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Original Article

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A Randomized Controlled Trial Comparing BioMime Sirolimus-Eluting Stent With Everolimus-Eluting Stent: Two-Year Outcomes of the meriT-V Trial

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Abstract

Background: Drug-eluting stents (DESs) based on biodegradable polymers (BPs) have been introduced to reduce the risk for late and very late stent thrombosis (ST), which were frequently observed with earlier generations of DES designs based on durable polymers (DPs); however, randomized controlled trials on these DES designs are scarce. The meriT-V trial is a randomized, active-controlled, non-inferiority trial with a prospective, multicenter design that evaluated the 2-year efficacy of a novel third-generation, ultra-thin strut, BP-based BioMime sirolimus-eluting stent (SES) versus the DP-based XIENCE everolimus-eluting stent (EES) for the treatment of *de novo* lesions.

Methods: The meriT-V is a randomized trial that enrolled 256 patients at 15 centers across Europe and Brazil. Here, we report the outcomes of the extended follow-up period of 2 years. The randomization of enrolled patients was in a 2:1 ratio; the enrolled patients received either the BioMime SES (n = 170) or the XIENCE EES (n = 86). The three-point major adverse cardiac event (MACE), defined as a composite of cardiac death, myocardial infarction (MI), or ischemia-driven target vessel revascularization (ID-TVR), was considered as the composite safety and efficacy endpoint. Ischemia-driven target lesion revascularization (ID-TLR) was evaluated as well as the frequency of definite/probable ST, based on the first Academic Research Consortium definitions.

Results: The trial had a 2-year follow-up completion rate of 98.44% (n = 252/256 patients), and the clinical outcomes assessment showed a nonsignificant difference in the cumulative rate of three-point MACE between both arms (BioMime vs. XIENCE: 7.74% vs. 9.52%, P = 0.62). Even the MI incidences in the BioMime arm were insignificantly lower than those of the XIENCE arm (1.79% vs. 5.95%, P = 0.17). Late ST was observed in 1.19% cases of the XIENCE arm, while there were no such cases in the BioMime arm (P = 0.16).

Conclusions: The objective comparisons between the novel BP-based BioMime SES and the well-established DP-based XIENCE EES in this randomized controlled trial show acceptable outcomes of both the devices in the cardiac deaths, MI, ID-TVR, and ST. Moreover, since there were no incidences of cardiac death in the entire study sample over the course of 2 years, we contend that the findings of the study are highly significant for both these DES designs. In this preliminary comparative trial, the device safety of BioMime SES can be affirmed to be acceptable, considering the lower three-point MACE rate and absence of late ST in the BioMime arm over the 2-year period.

Keywords: Coronary artery disease; Drug-eluting stent; Everolimus; Major adverse cardiac events; Percutaneous coronary intervention; Sirolimus; Stent thrombosis

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Introduction

Coronary artery disease (CAD) remains a current predominant cause of mortality for the global population, irrespective of ethnicity and despite the several technological advancements. Timely intervention is key to control the rising incidence of sudden cardiac death among elderly populations susceptible to CAD [1].

Table 1. Design Characteristics of the DES Used in the meriT-V Trial [2]

Stent	Alloy	Strut thickness	Drug (dose density)	Polymer	Coating thickness	Bare metal platform	Biodegradability of polymer coating (yes/no)	Polymer degradation (months)
XIENCE V (Abbott Vascular)	L605 CoCr	81 µm	Everolimus (1.0 µg/mm^2)	Permanent fluorinated PVDF polymer	7.6 µm	Vision®	-	Not applicable
BioMime (Meril Life Science)	L605 CoCr	65 µm	Sirolimus (1.25 µg/mm^2)	PLLA-PLGA	2 µm	Nexgen™ (Meril Life Sciences Pvt. Ltd., India)	✓	9

DES: drug-eluting stent; PLLA: poly-L-lactic acid; PLGA: poly-lactic co-glycolic acid; PVDF: polyvinylidine fluoride.

Totally percutaneous, catheter-based treatment utilizing balloon angioplasty and stent implantation remains as the mainstay of management of CAD, which transformed with the introduction of drug-eluting stents (DESs). The first-generation DES designs were composed of stainless steel and had a thick strut (> 100 µm), incorporating a thick polymer coating for carrying the antiproliferative drug. In the second-generation DES designs, both the polymer coating and strut were reduced in thickness, which minimized the bulkiness of the DES structure [2]. However, the second-generation DESs commonly had a permanent polymer coating, such as a fluorinated copolymer as is present in the well-established second-generation durable polymer (DP)-based everolimus-eluting stent (EES), XIENCE (Abbott Vascular, Santa Clara, CA, USA) (Table 1). This EES has an 81-µm strut structured on a L605 cobalt-chromium alloy frame. It has a 7.6-µm non-adhesive, fluorinated copolymeric coating that releases everolimus [2]. Emerging reports showed that although the second-generation DP-DES offered better flexibility and corrosion resistance in comparison to metallic stents, reduced the incidences of cardiac death and MI, and were able to maintain the low rates of restenosis and late stent thrombosis (ST) [3], the challenges related to delayed endothelialization [4] and risk for very late ST remain [5]. In addition to the relatively high rates of target lesion revascularization (TLR) and target vessel-related myocardial infarction (TV-MI) after 1 year, the propensity for delayed endothelialization and very late stent failure remains a challenge for all existing DES designs [4, 6]. Hence, comparative investigations between DES designs are necessary to ascertain the long-term implications of implanting them in increasing CAD populations. Furthermore, the advantages of DP-based DESs in comparison to stainless steel-based first-generation DESs are established. Even the advantages of biodegradable polymer (BP)-DESs in comparison to the first-generation DESs have been established; however, the comparisons between DP-based DES and BP-DESs remain controversial [7].

