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A comparison of an ultrathin-strut biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent for patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: rationale and design of the BIOSTEMI trial

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KEYWORDS

- drug-eluting stent
- STEMI
- thrombus-containing lesion

Abstract

Aims: A novel ultrathin-strut biodegradable polymer sirolimus-eluting stent (BP-SES) (Orsiro; Biotronik, Bülach, Switzerland) was shown to be superior to a thin-strut durable polymer everolimus-eluting stent (DP-EES) (XIENCE Xpedition/Alpine; Abbott Vascular, Santa Clara, CA, USA) with respect to the primary endpoint of target lesion failure (TLF) at 12 months in the pre-specified subgroup of patients with ST-segment elevation myocardial infarction (STEMI) included in the BIOSCIENCE trial. We designed a large-scale, randomised, clinical trial to assess the clinical superiority of ultrathin-strut BP-SES over thin-strut DP-EES among patients with STEMI undergoing primary percutaneous coronary intervention (PPCI).

Methods and results: BIOSTEMI (NCT02579031) is a prospective, multicentre, randomised, controlled, superiority trial that will randomly assign 1,250 patients with STEMI undergoing PPCI to treatment with BP-SES or DP-EES. The primary endpoint of TLF, a composite of cardiac death, target vessel reinfarction, and clinically indicated target lesion revascularisation within 12 months, will be analysed with Bayesian models applied to the BIOSTEMI data set (n=1,250) using robust historical priors to incorporate historical information from the BIOSCIENCE STEMI subgroup (n=407).

Conclusions: The BIOSTEMI trial will determine whether ultrathin-strut BP-SES are superior to thin-strut DP-EES with respect to TLF in patients with STEMI undergoing PPCI.

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Abbreviations

BMS	bare metal stent
BP-DES	biodegradable polymer drug-eluting stent
BP-SES	biodegradable polymer sirolimus-eluting stent
DES	drug-eluting stent
DP-DES	durable polymer drug-eluting stent
DP-EES	durable polymer everolimus-eluting stent
MACE	major adverse cardiac events
PCI	percutaneous coronary intervention
RR	rate ratio
STEMI	ST-segment elevation myocardial infarction
ST	stent thrombosis
TLF	target lesion failure
TLR	target lesion revascularisation
TVR	target vessel revascularisation

Introduction

Primary percutaneous coronary intervention (PPCI) is the reperfusion strategy of choice for patients with acute ST-segment elevation myocardial infarction (STEMI)[1]. However, PPCI during STEMI may predispose to stent malapposition due to stent undersizing and later thrombus resolution, thereby increasing the risk of stent thrombosis (ST) and in-stent restenosis[2]. In addition, vessel healing at the culprit site of STEMI is substantially delayed and may result in increased rates of late ST[3]. In this setting, early-generation durable polymer drug-eluting stents (DP-DES) were associated with substantial reductions in target vessel revascularisation (TVR) rates compared with bare metal stents (BMS)[4,5], but this early benefit was offset by an increased risk of very late ST during subsequent years[4,5], related to the persistence of durable polymers that results in chronic local inflammation, impaired endothelialisation and delayed arterial healing[3].

Newer-generation drug-eluting stents (DES) with thinner-strut stent platforms, biocompatible permanent polymer coatings and reduced sirolimus-analogue drug loads were associated with improved vascular healing and clinical outcomes compared with early-generation DP-DES[6]. Among patients with STEMI, the thin-strut durable polymer everolimus-eluting stent (DP-EES) was shown to reduce rates of repeat revascularisation and ST compared with BMS at one-[7] and two-year[8] follow-up, without increasing the risk of cardiac death or myocardial infarction (MI). Nevertheless, several randomised trials consistently failed to demonstrate clinical superiority of newer-generation biocompatible DP-DES over early-generation thick-strut DP-DES in STEMI patients treated with PPCI[9-12].

Newer-generation biodegradable polymer DES (BP-DES) were recently developed to overcome delayed vascular healing attributed to chronic inflammatory responses[13] and hypersensitivity reactions[14] induced by permanent polymer coatings, that result in persisting late adverse clinical events[15]. Newer-generation BP-DES were shown to be a safe and effective alternative to DP-DES in numerous randomised trials[16-24] and large-scale comprehensive network meta-analyses[25-27]. However, randomised evidence on the clinical efficacy and safety of BP-DES in STEMI patients undergoing PPCI is scarce. In the Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) trial, thick-strut biodegradable polymer biolimus-eluting stents (BP-BES) were associated with reduced short-[28] and long-term[29] rates of major adverse cardiac events (MACE) compared with BMS, mainly driven by lower risk of target vessel reinfarction and ischaemia-driven TLR. In a recent subgroup analysis of the randomised Limus Eluted From A Durable Versus ERodable Stent Coating (LEADERS) trial, thick-strut BP-BES were shown to reduce rates of MACE, cardiac death and definite ST throughout five years compared with early-generation thick-strut DP-DES[30]. These findings were recently confirmed by a pooled individual patient-level data analysis demonstrating significant reductions in rates of MACE and TLR at four years among STEMI patients treated with newer-generation thick-strut BP-BES compared with early-generation thick-strut DP-DES[31]. However, no randomised evidence is currently available comparing BP-DES with newer-generation DP-DES for PPCI.

The Orsiro DES (Biotronik, Bülach, Switzerland) is a novel biodegradable polymer sirolimus-eluting stent (BP-SES) consisting of an ultrathin-strut cobalt-chromium metallic stent platform and a unique hybrid combination of passive and active coatings[32]. The thin-layer, amorphous, silicon-carbide passive coating encapsulates the stent surface to reduce ion release from the metal stent platform and therefore minimises interaction with the surrounding tissue. The active coating contains a biodegradable poly-L-lactic acid (PLLA) polymer matrix that degrades completely within approximately 12-15 months and delivers sirolimus at a dose of 1.4 μg/mm^2 with elution kinetics optimised to release *in vivo* over approximately 100 days[32]. In the Ultrathin-strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus Eluting Stent for Percutaneous Coronary Revascularisation (BIOSCIENCE) randomised trial, ultrathin-strut BP-SES were shown to be non-inferior to current best-in-class thin-strut biocompatible DP-EES with respect to the primary composite endpoint of target lesion failure (TLF) at one- and two-year follow-up[22,33] in all-comers patients undergoing PCI. In the pre-specified subgroup of patients with STEMI, ultrathin-strut BP-SES were associated with significantly reduced rates of TLF during short- and long-term follow-up[34,35] compared with thin-strut DP-EES. Based on these hypothesis-generating findings, we designed a large-scale, randomised trial to assess the clinical superiority of ultrathin-strut BP-SES over thin-strut DP-EES in patients with STEMI undergoing PPCI.

