DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Wednesday February 26, 2014
1800 HOURS

LOCATION:
Curry Original
253A Ontario Street, Kingston

PRESENTING ARTICLES:
Dr. Melinda Fleming & Dr. Gita Raghavan

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

Risk of Elective Major Noncardiac Surgery After Coronary Stent Insertion

A Population-Based Study

Duminda N. Wijeysundera, MD, PhD; Harindra C. Wijeysundera, MD, PhD; Lingsong Yun, MSc; Marcin Wąsowicz, MD, PhD; W. Scott Beattie, MD, PhD; James L. Velianou, MD; Dennis T. Ko, MD, MSc

Background—Guidelines recommend that noncardiac surgery be delayed until 30 to 45 days after bare-metal stent implantation and 1 year after drug-eluting stent implantation.

Methods and Results—We used linked registry data and population-based administrative health care databases to conduct a cohort study of 8116 patients (≥40 years of age) who underwent major elective noncardiac surgery in Ontario, Canada between 2003 and 2009, and received coronary stents within 10 years before surgery. Approximately 34% (n=2725) underwent stent insertion within 2 years before surgery, of whom 905 (33%) received drug-eluting stents. For comparison, we assembled a separate cohort of 341 350 surgical patients who had not undergone coronary revascularization. The primary outcome was 30-day major adverse cardiac events (mortality, readmission for acute coronary syndrome, or repeat coronary revascularization). The overall rate of 30-day events in patients with coronary stents was 2.1% (n=170). When the interval between stent insertion and surgery was <45 days, event rates were high for bare-metal (6.7%) and drug-eluting (20.0%) stents. When the interval was 45 to 180 days, the event rate for bare-metal stents was 2.6%, approaching that of intermediate-risk nonrevascularized individuals. Adjusted analyses suggested that event rates were increased if this interval exceeded 180 days. For drug-eluting stents, the event rate was 1.2% once the interval exceeded 180 days, approaching that of intermediate-risk nonrevascularized individuals.

Conclusions—The earliest optimal time for elective surgery is 46 to 180 days after bare-metal stent implantation or >180 days after drug-eluting stent implantation. **(*Circulation*. 2012;126:1355-1362.)**

Key Words: complications ■ coronary artery disease ■ percutaneous transluminal coronary angioplasty ■ surgery

The management of noncardiac surgery after percutaneous coronary intervention (PCI) and coronary stent implantation is a frequent and important concern in perioperative care. Percutaneous coronary interventions are common, with 1.2 million procedures performed every year in North America alone.[1,2] Of patients who receive coronary stents, 5% subsequently undergo noncardiac surgery within 1 year,[3,4] corresponding to 60 000 patients annually in North America. The perioperative period poses important risks for such individuals. Risks of stent thrombosis and adverse cardiac events are increased as a result of the prothrombotic state induced by the surgical stress response,[5] as well as the potential disruption of antiplatelet medications. Conversely, if antiplatelet medications are continued to mitigate the risk of stent thrombosis, patients may suffer increased risks of major hemorrhage, which is itself associated with increased mortality.[6]

Editorial see p 1322
Clinical Perspective on p 1362

Given these opposing risks, practice guidelines recommend that elective noncardiac surgery be delayed until surgery can be performed safely using antiplatelet therapy with aspirin alone. The suggested delay is 30 to 45 days for bare-metal stents and 1 year for drug-eluting stents.[7,8] These recommendations have important implications, especially because 70%

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of North American patients who undergo PCI receive drug-eluting stents.[9] Specifically, many such individuals may not be able to defer their planned surgery for a year.

These recommendations are largely based on expert opinion, as well as reports that showed an increased risk of adverse cardiac events when noncardiac surgery was performed shortly after stent implantation.[4,10–13] However, these previous reports have important limitations. Some were single-center studies with limited generalizability.[11–13] In addition, the association between noncardiac surgery soon after PCI and adverse events may have been confounded by the inclusion of urgent-to-emergent surgeries in several studies.[4,10,12,13] Specifically, urgent-to-emergent procedures, which are likely to necessitate noncardiac surgery soon after PCI, are associated with an almost 4-fold increased risk of mortality.[6]

Given the important implications of current guideline recommendations for the perioperative care of patients with coronary stents, and the limitations to the related literature, we conducted a population-based cohort study to evaluate the outcomes of patients who underwent elective intermediate- to high-risk noncardiac surgery in Ontario, Canada after stent implantation.

Methods

The Cardiac Care Network of Ontario maintains a prospective clinical registry of all individuals who undergo cardiac catheterization, PCI, or coronary artery bypass grafting (CABG) surgery in Ontario, Canada.[14,15] All hospitals performing PCI are required to collect information on patients' clinical characteristics, as well as procedural information on the number of stents, characteristics of each stent, and location of stent placement. After research ethics approval from Sunnybrook Health Sciences Centre, we conducted a retrospective cohort study by linking this registry to several population-based administrative databases, namely the Discharge Abstract Database of the Canadian Institute for Health Information (hospital admissions), the Ontario Health Insurance Plan database (physician service claims), the Registered Persons Database (vital statistics), the Ontario Drug Benefit database (prescriptions for individuals ≥65 years of age), and the Canadian census. Although these databases lack physiological and laboratory measures (eg, blood pressure, hemoglobin), they have been validated for many outcomes, exposures, and comorbidities.[16–20] Because the Cardiac Care Network registry is prescribed under Ontario's health information privacy legislation, the need for informed consent was waived.

Cohort

We identified all Ontario residents who were ≥40 years of age, underwent any 1 of 16 prespecified elective noncardiac surgeries between April 1, 2003 and March 31, 2009, and underwent coronary stent implantation within 10 years before their index surgery. The included surgeries were abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular bypass, total hip replacement, total knee replacement, large bowel resection, partial liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, total abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy.[8,21,22] Information pertaining to the procedure performed and procedure status (elective versus nonelective) in this database is very accurate.[18] Individuals who underwent CABG surgery between the preoperative PCI and subsequent index noncardiac surgery were excluded. In addition, we excluded low-risk ambulatory surgeries, largely because they are associated with a very low risk of major complications.[23] Furthermore, many such procedures can be performed while patients receive dual antiplatelet therapy or delayed until dual therapy is no longer necessary.

Individuals in the cohort were categorized based on the type of stent implanted (bare-metal stent or drug-eluting stent) and duration between PCI and the index surgery. These categorizations were largely informed by practice guideline recommendations that elective noncardiac surgery be delayed until at least 45 days after bare-metal stent implantation and 365 days after drug-eluting stent implantation.[8] For individuals who underwent multiple PCI procedures before their index surgery, the categorization was based on the PCI closest to the surgery. The 9 categories were bare-metal stent within 1 to 45 days before surgery, bare-metal stent within 46 to 180 days before surgery, bare-metal stent within 181 to 365 days before surgery, bare-metal stent within 366 to 730 days before surgery, drug-eluting stent within 1 to 45 days before surgery, drug-eluting stent within 46 to 180 days before surgery, drug-eluting stent within 181 to 365 days before surgery, drug-eluting stent within 366 to 730 days before surgery, and any stent within 731 days to 10 years before surgery. Patients with remote histories of stent implantation (ie, 731 days to 10 years before surgery) served as the control group against which we compared individuals who underwent more recent stent implantation.

Outcomes and Comorbidities

Patients were tracked for 1 year after surgery for mortality, hospital readmission for an acute coronary syndrome (myocardial infarction or unstable angina), and repeat coronary revascularization (PCI or CABG surgery). The Discharge Abstract Database (in-hospital mortality, revascularization, hospital readmission for acute coronary syndrome), Registered Persons Database (out-of-hospital mortality), and Cardiac Care Network registry (revascularization) were used to ascertain these outcomes. We identified hospitalizations for acute coronary syndromes using *International Classification of Diseases* 10th Revision diagnostic codes I21, I22, I20, I23.82, and I24.[24] The primary outcome was a major adverse cardiac event (MACE), defined as mortality, readmission for acute coronary syndrome, or coronary revascularization, within 30 days after the index surgery. The secondary outcome was MACE within 1 year after surgery.

Demographic information was obtained from the Registered Persons Database, and validated algorithms were used to identify diabetes and hypertension.[17,19] The Ontario Health Insurance Plan database was used to identify anyone who required dialysis before surgery. Using the Discharge Abstract Database, we used previously described methods to identify other comorbidities based on *International Classification of Diseases* (9th or 10th Revision) codes from hospitalizations within 3 years preceding surgery: congestive heart failure, cerebrovascular disease, peripheral vascular disease, pulmonary disease, and chronic renal insufficiency.[25] We determined patients' socioeconomic status based on their neighborhood median income in the Canadian census and their residence (rural versus urban) using Statistics Canada definitions.[26]

Perioperative cardiac risk was also estimated based on the Revised Cardiac Risk Index.[27] This predictive index consists of 6 equally weighted components: coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, renal insufficiency, and high-risk surgery (major vascular, intraperitoneal, or intrathoracic procedures). It is suggested that a Revised Cardiac Risk Index score of 0 points corresponds to low risk, 1 to 2 points corresponds to intermediate risk, and 3 or more points corresponds to high risk.[28]

As an additional comparison, we used the same databases to describe the characteristics and outcomes of individuals who were ≥40 years of age, underwent eligible surgeries during the study period, and had not undergone any revascularization (PCI or CABG surgery) within 10 years before their index surgery.

To describe the preoperative use of antiplatelet medications, the Ontario Drug Benefits database was used to ascertain preoperative prescriptions for thienopyridines (clopidogrel or ticlopidine) in the 100 days before the index surgery. Because these data are only available for individuals ≥65 years of age, and a 100-day look-back period was used, this analysis was performed in the subgroup of individuals ≥66 years of age.

Analyses

We used appropriate tests (analysis of variance, Kruskal-Wallis test, χ^2 test) to compare the characteristics of patients who had or had not received a bare-metal stent or drug-eluting stent within 2 years before their index surgeries. Descriptive statistics were used to characterize event rates of the primary and secondary outcomes among individuals who had undergone previous PCI (categorized based on stent type and PCI-to-surgery interval), and among nonrevascularized individuals (categorized based on Revised Cardiac Risk Index score).[27]

We then used multivariable logistic regression to determine the adjusted association between the 9 categories of stent type and PCI-to-surgery interval with the primary and secondary outcomes. The reference category, against which the different categories of the primary exposure were compared, was a history of remote stenting (ie, bare-metal or drug-eluting stent within 731 days to 10 years before surgery). The other covariates in the regression model were age, sex, surgery, congestive heart failure, cerebrovascular disease, peripheral vascular disease, hypertension, diabetes mellitus, and renal disease. Surgeries were categorized as major vascular (abdominal aortic aneurysm repair, peripheral vascular bypass), high-intermediate risk (large bowel resection, partial liver resection, Whipple procedure, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy cystectomy, nephrectomy), and low-intermediate risk (carotid endarterectomy, total hip replacement, total knee replacement, total abdominal hysterectomy, radical prostatectomy) procedures.[29] Model discrimination was measured using the c-statistic, and calibration was estimated using the Hosmer-Lemeshow statistic.

