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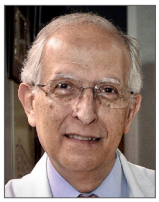
Randomised evaluation of a novel biodegradable polymer-based sirolimus-eluting stent in ST-segment elevation myocardial infarction: the MASTER study



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KEYWORDS

- bare metal stent
- drug-eluting stent
- STEMI

Abstract

Aims: The MASTER study was designed to compare the performance of a new biodegradable polymer sirolimus-eluting stent (BP-SES) with a bare metal stent (BMS) in patients with ST-segment elevation myocardial infarction (STEMI).

Methods and results: The study was a prospective, randomised (3:1), controlled, single-blind multicentre trial that enrolled 500 STEMI patients within 24 hours of symptom onset during 2013-2015. Three hundred and seventy-five patients were treated with BP-SES and 125 with BMS. One hundred and four (104) randomised patients underwent angiographic follow-up at six months. The primary clinical endpoint was target vessel failure (TVF), defined as cardiac death, MI not clearly attributable to a non-target vessel, or clinically driven target vessel revascularisation (TVR) at 12 months. The primary angiographic endpoint was in-stent late lumen loss (LLL) at six months in the angiographic cohort. The major secondary endpoint for safety was a composite of all-cause death, recurrent MI, unplanned infarct-related artery revascularisation, stroke, definite stent thrombosis (ST) or major bleeding at one month. At 12 months, TVF had occurred in 6.1% of BP-SES and 14.4% of BMS patients ($p_{non\text{-}inferiority}$=0.0004), mainly driven by a higher rate of repeat revascularisation in BMS patients. The safety endpoint occurred in 3.5% of BP-SES and 7.2% of BMS patients (p=0.127). In-stent LLL demonstrated the superiority (p=0.0125) of BP-SES (0.09±0.43 mm) over BMS (0.79±0.67 mm).

Conclusions: The study showed clinical non-inferiority and angiographic superiority of BP-SES versus a comparator BMS, suggesting that this novel DES may be a potential treatment option in STEMI. Clinical Trials Registration: https://clinicaltrials.gov/NCT02828683

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Abbreviations

BMS	bare metal stent
BP-BES	biodegradable polymer biolimus-eluting stent
BP-DES	biodegradable polymer drug-eluting stent
BP-SES	biodegradable polymer sirolimus-eluting stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
Co-Cr	cobalt-chromium
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DP-DES	durable polymer drug-eluting stent
DP-EES	durable polymer everolimus-eluting stent
IRA	infarct-related artery
LLL	late lumen loss
MLD	minimum lumen diameter
POCE	patient-oriented composite endpoint
pPCI	primary percutaneous coronary intervention
QCA	quantitative coronary angiography
RVD	reference vessel diameter
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
TIA	transient ischaemic attack
TLF	target lesion failure
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation

Introduction

In patients with ST-segment elevation myocardial infarction (STEMI), the use of drug-eluting stents (DES) has been associated with favourable outcomes compared with bare metal stents (BMS)[1,2]. However, stent platform design and polymer technology seem to impact on the clinical outcomes of different DES, as evidenced by the reduced rates of stent thrombosis (ST) with the newer-generation biodegradable polymer (BP) compared with the first generation of durable polymer (DP) DES[3]. So far, head-to-head randomised comparisons between newer-generation DP-DES versus BP-DES have revealed no significant differences in clinical outcomes, albeit with an inclusion of a mixed population of patients, with a limited number of STEMI[4-9]. As STEMI patients have a higher risk of repeat ischaemic events, biodegradable polymer DES may reduce long-term stent-related complications[10] while providing antiproliferative effects with drug elution[11]. Despite the diminishing role of BMS in contemporary practice, their use has been maintained in specific patient subsets, including STEMI[12]. The study presented here aimed to evaluate the outcomes of a new DES, coated with a sirolimus-eluting biodegradable polymer (BP-SES), designed to resorb within three to four months after implantation, thus potentially improving vessel healing and consequently long-term clinical outcomes[8,13] in STEMI patients undergoing primary percutaneous coronary intervention (pPCI).