One novel BP-based DES is the BioMime sirolimus-eluting coronary stent system (Meril Life Sciences Pvt. Ltd., India), which has aroused recent research attention. This is a Conformite Europeenne (CE)-marked device having an ultrathin strut thickness (65 µm) and a proprietary co-polymer matrix (BioPoly™) consisting of biocompatible and bioabsorbable polymers: poly-L-lactic acid (PLLA) and poly-lactic-co-glycolic acid (PLGA). The polymer coating pattern of BioMime sirolimus-eluting stent (SES) is conformal [8], which degrades within 30 - 60 days after complete elution of the drug (sirolimus) that occurs within 30 days [8-11]. The stent is composed of L605 cobalt-chromium alloy, which permits the design of ultrathin struts with a higher yield strength [2, 3, 11, 12]. This SES has a hybrid structure composed of open and closed cells that exclusively prevents side-branch jailing. The novel stent design incorporating the Nexgen™ platform reduces the likelihood of edge dissection and favors adequate stent expansion because of the unique strut width variability that ensures < 3% recoil and 0.29% foreshortening [10, 11]. Earlier, various single-arm investigations of the BioMime SES have been conducted with angiographic and clinical endpoint assessments, which demonstrated satisfactory clinical outcomes, including high procedural success and absence of major adverse cardiac events (MACEs) or ST, as evidenced in the series of meriT trials [9, 13, 14] (Table 2) and the 9-month clinical and angiographic outcomes of the meriT-V trial established that the BioMime SES is not inferior to its contemporary XIENCE EES in terms of minimizing the in-stent late lumen loss (LLL) (0.15±0.27 vs. 0.15±0.29; 95% confidence interval (CI): -0.006 (-0.09; 0.07), P = 0.87) [15].

The long-term implications of implanting different DES devices with respect to the effect of eluting everolimus or sirolimus remain to be clarified. Moreover, the factors contributing to the reduction of the late revascularization rates remain unassorted until now [6, 16], even though there have been large clinical investigations on different BP-DESs and DP-DESs eluting paclitaxel or rapamycin analogues. In that regard, the meriT-V trial compared the novel BP-based SES with the well-established second-generation DP-based XIENCE V [15] (Table 2). Herein, we report the 2-year clinical efficacy and safety among patients with ischemic heart disease randomized and implanted with either BioMime SES or XIENCE EES systems for the treatment of coronary lesions.

Materials and Methods

Trial design and study population

The meriT-V trial was a prospective, randomized, active-controlled trial with a multicenter, open-label design. The study design and trial methodology including the randomization process have been published earlier [15]. Overall, 256 subjects underwent percutaneous coronary intervention (PCI) using

Table 2. Clinical Outcomes of meriT Series Trials

meriT-1 [9]	meriT-2 [13]	meriT-3 [14]	meriT-V [15]
Single-center/first in man	Multicenter	Multicenter/post-marketing	Multicenter
India	India (11 sites)	India (15 sites)	Europe (15 sites), Brazil (three sites)
30 patients/30 *de novo* lesions	250 patients/355 *de novo* lesions	All-comers patients 1,161/1,312 lesions	Randomized; 256 patients (BioMime 170/182 lesions vs. 86/95 lesions XIENCE)
8-month angiographic follow-up	8-month angiographic follow-up	-	9-month angiographic follow-up
Key results (1 year)	Key results (1 year)	Key results (1 year)	Key results (9-month follow-up)
Procedural success: 100%	Procedural success: 99.2%	High procedural success rate	Procedural success: BioMime 99.41% vs. 98.84%
In-stent LLL: 0.15 mm; in-segment LLL: 0.17 mm; binary restenosis: 0%	In-stent LLL: 0.12 mm; in-segment LLL: 0.11 mm	-	-
MACE (cardiac death, MI and TLR); ST: 0%	MACE (cardiac death 0.8%, MI 0.4% or any TLR 5.2%): 6%; ST: 0.4%	MACE (cardiac death 1.4%, MI 0.35% and any TLR 0.52%): 2.35%; ST: 0.1%	MACE (cardiac death, any MI and ID-TVR): BioMime 2.98 vs. XIENCE 7.14%; BioMime vs. XIENCE; Death 0% for both; MI 0.6% vs. 4.76% (any MI); ID-TLR/ID-TVR: 2.38% in both groups; ST: 0% in both groups; TV-MI: BioMime 0.6% vs. XIENCE 1.19%
Indications: silent ischemia	CAD/IHD	CAD	IHD

CAD: coronary artery disease; ID-TLR: Ischemia-driven target lesion revascularization; ID-TVR: Ischemia-driven target vessel revascularization; IHD: ischemic heart disease; LLL: late lumen loss; MACE: major adverse cardiac event; ST: stent thrombosis; TV-MI: target vessel-related myocardial infarction.

the BioMime SES or the XIENCE EES with a 2:1 randomization. This report presents the data of patients who successfully completed the 2-year observation period at 15 different clinical centers in Europe and Brazil.

Eligibility criteria

The intended patient population included patients with myocardial ischemia (including silent ischemia) and ischemic heart disease. In brief, the inclusion criteria were: 1) patient age ≥ 18 years, 2) patients with documented evidence of silent ischemia/angina, *de novo* coronary lesions, 3) lesion length ≤ 46 mm, target lesion reference vessel diameter between 2.5 and 3.5 mm, and 4) willing to attend clinical and angiographic follow-up and provide consent for the total study duration. Exclusion criteria were as follows: patients with 1) evidence of Q-wave or non-Q-wave myocardial infarction (MI) within 72 h preceding the index procedure, unless the creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) enzymes are less than twice the upper limit of normal, 2) prior PCI near the target lesion (within 10 mm or at the lesion site), 3) an untreated significant lesion of > 40% diameter stenosis (DS) remaining proximal or distal to the target site after the planned intervention, 4) significant side-branch lesion (branch diameter > 2 mm) that potentially could be covered by stenting, 5) known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus, everolimus or the contrast media, 6) left main CAD, aorto-ostial lesion, unprotected left main lesion, or a lesion within 5 mm of the origin of the left anterior descending or left circumflex, and 7) calcified target vessel or lesion [15].

Ethical compliance statement

This study was initiated after protocol was reviewed and approved by the local ethics committee and Institutional Review Board by the respective sites according to local regulations. The study was conducted in conformity with the protocol and as per the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP).

Study endpoints

The endpoint of three-point MACEs inclusive of cardiac death, ischemia-driven target vessel revascularization (ID-TVR), and all MI was considered for the combined safety and efficacy evaluation at the 2-year landmark. Other efficacy endpoints were individually evaluated, including ischemia-driven target lesion revascularization (ID-TLR) and late ST for the population that completed the 2-year follow-up. MI was adjudicated as any MI recorded on the basis of clinical symptoms of ischemia or infarction, in association with the electrocardiographic findings and cardiac biomarker findings or pathologic evidence of infarction [17, 18]. Periprocedural MI was defined as total CK-MB elevation > 3× the upper limit of normal [17, 19]. Spontaneous MI, periprocedural MI, and TV-MI were included in the MI event records as per the first

Universal Definition of MI [17, 19]. According to the 2007 Academic Research Consortium (ARC) definitions, ID-TVR was defined as a repeat PCI or coronary artery bypass grafting (CABG) of the target vessel associated with ≥ 50% diameter reduction together with documented ischemia [20]. ID-TLR was defined as revascularization by PCI or CABG associated with DS of ≥ 50% with ischaemia-related symptoms, or DS of ≥ 70% observed even without any signs and symptoms of ischemia at the time of follow-up angiography, as per the 2007 ARC definition [20]. The cases of ST were assessed based on the definitions by the 2007 ARC document [20].

Statistical analysis

The results were reported as mean ± standard deviations for continuous variables and as counts and percentages for categorical variables. The P-values were calculated using the one-sided, two sample, equal-variance *t*-test for continuous data and Fischer's exact test or Pearson's Chi-squared test for categorical data. The P-value < 0.05 was considered for statistical significance. With reference to the SPIRIT III study [21] for the XIENCE arm and the meriT-2 study for the BioMime arm, we had earlier estimated the true difference (δ) = (μT - μS) between both groups to be 0.04 mm as the mean composite endpoint rate difference at the 9-month follow-up with standard deviation (σ) of 0.41 mm for both treatment groups (0.41 mm being the highest σ for XIENCE V as per SPIRIT III study).

Since the primary endpoint was in-stent LLL that is measured per lesion, with a randomization ratio of 2:1 and a non-inferiority margin of 0.195 mm, the minimum necessary study sample size was 258 patients (control arm: 86 and study arm: 172). This sample size was deemed adequate to reach the minimum necessary sample size of 231 subjects for the efficacy evaluation. As per the *post-hoc* power calculation using the one-sided, two-sample, equal-variance, *t*-test with a significance level (α) = 0.05 (α = 0.05, β = 0.10, both one-sided) and assuming 1.2 lesions per patient, 154 patients for BioMime SES arm and 77 for XIENCE EES arm were required to achieve target 88.4% power for non-inferiority determination. Whereas, the *post-hoc* power calculation revealed that the meriT-V achieved 88.6% power after accounting the drop-out rates and applying the exclusion criteria; the actual arm sizes were 170 and 86 subjects.

