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Perioperative Cardiovascular Risk of Prior Coronary Stent Implantation Among Patients Undergoing Noncardiac Surgery

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ABSTRACT

BACKGROUND Previous studies have observed high rates of perioperative cardiovascular events in patients with coronary stents undergoing noncardiac surgery (NCS). It is uncertain whether this finding reflects an independent association.

OBJECTIVES The goal of this study was to assess the independent relationship between prior coronary stent implantation and the occurrence of perioperative major adverse cardiac and cerebrovascular events (MACCE) and bleeding and its relation with time from stenting to NCS.

METHODS A total of 24,313 NCS cases at the Mayo Clinic (Rochester, Minnesota) from 2006 through 2011 were included in the study; 1,120 (4.6%) cases involved patients with coronary stents. MACCE was defined as death, myocardial infarction, cardiac arrest, or stroke. Age-adjusted odds ratios (aORs) were calculated after propensity adjustment for Revised Cardiac Risk Index factors and other conventional risk factors.

RESULTS The 30-day MACCE rates were 3.7% and 1.5% in stented and unstented patients, respectively ($p < 0.001$). The risk of MACCE was largely related to the time from stent implantation to NCS, indicating substantially elevated risk in the first year after stenting (aOR: 2.59; 95% confidence interval [CI]: 1.36 to 4.94) but not thereafter (aOR: 0.89; 95% CI: 0.59 to 1.36). Bleeding displayed a similar pattern, indicating elevated risk in the first year after stenting (aOR: 2.23; 95% CI: 1.55 to 3.21) but not thereafter (aOR: 1.07; 95% CI: 0.89 to 1.28). Subgroup analysis in patients with known stent type found that the increased risk of both MACCE and bleeding >1 month after stent implantation was not limited to only those with drug-eluting stents.

CONCLUSIONS This study found that prior coronary stent implantation is an independent risk factor for MACCE and bleeding when time from stenting to NCS is <1 year, both in patients with bare-metal and drug-eluting stents.
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With an estimated number of 454,000 procedures in the United States in 2010 alone, percutaneous coronary intervention (PCI) with implantation of bare-metal stents (BMS) or drug-eluting stents (DES) has become the cornerstone of the invasive management of patients with ischemic heart disease (1). As the number of patients with coronary stents increases, clinicians more commonly encounter patients with previously implanted stents who require noncardiac surgery

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(NCS) for other conditions. Numerous studies among patients early after stenting have observed high rates of perioperative cardiovascular events in the setting of NCS (2–9). International guidelines now recommend delaying nonurgent NCS for at least 1 month after BMS implantation and 6 to 12 months after DES implantation (10,11). Recent studies, however, reporting on elevated risk up to 6 to 12 months after both BMS and DES implantation suggest that this time frame may not be enough (2–4). It is important to note that most studies thus far have been conducted exclusively in patients with coronary stents and that the lack of a control group limits assessment of the independent risk associated with prior coronary stent implantation.

SEE PAGE 1050

The goal of the present study was to investigate if prior stent implantation is an independent risk factor for the perioperative occurrence of major adverse cardiac and cerebrovascular events (MACCE) and bleeding and whether this risk depends on time from stent implantation to NCS in an unselected cohort of patients undergoing NCS.

METHODS

STUDY DESIGN. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) is the leading source of short-term general and vascular surgical outcomes in the United States, and the Mayo Clinic in Rochester, Minnesota, has been a contributor to this database since it started participating in April 2006. Details on the ACS NSQIP database have previously been published, including sampling methods (12), variable definitions (12,13), and methods to ensure that data are of high quality and reliable (14). Briefly, hospitals participating in the ACS NSQIP program prospectively submit preoperative through 30-day postoperative data on a random sample of 15% to 20% of their surgical practice to the ACS NSQIP database. Data are collected by trained nurses using a variety of methods, including medical chart review and telephone follow-up. Definitions are determined by a central committee, and participating centers are audited to assure appropriate sampling and data collection. According to these audits, the overall disagreement rate for all participating centers is approximately 1.8% (12). The ACS NSQIP database does not cover patients aged <18 years, acute trauma cases, or cases of cardiac surgery, ophthalmologic surgery, or transplantation.

After obtaining institutional review board permission, the ACS NSQIP database was interrogated for the present study to obtain baseline, procedural, and outcome data on patients undergoing NCS from 2006 through 2011 at the Mayo Clinic in Rochester, Minnesota. Data on prior coronary stent implantation were acquired by matching the surgical database with the Mayo Clinic PCI Registry. In addition, medical charts were reviewed to identify all prior stent implantations performed elsewhere. Because the youngest patient with a stent was 28 years old, patients without stents age <28 years were not deemed to be appropriate control subjects and were excluded. No further inclusion or exclusion criteria were applied.

METHODS OF MEASUREMENT. Baseline, procedural, and 30-day postoperative outcome data were obtained from the ACS NSQIP database; full data definitions have been published previously (12,13). Current smoking was defined as having smoked cigarettes in the past year. Prior cardiac surgery was defined as previous major coronary or noncoronary cardiac surgery (thus excluding pacemaker and implantable cardioverter-defibrillator insertions), and peripheral vascular disease was defined as a history of revascularization or amputation for peripheral vascular disease. Functional status reflected the patient's ability to perform activities of daily living in the 30 days before surgery and was coded as independent versus partially/totally dependent. Revised Cardiac Risk Index factors (15) were also available and were coded as diabetes mellitus requiring insulin treatment, congestive heart failure in the last 30 days, recent angina (<1 month preoperatively) or myocardial infarction (<6 months preoperatively), prior cerebrovascular disease (any prior stroke or transient ischemic attack), renal failure (preoperative serum creatinine >177 μmol/l [>2.0 mg/dl]) or preoperative dialysis dependence, and performance of vascular surgery. Classes according to American Society of Anesthesiologist guidelines were graded by the attending anesthesiologist, as described previously (16). Due to a high rate of stent implantations performed in outside institutions, interrogation of the PCI registry and medical chart review could only disclose the most recently implanted type of stent in 69% of patients (85% when time from stenting to NCS was <1 year). All other reported data were available in ≥99% of patients, except for preoperative serum creatinine level (81%).