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Methods

STUDY POPULATION

This was a prospective, single-blind, multicentre, randomised and controlled clinical study enrolling 500 STEMI patients at 12 European sites and one site in Brazil. STEMI was defined as chest pain >20 minutes and ST-segment elevation of >1 mm in >2 contiguous leads, or (presumably new) left bundle branch block, or true posterior MI with ST depression of >1 mm in >2 contiguous anterior leads on ECG. Primary PCI was performed within 24 hours of symptom onset. At least one acute infarct-related artery (IRA) had to be identified as the target vessel with one or more coronary artery stenoses in a 2.5-4.0 mm native coronary artery which could be treated with one or multiple stents. Key exclusion criteria are listed in **Supplementary Appendix 1**.

The study was conducted in compliance with the Declaration of Helsinki and an ethics review committee at each participating site approved the study protocol. Written informed consent was obtained from each patient.

RANDOMISATION

Patients were randomly assigned (3:1) to undergo pPCI with either BP-SES or BMS. Randomisation was performed at each site using a sealed envelope system.

STUDY ENDPOINTS

The primary clinical endpoint was target vessel failure (TVF), defined as cardiac death, MI not clearly attributable to a non-target vessel, or clinically driven target vessel revascularisation (TVR) at 12 months. The primary pre-specified angiographic endpoint was in-stent late lumen loss (LLL) at six months post stent implantation in a subset of 104 patients undergoing angiographic follow-up. The major safety secondary endpoint was the composite of all-cause death, recurrent MI, unplanned IRA revascularisation, stroke, definite ST or major bleeding at one month. Other secondary endpoints included target lesion failure (TLF), defined as the composite of cardiac death, MI not clearly attributable to a non-target vessel and clinically driven target lesion revascularisation (TLR) up to 30 days, 6 months, 12 months and annually thereafter up to 3 years. Stent thrombosis was adjudicated according to the Academic Research Consortium definition. Bleeding endpoints were adjudicated according to the Bleeding Academic Research Consortium definition.

A more detailed description of the study endpoints, treatment procedure, blinding and monitoring process and quantitative coronary angiography can be found in **Supplementary Appendix 1**.

DEVICE DESCRIPTION

The Kaname® BMS stent (Terumo Corporation, Tokyo, Japan) consists of a thin-strut cobalt-chromium (Co-Cr) L605 mesh tube, with an open-cell design. For a 3.0 mm stent, the metallic surface area (nominal) is 15% with a strut thickness of 80 µm and a crossing profile of 0.041". The available stent lengths were 9, 12, 15, 18, 24, and 28 mm. The Ultimaster® (Terumo Corporation,

Tokyo, Japan) consists of the Kaname stent platform, abluminally coated with poly D,L-lactic acid-polycaprolactone (PDLLA-PCL) as a carrier of the immunosuppressant drug sirolimus (3.9 µg/mm stent length). The purpose of the gradient coating is to reduce potential cracking and delamination of the polymer. The drug release profile allows an initial stronger release immediately following stent implantation. Then the drug is released continuously until the polymer bioabsorption is completed within three to four months. For a stent size of 3.0×15 mm, the median maximum concentration (Cmax) was 36.8 pg/mL (range between 22.9 and 41.5 pg/mL), according to the previously published detailed information on the pharmacokinetic profile[14].

SAMPLE SIZE AND STATISTICAL ANALYSIS

Sample size calculation for the primary endpoint (TVF) at 12 months was based on expected TVF rates of 4.3% and 8.7% at 12 months in the BP-SES and BMS arms, respectively[1]. The non-inferiority margin was set at 3% (absolute %TVF for BP-SES no more than 3% higher than BMS) with a one-sided alpha error of 5% and a power of 90%. This required a total of 492 (123 BMS and 369 BP-SES) patients to be randomised. For the primary angiographic efficacy endpoint (in-stent LLL at six months), the following assumptions were used: LLL in the BP-SES and BMS arms was expected to be 0.04±0.35 and 0.80±0.43 mm, respectively. Based on a superiority margin of 0.40 mm with a two-sided alpha error of 5% and a power of 90%, the sample size required was 80 patients (20 BMS and 60 BP-SES). The expected dropout rate for the angiographic follow-up subgroup was 20%.

The primary statistical analysis was performed on the intention-to-treat population. For the comparison of frequencies and means, χ^2 statistics or Fisher's exact test and unpaired t-test (with F-test) or non-parametric test (Mann-Whitney or Kruskal-Wallis test for multiple groups comparison) were used, respectively.