Methods

STUDY DESIGN AND PRIMARY HYPOTHESIS

BIOSTEMI (A Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent With a Durable Polymer Everolimus-Eluting Stent for Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention) is a prospective, multicentre,

assessor-blind, randomised, controlled trial comparing the ultrathin-strut Orsiro BP-SES with the state-of-the-art thin-strut biocompatible DP-EES (XIENCE Xpedition®/Alpine™; Abbott Vascular, Santa Clara, CA, USA) in patients with STEMI undergoing PPCI **(Figure 1)**. The study protocol was designed by the steering committee, and all data are managed by the Clinical Trials Unit (CTU) Bern, University of Bern, Switzerland. The study organisation is detailed in **Supplementary Table 1**. The trial is registered at www.clinicaltrials.gov (Identifier: NCT02579031). The first patient was included in April 2016.

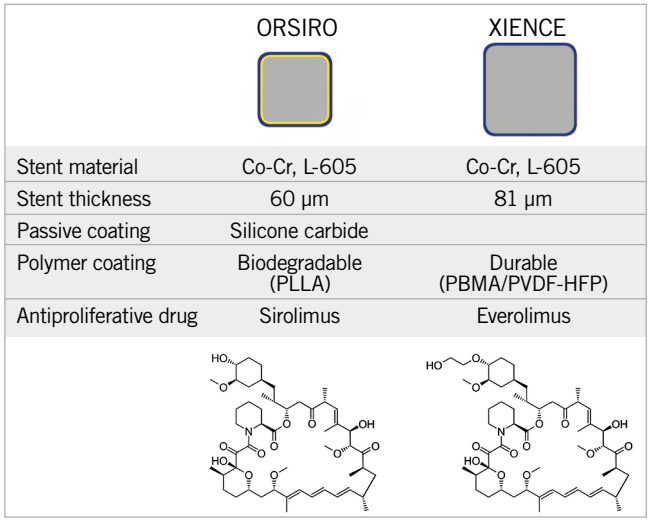

Figure 1. *Overview of the principal characteristics of the study stents. Co: cobalt; Cr: chromium; PBMA: poly n-butyl methacrylate; PLLA: poly-L-lactic acid; PVDF-HFP: poly-vinylidene fluoride-co-hexafluoropropylene*

The primary objective of the BIOSTEMI trial is to investigate the study hypothesis that ultrathin-strut BP-SES are superior to thin-strut DP-EES in STEMI patients undergoing PPCI. The study will combine data from the previously initiated BIOSCIENCE study[22] with prospective evidence from the BIOSTEMI trial using a robust Bayesian approach **(Figure 2)**. The main features of the BIOSCIENCE and BIOSTEMI study designs and inclusion criteria are summarised in **Supplementary Table 2**. The Bayesian approach quantitatively combines data from the similarly designed BIOSCIENCE and BIOSTEMI studies, which allows a more precise estimation of the clinical performance of the two study stents for the treatment of patients with STEMI. The U.S. Food and Drug Administration (FDA) has recently recognised that Bayesian analyses may lead to smaller trials while still retaining full validity of the results, by making better usage of pre-existing high-quality evidence (Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials; issued on 5 February 2010 by the FDA).

STUDY ENDPOINTS

The primary endpoint of the BIOSTEMI trial is the rate of TLF, a composite of cardiac death, target vessel reinfarction, or clinically indicated TLR, within 12 months of the index procedure. Secondary endpoints include all-cause death, cardiac death, Q-wave and non-Q-wave MI, clinically indicated and non-clinically indicated TLR, clinically indicated and non-clinically indicated TVR, target vessel failure, definite ST, and definite or probable ST at one and two years, and TLF at two years. All primary and secondary endpoint definitions are outlined in detail in the **Supplementary Appendix**. The study endpoints will be adjudicated by a blinded and independent clinical events committee (CEC).

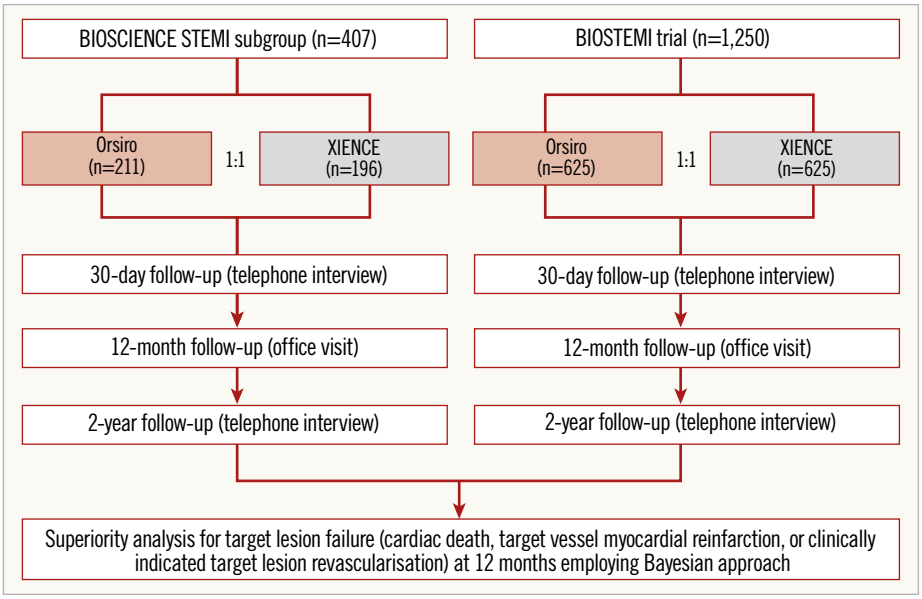

Figure 2. *BIOSTEMI study design. STEMI: ST-elevation myocardial infarction*

STUDY POPULATION

All subjects with STEMI within 24 hours of symptom onset and who qualify for PPCI according to current guidelines[1] are eligible. Subjects with coronary artery lesions suitable for DES implantation will be enrolled according to the inclusion and exclusion criteria detailed in **Supplementary Table 3**.

INFORMED CONSENT

All subjects will provide informed consent prior to randomisation. Considering the particular situation of subjects with STEMI requiring urgent PPCI, a specific informed consent process was developed for the purpose of the study and is detailed in the **Supplementary Appendix**. The study protocol, including the informed consent process, was approved by the responsible ethics committee.

RANDOMISATION

After successful crossing of the acute infarct artery target lesion, patients will be randomised in a 1:1 ratio to treatment with either BP-SES or DP-EES. Random stent allocation will be performed using an electronic web database (Cardiobase, copyright by Department of Cardiology, CTU Bern, Switzerland, and 2mt Software GmbH, Ulm, Germany) and will be stratified according to study centre, diabetes status, and presence or absence of multivessel coronary artery disease.

REVASCULARISATION PROCEDURE

PPCI will be performed according to current guidelines[1]. In patients with multivessel disease, revascularisation of all lesions in non-culprit vessels will be performed with the uniform use of the randomly allocated study stent within the same procedure or during subsequent staged procedures at the investigator's discretion. Staged procedures for the treatment of non-culprit vessels are permitted within three months of the index procedure. There is no restriction with respect to type or number of lesions that are treated.