ENDPOINTS. Our primary endpoint was the intraoperative through 30-day postoperative occurrence of MACCE. This composite measure included death, myocardial infarction, cardiac arrest, and stroke.

ABBREVIATIONS AND ACRONYMS

ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program

aOR = adjusted odds ratio

BMS = bare-metal stents

CI = confidence interval

DES = drug-eluting stents

MACCE = major adverse cardiac and cerebrovascular events

NCS = noncardiac surgery

PCI = percutaneous coronary intervention

Death was defined as all-cause mortality. Myocardial infarction was defined as the presence of 1 of the following: 1) documentation of electrocardiogram changes indicative of acute myocardial infarction, which included ≥1 of the following: ST-segment elevation >1 mm in ≥2 contiguous leads, new left bundle branch block, and new Q waves in ≥2 contiguous leads; or 2) new elevation in troponin >3 times the upper level of the reference range in the setting of suspected myocardial ischemia (12,13). Cardiac arrest was defined as the absence of cardiac rhythm or the presence of chaotic cardiac rhythm that resulted in loss of consciousness requiring the initiation of any component of basic and/or advanced cardiac life support. This approach did not include patients who had implantable cardioverter-defibrillator discharges without loss of consciousness. Stroke was defined as the development of an embolic, thrombotic, or hemorrhagic vascular accident with motor, sensory, or cognitive dysfunction that persisted for ≥24 h (12).

Our secondary endpoint was bleeding. Due to a change in definitions, this endpoint was coded differently in patients undergoing surgery before and after 2010. Before 2010, bleeding was defined as the need for transfusion (including autologous) of ≥1 U of packed red blood cells or whole blood intraoperatively or >4 U up to and including 72 h postoperatively. As of 2010, the requirement for >4 U for postoperative bleeding was changed to ≥1 U. All primary and secondary endpoints were available in all patients.

TABLE 1 Baseline and Procedural Characteristics According to Prior Stent Implantation

	Stent (n = 1,120)	No Stent (n = 23,193)	p Value
Baseline			
Age, yrs	70.0 ± 10.4	59.8 ± 14.4	<0.001
Male	815 (73.0)	10,661 (46.0)	<0.001
White race	1,048 (94.0)	20,813 (90.0)	<0.001
Body mass index, kg/m^2	30.3 ± 6.3	29.7 ± 7.5	0.004
Hypertension	920 (82.0)	10,040 (43.0)	<0.001
Current smoker	154 (14.0)	3,236 (14.0)	0.848
Recent myocardial infarction (<6 months)	39 (3.5)	77 (0.3)	<0.001
Prior cardiac surgery	244 (22.0)	1,258 (5.4)	<0.001
Peripheral vascular disease	85 (7.6)	471 (2.0)	<0.001
Chronic obstructive pulmonary disease	104 (9.3)	868 (3.7)	<0.001
Disseminated malignancy	32 (2.9)	851 (3.7)	0.156
Functional status, partially or totally dependent	115 (10.0)	1,337 (5.8)	<0.001
Revised Cardiac Risk Index factors			
Diabetes on insulin	149 (13.0)	918 (4.0)	<0.001
Recent congestive heart failure	17 (1.5)	66 (0.3)	<0.001
Recent angina or myocardial infarction	59 (5.3)	116 (0.5)	<0.001
Prior cerebrovascular disease	141 (13.0)	1,109 (4.8)	<0.001
Dialysis dependence	27 (2.4)	127 (0.5)	<0.001
Renal failure or dialysis (n = 19,582)	54 (5.4)	375 (2.0)	<0.001
Vascular surgery	221 (20.0)	1,619 (7.0)	<0.001
Procedural			
General anesthesia	1,022 (91.0)	21,693 (94.0)	0.003
Emergency surgery	86 (7.7)	1,144 (4.9)	<0.001
Surgical specialty			<0.001
General	380 (34.0)	10,685 (46.0)	
Orthopedics	231 (21.0)	4,260 (18.0)	
Vascular	221 (20.0)	1,619 (7.0)	
Urology	94 (8.4)	1,726 (7.4)	
Neurosurgery	64 (5.7)	1,275 (5.5)	
Otolaryngology	55 (4.9)	1,070 (4.6)	
Gynecology	14 (1.3)	1,045 (4.5)	
Plastic	23 (2.1)	821 (3.5)	
Thoracic	38 (3.4)	692 (3.0)	
ASA class			<0.001
1, No disturbance	1 (0.1)	1,192 (5.1)	
2, Mild systemic disease	170 (15.0)	13,117 (57.0)	
3, Severe systemic disease	860 (77.0)	8,404 (36.0)	
4, Life-threatening systemic disease	85 (7.6)	459 (2.0)	
5, Moribund	4 (0.4)	20 (0.1)	
Operation time, min	140 (90–234)	136 (87–217)	0.017
Total hospital stay, days	3 (1–7)	3 (1–5)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).
ASA = American Society of Anesthesiologists.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean ± SD, median and interquartile range, or ranges; discrete variables were presented as numbers and percentages. To compare groups, we used the Student *t* test or analysis of variance for normally distributed continuous variables, the Mann-Whitney *U* test or Kruskal-Wallis test for nonnormally distributed continuous variables, and Pearson's chi-square test for categorical variables. In patients with stents, the unadjusted probability of MACCE was plotted against the time from stenting to NCS by using a fractional polynomial (17). To determine the perioperative risk of prior coronary stent implantation, propensity-adjusted, age-adjusted logistic regression models were used. Propensity scores were calculated for any prior stent implantation and for patients with time from stenting to NCS of <6 months, 1 to 6 months, 6 to 12 months, <12 months, and ≥12 months to account for the possible time-dependent relationship between stenting and perioperative outcome. Variables included in the propensity scores were the Revised Cardiac Risk Index factors (Table 1), peripheral vascular disease, functional status, general anesthesia, and emergency surgery. Residual imbalances were identified by calculation of standardized differences. Minor residual imbalances were resolved by adding the responsible covariate to the logistic regression model as well (18).

