Drug-Eluting Stents Versus Bare-Metal Stents in Diabetic Patients With ST-Segment Elevation Acute Myocardial Infarction: A Pooled Analysis of Individual Patient Data From 7 Randomized Trials

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Introduction and objectives. The performance of drug-eluting stents (DES) in high-risk patients with diabetes and acute ST-elevation myocardial infarction (STEMI) who have undergone primary angioplasty has not been previously studied. The objective was to evaluate the efficacy and safety of DESs in diabetic patients with STEMI.

Methods. We performed a pooled analysis of individual patient data from 7 randomized trials that compared DES (ie, sirolimus- or paclitaxel-eluting stents) with bare-metal stent (BMS) in patients with STEMI. The analysis involved 389 patients with diabetes mellitus from a total of 2476 patients. The outcomes of interest were target-lesion revascularization, stent thrombosis, death, and the composite endpoint of death or recurrent myocardial infarction during a follow-up of 12-24 months.

Results. Overall, 206 diabetic patients received a DES and 183, a BMS. The risk of target-lesion revascularization was significantly lower in patients treated with a DES compared to those treated with a BMS (hazard ratio [HR] = 0.44; 95% CI, 0.23-0.88; P=.02). There was no significant difference in the risk of stent thrombosis between those treated with a DES or a BMS (HR=0.33; 95% CI, 0.09-1.13; P=.08). Similarly, the risk of the combined endpoint of death or myocardial infarction was not significantly different between patients treated with a DES or a BMS (HR=0.64; 95% CI, 0.36-1.13; P=.12).

Conclusions. Compared with BMSs, DES use improved clinical outcomes in diabetic patients undergoing primary angioplasty for STEMI: the need for reintervention was reduced, with no increase in mortality or myocardial infarction.


Stents liberadores de fármacos frente a stents convencionales en pacientes diabéticos con infarto agudo de miocardio con elevación del segmento ST: un análisis combinado de los datos de pacientes individuales de 7 ensayos aleatorizados

Introducción y objetivos. Los resultados obtenidos con los stents liberadores de fármacos (SLF) en el grupo de pacientes de alto riesgo formado por los pacientes...
diabéticos con infarto agudo de miocardio con elevación del segmento ST (IAMCEST) tratados con angioplastia primaria no se han estudiado con anterioridad. Nuestro objetivo fue evaluar la eficacia y la seguridad de los SLF en pacientes diabéticos con IAMCEST.

**Métodos.** Llevamos a cabo un análisis combinado de los datos de pacientes individuales de 7 ensayos aleatorizados en los que se comparó el empleo de stents libera- dores de sirolimus o de paclitaxel (SLF) con el de stents convencionales (SC) en el contexto de un IAMCEST. Se incluyó en este análisis a 389 pacientes con diabetes mellitus de un grupo total de 2.476. Los objetivos del estudio fueron la revascularización de la lesión diana, la trombosis del stent, la muerte y la variable combinada de muerte o infarto de miocardio recurrente durante un período de seguimiento de 12-24 meses.

**Resultados.** Hubo 206 pacientes diabéticos tratados con SLF y 183 tratados con SC. El riesgo de que se practicara una revascularización de la lesión diana fue significativamente inferior en los pacientes tratados con SLF en comparación con los pacientes tratados con SC (razón de riesgos [HR] = 0,44; intervalo de confianza [IC] del 95%, 0,23-0,88; p = 0,02). El riesgo de trombosis del stent no presentó diferencias significativas entre los pa- cientes tratados con SLF y los tratados con SC (HR = 0,33; IC del 95%, 0,09–1,13; p = 0,08). De forma análoga, el riesgo de la variable de valoración combinada formada por la muerte y el infarto de miocardio no presentó diferentes significativas entre los pacientes tratados con SLF y los tratados con SC (HR = 0,64; IC del 95%, 0,36-1,13; p = 0,12).

**Conclusiones.** En comparación con los SC, los SLF mejoran los resultados clínicos en los pacientes diabéti- cos a los que se practica una angioplastia primaria por un IAMCEST, al reducir la necesidad de reintervención sin incrementar la tasa de mortalidad o infarto de miocar- dio.


