Risk of Adverse Cardiac and Bleeding Events Following Cardiac and Noncardiac Surgery in Patients With Coronary Stent

How Important Is the Interplay Between Stent Type and Time From Stenting to Surgery?

Francesco Saia, MD, PhD, FESC; Laura Maria Beatrice Belotti, MSc; Paolo Guastaroba, MSc; Alessandra Berardini, MD; Roberta Rossini, MD; Giuseppe Musumeci, MD; Giuseppe Tarantini, MD, PhD; Gianluca Campo, MD; Vincenzo Guiducci, MD; Fabio Tarantino, MD; Alberto Menozzi, MD; Elisabetta Varani, MD; Andrea Santarelli, MD; Stefano Tondi, MD; Rossana De Palma, MD; Claudio Rapezzi, MD, FESC; Antonio Marzocchi, MD

Background—Epidemiology and consequences of surgery in patients with coronary stents are not clearly defined, as well as the impact of different stent types in relationship with timing of surgery.

Methods and Results—Among 39 362 patients with previous coronary stenting enrolled in a multicenter prospective registry and followed for 5 years, 13 128 patients underwent 17 226 surgical procedures. The cumulative incidence of surgery at 30 days, 6 months, 1 year, and 5 years was 3.6%, 9.4%, 14.3%, and 40.0%, respectively, and of cardiac and noncardiac surgery was 0.8%, 2.1%, 2.6%, and 4.0% and 1.3%, 5.1%, 9.1%, and 31.7%, respectively. We assessed the incidence and the predictors of cardiac death, myocardial infarction, and serious bleeding event within 30 days from surgery. Cardiac death occurred in 438 patients (2.5%), myocardial infarction in 256 (1.5%), and serious bleeding event in 1099 (6.4%). Surgery increased 1.58× the risk of cardiac death during follow-up. Along with other risk factors, the interplay between stent type and time from percutaneous coronary intervention to surgery was independently associated with cardiac death/myocardial infarction. In comparison with bare-metal stent implanted >12 months before surgery, old-generation drug-eluting stent was associated with higher risk of events at any time point. Conversely, new-generation drug-eluting stent showed similar safety as bare-metal stent >12 months and between 6 and 12 months and appeared trendly safer between 0 and 6 months.

Conclusions—Surgery is frequent in patients with coronary stents and carries a considerable risk of ischemic and bleeding events. Ischemic risk is inversely related with time from percutaneous coronary intervention to surgery and is influenced by stent type. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:39-47. DOI: 10.1161/CIRCOUTCOMES.115.002155.)**

Key Words: bleeding ■ drug-eluting stent ■ risk stratification ■ stent thrombosis ■ surgery

Percutaneous coronary intervention (PCI) is the most common strategy for myocardial revascularization and in the vast majority of the cases is accomplished with coronary stenting. To prevent the occurrence of stent thrombosis and its serious clinical consequences, dual antiplatelet therapy is recommended for at least 1 month after bare-metal stent (BMS) implantation and for 6 to 12 months after drug-eluting stent (DES) implantation.[1–3] This different therapeutic approach is because of delayed endothelialization associated with DES, a phenomenon that extends the time window for the risk of stent thrombosis.

Among patients who receive coronary stents, a considerable proportion subsequently need surgery,[4,5] and this represents a risk factor for both ischemic and bleeding events,

Received April 8, 2015; accepted November 13, 2015.

From the Institute of Cardiology, Cardio-thoraco-vascular Department, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy (F.S., A.B., C.R., A. Marzocchi); Regional Health Care and Social Agency, Bologna, Italy (L.M.B.B., P.G., R.D.P.); Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo, Italy (R.R., G.M.); Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy (G.T.); Cardiology Unit, Department of Medical Sciences, Azienda Ospedaliero-Universitaria S.Anna, Cona (Ferrara), Italy (G.C.); Interventional Cardiology Unit, S. Maria Nuova Hospital, Reggio Emilia, Italy (V.G.); Interventional Cardiology Unit, Morgagni Hospital, Forlì, Italy (F.T.); Cardiovascular Department, Maggiore Hospital, Parma, Italy (A. Menozzi); Cardiovascular Department, S. Maria delle Croci Hospital, Ravenna, Italy (E.V.); Cardiology department, Ospedale degli Infermi, Rimini, Italy (A.S.); and Department of Cardiology, Baggiovara Hospital, Modena, Italy (S.T.).

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.002155/-/DC1.

Correspondence to Francesco Saia, MD, PhD, FESC, Institute of Cardiology, Cardio-thoraco-vascular Department, University of Bologna, Policlinico S.Orsola-Malpighi (Pad 21), Via Massarenti, 9, 40138 Bologna, Italy. E-mail francescosaia@hotmail.com

WHAT IS KNOWN

- In patients with coronary stents, surgery carries a considerable risk of ischemic and bleeding events.
- In the perioperative phase, discontinuation of antiplatelet therapy increases the risk of stent thrombosis and cardiac ischemic events, in general, whereas continuation of antithrombotics increases the risk of bleeding.
- Bare-metal stents are usually preferred for coronary revascularization when surgery is planned at the time of percutaneous coronary intervention.

WHAT THE STUDY ADDS

- Surgery is frequent during follow-up of patients with previous coronary stenting, and its incidence is generally underestimated.
- Perioperative ischemic risk is inversely related with time from percutaneous coronary intervention to surgery and is influenced by stent type, with new-generation drug-eluting stent appearing at least as safe as bare-metal stent at any time window.

with an inverse relationship with time.[6] Indeed, premature cessation of dual antiplatelet therapy is a strong predictor of stent thrombosis, and surgery is a common reason for premature discontinuation of either single or dual antiplatelet therapy (DAPT) antiplatelet therapy.[7] The hypercoagulable state associated with surgery can further contribute to increase the overall ischemic risk. On the opposite front, continuation of antiplatelet therapy may increase the risk of perioperative bleeding.[8] The risk of perioperative complications, however, depends also on other factors, including patient status, type, and magnitude of surgery and prevalence of comorbidities.[3] Cardiac risk, therefore, extends well beyond the recommended period of dual antiplatelet therapy. Further, the influence of stent type and period of risk still have to be defined, and a recent study did not show temporal differences in outcomes between DES and BMS for at least 2 years after PCI.[4]

The aims of this study were to describe the incidence and type of cardiac (CS) and noncardiac surgery (NCS) after PCI and stenting during long-term follow-up and to assess predictors of periprocedural adverse ischemic and bleeding events. In addition, we sought to assess the risk associated with the interplay between different stent types and time from stenting to surgery.