A secondary analysis was conducted to account for BMS or DES implantation in the subgroup of patients

with available stent type. To avoid exclusion of patients with missing preoperative serum creatinine measurements, renal failure was defined as preoperative dialysis dependence in the primary analyses. Preoperative creatinine was subsequently accounted for in a sensitivity analysis. In a second sensitivity analysis, patients with recent (<6 months) myocardial infarction were excluded. To further validate the findings of the primary analysis, a third sensitivity analysis was conducted. In this analysis, patients with nonoverlapping propensity scores were excluded, as these patients at either very high or very low risk may not have had appropriate counterparts. Addition of sex or race to the models did not materially change the estimates for stent implantation and was thus considered to be redundant. Similarly, no meaningful change in the estimates for bleeding were seen when they were adjusted for the applied definition. Statistical analyses were performed with Stata version 11.0 (Stata Corp., College Station, Texas), and statistical significance was set at $p < 0.05$ (2-tailed).

RESULTS

A total of 25,592 NCS procedures performed at the Mayo Clinic from April 26, 2006, through December 31, 2011, were captured in the ACS NSQIP database. After exclusion of 1,279 procedures (5.0%) performed in patients aged <28 years, our final study population consisted of 24,313 surgical cases performed in 22,853 unique patients. Among the total number of 24,313 NCS procedures, 1,120 (4.6%) were performed in patients who had previously undergone PCI with coronary stent implantation.

BASELINE AND PROCEDURAL CHARACTERISTICS. Baseline and procedural characteristics of the included patients are listed in Table 1. There were substantial differences between patients with and without stents. Patients with stents were on average >10 years older (70.0 vs. 59.8 years; $p < 0.001$) and were more often male (73% vs. 46%; $p < 0.001$). Compared with patients without stents, those who had undergone stenting had higher rates of all cardiac risk factors considered in the Revised Cardiac Risk Index. Stent type was available in 777 stented patients; of these, 48% underwent implantation of BMS and 52% underwent implantation of DES. Baseline characteristics in patients with BMS and DES were generally well balanced (Online Table 1).

UNADJUSTED OUTCOMES. Overall, the rate of 30-day MACCE was low and occurred in 3.7% of patients with a stent and 1.5% of patients without a stent ($p < 0.001$). Stented patients exhibited significantly higher perioperative rates of death (2.5% vs. 1.0%; $p < 0.001$) and myocardial infarction (1.3% vs. 0.3%; $p < 0.001$), but this was not the case for cardiac arrest (0.6% vs. 0.3%; $p = 0.077$) or stroke (0.4% vs. 0.3%; $p = 0.637$). The rate of bleeding was 20% in patients with stents and 11% in patients without stents ($p < 0.001$). Despite the change in definition, the overall rate of bleeding remained stable before (11.9%) and after (11.6%) 2010. Details on the invasive management and outcome of patients with perioperative myocardial infarction are listed in Table 2. Invasive measures were commonly used in these patients, including angiography (39%), PCI (14%), and coronary artery bypass grafting (10%). Angiographic review revealed stent thrombosis in only 2 patients who had had an unknown stent type implanted 3.2 and 4.6 years before NCS. Two other patients experienced perioperative myocardial infarction due to a new lesion in a previously stented vessel >1 year after stent implantation. The stented segment was patent in both of these patients. Thirty-day mortality was high in patients with perioperative myocardial infarction (21%). The MACCE rate was 4.8% in patients with BMS and 2.0% in patients with DES ($p = 0.030$) (Online Table 1). These rates were 21% and 19% for bleeding, respectively ($p = 0.694$). MACCE and bleeding rates according to surgical specialty are listed in Online Table 2.

TIME DEPENDENCY OF RISK. In patients with stents, the median time from stenting to NCS was 4.5 years

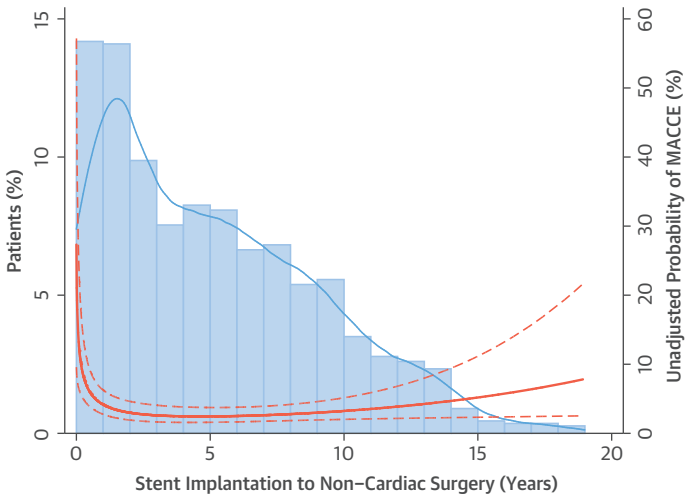
TABLE 2 Angiographic Findings and Invasive Management of Patients With Perioperative Myocardial Infarction

	Stent (n = 14)	No Stent (n = 66)	p Value
Angiography	7 (50)	24 (37)	0.363
Noncardiac surgery to angiography, days	7 (0–25)	4 (0–19)	
Final diagnosis after angiography			
Type 1 myocardial infarction, new lesion(s)	2 (29)	17 (71)	
Type 1 myocardial infarction, stent thrombosis	2 (29)	NA	
Type 2 myocardial infarction, supply/demand imbalance	3 (43)	7 (29)	
PCI	3 (21)	8 (12)	0.371
Noncardiac surgery to PCI, days	2 (0–25)	5 (2–19)	
CABG	0	8 (12)	0.166
Noncardiac surgery to CABG, days		6 (1–16)	

Values are n (%) or median (range).

CABG = coronary artery bypass grafting; NA = not applicable; PCI = percutaneous coronary intervention.

