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Risk of Myocardial Infarction and Death After Noncardiac Surgery Performed Within the First Year After Coronary Drug-Eluting Stent Implantation for Acute Coronary Syndrome or Stable Angina Pectoris

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This study aimed to examine the 30-day risk of myocardial infarction (MI) and death in patients who underwent noncardiac surgery within 1 year after coronary drug-eluting stent implantation for acute coronary syndrome (ACS) or stable angina pectoris (SAP) and to compare it with the risk in surgical patients without known coronary artery disease. Patients with drug-eluting stent implantation for ACS (n = 2,291) or SAP (n = 1,804) who underwent noncardiac surgery were compared with a cohort from the general population without known coronary artery disease matched on the surgical procedure, hospital contact type, gender, and age. In patients with ACS, the 30-day MI risk was markedly increased when surgery was performed within 1 month after stenting (10% vs 0.8%; adjusted odds ratio [OR_{adj}] 20.1, 95% confidence interval [CI] 8.85 to 45.6), whereas mortality was comparable (10% vs 8%, OR_{adj} 1.17, 95% CI 0.76 to 1.79). When surgery was performed between 1 and 12 months after stenting, the 30-day absolute risk for MI was low but higher than in the comparison cohort (0.6% vs 0.2%, OR_{adj} 2.18, 95% CI 0.89 to 5.38), whereas the mortality risks were similar (2.0% vs 1.8%, OR_{adj} 1.03, 95% CI 0.69 to 1.55). In patients with SAP, the 30-day MI risk was low but higher than in the comparison cohort (0.4% vs 0.2%, OR_{adj} 1.90, 95% CI 0.70 to 5.14), whereas the mortality risks were similar (2.2% vs 2.1%, OR_{adj} 0.91, 95% CI 0.61 to 1.37). In conclusion, patients with ACS and SAP who underwent surgery between 1 and 12 months after stent implantation had a risk for MI and death that was similar to the risk observed in surgical patients without coronary artery disease. **(Am J Cardiol 2021;160:14−20)**

Approximately 1 in 5 patients undergo noncardiac surgery within the first year after a drug-eluting stent (DES) implantation.[1−3] For these patients, it is recommended that a multidisciplinary team, including cardiologists and surgeons, evaluates the indication for and timing of the surgery and the consequences of interrupting dual antiplatelet therapy (DAPT). Such consequences include an increased risk of thrombotic events such as stent thrombosis and risk of bleeding associated with surgery.[4,5] Based on 2 recent cohort studies,[3,6] the 2018 European Society of Cardiology DAPT consensus document suggested that when surgical delay is undesired, elective surgery may be considered 1 month after DES implantation for stable angina pectoris (SAP) and 6 months after DES implantation for acute coronary syndrome (ACS).[5] However, the evidence for this recommendation is limited. In particular, it is unknown whether noncardiac surgery can be safely performed in patients treated for ACS earlier than 6 months after DES implantation. We therefore examined the 30-day risk of myocardial infarction (MI) and death after noncardiac surgery performed within the first year after DES implantation for ACS or SAP. The risk in patients treated for ACS or SAP was compared separately with the risk in a comparison cohort of patients from the general population without coronary artery disease who underwent similar surgical procedures.

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See page 20 for disclosure information.

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Methods

In a matched cohort study using patient-level record linkage between registries, we compared the risk of MI and all-cause mortality within the first 30 days after noncardiac surgery in patients with a previous DES implantation for ACS or SAP with the risk in surgical patients sampled from the general population without known coronary artery disease who underwent the same surgical procedures. People in Denmark have free access to tax-supported health care.[7]

Patients treated with DES implantation between May 2005 and January 2012 and with a surgical procedure within 1 year after DES implantation were included. Patients were divided according to the indication for stent implantation and only patients with ACS or SAP were included in these analyses. The general population surgical procedure comparison cohort consisted of patients without known coronary artery disease who underwent the same surgical procedures. For each patient with stent implantation, up to 4 subjects were matched individually based on the type of surgical procedure, hospital contact type (in-patient, out-patient, or emergency room), gender, and age (±5 years). Patients from the 2 cohorts who received anticoagulants were excluded. The cohort has been described in detail previously.[3] The stent implantations were performed within the catchment area of the Western Denmark Heart Registry, whereas the surgical procedures were recorded in the Danish National Patient Register covering all Danish hospitals.[8]