Methods

Patient Population and Surgical Procedures

Among 39 362 consecutive patients undergoing PCI and stenting between July 2002 and December 2011 enrolled in the all comers multicenter Registro regionale AngiopLastiche dell'Emilia-Romagna (REAL) Registry,[9–12] we identified those who underwent surgery up to December 31, 2012 (median follow-up 4.8 years, interquartile range 2.8–6.9 years). As previously reported,[9–12] for reimbursement and health policy issues, the Regional Healthcare and Social Agency of the Region Emilia-Romagna is able to identify all hospital admissions occurring within the entire Italian country for patients who are resident in the Region. This ensures a complete follow-up for all patients enrolled in the registry, with a maximum delay of 1 year. Surgical procedures occurring abroad, which are known to be extremely rare, could theoretically be missed. Follow-up is updated every 3 months. In addition, the Regional Government, through the analysis of mortality registries, keeps track of vital status of all patients who are resident in the region and is able to identify all deaths occurring within and outside the national territory. A total of 1512 types of interventions and 17 226 elective or urgent surgical procedures of interest were identified. Surgery was divided into CS and NCS. Distinction between elective and urgent surgery was reported in the hospital discharge records. Electrophysiology procedures with a surgical approach (eg, pace maker implantation and implantation of implantable cardiac defibrillator) were taken into account to assess the overall incidence of surgery but were excluded from multivariable analyses.

End Points and Definitions

Cardiac risk associated with each surgical procedure was classified according to current European Society of Cardiology guidelines as low, intermediate or high based on estimated 30-day cardiac event rates (Table I in the Data Supplement).[3] Bleeding risk associated with each procedure was classified into low, intermediate, or high on the basis of available literature coupled with expert opinion (Table II in the Data Supplement).[13] For this purpose, a large number of surgeons were previously involved, and the result of this multidisciplinary collaboration have been summarized in an intersociety consensus document on perioperative management of antiplatelet therapy in patients undergoing surgery after coronary stent implantation. The document was endorsed by 16 national societies of cardiology, anaesthesiology, and surgery. Stent thrombosis risk associated with previous stenting was categorized based on the type of stent implanted (BMS versus DES) and time between index PCI and surgery. Stent thrombosis risk was defined low >6 months after BMS and >12 months after DES; intermediate 1 to 6 months after BMS or 6 to 12 months after DES; and high <1 month after BMS or <6 months after DES (Table 1).[13] For patients with multiple PCI procedures, only the procedure carrying the highest thrombotic risk based on the classification above was selected for the analysis. Patients with DES were further differentiated between old-generation DES (oDES; Cypher and Cypher Select [Cordis Corporation], Taxus Express and Taxus Liberté [Boston Scientific], Endeavor with PC polymer[Medtronic Inc]) and new-generation DES (nDES; Biomatrix [Biosensors Interventional Technologies Pte Ltd], Nobori [Terumo Corp], Endeavor Resolute with biolinx polymer [Medtronic Inc], Optima [Sorin Biomedica], Cre8 [CID], Promus [Boston Scientific], Xience V and Xience Prime [Abbott Laboratories]).

In patients undergoing surgery, the incidence of cardiovascular death, myocardial infarction (MI), and serious bleeding event (SBE) was assessed at 30 days. Follow-up was obtained directly and independently from the Emilia-Romagna Regional Healthcare and Social Agency through the analysis of the Hospital Discharge Records and the Mortality Registries. This administrative process ensures complete follow-up for all the patients who are resident in the Region, provided they are admitted in an Italian hospital. Follow-up for mortality comprises out-of-hospital deaths. Cardiac death was defined as the combination of death from a clearly identifiable cardiovascular cause or sudden/unexplained death. An SBE was defined as hemorragic stroke and any bleeding requiring intervention or unplanned red blood cell transfusion or leading to death or a new hospitalization.[14] Repeated PCI was collected both from hospital discharge records and from the prospective REAL registry database, which collects data from 13 catheterization laboratories. There was no formal event adjudication, and so all events were diagnosed by physicians involved in patients' care.

Statistical Analysis

Continuous variables were expressed as mean±SD and compared using Student's unpaired *t* test. Categorical variables were expressed as counts and percentages, and χ^2 test was used for comparison.

Table 1. Definition of Stent Thrombosis Risk Associated With Stent Type and Time From Stenting to Surgery

High Risk	Intermediate Risk	Low Risk
<1 mo after BMS	1–6 mo after BMS	> 6 mo after BMS
<6 mo after DES	6–12 mo after DES	> 12 mo after DES

BMS indicates bare-metal stent; and DES, drug-eluting stent.

The incidence of surgery during follow-up was estimated with the Kaplan–Meier method. To estimate the cumulative incidence of surgery, only the first surgery was used as the event of interest without considering recurrent events. Multivariate time-dependent Cox regression analysis was performed to identify factors independently associated with cardiac detah during follow-up, using all clinical, angiographic, and procedural variables included in Table 2. Surgery and treatment were used as time-dependent covariates. Considering surgery as a time-varying variable enable to avoid immortal time bias[15] by acknowledging a change in exposure status: all patients were considered unexposed (ie, without surgery) from the time of study entry until the date of surgery; patients who received surgery were considered exposed from the time of surgery until death or the end of the study.[16] Differently, the incidence of adverse events within 30 days was calculated for every single surgical procedure, including repeated interventions. Accordingly, to estimate odds ratios (OR) for events of interest, stent thrombosis risk, surgical risk, and bleeding risk were reclassified for each single surgical procedure (see examples in the Data Supplement). Stepwise multivariable logistic regression analyses were performed to identify predictors of cardiac death/MI or SBE within 30 days from surgery, using the following variables with a probability of inclusion =10%: urgent surgery, thrombotic risk, bleeding risk, surgical risk, age, sex, diabetes mellitus, liver cirrhosis, hypertension, cerebrovascular disease, chronic kidney disease, cancer, chronic obstructive pulmonary disease, previous red blood cell transfusion, diagnosis at admission for PCI, ejection fraction, target vessel, total lesion length, heart failure, and NCS versus CS. The first 4 variables were forced into the model. Additional variables that were not significant at univariable analyses, such as in-stent restenosis, chronic total occlusion, bifurcation, stent size, and total stent length, were not included in the final multivariable analyses. Model discrimination was measured using the c-statistic, and calibration was estimated using the Hosmer–Lemeshow statistic. A second multivariable analysis was performed replacing the variable stent thrombosis risk with the following variables: BMS >360 days (reference, hazard ratio =1), oDES >360 days, nDES >360 days, BMS 180 to 360 days, oDES 180 to 360 days, nDES 180 to 360 days, BMS 0 to 180 days, oDES 0 to 180 days, and nDES 0 to 180 days. The statistical threshold for significance was set at $P<0.05$ for a 2-tailed test. All analyses were performed with the SAS 9.3 system (SAS Institute, Cary, NC).

