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CORRESPONDENCE

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Noncardiac Surgery After Coronary Stenting: Early Surgery and Interruption of Antiplatelet Therapy Are Associated With an Increase in Major Adverse Cardiac Events

To the Editor: Noncardiac surgery early after percutaneous coronary intervention (PCI) with stenting has been associated with adverse cardiac events in the perioperative period (1,2). However, these reports were on patients with bare-metal stents, did not include drug-eluting stents, and did not compare patients who continued their antiplatelet therapy during surgery with those who interrupted this therapy. Therefore, we conducted the current study.

Patients who underwent noncardiac surgery between 1999 and 2005 and had a successful PCI because of unstable coronary artery disease within the 2 years before surgery were enrolled. The data on PCI procedures were part of a prospectively maintained registry including a total of 574 procedures. Data on the surgical procedure, as well as 30-day cardiovascular outcome, were retrospectively collected by screening of medical charts. The medical ethics committee of our hospital approved the study. All patients underwent PCI using either bare-metal or drug-eluting stents (paclitaxel or sirolimus). Patient characteristics included the indication for PCI, the number of affected and stented coronary arteries, whether the procedure was successful, left ventricular function, and medication use during and after PCI. In addition, cardiac risk factors were scored. Patients with bare-metal stents were prescribed lifelong aspirin and clopidogrel for at least 1 month at the discretion of the treating physician (median 30 days, interquartile range 30 to 90 days). Patients with drug-eluting stents usually received lifelong aspirin as well as clopidogrel for at least 3 months (sirolimus, median 90 days, interquartile range 60 to 180 days) to 6 months (paclitaxel, median 180 days, interquartile range 180 to 180 days), or longer at the discretion of the treating physician.

The surgical procedures were categorized according to surgical risk, based on the definition of the Revised Cardiac Risk Index (3). Furthermore, the cardiac risk factors and medication use assessed during the initial PCI procedures were updated at the time of operation and were used to assess the Revised Cardiac Risk Index for each patient (3). Importantly, there was no protocol for perioperative antiplatelet use in the population studied. Consequently, some patients received aspirin and/or clopidogrel throughout the surgical procedure, whereas in other patients aspirin and clopidogrel were stopped 1 week before operation.

Medical charts were reviewed for the composite end points of 30-day major adverse cardiac events (MACE), defined as nonfatal myocardial infarction and/or cardiac death as previously defined according to guidelines of the American College of Cardiology/European Society of Cardiology (4). Patients with an increased cardiac risk (i.e., previous PCI) were routinely screened for postoperative cardiac end points using serial troponin T and electrocardiographic monitoring on days 1, 3, and 7 after surgery. Additional tests were performed at the discretion of the treating physician. Blood loss during operation and the necessity and quantity of perioperative transfusion requirements were noted in all patients.

Table 1 Baseline Characteristics of All Patients

	n = 192
Medical history	
Ischemic heart disease	192 (100%)
Congestive heart failure	5 (3%)
Diabetes mellitus	47 (25%)
Renal impairment	29 (15%)
History of CVA or TIA	23 (12%)
Revised cardiac risk index	
1 risk factor	65 (34%)
2 risk factors	74 (39%)
3 or more risk factors	53 (28%)
Medical therapy	
Beta-blockers	131 (68%)
Statins	136 (71%)
Calcium antagonists	50 (26%)
Nitrates	20 (10%)
Diuretics	24 (13%)
ACE inhibitors	47 (24%)
Antiplatelet therapy during surgery	101 (53%)
Coronary stenting	
Bare-metal	93 (48%)
Drug-eluting	99 (52%)
Number of vessels dilated	
1	91 (47%)
2	60 (31%)
3	41 (21%)
Stenting successful	192 (100%)
Type of noncardiac surgery	
Abdominal	31 (16%)
Vascular peripheral	30 (16%)
Eye	23 (12%)
Urologic	24 (13%)
Orthopedic	23 (12%)
Renal transplantation	12 (6%)
ENT	10 (5%)
Aortic	9 (5%)
Reconstructive	9 (5%)
Gynecologic	5 (3%)
Neurologic	4 (2%)
Carotid	3 (2%)
Other	9 (5%)

ACE = angiotensin-converting enzyme; CVA = cerebrovascular accident; ENT = ear/nose/throat; TIA = transient ischemic attack.