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC), and a 2-tailed P value <0.05 was used to define statistical significance.

Results

The cohort consisted of 8116 patients who underwent stent implantation within 10 years before their noncardiac surgery. Approximately 34% (n=2725) underwent stent implantation within 2 years before surgery; of these individuals, 905 (33%) received drug-eluting stents. The proportion that had received drug-eluting stents within 2 years before surgery varied over the study period (Figure I in the online-only Data Supplement). Compared with individuals with remote histories of stent implantation (ie, 731 days to 10 years before noncardiac surgery), patients who received bare-metal or drug-eluting stents within 2 years before surgery differed with regard to surgical procedure and comorbidities (Table).

The separate comparator group of patients, who were ≥40 years of age, underwent eligible surgeries, and had not undergone coronary revascularization within 10 years before their index surgery, consisted of 341 350 individuals. Their characteristics are presented in Table I in the online-only Data Supplement.

Among individuals who had undergone previous PCI, the overall risk of 30-day MACE was relatively low at 2.1% (n=170), whereas the risk of 1-year MACE was 9.8% (n=798). The rate of postoperative mortality was 1.2% (n=100) at 30 days and 5.2% (n=419) at 1 year. The incidence of MACE over the first year after surgery is presented in Figure II in the online-only Data Supplement.

The unadjusted risk of cardiac events at 30 days (Figure 1) and 1 year (Figure III in the online-only Data Supplement) after surgery varied based on the type of stent implanted and the time interval from stent implantation to surgery. Once the interval between PCI and surgery exceeded 45 days, the 30-day risk of MACE in a patient with a bare-metal stent approached that of an intermediate-risk nonrevascularized individual with 1 to 2 clinical risk factors (Figure 1). Once the interval exceeded 180 days, the 30-day risk of MACE in a patient with a drug-eluting stent approached that of an intermediate-risk nonrevascularized individual with 1 risk factor (Figure 1).

Using multivariable logistic regression, we determined the adjusted association of coronary stent type and PCI-to-surgery time interval with postoperative MACE at 30 days (Figure 2) and 1 year (Figure IV in the online-only Data Supplement) after surgery. The confidence intervals were generally wide, especially with respect to adjusted odds ratios for 30-day MACE. However, these analyses were suggestive of an increased 30-day risk of MACE when surgery was performed within 45 days of either bare-metal or drug-eluting stent insertion, or within 181 to 365 days after bare-metal stent insertion (Figure 2).

For the subgroup ≥66 years of age at the time of surgery (n=5381), the proportion receiving preoperative thienopyridines was 60.6% (n=734) among the 1211 individuals who received a bare-metal stent within 2 years before surgery, 68.9% (n=404) among the 586 individuals who received a drug-eluting stent within 2 years before surgery, and 12.8% (n=460) among the 3584 individuals who had received any stent within 2 to 10 years before surgery. The specific proportions within subgroups defined by stent type and PCI-to-surgery time interval are presented in the Table II in the online-only Data Supplement.

Discussion

In this population-based study, we found that the risk of perioperative MACE was highest when major elective noncardiac surgery was performed <45 days after coronary stent implantation. The earliest optimal time for performing surgery appeared to be from 46 to 180 days after bare-metal stent implantation or >180 days after drug-eluting stent implantation. Thus, these findings help inform clinical decision-making regarding the timing of major elective noncardiac surgery after recent PCI.

Implications

Our findings suggest that elective noncardiac surgery can be performed reasonably safely in carefully selected patients once at least 6 months have elapsed since drug-eluting stent implantation. There may also be an optimal time window for performing surgery within the year after bare-metal stent implantation, namely from 46 to 180 days after PCI. Although the presence of this optimal window is not certain, especially because its associated adjusted odds ratio is imprecise, this window is biologically plausible. It represents the period when re-endothelialization is largely complete after bare-metal stent implantation[30] but when in-stent restenosis has yet to completely manifest itself.[31] Conversely, once >1 year has elapsed since either bare-metal or drug-eluting stent implantation, physicians can be reassured that the associated perioperative cardiac risk has reached a plateau, with risks similar to that of individuals with remote histories of previous PCI (ie, 2 to 10 years before surgery).

Table. Characteristics of Main Study Cohort*

	BMS 0 to 2 Years Before Surgery (n=1820)	DES 0 to 2 Years Before Surgery (n=905)	Stent 2 to 10 Years Before Surgery (n=5391)	*P* Value
Demographics				
Female sex	590 (32.4%)	314 (34.7%)	1,681 (31.2%)	0.09
Age (y), mean (SD)	69.1 (9.3)	68.8 (9.5)	69.2 (9.0)	0.45
Income quintile				
First (lowest)	364 (20.1%)	175 (19.3%)	1,009 (18.8%)	
Second	325 (17.9%)	196 (21.7%)	1,133 (21.1%)	
Third	387 (21.3%)	175 (19.3%)	1,097 (20.4%)	0.12
Fourth	371 (20.5%)	165 (18.2%)	1,084 (20.1%)	
Fifth (highest)	366 (20.2%)	194 (21.4%)	1,057 (19.6%)	
Missing	7 (0.4%)	0 (0%)	11 (0.2%)	
Rural residence	314 (17.3%)	152 (16.8%)	974 (18.1%)	0.54
Comorbid disease				
Congestive heart failure	202 (11.1%)	71 (7.8%)	313 (5.8%)	<0.001
Cerebrovascular disease	116 (6.4%)	57 (6.3%)	212 (3.9%)	<0.001
Peripheral vascular disease	369 (20.3%)	169 (18.7%)	817 (15.2%)	<0.001
Hypertension	1,501 (82.5%)	779 (86.1%)	4,640 (86.1%)	<0.001
Diabetes mellitus	591 (32.5%)	372 (41.1%)	1,939 (36.0%)	<0.001
Pulmonary disease	163 (9.0%)	81 (9.0%)	436 (8.1%)	0.41
Renal disease	113 (6.2%)	60 (6.6%)	290 (5.4%)	0.19
Procedure				
AAA repair	161 (8.8%)	48 (5.3%)	323 (6.0%)	
Carotid endarterectomy	92 (5.1%)	68 (7.5%)	265 (4.9%)	
Peripheral vascular bypass	157 (8.6%)	89 (9.8%)	350 (6.5%)	
Total hip replacement	304 (16.7%)	137 (15.1%)	964 (17.9%)	
Total knee replacement	482 (26.5%)	279 (30.8%)	1,929 (35.8%)	
Large bowel surgery	280 (15.4%)	130 (14.4%)	563 (10.4%)	<0.001
Liver resection	17 (0.9%)	6 (0.7%)	29 (0.5%)	
Whipple procedure	6 (0.3%)	8 (0.9%)	24 (0.4%)	
Lung resection	67 (3.7%)	21 (2.3%)	155 (2.9%)	
Gastrectomy or esophagectomy	33 (1.8%)	13 (1.4%)	85 (1.6%)	
Abdominal hysterectomy	73 (4.0%)	47 (5.2%)	215 (4.0%)	
Radical prostatectomy	59 (3.2%)	26 (2.9%)	277 (5.1%)	
Nephrectomy	70 (3.8%)	25 (2.8%)	47 (0.9%)	
Cystectomy	19 (1.0%)	8 (0.9%)	47 (0.9%)	
Revised Cardiac Risk Index				
1 point	597 (32.8%)	317 (35.0%)	2,181 (40.5%)	
2 points	756 (41.5%)	343 (37.9%)	2,193 (40.7%)	<0.001
3 points	351 (19.3%)	181 (20.0%)	800 (14.8%)	
4 or more points	116 (6.4%)	64 (7.1%)	217 (4.0%)	

AAA indicates abdominal aortic aneurysm; BMS, bare-metal-stent; DES, drug-eluting-stent; and SD, standard deviation.
*Values are expressed as No. (percentage) unless indicated otherwise.

Importantly, our results also indicate that the absolute magnitude of short-term postoperative risk is not unreasonable during these periods, namely 45 to 180 days after bare-metal stent implantation and >180 days after drug-eluting stent implantation. Specifically, perioperative risks during these intervals approach that of an intermediate risk nonrevascularized patient with 1 to 2 risk factors. This absolute risk is important for clinicians to consider when weighing the risks of proceeding with elective surgery after PCI against the risks of not operating in individuals who require surgery for conditions such as cancer.

Our study has implications for current guideline recommendations pertaining to the perioperative care of patients with coronary stents. Although our results do support the recommendation to delay elective noncardiac surgery until at least 30 to 45 days have elapsed since bare-metal stent implantation, they further suggest that excessive delays are not helpful. Specifically, short-term perioperative cardiac risk