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**ABBREVIATIONS**

BMS: bare-metal stent  
DES: drug-eluting stents  
STEMI: ST-segment elevation myocardial infarction

**INTRODUCTION**

Primary coronary angioplasty has been established as the treatment of choice for patients with acute ST-segment elevation myocardial infarction (STEMI). Implantation of bare metal stents (BMS) further reduces the incidence of major adverse cardiac events mainly by decreasing the need for reintervention. Nevertheless, many STEMI patients treated with primary bare-metal stenting still require repeat revascularization procedures. Drug-eluting stents (DESs) have been shown effective in reducing restenosis and need for reintervention in several patient subsets. Recently, several randomized trials and a meta-analysis of these trials which compared DESs (sirolimus-eluting or paclitaxel-eluting stents) with BMS among STEMI patients demonstrated that DESs improve clinical outcome by reducing the risk of reintervention. On the other hand, in spite of some concerns about an increased risk of stent thrombosis with these devices in STEMI patients, they showed a good safety profile.

Diabetes mellitus portends a higher risk for adverse outcomes in patients with coronary artery disease undergoing percutaneous coronary interventions. Diabetic patients experience a higher incidence of thrombotic events and more frequently require reintervention procedures. Studies which have excluded patients with STEMI have shown that DESs reduce the risk of repeat revascularization, while there has been concern about the safety of these devices in diabetic patients. However, the efficacy and safety of DESs in diabetic patients with STEMI treated with primary stenting has not been studied before. The numbers of STEMI patients with diabetes mellitus in the individual studies which were previously mentioned were too small to allow meaningful analysis. Therefore, we performed a pooled analysis based on individual data of diabetic patients enrolled in 7 randomized trials that evaluated the effectiveness and safety of DESs versus BMS in patients with STEMI.

**METHODS**

We searched for randomized studies comparing DESs (sirolimus- or paclitaxel-eluting stents) with BMS in patients undergoing primary angioplasty for STEMI. They were included in this pooled analysis if results regarding diabetes mellitus status and a mean follow-up period of at least 12 months were reported or made available by the trial investigators.

To identify the studies of interest we searched PubMed database, U.S. National Institute of Health, Cochrane Central Register of Controlled Trials, and the proceedings of the American Heart Association, American College of Cardiology, and European Society of Cardiology. Internet-based sources of information on the results of clinical trials in cardiology were also searched. We also identified relevant reviews and editorials from
major medical journals published within the last year and assessed for possible information on trials of interest. The last search was performed in November 2007. A total of 7 trials were available for this pooled analysis.10-16

The primary efficacy end point of pooled analysis was the need for reintervention (target lesion revascularisation). The primary safety end point of this pooled analysis was stent thrombosis. According to the protocols used in the original clinical trials, stent thrombosis was defined as angiographic evidence of thrombus in the presence of ischemic signs. Secondary end points were death and the composite of death or and recurrent myocardial infarction. The adjudication of events in each trial was performed by the same event committee over the entire follow-up period. Survival was calculated from the date of randomization to the date of death. Data for surviving patients were censored on the date of last follow-up. An electronic form containing the data fields to be completed for individual patients was sent to all principal investigators of the trials.

The data requested for each enrolled patient included the date of randomization, allocated treatment, diabetes status, event status (including death, recurrent myocardial infarction, coronary revascularisation [percutaneous or surgical], stent thrombosis, and their respective dates of occurrence) and date of last follow-up. All data were thoroughly checked for consistency (logical checking and checking against the original publications). Any queries were resolved and the final database entries verified by the responsible trial investigator.

Statistical Analysis

We used the Mantel-Cox method stratified by trial to perform survival analysis. Hazard ratios and their 95% confidence intervals were calculated by means of the log-rank test. Trials in which the event of interest was not observed in any of the treatment groups were not included in the analysis of that event. For trials in which only one of the treatment groups had no events of interest, the treatment effect estimate and its standard error were approximated from 2 × 2 contingency tables after adding 0.5 to each cell.23 We used the Cochran test to assess heterogeneity across trials. Also, we calculated the I2 statistic to measure the consistency between trials with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively.24 Hazard ratios from individual trials were pooled using the DerSimonian and Laird method for random effects.25 Results were considered statistically significant at 2-sided P<.05. Statistical analysis was performed by using the Stata software, version 9.2 (Stata Corp, College Station, Tex). Survival curves are presented as simple, non-stratified Kaplan-Meier curves across all trials and constructed with the use of S-Plus software version 4.5. (Insightful Corporation, Seattle, WA).