Table 2 Characteristics of Patients With Perioperative Major Adverse Cardiac Events

Patient	Age (yrs)	Gender	Type of Surgery	Time From PCI	Target Vessel	Type of Stent	Aspirin Withheld	Clopidogrel Withheld
A	58	M	Abdominal	1	LAD	Bare-metal	Yes	Yes
B	69	M	Esophagectomy	28	RCA, LCx	Bare-metal	Yes	Yes
C	64	M	Abdominal	30	RCA	Paclitaxel	Yes	Yes
D	47	M	ENT	80	RCA, LAD	Sirolimus	Yes	Yes
E	65	M	Urologic	253	LAD,RCA,LCx	Paclitaxel	Yes	N/A

Patient	Complication
A	MI, thrombosis LAD stent (angiography)
B	MI, thrombosis RCA stent (autopsy)
C	MI, left main thrombosis, no stent thrombosis (autopsy)
D	MI, thrombosis LAD stent (ECG)
E	MI, thrombosis LAD stent (angiography)

ECG = electrocardiogram; ENT = ear/nose/throat; LAD = left anterior descending coronary artery; LCx = left circumflex artery; MI = myocardial infarction; N/A = not available; RCA = right coronary artery.

In total, 192 patients underwent surgery within 2 years after the initial PCI procedure (Table 1). Patients were arbitrarily divided in an early-surgery group (defined as noncardiac surgery during which clopidogrel was required during the trials that led to approval of these devices and according to their labels: bare-metal stents 1 month, sirolimus-eluting stents 3 months, paclitaxel-eluting stents 6 months) and a late-surgery group. Thirty patients underwent early surgery according to this classification.

During the first 30 postoperative days, 5 patients (2.6%) experienced a MACE (all fatal, see Table 2 for characteristics of these patients). In the early-surgery group, 4 MACEs (13.3%) occurred, whereas in the late-surgery group, only 1 MACE (0.6%) occurred (Fisher exact test $p = 0.002$) (Table 3). In 91 patients (47%), antiplatelet medication was interrupted during the perioperative period. There was no significant difference in surgical risk between patients in whom antiplatelet therapy (both clopidogrel and aspirin) was interrupted versus those in whom antiplatelet therapy was continued. The interruption was associated with a significantly higher incidence of MACE in patients who stopped versus those who continued (5.5% vs. 0%, Fisher exact test $p = 0.023$). In the group of patients with a MACE, all 5 patients discontinued antiplatelet therapy, whereas in the group without a MACE, only 46% (86 of 187) patients discontinued their antiplatelet therapy. In particular, in patients in whom antiplatelet therapy was stopped before the required time for clopidogrel use (early-surgery group), the discontinuation of antiplatelet therapy had a detrimental effect: an incidence of MACEs of 30.7% in the discontinuation group versus 0% in patients who continued antiplatelet therapy (Fisher exact test $p = 0.026$) (Table 4). Again, all 4 patients with a MACE discontinued antiplatelet therapy, whereas only 35% (9 of 26) of the patients without a MACE discontinued antiplatelet therapy.

There was no difference in the incidence of MACE between patients with drug-eluting stents and those with bare-metal stents (2.2% vs. 3.0%, $p = 0.70$); neither was there a significant difference within the early-surgery group (28.6% for bare-metal stents and 8.7% for drug eluting stents, $p = 0.23$). Remarkably, in 57% of the patients with bare-metal stents, antiplatelet therapy was interrupted in the early-surgery group, whereas antiplatelet therapy was interrupted in 39.1% of the drug-eluting stent group.

Excessive blood loss during surgery was noted in the medical charts of 2 patients (1 receiving antiplatelet therapy). Blood transfusion was required in 44 patients (24% vs. 20% for those who continued vs. those who discontinued antiplatelet therapy, respectively, $p = 0.50$). In patients requiring blood transfusion, the number of units of homologues' blood did not differ between those who continued versus those who discontinued antiplatelet therapy (median 2 vs. 3 U, $p = 0.51$).

This study showed an association between early noncardiac surgery after coronary artery stenting and perioperative adverse cardiovascular events. Importantly, in patients undergoing early surgery, discontinuation of antiplatelet therapy during the perioperative period may be a major cause of the increase in MACE. The type of stent (i.e., bare-metal or drug-eluting) did not influence cardiovascular outcome in this cohort of patients.