Results

Between October 2013 and March 2015, 500 STEMI patients were enrolled, 375 of whom were assigned to undergo pPCI with implantation of BP-SES and 125 were treated with BMS; 98.4% (n=495) completed the 12-month clinical follow-up **(Figure 1)**. Overall, mean age was 60±11 years, 81% were men and 14.8% of patients had diabetes. There were no significant differences in baseline clinical characteristics between the two study groups **(Table 1)**. Time from symptom onset to first balloon inflation was 286±221 minutes and thrombectomy by manual aspiration was performed in 36% of the overall patient population, with no significant differences between the study groups **(Table 1)**. The DAPT rate did not differ between the groups **(Supplementary Table 1)**.

While most of the procedural characteristics did not differ significantly between patients receiving BP-SES vs. BMS, the number of implanted stents (1.5±0.9 vs. 1.3±0.6, p=0.039), as well as the mean implanted stent length (30±17 mm vs. 26±12 mm, p=0.012) were significantly greater in the BP-SES group. Staged PCI was performed in 81 patients in the BP-SES group and 16 patients in

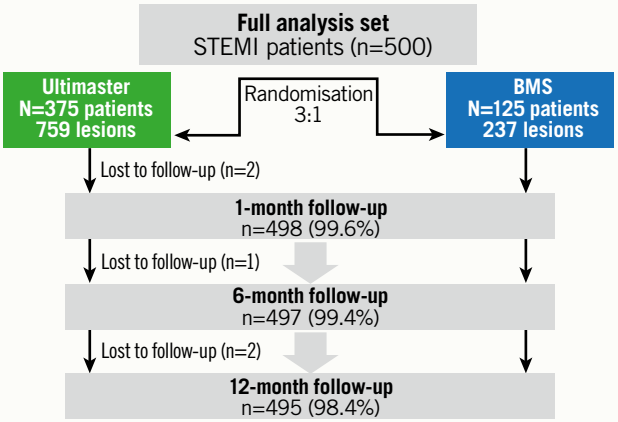

Figure 1. *Study flow chart: enrolment, randomisation and follow-up.*

Table 1. Baseline characteristics.

Variable	BP-SES	BMS	*p*-value
Number of patients	375	125	
Age, years (mean±SD)	60±11	62±11	0.23
Body mass index, kg/m^2 (mean±SD)	27.4±3.9	27.5±4.3	0.77
Male gender, %	81.1	80.1	0.79
Current smoker, %	50.7	48.0	0.68
Dyslipidaemia, %	39.0	36.0	0.60
Arterial hypertension, %	53.6	51.2	0.68
Family history of CAD, %	34.7	32.8	0.74
Previous PCI, %	1.3	3.2	0.24
Previous CABG, %	0.3	0	0.99
Previous cerebrovascular accident (stroke/TIA), %	3.2	3.2	0.99
Diabetes mellitus, %	15.5	12.8	0.56
Prior myocardial infarction, %	3.5	3.2	0.99
Renal disease, %	1.9	0	0.20
Clinical status at admission			
Symptom to balloon time, minutes (mean±SD)	294±223	263±213	0.20
Door to balloon time, minutes (mean±SD)	74±86	70±123	0.76
Time to staged procedure, days (mean±SD)	18±16	22±18	0.37
Medications			
Dual antiplatelet therapy on admission, %	1.6	4.8	0.08
Aspirin	16.8	17.6	0.89
Clopidogrel	1.9	5.6	0.05
Dual antiplatelet therapy pre-procedure, %	97.2	98.4	0.74
Aspirin	96.8	96.8	0.99
Clopidogrel	91.4	91.8	0.99
Prasugrel	4.4	4.1	0.99
Ticagrelor	3.1	2.5	0.99
GP IIb/IIIa inhibitor	26.1	18.2	0.09
Bivalirudin	3.1	2.5	0.99

BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack

the BMS group. In total (initial and staged procedure combined), there were more (p=0.003) stents implanted in patients assigned to the BP-SES group (1.8±1.2) versus the BMS group (1.5±0.9) **(Supplementary Table 2)**.

