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Short communication

Multivessel percutaneous coronary intervention with thin-strut biodegradable versus durable polymer drug-eluting stents in ST-segment elevation myocardial infarction: A subgroup analysis of the BIOSTEMI randomized trial

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ABSTRACT

Background: Randomized evidence comparing newer-generation drug-eluting stents for multivessel percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is limited. We sought to investigate clinical outcomes in STEMI patients undergoing multivessel PCI with thin-strut biodegradable polymer sirolimus-eluting stents (BP-SES) versus durable polymer everolimus-eluting stents (DP-EES).
Methods: We performed a subgroup analysis of the BIOSTEMI (NCT02579031) randomized trial, which included individual patient data from STEMI patients enrolled into the BIOSCIENCE (NCT02579031) study. STEMI patients randomly allocated to BP-SES or DP-EES were divided into those undergoing multivessel versus culprit lesion-only PCI. The primary endpoint was target lesion failure (TLF), a composite of cardiac death, target vessel myocardial re-infarction or clinically indicated target lesion revascularization (TLR), within 24 months.
Results: Among 1707 STEMI patients, 145 patients underwent multivessel PCI. At 2 years, TLF occurred in 2 patients (2.8%) treated with BP-SES and 13 patients (18.7%) treated with DP-EES (hazard ratio [HR], 0.14; 95% confidence interval (CI), 0.03–0.61; $p = 0.009$) in the multivessel PCI group, and in 40 (5.3%) and 61 (8.2%) patients treated with BP-SES and DP-EES respectively (HR, 0.64; 95%CI, 0.43–0.96; $p = 0.03$; p for interaction = 0.050) in the culprit lesion-only PCI group. In the multivessel PCI group, the rates of clinically indicated TLR (0% vs. 12.4%) and target vessel myocardial re-infarction (0% vs. 4.6%) at 2 years were lower in patients treated with BP-SES compared with DP-EES.
Conclusion: In a subgroup analysis of the BIOSTEMI trial, BP-SES were associated with lower 2-year TLF rates compared to DP-EES in STEMI patients undergoing multivessel PCI.

1. Introduction

Multivessel coronary artery disease (MVD) is common in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) [1] and is associated with worse outcomes compared with single-vessel coronary artery disease [1,2]. Complete multivessel revascularization by PCI provides superior long-term clinical outcomes compared to culprit lesion-only PCI in patients with STEMI and MVD [3,4]. Randomized evidence comparing differential clinical outcomes between newer-generation drug-eluting

Abbreviations: BP-SES, biodegradable polymer sirolimus-eluting stent; CI, confidence interval; DES, drug-eluting stent; DP-EES, durable polymer everolimus-eluting stent; HR, hazard ratio; MVD, multivessel disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization..

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stents (DES) in patients with STEMI undergoing multivessel PCI is however limited.

Newest-generation thin-strut biodegradable polymer sirolimus-eluting stents (BP-SES) are superior to second-generation durable polymer everolimus-eluting stents (DP-EES) with respect to target lesion failure (TLF) at 1 year among patients with STEMI, a difference driven by a lower risk of ischemia driven target lesion revascularization (TLR) [5]. Long-term clinical advantages of thin-strut BP-SES over DP-EES may therefore be anticipated in STEMI patients undergoing multivessel PCI, considering the beneficial effects of thin-strut BP-SES may accumulate with the increasing number of lesions treated. We therefore performed a subgroup analysis of the BIOSTEMI trial to investigate potential differences in clinical outcomes between thin-strut BP-SES and DP-EES among STEMI patients undergoing multivessel PCI.

2. Methods

BIOSTEMI (*NCT02579031*) was an investigator-initiated, prospective, multicentre trial that randomly assigned STEMI patients in a 1:1 ratio to thin-strut BP-SES or DP-EES [6]. Randomization was stratified according to the presence or absence of MVD, which was defined as ≥2 coronary stenoses in ≥2 vessels and/or in the left main coronary artery. In the present subanalysis, MVD patients were further divided into those undergoing multivessel versus culprit lesion-only PCI. Multivessel PCI using randomly allocated study stents in all stenoses was permitted during the index procedure or within 3 months, at the operator's discretion. The primary endpoint was TLF, a composite of cardiac death, target vessel myocardial re-infarction, or clinically indicated TLR, within 24 months. Secondary endpoints included individual components of the primary endpoint, all-cause death, myocardial re-infarction, any revascularization, target vessel failure (TVF) as a composite of cardiac death, myocardial re-infarction or target vessel revascularization, definite stent thrombosis, and definite or probable stent thrombosis at 2 years. The study protocol was approved by institutional ethics committees at participating sites and complied with the Declaration of Helsinki. All patients provided written informed consent for participation.

