Previous Coronary Stent Implantation and Cardiac Events in Patients Undergoing Noncardiac Surgery

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Background—Noncardiac surgery performed after coronary stent implantation is associated with an increased risk of stent thrombosis, myocardial infarction, and death. The influence of stent type and period of risk still have to be defined.

Methods and Results—We linked the Scottish Coronary Revascularisation Register with hospital admission data to undertake a Scotland-wide retrospective cohort study examining cardiac outcomes in all patients who received drug-eluting or bare-metal stents between April 2003 and March 2007 and subsequently underwent noncardiac surgery. Of 1953 patients, 570 (29%) were treated with at least 1 drug-eluting stent and 1383 (71%) with bare-metal stents only. There were no differences between drug-eluting and bare-metal stents in the primary end point of in-hospital mortality or ischemic cardiac events (14.6% versus 13.3%; P=0.3) or the secondary end points of in-hospital mortality (0.7% versus 0.6%; P=0.8) and acute myocardial infarction (1.2% versus 0.7%; P=0.3). Perioperative death and ischemic cardiac events occurred more frequently when surgery was performed within 42 days of stent implantation (42.4% versus 12.8% beyond 42 days; P<0.001), especially in patients revascularized after an acute coronary syndrome (65% versus 32%; P=0.037). There were no temporal differences in outcomes between the drug-eluting and bare-metal stent groups.

Conclusions—Patients undergoing noncardiac surgery after recent coronary stent implantation are at increased risk of perioperative myocardial ischemia, myocardial infarction, and death, particularly after an acute coronary syndrome. For at least 2 years after percutaneous coronary intervention, cardiac outcomes after noncardiac surgery are similar for both drug-eluting and bare-metal stents. (Circ Cardiovasc Interv. 2010;3:236-242.)

Key Words: angioplasty ■ myocardial infarction ■ stents ■ surgery ■ survival

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introduced in the 1990s, bare-metal coronary stent implantation revolutionized percutaneous coronary intervention by reducing abrupt vessel closure as well as recoil and restenosis after balloon angioplasty. However, their use is associated with restenosis due to neointimal hyperplasia at the site of implantation. Drug-eluting coronary stents were developed to address this problem and have reduced the need for target vessel revascularization by 50% to 70%. In Scotland, coronary stents are used in >90% of percutaneous coronary interventions, with drug-eluting stents, commercially available since 2003, used in ≈50% of procedures by 2006.

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Stent thrombosis after coronary stent implantation is a serious condition associated with poor clinical outcomes. Treatment of patients with dual antiplatelet therapy (aspirin and thienopyridine) for at least 4 weeks after bare-metal stent implantation has reduced the incidence of stent thrombosis to <1%. The optimal duration of dual antiplatelet therapy after implantation of a drug-eluting stent remains unknown. Recently, a number of randomized controlled trials and registries have reported a small risk of late (30 days to 12 months) and very late (>12 months) stent thrombosis after implantation of drug-eluting stents. These findings have been attributed to delays in stent endothelialization, hypersensitivity reactions to stent components, and the greater complexity of interventions being performed with drug-eluting stents. Current guidelines recommend 6 to 12 months of dual antiplatelet therapy after drug-eluting stent placement.

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Noncardiac surgery is associated with a proinflammatory and prothrombotic state. When circulating concentrations of procoagulant factors are increased, platelet activation occurs, and endogenous fibrinolysis is impaired, increasing the potential risk of stent thrombosis, particularly where endothelialization of a coronary stent is delayed or impaired. Because of concerns of excessive bleeding, antiplatelet therapy is often discontinued in the perioperative period, although this has emerged as one of the most important independent predictors of stent thrombosis.

Previous studies evaluating outcomes in patients undergoing noncardiac surgery after bare-metal stent placement reported extremely high rates of stent thrombosis, myocardial infarction, and death in patients having their surgery within 4 to 6 weeks of stent placement. It is unclear whether this risk is increased or prolonged in patients treated with drug-eluting stents. To address this issue, we undertook a Scotland-wide retrospective cohort study of patients undergoing noncardiac surgery after coronary stent implantation to compare perioperative risk by type of stent and to explore the temporal relationship.