RESULTS

Seven randomized trials including 2476 patients with STEMI treated with DESs or BMS were selected for this analysis. Of these, a total of 389 diabetic patients (15.7%) were identified and analyzed. The main characteristics and inclusion criteria of these trials are summarised in Tables 1 and 2. There were 206 diabetic patients allocated to the DESs group (127 patients with sirolimus-eluting stent and 79 patients with paclitaxel-eluting stent) and 183 diabetic patients to BMS group. Table 3 shows the definition of diabetes in each of trials. More specifically, sirolimus-eluting stent was tested in the SESAMI (Randomized Trial of Sirolimus Stent vs Bare Stent in Acute Myocardial Infarction trial) and the STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction trial) and the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angiography).12,13,15 Paclitaxel-eluting stent was tested in the HAMU-STENT (Helsinki area acute myocardial infarction-treatment re-evaluation—Should the patient get a drug-eluting or a normal stent trial) and PASSION (Paclitaxel-Eluting Stent vs Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial).10,11 Either sirolimus- or paclitaxel-eluting stents were tested in the BASKET-AMI (Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction trial) and the trial of Di Lorenzo et al.14,16 The recommended length of postprocedural thienopyridine therapy was 3,12 6,11,13,14,16 or 12 months.10,15 The mean length of follow-up ranged from 12 to 24.2 months. All trials were of open-label design and all but 2 trials11,16 had protocol-mandated follow-up angiography. No significant interaction was observed between diabetes and treatment effect achieved with DES in the entire population regarding reintervention (P=.60), stent thrombosis (P=.24), death (P=.30), and composite of death or recurrent myocardial infarction (P=.64).

Figure 1A shows the absolute numbers of patients who experienced the primary efficacy end point of reintervention in each trial by treatment group, with the hazard ratio for each trial. Overall, the use of DES was associated with a hazard ratio for reintervention of 0.44 (95% confidence interval [CI], 0.23-0.88; P=.02) compared with the use of BMS.
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of the curves is readily visible. The probability of reintervention was 6.8% in the DES group and 13.7% in the BMS group.

Figure 2A shows the number of patients who suffered the primary safety end point of stent thrombosis (as defined in the individual trials). The

TABLE 1. Main Characteristics of the Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Mean (years), y</th>
<th>Diabetic Patients, No. (%)</th>
<th>Type of DES</th>
<th>Primary End Point</th>
<th>Length of Thienopyridine Therapy, mo</th>
<th>Mean Length of Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-AMI</td>
<td>216</td>
<td>62.2</td>
<td>31 (14.4)</td>
<td>PES, SES</td>
<td>Cardiac death, myocardial infarction, or reintervention</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Di Lorenzo</td>
<td>270</td>
<td>64</td>
<td>59 (21.9)</td>
<td>PES, SES</td>
<td>Death, myocardial infarction, or reintervention</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>HAAMU-STENT</td>
<td>164</td>
<td>63</td>
<td>24 (14.6)</td>
<td>PES</td>
<td>Angiographic late lumen loss</td>
<td>12</td>
<td>16.7</td>
</tr>
<tr>
<td>PASSION</td>
<td>619</td>
<td>60.8</td>
<td>68 (11)</td>
<td>PES</td>
<td>Cardiac death, myocardial infarction, or reintervention</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>SESAMI</td>
<td>320</td>
<td>61.6</td>
<td>65 (20.3)</td>
<td>SES</td>
<td>Angiographic binary restenosis</td>
<td>12</td>
<td>12.3</td>
</tr>
<tr>
<td>STRATEGY</td>
<td>175</td>
<td>62.6</td>
<td>26 (14.9)</td>
<td>SES</td>
<td>Death, myocardial infarction, stroke, or angiographic binary restenosis</td>
<td>3</td>
<td>24.2</td>
</tr>
<tr>
<td>TYPHOON</td>
<td>712</td>
<td>59.3</td>
<td>116 (16.3)</td>
<td>SES</td>
<td>Cardiac death, myocardial infarction, or reintervention</td>
<td>6</td>
<td>12.1</td>
</tr>
</tbody>
</table>

BASKET-AMI indicates Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction trial; DES, drug-eluting stent.; HAAMU-STENT, the Helsinki area acute myocardial infarction-treatment re-evaluation-Should the patient get a drug-eluting or a normal stent trial; PASSION, the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SESAMI, the Randomized Trial of Sirolimus Stent versus Bare Stent in Acute Myocardial Infarction trial; STRATEGY, the Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent versus Abciximab and Bare Metal Stent in Myocardial Infarction trial; TYPHOON, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty.

