Long-term Outcomes with Biodegradable Polymer Sirolimus-eluting Stents versus Durable Polymer Everolimus-eluting Stents in ST-segment Elevation Myocardial Infarction: 5-year follow-up of the BIOSTEMI randomized trial

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On behalf of the BIOSTEMI Extended Survival (ES) investigators

Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Grant/Research Support	Biosensors, Biotronik, Concept Medical, Terumo Corp.
Consultant Fees/Honoraria	Biosensors, Biotronik, Concept Medical, Cordis, Medalliance, Medtronic, Pfizer, Terumo Corp.
Individual Stock(s)/Stock Options	No
Royalties/Patent Beneficiary	No
Executive Role/Ownership Interest	No
Other Financial Benefit	No

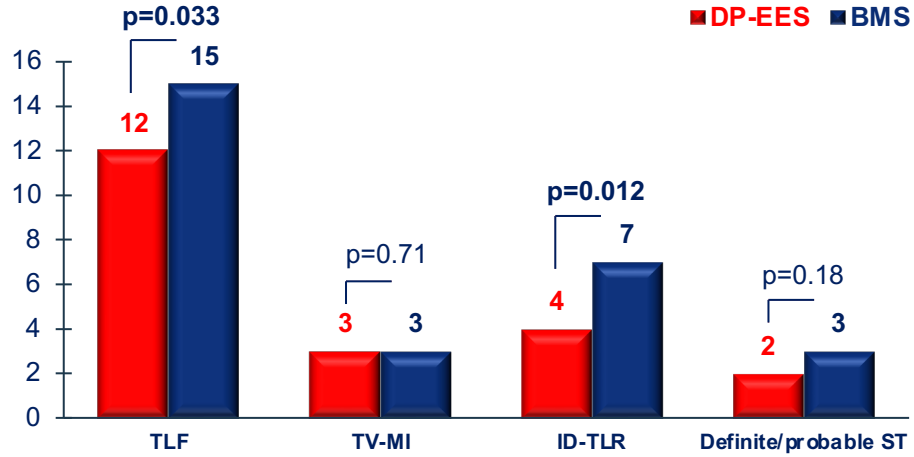
All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app

Background

EXAMINATION @ 5 years

Durable polymer everolimus-eluting stents vs. BMS in STEMI (n=1498)

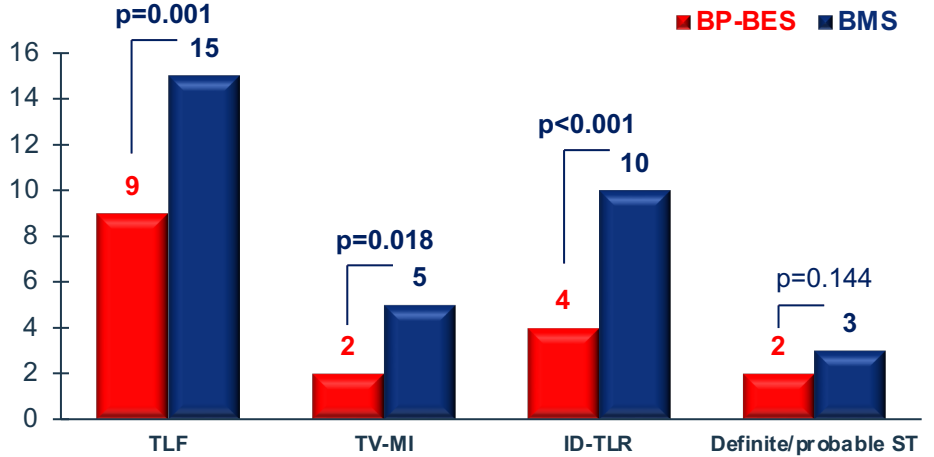
Sabaté M, et al., Lancet 2016;387(10016):357-366



COMFORTABLE-AMI @ 5 years

Biodegradable polymer biolimus-eluting stents vs. BMS in STEMI (n=1157)

Räber L, et al., Eur Heart J. 2019;40(24):1909-1919



Long-term outcomes of dedicated direct randomized comparisons between different newer-generation DES designs among patients with STEMI have not been reported to date.

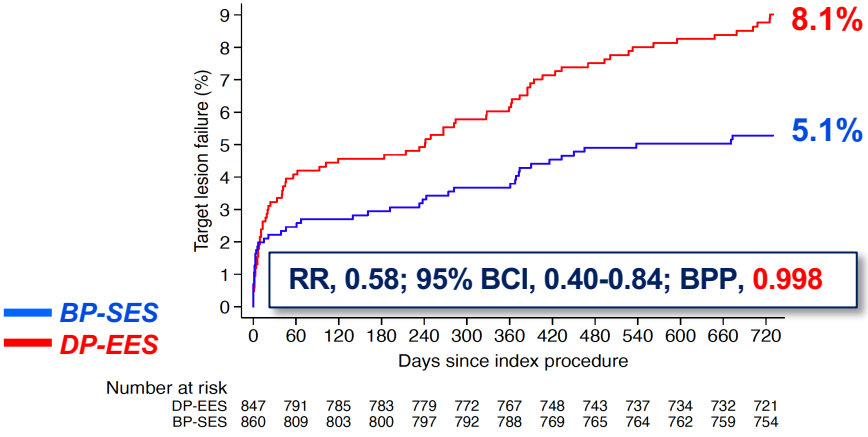
Background

BIOSTEMI

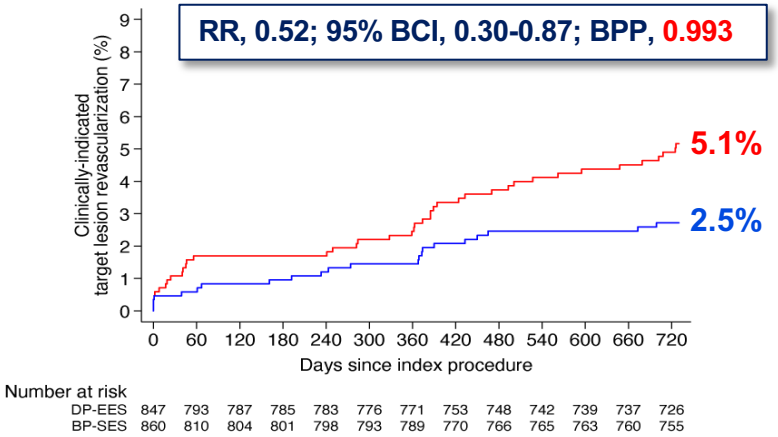
Biodegradable polymer sirolimus-eluting stents (BP-SES) vs. durable polymer everolimus-eluting stents (DP-EES) in STEMI (n=1300)