Results

Of the 256 patients enrolled, 98.44% patients (n = 252/256) completed the 2-year follow-up. The BioMime arm had a slightly higher cardiac risk status as the XIENCE arm, though without statistically significance. This arm included a higher proportion of patients having a previous MI (n = 37/168 patients). The total study population had a high proportion of patients with stable angina (BioMime vs. XIENCE: 68.24% vs. 70.9%, P = 0.66) (Table 3). Detailed baseline characteristics of the study population have already been published earlier [15]. For the study population that completed the 2-year follow-up, the three-point MACEs for both arms were slightly high (BioMime vs. XIENCE: 7.74% vs. 9.52%, P = 0.63) including significantly lower cumulative incidence of MI in the BioMime arm (BioMime vs. XIENCE: 1.79% vs. 5.95%; P = 0.17). This trend of non-significant differences was reflected in the incidences of ID-TVR as well, including the TLR incidence (BioMime vs. XIENCE: 5.95% vs. 3.57%; P = 0.45) (Table 4).

In the BioMime arm, definite or probable ST did not occur over the 2-year study period, while one instance (1.19%) was documented in the XIENCE arm (P = 0.16). During the entire observational period of the trial, no events of cardiac death had occurred while the ID-TVR (non-TLR) across both the study arms (2.38%; P = 0.99) were similar. The 2-year clinical outcomes have been summarized as cumulative frequencies with percentages (Table 4).

Discussion

The current study is the first-ever global randomized controlled clinical trial that provided long-term follow-up data on a novel ultrathin (65 µm) strut SES having the PLLA-PLGA coating and eluting sirolimus with the lowest drug dose density (1.25 µg/mm^2) [10] and the best-in-class second-generation DES, XIENCE V. Although the meriT-V trial enrolled a limited population, the outcomes data provide substantial evidence on the safety of both these devices, as minimal MACE, negligible deaths, and ST were observed until the 2-year follow-up. The cumulative MACE of the BioMime arm (7.74%) included 10 revascularizations of the target vessel including those of the non-target lesions, three MI (1.79%), and no cardiac deaths. The cumulative frequency of MI for this study device is quite low, in comparison to that reported for contemporary devices (Table 5) [22-28].

Both the stents studied have a cobalt-chromium platform and a conformal coating of polymer [8]. The different DES design characteristics (such as type of polymer, strut thickness) can affect the long-term clinical outcomes such as ID-TLR, ID-TVR, and incidence of MI. In this trial, all types of MI including spontaneous MI, periprocedural MI, and TV-MI were included in the endpoint assessments. Of the total eight MI incidences across both the arms, two were related to the target vessel (one in each arm). Whereas, the frequency of revascularizations was numerically higher in the BioMime arm (10 ID-TLR events) in comparison to the XIENCE arm (three ID-TLR events), which could be attributed to the 2:1 randomization that provided an unequally larger arm size of the BioMime arm. Hence, the current 2-year data of ID-TVR and ID-TLR have insignificant differences (BioMime vs. XIENCE = 5.95% vs. 3.57%, 95% CI: -3.86 to 8.62; P = 0.45). Furthermore, we observed that the frequency of MACE was high in the first 12 months, which slowed down considerably after the 1-year landmark. No revascularizations were recorded after 1 year following PCI for both the study arms and only two incidences of MI have occurred after 1 year. We have conducted a Kaplan-Meier analysis of the individual components of MACE except for cardiac death (Figs. 1 and 2).

Reduction in strut thickness affects the late-term clinical

Table 3. Baseline Characteristics and Medical History of the Patients in BioMime™ and XIENCE Arm [15]

Variables	BioMime™ SES (N = 170)	XIENCE EES (N = 86)	P-value (BioMime™ SES vs. XIENCE EES)
Age (years), mean ± SD	64.33 ± 9.57	64.70 ± 8.99	0.75
Male, n (%)	111 (65.29)	53 (61.63)	0.56
Body mass index (kg/m^2)	28.64 ± 4.45	29.40 ± 4.39	0.20
Cardiac risk factors, n (%)			
Diabetes mellitus	41 (24.12)	18 (20.93)	0.57
Hypertension	125 (73.53)	68 (79.07)	0.11
Dyslipidemia	118 (69.41)	59 (68.60)	0.89
Chronic lung disease	9 (5.29)	10 (11.63)	0.07
Smokers	71 (41.76)	41 (47.67)	0.37
History of CAD	67 (39.41)	29 (33.72)	0.37
Renal insufficiency	4 (2.35)	2 (2.33)	0.99
Previous MI	37 (21.76)	13 (15.12)	0.25
Previous PCI	31 (18.24)	14 (16.28)	0.69
Cardiac status, n (%)			
Stable angina	116 (68.24)	61 (70.9)	0.66
Unstable angina	25 (14.71)	12 (13.95)	0.87
Asymptomatic	16 (9.41)	5 (5.81)	0.32
STEMI	3 (1.76)	0 (0.0)	0.25
NSTEMI	10 (5.88)	8 (9.3)	0.31
LVEF, %	55.86 ± 7.22	56.82 ± 10.13	0.40

CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; N: number of patients; PCI: percutaneous coronary intervention; SD: standard deviation; ST: stent thrombosis; STEMI: ST elevation myocardial infarction.

outcomes, including the reduction of restenosis and incidence of target lesion failure (TLF). As pointed by Bangalore et al, in their meta-analysis of 10 randomized controlled trials (RCTs) (11,658 patients) [29], the newer-generation BioMime SES, Orsiro SES, and MiStent BP-DESs (60 - 65 µm) showed a moderate reduction (16%) in the incidence of TLF compared

Table 4. Cumulative Clinical Outcomes of Both Study Arms Through the 2-Year Follow-Up