This study was based on common practice, and regulatory authorities required written informed consent for PCI and for data collection, which was obtained for all patients. The study protocol is in accordance with the declaration of Helsinki.

Results

During follow-up after PCI and stenting, a total of 13 128 patients underwent 17 226 surgical procedures (6085 [35.3%] <12 months from PCI). The cumulative incidence of any surgery at 30 days, 6 months, 1 year, and 5 years was 3.6%, 9.4%, 14.3, and 40.0%, respectively. The cumulative incidence of CS and NCS during follow-up is shown in Figure 1. At 30 days, 6 months, and 1 year, the cumulative incidence of NCS was 1.3%, 5.1%, and 9.1% and of CS was 0.8%, 2.1%, and 2.6%, respectively. Overall, 79.8% of surgical procedures were noncardiac (Table 3). Around a third of the procedures (29.0%) were done on an urgent basis, with a wide range between different types of surgery (from 4.7% eye surgery to 53.1% electrophysiology; Figure I in the Data Supplement). The cumulative rates of urgent procedures at 30 days, 6 months, and 1 year were 2.7%, 4.5%, and 5.7%, respectively. The corresponding rates of nonurgent procedures were 0.9%, 5.0%, and 8.7%, respectively. Table 2 describes the baseline characteristics of patients who underwent surgery during follow-up in comparison to those who did not. BMS was used more often in patients who underwent surgery <1 year from PCI (Table III in the Data Supplement), probably reflecting a general preference for BMS in patients with planned surgery at the time of PCI. Considering the different categories of stent thrombosis risk associated with the type of stent (Figure 2), a total of 12 626 surgical procedures (73.3%) were at low risk, 2531 (14.7%) at intermediate risk, and 2069 (12.0%) at high risk. Considering the bleeding risk, 7624 (44.3%) procedures were performed with a low risk, 5209 (30.2%) with an intermediate risk, and 4393 with a high risk (25.5%). According to the cardiac risk associated with different surgical procedures, 9422 procedures (54.7%) were low risk, 4764 intermediate risk (27.7%), and 3040 (17.7%) high risk.

Within 30 days after surgery, death occurred in 754 patients (4.4%), cardiac death in 438 (2.5%), nonfatal MI in 256 (1.5%), and an SBE in 1099 (6.4%). Bleeding was fatal in 115 cases (10.5% of all SBE). Tables IV and V in the Data Supplement show the differences between patients who had perioperative events versus those who did not. The independent predictors of cardiac death/MI and SBE at 30 days are illustrated in Figure 3. Of interest, thrombotic risk was independently associated with periprocedural cardiac death/MI (OR=1.50 for intermediate risk and 2.17 for high risk), whereas surgical risk and bleeding risk were not. Conversely, stent thrombosis risk was not independently associated with periprocedural SBE, whereas operative risk category was a significant predictor of SBE (OR=1.62 for intermediate risk and 1.75 for high risk), and bleeding risk category was strongly related to SBE (OR=2.27 for intermediate risk and 4.09 for high risk). The interaction between stent type and timing from stenting to surgery showed an increased risk of ischemic events with oDES at any time point (0–180 days from PCI, OR=2.10; 6–12 months OR=1.90; >12 months OR=1.45; Figure 3C; Table VI in the Data Supplement). BMS and nDES were not significantly different >12 months and between 6 and 12 months after PCI, whereas nDES appeared somewhat safer between 0 and 180 days. A further analysis including the time frames 0 to 60 days and 60 to 180 days demonstrated that this advantage is all achieved beyond 2 months after stenting, a time frame where nDES have a neutral effect, whereas BMS and oDES significantly increased the risk (OR=1.45 and 2.41, respectively; Figure II in the Data Supplement). Sensitivity analyses excluding the Endeavor stent confirmed these results (Tables VII and VIII and Figure III in the Data Supplement). Finally, we evaluated the overall effect of surgery and timing of surgery with respect to PCI over cardiovascular mortality during follow-up and found that surgery was associated with an increased risk (hazard ratio =1.58), which was strongly influenced from the time span between PCI and surgery (Table IX in the Data Supplement).

Table 2. Baseline Clinical and Procedural Characteristics of Patients Who Underwent Surgery During Follow-Up in Comparison to Those Who Did Not