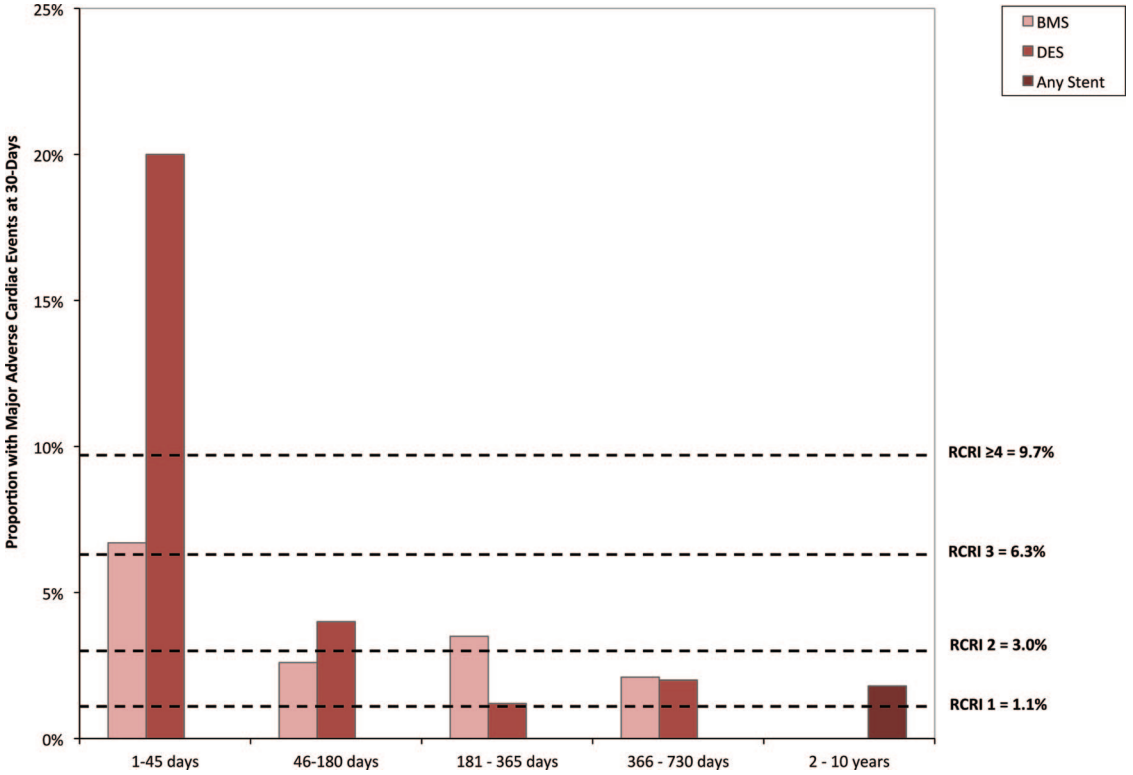

Figure 1. Proportion of patients with major adverse cardiac events (death, readmission for acute coronary syndrome, coronary revascularization) within 30 days after elective noncardiac surgery, based on the interval between the most recent coronary stent insertion and subsequent noncardiac surgery. The red columns represent proportions for individuals who received bare metal stents (BMS), drug eluting stents (DES), or either type of stent (for stent insertions 2 to 10 years before noncardiac surgery). For comparison, the horizontal dashed lines represent event rates for individuals who did not undergo coronary revascularization within 10 years before noncardiac surgery, as stratified by their Revised Cardiac Risk Index scores.

might rise once >180 days have elapsed since PCI. Conversely, whereas guidelines recommend that surgery be delayed until 1 year after drug-eluting stent implantation,[8] our findings instead suggest that surgery can be performed reasonably safely after a 6-month delay.

Our results have both important similarities and differences with respect to previous investigations of noncardiac surgery after coronary stent implantation. We confirmed observations of substantially increased risk when surgery is performed within 6 weeks of coronary stent implantation.[4,10,12,13] In addition, our study is largely consistent with previous research showing that cardiac risk is relatively low if elective surgery is delayed by 6 months or more after drug-eluting-stent implantation.[32–34] Our findings also corroborate a previous study where discontinuation of dual antiplatelet therapy after 6 months was not associated with increased rates of stent thrombosis after drug-eluting stent implantation.[35]

Conversely, our findings differ from some previous studies with respect to rates of perioperative MACE.[4,10,36] In 2 prospective cohort studies, Vincenzi et al[4] reported an adverse event rate of 44%, whereas Godet et al[36] reported a 12% rate of postoperative myocardial necrosis. These differences may be explained, in part, by their inclusion of urgent-to-emergent surgeries (28% in the study by Vincenzi et al and 8% in the study by Godet et al). These studies also differed from our investigation with respect to the definition of adverse events. Vincenzi et al included a broad range of complications—including cardiac death, myocardial infarction, repeat revascularization, bleeding, sepsis, and elevated troponin concentrations without clinical evidence of myocardial infarction—in their reported event rate. If only cardiac death, myocardial infarction, and repeat revascularization were considered, the event rate was 22% instead.[4] Similarly, whereas Godet et al reported a 12% rate of elevated troponin concentrations, the rate of myocardial infarction or death was 4%.[36]

In a previous study that used administrative databases, Cruden et al[10] reported a 14% rate of postoperative death or ischemic events. Notably, the adverse event rate remained elevated at 11% rate even when surgery was performed >1 year after PCI. These differences may be explained the investigators' use of administrative data to identify postoperative in-hospital cardiac complications. Previous research has shown that administrative data generally do not accurately capture in-hospital complications.[37] In contrast, the components of our primary outcome—mortality, readmission for acute coronary syndrome, or revascularization—are accurately captured by administrative databases.[18,24] Notably, rates of postoperative death, which are generally accurately captured by administrative data, in the study by Cruden et al were considerably lower at only 0.6%.

The major strength of our study is the generalizability associated with its population-based sample. Additionally, the cohort only included elective procedures, thereby focusing the analysis on the clinically relevant situation where

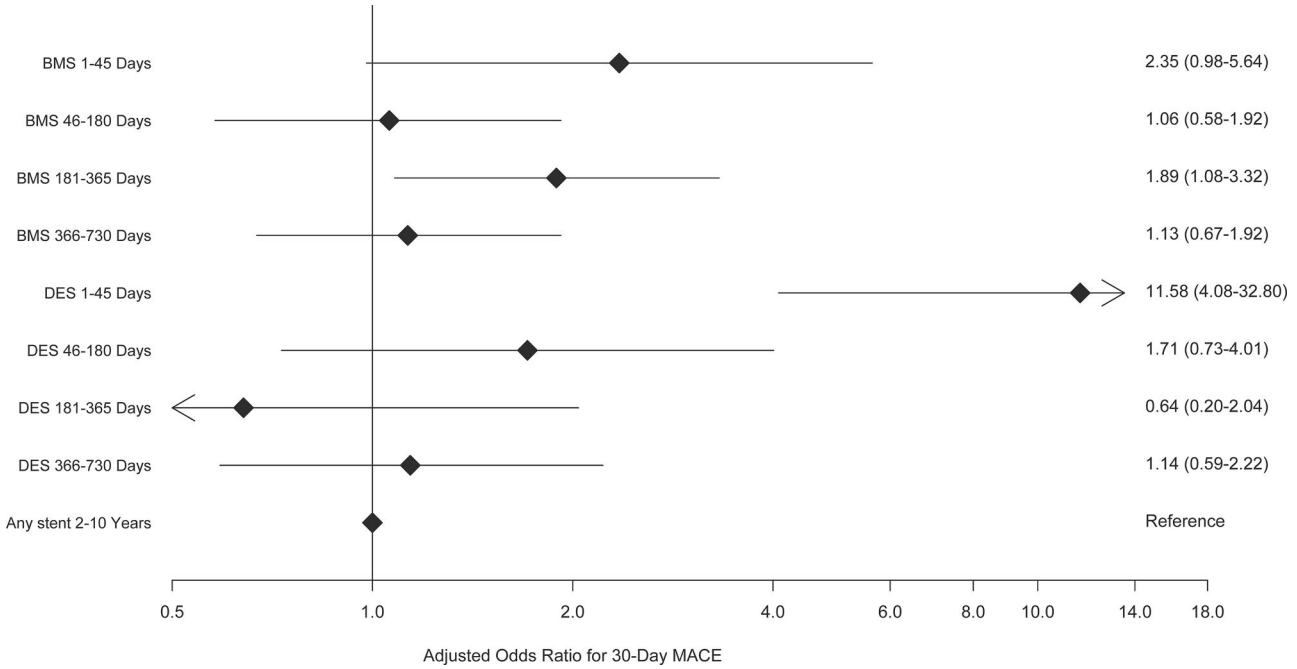

Figure 2. Adjusted association of stent type and time interval from stent insertion to surgery with major adverse cardiac events within 30 days after elective noncardiac surgery. The diamonds represent adjusted odds ratios (OR) for 30-day major adverse cardiac events, and the error bars are 95% confidence intervals (CI). The corresponding numeric values for these point estimates and CIs are presented on the right. The arrows denote CIs that extend beyond the scale of this graph. The reference category for the adjusted odds ratios was a remote history of stent insertion (ie, bare-metal or drug-eluting stent within 731 days to 10 years before surgery). The adjusted ORs were derived from a logistic regression model that adjusted for age, sex, surgery, congestive heart failure, cerebrovascular disease, peripheral vascular disease, hypertension, diabetes mellitus, and renal disease. This model had reasonable discrimination (c-index 0.71) and good calibration (Hosmer-Lemeshow statistic $P=0.63$).

physicians must decide whether to delay elective surgery to minimize perioperative risk related to coronary stents. Conversely, for nonelective procedures, surgery usually proceeds regardless of the interval since recent PCI, and the main issue is how best to manage patients' antiplatelet medications.

Our study also has several limitations. First, despite being one of the largest evaluations of noncardiac surgery after stent implantation, event rates were relatively low, thereby limiting our statistical power. Many estimates from multivariable analyses therefore had wide confidence intervals, and smaller subgroups within patients who underwent previous PCI (eg, strata defined by Revised Cardiac Risk Index score) could not be evaluated. Second, administrative databases generally do not accurately capture in-hospital complications.[37] We could not therefore ascertain several postoperative complications that are directly relevant to this study, such as nonfatal myocardial infarction, stent thrombosis, and clinically significant bleeding. Nonetheless, the primary outcome includes all significant sequelae of a postoperative myocardial infarction, namely death, repeat revascularization, or hospital readmission for acute coronary syndrome. Third, our databases did not capture in-hospital medications or outpatient aspirin use; furthermore, they did not describe whether patients had briefly discontinued their aspirin or thienopyridine use before surgery. Indeed, the absence of information on in-hospital medications may explain the paradoxically lower rate of thienopyridine use among patients who had noncardiac surgery <45 days after stent insertion (Table II in the online-only Data Supplement). Fourth, the PCI registry lacked some detailed procedural information (eg, bifurcational stenting, poor run-off) that may have influenced both patients' perioperative risks and clinicians' willingness to discontinue antiplatelet therapy earlier than recommended by practice guidelines.

Fifth, survivor bias and unmeasured confounding may explain, in part, the lower event rates among individuals with longer delays between PCI and noncardiac surgery. For example, when compared with anyone who underwent surgery shortly after PCI, such patients would have to survive longer after PCI without dying or needing repeat revascularization. Thus, any individual with unstable coronary artery disease requiring repeat revascularization would either be excluded if CABG was performed, or reclassified as having a shorter interval from PCI to surgery. In addition, the performance of elective surgery sooner after PCI may have been a marker of more urgent procedures that were themselves associated with increased perioperative risk. Sixth, changing practice guidelines might explain, in part, the reduced risk of MACE when surgery was performed >6 months after drug-eluting stent insertion. Specifically, before the updating of perioperative practice guidelines in 2007,[7] PCI-specific guidelines recommended clopidogrel therapy for only 3 months after sirolimus stent implantation and 6 months after paclitaxel stent implantation.[38] Performance of surgery >6 months after drug-eluting stent implantation may therefore be a marker of more compliant physicians whose patients generally had better overall outcomes.

