JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 68, NO. 24, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.09.960

EDITORIAL COMMENT

Surgery After DES Implantation

To Operate or Not to Operate: Is It Still a Question?*

Christian Spaulding, MD, PhD,[a] Marco G. Mennuni, MD[a,b]

One of the most challenging decisions in the contemporary cardiology era is whether to give the green light for noncardiac surgery after recent percutaneous coronary intervention with a drug-eluting stent (DES-PCI). Unfortunately, this frequent situation occurs in 5% to 34% of cases within 1 year of DES-PCI (Table 1). There are no randomized data to guide the clinician on the timing of surgery. The 2016 American College of Cardiology/American Heart Association guideline-focused update on duration of dual antiplatelet therapy (DAPT) strongly advises against elective noncardiac surgery <3 months after DES implantation (Class III: Harm, Level of Evidence: B-NR), but surgery may be considered 3 to 6 months after DES-PCI, with discontinuation of DAPT if the delayed surgery risk is greater than the stent thrombosis risk (Class IIb, Level of Evidence: C-EO) (1).

In daily practice, however, things are not that simple. The consequences of delaying surgery are difficult to determine, and the risk of stent thrombosis varies according to clinical and anatomical factors, such as recent acute coronary syndrome, bifurcation, and under-deployed stents. Decisions are most often made on an individual basis, after a difficult consensus reached by cardiologists, anesthesiologists, and surgeons. All interventional cardiologists can repeat quotes from these tense meetings such as "Why did you implant the stent?" or "I'm sorry, the surgery cannot be delayed. You must find a solution; after all you're the one who put the stent in!" or "You have your guidelines, I have a patient who needs surgery!"

Administration of DAPT after coronary stenting is based upon the fact that the stented coronary artery requires protection from thrombosis due to delayed endothelial healing. Late stent thrombosis, occurring after stent implantation, was reported with the first-generation DES, leading to the recommendation of prolonged DAPT for at least 1 year (2–4). However, with widespread use of new-generation DES, rates of stent thrombosis have been significantly reduced (5). Several randomized trials have now evaluated shorter durations of DAPT and a recent patient-level pooled analysis reported the safety of 3 to 6 months DAPT duration after DES-PCI (6).

However, data for the timing of surgery after DES-PCI and the management of DAPT in this setting are still lacking, and the fingers of interventional cardiologists are often crossed when DAPT must be stopped for <6 months after DES-PCI for unplanned surgery.

SEE PAGE 2622

In this issue of the *Journal*, Egholm et al. (7) provided an important contribution to the field. Between 2005 and 2012, 22,590 patients underwent DES-PCI in western Denmark. By linking the western Denmark Heart Registry records and the Danish National Patient Registry, the authors evaluated 4,303 DES-PCI patients who had a surgical procedure, comparing those individuals with a control group of patients without previous ischemic heart disease undergoing similar surgical procedures (n = 20,232). Surgery in DES-PCI patients was associated with an increased risk of myocardial infarction (1.6% vs. 0.2%,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Cardiology Department, European Hospital Georges Pompidou, INSERM U 970 and Sudden Death Expert Center, Paris Descartes University, Paris, France; and the [b]Cardiology Department, Humanitas Research Hospital, Milan, Italy. Dr. Spaulding has received research grants from the French Ministry of Health; consulting fees from Abiomed, Zoll, Medtronic, and Medpass; and speaker fees from AstraZeneca, Cordis, Servier, Lead-Up, Bayer, The Medicines Company, Eli Lilly, and WebMD. Dr. Mennuni has received a training grant from the European Society of Cardiology and consulting fees from Boston Scientific.

TABLE 1 Studies of Noncardiac Surgery After PCI

First Author (Ref. #)	Study Type	Country	Period	Time From PCI to Surgery, Months	Number of Patients Who Underwent PCI	Number of Patients (%) Who Underwent Surgery After PCI*	BMS	First-Generation DES	Second-Generation DES	Total ACEAS*	ACEAS BMS	ACEAS First-Generation DES	ACEAS Second-Generation DES
Berger et al. (10)	Multicenter registry	USA	2004–2005	12	4,637	206 (4.4)	–	206 (100%)	–	4† (1.9)	–	4† (1.9)	–
Cruden et al. (11)	National registry	Scotland	2003–2007	24	17,797	1,953 (10.9)	1,383 (70.8)	570 (29.2)	–	267 (13.6)	184 (13.3)	83 (14.6)	–
Gandhi et al. (12)	Single-center registry	Texas, USA	2005–2008	36	827	191 (23.0)	–	191 (100)	–	19 (9.9)	–	19 (9.9)	–
Hawn et al. (13)	National registry	USA	2000–2010	24	124,844‡	41,989‡ (33.6)	21,986‡ (52.3)	20,003‡ (47.7)	–	1,980‡ (4.7)	1,127‡ (5.1)	853‡ (4.3)	–
Holcomb et al. (14)	National registry	USA	2000–2010	24	–	20,590§	1,138§ (20.6)	2,511§ (45.5)	1,722§ (31.2)	152§ (2.8)	36§ (3.2)	70§ (2.8)	46§ (2.7)
Kałuza et al. (15)	Single-center registry	Texas, USA	1996–1998	1.5	–	40	40 (100)	–	–	9 (22.5)	9 (22.5)	–	–
Mahmoud et al. (16)	Single-center registry	Minnesota, USA	2006–2011	Unlimited	–	1,120	373‖ (48.0)	404‖ (52.0)	–	41 (3.7)	18‖ (4.8)	8‖ (2.0)	–
Reddy and Vaitkus (17)	Single-center registry	Illinois, USA	1999–2003	3	–	56	56 (100)	–	–	8 (14.0)	8 (14.0)	–	–
Wilson et al. (18)	Single-center registry	Minnesota, USA	1990–2000	2	–	207	207 (100)	–	–	8 (3.8)	8 (3.8)	–	–
Wijeysundera et al. (19)	Regional registry	Canada	1993–2009	120	–	8,116	7,211 (88.8)	905 (11.2)	–	170 (2.1)	–	–	–
Rossini et al. (20)	Multicenter registry	Italy	2003–2011	Unlimited	9,789	666 (6.8)	319 (47.9)	–	–	31 (4.2)	–	–	–

Values are n or n (%) unless otherwise indicated. *Values are n patients (percentage); ACEAS are reported as N events (percentage). †7-day outcome. ‡Number of procedures. §Stent type known in 777 patients. ‖Stent type known in 5,371 patients.
ACEAS = adverse cardiac events after surgery; BMS = bare-metal stent; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

TABLE 2 Clinical and Procedural Factors Influencing the Timing of Surgery After DES-PCI*

Surgery Between 1 and 3 Months	Wait 3 to 6 Months or Longer
Outcome strongly influenced by surgical delay	DES-PCI performed for ACS
Uncontrolled bleeding = surgical indication	Diabetes mellitus
Uncontrolled pain	Low left ventricular ejection fraction
	Stent undersized or malapposition
	Small stent diameter
	Long stent length
	Bifurcation stents
	Left main DES-PCI
	History of stent thrombosis

*Excludes emergency surgery.

