EDITORIAL

Patient With Coronary Stents Needs Surgery
What to Do?

Emmanouil S. Brilakis, MD, PhD; Subhash Banerjee, MD

One of the most common questions interventional cardiologists are being asked is: "My patient needs surgery and has a coronary stent; should I clear him/her for surgery and what should I do about the antiplatelet therapy?" With approximately 1 in 5 patients undergoing noncardiac surgery within 2 years after receiving a stent,[1] this will continue to be a frequent question in the years to come.

The fact that this question is being asked is encouraging and reflects that most physicians are aware of the possibility of perioperative stent thrombosis, a severe and sometimes life-threatening complication that can occur when patients with coronary stents undergo surgery.[2] Perioperative stent thrombosis is the result of several factors, such as incomplete stent endothelialization, antiplatelet therapy discontinuation, and the prothrombotic state caused by surgery, and carries significant morbidity and mortality.[2]

What is currently known about perioperative stent thrombosis? First, the risk is estimated at 0.86% to 2.33%[3] and is highest early after stent implantation and declines over time. Second, the type of stent is important: surgery is generally considered safe if performed more than 6 weeks after bare metal stent (BMS) implantation, whereas the risk for stent thrombosis remains even years after drug-eluting stent (DES) implantation[4] because of delayed stent endothelialization due to the drug. Avoiding surgery for 12 months after DES implantation is currently recommended by the American College of Cardiology/American Heart Association perioperative management guidelines.[5] Third, continuation of at least 1 antiplatelet agent (aspirin) or preferably 2 antiplatelet agents (aspirin and an oral $P2Y_{12}$ adenosine-diphosphate receptor inhibitor) decreases the risk for perioperative stent thrombosis, if the effects on perioperative bleeding risk are considered acceptable.[2]

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In this issue of the *JAMA*, Hawn et al[6] take advantage of the power of the large Veterans Affairs electronic medical record system to determine the perioperative risk of patients undergoing surgery after coronary artery stent implantation. The authors examined the largest cohort reported to date of patients with coronary stents undergoing surgery (41 989 operations) and documented an overall rate of major adverse cardiac events (MACE) of 4.7% (1980 events). The study confirms that the risk of MACE declines with increasing time from surgery, stabilizing after 6 months; demonstrates higher risk for MACE with BMS than DES (5.1% vs 4.3%); and suggests that complete cessation of antiplatelet therapy was associated with a similar risk of MACE as continuation of dual antiplatelet therapy during surgery.

The first finding is consistent with prior studies[3] and with recent reports suggesting that less than 12 months of dual antiplatelet therapy duration may be adequate after DES implantation.[7] The second finding is likely due to patient selection, because sicker patients or patients who are known to require surgery early after stent placement are more likely to receive BMS. The third finding is counter to currently accepted approaches; the lack of a "protective effect" of dual antiplatelet therapy on MACE could be due to increased bleeding or may reflect the inclusion of all MACE as the primary end point without specifically addressing stent thrombosis.[2] Eisenberg et al[8] have shown that the risk of stent thrombosis is lower when $P2Y_{12}$ inhibitors are discontinued if aspirin is continued.

How should the findings by Hawn et al[6] and other recent studies[7] influence the approach for patients who need surgery after stents? The approach for patients with BMS should not change; these patients usually can undergo surgery within 6 weeks after coronary stent implantation with very low risk of stent thrombosis.[2] For patients with DES, surgery performed at least 6 months after DES implantation appears to carry low risk for stent thrombosis, especially with contemporary, second-generation DES, which have more biocompatible, durable polymer coatings.[7] Hence, nonurgent operations should be postponed until 6 months after stent implantation. Although the evidence is not definitive, continuing antiplatelet therapy during the perioperative period could decrease the risk of stent thrombosis[2] and may carry low risk for bleeding, especially for minor surgeries; urgent surgeries can be performed before 6 months, if dual or at least single antiplatelet therapy can be continued. If all antiplatelet therapy needs to be discontinued (for example, to perform intracranial or spine surgery), consideration should be given to "bridging" therapy with short-acting antiplatelet agents (such as glycoprotein IIb/IIIa inhibitors or cangrelor),[2] taking into account that the highest-risk period for perioperative stent thrombosis is the first postoperative day[1] and that little is known about the safety and efficacy of such treatments.[9] Perioperative bridging therapy may be most beneficial when surgery is needed within 6 weeks after DES (or BMS) implantation, which is the highest risk period for stent thrombosis.[6]

Patients with coronary stents should ideally undergo surgery at centers with primary percutaneous coronary

intervention capability, to allow prompt treatment if perioperative stent thrombosis occurs.[2] Close communication and collaboration should be maintained among the surgeon, cardiologist, and anesthesiologist.[2] Restarting antiplatelet therapy shortly after surgery (ideally during the first postoperative day,[1] if considered safe by the surgeon) could help reduce the risk of stent thrombosis. Aspirin and clopidogrel (with a 600-mg loading dose) should be administered, avoiding more potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) to minimize the bleeding risk early after surgery.