Clinical events	Follow-up						
	In-hospital (N = 256)		1 year (N = 252)		2 years (N = 252)		P-value (at 2 years)
	BioMime (N = 170)	XIENCE (N = 86)	BioMime (N = 168)	XIENCE (N = 84)	BioMime (N = 168)	XIENCE (N = 84)	BioMime vs. XIENCE
Death, n (%)							
Cardiac death	0	0	0	0	0	0	NA
Non-cardiac death	0	0	1 (0.6%)	0	2 (1.19%)	0	0.32
Myocardial infarction	1 (0.59%)	1 (1.16%)	2 (1.19 %)	4 (4.76%)	3 (1.79%)	5 (5.95%)	0.17
ID-TLR	0	0	10 (5.95%)	3 (3.57%)	10 (5.95%)	3 (3.57%)	0.45
ID-TVR (including TLR)	0	0	10 (5.95%)	3 (3.57%)	10 (5.95%)	3 (3.57%)	0.45
ID-TVR (non-TLR)	0	0	4 (2.38%)	2 (2.38%)	4 (2.38%)	2 (2.38%)	0.99
Stent thrombosis, n (%)							
Definite or probable/probable	0	0	0	1 (1.19%)	0	1 (1.19%)	0.16
Total of three-point MACE	1 (0.59%)	1 (1.16%)	11 (6.55%)	7 (8.33%)	13 (7.74%)	8 (9.52%)	0.6170

Values are presented as n (%). ID-TLR: ischemia-driven target lesion revascularization; ID-TVR: ischemia-driven target vessel revascularization; MACE: major adverse cardiac event; N: number of patients.

Table 5. Clinical Outcomes of Contemporary Trials on BP-DES and DP-DES Designs

Trials	Study details	Cardiac death	TLR	TVR	MI	TV-MI	Late ST	ST	Other events
BIOSCIENCE (2-year follow-up) [24]	Orsiro arm: 1,063 patients (1,594 lesions); XIENCE arm: 1,056 patients (1,545 lesions); patients with presence or absence of STEMI	3.2% vs. 3.2%	6.4% vs. 5.8 %	8.1% vs. 7.5%	6.1% vs. 7.2%	4.1% vs. 4.5%	-	Definite/probable 3.9% vs. 4.9%; definite 1.1% vs. 0.8%	CI-TVR 7.7% vs. 6.8%; CI-TLR: 6.0% vs. 5.1%; TLF 10.5% vs. 10.4%; TVF 12.2% vs. 12.3%
DESSOLVE III (2-year follow-up) [25]	MiSTENT (703/1,398 patients) vs. XIENCE (695/1,398 patients); 20 centers in Europe; all comers	3.0% vs. 2.0%	5.1% vs. 6%	6.9% vs. 8.5%	3.0% vs. 2.8%	2.7% vs. 2.3%	Late 0.4% vs. 0.6%; very late ST 0.3% vs. 0.3%	Definite/probable 0.9% vs. 1.3%; definite 0.6% vs. 1%	CI-TVR 5.9% vs. 7.7%; CI-TLR: 4.6% vs. 5.4%; DOCE/ TLF: 8.7% vs. 8.6%
BIOSTEMI trial (2-year follow-up) [22]	Orsiro (649/1,300 patients/651 lesions) vs. XIENCE (651/1,300 patients/806 lesions); 10 centers in Switzerland; first STEMI	2.9% vs. 3.2%	2.8% vs. 5.2%	3.4% vs. 6.3%	3.7% vs. 3.1%	1.5% vs. 2.0%	-	Definite/probable 2.0% vs. 2.3%; definite 1.4% vs. 1.8%	TLF: 5.1% vs. 8.1%; CI-TVR 3.1% vs. 6.1%; CI-TLR: 2.5% vs. 5.1%; TVF 6% vs. 9.4%
BIOFLOW-V trial (3-year follow-up) [23]	Orsiro (884/1,334 patients/1,051 lesions) vs. XIENCE (450/1,334 patients/561 lesions); 92 international randomized study centers; non-STEMI/ACS	1.1% vs. 1.2%	-	-	-	5% vs. 9.2%	Late and very late ST 0.1% vs. 1.2%	-	ID-TLR: 3.2% vs. 6.7%; MACE: 11.5% vs. 17.5%; TVF: 9.7% vs. 16.2; TLF: 8.2% vs. 13.6%
BIOFLOW-II trial (5-year follow-up) [26]	Orsiro (298 patients/332 lesions) vs. XIENCE (154 patients/173 lesions); 24 centers in eight European countries; *de novo* lesions	1.7% vs. 2.8%	-	-	4.5% vs. 6.2%	3.4% vs. 3.3%	-	Overall ST 0.7% vs. 2.8%; definite 0% vs. 0.7%; probable 0%	CI-TVR 12.6% vs. 10.1%; CI-TLR: 6.3% vs. 6.7%; TLF 10.4% vs. 12.7%; TVF 15.6% vs. 12.7%
BIOFLOW-V trial (5-year follow-up) [23]	Orsiro (884 patients) vs. XIENCE (450 patients); 92 randomized study centers; non-STEMI/ACS	2.6% vs. 1.9%	-	-		6.6% vs. 10.3%	Late and very late ST 0.3% vs. 1.6%	-	ID-TLR: 5.9% vs. 7.7%; ID-TVR: 9.6% vs. 12.4%; TLF 12.3% vs. 15.3%; TVF 15.2% vs .19%; MACE: 18.3% vs. 21.4%
BIORESORT trial (3-year follow-up) [27]	1,506/3,514 patients; Orsiro (525) vs. synergy (496) vs. resolute integrity (485); four clinical sites; all-comer trial	1.3% vs. 1.8% vs. 2.1%	1.7% vs. 2.5% vs. 4.4%	-	-	2.7% vs. 2.7% vs. 4.0%	-	Definite or probable ST 0.6% vs. 1.2% vs. 1.5%; definite ST 0.4% vs. 0.6% vs. 1.1%	TLF: 5.2% vs. 6.5% vs. 8.7%
SCAAR registry [28]	4,561 patients implanted with Orsiro and 69,570 n-DES group (XIENCE PRIME, XIENCE Xpedition and XIENCE ProX, PROMUS Element, Plus and Promus PRIMER, Resolute Integrity and Resolute, Onyx, SYNERGY; undergoing PCI	-	1.6% vs. 2.3%		6.0% vs. 5.2%		Late ST: 0.5% vs. 0.6%; very late ST: 0.7% vs. 0.8%	Definite ST: 0.7% vs. 0.8%	