Methods

Data Sources
The Scottish Coronary Revascularisation Register has prospectively collected comprehensive data on all percutaneous coronary interventions performed in Scottish National Health Service (NHS) hospitals since April 1997. The information collected includes patient demographics, clinical indication, procedure urgency, stent details (location, number, length, size, and type), pre- and postprocedure thrombolysis in myocardial infarction flow, estimated left ventricular ejection fraction, glycoprotein Ib/IIa receptor antagonist use at the time of coronary intervention, and residual stenosis after intervention. The Information Services Division of NHS Scotland collates data on all NHS hospital admissions through the Scottish Morbidity Record, including urgency of admission and any procedures undertaken. This analysis was performed with the written approval of the NHS Caldicott Guardian responsible for these data.

Data Analysis Protocol
The revascularization register was linked with subsequent hospital admissions to identify all patients who received a coronary stent between April 2003 and March 2007 and subsequently underwent noncardiac surgery (study cohort). In-hospital cardiovascular outcomes after noncardiac surgery were examined for patients who had received at least 1 drug-eluting stent and those who received only bare-metal stents. Where patients underwent percutaneous coronary intervention on ≥2 occasions during the study period, the most recent coronary intervention was used for time-dependent analysis. We excluded patients from the time-dependent analysis who underwent serial coronary interventions and received bare-metal stents after at least 1 drug-eluting stent.

Definitions
Surgical procedures were defined as those that required significant surgical incision with the potential for perioperative bleeding. The primary outcome was the composite end point of in-hospital death or ischemic cardiac event (International Classification of Diseases, 10th Revision, codes I20.0, I20.1, I20.8 to I21.4, I21.9 to I22.1, I22.8, I22.9, I24.0, and I24.9 to I25.1) after noncardiac surgery. Secondary outcomes were in-hospital death and acute myocardial infarction (International Classification of Diseases, 10th Revision, codes I21.0 to I21.4, I21.9 to I22.1, I22.8, and I22.9).

Statistical Analysis
To detect a 5% absolute difference in the primary end point between the bare-metal and drug-eluting stent groups at 80% power and 2-sided \( P < 0.05 \), we needed a study population of \( n = 1000 \) (\( n = 500 \) in each group), assuming an event rate of 10% in the bare-metal stent group. Database linkage provided follow-up information until July 30, 2007. Statistical analyses were performed with \( \chi^2 \) test, Fisher exact test, unpaired Student \( t \) test, or Mann–Whitney test as stated. To assess the temporal risk of noncardiac surgery according to coronary artery stent type, outcomes were examined categorically for surgical admissions occurring <42 days, 42 days to 12 months, and >12 months from coronary stent implantation. These time categories were chosen on the basis of previous data and to be consistent with the definition of very late stent thrombosis (>12 months after implantation). Univariate and multivariable logistic regression analyses were performed to identify variables potentially associated with perioperative ischemic cardiac events. Data are presented as mean ± SD or median (interquartile range). In all cases, 2-tailed tests were performed, and statistical significance was taken at the 5% level.

Results
Of the 17 797 patients who underwent coronary stent implantation, 1953 (11.0%) subsequently underwent noncardiac surgery (Table 1). Five hundred seventy patients (29%) received at least 1 drug-eluting stent, and 1383 (71%) received only bare-metal stents. Overall, the mean age at percutaneous coronary intervention was 64 years. Compared with patients who received only bare-metal stents, patients treated with drug-eluting stents had a higher frequency of diabetes mellitus, hypertension, and stable angina (Table 2). They also had longer and more calcified lesions, a higher frequency of lesions affecting the left main stem, left anterior descending, and coronary ostia as well as chronic total occlusions (Table 3). Patients treated with drug-eluting stents had a larger number of stents implanted, and the stents they received tended to have smaller diameters. The mean duration from percutaneous coronary intervention to noncardiac surgery was greater for bare-metal than for drug-eluting stents (median, 503 days [interquartile range, 244 to 848] versus median, 371 days [interquartile range, 194 to 603]; \( P < 0.001 \); Mann–Whitney). There were no differences in the primary end point of in-hospital death or any ischemic cardiac event (13.3% versus 14.6%; \( P = 0.3 \)) or the secondary end points of death alone (0.6% versus 0.7%; \( P = 0.8 \)) or acute myocardial
infarction (0.7% versus 1.2%; \(P=0.3\)) between the bare-metal and drug-eluting stent groups, respectively.