Medicine is both an art and a science. The study by Hawn et al[6] provides good scientific evidence to a field and a common clinical question that have been, and continue to be, dominated by expert opinion.

ARTICLE INFORMATION

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REFERENCES

1. 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.

2. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol*. 2007;49(22):2145-2150.

3. Alshawabkeh LI, Banerjee S, Brilakis ES. Systematic review of the frequency and outcomes of non-cardiac surgery after drug-eluting stent implantation. *Hellenic J Cardiol*. 2011;52(2):141-148.

4. 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.

5. Fleisher LA, Beckman JA, Brown KA, et al; 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); 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; Society for Vascular Surgery. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol*. 2007;50(17):e159-e241.

6. Hawn MT, Graham LA, Richman JS, Itani KMF, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA*. doi:10.1001/jama.2013.278787.

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

8. Eisenberg MJ, Richard PR, Libersan D, Filion KB. Safety of short-term discontinuation of antiplatelet therapy in patients with drug-eluting stents. *Circulation*. 2009;119(12):1634-1642.

9. Alshawabkeh LI, Prasad A, Lenkovsky F, et al. Outcomes of a preoperative "bridging" strategy with glycoprotein IIb/IIIa inhibitors to prevent perioperative stent thrombosis in patients with drug-eluting stents who undergo surgery necessitating interruption of thienopyridine administration. *EuroIntervention*. 2013;9(2):204-211.

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

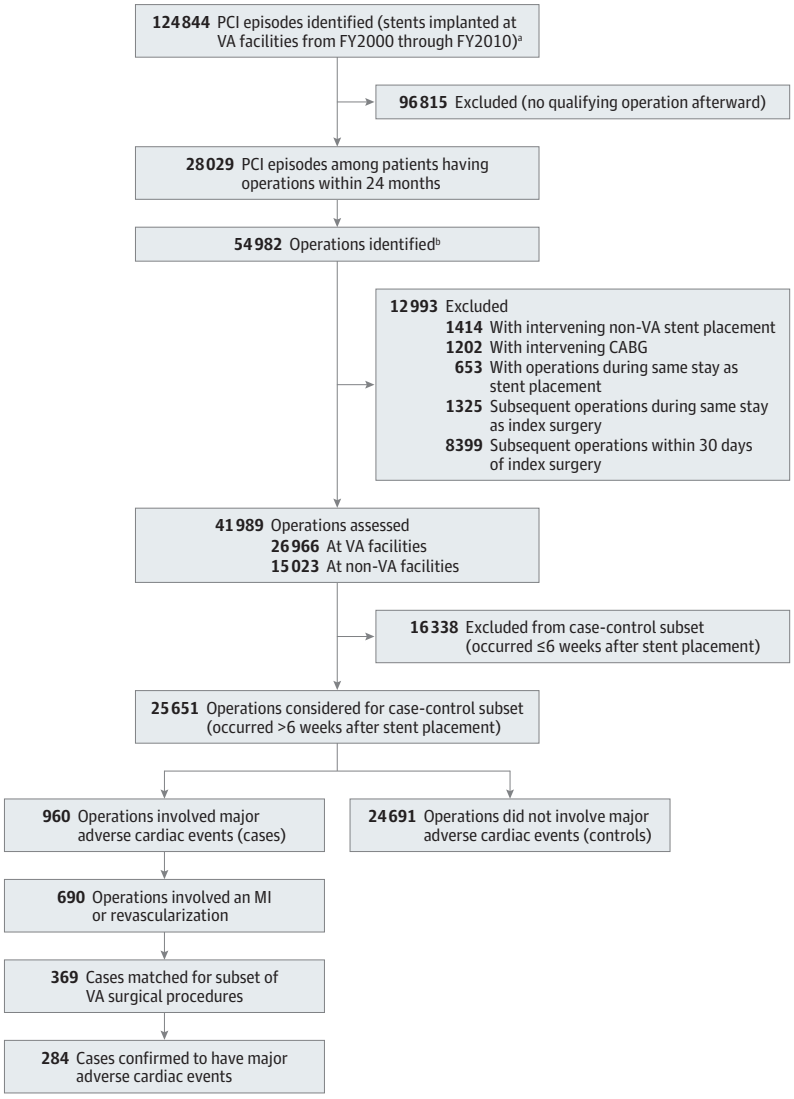
Cardiac stents were identified in the VA's National Patient Care Databases (NPCD) and the VA Clinical Assessment, Reporting, and Tracking (CART) Program. Noncardiac surgery occurring in the VA was identified in the VA Surgical Quality Improvement Program database (VASQIP) and noncardiac surgery occurring 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]

