Article type : Original Paper

**Coronary stent implantation and adverse cardiac events after surgery**

Troels Thim, MD, PhD,² Gro Egholm, MD, PhD,² Kevin Kris Warnakula Olesen, MD,² Morten Madsen, MSc, b Svend Eggert Jensen, MD, PhD, c Lisette Okkels Jensen, MD, DMSc, d Hans Erik Bøtker, MD, DMSc, a Steen Dalby Kristensen, MD, DMSc, a Michael Maeng, MD, PhD a

² Department of Cardiology, Aarhus University Hospital, Denmark
b Department of Clinical Epidemiology, Aarhus University Hospital, Denmark
c Department of Cardiology, Aalborg University Hospital, Denmark
d Department of Cardiology, Odense University Hospital, Denmark

**Running head:** Coronary drug-eluting stents and non-cardiac surgery

**Correspondence and reprints:** Troels Thim, Aarhus University Hospital, Department of Cardiology, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark. E-mail: troels.thim@clin.au.dk.

**Conflict of interest:** None.
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/eci.13030
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Funding: Department of Cardiology, Aarhus University Hospital, Denmark

Abstract

Background: In the risk-assessment of patients considered for non-cardiac surgery and with recent coronary stent implantation, coronary drug-eluting stent implantation procedure characteristics may be taken into account. We aimed to evaluate associations between coronary drug-eluting stent implantation procedure characteristics and the risk of myocardial infarction and all-cause death within 30 days after non-cardiac surgery.

Design: Patients with coronary drug-eluting stents were identified using the Western Denmark Heart Registry. Surgical procedures performed after stent implantation were detected using the Danish National Patient Registry. We used registry based detection of myocardial infarction and all-cause death.

Results: Of 22,590 patients treated with drug-eluting stents between 2005 and 2012, 4,046 underwent non-cardiac surgery within 1 and 12 months after stent implantation. We found no significant association between the risk of myocardial infarction or all-cause death within 30 days after surgery and number of arteries treated (1 (reference) versus more), number of lesions treated (1 (reference) versus more), segments treated (left main and proximal left anterior descending artery versus other (reference), total stent length (< 20mm (reference) versus ≥20mm), number of stents (1 (reference) versus >1), and largest balloon diameter (≥3mm (reference) versus <3mm). All-cause death, but not myocardial infarction, risk was lower among patients treated with first generation versus second generation stents (odds ratio 0.58).
Conclusions: We identified no significant associations between stent implantation procedure characteristics and risk of myocardial infarction or all-cause death among patients undergoing non-cardiac surgery. All-cause death was lower with first versus second generation drug eluting stents.

Key words: drug-eluting stents, non-cardiac surgery, myocardial infarction, all-cause death

Introduction

After coronary stent implantation, 5–25% of patients require non-cardiac surgery within 5 years after stent implantation.\(^1\) Guidelines advocate postponing surgery until termination of dual antiplatelet therapy.\(^1,2\) When surgery cannot be postponed, it is recommended that a multidisciplinary team assess the individual risk associated with surgery and make a plan for the surgery, including perioperative management of antiplatelet therapy, taking the risk of ischemic and bleeding events into account.\(^1,2\) In the risk assessment, individual factors such as stent implantation procedure characteristics (e.g., stent type, stent length, number of stents and stented vascular segment) may be taken into account. However, data justifying that procedural characteristics influence outcomes in relations to subsequent non-cardiac surgery are scarce.\(^3–5\) We aimed to evaluate the association between stent implantation procedure characteristics and risk of myocardial infarction and all-cause death among patients undergoing non-cardiac surgery between 1 and 12 months after coronary drug-eluting stent implantation.
Methods

The study was an observational registry-based study. In Denmark, registry-based studies do not require ethical approval. The study was approved by the Danish Data Protection Agency (2012-41-0164).

We evaluated the association between variables related to the drug-eluting stent implantation procedure and the risk of myocardial infarction and all-cause death. Patients undergoing non-cardiac surgery between 1 and 12 months after drug-eluting stent implantation were included.