DATA COLLECTION

The schedule of measurements and follow-up plan are detailed in **Supplementary Table 4**. Patient data are collected in a web-based data entry system hosted at the CTU Bern. Data entry will be performed by the on-site study personnel. Central and on-site data monitoring will be organised by the CTU Bern according to a pre-specified monitoring plan. All electronic case report forms will undergo central data monitoring. On-site monitoring will be performed on the complete case report forms of the first 10 patients included at each participating site, followed by a random sample of 20% at each site. All serious adverse events will be submitted to the CTU Bern in a blinded fashion. Any death, myocardial reinfarction, revascularisation procedure, ST, cerebrovascular event, or bleeding complication will be independently adjudicated by a blinded CEC.

STATISTICAL ANALYSIS

BIOSTEMI is a superiority trial powered for the primary composite endpoint of TLF within 12 months after the index procedure. New data from patients prospectively enrolled in the BIOSTEMI trial will be combined with historical data from the subgroup of patients with STEMI included in the BIOSCIENCE trial (BIOSCIENCE STEMI) that contributed to the primary clinical endpoint analysis[22,34], employing a Bayesian approach based on robust historical priors (RHP). Compared to conventional meta-analytic approaches, RHP will down-weight historical information on the primary endpoint rates, if this information turns out to be inconsistent with the new data acquired on the primary endpoint rates, for each arm separately. The analysis method is based on Schmidli et al[36] and adapted to the case of a single historical trial and estimation of rates and rate ratios (RR). A detailed description of the statistical analysis is provided in the **Supplementary Appendix**, **Supplementary Table 5**-**Supplementary Table 7**, **Supplementary Figure 1**, and **Supplementary Figure 2**.

All patients undergoing randomisation will be included in the analysis of primary and secondary clinical outcomes in the study arm to which they were originally allocated according to the intention-to-treat principle. The primary and secondary endpoints will be analysed with Bayesian log-Poisson models applied to new data from the BIOSTEMI patients with RHP that incorporate historical information from BIOSCIENCE STEMI patients. The individual observation time of each patient will be included in these models, and incidence rates and incidence RR will be provided. The RR will be reported as the median of the posterior distribution with two-sided 95% credibility interval (CrI). Superiority of BP-SES over DP-EES will be declared if the upper limit of the CrI is ≤ 1.

SAMPLE SIZE

The BIOSTEMI trial is powered for superiority on the primary endpoint at 12 months using a robust Bayesian approach that incorporates historical information adopted by Schmidli et al[36] and modified as detailed in the **Supplementary Appendix**. Power calculation was based on a Monte Carlo simulation, where information from the 407 BIOSCIENCE STEMI patients was included via RHP. Power was estimated as the number of simulated trials where superiority is declared divided by the total number of simulated trials. In BIOSCIENCE STEMI, an RR of 0.38 for BP-SES/DP-EES with respect to the primary endpoint TLF was observed at 12 months[24,36]. To be conservative, a less pronounced RR of 0.60, with an incidence rate for the primary endpoint of 4.2% in the BP-SES and 7.0% in the DP-EES arm, respectively, will be used for sample size calculation in the BIOSTEMI trial. We assumed a dropout rate of 5% at 12 months. With a 1:1 allocation ratio and a two-sided α=0.05, we found that enrolment of a total of 1,250 patients (625 per treatment arm) in the BIOSTEMI trial would provide more than 80% power to detect superiority of BP-SES over DP-EES.

PRE-SPECIFIED ANALYSES

Stratified analyses of the primary endpoint across major subgroups based on the BIOSTEMI subjects will be performed. Subgroup analyses of the primary endpoint will be performed with respect

to diabetes, gender, age ≥65 years, BMI ≥30 kg/m^2, multivessel disease, and chronic renal failure. Rates of cerebrovascular events and bleeding complications will be analysed according to the type and duration of the anticoagulant and antiplatelet strategies, as detailed in the **Supplementary Appendix**.

Conclusions

BIOSTEMI is a prospective, multicentre, assessor-blind, randomised, controlled trial assessing the superiority of ultrathin-strut BP-SES over thin-strut DP-EES with respect to the primary endpoint of TLF in patients with STEMI undergoing PPCI. BIOSTEMI is the first randomised controlled clinical trial comparing ultrathin-strut BP-DES with thin-strut DP-DES for PPCI.

Impact on daily practice

The optimal DES therapy for PPCI in patients with STEMI remains unclear. A novel ultrathin-strut BP-SES may improve clinical outcomes compared with the current best-in-class newer-generation DP-EES among patients with STEMI, thus potentially advancing current management strategies for PPCI. The results of the BIOSTEMI trial may entail important clinical implications for the future management of patients with STEMI undergoing PPCI in clinical practice.

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Conflict of interest statement

J.F. Iglesias reports receiving research grants to the institution from AstraZeneca and Biotronik, educational grants to the institution from Philips Volcano, and honoraria/speaker fees from AstraZeneca, Biotronik, Medtronic, Philips Volcano and Terumo. O. Muller reports receiving research grants to the institution from AstraZeneca and Biotronik, and honoraria/speaker fees from Medtronic and St. Jude Medical/Abbott. M. Roffi reports receiving institutional research grants from Abbott Vascular, Medtronic, Boston Scientific, Terumo, and Biotronik. P. Jüni reports receiving research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as an unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company. M. Valgimigli reports receiving grants from AstraZeneca, and personal fees from Abbott, Amgen and Bayer, outside the submitted work. S. Windecker reports receiving grants to the institution from Biotronik, Boston Scientific, Bracco Pharmaceutical, Edwards Lifesciences, Medtronic, Terumo, and St. Jude Medical. T. Pilgrim reports receiving research grants to the institution from Biotronik, Edwards Lifesciences and Symetis, speaker fees from Boston Scientific, and reimbursement for travel from St. Jude Medical. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix. Study organisation, study design, inclusion and exclusion criteria, study endpoint definitions.

Supplementary Table 1. Study organisation.

Supplementary Table 2. Study design of trials contributing to the Bayesian analysis.

Supplementary Table 3. Inclusion and exclusion criteria.

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Supplementary Table 7. Type I error and power obtained by Monte Carlo simulation under several scenarios for the event rate expected in the new BIOSTEMI trial and for values of the weighting parameter.

Supplementary Figure 1. Graphical description of how the robust historical priors are constructed.

Supplementary Figure 2. Graphical description of how the primary endpoint and secondary endpoints will be analysed.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/139th_issue/120

Supplementary data

Supplementary Appendix. Study organisation, study design, inclusion and exclusion criteria, study endpoint definitions

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1. STUDY ORGANISATION

The BIOSTEMI study organisation is detailed in **Supplementary Table 1**.

