Biolimus-Eluting vs. Other Limus-Eluting Stents in NSTE-ACS: a pooled analysis of GLASSY and TWILIGHT

Running title: Biolimus-Eluting Stents in NSTE-ACS patients

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Abstract

Background: Biodegradable polymer biolimus-eluting stents (BP-BES) may be associated with better outcomes in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) compared to other current-generation limus-eluting stents (LES).

Aims: To compare BP-BES with other current-generation LES in ACS patients undergoing PCI.

Methods: We pooled individual data of Non-ST-segment elevation (NSTE)-ACS patients from two large randomized controlled trials (GLASSY and TWILIGHT). The BP-BES groups consisted mostly of GLASSY patients, while the control group (other current-generation LES) included exclusively TWILIGHT patients. The primary outcome was major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, or stent thrombosis; the key secondary outcome was target-vessel failure (TVF). To account for trial design differences, outcomes were assessed at 3 months (short-term) and between 3 to 12 months (long-term) after PCI and subsequently pooled to estimate the 12-month hazards.

Results: Of 7,107 and 6,053 NSTE-ACS patients included in the short- and long-term analysis, 32.7% and 36.5% received a BP-BES, respectively. Risk of MACE associated with BP-BES versus other LES was similar at short-term (1.1% vs 1.4%, adjusted HR 0.81, 95%CI 0.51-1.29), lower at long-term (1.7% vs 3.1%, adjusted HR 0.46, 95%CI 0.32-0.67), and lower in the entire 12-month period (pooled adjusted HR 0.58, 95%CI 0.43-0.77). The cumulative 12-month risk of TVF was reduced with BP-BES (adjusted HR 0.52, 95%CI 0.38-0.70).

Conclusion: BP-BES was associated with lower 12-month risks of MACE and TVF compared to other current generation LES among NSTE-ACS patients treated with abbreviated or standard ticagrelor-based DAPT. These non-randomized findings are hypothesis-generating.

Key words: biolimus eluting stent; biodegradable polymer; ticagrelor; percutaneous coronary intervention; outcomes.

Condensed abstract

Differences in clinical outcomes may exist between biodegradable polymer biolimus-eluting stents (BP-BES) and other current-generation limus-eluting stent (LES) in patients with acute coronary syndrome (ACS). We pooled individual data of about 7,000 Non-ST-segment elevation ACS patients undergoing PCI and treated with ticagrelor with or without aspirin from two large randomized controlled trials (GLASSY and TWILIGHT). BP-BES patients derived very largely from GLASSY and other LES patients from TWILIGHT. In this population, BP-BES compared to other current generation LES, were associated with a lower 12-month risk of major adverse cardiovascular events and target-vessel failure.

Abbreviations

ACS= Acute coronary syndrome

BARC= Bleeding academic research consortium

BP-BES= Biodegradable polymer biolimus-eluting stents

DAPT= Dual antiplatelet therapy

DES= Drug eluting stent

GLASSY= GLOBAL LEADERS Adjudication Sub-Study

LES= Limus-eluting stent

PCI= Percutaneous coronary intervention

NSTE-ACS= Non-ST-segment elevation acute coronary syndrome

TWILIGHT= Ticagrelor with Aspirin or Alone in High-Risk Patients After Coronary Intervention

Introduction

Advances in coronary stent technology have improved outcomes of patients undergoing percutaneous coronary intervention (PCI) (1,2). First generation drug-eluting stents (DES) reduced the risk of in-stent restenosis and need for repeat revascularization compared with bare metal stents (BMS) (3). However, these benefits came at expense of an increase in very late (>12 months) stent thrombosis (4), a complication that was significantly reduced with the introduction of newer or current generation DES (5). The durable polymer (DP) has been suggested as a possible cause of the residual thrombogenicity observed with current generation DES (6). Biodegradable polymer (BP)-DES were developed to combine the advantages of BMS (i.e., low risk of very late stent thrombosis) and current generation DES (i.e., low risk of restenosis). Biolimus, a sirolimus derivative with improved pharmacokinetics and lipophilicity, was designed to provide a more powerful and sustained immunosuppressant and anti-inflammatory effect on the vessel wall (7).

Several randomized controlled trials (RCTs) and meta-analyses have shown BP-biolimus eluting stent (BP-BES) to be superior to BMS and first generation DES, but similar to current generation DES with DP or BP with respect to the risk of stent thrombosis and myocardial infarction (MI) (8-14). However, in the vast majority of these studies high ischemic risk patients such as those with acute coronary syndrome (ACS) were underrepresented and dual antiplatelet therapy (DAPT) was prescribed for at least 6 months. Therefore, the potential benefits of BP-BES over other current generation DES may have been underestimated. Recently, a large registry of MI patients treated with standard DAPT regimens showed better outcomes with BP-BES compared to other contemporary DES (15).

The aim of the current study was to assess the impact of BP-BES vs other current generation limus-eluting stents (LES) in Non-ST-segment elevation (NSTE)-ACS patients receiving standard or abbreviated DAPT regimens.

METHODS

Study population

Individual patient-level data from two RCTs, the *GLOBAL LEADERS Adjudication Sub-Study* (GLASSY) and the *Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention* (TWILIGHT) were pooled together in the biodegradable polymer biolimus-eluting stent and single versus dual antiplatelet therapy (Bio-Sidney) collaboration. Details regarding trial design and their main results have been published previously (16,17). GLASSY was a prespecified ancillary study of GLOBAL LEADERS, a multicenter open-label RCT, in which patients ≥18 years old were randomized immediately prior to PCI to 1-month DAPT (ticagrelor-based DAPT followed by 23-month ticagrelor 90 mg twice daily monotherapy) or 12-month DAPT (clopidogrel-based in patients with chronic coronary syndrome (CCS) and or ticagrelor-based in ACS patients) followed by aspirin alone for 12 months. All patients received at least one BP-BES (Biomatrix™ or Biomatrix Flex™, Biosensors, Switzerland) and were followed up to 24 months after index PCI. In GLASSY all events of the 7,585 patients from the top 20 GLOBAL LEADERS enrolling sites were adjudicated by a clinical event committee (CEC) unaware of treatment assignment (16).