ACS = acute coronary syndrome; DES-PCI = percutaneous coronary intervention with drug-eluting stent (≥1 stents).

respectively; odds ratio [OR]: 4.82; 95% confidence interval [CI]: 3.25 to 7.16) and cardiac death (1.0% vs. 0.2%, respectively; OR: 5.87; 95% CI: 3.60 to 9.58) but not all-cause mortality (3.1% vs. 2.7%, respectively; OR: 1.12; 95% CI: 0.91 to 1.38). When waiting time was stratified by time from DES-PCI to surgery, only surgery within the first month was associated with an increased risk of events. Such novel findings suggested that surgery may be performed safely 1 month after DES-PCI. However, we are left without a clear answer for the management of DAPT during surgery as limited information for DAPT administration was gathered in the study. Can $P2Y_{12}$ inhibitors be stopped safely before surgery performed 1 month after DES-PCI? Part of the answer can be found in the PARIS (Patterns of non-adherence to Anti-platelet Regimens In Stented patients) registry, in which a physician-guided DAPT interruption of up to 14 days was not associated with subsequent thrombotic events (8). Similar findings from a multicenter Spanish registry were reported by Ferreira-Gonzalez et al. (9). However, the overall rate of interruption and events was low in both studies, limiting the power to detect small differences.

Will the study by Egholm et al. (7) change our clinical practice? Data from a single registry will probably not be enough to modify current guidelines. However, this study added an important component to the difficult decision-making process for non-cardiac surgery after DES-PCI. A green (or at least cautionary yellow) light may be given based on consensus between cardiologists, anesthesiologists, and surgeons after balancing the need for surgery, risk of stent thrombosis, and bleeding risks (**Table 2**). The data presented by Egholm et al. (7) suggest that if surgery cannot be delayed, it can probably be performed safely 1 month after DES-PCI in selected patients, with support from the PARIS registry showing that physician-guided interruption of DAPT for <14 days may be safe as well in terms of thrombotic events.

The practice of cardiology in the 21st century remains a science based, in most cases, on clear guidelines supported by large randomized trials. There are still difficult cases, and decisions must be based on multiple factors. Surgery early after DES-PCI is a gray zone where cardiologists cannot rely solely on science; instead, we must become doctors practicing tailored medicine for individual patients.

Unsolved doubt, a motif of Prince Hamlet's dilemma, is difficult in clinical practice. The study by Egholm et al. (7) performed in Danish patients helps solve the Hamletic dilemma "to operate or not to operate" after recent DES-PCI. This new study is a bright testimony to the value of the large national Danish registries, which bring answers to questions that cannot be solved by randomized trials.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Christian Spaulding, Hôpital Européen Georges Pompidou, 20 rue Leblanc, Paris, Ile-de-France 75015, France. E-mail: christian.spaulding@aphp.fr.

REFERENCES

1. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

2. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.

3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.

4. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. N Engl J Med 2008;359:1330–42.

5. Camenzind E, Boersma E, Wijns W, et al. Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type. Eur Heart J 2014;35:1932–48.

6. Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol 2015;65:1092–102.

7. Egholm G, Kristensen SD, Thim T, et al. Risk associated with surgery within 12 months after coronary drug-eluting stent implantation. J Am Coll Cardiol 2016;68:2622–32.

8. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac

events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

9. Ferreira-Gonzalez I, Marsal JR, Ribera A, et al. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. J Am Coll Cardiol 2012;60:1333–9.

10. 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 (Evaluation of Drug-Eluting Stents and Ischemic Events) registry. J Am Coll Cardiol Intv 2010;3:920–7.

11. 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.

12. Gandhi NK, Abdel-Karim AR, Banerjee S, Brilakis ES. Frequency and risk of noncardiac surgery after drug-eluting stent implantation. Catheter Cardiovasc Interv 2011;77:972–6.

13. Hawn MT, Graham LA, Richman JS, et al. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. JAMA 2013;310:1462–72.

14. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. J Am Coll Cardiol 2014;64:2730–9.

15. Kałuza GL, Joseph J, Lee JR, et al. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288–94.

16. Mahmoud KD, Sanon S, Habermann EB, et al. Perioperative cardiovascular risk of prior coronary stent implantation among patients undergoing noncardiac surgery. J Am Coll Cardiol 2016;67:1038–49.

17. Reddy PR, Vaitkus PT. Risks of noncardiac surgery after coronary stenting. Am J Cardiol 2005;95:755–7.

18. 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.

19. Wijeysundera DN, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. Circulation 2012;126:1355–62.

20. Rossini R, Musumeci G, Capodanno D, et al. Perioperative management of oral antiplatelet therapy and clinical outcomes in coronary stent patients undergoing surgery. Results of a multicentre registry. Thromb Haemost 2015;113:272–82.

KEY WORDS drug-eluting stents, dual antiplatelet therapy, registry, risk, surgery

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 68, NO. 24, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.09.967

Risk Associated With Surgery Within 12 Months After Coronary Drug-Eluting Stent Implantation

Gro Egholm, MD, PhD,[a,b] Steen Dalby Kristensen, MD, DMSc,[a] Troels Thim, MD, PhD,[a] Kevin K.W. Olesen, MD,[a] Morten Madsen, MSc,[b] Svend E. Jensen, MD, PhD,[c] Lisette O. Jensen, MD, PhD, DMSc,[d] Henrik T. Sørensen, MD, PhD, DMSc,[b] Hans E. Bøtker, MD, PhD, DMSc,[a] Michael Maeng, MD, PhD[a]

ABSTRACT

BACKGROUND Guidelines recommend postponing surgery for at least 6 months after treatment with a drug-eluting stent by percutaneous coronary intervention (DES-PCI).

OBJECTIVES The goal of this study was to evaluate the surgical risk associated with DES-PCI compared with that in nonstented patients without ischemic heart disease (IHD).

METHODS Between 2005 and 2012, a total of 22,590 patients underwent DES-PCI in western Denmark. By record-linking the Western Denmark Heart Registry and the Danish National Patient Register, we evaluated 4,303 DES-PCI–treated patients with a surgical procedure and compared them with a control group of patients without previous IHD undergoing similar surgical procedures (n = 20,232). Events of interest were myocardial infarction (MI), cardiac death, and all-cause mortality within 30 days after surgery.

RESULTS Surgery in DES-PCI–treated patients was associated with an increased risk of MI (1.6% vs. 0.2%; odds ratio [OR]: 4.82; 95% confidence interval [CI]: 3.25 to 7.16) and cardiac death (1.0% vs. 0.2%; OR: 5.87; 95% CI: 3.60 to 9.58) but not all-cause mortality (3.1% vs. 2.7%; OR: 1.12; 95% CI: 0.91 to 1.38). When stratified for time from PCI to surgery, only surgery within the first month was associated with a significant increased risk of events.

CONCLUSIONS Patients requiring surgery within 12 months after DES-PCI had an increased risk of MI and cardiac death compared with patients without IHD. The increased risk was only present within the first month after DES-PCI, suggesting that surgery might be undertaken earlier than currently recommended. (J Am Coll Cardiol 2016;68:2622–32)

Drug-eluting coronary stent (DES) implantation has become the standard of care in patients undergoing percutaneous coronary intervention (PCI) (1). Compared with bare-metal stent (BMS) implantation, earlier generations of DES-PCI delay the healing process after stent implantation (2,3). Consequently, patients are instructed to take dual antiplatelet therapy (DAPT) for 6 to 12 months to reduce the risk of stent thrombosis (4,5). A systematic review has estimated that approximately 4% to 15% of all patients undergoing DES-PCI need surgery within 12 months after stent

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; and the [d]Department of Cardiology, Odense University Hospital, Odense, Denmark. This work was supported by unrestricted grants from TrygFonden, Knud og Edith Eriksens Mindefond, Snedkermester Sophus Jacobsen og hustru Astrid Jacobsens Fond, Region Midtjyllands Sundhedsvidenskabelige Forskningsfond, and the Department of Cardiology, Aarhus University Hospital. Dr. Egholm has received speaker honorarium from Bayer. Dr. Kristensen is supported by a senior research grant from the Novo-Nordic Foundation. Dr. Thim has received an educational grant from St. Jude Medical; and a travel grant from Biosensors. The work of Dr. Sørensen was funded by the Program for Clinical Research Infrastructure established by the Lundbeck Foundation and the Novo Nordisk Foundation and administered by the Danish Regions. Dr. Bøtker is a member of the advisory board of AstraZeneca and Novo Nordisk. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 5, 2016; revised manuscript received August 28, 2016, accepted September 27, 2016.

implantation (6). The risk of adverse cardiac events ranges from 3% to 11% depending on the definition of adverse cardiac events, the timing of surgery after DES-PCI, and the different types of surgery (6–9).