Pilgrim T, et al. JACC Cardiovasc Interv. 2021;14(6):639-648

TARGET LESION FAILURE @ 2 YEARS

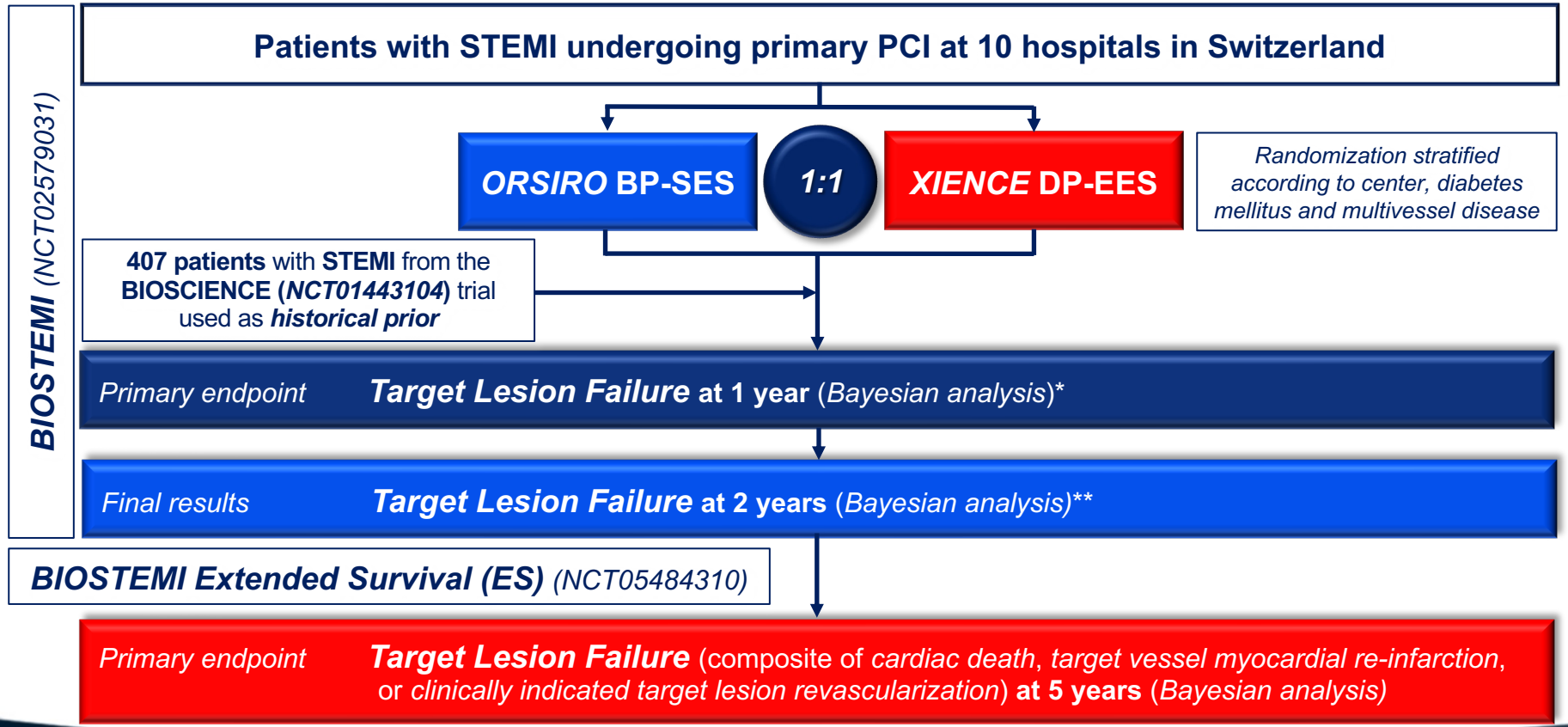


CLINICALLY INDICATED TLR @ 2 YEARS



Whether clinical *superiority* of biodegradable polymer DES is sustained after *complete degradation* of its polymer coating remains uncertain

Study design



*Iglesias JF, et al., Lancet 2019;394(10205):1243-1253; **Pilgrim T, et al. JACC Cardiovasc Interv. 2021;14(6):639-648

