Comparison between drug-eluting and bare metal stent on ST-elevation myocardial infarction outcome: Should second-generation drug-eluting stent be preferred?

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**Article info**

**Article history:**
Received 17 April 2013
Received in revised form 6 September 2013
Accepted 9 September 2013
Available online 22 December 2013

**Keywords:**
STEMI
Primary PCI
Bare metal PCI
Drug-eluting PCI
Outcome

**Abstract**

**Background and purpose:** Although several studies reported that drug-eluting stents (DES) are able to reduce restenosis incidence without increasing mortality, concerns still exist about their safety in ST-segment elevation myocardial infarction (STEMI) patients mainly for a possible higher rate of in-stent thrombosis. Recent evidence suggests a better safety profile of second-generation DES, but data on their outcome in STEMI are still poor. In this study, we evaluated the impact on mortality and target lesion revascularization (TLR) of DES or bare metal stent (BMS) implantation in STEMI patients submitted to primary angioplasty.

**Methods and subjects:** We analyzed mortality and TLR in 1150 STEMI patients during a mean 43-month follow-up after DES (44.6%) or BMS (55.4%) implantation. A propensity score method was used to minimize bias. During follow-up, 223 deaths occurred.

**Essential results:** Unadjusted for potential confounders, DES implantation was associated with a significant reduction in all-cause mortality [hazard ratio (HR) 0.40; 95%CI 0.30–0.54] and TLR (HR 0.55; 95%CI 0.36–0.86); this latter was confirmed after propensity score analysis (HR 0.39; 95%CI 0.21–0.67). Second-(n = 179) vs. first-(n = 337) generation DES showed a further reduction in TLR (HR 0.17; 95%CI 0.05–0.57). Adjusted analyses showed a significant reduction in the combined end-point of all-cause mortality or TLR after both first- and second-generation DES vs. BMS implantation with a trend to a lower risk for second- vs. first-generation DES.

**Principal conclusions:** DES implantation in STEMI patients showed a significant reduction in TLR and in the combined endpoint of TLR or mortality. Second-generation DES showed a more protective effect on the combined endpoint, suggesting that they would be preferred in this setting.

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**Introduction**

Primary percutaneous coronary intervention (PCI) is the gold standard therapy for ST-segment elevation myocardial infarction (STEMI), its main aim being to obtain a rapid and effective myocardial reperfusion through the culprit vessel re-opening, thereby reducing mortality. Several randomized controlled trials demonstrated that routine bare metal stent (BMS) implantation, during primary PCI, was superior to balloon angioplasty alone for its ability to reduce reocclusion or reinfarction [1–4]. However, angiographic follow-up of STEMI patients treated with BMS showed a very high rate of in-stent restenosis [5–7]. Conversely, the use of drug-eluting stents (DES) in the setting of primary PCI was associated with a lower rate of in-stent restenosis with a consequently lower need for repeat revascularizations [8]. However, no definitive conclusions have been drawn regarding their effect on long-term mortality and the incidence of cardiovascular events in this group of patients [9–16]. Furthermore, some concerns still exist about the safety of DES in the setting of acute myocardial infarction for two main reasons. Firstly, fears relating...
to the higher rate of early and late in-stent thrombosis reported in several studies leading to a higher mortality rate [17]. Secondly, the reduced possibility, in an urgent setting such as primary PCI, of completely ruling out all the possible contraindications to a prolonged dual antiplatelet therapy (DAPT). However, conflicting results regarding DES in STEMI patients were related almost exclusively to first-generation DES [9–11,13,14,18]. Recently, new evidence has demonstrated a better safety profile of second- vs. first-generation DES in patients with acute coronary syndromes, with a reduced incidence of in-stent thrombosis [19,20], but data on outcome in the specific setting of STEMI are still poor. Therefore, the choice of the safest stent in STEMI patients is still a matter for debate.

The aim of the present study was to evaluate, in STEMI patients submitted to primary PCI, the impact of the type of stent implanted, either BMS or first- or second-generation DES, on repeat revascularization rate and long-term mortality.

Methods

Between January 2004 and December 2009, 2058 patients with STEMI were submitted to primary PCI in the catheterization laboratory of the University of Florence, a tertiary care facility.