Values are n (%). ACS: acute coronary syndrome; BP: biodegradable polymer; CI-TLR: clinically-indicated target lesion revascularization; CI-TVR: clinically-indicated target vessel revascularization; DP: durable polymer; ID-TLR: ischemia-driven target lesion revascularization; ID-TVR: ischemia-driven target vessel revascularization; MACE: major adverse cardiac event; N: number of patients; n-DES: new-generation drug-eluting stent; PCI: percutaneous coronary intervention; ST: stent thrombosis; STEMI: ST elevation myocardial infarction; TLF: target lesion failure; TVF: target vessel failure; TV-MI: target vessel-related myocardial infarction.

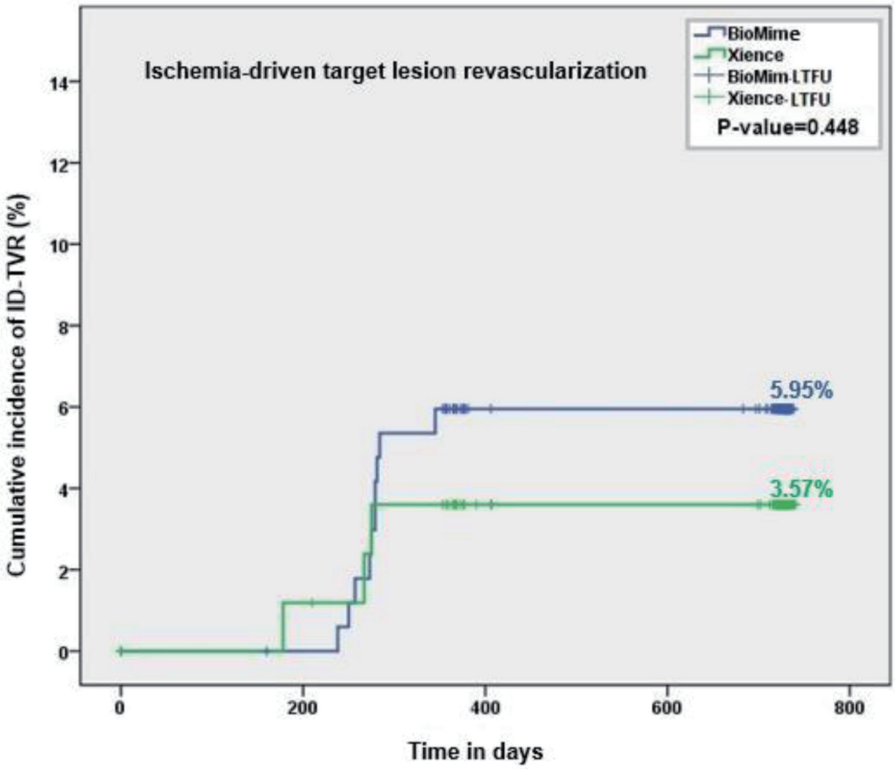

Figure 1. Kaplan-Meier analysis of ID-TVR up to the 2-year follow-up. ID-TVR: ischemia-driven target vessel revascularization.

