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The Risk of Adverse Cardiac and Bleeding Events Following Noncardiac Surgery Relative to Antiplatelet Therapy in Patients With Prior Percutaneous Coronary Intervention

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Noncardiac surgery (NCS) may be required within the first year after percutaneous coronary intervention (PCI) in approximately 4% of patients and is the second most common reason for premature discontinuation of antiplatelet therapy (APT),which may, in turn, increase the risk of perioperative ischemic events, particularly stent thrombosis. Its continuation may increase the risk of perioperative bleeding. We review current information on the incidence of these events, particularly related to APT, describe potentially useful strategies to minimize the risks of adverse outcomes, and provide recommendations on APT use. (J Am Coll Cardiol 2012;60: 2005–16) © 2012 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is the most common strategy for myocardial revascularization, with more than a million procedures performed annually in the United States alone (1). Enthusiasm has been tempered by the potentially lethal complication of stent thrombosis (ST) (2). The most important ST predictor is premature discontinuation of dual antiplatelet therapy (DAPT) (3,4). Apart from noncompliance, the second most common reason for early discontinuation of either DAPT or single antiplatelet therapy (APT) is the need for noncardiac surgery (NCS), accounting for one-third of cases (4).

In both retrospective (5) and prospective (6) studies, approximately 4% of patients undergo NCS within the first year after index PCI (approximately 40,000 patients in the United States by current PCI usage). This large cohort presents a challenge for the treating surgeon, anesthesiologist, and cardiologist in managing APT in the perioperative period. On the basis of current American College of Cardiology/American Heart Association guidelines, approximately two-thirds of all NCS procedures in the first year after index PCI are classified as moderate to high risk for major adverse cardiac events (MACE) (5–7). Surgical stress creates a prothrombotic state due to increased platelet activation and decreased fibrinolysis, explaining in part the well-described MACE increase in the perioperative period (8–10).

The small, but persistent, ST risk long after PCI raises the important issue of perioperative management. On the one hand, MACE, particularly ST, is a concern after APT discontinuation; with its continuation, bleeding looms as a persistent danger. In this paper, we review studies of NCS outcomes following PCI with either bare-metal stents (BMS) or drug-eluting stents (DES), particularly in relation to APT, and potential strategies to decrease these risks.

Methods

We performed a PubMed search for full-length articles published within the last 10 years in the English language (abstracts were excluded) with the following key terms: "noncardiac surgery, coronary stent" and "noncardiac surgery, percutaneous coronary intervention." We identified 6 studies with BMS (11–16), 13 with DES (6,17–28), and 6 with both BMS and DES (5,29–33). In 1 study of 103 patients (34), stent type (BMS vs. DES) was unavailable in 75% of patients; we excluded this study except to discuss it relative to anticoagulation strategies. Another paper was excluded because the myocardial infarction (MI) endpoint, although well defined, was not clearly presented (23). We reviewed each study for definitions and incidence of MACE and bleeding, APT status, and factors associated with adverse outcomes. We also performed an extensive English literature search for strategies to prevent MACE. In this presentation, the ischemic risk of surgery was defined as "low,"

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Abbreviations and Acronyms

APT = antiplatelet therapy
ASA = aspirin
BA = balloon angioplasty
BMS = bare-metal stent(s)
DAPT = dual antiplatelet therapy
DES = drug-eluting stent(s)
LMWH = low-molecular-weight heparin
MACE = major adverse cardiac event(s)
MI = myocardial infarction
NCS = noncardiac surgery
PCI = percutaneous coronary intervention
ST = stent thrombosis

"intermediate," or "high," using the American College of Cardiology/American Heart Association guidelines (7).

Current guidelines for management of patients undergoing NCS after PCI. The 2009 American College of Cardiology/American Heart Association and 2010 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines provide a framework for APT management in the perioperative period following PCI (7,35). Given the lack of prospective randomized clinical trials, recommendations are based primarily on expert opinion and relatively small, and mostly retrospective, studies.

Four important variables cited in decision making regarding APT use in the perioperative period include urgency of surgery, PCI type (balloon angioplasty [BA] vs. stenting), stent type (DES vs. BMS), and the duration between PCI and NCS.

Guidelines recommend that elective surgery be postponed for at least 2 weeks after BA, 1 month after BMS, and 1 year after DES. The rationale relates to the time frame for vascular healing and re-endothelialization in animal studies (36). Current guidelines recommend that aspirin (ASA) (81 to 325 mg/day) be continued through the perioperative period if the risk of surgical bleeding is not prohibitive. The decision regarding APT continuation with urgent or emergent surgery is governed by the relative risks of bleeding versus ST in an individual patient. This consideration is reflected in the 2010 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines, where a "case by case" approach is suggested (35).

Limitations of current guidelines and studies. Most published studies are retrospective, single center, and/or with small sample size, limiting generalizability of the results (Table 1). In addition, definition of adverse events, both cardiac and bleeding, details of perioperative APT, and duration of post-operative monitoring vary, making comparisons among studies difficult. Thus, the reader must take these caveats into consideration in drawing conclusions about the risks and efficacy of APT in PCI patients undergoing NCS. In addition, current guidelines provide APT recommendations for only the first year after PCI. The small, but persistent, MACE risk including ST beyond the first year is not addressed. Finally, it should be mentioned that MACE definitions vary in each study; thus, the reader should refer to Tables 2 to 4 to determine what constitutes MACE in each study.