TWILIGHT was a multicenter RCT, which enrolled 9,006 patients who underwent PCI with DES implantation and had at least one clinical and one angiographic feature associated with high risk of ischemic or bleeding events. After three months of DAPT with aspirin and ticagrelor, 7,119 patients free from cardiovascular complications (bleeding BARC type 3b or higher, myocardial infarction (MI), definite or probable stent thrombosis, coronary revascularization or any stroke) were randomized in a double-blind fashion to receive ticagrelor 90 mg twice daily either with placebo (experimental group) or aspirin 81 to 100 mg (control group) for an additional 12 months. The type of DES implanted was left at discretion of the treating physician. All events

were adjudicated by an independent and blinded CEC (17).

Definitions of outcomes were harmonized in the pooled population (**supplementary tables 1** and **2**). To further assess the consistency between these two trials with respect to CEC processes and definitions, 100 randomly selected Investigator/Site reported events from the GLASSY trial were re-adjudicated by the CEC of TWILIGHT and 100 randomly selected Investigator/Site events from TWILIGHT were re-adjudicated by the CEC of GLASSY, yielding an agreement of ≥94.5% and kappa values ≥0.86 (**supplementary table 3**) (18).

In this analysis, only patients with NSTE-ACS who received at least one current generation limus-eluting stent (LES) were included. Exclusion criteria were: ST-elevation myocardial infarction (STEMI); implantation of BMS, 1st generation DES, current generation non-limus eluting stent, unclear or mixed (BP-BES and other current generation DES) stent types at time of index PCI; fatal or non-fatal events during index hospitalization; fulfillment of any exclusion criterion of one of the two trials (**Figure 1**) (16,17).

Given that randomization occurred at different time points in the two studies (immediately before index PCI in GLASSY and at 3 months after PCI in TWILIGHT), outcomes between hospital discharge and up to 3 months (short-term analysis) and between 3 and 12 months post-PCI (long-term analysis) were assessed separately. The short-term analysis included all patients randomized in GLASSY and TWILIGHT patients regardless of whether they were randomized at 3 months. In the long-term analysis, GLASSY patients who were not event-free at 3 months according to the TWILIGHT eligibility criteria and TWILIGHT patients not randomized at 3 months were excluded. In both analyses, patients were assigned to the BP-BES or other current generation LES group based on the stent type received at index PCI (**Figure 1**). More than 99% of BP-BES patients derived from GLASSY, whereas the other LES group consisted exclusively of TWILIGHT patients.

Each RCT was approved by its local medical ethics committee, and all patients provided written informed consent. Additionally, Ethics Committee of Mount Sinai Hospital (New York, USA) gave a specific approval for the current pooled analysis.

Clinical endpoints

The primary outcome was major adverse cardiovascular events (MACE) – a composite of cardiovascular death, MI, or definite or probable stent thrombosis. The key secondary outcome was target-vessel failure (TVF) – a composite of cardiovascular death, target-vessel MI, definite or probable stent thrombosis, or clinically driven target vessel revascularization (TVR). Other secondary outcomes were the individual components of the primary and secondary composite outcomes; all-cause death; ischemic stroke. The outcome definitions are reported in the **Supplementary Table 1**.

Statistical analysis

Baseline and procedural continuous variables were summarized by means and standard deviations, categorical variables by counts and percentages. Chi-square and Student's t-test were used to compare data, as appropriate. Outcome incidence was calculated with the Kaplan-Meier method and compared between groups using the log-rank test for the time to first event. The short-term analysis evaluated occurrences between hospital discharge and 3 months after PCI, while the long-term analysis included events between 3 and 12 months after PCI.Cox proportional hazard models were used to compare the unadjusted and adjusted risk for the primary and secondary outcomes between patients treated with BP-BES vs other current generation LES. Risks are expressed as hazard ratios (HR) and 95% confidence intervals (CI). Covariates included in the final multivariable model were selected through a forward stepwise approach with an inclusion criterion

of p-value <0.05 with forcing in age and sex from a pool of variables imbalanced between the two stent groups or relevant for the outcome of interest. The model obtained for the primary outcome was applied to the secondary endpoints. The final model for the short-term analysis included: age, sex, left ventricular ejection fraction (LVEF), hemoglobin, prior PCI, prior coronary artery bypass graft (CABG), and indication for PCI; for the long-term analysis: age, sex, prior MI, peripheral artery disease, troponin elevation, diabetes, prior coronary artery bypass graft, creatine kinase elevation, hypercholesterolemia, LVEF, current smoker and estimated glomerular filtration rate<60ml/min 1.73m^2. No major violations of the proportional hazards assumption was observed using Schoenfeld residuals and log-minus-log plots. HRs were calculated separately in the short and long-term analyses and then pooled by taking the average of two estimates weighted using inverse of variances to obtain a risk estimate of the whole 12-month study period.

Additionally, the adjusted risk for the primary outcome was estimated with propensity score analysis using three different approaches: 1) Inverse probability of treatment weighting (IPTW) with no trimming; 2) IPTW trimming the lowest and highest 2 percentiles 3) stratification in 5 strata.

All probability testing was 2-sided and p-value of <0.05 was considered statistically significant for all tests. All data were independently analyzed at the London School of Hygiene and Tropical Medicine using Stata version 16 (StataCorp, College Station, Texas).

RESULTS

Population characteristics

The populations for the short-term analysis (0-3 months after PCI) and long-term analysis (3-12 months after PCI) consisted of 7,055 and 6,053 patients NSTE-ACS patients, respectively. In the two analyses, patients receiving BP-BES at index PCI were 2,321 (32.7%) and 2,211

(36.5%), respectively, and more than 99% of them derived from GLASSY. The control group (other current generation LES) groups consisted exclusively of TWILIGHT patients (**Figure 1**).

Baseline and procedural characteristics are reported in **Table 1**, **Table 2 and Supplementary Table 4**. All patients in the BP-BES group and one-third in the control group were enrolled in Europe. Overall, patients with BP-BES had fewer comorbidities, except for hypercholesterolemia and hypertension, and more frequently presented with non-ST-segment elevation MI compared with the control group. In BP-BES patients, femoral access, revascularization of left anterior descending or left main artery, of multiple vessels or lesions, or of coronary occlusions (preprocedural TIMI flow of 0 or 1) and presence of thrombus were less frequent, total stent length implanted was shorter, while bifurcation lesions more common than in the control group.

