Everolimus-eluting stent versus bare metal stent in proximal left anterior descending ST-elevation myocardial infarction: Insights from the EXAMINATION trial

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Background ST-elevation myocardial infarctions (STEMI) caused by proximal left-anterior descending (LAD) lesions have more myocardium at risk and worse outcomes than those located in other segments. The aim is to compare outcomes of patients with STEMI and proximal-LAD lesions treated with bare-metal stents (BMS) versus everolimus-eluting stents (EES).

Methods The EXAMINATION trial randomized 1498 STEMI patients to BMS versus EES. The primary end point was the patient-oriented combined of all-cause death, any-recurrent myocardial infarction (MI) and any-revascularization. The secondary end point included the device-oriented combined of cardiac death, target-vessel MI and target-lesion revascularization (TLR).

Results STEMI with a proximal-LAD occlusion was observed in 290 patients (BMS = 132 and EES = 158). Both groups were similar except for diabetes (12.9% vs 24.1%; \( P = .016 \)). At 1 year, the primary end point was observed in 18.9% and 9.5% of patients treated with BMS and EES, respectively (\( P = .023 \)). The secondary end point was observed in 11.4% and 5.1%, respectively (\( P = .053 \)). There were no differences in cardiac death (4.5% vs 3.8%; \( P = .750 \)) and MI (1.5% vs 0%; \( P = .121 \)). BMS had higher rate of TLR compared to EES (6.8% vs 1.3%; \( P = .014 \)).

Patients with proximal-LAD STEMI had higher mortality than patients with non proximal-LAD STEMI (5.5% vs 2.9%; \( P = .027 \)). Proximal-LAD lesions treated with BMS tended to increase the risk of the primary end point compared with other segments (18.9% vs 13.0%; \( P = .079 \)). However, EES implanted in proximal-LAD had similar outcomes compared with other locations (9.5% vs 12.0%; \( P = .430 \)). Adjusting for confounders, the interaction between BMS and proximal-LAD location was associated with the primary end point.

Conclusion Patients with STEMI and proximal-LAD lesions treated with EES have better outcomes compared with BMS at 1 year. Although further investigations are required, it seems reasonable to consider EES for proximal-LAD STEMI lesions. (Am Heart J 2013;166:119-126.e1.)

Percutaneous coronary intervention (PCI) is the standard of treatment in ST-elevation myocardial infarction (STEMI). Drug eluting stents (DES) have shown a remarkable reduction in target-vessel revascularization (TVR) compared with bare-metal stents (BMS) in patients with STEMI. However, DES have failed to decrease all-cause mortality and risk of re-infarction at follow-up.

Culprit lesions located in the proximal-left anterior descending (proximal-LAD) artery are observed in approximately 25% of patients with STEMI. The
proximal-LAD supplies blood to a large portion of the myocardium. Therefore, in STEMI patients, the myocardium at risk is usually larger when the culprit lesion is located in the proximal-LAD than when located in other coronary segments. For this reason, culprit STEMI lesions located in the proximal-LAD are related to higher rate of adverse cardiac events than culprit STEMI lesions located in other coronary segments. Moreover, it has been shown that re-infarction and stent restenosis at follow-up can be severe complications after the acute phase of a STEMI, but especially when the culprit lesion was located in the proximal-LAD.5,6

The EXAMINATION all-comers trial randomized 1498 patients with STEMI to BMS versus EES. In the EXAMINATION trial, EES failed to decrease the patient-oriented primary end point (combination of all-cause death, any recurrent myocardial infarction and any repeat revascularization) compared to BMS at 1 year.

It is uncertain if the new generation of DES are associated with better outcomes than BMS in STEMI patients with culprit lesions located in the proximal-LAD. The objective of this study is to compare the clinical outcomes of STEMI patients with proximal-LAD and non-proximal-LAD culprit lesions treated with BMS versus EES at 1 year.

Methods

This study is a sub-study of the all-comers, multicentre, controlled, randomized, EXAMINATION trial (Evaluation of the Xience-V stent in Acute Myocardial INfarCTION) (NCT00828087). The EXAMINATION trial randomized 1:1 a total of 1498 patients with STEMI undergoing PCI to everolimus-eluting stent (EES; Xience; Abbott Vascular, Santa Clara, CA) or Multilink Vision BMS (Abbott Vascular, Santa Clara, CA). The EXAMINATION trial was powered to detect 30% reduction of the patient-oriented primary end point with EES compared to BMS. The results of the EXAMINATION trial have been previously reported.