Only patients who had at least one DES or one BMS implanted in the course of the primary PCI were included in this analysis: 245 patients who were treated for the index event only with balloon angioplasty or with both types of stent were excluded from the study. Among the remaining 1813 patients, 1150 were resident in the Florence area (33 municipalities) and 663 in the surrounding provinces. We limited our analysis to the 1150 inhabitants in the Florence area. The study was approved by the local ethics committee.

Patients were divided into two groups according to the type of stent implanted in the infarct-related artery (IRA) either BMS (Liberte’ and Express Stent, Boston Scientific, Natick, MA, USA; Multi Link Vision and Multi Link Mini-Vision Stent, Abbott Vascular, Abbott Park, IL, USA; Driver and MicroDriver, Medtronic, Minneapolis, MN, USA; Tecnic Carbostent, Sorin Biomedica, Milan, Italy) or DES (Paclitaxel Eluting Stent-PES, Taxus, Boston Scientific; Sirolimus Eluting Stent—SES, Cypher, Cordis, Bridgewater, NJ, USA; Everolimus Eluting Stent-EES, Promus, Boston Scientific or XIENCE-V, Abbott Vascular; Zotarolimus Eluting Stent-ZES, Endeavor and Endeavor Resolute, Medtronic).

The DES patients’ group was divided into two further groups: (a) 337 patients implanted with a first-generation DES (PES, SES) and (b) 179 patients implanted with a second-generation DES (EES, ZES). All PCI were performed according to the international guidelines on myocardial revascularization [21]. Coronary angiography was performed through either the radial or the femoral approach. Before PCI all patients received a bolus of 70IU/kg of unfractionated heparin, 325mg of aspirin, and 300/600mg of clopidogrel loading dose. Administration of glycoprotein (Gp) IIb/IIIa receptor inhibitors, the use of thrombus aspiration systems, and intravascular ultrasound analysis, as well as the type of stent implanted were at the Interventional cardiologist’s discretion. Post-PCI, all patients received 75mg/day of clopidogrel for at least 12 months, 100mg/day of aspirin indefinitely, in addition to beta-blockers, angiotensin-converting enzyme inhibitors, and statins if not contraindicated. Primary PCI was performed only in the IRA with the exception of patients with cardiogenic shock: an intra-aortic balloon pump was used in patients with severe hemodynamic instability or with cardiogenic shock.

Endpoints

The primary endpoints were: all-cause mortality, the occurrence of TLR, and the combined endpoint of all-cause mortality or TLR during follow-up.

Life status after hospital discharge was assessed in December 2011 by consulting the Registry Office of the municipalities of residence. TLR was defined as a PCI of the target lesion due to restenosis or reocclusion within the stent or in an adjacent segment of 5 mm distally or proximally to the edges of the stent. Data regarding TLR were obtained by consulting the hospital discharge database following the index hospitalization and the procedural details were obtained from the local catheterization laboratory database. All PCIs performed in the study population after the index revascularization were ischemia-driven and all the procedures were reviewed by two interventional cardiologists unaware of the type of stent implanted in the index procedure to establish the occurrence of TLR as described above.

Subsequent revascularizations of other coronary arteries did not constitute an endpoint.

Endpoints were assessed for the entire follow-up period.

Statistical analysis

Categorical variables were given as a percentage and compared with the χ² test. As continuous variables were non-normally distributed at the Shapiro–Wilk test, they were described as median and interquartile range and compared using the Wilcoxon’s rank-sum test.

A propensity score method was used to minimize bias related to the nonrandom assignment of stent type. The propensity score was calculated introducing in the final model the following variables: age-classes, gender, diabetes mellitus, smoking habit, dyslipidemia, chronic obstructive pulmonary disease, Killip class, heart rate, and coronary angiographic characteristics (statistically significant at univariate analysis) as well as other variables such as previous acute myocardial infarction, primary PCI, and hypertension (not statistically significant at univariate analysis, but potential predictors).

The propensity score reflects the individual patient’s predicted probability of receiving treatment with DES given the observed set of covariates and it is used to make an adjustment for covariates during calculation of the prognostic effect. When building the propensity score using a logistic regression model, only covariates that occurred pre-treatment were included (baseline conditions and clinical presentation). Two separate methods were used to compare outcomes after DES or BMS:

(1) A classical approach using the Cox proportional hazards regression model to estimate the effect of the type of stent on all-cause mortality, TLR, and the combined endpoints, adjusting for procedural aspects (thrombus aspiration and Gp IIb/IIIa inhibitor use) and propensity score included as a continuous covariate. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The methods proposed by Grambsch and Therneau [22] and by May and Hosmer [23] were used to check the proportional hazard assumption and the goodness-of-fit of the models, respectively. Ap-value <0.05 was considered statistically significant.

