Sirolimus-Eluting Stent Treatment at High-Volume Centers Confers Lower Mortality at 6-Month Follow-Up

Results From the Prospective Multicenter German Cypher Registry

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Background—Studies continue to identify percutaneous coronary intervention procedural volume both at the institutional level and at the operator level as being strongly correlated with outcome. High-volume centers have been defined as those that perform >400 percutaneous coronary intervention procedures per year. The relationship between drug-eluting stent procedural volume and outcome is unknown. We investigated this relationship in the German Cypher Registry.

Methods and Results—The present analysis included 8201 patients treated with sirolimus-eluting stents between April 2002 and September 2005 in 51 centers. Centers that recruited >400 sirolimus-eluting stent patients in this time period were considered high-volume centers; those with 150 to 400 patients were considered intermediate-volume centers; and those with <150 patients were designated as low-volume centers. The primary end point was all death, myocardial infarction, and target-vessel revascularization at 6 months. This end point occurred in 11.3%, 12.1%, and 9.0% of patients in the low-, intermediate-, and high-volume center groups, respectively (P=0.0001). There was no difference between groups in the rate of target-vessel revascularization (P=0.2) or cerebrovascular accidents (P=0.5). The difference in death/myocardial infarction remained significant after adjustment for baseline factors (odds ratio 1.85, 95% confidence interval 1.31 to 2.59, P<0.001 for low-volume centers; odds ratio 1.69, 95% confidence interval 1.29 to 2.21, P<0.001 for intermediate-volume centers). Patient and lesion selection, procedural features, and postprocedural medications differed significantly between groups.

Conclusions—The volume of sirolimus-eluting stent procedures performed on an institutional level was inversely related to death and myocardial infarction but not to target-vessel revascularization at 6-month follow-up. Safety issues are better considered in high-volume centers. These findings have important public health policy implications. (Circulation. 2009;120:600-606.)

Key Words: stents ▪ restenosis ▪ mortality

Practice guidelines limit the performance of percutaneous coronary intervention (PCI) procedures to hospitals and/or operators demonstrating a certain threshold activity level.1 Although controversial, the rationale behind this recommendation has been derived from numerous studies showing an inverse relationship between institutional/operator volumes and adverse procedural outcomes after balloon angioplasty or stent placement.2–5 A threshold of 400 procedures annually on the institutional level defines a high-volume center, and the performance of 75 procedures per year on an operator level was found acceptable for elective PCI. Hospitals/operators exceeding this activity level reported significantly less mortality and fewer cases of urgent target-vessel revascularization (TVR), myocardial infarction, and cerebrovascular accidents during the index hospitalization and up to 30 days thereafter. Although they are related disciplines, it was shown that operator experience in elective PCI is not sufficient to confer expertise in primary PCI for ST-segment elevation myocardial infarction; rather, independent experience with primary PCI for ST-segment elevation myocardial infarction is necessary to translate into favorable outcomes.6,7

Drug-eluting stents (DES) represent a continuance of bare-metal stents, yet they are distinct devices that involve...

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different technical and cognitive processes. To date, no study has analyzed the volume-outcome relationship for DES separately. It seems wise when studying such a relationship to look beyond the first 30 days after implantation, bearing in mind a tendency for delayed events to occur after DES. We investigated the relationship of institutional sirolimus-eluting stent (SES) procedural volume and 6-month outcomes in the prospective, multicenter German Cypher Registry.

Methods

Design and Population

The German Cypher Registry is a project of the Deutsche Gesellschaft für Kardiologie (German Society of Cardiology), the Bund der Niedergelassenen Kardiologen (Association of Out-of-Hospital Cardiologists), and the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (Working Group of Hospital Cardiologists), which are nonprofit organizations. Details of the registry have been described elsewhere. In brief, the aim of this prospective, multicenter registry was to monitor current use and outcomes of SES in daily clinical practice and to evaluate safety, effectiveness, and socioeconomic data.