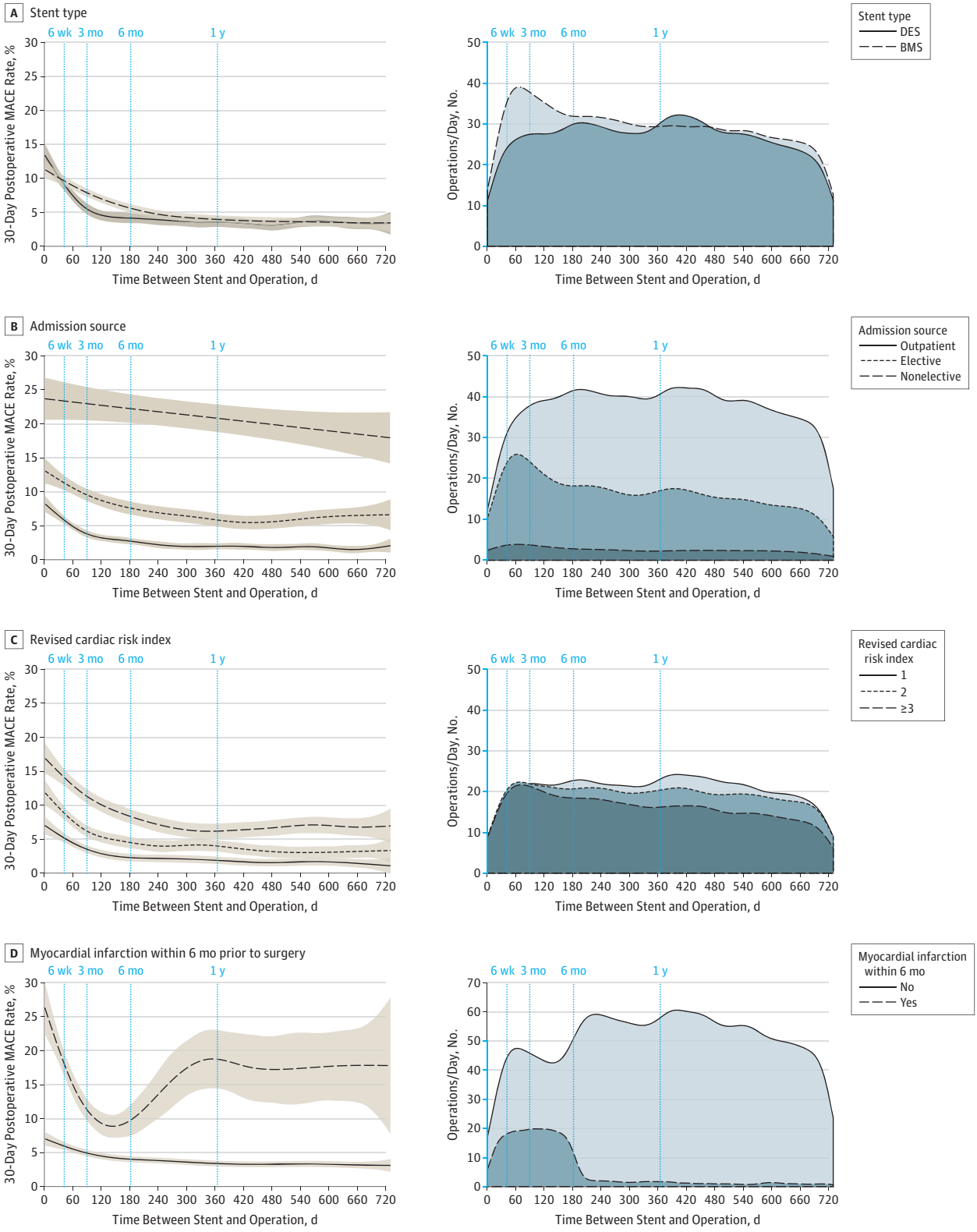
[c] Primary *Current Procedural Terminology* codes of general (10000-10039), hemic and lymphatic (38100-39999), and endocrine (60000-60999) operations.