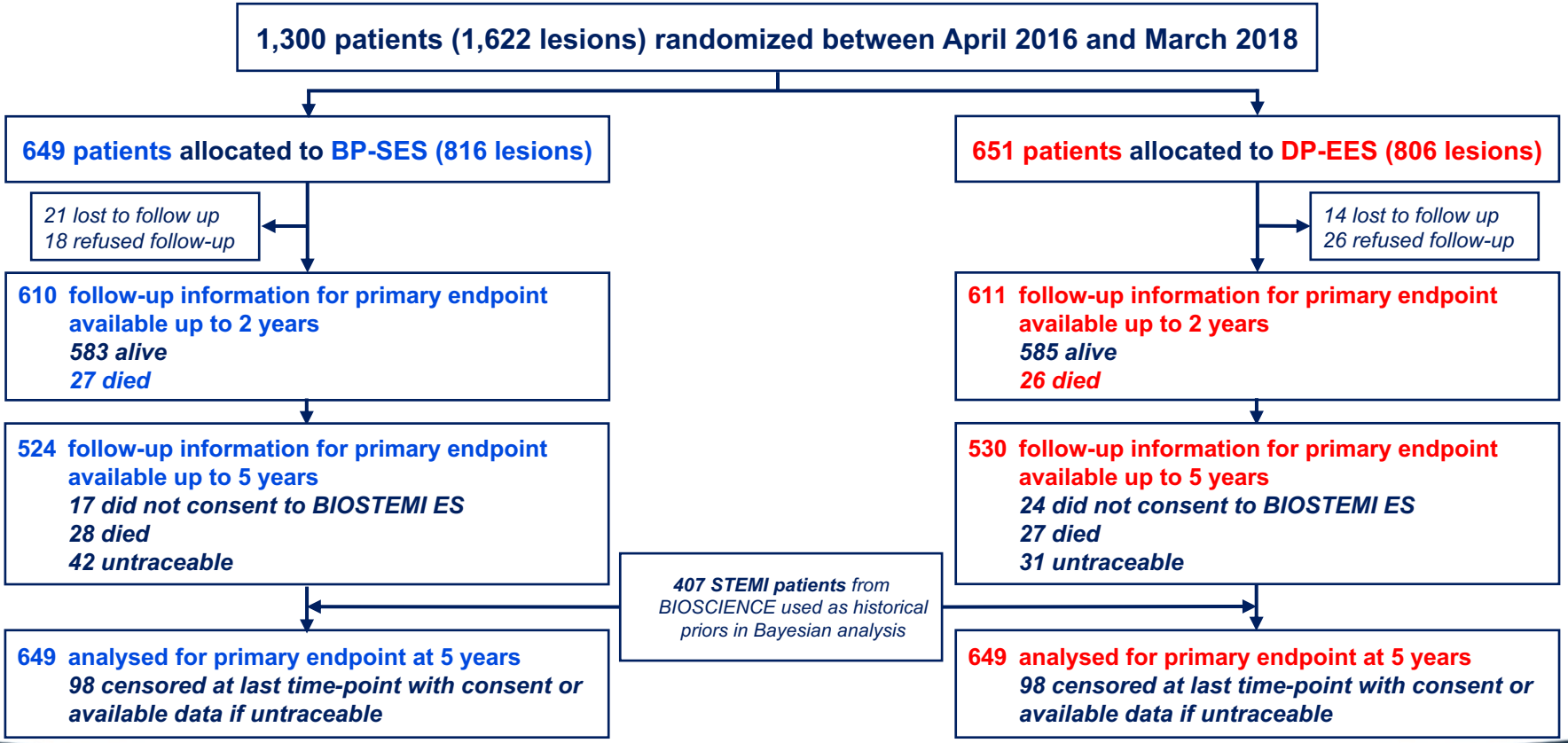
Study stents

	BIODEGRADABLE POLYMER SIROLIMUS-ELUTING STENT ORSIRO (*Biotronik*)	DURABLE POLYMER EVEROLIMUS-ELUTING STENT XIENCE (*Abbott Vascular*)
PLATFORM	Cobalt - Chromium, L-605  ≤3.0 mm >3.0 mm	Cobalt - Chromium, L-605  All diameters
POLYMER	Hydrogen-rich silicon-carbide passive coating **Biodegradable** (within *24 months*) **Poly-L-lactic acid (PLLA)**	**Durable** poly-n-butylmethacrylate (PBMA)/poly-vinylidene fluoride-co-hexafluoropropylene (PVDF-HFP)
DRUG	**Sirolimus** **(1.4 µg/mm²)**	**Everolimus** **(1.0 µg/mm²)**

Methods

- **Investigator-initiated *follow-up extension study*** of the **BIOSTEMI** multicenter, prospective, open-label, single-blind, randomized ***superiority*** trial.
- ***Bayesian analysis*** incorporating **historical information** from **407 patients** with **STEMI** included in the **BIOSCIENCE** randomized trial.
- **Bayesian log Poisson models** with **minimally informative priors** (μ=0, τ=0.111) and an **offset term** (log of the time at risk) to model *incidence rates*.
- ***Robust priors*** for each endpoint were a **50:50 mixture** between the **historical informative prior** (μ=posterior mean [BIOSCIENCE], τ=posterior SD [BIOSCIENCE]), and a **vague prior** (μ=0, τ=0.111) based on Bernoulli distributions.
- ***Rate Ratios*** (RR) estimates reported as the **median** of the ***Bayesian posterior distribution***.
- ***95% Bayesian credibility intervals*** (BCI) reported as the **2.5th** and **97.5th percentiles** of the **posterior distribution**.
- ***Superiority*** declared if the ***posterior probability*** *for a* ***RR <1*** was ***>0.975*** with ***≥80% power***.
- All analyses performed with **individual participant** as the **unit of analysis** and according to the ***intention-to-treat*** principle.

Study flowchart



Baseline clinical characteristics

	BP-SES (n=649)	DP-EES (n=651)
Age (years) — mean ± SD	62.2 ± 11.8	63.2 ± 11.8
Male gender — n (%)	513 (79%)	477 (73%)
Diabetes mellitus — n (%)	73 (11%)	82 (13%)
Hypertension — n (%)	281 (44%)	297 (46%)
Hypercholesterolemia — n (%)	304 (47%)	302 (47%)
Active smoker — n (%)	294 (46%)	250 (39%)
Prior myocardial infarction — n (%)	27 (4%)	24 (4%)
Prior percutaneous coronary intervention — n (%)	29 (5%)	34 (5%)
Prior coronary artery bypass surgery — n (%)	2 (0.3%)	8 (1%)
Chronic renal failure (GFR<60 ml/min) — n (%)	76 (12%)	78 (12%)
Left ventricular ejection fraction (%) — mean ± SD	49.0 ± 11.0	48.4 ± 11.2

