Perioperative Complications After Noncardiac Surgery in Patients With Insertion of Second-Generation Drug-Eluting Stents

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The perioperative outcomes of noncardiac surgery in patients who have received second-generation drug-eluting stents (DESs) have received limited study. We reviewed the medical records of 1,748 consecutive patients who received DES at our institution (1,789 procedures) from January 1, 2009, to July 1, 2012, to determine the outcomes of subsequent noncardiac surgery. During a median follow-up of 43 months, 221 patients underwent 345 noncardiac surgeries (138 low risk, 130 intermediate risk, and 77 high risk), of which 278 were in patients with previous second-generation DES implantation. The incidence of noncardiac surgery in patients with previous second-generation DES implantation was 4.5% at 1 year, 11.6% at 2 years, and 15.2% at 3 years. The mean time from stent implantation to surgery was 21 ± 12.9 months. Mean age was 66 ± 8 years, 99% were men, and 11% had a perioperative complication, including 5.8% major bleeding, 2.5% acute kidney injury, 2.2% major adverse cardiac event, and 1.4% stroke. Perioperative stent thrombosis occurred in 2 patients (0.7%, 95% confidence interval 0.2% to 2.6%): 1 patient had received a DES 14 months before surgery and had stent thrombosis on the day of surgery and the other had a DES implanted 21 months before surgery and developed stent thrombosis the day after surgery. In conclusion, the incidence of perioperative complications with noncardiac surgery after second-generation DES implantation was 11% and consisted mainly of bleeding (5.8%). The incidence of definite stent thrombosis was 0.7%. Published by Elsevier Inc. (Am J Cardiol 2014;114:230−235)

Drug-eluting stents (DESs) significantly reduce the rates of in-stent restenosis compared with bare metal stent implantation.[1] However, concerns emerged for increased risk of stent thrombosis, even many years after DES implantation.[2−5] The perioperative period is a time of increased concern for stent thrombosis, as surgery causes a prothrombotic state and antiplatelet medications are often discontinued.[6−8] Second-generation DESs are made of cobalt-chrome or platinum-chrome platforms and have thinner strut thickness and more biocompatible, durable polymer coatings compared with first-generation DESs. Second-generation DESs further improved the outcomes achieved with first-generation DESs by reducing the risk of restenosis, myocardial infarction (MI), and stent thrombosis.[9,10] The impact of second-generation DESs on the incidence of perioperative stent thrombosis after noncardiac surgery has received limited evaluation[11−13] and formed the focus of the present study.

Methods

We reviewed the records of 1,748 consecutive patients who underwent DES implantation at our institution (1,789 procedures) from January 1, 2009, to July 1, 2012, to determine whether they subsequently underwent noncardiac surgery and whether they developed any perioperative complications.

Stent thrombosis was defined according to the Academic Research Consortium criteria.[14] If patients had multiple stent placements, time to surgery was recorded from the most recent DES placement. First-generation DESs included sirolimus- and paclitaxel-eluting stents (Cypher [Cordis, Warren, New Jersey] and Taxus [Boston Scientific, Natick, Massachusetts]). Second-generation DESs included everolimus-, zotarolimus-, and paclitaxel-eluting platinum chromium stents (Promus [Boston Scientific, Natick, Massachusetts], Xience [Abbott Vascular, Santa Clara, California], Endeavor and Resolute [Medtronic Vascular, Santa Rosa, California], and Ion [Boston Scientific, Natick, Massachusetts]). Patients were considered to have continued preoperative aspirin or ADP P2Y12 inhibitors if the medications were not discontinued or held ≥5 days before surgery. Major adverse cardiac events (MACEs) were defined as perioperative MI, coronary revascularization, and all-cause death. MI was defined as an increase in cardiac biomarkers (creatine kinase, creatine kinase myocardial band, or troponin) ≥3 times upper limit of normal, with at least one of the following: electrocardiographic changes suggestive of ischemia or patient report of chest pain lasting at least 20 minutes. Major bleeding was defined as any bleeding associated with hypotension, estimated blood loss >500 mL, or transfusion of at least 2 units of packed red blood cells. Acute renal failure was defined as a twofold

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See page 234 for disclosure information.