All participating centers submitted and received the approval of their Medical Ethics Committee for the protocol and for the informed consent. The study was conducted in compliance with the protocol, the Declaration of Helsinki, BS EN ISO 14155 Part 1 and Part 2, and applicable local requirements. All patients provided written informed consent. The EXAMINATION trial has been funded by the Spanish Heart Foundation.

Population and procedure characteristics

All patients with STEMI within the first 48 hours after the onset of symptoms that underwent PCI were eligible for the study. The inclusion and exclusion criteria, as well as the procedural characteristics, are listed in the online Appendix. Proximal-LAD lesions were defined as culprit lesions located proximal to the first septal branch of the LAD coronary artery.

Study end points

The primary end point of the study was the patient-oriented end point of all-cause death, any recurrent myocardial infarction and any repeat revascularization at 1 year. Secondary end points of the study included the device-oriented combined end point of cardiac death, target-vessel myocardial infarction and target-lesion revascularization at 1 year. In addition, the following secondary endpoints were examined at 1-year: all cause and cardiac death; recurrent myocardial infarction (World Health Organization extended definition); target lesion revascularization; TVR; stent thrombosis (according to the Academic Research Consortium definitions); device and procedural success; major and minor bleeding. Detailed definitions of the endpoints have been reported elsewhere. All clinical events were adjudicated by an independent Clinical Event Committee (Cardialysis, Rotterdam, The Netherlands).

Statistical analysis

Continuous variables were explored for normal distribution with the Kolmogorov-Smirnov test. Variables following normal distribution were expressed as mean (1 SD) and variables not following a normal distribution were expressed as median (inter-quartile range). Categorical variables were expressed as number (percentage). Comparisons between continuous variables were performed with the t-student or Mann-Whitney tests as appropriate. Comparisons between categorical variables were performed with the chi-square test. Event-free survival curves were generated with Kaplan-Meier. Survival curves among groups were compared using the log-rank test.

A total of 3 multivariate models using all the examination population and 3 multivariate models using the proximal-LAD population have been performed. The variables included in each model are reported in the online Appendix. All P values were 2-tailed, with statistical significance set at a level of < .025 (Bonferroni correction). Statistical analyses were performed using SPSS Statistics 20.0 (SPSS Inc, Chicago, IL).

Results

The EXAMINATION trial randomized 1498 patients with STEMI to BMS (n = 747) or EES (n = 751). A total of 290 patients presented with culprit lesions located in the proximal-LAD and were allocated to BMS (n = 132; 45.5%) or EES (n = 158; 54.5%).

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of all patients are shown in Table 1. Patients with proximal-LAD STEMI presented with lower percentage of prior myocardial infarction than patients with other STEMI locations (2.3% vs 6.0%, respectively; P = .029). However, the clinical status on hospital admission was worse in patients with proximal-LAD STEMI than in patients with other STEMI locations (22.1% vs 7.6% of patients presented with Killip class > 1, respectively; P < .001).

Baseline demographic and clinical characteristics among patients with proximal-LAD STEMI were similar between patients allocated to BMS and EES except for diabetes mellitus (12.9% vs 24.1%, respectively; P = .016).
and total stent length ≥30 mm (20.5% vs 31.0%, respectively; \(P = .050\)).

Baseline procedural characteristics

Baseline procedural characteristics of all patients are shown in Table II. Patients with non proximal-LAD and proximal-LAD STEMI had similar baseline procedural characteristics except for ST segment resolution after stent implantation. Patients with proximal-LAD STEMI had similar procedural characteristics between the BMS and EES groups.

Clinical outcomes

After 1 year of follow-up, 85.6% of patients with non proximal-LAD STEMI and 88.0% of patients with proximal-LAD STEMI were under dual antiplatelet therapy with aspirin plus clopidogrel (\(P = .232\)). Within the proximal-LAD population, 80.5% of patients treated with BMS and 94.0% of patients treated with EES were under dual antiplatelet therapy (\(P = .006\)).

Clinical outcomes at 1 year are shown in Table III. Figure 1 shows the Kaplan-Meier curves among patients with proximal-LAD STEMI. Figure 2 shows the Kaplan-Meier curves of all patients included in the EXAMINATION trial.