We used registry-based detection of the events, MI and all-cause mortality, which were extracted from the Danish National Patient Register and the Danish Civil Registration System, respectively. Events were recorded within the first 30 days after the surgery. In the Danish Civil Registration System, all citizens have a unique personal identifier that allows cross-linkage of registries. The Danish Civil Registration System also contains an updated vital status of the citizens, which we used for the registration of all-cause mortality.[9] From the Western Denmark Heart Registry, we collected the baseline patient characteristics and information regarding stent implantation procedures, including treatment indication and date. This registry contains information on all coronary procedures performed at the 3 centers that perform coronary interventions in Western Denmark (Odense University Hospital, Aarhus University Hospital, and Aalborg University Hospital). These centers serve approximately 3 million inhabitants corresponding to approximately 55% of the Danish population.[10] From the Danish National Patient Register, we collected dates of surgery, hospital contact type, surgical codes, and information on co-morbidities. We also used the Danish National Patient Register to identify eligible general population comparison subjects defined as individuals without the International Classification of Diseases, Tenth Revision, codes I20 to I25 since 1995. Incidence of MI was detected using the Danish National Patient Register and defined as an acute admission under the International Classification of Diseases, Tenth Revision, diagnosis code I21, as described previously.[11] The Danish National Patient Register contains information on all admissions in Denmark, including surgical codes and discharge diagnoses.[8] From the Danish Register of Medical Product Statistics, we collected information on redeemed prescriptions.[12] Patients were considered to have received drug treatment if they had redeemed a prescription within 100 days before the surgery. The outcomes in the cohort of patients treated with stent implantation for ACS or SAP were compared separately with those of the comparison cohort.

The events, MI and all-cause mortality, were reported as cumulative incidence rates and counts (percentages). Unadjusted odds ratios and odds ratios as measures of the relative risks adjusted for admission type for surgery (elective or acute) and odds ratios adjusted for admission type for surgery (elective or acute) and co-morbidities (Charlson co-morbidity index without MI) with 95% confidence intervals were computed for the events using conditional logistic regression. We reported the outcomes overall, with surgery within 30 days after DES implantation, and with surgery within 31 to 365 days after DES implantation. In the supplement, we reported the outcomes overall; with surgery within 30 days, 31 to 91 days, 92 to 182 days; and 183 to 365 days after DES implantation.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). The Danish Data Protection Agency approved the study (2012-41-0164). Ethical committee approval is not required for registry-based studies in Denmark.

Results

Figure 1 shows selection of the 2 cohorts. Table 1 describes the patient and stent implantation characteristics and surgical procedures. The table shows the matching based on surgical procedure, hospital contact type, gender, and age, which also reflects the noncardiac surgery risk recorded as suggested by the European Society of Cardiology/European Society of Anaesthesiology Guidelines.[4] Supplementary Table 1 describes information on co-morbidities and the use of prescribed medication. In general, the burden of co-morbidity was higher, and the use of the recorded cardiovascular medications was more frequent in patients with stent implantation than in the general population.

Table 2 shows the number of events and the unadjusted and adjusted odds ratios for the events in patients with stent implantation for ACS. Figure 2 displays the cumulative incidence rates for MI and all-cause mortality in patients with stent implantation for ACS and those in the comparison cohort. The odds ratio for acute MI within 30 days after surgery was 6- to 10-fold higher in patients with stent implantation for ACS, whereas there was a similar all-cause mortality. The odds ratio for surgery-related MI in patients with stent implantation for ACS was high within the first 30 days after DES implantation. However, when the surgery was performed between 30 days and 12 months after DES implantation, there was only a small risk difference between the 2 cohorts. Of the 39 patients with MI after noncardiac surgery was performed within 30 days after stenting for ACS, 32 patients had surgery during an acute admission. Similarly, of the 38 patients who died after noncardiac surgery was performed within 30 days after stenting for ACS, 31 patients had surgery during an acute admission. Table 3