Consistent with the main analysis [5], we included individual patient data from STEMI patients enrolled into BIOSCIENCE (*NCT02579031*), a prospective, multicenter, randomized, non-inferiority trial that compared BP-SES and DP-EES with respect to TLF in all-comers patients undergoing percutaneous coronary revascularization [7]. *p*-values for main effects of stent type within subgroups were obtained from Chi-squared, Fisher's exact or Student's *t*-tests, as appropriate. *p*-values for interactions between subgroups and stent types were calculated using generalized linear, Poisson and logistic models (mixed-effects for lesion-level). Hazard ratios (HR), 95% confidence intervals (CI), *p*-values for main effects and *p*-values for interactions were obtained from mixed-effect survival models, in which the trial identity (BIOSTEMI or BIOSCIENCE) was fitted as random intercept [8]. We reported time-to-first event for outcomes, and numbers of patients and Kaplan-Meier estimates of cumulative incidence. Statistical analyses were conducted using R Studio version 3.5.2 and STATA version 15.

Table 1
Clinical outcomes at 2 years in multivessel versus culprit lesion-only PCI groups.

	Multivessel PCI				Culprit lesion-only PCI				*p*-Value for interaction
	BP-SES	DP-EES	HR (95% CI)	*p*-value	BP-SES	DP-EES	HR (95% CI)	*p*-value	
Patients – no.	*n* = 72	*n* = 73			*n* = 781	*n* = 774			
Target lesion failure[a]	2 (2.8)	13 (18.7)	0.14 (0.03–0.61)	0.009	40 (5.3)	61 (8.2)	0.64 (0.43–0.96)	0.030	0.050
All-cause death	4 (5.6)	7 (9.7)	0.54 (0.16–1.86)	0.333	31 (4.1)	28 (3.7)	1.10 (0.66–1.83)	0.715	0.301
Cardiac death	2 (2.8)	5 (7.0)	0.38 (0.07–1.97)	0.250	20 (2.6)	25 (3.3)	0.79 (0.44–1.43)	0.444	0.409
Myocardial re-infarction	1 (1.5)	5 (7.7)	0.18 (0.02–1.57)	0.121	27 (3.7)	25 (3.4)	1.07 (0.62–1.85)	0.801	0.118
Target vessel myocardial re-infarction	0 (0.0)	3 (4.6)	NA	NA	12 (1.6)	16 (2.2)	0.74 (0.35–1.56)	0.428	NA
Cardiac death or any myocardial re-infarction	3 (4.3)	10 (14.3)	0.27 (0.08–1.00)	0.049	45 (6.0)	49 (6.5)	0.91 (0.61–1.37)	0.656	0.082
Revascularization (any)	4 (5.9)	11 (16.8)	0.32 (0.10–1.02)	0.054	47 (6.4)	63 (8.7)	0.73 (0.50–1.07)	0.108	0.185
Target lesion revascularization (any)	0 (0.0)	9 (13.9)	NA	NA	24 (3.3)	34 (4.7)	0.70 (0.41–1.17)	0.175	NA
Clinically indicated target lesion revascularization	0 (0.0)	8 (12.4)	NA	NA	22 (3.0)	33 (4.6)	0.66 (0.38–1.13)	0.128	NA
Target vessel revascularization (any)	3 (4.4)	11 (16.9)	0.24 (0.07–0.87)	0.030	29 (3.9)	43 (5.9)	0.66 (0.41–1.06)	0.087	0.149
Clinically indicated target vessel revascularization	3 (4.4)	10 (15.5)	0.27 (0.07–0.99)	0.048	27 (3.7)	42 (5.8)	0.63 (0.39–1.02)	0.062	0.230
Target vessel failure[b]	5 (7.1)	16 (23.0)	0.28 (0.10–0.76)	0.013	47 (6.2)	70 (9.4)	0.66 (0.45–0.95)	0.026	0.117
All-cause death, myocardial re-infarction or any revascularization	8 (11.2)	19 (26.6)	0.37 (0.16–0.85)	0.019	81 (10.7)	92 (12.3)	0.87 (0.64–1.17)	0.349	0.056
Definite stent thrombosis	0 (0.0)	2 (3.1)	NA	NA	10 (1.3)	12 (1.6)	0.82 (0.36–1.91)	0.651	NA
Definite or probable stent thrombosis	0 (0.0)	3 (4.4)	NA	NA	16 (2.1)	22 (2.9)	0.72 (0.38–1.36)	0.309	NA