The patient-oriented primary end point was observed similarly in patients with non proximal-LAD and proximal-LAD STEMI (12.5% vs 13.8%, respectively; \(P = .557\)). However, in patients with proximal-LAD STEMI, the primary end point was observed more frequently with BMS than with EES (18.9% vs 9.5%, respectively; \(P = .023\)). In contrast, in patients with non proximal-LAD STEMI, the primary end point was similarly observed between BMS and EES groups (13.0% vs 12.0%, respectively; \(P = .594\)).

Patients with non proximal-LAD STEMI had less all-cause death compared to patients with proximal-LAD STEMI (2.9% vs 5.5%, respectively; \(P = .027\)). However, in patients with proximal-LAD STEMI, all-cause mortality was similar between BMS and EES groups (6.8% vs 4.4%, respectively; \(P = .375\)). TVR was similar between non proximal-LAD and proximal-LAD STEMI (5.6% vs 4.1%, respectively; \(P = .354\)). In patients with proximal-LAD STEMI, TVR was more frequent in patients treated with BMS than with EES (7.6% vs 1.3%, respectively; \(P = .007\)).
Multivariate models

Within the proximal-LAD population, three multivariate models were performed for primary end point, secondary end point and clinically-driven TVR. The multivariate models included the following variables: diabetes mellitus, thrombus aspiration, stent length \( \geq 30 \) mm, stent diameter \( \geq 3.0 \) mm, ST-segment resolution \( \geq 70\% \), treatment with dual antiplatelet therapy at 1 year and stent type. In these models, use of BMS was associated with a higher risk of primary end point (odds ratio = 2.881; CI 95% = 1.122 - 7.394; \( P = .025 \)). Use of BMS was also associated with a trend towards a higher risk of secondary end point and clinically driven TVR with an odds ratio of 10.707 (CI 95% = 1.256-91.280; \( P = .041 \)), respectively.

Within all the EXAMINATION trial population, three multivariate models were investigated for primary end point, secondary end point and clinically driven TVR. Table IV shows the odds ratio (95% CI) of the variables included in the model and its \( P \) values. Multivariate models were performed for primary end point, secondary end point and clinically-driven TVR. The multivariate models included the following variables: diabetes mellitus, thrombus aspiration, stent length \( \geq 30 \) mm, stent diameter \( \geq 3.0 \) mm, ST-segment resolution \( \geq 70\% \), treatment with dual antiplatelet therapy at 1 year and stent type. In these models, use of BMS was associated with a higher risk of primary end point (odds ratio = 2.881; CI 95% = 1.122 - 7.394; \( P = .025 \)). Use of BMS was also associated with a trend towards a higher risk of secondary end point and clinically driven TVR with an odds ratio of 10.707 (CI 95% = 1.256-91.280; \( P = .041 \)), respectively.

Discussion

The major findings of this study are (1) Patients with proximal-LAD STEMI have higher all-cause mortality than non proximal-LAD STEMI, with no differences in myocardial infarction and TVR at 1 year; (2) In STEMI patients with culprit lesions located in the proximal-LAD, EES decreased the primary end point and tended to decrease the device-oriented secondary end point mainly...
by the reduction of TVR at 1 year, whereas in patients with non proximal-LAD related STEMI, EES presented with a similar number of primary and device-oriented secondary end point as BMS at 1 year.

Current guidelines recommend the use of DES in STEMI patients with no contraindications to prolonged dual antiplatelet therapy. However, the use of DES in STEMI patients undergoing primary PCI is still low (around 30%-35%) in North America and Europe.STEMI patients undergoing primary PCI is still lower than in STEMI caused by culprit lesions located in other coronary segments. In addition, a proximal-LAD STEMI is associated with larger microvascular obstruction compared to a STEMI caused by the occlusion of other coronary segments. For these reasons, patients with proximal-LAD STEMIIs have poorer clinical outcomes and lower ejection fraction than patients with STEMI caused by mid or distal LAD occlusions. According to previous studies, this study found differences in Killip class on admission, ejection fraction, ST-segment resolution and all-cause mortality or myocardial infarction. These differences in ischemic-driven TVR between BMS and EES were also present with higher rate of ischemic-driven TVR than patients treated with EES, with no differences in all-cause mortality or myocardial infarction. These differences in ischemic-driven TVR between BMS and EES were also observed in patients with non proximal-LAD STEMI. However, the present study found a significant interaction between stent type and proximal-LAD location of the culprit lesion. Patients with culprit lesions located in the proximal-LAD treated with BMS tended to present with higher number of adverse events than patients with culprit lesions located in different coronary segments also treated with BMS. In contrast, patients treated with EES presented with similar clinical outcomes independently of the location of the culprit lesion.