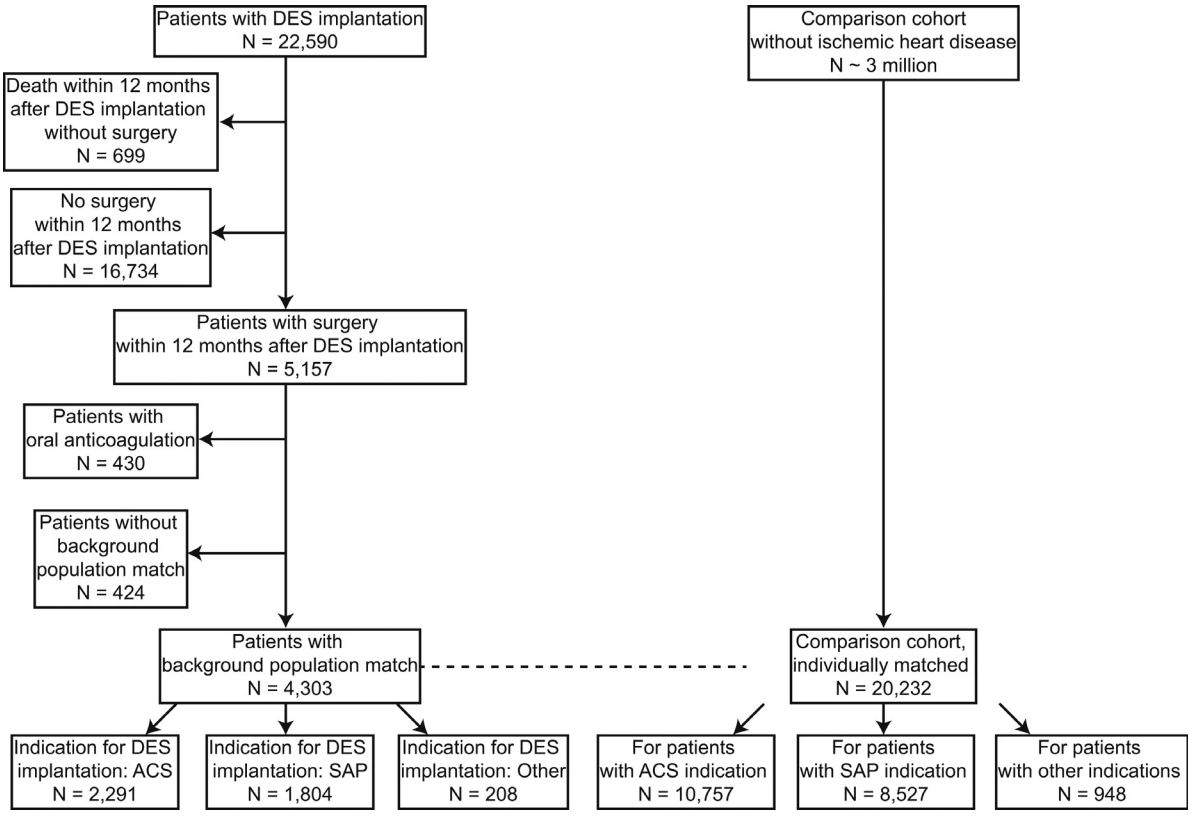

Figure 1. Flow diagram. Comparison cohort included up to 5 individuals matched individually based on surgical procedure, hospital contact type (in-patient, out-patient, or emergency room), gender, and age (±5 years). Other = indications other than ACS or SAP such as arrhythmia and heart failure.