There was no heterogeneity across trials ($I^2=0\%$) and no significant interaction ($P=.52$) between treatment effect and type of DES (sirolimus-eluting stent or paclitaxel-eluting stent) used. Figure 1B shows 1-year probability curves for reintervention in the 2 treatment arms. A continuous separation of the curves is readily visible. The probability of reintervention was 6.8% in the DES group and 13.7% in the BMS group.

Figure 2A shows the number of patients who suffered the primary safety end point of stent thrombosis (as defined in the individual trials). The

TABLE 2. Main Inclusion/Exclusion Criteria of the Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASKET-AMI</td>
<td>Acute myocardial infarction within 12 hours</td>
<td>Target vessel diameter ≥4 mm, restenotic lesion, no consent</td>
</tr>
<tr>
<td>Di Lorenzo</td>
<td>Initial onset of chest pain within 12 hours</td>
<td>Active internal bleeding or a history of bleeding diathesis within the previous 30 days. Thrombolytic/fibrinolytic therapy within 24 hours</td>
</tr>
<tr>
<td>HAAMU-STENT</td>
<td>Initial onset of chest pain within 12 hours</td>
<td>Contraindication for thrombolytic treatment, left bundle branch block, no consent</td>
</tr>
<tr>
<td>PASSION</td>
<td>Age 18-80 years, reperfusion to be achieved within 6 hours, suitable anatomy for primary stenting</td>
<td>Prior thrombolysis, infarction caused by restenosis/thrombosis, cardiogenic shock, intubation/ventilation, intracranial disease</td>
</tr>
<tr>
<td>SESAMI</td>
<td>Age &gt;18 years, symptom duration ≥30 minutes and ≤12 hours</td>
<td>Cardiogenic shock, bleeding diathesis, severe hepatic/renal dysfunction, left main/graft disease, no consent</td>
</tr>
<tr>
<td>STRATEGY</td>
<td>Chest pain duration ≥30 minutes, admission within 12 hours from pain onset or between 12-24 hours with ischemia</td>
<td>Thrombolysis within 30 days, bleeding diathesis, major surgery within 15 days, stroke within 6 months</td>
</tr>
<tr>
<td>TYPHOON</td>
<td>Symptoms began &lt;12 hours before catheterization</td>
<td>Prior thrombolysis, overt heart failure, prior myocardial infarction, left ventricular ejection fraction &lt;30%</td>
</tr>
</tbody>
</table>

BASKET-AMI indicates Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction trial; DES, drug-eluting stent.; HAAMU-STENT, the Helsinki area acute myocardial infarction-treatment re-evaluation-Should the patient get a drug-eluting or a normal stent trial; PASSION, the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation trial; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SESAMI, the Randomized Trial of Sirolimus Stent versus Bare Stent in Acute Myocardial Infarction trial; STRATEGY, the Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent versus Abciximab and Bare Metal Stent in Myocardial Infarction trial; TYPHOON, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty.
figure 3a shows the absolute numbers of deaths in each trial according to treatment group, with the hazard ratio for each trial. there was no statistical evidence of heterogeneity across the 7 trials. in total, there were 15 death in patients with des and 18 deaths in patients with bms. there was no heterogeneity across trials (i²=0%) and no significant interaction (p=.98) between treatment effect and type of des used (sirolimus- or paclitaxel-eluting stent). figure 2b shows 1-year curves of stent thrombosis probability for the 2 treatment groups. the probability of stent thrombosis was 1.5% in the des group and 4.4% in the bms group.

figure 4a shows the absolute numbers of patients who died or had a recurrent myocardial infarction in each trial according to treatment group, with the hazard ratio for each trial. there was no statistical evidence of heterogeneity across trials. overall, use of des was associated with a hazard ratio for death or myocardial infarction of 0.64 (95% ci, 0.36-1.13; \( p=.12 \)), as compared with use of bms. figure 4b shows 1-year event curves for the 2 treatment groups. the probability of death or myocardial infarction was 12.6% in the des group and 13.1% in the bms group.