Characteristics	Surgery (N=13 128)	No surgery (N=26 234)	*P* Value
Demographics			
Age, y	69.2±10.5	67.3±12.2	<0.0001
Male, % (n)	74.5 (9774)	72.5 (19 008)	<0.0001
BMI, mean±SD	27.8±43.9	27.2±4.5	0.07
Risk factors			
Diabetes mellitus, % (n)	26.3 (3455)	23.2 (6080)	<0.0001
Hypertension, % (n)	74.7 (9813)	71.1 (18 649)	<0.0001
Dyslipidemia, % (n)	59.3 (4704)	63.0 (10 264)	<0.0001
Current smoker, % (n)	19.8 (2596)	23.2 (6095)	<0.0001
Family history, % (n)	22.4 (2596)	23.4 (5399)	0.03
Clinical history			
Previous MI, % (n)	31.5 (4139)	29.4 (7710)	<0.0001
Previous PCI, % (n)	23.0 (3019)	22.1 (5798)	0.04
Previous CABG, % (n)	7.6 (996)	6.3 (1645)	<0.0001
Heart failure, % (n)	13.4 (1757)	10.8 (2846)	<0.0001
Cerbrovascular disease, % (n)	10.5 (1380)	8.1 (2118)	<0.0001
Peripheral vascular disease, % (n)	8.7 (1137)	5.2 (1361)	<0.0001
Chronic kidney disease, % (n)	8.6 (1134)	6.3 (1655)	<0.0001
Chronic obstructive pulmonary disease, % (n)	10.4 (1369)	8.3 (2181)	<0.0001
Liver cirrhosis, % (n)	1.2 (163)	0.8 (214)	<0.0001
Dementia, % (n)	0.7 (98)	0.8 (198)	0.93
Cancer, % (n)	9.4 (1235)	5.9 (1542)	<0.0001
Peptic ulcer, % (n)	1.5 (196)	1.1 (287)	0.0007
Previous RBCs transfusion, % (n)	2.9 (386)	2.2 (585)	<0.0001
Clinical presentation			
STEMI, % (n)	23.5 (3090)	25.5 (6694)	<0.0001
Non-ST elevation ACS, % (n)	41.7 (5475)	41.5 (10 900)	0.77
Stable coronary disease, % (n)	34.8 (4563)	32.9 (8640)	0.0003
Cardiogenic shock, % (n)	3.7 (476)	3.3 (843)	0.03
LVEF<35, % (n)	5.9 (777)	4.5 (1170)	<0.0001
Procedural characteristics			
Multivessel disease, % (n)	76.1 (6620)	74.9 (12 578)	0.03
Target lesion			
Left main, % (n)	3.5 (463)	3.6 (949)	0.65
Left anterior descending, % (n)	50.7 (6653)	52.1 (13 675)	0.007
Proximal, % (n)	25.7 (3373)	26.0 (6823)	0.50
Left circumflex, % (n)	31.9 (4182)	31.4 (8233)	0.34
Right, % (n)	36.0 (4721)	34.3 (9007)	0.001
Saphenous vein graft, % (n)	2.7 (349)	2.2 (587)	0.01
Total lesion length, mean±SD	24.9±16.0	25.1±15.9	0.13
Total stent length, mean±SD	28.4±18.0	28.6±17.9	0.22
In-stent restenosis	5.6 (739)	5.7 (1484)	0.91
Chronic total occlusion	6.7 (877)	7.6 (1980)	0.002
Bifurcation	22.8 (2893)	23.6 (5920)	0.12
Stent type			
BMS, % (n)	65.4 (8580)	61.2 (16 059)	<0.0001
DES, % (n)	34.6 (4548)	38.8 (10 175)	<0.0001

ACS indicates acute coronary syndrome; BMI, body mass index; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-elutingt stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

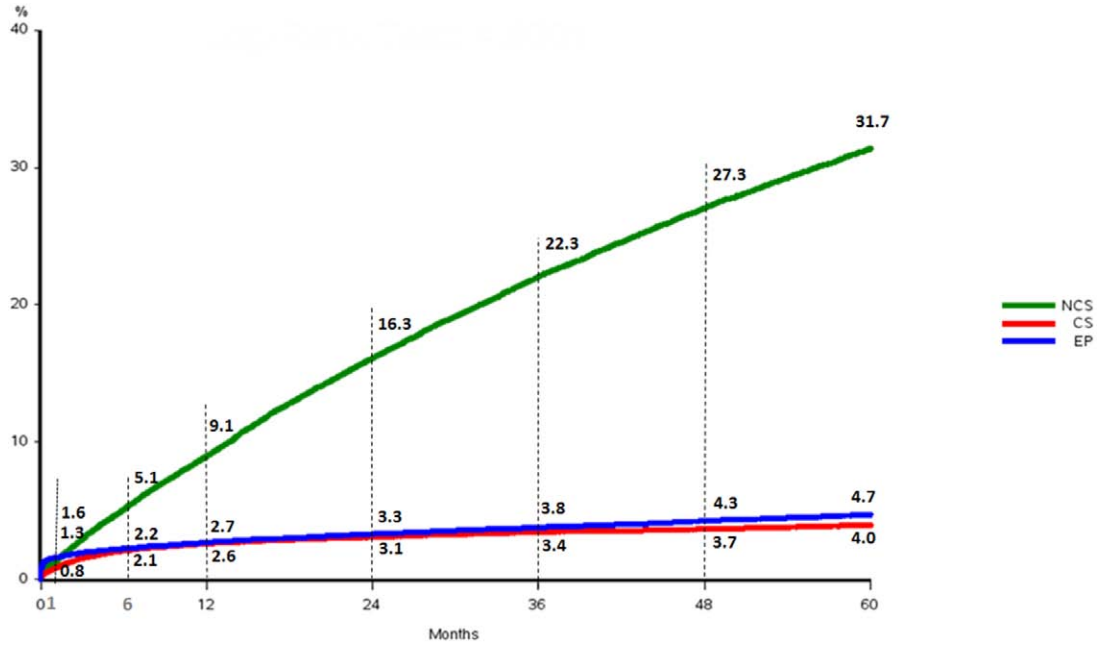


Figure 1. Cardiac surgery (CS), noncardiac surgery (NCS), and surgical electrophysiology (EP) procedures during follow-up. Kaplan–Meier estimate of the cumulative incidence ≤5 years of follow-up after stenting.

Discussion

The principal findings of our population-based study can be summarized as follows: (1) around 14% of the patients who received coronary stents underwent surgery during the first year after the procedure and 40% did so within 5 years; (2) surgery is associated with an increased risk of cardiovascular mortality during follow-up; (3) around 18% of the surgical procedures carry a high cardiac risk and 25% a high bleeding risk, and in 12% of the cases surgery is performed in patients with a high risk of stent thrombosis; (4) urgent surgery is a strong predictor of both ischemic and bleeding events in the periprocedural phase; (5) along with conventional risk factors, thrombotic risk associated with the interplay between type of stent and time from PCI to surgery provides reliable risk stratification for the occurrence of cardiac death/MI within 30 days after surgery; (6) nDES seem safer than oDES and BMS when surgery is performed between 0 and 6 months after PCI and safer than oDES and comparable to BMS between 6 and 12 months and beyond 1 year.