Table 1
Patient and procedure characteristics

Variable	Patients with ACS as indication for DES implantation N = 2,291	Comparison cohort N = 10,757	Patients with SAP as indication for DES implantation N = 1,804	Comparison cohort N = 8,527
Demographics				
Age (years)	68 (60;76)	68 (60;76)	69 (61;76)	69 (61;76)
Men	1,621 (70.8%)	7578 (70.4%)	1267 (70.2%)	6007 (70.4%)
Stent implantation				
More than 1 stent	873 (38.1%)	-	766 (42.5%)	-
More than 20mm stent	1,260 (55.0%)	-	971 (53.8%)	-
First generation	1370 (59.8%)	-	1082 (60.0%)	-
Surgical procedures				
Urology (minor)	119 (5.2%)	560 (5.2%)	72 (4.0%)	339 (4.0%)
Urology (major)	67 (2.9%)	328 (3.0%)	44 (2.4%)	219 (2.6%)
Gynaecology	45 (2.0%)	219 (2.0%)	33 (1.8%)	165 (1.9%)
Orthopaedic (minor)	51 (2.2%)	255 (2.4%)	55 (3.0%)	259 (3.0%)
Orthopaedic (major)	243 (10.6%)	1,161 (10.8%)	193 (10.7%)	911 (10.7%)
Peripheral vessels	140 (6.1%)	563 (5.2%)	113 (6.3%)	486 (5.7%)
Skin	261 (11.4%)	1,273 (11.8%)	205 (11.4%)	987 (11.6%)
Nervous system	58 (2.5%)	277 (2.6%)	44 (2.4%)	220 (2.6%)
Endocrinology	11 (0.5%)	55 (0.5%)	6 (0.3%)	26 (0.3%)
Ophthalmology	232 (10.1%)	1,140 (10.6%)	236 (13.1%)	1,163 (13.6%)
Otorhinolaryngology	232 (10.1%)	1,146 (10.7%)	224 (12.4%)	1,099 (12.9%)
Dental	63 (2.7%)	298 (2.8%)	51 (2.8%)	214 (2.5%)
Heart and great vessels	72 (3.1%)	132 (1.2%)	52 (2.9%)	138 (1.6%)
Pulmonary	162 (7.1%)	779 (7.2%)	71 (3.9%)	343 (4.0%)
Mamma	17 (0.7%)	77 (0.7%)	16 (0.9%)	78 (0.9%)
Abdominal, minor	318 (13.9%)	1,550 (14.4%)	226 (12.5%)	1,106 (13.0%)
Abdominal, major	200 (8.7 %)	944 (8.8%)	163 (9.0%)	774 (9.1%)
Hospital contact type				
In-patient	1,004 (43.8%)	4,465 (41.5%)	734 (40.7%)	3,326 (39.0%)
Out-patient	1,171 (51.1%)	5,724 (53.2%)	982 (54.4%)	4,778 (56.0%)
Emergency room	116 (5.1%)	568 (5.3%)	88 (4.9%)	423 (5.0%)
ESC/ESA risk group				
Low	1,578 (68.9%)	7,669 (71.3%)	1,297 (71.9%)	6,240 (73.2%)
Intermediate	594 (25.9%)	2,749 (25.6%)	419 (23.2%)	1,981 (23.2%)
High	119 (5.2%)	339 (3.2%)	88 (4.9%)	306 (3.6%)

Age is presented as median (twenty-fifth percentile; seventy-fifth percentile). All other variables are presented as numbers (percentages).

ACS = acute coronary syndrome; DES = drug-eluting stent; ESC/ESA = European Society of Cardiology/European Society of Anaesthesiology; SAP = stable angina pectoris.

Table 2
Myocardial infarction and death within 30 days after noncardiac surgery in patients with previous drug-eluting stent implantation for ACS and in a general population comparison cohort

	Number of patients with stent implantation	Comparison cohort	Events among patients with stent implantation	Events in the comparison cohort	Unadjusted OR (95% CI)	OR adjusted for acute admission for surgery (95% CI)	OR adjusted for acute admission for surgery and comorbidity* (95% CI)
Myocardial infarction							
Time from DES implantation to surgery							
0 to 365 days (all)	2,291	10,757	50 (2.2%)	32 (0.3%)	6.01 (3.76 - 9.59)	8.04 (4.85 - 13.3)	7.77 (4.66 - 12.9)
0 to 30 days	375	1,666	39 (10%)	13 (0.8%)	12.9 (6.60 - 25.2)	19.0 (8.65 - 41.6)	20.1 (8.85 - 45.6)
31 to 365 days	1,916	9,091	11 (0.6%)	19 (0.2%)	1.95 (0.88 - 4.32)	2.49 (1.06 - 5.84)	2.18 (0.89 - 5.38)
Death							
Time from DES implantation to surgery							
0 to 365 days (all)	2,291	10,757	76 (3.3%)	295 (2.7%)	1.15 (0.87 - 1.53)	1.21 (0.91 - 1.61)	1.10 (0.82 - 1.47)
0 to 30 days	375	1,666	38 (10%)	133 (8.0%)	1.29 (0.86 - 1.95)	1.26 (0.83 - 1.92)	1.17 (0.76 - 1.79)
31 to 365 days	1,916	9,091	38 (2.0%)	162 (1.8%)	1.04 (0.71 - 1.54)	1.16 (0.78 - 1.71)	1.03 (0.69 - 1.55)

* Charlson co-morbidity index without myocardial infarction.
ACS = acute coronary syndrome; CI = confidence interval; DES = drug-eluting stent; OR = odds ratio.