QUANTITATIVE CORONARY ANGIOGRAPHY

Figure 2 shows the patient flow in the angiographic subset. Pre-intervention measurements showed similar lesion length, minimum lumen diameter (MLD), %DS and reference vessel diameter (RVD) in both groups **(Table 2)**. Post-procedural QCA revealed similar acute luminal gain and residual stenosis after implantation of BP-SES and BMS. At six months, in-stent MLD was larger in BP-SES vs. BMS patients, resulting in significantly lower LLL in BP-SES (0.09±0.43 vs. 0.79±0.67 mm, $p_{superiority}$=0.0125), hence meeting the primary angiographic efficacy endpoint of the study **(Table 2)**.

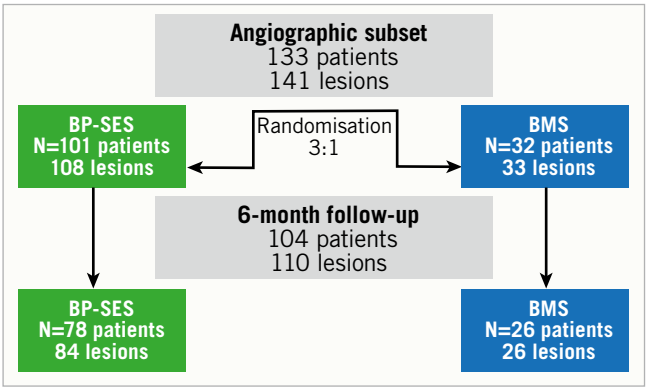

Figure 2. *Patient flow in the angiographic subset.*

Table 2. Quantitative coronary angiography before and after primary percutaneous coronary intervention.

Variable		BP-SES	BMS	*p*-value
Pre-procedure				
Patients, n		101	32	
Lesions, n		108	33	
RVD, pre- (mm) in-lesion		2.68±0.54	2.47±0.58	0.34
MLD, pre- (mm) in-lesion		0.22±0.40	0.22±0.34	0.93
% DS, pre- in-segment		92.16±13.10	91.39±12.92	0.77
Post-procedure				
Patients, n		101	32	
Lesions, n		108	33	
MLD, mm	in-stent	2.49±0.43	2.51±0.37	0.84
	in-segment	2.14±0.56	2.17±0.38	0.78
% DS	in-stent	10.22±7.43	12.21±7.88	0.19
	in-segment	20.53±10.88	21.85±9.24	0.53
Acute gain (mm)	in-stent	2.27±0.54	2.29±0.49	0.82
	in-segment	1.92±0.64	1.95±0.52	0.81
Six months after procedure				
Patients, n		78	26	
Lesions, n		84	26	
MLD, mm	in-stent	2.44±0.54	1.61±0.63	<0.001
	in-segment	2.20±0.55	1.56±0.56	<0.001
% DS	in-stent	15.1±14.9	42.2±23.0	<0.001
	in-segment	22.17±15.05	42.85±22.43	<0.001
Late lumen loss (mm)		0.09±0.43	0.79±0.67	0.0125

BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stent; MLD: minimum lumen diameter; RVD: reference vessel diameter

CLINICAL OUTCOMES

At 12 months, BP-SES was non-inferior to BMS with regard to TVF (the primary efficacy endpoint), which occurred in 6.1% vs. 14.4% of patients, respectively, $p_{non\text{-}inferiority}$=0.0004 **(Table 3, Figure 3)**. This result was predominantly driven by a significant reduction in the rates of TLR/TVR in BP-SES-treated over BMS-treated patients **(Table 3)**.

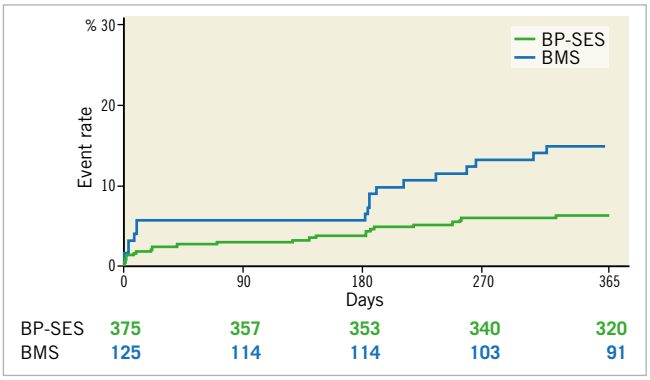

Figure 3. *Kaplan-Meier curves of target vessel failure at 12 months.*

At 30 days, the composite safety endpoint (all-cause death, recurrent MI, unplanned IRA revascularisation, stroke, definite ST or major bleeding) and the individual components did not differ between the two study groups **(Table 3)**.