FIGURE 1 Time From Stenting to NCS and Time Dependence of Perioperative Cardiovascular Risk in Stented Patients



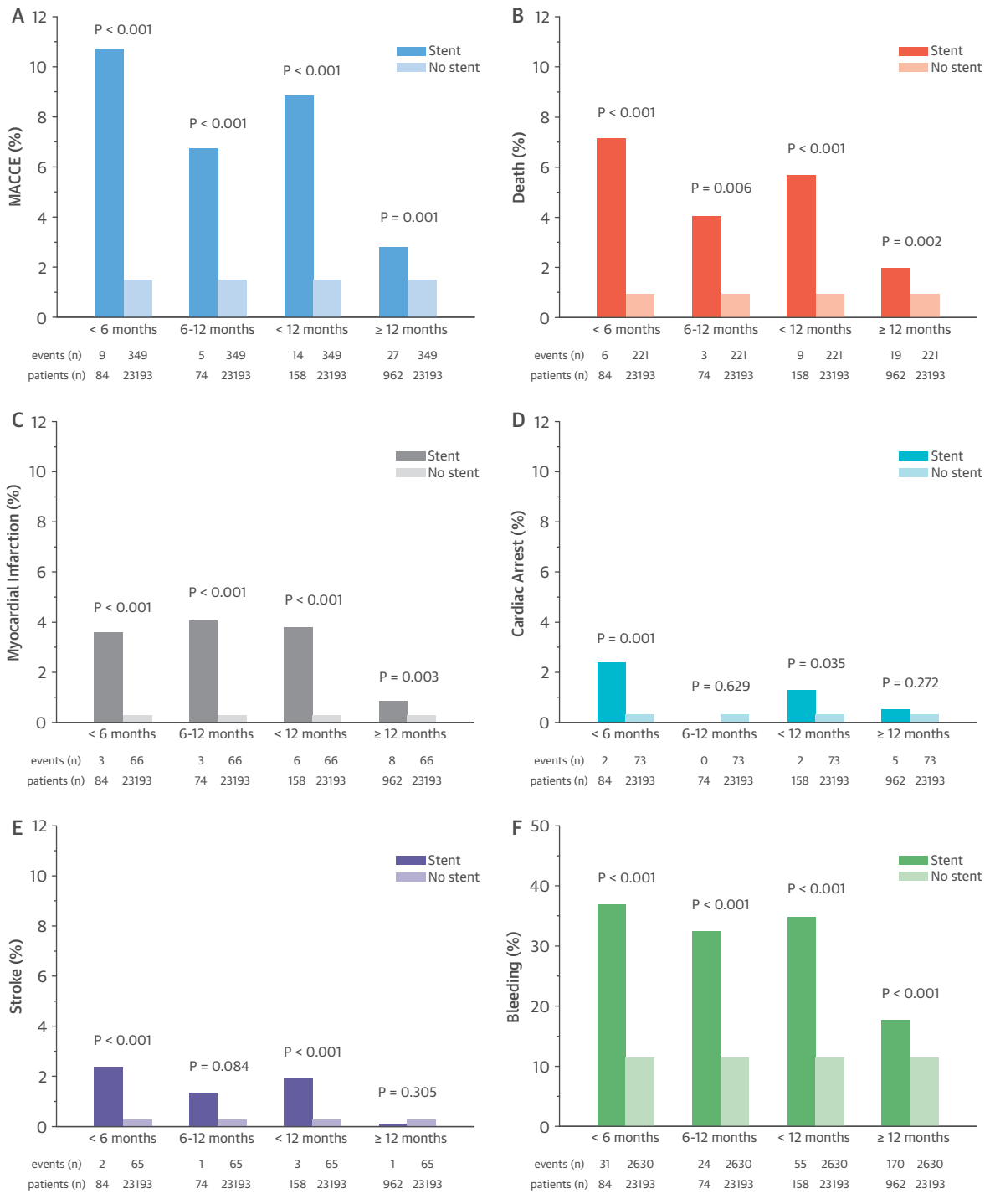
The distribution of time from stenting to noncardiac surgery (NCS) in stented patients is shown as a bar chart and a smoothed Kernel density function **(blue line)**. The **orange line** shows the time-dependent unadjusted probability of major adverse cardiac and cerebrovascular events (MACCE) with a **dashed** 95% confidence interval (p = 0.006).

(interquartile range 1.7 to 8.0 years). As shown in Figure 1, most surgical procedures were performed in the first 2 years after stenting. Eighty-four patients (7.5%) underwent NCS within 6 months of stent implantation, 74 (6.6%) between 6 and 12 months, and 157 (14%) between 12 and 24 months. Baseline and procedural characteristics according to time from stenting to NCS are listed in Online Table 3. The unadjusted probability of MACCE was dependent on time from stenting to NCS, demonstrating a high risk of MACCE when NCS was performed early after stent implantation and a progressive decline of the perioperative risk over time (p = 0.006). Figure 2 displays the event rates for primary and secondary outcomes stratified according to the time-dependent presence of a stent.

ADJUSTED OUTCOMES. Propensity-adjusted outcomes are displayed in the Central Illustration and Figure 3. Any prior stent implantation was not associated with MACCE (adjusted odds ratio [aOR]: 1.10; 95% confidence interval [CI]: 0.77 to 1.59) or any of its components, with the exception of perioperative myocardial infarction (aOR: 2.14; 95% CI: 1.15 to 3.99). However, the risk strongly depended on time from stenting to NCS. The perioperative risk of MACCE was substantially elevated in patients with prior stent implantation in the past year (aOR: 2.59; 95% CI: 1.36 to 4.94), and this outcome was also true for death (aOR: 2.65; 95% CI: 1.21 to 5.82) and myocardial infarction (aOR: 7.04; 95% CI: 2.72 to 18.22) but not for cardiac arrest or stroke. Patients who underwent recent stent implantation were further subdivided into <6 months, 1 to 6 months, and 6 to 12 months. Five patients underwent NCS within 1 month of DES implantation, and 2 patients underwent NCS within 1 month of BMS implantation. Of these 7 patients, MACCE occurred in 1 patient (14%) with recent BMS implantation (death due to cardiac arrest). The risk of NCS <6 months and 1 to 6 months after stent implantation was largely comparable to the risk of NCS <1 year after stenting. In the group undergoing NCS 6 to 12 months after stent implantation, slight attenuation of the perioperative risk was reported. Prior stent implantation between 6 and 12 months was not significantly associated with MACCE or death, although the risk of perioperative myocardial infarction was still markedly elevated (aOR: 6.92; 95% CI: 1.99 to 24.14). Patients with time from stent implantation to NCS ≥12 months were not at higher risk of MACCE or any of its components. Only 2 more MACCE occurred in the 157 patients with time from stenting to NCS of 12 to 24 months (1.3%), thereby indicating mitigation of the initial perioperative risk and making it unfeasible to conduct further analysis in this specific subgroup.