Number of events and percentages are reported. HR, hazard ratio; CI, confidence interval. BP-SES, biodegradable polymer sirolimus-eluting stent; DP-EES, durable polymer everolimus-eluting stent; PCI, percutaneous coronary intervention.

[a] Composite of cardiac death, target vessel myocardial re-infarction, and clinically indicated target lesion revascularization (primary endpoint).

[b] Composite of cardiac death, any myocardial re-infarction, or any target vessel revascularization.

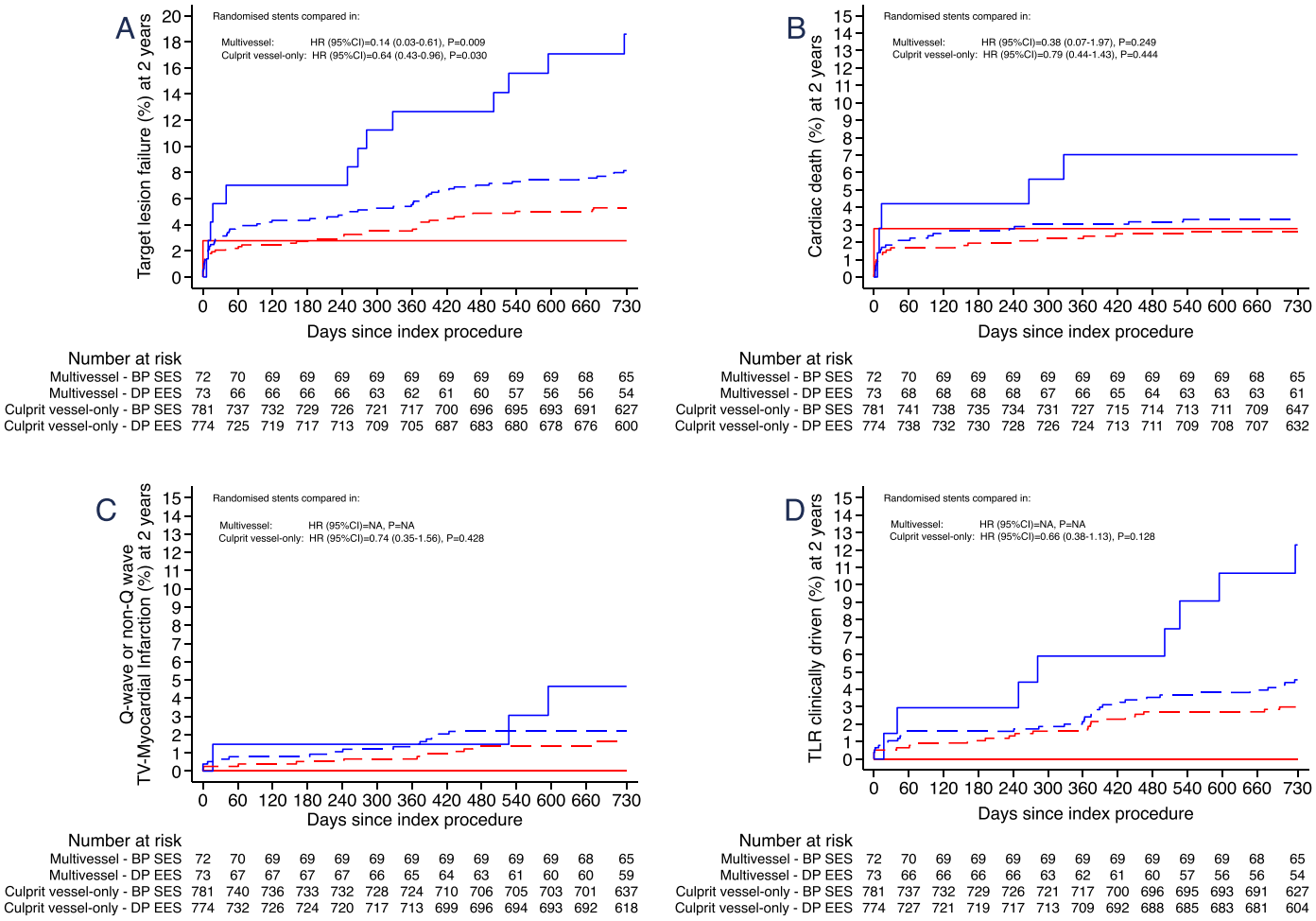

Fig. 1. Time-to-event curves for target lesion failure and its individual components at 2-year follow-up. A, target lesion failure; B, cardiac death; C, target vessel (TV) myocardial re-infarction; D, clinically indicated target lesion revascularization (TLR). *Red lines*, biodegradable polymer sirolimus-eluting stent (BP-SES); *blue lines*, durable polymer everolimus-eluting stent (DP-EES); *solid lines*, multivessel percutaneous coronary intervention (PCI); *dash lines*, culprit lesion-only primary PCI. HR, hazard ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

Among 1707 STEMI patients enrolled into BIOSCIENCE ($n = 407$) and BIOSTEMI ($n = 1300$) trials, 145 patients underwent multivessel PCI with BP-SES ($n = 72$) or DP-EES ($n = 73$), of which 45 and 100 patients were included in BIOSCIENCE and BIOSTEMI trials, respectively. Among patients who underwent multivessel PCI, the median time from primary PCI to the staged procedure was 37.3 ± 22.7 days. Baseline clinical, angiographic and procedural characteristics did not significantly differ between groups (Supplementary Tables 1 and 2). The 2-year TLF risk was numerically higher among patients undergoing multivessel PCI as compared to culprit lesion-only PCI (10.7% vs. 6.7%; $p = 0.089$) (Supplementary Table 3). At 2 years, TLF occurred in 2 patients (cumulative incidence, 2.8%) treated with BP-SES and 13 patients (18.7%) treated with DP-EES (HR, 0.14; 95% CI, 0.03–0.61; $p = 0.009$) in the multivessel PCI group, and in 40 (5.3%) and 61 (8.2%) patients treated with BP-SES and DP-EES respectively (HR, 0.64; 95% CI, 0.43–0.96; $p = 0.03$; p for interaction = 0.050) in the culprit lesion-only PCI group (Table 1; Fig. 1). In the multivessel PCI group, differences in 2-year TLF rates between BP-SES and DP-EES were consistent among patients included in BIOSCIENCE and BIOSTEMI trials (Supplementary Table 4). The rates of cardiac death (2.8% vs. 7.0%), target vessel myocardial re-infarction (0% vs. 4.6%) and clinically indicated TLR (0% vs. 12.4%) at 2 years were lower among patients undergoing multivessel PCI with thin-strut BP-SES as compared to those treated with DP-EES (Table 1; Fig. 1). Patient-oriented composite endpoints including cardiac death or myocardial re-infarction (4.3% vs. 14.3%; HR, 0.27; 95% CI, 0.08–1.00; $p = 0.049$), all-cause death, myocardial re-infarction or any revascularization (11.2% vs. 26.6%; HR, 0.37; 95% CI, 0.16–0.85; $p = 0.019$), and TVF (7.1% vs. 23.0%; HR, 0.28; 95% CI, 0.10–0.76; $p = 0.013$) at 2 years of follow-up were significantly lower among patients undergoing multivessel PCI with BP-SES compared to DP-EES (Table 1).