Discussion

The main findings of this study comparing a novel BP-SES to a comparator BMS in STEMI patients undergoing pPCI are as follows: 1) this novel DES showed non-inferiority with regard to TVF at 12 months versus BMS, coupled with a reduction in clinically driven repeat revascularisation; 2) in the angiographic subgroup, BP-SES was associated with a significant decrease in late lumen loss compared with BMS, which may explain the significantly lower rate of clinically driven TLR in patients treated with BP-SES; and 3) the cumulative rate of all-cause death, recurrent MI, unplanned IRA revascularisation, stroke, definite ST or major bleeding at one month did not differ between the groups.

The results of recent studies support the hypothesis that a new-generation thin-strut DES with a bioresorbable polymer may be a valuable treatment option for STEMI patients[10,15]. Although two previous studies have already investigated the effects of

Table 3. Clinical endpoints at 30 days and 12 months.

Variable	BP-SES	BMS	*p*-value
Patients	375	125	
30 days			
All-cause death, % (n)	2.4 (9)	4.8 (6)	0.22
All myocardial infarction, % (n)	0.8 (3)	1.6 (2)	0.60
All unplanned IRA revascularisation, % (n)	0.8 (3)	3.2 (4)	0.069
Stroke, % (n)	0.53 (2)	0.0 (0)	1.00
Major bleeding, % (n)	0.8 (3)	0.0 (0)	0.58
Definite stent thrombosis, % (n)	0.8 (3)	3.2 (4)	0.069
Composite (all-cause death, recurrent MI, unplanned IRA revascularisation, stroke, definite ST or major bleeding), % (n)	3.5 (13)	7.2 (9)	0.13
12 months			
All-cause death, % (n)	4.8 (18)	5.6 (7)	0.81
Cardiac death, % (n)	3.2 (12)	4.0 (5)	0.78
MI not clearly attributable to a non-target vessel, % (n)	0.8 (3)	1.6 (2)	0.60
MI clearly attributable to a non-target vessel, % (n)	0.27 (1)	0.0 (0)	1.00
All clinically driven revascularisation, % (n)	4.8 (18)	13.6 (17)	0.002
Clinically driven TLR, % (n)	2.7 (10)	11.2 (14)	<0.001
Clinically driven TVR, % (n)	3.2 (12)	11.2 (14)	0.0016
All unplanned IRA revascularisation, % (n)	3.2 (12)	12.8 (16)	0.0002
Definite+probable ST, % (n)	1.9 (7)	4.8 (6)	0.1000
Primary efficacy endpoint: TVF, % (n)	6.1 (23)	14.4 (18)	<0.001

BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stent; IRA: infarct-related artery; MI: myocardial infarction; TLR: target lesion revascularisation; TVF: target vessel failure; TVR: target vessel revascularisation; ST: stent thrombosis

newer-generation DES in STEMI patients[1,2], to the best of our knowledge this is the first randomised study to compare the results of a thin-strut DES with biodegradable polymer applied abluminally in a gradient fashion, versus a BMS.

The everolimus-eluting stent versus bare metal stent in ST-segment elevation myocardial infarction (EXAMINATION) trial compared a thin-strut (81 µm) DP everolimus-eluting stent (DP-EES) with a BMS. The study did not meet its primary endpoint, defined as a reduction in the patient-oriented composite endpoint (POCE) at one year, which consisted of any death, any reinfarction and any revascularisation[2]. The rate of TLR up to one year in our study in BP-SES patients (2.7%) was similar to that of DP-EES in the EXAMINATION trial (2.1%), and significantly lower compared to BMS in both trials[2].