Inclusion started simultaneously with the launch of the sirolimus-eluting Cypher stent (Cordis, Johnson & Johnson, Miami, Fla) in Germany on April 14, 2002, and recruitment of the scientific database of the registry was closed on September 30, 2005. Case report forms were collected via the Internet, with descriptions of the target lesion and interventional characteristics given by the implanting physician. Clinical and angiographic inclusion and exclusion criteria were not specified before enrolment; therefore, all Cypher stents implanted in the participating centers were included in the present registry. During this time period, the rate of DES implantation ranged between 10% and 50% of the total stent volume of the participating centers. The majority of indications were patients not previously studied in randomized trials (off-label use), as we reported previously. The antithrombotic regimen, especially the use of glycoprotein IIb/IIIa antagonists, was left to the operator’s discretion. All patients were advised to maintain combined antiplatelet therapy of aspirin (100 mg) and clopidogrel (75 mg) daily for at least 2 months (in accordance with the instructions for use in 2002) and then to continue taking aspirin monotherapy indefinitely.

The study population included 8201 patients treated with SES in 51 centers. Institutional volumes were divided into tertiles. Centers and then to continue taking aspirin monotherapy indefinitely. At least 2 months (in accordance with the instructions for use in 2002) and then to continue taking aspirin monotherapy indefinitely.

Follow-Up and Outcome

Clinical follow-up was performed at a median of 6.4 months (quartiles from 6.0 to 7.4 months) after stent implantation and was completed for 93.5% of patients. This interval was predefined in the protocol generated in early 2002. The follow-up was performed either by the data center in Ludwigshafen, Germany, or by the treating hospital. All patients were contacted by telephone. All events were verified by hospital charts or by direct contact with the treating physician. If patients could not be reached, the Einwohnermeldeamt (local government registration office) was contacted to document deaths.

Monitoring and Quality Assurance

Query management was established for missing or implausible data. Announced source-data verification was performed at 15 hospitals selected by chance, with comparison of the documented data with the hospital charts. An independent physician reviewed and verified all adverse events reported during in-hospital and 6-month follow-up.

End Points and Definitions

All deaths were documented, and differentiation between cardiac, noncardiac, and unknown causes was made. All repeat revascularization procedures were documented. TVR was defined as either percutaneous intervention or bypass surgery for the initially treated coronary vessel. Creatine kinase, creatine kinase-MB, and troponin elevations were reported after each procedure. Myocardial infarction included Q-wave and non-Q-wave myocardial infarction. Angiographic follow-up was optional. The primary end point for the present analysis was a composite of all deaths, myocardial infarction, and TVR at 6-month follow-up. Death and myocardial infarction at 6 months were used as the safety end point, whereas TVR reflected the effectiveness.

Role of the Funding Source

The design of the German Cypher Registry and the collection, analysis, and interpretation of the data were all independent of Cordis Corporation, a Johnson & Johnson company, which supported the study by an unrestricted grant. The registry was approved by the research and ethics committee at the institutions involved, and the patients gave written informed consent for inclusion in the registry and processing of their anonymous data.

Statistical Analysis

Absolute numbers and percentages were computed to describe the patient population. Medians (with quartiles) or means (with standard deviation) were computed as appropriate. Categorical values were compared by χ² test, and continuous variables were compared by 2-tailed Wilcoxon rank sum test. P values <0.05 were considered significant. All P values were the result of 2-tailed tests. A Kaplan–Meier curve for death during follow-up was generated. A multivariable logistic regression model was used to analyze factors associated with the combined end point of death and myocardial infarction. The model included age, male gender, diabetes mellitus, hypertension, renal insufficiency, acute coronary syndromes (unstable angina pectoris, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction), multivessel disease, and ejection fraction <40%. The variables entered into this model are a result of a previous analysis from the same registry that examined predictors of death and myocardial infarction at 6 months after SES treatment. In that previous analysis, all baseline and procedural characteristics with a P value <0.1 in the univariate analysis were entered into a multivariable regression model. The previous model did not include center volume. Therefore, institutional volume (low or intermediate) was added to the previously determined predictors in the current multivariable logistic regression model. The tests were performed with the SAS statistical package, version 8.2 (Cary, NC). Because patients nested within centers may have correlated outcomes, the analysis was redone with generalized estimating equation models (SAS procedure GENMOD) that incorporated “center” as a random effect. Finally, the multivariable model was performed for patients who presented with acute coronary syndrome and those who presented with stable angina pectoris/silent ischemia, separately.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline and Procedural Characteristics