We evaluated the risk in relation to surgery within the first year after coronary drug-eluting stent implantation since the standard recommendation for dual antiplatelet therapy after coronary drug-eluting stent implantation was one year during the study period. Surgery performed within in the first month after coronary drug-eluting stent implantation was excluded since surgery performed within this period is most often urgent surgery associated with a higher risk than surgery performed more than one month after coronary DES implantation.6 We assessed 30-day postoperative risk of myocardial infarction and all-cause-death.

All patients treated with drug-eluting stent implantation between May 2005 and January 2012 as registered in the Western Denmark Heart Registry and with a non-cardiac surgical procedure in the Danish National Patient Registry within 1 to 12 months after drug-eluting stent implantation were included in the analysis. The cohort of patients treated with drug-eluting stent implantation between May 2005 and January 2012 has been previously described.6 We used registry-based event detection.7
We evaluated the following stent implantation procedure characteristics:

- number of arteries treated (1 (reference) versus >1),
- number of lesions treated (1 (reference) versus >1),
- treated segments (left main and proximal left anterior descending artery versus other segments (reference)),
- total stent length (<20mm (reference) versus ≥20mm),
- number of stents (1 (reference) versus >1),
- drug-eluting stent generation (first versus second (reference)),
- and largest balloon diameter (<3mm versus ≥3mm (reference)).

We evaluated associations between these characteristics and the outcomes, myocardial infarction and all-cause death using odds ratios. Myocardial infarction was defined as a discharge diagnosis of myocardial infarction from and acute admission as registered in the Danish National Patient Registry. This definition has recently been validated using patient chart review. All-cause death data were retrieved from the Danish Central Person Register.

The included non-cardiac surgical procedures have been published earlier. Cardiac surgery was not included.

Baseline patient demographics and stent implantation procedure characteristics (including procedure dates) were retrieved from the Western Denmark Heart Registry. This registry collects patient and procedure characteristics on all coronary procedures performed in Western Denmark, which covers 3 million inhabitants (55% of the Danish population).

Dates of surgery, surgical procedure codes, and myocardial infarction diagnoses were retrieved from the Danish National Patient Registry. This registry collects data on all hospital admissions and outpatient clinic visits in all of Denmark. The collected data include codes for procedures and examinations as well as admission types and discharge diagnoses.

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The Danish Central Person Register contains vital status on all Danish citizens and is updated daily. The Civil Personal Register number assigned to all Danish citizens in this registry allows for individual-level record linkage across the used registries.

We used logistic regression to estimate crude odds ratios and odds ratios adjusted for age (≤ or >70 years) and gender. Kaplan-Meier failure estimate graphs were constructed for the myocardial infarction and all-cause death. Data were summarised and analysed using Stata/IC 13.1 for Windows.

In a supplemental analysis, we adjusted the crude odds ratios for acute coronary syndrome as indication for stent implantation, year of stent implantation, time from stent implantation to surgery, and for European Society of Cardiology/European Society of Anesthesiology non-cardiac surgery risk group.

Results

A total of 22,590 patients were treated with drug-eluting stents in the study period (Figure 1). Of these, 4,046 patients underwent a subsequent surgical procedure within 1 to 12 months after coronary stent implantation. The baseline patient demographics and drug-eluting stent implantation procedure characteristics of these 4,046 patients are given in Tables 1 and 2. The surgical procedures were performed within a wide range of surgical specialties and were categorized as European Society of Cardiology/European Society of Anesthesiology non-cardiac surgery low (n=2,945), intermediate (n=1,014) and high (n=87) risk groups.

Among 4,046 patients with a surgical procedure within 1 to 12 months after coronary stent implantation, 18 patients (0.4%) suffered a myocardial infarction and 88 patients (2.2%) died within 30 days after surgery (Figure 2).
The odd ratios for myocardial infarction and all-cause death after non-cardiac surgery according to stent implantation procedure characteristics are given in Table 3.

Overall, the 95% confidence intervals were wide as a consequence of the low event rates. Only, the odds ratio for the association between stent generation and all-cause death had a 95% confidence interval that did not span one with first generation stents being associated with a lower risk of death.