Table 1 Limitations of Current Studies

First Author (Ref. #)	Year	Small Sample Size (N < 100)	Retrospective	APT Status Not Well Defined	MACE Not Well Defined	Bleeding Endpoints Not Well Defined	Single Center	Questionnaire-Based Study
Kaluza et al. (11)	2000	+	+	+			+	
Wilson et al. (12)	2003		+				+	
Sharma et al. (13)	2004	+	+	+			+	
Reddy et al. (14)	2005	+	+	+			+	
Brichon et al. (15)	2006	+	+					
Kim et al. (29)	2008		+	+		+	+	
Nuttal et al. (16)	2008		+	+			+	
Compton et al. (17)	2006	+	+	+			+	
Brotman et al. (18)	2006		+				+	
Conroy et al. (19)	2007	+	+	+	+	+	+	
Schouten et al. (30)	2007	+	+	+		+	+	
Rhee et al. (20)	2008		+			+	+	
Godet et al. (21)	2008	+		+		+	+	
Rabbitts et al. (22)	2008		+	+			+	
Anwaruddin et al. (25)	2009		+			+	+	
Assali et al. (26)	2009	+	+				+	
Van Kuijk et al. (31)	2009		+	+				
Choi et al. (23)	2010	+	+		+		+	
Chia et al. (24)	2010		+			+		+
Berger et al. (6)	2010			+		+		
Gandhi et al. (27)	2010		+	+			+	
Cruden et al. (5)	2010		+	+		+		
Brilakis et al. (28)	2011		+	+		+		
Albaladejo et al. (32)	2011			+				
Brancati et al. (33)	2011		+				+	

+ = limitation present; APT = antiplatelet therapy; MACE = major adverse cardiac event(s); pts= patients.

Table 2 NCS Following PCI With BMS

First Author (Ref. #)	Year	N	Type of Surgery (%) L	I	H	C	U	PCI to NCS (days)	MACE Component	MACE (%)	APT in Periop Period (%) ASA	$P2Y_{12}$ Inh	DAPT	Major Bleeding Component	(%)	Comments
Kaluza et al. (11)	2000	40		33	65	2		13	D	20	5	12.5	2.5	Tx or reop	27	1. All MACE <2 weeks after PCI
									MI	17.5						2. ST presumed to be cause of all MI
Wilson et al. (12)	2003	207		36	58		6	1–60	D, MI, ST, or Revasc	4	51	14	26	"Excessive" surgical site bleed	2	
														Tx	33	
Sharma et al. (13)	2004	47		68	30		2	<21 (n = 27)	D or MI	25 (<21 days)	NA	74	NA	Tx	29	6 of 7 deaths in first 21 days considered probable ST
								21–90 (n = 20)		15 (21–90 days)		70		Reop	0	
Reddy et al. (14)	2005	56	10	60	20		10	<42	MI or CVD	14	79*	32*		Reop, Tx >2 PRBC, Hb drop >2 g/dl or IC, IO, or RP bleed	5	All 3 bleeding episodes were in patients receiving $P2Y_{12}$ inhibitor
Brichon et al. (15)	2006	32		100				<90	ST	9	66	0	0	Hemothorax or RP bleed	10	30% of patients received only heparin
Nuttal et al. (16)	2008	899	21	46	33			64	D, MI, ST, or TLR	Overall: 5.2 <30 days −10.5 30–90 days −3.8 90–365 days −2.8		64.5†		Need for non-PRBC Tx	5	

*Percentage of patients taking both ASA and $P2Y_{12}$ inhibitor not provided; †rates of individual or dual APT not provided.

ASA = aspirin; BMS = bare-metal stent(s); C = cardiac; CABG = coronary artery bypass grafting; cryo = cryoprecipitate; CT = clotting time; CVD = cardiovascular death; D = death; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); FFP = fresh frozen plasma; H = high; Hb = hemoglobin; I = intermediate; IC = intracranial; inh = inhibitor; IO = intraocular; L = low; MI = myocardial infarction; NA = not available; NCS = noncardiac surgery; PCI = percutaneous coronary intervention; periop= perioperative; plt = platelet; post-op = post-operative; PRBC = packed red blood cells; $P2Y_{12}$ inhibitor = thienopyridine; reop= reoperation; RP = retroperitoneal; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; Tx = transfusion; U = unknown.

Table 3 NCS Following PCI With DES

First Author (Ref. #)	Year	N (n)	Type of Surgery (%)					PCI to NCS (days)	MACE		APT in Periop Period (%)			Major Bleeding		Comments
			L	I	H	C	U		Component	(%)	ASA	$P2Y_{12}$ Inh	DAPT	Components	(%)	
Compton et al. (17)	2006	38 (59)	31	35	15		19	260	MI	0	83	40	*	Post-op Tx	3	
Brotman et al. (18)	2007	114	52	42	6			236	MI, ST, or D	1.8	1.8	0	21	Reop or IC or RP bleed	0.9	No ST despite low APT use
Conroy et al. (19)	2007	24 (42)						NA	Isch on ECG, trop elev, or ST	7	NA	50	NA	Surgical site bleed or reop	2.4	1 LST, 2 VLST (clopidogrel was held in all)
Rhee et al. (20)	2008	141		96		4		228	ST	5	5	0	0	NA	NA	>7 days of $P2Y_{12}$ inhibitor discontinuation was associated with ST
Godet et al. (21)	2008	96		26	74			425	Trop elev	12	70	38	NA	NA	NA	26% of pts received LMWH in periop period
									ST	2						
Rabbitts et al. (22)	2008	520	18	56	25			204	D, MI, ST, or revasc	5.4	70	33	*	Surgical site	1	
		<1 yr = 400								<1 yr = 6				"excessive bleed"		
		>1 yr = 12,0								>1 yr = 3.3						
Chia et al. (24)	2010	710						348	MI or ST	1.5	14	9	18	NA	NA	
Anwaruddin et al. (25)	2009	481 (606)	5.6	55.6	20	22		390	1^0–ST (def + mod prob)	2	15	1	21	NA	NA	Risk of MACE higher if NCS <30 days after PCI
									2^0–D, nonfatal MI, ST							
										9						
Assali et al. (26)	2009	78		81	19			414	MI, ST, or CD	7.7	18	42	21	Hb drop >2 g/dl	16.7	1) No difference in MACE between 6–12 vs. >12 months 2) Most MACE occurred <1 week after NCS
Berger et al. (6)	2010	206		76	20		4	179	CD, MI, or DST	1.9	NA	NA	NA	NA	NA	
Gandhi et al. (27)	2011	135 (191)	23	62	15			547	DST	0.5	54	30	NA	Bleeding with hypotension, blood loss >500 ml or >2 U PRBC Tx	6	APT was not associated with bleeding complications
									MI	2						
Brilakis et al. (28)	2011	164	100					<365	D, MI, or ST	0.6	NA	NA	NA	NA	NA	

N (n) indicates the number of subjects (the number of noncardiac surgeries). *Percentage of patients taking both ASA and $P2Y_{12}$ not provided.

def = definite; DST = definite stent thrombosis; Isch = ischemia; IV = intravenous; L = low; LMWH = low-molecular -weight heparin; LST = late stent thrombosis; mod prob = modified probable; revasc = revascularization; trop elev = troponin elevation; VLST= very late stent thrombosis; 1^0 = primary; 2^0 = secondary; other abbreviations as in Tables 1 and 2.