In both study populations (short- and long-term analysis), nearly 80% of stent implanted in the control group were DP-DES, with everolimus eluting stent being the most frequent, approximately 19% consisted of BP everolimus- or BP sirolimus-eluting stent, and around 1% were polymer free stent (**Table 2**).

In the short-term analysis (up to three months post-PCI), 50% of patients in the BP-BES group received 1-month of a ticagrelor-based DAPT followed by ticagrelor monotherapy, while the remaining 50% of the BP-BES group and all the patients in the control group received a ticagrelor-based DAPT for 3 months. In the long-term analysis (from 3 to 12 months), half of patients received ticagrelor monotherapy and the other half ticagrelor plus aspirin in both the BP-BES and the control group (**Supplementary Figure 1**).

Primary outcome

At 3 months after PCI, MACE occurred in 26 (1.1%) BP-BES patients and in 59 (1.3%) patients in the control group; between 3- and 12-months post-PCI in 38 (1.7%) BP-BES and 117 (3.1%) LES patients (**Figure 2**, **Table 3 and Supplementary Table 5**). After multivariable adjustment, the risk of MACE associated with BP-BES vs other LES was similar at 3 months (adjusted HR 0.86, 95%CI 0.53-1.38, p-value= 0.53), whereas it was lower between 3 and 12 months (adj. HR 0.49, 95% CI 0.34-0.72, p-value <0.001), leading to cumulative lower risk at 12 months (pooled adj. HR 0.61, 95% CI 0.45-0.82, p-value 0.001) (**Figure 3**). Results of the propensity score-adjusted sensitivity analyses were largely consistent with the primary analysis (**Supplementary Table 6 and Supplementary Figures 2-4**).

Secondary outcomes

In the BP-BES and control group, TVF occurred in 26 (1.1%) and 56 (1.3%) patients at 3 months, and in 32 (1.5%) and 170 (4.4%) patients, respectively, between 3 and 12 months (**Table 3** and **Supplementary Table 5**).

Use of BP-BES vs other-LES was associated with a similar adjusted risk of TVF at 3 months (adj. HR 0.99, 95% CI 0.61-1.60, p=0.96), but with a lower hazard between 3 and 12 months (adj. HR 0.34, 95% CI 0.23-0.50, p<0.001) and in the overall study period (pooled adj. HR 0.52, 95% CI 0.38-0.70, p <0.001) (**Figure 3**).

With respect to the individual ischemic outcomes, the 12-month hazards of MI, and TVR were lower in the BP-BES group than in the control group, whereas there were no differences concerning the risk of stent thrombosis, even though the risk for this adverse event was significantly lower between 3 and 12 months. The risks of all-cause death and cardiovascular death were similar in the two stent groups in the short-, long-term, and pooled analysis. Stroke rates were low overall and did not differ between groups (**Table 3** and **Figure 3**).

DISCUSSION

In a pooled analysis combining individual patient data from two RCTs, GLASSY and TWILIGHT, we compared BP-BES versus other current generation LES with regards to 12-month outcomes among NSTE-ACS patients randomized to an abbreviated versus standard DAPT treatment. We found that compared with other LES, use of BP-BES was associated with a lower risk of MACE and of TVF at 12 months.

Newer generation DES represents the standard of care in patients undergoing PCI irrespective of clinical presentation, lesion features, and type and duration of antithrombotic therapy (19,20). Indeed, current generation DES are associated with a lower risk of in-stent restenosis, stent thrombosis, and MI compared with BMS or first-generation DES (3-5). BP-DES were developed to further reduce the residual risk of late stent thrombosis associated with durable polymer coatings (21,22). Biolimus A9, a sirolimus derivative with improved pharmacokinetics and lipophilicity, was conceived to provide a more powerful and sustained immunosuppressant and anti-inflammatory effect on the vessel wall. Previous RCTs confirmed the superiority of BP-BES over BMS and first-generation DES but showed that BP-BES have a similar efficacy and safety compared to other current generation DES (8-14). However, since the vast majority of these studies was not focused on ACS patients and DAPT was prescribed for at least 6 months, the potential advantages of BP-BES may have been underestimated.

In this pooled analysis of GLASSY and TWILIGHT, we compared BP-BES with other new generation LES in NSTE-ACS patients, half of whom received ticagrelor-based DAPT for no longer than 3 months followed by ticagrelor monotherapy. Of note, BP-BES patients derived almost exclusively from GLASSY while patients receiving other LES were derived from TWILIGHT. Nearly all (>99%) the patients in BP-BES group received Biomatrix® or Biomatrix Flex™ (Biosensors Interventional Technologies Pte Ltd., Singapore) and very few patients

Nobori™ (Terumo, Japan). In the control group, the majority (nearly 80%) of stent were DP-DES (mostly eluting everolimus or zotarolimus), approximately 19% consisted of BP-DES (releasing everolimus or sirolimus), and around 1% were polymer free stents. We found that BP-BES was associated with a lower 1-year hazard of MACE (a composite of cardiovascular death, MI, and definite or probable stent thrombosis), TVF (a composite including cardiovascular death, target-vessel MI, definite or probable stent thrombosis and clinically driven TVR) than the control group. The reduction in ischemic events was driven by lower rates of MI and TVR in patients treated with BP-BES, whereas cardiovascular or all-cause mortality and stent thrombosis were similar in the two stent groups. The rate of ischemic complications was similar between the 2 stent types in the first three months after stent implantation; only thereafter a signal of superiority of BP-BES became apparent.

These findings might be explained by the pharmacologic properties of the BP, whose degradation takes place two to nine months after stent implantation. After this time-frame, the residual inflammation in the vessel wall and the risk of stent thrombosis or in-stent restenosis may significantly decrease, especially in higher-risk patients, such as those with ACS (21,22). Recently, the BIOSTEMI trial (23), showed that in 1,300 STEMI patients BP-sirolimus eluting stent was superior to DP-everolimus eluting stent with respect to target lesion failure at 1 year, mostly due to a reduction in ischemia-driven TLR. An additional explanation for the lower rates of events in the BP-BES group could reside in the pharmacokinetics properties and higher lipophilicity of Biolimus A9, which may exert a more potent and longer anti-inflammatory effect on the vessel wall compared to other immunosuppressive agents (7). Moreover, it remains possible that aspirin discontinuation, which occurred at the latest after 3 months in half of the study population, might have negatively impacted the outcomes of patients receiving other LES but not of BP-BES patients, although this interpretation of the findings remains hypothetical.