Fourteen patients who had received bare-metal stents after at least 1 drug-eluting stent were excluded from the time-dependent analysis. Overall, there were more in-hospital deaths and ischemic cardiac events where noncardiac surgery was performed within 42 days of stent implantation (Figure A; Table 4). There were no temporal differences in cardiovascular outcomes between the drug-eluting and bare-metal stent groups for in-hospital death or ischemic cardiac events \((P=0.7)\), death alone \((P=1.0)\), or acute myocardial infarction \((P=1.0)\) (Table 4). Patients undergoing noncardiac surgery within 1 month of stent implantation for an acute coronary syndrome were at greater risk of in-hospital death or an ischemic cardiac event than patients who underwent stent implantation for stable coronary artery disease (65% versus 32%; \(P=0.037\); Figure B).

On univariate analysis, previous coronary artery bypass graft surgery and increasing age, but not stent type, were associated with an increased risk of in-hospital death or ischemic cardiac events. Compared with elective procedures, there was a trend toward an association between urgent and emergent noncardiac surgery and an increased risk of in-hospital death or ischemic cardiac events \((12.8%\) versus 16.2%, respectively; \(P=0.057)\). After multivariate adjustment, previous coronary artery bypass graft surgery (odds ratio, 1.55; 95% CI, 1.07 to 2.26) and increasing age (odds ratio, 1.22; 95% CI, 1.06 to 1.39 per decade) remained predictors of the primary end point.

### Discussion

This national cohort study is the first to our knowledge to systematically compare adverse cardiac outcomes in patients treated with drug-eluting or bare-metal stents who underwent noncardiac surgery. Importantly, for at least the first 2 years after percutaneous coronary intervention, cardiac outcomes after noncardiac surgery are similar with both drug-eluting and bare-metal stents. In keeping with previous data, noncardiac surgery performed within 6 weeks of coronary stent implantation was associated with greater in-hospital mortality and adverse ischemic cardiac events. This excess hazard was particularly prominent in those patients who underwent stent implantation after an acute coronary syndrome.

These findings have important implications for a large number of patients. In the present study, 4.4% of patients who underwent percutaneous coronary intervention also underwent noncardiac surgery within 1 year of coronary stent implantation. Current guidelines recommend that patients treated with bare-metal stents should complete a minimum of 4 weeks of dual antiplatelet therapy before undergoing noncardiac sur-
In contrast, patients treated with drug-eluting stents should complete a 6- to 12-month course of dual antiplatelet therapy before undergoing noncardiac surgery. Delaying noncardiac surgery for up to 12 months often has a major impact on patients’ quality of life as well as progression of the underlying condition for which noncardiac surgery is indicated.

One interpretation of our data might be that noncardiac surgery can be performed beyond 6 weeks after stent implantation without incurring major excess cardiac risk, irrespective of the type of stent implanted. However, we would caution against such a conclusion. Although the risk associated with noncardiac surgery performed beyond 6 weeks was significantly lower than the high rates observed before 6 weeks, mortality was 4-fold higher for surgery performed between 6 weeks and 1 year compared with beyond 1 year. Although a direct comparison with national perioperative mortality data in Scotland is difficult, annual figures published by the Information Services Division of the NHS in Scotland report a crude mortality rate for noncardiac surgery of 0.24% to 0.31% for the period 2003–2007. It should be highlighted that these data reflect 30-day mortality after surgery and specifically relate to 12 major surgical procedures performed electively, limiting comparison with the present study. Acknowledging these limitations and the difficulties in identifying an appropriately matched control population, these data provide further evidence that the perioperative cardiac risk associated with noncardiac surgery may remain elevated for up to 1 year after coronary stent implantation.