### Table III. Clinical outcomes at 1-year followup

<table>
<thead>
<tr>
<th></th>
<th>Non proximal-LAD (n = 1208)</th>
<th>Proximal-LAD (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n = 1208)</td>
<td>BMS (n = 615)</td>
</tr>
<tr>
<td>Primary end point, n (%)</td>
<td>151 (12.5)</td>
<td>80 (13.0)</td>
</tr>
<tr>
<td>Secondary end point, n (%)</td>
<td>79 (6.5)</td>
<td>46 (7.5)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>35 (2.9)</td>
<td>17 (2.8)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>32 (2.7)</td>
<td>15 (2.4)</td>
</tr>
<tr>
<td>Myocardial infarction (ARC definition), n (%)</td>
<td>21 (1.7)</td>
<td>13 (2.1)</td>
</tr>
<tr>
<td>Myocardial infarction (WHO definition), n (%)</td>
<td>13 (1.1)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Revascularization, n (%)</td>
<td>114 (9.4)</td>
<td>62 (10.1)</td>
</tr>
<tr>
<td>Target lesion</td>
<td>42 (3.5)</td>
<td>28 (4.6)</td>
</tr>
<tr>
<td>Target vessel</td>
<td>67 (5.6)</td>
<td>41 (6.7)</td>
</tr>
<tr>
<td>Non-target vessel</td>
<td>64 (5.3)</td>
<td>30 (4.9)</td>
</tr>
<tr>
<td>Definite/probable stent thrombosis, n (%)</td>
<td>22 (1.8)</td>
<td>16 (2.6)</td>
</tr>
<tr>
<td>Definite</td>
<td>17 (1.4)</td>
<td>13 (2.1)</td>
</tr>
<tr>
<td>Probable</td>
<td>5 (0.4)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Bleeding, n (%)</td>
<td>58 (4.8)</td>
<td>36 (5.6)</td>
</tr>
<tr>
<td>Major</td>
<td>16 (1.3)</td>
<td>10 (1.6)</td>
</tr>
<tr>
<td>Minor</td>
<td>45 (3.7)</td>
<td>26 (4.2)</td>
</tr>
</tbody>
</table>

Primary end point = all-cause death, any-recurrent myocardial infarction and any-repeat revascularization at 1 year; secondary end point = cardiac death, target-vessel myocardial infarction and target-lesion revascularization at 1 year.

ARC, Academic research consortium; WHO, World Health Organization.

* P-value for the comparison between the non proximal-LAD vs proximal-LAD groups.
In a sub-study of the HORIZONS-AMI trial, STEMI patients treated with paclitaxel-eluting stents had lower risk of TLR compared to BMS at 12 months. The independent predictors of TLR in patients treated with BMS were: insulin-treated diabetes mellitus, reference vessel diameter ≤ 3.0 mm and lesion length ≥ 30 mm. In another study, Shugman et al. found that proximal-LAD was also an independent predictor of TVR. In our study, BMS was the only independent predictor factor of clinically-driven TVR. However, stent diameter <3 mm, total stent length ≥ 30 mm and implantation of BMS in proximal-LAD tended to be associated with TVR. Therefore, it seems advisable to consider EES in culprit STEMI lesions with reference vessel diameter <3 mm, lesion length ≥30 mm and lesions located in proximal-LAD. It is noteworthy that >80% of patients with proximal-LAD culprit lesions were treated with a stent ≥3.0 mm diameter. Moreover, taking into account the total stent length, stent diameter and diabetes mellitus; implantation of BMS was still associated with higher risk of restenosis.

The higher rate of ischemic-driven TVR observed in patients with proximal-LAD STEMI treated with BMS compared to non proximal-LAD lesions treated with BMS can be explained by the increased viable myocardium. It is probable that many cases with stent restenosis at non proximal-LAD were asymptomatic; whereas most of the cases with stent restenosis at the proximal-LAD had symptoms and required TVR. For this reason, in clinical stent trials without planned angiography at follow-up comparing STEMI and non-STEMI acute coronary syndromes, patients with STEMI had less ischemic-driven TVR than patients with non-STEMI.