In the supplemental analysis, adjustment for acute coronary syndrome as indication for stent implantation, year of stent implantation, time from stent implantation to surgery, and for European Society of Cardiology/European Society of Anesthesiology non-cardiac surgery risk group did not change the crude odds ratios markedly (please, see the Supplementary table 1 and 2). Combining the endpoints myocardial infarction and all-cause death did not change the results (please see Supplementary table 3).

The time interval between stent implantation and surgery did not differ between patients treated with first and second generation stents. Supplementary table 4 and 5 show the number of non-cardiac surgical procedures and risk of myocardial infarction and death according to time between stent implantation and non-cardiac surgery in the intervals 31-60 days, 61-90 days, 91-180 days, 181-270 days, 271-365 days stratified according to stent generation.

Discussion

The main findings of the study are that the rates of myocardial infarction (0.4%) and all-cause death (2.2%) within 30 days after surgery were low and that there were no statistically significant associations between stent implantation procedure characteristics and risk of these events. However, there was a general trend towards a higher post-operative risk with coronary stent treatment for more extensive or severe disease.
The observed rates of myocardial infarction and all-cause death within 30 days after non-cardiac surgery within 1 to 12 months after coronary drug eluting stent implantation were low. In previous studies, rates of myocardial infarction and death after non-cardiac surgery among patients with prior coronary drug-eluting stent implantation vary.\textsuperscript{3–5,12–15} These studies are heterogeneous. Some include patients treated with BMS or DES and others only include patients treated with DES. The follow-up intervals after stent implantation also differed. Moreover, the time intervals between stent implantation and surgery, the types of non-cardiac surgery included, and the follow-up time after surgery have varied and may have impacted results. For myocardial infarction, differences in definition of myocardial infarction and practices for assessment of biochemical markers of myocardial injury after surgery may lead to differences in detection.

Although we included all patients treated with coronary drug-eluting stent implantation within the study period, selection of patients for surgery by the treating clinicians may have contributed to the observed low event rates. I.e., patients assumed to have a low risk in relation to surgery would be more likely to have surgery performed, whereas patients assumed to have higher risk would be more likely to have surgery deferred or postponed. In the available studies,\textsuperscript{3–5,12–15} including the current study, data describing the numbers and characteristics of patients considered for surgery after stent implantation, but who had surgery deferred or postponed, are lacking. Thus, the processes for selection of patients for surgery were not described. Therefore, the observed low risks of post-operative events may not apply to all patients, in whom surgery is considered during the first year after coronary drug-eluting stent implantation. Particularly, patients in the European Society of Cardiology/European Society of Anesthesiology non-cardiac surgery high risk group were not well-represented in this study.
Only the association between first generation drug-eluting stents and lower all-cause death was statistically significant. Since first generation drug-eluting stents are not currently implanted, this result no longer has clear clinical impact. The result seems counterintuitive and conflicting with previous data.\textsuperscript{12} The result could be a chance finding. However, it may also represent temporal changes in practice regarding the performance of surgery within the first year after implantation. First generation stents were implanted earlier in the study period than second generation stents and a more critical selection of very low risk patients for surgery during this period, with focus on late stent thrombosis, may have contributed to this result.

Regarding the remaining stent procedure characteristic, there may be a general trend towards a higher post-operative risk with coronary stent treatment for more extensive or severe disease. The observed odds ratios have wide 95% confidence intervals as a consequence of the observed low event rates. However, the best estimates in this study are that the risk of myocardial infarction is increased approximately 77% with stent treatment of the left main or proximal left anterior descending artery, 34% with total stent length $\geq 20$mm, and 15%-20% with number of stents, treated arteries, or treated lesions $> 1$. Whether these risks are related to the stent treatment per se or the underlying more extensive disease requiring more extensive stent treatment remains unresolved. More extensive or severe disease may also be associated with important comorbidities that can adversely affect the post-operative risk of myocardial infarction and death. We adjusted results for age and gender but did not adjust for other potential confounding comorbidities in consideration of the low number of events.
The observed higher post-operative risk with coronary stent treatment for more extensive or severe disease, although without statistically significant associations, is in agreement with previous, smaller, studies in patients treated with bare metal stents.\textsuperscript{3,4} In some larger studies, with higher event rates after surgery, factors such as incomplete revascularisation, ostial lesions, distal lesions, and calcified lesions were associated with adverse cardiac events after surgery.\textsuperscript{16,17}