[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.

ARTICLE INFORMATION

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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.

1. Msall ME, Phelps DL, DiGaudio KM, et al; Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. *Pediatrics*. 2000;106(5):998-1005.

2. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003;289(9):1124-1129.

3. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: natural history ROP: ocular outcome at 5(1/2) years in premature infants with birth weights less than 1251 g. *Arch Ophthalmol*. 2002;120(5):595-599.

4. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993-1999. *Pediatrics*. 2005;115(6):1645-1651.

5. Doyle LW, Roberts G, Anderson PJ; Victorian Infant Collaborative Study Group. Changing long-term outcomes for infants 500-999 g birth weight in Victoria, 1979-2005. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(6):F443-F447.

6. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.

COMMENT & RESPONSE

Cardiovascular Event Risk After Noncardiac Surgery

To the Editor Dr Hawn and colleagues[1] evaluated the risk of undergoing noncardiac surgery following coronary stent placement. The analysis, which examines the outcomes of 28 029 veterans undergoing noncardiac surgery within 24 months of coronary stent implantation, found that emergency surgery and severity of cardiac disease were the principal factors associated with postoperative major adverse cardiovascular events (MACE).

Stent type (drug-eluting vs bare metal) and antiplatelet therapy cessation were not associated with MACE. As physicians involved in the care of patients who have presented with stent thrombosis shortly after discontinuing antiplatelet therapy in anticipation of surgery, we note that such adverse events would not have been included in this analysis because the study population included only those who ultimately underwent surgery. Exclusion of patients whose surgery was delayed or cancelled due to MACE could lead to selection bias, potentially influencing the study results, particularly those related to antiplatelet therapy cessation and stent type.

One of the most feared complications of surgery following coronary stent placement is stent thrombosis. The mechanism of stent thrombosis is related to multiple factors, of which early cessation of dual antiplatelet therapy and proinflammatory postsurgical state are major contributors.[2] Current guidelines recommend delaying elective surgery for 1 year following implantation of drug-eluting stents or at least 4 to 6 weeks for bare metal stents and reflect concern for stent thrombosis occurring not only in the postoperative period (as assessed in this study), but also in the preoperative period.[3]

In one of the original descriptions of late thrombosis associated with drug-eluting stents, McFadden et al[4] presented 4 cases, of which 3 were related to premature cessation of dual antiplatelet therapy leading up to surgery. Notably, 2 patients had events prior to surgery and would have been excluded from the current analysis.

Hawn et al[1] have conducted a comprehensive investigation of postoperative outcomes in patients with previous coronary stents; however, inferences on preoperative management and events are less clear. Whether current guidelines emphasizing stent type and surgical timing require reevaluation based on this evidence hinges, in part, on the magnitude of potential bias introduced by their cohort selection.

Selection of a cohort of patients scheduled to undergo surgery (analogous to an intention-to-treat analysis for a randomized trial) could overcome such a limitation and may be necessary to fully characterize the true risk of undergoing surgery in this population.

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1. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA*. 2013;310(14):1462-1472.

2. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol*. 2007;49(22):2145-2150.

3. 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 [published correction appears in *J Am Coll Cardiol*. 2008;52(9):794-797]. *J Am Coll Cardiol*. 2007;50(17):1707-1732.

4. 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.

In Reply Drs Rassi and Yeh raise an important limitation of our study addressing the risk of noncardiac surgery in patients with recent coronary stent placement. They correctly point out that our study only included patients who successfully underwent surgery. As such, patients scheduled for surgery who had an intervening acute coronary event (potentially due to antiplatelet therapy cessation) would not be included in our cohort.

Therefore, we could be underreporting the actual rate of MACE due to antiplatelet therapy cessation in relation to planned surgery. During our chart review for the study, we identified a single case in which a patient was admitted with an acute coronary event following antiplatelet therapy cessa-

tion for surgery and the scheduled surgery was cancelled. The patient subsequently had surgery following stabilization and thus entered our cohort. Nevertheless, our study design did not allow for systematic identification of this clinical scenario.