The incidence of NCS within 1 year after PCI is commonly reported to be around 5%.[2,4,17,18] In our study, we found that this proportion was definitely higher, being around 9% for NCS and around 14% including CS and surgical electrophysiology procedures, which is consistent with findings of a recent study based on the Veterans Administration databases.[19] The fact that around 35% of surgical procedures recorded were performed <12 months from PCI and that ≤40% of the patients needed surgery within 5 years after stenting describes the magnitude of the problem for perioperative risk management. In these patients, the tradeoff between reduction of ischemic risk with antithrombotics and increased bleeding risk is difficult, and in many instances, therapeutic decisions are arbitrary and not evidence-based. To minimize ischemic risk, current guidelines provide a general recommendation that elective surgery be delayed until 30 to 45 days after BMS implantation and 1 year after DES,[1,2] whereas elective NCS may be considered beyond 6 months after DES in selected cases but is generally discouraged. Yet, surgery represents a common reason for early discontinuation of DAPT, a relevant risk factor for stent thrombosis, and the first cause of late (>12 months) discontinuation of aspirin because of the concerns of perioperative bleeding.[7] It is worth noting that the risk of stent thrombosis and adverse ischemic events persists for inpatient surgery >12 months after PCI, especially for DES, extending at least 2 to 3 years.[20] In addition, aspirin withdrawal at any time has been associated with an adverse prognosis in subjects

Table 3. Type of Surgery and Relative Frequency

	Frequency of surgery (n=17 226)
Noncardiac surgery	13 737 (79.8)
General surgery	3311 (19.2)
Orthopedic	2428 (14.1)
Urologic	1847 (10.7)
Vascular	1487 (8.6)
Ophthalmology	1156 (6.7)
Neurosurgery	1000 (5.8)
Dermatology	827 (4.8)
Otolaryngology	534 (3.1)
Plastic surgery	371 (2.2)
Thoracic	309 (1.8)
Gynecological	252 (1.5)
Maxillofacial	153 (0.9)
Dentistry	72 (0.4)
Cardiac surgery	1593 (9.2)
Electrophysiology with surgical access*	1896 (11.0)

*Includes pace-maker, implantable cardioverter defibrillator, and cardiac resynchronization therapy.

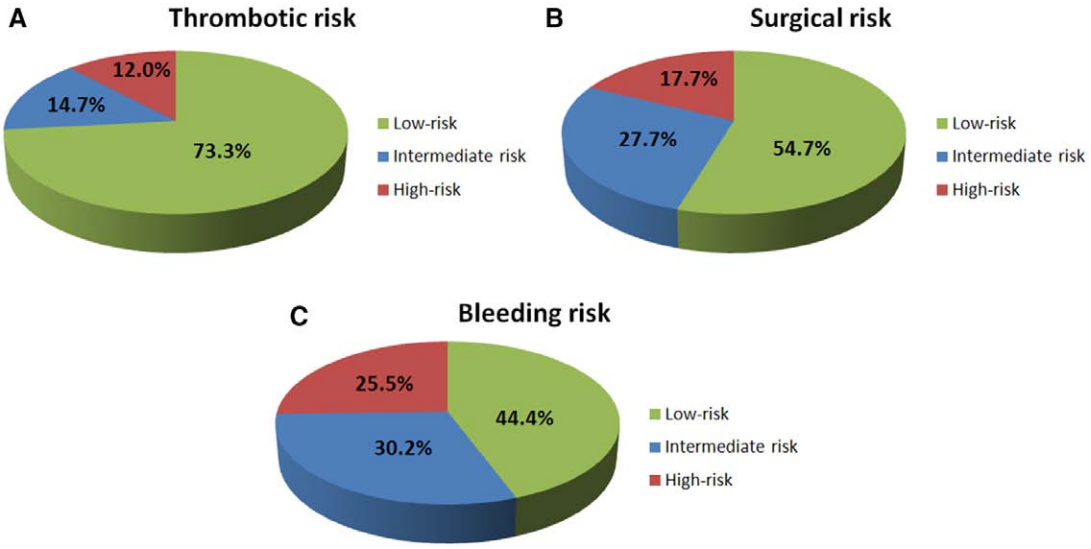


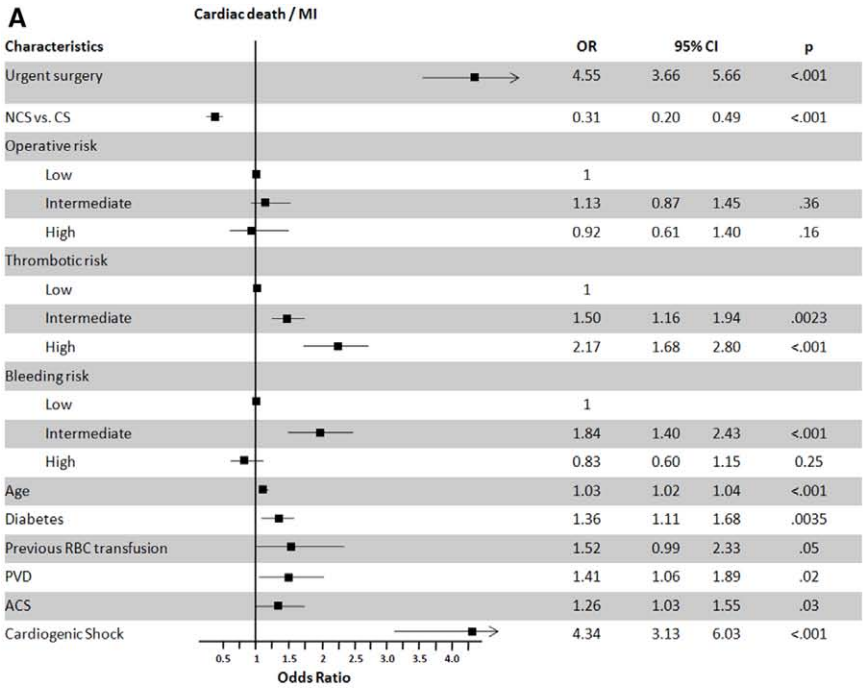
Figure 2. Distribution of ischemic and bleeding risks at the time of surgery. **A**, Thrombotic risk according to the type of stent and time from percutaneous coronary intervention (PCI) to surgery. **B**, Operative risk according to the type of intervention. **C**, Bleeding risk based on the type of intervention.