Surgery within the first 6 months after DES-PCI is associated with an increased risk of adverse events compared with surgery performed >6 months after DES-PCI (10,11). Therefore, current guidelines from the European Society of Cardiology (ESC) recommend postponing elective surgery for 6 to 12 months after DES-PCI for stable coronary artery disease and for 12 months in patients with acute coronary syndrome (ACS) (4). U.S. guidelines recommend delaying surgery for 12 months after DES-PCI unless the risk associated with surgical delay is considered larger than the risk of stent thrombosis (5).

SEE PAGE 2633

Using Danish population-based registries and individual-based record linkage of Danish registries, we present the results of a population-based comparison of the risk associated with surgery among DES-PCI-treated patients compared with patients without ischemic heart disease (IHD) undergoing a similar operation.

METHODS

We conducted a matched-cohort study on the basis of patient-level record linkage of the Western Denmark Heart Registry (WDHR) and the Danish National Patient Register (DNPR) evaluating patients with DES-PCI undergoing a surgical procedure within 12 months after the index DES-PCI procedure. The study compared the risk of myocardial infarction (MI), cardiac death, and all-cause mortality between DES-PCI-treated patients and patients without IHD, sampled from the general population, who underwent the same surgical procedure.

STUDY SETTING AND POPULATION. All patients treated with a DES-PCI procedure between May 2005 and January 2012 were identified by using the WDHR (12). The registry assembles patient and procedural information from all coronary procedures performed at the 3 large PCI centers in western Denmark (Odense University Hospital, Aarhus University Hospital, and Aalborg University Hospital) covering the region's population of approximately 3 million inhabitants, corresponding to 55% of the Danish population.

For each patient, the first PCI procedure performed during the study period was included as the index procedure. Because >90% of the PCI procedures at our centers are currently performed with DES, patients treated with balloon dilation alone or with BMS were not included.

The Danish Civil Registration System provides each citizen with a unique personal identification number on birth or immigration; we were thus able to collect individual-level linked information throughout the national and regional administrative registries (13). Data from WDHR were linked with data from the DNPR to identify patients who required surgery within 12 months after the DES-PCI. The DNPR contains data on all Danish hospital admissions since 1995, including dates of hospitalization, outpatient visits, and discharge diagnosis/surgical procedures coded according to the International Classification of Diseases-10th Revision (ICD-10). The Danish National Health Service provides tax-supported health care, guaranteeing access to general practitioners and hospitals, as well as partial reimbursement for prescribed medications. This approach ensures a high coverage in the registries used (14).

Surgery was categorized as low- to high-risk procedures according to the latest version of the ESC guidelines on noncardiac surgery (4) and could be performed under local, spinal, or general anesthesia. The ESC guidelines recommend risk assessment on the basis of estimates of 30-day risk of MI and cardiovascular death after noncardiac surgery. In this study, cardiac surgery was considered a high-risk procedure. Noninvasive endoscopic procedures, closed orthopedic repositions, heart transplantations, or insertion of left ventricular assist devices were not included. Surgical procedures were grouped according to the surgery performed (endocrine, ophthalmic, otorhinolaryngologic, oral and maxillofacial, heart and central vascular; respiratory, mammary, abdominal surgery minor/major, urologic minor/major, gynecologic, orthopedic minor/major, peripheral vascular, dermatologic, or neurosurgery) (Online Table 1).

Patients without IHD were identified by using the DNPR and sampled from the general population. First, we included all patients with no history of IHD, defined as diagnosis ICD-10 codes I20 to I25 and without a prescription for anticoagulation therapy. Second, we matched DES-PCI-treated patients versus patients without IHD. Each DES-PCI-treated patient was matched individually with at least 1 and up to 5 patients without IHD. The matching was based on type of surgical procedure according to surgical procedure codes (ICD-10), inpatient/outpatient admission at surgery, age (±5 years), and sex. DES-PCI-treated patients

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BMS = bare-metal stent(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

DNPR = Danish National Patient Register

ESC = European Society of Cardiology

ICD-10 = International Classification of Diseases-10th Revision

IHD = ischemic heart disease

MI = myocardial infarction

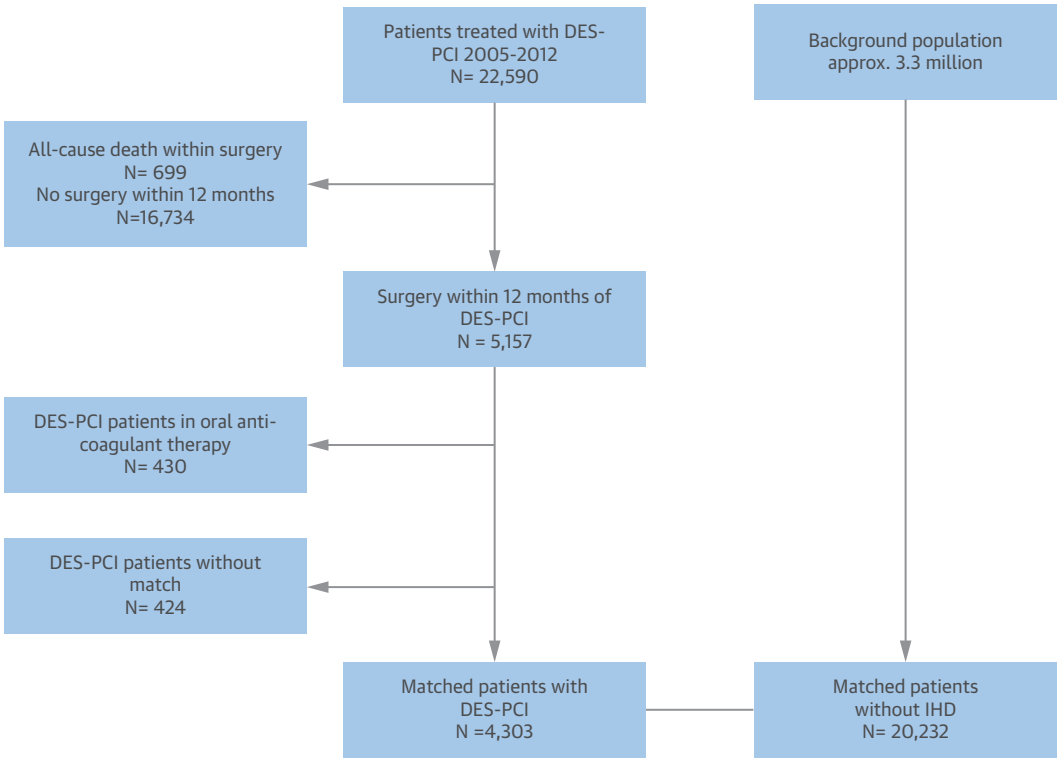
OR = odds ratio

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

WDHR = Western Denmark Heart Registry

FIGURE 1 Study Flowchart



Starting with a study population of 22,590 patients treated with a drug-eluting stent implanted by using percutaneous coronary intervention (DES-PCI), the surgical comparison cohorts included 4,303 DES-PCI–treated patients who were matched with 20,232 patients without ischemic heart disease (IHD) sampled from the general population.

undergoing anticoagulation therapy (warfarin and novel oral anticoagulant agents) were not included because these patients were likely in a different risk category.