The investigated stent procedure characteristics are not independent, i.e. patients treated in more than one artery are treated for more than one lesion and are more likely to be treated with more than one stent and longer total stent length. Also, patients treated for lesions in the proximal segments of the left coronary artery (segments 5,6,7) are more likely to be treated with larger balloon diameters than patients treated for more distal lesions.

As the current study was registry based, we did not have individual level information on antiplatelet therapy in relation to surgery. This is a limitation since the perioperative handling of antiplatelet therapy in relation to surgery has impact on ischemic events.\textsuperscript{18} It is also a limitation that we were not able to include data on stroke, repeat revascularisation or bleeding after surgery. Since we used the Danish National Patient Registry for event detection, we were unable to account for stent thrombosis specifically; however, any stent thromboses should be detected as either myocardial infarction or death.

The guidelines generally recommend a careful individual risk assessment before undertaking surgery in patients on dual antiplatelet therapy because of recent drug-eluting stent implantation.\textsuperscript{1,2} With the current evidence, it remains uncertain how stent implantation procedure characteristics should be weighed in this risk assessment. It may be
reasonable, in general terms, to consider more extensive coronary drug-eluting stent treatment as a risk factor.

The main limitations of the study are, thus, the missing information on the processes for selection of patients for surgery and handling of antiplatelet therapy in relation to surgery. The lack of information on the processes for selection of patients for surgery is shared with the other studies in this field. The relatively low number of events limited the statistical power of the study.

In conclusion, we identified no significant associations between stent implantation procedure characteristics and risk of myocardial infarction or all-cause death among patients undergoing non-cardiac surgery within 1-12 months after coronary drug-eluting stent implantation. All-cause death was lower with first versus second generation drug-eluting stents.

Acknowledgements

The study was supported by the Department of Cardiology, Aarhus University Hospital and the Department of Clinical Epidemiology, Aarhus University Hospital.

References


Figure 1. Study flow chart

Patients with coronary drug-eluting stent implantation 2005-2012
N = 22,590

Death within 12 months after stent implantation without surgery, N = 699
No surgery within 12 months after stent implantation, N = 16,734

Surgery within 12 months after coronary drug-eluting stent implantation
N = 5,157

Cardiac surgery, N = 399
Surgery within 1 month after stent implantation, N = 712

Non-cardiac surgery within 1 to 12 months after coronary drug-eluting stent implantation
N = 4,046

Figure 2: Kaplan-Meier failure estimate for myocardial infarction (A) and for all-cause death (B)