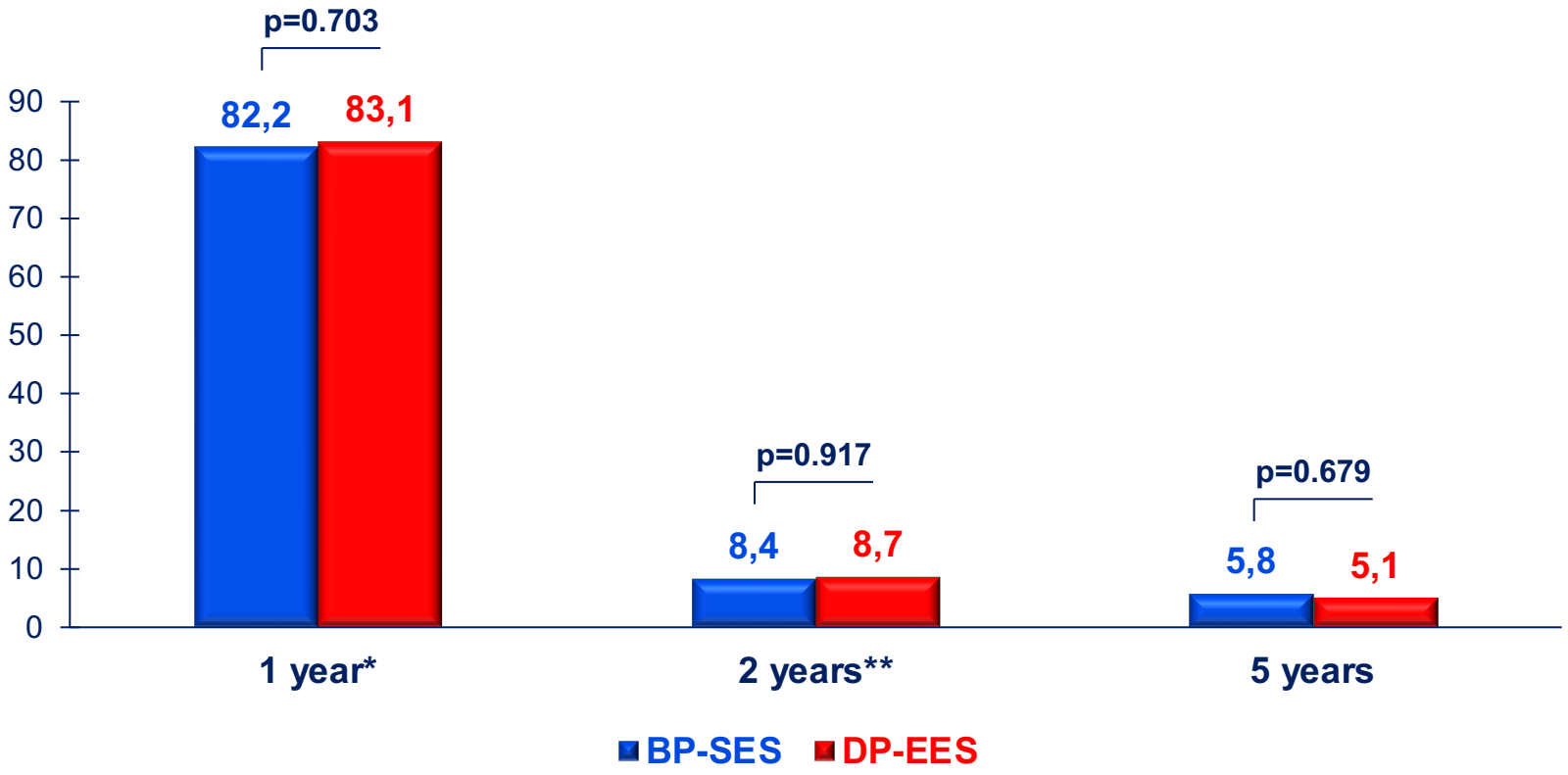
Iglesias JF, et al., Lancet 2019;394(10205):1243-1253

Baseline angiographic and procedural characteristics

	BP-SES (n=649)	DP-EES (n=651)	p-value
Target vessel location per lesion — n (%)			0.13
Left main coronary artery	10 (1%)	9 (1%)	
Left anterior descending artery	316 (39%)	357 (44%)	
Left circumflex artery	143 (18%)	137 (17%)	
Right coronary artery	346 (42%)	302 (38%)	
Number of lesions treated per patient — mean ± SD	1.26 ± 0.57	1.24 ± 0.52	0.76
Thrombus aspiration — n (%)	243 (30%)	250 (31%)	0.68
Total number of stents implanted — mean ± SD	1.37 ± 0.64	1.39 ± 0.66	0.79
Total stent length (mm) — mean ± SD	31.91 ± 18.21	33.92 ± 19.76	0.051
Maximum stent diameter (mm) — mean ± SD	3.17 ± 0.52	3.16 ± 0.50	0.71
Small vessel (minimum stent diameter <3.0 mm) — n (%)	292 (36%)	321 (40%)	0.13

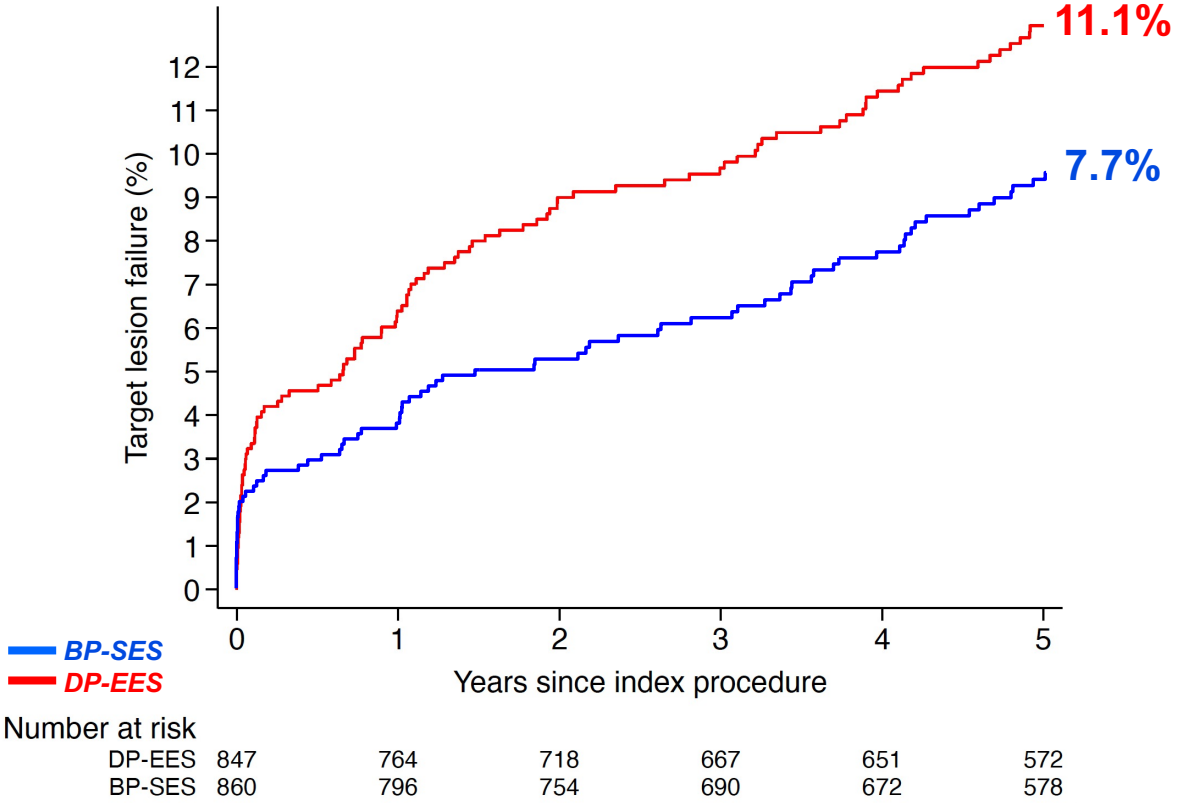
Iglesias JF, et al., Lancet 2019;394(10205):1243-1253