Our results are consistent with some prior reports comparing BP-BES with other current generation stent devices. In the CHOICE (Comparing Three 2nd Generation Drug-Eluting Stents in Real-World Practice) trial, an open-label, randomized, noninferiority, multicenter study including 1,911 patients (75% with ACS), the rate of the device-oriented (cardiac death, target-vessel MI, or clinically indicated TVR) and patient-oriented (any death, any MI, or any revascularization) composite outcomes at 24 months was numerically lower in the BP-BES group (Biomatrix Flex^{TM}) than in the two control groups treated with 2nd generation DP-everolimus eluting and DP-zotarolimus eluting stents, respectively (12). BP-BES met the criteria of noninferiority, whereas superiority was not tested. Of note, the overall results of this trial must be interpreted with caution since it was terminated prematurely because of slow enrolment and low events rate. Similarly, in the noninferiority randomized trial SORT-OUT VI (Scandinavian Organization for Randomized Trials with Clinical Outcome VI) enrolling 2,999 patients treated with 12-month DAPT, 50% of which presented with ACS, 1-year rates of MI, TLR and ST were numerically lower in the BP-BES than in the DP-ZES group (24). However, this trend was non confirmed at 3-year follow-up (11). Furthermore, the HOST-REDUCE-POLYTECH-ACS found that in 3,413 ACS subjects enrolled in South-Korea, 2nd generation DP-DES versus mixed types of BP-DES (BES: Biomatrix®, Biomatrix Flex^{TM}, Nobori®; SES: Ultimaster®, Orsiro®) were associated with a similar risk of all-cause death, non-fatal MI, or repeat revascularization at 1 year (10). Also in this study, all patients received a 12-month DAPT, consisting of aspirin and prasugrel 5 or 10 mg in two-thirds of patients.

Recently, a large observational study based on the data of Korea Acute Myocardial Infarction Registry (KAMIR) showed significantly better outcomes in patients with MI treated with BP-BES (75% Biomatrix® and 25% Nobori®) compared to those treated with either DP everolimus- or zotarolimus- eluting stents (15).

The less prominent benefits of BP-BES vs other current generation LES in the setting of ACS observed in the above-mentioned studies might be due to the type and duration of DAPT, which was of only 3 months in 50% of patients of our study. However, other factors, such as patient's ethnicity and differences concerning the stents used in the comparison group may explain the partial discrepancies. Specific stent features, such as the type of alloy, the strut thickness and the architectural design might have an impact on stent and non-stent related ischemic events after PCI (1,2).

Adequately powered RCT are needed to confirm the results of our analysis and before recommending the preferential use of BP-BES in NSTE-ACS patients receiving ticagrelor monotherapy.

Limitations

The findings of this study should be interpreted in light of several limitations. This was a post-hoc analysis of two RCTs in which randomization concerned the antiplatelet regimen and not the stent type. Nevertheless, our analysis comprised a sizeable patient level dataset with prospective data collection. Moreover, the results of the comparison between stent types were affected by between trials differences; indeed, all the BP-BES patients were derived from GLASSY, whereas the control group consisted exclusively of patients from the TWILIGHT trial. The two studies had different designs and methods of events ascertainment and assessment. Extensive efforts were made to minimize these differences by inclusion of patients with similar inclusion and exclusion criteria from the two studies, performing the short-term and long-term analyses separately, and controlling for confounders using four different statistical methods. Moreover, the results of events cross-adjudication showed a high agreement on methods of assessment between the two trials. Nonetheless, residual differences that could have affected the results of the stent comparison may

persist. In addition, the 12-month risk of adverse events should be interpreted with caution, since those were obtained by pooling the estimates of two different follow-up periods of two slightly different cohorts. Finally, the statistical significance of some secondary outcomes might be due to over-adjustment of the multivariable models. For these reasons, the findings should be considered exploratory and hypothesis-generating.

CONCLUSIONS

Among NSTE-ACS patients undergoing PCI treated with an abbreviated or standard ticagrelor-based DAPT, BP-BES compared with other current generation LES was associated with a lower 1-year risk of MACE and TVF, mostly due to a reduction of MI and clinically driven TVR. These non-randomized findings should be considered exploratory and need further confirmation.

Acknowledgments

None

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Figure legends

Figure 1. Flow chart showing the study population of the short-term (A) and long-term (B) analysis. Included patients derived from two randomized clinical trials, GLASSY and TWILIGHT, which compared an abbreviated versus a standard duration of a ticagrelor-based dual antiplatelet therapy.

BP-BES= Biodegradable polymer biolimus eluting stent; CCS= chronic coronary syndrome; LES= limus-eluting stent; STEMI= ST-elevation myocardial infarction.

[#]Bare metal stent, first generation DES, current generation non-limus eluting stent, unclear stent types
[†]BP-BES and other current generation DES

Figure 2. Kaplan-Meier curves for the primary outcome in the BP-BES and LES group. The primary outcome was a composite of cardiovascular death, myocardial infarction, or stent thrombosis. Different inclusion and exclusion criteria were applied to select the population of the short-term and long-term analysis (see methods for further details).

BP-BES= Biodegradable polymer biolimus eluting stent; CABG= Coronary artery bypass graft surgery; eGFR= estimated glomerular fraction rate; HR= Hazard ratio; LES= limus eluting stent; LVEF= left ventricular ejection fraction; MI= myocardial infarction; PCI= Percutaneous coronary intervention.

Figure 3. Adjusted risk for the primary and secondary outcomes. The results were obtained from a Cox proportional hazard model. Covariates included in the final multivariable model were selected through a forward stepwise approach with a criterion of p-value <0.05 forcing in age and sex. Risks were calculated separately in the short and long-term analyses and then pooled to obtain a risk estimate for the whole 12-month study period.