In recent studies, an association between early noncardiac surgery after PCI and adverse cardiac outcome has been reported as well (1,2,5). However, these reports did not include the use of drug-eluting stents. The excessive risk of early surgery after PCI might be attributable to the high risk of in-stent thrombosis during the perioperative period. This thrombosis risk is possibly increased by the stress response to major surgery. The stress response includes sympathetic activation promoting shear stress on arterial plaques, enhanced vascular reactivity conducive to vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability. Because procoagulant clotting factors increase while fibrinolysis decreases, the surgical patient is in a hypercoaguable state. Furthermore, coronary stenting results in denudation of the endothelial surface. This might also contribute to the high risk of patients with early surgery because re-endothelization takes up to

Table 3 Incidence of Nonfatal MI or Cardiac Death Within 30 Days After Noncardiac Surgery

	Late Surgery (n = 162)	Early Surgery (n = 30)
No MACE	161 (99.4%)	26 (86.7%)
MACE	1 (0.6%)	4 (13.3%)

MACE = major adverse cardiac events; MI = myocardial infarction.

Table 4 Incidence of Nonfatal MI or Cardiac Death Within 30 Days After Noncardiac Surgery in Patients With Early (n = 30) Surgery After PCI Who Either Continued or Discontinued Antiplatelet Therapy

	Continued (n = 17)	Discontinued (n = 13)
No MACE	17 (100%)	9 (69.3%)
MACE	0 (0%)	4 (30.7%)

MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

8 weeks. This hypothesis is supported by our finding that all MACEs in the early-surgery group occurred in patients in whom antiplatelet therapy was discontinued, including 3 events in the 17 patients with bare-metal stents in whom antiplatelet therapy was discontinued and 2 events in 9 patients with drug-eluting stents without antiplatelet therapy. In contrast to our findings, Reddy et al. (5) did not show an association between discontinuation of antiplatelet therapy and perioperative MACEs in 56 patients with prior bare-metal stenting. This might have been attributable to the small number of events in their study.

The small number of events is also a limitation of the current study. Multivariate analysis could not be performed because of this small number. However, the difference found between those patients who continued their antiplatelet therapy and those who did not deserves attention, and, until more evidence is available, antiplatelet therapy during surgery should be continued unless there is an absolute contraindication.

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Letters to the Editor

Time Dependence of Defibrillator Benefit Postcoronary Revascularization

In a recent issue of the *Journal,* Goldenberg et al. (1), in a subgroup analysis of MADIT-II (Multicenter Automatic Defibrillator Implantation Trial) (2), showed that in patients with ischemic left ventricular dysfunction who underwent coronary revascularization (CR), the efficacy of implantable cardioverter-defibrillator (ICD) therapy was not apparent when the device was implanted 6 months or less following CR. The authors concluded a time dependence of the ICD therapy efficacy and raised the question of the optimal timing of device implantation following CR. In our opinion, the issues raised by the study should instead focus on the reasons why the ICD benefit was only apparent when implanted after long time frames following revascularization.

In view of the elapsed time following CR by the time of patient enrollment, we can assume that the distinguishing feature between patients enrolled early and those enrolled late after CR resides in the probability of recurrent ischemia. This was moreover the rationale of the selected time frames based on the probability of coronary artery disease progression. Because several observations suggest a role for silent (or overt) ischemia as at least a contributing factor to sudden death (3,4), the lack of survival benefit of ICD therapy in the group characterized by a lower probability of ischemia may therefore be attributed to the prevention of recurrent ischemia by revascularization. This hypothesis is further substantiated by the CABG (Coronary Artery Bypass Graft)-Patch trial (5) where no survival benefit was conferred by prophylactic ICD in patients undergoing CABG with depressed left ventricular function.

Accordingly, this subgroup analysis (1) further confirms the importance of revascularization to lower the risk of sudden cardiac death. As it is reasonable to first treat the contributing factors rather than the consequences, a systematic evaluation of the coronary artery status with CR if required prior to prophylactic ICD implantation should be the conclusion to draw from this subset of the MADIT-II study. The investigators raised the question of the optimal timing of device implantation. However, considering time frames from up to and more than 5 years following CR, the "timing" for a significant life-saving benefit of ICD to become apparent also coincides with an increasing probability of progression of coronary artery lesions. We may then assume that a substantial proportion of patients in these time frames would actually have qualified for a coronary evaluation prior to ICD implantation.