PATIENT CHARACTERISTICS AND EVENT DEFINITIONS. The stents used in the cohort were both first-generation DES; sirolimus-eluting stent (Cypher, Cordis, Johnson & Johnson, New Brunswick, New Jersey) and the paclitaxel-eluting stent (Taxus, Boston Scientific Corp., Marlborough, Massachusetts) and second-generation DES; zotarolimus-eluting stent (Endeavor, Medtronic, Minneapolis, Minnesota) and the everolimus-eluting stent (Xience V, Abbott Vascular, or PROMUS, Abbott's privately labeled Xience V Everolimus Eluting Coronary Stent, Boston Scientific Corp.) and second-generation DES. Demographic and patient characteristics were retrieved from the WDHR and the Danish Register of Medical Product Statistics for DES-PCI-treated patients; the latter contains information on all prescriptions dispensed in Danish pharmacies since 1994. Patients were considered to be in treatment if a prescription was redeemed 100 days before surgery. Demographic and patient characteristics were retrieved for DES-PCI-treated patients and for patients without IHD. The Charlson Comorbidity Index was used to quantify comorbidity in the 2 groups, and data were retrieved from the DNPR (15). We used both the Charlson Comorbidity Index and a modified Charlson Comorbidity Index, excluding peripheral artery disease (PAD), diabetes mellitus, and renal disease, allowing these factors to be evaluated separately.

MI within the first 30 days' post-surgery was defined as the listing of MI as the primary or secondary discharge diagnosis (ICD-10 code I21) and acute hospital admission collected from the DNPR. This definition of MI has a sensitivity of 94% and a specificity of 98% (16). The discharge diagnosis of MI is decided by the discharging physician in accordance with the universal definition of MI (17). Cardiac death within the first 30 days after surgery was defined as death resulting from IHD, sudden cardiac death, death from ventricular tachycardia, death caused by heart failure, and sudden death undefined

(ICD-10 codes I20 to I25, I46, I47.2, I50, and R96, respectively); this information was retrieved from the Danish Registry of Causes of Death (18). All other deaths were recorded as noncardiac deaths.

All-cause mortality was identified within 30 days after surgery from the Civil Registration System (19). Events were included from any Danish hospital.

STATISTICAL ANALYSIS. Events were summarized as 30-day cumulative incidence and reported as counts (percentages). Patient demographic and surgical characteristics were stated as counts (percentages), mean ± SD, and age and time from PCI to surgery as median (interquartile range). Crude and adjusted odds ratios with 95% confidence intervals were computed for each adverse event (MI, cardiac death, and all-cause mortality).

To evaluate risk factors in DES-PCI-treated patients, bivariate logistic regression models were used. When assessing the impact of time from index PCI to surgery, Kaplan-Meier curves were determined to evaluate events as a function of time. Thereafter, we divided time from PCI to surgery according to period, as follows: 0 to 30 days, >1 to 2 months, >2 to 3 months, >3 to 6 months, >6 to 9 months, and >9 to 12 months (reference) for patients treated with DES-PCI. Subsequently, the information from these analyses was used to dichotomize time from index PCI to surgery into ≤1 month versus >1 to 12 months when evaluating risk factors in DES-PCI-treated patients.

Cumulative incidence proportion was calculated for patients without IHD matched with DES-PCI-treated patients with surgery within 0 to 30 days, >1 to 2 months, and >2 to 12 months after stent implantation. Patient-level matching was maintained for each of these groups; that is, a specific control subject was matched with a specific DES-PCI-treated patient and, thus, only appears in 1 of these groups Conditional logistic regression analyses were used to assess the risk of DES-PCI in the surgical setting. Covariates used in the comparative models were emergency versus elective surgery; they were further adjusted for PAD, diabetes mellitus, and renal disease, and categorized for the Charlson Comorbidity Index.

Statistical analyses were performed by using Stata version 13 (Stata Corp., College Station, Texas) and SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina). The study was approved by the Danish Data Protection Agency. Registry-based studies do not require ethical approval in Denmark.

RESULTS

Among 22,590 DES-PCI-treated patients, 5,157 (23%) individuals undergoing surgery within 12 months of the index PCI were identified. DES-PCI-treated patients receiving oral anticoagulation therapy (n = 430) were excluded, yielding a total of 4,727 patients treated with DES-PCI who were eligible for matching with patients without IHD. Because the comparison was limited to patients without IHD, 424 patients undergoing coronary artery bypass grafting were also excluded (Figure 1). For this unmatched DES-PCI population, the rates of MI (n = 11), cardiac death (n = 9; information limited to 408 patients), and all-cause mortality (n = 20) were 2.6%, 2.2%, and 4.7%, respectively.

Demographic and patient characteristics for DES-PCI-treated patients (n = 4,303) and patients without IHD (n = 20,232) are listed in Table 1. There were major differences in drug therapy related to IHD, such as statins, beta-blockers, nitrates, proton pump inhibitors, $P2Y_{12}$ inhibitors, and aspirin (the latter 2 comprising the components of DAPT). The surgical

TABLE 1 Patient Characteristics

	DES-PCI (n = 4,303)	Without IHD (n = 20,232)
Demographic characteristics		
Age, yrs	68 (60–75)	68 (60–75)
Male	3,038 (70.6)	14,293 (70.6)
Body mass index >30 kg/m^2	796 (23.4)	-
Smoking	1,117 (26.2)	-
Drug exposure		
$P2Y_{12}$ inhibitor	3,387 (78.7)	126 (0.6)
Aspirin	3,172 (73.7)	3,681 (18.2)
Proton pump inhibitors	1,270 (29.5)	2,272 (11.2)
Statins	3,133 (72.8)	3,105 (15.3)
NSAID	303 (7.0)	1,901 (9.4)
COX-2 inhibitor	194 (4.5)	1,205 (6.0)
Oral glucocorticoids	314 (7.3)	945 (4.7)
Calcium antagonist	1,210 (28.1)	2,659 (13.1)
Beta-blockers	2,915 (67.7)	2,038 (10.1)
Nitrates	1,185 (27.5)	175 (0.9)
Surgical characteristics		
Emergency surgery	1,123 (26.1)	5,458 (27.0)
ESC low-risk group	2,994 (69.6)	14,481 (71.6)
ESC intermediate-risk group	1,083 (25.2)	5,051 (25.0)
ESC high-risk group	226 (5.3)	700 (3.5)
Inpatients	1,862 (43.3)	8,328 (41.2)
Time from DES-PCI to surgery, d	147 (61–249)	-
Lesion and procedural characteristics		
No. of stents ≥1	1,729 (40.2)	-
Stent length ≥20 mm	2,269 (52.7)	-
First-generation DES	2,594 (60.3)	-
Acute coronary syndrome	2,291 (56.0)	-

Values are median (interquartile range) or n (%).