Conclusions

In this population-based study, the earliest optimal time for performing elective noncardiac surgery appeared to be from 46 to 180 days after bare-metal-stent implantation, or >180 days after drug-eluting-stent implantation. In addition to being relevant to future practice guidelines, these findings will help inform clinical decision-making when weighing the risks of operative versus nonoperative therapy in patients being considered for major elective noncardiac surgery after recent coronary stent implantation.

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Disclosures

None.

References

1. Gurevich Y, LeMay T, Capan DD, Herring J. Health indicators 2009: a focus on cardiac care in Canada. *Healthc Q*. 2010;13:18–21.
2. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics - 2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.
3. Berger PB, Kleiman NS, Pencina MJ, Hsieh WH, Steinhubl SR, Jeremias A, Sonel A, Browne K, Barseness G, Cohen DJ, and EVENT Investigators. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry. *J Am Coll Cardiol Cardiovasc Interv*. 2010;3:920–927.
4. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery - a prospective outcome study. *Br J Anaesth*. 2006;96:686–693.
5. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ*. 2005;173:627–634.
6. POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371:1839–1847.
7. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SCJ, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Tarkington LG, Yancy CW. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2007;116:e418–e499.
8. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;120:e169–e276.
9. Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001–2008. *JAMA*. 2011;305:1769–1776.
10. Cruden NL, Harding SA, Flapan AD, Graham C, Wild SH, Slack R, Pell JP, Newby DE. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ Cardiovasc Interv*. 2010;3:236–242.
11. Kałuza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol*. 2000;35:1288–1294.
12. Nuttall GA, Brown MJ, Stombaugh JW, Michon PB, Hathaway MF, Lindeen KC, Hanson AC, Schroeder DR, Oliver WC, Holmes DR, Rihal CS. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. *Anesthesiology*. 2008;109:588–595.
13. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, Melby S, Berger PB. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol*. 2003;42:234–240.
14. Ko DT, Chiu M, Guo H, Austin PC, Goeree R, Cohen E, Labinaz M, Tu JV. Safety and effectiveness of drug-eluting and bare-metal stents for patients with off- and on-label indications. *J Am Coll Cardiol*. 2009;53:1773–1782.
15. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med*. 2007;357:1393–1402.
16. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144:290–296.
17. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25:512–516.
18. Juurlink D, Preya C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. ICES Investigative Report.* Toronto, ON: Institute for Clinical Evaluative Sciences; 2006.
19. Tu K, Campbell NRC, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Medicine*. 2007;1:E18–E26.
20. Williams JI, Young W. Appendix: a summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams JI, Anderson GM, Blackstein-Hirsch P, Fooks C, Naylor CD, eds. *Patterns of Health Care in Ontario. The ICES Practice Atlas.* Ottawa, ON: Canadian Medical Association; 1996.
21. *Technical Supplement: Health Care in Canada 2005.* Ottawa, ON: Canadian Institute for Health Information; 2005.
22. Bourne RB, DeBoer D, Hawker G, Kreder H, Mahomed N, Paterson JM, Warner S, Williams J. Chapter 5: Total hip and knee replacement. In: Tu JV, Pinfold SP, McColgan P, Laupacis A, eds. *Access to Health Service in Ontario: ICES Atlas.* Toronto, ON: Institute for Clinical Evaluative Sciences; 2005.

23. Warner MA, Shields SE, Chute CG. Major morbidity and mortality within 1 month of ambulatory surgery and anesthesia. *JAMA*. 1993;270:1437–1441.
24. Ko DT, Newman AM, Alter DA, Austin PC, Chiu M, Cox JL, Goodman SG, Tu JV. Secular trends in acute coronary syndrome hospitalization from 1994 to 2005. *Can J Cardiol*. 2010;26:129–134.
25. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
26. du Plessis V, Beshiri R, Bollman RD, Clemeson H. *Definitions of "rural." Agriculture and Rural Working Paper Series, No. 61*. Ottawa, ON: Statistics Canada; 2002.
27. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.
28. Auerbach A, Goldman L. Assessing and reducing the cardiac risk of noncardiac surgery. *Circulation*. 2006;113:1361–1376.
29. Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology*. 2010;112:1105–1115.
30. Ueda Y, Nanto S, Komamura K, Kodama K. Neointimal coverage of stents in human coronary arteries observed by angioscopy. *J Am Coll Cardiol*. 1994;23:341–346.
31. Weintraub WS. The pathophysiology and burden of restenosis. *Am J Cardiol.* 2007;100:3K–9K.
32. Assali A, Vaknin-Assa H, Lev E, Bental T, Ben-Dor I, Teplitsky I, Brosh D, Fuchs S, Eidelman L, Battler A, Kornowski R. The risk of cardiac complications following noncardiac surgery in patients with drug eluting stents implanted at least six months before surgery. *Catheter Cardiovasc Interv*. 2009;74:837–843.
33. Brotman DJ, Bakhru M, Saber W, Aneja A, Bhatt DL, Tillan-Martinez K, Jaffer AK. Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents: a retrospective cohort study. *J Hosp Med*. 2007;2:378–384.
34. Rabbitts JA, Nuttall GA, Brown MJ, Hanson AC, Oliver WC, Holmes DR, Rihal CS. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology*. 2008;109:596–604.
35. Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116:745–754.
36. Godet G, Le Manach Y, Lesache F, Perbet S, Coriat P. Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery: is it always a problem? *Br J Anaesth*. 2008;100:472–477.
37. Romano PS, Schembri ME, Rainwater JA. Can administrative data be used to ascertain clinically significant postoperative complications? *Am J Med Qual*. 2002;17:145–154.
38. Smith SC, Feldman TE, Hirshfeld JW, Jacobs AK, Kern MJ, King SB, Morrison DA, O'Neill WW, Schaff HV, Whitlow PL, Williams DO. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2006;47:e1–e121.

CLINICAL PERSPECTIVE

For patients with coronary stents, practice guidelines recommend that elective noncardiac surgery be delayed until surgery can be performed safely using antiplatelet therapy with aspirin alone. The suggested delay is 30 to 45 days for bare-metal stents and 1 year for drug-eluting stents. However, these recommendations are largely based on expert opinion and limited data. We therefore conducted a population-based cohort study in Ontario, Canada to describe the risks of major elective noncardiac surgery after stent implantation. After linking population-based administrative databases to a province-wide coronary stent registry, rates of 30-day major adverse cardiac events (mortality, readmission for acute coronary syndrome, repeat coronary revascularization) were measured among patients who underwent major elective noncardiac surgery from 2003 to 2008 after previous stent implantation. We found that when the interval between stent implantation and surgery was <45 days, event rates were high for bare-metal (6.7%) and drug-eluting (20.0%) stents. When the interval was 45 to 180 days, the event rate for bare-metal stents was 2.6%, which approached that of nonrevascularized individuals with Revised Cardiac Risk Index scores of 1 to 2. Adjusted analyses suggested this event rate increased further if this interval exceeded 180 days. For drug-eluting stents, the event rate was 1.2% once the interval exceeded 180 days, approaching that of nonrevascularized individuals with Revised Cardiac Risk Index scores of 1. These results suggest that the earliest optimal time for performing major elective noncardiac surgery is 46 to 180 days after bare-metal stent implantation and >180 days after drug-eluting stent implantation.

Original Investigation

Risk of Major Adverse Cardiac Events Following Noncardiac Surgery in Patients With Coronary Stents

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IMPORTANCE Guidelines recommend delaying noncardiac surgery in patients after coronary stent procedures for 1 year after drug-eluting stents (DES) and for 6 weeks after bare metal stents (BMS). The evidence underlying these recommendations is limited and conflicting.

OBJECTIVE To determine risk factors for adverse cardiac events in patients undergoing noncardiac surgery following coronary stent implantation.

DESIGN, SETTING, AND PARTICIPANTS A national, retrospective cohort study of 41 989 Veterans Affairs (VA) and non-VA operations occurring in the 24 months after a coronary stent implantation between 2000 and 2010. Nonlinear generalized additive models examined the association between timing of surgery and stent type with major adverse cardiac events (MACE) adjusting for patient, surgery, and cardiac risk factors. A nested case-control study assessed the association between perioperative antiplatelet cessation and MACE.

MAIN OUTCOMES AND MEASURES A composite 30-day MACE rate of all-cause mortality, myocardial infarction, and cardiac revascularization.

RESULTS Within 24 months of 124 844 coronary stent implantations (47.6% DES, 52.4% BMS), 28 029 patients (22.5%; 95% CI, 22.2%-22.7%) underwent noncardiac operations resulting in 1980 MACE (4.7%; 95% CI, 4.5%-4.9%). Time between stent and surgery was associated with MACE (<6 weeks, 11.6%; 6 weeks to <6 months, 6.4%; 6-12 months, 4.2%; >12-24 months, 3.5%; $P < .001$). MACE rate by stent type was 5.1% for BMS and 4.3% for DES ($P < .001$). After adjustment, the 3 factors most strongly associated with MACE were nonelective surgical admission (adjusted odds ratio [AOR], 4.77; 95% CI, 4.07-5.59), history of myocardial infarction in the 6 months preceding surgery (AOR, 2.63; 95% CI, 2.32-2.98), and revised cardiac risk index greater than 2 (AOR, 2.13; 95% CI, 1.85-2.44). Of the 12 variables in the model, timing of surgery ranked fifth in explanatory importance measured by partial effects analysis. Stent type ranked last, and DES was not significantly associated with MACE (AOR, 0.91; 95% CI, 0.83-1.01). After both BMS and DES placement, the risk of MACE was stable at 6 months. A case-control analysis of 284 matched pairs found no association between antiplatelet cessation and MACE (OR, 0.86; 95% CI, 0.57-1.29).

CONCLUSIONS AND RELEVANCE Among patients undergoing noncardiac surgery within 2 years of coronary stent placement, MACE were associated with emergency surgery and advanced cardiac disease but not stent type or timing of surgery beyond 6 months after stent implantation. Guideline emphasis on stent type and surgical timing for both DES and BMS should be reevaluated.