A total of 1140 patients (13.9%) were treated in low-volume centers, 2360 (28.8%) in intermediate-volume centers, and 4701 (57.3%) in high-volume centers. Clinical and angiographic baseline characteristics and procedural data are shown in Tables 1 and 2. Patients treated at lower-volume centers were significantly younger in age, more frequently had diabetes mellitus, and more frequently presented with acute coronary syndromes. Several procedural details differed significantly between groups: Direct stenting without balloon...
predilation was more frequently applied in lower-volume centers; stent diameter and total stent length were less in patients treated in lower-volume centers; and lower implantation pressures were applied in lower-volume centers.

**Early Outcome**

At initial hospital discharge, a significant difference in outcome was documented between groups: The combined end point of all deaths, postprocedural myocardial infarction, and all urgent revascularization procedures occurred in 4.4%, 2.8%, and 1.6% of patients treated in low-, intermediate-, and high-volume centers, respectively (P<0.0001), as shown in Table 3.

**Six-Month Outcome**

The primary end point, which was a composite of all deaths, myocardial infarction, and TVR at 6 months, occurred in 11.3%, 12.1%, and 9.0% of patients in the low-, intermediate- and high-volume center groups, respectively (P=0.0001). There was no difference between groups for TVR (P=0.2) or cerebrovascular accidents (P=0.5). Figure 1 plots the time points of death until the end of follow-up. The difference in deaths and myocardial infarction remained significant after adjustment for baseline factors (odds ratio [OR] 1.85, 95% confidence interval [CI] 1.31 to 2.59, P<0.001 for low-volume centers; OR 1.69, 95% CI 1.29 to 2.21, P<0.001 for intermediate-volume centers). The 6-month outcome results are shown in Table 4. Table 5 displays medications received by patients at time of follow-up; patients treated at lower-volume centers received dual antiplatelet agents for significantly shorter durations and were less frequently given statins and β-blockers. Risk factors associated with death and myocardial infarction at 6 months are shown in Figure 2 and Table 6. The generalized estimating equation model showed that the institutional volume effect remained significant (low-volume centers: OR 1.75, 95% CI 1.08 to 2.86, P=0.024; intermediate-volume centers: OR 1.61, 95% CI 1.01 to 2.55, P=0.044).

**Volume-Outcome Relation According to Clinical Syndrome Acuity**

A total of 3390 patients were treated for acute coronary syndromes and 4811 for stable angina pectoris or silent ischemia. Among acute coronary syndrome patients, the combined end point of death, postprocedural myocardial infarction, or urgent revascularization procedures during initial hospitalization occurred in 6.0%, 3.9%, and 2.4% of patients treated in low-, intermediate-, and high-volume centers, respectively (P<0.001). For stable patients, these events were documented among 2.8%, 1.8%, and 1.2% of patients, respectively (P<0.01). With regard to the primary end point (death, myocardial infarction, and TVR at 6 months), the risk of this composite end point occurring among acute coronary syndrome patients was significantly higher when the patients were treated in lower-volume centers owing to higher death and myocardial infarction rates (adjusted OR for death and myocardial infarction 2.09, 95% CI 1.35 to 3.24 for low-volume centers and OR 1.79, 95% CI 1.24 to 2.57 for intermediate-volume centers). Among stable patients, this difference was not significant after adjustment (OR 1.48, 95% CI 0.85 to 2.59 for low-volume centers and OR 1.49, 95% CI 0.99 to 2.24 for intermediate-volume centers).