COX = cyclooxygenase; DES-PCI = drug-eluting stent implanted at percutaneous coronary intervention; ESC = European Society of Cardiology; IHD = ischemic heart disease; NSAID = nonsteroidal anti-inflammatory drug.

TABLE 2 Comorbidities

	DES-PCI (n = 4,303)	Without IHD (n = 20,232)
Comorbidity		
Myocardial infarction	52.0	0
Congestive heart failure	13.8	1.5
Peripheral vascular disease	12.7	5.2
Cerebrovascular disease	8.9	6.0
Dementia	0.5	1.0
Chronic pulmonary disease	10.6	5.2
Connective tissue disease	4.3	1.8
Gastroduodenal ulcer	3.4	1.2
Mild liver disease	0.8	0.8
Diabetes mellitus	16.7	4.3
Hemiplegia	0.1	0.1
Renal disease	5.7	1.6
End-organ disease caused by diabetes	9.5	2.9
Any tumor	8.1	5.1
Leukemia	0.5	0.3
Lymphoma	0.7	0.5
Liver disease	0.2	0.2
Metastatic solid tumor	0.6	0.7
AIDS	0.2	0.1
Charlson Comorbidity Index score		
0	23.1	72.4
1	33.9	14.3
2	19.8	8.2
≥3	23.2	5.1

Values are %.
AIDS = acquired immunodeficiency syndrome; other abbreviations as in Table 1.

characteristics were matched, and the rate of emergency surgery was 25.6%. In the patients treated with DES-PCI, 61% of DES used were first generation, and 56% of the DES-PCI procedures were performed in patients with ACS. Comorbidity, as assessed by using the Charlson Comorbidity Index, was more frequent in patients treated with DES-PCI, of whom 76.9% had at least 1 comorbidity compared with 27.6% in patients without IHD (Table 2). Thus, the DES-PCI-treated patients had more comorbidities than patients without IHD. The different surgical fields and their related events are displayed in Online Table 2.

RISK FACTORS AND RISKS WITH SURGERY. First, we evaluated the possible risk factors associated with events among the patients treated with DES-PCI. Surgery was more common within the first 3 months (34%) than at >3 to 6 months (25%), >6 to 9 months (21%), and >9 to 12 months (20%) after index PCI. Time from index PCI was significantly associated with the risk of events. The risks of surgery for each of the first 3 months as well as for the periods >3 to 6 months, >6 to 9 months, and using surgery >9 to 12 months after DES-PCI as reference, are presented in Online Table 3, which shows that surgery within the first month after DES-PCI was associated with a significantly increased risk of all events. Beyond the first month, however, no significant differences were observed compared with surgery at >9 to 12 months. According to the unadjusted ORs of clinical, PCI-related, or surgical risk factors related to post-operative adverse events (Table 3), the factors associated with the highest risk of events were timing of surgery (≤1 month vs. >1 to 12 months), emergency surgery (acute vs. elective), and ACS as an indication for DES-PCI, PAD, and renal disease.

Compared with certain stent-related factors (DES generation, total stent length per patient, and number of stents implanted per patient), diabetes mellitus, sex, and Charlson Comorbidity Index score were less strongly associated with events (Table 3).

We also evaluated the risk of surgery and subsequent events in DES-PCI-treated patients compared with patients without IHD (Table 4). Surgery in DES-PCI-treated patients was associated with an increased risk of MI (64 [1.6%] vs. 49 [0.2%]; OR: 4.82; 95% CI: 3.25 to 7.16) and cardiac death (44 [1.0%] vs. 31 [0.2%]; OR: 5.87; 95% CI: 3.60 to 9.58) but not all-cause mortality (137 [3.1%] vs. 551 [2.7%]; OR: 1.12; 95% CI: 0.91 to 1.38). After adjusting for emergency surgery, the risk of MI and cardiac death increased among DES-PCI-treated patients compared with patients without IHD, whereas all-cause mortality remained almost unaffected. Further adjustment for comorbidity by using the modified Charlson Comorbidity Index with separate inclusion of PAD, diabetes mellitus, and renal disease had very little effect on the risk estimates.

When stratifying for timing of surgery in relation to index DES-PCI, surgery performed within 1 month after index DES-PCI was associated with an increased risk in DES-PCI-treated patients compared with patients without IHD. However, the risk associated with surgery was also increased in patients without IHD undergoing similar operations with a matched degree of urgency, indicating that part of the increased risk was related to the type and urgency of surgery and not solely explained by surgery early after PCI (Central Illustration, Figure 2).

Comparing patients treated with PCI >1 to 2 months and >2 to 12 months versus their respectively matched patients without IHD, we found that surgery in these groups had a low and similar risk (Central Illustration, Figure 2).

TABLE 3 Risk Factors Associated With Adverse Cardiac Events

	n	Myocardial Infarction	Myocardial Infarction OR (95% CI)	Cardiac Death	Cardiac Death OR (95% CI)	All-Cause Mortality	All-Cause Mortality OR (95% CI)
Timing of surgery*							
≤1 month	635	46 (7.2)	15.84 (9.12–27.50)	31 (5.0)	13.71 (7.13–26.35)	57 (9.0)	4.42 (3.11–6.28)
>1–12 months	3,668	18 (0.5)		13 (0.4)		80 (2.1)	
ACS†							
ACS	2,291	50 (2.2)	3.64 (1.89–7.01)	32 (1.5)	5.14 (2.00–13.23)	76 (3.3)	1.41 (0.96–2.05)
SAP	2,012	11 (0.5)		5 (0.2)		43 (2.1)	
Emergency surgery							
Acute	1,123	42 (4.5)	5.58 (3.31–9.38)	28 (3.2)	4.92 (2.65–9.13)	93 (10.1)	6.44 (4.47–9.27)
Elective	3,180	22 (0.7)		16 (0.5)		44 (1.4)	
Stent generation							
First	2,594	36 (0.6)	0.84 (0.51–1.39)	25 (1.0)	0.75 (0.41–1.37)	69 (2.7)	0.66 (0.47–0.92)
Second	1,709	28 (1.6)		19 (1.1)		68 (4.0)	
Stent length							
>20 mm	2,269	37 (1.6)	0.81 (0.49–1.34)	28 (1.2)	0.64 (0.34–1.18)	79 (3.5)	0.81 (0.58–1.15)
≤20 mm	2,034	27 (1.3)		16 (0.8)		58 (2.8)	
No. of stents							
>1	1,729	24 (1.4)	1.12 (0.67–1.87)	23 (1.3)	0.62 (0.34–1.12)	61 (3.5)	0.83 (0.59–1.17)
1	2,574	40 (1.6)		21 (0.9)		76 (3.0)	
Age							
>70 yrs	1,789	26 (1.5)	0.96 (0.58–1.59)	25 (1.5)	1.88 (1.04–3.44)	88 (4.9)	2.60 (1.82–3.70)
≤70 yrs	2,514	38 (1.5)		19 (0.7)		49 (1.9)	
Sex							
Female	1,265	13 (1.0)	0.61 (0.33–1.12)	11 (0.9)	0.80 (0.41–1.60)	47 (3.7)	1.26 (0.88–1.81)
Male	2,987	51 (1.7)		33 (1.1)		90 (3.0)	
Comorbidity‡							
>1	673	13 (1.9)	1.04 (0.83–1.30)	8 (1.2)	1.04 (0.80–1.36)	27 (4.0)	1.23 (0.96–1.28)
0–1	3,630	51 (1.4)		36 (1.0)		110 (3.0)	
Diabetes mellitus							
Yes	719	8 (1.1)	0.71 (0.34–1.49)	6 (0.8)	0.79 (0.33–1.88)	27 (3.8)	1.23 (0.80–1.89)
No	3,584	56 (1.6)		38 (1.0)		110 (3.0)	
Peripheral artery disease							
Yes	547	9 (1.6)	1.13 (0.55–2.29)	8 (1.6)	1.53 (0.71–3.32)	29 (5.3)	1.88 (1.24–2.88)
No	3,756	55 (1.5)		36 (1.0)		108 (2.9)	
Renal disease§							
Yes	244	5 (2.0)	1.42 (0.56–3.57)	10 (4.2)	4.98 (2.43–10.20)	19 (7.8)	2.82 (1.70–4.66)
No	4,059	59 (1.5)		34 (0.8)		118 (2.9)	

