *versus* time period between percutaneous coronary intervention (PCI) and surgery: the percentage of patients who experience MACEs (death, ST-elevation myocardial infarction, non–ST-elevation myocardial infarction, stent thrombosis, and repeating revascularization with either coronary artery bypass grafting or repeat angioplasty of the target vessel) *versus* different time.

Antiplatelet Therapy

Two hundred forty-five patients (47.1%) were taking a thienopyridine in the month before NCS, and in 175 cases this was continued into the perioperative period (less than 7 days before surgery). Four hundred twenty-five patients (81.7%) were taking aspirin in the month before NCS, and in 365 cases this was continued into the perioperative period (less than 7 days before NCS).

Use of thienopyridine less than 7 days from NCS was associated with an increased rate of MACEs in univariate analysis (overall $P = 0.040$; OR = 2.2; 95% CI, 0.63–7.97 compared with those who discontinued thienopyridine 7–30 days before surgery; OR = 2.9; 95% CI, 1.23–6.61 compared with those not taking thienopyridine within the 30 days before surgery). Given the small number of patients with MACEs (n = 28), we did not pursue exhaustive multivariable analyses to assess whether thienopyridine use was an independent risk factor for MACEs. However, from an analysis that adjusted for emergent NCS (the variable with the strongest univariate association), the association between thienopyridine use and MACEs was no longer statistically significant ($P = 0.057$).

Bleeding Complications and Transfusion

There were 5 cases of excessive surgical bleeding in the operative note (1 of these patients was taking a thienopyridine and 4 were not taking a thienopyridine before NCS). Seventy-seven patients (14.8%) required erythrocyte transfusion, and 10 patients (1.9%) required transfusion of other blood products, including platelets, fresh frozen plasma, and cryoprecipitate. Of the patients who were taking a thienopyridine within 7 days of NCS, 27 (15.4%) received an erythrocyte transfusion, compared with 50 patients (15.0%) not taking a thienopyri-

Table 4. Frequency of MACEs in Patients Undergoing Noncardiac Surgery after PCI*

	Days from PCI to Surgery				
	≤ 90	91–180	181–365	≥ 366	*P* Value*
Surgeries, n	125	105	170	120	
Events, n (%)	8 (6.4)	6 (5.7)	10 (5.9)	4 (3.3)	
Unadjusted					
OR	2.0	1.8	1.8	1.0	0.727
95% CI	(0.6–6.8)	(0.5–6.4)	(0.6–5.9)		
Adjusted					
OR	0.7	1.3	1.6	1.0	0.565
95% CI	(0.2–2.8)	(0.3–4.7)	(0.5–5.3)		

* Logistic regression was used to assess whether the likelihood of major adverse cardiac events (MACEs) differed across timing groups. For the logistic regression analyses, the *P* value presented corresponds to the 3 *df* test comparing all four timing groups simultaneously. In addition, the odds ratio (OR) and corresponding 95% confidence interval (CI) are presented for the three shorter interval groups (≤ 90, 91–180, and 181–365 days) with the largest interval group (≥ 366 days) as the reference. Both unadjusted and adjusted logistic regression analyses were performed. A balance score for the timing from percutaneous coronary intervention (PCI) to surgery was calculated for each patient based on all the variables in table 1. This score was then used as a covariate while assessing the effect of time in the adjusted analysis. When analyzing time as a continuous variable, the *P* values in the unadjusted and adjusted models are 0.337 (OR = 0.97; 95% CI, 0.91–1.03 per 30-day increase) and 0.643 (OR = 1.02; 95% CI, 0.95–1.09 per 30-day increase), respectively.

dine. Of the 5 patients who received platelet transfusions, 3 were taking thienopyridine before NCS and 2 were not (table 5).