Dual antiplatelet therapy adherence



*Iglesias JF, et al., Lancet 2019;394(10205):1243-1253; **Pilgrim T, et al. JACC Cardiovasc Interv. 2021;14(6):639-648

Primary endpoint: Target lesion failure @ 5 years



BIOSTEMI with historical information

Absolute risk difference: -3.4%

RR, 0.70; 95% BCI, 0.51-0.95

Bayesian posterior probability, 0.988

Prespecified criterion for superiority met

BIOSTEMI only

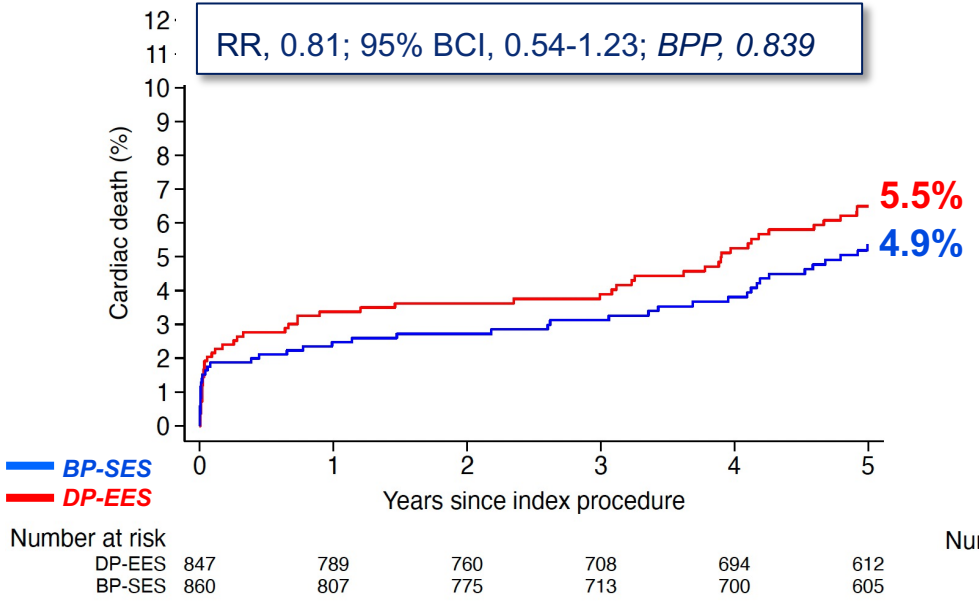
RR, 0.68; 95% BCI, 0.47-0.98

Bayesian posterior probability, 0.981

BCI, Bayesian credibility interval.