Within 30 days after surgery among patients treated with DES; second line of each variable represents comparison group. *Refers to the time from index PCI to surgery (≤1 month vs. >1 to 12 months). †Refers to acute coronary syndrome (ACS) as an indication for PCI. ‡Comorbidity using modified Charlson Comorbidity Index. §Refers to diagnosed renal disease (data from the Danish National Patient Register).

CI = confidence interval; OR = odds ratio; SAP = stable angina pectoris; other abbreviations as in Table 1.

DISCUSSION

The present study compared risk associated with surgery in patients treated with DES-PCI versus patients without IHD, the latter sampled from the general population after excluding patients with previous IHD. The main findings were as follows: 1) surgery in patients treated with DES-PCI was associated with an increased 30-day risk of MI; 2) surgery among DES-PCI-treated patients did not increase 30-day all-cause mortality; and 3) beyond the first month after stent implantation, DES-PCI-treated patients had the same perioperative risk as surgery in patients without IHD.

The current guidelines on noncardiac surgery from the ESC (4) and the American College of Cardiology/American Heart Association (5) recommend delaying surgery after DES-PCI for 6 to 12 months. Our results suggest that surgery after DES-PCI might be performed earlier without increased risk.

SURGERY AFTER DES-PCI. By evaluating a DES-PCI cohort alone and by comparing it with a matched cohort of patients without IHD, we confirmed that the risk of MI after surgery declined over time from DES-PCI (8,20,21). Similar to previous studies (10,11), we found that surgery performed within the first month

TABLE 4 Risk Associated With Surgery

	DES-PCI*	DES-PCI,* Events	Without IHD	Without IHD, Events	Crude OR (95% CI)	Adjusted OR† (95% CI)	Adjusted OR‡ (95% CI)
Myocardial infarction	4,303	64 (1.5)	20,207	49 (0.2)	4.82 (3.25–7.16)	7.55 (4.80–11.9)	7.48 (4.72–11.9)
Time from DES-PCI to surgery ≤1 month	635	46 (7.2)	2,818	14 (0.5)	14.3 (7.49–27.4)	26.6 (11.2–62.8)	NR§
Time from DES-PCI to surgery >1–2 months	442	6 (1.4)	1,990	10 (0.5)	1.23 (0.42–3.66)	NR§	NR§
Time from DES-PCI to surgery >2–12 months	3,239	12 (0.4)	15,399	25 (0.8)	1.80 (0.87–3.72)	2.32 (1.08–4.96)	NR§
Cardiac death	4,059	44 (1.1)	20,205	31 (0.2)	5.87 (3.60–9.58)	7.79 (4.52–13.4)	7.51 (4.26–13.2)
Time from DES-PCI to surgery ≤1 month	626	31 (5.0)	2,818	9 (0.3)	15.1 (6.86–33.3)	15.1 (6.85–33.4)	NR§
Time from DES-PCI to surgery >1–2 months	429	2 (0.4)	1,989	4 (0.2)	1.35 (0.22–8.34)	NR§	NR§
Time from DES-PCI to surgery >2–12 months	3,004	11 (0.4)	15,398	18 (0.1)	2.50 (1.13–5.57)	3.54 (1.42–8.81)	NR§
All-cause mortality	4,299	137 (3.2)	20,207	551 (2.7)	1.12 (0.91–1.38)	1.19 (0.97–1.47)	1.07 (0.86–1.32)
Time from DES-PCI to surgery ≤1 month	635	57 (9.0)	2,818	198 (7.0)	1.30 (0.92–1.82)	1.32 (0.93–1.86)	1.18 (0.82–1.69)
Time from DES-PCI to surgery >1–2 months	442	12 (2.7)	1,990	64 (3.2)	0.79 (0.40–1.52)	0.89 (0.45–1.76)	0.90 (0.45–1.80)
Time from DES-PCI to surgery >2–12 months	3,222	68 (2.1)	15,399	289 (1.9)	1.09 (0.82–1.45)	1.17 (0.88–1.57)	1.02 (0.75–1.38)

Values are n or n (%) unless otherwise indicated. *Time from DES-PCI to surgery as a time-dependent risk associated with surgery only in patients with DES-PCI. †Adjusted for type of surgery (emergency vs. elective). ‡Further adjusted for comorbidity, using a modified Charlson Comorbidity Index in which peripheral artery disease, diabetes mellitus, and renal disease are included separately. §ORs are not reported (NR); adjustment not valid due to the low number of myocardial infarctions and cardiac deaths.

Abbreviations as in Tables 1 and 3.

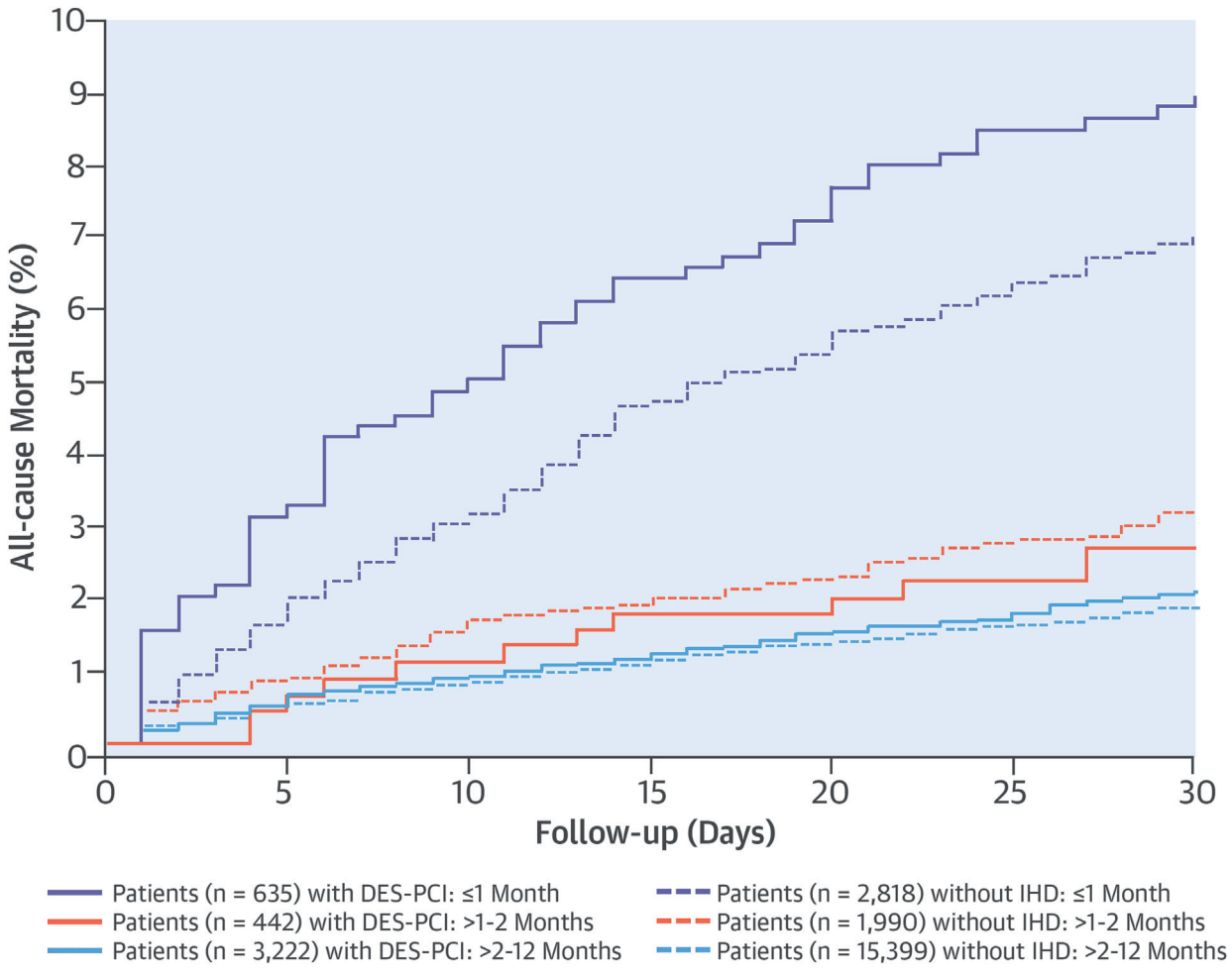
after DES-PCI was associated with the highest risk. Others have reported that surgery-associated risk in DES-PCI-treated patients reached a stable level after 3 to 6 months (8,20,22,23). Such temporal comparisons are only valid if the operations performed within the specified time intervals are comparable or if a surgical comparison cohort is included. Because previous studies did not include a surgical comparison cohort, the results are potentially influenced by the type and urgency of the surgical procedures.