2. STUDY DESIGN

BIOSTEMI is a prospective, multicentre, assessor-blind, randomised controlled trial comparing an ultrathin-strut biodegradable polymer sirolimus-eluting stent (BP-SES) (Orsiro; Biotronik, Bülach, Switzerland) with a thin-strut biocompatible durable polymer everolimus-eluting stent (DP-EES) (XIENCE Xpedition™/Alpine; Abbott Vascular, Santa Clara, CA, USA) in unselected patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). The BIOSTEMI trial will combine data from the previously initiated BIOSCIENCE randomised study [22] with prospective evidence from the BIOSTEMI trial by using a robust Bayesian approach. The main features of BIOSCIENCE and BIOSTEMI study designs and inclusion criteria are summarised in **Supplementary Table 2**.

3. INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria of the BIOSTEMI trial are outlined in **Supplementary Table 3**.

4. STUDY ENDPOINT DEFINITIONS

4.1 Death

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Cardiac death includes any death due to immediate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), death related to the procedure, unwitnessed death, and death of unknown cause.

Cardiovascular death includes any death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular causes.

Non-cardiovascular death includes any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

4.2 Myocardial reinfarction

Spontaneous myocardial reinfarction is defined as a typical rise and gradual fall of cardiac biochemical markers (preferentially troponin; alternatively, creatinine kinase [CK] or CK-MB fraction) >1 times the upper limit of normal (ULN), in combination with any one of the following characteristics: ischaemic symptoms, development of new pathologic Q-waves on the ECG according to the Minnesota code, ECG changes indicative of ischaemia (ST-segment elevation or depression),

pathologic findings of an acute myocardial infarction, development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biochemical marker assessment during the acute event. Myocardial reinfarction is categorised according to the electrocardiographic criteria of the Minnesota code manual into Q-wave and non-Q-wave myocardial reinfarction. Q-wave myocardial reinfarction is defined as development of new pathologic Q-waves on the ECG in two or more contiguous leads (according to the Minnesota code) with or without post-procedural increase of cardiac biochemical markers (troponin, CK, or CK-MB fraction). All other myocardial reinfarctions are defined as non-Q-wave myocardial reinfarctions.

Myocardial reinfarction occurring within 48 hours after percutaneous coronary intervention or within seven days after coronary artery bypass grafting is defined as periprocedural myocardial reinfarction. Periprocedural myocardial reinfarction in the setting of evolving acute myocardial infarction is defined as recurrent chest pain lasting >20 minutes (or new ECG changes consistent with myocardial reinfarction) in combination with a >50% elevation of peak CK (or CK-MB in the absence of CK) level above the previous level measured within 24 hours after the event. If the elevated CK (or CK-MB) levels from the index myocardial infarction are falling or have returned to normal within 24 hours post index percutaneous coronary intervention, a new elevation of CK >2x ULN within 24 hours post index percutaneous coronary intervention if the CK level has returned to <ULN, or a rise by >50% above the previous nadir level if the CK level has not returned to <ULN are defined as periprocedural myocardial reinfarction.

4.3 Target vessel

The target vessel is defined as the index major coronary artery (left anterior descending artery, left circumflex artery, or right coronary artery, and their side branches), which was in physical contact with any component (guiding catheter, guidewire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure.

4.4 Target vessel myocardial reinfarction

Target vessel myocardial reinfarction is defined as any myocardial reinfarction that is not clearly attributable to a non-target vessel.

4.5 Target vessel revascularisation

Target vessel revascularisation is defined as any revascularisation within the entire major coronary vessels proximal or distal to a target lesion including upstream and downstream side branches and the target lesion itself. Target vessel revascularisation is deemed clinically indicated if the stenosis of the treated lesion is ≥50% of the lumen diameter in the presence of signs or symptoms of ischaemia, or if the diameter stenosis is ≥70% of the lumen diameter, irrespective of the presence or absence of ischaemic signs and symptoms.

4.6 Target vessel failure

Target vessel failure is defined as target vessel revascularisation, Q-wave or non-Q wave myocardial reinfarction, or cardiac death that cannot be clearly attributed to a vessel other than the target vessel.

4.7 Target lesion

The target lesion is defined as the treated lesion starting 5 mm proximal of the stented lesion and ending 5 mm distal of the stented lesion. The culprit lesion is defined as the lesion responsible for the index acute myocardial infarction, based on ECG, wall motion abnormalities, and/or angiographic lesion morphology (e.g., ulceration and/or thrombus consistent with plaque rupture). Non-culprit lesions are defined as any lesions in the entire coronary artery tree outside the culprit lesion.

4.8 Target lesion revascularisation

Target lesion revascularisation is defined as any repeat percutaneous or surgical intervention due to a stenosis or occlusion within the stent or within the 5 mm borders proximal or distal to the stent. Target lesion revascularisation is deemed clinically indicated if the stenosis of the treated lesion is ≥50% of the lumen diameter in the presence of signs or symptoms of ischaemia, or if the diameter stenosis is ≥70% of the lumen diameter, irrespective of the presence or absence of ischaemic signs and symptoms.

4.9 Stent thrombosis

Stent thrombosis is defined as definite, probable, and possible according to the definitions provided by the Academic Research Consortium [37].

4.10 Device success

Device success is defined as the attainment of <30% residual stenosis by quantitative coronary angiography (or <20% by visual assessment), using the assigned device only.

4.11 Lesion success

Lesion success is defined as the attainment of <30% residual stenosis by quantitative coronary angiography (or <20% by visual assessment), using any percutaneous method.

4.12 Procedure success

Procedural success is defined as the attainment of <30% residual stenosis by quantitative coronary angiography (or <20% by visual assessment) in all lesions using any percutaneous method, without the occurrence of death, myocardial reinfarction, or repeat revascularisation of the target vessel during the hospital stay.

4.13 Bleeding

Bleeding events are defined according to the definitions provided by the Bleeding Academic Research Consortium [38].

5. INFORMED CONSENT

The BIOSTEMI trial presents an all-comers study design with broad inclusion and minimal exclusion criteria to reflect the routine management of STEMI patients undergoing PPCI in contemporary practice. A specific informed consent process was developed for the purpose of the study to allow broad patient inclusion, including unconscious patients, while minimising the delay to PPCI. Patients with cardiogenic shock will also be enrolled in the trial.

5.1 Conscious patients

Conscious patients will be asked for a written informed consent. In case the conscious patient is unable to provide written informed consent, a verbal informed consent will be obtained. After PPCI, the patient will be asked for written informed consent.

5.2 Unconscious patients

In case the patient is unconscious and there is no indication that the patient is opposed to participating in the trial, an independent physician who is not involved in the study will be asked to safeguard the patient's interests and decide about the involvement of the patient in the study. In case the unconscious patient dies before providing written informed consent or the presumed consent is withdrawn by a legally accepted patient representative, the health-related personal data of the patient collected up to this point will be anonymised.

5.3. Informed consent withdrawal

In case the patient withdraws verbal or written informed consent, the health-related personal data of the patient collected up to the time of withdrawal will be anonymised after data evaluation has been completed.