(2) In the second approach, one-to-one nearest neighbor matching was performed to compare outcomes after undergoing PCI (matched-pair analysis). In this case, the matched pairs were characterized by having a similar propensity score. To evaluate the success of the propensity score matching we compared covariates in the groups before and after matching. All baseline characteristics that had been significantly different
(unbalanced) between groups in the overall study were balanced on the propensity-matched pairs.

Cox proportional hazard models adjusted for procedural aspects and stratified were fitted on the matched pairs [24]. These two approaches are well-accepted methods of applying propensity scores [24–26]. Analyses were performed using STATA statistical package (version 11.0, Stata Corporation, College Station, TX, USA).

**Results**

Out of 1150 STEMI patients with primary PCI (mean age: 68.2 ± 12.5 years), 634 (55.4%) received a BMS and 516 (44.6%) received a DES in the IRA.

In comparison with BMS patients, DES patients were significantly younger, more often men, and more likely to be current smokers and dyslipidemic. Among cardiovascular and non-cardiovascular comorbidities, only chronic obstructive pulmonary disease was less frequent in DES patients (p = 0.035) (Table 1).

Patients who received DES showed significantly lower levels of glycemia and troponin I, a lower Killip class, a higher ejection fraction (EF) (Table 1) and a higher grade of anterograde flow pre-PCI in the IRA (Table 2). In comparison to BMS, DES were significantly longer and with a diameter less than 3 mm, more frequently implanted in the left anterior descending artery (LAD), and associated with Gp IIb–IIa inhibitor administration (Table 2).

**Impact of type of stent on all-cause mortality**

During the follow-up period (mean duration 43 months), 223 deaths occurred. The overall survival probability for the entire cohort was 79% (72% for BMS; 88% for DES, p < 0.001).

In the unadjusted analysis, DES was associated with a statistically significant 60% reduction in all-cause mortality (HR 0.40; 95% CI 0.30–0.54). The reduction was not significant anymore when the propensity score was included as a continuous covariate (HR 0.76; 95% CI 0.53–1.10) and when the analysis was stratified by the DES generation group. Nevertheless, the matched-pair analysis indicated a significant reduction in mortality in the DES group (HR 0.61; 95% CI 0.39–0.95) (Table 3).

Moreover, during follow-up, we observed 49 myocardial reinfections without any significant difference in relation to the type of stent implanted [26 events (4.1%) in patients treated with BMS vs. 23 events (4.4%) in those treated with DES, p = n.s.]. As far as the causes of death are concerned, data are available only for 92 patients who died in hospital during the index admission or in a subsequent hospitalization. In particular, 63 of them died of cardiac causes (49 myocardial infarction, 7 other ischemic heart diseases, 2 cardiac arrest, and 5 heart failure).

**Impact of type of stent on TLR occurrence**

During the follow-up period, 89 TLR were performed (84% during the first year after the index event).

The TLR-free survival probability for the entire cohort was 92% (91% for BMS; 94% for DES, p < 0.028).

Unadjusted for any potential confounders, DES was associated with a statistically significant 45% reduction in TLR occurrence (HR 0.55; 95% CI 0.36–0.86). This association remained significant when the propensity score was included in the model as a continuous covariate (HR 0.39; 95% CI 0.21–0.67) and in the analysis stratified by DES generation group, with a strong reduction for the second-generation DES (HR 0.17; 95% CI 0.05–0.57). Results were

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**Table 1** Baseline characteristics at presentation of patients undergoing PCI by stent type.