Table 4 NCS Following PCI With Either BMS or DES

First Author (Ref. #)	Year	n		Type of Surgery (%)				PCI to NCS (days)	MACE			APT in Periop Period (%)			Major Bleeding		Comments
										(%)							
		BMS	DES	L	I	H	U		Component	BMS	DES	ASA	I	DAPT	Component	(%)	
Kim et al. (29)	2008	101	138					NA	CD, ST, or MI	0	2.2	NA	NA	NA	NA	NA	Higher prevalence of comorbidities in DES group
Schouten et al. (30)	2007	93	99	12	60	23	5	<730	MI or CD	2	3	53 (either single or dual APT)			NA	NA	APT interruption was associated with higher MACE (5.5% vs. 0.0%, p = 0.023) No difference in MACE between BMS and DES
Van Kuijk et al. (31)	2009	174	376	33	51	15		BMS 1,314	D, MI, ST, or revasc	6	13	91*		9**	Severe= fatal, IC, reop, or Tx of >4 units	10 (severe)	Bleeding complications significantly higher with DAPT in both groups
				31	47	22		DES 511				70*		30**	Moderate = Tx of 1–3 units	8 (mod)	Early NCS in either group was associated with MACE (overall p < 0.001) BMS < 30 days = 50% 30–90 days = 14%, and >90 days = 4% DES <30 days = 35%, 30–90 days = 13%, 90–180 days = 15%, 180–365 days = 6% and >365 days = 9%
Cruden et al. (5)	2010	1,383	570	19	71	10		BMS 503	1^{o}–in-hospital D + ischemic cardiac events	1^{o}–13.3	1^{o}–14.6	NA	NA	NA	NA	NA	No significant difference between BMS and DES
								DES 371	2^{o}–In-hospital D + MI	2^{o}–1.3	2^{o}–1.9						MACE higher if NCS <6 weeks vs >6 weeks after PCI (42.4% vs. 12.8%, p < 0.001)
Albaladejo et al. (32)	2011	623	367	20	40	26	14	II	MI, ST, HF, CS, SA, or stroke	10.9†		NA	NA	NA	Major= fatal, >2 unit Tx, >2 g/dl fall in Hb, IC, IO, IS, Pe, RP, or need for reop Minor = Abnormal bleeding as defined by surgeon or physician and not meeting criteria for major bleeding	9.5‡	Unknown stent type in 12.7%
Brancati et al. (33)	2011	70	31	26	65	9	0	288	D, MI, ST, or revasc	6	6	47* 19*		36 68	Need for Tx or surgical hemostasis	BMS 14 DES 6	

*Single APT either ASA or clopidogrel; **dual APT; †individual MACE rates not provided; ‡includes both major and minor bleed; §In 82.2% of individuals, interval between PCI and NCS was >1 year (median interval is not provided).
Abbreviations as in Table 2.

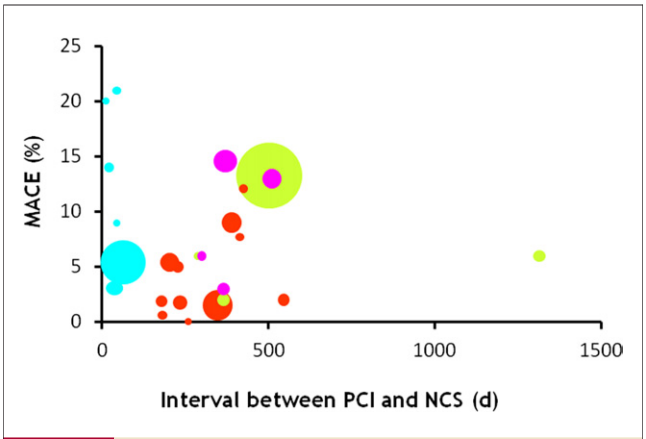

Figure 1 **The Incidence of MACE in Published Series**

The reader should refer to Tables 2 to 4 for major adverse clinical events (MACE) definition for each study. The time interval in days (d) between percutaneous coronary intervention (PCI) and noncardiac surgery (NCS) represents either the mean or median time after NCS or the mid-point of the time range as described in the individual study. The circle size approximates the study sample size. Small modifications in circle size were made to allow graphical representation. The exact sample sizes are described in Tables 2 to 4. The colors of the circles represent the following: **aqua** = studies with bare-metal stents (BMS) only; **red** = studies with drug-eluting stents (DES) only; **lime** = BMS patients in studies with both BMS and DES stents; and **pink** = DES patients in studies with both stent types.

Cardiac risks from NCS in patients with prior PCI. NCS FOLLOWING PCI WITH BMS. MACE following NCS with BMS was first reported by Kaluza et al. (11) who found a 17.5% (7 of 40) incidence of MI presumed to be secondary to ST. Total mortality (ischemic + bleeding) was 20%. All MACE occurred within the first 2 weeks after PCI. Subsequent studies provide evidence that the high-risk period for MACE may extend to 6 weeks, though the risk seems to be lower between 3 to 6 weeks as compared with the initial 2 weeks (12–14) (Fig. 1, Tables 2 to 5).

Nuttal et al. (16) in 899 patients showed an overall MACE rate of 5.2%. APT (single vs. dual not specified) was used perioperatively in 72% when the interval between PCI and NCS was <30 days and in approximately 60% >30 days. NCS within 1 month of PCI carried the highest MACE risk (10.5%). The risk between 30 and 90 days was 3.8%, with a persistent 2.8% risk between 90 and 360 days. Other risk factors included general anesthesia (odds ratio: 2.79, 95% confidence interval: 1.27 to 6.13, $p < 0.01$) and shock before the index PCI (odds ratio: 8.06, 95% confidence interval: 3.53 to 18.41, $p < 0.001$). A small study (32 patients) suggested that the high-risk period may extend to 3 months because 2 of 3 ST occurred >30 days after PCI (15).