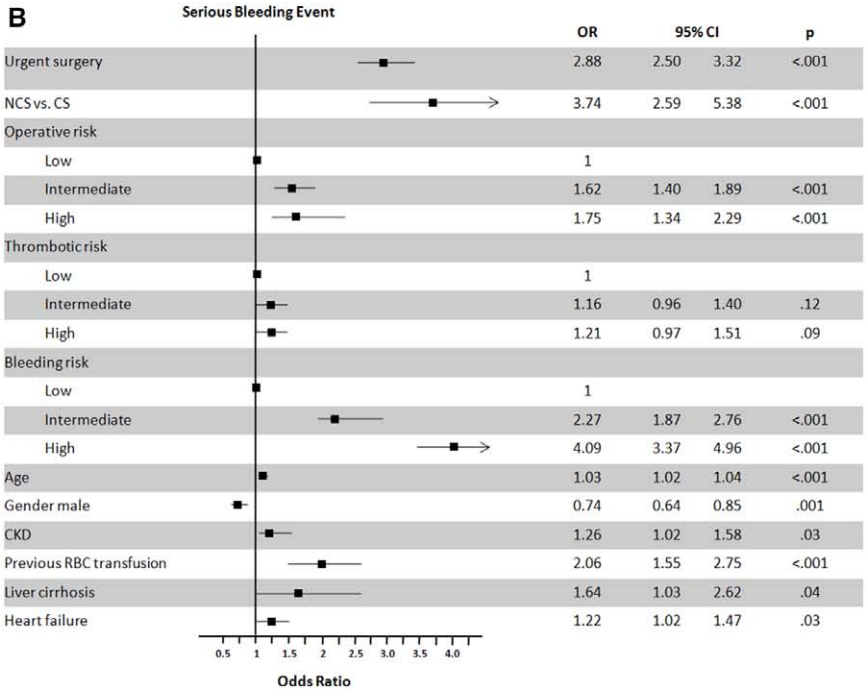
with coronary artery disease[8] and coronary stents.[21] On the other hand, previous studies suggested that continuation of antiplatelet therapy until surgery does not provide complete protection against ischemic events[22] and may actually increase bleedings,[23] especially for some types of procedures.[6]

Our study confirms that careful cardiovascular risk stratification, including assessment of intrinsic surgical cardiac risk, bleeding risk, and thrombotic risk associated with the stent, may be helpful in predicting the risk of periprocedural events and should always be adopted (Figure 3). Although there is a general agreement on surgical risk estimate for the principal surgical procedures,[3] a standardization of bleeding risk and ischemic risk associated with the type of stent implanted and the time elapsed from PCI is missing. For the purpose of this study, expert surgeons classified bleeding risk and their classification actually reflected the risk of SBEs (Figure 3B), with a more than double risk of SBE in patients at intermediate risk and a 4.09× higher risk in patients deemed at high risk. Considering the fact that SBEs were numerically higher than cardiac death and MI, a standardized bleeding classification of surgical procedures seems helpful, and interesting attempts in this direction are ongoing.[13]

In our study, thrombotic risk stratification on the basis of stent type (DES versus BMS) and time from PCI showed a good correlation with the incidence of cardiac death/MI within 30 days after surgery (Figure 3A). Patients with intermediate thrombotic risk exhibited a 50% higher risk of cardiac death and MI, and patients classified at high risk showed a risk of cardiac death/MI 2.17× higher than patients at low thrombotic risk. Two recent studies suggested that 6 months might be the earliest optimal time for surgery after DES implantation.[24,25] Our findings support guidelines' emphasis on stent type and surgical timing and raise the hypothesis that further risk stratification could be performed with differentiation between oDES and nDES (Figure 3C). Indeed beyond 1 year after implantation, there was no apparent difference between BMS and nDES (whereas for oDES, there was still an increased risk). Similarly, focusing on the interval between 6 and 12 months, the risk of cardiac death and MI seems significantly higher with oDES (OR=1.90), whereas it was comparable between BMS and nDES (and numerically lower than with BMS >12 months, a timing when restenosis could be detrimental for BMS). These observations are consistent with several reports of improved vessel healing and reduced stent thrombosis risk associated with new generation DES.[26] Remarkably, nDES was not associated with a significant increase of death and MI when surgery was performed within 6 months from PCI, whereas the risk for BMS (OR=2.00) and oDES (OR=2.10) was higher. A further analysis demonstrated that this potential advantage of nDES was gained between 2 and 6 months after stenting. Possible explanation for this apparent better safety of nDES even when surgery occurs early after PCI may be the thinner stent struts design and the presence of thromboresistant or bioabsorbable polymers. Further studies are necessary to better investigate these findings. In this scenario, it is worth mentioning that shorter duration of mandatory dual antiplatelet therapy after nDES has been approved in many countries and that the current attitude to prefer BMS in patients who are candidates for elective surgery could be challenged.

As previously mentioned, our study further highlight the need for dedicated pharmacological strategies aimed at minimizing both ischemic and bleeding risk in patients with coronary stents undergoing surgery. A bridging strategy using the short-acting glycoprotein IIb/IIIa inhibitor tirofiban has been proposed for patients at high risk for stent thrombosis undergoing urgent surgery.[27] Although initial results are promising, this strategy has important potential drawbacks, including excessive level of antiplatelet inhibition and slow return to baseline platelet function, and convincing evidence is still lacking. An attractive alternative is cangrelor, an intravenous antagonist of the Adenosine diphosphate $P2Y_{12}$ receptor characterized by rapid and reversible platelet inhibition and fast (<1 hour) offset of effect. In a randomized trial, among patients undergoing CS who discontinued thienopyridine therapy, cangrelor was