shows the numbers of patients in the DES and general population cohorts and events and the unadjusted and adjusted odds ratios for the events in patients with stent implantation for SAP. Figure 2 displays the cumulative incidence rates for MI (Figure 2) and all-cause mortality (Figure 2) in patients with stent implantation for SAP and those in the comparison cohort. The odds ratio for acute MI within 30 days after surgery was 2-fold higher in patients with stent implantation for SAP overall, whereas there was a similar all-cause mortality. The number of events and the unadjusted and adjusted odds ratios for the events in patients with previous stent implantation for ACS or SAP stratified further for time between stent implantation and surgery are shown in Supplementary Tables 2 and 3. In these stratified analyses, the numbers of events are low in some of the strata, particularly for acute MI in patients with stent implantation for SAP, and the odds ratios should therefore be interpreted with caution. However, no consistent difference in the risk for adverse events was found when the period from 1 to 12 months was subdivided into 1 to 3, 3 to 6, and 6 to 12 months.

Discussion

The main findings of our study are as follows: (1) Noncardiac surgery within the first month after DES implantation in patients with ACS was associated with a 30-day risk for both MI and death that approximated 10%. Compared with the comparison cohort, the 30-day rate of MI was markedly increased, whereas the risk for death was comparable with the comparison cohort when surgery was performed within the first month after DES implantation. (2) Noncardiac surgery performed later than 1 month after DES implantation for ACS was associated with a <1% risk of MI and an approximately 2% risk of death, which was comparable with the risk of MI and death in the comparison cohort. (3) Noncardiac surgery performed after stent implantation for SAP was associated with risks of MI of 2% within the first month after DES implantation and <1% later than 1 month after DES implantation and the risk of death of approximately 4% within the first month after stent implantation and approximately 2% later than 1 month after DES implantation. These results confirmed previous results that showed a low risk associated with noncardiac surgery after DES implantation in stable patients.[3] (4) Acute admission for noncardiac surgery was the major driver of the differences between the unadjusted and adjusted odds ratios, whereas further adjustment for co-morbidities had little impact.

Within the first month after DES implantation for ACS, the risk of death and MI after noncardiac surgery is high and our data support that surgery should be avoided, whenever possible, within the first month after DES implantation for ACS. Most of the surgeries that were performed within 30 days after stenting for ACS were performed during an acute admission. In these patients, postponing surgery may have been associated with detrimental outcomes.

In this study, the risk of death after noncardiac surgery when performed later than 1 month after DES implantation for ACS was approximately 2%. A similar risk of death was observed in the comparison cohort and in patients who