There are case reports of very late ST, that is, >1 year from BMS implantation following NCS; the incidence of these events, however, and their relationship to APT use is uncertain (37–39).

NCS FOLLOWING PCI WITH DES. There is a wide variation in the reported MACE risk in DES patients (Fig. 1, Tables 3 and 5). Two early studies suggested it was low (<2%) (17,18). These studies were notable for a long interval between PCI and NCS (>6 months), frequent APT use in the perioperative period (17), and relatively low-risk NCS. Similarly, in a questionnaire-based study, a low MACE risk (1.5%) was reported (24).

Other studies, however, suggest a higher MACE rate. Rhee et al. (20) reported a 5% ST incidence following NCS within 1 year of PCI. In this series, all oral APT agents were withheld. Assali et al. (26) identified a 7.7% MACE risk following NCS at least 6 months after PCI despite continuation of single or dual APT in approximately 80% of cases.

The incidence of late ST (31 to 365 days after implantation) in real-world practice in non-NCS patients is approximately 0.6% (40). A prospective registry reported 2% incidence of ST following NCS (21). In a single-center retrospective study (N = 520), MACE was 5.4% within the first year of PCI and 3.3% thereafter (22). There was no significant MACE difference whether NCS was performed <90, 90 to 180, 181 to 360, or >365 days from PCI. There was a significant univariate association between MACE and advanced age, emergent surgery, shock at index PCI, and thienopyridine use in the perioperative period. However, thienopyridine use was not associated with MACE after adjustment for emergency surgery. ASA was used within 7 days of NCS in 70% of cases and thienopyridine in 33%, whereas DAPT usage was not reported.

In another relatively large retrospective study (481 patients, 606 procedures), the risk of definite and probable ST with an average delay between PCI and surgery of about a year was 2% (25). ST risk was 6% if NCS was performed within 1 month of PCI and 1.5% thereafter ($p = 0.04$). Other ST predictors were NCS being emergent, previous MI, pre-operative heparin use, and longer stent length. ASA and/or clopidogrel in the perioperative period was not associated with either improved or worsened MACE risk.

In a prospective registry of 206 patients, MACE was 1.9% (6). However, the incidence was 27 times higher if NCS was performed <1 week of index PCI as compared with any time period thereafter. A history of heart failure and serum creatinine >2.0 mg/dl also predicted MACE. In the same registry, MACE associated with minor NCS (defined as surgery without a large surgical incision) <1 year after DES was very low, with only 1 ST case in the first week following NCS among 164 subjects (28). APT status was not described.

NCS beyond 1 year of index PCI may have a lower MACE risk. A study of 135 DES patients undergoing 191 NCS procedures with an average delay of 18 months had a low MACE rate (ST: 0.5%, MI: 2%) (27). ASA was continued during the perioperative period in 54% and clopidogrel in 30%. It was stated that there was no MACE difference between patients who received clopidogrel versus who did not, but the DAPT rates in the perioperative period were not reported. Of all reported complications (ischemic + bleeding), 74% occurred within the first 3 days

Table 5 Incidence of ST After NCS

Thrombosis	First Author (Ref. #)	Patients	N	Definition of ST	Incidence ST (%)
Bare-metal stent					
	Kaluza et al. (11)	40	7	ARC def (2) or prob (5)	17.5
	Wilson et al. (12)	207	4	ND	1.93
	Sharma et al. (13)	47	7	ND	14.8
	Reddy et al. (14)	56	5	ARC def	8.9
	Brichon et al. (15)	32	3	ARC def	9.0
	Nuttal et al. (16)	899	9	ARC def	1.0
	Kim et al. (29)	101	0	0	0.0
	Schouten et al. (30)	93	2	ARC def	2.1
	Van Kuijk et al. (31)	174	0	ND	0.0
	Brancati et al. (33)	71	4	ARC prob	5.63
	Total	1,586	41	ARC ST: def 21; prob 9; U 11	2.58*
Drug-eluting stent					
	Compton et al. (17)	59	0	ND	0.0
	Brotman et al. (18)	114	0	ARC def	0.0
	Conroy et al. (19)	43	3	ARC def	6.97
	Rhee et al. (20)	141	7	ARC def/prob/poss*	5.0
	Godet et al. (21)	96	2	ARC def	2.0
	Rabbitts et al. (22)	520	4	ARC def	0.76
	Chia et al. (24)	710	3	ARC def	0.42
	Anwaruddin et al. (25)	606	11	ARC def (4) or prob (7)	2.0
	Assali et al. (26)	78	2	ND	2.8
	Berger et al. (6)	206	0	ARC def	0.0
	Gandhi et al. (27)	191	1	ARC def	0.52
	Brilakis et al. (28)	164	1	ND	0.6
	Kim et al. (29)	138	3	ARC def (2) or prob (1)	2.17
	Schouten et al. (30)	99	2	ARC def	2.02
	Van Kuijk et al. (31)	376	6	ND	1.59
	Brancati et al. (33)	30	2	ARC def	6.6
	Total	3,571	47	ARC ST: def 23; prob 8 U 16	1.31*

Academic Research Consortium (ARC) definition of definite (def), probable (prob), or possible (poss); n = number of stent thrombosis events; ND indicates ST not prospectively defined in the *Methods*. Please note that many studies did not prospectively define ST by using ARC criteria; case descriptions were classified by the authors into 1 of the categories. If coronary angiography was required for ST, this event was defined as "ARC def." The number in parenthesis is the number of patients in each ARC category of that study. *The results of this study did not allow for clarification of the ARC category.

Abbreviations as in Table 2.

following NCS, highlighting the first post-operative week as carrying the highest MACE risk.

Individual very late ST cases with DES after NCS have been described, but the incidence is uncertain (19,21,25,41–43).