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Noncardiac surgery after recent coronary stent placement is associated with increased risk of adverse cardiac events. Consequently, it is desirable to delay elective surgery as long as possible after coronary stent placement. In 2004, drug-eluting stents (DES) were approved and overtook bare metal stents (BMS) as the preferred revascularization strategy.[1] Reports of unanticipated late stent thrombosis after cessation of dual antiplatelet therapy (APT) and case reports of stent thrombosis in patients with DES undergoing noncardiac surgery led to a revision of the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines in 2007.[1-8] The revised guidelines recommend continuing dual APT for all patients at least 1 year after DES implantation.[9] For patients with DES undergoing noncardiac surgery, class IIa recommendations, based on level C evidence, state the following: (1) elective surgery after DES implantation should be delayed until completion of 1 year of dual APT, or (2) if the surgery is urgent, the surgery should be performed without cessation of APT. The guidelines for DES differ from those for BMS, which recommend a delay in surgery and temporary cessation of APT after 4 to 6 weeks from stent placement.[10]

Approximately 600 000 percutaneous coronary stent procedures are performed annually in the United States.[11,12] Twelve percent to 23% of these patients undergo noncardiac surgery within 2 years of coronary stent placement.[13-17] Delaying necessary noncardiac surgery can pose a significant clinical dilemma for a large number of patients. The delays in surgery recommended by the guidelines are based on a limited and conflicting evidence base. Case series early in the DES experience suggested high rates of major adverse cardiac events (MACE) after noncardiac surgery. However, subsequent, larger multicenter cohort studies reported MACE rates similar to BMS MACE rates.[13,14,18] Small series assessing perioperative APT management found no evidence that continued perioperative APT mitigates the risk of MACE. It is not clear whether the lower observed MACE rates in more recent studies are attributable to the effectiveness of guideline-driven delays of elective surgery together with continuing perioperative APT or reflect more reliable estimates of perioperative MACE rates in populations with stents, or both.

APT *antiplatelet therapy*
BMS *bare metal stent*
CHF *congestive heart failure*
DES *drug-eluting stent*
MACE *major cardiac adverse event*
PCI *percutaneous coronary intervention*

To better understand the relationship between stent type, APT, and MACE associated with noncardiac surgery after coronary stent placement, we evaluated a national cohort of Veterans Affairs (VA) patients who had either coronary BMS or DES placed between 2000 and 2010. We hypothesized that early surgery is associated with higher MACE rates after coronary stent placement, particularly in patients with DES, and that continued APT reduces the risk of postoperative MACE.

Methods

We conducted a retrospective cohort study of patients undergoing noncardiac surgery within 2 years after cardiac stent implantation to examine the relationship between stent type and time from stent to surgery with a composite adverse event of myocardial infarction (MI), revascularization, and all-cause mortality (MACE). We conducted 3 analyses to address the hypotheses. First, we constructed a multivariable regression model to determine risk factors for MACE and the strength of their association. Second, we assessed MACE rates as a function of time between stent and surgery and stent type. Third, we assessed the association of APT cessation with MACE. The study protocol was reviewed and approved by the local VA institutional review board of each coauthor with waiver of informed consent.

Data Sources

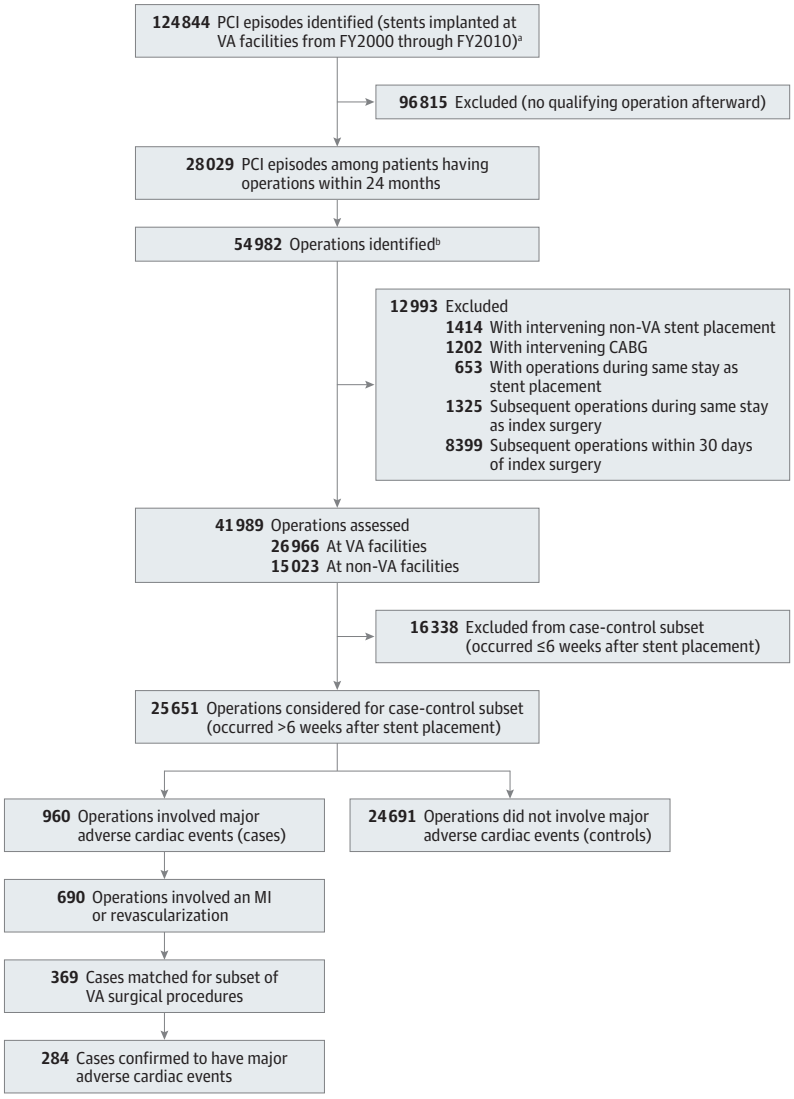
Cardiac stents were identified in the VA's National Patient Care Databases (NPCD) and the VA Clinical Assessment, Reporting, and Tracking (CART) Program. Noncardiac surgery occurring in the VA was identified in the VA Surgical Quality Improvement Program database (VASQIP) and noncardiac surgery occurring outside of the VA was identified using Centers for Medicare & Medicaid Services (CMS) data for the 73% of veterans in the cohort who had dual VA-Medicare eligibility. Demographics and comorbidities were obtained from the VA NPCD or CMS inpatient, outpatient, and carrier base files. Death was obtained from the VA Vital Status File. Additional laboratory results and medication prescriptions were obtained from the VA Decision Support System.

For the nested case-control portion of this study, we abstracted data from the VA electronic health record. Chart abstraction began March 2012 and concluded in March 2013. Standardized data collection forms were developed, and all chart abstractors were trained in accordance with the procedure manual.

Patient Sample

We identified all coronary stents implanted in VA facilities between 2000-2010 using codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) (36.06 for BMS or 36.07 for DES) and direct abstraction from the CART Program data files. Percutaneous coronary intervention (PCI) care episodes were defined as a single visit to the catheterization laboratory for a PCI procedure, where 1 or more stents were implanted. Noncardiac surgical procedures were defined using *Current Procedural Terminology* (*CPT*) codes 10000 to 32999 and 34000 to 69999. We excluded minor surgeries, such as endoscopic procedures (*CPT* 43200-43272, 45300-45392, 46600-46608), and minor musculoskeletal procedures, such as application of a cast and joint aspiration (29000-29750). Operations preceded by an intervening coronary artery bypass graft surgery or non-VA stent or occurring during the same hospitalization as the PCI were excluded (**Figure 1**). The unit of analysis was the first surgical procedure occurring during a hospitalization within 2 years after a

Figure 1. Study Population With Exclusion Criteria



CABG indicates coronary artery bypass graft surgery; CMS, Centers for Medicare & Medicaid Services; FY, fiscal year; MI, myocardial infarction; VA, Veterans Affairs.
[a]Patients may have had more than 1 percutaneous coronary intervention (PCI) care episode over the 10-year study period.
[b]Patients may have had more than 1 surgical episode in the 24 months after a PCI episode.

coronary stent placement. Because outcomes were assessed over a 30-day period after surgery, any subsequent surgeries occurring within 30 days after the index procedure were excluded from the analysis. For patients with multiple PCI care episodes, the timing between stent and surgery was measured from the most recent PCI care episode prior to surgery. Further details on the construction of the study cohort have been published.[17]

Study Variables

The outcome variable for the study was MACE within 30 days of exposure to noncardiac surgery. MACE was a composite variable including death from any cause, MI (*ICD-9-CM* codes 410.xx or VASQIP nurse-abstracted MI), or coronary revascularization (*ICD-9-CM* 00.66, 36.01-36.09; *CPT*: 33510-33519, 33520-33523, 33530-33536, 92973-92984, 92995-92998).

Noncardiac surgery was categorized using the primary *CPT* code: integumentary, 10040-19999; musculoskeletal, 20000-29999 (except amputation classified under vascular); respiratory, 30000-32999; vascular, 34000-37799 plus 27290, 27295, 27598, 27880-27899, 28801-28825; digestive, 40000-49999; genitourinary, 50000-58999; nervous, 61000-64999; or eye/ear, 65000-69999. Procedures with *CPT* codes not listed here were categorized as "other." Procedure complexity was estimated from 2011 CMS work relative value units for the primary *CPT* code.

A patient's cardiac risk at the time of noncardiac surgery was estimated from the 6-point revised cardiac risk index (rCRI) using administrative diagnosis codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*). The rCRI was calculated from *ICD-9* diagnostic codes for congestive heart failure (CHF), stroke, MI, and diabetes; *CPT* codes associated with high-risk surgery; and laboratory data identifying 1 or more serum creatinine values greater than 2 mg/dL in the year prior to surgery.[19] An insulin prescription in the Decision Support System pharmacy data within 12 months of surgery was used

to identify insulin-dependent diabetes in patients with an *ICD-9* code for diabetes. The rCRI was analyzed as both an ordinal and categorical variable: low risk (1 point), moderate risk (2 points), or high risk (≥3 points). Additional comorbidities at the time of surgery were identified in the VA NPCD and CMS data using *ICD-9* diagnosis codes (listed in eAppendix 1 in the Supplement).