**Discussion**

A volume-outcome relationship was demonstrated in the present era, and it remained significant after the introduction of multivariable predictors.
of coronary stents and other technical advancements in the modern PCI era. The main outcome measures were emergent bypass surgery and mortality at 30 days, although other outcome measures have also been used. No study has examined the volume-outcome relationship for DES or for outcomes beyond the first month. The principal findings of the present study are as follows: (1) A volume-outcome relation-ship for SES-based procedures exists, with higher rates of the combined end point of death, postprocedural myocardial infarction, and urgent revascularization (PCI or surgery) procedures during initial hospitalization among lower-volume centers; and (2) this relationship was protracted, with higher death and myocardial infarction rates at 6 months after PCI among lower-volume centers.

Table 2. Angiographic and Procedural Characteristics of Patients Treated With SES in Low-, Intermediate-, or High-Volume Centers

| Variable                          | Low Volume (Lesion =1275) | Intermediate (Lesion =2737) | High Volume (Lesion =5873) | \( P \)  \\
|-----------------------------------|---------------------------|----------------------------|---------------------------|---------  \\
| Ostial lesion                     | 11.0                      | 12.7                       | 7.9                       | <0.001  \\
| Bifurcated lesion                 | 14.6                      | 17.0                       | 12.9                      | <0.001  \\
| Chronic total occlusion           | 5.6                       | 5.6                        | 7.9                       | <0.001  \\
| In-stent restenosis               | 22.8                      | 23.9                       | 16.6                      | <0.001  \\
| Direct stenting                   | 37.3                      | 32.8                       | 33.0                      | 0.009   \\
| Visual thrombi                    | 8.9                       | 6.4                        | 5.7                       | <0.001  \\
| Percent diameter stenosis         | 90 (80–95)                | 90 (80–95)                 | 90 (75–95)                | <0.001  \\
| Left main artery                  | 1.7                       | 2.7                        | 3.0                       | 0.030   \\
| Left anterior descending artery   | 57.7                      | 54.3                       | 60.6                      | <0.001  \\
| Left circumflex artery            | 14.8                      | 14.0                       | 14.2                      | 0.78    \\
| Right coronary artery             | 25.7                      | 29.0                       | 22.2                      | <0.001  \\
| Coronary bypass graft             | 5.4                       | 5.2                        | 2.7                       | <0.001  \\
| High-pressure inflation \( \geq 16 \) atm | 26.2                      | 33.8                       | 35.5                      | <0.001  \\
| Inflation pressure, atm           | 13 (12–16)                | 14 (12–16)                 | 14 (12–16)                | <0.001  \\
| Stent diameter, mm                | 2.89 ±0.31                | 2.94 ±0.32                 | 2.94 ±0.64                | <0.001  \\
| Stented length, mm                | 17.9 ±6.3                 | 17.9 ±7.4                  | 20.4 ±7.9                 | <0.001  \\
| Pretreated with aspirin           | 98.4                      | 97.3                       | 98.0                      | 0.06    \\
| Pretreated with clopidogrel       | 88.1                      | 88.9                       | 93.3                      | <0.001  \\
| Use of glycoprotein IIb/IIIa antagons | 20.8                      | 19.1                       | 21.1                      | 0.14    \\
| Residual coronary dissections     | 2.7                       | 2.8                        | 1.9                       | 0.013   \\
| Residual stenosis \( \geq 30\% \) | 1.4                       | 1.3                        | 0.6                       | <0.001  \\
| Final TIMI flow <3                | 3.1                       | 2.2                        | 2.3                       | 0.17    \\

TIMI indicates Thrombolysis In Myocardial Infarction. Values are percentages, mean ±SD, or mean (median).