<table>
<thead>
<tr>
<th>BMS group</th>
<th>DES group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>634</td>
<td>516</td>
</tr>
<tr>
<td>Age, years*</td>
<td>74 (63–82)</td>
<td>51 (53–71)</td>
</tr>
<tr>
<td>Males, %</td>
<td>33.7</td>
<td>49.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 (23–28)</td>
<td>26 (24–28)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>28.5</td>
<td>22.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55.9</td>
<td>49.6</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>56.3</td>
<td>65.5</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>33.2</td>
<td>41.9</td>
</tr>
<tr>
<td>Chronic kidney disease, %</td>
<td>5.9</td>
<td>5.2</td>
</tr>
<tr>
<td>COPDx</td>
<td>10.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Previous AML</td>
<td>11.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Previous angina, %</td>
<td>21.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Previous PCI, %</td>
<td>8.3</td>
<td>11.4</td>
</tr>
<tr>
<td>Previous CABC, %</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Systolic pressure*</td>
<td>130 (115–146)</td>
<td>130 (115–150)</td>
</tr>
<tr>
<td>Heart rate*</td>
<td>78 (67–88)</td>
<td>75 (66–85)</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II, %</td>
<td>86.8</td>
<td>92.1</td>
</tr>
<tr>
<td>III–IV, %</td>
<td>13.2</td>
<td>7.9</td>
</tr>
<tr>
<td>EF*</td>
<td>45 (37–50)</td>
<td>48 (40–55)</td>
</tr>
<tr>
<td>Glycemia*</td>
<td>1.39 (1.14–1.81)</td>
<td>1.25 (1.06–1.52)</td>
</tr>
<tr>
<td>Serum creatinine*</td>
<td>0.9 (0.8–1.2)</td>
<td>0.9 (0.8–1.1)</td>
</tr>
<tr>
<td>CK-MB*</td>
<td>172 (79–331)</td>
<td>155 (65–294)</td>
</tr>
<tr>
<td>Tn (ng/mL)*</td>
<td>80 (35–174)</td>
<td>64 (26–147)</td>
</tr>
</tbody>
</table>

BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary interventional; EF, ejection fraction; PCI, percutaneous coronary intervention; TLR, thrombolysis in myocardial infarction.

* Median and interquartile range.
similar in the matched-pair analysis (OR 0.41; 95% CI 0.23–0.73) (Table 3).

Impact of type of stent on combined endpoint (all-cause mortality or TLR occurrence)

Finally, we considered the effect of type of stent on the combined endpoint of all-cause mortality and TLR occurrence during the entire follow-up period. Unadjusted analysis showed a 57% reduction on combined endpoint for patients treated with DES (HR 0.43; 95% CI 0.33–0.55). All adjusted models showed significant results, and a consistent risk reduction of between 40% and 60% was found in the different analytical approaches (Table 3).

A detailed analysis was performed on a 1-year combined endpoint.

Fig. 1 shows the observed 1-year event-free survival Kaplan–Meier curves (a) and estimated (adjusted for propensity score as a continuous variable, thrombus aspiration and Gp IIb/IIIa inhibitors) curves (b) among BMS and first- as well as second-generation DES patients. The adjusted analysis (Fig. 2) showed a statistically significant lower risk of the combined endpoint in the first year of follow-up in DES groups (HR 0.50; 95% CI 0.34–0.73) in comparison with BMS (reference category) and suggested a lower risk in second-generation DES (HR 0.42; 95% CI 0.23–0.77) compared with first-generation DES (HR 0.55; 95% CI 0.36–0.85).

Discussion

The present study again raises questions regarding the choice of the better stent for STEMI patients; indeed, over the past few years, the use of DES for primary PCI has generated a variety of responses ranging from enthusiasm to consternation [27]. In our study population of unselected STEMI patients who underwent primary PCI,
DES implantation was associated with a significant reduction in the need for TLR. Considering long-term mortality, a significant reduction with DES was found only when a more sophisticated statistical method was applied, whereas no significant differences were found between patients treated with DES or BMS in the other methodological approaches.

Nevertheless, when the combined endpoint of all-cause mortality or TLR was considered, DES confirmed a more protective effect than BMS.

In addition, all the analyses considering the different endpoints suggested a further lower risk associated with the use of second-generation DES.

Therefore, our results are in agreement with previous studies reporting a reduction in TLR in STEMI patients treated with DES implantation [12,14] but, at variance with them, they also suggest a reduction in all-cause mortality with DES and a more protective effect on the different outcomes of second-generation DES.

Although the main aim of primary PCI is a rapid and effective myocardial reperfusion, the reduction in TLR rate can also be considered an important goal in STEMI patients for two main reasons: firstly, a reduction in repeat revascularization improves the patient’s quality of life; secondly, in a significant percentage of cases, restenosis can express itself as an acute coronary syndrome, hazardous for the patient and with high costs for the community [28].

Therefore, the ability of DES implantation in reducing TLR can be considered favorable also for STEMI patients on condition that the use of this type of stent does not increase the incidence of other major adverse events likely to increase the mortality rate.