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Table 1
Characteristics of the study patients

Variable	All (221 Patients, 345 Noncardiac Procedures)	Second-Generation DES (180 Patients, 278 Procedures)	First-Generation DES (35 Patients, 58 Procedures)	Both (6 Patients, 9 Procedures)	p
Age (years)	65 ± 8	66 ± 8	65 ± 6	67 ± 7	0.871
Men	219 (99.1%)	178 (98.9%)	35 (100%)	6 (100%)	0.662
Previous myocardial infarction	78 (35%)	65 (36%)	8 (23%)	5 (83%)	0.015
Previous coronary bypass graft surgery	64 (29%)	54 (30%)	8 (23%)	2 (33%)	0.666
Current smoker	66 (33%)	57 (36%)	6 (19%)	3 (50%)	0.107
Ever smoked	164 (82%)	136 (84%)	22 (69%)	6 (100%)	0.042
Average smoking (pack-years)	41 ± 35	43 ± 36	26 ± 25	46 ± 27	0.079
Hyperlipidemia*	197 (89%)	160 (89%)	32 (91%)	5 (83%)	0.820
Hypertension†	197 (89%)	160 (89%)	31 (89%)	6 (100%)	0.496
Diabetes mellitus	122 (55%)	95 (53%)	26 (74%)	1 (17%)	0.008
Diabetes mellitus on insulin	53 (24%)	40 (22%)	13 (37%)	0 (0%)	0.037
Peripheral arterial disease	48 (22%)	42 (23%)	6 (17%)	0 (0%)	0.160
Glomerular filtration rate (ml/min)	75 ± 33	75 ± 31	71 ± 41	90 ± 26	0.253
Chronic renal insufficiency	40 (18%)	32 (18%)	7 (20%)	1 (17%)	0.949
End stage renal disease	14 (6%)	10 (6%)	4 (11%)	0 (0%)	0.328
Left ventricular ejection fraction (%)	51 ± 12	52 ± 12	49 ± 11	52 ± 10	0.418
Number of coronary vessels stented					0.046
1	163 (74%)	138 (77%)	22 (63%)	3 (50%)	
2	49 (22%)	34 (19%)	13 (37%)	2 (33%)	
3	9 (4%)	8 (4%)	0 (0%)	1 (17%)	
Type of coronary stents implanted					<0.001
Paclitaxel	10 (5%)		9 (26%)	1 (17%)	
Sirolimus	28 (13%)		26 (74%)	2 (33%)	
Everolimus	104 (47%)	101 (56%)		3 (50%)	
Zotarolimus	77 (35%)	77 (43%)		0 (0%)	
ION paclitaxel	2 (1%)	2 (1%)		0 (0%)	
Indication for PCI					0.020
Elective	106 (48%)	94 (52%)	11 (31%)	1 (17%)	
Acute coronary syndrome	115 (52%)	86 (48%)	24 (69%)	5 (83%)	
Medications used before surgery					
Aspirin	309 (90%)	249 (90%)	52 (90%)	8 (89%)	1.00
Clopidogrel	200 (58%)	167 (60%)	28 (48%)	5 (56%)	0.255
Prasugrel	11 (3%)	10 (4%)	1 (2%)	0 (0%)	0.546
Ticagrelor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
Beta-blocker	299 (87%)	244 (88%)	48 (83%)	7 (78%)	0.463
Angiotensin-converting enzyme inhibitor	195 (57%)	161 (58%)	26 (45%)	8 (89%)	0.019
Angiotensin receptor blocker	56 (16%)	44 (16%)	12 (21%)	0 (0%)	0.134
Calcium channel blocker	88 (26%)	79 (28%)	8 (14%)	1 (11%)	0.028
Statin	303 (88%)	240 (86%)	54 (93%)	9 (100%)	0.098
Preoperative aspirin	229 (66%)	188 (68%)	39 (67%)	2 (22%)	0.022
Preoperative thienopyridine	100 (29%)	85 (31%)	13 (22%)	2 (22%)	0.392
Preoperative dual antiplatelet therapy	88 (26%)	76 (27%)	11 (19%)	1 (11%)	0.213
No preoperative antiplatelet therapy	103 (30%)	80 (29%)	17 (29%)	6 (67%)	0.070