Nested Case-Control Subset

The nested case-control subset was restricted to (1) VA operations (because these were the only records available for review), (2) MI or revascularization end points, and (3) surgeries occurring more than 6 weeks after stent placement. Operations that occurred in the first 6 weeks after stent placement and operations followed by death alone were excluded (Figure 1). After exclusions, we matched cardiac MACE by fiscal year of operation, *CPT* category, work relative value unit (within 6 units), stent type, rCRI, and time from stent to operation (within 2 weeks) using 24 691 potential controls from VA surgeries that were not followed by a MACE (eAppendix 2 in the Supplement). Separate abstraction forms were assigned for exposure (preoperative antiplatelet management) and outcome (MACE and bleeding) so that an abstractor did not assess both for the same patient (eAppendix 3 in the Supplement). Uncertainty of an exposure or outcome variable was adjudicated by 2 of the senior investigators (M.T.H., T.M.M.).

Statistical Analyses

To determine factors associated with MACE, generalized additive models were used to determine the relationship between time from stent to surgery and MACE with adjustment for stent type, surgical characteristics, cardiac risk factors, and comorbid conditions. Generalized additive models were used to allow time between stent and surgery to be fit as a linear or nonlinear term in assessing the relationship between surgical timing and MACE.[20] The approximate *P* values for spline terms are derived using a score test and algorithmically estimated degrees of freedom. To examine the relative contribution of variables in the adjusted models, we calculated the analysis of variance χ^2 for each variable minus its degrees of freedom ($\chi^2 - df$).[21] The statistical threshold for significance was set at $P = .05$ for a 2-tailed test. To account for confounding by indication in choice of stent type, we conducted analyses using propensity score quintiles and inverse propensity weighting. We restricted this analysis to patients with stents placed after fiscal year 2003, when DES were widely available for implantation. Inverse probability weights were divided into quintiles and incorporated into the models.

All univariable and bivariable statistics were calculated using SAS version 9.2 (SAS Institute) and generalized additive models used R package MGCV for spline models. Plots of unadjusted data were created with R package GGPLOT2[22] and smoothed trends were fitted using the loess algorithm. For the nested case-control study, univariable and bivariable statistics were calculated to examine differences in medication management by MACE. Odds ratios (ORs) were calculated with conditional logistic regression to account for matched pairs.[23]

Results

Of the 124 844 PCI episodes of care occurring in 2000-2010, a total of 28 029 patients (22.5%) met study inclusion criteria and underwent 41 989 surgical procedures within 24 months (22.5%; 95% CI, 22.2%-22.7%) (Figure 1). Patient demographics and comorbidities along with stent and surgical characteristics are shown in **Table 1** and **Table 2**. A total of 1980 MACE (4.7%) occurred within 30 days of surgery: 1170 MI or repeat revascularization without death, 141 MI or repeated revascularization with death, and 669 death alone. In unadjusted analyses, MACE rates differed significantly by stent type: BMS (5.1%) vs DES (4.3%, $P < .001$). Markers of ischemic heart disease were associated with MACE, including MI or CHF in the past 6 months (13.6% and 12.0%, respectively), and rCRI score (Table 1). In addition, operations occurring after publication of the 2007 ACC/AHA guidelines were associated with lower MACE rates (3.5%) compared with before the guidelines' publication (5.1%, $P < .001$).

The results of the generalized additive models of MACE assessing time from stent to surgery as a continuous linear or nonlinear term and the relative contribution of model covariates ($\chi^2 - df$) to MACE are shown in **Table 3**. In the overall model of MACE, nonelective presentation for the surgical hospitalization was the most explanatory determinant, followed by conditions associated with ischemic cardiac disease, including recent MI or CHF, and higher rCRI score, whereas stent type was not significantly associated with MACE and was ranked 12th in explanatory importance of the 12 variables in the model. There was no significant interaction between stent type and time to surgery ($P = .56$ for BMS and $P = .20$ for DES). The plot of the adjusted OR over time by stent type is provided in the eFigure in the Supplement. Because of the possibility of multicolinearity between variables included in the rCRI and as independent variables in the model (ie, history of coronary artery disease and recent MI), we assessed maximum variance inflation factors for all rCRI component variables and found it to be less than 1.1 for all variables assessed. In addition, a comparison of the model output excluding variables that are also considered in rCRI (operation type, MI in past 6 months, CHF admission in past 6 months, chronic kidney disease) is provided in the eTable in the Supplement, and the estimates for rCRI and stent type did not change substantively.

Time from stent to surgery was correlated with MACE, with higher rates observed for surgery closer to stent implantation (**Figure 2**A), nonelective admission source (Figure 2B), rCRI category (Figure 2C), and recent MI (Figure 2D). After adjustment, the odds of a MACE for surgery between 6 weeks and 6 months after DES placement was lower than for BMS (adjusted OR [AOR], 0.75; 95% CI, 0.62-0.91) and not significantly different for surgery less than 6 weeks (AOR, 1.1; 95% CI, 0.8-1.5) or more than 6 months after stent implantation (AOR, 0.92; 95% CI, 0.82-1.05). In the propensity analysis, stent type was significant ($P = .001$) with lower odds of MACE for surgery after DES placement (AOR, 0.87; 95% CI, 0.80-0.94) (eTable in the Supplement). Because the direction of the estimate did not rectify concern for confounding by indication for stent type,

Table 1. Patient Characteristics at the Time of Surgery, Overall and by 30-Day Postoperative MACE

	No. (%)			
	Overall	No MACE	MACE	*P* Value
Overall	41 989	40 009 (95.3)	1980 (4.7)	
Age, y				
<60	8149 (19.4)	7817 (95.9)	332 (4.1)	.002
≥60	33 840 (80.6)	32 192 (95.1)	1648 (4.9)	
Race				
White	36 857 (89.6)	35 168 (95.4)	1689 (4.6)	.20
Black	3794 (9.2)	3596 (94.8)	198 (5.2)	
Other	501 (1.2)	479 (95.6)	22 (4.4)	
Sex				
Male	41 311 (98.4)	39 363 (95.3)	1948 (4.7)	.90
Female	678 (1.6)	646 (95.3)	32 (4.7)	
Revised cardiac risk index				
1	15 455 (36.8)	15 110 (97.8)	345 (2.2)	<.001
2	14 448 (34.4)	13 810 (95.6)	638 (4.4)	
≥3	12 086 (28.8)	11 089 (91.8)	997 (8.3)	
History of coronary artery disease				
No	95 (0.2)	90 (94.7)	5 (5.3)	.80
Yes	41 894 (99.8)	39 919 (95.3)	1975 (4.7)	
Myocardial infarction in past 6 mo				
No	37 921 (90.3)	36 495 (96.2)	1426 (3.8)	<.001
Yes	4068 (9.7)	3514 (86.4)	554 (13.6)	
History of congestive heart failure				
No	23 895 (56.9)	23 139 (96.8)	756 (3.2)	<.001
Yes	18 094 (43.1)	16 870 (93.2)	1224 (6.8)	
Congestive heart failure in past 6 mo				
No	40 278 (95.9)	38 504 (95.6)	1774 (4.4)	<.001
Yes	1711 (4.1)	1505 (88.0)	206 (12.0)	
History of cerebrovascular disease				
No	34 016 (81.0)	32 538 (95.7)	1478 (4.3)	<.001
Yes	7973 (19.0)	7471 (93.7)	502 (6.3)	
Hypertension in past year				
No	3516 (8.4)	3378 (96.1)	138 (3.9)	.02
Yes	38 473 (91.6)	36 631 (95.2)	1842 (4.8)	
CABG in past 2 y				
0	41 167 (98.0)	39 215 (95.3)	1952 (4.7)	.20
1	728 (1.7)	703 (96.6)	25 (3.4)	
≥2	94 (0.2)	91 (96.8)	3 (3.2)	
Diabetes				
No	21 246 (50.6)	20 363 (95.8)	883 (4.2)	<.001
Non-insulin dependent	13 286 (31.6)	12 619 (95.0)	667 (5.0)	
Insulin dependent	7457 (17.8)	7027 (94.2)	430 (5.8)	
Chronic kidney disease in past year				
No	40 140 (95.6)	38 306 (95.4)	1834 (4.6)	<.001
Stage 1-5	1341 (3.2)	1256 (93.7)	85 (6.3)	
Chronic dialysis, stage 6	508 (1.2)	447 (88.0)	61 (12.0)	
Stent type				
Bare metal	21 986 (52.4)	20 859 (94.9)	1127 (5.1)	<.001
Drug-eluting	20 003 (47.6)	19 150 (95.7)	853 (4.3)	
PCI in past 2 y				
Index only	35 897 (85.5)	34 271 (95.5)	1626 (4.5)	<.001
1	5056 (12.0)	4764 (94.2)	292 (5.8)	
≥2	1036 (2.5)	974 (94.0)	62 (6.0)	

Abbreviations: CABG, coronary artery bypass graft surgery; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.

Table 2. Operation Characteristics at the Time of Surgery, Overall and by 30-Day Postoperative MACE

	No. (%)			
	Overall	No MACE	MACE	*P* Value
Overall	41 989	40 009 (95.3)	1980 (4.7)	
Timing of operation				
Before guidelines	32 102 (76.5)	30 473 (94.9)	1629 (5.1)	<.001
After guidelines	9887 (23.5)	9536 (96.5)	351 (3.5)	
Work relative value unit				
<10	25 781 (61.4)	24 727 (95.9)	1054 (4.1)	<.001
10-20	12 333 (29.4)	11 752 (95.3)	581 (4.7)	
>20	3871 (9.2)	3526 (91.1)	345 (8.9)	
Operation type				
Eye/ear	7181 (17.1)	7062 (98.3)	119 (1.7)	<.001
Integumentary	8061 (19.2)	7820 (97.0)	241 (3.0)	
Nervous	2027 (4.8)	1958 (96.6)	69 (3.4)	
Genital/urinary	6728 (16.0)	6481 (96.3)	247 (3.7)	
Musculoskeletal	5654 (13.4)	5418 (95.8)	236 (4.2)	
Other[a]	499 (1.2)	463 (92.8)	36 (7.2)	
Digestive	4256 (10.1)	3911 (91.9)	345 (8.1)	
Vascular	5408 (12.9)	4951 (91.6)	457 (8.4)	
Respiratory	2175 (5.2)	1945 (89.4)	230 (10.6)	
Admission status				
Outpatient	27 677 (65.9)	27 018 (97.6)	659 (2.4)	<.001
Elective inpatient	12 357 (29.4)	11 449 (92.7)	908 (7.3)	
Nonelective inpatient	1955 (4.7)	1542 (78.9)	413 (21.1)	
Location				
VA facility	26 966 (64.2)	25 818 (95.7)	1148 (4.3)	<.001
Non-VA facility	15 023 (35.8)	14 191 (94.5)	832 (5.5)	
ASA class, VA only				
≤2	2481 (10.5)	2427 (97.8)	54 (2.2)	<.001
3	17 079 (71.9)	16 513 (96.7)	566 (3.3)	
≥4	4192 (17.7)	3819 (91.1)	373 (8.9)	
Time since stent placement				
<6 wk	2094 (5.0)	1852 (88.4)	242 (11.6)	<.001
6 wk to <6 mo	9040 (21.5)	8465 (93.6)	575 (6.4)	
6 mo to <12 mo	10 792 (25.7)	10 334 (95.8)	458 (4.2)	
12 mo to 24 mo	20 063 (47.8)	19 358 (95.8)	705 (3.5)	

Abbreviations: ASA, American Society of Anesthesiologists; CMS, Centers for Medicare & Medicaid Services; MACE, major adverse cardiac event; VA, Veterans Affairs.