6. ANTITHROMBOTIC REGIMEN

The routine administration of potent $P2Y_{12}$ receptor inhibitors (ticagrelor or prasugrel) is recommended as the antiplatelet therapy of choice [1]. Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (≥250 mg loading dose) and ticagrelor (180 mg loading dose) or prasugrel (60 mg loading dose) is administered prior to the procedure in all patients according to local protocols. If both ticagrelor and prasugrel are either not available or contraindicated, clopidogrel (600 mg loading dose) will be administered. Unfractionated heparin at a minimal dose of 5,000 international units (IU) or 70-100 IU/kg body weight is administered during the procedure to maintain an activated clotting time ≥250 seconds. The use of glycoprotein IIb/IIIa inhibitors is left to the investigator's discretion. After the procedure, DAPT with aspirin (75-100 mg once daily) and ticagrelor (90 mg twice daily) or prasugrel (5 mg [if age ≥75 years or body weight <60 kg] or 10 mg once daily) will be prescribed in all

patients for 12 months. If both ticagrelor and prasugrel are either not available or contraindicated, clopidogrel (75 mg once daily) will be prescribed for 12 months.

7. FOLLOW-UP

The schedule of measurements performed during the index admission and the follow-up plan are summarised in **Supplementary Table 4**. Patients will be followed up at 30 days, one year and two years after the index procedure. Telephone contacts will be conducted at 30 days and two years after the index procedure to assess vital status, cardiovascular drug use, hospitalisations, and intervening major clinical events since the last in-hospital visit. On-site clinical visits will be conducted at 1 year after the index procedure to identify cardiovascular drug use, hospitalisations, and intervening adverse clinical events since the last telephone contact. The study primary and secondary endpoints will be assessed during the one-year on-site visit. No angiographic follow-up is mandated per protocol. Thus, any follow-up coronary angiography will be clinically indicated.

8. STATISTICAL ANALYSIS

8.1 Definitions

In this document, the Normal distribution $Normal(\mu, \tau)$ is parametrised with the mean μ and the precision τ, where $\tau = 1/\sigma^2$.

STEMI: ST-segment elevation myocardial infarction.

The STEMI subgroup of the BIOSCIENCE trial (N=407) is called *historical* trial hereafter.

The current trial, BIOSTEMI (N=1,250), is called *present* trial hereafter.

BP-SES: treatment arm, biodegradable polymer sirolimus-eluting stent.

DP-EES: control arm, durable polymer everolimus-eluting stent.

Primary endpoint: TLF, first occurrence of target lesion failure until and including 365 days post index procedure.

Secondary endpoints: first occurrence of other clinical outcomes.

Type I error: the proportion of simulations under the assumption of a rate ratio equal to 1 that resulted in a credible interval of the rate ratio not containing 1.

8.2. Analysis of primary and secondary clinical endpoints

8.2.1 Minimally informative model

The aim of the study is to compare the average incidence rate of clinical outcomes between two treatment arms measured in units of *number of events per patient-year*. The analysis is Bayesian but posterior 95% credible intervals will be used to construct a frequentist statistical test. This is a superiority trial defined by:

- H0: TLF rate is equal in BP-SES and DP-EES
- H1: TLF rate is lower in BP-SES compared to DP-EES, hence BP-SES is clinically superior to DP-SES

Although the clinically relevant alternative hypothesis (H1) is one-sided, two-sided tests will be performed at the conventional alpha level of 5%. We use a generalised linear model approach with a Poisson distributed response. The single categorical predictor has two categories: treatment (T) and control (C). There are N patients indexed by *i*, the outcome variable Y_i indicates whether an event was recorded and t_i is the time of the first event or of censoring (in units of years). There are two categories, treatment (T) and control (C), where $x_{Ti}\ and\ x_{Ci}$ are binary variables that indicate if patient *i* belongs to the treatment or control arm. The model is given by

$$\mathrm{Y}_i \sim \mathrm{Poisson}(\lambda_i)\ ;\ \mathrm{E}(\mathrm{Y}_i) = \mathrm{Var}(\mathrm{Y}_i) = \lambda_i \qquad \text{(eq.1)}$$

$$\log(\lambda_i) = x_{Ti}\beta_T + x_{Ci}\beta_C + \log(\mathrm{t}_i) \qquad \text{(eq.2)}$$

To estimate incidence rates, we included the offset term $\log(\mathrm{t}_i)$, with time at risk t_i. This model estimates the log incidence rate in each arm and the rates can be obtained by $\exp(\beta_T)$ and $\exp(\beta_C)$. The rate ratio is obtained by $\mathrm{RR} = \exp(\beta_T - \beta_C)$. For Bayesian inference, we need to define the prior distribution of the two log-rates $P(\beta_T)$ and $P(\beta_C)$. For a model assuming minimal prior knowledge, we will use vague priors defined as follows

$$P_V(\beta_T) = P_V(\beta_C) \sim Normal(\mu = 0, \tau = 0.111) \qquad \text{(eq.3)}$$

The above model formulation allows setting exactly the same prior in both arms and thus assumes that there is no prior difference between the arms. The prior 95% credibility interval of $P_V(\beta)$ is 0.003 to 356 events per patient-years. Since we expect an events rate of between 0.01 and 0.10 (1% to 10%), this prior provides only minimal information to the analysis. More biologically plausible prior distributions could also be selected. The level of information provided by this prior has been confirmed to be negligible by comparing to results from a frequentist analysis obtained on the N=407 BIOSCIENCE STEMI patients **(Supplementary Table 5)**. In addition, a Bayesian Cox model could have been used. **Supplementary Table 5** also shows that the usage of the Bayesian Poisson model instead of a (frequentist) Cox model also resulted in negligible differences.

8.2.2 Robust historical priors

Since only one historical trial is available, the posterior predictive distribution [36] cannot be obtained; here we use the posterior distribution of the parameter instead. The posterior of the log-rate (β) obtained from the historical data (N=407 patients) will serve as informative prior and its robust version will flow into analysis of the BIOSTEMI data. Historical data are analysed with the model given by eq. 1 – 3, which results in posterior distributions for β_T and β_C. These posterior

distributions have been confirmed to be approximately normal and thus it is sufficient to keep the mean and standard deviation as summary. For the primary endpoint TLF, the values are provided in **Supplementary Table 6**.

For the primary endpoint TLF, the historical priors are thus approximated by:

$$P_H(\beta_T) \sim Normal(\mu = -3.422, \tau = 7.036) \quad \text{(eq.4a)}$$

$$P_H(\beta_C) \sim Normal(\mu = -2.458, \tau = 16.796) \quad \text{(eq.4b)}$$

and the robust versions are obtained by weighted sum with the mixing weight W_R, where $W_R = 0.5$ is used for the present trial.

$$P_{ROB}(\beta_T|W_R) = (1 - W_R)\, P_H(\beta_T) + W_R\, P_V(\beta_T) \quad \text{(eq.5a)}$$

$$P_{ROB}(\beta_C|W_R) = (1 - W_R)\, P_H(\beta_C) + W_R\, P_V(\beta_C) \quad \text{(eq.5b)}$$

An overview of construction of RHPs is given in **Supplementary Figure 1**. As a guidance: With W_R = 0, the historical information gets full weight and is included as a standard informative prior. With W_R = 1, the historical information is completely ignored. With W_R = 0.5, the historical information is down-weighted if it is inconsistent with the current data.