The effect of a biodegradable polymer DES vs. BMS on cardiovascular events among patients with MI was also tested in the COMFORTABLE AMI trial, that compared a BP biolimus-eluting stent (BP-BES) with 120 µm strut thickness against a corresponding BMS[1]. The study did meet its primary endpoint as there was a 50% reduction in the combined one-year occurrence of cardiac death, target vessel-related reinfarction, and ischaemia-driven TLR in patients treated with BP-BES. Indeed, the TLR rate in patients treated with BP-BES was significantly lower than that in patients receiving BMS (2.0% vs. 6.2%, p<0.001), and was comparable to the rate found in our BP-SES patients. In our study, the low TLR rate was paralleled by an in-stent LLL of 0.09±0.43 mm at six-month angiographic follow-up. This was lower compared with the previously reported in-stent LLL of 0.19±0.35 mm[16] and 0.14±0.36 mm[7] after DP-EES implantation, though assessed at a longer (eight to nine months) angiographic follow-up. A pooled analysis of the EXAMINATION and COMFORTABLE AMI trials showed that treatment with DES (DP-EES or BP-BES) was an independent predictor of a lower risk of definite ST (OR 0.35, 95% CI: 0.16-0.74)[17]. In our study, BP-SES showed a tendency towards lower definite/probable ST rates **(Table 3)**, with most of the observed BMS-related ST occurring in the early post-implantation period **(Supplementary Table 3)**. Although underpowered for this individual endpoint, due to the non-inferiority trial design based on the occurrence of TVF, the tendency to reduce the ST rate may be an indicator of improved prognosis for new-generation DES over BMS in STEMI. As permanent polymer, particularly in first-generation DES, has been associated with impaired vascular healing that may result in increased risk of long-term ST and restenosis[18], bioresorbable polymer technology may play a role in minimising the risk of very late ST. However, it should be noted that the observed tendency of BP-SES to reduce the risk of definite/probable ST in the present study was also found in the EXAMINATION trial, indicating that not all permanent polymers are equal in terms of ST risk. In the EXAMINATION trial, the implantation of DP-EES was associated with a significant reduction of definite or probable ST, compared with BMS, at one year (0.9% vs. 2.5%, p=0.02)[2]. Nevertheless, replacing a permanent polymer layer with a polymer coating that degrades gradually as the drug is released over time (the DES technology tested in the current study)[13], thus resulting in a stent surface similar to that of a BMS, has less potential to provide a chronic inflammatory stimulus. The outcomes of the present study seem to support the premise that this type of BP-DES may combine an efficacious antiproliferative effect, as evidenced by the significant TLR and LLL reduction, with an improved safety profile provided by the stent surface and the vessel wall that are free from a polymer. Longer follow-up (five years) will be necessary to confirm this argument further.

The stent thrombosis rate in the present study was slightly higher than in the EXAMINATION and COMFORTABLE AMI studies. However, it is important to note important different aspects between the studies. In the MASTER trial, the studied population was treated with more stents (1.4 vs. 1.1 in the other two studies), longer segments were covered (37 vs. 23 mm), patients were treated less frequently with IIb/IIIa inhibitors (approximately 24% vs. >45%) and less potent antiplatelet regimens were used,

compared to the other two trials (mostly clopidogrel and aspirin vs. prasugrel and aspirin). Also, the reported average reference vessel diameter in our study may have been smaller **(Table 2)** compared to previous studies in STEMI patients. All these things considered, comparisons of the event rates across the studies should be interpreted with caution.

Study limitations

This study has several limitations. First, the study was not powered for individual hard clinical endpoints, and the single-blind design limits robustness. Second, most of the patients were treated with clopidogrel which may not reflect the current standard of care in STEMI patients. Third, a possible imbalance in lesion complexity may have contributed to a higher rate of ST in the BMS group. Fourth, the TLR rate may have, at least in part, been impacted by the six-month angiographic follow-up. However, BMS was associated with a numerically higher rate of TLR also in patients without follow-up angiography **(Supplementary Table 4)**. Fifth, both stroke and major bleeding, as pre-specified parts of the composite safety endpoint, occurred infrequently (together only five events, all in the BP-SES group). When stroke and major bleeding are excluded, BP-SES is associated with a statistically lower rate of the composite of all-cause death, recurrent MI, unplanned IRA revascularisation, or definite ST, as compared with BMS (2.9% vs. 7.2%, respectively, p=0.04). Sixth, despite randomisation, there was an imbalance regarding the staged procedures, in favour of the BP-SES group. Seventh, the protocol allowed the use of non-study stents in staged procedures, so that four patients assigned to a Kaname BMS at index procedure received DES during staged procedures and two patients assigned to an Ulitmaster DES received either BMS or other DES during staged procedures. Importantly, none of these patients had ischaemic events in the follow-up. Finally, longer-term follow-up should be awaited to rule out very late risks with the novel DES technology presented here.