BP-BES= Biodegradable polymer biolimus eluting stent; LES= limus eluting stent; TVR= target vessel revascularization;
P-values for heterogeneity between the 0-3 month and 3-12 month estimates: primary outcome 0.17; TVF 0.001; cardiovascular death 0.28; MI 0.47; definite/probable ST 0.08; clinically driven TVR <0.001; ischemic stroke 0.56.
The x-axis displays values in a log-transformed scale with a 10 basis.
*Adjusted for age, sex, left ventricular ejection fraction (LVEF), haemoglobin, prior PCI, prior coronary artery bypass graft (CABG), and clinical presentation (Non-ST-elevation ACS versus chronic coronary syndrome)
[#]Adjusted for age, sex, prior MI, peripheral artery disease, troponin elevation, diabetes, prior coronary artery bypass graft, creatine kinase elevation, hypercholesterolemia, LVEF, current smoker and estimated glomerular filtration rate<60ml/min 1.73m2.
[†]Composite of cardiovascular death, MI and definite/probable stent thrombosis
[‡]Composite of cardiovascular death, target-vessel MI and definite/probable stent thrombosis and clinically driven target vessel revascularization

608 **Table 1: Baseline characteristics.** Two different population were selected for the short- and
609 long-term analysis. For details see the methods section.

	Short Term Analysis (0-3 months)			Long Term Analysis (3-12 months)		
Variable	**BP-BES N=2,321**	**Other LES N=4,786**	**P-value**	**BP-BES N=2,211**	**Other LES N=3,842**	**P-value**
Age, years	64.7 (10.7)	63.4 (10.4)	<0.001	64.6 (10.7)	62.8 (10.3)	<0.001
Female sex	555 (23.9)	1234 (25.8)	0.09	524 (23.7)	949 (24.7)	0.38
Region			<0.001			<0.001
Asia	0 (0.0)	1109 (23.2)		0 (0.0)	991 (25.8)	
North America	0 (0.0)	2277 (47.6)		0 (0.0)	1678 (43.7)	
Europe	2321 (100)	1400 (29.2)		2211 (100)	1173 (29.5)	
BMI, kg/m2, median (IQR)	27.5 (24.9-30.5)	27.8 (24.9-31.7)	0.004	27.5 (24.9-30.5)	27.8 (24.8-31.6)	0.008
Current smoker	724 (31.2)	1144 (23.9)	<0.001	691 (31.3)	941 (24.5)	<0.001
Diabetes mellitus	536 (23.1)	1737 (36.3)	<0.001	510 (23.1)	1342 (34.9)	<0.001
Hypercholesterolemia	1396 (63.2)	2718 (56.8)	<0.001	1323 (62.9)	2096 (54.6)	<0.001
Hypertension	1657 (71.7)	3308 (69.1)	0.03	1574 (71.5)	2606 (67.8)	0.003
Prior MI	548 (23.6)	1244 (26.0)	0.03	510 (23.1)	982 (25.6)	0.03
Prior PCI	697 (30.1)	1748 (36.5)	<0.001	662 (30.0)	1329 (34.6)	<0.001
Prior CABG	116 (5.0)	503 (10.5)	<0.001	106 (4.8)	358 (9.3)	<0.001
PAD	160 (6.9)	343 (7.2)	0.70	150 (6.8)	231 (6.0)	0.22
CKD*	369 (15.9)	746 (16.2)	0.79	343 (15.5)	532 (14.4)	0.23
Prior bleeding	8 (0.3)	48 (1.0)	0.003	6 (0.3)	36 (0.9)	0.003
Anemia	310 (13.7)	965 (20.9)	<0.001	291 (13.5)	743 (20.0)	<0.001
COPD	122 (5.3)	227 (5.2)	0.93	115 (5.2)	197 (5.2)	0.99
LVEF, %	53.8 (11.3)	53.3 (10.1)	0.15	54.0 (11.2)	53.5 (10.0)	0.25
Clinical presentation			<0.001			<0.001
Unstable angina	927 (39.9)	2593 (54.2)		893 (40.4)	2054 (53.5)	
NSTEMI	1394 (60.1)	2193 (45.8)		1318 (59.6)	1788 (46.5)	
Troponin elevation†	1398 (95.2)	2124 (64.4)	<0.001	1337 (95.4)	1742 (64.9)	<0.001
CK elevation†	526 (37.4)	525 (28.5)	<0.001	508 (37.8)	433 (28.6)	<0.001
CK-MB elevation†	501 (36.4)	526 (28.8)	<0.001	483 (36.4)	440 (29.0)	<0.001
Randomized treatment			0.54			0.39
Ticagrelor plus Aspirin	1145 (49.8)	1945 (50.6)		1094 (49.5)	1945 (50.6)	
Ticagrelor plus Placebo	1153 (50.2)	1897 (49.4)		1117 (50.5)	1897 (49.4)	
Discharge medication						
Aspirin	2316 (99.8)	4786 (100.0)	0.004	2207 (99.9)	3842 (100.0)	0.02
Ticagrelor	2244 (96.7)	4786 (100.0)	<0.001	2143 (97.0)	3842 (100.0)	<0.001
Prasugrel	24 (1.0)	0 (0.0)	<0.001	24 (1.1)	0 (0.0)	<0.001
Clopidogrel	24 (1.0)	0 (0.0)	<0.001	22 (1.0)	0 (0.0)	<0.001
ACEi/ARB	1563 (67.5)	3366 (70.3)	0.02	1487 (67.4)	2713 (70.6)	0.01
Beta-blocker	1906 (82.3)	3847 (80.4)	0.05	1817 (82.3)	3103 (80.8)	0.13
Statin	2172 (93.8)	4528 (94.6)	0.16	2074 (94.0)	3647 (94.9)	0.12
PPI	1412 (60.8)	2278 (47.6)	<0.001	1339 (60.6)	1875 (48.8)	<0.001

610 *Defined as eGFR<60ml/min 1.73m2 according to the CKD-EPI formula.
611 †Elevation above the upper reference limit before or after PCI
612 ACEi= angiotensin-converting enzyme inhibitor; ARB= Angiotensin receptor blocker; BMI= Body Mass index; BP-
613 BES= Biodegradable polymer biolimus-eluting stents; CABG= Coronary artery bypass graft surgery; CK= creatine
614 kinase; CKD= Chronic kidney disease; CK-MB= Creatine kinase-MB; COPD= Chronic obstructive pulmonary
615 disease; IQR= *interquartile range*; LES= limus-eluting stents; LVEF= Left ventricular ejection fraction; MI=
616 Myocardial infarction; NSTEMI= non-ST-elevation myocardial infarction; PAD= Peripheral arterial disease; PCI=
617 Percutaneous coronary intervention; PPI= Proton pump inhibitor
618

Table 2: Procedural characteristics. Two different populations were selected for the short- and long-term analysis. For details see the methods section.