The RHPs in equations 5a and 5b depict marginalised priors over two arm-specific selection indicators I_T and I_C that are Bernoulli distributed with a prior probability W_R=0.5. Thus, these indicators will be updated and their posterior means [E(I_T|Y) and E(I_C|Y)] will depict the new mixture proportions and whether there was an agreement between BIOSCIENCE and BIOSTEMI.

8.2.3 Analysis of the BIOSTEMI data and decision on superiority

The present trial data (N=1,250) are analysed with eq.1 and eq.2 and the priors from eq.5a and eq.5b. The parameter of interest is the rate ratio (RR) defined as rate (BP-SES)/rate (DP-EES). A graphical overview of analyses is given in **Supplementary Figure 2**. We will report the median of the posterior distribution of the RR and two-sided 95% credibility intervals (CrI). Superiority of BP-SES will be declared if the upper limit of this 95% CrI is ≤1. Equivalently, the posterior probability of the rate ratio being lower than 1 should be less than 97.5%, i.e., P (RR|Y<1) >97.5%.

8.3. Validation

8.3.1 Validation method

The frequentist operating characteristics (Type I error and power) of the model from section one were assessed under several scenarios obtained from Monte Carlo simulation. In all cases we assume a sample size at baseline of N=625 in each arm and 5% lost to follow-up at one year, thus the sample

size at FUP is N=594 in each arm. The binary decision of the superiority test is obtained by comparing the 95% CrI of the RR to a reference value of 1 with a two-sided alpha = 0.05. Type I error and power were estimated as the number of simulated trials where superiority is declared divided by the total number of simulated trials. Of note, Type I error values are obtained under the assumption that the RR = 1 in the new trial.

8.3.2 Results

Under the primary scenario and if there was no difference between the stents in the new population (**** in Supplementary Table 7**), the Type I error is 8.1% with the RHP. This is closer to the nominal value of 5% compared to the non-robust historical priors which have a Type I error of 11.4%. The vague prior achieves a Type I error of 5.1% which is very close to the nominal 5% but its power is considerably lower (54.9%) than the RHP (power = 81.8%). More results can be found in **Supplementary Table 7**.

8.3.3 Conclusion

The model with RHP offers a good trade-off between conservation of sufficient power if new and historical data are consistent vs. down-weighting of historical evidence that is inconsistent with new data. This conclusion also holds for the secondary scenarios of higher and lower overall incidence rates.

8.4. Sample size calculation

In the STEMI subgroup of the BIOSCIENCE trial, a rate ratio for BP-SES/DP-EES of 0.38 was found [22]. To be conservative, a less pronounced rate ratio of 0.60 was assumed for the BIOSTEMI trial and used for the present sample size calculation. The BIOSTEMI trial is powered for superiority on the primary endpoint at 1 year using the robust Bayesian approach that incorporates historical information as described above. Power calculation was based on a Monte Carlo simulation where information from the 407 BIOSCIENCE STEMI patients was included via RHPs and outcomes for the BIOSTEMI patients were simulated from a binomial distribution. Power was estimated as the number of simulated trials where superiority is declared divided by the total number of simulated trials. We assumed a rate ratio of the primary endpoint of 0.60 with an incidence rate of 4.2% in BP-SES and 7.0% in DP-EES. The dropout rate was assumed to be 5% at one year. With a 1:1 allocation ratio and a two-sided α=0.05 we found that enrolment of a total of 1,250 patients (625 per arm) in the BIOSTEMI trial would provide over 80% power **(Supplementary Table 7)**. Alternative methodologies could also be considered by placing a prior distribution over the treatment effect.

8.5. Pre-specified analyses

All subgroup analyses will be conducted using the same approach as the main analysis. Specifically, RHP will be constructed by analysing the primary endpoint in each subgroup of BIOSCIENCE STEMI

patients and, similarly to the primary endpoint analysis, a data-driven subgroup-specific down-weighting of the historical information will be allowed if the results of the BIOSCIENCE and BIOSTEMI trials disagree. These subgroup-specific RHP will be employed to analyse the data from BIOSTEMI patients. The difference of log-rate ratios will depict an interaction term. An interaction will be inferred if the 95% CrI of this term does not include 0.

9. SUPPLEMENTARY TABLES

Supplementary Table 1. Study organisation.

Principal investigators	Juan F. Iglesias, MD; Olivier Muller, MD, PhD; Thomas Pilgrim, MD.
Co-investigators	Eric Eeckhout, MD, PhD; Stephan Windecker, MD.
Steering committee	Juan F. Iglesias, MD (co-principal investigator); Olivier Muller, MD, PhD (co-principal investigator); Thomas Pilgrim, MD (co-principal investigator); Peter Jüni, MD (statistician); Eric Eeckhout, MD, PhD (co-investigator); Stephan Windecker, MD (co-investigator, chair).
Data co-ordination and analysis	Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland.
Site management and on-site data monitoring	Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland.
Central data monitoring	Clinical Trials Unit Bern, Bern University Hospital, Bern, Switzerland.
Data safety and monitoring board	None.
Sponsor	Department of Cardiology, Bern University Hospital, Bern, Switzerland.
Funding	Dedicated grant from Biotronik, Bülach, Switzerland.

Supplementary Table 2. Study design of trials contributing to the Bayesian analysis.

	BIOSCIENCE STEMI	BIOSTEMI
STUDY DESIGN	• Prospective • Multicentre • Randomised (1:1) • Orsiro BP-SES versus XIENCE™ (Prime/Xpedition) DP-EES	• Prospective • Multicentre • Randomised (1:1) • Orsiro BP-SES versus XIENCE™ (Xpedition/Alpine) DP-EES
LOCATION	Switzerland	Switzerland
STUDY ENDPOINTS	Target lesion failure* at 12 months	Target lesion failure* at 12 months
NUMBER OF SUBJECTS RANDOMISED	407 (Orsiro: 211, XIENCE: 196)	1,250 (Orsiro: 625, XIENCE: 625)
INCLUSION CRITERIA	1. Age ≥18 years; 2. Symptomatic coronary artery disease, including patients with chronic stable angina, silent ischaemia, and ACS (NSTEMI and STEMI); 3. ≥1 coronary artery stenosis >50% in a native coronary artery or a saphenous bypass graft that can be covered with one or multiple coronary stents; and 4. RVD ≥2.25 mm and ≤4.0 mm.	1. Age ≥18 years; 2. STEMI treated with PPCI within 24 hours of symptom onset; 3. ≥1 acute infarct artery target vessel with one or more coronary artery stenoses in a native coronary artery that can be covered with one or multiple coronary stents (no limit about the number of treated lesions, vessels, or complexity). 4. RVD ≥2.25 mm and ≤4.0 mm.
FOLLOW-UP	30 days, 1 year, 2 years, and 5 years: clinical	30 days, 1 year, and 2 years: clinical

* composite of cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularisation. ACS: acute coronary syndrome; BP-SES: biodegradable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; NSTEMI: non-ST-elevation myocardial

infarction; PPCI: primary percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction

Supplementary Table 3. Inclusion and exclusion criteria.