Conclusions

New-generation thin-strut BP-SES exhibited a comparable safety profile to BMS with identical design up to one-year follow-up in STEMI patients. Moreover, lower LLL translated into significantly reduced TVF at 12 months, driven mainly by the TLR reduction. Together, these findings may suggest BP-SES to be another option in percutaneous treatment of patients with STEMI.

Impact on daily practice

Previous research has shown the potential of new-generation DES to improve outcomes over BMS in STEMI patients. Novel technology, including biodegradable polymer DES, may lead to further improvements in the outcomes of patients with STEMI. The MASTER randomised study demonstrated favourable clinical and angiographic results of BP-SES versus a comparator BMS up to 12-month follow-up, indicating that this novel DES may be another treatment option in STEMI.

Funding

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Conflict of interest statement

H. Garcia-Garcia declares consultancy fees from Terumo (minor). C. Tamburino reports personal fees from Abbott, personal fees from Medtronic, Stentys, Symetis, and St. Jude, outside the submitted work. M. Zivkovic reports other from Clinical Center Nis during the conduct of the study and is a clinical investigator for the MASTER trial. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Table 1. The rates of dual antiplatelet therapy in patients treated with BP-SES vs. BMS.

Supplementary Table 2. Procedure and lesion characteristics.

Supplementary Table 3. Occurrence of stent thrombosis.

Supplementary Table 4. The rates of TLR in patients treated with BP-SES vs. BMS, in the subgroup of patients with and without angiographic follow-up at six months.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/151st_issue/323

Supplementary data

Supplementary Appendix 1. Methods

Study population

Key exclusion criteria were: women of childbearing potential who had not undergone tubal ligation, oophorectomy or hysterectomy; known intolerance to aspirin, clopidogrel, heparin, bivalirudin, cobalt, chromium, nickel, sirolimus or contrast material; mechanical complications of acute MI; acute MI secondary to stent thrombosis (ST); previously stented IRA; planned surgery within 6 months of PCI unless dual antiplatelet therapy (DAPT) was maintained throughout the peri-surgical period; patients with non-cardiac comorbidities with life expectancy <1 year or that may result in protocol non-compliance; history of bleeding diathesis or known coagulopathy; and use of oral anticoagulants.

Study endpoints

Cardiac death was defined as any death due to proximate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment.

Myocardial infarction (MI) was defined either as the development of pathological Q-waves in at least two contiguous leads with or without elevated cardiac enzymes or, in the absence of pathological Q-waves, as an elevation in creatinine kinase levels to greater than twice the upper limit of normal in the presence of an elevated level of CK-MB fraction or troponin.

Stroke (cerebrovascular accident [CVA]) was defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as haemorrhage, embolism, thrombosis, or rupturing aneurysm that persists >24 hours.

Target lesion revascularisation and target vessel revascularisation were assessed as clinically driven based on the following definitions:

- a positive history of recurrent angina pectoris, presumably related to the target vessel;

- objective signs of ischaemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;

- abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve, fractional flow reserve);

- diameter stenosis ≥70% (by core lab QCA assessment) even in the absence of the above-mentioned ischaemic signs or symptoms.

An independent clinical events committee (CEC) adjudicated all rePCI events and assessed whether they were clinically driven.

Treatment procedure

Lesion preparation was left to the discretion of the investigators including, but not limited to, predilation, use of manual thrombectomy, optimisation of post-stenting result and adjuvant periprocedural pharmacological treatment. In case of non-culprit lesion PCI, staged procedures were to be performed within six weeks of the index procedure using the assigned study stent. A staged procedure performed more than six weeks after hospital discharge following pPCI was considered a reintervention (adverse event) and not a planned staged procedure. Angina status assessment, ECG and cardiac enzymes (CK-MB or troponin at least 6-12 hours after PCI) were mandatory parts of post-procedural evaluation. Patients were encouraged to continue DAPT for a period of at least six months. Any interruption of DAPT was required to be documented in the patient record and case report forms, including the date, reason and duration of interruption.