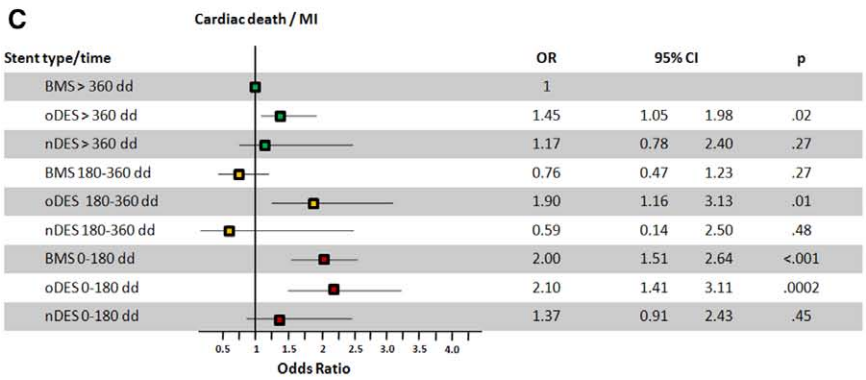


Figure 3. Independent predictors of cardiac death/myocardial infarction (MI) and serious bleeding event (SBE) within 30 days after surgery. **A**, Cardiac death/MI; c=0.84, Hosmer and Lemeshow goodness-of-fit test *P*=0.88. **B**, Serious bleeding events; c=0.77, Hosmer and Lemeshow goodness-of-fit test *P*=0.18. **C**, Impact of stent type and timing of surgery in relationship with percutaneous coronary intervention (PCI); c=0.84, Hosmer and Lemeshow goodness-of-fit test *P*=0.69. ACS indicates acute coronary syndrome; BMS, bare-metal stents; CI, confidence interval; CKD, chronic kidney disease; CS, cardiac surgery; NCS, noncardiac surgery; nDES, new-generation drug-eluting stent; oDES, old-generation drug-eluting stent; OR, odds ratio; and RBC, red blood cells.

shown superior to placebo in maintenance of platelet inhibition throughout the periprocedural phase, without increasing major bleedings.[28] Clinical efficacy of this strategy in patients undergoing CS and NCS must be confirmed in larger studies.

This study presents several limitations because of its retrospective nature. Most importantly, we did not have information on pharmacological treatment at the time of surgery and in patients with adverse events, so our study must be viewed as a picture of current situation assuming that physicians did their best to minimize the risk of perioperative adverse events. Adverse events occurring in patients scheduled to undergo surgery while preparing for surgery (ie, while stopping DAPT) were not captured unless the patient was already hospitalized, thus possibly underestimating the ischemic risk. Some of the findings about different stent types might have been influenced by different pharmacological choices rather than the stent type itself. Although our analysis took into account a large number of surgical procedures, outpatient surgery and invasive diagnostic procedures were not captured. These procedures are associated with a low risk of major complications and in most of the cases can be performed while patients receive DAPT or delayed until DAPT is no longer necessary, but they are not infrequently the cause of premature antiplatelet discontinuation. Finally, use of DES was generally low, reflecting average use in our catheterization laboratories during the study period. However, the general validity of our findings should not be influenced by this premise, being the absolute number of patients enrolled and surgical procedures considered high enough to allow reliable multivariable analyses. Yet, the number of patients treated with nDES in relationship with other subgroups is small, and this expose to a sizable risk of type II error. Hence, our findings about nDES can only be viewed as hypothesis generating.

Conclusions

Surgery is frequent in patients with coronary stents and poses important problems for perioperative management. Stratification of thrombotic and bleeding risk may help decision-making for the most appropriate perioperative management. nDES seem safer than oDES when surgery is performed <1 year after PCI and at least as safe as BMS at any time point.

Disclosures

Dr Saia reports receiving consulting fees from Abbott Vascular, Eli Lilly, Astra Zeneca, and St Jude Medical and speaker's fees from Abbott Vascular, Eli Lilly, Astra Zeneca, St Jude Medical, Terumo, Biosensors, Edwards, and Boston Scientific; Drs Musumeci and Rossini received speaker's fees from St Jude, Astra Zeneca, The Medicines Company, and Lilly-Daichii and received consulting fees from Lilly-Daichii, Astra Zeneca, and the Medicines Company.

References

1. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN; American College of Cardiology; American Heart Association. 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–e137. doi: 10.1016/j.jacc.2014.07.944.
2. Authors/Task Force members; Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541–2619. doi: 10.1093/eurheartj/ehu278.
3. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C; Authors/Task Force Members. 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;35:2383–2431. doi: 10.1093/eurheartj/ehu282.
4. Cruden NL, Harding SA, Flapan AD, Graham C, Wild SH, Slack R, Pell JP, Newby DE; Scottish Coronary Revascularisation Register Steering Committee. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ Cardiovasc Interv*. 2010;3:236–242. doi: 10.1161/CIRCINTERVENTIONS.109.934703.
5. Kałuza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol*. 2000;35:1288–1294.
6. Savonitto S, Caracciolo M, Cattaneo M, DE Servi S. Management of patients with recently implanted coronary stents on dual antiplatelet therapy who need to undergo major surgery. *J Thromb Haemost*. 2011;9:2133–2142. doi: 10.1111/j.1538-7836.2011.04456.x.
7. Ferreira-González I, Marsal JR, Ribera A, Permanyer-Miralda G, García-Del Blanco B, Martí G, Cascant P, Masotti-Centol M, Carrillo X, Mauri J, Batalla N, Larrousse E, Martín E, Serra A, Rumoroso JR, Ruiz-Salmerón R, de la Torre JM, Cequier A, Gómez-Hospital JA, Alfonso F, Martín-Yuste V, Sabatè M, García-Dorado D. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. *J Am Coll Cardiol*. 2012;60:1333–1339. doi: 10.1016/j.jacc.2012.04.057.
8. Burger W, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention - cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation - review and meta-analysis. *J Intern Med*. 2005;257:399–414. doi: 10.1111/j.1365-2796.2005.01477.x.
9. Campo G, Saia F, Guastaroba P, Marchesini J, Varani E, Manari A, Ottani F, Tondi S, De Palma R, Marzocchi A. Prognostic impact of hospital readmissions after primary percutaneous coronary intervention. *Arch Intern Med*. 2011;171:1948–1949. doi: 10.1001/archinternmed.2011.536.
10. Marzocchi A, Saia F, Piovaccari G, Manari A, Aurier E, Benassi A, Cremonesi A, Percoco G, Varani E, Magnavacchi P, Guastaroba P, Grilli R, Maresta A. Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation*. 2007;115:3181–3188. doi: 10.1161/CIRCULATIONAHA.106.667592.
11. Saia F, Piovaccari G, Manari A, Guastaroba P, Vignali L, Varani E, Santarelli A, Benassi A, Liso A, Campo G, Tondi S, Tarantino F, De Palma R, Marzocchi A. Patient selection to enhance the long-term benefit of first generation drug-eluting stents for coronary revascularisation procedures. Insights from a large multicentre registry. *EuroIntervention*. 2009;5:57–66.
12. Saia F, Piovaccari G, Manari A, Santarelli A, Benassi A, Aurier E, Sangiorgio P, Tarantino F, Geraci G, Vecchi G, Guastaroba P, Grilli R, Marzocchi A. Clinical outcomes for sirolimus-eluting stents and polymer-coated paclitaxel-eluting stents in daily practice: results from a large multicenter registry. *J Am Coll Cardiol*. 2006;48:1312–1318. doi: 10.1016/j.jacc.2006.03.063.
13. Rossini R, Musumeci G, Visconti LO, Bramucci E, Castiglioni B, De Servi S, Lettieri C, Lettino M, Piccaluga E, Savonitto S, Trabattoni D, Capodanno D, Buffoli F, Parolari A, Dionigi G, Boni L, Biglioli F, Valdatta L, Droghetti A, Bozzani A, Setacci C, Ravelli P, Crescini C, Staurenghi G, Scarone P, Francetti L, D'Angelo F, Gadda F, Comel A, Salvi L, Lorini L, Antonelli M, Bovenzi F, Cremonesi A, Angiolillo DJ, Guagliumi G; Italian Society of Invasive Cardiology (SICI-GISE); Italian Association