Individual components of TLF @ 5 years

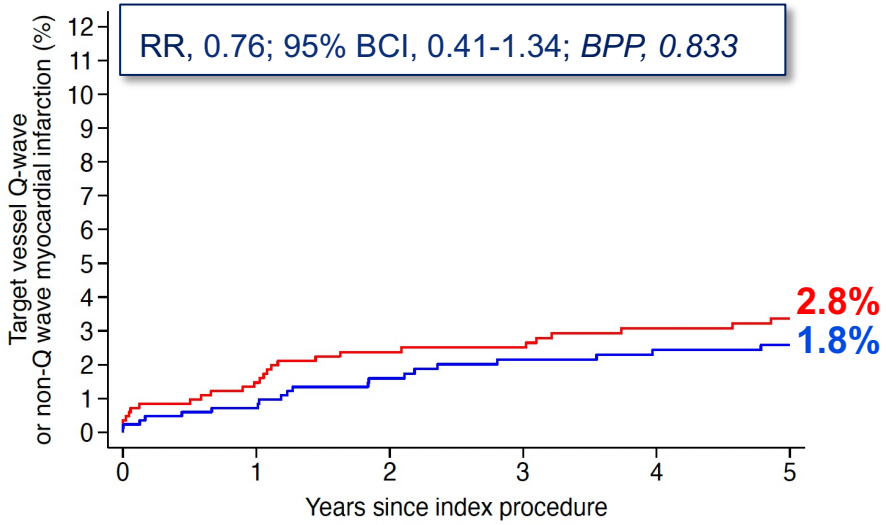
CARDIAC DEATH



Number at risk

DP-EES	847	789	760	708	694	612
BP-SES	860	807	775	713	700	605

TV MYOCARDIAL RE-INFARCTION

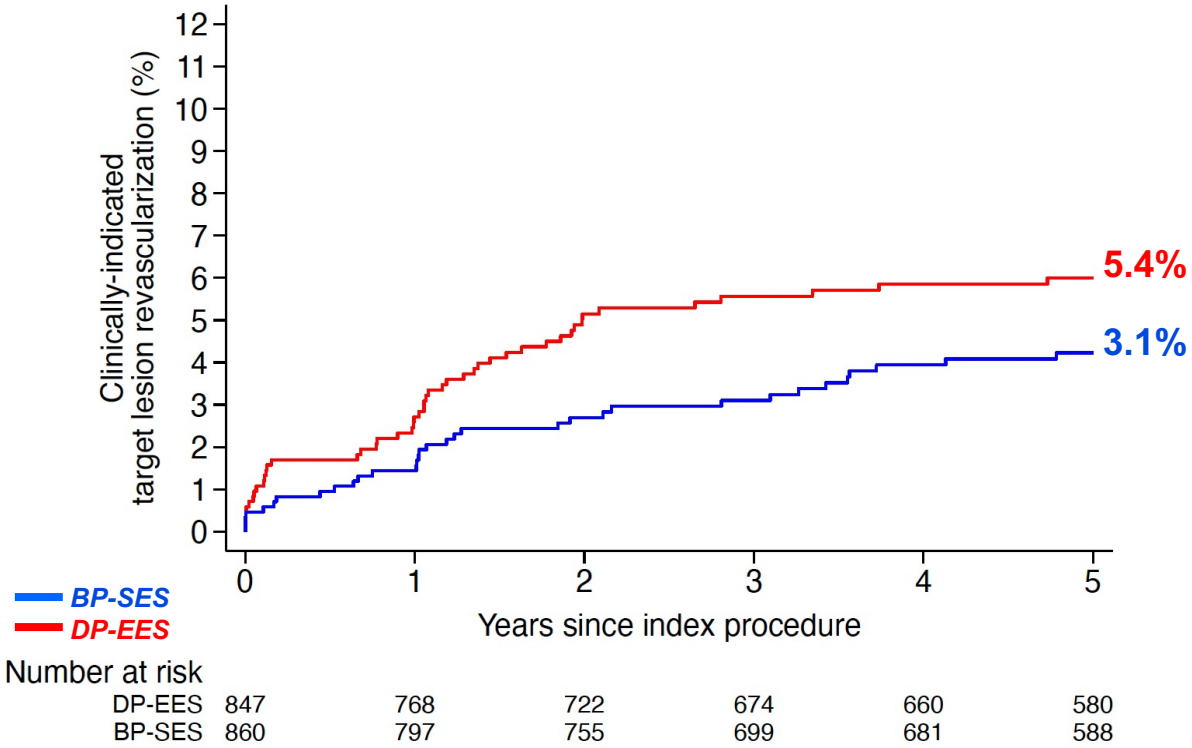


Number at risk

DP-EES	847	777	743	691	675	594
BP-SES	860	803	764	700	686	593

BCI, Bayesian credible interval; BPP, Bayesian posterior probability; RR, rate ratio.

Clinically indicated TLR @ 5 years



BIOSTEMI with historical information

RR, 0.68; 95% BCI, 0.40-1.06

Bayesian posterior probability, 0.956

BIOSTEMI only

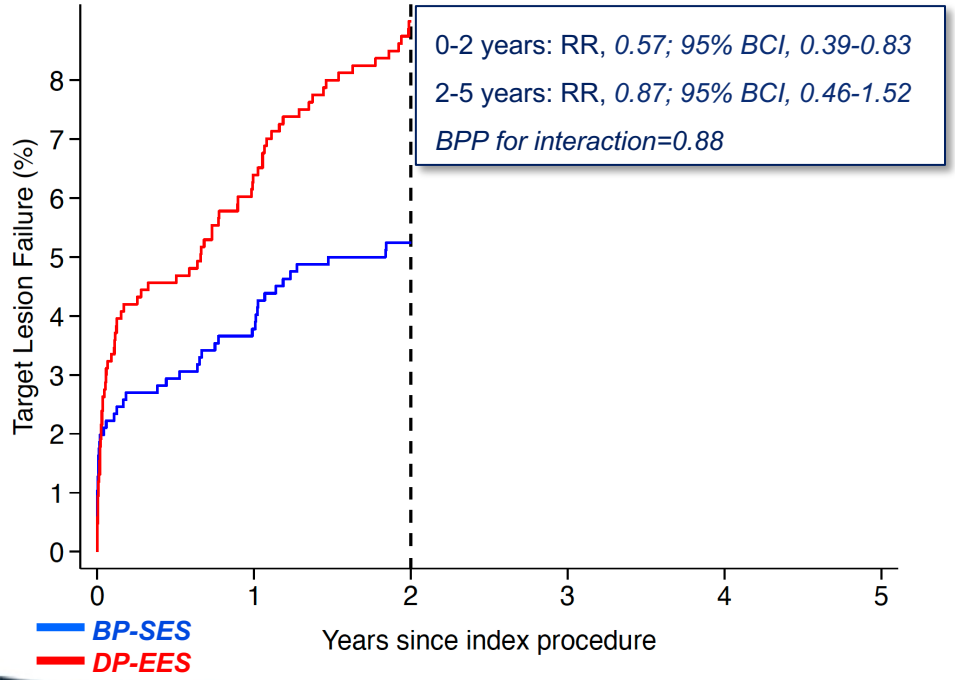
RR, 0.56; 95% BCI, 0.32-0.96

Bayesian posterior probability, 0.982

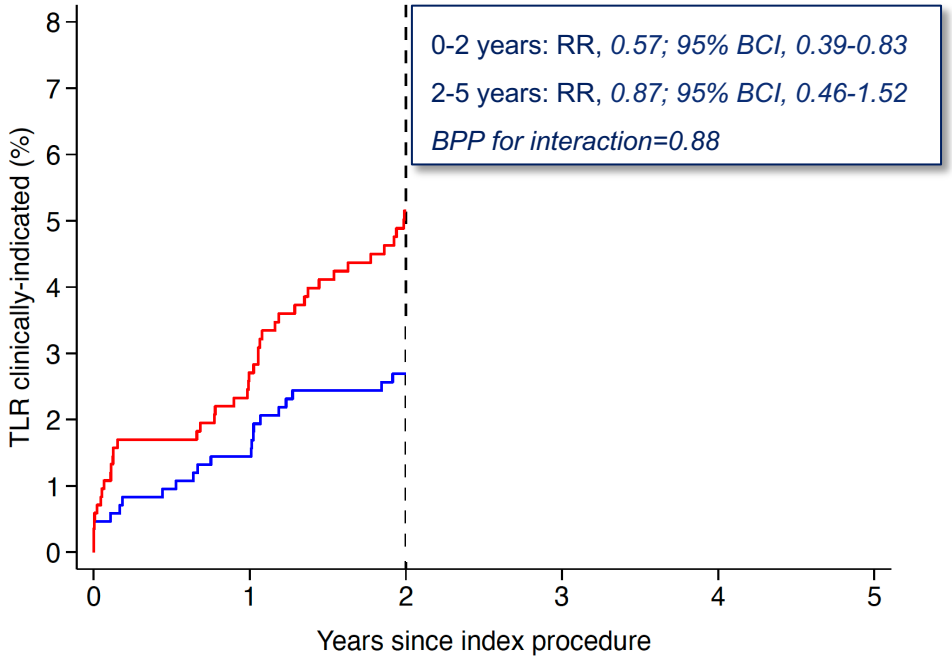
BCI, Bayesian credible interval; TLR, target lesion revascularization.