To overcome this limitation, we included a matched cohort of patients without IHD. This evaluation of the comparative risk associated with surgery in DES-PCI-treated patients versus patients without IHD revealed an increased overall risk for MI and cardiac death in the patients with previous DES-PCI. However, this difference was highly time dependent and limited to the first month after DES-PCI. Furthermore, the increased risk associated with surgery within the first month after DES-PCI was not solely associated with DES-PCI. Matching for the specific surgical procedure and the urgency of the operation showed that the increased risk associated with surgery after DES-PCI within the first month was in part related to these parameters. Nevertheless, our data confirmed that surgery, if possible, should be delayed for at least 1 month after DES-PCI. Beyond the first 30 days after PCI, the DES-PCI-treated patients exhibited the same low risk as patients without previous IHD, even though the DES-PCI-treated patients had a higher number of comorbid conditions. This novel finding suggests that these patients, in whom delaying surgery might be associated with pain or increased risk of morbidity or mortality, can safely undergo surgical procedures earlier than current guidelines recommend (4,5).

We have been unable to identify any reports using a similar comparative design in patients treated with DES-PCI. In particular, no other study has compared DES-PCI-treated patients versus a control group of patients without previous IHD. However, we did identify a single study, combining DES and BMS, which had a comparison group (21). In that study, data for patients with coronary stents implanted in Veteran Affairs hospitals from 2000 to 2010 were matched with Veteran Affairs Surgical Quality Improvement Program data to identify noncardiac surgery within 24 months of stent placement. Similar to our results, the investigators reported an increased risk of MI but no difference in mortality. The same group of investigators used Veteran Affairs data to compare patients with stents undergoing surgery within 2 years versus patients with stents but without surgery (22). The 2 groups had the exact similar risk of adverse cardiac events during 2 years of follow-up. Patients with stents, however, had a higher risk of adverse cardiac events within the 30-day post-operative period. As in our study, this increased risk was particularly present within the first 4 to 6 weeks.

The main difference between this latter study and our data was the use of a nonsurgical group with IHD (22) versus a surgical non-IHD matched control group. The result obtained from U.S. Veterans Affairs hospitals may not be as representative of

CENTRAL ILLUSTRATION **All-Cause Mortality Stratified According to Time From Stent Implantation to Surgery**



Egholm, G. et al. J Am Coll Cardiol. 2016;68(24):2622-32.

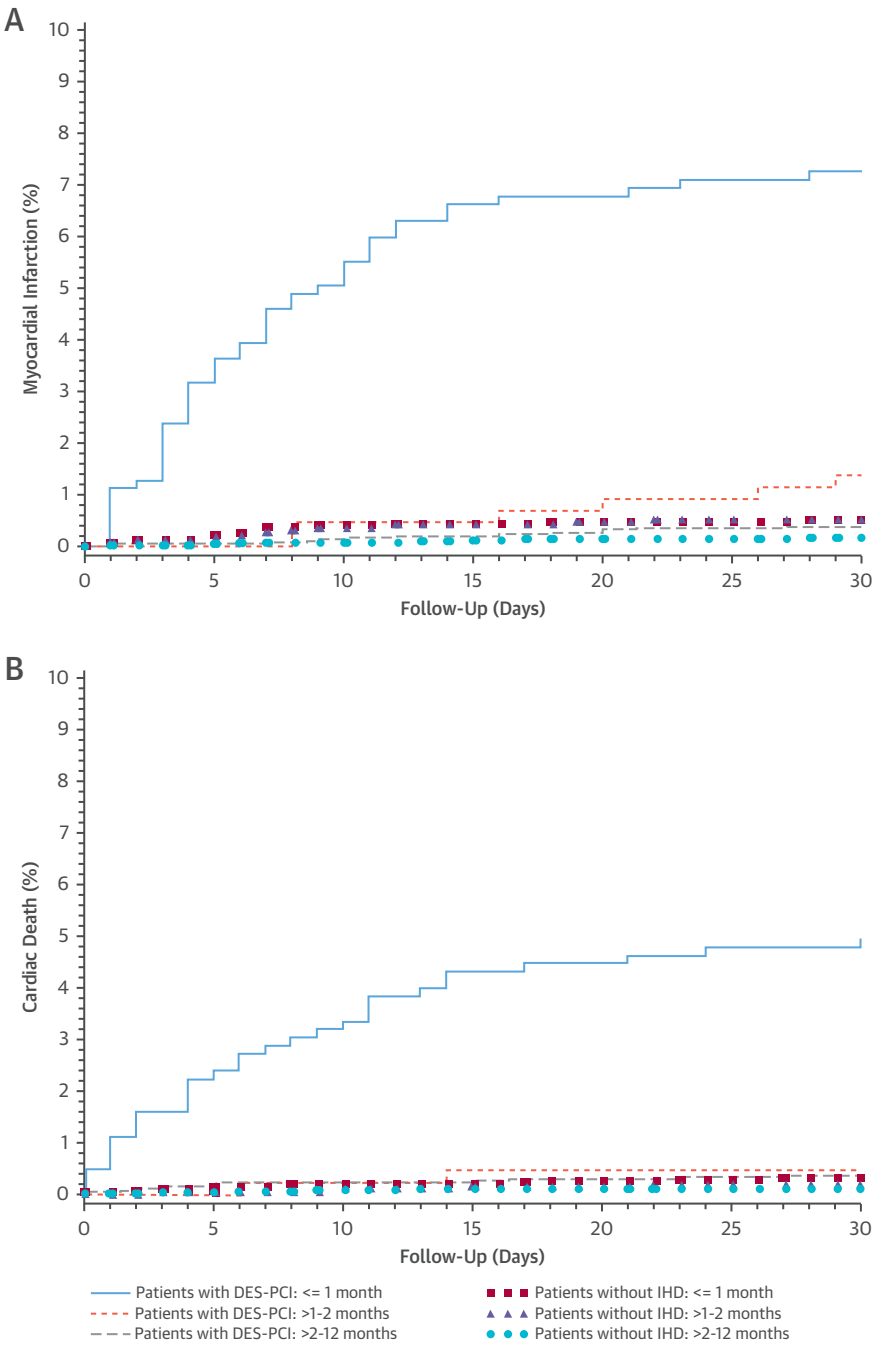
Although guidelines recommend delaying surgery until at least 6 months after treatment with a drug-eluting stent by percutaneous coronary intervention (DES-PCI), it is unknown whether associated risk is higher in these patients compared with those with ischemic heart disease (IHD). In this study, highest all-cause mortality risk was seen in DES-PCI–treated patients undergoing surgery within the first month after stent implantation; this finding was greater than mortality in matched patients without IHD. However, beyond the first month after stent implantation, DES-PCI–treated patients had the same mortality as matched patients without IHD.