of Hospital Cardiologists (ANMCO); Italian Society for Cardiac Surgery (SICCH); Italian Society of Vascular and Endovascular Surgery (SICVE); Italian Association of Hospital Surgeons (ACOI); Italian Society of Surgery (SIC); Italian Society of Anaesthesia and Intensive Care Medicine (SIAARTI); Lombard Society of Surgery (SLC); Italian Society of Maxillofacial Surgery (SICMF); Italian Society of Reconstructive Plastic Surgery and Aesthetics (SICPRE); Italian Society of Thoracic Surgeons (SICT); Italian Society of Urology (SIU); Italian Society of Orthopaedics and Traumatology (SIOT); Italian Society of Periodontology (SIdP); Italian Federation of Scientific Societies of Digestive System Diseases Lombardia (FISMAD); Association of Obstetricians Gynaecologists Italian Hospital Lombardia (AOGOI); Society of Ophthalmology Lombardia (SOL). Perioperative management of antiplatelet therapy in patients with coronary stents undergoing cardiac and non-cardiac surgery: a consensus document from Italian cardiological, surgical and anaesthesiological societies. *EuroIntervention*. 2014;10:38–46. doi: 10.4244/EIJV10I1A8.

14. Ducrocq G, Wallace JS, Baron G, Ravaud P, Alberts MJ, Wilson PW, Ohman EM, Brennan DM, D'Agostino RB, Bhatt DL, Steg PG; REACH Investigators. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. *Eur Heart J*. 2010;31:1257–1265. doi: 10.1093/eurheartj/ehq021.
15. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.
16. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol*. 2005;162:1016–1023. doi: 10.1093/aje/kwi307.
17. Berger PB, Kleiman NS, Pencina MJ, Hsieh WH, Steinhubl SR, Jeremias A, Sonel A, Browne K, Barseness G, Cohen DJ; 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;3:920–927. doi: 10.1016/j.jcin.2010.03.021.
18. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery–a prospective outcome study. *Br J Anaesth*. 2006;96:686–693. doi: 10.1093/bja/ael083.
19. Hawn MT, Graham LA, Richman JR, Itani KM, Plomondon ME, Altom LK, Henderson WG, Bryson CL, Maddox TM. The incidence and timing of noncardiac surgery after cardiac stent implantation. *J Am Coll Surg*. 2012;214:658–666; discussion 666. doi: 10.1016/j.jamcollsurg.2011.12.011.
20. Anwaruddin S, Askari AT, Saudye H, Batizy L, Houghtaling PL, Alamoudi M, Militello M, Muhammad K, Kapadia S, Ellis SG. Characterization of post-operative risk associated with prior drug-eluting stent use. *JACC Cardiovasc Interv*. 2009;2:542–549. doi: 10.1016/j.jcin.2009.03.014.
21. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol*. 2005;45:456–459. doi: 10.1016/j.jacc.2004.11.041.
22. van Kuijk JP, Flu WJ, Schouten O, Hoeks SE, Schenkeveld L, de Jaegere PP, Bax JJ, van Domburg RT, Serruys PW, Poldermans D. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am J Cardiol*. 2009;104:1229–1234. doi: 10.1016/j.amjcard.2009.06.038.
23. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370:1494–1503. doi: 10.1056/NEJMoa1401105.
24. 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;310:1462–1472. doi: 10.1001/jama.2013.278787.
25. Wijeysundera DN, Wijeysundera HC, Yun L, Wąsowicz M, Beattie WS, Velianou JL, Ko DT. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation*. 2012;126:1355–1362. doi: 10.1161/CIRCULATIONAHA.112.102715.
26. Vignali L, Saia F, Belotti LM, Solinas E, Guastaroba P, Rubboli A, Manari A, Mehran R, Ardissino D, De Palma R. New-generation drug-eluting stents reduce stent thrombosis and myocardial infarction: a propensity-score-adjusted analysis from the multicenter REAL registry (REgistro Regionale AngiopLastiche Dell'Emilia-Romagna). *Catheter Cardiovasc Interv*. 2015;85:797–806. doi: 10.1002/ccd.25675.
27. Savonitto S, D'Urbano M, Caracciolo M, Barlocco F, Mariani G, Nichelatti M, Klugmann S, De Servi S. Urgent surgery in patients with a recently implanted coronary drug-eluting stent: a phase II study of 'bridging' antiplatelet therapy with tirofiban during temporary withdrawal of clopidogrel. *Br J Anaesth*. 2010;104:285–291. doi: 10.1093/bja/aep373.
28. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ; BRIDGE Investigators. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA*. 2012;307:265–274. doi: 10.1001/jama.2011.2002.