Values are mean ± SD or *n* (%).
DES = drug-eluting stent; PCI = percutaneous coronary intervention.
* Hyperlipidemia was defined as low-density cholesterol >100 mg/ml or use of antilipidemic medications.
† Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertensive medications.

increase in creatinine or decrease by 50% in glomerular filtration rate. Stroke was defined as pathological, imaging, or other objective evidence of cerebral, spinal, or retinal focal ischemic injury in a defined vascular distribution or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms lasting ≥24 hours or until death, with other etiologies excluded. An event was considered to be postoperative if it occurred within 30 days from noncardiac surgery.

Surgeries were classified as low, intermediate, or high risk according to the American College of Cardiology/American Heart Association guidelines. Low-risk surgeries included endoscopic, superficial, cataract, breast, and ambulatory procedures; intermediate-risk surgeries included intraperitoneal, intrathoracic, carotid endarterectomy, head and neck, and prostate procedures; high-risk surgeries included aortic and other major vascular surgery, peripheral vascular surgery, and emergent surgeries.[15] Simple epidural injections and nerve blocks were excluded from the study.

Continuous parameters were reported as mean ± SD and compared using the Wilcoxon rank-sum test. Discrete parameters were reported as percentages and compared

Table 2
Incidence of complications within 30 days from noncardiac surgery

Outcome	All Procedures (n = 345)	Procedures in Patients with Second-Generation DES (n = 278)	Procedures in Patients With First-Generation DES (n = 58)	p
Any Complication*	38 (11%)	31 (11%)	8 (14%)	0.281
Major bleeding	21 (6.1%)	16 (5.8%)	5 (8.6%)	0.414
MACE	10 (2.9%)	6 (2.2%)	4 (6.9%)	0.172
Acute renal failure	9 (2.6%)	7 (2.5%)	2 (3.5%)	0.729
Stroke	4 (1.1%)	4 (1.4%)	0 (0%)	0.419
Stent thrombosis	2 (0.6%)	2 (0.7%)	0 (0%)	0.648
Syncope	0 (0%)	0 (0%)	0 (0%)	N/A

Values are *n* (%).
DES = drug-eluting stent; MACE = major adverse cardiac event.
* Any complication includes any patient who had perioperative major bleeding, MACE, acute renal failure, stroke, stent thrombosis, or syncope.

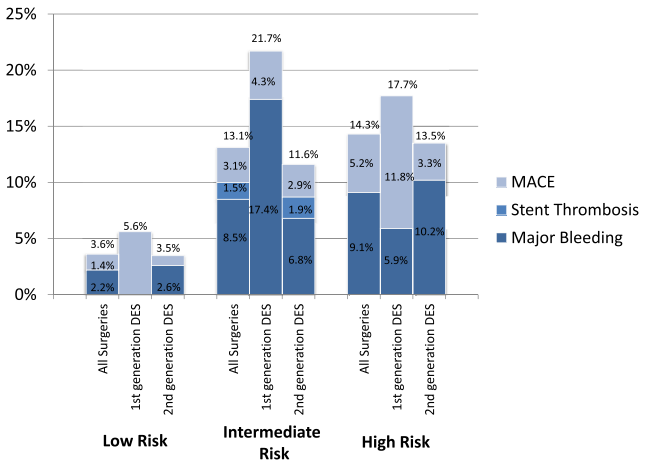

Figure 1. Rates of perioperative MACE, stent thrombosis, and major bleeding classified according to surgical risk.