NCS FOLLOWING PCI WITH EITHER BMS OR DES. The relative MACE incidence with BMS and DES following NCS has been compared in a few studies (Tables 4 and 5). Cruden et al. (5) compared BMS (n = 1,383) with DES (n = 570), with a median interval between PCI and NCS >1 year. APT use was not reported. MACE frequency was 13.3% for BMS and 14.6% with DES (p = 0.3). High MACE rates in this study likely reflected broad endpoint criteria (primary endpoint: in-hospital death or ischemic cardiac event, ICD-10 (International Classification of Diseases-10) codes 120.0, 120.1, 120.8–121.4, 121.9–122.1, 122.8, 122.9, 124.0, and 124.9–125.1; secondary endpoint: in-hospital death and MI, codes 121.0–121.4, 121.9–122.1, 122.8, and 122.9). Similar, but smaller, studies have also failed to link MACE risk to stent type (30,33). By contrast, a relatively small study (BMS = 101, DES = 138) identified higher MACE with DES (2.2%) versus BMS (0%) (29), probably reflecting higher baseline comorbidity in the DES cohort (increased prevalence of hypertension and diabetes mellitus, longer stent length, and multivessel intervention) (29). In these studies, a short period (<4 to 6 weeks) between PCI and NCS was associated with higher MACE regardless of stent type (31,33).

In a prospective multicenter observational study of 1,134 NCS procedures (82% performed >1 year after PCI), MACE risk was 10.9% (32). This study did not report complications by stent type. A multivariate analysis did identify complete APT interruption >5 days prior to NCS as well as creatinine clearance <30 ml/min, pre-operative hemoglobin <10 g/dl, and urgent and high-risk surgery as significant predictors for MACE.

Table 5 lists the incidence of ST in studies in which it was specifically stated. The apparently lower DES ST rate may reflect a lack of studies during the very-high-risk period as compared with BMS studies, where many were performed during this time, as seen in Figure 1.

NCS following BA. BA is rarely used as an isolated procedure. However, it may have some utility as a "holding"

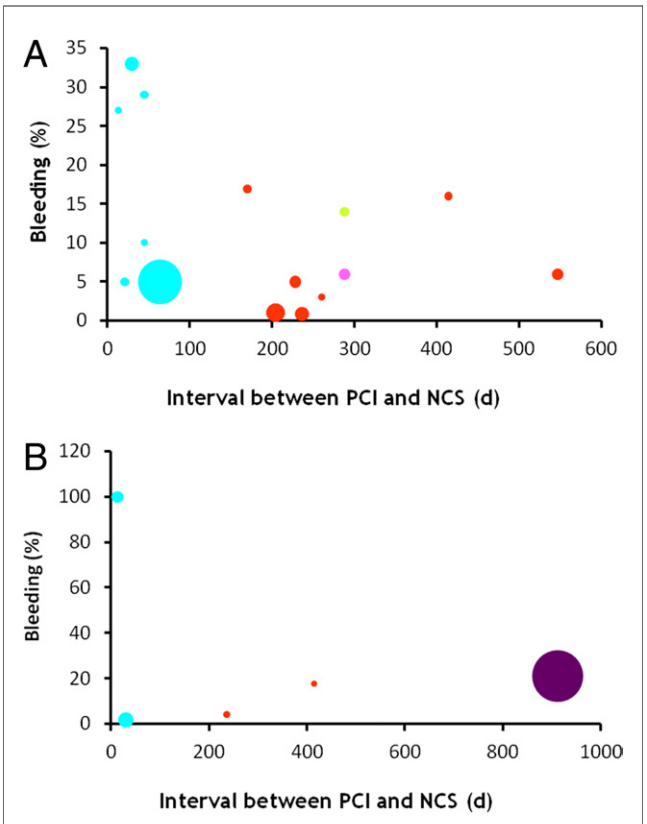

Figure 2 The Incidence of Bleeding Events

(A) The incidence of bleeding events and **(B)** the incidence of bleeding limited to dual antiplatelet therapy (DAPT) in published series. The colors are as in Figure 1 except **purple (B)** are studies with both BMS and DES. Abbreviations as in Figure 1.

procedure for NCS in certain circumstances. In a retrospective study of 350 patients undergoing NCS <2 months of BA, Brilakis et al. (44) reported 3 adverse events (0.9%) including one death and 2 MI. All events occurred among the 188 patients undergoing NCS within 2 weeks of BA. Aspirin was used in 78% and thienopyridine in 4%. Leibowitz et al. (45) comparing BA (n = 122) with stenting (n = 94) did not identify any significant difference in MACE risk regardless of NCS timing (<2 or >2 weeks). MI incidence was 6% in the BA group. It should be noted that the relatively high MI rate may have been related to the fact that MACE incidence included events up to 6 months after NCS.

Risk of bleeding in the setting of NCS following PCI. It is intuitive that APT, particularly DAPT, continued in the perioperative period increases the bleeding risk, but the level of risk remains uncertain.

Results from multiple studies report a variable frequency of significant bleeding, in part due to different bleeding endpoint definitions. Timing of NCS following PCI has been variably associated with the bleeding risk with either single APT or DAPT (Figs. 2A and 2B, Tables 2 to 4 and 6). Though some studies (11,13) suggest higher bleeding risk if NCS is performed within 2 to 3 weeks of PCI, a large retrospective study (16) did not identify any significant association, although there was a trend toward a higher bleeding risk if NCS was <30 days of PCI (<30: 6.9%, 30 to 90: 4.6%, >90: 3.6%). In a prospective study of 103 stented patients, there were only 4 major bleeding episodes, defined as "unusually high post-operative blood loss as assessed by the surgeon" despite APT continuation (84% ASA, 44% clopidogrel) or discontinuation for <3 days, in addition to either the use of unfractionated or low-molecular-weight heparin (LMWH) (34). Other retrospective studies also have not identified a significant relationship between APT use and with the risk of perioperative bleeding (13,22).

There seems to be a higher bleeding risk with DAPT versus single APT, although very few studies, even retrospective ones, provide this comparison. Table 6 lists the incidence of bleeding in the perioperative period following NCS with the use of either single or dual APT. The mean bleeding risk from studies in which adequate information was available was 4.1% for single APT versus 14.7% for DAPT, driven in large part by the study of Van Kuijk et al. (31). They reported significant bleeding in 21% of DAPT and 4% of single APT patients ($p \leq 0.001$). These results differ from the expected 1% increase in bleeding risk with DAPT (vs. ASA alone) in the nonsurgical setting (46).