	Short Term Analysis (0-3 months)			Long Term Analysis (3-12 months)		
Variable	**BP-BES N=2,321**	**Other LES N=4,786**	**P-value**	**BP-BES N=2,211**	**Other LES N=3,842**	**P-value**
Radial access	1795 (77.7)	3475 (72.6)	<0.001	1713 (77.8)	2888 (75.2)	0.02
Femoral access	513 (22.2)	1301 (27.2)	<0.001	486 (22.1)	946 (24.6)	0.03
Other access	17 (0.7)	10 (0.2)	<0.001	16 (0.7)	8 (0.2)	0.002
Left main vessel	65 (2.8)	236 (4.9)	<0.001	63 (2.8)	196 (5.1)	<0.001
LAD	1043 (45.0)	2712 (56.7)	<0.001	996 (45.0)	2204 (57.4)	<0.001
LCX	764 (32.9)	1588 (33.2)	0.84	733 (33.2)	1271 (33.1)	0.96
RCA	732 (31.6)	1675 (35.0)	0.004	698 (31.6)	1323 (34.4)	0.02
Venous bypass graft	36 (1.6)	110 (2.3)	0.04	30 (1.4)	78 (2.0)	0.06
No. vessels treated			<0.001			<0.001
One	1941 (84.4)	3536 (73.9)		1845 (84.2)	2823 (73.5)	
Two	338 (14.7)	1085 (22.7)		328 (15.0)	893 (23.2)	
Three or more	20 (0.9)	165 (3.4)		19 (0.9)	126 (3.3)	
No. lesions treated			<0.001			<0.001
One	1758 (76.5)	2873 (60.0)		1675 (76.4)	2325 (60.5)	
Two	436 (19.0)	1433 (29.9)		418 (19.1)	1151 (30.0)	
Three or more	105 (4.6)	480 (10.0)		99 (4.5)	366 (9.5)	
Multi-vessel procedure	358 (15.6)	1250 (26.1)	<0.001	347 (15.8)	1019 (26.5)	<0.001
Bifurcation	383 (16.6)	578 (12.1)	<0.001	361 (16.4)	481 (12.5)	<0.001
Thrombus	119 (5.2)	731 (15.3)	<0.001	116 (5.3)	622 (16.2)	<0.001
TIMI flow 0-1 (before PCI)	301 (13.5)	685 (16.8)	<0.001	286 (13.5)	555 (14.4)	<0.001
Total stent length, mm, median (IQR)	28.0 (18.0-43.0)	33.0 (22.0-50.0)	<0.001	28.0 (18.0-42.0)	33.0 (22.0-51.0)	<0.001
Stent type						
BP-BES	2321 (100)	0 (0.0)	<0.001	2211 (100)	0	<0.001
DP-EES	0 (0.0)	2803 (58.6)	<0.001	0 (0.0)	2242 (58.4)	<0.001
DP-ZES	0 (0.0)	1351 (28.2)	0.002	0 (0.0)	1086 (28.3)	0.01
DP-SES	0 (0.0)	54 (1.1)	0.59	0 (0.0)	42 (1.1)	0.66
BP EES	0 (0.0)	396 (8.3)	0.13	0 (0.0)	310 (8.1)	0.21
BP SES	0 (0.0)	520 (10.9)	0.08	0 (0.0)	451 (11.7)	0.12
Polymer free SES	0 (0.0)	56 (1.2)	0.58	0 (0.0)	45 (1.2)	0.64
Polymer free TES	0 (0.0)	1 (0.0)	0.94	0 (0.0)	0 (0.0)	.

BES= biolimus-eluting stents; BP= Biodegradable polymer; DP= durable polymer; EES= everolimus-eluting stents; LAD= left anterior descending artery; LCX= Left Circumflex artery; LES= limus-eluting stents; PCI= Percutaneous coronary intervention; RCA= Right coronary artery; SES= sotarolimus-eluting stents; TES= Tetramethylpyrazine-eluting stents; TIMI= Thrombolysis in Myocardial Infarction; ZES= zotarolimus-eluting stents

Table 3. Kaplan-Meier event rate estimates between hospital discharge and 3 months after PCI (short-term analysis) and between 3 and 12 months (long-term analysis).

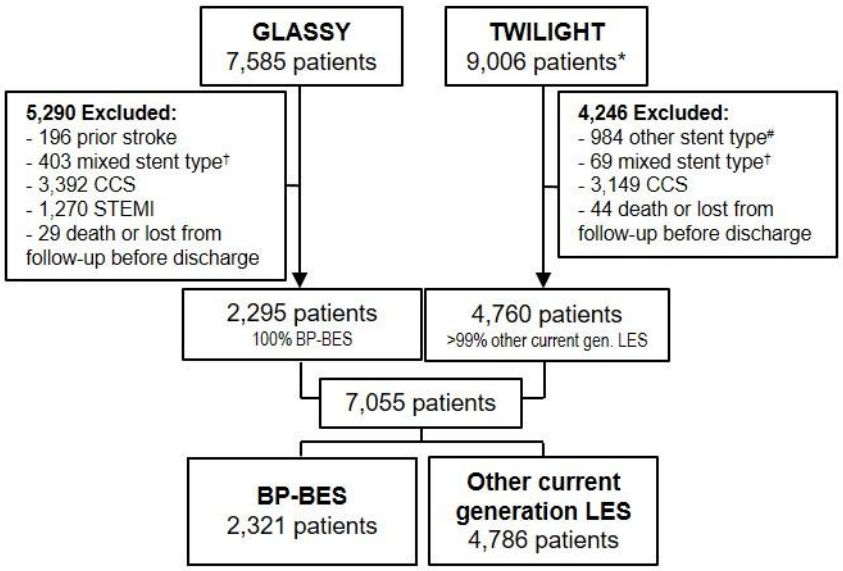
	0-3 months			3-12 months		
Outcomes	**BP-BES N=2,321**	**Other LES N=4,786**	**p-value***	**BP-BES N=2,211**	**Other LES N=3,842**	**p-value***
Primary outcome						
Cardiovascular death, myocardial infarction or stent thrombosis	26 (1.1)	59 (1.3)	0.48	38 (1.7)	117 (3.1)	0.002
Secondary outcomes						
Target-vessel failure†	26 (1.1)	56 (1.3)	0.62	32 (1.5)	170 (4.4)	<0.001
Cardiovascular death	11 (0.5)	10 (0.2)	0.09	12 (0.6)	30 (0.8)	0.28
Myocardial infarction	16 (0.7)	48 (1.1)	0.12	28 (1.3)	97 (2.6)	<0.001
Definite/probable stent thrombosis	6 (0.3)	20 (0.4)	0.26	1 (0.1)	11 (0.3)	0.04
Target-vessel revascularization	14 (0.6)	46 (1.1)	0.07	18 (0.8)	140 (3.7)	<0.001
Ischemic stroke	3 (0.1)	12 (0.3)	0.25	7 (0.3)	9 (0.2)	0.55