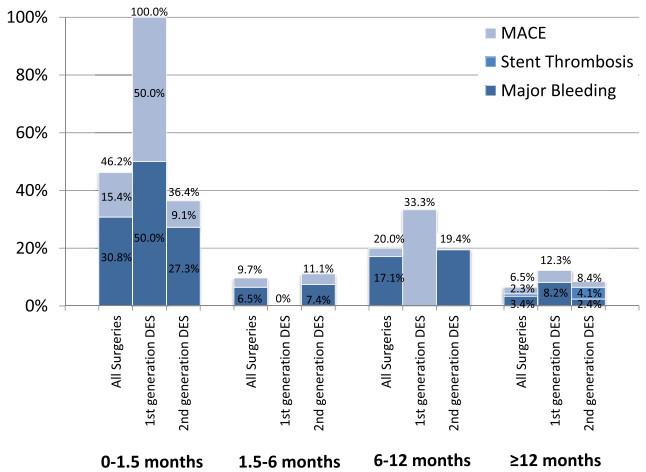

Figure 2. Rates of perioperative MACE, stent thrombosis, and major bleeding classified according to time from DES implantation to noncardiac surgery.

using the chi-square or the Fisher's exact test, as appropriate. A 2-sided p value of <0.05 was considered statistically significant. All analyses were done using JMP 11.0 (SAS Institute, Cary, North Carolina). The study was approved by the Institutional Review Board.

Results

During a median follow-up of 43 months, 221 of the 1,748 DES patients underwent 345 noncardiac surgeries. Of those 345 noncardiac surgeries, 278 occurred in patients who had received a second-generation DES, 58 in patients who had received a first-generation DES, and 9 in patients who had received both a first- and a second-generation DES. The mean time from DES implantation to surgery was 21 ± 12.9 months for second-generation DES and 22 ± 11.3 months for first-generation stents (p = 0.138). The incidence of noncardiac surgery for second-generation DES was 4.5% at 1 year, 11.6% at 2 years, and 15.2% at 3 years. The incidence of noncardiac surgery for first-generation DES was 3.8% at 1 year, 13.3% at 2 years, and 22.5% at 3 years. The characteristics of the study patients are listed in Table 1. The most common types of surgery were (1) general (n = 77, 22.3%), (2) vascular (n = 77, 22.3%), and (3) ophthalmologic (n = 72, 20.9%). The least common surgeries were podiatric (n = 2, 0.6%), neurosurgical, dermatologic, and dental (each n = 5, 1.5%). There were no significant differences in the type of surgery among patients who had undergone first- or second-generation DES (p = 0.630).

The rates of stent thrombosis, MACE, major bleeding, acute renal failure, syncope, and stroke up to 30 days after noncardiac surgery are listed in Table 2. Perioperative stent thrombosis occurred in 2 patients (0.6% of all patients, 95% confidence interval 0.2% to 2.1%, and 0.7% of second-generation DES patients, 95% confidence interval 0.2% to 2.6%). Overall, there was a trend toward lower incidence of perioperative complications in patients who had received a second-generation DES compared with those who had received a first-generation DES before surgery.

The first patient who developed perioperative stent thrombosis was a 62-year-old man who underwent elective transurethral resection of the prostate for gross refractory hematuria 14 months after implantation of an Endeavor zotarolimus-eluting stent into the right coronary artery for stable angina. Aspirin and prasugrel were held before surgery, and eptifibatide was administered. Three hours after surgery and before eptifibatide could be restarted, he developed severe chest pain, bradycardia, and lateral ST-segment elevation. Emergent coronary angiography

Table 3
Incidence of complications according to time from DES implantation to noncardiac surgery

Time from DES Implantation to Noncardiac Surgery	Months				p for <1.5 months vs ≥1.5–6 months	p for <6 months vs ≥6 months	p for <12 months vs ≥12 months
	<1.5	≥1.5–6	≥6–12	≥12			
All noncardiac surgeries (n = 345)							
Major bleeding	4/13 (30.8%)	2/31 (6.5%)	6/35 (17.1%)	9/266 (3.4%)	0.041	0.046	0.001
MACE	2/13 (15.4%)	1/31 (3.2%)	1/35 (2.9%)	6/266 (2.3%)	0.167	0.145	0.220
Stent thrombosis	0/13 (0%)	0/31 (0%)	0/35 (0%)	2/266 (0.8%)	N/A	0.459	0.307
Surgeries with second-generation DES (n = 278)							
Major bleeding	3/11 (27.3%)	2/27 (7.4%)	6/31 (19.4%)	5/209 (2.4%)	0.118	0.061	0.0001
MACE	1/11 (9.1%)	1/27 (3.7%)	0/31 (0%)	4/209 (1.9%)	0.520	0.214	0.637
Stent thrombosis	0/11 (0%)	0/27 (0%)	0/31 (0%)	2/209 (4.1%)	N/A	0.442	0.284