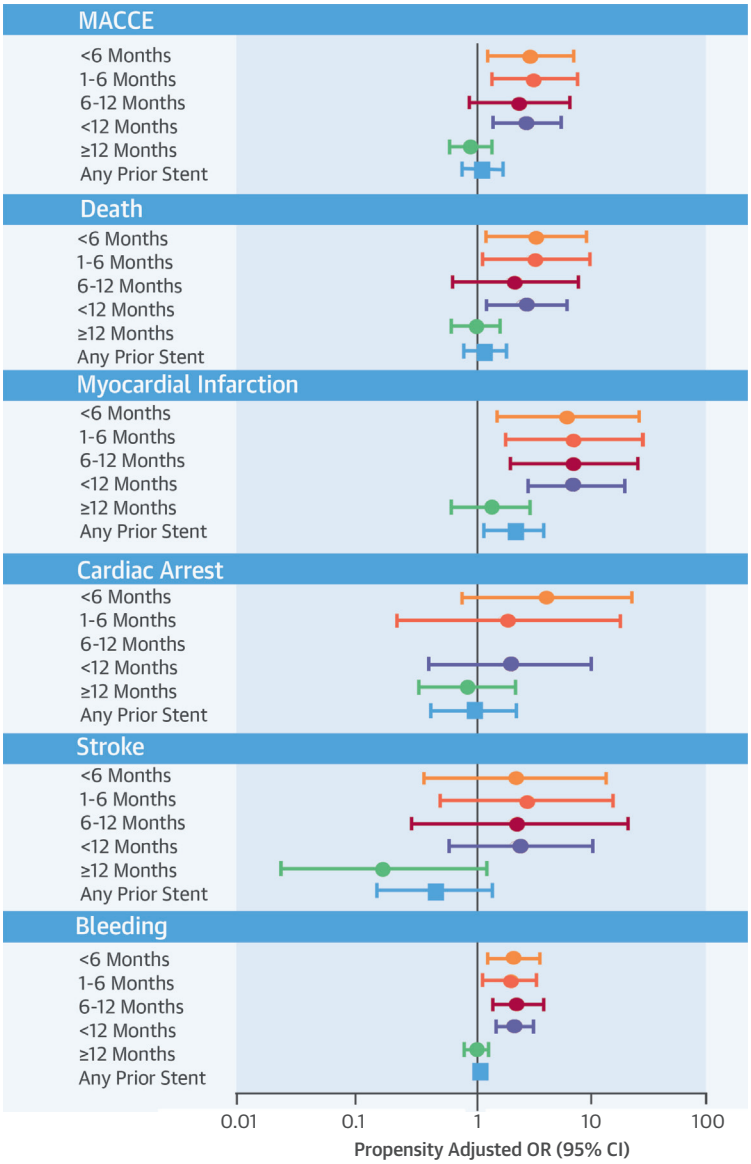
The risk of bleeding was slightly elevated in patients with stents (aOR: 1.20; 95% CI: 1.02 to 1.41) (Central Illustration, Figure 3) but followed a similar time-dependent pattern. The risk of perioperative bleeding was substantially elevated in patients with stent implantation in the past year (aOR: 2.23; 95% CI: 1.55 to 3.21) but not in patients with stents that were in place ≥12 months (aOR: 1.07; 95% CI: 0.89 to 1.28). This was also true for patients undergoing NCS 12 to 24 months after stent implantation (aOR: 1.02; 95% CI: 0.66 to 1.59). Patients who experienced a bleeding episode were also at higher risk of perioperative MACCE (aOR: 4.10; 95% CI: 3.25 to 5.18) and myocardial infarction (aOR: 3.27; 95% CI: 1.95 to 5.48). A sensitivity analysis demonstrated that the primary results of our study were not materially altered when preoperative serum creatinine level was accounted for (Online Figure 1). Exclusion of patients with recent myocardial infarction attenuated the risk of death (aOR: 3.00; 95% CI: 0.93 to 9.67; p = 0.067) but not MACCE (aOR: 3.05; 95% CI: 1.15 to 8.08; p = 0.025) in the first 6 months after stent implantation (Online Figure 2). Moreover, the risk of MACCE for patients undergoing NCS 6 to 12 months after stent implantation now reached significance (aOR: 2.79; 95% CI: 1.10 to 7.07; p = 0.031), indicating that

FIGURE 2 **Perioperative Occurrence of Cardiovascular Events by Time From Stent Implantation to Noncardiac Surgery**



Occurrence of **(A)** major adverse cardiac and cerebrovascular events; **(B)** death; **(C)** myocardial infarction; **(D)** cardiac arrest; **(E)** stroke; and **(F)** bleeding by time from stent implantation to noncardiac surgery. Time from stent implantation to noncardiac surgery is broken down into <6 months, 6-12 months, <12 months, and ≥12 months.