That being said, DAPT may have an acceptable bleeding risk if future data provide evidence that there is a MACE decrease compared with DAPT discontinuation preoperatively. At least 1 surgical series suggests that DAPT may be used with an acceptable bleeding risk. In 108 non-PCI patients (47), the bleeding risk with limb ischemia surgery in patients maintained on 75 mg of aspirin in the perioperative period and then randomly assigned to either clopidogrel or matched placebo was evaluated. There was no

Table 6 Incidence of Bleeding on Single APT or DPT After NCS

First Author (Ref. #)	Patient on DAPT at Time of NCS	DAPT Patients With Bleeding	DAPT Patients With Bleeding (%)	Patients on Single APT at Time of NCS	Single APT Patients With Bleeding	Single APT Patients With Bleeding (%)
Kaluza et al. (11)	1	1	100.00	—	—	—
Wilson et al. (12)	54	1	1.85	134	1	0.7
Brotman et al. (18)	24	1	4.00	2	0	0.0
Assali et al. (26)	17	3	17.60	47	7	15.0
Van Kuijk et al. (31)	128	27	21.00	421	17	4.0
Total	224	33	14.70	604	25	4.1

Abbreviations as in Tables 1 and 2.

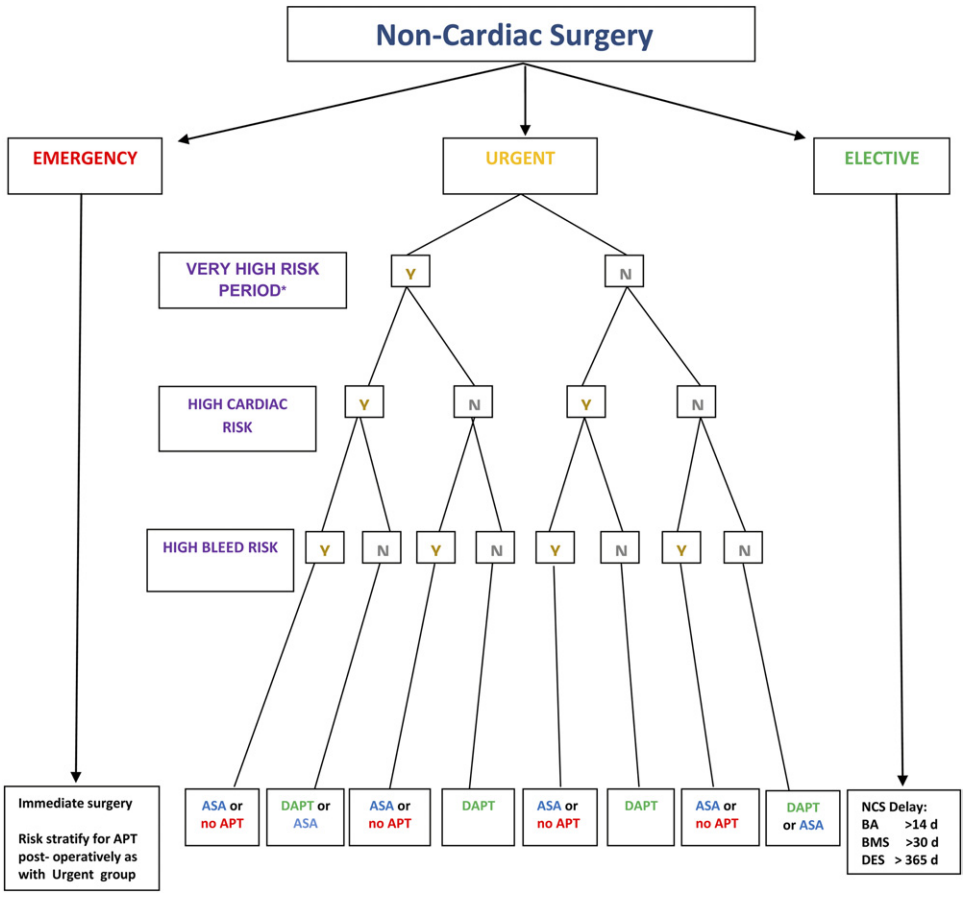

Figure 3 A Guide to APT in the Perioperative Period

The illustration uses a "case-by-case" approach. *High-risk period is <4 weeks after stent implantation. APT = antiplatelet therapy; ASA = aspirin; BA = balloon angioplasty; N = no; Y = yes; other abbreviations as in Figures 1 and 2.

increase in major bleeding, but the transfusion requirement was increased with DAPT (28%) versus ASA alone (12.6%) ($p = 0.037$). Though this study does not specifically address patients with previous PCI undergoing NCS, it does provide evidence that DAPT may not increase major bleeding even in patients undergoing high-risk surgery.

Given the lack of large randomized studies, current guidelines recommend a case-by-case approach, weighing MACE versus bleeding risk (7,35).

Strategies to reduce adverse cardiac ischemic complications in stented patients following NCS. Given the high frequency of NCS in the year after PCI and potential increase in MACE (including ST) with both DES and BMS, it has become imperative to develop better strategies to decrease the risk of stent-related MACE. Potential strategies include the following:

DAPT CONTINUATION IN THE PERIOPERATIVE PERIOD. DAPT continuation in the perioperative period is 1 strategy to prevent or reduce MACE. As previously noted, ASA is recommended by guidelines unless the bleeding risk is prohibitive. It should be noted that there have been conflicting data from previous studies whether DAPT continuation is actually effective in preventing ST and/or MACE (please see the preceding text). Current data suggest that minor bleeding and bleeding severe enough to warrant transfusion may be more frequent with DAPT, but major or life-threatening bleeds, depending on the bleeding definition, may not be more frequent. Therefore, adoption of DAPT as a "fallback" position for NCS in patients who have an "acceptable" pre-operative bleeding risk may improve cardiac outcomes. Further data are required to determine whether such a fallback position carries a favorable risk–benefit ratio.

We provide a suggested approach to APT use in Figure 3. It assumes that APT, and particularly DAPT, decrease MACE and ST and increase perioperative bleeding. The flow diagram is presented as a suggested approach for the clinician to individualize treatment in the absence of definitive data.