Landmark analysis of TLF and clinically indicated TLR

TARGET LESION FAILURE



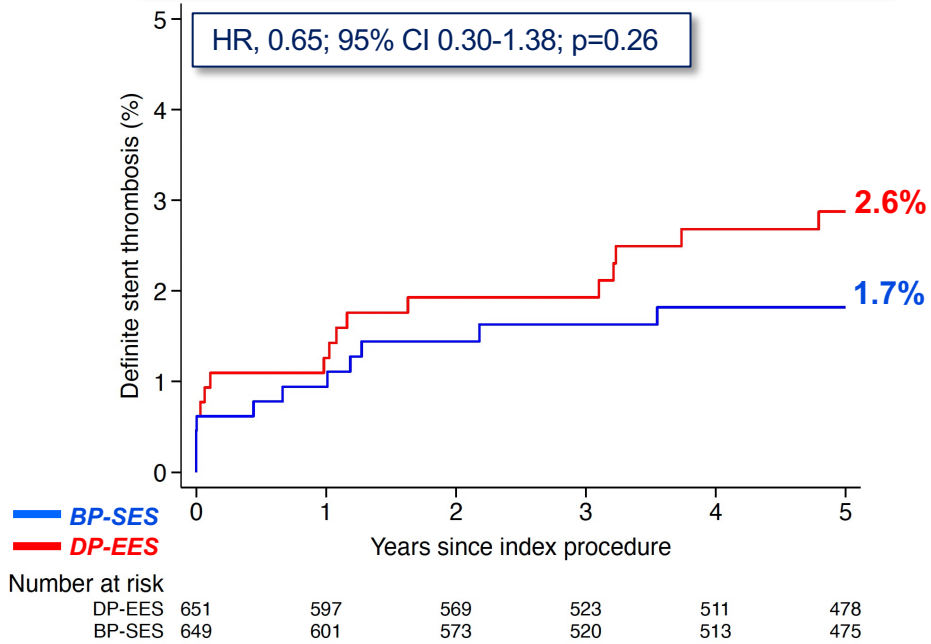
CLINICALLY INDICATED TLR



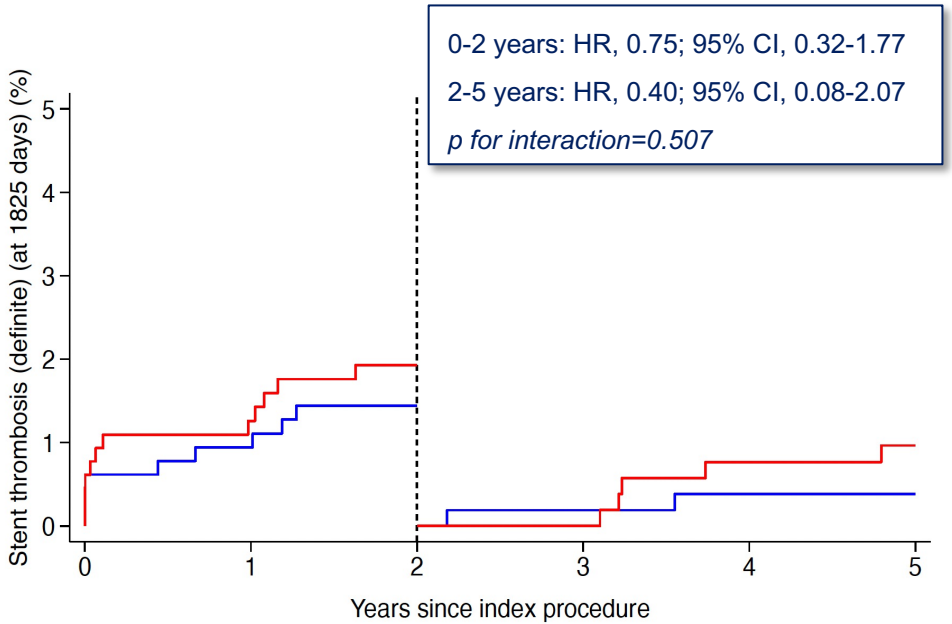
BCI, Bayesian credible interval; BPP, Bayesian posterior probability; RR, rate ratio.