In our study population, not only we observed no increase in all-cause mortality in patients treated with DES but, when a propensity score matching-pair analysis was performed, we saw that the all-cause mortality rate was significantly lower in the DES group than in the BMS group. Although, in-stent thrombosis was not included as an endpoint in our study and we were consequently unable to know its real incidence, we can nevertheless assume that DES implantation in our patients was not associated with an increased occurrence of this complication that in previous reports was fatal in 50% of cases [29].

Moreover, the mean duration of our follow-up was 43 months, a significantly longer period than the 12 months usually recommended for the DAPT, suggesting that, also after the discontinuation of this therapy, DES implantation in our STEMI patients was not associated with an increased mortality rate in comparison to BMS.

The risk of a higher incidence of in-stent thrombosis in STEMI patients treated with DES, leading to an increase in mortality thereby wiping out the advantages of a rapid reperfusion due to the primary PCI, has become a pivotal issue over the past few years and only recently both randomized controlled clinical trials [19] and meta-analysis [30] suggested the safety and efficacy of DES in primary PCI [31]. In particular, our analysis strengthens this latter issue through the results of a real world study that faithfully reflects the daily activity of our tertiary center. Nevertheless, cardiologists are still suspicious about DES implantation in STEMI patients, especially because of the difficulty in obtaining clinical history in the setting of primary PCI with an incomplete overseeing of contraindications to a prolonged DAPT. However, in our opinion, asking some simple questions, which can be done in the catheterization laboratory during primary PCI (regarding a possible planned surgical intervention that cannot be postponed, a history of gastrointestinal or urological bleeding, previous allergic reactions to aspirin, and the willingness of the patient to undergo DAPT for at least 12 months), can aid the interventional cardiologist in the choice of the better stent for each individual patient.

Our results also showed a significant reduction in the combined endpoint of all-cause mortality or TLR occurrence with the use of DES in comparison to BMS. As new evidence has emerged on an improved safety profile of second-generation DES [32], we also performed a sub-analysis on patients treated with second-generation DES. Patients who underwent EES or ZES implantation showed a consistent reduction in the combined endpoint of all-cause mortality or TLR compared to BMS and to first-generation DES. This result was significantly maintained after multivariate analysis and propensity score matching (Figs. 1 and 2).

There are some significant differences between second- and first-generation DES. First, the drug elution profile is different. In the ZES and EES systems, most of the anti-proliferative drug is eluted by the first month post-PCI, when most of the proliferative activity exists. After this period, the drug does not inhibit healing and the coverage of stent struts, thus reducing the occurrence of late and very late stent thrombosis [33,34]. The second difference is that ZES are coated with biocompatible hydrophilic phosphorylcholine polymers and have low-profile thin stent struts capable of inducing less inflammation when compared to first-generation DES [35] and ensuring an early endothelial coverage [36].

Limitations

Our study had several limitations. First, this study was observational on prospectively collected data, therefore it was prone to a number of biases. To address some of these limitations, we conducted a propensity score analysis. The score analysis may reduce selection bias, but can only check for measured characteristics, and is therefore unable to completely replicate the random treatment assignment of a clinical trial. Thus, biases may remain that are not accounted for in this analysis, such as the presence of cancer or the reason for which in a single patient, a DES was chosen over a BMS. However, we extensively analyzed baseline clinical and angiographic characteristics predictive for DES implantation: younger age, LAD as culprit vessel, and a grade of occlusion less than 98%.

Another limitation is the lack of knowledge regarding the duration of DAPT used in the 2 groups of patients even though, at our institution, this therapy is recommended for at least a 12-month period in all patients with STEMI submitted to primary PCI, regardless of the type of stent implanted. Finally, myocardial infarction and stent thrombosis were not included as endpoints. This is potentially important considering the concerns about stent thrombosis of DES in STEMI patients.

Conclusions

In conclusion, our data, despite several limitations, suggested that DES implantation in STEMI patients can be considered safe, in fact DES in our analysis did not determine an increased mortality showing a positive trend toward its reduction. It also seems preferable to BMS because of its ability to reduce TLR and the combined endpoint of all-cause mortality or TLR. Our data suggest that the advantages are more evident in patients treated with second-generation DES in comparison to BMS and first-generation DES.

Therefore, on the basis of our results, we suggest that currently second-generation DES should be preferred during primary PCI, in particular for their impact on death or TLR. However, it is reasonable to suppose that further advantages will soon be forthcoming thanks to the use of new third-generation stents.

References
