Long-Term Outcome After Drug-Eluting Versus Bare-Metal Stent Implantation in Patients With ST-Segment Elevation Myocardial Infarction

3-Year Follow-Up of the Randomized DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) Trial

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Objectives
The purpose of this study was to compare long-term clinical outcomes after implantation of drug-eluting stents (DES) and bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI).

Background
The evidence of long-term efficacy and safety after implantation of DES in patients with complex lesions is scarce.

Methods
We randomly assigned 626 patients with STEMI referred within 12 h to have a DES or a BMS implanted in the infarct-related lesion with or without distal protection during primary percutaneous coronary intervention.

Results
At 3 years, target lesion revascularization was 6.1% in the DES group compared with 16.3% in the BMS group (p < 0.001), and the rate of major adverse cardiac events was 11.5% versus 18.2%, respectively (p < 0.02). Whereas all-cause mortality did not differ significantly, the rate of cardiac death was higher in the DES group, 6.1% versus 1.9% for the BMS group (p = 0.01). The occurrence of reinfarction, stroke, and stent thrombosis was similar.

Conclusions
Implantation of DES in patients with STEMI reduces the long-term rate of major adverse cardiac events compared with BMS, but patients with DES had a higher risk of cardiac death not attributed to myocardial infarction or stent thrombosis. (Drug Elution and Distal Protection During Percutaneous Coronary Intervention in ST Elevation Myocardial Infarction [DEDICATION]; NCT00192868) (J Am Coll Cardiol 2010;56:641–5) © 2010 by the American College of Cardiology Foundation

Primary percutaneous coronary intervention (PCI) including stent implantation is the preferred treatment of patients with ST-segment elevation myocardial infarction (STEMI). Drug-eluting stents (DES) have proven more effective than bare-metal stents (BMS) to prevent coronary restenosis and the need for repeat revascularization in a variety of patients (1–5). However, concerns have arisen about the long-term benefit of DES, because DES may predispose to stent thrombosis (6–11).

Some analyses have been in favor of DES implantation during primary PCI (12,13), whereas others have shown more diversified results (14,15). The DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction) trial evaluated how implantation of DES compared with BMS affects the outcome in patients with STEMI (16–18). The DES implantation reduced neointimal hyperplasia and the need for repeat revascularization at 8 months, but a tendency to increased cardiac mortality in the DES group called for extended follow-up of the patients.

Methods
Study design and patient population. Patients with a high-grade stenosis/occlusion of a native coronary artery...
Patients were followed up for at least 3 years, and clinical end points were evaluated from Danish population registries (19).

Study end points and definitions. The main end point was the occurrence of major adverse cardiac events (MACE), defined as cardiac death, nonfatal recurrent myocardial infarction, and target lesion revascularization (TLR). The clinical events committee adjudicated the clinical end points, having all data sources available (20).

A myocardial infarction occurring during follow-up was defined as an increase above the upper normal limit of creatine kinase-myocardial band or troponins in the presence of an acute coronary syndrome. Reinfarction was present if the myocardial infarction was related to the target vessel. Stroke was defined as the development of disabling neurologic symptoms and objective findings lasting at least 24 h. TLR was defined as revascularization of the target lesion in the presence of recurrent angina, and target vessel revascularization (TVR) was defined as revascularization anywhere in the index vessel. Stent thromboses were categorized according to the Academic Research Consortium (20).

Statistical analysis. Inclusion of 600 patients was sufficient to detect a 50% reduction in MACE (power 80%, type-1 error 5%). Categorical variables were compared using the chi-square test or Fisher’s exact test. Continuous variables were compared using the Mann–Whitney U test and the Student t test. The Kaplan–Meier method was used to create survival estimates, and the log-rank test was used for interaction analyses. Interaction analyses were performed by Cox proportional hazards models. All p values were 2-sided.

Results

Baseline demographics and procedural results. Of the included patients, 313 received a DES (46% were sirolimus-eluting stents, 41% paclitaxel-eluting stents, and 13% zotarolimus-eluting stents), and 313 received a BMS (38% made of cobalt alloy, 62% of stainless steel) (Table 1).

Events. Patients were followed up for a median of 1,256 days (maximum 1,559 days). The 3-year clinical outcomes are depicted in Figure 1, and the clinical events in Table 2. The MACE rate was reduced in the DES group (Fig. 2A) as was the need for repeat revascularization.