INCLUSION CRITERIA
1. Age ≥18 years; 2. ST-segment elevation myocardial infarction, defined as: • new, or presumed new, persistent ST-segment elevation ≥1 mm in ≥2 contiguous leads, or • new, or presumed new, left bundle branch block, or • new, or presumed new, horizontal or down-sloping ST-segment depression ≥1 mm in leads V_1-V_3; 3. Primary percutaneous coronary intervention within 24 hours of symptom onset; 4. ≥1 acute infarct artery target vessel with one or more coronary artery stenosis in a native coronary artery that can be covered with one or multiple coronary stents (no limit about the number of treated lesions, vessels, or complexity); 5. Reference vessel diameter ≥2.25 mm and ≤4.0 mm.
EXCLUSION CRITERIA
1. Known allergy to aspirin, ticagrelor, prasugrel, clopidogrel, sirolimus, everolimus or contrast media; 2. Inability to provide informed consent; 3. Currently participating in another trial before reaching the primary endpoint; 4. Planned surgery within 6 months of primary percutaneous coronary intervention, unless dual antiplatelet therapy could be maintained throughout the perisurgical period; 5. Non-cardiac comorbid conditions with life expectancy of less than 1 year; 6. Mechanical complication of acute myocardial infarction; 7. Acute myocardial infarction due to stent thrombosis.

Supplementary Table 4. Schedule of measurements and follow-up plan.

	INDEX ADMISSION			FOLLOW-UP		
	BASELINE	PROCEDURE	POST-PROCEDURE TO HOSPITAL DISCHARGE	30 DAYS ± 7 DAYS	1 YEAR ± 30 DAYS	2 YEARS ± 30 DAYS
Follow-up (type of contact)				Telephone interview	In-hospital visit	Telephone interview
Patient information, informed consent	X					
Inclusion/exclusion criteria	X					
Demographics	X					
Medical history	X			X	X	X
Physical examination	X				X	
Vital signs	X	X	X		X	
Complete blood count, blood chemistry, lipids, glucose[1]	X		X			
Cardiac biomarkers: troponin, CK, CK-MB[2]	X		X			
12-lead ECG[3]	X		X		X	
Pregnancy test[4]	X					
Randomisation		X				
Coronary angiography		X				
Assessment for primary endpoint					X	
Assessment for secondary endpoints		X		X	X	X
Concomitant medical therapy	X	X	X	X	X	X
Serious adverse events		X	X	X	X	X

[1] Within 24 hours prior to or immediately after the index procedure. [2] Troponin T/troponin I/high-sensitive troponin, whichever is clinical routine. CK and CK-MB are determined prior to percutaneous coronary intervention and every 6-8 hours until CK maximum level has been reached. [3] ECG prior to primary percutaneous coronary intervention, 24 hours post-procedure and at discharge. [4] Female of childbearing potential (age <50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy. CK: creatine kinase; CK-MB: creatine kinase-MB isoenzyme; ECG: electrocardiogram

Supplementary Table 5. Comparison of rate ratios and CIs obtained by frequentist and Bayesian methods with the vague prior given in eq.3.

	BP-SES	DP-EES	Mantel-Cox method with two-sided p-values from log-rank test		Bayesian Poisson model with prior normal (μ=0, τ=0.111)	
	N=211	N=196	Rate ratio [BP-SES/DP-EES]	*p*-value	Rate ratio [BP-SES/DP-EES]	*p*-value
	n (%)	n (%)	95% CI		95% CI	
All-cause death	6 (2.9)	9 (4.7)	0.62 (0.22-1.74)	0.36	0.62 (0.21 to 1.71)	0.36
Cardiac death	3 (1.5)	9 (4.7)	0.31 (0.08-1.14)	0.06	0.32 (0.08 to 1.05)	0.06
Reinfarction (any)	3 (1.5)	5 (2.6)	0.55 (0.13-2.32)	0.41	0.58 (0.13 to 2.20)	0.43
Q-wave	0 (0.0)	3 (1.6)	0.13 (0.01-2.50)	0.11	0.13 (0.00 to 1.26)	0.08
Non-Q-wave	3 (1.5)	2 (1.1)	1.40 (0.23-8.42)	0.71	1.34 (0.25 to 8.26)	0.73
Target vessel reinfarction	1 (0.5)	5 (2.6)	0.18 (0.02-1.57)	0.08	0.23 (0.03 to 1.19)	0.08
Q-wave	0 (0.0)	3 (1.6)	0.13 (0.01-2.50)	0.11	0.13 (0.00 to 1.30)	0.09
Non-Q-wave	1 (0.5)	2 (1.1)	0.47 (0.04-5.12)	0.52	0.54 (0.05 to 4.10)	0.54
Cardiac death or MI	6 (2.9)	14 (7.3)	0.39 (0.15-1.03)	0.05	0.40 (0.15 to 0.99)	0.05
Any repeat revascularisation	10 (4.9)	9 (4.7)	1.02 (0.41-2.51)	0.96	1.04 (0.42 to 2.58)	0.94
Any TLR	3 (1.5)	5 (2.7)	0.55 (0.13-2.31)	0.41	0.57 (0.13 to 2.21)	0.42
Clinically indicated TLR	3 (1.5)	4 (2.1)	0.69 (0.16-3.10)	0.63	0.71 (0.16 to 2.99)	0.64
Clinically indicated TVR	6 (3.0)	5 (2.7)	1.12 (0.34-3.66)	0.86	1.12 (0.34 to 3.82)	0.86
Any TVR	6 (3.0)	6 (3.2)	0.92 (0.30-2.87)	0.89	0.93 (0.30 to 2.93)	0.90
Clinically indicated TLR or surgical TVR	3 (1.5)	5 (2.7)	0.55 (0.13-2.32)	0.41	0.58 (0.13 to 2.25)	0.43
Cerebrovascular event	4 (2.0)	4 (2.1)	0.93 (0.23-3.71)	0.91	0.93 (0.23 to 3.75)	0.92
Target lesion failure	7 (3.4)	17 (8.8)	0.38 (0.16-0.91)	0.02	0.39 (0.15 to 0.89)	0.02
Target vessel failure	10 (4.9)	18 (9.3)	0.51 (0.24-1.11)	0.08	0.52 (0.24 to 1.09)	0.08
Death, MI, repeat revascularisation	17 (8.3)	19 (9.8)	0.82 (0.43-1.59)	0.56	0.83 (0.43 to 1.60)	0.57

BP-SES: biodegradable polymer sirolimus-eluting stent; CI: confidence interval; DP-EES: durable polymer everolimus-eluting stent; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation

Supplementary Table 6. Gaussian summary of the posterior log-rate (β) of TLF obtained from the historical data, which will serve as informative prior for construction of the robust historical priors. The precision $\tau = 1/\sigma^2$.