Values are *n* (%).
DES = drug-eluting stent; MACE = major adverse cardiac event.

confirmed thrombosis of the proximal right coronary artery stent, which was successfully treated with percutaneous coronary intervention followed by uneventful recovery.

The second patient who developed perioperative stent thrombosis was a 53-year-old man who presented for elective open sigmoidectomy with diverting loop ileostomy for repeated episodes of diverticulitis 21 months after stenting of the first obtuse marginal artery for non-ST-segment elevation MI with an Endeavor zotarolimus-eluting stent. Aspirin was continued during the perioperative period, but clopidogrel was discontinued 7 days before surgery. Thirty hours after surgery, the patient became dyspneic, diaphoretic, and tachycardic and developed ST-segment depressions in leads V2 to V3. He had no chest pain. Cardiac biomarkers were markedly elevated (creatine kinase myocardial band, >300 ng/ml and troponin I >100 ng/ml). Coronary angiography confirmed first obtuse marginal stent thrombosis, and percutaneous coronary intervention was performed. The patient developed severe hypotension. Despite insertion of an intra-aortic balloon pump and multiple vasopressors, he died on the second postoperative day.

Of 345 cases of noncardiac surgery, 138 were low-risk, 130 were intermediate-risk, and 77 were high-risk procedures. The risk of MACE (p = 0.295) and major bleeding (p = 0.029) was lower in low-risk surgeries compared with intermediate- and high-risk surgeries (Figure 1). The risk of any perioperative complication (5.8% vs 15.4% vs 13.0%, respectively, p = 0.028) was likewise lower in low-risk surgeries compared with intermediate- and high-risk surgeries. Among the 278 noncardiac surgeries in patients with previous second-generation DES, the risk of MACE (p = 0.406), major bleeding (p = 0.099), and any perioperative complication (6.0% vs 15.5% vs 11.9%, respectively, p = 0.070) was lower in low-risk surgeries compared with intermediate- and high-risk surgeries.

The rates of major bleeding, MACE, and stent thrombosis according to the time of noncardiac surgery after DES implantation are shown in Figure 2. Patients had higher rates of both major bleeding and MACE when noncardiac surgery was performed <1.5 months after DES implantation (Table 3). When only second-generation DESs were evaluated, there was no significant difference in MACE when noncardiac surgery was done <1.5 months, <6 months, and <1 year after stenting, although there were higher rates of major bleeding when noncardiac surgery was done <1 year after DES implantation rather than after 1 year.

Of the patients who were prescribed aspirin and an ADP P2Y12 inhibitor, three quarters continued aspirin perioperatively and half continued taking an ADP P2Y12 inhibitor perioperatively (Table 1). The incidence of major bleeding (6.6% vs 5.2%, respectively, p = 0.623) and MACE (2.2% vs 4.4%, respectively, p = 0.273) was similar in patients who continued aspirin preoperatively compared with those who did not. Likewise, the incidence of major bleeding (6.0% vs 6.2%, respectively, p = 0.959) and MACE (5.0% vs 2.1%, respectively, p = 0.158) was similar in patients who continued to take an ADP P2Y12 inhibitor preoperatively compared with those who did not. Patients who received dual antiplatelet therapy during the perioperative period had similar incidence of major bleeding (p = 0.749) and MACE (p = 0.820) compared with patients in whom both aspirin and ADP P2Y12 inhibitors were discontinued before surgery.