CENTRAL ILLUSTRATION **Risk of Coronary Stents in Noncardiac Surgery: Propensity-Adjusted Risk**



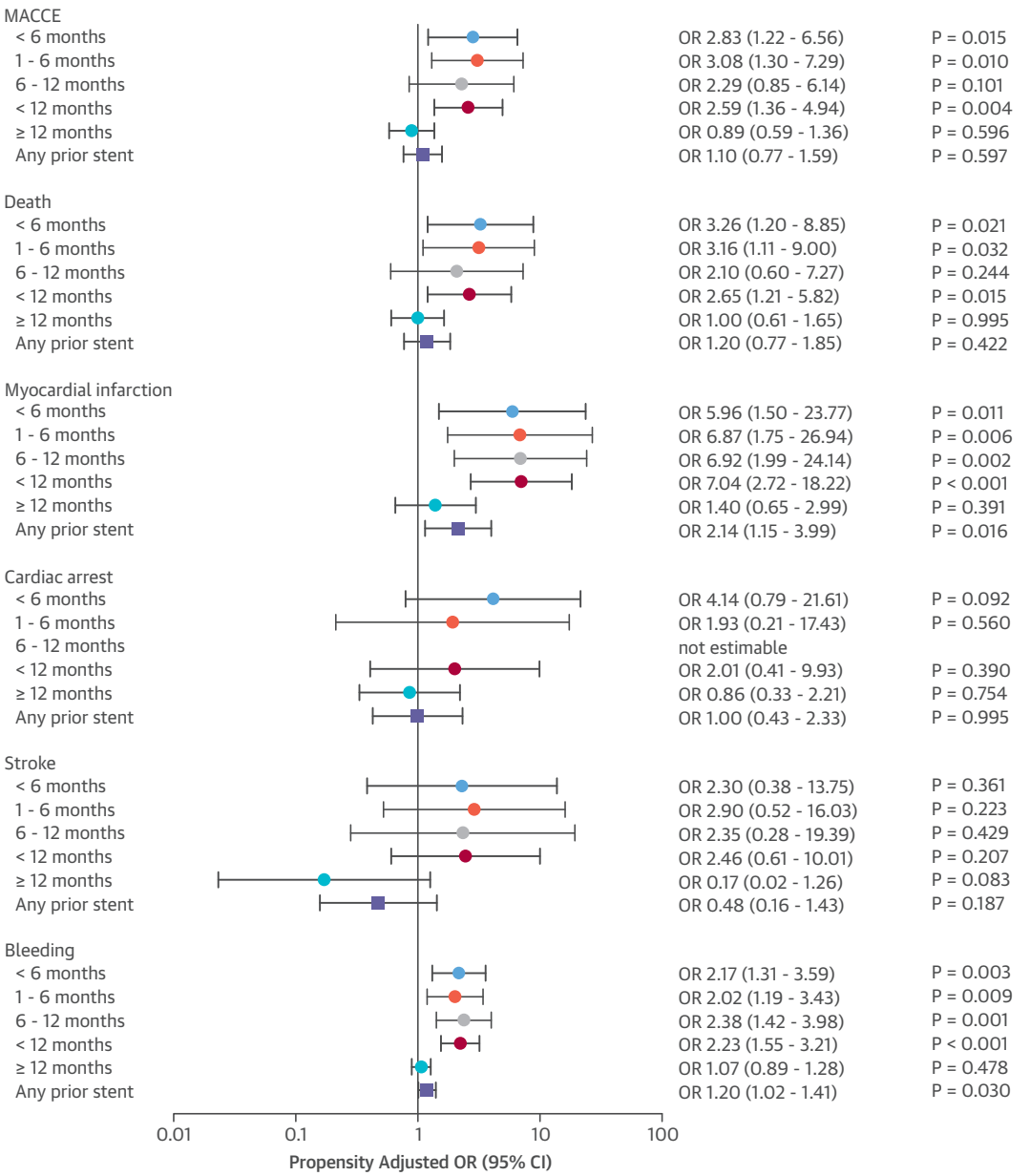
Mahmoud, K.D. et al. J Am Coll Cardiol. 2016; 67(9):1038–49.

Perioperative cardiovascular events associated with any prior stent implantation and stratified according to time from stenting to noncardiac surgery. The reported risk is relative to that of unstented control subjects. Estimates for 1 to 12 months were similar to <12 months, except for attenuation of the risk of cardiac arrest. MACCE = major adverse cardiac and cerebrovascular events.

the perioperative risk could also be seen in a group of patients deemed to have more stable coronary disease. After exclusion of patients with nonoverlapping propensity scores (1 to 2,189 patients, depending on the analysis), the perioperative risk of MACCE for patients with prior coronary stent implantation 6 to 12 months before NCS reached significance (aOR: 2.84; 95% CI: 1.12 to 7.19; p = 0.028) (Online Figure 3). Results were otherwise similar.

STENT TYPE. Results of the primary analyses were recalculated in patients with known stent type

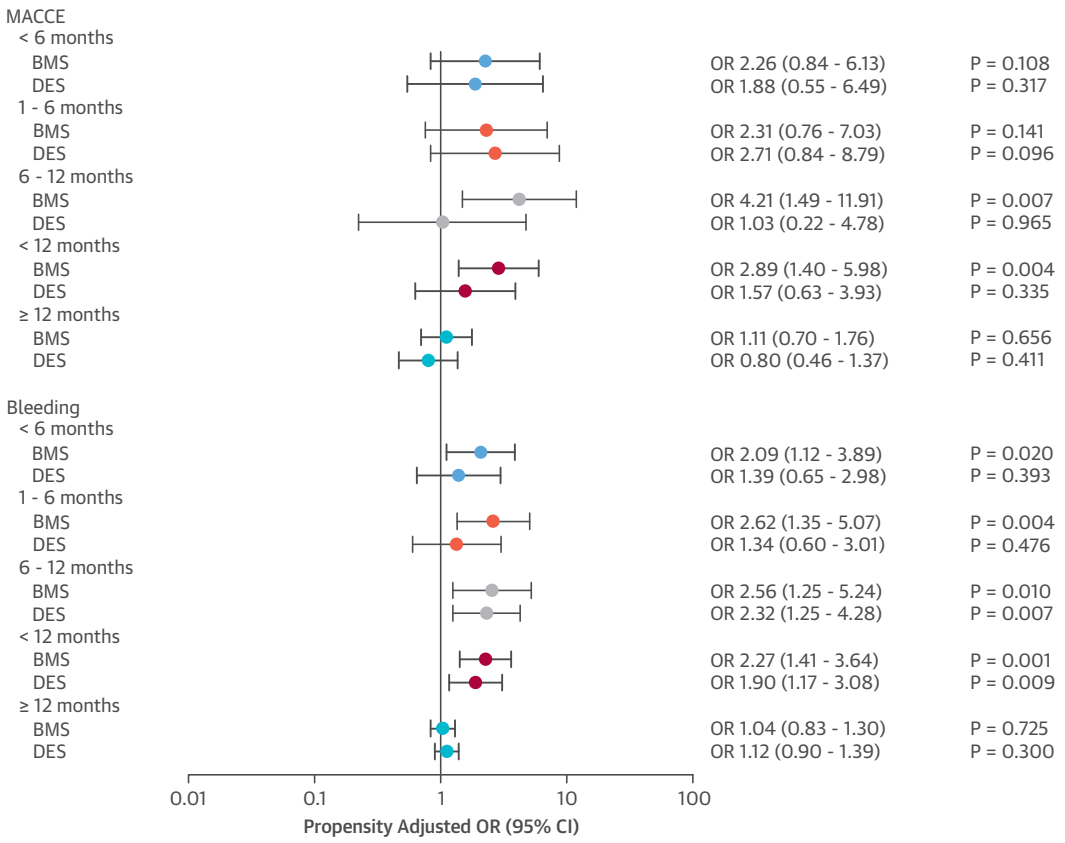
FIGURE 3 **Propensity-Adjusted Risk of Perioperative Cardiovascular Events in Stented Patients**