Table 3. Adverse Events During Initial Hospitalization Among Patients Treated With SES in Low-, Intermediate-, and High-Volume Centers

| Variable                          | Low Volume (n =1140) | Intermediate (n =2360) | High Volume (n =4701) | \( P \)  \\
|-----------------------------------|----------------------|-----------------------|-----------------------|---------  \\
| Cause of death                    |                      |                       |                       |         \\
| All-cause mortality               | 0.7                  | 0.6                   | 0.3                   | 0.08    \\
| Cardiac mortality                 | 0.7                  | 0.5                   | 0.3                   |         \\
| Noncardiac mortality              | 0                    | 1 Patient             | 0                     |         \\
| Unknown                            | 0                    | 1 Patient             | 0                     |         \\
| Myocardial infarction             | 1.7                  | 1.2                   | 0.5                   | <0.001  \\
| Urgent revascularization          | 2.8                  | 1.4                   | 1.1                   | <0.001  \\
| Death/myocardial infarction       | 2.4                  | 1.9                   | 0.8                   | <0.001  \\
| Death/myocardial infarction/urgent revascularization | 4.4                  | 2.8                   | 1.6                   | <0.001  \\

Values are percentages, unless otherwise indicated.

Figure 1. Kaplan–Meier curve of all deaths occurring from stent implantation until the end of the 6-month follow-up among patients treated with SES in low-, intermediate-, or high-volume centers.
source of this association. Previous explanations for volume-outcome relationships included a learning effect whereby the higher-volume centers, by performing more procedures, become more skilled and have fewer adverse outcomes. Alternatively, patients or referring facilities may seek out hospitals with lower complication rates and higher success rates, thus increasing the procedure volume at hospitals with better performance.12

The primary end point of the present analysis was a combined safety and effectiveness end point composed of all deaths, myocardial infarctions, and TVRs at 6 months. There was no difference in device effectiveness, as expressed by similar TVR rates of <10% in different-volume centers.1 However, the risk-adjusted safety end point was significantly different between groups, with higher death and myocardial infarction rates among patients treated at lower-volume centers.

Stent thrombosis, although rare, usually manifests by death or large myocardial infarctions. Real-world experience suggests that the off-label use of DES is associated with higher rates of early and late stent thrombosis, manifested by fatal or nonfatal infarctions.13,14 A clinical alert report from the Society of Cardiovascular Angiography and Interventions DES task force summarized the following patient and lesion features associated with increased DES thrombosis: Discontinuation of dual antiplatelets; diabetes mellitus; acute coronary syndromes; low ejection fraction; renal failure; bifurcations; longer stent length; residual dissection; small stent diameter and/or severe underexpansion; and stent malpositioning.15 In the present cohort, lower-volume centers treated significantly more patients with diabetes mellitus, more acute coronary syndrome patients, more patients with renal insufficiency, and more patients with bifurcational lesions; furthermore, more residual dissections were recorded in lower-volume centers, smaller stents were implanted, and stent malpositioning and underexpansion were probably more frequent owing to the significantly lower inflation pressures applied. Sirolimus-eluting Cypher stent underexpansion is common when the stent is deployed at conventional pressures (14 atm); therefore, increasing balloon delivery pressure to 20 atm appears warranted to ensure adequate deployment.16 Although high-volume centers ultimately had a significantly longer stent length, they also had fewer residual dissections, which therefore could have translated into a net clinical benefit during