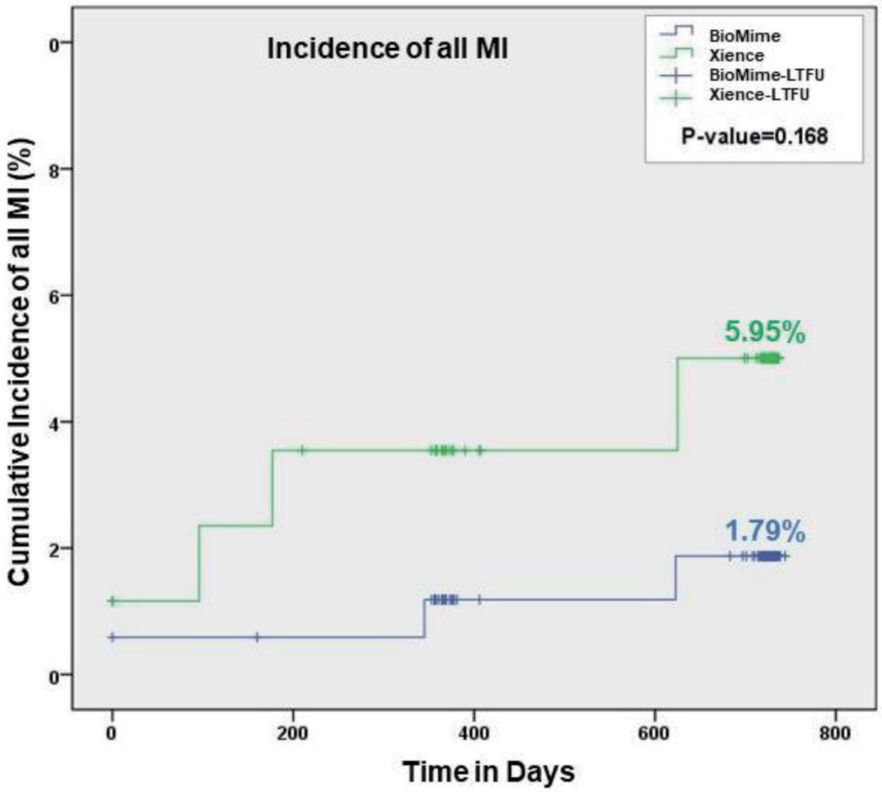

Figure 2. Kaplan-Meier curve of the cumulative incidence of all MI events in both study arms. MI: myocardial infarction.

to the thicker strut DES counterparts—Resolute Integrity, Nobori, and XIENCE (81 - 120 µm). In this meta-analysis, TLF was a composite of cardiovascular death, TV-MI, or ID-TLR and evaluated for 1-year follow-up. Furthermore, Bangalore et al noted that the low risk of TV-MI with BP-DESs contributed to the reduction in TLF [29]. Among the BP-DESs assessed in that meta-analysis, BioMime has a consistent ultrathin strut thickness (65 µm) along with MiStent (64 µm), in contrast to Orsiro SES that has a 60-µm strut for stents up to the 3.0 mm diameters and 80 µm struts for 3 to 4.5 mm diameters [22].

The newer-generation BP-DES Orsiro has shown substantial reduction in the incidence of TLF, as observed in the BIOFLOW V trial over 12 months (6%), 3 years (8.2%), and 5 years (12.3%) [23, 30, 31] (Table 5). In comparison, the 2-year MACEs of the BioMime arm in this trial seem well-consistent; however, extended follow-up studies would be necessary to ascertain the long-term outcomes. From the meta-analysis conducted by El-Hayek et al on RCTs evaluating the efficacy and safety between DP-based and BP-based DESs (16 RCTs, 19,886 patients), it is clarified that BP-DESs are superior to first-generation DP-DES designs in reducing the incidence of MI and cardiac death. Moreover, they also remarked that very few studies (six of 16) have evaluated the outcomes after the 1-year landmark. They reported that the risk for TVR was similar between BP-DES and DP-DES (risk ratio (RR): 1.12, 95% CI: 0.93 to 1.35; P = 0.25). Even the incidence of very late ST was comparable between both arms (BP-DES vs. DP-DES: 0.37% vs. 0.45%, RR: 0.87, 95% CI: 0.49 to 1.53; P = 0.62) [7]. This meta-analysis concluded that in terms of TVR, cardiac mortality, and late ST, both BP-DES and DP-DES are comparable, while the frequency of very late ST (beyond 1 year) was only slightly higher for DP-DES without statistical significance (0.98% vs. 1.15%). The authors postulated that the current generation of BP-DESs and DP-DESs have a similar safety and efficacy profile [7].

The novel sirolimus-eluting ultrathin-strut BioMime stent is a CE-marked, newer-generation device incorporating a biodegradable copolymeric matrix with favorable reports of biocompatibility and enhanced drug deliverability [31]. Its novel design with an ultrathin-strut thickness (65 µm) is aimed at reducing intra-arterial injury and improving the deliverability of sirolimus through the 2-µm BP coating that degrades within 30-60 days [9, 10, 32].

In continuation of the previously reported single-arm meriT trials that show acceptable safety and efficacy outcomes of the BioMime SES up to the 1-year follow-up (Table 4), the 9-month outcomes of meriT-V trial show the non-inferiority between both DESs in terms of LLL (0.15±0.27 vs. 0.15±0.29; 95% CI: -0.006 (-0.09; 0.07), P = 0.87) [15]. Furthermore, the cumulative MACE of 8.1% (inclusive of 2.09% cases of cardiac deaths, 1.34% cases of MI, and 0.5% ST) was reported in the Billar registry for a large study population (n = 696) comprising patients with long, diffuse lesions treated using the non-tapered BioMime SES [33].