Discussion

To eliminate the premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents, the recent advisory by the AHA–ACC included a recommendation to defer elective procedures with significant risk of bleeding until 12 months after DES, when patients have completed the course of thienopyridine therapy. In our study, the rate of MACEs did seem to decrease with NCS more than 1 yr after PCI with DES, which is consistent with the AHA–ACC advisory, but this was not statistically significant. Therefore, we do not have evidence that either supports or contradicts their recommendations; however, our study is underpowered to detect the observed differences. A sample size of 1,900 (950 per group) would be required to provide statistical power (two-tailed, $\alpha = 0.05$) of 80% to detect a difference between groups, under the assumption that the true rate of MACEs is 3.3% in one group and 6% in the other.

Patients with DESs who underwent emergent surgery had a disconcertingly high rate of MACEs (17.9%). Patients with DESs who undergo emergent surgical procedures warrant aggressive preventative measures and monitoring for ischemia, especially because perioperative ischemia is often underdiagnosed.[20]

The higher rate of perioperative ischemic events in patients whose thienopyridine therapy was continued until less than 7 days of NCS by univariate analysis contradicts the concept that perioperative antiplatelet therapy decreases the rate of DES thrombosis.[11] The most likely cause for this is the association of continuation of thienopyridine therapy with emergent NCS. In our analysis that adjusted for emergent NCS (the variable with the strongest univariate association), the association between thienopyridine use and MACEs was no longer statistically significant. It is also possible that patients who were deemed to be at high risk for perioperative ischemia by their physicians or who had more recent PCI with a DES are more likely to be continued on a thienopyridine through the perioperative period. Continuation of thienopyridine therapy may not be risk factor for MACEs, but rather an indicator of patients at increased risk for MACEs.

Patients who were no longer taking a thienopyridine had the lowest rate of MACEs (3.4%), which supports the AHA–ACC recommendation of delaying NCS after PCI with DES after the course of thienopyridine therapy has been completed. These patients did not have acute withdrawal of thienopyridine therapy preoperatively. However, this may also be because the surgeries in these patients were performed further out after DES placement (table 3).

An important finding of this study was the low incidence of surgical bleeding complications despite the high rate of antiplatelet therapy use. The incidence of

Table 5. Discontinuation of Medication before Noncardiac Surgery and Bleeding Complications (n = 520)

Thienopyridine Use	n	Bleeding Complications	Erythrocyte Transfusion, No. Patients (%)	Nonerythrocyte Transfusion	Platelet Transfusion, No. Patients (%)
Used within 7 days before surgery	175	1	27 (15.4)	6 (3.4)	3 (1.7)
Used within 30 days, but stopped > 7 days before surgery	70	0	9 (12.9)	0	0 (0.0)
No use within 30 days before surgery	264	4	41 (15.5)	4 (1.5)	2 (0.8)

bleeding complications and of transfusion requirements did not seem to be related to the use of antiplatelet therapy. Although the time between PCI with DES and NCS was not a significant risk factor for MACEs, the fact that perioperative antiplatelet therapy is not associated with perioperative bleeding events may help to provide evidence for guidelines on perioperative antiplatelet management in certain subsets of surgical patients.

Comparison with BMSs

This study was conducted according to similar methods as our study in patients with BMSs to allow comparison of the results.[2] The patient characteristics and surgeries performed were similar in the two studies.

The rate of MACEs after NCS was similar in the two studies. In the patients with DESs, the rate of MACEs was 5.4% (28 of 520 patients), compared with a rate of 5.2% (47 of 899 patients) in the study on patients with BMSs. In patients with BMSs, the rate of MACEs decreased with increasing time between PCI and NCS. However, in the patients with DESs, the rate did not change significantly with time from PCI to NCS. It is interesting to note that while the patients with DESs had a lower risk of MACEs if NCS was performed soon after stent placement (6.4% with NCS $<$ 90 days after DES *vs.* 10.5% and 3.8% with NCS $\leq$ 30 and 31–90 days, respectively, after BMS), the risk did not decrease with time as much as was seen in the patients with BMSs (5.7% and 5.9% with NCS 91–180 and 181–365 days, respectively, after DES *vs.* 3.0%, 2.6%, and 2.7% with NCS 91–180, 181–270, and 271–365 days, respectively, after BMS).