Previous studies evaluating outcomes in patients treated with drug-eluting stents undergoing noncardiac surgery have reported variable findings. Compton et al reported no major adverse outcomes in 28 patients undergoing 41 major noncardiac surgical procedures with a median time from drug-eluting stent implantation to surgery of 260 days. Brotman et al also reported a low incidence of adverse outcomes in 114 patients undergoing noncardiac surgery with a median of 236 days from drug-eluting stent implantation. In the latter study, 2 patients suffered a myocardial infarction.
unrelated to the stented coronary segment, and there were no deaths after noncardiac surgery.25

Two larger single-center retrospective studies performed in North America have examined perioperative outcomes in patients treated with drug-eluting stents.26,27 Rabbitts et al26 reported an adverse cardiac event rate of 5.4% in 520 patients undergoing noncardiac surgery after stent placement (median time to surgery, 204 days) but failed to demonstrate an association between time from stent implantation to surgery and adverse cardiac events. One explanation for this disparity may be the authors did not look specifically at early surgery after percutaneous coronary intervention but grouped all patients who had undergone surgery within 3 months of stent implantation. In contrast, Anwaruddin et al27 reported a combined postoperative rate of death, myocardial infarction, and stent thrombosis of 9% in 481 patients undergoing noncardiac surgery after drug-eluting stent placement. In keeping with our data, the rate of adverse events was highest (>25%) where surgery was performed within 1 month of stent implantation, falling to ≈6% in patients undergoing surgery beyond 6 months.27 Perioperative cardiac outcomes in patients treated with bare-metal stents were not reported.27 Importantly, our findings clearly demonstrate that the temporal risk of adverse cardiac events in patients undergoing noncardiac surgery after stent implantation is similar for both drug-eluting and bare-metal stents.

In keeping with previous data,14,15,19,21,27,28 we have demonstrated that patients undergoing surgery within 4 to 6 weeks of coronary stent implantation are at greatest risk of adverse cardiac events. Our findings provide the largest and most robust assessment to date of perioperative cardiac risk in patients undergoing noncardiac surgery after implantation of a coronary stent. We believe that our findings support current recommendations that noncardiac surgery should be deferred for at least 6 weeks after bare-metal stent implantation.8,9 Furthermore, our findings would suggest that the increased cardiac risk, although diminishing in magnitude, may extend beyond 6 weeks, irrespective of the type of stent used. Furthermore, large-scale studies are required to confirm the perioperative cardiac risk in patients with previous coronary stents undergoing noncardiac surgery during this period before changes to the guidelines can be recommended.29

Recently published data from the Acute Catheterization and Urgent Intervention Triage Strategy trial would suggest that early stent thrombosis occurs more frequently in patients undergoing coronary intervention for an acute coronary syndrome compared with those undergoing stent implantation for stable disease.30 In keeping with these data, we have demonstrated that the early excess cardiac risk with noncardiac surgery is greatest in patients who underwent recent coronary stent implantation after an acute coronary syndrome. Importantly, however, this excess hazard did not extend to patients undergoing noncardiac surgery beyond 1 month from stent implantation.

A number of potential mechanisms may explain the observed excess in perioperative cardiac events early after noncardiac surgery. Physiological stressors such as anemia, hypotension, and hypoxia may lead to myocardial ischemia in the presence of fixed coronary obstruction. In addition, withdrawal of antiplatelet therapy may lead not only to an increase in the risk of stent thrombosis,31 but also to an increase in the incidence of atherothrombotic coronary events in general.31 Finally, the proinflammatory state associated with noncardiac surgery may contribute to the development of vulnerable or inflamed plaques within the coronary vascular bed.32

The end points used in this study were obtained from routine administrative hospital and death records.33 Although postoperative cardiac enzymes and ECGs were not routinely performed, stent thrombosis is associated with a high morbidity and is likely to have been clinically evident in the majority of cases. For this reason, a relatively broad and inclusive combined primary end point (death or any ischemic cardiac event) was chosen to ensure optimal collection of clinically relevant end points. It is reassuring that the temporal trends observed for the combined primary end point were mirrored in the more-specific secondary end points of in-hospital death and acute myocardial infarction alone. We also do not believe that there would have been any systematic bias in recording any of the end points between the 2 stent groups.