Second-generation DES, such as the EES, are aimed to decrease the risk of TVR by thinning the strut thickness and by reducing the thrombogenicity of durable polymers compared to first generation DES. In a sub-study of the COMPARE trial including all STEMI patients, EES reduced the risk of TVR compared to the paclitaxel first-generation DES. In the XAMI trial, EES failed to decrease TVR compared to the sirolimus first-generation DES. However, in both studies, EES reduced the risk of...
definite and probable stent thrombosis. The CON-FORTABLE AMI trial compared BMS with a new-generation of biolimus-eluting stents with erodible coating. Biolimus-eluting stent presented with lower risk of target vessel-related re-infarction and a trend towards lower stent thrombosis than BMS. In the EXAMINATION trial, EES presented with lower stent thrombosis than BMS at 1-year follow-up. It is uncertain if proximal-LAD lesions are prone to higher suitability for stent thrombosis. The few number of stent thrombosis in proximal-LAD warrants further investigations.

**Limitations**

This study is a post-hoc analysis of the EXAMINATION trial. The sample size of the EXAMINATION trial was estimated for the primary end point in all STEMI locations. Therefore, the number of patients with proximal-LAD related STEMI can be undersized for this sub-study. Moreover, the EXAMINATION trial did not meet its primary end point and subsequent subset analyses have to be taken as hypothesis generating studies. In addition, the clinical follow-up of this study is limited to 1 year. It is well known that DES are associated with higher risk of very-late thrombosis compared to BMS. Finally, anatomical variations of coronary arteries have not been taken into account in the present manuscript. It is possible that proximal segments of large right or left circumflex coronary arteries may have similar results than proximal-LAD culprit lesions in STEMI patients.

**Conclusions**

At 1 year, patients with STEMI caused by proximal-LAD culprit lesions have higher mortality than patients with STEMI caused by culprit lesions located in other coronary segments. Treatment of proximal-LAD lesions with EES had better clinical outcomes than with BMS; mainly caused by the reduction of TLR. Patients with proximal-LAD lesions treated with BMS tended to present with higher number of adverse cardiac events than those with culprit lesions located in other coronary segments.
whereas implantation of EES at proximal-LAD segments implied similar outcomes compared with other coronary locations. Although further investigations with adequate pre-specified powered studies are required, it seems reasonable to consider EES for patients with STEMI and culprit lesions located in proximal-LAD.

### References


Appendix

Inclusion and exclusion criteria

Patients with STEMI <12 hours after the onset of symptoms were classified as primary PCI group; patients with failed thrombolysis undergoing urgent PCI were classified as rescue PCI group; PCI indicated early (<24 hours) after effective thrombolysis were classified as PCI post-successful thrombolysis group, and patients presenting late with STEMI (>12 to <48 hours after the onset of symptoms) were classified as latecomer group. Exclusion criteria included: lesions requiring stent sizes <2.25 or >4 mm, STEMI caused by stent thrombosis, age <18 years, pregnancy, patients with known intolerance to aspirin, clopidogrel, heparin, cobalt-chromium, or other components of the stents. Patients on chronic treatment with anti-vitamin K agents were also excluded.

Procedure and angiographic characteristics

PCI was performed according to the standard medical practices in each participating centre. Unfractionated heparin, low-molecular-weight heparin or bivalirudin were used for procedural anticoagulation. The use of glycoprotein IIb/IIIa inhibitors was left to operator’s criteria. A loading dose of aspirin (≥250 mg) and clopidogrel (≥300 mg) was administered to the patient before PCI. Aspirin (≥100 mg/d) was prescribed indefinitely and clopidogrel (75 mg/d) was prescribed for at least one year in both groups.

Statistical methods

In order to adjust for potential confounders between BMS and EES groups in the proximal-LAD population, three multivariate models were performed for primary end point, secondary end point and clinically-driven TVR. All covariates with a difference between the BMS and EES groups with \( P < .10 \) were included in the multivariate regression analyses.

In order to assess the effect of stent type according to the location of the culprit lesion (proximal-LAD vs non proximal-LAD), three multivariate models were investigated for the primary end point, secondary end point and clinically-driven TVR using all the Examination trial population. Univariate analyses of all potential clinical and procedural characteristics were performed. All covariates associated with the primary and secondary end points and with clinically-driven TVR with a \( P < .10 \) were included in the multivariate regression analyses. For these specific models, the interaction between stent type and proximal-LAD location of the culprit STEMI lesion were included.

All multivariate analyses have been performed as Generalized linear models with binary logistic response. All interactions included in the model have been treated taking into account the hierarchical principle. Results were reported as OR, together with the 95% CI and \( P \) values.