Stent thrombosis @ 5 years

DEFINITE STENT THROMBOSIS

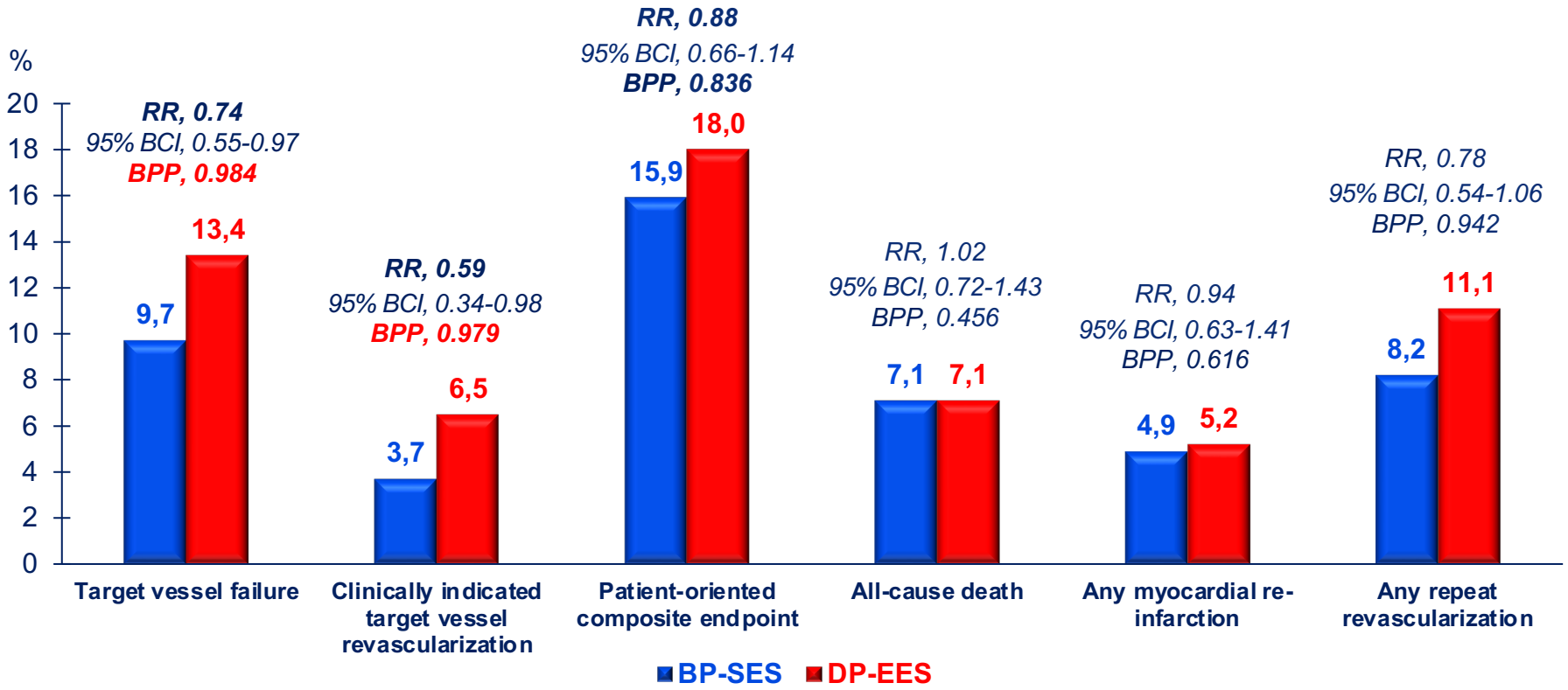


LANDMARK ANALYSIS



Patients included in BIOSTEMI trial only (without historical information from BIOSCIENCE). CI, confidence interval; HR, hazard ratio.

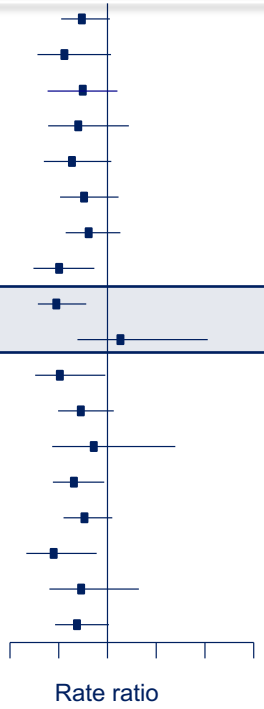
Secondary endpoints @ 5 years



BCI, Bayesian credibility interval; BPP, Bayesian posterior probability; RR, rate ratio.

Stratified analysis of the primary endpoint @ 5 years

		BP-SES	DP-EES	Rate Ratio (95% BCI)	BPP	BPP for interaction
Diabetes	no	42/575	58/569	0.74 (0.53-1.02)	0.964	**0.797**
	yes	7/73	14/82	0.56 (0.28−1.04)	0.970	
Gender	male	37/513	48/477	0.75 (0.52-1.06)	0.948	**0.577**
	female	13/136	24/174	0.70 (0.39-1.22)	0.905	
Age	< 65 years	19/381	31/376	0.64 (0.35-1.04)	0.965	**0.712**
	≥ 65 years	31/268	41/275	0.76 (0.51-1.11)	0.920	
BMI	< 30 kg/m2	42/513	53/518	0.81 (0.57-1.13)	0.898	**0.928**
	≥ 30 kg/m2	8/134	17/131	0.50 (0.24-0.87)	0.991	
Chronic renal failure	eGFR ≥60	27/557	53/555	0.48 (0.29-0.78)	0.999	**0.993**
	eGFR <60	22/76	19/78	1.13 (0.69-2.03)	0.315	
Small vessel	no	9/214	18/220	0.51 (0.26-0.98)	0.979	**0.819**
	yes	40/429	54/431	0.73 (0.49-1.06)	0.949	
Long lesion	no	12/139	16/152	0.86 (0.43-1.70)	0.667	**0.752**
	yes	37/504	56/499	0.66 (0.44-0.97)	0.983	
Multivessel disease	no	46/598	63/601	0.76 (0.55-1.05)	0.952	**0.929**
	yes	4/50	9/50	0.45 (0.17-0.89)	0.985	
Total vessel occlusion	no	20/263	23/228	0.73 (0.40-1.32)	0.861	**0.570**
	yes	30/385	49/423	0.69 (0.46-1.01)	0.970	



BCI, Bayesian credible interval; BMI, body mass index; eGFR, glomerular filtration rate; BPP, Bayesian posterior probability; RR, rate ratio.

Limitations

- Study powered for **superiority** on the primary endpoint of **TLF** at **5 years** using ***Bayesian methods***.
  - *Differences in individual components of TLF and secondary endpoints should be interpreted with caution and are hypothesis-generating.*
- Study DES designs *differ* in terms of **stent platforms**, **polymer characteristics**, presence/absence of a **passive coating**, and **antiproliferative agents**.
  - *Relative contribution of individual components to differences in clinical outcomes between BP-SES and DP-EES cannot be definitively differentiated.*
- *Follow-up information* **missing** for a **significant number of patients (n=193)** at **5 years** because of *refusal* or *loss to follow-up*.
  - *In a sensitivity analysis using multiple imputations of the primary endpoint, we found similar estimates of the RR for TLF at 5 years between BP-SES and DP-EES.*

Conclusions

- In patients with **STEMI** undergoing primary PCI, **BP-SES** are ***superior*** to **DP-EES** with respect to the rates of **TLF** at **5 years** of follow-up, a difference driven by a numerically **lower risk** for **ischemia-driven TLR**.
- **Differences** in **TLF** between **BP-SES** and **DP-EES** at **5 years** remain ***consistent*** after **exclusion** of the ***historical information*** from the BIOSCIENCE trial.
- **BIOSTEMI ES** is the first *head-to-head* randomized trial with a *superiority* design and *long-term follow-up* demonstrating (1) **significant differences** in **clinical outcomes** between **two contemporary DES** for the treatment of patients with **STEMI**, and (2) the *absence* of **late catch-up phenomenon** with **newer-generation biodegradable polymer DES** after complete degradation of the polymer coating.
- In the current era of *newer-generation DES*, *potent antithrombotic therapies*, and *effective secondary preventive treatments*, **differences** in **long-term stent-related outcomes** between **newer-generation DES designs** *do not* translate into significant **differences** in **patient-oriented clinical outcomes** at **5 years** of follow-up.

Long-term outcomes with biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in ST-segment elevation myocardial infarction: 5-year follow-up of the BIOSTEMI randomised superiority trial

Juan F Iglesias, Marco Roffi, Sylvain Losdat, Olivier Muller, Sophie Degrauwe, David J Kurz, Laurent Haegeli, Daniel Weilenmann, Christoph Kaiser, Maxime Tapponnier, Stéphane Cook, Florim Cuculi, Dik Heg, Stephan Windecker, Thomas Pilgrim

BIOSTEMI ES manuscript available online as of October 25, 2023 in The Lancet