*Calculated using log-rank tests

†Composite of cardiovascular death, target-vessel MI, definite or probable ST, or clinically driven target vessel revascularization (TVR)

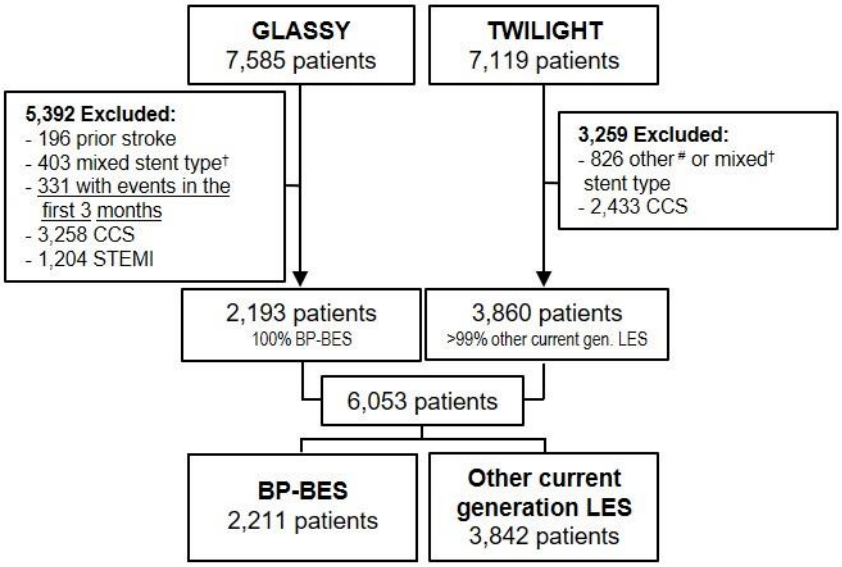
BARC= Bleeding Academic Research Consortium; BP-BES= Biodegradable polymer biolimus-eluting stents; LES= limus-eluting stents;