The design of this ultrathin-strut BP-DES incorporates a L605 cobalt-chromium platform (Nexgen™), which is considered superior to the stainless steel-based metallic platforms in terms of: 1) higher yield strength, 2) better radiopaque visibility, and 3) enabling the design of ultrathin struts that is targeted at reducing ST and late restenosis [8]. Hence, we can assert that this device has potential features necessary for reducing late (> 6 months) restenosis and ST, as observed in earlier single-arm multicenter studies on this device (Table 4), where minimal ST rates were reported (0-0.4%) up to the 1-year follow-up [9, 13, 14]. Similarly, minimal ST was observed in the meriT-V trial at the completion of 2-year follow-up for both XIENCE and BioMime arms.

As reported above, the 2-year outcomes of the meriT-V trial are congruent with the outcomes reported in contemporary literature for respective DESs (Table 5). The overall outcomes of the BioMime arm suggest that the BioMime SES possesses the potential characteristics necessary for reducing the late-term incidence of ID-TVR, MI, cardiac death, and very late ST (Table 4).

Regarding the numerical differences in the incidences of all MI between both study arms, we noted that in the BioMime SES arm, one elderly patient aged 76 years had prior PCI and MI, with liver disease, chronic lung disease, renal insufficiency, peripheral vascular disease, along with traditional cardiac risk factors (dyslipidemia and hypertension). This patient experienced recurrent MI after few months of the index PCI and underwent repeat PCI. The MI incidences in this group are relatively low (1.79%). Whereas, in the XIENCE arm (5.95%), one younger, highly comorbid patient experienced two recurrent MI events, which contributed to the high MI incidence rate in the XIENCE arm. This patient had lung and renal disease, along with peripheral vascular disease and was a regular smoker. The other MI incidences recorded of the XIENCE arm were among non-smoking patients who had significant underlying systemic diseases (liver disease, anemia, lung disease, and renal insufficiency) and cardiac risk factors (hypertension, and peripheral vascular disease). These factors may have contributed to the relatively higher MI frequency in the XIENCE arm.

It is worth noting that among the 10 patients in the BioMime arm who underwent repeat revascularizations, there were commonly younger patients. Moreover, 50% of these patients had diabetes. The revascularizations were more frequent in patients with prior MI or prior PCI in this arm. In addition, four of the revascularizations were in the non-target lesion. These potentially contributory factors were notable in the BioMime arm for the slightly high ID-TVR endpoint rate.

Limitations

The limitations of the trial need to be acknowledged, including the small sample size and the short length of follow-up. However, since it is a prospective study, we believe that the study results hold high clinical significance particularly for the management of the patients with stable CAD, including myocardial ischemia. We have performed a *post-hoc* power calculation using a one-sided, two-sample, equal-variance *t*-test with the actual trial drop-out rates, which revealed that the study had obtained 88.6% power. Nevertheless, we ascertain the need for further larger randomized controlled studies with both devices that have a longer duration of observation. The increasing evidence of the efficacy and clinical outcomes of BioMime SES

compared with contemporary BP- and DP-based designs would further establish its efficacy among DESs.

Conclusion

The objective comparisons between the newer-generation DES (BioMime SES) and the conventional DP-based XIENCE EES affirm that both the devices had acceptable safety outcomes up to the 2-year follow-up. Most importantly, the frequencies of ID-TVR, ID-TLR, and MI declined considerably after the 1-year timeframe in both the arms. Hence, the study shows acceptable efficacy of the respective devices in reducing the need for repeat vascularization and late-term ST. Since this trial had a moderate sample size, further research on these devices would be necessary to ascertain the satisfactory long-term safety and efficacy for increasing CAD populations.

Acknowledgments

None to declare.

Financial Disclosure

Meril Life Sciences Pvt. Ltd., India, sponsored the meriT-V trial.

Conflict of Interest

Dr. Udita Chandra is a fulltime employee of Meril Life Sciences Pvt. Ltd., India. The other authors affirm that that the study was carried out without any commercial or financial ties that might be viewed as a potential conflict of interest.

Informed Consent

Prior to enrolment, written informed consent was obtained from all subjects randomized in the study arms.

Author Contributions

All authors conceptualized and planned the study particulars. AA, RC, SK, EK, ST, AE, OH, MM, FF-O, KM, PL, RB, AI, JK, PK, LJ recruited and conducted the trial protocol at their respective sites. UC was involved in the drafting, editing, and reviewing of the manuscript. All authors have reviewed the final manuscript and agree to take responsibility for the content of the published manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ACS: acute coronary syndrome; ARC: Academic Research Consortium; BP: biodegradable polymer; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CE: Conformite Europeenne; CK: creatine kinase; CK-MB: creatine kinase-myocardial band; DES: drug-eluting stent; DP: durable polymer; DS: diameter stenosis; EES: everolimus-eluting stent; ICH-GCP: International Conference on Harmonization Guideline for Good Clinical Practice; ID-TLR: ischemia-driven target lesion revascularization; ID-TVR: ischemia-driven target vessel revascularization; LLL: late lumen loss; MACE: major adverse cardiac event; MI: myocardial infarction; PCI: percutaneous coronary intervention; PLLA: poly-L-lactic acid; PLGA: poly-lactic co-glycolic acid; RCTs: randomized controlled trials; SES: sirolimus-eluting stent; ST: stent thrombosis; TLF: target lesion failure; TLR: target lesion revascularization; TV-MI: target vessel-related myocardial infarction

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