A

B

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### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=4,046)</th>
<th>Myocardial infarction</th>
<th>All-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (years)</td>
<td>68 (61-76)</td>
<td>70 (62-81)</td>
<td>68 (61-76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76 (69-83)</td>
<td>68 (60-75)</td>
</tr>
<tr>
<td>Male gender</td>
<td>2,860 (71%)</td>
<td>12 (67%)</td>
<td>2,848 (71%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52 (59%)</td>
<td>2,808 (71%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1,029 (25%)</td>
<td>4 (22%)</td>
<td>1,025 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (19%)</td>
<td>1,012 (26%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2,189 (54%)</td>
<td>12 (67%)</td>
<td>2,177 (54%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44 (50%)</td>
<td>2,145 (54%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2,027 (50%)</td>
<td>11 (61%)</td>
<td>2,016 (50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 (55%)</td>
<td>1,979 (50%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>641 (16%)</td>
<td>2 (11%)</td>
<td>639 (16%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (17%)</td>
<td>626 (16%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>751 (19%)</td>
<td>6 (33%)</td>
<td>745 (18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 (22%)</td>
<td>732 (18%)</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention</td>
<td>614 (15%)</td>
<td>5 (28%)</td>
<td>609 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (19%)</td>
<td>597 (15%)</td>
</tr>
<tr>
<td></td>
<td>All patients (n=4,046)</td>
<td>Myocardial infarction</td>
<td>All-cause death</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>-----------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>Yes (n = 18)</td>
<td>No (n = 4,028)</td>
<td>Yes (n = 88)</td>
</tr>
<tr>
<td>Number of arteries treated (&gt; 1)</td>
<td>792 (20%)</td>
<td>4 (22%)</td>
<td>788 (20%)</td>
</tr>
<tr>
<td>Number of lesions treated (&gt; 1)</td>
<td>1,230 (30%)</td>
<td>6 (33%)</td>
<td>1,224 (30%)</td>
</tr>
<tr>
<td>Treated segments (5, 6, 7*)</td>
<td>1,906 (47%)</td>
<td>11 (61%)</td>
<td>1,895 (47%)</td>
</tr>
<tr>
<td>Total stent length (≥ 20mm)</td>
<td>2,188 (54%)</td>
<td>11 (61%)</td>
<td>2,177 (54%)</td>
</tr>
<tr>
<td>Number of stents (&gt; 1)</td>
<td>1,611 (40%)</td>
<td>8 (44%)</td>
<td>1,603 (40%)</td>
</tr>
<tr>
<td>Stent generation (first generation)</td>
<td>2,488 (61%)</td>
<td>9 (50%)</td>
<td>2,479 (62%)</td>
</tr>
<tr>
<td>Largest balloon diameter (&lt; 3 mm)</td>
<td>997 (25%)</td>
<td>4 (22%)</td>
<td>993 (25%)</td>
</tr>
</tbody>
</table>

* Segment 5: left main stem. Segments 6-7: proximal left anterior descending coronary artery.
**Table 3.** Odd ratios for myocardial infarction and all-cause death within 30 days after non-cardiac surgery according to stent implantation procedure characteristics

<table>
<thead>
<tr>
<th></th>
<th>Crude OR</th>
<th>Adjusted OR</th>
<th>Crude OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of arteries treated (&gt; 1)</td>
<td>1.17 (0.39-3.58)</td>
<td>1.15 (0.38-3.52)</td>
<td>0.91 (0.53-1.58)</td>
<td>0.83 (0.48-1.43)</td>
</tr>
<tr>
<td>Number of lesions treated (&gt; 1)</td>
<td>1.15 (0.43-3.06)</td>
<td>1.13 (0.42-3.02)</td>
<td>1.01 (0.64-1.60)</td>
<td>0.94 (0.59-1.49)</td>
</tr>
<tr>
<td>Treated segments (5, 6, 7*)</td>
<td>1.77 (0.68-4.57)</td>
<td>1.77 (0.68-4.57)</td>
<td>1.13 (0.74-1.72)</td>
<td>1.10 (0.72-1.68)</td>
</tr>
<tr>
<td>Total stent length (≥ 20mm)</td>
<td>1.34 (0.52-3.45)</td>
<td>1.34 (0.52-3.48)</td>
<td>1.12 (0.73-1.72)</td>
<td>1.13 (0.74-1.74)</td>
</tr>
<tr>
<td>Number of stents (&gt; 1)</td>
<td>1.21 (0.48-3.07)</td>
<td>1.20 (0.47-3.05)</td>
<td>1.10 (0.72-1.69)</td>
<td>1.06 (0.69-1.62)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent generation (first)</td>
<td>0.62 (0.25-1.58)</td>
<td>0.63 (0.25-1.59)</td>
<td>0.56 (0.37-0.86)</td>
<td>0.58 (0.38-0.89)</td>
</tr>
<tr>
<td>Largest balloon diameter (&lt; 3 mm)</td>
<td>0.87 (0.29-2.66)</td>
<td>0.86 (0.28-2.61)</td>
<td>1.29 (0.81-2.05)</td>
<td>1.20 (0.76-1.92)</td>
</tr>
</tbody>
</table>

OR=odds ratio, presented as OR (95% confidence interval). Adjusted for age (≤ or >70 years) and gender.

* Segment 5: left main stem. Segments 6-7: proximal left anterior descending coronary artery.