Discussion

The main finding of our study is that patients who underwent noncardiac surgery after second-generation DES implantation have significant risk for perioperative complications, which was higher for surgeries classified as high and intermediate risks compared with low risk. Perioperative bleeding accounted for approximately half of all complications. Although the incidence of perioperative stent thrombosis was low (0.7%), it persisted even when surgery was performed >12 months post implantation. Stent thromboses occurred during the first 48 hours after surgery.

Second-generation DESs have lower rates of stent thrombosis compared with first-generation DESs. In SPIRIT IV, the 1-year incidence of definite stent thrombosis was 0.3% for everolimus-eluting stents and 0.8% for paclitaxel-eluting stents (p = 0.02).[9] Palmerini et al[16] performed a meta-analysis of 49 trials including 50,844 patients, finding that everolimus-eluting stents had lower rates of definite stent thrombosis compared with paclitaxel DES, even 2 years after DES implantation (odds ratio 0.34, 95% confidence interval 0.19 to 0.62). We previously reported the perioperative stent thrombosis rate after noncardiac surgery at our institution for first-generation DES to be approximately 0.5%,[17] which is similar to the 0.7% rate observed with second-generation DES in the present study. The protective effect of second-generation DES against stent

thrombosis may be overwhelmed by the prothrombotic state induced by surgery and interruption of antiplatelet therapy.[6,7]

Our study is the first to examine the rates of stent thrombosis after noncardiac surgery in patients with second-generation DES. Two recent large observational studies examined risk of MACE after noncardiac surgery in patients with cardiac stents.[6,18] However, these studies did not examine actual rates of stent thrombosis, nor did they specifically assess rates of MACE in patients with previous second-generation DES separately from first-generation DES. Hawn et al[18] found a 30-day MACE rate for combined first- and second-generation DESs to be 4.3%, and Wijeysundera et al[6] found a 30-day MACE rate for all previous stents to be 2.1%. Our finding of a 30-day MACE rate for patients with any previous DES of 2.9%, and specifically for second-generation DES of 2.2%, is similar to the above reports. We also confirmed findings of substantially increased risk when surgery is performed within 6 weeks of coronary stent implantation; a major bleed occurred in 30.8% and MACE in 15.4% within this time frame (Table 3).[6,18–20] However, as with previous studies, the association between noncardiac surgery soon after percutaneous coronary intervention and adverse events may be confounded by including emergent surgeries, which carry higher risk compared with elective surgeries.[6,21]

Both perioperative stent thromboses that occurred in our cohort were very late stent thromboses, occurring >1 year after DES implantation, although recent studies have shown that the risk is low and stable after 6 months after DES implantation.[18] One patient stopped both aspirin and prasugrel preoperatively and was bridged with eptifibatide, whereas the other continued aspirin but stopped clopidogrel 7 days before surgery. Similar to previous studies, we found no association between antiplatelet therapy cessation during the perioperative period and the risk of adverse events.[18,22] As we recently reported, preoperative "bridging" with a glycoprotein IIb/IIIa inhibitor was not 100% effective in preventing perioperative stent thrombosis.[23] We also found bleeding rates to be the same irrespective of antiplatelet use, possibly because surgeons are more likely to stop antiplatelet therapy for surgeries at high risk for bleeding and more likely to continue antiplatelet therapy for surgeries that carry low risk of bleeding.

This study has several limitations. First, it was a small single-center study, with limited power to detect differences between the compared groups, yet it provided detailed assessment of all adverse outcomes. Second, nearly all study patients were men, limiting extrapolation to women. Third, our study did not include patients who had noncardiac surgery or DES placement at a different institution. Future prospective studies of a large number of patients will be important to better characterize the perioperative risk of patients with previous implantation of second-generation DES.

Disclosures

Dr. Banerjee receives research grants from Gilead and the Medicines Company, consultant/speaker honoraria from Covidien and Medtronic, ownership in MDCARE Global (spouse), and intellectual property in HygeiaTel. Dr. Brilakis receives consulting honoraria/speaker fees from Sanofi, Janssen, St Jude Medical, Terumo, Asahi, Abbott Vascular, and Boston Scientific and receives research grant from Guerbet; spouse is an employee of Medtronic. All other authors have no conflicts of interest to disclose.

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