[a] Primary *Current Procedural Terminology* codes of general (1000-10039), hemic and lymphatic (38100-39999), and endocrine (60000-60999) operations.

and given the need to truncate the cohort, we elected to not pursue modeling with propensity for DES. A prior study has also found limited value of propensity adjustment over multivariable regression modeling for outcomes by stent type.[24]

To investigate the association between APT management around the time of surgery and MACE, we performed a case-control study on the subset of VA surgical procedures. Of the 369 abstracted VA cases, a MACE was confirmed in 284 (77.0%). There was no significant difference in the likelihood of receiving dual APT prior to surgery (59.9% cases vs 55.6% controls; $P = .43$) or completely stopping APT for at least 5 days (22.9% cases vs 25.4% controls; $P = .49$) (**Table 4**). In matched analyses, there was no association between complete APT cessation and adverse cardiac events (OR, 0.86; 95% CI, 0.57-1.29). Post hoc power analyses indicated that the cohort had 80% power to detect an OR of 1.68 with α of .05.

To assess the robustness of these findings, we conducted several sensitivity analyses. First, to understand the association of the 2007 perioperative guidelines with the findings and its potential relationship with stent selection, we restricted the cohort to the 32 102 operations occurring prior to 2007 and observed no association between DES and higher MACE rates prior to publication of the ACC/AHA guidelines (AOR, 0.97; 95% CI, 0.86-1.09 compared with BMS). Second, to understand MACE rates among elective operations only, we restricted the cohort to only elective and outpatient procedures and obtained similar results (DES AOR, 0.90; 95% CI, 0.81-1.01 compared with BMS). Third, we restricted the end points to MI or revascularization and MI or death and observed no difference in the estimate for DES (DES AOR, 0.91; 95% CI, 0.81-1.02 and DES AOR, 0.90; 95% CI, 0.82-1.00 compared with BMS, respectively) (eTable in the Supplement).

Table 3. Best-Fit Model of Perioperative Major Adverse Cardiac Event[a]

	OR (95% CI)	*P* Value	Partial Effects Analysis[b] $\chi^2 - df$	Rank
Admission status				
Outpatient	1 [Reference]	<.001	388.9	1
Elective inpatient	2.42 (2.10-2.79)			
Nonelective inpatient	4.77 (4.07-5.59)			
Myocardial infarction in past 6 mo				
No	1 [Reference]	<.001	230.0	2
Yes	2.63 (2.32-2.98)			
Revised cardiac risk index				
1	1 [Reference]	<.001	119.6	3
2	1.50 (1.31-1.73)			
≥3	2.13 (1.85-2.44)			
Operation type				
Eye/ear	1 [Reference]	<.001	86.1	4
Integumentary	1.38 (1.09-1.74)			
Genital/urinary	1.71 (1.36-2.16)			
Musculoskeletal	1.62 (1.27-2.05)			
Nervous	1.71 (1.25-2.33)			
Vascular	1.88 (1.50-2.37)			
Digestive	2.30 (1.82-2.90)			
Other[c]	2.42 (1.61-3.63)			
Respiratory	2.80 (2.18-3.59)			
Time between stent and surgery, wk[d]		<.001	45.0	5
Congestive heart failure in past 6 mo				
No	1 [Reference]	<.001	17.7	6
Yes	1.45 (1.23-1.72)			
PCI in past 2 y				
Index only	1 [Reference]	<.001	13.8	7
1 more	1.30 (1.13-1.48)			
≥2 more	1.25 (0.95-1.65)			
Age at surgery, y				
<60	1 [Reference]	.001	7.0	8
≥60	1.20 (1.06-1.36)			
Work relative value unit, continuous	1.01 (1.00-1.02)	.01	5.8	9
Chronic kidney disease in past year				
None	1 [Reference]	.02	5.7	10
Stage 1-5	0.95 (0.75-1.21)			
Dialysis	1.50 (1.12-2.02)			
Timing of operation				
Before guidelines	1 [Reference]	.04	3.4	11
After guidelines	0.89 (0.80-1.0)			
Stent type				
Bare metal	1 [Reference]	.08	2.1	12
Drug-eluting	0.91 (0.83-1.01)			

Abbreviations: OR, odds ratio; PCI, percutaneous coronary intervention; VA, Veterans Affairs.

[a] The final model is adjusted for operation facility (VA vs non-VA). After including the covariates, the −2 log likelihood was reduced from 15 959.8 to 13 866.7. Hypertension within the past year was also tested but excluded from the final model at $P = .29$.

[b] To examine the relative contribution of variables in the adjusted model, we calculated $\chi^2 - df$ for each variable and ranked the variables by this value.[21]

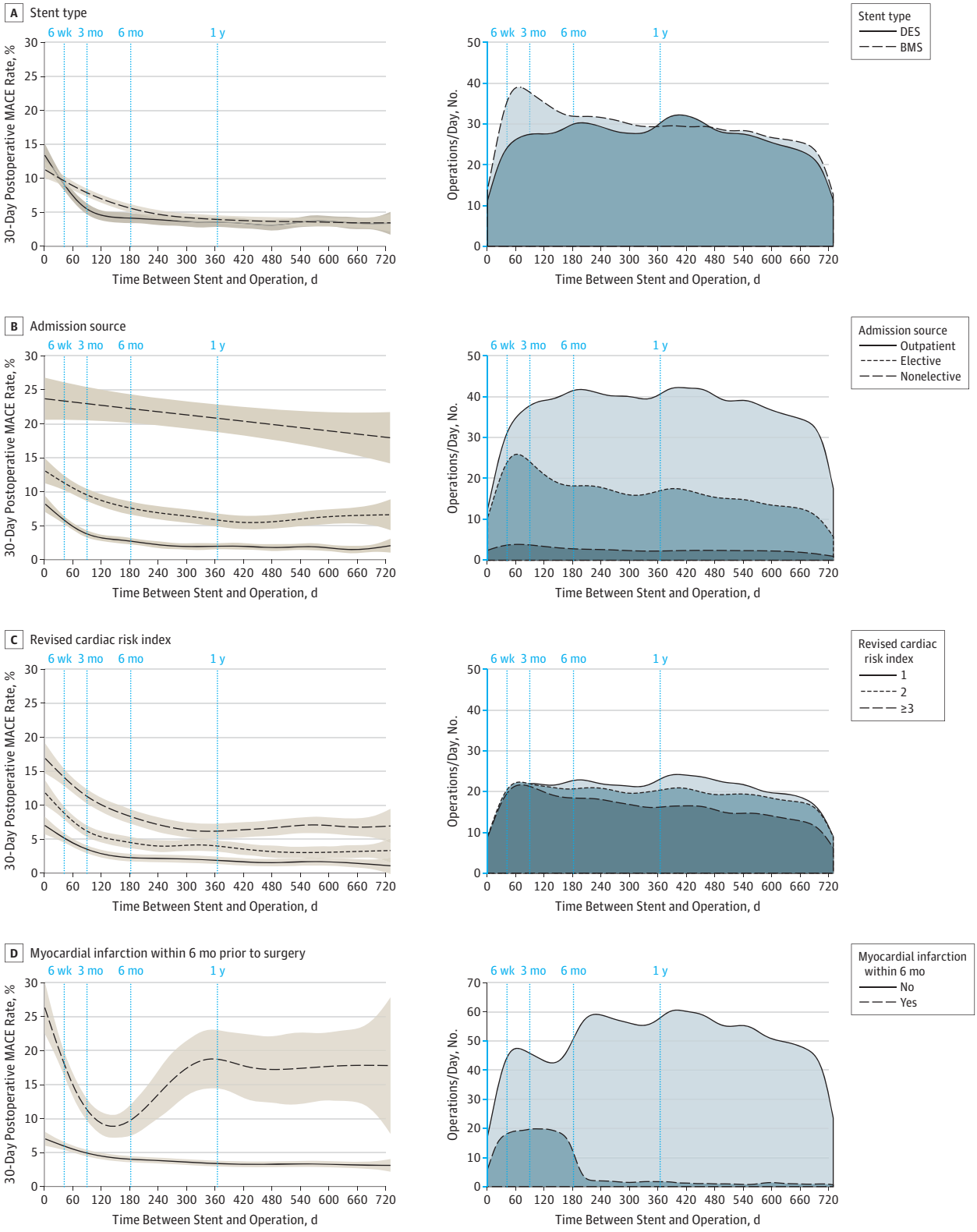
[c] Primary *Current Procedural Terminology* codes of general (1000-10039), hemic and lymphatic (38100-39999), and endocrine (60000-60999) operations.

[d] Time is considered a nonlinear effect; thus, ORs vary across time. Refer to Figure 2 for a plot of adjusted ORs across time.

Discussion

This study assessing the risk of major adverse cardiac events after noncardiac surgery in patients with recent coronary stenting identified several factors, principally acuity of clinical presentation for surgery and several markers of advanced cardiac disease. Although the time from stent placement to surgery was associated with MACE, this was principally observed for surgery in the first 6 months after the stent procedure, whereas timing of surgery more than 6 months after the stent procedure was not significantly associated with MACE. While the data suggest that the risk of surgery after DES placement may stabilize earlier, the potential confounding and nonrandomized nature of this observational study does not allow for direct comparison of outcomes by stent type. Stent type was not

Figure 2. Unadjusted 30-Day Rate of Postoperative MACE After Noncardiac Surgery by Time Between Stent Date and Surgery Date



Left, plots created with R package GGPLOT2[22]; smoothed trends were fitted using the loess algorithm. The lines represent the estimate of the rate and the shaded area around the line represents the 95% CI. Right, density plots of number of operations per day; y-axis intervals in blue indicate range from 0 to 50 operations/day. BMS indicates bare metal stent; DES, drug-eluting stent; MACE, major adverse cardiac event.