Quantitative coronary angiography

Angiograms obtained at baseline and at six-month follow-up in patients included in the angiographic subgroup were assessed by an independent core laboratory (CERC, Paris, France). At baseline, the main angiographic parameters were minimum lumen diameter (MLD) before and after the procedure, diameter stenosis percentage (%DS) and acute gain (change in MLD from baseline to the final angiogram). At six-month follow-up, the following parameters were calculated: angiographic binary restenosis rate (≥50% DS), MLD, %DS and in-stent and in-segment late lumen loss, which was expressed as the difference in

MLD between measurements at the end of the procedure and at follow-up. Commercially validated software CAAS Workstation version 5.10 (Pie Medical Imaging BV, Maastricht, the Netherlands) was used for all analyses.

Clinical follow-up and data monitoring

Monitoring was conducted by the sponsor or sponsor designee (i.e., local clinical research organisation) in all centres and data verification including that of device malfunctions and serious adverse events was performed. An independent clinical events committee (CEC) and data monitoring committee (DMC) comprised of interventional cardiologists adjudicated all clinical events and clinical endpoints based on protocol definitions and assessed the safety of the study. The CEC/DMC members were not participants in the study.

Blinding

Members of the Steering Committee, DMC, CEC and core laboratory were blinded to patient assignment, whereas study personnel and investigators were not. Patients were not informed of the type of device they were treated with, unless they specifically requested.

Supplementary Table 1. The rates of dual antiplatelet therapy in patients treated with BP-SES vs. BMS.

	BP-SES	**BMS**	***p*-value**
DAPT at 1 month	98.4	96.7	0.26
DAPT at 6 months	96.7	94.1	0.21
DAPT at 12 months	79.7	79.7	0.99

BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stent

Supplementary Table 2. Procedure and lesion characteristics.

Variable	BP-SES	BMS	*p*-value
Initial procedure			
Lesions, n	443	149	
Target vessel, %			0.51
RCA	48.2	44.3	
LAD	36.7	39.6	
LCX	14.3	16.1	
LM	0.7	0.0	
Bifurcation lesion, %	7.2	2.8	0.07
Lesion preparation			
Balloon dilatation, %	50.0	48.3	0.78
Manual thrombectomy, %	35.5	37.6	0.69
Post-dilatation, %	32.2	28.4	0.41
TIMI flow post procedure, %			
0	0.91	0.67	0.99
1	0.45	0.67	0.99
2	3.0	4.03	0.59
3	95.7	94.6	0.65
Stents implanted per patient, mean±SD	1.47±0.87	1.33±0.58	0.04
Total implanted stent length (mm), mean±SD	29.7±17.2	26.1±11.9	0.012
Stent diameter (per stent), %			0.49
2.5 mm	19.4	16.3	
3.0 mm	50.9	53.0	
3.5 mm	5.4	4.2	
4.0 mm	24.3	26.5	
Staged procedure			
Patients, n	81	16	
Lesions, n	111	22	
Stents implanted per patient, mean±SD	1.63±0.94	1.50±0.97	0.62
Cumulative, initial + staged			
Lesions, mean±SD	1.48±0.82	1.37±0.82	0.19
Stents implanted per patient, mean±SD	1.82±1.23	1.52±0.89	0.003

BMS: bare metal stent; BP-SES biodegradable polymer sirolimus-eluting stent

Supplementary Table 3. Occurrence of stent thrombosis.

Stent thrombosis	**BP-SES**	**BMS**	***p*-value**
Acute			
Definite	0.5	1.6	0.25
Probable	0	0	
Definite/probable	0.5	1.6	0.25
Subacute			
Definite	0.3	1.6	0.095
Probable	0.5	1.6	0.25
Definite/probable	0.8	3.2	0.048
Late			
Definite	0.5	0	0.41
Probable	0	0	
Definite/probable	0.5	0	

Supplementary Table 4. The rates of TLR in patients treated with BP-SES vs. BMS, in the subgroup of patients with and without angiographic follow-up at six months.

	Angiographic FU at 6 months		*p*-value	No angiographic FU at 6 months		*p*-value
	BP-SES	**BMS**		**BP-SES**	**BMS**	
CD-TLR at 6 months	3/78 (3.9%)	5/26 (19.2%)	0.01	3/297 (1.0%)	3/99 (3.0%)	0.15
CD-TLR at 12 months	3/78 (3.9%)	8/26 (30.8%)	<0.001	7/297 (2.4%)	6/99 (6.1%)	0.07

BMS: bare metal stent; BP-SES: biodegradable polymer sirolimus-eluting stent; CD: clinically driven; TLR: target lesion revascularisation