Propensity-adjusted risk of perioperative cardiovascular events associated with any prior stent implantation and stratified by time from stenting to noncardiac surgery. The reported risk is relative to that of unstented control subjects. Estimates for 1 to 12 months were similar to <12 months, except for attenuation of the risk of cardiac arrest (OR: 0.97; 95% CI: 0.12 to 8.11; p = 0.979). CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular events; OR = odds ratio; MACCE = major adverse cardiac and cerebrovascular events.

(Figure 4). Remarkably, an elevated risk of MACCE was seen in patients undergoing NCS 6 to 12 months after implantation of BMS (aOR: 4.21; 95% CI: 1.49 to 11.91) but not DES (aOR: 1.03; 95% CI: 0.22 to 4.78). The risk of bleeding was only elevated in the first year after stent implantation, irrespective of stent type. Although these analyses should be interpreted with caution due to limited statistical power, they indicate that the excess perioperative risk between 6 and 12 months after stent implantation could not be fully attributed to patients who had previously undergone DES implantation. Results were similar after

FIGURE 4 Propensity-Adjusted Risk of Perioperative Cardiovascular Events in Stented Patients by Stent Type



Propensity-adjusted risk of perioperative cardiovascular events in patients with prior bare-metal stent (BMS) implantation (n = 375) and drug-eluting stent (DES) implantation (n = 402) compared with unstented control subjects. Estimates for 1 to 12 months were similar to <12 months. Abbreviations as in Figure 3.

exclusion of patients with nonoverlapping propensity scores (Online Figure 4).

DISCUSSION

The goal of this study was to assess the perioperative risk of prior coronary stent implantation among patients undergoing NCS. We found that any prior stent implantation was not associated with MACCE after propensity adjustment for conventional risk factors. However, this risk heavily depended on time from stent implantation to NCS, revealing a markedly elevated risk of perioperative MACCE and bleeding in the first year after stent implantation. Although we found that the risk of overall MACCE and death seemed to decline after 6 months, patients undergoing NCS after 6 to 12 months of stent implantation still exhibited a >6-fold risk of myocardial infarction and a >2-fold risk of bleeding compared with control subjects after adjustment for conventional risk factors. After 1 year, the initial perioperative risk was completely mitigated and comparable to that of the unstented counterparts who had an equivalent baseline risk. By conducting a study in an unselected cohort of patients undergoing NCS, our approach is fundamentally different from most previous studies that were exclusively conducted in patients with stents (3–9). Inclusion of a control group allowed us to more accurately estimate the true independent risk of prior stent implantation, thereby providing the clinician with periprocedural risks that can be weighted against the risk of delaying surgery.

To the best of our knowledge, there has been only 1 other controlled observational study on this topic to date (2). This matched cohort study conducted in

the Veterans Affairs Database found an increased risk of perioperative myocardial infarction and coronary revascularization when NCS was timed in the first year after coronary stent placement. This risk was seen in patients with DES as well as BMS. This later finding is in accordance with the results of our subgroup analysis, which showed that the residual perioperative risk 6 to 12 months after stenting could be at least in part attributable to patients with BMS.

Together with similar signals from recent uncontrolled studies (3,4), accumulating data suggest that implantation of BMS in patients expected to require NCS within 1 year of stent implantation may not reduce perioperative MACCE and bleeding compared with implantation of DES. These findings warrant reevaluation of the current international guidelines statement to delay elective NCS only 1 month after BMS implantation (10,11). This recommendation seems to assume that stent thrombosis is the primary mechanism of perioperative myocardial infarction and that re-endothelialization provides protection against it. As was shown by our angiographic review, stent thrombosis was an uncommon mechanism, and most perioperative myocardial infarctions were actually the result of new lesions or supply/demand imbalance. Thus, there seems to be a vulnerable period of up to 1 year in which a patient undergoing stenting is particularly susceptible to the prothrombotic state and hemodynamic variations that surgery may produce (19).

Perioperative outcome after NCS in patients with stents represents a highly complex interplay between time, patient's surgical and cardiac risk, clinical decision-making, and the initial need for dual antiplatelet therapy after stenting. Therefore, the findings of our study should be seen as complimentary to studies reporting on other important aspects of this process that we were unable to elucidate, such as the role of antiplatelet therapy. Antiplatelet therapy has traditionally been seen as the mediator for both ischemic events and bleeding. The recently published POISE-2 (Perioperative Ischemic Evaluation-2) trial has questioned this belief by showing that the perioperative use of aspirin did not reduce the incidence of myocardial infarction in NCS but did result in a higher rate of bleeding (20). In POISE-2, as well as in our study, patients who experienced bleeding were also at higher risk of myocardial infarction, which may be explained by a mismatch between supply and demand of myocardial oxygen. Importantly, the generalizability of the results of POISE-2 to patients undergoing recent stenting is unclear, as they were excluded from the trial. Nonetheless, recent observational data yield similar findings. In the intercontinental PARIS (patterns of nonadherence to anti-platelet regimens in stented patients) registry, physician-guided interruption (<14 days) of dual antiplatelet therapy for surgery was only predictive of major adverse cardiac events in the first 6 months after stenting (21). A large study in the Veterans Affairs Database found no independent association between discontinuation of perioperative dual antiplatelet therapy and major adverse cardiac events among patients undergoing NCS within 2 years of stenting (4). An analysis of the Japanese CREDO-Kyoto registry yielded similar results (6). These findings may reflect advances in PCI, stent design, and/or NCS, but they could also reflect residual confounding (e.g., physicians continue antiplatelet therapy in patients at higher risk of perioperative events).