HEPARIN AND LMWH. ST prevention likely requires some degree of platelet inhibition. Thus, it remains unclear

whether DAPT cessation and anticoagulation therapy alone is a useful strategy. A 103-patient study (unknown stent type: 77%) undergoing NCS <1 year after PCI evaluated addition of either unfractionated or LMWH perioperatively in addition to continuation of some type of APT (ASA 85%, clopidogrel 44%) (34). Though the incidence of significant bleeding was low, the risk of overall adverse events was high (approximately 44%), likely due in part to the primary composite endpoint definition that included cardiac death, MI, revascularization (PCI or coronary artery bypass grafting), congestive heart failure, unstable angina, significant arrhythmias, biochemical evidence of myocardial necrosis, sepsis, surgical bleeding, and nonsurgically related bleeding. Given the paucity of data, the value of heparin or LMWH is uncertain, and further data are required.

INTRAVENOUS GLYCOPROTEIN IIB/IIIA THERAPY. DAPT discontinuation preoperatively and use of a short-acting intravenous APT in addition to ASA is another potential strategy. Savonitto et al. (48) used tirofiban in 30 DES patients undergoing urgent surgery <1 year after DES implantation. Clopidogrel was stopped 5 days preoperatively and tirofiban continued up to 4 h before surgery. There was no MACE and only 1 major bleeding episode. This study may have underestimated the bleeding risk because patients with high baseline bleeding risk were excluded. A similar protocol was tested in 36 DES patients (ASA continued in 80%) undergoing cardiac surgery (n = 15) or NCS (n = 21) (49). There was no MACE and 6 bleeding episodes (5 transfusions, 1 re-operation). Based on these small studies, a "bridging strategy" using short-acting intravenous APT may be an alternative to prevent MACE in high-risk patients, but further data are required.

Newer antiplatelet agents and NCS. The TIMI-38 (Thrombolysis In Myocardial Infarction 38) trial demonstrated that in acute coronary syndrome patients, prasugrel had a lower ST risk versus clopidogrel, whereas bleeding complications were more frequent (50). Although there are no studies of prasugrel in the NCS setting, the same considerations as with clopidogrel regarding bleeding complications are applicable. Because of its longer half-life, it is recommended to withhold prasugrel 7 days before surgery.

Ticagrelor is a reversible $P2Y_{12}$ inhibitor that has been shown to compare favorably with clopidogrel in terms of both efficacy and safety (51). This agent may be useful during NCS because it is reversible and has a rapid onset of action; however, its action offset may be as long as 5 to 7 days and thus does not appear to offer an advantage over other $P2Y_{12}$ inhibitors in allowing NCS with a minimal break in platelet inhibition from an oral agent (52). At present, there are no published data in patients undergoing NCS.

Cangrelor, currently investigational, is an intravenous non-thienopyridine $P2Y_{12}$ receptor inhibitor, with a 3-min half-life (52). The recently reported BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) trial (53) demonstrated that cangrelor could provide adequate platelet inhibition before surgery after oral thienopyridine discontinuation. Bleeding events were not increased in patients who received cangrelor compared with placebo nor was there any difference in ischemic events. It should be noted that at the time of surgery, the cangrelor group did not demonstrate any difference in platelet inhibition compared with placebo; as such, the BRIDGE study showed a means to maintain platelet inhibition before, but not during, surgery. Cangrelor's value in reducing MACE with an acceptable bleeding risk during surgery requires a large-scale randomized study.

Conclusions and Recommendations

The current, rather limited, data suggest the following regarding the MACE and bleeding risks after NCS, and methods to decrease them:

1. The actual MACE risk after NCS remains uncertain, with wide variations reported (Fig. 1, Tables 2 to 5). There does seem to be a consensus, however, that the highest-risk period for ST after PCI with either BMS or DES following NCS is the first 4 weeks. Therefore, it seems reasonable to withhold NCS, if possible, for at least 4 weeks after PCI.
2. In the non-NCS situation, it is recommended that DAPT be continued for 1 to 12 months with BMS and at least 12 months for DES. Should NCS be required during this period, consideration to continue DAPT during NCS should be given, understanding that the risks and benefits of such an approach remain unclear based on current data (Fig. 3). However, it seems reasonable until more definitive data are forthcoming to recommend ASA in most cases as per guidelines unless the risk of bleeding is prohibitive and to recommend DAPT when the risk of bleeding is less than severe.
3. An important issue that has emerged is the persistent MACE risk even beyond the conventional "high-risk" period. The value of APT is uncertain. It seems reasonable to consider ASA unless the risk of bleeding is more than moderate, although further data are required to strengthen this recommendation.
4. The frequency of the combination of prior stent implantation and NCS recommends a randomized prospective trial to determine whether, and to what extent, APT, either single or dual, affects MACE, ST, and bleeding incidence after NCS.
5. At present, decision making regarding APT in the perioperative period in an individual patient will have to balance bleeding versus MACE risk. Recent strategies evaluating use of glycoprotein IIb/IIIa inhibitor or newer $P2Y_{12}$ receptor antagonists look promising, but further studies are required. A coordinated treatment plan by the cardiologist, anesthesiologist, and surgeon is essential.