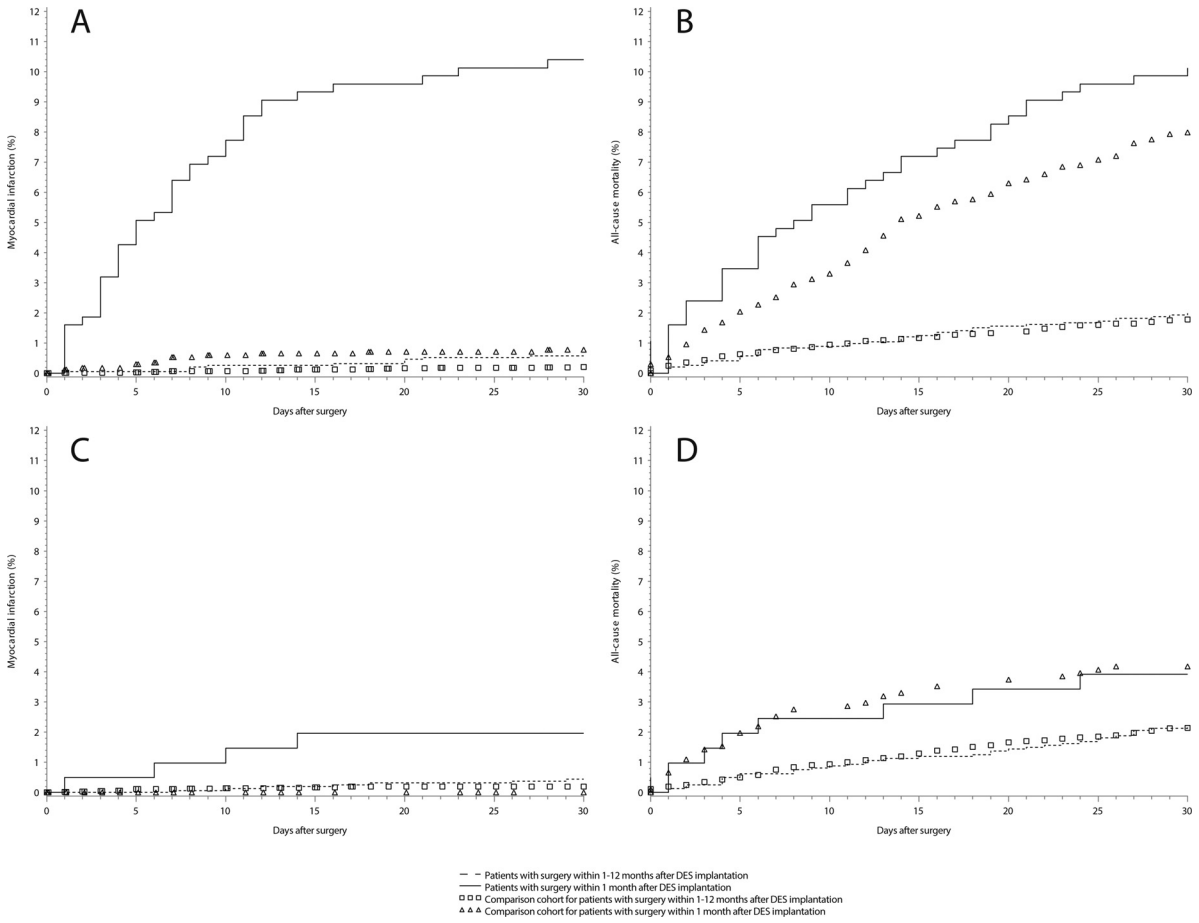

Figure 2. Cumulative incidence rates for myocardial infarction and death. Myocardial infarction (*A*) and all-cause mortality (*B*) among patients with previous DES implantation for acute coronary syndromes versus matched comparison cohort individuals. Myocardial infarction (*C*) and all-cause mortality (*D*) among patients with DES implantation for stable angina pectoris and their comparison cohort members.

underwent noncardiac surgery later than 1 month after stent implantation for SAP. In a similar study based on the US Veterans Affairs National Patient Care Databases, the 30-day risk of death after noncardiac surgery within 2 years after stent implantation was 1.9% and 1.8% in controls without stent implantations.[6] Our Danish consecutive "all-comers" cohorts differ in many aspects from the US Veteran Affairs cohort, but the similarities in the results from these 2 studies support the robustness of the findings. The results indicate that noncardiac surgery performed later than 1 month after stent implantation for ACS is not associated with excess mortality compared with the comparison cohort or with patients with stent implantation for SAP. Thus, in selected patients with DES implantation for ACS, noncardiac nonacute surgery might be considered as early as 1 month after stent implantation when there is a clinical need. The latter indication may include cancer suspicion and patients with severe chronic pain.

Despite similar death risks after surgery, patients with DES implantation have consistently been reported to have increased risks of MI and cardiac death.[1–3,6,13] Death as an outcome is indisputable. Because the observed increased risks for MI did not translate into increased overall death rates, it may be that this outcome measure is biased to some extent. It has been reported that troponin evaluation after surgery is more frequent in patients with previous stent implantation than in patients without stent implantation, and troponin evaluation was more frequent early after stent implantation than later.[6] It can be speculated that suspicion of MI and thus troponin evaluation after surgery may have been higher after stent implantation for ACS than after stent implantation for SAP or in the comparison cohort in our study. Assessment of cardiac biomarkers was not routine after noncardiac surgery. Furthermore, we have previously reported that International Classification of Diseases-based detection of MI is less accurate in the first 30 days after stenting because of the potential double registration of MIs when patients are transferred from the percutaneous coronary intervention center back to the referral hospital.[11] Thus, detection bias and registration may partly explain the increased risk for MI observed in the group of patients who underwent noncardiac surgery in the first month after DES implantation.