Current guidelines recommend the use of a validated risk score to assess the perioperative cardiovascular risk of patients undergoing NCS (10,11). Currently recommended risk scores are the Revised Cardiac Risk Index (15) and the ACS NSQIP risk calculator (13). Although both scores include baseline, cardiac, and surgical risk factors, prior coronary stent implantation was not evaluated as a possible risk factor in the development of these models. The results of our study show that prior stent implantation <1 year before NCS is an important risk factor for the occurrence of perioperative MACCE and bleeding, even after adjustment for the Revised Cardiac Risk Index and other factors. Collaboration between different medical specialties to create large databases that include detailed cardiovascular and surgical data is key to optimizing prediction of perioperative cardiovascular events and to developing interventions to prevent their occurrence in high-risk patients. This approach is also necessary to determine if prior stent implantation is an actual risk factor or merely a marker of more specific variables (e.g., antiplatelet use, coronary anatomy).

STUDY LIMITATIONS. By choosing patients undergoing NCS as a denominator for our analysis, we were able to estimate the independent perioperative risk of prior stent implantation. However, this method was at the expense of detailed stent-related data because many of the stent implantations were performed elsewhere. Specifically, we cannot provide data on the use of new-generation DES, which exhibit excellent safety and efficacy and may not require a 1-year dual antiplatelet regimen (22). Second, our stented population consisted primarily of older, white male subjects who often had comorbidities, and baseline

differences with the control group were profound. Although we rigorously adjusted the analyses for conventional risk factors, we cannot exclude the possibility of residual confounding. However, the fact that perioperative risk completely returned to baseline levels in patients undergoing NCS after 1 year of stent implantation is both biologically plausible and indicative of adequate adjustment for confounders. In addition, the results were not materially different when patients with nonoverlapping propensity scores were excluded. Future studies are required to determine the generalizability of our findings to other populations. Third, data on antiplatelet therapy use were lacking. Fourth, the low event rate in our study limits statistical power to demonstrate modest but relevant risks. This may particularly have been a problem in the subgroup analysis by stent type and for the cardiac arrest and stroke endpoints, thus warranting cautious interpretation. Fifth, it should be noted that the ACS NSQIP definition of myocardial infarction is stringent, whereas the bleeding definition is rather liberal. Finally, in the absence of data on the operator's intentions at the time of stent implantation, it is possible that patients at higher risk of adverse events were more likely to receive BMS despite multivariable adjustment (i.e., reverse causality).

CONCLUSIONS

Patients undergoing NCS are at higher risk of perioperative MACCE (particularly myocardial infarction) and bleeding in the first year after coronary stent implantation. A subgroup analysis in patients with known stent type indicated that the perioperative risk beyond 6 months could be at least in part attributable to patients with prior BMS implantation. This later finding is in line with other recent reports and contradicts the common belief that perioperative risk is only elevated in the first month after BMS implantation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with ischemic heart disease undergoing NCS are at risk of perioperative cardiovascular events and bleeding, particularly within the first year after deployment of coronary stents, and use of BMS may not reduce the rate of these perioperative events compared with DES.

TRANSLATIONAL OUTLOOK: Additional research is needed to establish optimum approaches to perioperative continuation or interruption of antiplatelet therapy in patients with coronary stents undergoing NCS.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29–322.

2. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of coronary stents on postoperative adverse events: a matched cohort study. Ann Surg 2015 Apr 17 [E-pub ahead of print].

3. Wijeysundera DN, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. Circulation 2012;126:1355–62.

4. Hawn MT, Graham LA, Richman JS, et al. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. JAMA 2013;310:1462–72.

5. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. J Am Coll Cardiol 2014;64:2730–9.

6. Tokushige A, Shiomi H, Morimoto T, et al. 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;5:237–46.

7. Albaladejo P, Marret E, Samama CM, et al. Non-cardiac surgery in patients with coronary stents: the RECO study. Heart 2011;97:1566–72.

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

9. Nuttall GA, Brown MJ, Stombaugh JW, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. Anesthesiology 2008;109:588–95.

10. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2014;64:e77–137.

11. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on Non-Cardiac Surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383–431.

12. ACS NSQIP user guide for the 2011 participant use data file. Available at: https://www.facs.org/~/media/files/quality%20programs/nsqip/ug11.ashx. Accessed June 14, 2015.

13. Gupta PK, Gupta H, Sundaram A, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. Circulation 2011;124:381–7.

14. Shiloach M, Frencher SK Jr., Steeger JE, et al. Toward robust information: data quality and inter-rater reliability in the American College of Surgeons national surgical quality improvement program. J Am Coll Surg 2010;210:6–16.

15. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple

index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043–9.

16. Saklad M. Grading of patients for surgical procedures. Anesthesiology 1941;2:281–4.

17. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. Appl Statist 1994;43:429–67.

18. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J 2011;32:1704–8.

19. Arnesen H, Dahl OE, Aspelin T, et al. Sustained prothrombotic profile after hip replacement surgery: the influence of prolonged prophylaxis with dalteparin. J Thromb Haemost 2003;1:971–5.

20. Devereaux PJ, Mrkobrada M, Sessler DI, et al. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014;370:1494–503.

21. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

22. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ 2015;350:h1618.

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APPENDIX For supplemental tables and figures, please see the online version of this article.