Table 4. Association With Perioperative Antiplatelet Management and 30-Day Postoperative Major Adverse Cardiac Event in Matched Case-Control Cohort

	No. (%)			
	Overall	MACE	No MACE	*P* Value
Antiplatelet medication prior to surgery				
Dual	328 (57.8)	170 (59.9)	158 (55.6)	.43
Single	206 (36.3)	100 (35.2)	106 (37.3)	
None	34 (6.0)	14 (4.9)	20 (7.0)	
Antiplatelet management at surgery				
Dual therapy				
All therapy continued	216 (65.9)	114 (67.1)	102 (64.6)	.82
Clopidogrel held	36 (11.0)	16 (9.4)	20 (12.7)	
Aspirin held	14 (4.3)	7 (4.1)	7 (4.4)	
All therapy held	62 (18.9)	33 (19.4)	29 (18.4)	
Aspirin only				
Continued	143 (82.7)	70 (87.5)	73 (78.5)	.12
Held	30 (17.3)	10 (12.5)	20 (21.5)	
Clopidogrel only				
Continued	22 (66.7)	12 (60.0)	10 (77.0)	.31
Held	11 (33.3)	8 (40.0)	3 (23.1)	
Antiplatelet cessation >5 d, all held				
Yes	137 (24.1)	65 (22.9)	72 (25.4)	.49
No	431 (75.9)	219 (77.1)	212 (74.7)	

Abbreviation: MACE, major adverse cardiac event.

significantly associated with MACE for surgeries more than 6 months after stent placement, and we did not observe an association between APT cessation with MACE.

Of the 600 000 coronary stent procedures performed annually, nearly 20% are followed by at least 1 surgical procedure in the ensuing 2 years.[11-17] The present findings suggest that underlying surgical and cardiac risk, rather than stent type, are the primary factors associated with perioperative MACE; that event rates stabilize by 6 months; and that APT continuation does not substantially mitigate risk. Accordingly, the current focus of the guidelines on differential timing recommendations by stent type may warrant reconsideration, and greater concentration may need to be placed on assessing and optimizing cardiac risk.

The antiproliferative properties of DES protect against neointimal hyperplasia and the subsequent in-stent restenosis, but this benefit results in delayed endothelialization of DES, compared with BMS, leading to increased risk for stent thrombosis.[2] A meta-analysis of 4 randomized clinical trials showed an increased rate of stent thrombosis 1 year after the implantation of DES compared with BMS.[25] In response to this concern, the 2007 revised ACC/AHA guidelines specifically emphasized both timing and antiplatelet management for patients with DES undergoing noncardiac surgery. These recommendations were based largely on limited evidence of case series reporting stent thrombosis in surgical patients and reports of stent thrombosis after dual APT cessation within 1 year of DES implantation.

The differential MACE rate based on timing of noncardiac surgery by stent type is supported by limited and conflicting evidence. A report from the CREDO-Kyoto registry on 1878 patients (17%) who underwent a noncardiac surgery within 2 years of stent placement observed an overall MACE rate of 3.2% and similar rates between BMS (3.5%) and DES (2.9%).[25] Similarly, a study of the Ontario stent registry cohort with linked administrative data reported on 2725 patients undergoing surgery within 2 years of stent placement. They reported the optimal time of surgery as 46 to 180 days for BMS and after 180 days for DES, with the only statistically significant difference by stent type being higher MACE rate for DES when surgery was less than 45 days and for BMS when surgery was between 181 and 365 days.[14] We observed higher MACE rates for BMS compared with DES, particularly in a window where it was thought safe to proceed with surgery for patients with BMS (45-180 days) but not DES.

These prior studies and the current analysis are observational, meaning that neither stent type nor surgery timing was randomized and other factors could be confounding the results. Considering the current findings in the context of the prior studies, we recommend future prospective studies to assess the safety of noncardiac surgery at 6 months after DES implantation. In addition, the findings challenge the current focus on stent type and timing of surgery as the primary decision points of perioperative risk assessment in patients with prior coronary stents. Additional cardiac risk factors of recent MI, higher rCRI, and recent CHF exacerbation warrant more attention in the algorithms for risk stratification in patients with stents.

The efficacy of APT in reducing perioperative ischemic cardiac events is established.[26] However, the effectiveness of continued APT agents in reducing perioperative MACE events in patients with coronary stents is less clear. In the CREDO-Kyoto registry, 2398 patients had a surgical procedure within 3 years of stent implantation. They found that

30-day MACE rates were 4.9% for dual APT, 1.1% for single APT, and 2.3% for no APT, although the results were not significant.[25] Other studies have also reported higher rates of MACE after surgery with continued dual APT compared with single APT.[27,28] These observational studies, including the present study, are likely confounded by the fact that patients with the highest cardiac risk are most likely to both be taking dual APT and have it continued perioperatively. Nonetheless, matched-pair analysis did not find an association between continued APT and MACE. One potential explanation behind this finding may be that the anti-ischemic properties of APT are offset by a higher risk of bleeding. A prospective study of 103 patients undergoing noncardiac surgery reported a cardiac related mortality of 5% despite continued APT, and bleeding events occurred more frequently among those with MACE.[29] Thus, bleeding events and their sequelae may be in the causal pathway of MACE and confound potential protective effects of continued APT.

Several considerations need to be given to the present findings. First, the study sample comprised primarily older male patients, thus limiting the generalizability to women or younger men. Second, the clinical decision-making factors that influenced stent selection were largely unavailable to us and limited the ability to account for them in the models. Accordingly, the results could be confounded by those factors. Third, many patients underwent more than 1 PCI procedure during the dates of the study cohort, which could result in misclassification bias for time from stent placement to surgery. However, based on these and others' data, the PCI care episode closest to the surgery likely possesses the highest risk. Fourth, the surgical population by design is heterogeneous, with procedures ranging from minor outpatient to emergent inpatient operations. Although this improves the generalizability, it limits the ability to make recommendations regarding specific surgical populations or clinical scenarios. Fifth, we relied on administrative data to determine the end points, which could result in misclassification bias. Sixth, the case-control analysis of APT management had limited power to detect a true association. Seventh, the observational nature of the cohort and its inherent selection bias in stent type and surgery renders the findings as hypothesis generating only. As such, it suggests important areas for inquiry, ideally with randomized trials, to improve the evidence base supporting guideline recommendations.

Conclusions

Predominant risk factors for MACE after noncardiac surgery in patients with recent coronary stent implantation included nonelective surgical presentation and conditions associated with advanced ischemic cardiac disease. The time between coronary stent implantation and noncardiac surgery provided less explanatory importance. Stent type among those patients undergoing surgery more than 6 months after stent placement was not significantly associated with MACE. Complete APT cessation in the perioperative period was also not associated with MACE. Guidelines recommending prolonged delay and continued use of APT for patients with DES should be reevaluated.

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REFERENCES

1. Malenka DJ, Kaplan AV, Lucas FL, Sharp SM, Skinner JS. Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. *JAMA*. 2008;299(24):2868-2876.

2. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193-202.

3. Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115(18):2435-2441.

4. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med*. 2006;119(12):1056-1061.

5. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020-1029.

6. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364(9444):1519-1521.

7. Murphy JT, Fahy BG. Thrombosis of sirolimus-eluting coronary stent in the

postanesthesia care unit. *Anesth Analg*. 2005;101(4):971-973.

8. Nasser M, Kapeliovich M, Markiewicz W. Late thrombosis of sirolimus-eluting stents following noncardiac surgery. *Catheter Cardiovasc Interv*. 2005;65(4):516-519.

9. Grines CL, Bonow RO, Casey DE Jr, et al; American Heart Association; American College of Cardiology; Society for Cardiovascular Angiography and Interventions; American College of Surgeons; American Dental Association; American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. *Circulation*. 2007;115(6):813-818.

10. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50(17):1707-1732.

11. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. *J Am Coll Cardiol*. 2012;60(20):2017-2031.

12. Auerbach D, Maeda J, Steiner C. Hospital stays with cardiac stents, 2009 [Healthcare Cost and Utilization Project Statistical Brief No. 128]. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb128.pdf. Accessed September 11, 2013.

13. Berger PB, Kleiman NS, Pencina MJ, et al; EVENT Investigators. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry. *JACC Cardiovasc Interv*. 2010;3(9):920-927.

14. Wijeysundera DN, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation*. 2012;126(11):1355-1362.

15. Gandhi NK, Abdel-Karim AR, Banerjee S, Brilakis ES. Frequency and risk of noncardiac surgery after drug-eluting stent implantation. *Catheter Cardiovasc Interv*. 2011;77(7):972-976.

16. To AC, Armstrong G, Zeng I, Webster MW. Noncardiac surgery and bleeding after percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2009;2(3):213-221.

17. Hawn MT, Graham LA, Richman JR, et al. The incidence and timing of noncardiac surgery after cardiac stent implantation. *J Am Coll Surg*. 2012;214(4):658-666.

18. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology*. 2008;109(4):596-604.

19. 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(10):1043-1049.

20. Wood SN. *Generalized Additive Models: An Introduction With R*. New York, NY: Chapman & Hall/CRC; 2006.

21. Harrell FE Jr. *Regression Modeling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer; 2001.

22. Wickham H. *GGPLOT2: Elegant Graphics for Data Analysis*. New York, NY: Springer; 2009.

23. Stokes ME, Davis CS, Koch GG. *Categorical Data Analysis Using the SAS System*. Cary, NC: SAS Institute; 1991.

24. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007;297(3):278-285.

25. Tokushige A, Shiomi H, Morimoto T, et al; CREDO-Kyoto PCI/CABG registry cohort-2 investigators. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: a report from the CREDO-Kyoto PCI/CABG registry cohort-2. *Circ Cardiovasc Interv*. 2012;5(2):237-246.

26. Brilakis ES, Patel VG, Banerjee S. Medical management after coronary stent implantation: a review. *JAMA*. 2013;310(2):189-198.

27. Assali A, Vaknin-Assa H, Lev E, et al. The risk of cardiac complications following noncardiac surgery in patients with drug eluting stents implanted at least six months before surgery. *Catheter Cardiovasc Interv*. 2009;74(6):837-843.

28. van Kuijk JP, Flu WJ, Schouten O, et al. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am J Cardiol*. 2009;104(9):1229-1234.

29. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery: a prospective outcome study. *Br J Anaesth*. 2006;96(6):686-693.