Both studies found a similarly increased rate of MACEs in patients undergoing emergent surgery. The rate of MACEs with emergent surgery in patients with DESs was 17.9%, compared with 4.7% in patients with nonemergent surgery. In patients with BMSs, the rate of MACEs was 11.7% with emergent surgery and 4.4% with nonemergent surgery.

We could not assess the characteristics associated with bleeding complications in patients with DESs because the bleeding complications were too few.

Comparison with Previous Studies

There has been growing concern about performing PCI with DES before NCS and about performing NCS in patients with recently placed DESs. This concern arose after case reports of late thrombosis of DESs in nonsurgical patients. In 2001, Liistro and Colombo[7] reported a case of thrombosis of a paclitaxel-eluting stent 7 months after insertion. In 2004, McFadden *et al.* [9] reported two cases of paclitaxel-eluting stent thrombosis at 343 and 442 days, and two cases of sirolimus-eluting stent thrombosis at 335 and 375 days. Also in 2004, Virmani *et al.*[10] reported a case of thrombosis of a sirolimus-eluting stent 18 months after insertion. In contrast to these reports, our case series found that NCS after PCI with DES might be performed with acceptable rates of MACEs when the patients receive proper care and close attention to antiplatelet drug management.

A recent study by Schouten *et al.*[21] found an even lower rate of MACEs (2.2% in 99 patients with DESs who underwent NCS). Similar to our studies, Schouten *et al.* did not find a difference in rate of MACEs in patients with DESs compared with BMSs, but this could have been because of the low number of adverse events found (total of five MACEs in 99 patients with DESs and 93 patients with BMSs).

Previous work by Iakovou *et al.*[12] found premature discontinuation of antiplatelet therapy to be the strongest predictor of late thrombotic occlusion in nonsurgical patients with DESs. Pfisterer *et al.*[13] similarly found that discontinuation of antiplatelet therapy may increase cardiac events in patients with DESs. The findings of Schouten *et al.*, however, were consistent with the findings of Iakovou *et al.* and Pfisterer *et al.* All of the adverse cardiac events in patients with BMSs and DESs who underwent early surgery in the study of Schouten *et al.* were in patients whose antiplatelet therapy was discontinued, though there were only four such events. Similar to our study, they found no increase in blood transfusion in patients continued on antiplatelet therapy through NCS, and there were very few bleeding complications (2 in 196 patients).[21]

Limitations

Our study has the inherent limitations of a retrospective design. There is a possibility of referral bias, and the care of the patients was not controlled by a study protocol. We did not include patients who underwent PCI elsewhere and then had NCS at our institution or underwent PCI at our institution and then went elsewhere for NCS. We also only reported events that occurred during the hospital stay. If any patients were admitted to another hospital with postoperative complications or if they experienced an event at home, these events were not included. The practice of routinely following postoperative cardiac markers and electrocardiographs varies between providers and MACEs could therefore have been underdiagnosed. Data recorded in the medical record can be subjective, *e.g.*, the recording of bleeding complications may have been inaccurate. As noted previously, the low rate of MACEs in the study may have limited the power to detect differences in the rate of MACEs between groups. A limitation of our study is that we did not collect information on β-blocker and statin use. Another limitation of our study is a lack of a control group that underwent coronary angiography, had documented coronary artery disease that was not treated with PCI or coronary artery bypass grafting, and then went on to have NCS. Ashton *et al.*[22] found a 4.1% incidence of MI (defined as at least two of the following: development of new Q waves, typical change in creatine kinase MB,

and positive technetium pyrophosphate scintigraphy) in patients with known coronary disease. Finally, we were unable to determine whether PCI was being performed specifically for the subsequent noncardiac surgery, but we suspect that the majority of PCI procedures were not performed for a planned subsequent surgery.

Conclusions

The rate of MACEs in patients with DESs undergoing NCS was 5.4%. No association was found between MACEs and duration of time from stenting to surgery, but observed rates of MACEs were lowest after 1 yr. Elderly patients and patients undergoing emergent surgery after PCI with DES should be closely monitored for MACEs. Bleeding complications were few and were not associated with antiplatelet therapy.

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