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REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics. Circulation 2009;119:e21–181.
2. van Werkum JW, Heestermans AA, de Korte FI, et al. Long-term clinical outcome after a first angiographically confirmed coronary stent thrombosis. Circulation 2009;119:828–34.
3. van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis registry. J Am Coll Cardiol 2009;53:1399–409.
4. Ferreira-Gonzalez I, Marsal JR, Ribera A, et al. Background, incidence, and predictors of antiplatelet therapy discontinuation during the first year after drug-eluting stent implantation. Circulation 2010; 122:1017–25.
5. Cruden NL, Harding SA, Flapan AD, et al. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. Circ Cardiovasc Interv 2010;3:236–42.
6. Berger PB, Kleiman NS, Pencina MJ, et al. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement: results from the EVENT registry. J Am Coll Cardiol Intv 2010;3:920–7.
7. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; 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; Society for Vascular Surgery, Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. J Am Coll Cardiol 2009;54:e13–118.
8. Rajagopalan S, Ford I, Bachoo P, et al. Platelet activation, myocardial ischemic events and postoperative non-response to aspirin in patients undergoing major vascular surgery. J Thromb Haemost 2007;5:2028–35.
9. Haggart PC, Adam DJ, Ludman PF, Ludman CA, Bradbury AW. Myocardial injury and systemic fibrinolysis in patients undergoing repair of ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 2001;21:529–34.
10. Diamantis T, Tsiminikakis N, Skordylaki A, et al. Alterations of hemostasis after laparoscopic and open surgery. Hematology 2007;12: 561–70.
11. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94.
12. Wilson SH, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42:234–40.
13. Sharma AK, Ajani AE, Hamwi SM, et al. Major noncardiac surgery following coronary stenting. Cathet Cardiovasc Interv 2004;63:141–5.
14. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. Am J Cardiol 2005;95:755–7.
15. Brichon PY, Boitet P, Dujon A, et al. Perioperative in-stent thrombosis after lung resection performed within 3 months of coronary stenting. Eur J Cardiothorac Surg 2006;30:793–6.
16. Nuttall GA, Brown MJ, Stombaugh JW, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. Anesthesiology 2008;109:588–95.
17. Compton PA, Zankar AA, Adesanya AO, Banerjee S, Brilakis ES. Risk of noncardiac surgery after coronary drug-eluting stent implantation. Am J Cardiol 2006;98:1212–3.
18. Brotman DJ, Bakhru M, Saber W, et al. Discontinuation of antiplatelet therapy prior to low-risk noncardiac surgery in patients with drug-eluting stents. J Hosp Med 2007;2:378–84.
19. Conroy M, Bolsin SN, Black SA, Orford N. Perioperative complications in patients with drug-eluting stents: a three-year audit at Geelong Hospital. Anaesth Intensive Care 2007;35:939–44.
20. Rhee SJ, Yun KH, Lee SR, et al. Drug-eluting stent thrombosis during perioperative period. Int Heart J 2008;49:135–42.
21. Godet G, Le Manach Y, Lesache F, Perbet S, Coriat P. Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery. Br J Anaesth 2008;100:472–7.
22. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. Anesthesiology 2008;109:596–604.
23. Choi CU, Rha SW, Jin Z, et al. The optimal timing for non-cardiac surgery after percutaneous coronary intervention with drug-eluting stents. Int J Cardiol 2010;139:313–6.
24. Chia KK, Park JJ, Postle J, Cottrill A, Ward MR. Frequency of late drug-eluting stent thrombosis with non-cardiac surgery. Am J Cardiol 2010;106:1–3.
25. Anwaruddin S, Askari AT, Saudye H, et al. Characterization of post-operative risk associated with prior drug-eluting stent use. J Am Coll Cardiol Intv 2009;2:542–9.
26. 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. Cathet Cardiovasc Interv 2009;74:837–43.
27. Gandhi NK, Abdel-Karim AR, Banerjee S, Brilakis ES. Frequency and risk of noncardiac surgery after drug-eluting stent implantation. Cathet Cardiovasc Interv 2011;77:972–6.
28. Brilakis ES, Cohen DJ, Kleiman NS, et al. Incidence and clinical outcome of minor surgery in the year after drug-eluting stent implantation. Am Heart J 2011;161:360–6.
29. Kim HL, Park KW, Kwak JJ, et al. Stent-related cardiac events after non-cardiac surgery. Int J Cardiol 2008;123:353–4.
30. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting. J Am Coll Cardiol 2007;49:122–4.
31. 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;104:1229–34.
32. Albaladejo P, Marret E, Samama CM, et al. Non-cardiac surgery in patients with coronary stents: the RECO study. Heart 2011;97:1566–72.
33. Brancati MF, Giammarinaro M, Burzotta F, et al. Outcome of non-cardiac surgery after stent implantation in the DES era. J Invasive Cardiol 2011;23:44–9.
34. Vicenzi MN, Meislitzer T, Heitzinger B, Halaj M, Fleisher LA, Metzler H. Coronary artery stenting and non-cardiac surgery. Br J Anaesth 2006;96:686–93.
35. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2010;38 Suppl:S1–S52.
36. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans. J Am Coll Cardiol 2006;48:193–202.
37. Ali M, McDonald K. Very late bare-metal stent thrombosis, rare but stormy! J Invasive Cardiol 2011;23:E208–10.
38. Rossi ML, Zavalloni D, Gasparini GL, Presbitero P. Very late multivessel thrombosis of bare metal stents with concomitant patent drug-eluting stents after withdrawal of aspirin. Int J Cardiol 2008;131: e7–9.
39. Willis N, Sachdeva R, Uretsky BF. Bare-metal stent thrombosis after noncardiac surgery greater than 10 years after stent implantation. Cathet Cardiovasc Interv 2011;78:234–6.
40. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice. Lancet 2007;369:667–78.
41. Choi HS, Jeong MH, Seo IK, et al. Very late stent thrombosis in a drug-eluting stent due to interruption of anti-platelet agents in patients with acute myocardial infarction and thrombocytosis. Korean Circ J 2011;41:417–20.
42. de Souza DG, Baum VC, Ballert NM. Late thrombosis of a drug-eluting stent presenting in the perioperative period. Anesthesiology 2007;106:1057–9.
43. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
44. Brilakis ES, Orford JL, Fasseas P, et al. Outcome of patients undergoing balloon angioplasty in the two months prior to noncardiac surgery. Am J Cardiol 2005;96:512–4.

45. Leibowitz D, Cohen M, Planer D, et al. Comparison of cardiovascular risk of noncardiac surgery following coronary angioplasty with versus without stenting. Am J Cardiol 2006;97:1188–91.
46. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17.
47. Burdess A, Nimmo AF, Garden OJ, et al. Randomized controlled trial of dual antiplatelet therapy in patients undergoing surgery for critical limb ischemia. Ann Surg 2010;252:37–42.
48. Savonitto S, D'Urbano M, Caracciolo M, et al. Urgent surgery in patients with a recently implanted coronary drug-eluting stent. Br J Anaesth 2010;104:285–91.
49. Marcos EG, Da Fonseca AC, Hofma SH. Bridging therapy for early surgery in patients on dual antiplatelet therapy after drug-eluting stent implantation. Neth Heart J 2011;19:412–7.
50. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
51. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
52. Angiolillo DJ, Capranzano P. Pharmacology of emerging novel platelet inhibitors. Am Heart J 2008;156 Suppl:S10–5
53. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. JAMA 2012;307:265–74.

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