## discussion

in this study we performed a pooled analysis of patient-level data from 7 randomized trials comparing sirolimus- or paclitaxel-eluting stents with bms in diabetic patients undergoing primary angioplasty for stemi. the findings of this study show that use of des dramatically reduces the risk of repeat revascularization without any increase in the risk of thrombotic related events as compared with the use of bms.

although it has been established that des are generally highly effective in reducing restenosis and need of reinterventions in various patient and lesion subsets, until recently there has been only limited evidence on the use of des in patients with acute myocardial infarction. an increased risk of acute and sub-acute stent thrombosis has constituted a major concern regarding the use of des in this group of patients. this increased risk has been explained by enhanced platelet reactivity in acute myocardial infarction, presence of a pronounced inflammatory and thrombogenic environment of the exposed necrotic core to flowing blood, prothrombogenic effects of the non-erodible polymer and drugs loaded onto the stent platform. the risk of stent thrombosis with des could be even higher and the effectiveness of these devices could be lower in patients with diabetes mellitus undergoing primary stenting for stemi. evidence shows the presence of diabetes mellitus is associated with a worse outcome among patients with acute myocardial infarction; diabetic patients have a higher rate of mortality and postintervention coronary restenosis than non-diabetic patients. this poor prognosis of diabetic patients with acute myocardial infarction has been linked to various factors including hypercoagulability, endothelial and platelet dysfunction, widespread atherosclerosis,
and comorbidities. Considering that the prevalence of diabetes mellitus among patients with acute myocardial infarction has increased during the last decade and the prognosis of patients with diabetes mellitus has remained worse despite advances in the management of myocardial infarction, the evaluation of the efficacy and safety of DES in diabetic patients with STEMI constitutes an issue of great interest. Nevertheless, there have been no dedicated studies on diabetic patients treated with DES for STEMI. On the other hand, previous reports on the use of DES in diabetic patients without STEMI have shown the superiority of DES over BMS in reducing repeat revascularization rates but have also raised some concerns regarding a higher risk of thrombosis-related events with DES.

Within the last 2 years the results of several randomized studies of DES versus BMS in patients undergoing primary stenting for STEMI have been reported. These studies showed the safety and efficacy of using DES in STEMI patients. However, there were no separate analyses for diabetic patients in these studies. The numbers of patients with diabetes mellitus in the individual studies were too small, varying from 24 to 116 patients thus preventing the performance of any meaningful subset analysis. In a pooled analysis of 389 patients with diabetes mellitus undergoing primary stenting...
for STEMI in 7 randomized trials we found that use of DES was associated with a 56% reduction in the hazards of repeat reintervention. This figure is comparable to the 62% reduction in the hazards of reintervention reported recently from a meta-analysis including all patients of randomized trials comparing DES with BMS in STEMI. Furthermore, we did not find evidence for a higher rate of stent thrombosis, death or the composite endpoint of death or myocardial infarction. The 1-year probability of stent thrombosis was 4.4% in the BMS group. Available information on the incidence of this complication in diabetic patients with STEMI treated with BMS is very limited. It has been as high as 18% in a very small cohort of diabetics in the study of Silva et al. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, the incidence of stent thrombosis was not reported for diabetic patients; however, the patients had a 1-year rate of 6.1% for mortality and 3.4% for recurrent infarction. It has been suggested that DES increase the risk of late stent thrombosis as compared with BMS not only in a recent meta-analysis, but also in a recent registry of STEMI. Thus it is possible that our mean follow-up of more than 15 months has limited our capacity to detect the true incidence of very late stent thrombosis in our
and BMS. Despite the larger number of patients available for this pooled analysis as compared with the individual trials, the results of this analysis should be interpreted with caution. Not only the number of diabetic patients is relatively limited but this study also represents a post hoc subset analysis. In the setting of a subset analysis, randomization could have been ineffective. Adequately powered studies with longer follow-up are required to provide definitive answers to the issues of efficacy and safety of DES implantation in diabetic patients with STEMI. Furthermore, it should be noted that
CONCLUSIONS

In conclusion, use of DES in diabetic patients undergoing primary stenting for STEMI reduces the need for repeat intervention without increasing the rate of thrombosis-related events as compared to BMS.

STEMI is still an off-label indication for DES. The results of this meta-analysis apply to the type of patients enrolled in the trials which were included in this meta-analysis. However, recent evidence from patients outside the setting of clinical trials suggests similar benefit with drug-eluting stents in the setting of acute myocardial infarction.33,34

Figure 4. A: absolute numbers of patients experiencing death or recurrent myocardial infarction and hazard ratios for this endpoint with drug-eluting stent versus bare-metal stents for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. B: Kaplan-Meier curves of death or recurrent myocardial infarction in each of the stent groups for the pooled population. BMS indicates bare-metal stent; DES, drug-eluting stent.
REFERENCES


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