Although we included all patients treated with coronary stents in Scotland over a 4-year period who subsequently underwent noncardiac surgery, we must acknowledge a number of limitations associated with the retrospective, nonrandomized design. Compared with the bare-metal stent group, fewer patients in the drug-eluting stent group underwent percutaneous coronary intervention after presentation with an acute coronary syndrome. In contrast, differences in stent size and usage and lesion morphology would have favored an increase in the risk of stent thrombosis in the drug-eluting stent group. However, none of these factors were identified as predictors of adverse perioperative cardiac events by univariate analysis or in our multivariate model.

Finally, national data on perioperative antiplatelet therapy use

Table 4. Cardiovascular Outcomes According to Time Delay Between Stent Implantation and Noncardiac Surgery

<table>
<thead>
<tr>
<th>Time Delay</th>
<th>Death/any IHD Event (%)</th>
<th>Death (%)</th>
<th>Myocardial Infarction (%)</th>
<th>BMS (%)</th>
<th>DES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;42 d</td>
<td>25 (42.4)</td>
<td>3 (5.1)</td>
<td>5 (8.5)</td>
<td>n=40</td>
<td>n=477</td>
</tr>
<tr>
<td>42 d to 1 y</td>
<td>106 (14.5)</td>
<td>7 (0.9)</td>
<td>5 (0.7)</td>
<td>n=732</td>
<td>n=1148</td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>134 (11.7)</td>
<td>2 (0.2)</td>
<td>7 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%), unless otherwise indicated. BMS indicates bare-metal coronary stent; DES, drug-eluting coronary stent; IHD, ischemic heart disease.

*χ² test for events (n) by time from stent implantation to surgery.
†χ² test for rate per 100 population (BMS versus DES).
‡P=1.0.
§P=1.0, Fisher exact test for rate per 100 population (BMS versus DES).
and perioperative bleeding complications are not currently available in Scotland, and we have no information on the perioperative use or withdrawal of antiplatelet therapies in our patient cohort.

In summary, we have demonstrated in a large-scale cohort analysis that the risk of in-hospital death or adverse ischemic cardiac events after noncardiac surgery is greatest where surgery is performed within 6 weeks of coronary stent implantation and is not influenced by the type of stent implanted. This early excess risk appears to be greatest where coronary stents are implanted after presentation with an acute coronary syndrome.

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Disclosures
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References
Patients treated with coronary stent implantation before undergoing noncardiac surgery seem to be at increased risk for adverse perioperative cardiac events. The period of risk and the influence of stent type on outcome remain to be determined in a large-scale multicenter study. To specifically address these issues, we performed a systematic, large-scale retrospective cohort study in Scotland linking the national angioplasty registry with hospital admission data to examine outcomes in all patients treated with coronary stenting over a 4-year period who subsequently underwent noncardiac surgery (n = 1953). Approximately 5% of patients underwent noncardiac surgery within 1 year of coronary stent implantation. Perioperative death and ischemic cardiac events were more common when surgery was performed within 6 weeks of stent implantation, especially where revascularization was performed after an acute coronary syndrome. For at least 2 years after coronary stent implantation, no difference in cardiac outcomes after noncardiac surgery was evident according to whether the initial stent was drug eluting or bare metal. Our findings support current guideline recommendations that noncardiac surgery should be deferred for at least 4 to 6 weeks after implantation of a bare-metal coronary stent. Although our findings suggest similar perioperative outcomes for patients treated with drug-eluting stents, further prospective large-scale studies are required before any change to the current guideline recommendations that noncardiac surgery be deferred for 6 to 12 months after drug-eluting stent implantation can be supported.

CLINICAL PERSPECTIVE


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