Three-year all-cause mortality only tended to be different between groups (Fig. 2B), but cardiac mortality was increased in the DES group (Fig. 2C). In the DES group, 12 patients died before discharge: 4 classified as probable stent thrombosis (but might also have been caused by malignant arrhythmias), 8 as progressive heart failure (Table 3, Fig. 3). Seven deaths occurred after discharge, 5 suddenly (possible stent thrombosis) and 2 due to progressive heart failure. In the BMS group, 4 patients died before discharge (3 of progressive heart failure and 1 of cardiac rupture) and 2 occurred after discharge: 1 suddenly (possible stent thrombosis) and 1 due to progressive heart failure. In a Cox proportional hazards model with information on randomization as the only variable, the hazard ratio for the DES versus BMS group was 3.2 (95% confidence interval: 1.3 to 8.1, p = 0.01) with no influence by distal protection (p value for interaction 0.50).

Myocardial infarctions and stroke occurred with similar frequencies (Fig. 1). All but 1 patient had myocardial infarctions that resulted in creatine kinase-myocardial band levels more than twice the upper reference value. We found no significant interactions between distal protection and stent type with regard to clinical end points.

Discussion

We evaluated the long-term clinical outcome of STEMI patients randomly assigned to have a DES or a BMS implanted in the infarct-related lesion and showed a significantly reduced need for revascularization in the DES group. The rate of all-cause mortality was not significantly different, but the rate of cardiac mortality was significantly
In the DES group, which is in contrast to most previous studies.

In the PASEO (Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) trial, the sirolimus-eluting and paclitaxel-eluting stent were both safe and effective compared to a BMS, with a similar total mortality between 8% and 11% (cardiac mortality not reported) (21). The STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus Eluting Stent Versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction) trial found a lower rate of TVR with the tirofiban and sirolimus stent regimen and a total mortality between 11% and 14% (no report on cardiac mortality) (22). In the PASSION (Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial, implantation of a paclitaxel-eluting stent did not improve clinical outcome at 2 years (23). The SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction) trial, the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty) trial, and the MULTI-STRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction) study all reported a reduced TLR rate within 12 months after implantation of a sirolimus-eluting stent without raising any safety concerns (24–26). Similar results were reported in the large HORIZONS (Harmonizing Outcomes With Revascularization and Stents in AMI) trial after implantation of a paclitaxel-eluting stent compared with a BMS, and cardiac death was between 2.4% and 2.7% after 1 year (27).

In the meta-analysis by Kastrati et al. (28), there was no difference in 1-year mortality rates (4% and 5% in the DES group and BMS group, respectively); and in a review of patients included in registries or randomized trials, Brar et al. (14) did not find any increase in death associated with DES treatment.

A multinational registry comparing 2-year outcomes of patients treated with DES or BMS for a STEMI reported similar prognosis in the 2 groups. However, extension of the observation period up to 2 years revealed an increased late mortality in the DES group (29). With the observational nature of registries in mind, these results should be interpreted with caution. Nevertheless, the risk of late and very late stent thrombosis seems to continue after implantation.

### Table 2 Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DES (n = 313)</th>
<th>BMS (n = 313)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events at 8 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>28 (8.9)</td>
<td>45 (14.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Death</td>
<td>16 (5.1)</td>
<td>8 (2.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>13 (4.2)</td>
<td>5 (1.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>MI</td>
<td>5 (1.6)</td>
<td>8 (2.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>20 (6.4)</td>
<td>50 (16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>16 (5.1)</td>
<td>41 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Events at 3 yrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>36 (11.5)</td>
<td>57 (18.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>33 (10.5)</td>
<td>20 (6.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>19 (6.1)</td>
<td>6 (1.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>9 (4.2)</td>
<td>15 (5.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>28 (8.9)</td>
<td>62 (19.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>19 (6.1)</td>
<td>51 (16.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are n (%).

MACE = major adverse cardiac events (cardiac death, reinfarction, and target lesion revascularization); MI = myocardial infarction; other abbreviations as in Table 1.
of different types of DES, with an increased rate among patients with acute coronary syndromes (30).

The very low cardiac mortality rate in our BMS group is hard to interpret, and the excess cardiac DES mortality should be interpreted accordingly and might have occurred by chance.

**Conclusions**

The present randomized study with long-term follow-up shows that in patients with STEMI, implantation of a DES, compared with a BMS, significantly reduces the rate of MACE and the need for revascularization. Despite this reduction, patients with STEMI who have a DES implanted seem to have a higher risk of cardiac death that cannot be attributed to reinfarction or stent thrombosis.
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Key Words: acute MI ▪ drug-eluting stent ▪ reinfarction ▪ stent thrombosis ▪ primary PCI.