However, 2 recent multicenter registry studies have defined the incidence and outcome of dual antiplatelet therapy cessation in patients after coronary stent implantation. The Patterns of Non-adherence to Anti-platelet Regimens in Stented Patients registry reported patterns of antiplatelet therapy interruption and their association with MACE, a composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or target-lesion revascularization.[1]

Overall, 5018 patients were enrolled and 4678 (93%) were followed up prospectively for 24 months after stent implantation. Three categories of cessation were assessed: (1) physician-recommended discontinuation, (2) brief interruption (ie, for surgery), and (3) disruption (noncompliance or complication, ie, bleeding). The incidence of antiplatelet therapy cessation during the 24-month follow-up was 57.3%, and brief interruption occurred in 10.4%.

Brief interruption was not significantly associated with MACE (hazard ratio [HR], 1.41; 95% CI, 0.94-2.12) or any of the composite end points except target-lesion revascularization (HR, 1.97; 95% CI, 1.23-3.17). Moreover, 74% of the MACE events occurred when patients were receiving dual antiplatelet therapy. This is consistent with our findings that higher risk patients are more likely to have antiplatelet therapy continued and continuation is not completely protective against MACE. In addition, their analysis[1] found that the highest risk for all MACE following dual antiplatelet therapy cessation occurred within the first 6 months, consistent with our findings.

These results are also consistent with a second multisite study of 1622 consecutive patients followed up for 1 year after drug-eluting stent implantation.[2] Discontinuation was defined as interruption of 1 or both antiplatelet therapies and occurred in 10.4% within 1 year after stent implantation. Similar rates of MACE occurred in those with discontinuation compared with those without discontinuation (HR, 1.32; 95% CI, 0.56-3.12).

Even though our study could not estimate the overall MACE rate for patients planning to undergo noncardiac surgery following coronary stent implantation, these 2 registry studies provide support for the low risk of temporary antiplatelet therapy cessation following coronary stent placement. Moreover, the majority of adverse events occurred in the first 6 months, consistent with the findings in our report, and together these further support revisiting the guidelines for noncardiac surgery following coronary stenting.

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1. 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(9906):1714-1722.

2. Ferreira-González I, Marsal JR, Ribera A, et al. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. *J Am Coll Cardiol*. 2012;60(15):1333-1339.

Treatment Options for Asymptomatic Carotid Artery Stenosis

To the Editor Dr Beckman[1] discussed the available options for the management of asymptomatic carotid artery stenosis, using a 78-year-old female patient with severe stenosis as the case. Beckman summarized the results of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST),[2] demonstrating that in asymptomatic patients, carotid artery stenting (CAS) is associated with similar outcomes compared with carotid endarterectomy (CEA). The patient preferred revascularization over optimal medical therapy and consequently underwent uneventful CAS.[1]

The results of a subsequent CREST subgroup analysis[3] on the influence of sex on outcomes after CAS compared with CEA were not discussed in the article,[1] but are quite relevant. The subgroup analysis by sex showed that women assigned to CAS had higher periprocedural stroke rates compared with those undergoing CEA (5.5% vs 2.2%, respectively; hazard ratio [HR], 2.63 [95% CI, 1.23-5.65]; $P = .01$). As the CREST authors commented,[3] "women might be at higher risk of periprocedural stroke and death because of technical difficulties related to the fact that they have smaller internal carotid arteries than men; women, on average, have 40% smaller internal carotid arteries than men." This sex-specific association was not affected by symptomatic status ($P = .33$ for interaction).[3]

The results of another CREST subgroup analysis[4] by age are also relevant. This subgroup analysis[4] demonstrated that "for patients 70 years and older, the risk of events in CAS-treated patients was approximately twice that for CEA-treated patients (HR, 2.04; 95% CI, 1.48-2.82)"; and "there was no evidence that the age-by-treatment relationships differed by symptomatic status or sex." A recent meta-analysis (n = 44 studies; 512 685 CEAs and 75 201 CAS procedures) verified that CAS is associated with an increased incidence of stroke in older compared with younger patients (odds ratio, 1.56; 95% CI, 1.40-1.75).[5]

CREST reported that for asymptomatic patients, CAS is associated with similar outcomes compared with CEA.[1,2] However, based on the CREST subgroup analyses by sex[3] and age,[4] as well as the recent meta-analysis,[5] it seems that CAS is associated with higher stroke rates compared with CEA for the management of a 78-year-old asymptomatic female patient with severe carotid stenosis, such as the one discussed in the article.[1] The results of CREST 2 and other trials comparing the effects of optimal medical therapy with CAS and CEA in asymp-