Guidelines currently recommend postponing noncardiac surgery for at least 1 month after stent implantation for SAP and for 6 months after stent implantation for ACS.[5] It should be noted that guidelines generally recommend postponing noncardiac surgery until completion of the full planned course of DAPT. The clinical reality, however, is that many patients undergo noncardiac surgery within

Table 3
Myocardial infarction and death within 30 days after noncardiac surgery in patients with previous drug-eluting stent implantation for SAP and in the comparison cohort

	Number of patients with stent implantation	Comparison cohort	Events among patients with stent implantation	Events in the comparison cohort	Unadjusted OR (95% CI)	OR adjusted for acute admission for surgery (95% CI)	OR adjusted for acute admission for surgery and comorbidity* (95% CI)
Myocardial infarction							
Time from DES implantation to surgery							
0 to 365 days (all)	1,804	8,527	11 (0.6%)	15 (0.2%)	2.15 (0.94 - 4.95)	3.46 (1.44 - 8.29)	2.88 (1.18 - 7.02)
0 to 30 days	204	912	4 (2.0%)	0 (0.0%)	-	-	-
31 to 365 days	1,600	7,615	7 (0.4%)	15 (0.2%)	1.28 (0.49 - 3.36)	2.36 (0.89 - 6.30)	1.90 (0.70 - 5.14)
Death							
Time from DES implantation to surgery							
0 to 365 days (all)	1,804	8,527	43 (2.4%)	201 (2.4%)	0.95 (0.66 - 1.36)	1.02 (0.71 - 1.46)	0.88 (0.60 - 1.28)
0 to 30 days	204	912	8 (3.9%)	38 (4.2%)	0.80 (0.33 - 1.97)	0.89 (0.36 - 2.20)	0.65 (0.23 - 1.80)
31 to 365 days	1,600	7,615	35 (2.2%)	163 (2.1%)	0.98 (0.66 - 1.45)	1.04 (0.70 - 1.54)	0.91 (0.61 - 1.37)

* Charlson co-morbidity index without myocardial infarction.
CI = confidence interval; DES = drug-eluting stent; OR = odds ratio; CI = confidence interval; SAP = stable angina pectoris.

the planned DAPT period.[1−3,6,13−15] In these instances, a multidisciplinary approach to individual risk evaluation and management, including DAPT management, is recommended.[4,16] Our results suggest that selected patients with DES implantation for ACS might be considered for noncardiac surgery earlier than generally recommended in the current guidelines.

The increased risk associated with acute admission for noncardiac surgery is noteworthy. This finding indicates that these patients require careful attention from a multidisciplinary team. Although acute or subacute surgery may be unavoidable, a multidisciplinary team still needs to decide on adjunctive therapies such as antiplatelet therapy, proper monitoring, and pre- and postoperative investigations. In multidisciplinary discussions, the relevance of the number of implanted stents may also arise. In the overall cohort, we previously found no association between the number of implanted stents and the risk of MI or all-cause death within 30 days after surgery.[17]

The Danish registries used in this study include large cohorts across all social classes and both genders and provide validated outcome measures with very limited loss to follow-up.[8−12,18] However, being a database study it lacks clinical detail, and we have no information on peri-operative management of DAPT, which may impact the outcomes assessed in this study.[19−21] In other studies, the same limitations regarding the lack of information on DAPT apply.[1−3,6,13−15]

Although our study included all patients who underwent surgery within the first year after stent implantation, we did not have information on all patients for whom surgery was considered but was deferred or postponed because of a recent stent implantation. Lack of information on selection of patients for surgery represents a potential limitation to the generalizability of the results. In similar registry studies, the selection of patients for noncardiac surgery was not described either.[1−3,6,13−15]

Our study is truly population based and, like other studies on this topic that include "all-comers," there was a moderate male preponderance because of the higher risk of coronary artery disease among men.[2] In comparison, studies performed using the US Veterans Affairs National Patient Care Databases included a more selected cohort that was almost exclusively males.[1] Females are thus underrepresented in the currently available data. We used logistic regression and odds ratios to estimate the relative risks. The odds ratios may overestimate the relative risks when an outcome is common.

Recent registry studies included patients treated with bare-metal stents and patients treated with DES.[1,2] In this study, we included only patients treated with DES, which represents the mainstay in coronary stent implantation today.[22] In this study, approximately 40% received newer-generation DES. Because stent thrombosis was very rare and is expected to be even rarer with newer-generation DES, the conclusions are unlikely to be different in a cohort restricted to newer-generation stents.[19]

In conclusion, patients with ACS requiring surgery between 1 and 12 months after DES implantation had a risk of MI and death that was comparable with the risk observed in the general population cohort without known coronary artery disease. This suggests that noncardiac surgery can be

safely performed earlier than previously anticipated. This information seems informative for multidisciplinary teams in their strategy for planning of noncardiac surgery in patients with DES implantation.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.08.040.

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