TRIAL ARM	exp(μ) = event rate	μ	σ	T
BP-SES (T)	3.26%	-3.422	0.377	7.036
DP-EES (C)	8.56%	-2.458	0.244	16.796

BP-SES: biodegradable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent

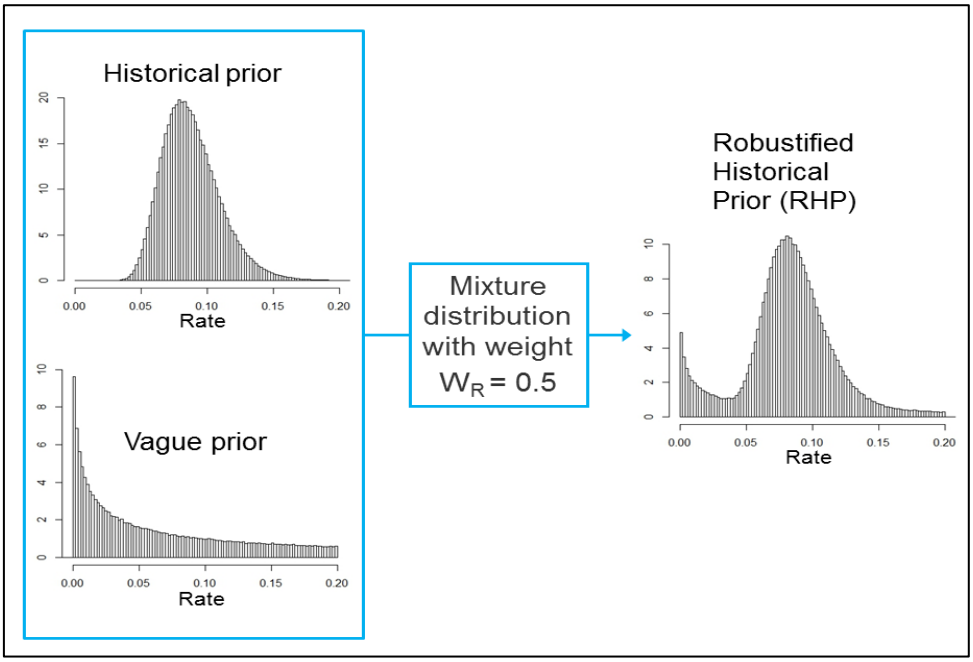
Supplementary Table 7. Type I error and power obtained by Monte Carlo simulation under several scenarios for the event rate expected in the new BIOSTEMI trial and for values of the weighting parameter.

Rate (BP-SES)	Rate (DP-EES)	Rate ratio		Vague priors	Robust historical priors	Historical priors	FE meta-analysis
				W_R=1.0	W_R=0.5	W_R=0.0	
Secondary scenario: overall incidence rate is higher							
0.060	0.100	0.6	Power (%)	70.2	81.6	88.7	91.8
0.100	0.100	1.0	Type I error (%)	3.6	3.6	5.9	10.8
Primary scenario							
0.042	**0.070**	**0.6**	***Power (%)**	**54.9**	**81.8**	**87.3**	**86.5**
0.070	**0.070**	**1.0**	****Type I error (%)**	**5.1**	**8.1**	**11.4**	**13.3**
Secondary scenario: overall incidence rate is lower							
0.034	0.056	0.6	Power (%)	44.8	71.3	86.5	81.7
0.056	0.056	1.0	Type I error (%)	4.6	11.3	16.4	15.0

Each scenario (row) is based on 2,000 Monte Carlo iterations. *RR=0.6 is the scenario of the pre-specified sample size calculation. **RR=1.0 is the null hypothesis that both stents perform equally. BP-SES: biodegradable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent; FE: fixed effects

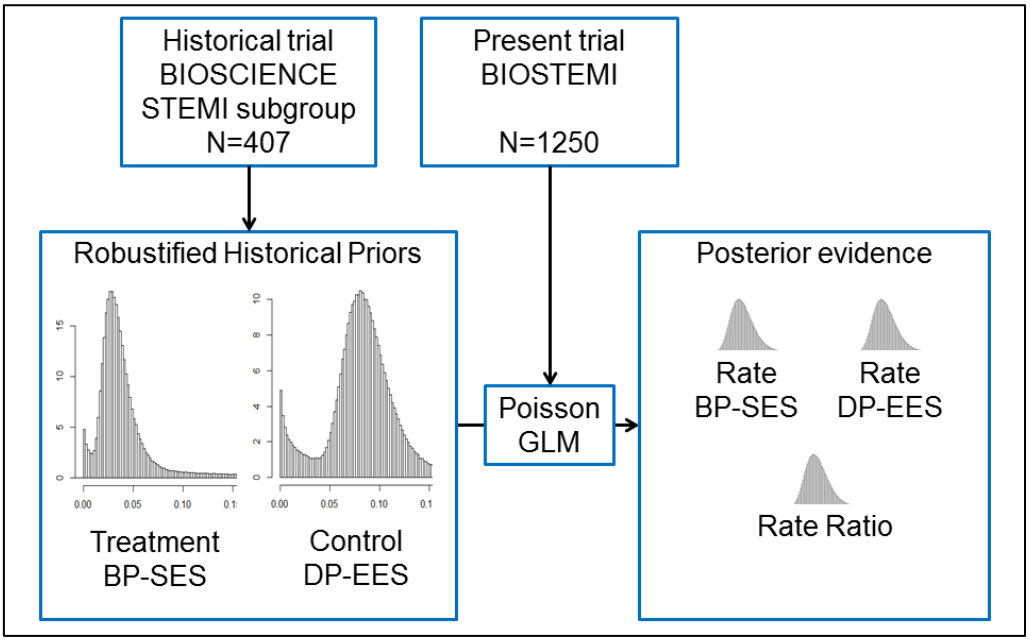
10. SUPPLEMENTARY FIGURES

Supplementary Figure 1. Graphical description of how the robust historical priors are constructed.



Exemplified here with the historical event rate from the DP-EES arm. Distributions are shown in the rate scale.

Supplementary Figure 2. Graphical description of how the primary endpoint and secondary endpoints will be analysed.



Exemplified here with the primary endpoint target lesion failure. Distributions are shown in the rate scale. BP-SES: biodegradable polymer sirolimus-eluting stent; DP-EES: durable polymer everolimus-eluting stent