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Volume (n=1052)</th>
<th>Intermediate (n=2132)</th>
<th>High Volume (n=4489)</th>
<th>P</th>
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<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.9</td>
<td>2.0</td>
<td>1.3</td>
<td>0.047</td>
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<tr>
<td>Cardiac mortality</td>
<td>0.7</td>
<td>1.2</td>
<td>0.5</td>
<td>0.006</td>
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<td>Noncardiac mortality</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.92</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9</td>
<td>0.5</td>
<td>0.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.1</td>
<td>1.8</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0.5</td>
<td>0.3</td>
<td>0.5</td>
<td>0.54</td>
</tr>
<tr>
<td>TVR</td>
<td>7.2</td>
<td>7.8</td>
<td>6.9</td>
<td>0.38</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>11.7</td>
<td>11.1</td>
<td>12.7</td>
<td>0.14</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>32.0</td>
<td>25.6</td>
<td>18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.4</td>
<td>1.1</td>
<td>1.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Death/myocardial infarction/TVR</td>
<td>3.4</td>
<td>4.0</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are percentages.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Volume (n=1052)</th>
<th>Intermediate (n=2132)</th>
<th>High Volume (n=4489)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>91.5</td>
<td>90.5</td>
<td>91.9</td>
<td>0.19</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>98.4</td>
<td>97.3</td>
<td>98</td>
<td>0.08</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>57.9</td>
<td>61.3</td>
<td>40.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of intake, wk (median)</td>
<td>12 (6–21)</td>
<td>24 (12–26)</td>
<td>26 (12–26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intake &lt;8 wk</td>
<td>27.6</td>
<td>11.2</td>
<td>11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>99.3</td>
<td>99.5</td>
<td>99.6</td>
<td>0.35</td>
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<tr>
<td>Oral anticoagulants</td>
<td>3.6</td>
<td>5.5</td>
<td>6.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>4.7</td>
<td>7.0</td>
<td>7.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>80.5</td>
<td>84.9</td>
<td>87.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>85.5</td>
<td>87.8</td>
<td>89.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers</td>
<td>71.3</td>
<td>78.7</td>
<td>76.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>78.2</td>
<td>82.4</td>
<td>79.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>15.2</td>
<td>15.6</td>
<td>15.4</td>
<td>0.97</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>12.3</td>
<td>12.1</td>
<td>15.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>81.6</td>
<td>87</td>
<td>90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At initial discharge</td>
<td>88</td>
<td>91.3</td>
<td>92.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are percentages.
initial hospitalization and at follow-up. Because the data collection did not include lesion length, vessel diameter, or degree of lesion calcification, it is difficult to tell whether these procedural differences were due to lesion-based characteristics or device-based technical considerations with which high-volume centers were more familiar. Moreover, lower-volume center patients received dual-antiplatelet drugs for significantly shorter durations, even less than the minimum recommended duration in a considerable percentage of patients.

A recently identified predictor for DES thrombosis was younger age, a feature we witnessed more frequently in the lower-volume centers. Several definitions for stent thrombosis exist, with the Academic Research Consortium definition being the most recent and most sensitive; the present data collection effort was not sufficient to classify all events accordingly. However, we were able to document several features known to be associated more frequently with increased DES thrombosis in lower-volume centers. Moreover, it was apparent that significantly fewer patients in the lower-volume centers received a guideline-oriented second-prevention medical therapy. Because we cannot clearly state the underlying cause of these deaths and infarction cases, it remains speculative how many of these events were device related and how many represented new disease activity. Irrespective of their nature, we may conclude that in addition to other well-known predictors of adverse outcome, patients receiving SES at high-volume centers have fewer adverse events during initial hospitalization and lower mortality and myocardial infarction rates at 6-month follow-up. Patient and lesion selection, procedural techniques, and post-procedural medical therapy differ significantly according to institutional volume, with a higher adherence to current recommendations found among high-volume centers. These findings have important public health policy implications.