an "all-comers" population as our study due to differences in sex (male subjects, 98% vs. 70%), presence of diabetes (49% vs. 17%), and probably a narrower social class (veterans vs. all social classes) (21). Our data are derived from a society with a tax-supported health care system with a guarantee for free access to general practitioners and hospitals. Clearly, therefore, the studies are performed in societies with different access to hospital care and surgery. Moreover, different strategies related to DAPT in relation to surgery are possible. However, the similarities of the results from the 2 studies performed in different settings supported the robustness of these findings.

STUDY LIMITATIONS. The major strength of this study was our use of population-based registries, which enabled us to collect procedural and diagnostic information on patients without previous IHD as well as DES-PCI-treated patients. Similarly, the use of registries permitted inclusion of consecutive patients over an 8-year period.

Some limitations must be acknowledged. First, our study had a retrospective design despite being based on prospectively registered data. Second, data on

FIGURE 2 Cumulative Incidence Proportion of Events



Cumulative incidence proportion of **(A)** myocardial infarction and **(B)** cardiac death are shown for patients with a DES-PCI and patients without IHD stratified according to time from index PCI to surgery. Abbreviations as in Figure 1.

timing of surgery might be affected by confounding by indication because the use of DAPT might have led to delay or even cancellation of some major surgical procedures (23). In addition, we did not have data on the antithrombotic therapy management during the surgery procedures for all 22,590 patients. We did, however, have data from a nested case-control study based on this cohort in which we evaluated the

medical charts of 458 patients who had been treated with DES-PCI and underwent surgery during the subsequent 12 months (24). In the control group (n = 230), who did not differ significantly from patients with adverse cardiac events or reoperation for bleeding, 58% of patients received both aspirin and a $P2Y_{12}$ inhibitor within 3 days before surgery, 3% received a $P2Y_{12}$ inhibitor only, 13% aspirin only, and 28% neither aspirin nor a $P2Y_{12}$ inhibitor. Also, the high rate of events within the first month of DES-PCI might have indicated that the concomitant therapy with antiplatelet therapy unmasked malignant conditions or that the PCI-related hospitalization revealed conditions that led to accelerated surgical procedures. Such comorbidities were not accounted for in the matching of DES-PCI-treated patients and patients without IHD, and this issue represents a potential bias.

Finally, the risk of being classified as a cardiac death was overall increased among patients with known IHD (DES-PCI-treated patients) compared with patients with no previous IHD. Without a difference in all-cause death, the difference in cardiac death (and noncardiac death) between patients treated with DES-PCI and patients without IHD is striking and is most likely caused by differential classification. It is unclear whether this difference was caused by too many deaths classified as cardiac among DES-PCI-treated patients, too few among patients without IHD, or a combination of these factors.

CONCLUSIONS

Patients requiring surgery within 12 months after DES-PCI had an increased risk of MI and cardiac death compared with patients without IHD. The increased risk was only present within the first month after DES-PCI, suggesting that surgery might be undertaken earlier than currently recommended.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gro Egholm, Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. E-mail: grochi@rm.dk.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although surgery within 30 days after implantation of DES increases the risk of MI, cardiac death, and all-cause mortality, surgery performed beyond this period but within 12 months after DES implantation demonstrated a 30-day mortality equivalent to that of patients without IHD.

TRANSLATIONAL OUTLOOK: Further studies are needed to define the optimal approach to antithrombotic therapy in patients undergoing noncardiac surgery in the 12 months after DES implantation.

REFERENCES

1. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med 2015;373:2038–47.

2. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. Arterioscler Thromb Vasc Biol 2007;27:1500–10.

3. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.

4. Kristensen SD, Knuuti J, Saraste A, et al. 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;35:2383–431.

5. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.

6. Hollis RH, Graham LA, Richman JS, et al. Adverse cardiac events in patients with coronary stents undergoing noncardiac surgery: a systematic review. Am J Surg 2012;204:494–501.

7. Alshawabkeh LI, Banerjee S, Brilakis ES. Systematic review of the frequency and outcomes of non-cardiac surgery after drug-eluting stent implantation. Hellenic J Cardiol 2011;52:141–8.

8. Hawn MT, Graham LA, Richman JS, et al. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. JAMA 2013;310:1462–72.

9. Hawn MT, Graham LA, Richman JR, et al. The incidence and timing of noncardiac surgery after cardiac stent implantation. J Am Coll Surg 2012;214:658–66.

10. 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.

11. Tokushige A, Shiomi H, Morimoto T, et al. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: a report from the CREDO-Kyoto PCI/CABG Registry Cohort-2. Circ Cardiovasc Interv 2012;5:237–46.

12. Schmidt M, Maeng M, Jakobsen CJ, et al. Existing data sources for clinical epidemiology: the Western Denmark Heart Registry. Clin Epidemiol 2010;2:137–44.

13. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.

14. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol 1996;25:435–42.

15. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.

16. Egholm G, Madsen M, Thim T, et al. Evaluation of algorithms for registry-based detection of acute myocardial infarction following percutaneous coronary intervention. Clin Epidemiol 2016;8:415–23.

17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67.

18. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39 Suppl 7:26–9.

19. Pedersen CB. The Danish Civil Registration System. Scand J Public Health 2011;39 Suppl 7:22–5.

20. Saia F, Belotti LM, Guastaroba P, et al. 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? Circ Cardiovasc Qual Outcomes 2016;9:39–47.

21. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of coronary stents on postoperative adverse events: a matched cohort study. Ann Surg 2016;263:924–30.

22. Holcomb CN, Graham LA, Richman JS, et al. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. J Am Coll Cardiol 2014;64:2730–9.

23. Graham LA, Hollis RH, Richman JS, Hawn MT. Frequency of surgery cancellations associated with myocardial infarction or death 6 months after coronary stent placement. JAMA Surg 2015;150:1199–201.

24. Egholm G, Thim T, Olesen KK, et al. Dual antiplatelet therapy after coronary drug-eluting stent implantation and surgery-associated major adverse events. Thromb Haemost 2016;116:172–80.

KEY WORDS coronary artery disease, epidemiology, interventional cardiology, noncardiac surgery

APPENDIX For supplemental tables, please see the online version of this article.