4. Discussion

In a subgroup analysis of the BIOSTEMI randomized trial, we found significant differences in 2-year rates of TLF favoring thin-strut BP-SES over DP-EES among STEMI patients undergoing multivessel PCI. This difference was mainly caused by higher rates of major adverse cardiac events, including cardiac death, target vessel myocardial re-infarction, and ischemia driven TLR, among STEMI patients undergoing multivessel PCI with DP-EES as compared to thin-strut BP-SES. Overall, there was a borderline significant treatment interaction suggesting incremental clinical benefits with thin-strut BP-SES over DP-EES with respect to the 2-year TLF risk in patients with STEMI undergoing multivessel PCI. To the best of our knowledge, the present is the first study suggesting differential clinical outcomes between newer-generation DES in patients with STEMI undergoing multivessel PCI. Thick-strut biodegradable

polymer DES have shown similar safety and efficacy outcomes at 1 year of follow-up compared with second-generation durable polymer-based DES among STEMI patients undergoing multivessel PCI [9]. Our findings suggest that most recent DES iterations combining thinner stent platforms with biodegradable polymers may provide incremental clinical benefits compared to second-generation polymer-based DES in STEMI patients undergoing multivessel PCI by reducing the risk of repeat revascularization. The observed lower TLR rates among patients treated with thin-strut BP-SES compared with contemporary newer-generation DES are consistent with the results from a recent large-scale, real-life, all-comers registry [10]. The present study suggests particular clinical benefits from thin-strut BP-SES in patients with STEMI undergoing multivessel PCI, in which the lower risk of TLR with thin-strut BP-SES over DP-EES may accumulate with the number of stents used. The potential mechanism by which thin-strut BP-SES reduce TLF compared to DP-EES in STEMI patients undergoing multivessel PCI remains unclear and warrants further dedicated studies. In addition to strut thickness and polymer characteristics, BP-SES and DP-EES also differ in terms of stent platform geometry, polymer composition, thickness or distribution, and antiproliferative drug composition or elution kinetics, all of which may potentially impact on clinical outcomes.

5. Limitations

The present analysis is underpowered to assess clinical differences between BP-SES and DP-EES due to the small sample size and these findings are therefore hypothesis-generating. Future properly powered studies are warranted to investigate the comparative effects of thin-strut BP-SES versus DP-EES in STEMI patients undergoing multivessel PCI. Finally, the results of the present study should be interpreted in view of higher 2-year rates of ischemia-driven TLR and stent thrombosis than those observed in previous randomized clinical trials including STEMI patients treated with DP-EES [11].

6. Conclusion

In conclusion, in a subgroup analysis of the BIOSTEMI randomized trial, thin-strut BP-SES were associated with significantly lower TLF rates at 2 years of follow-up compared with DP-EES in patients with STEMI undergoing multivessel PCI.

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Statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Potential conflicts of interest

JFI reports research grants to the institution and personal fees from Biotronik during the conduct of the study; grants and personal fees from Biotronik, Philips Volcano, and AstraZeneca and personal fees from Terumo, Medtronic, and Cardinal Health, outside the submitted work. SL is affiliated with Clinical Trials Unit Bern (CTU Bern), University of Bern (Bern, Switzerland), which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organisations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see www.ctu.unibe.ch/ research/declaration_of_interest/index_eng.html. MR reports institutional research grants from Terumo, Boston Scientific, Medtronic, Abbott Vascular, and Biotronik, outside the submitted work. DJK reports grants from the University Clinic for Cardiology, Inselspital Bern, Swizerland, during the conduct of the study. MV reports grants and personal fees from Abbott, Terumo, and AstraZeneca, personal fees from Bayer, Dalichi Sankyo, Amgen, Alvimedica, Idorsia, Coreflow, Vifor, Bristol-Myers Squibb, and iVascular, and grants from Medicure, ouside the submitted work. SW received research grants to their institution from Amgen, Abbott, Bayer, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Edwards Lifesciences, Medtronic, Polares, and Sinomed, outside the submitted work, and research grants from Biotronik during the conduct of the study. TP received research grants to the institution and speaker fees from Biotronik during the conduct of this study, research grants to the institution and speaker fees from Boston Scientific, outside the submitted work, and serves as a consultant for HighLife SAS. All other authors declare no competing interests.

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Appendix A. Supplementary data

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