A **SHORT-TERM ANALYSIS (0-3 months)**



*including randomized and enrolled but non randomized patients

B **LONG-TERM ANALYSIS (3-12 months)**



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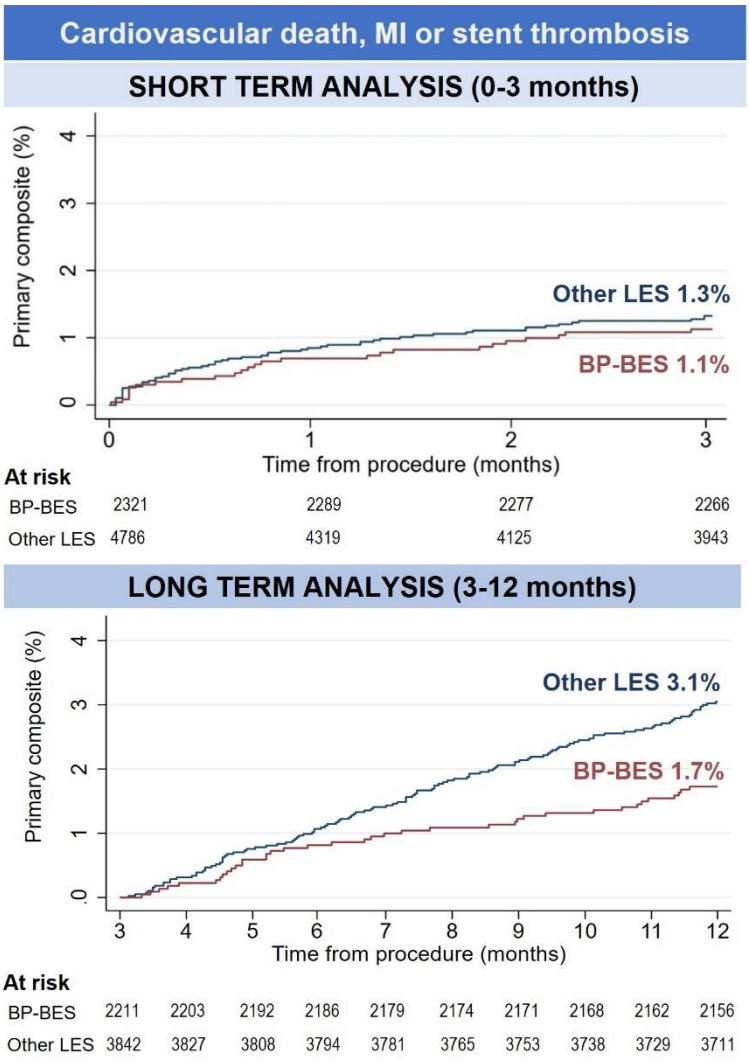
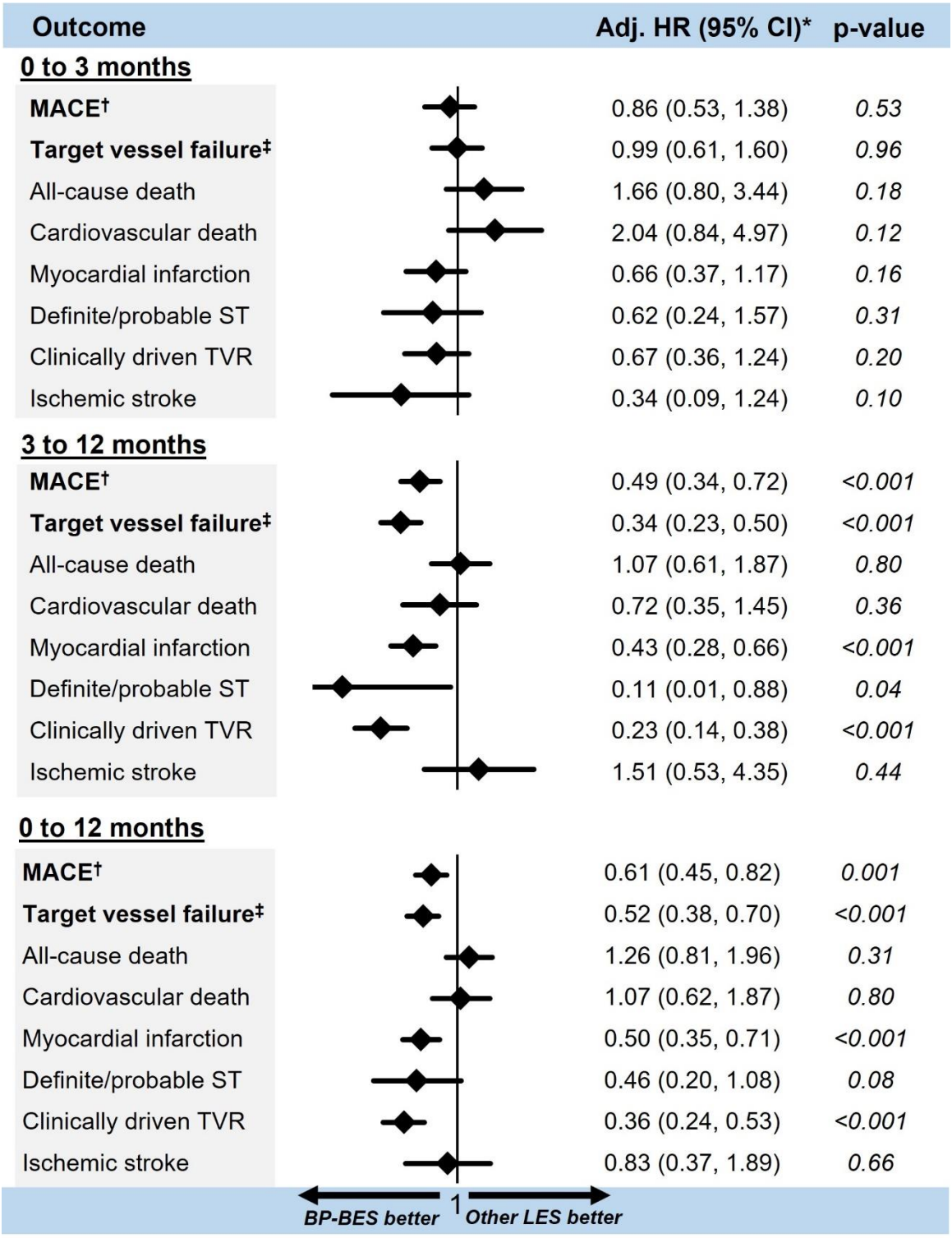

Cardiovascular death, MI or stent thrombosis
SHORT TERM ANALYSIS (0-3 months)
Primary composite (%)
0
1
2
3
4
Other LES 1.3%
BP-BES 1.1%
0
1
2
3
Time from procedure (months)
At risk
BP-BES 2321 2289 2277 2266
Other LES 4786 4319 4125 3943
LONG TERM ANALYSIS (3-12 months)
Primary composite (%)
0
1
2
3
4
Other LES 3.1%
BP-BES 1.7%
3
4
5
6
7
8
9
10
11
12
Time from procedure (months)
At risk
BP-BES 2211 2203 2192 2186 2179 2174 2171 2168 2162 2156
Other LES 3842 3827 3808 3794 3781 3765 3753 3738 3729 3711

638


Outcome
Adj. HR (95% CI)*
p-value
0 to 3 months
MACE†
0.86 (0.53, 1.38)
0.53
Target vessel failure‡
0.99 (0.61, 1.60)
0.96
All-cause death
1.66 (0.80, 3.44)
0.18
Cardiovascular death
2.04 (0.84, 4.97)
0.12
Myocardial infarction
0.66 (0.37, 1.17)
0.16
Definite/probable ST
0.62 (0.24, 1.57)
0.31
Clinically driven TVR
0.67 (0.36, 1.24)
0.20
Ischemic stroke
0.34 (0.09, 1.24)
0.10
3 to 12 months
MACE†
0.49 (0.34, 0.72)
<0.001
Target vessel failure‡
0.34 (0.23, 0.50)
<0.001
All-cause death
1.07 (0.61, 1.87)
0.80
Cardiovascular death
0.72 (0.35, 1.45)
0.36
Myocardial infarction
0.43 (0.28, 0.66)
<0.001
Definite/probable ST
0.11 (0.01, 0.88)
0.04
Clinically driven TVR
0.23 (0.14, 0.38)
<0.001
Ischemic stroke
1.51 (0.53, 4.35)
0.44
0 to 12 months
MACE†
0.61 (0.45, 0.82)
0.001
Target vessel failure‡
0.52 (0.38, 0.70)
<0.001
All-cause death
1.26 (0.81, 1.96)
0.31
Cardiovascular death
1.07 (0.62, 1.87)
0.80
Myocardial infarction
0.50 (0.35, 0.71)
<0.001
Definite/probable ST
0.46 (0.20, 1.08)
0.08
Clinically driven TVR
0.36 (0.24, 0.53)
<0.001
Ischemic stroke
0.83 (0.37, 1.89)
0.66
1
BP-BES better
Other LES better

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