Table 6. ORs and 95% CIs for Predictors of Death and Myocardial Infarction at 6 Months Among Patients Treated With SES

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-volume center</td>
<td>1.39</td>
<td>1.03–1.87</td>
</tr>
<tr>
<td>Intermediate-volume center</td>
<td>1.72</td>
<td>1.36–2.17</td>
</tr>
<tr>
<td>Age</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.77</td>
<td>0.62–0.96</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.75</td>
<td>1.42–2.16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.14</td>
<td>0.86–1.53</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2.60</td>
<td>2.02–3.33</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>3.68</td>
<td>2.75–4.92</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.81</td>
<td>1.40–2.34</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2.16</td>
<td>1.75–2.65</td>
</tr>
<tr>
<td><strong>Multivariable analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-volume center</td>
<td>1.84</td>
<td>1.31–2.59</td>
</tr>
<tr>
<td>Intermediate-volume center</td>
<td>1.68</td>
<td>1.28–2.21</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.00–1.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.79</td>
<td>0.60–1.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.42</td>
<td>1.10–1.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.88</td>
<td>0.62–1.26</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.96</td>
<td>1.45–2.65</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>2.35</td>
<td>1.68–3.27</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.59</td>
<td>1.16–2.16</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1.89</td>
<td>1.48–2.41</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction.

Study Limitations
The volume-outcome relationship has been generally criticized as being a mere statistical association that does not necessarily reflect quality. We cannot explain the cause of this association; furthermore, the registry was not designed to classify adverse events according to their underlying cause. Moreover, we did not study the operator volume-outcome relationship, which would have been of interest. Postprocedural myocardial infarctions were not centrally defined, which may have contributed to differences based on differences in self-reports. The design of the registry does not enable conclusions to be drawn about the incidence of stent thrombosis. The study has all the shortcomings of a registry, yet its value lies in the fact that despite broad effectiveness in real-world use, safety issues must be considered with SES implantation. A longer follow-up would have added to the robustness of the outcome data.
Appendix

Organization of the German Cypher Stent Registry

**Steering committee:** Christian W. Hamm (Chair), Tassilo Bonzel, Malte Kelm, Benny Levenson, Christoph A. Nienaber, Gert Richardt, Georg Sabin, Jochen Senges, Ulrich Tebbe, and Thomas Pfannebecker (Cordis).

**Internet data acquisition** (Institute of Clinical Research of the German Cardiac Society): Thomas Fetsch and Petra Kremer.

**Statistical analysis** (KL Neuhaus Datenzentrum, Heart Center Ludwigshafen): Steffen Schneider.

**Study coordination:** Thomas Fetsch.

The participating centers are reported elsewhere. According to the volume definition applied in the present analysis, 6 of the authors are affiliated with high-volume centers, 3 with intermediate-volume centers, and 2 with low-volume centers.

Sources of Funding

This study was supported by Cordis Corp, a Johnson & Johnson Company.

Disclosures

T. Pfannebecker is an employee of Cordis, Germany. The remaining authors report no conflicts.

References


CLINICAL PERSPECTIVE

Drug-eluting stents remain a very effective method for the treatment of coronary artery disease. In light of the observed small increased incidence of late thrombosis after implantation of drug-eluting stents, which may manifest by death or large infarctions, certain safety issues should be considered in the complex process of patient selection for patients subjected to this kind of revascularization, implantation techniques, and postprocedural medical therapy. In the present analysis, which included 8201 patients from the multicenter prospective German Cypher Registry who were treated with sirolimus-eluting stents, we found that hospitals with a lower volume of sirolimus-eluting stent–based procedures had significantly higher rates of death and myocardial infarction at 6-month follow-up than high-volume centers. After adjustment for different baseline factors known to be associated with higher mortality and infarction, institutional volume remained an independent risk predictor for death and infarction at 6 months (odds ratio 1.85, 95% confidence interval 1.31 to 2.59, P<0.001 for low-volume centers; odds ratio 1.69, 95% confidence interval 1.29 to 2.21, P<0.001 for intermediate-volume centers). It was also obvious that patient selection, procedural details, and postprocedural medication differed significantly according to hospital volume, with a stricter implementation of current recommendations in high-volume centers.
Sirolimus-Eluting Stent Treatment at High-Volume Centers Confers Lower Mortality at 6-Month Follow-Up: Results From the Prospective Multicenter German Cypher Registry
for the German Cypher Registry

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