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Five-year outcomes of chronic total occlusion treatment with a biolimus A9-eluting biodegradable polymer stent versus a sirolimus-eluting permanent polymer stent in the LEADERS all-comers trial

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Abstract

Background: *Few data are available on long-term follow-up of drug-eluting stents in the treatment of chronic total occlusion (CTO). The LEADERS CTO sub-study compared the long-term results in CTO and non-CTO lesions of a Biolimus A9™-eluting stent (BES) with a sirolimus-eluting stent (SES).*

Methods: *Among 1,707 patients enrolled in the prospective, multi-center, all-comers LEADERS trial, 81 with CTOs were treated with either a BES (n = 45) or a SES (n = 36). The primary endpoint was the occurrence of major adverse cardiac events (MACE): cardiac death, myocardial infarction (MI) and clinically-indicated target vessel revascularization (TVR).*

Results: *At 5 years, the rate of MACE was numerically higher in the CTO group than in the non-CTO group (29.6% vs. 23.3%; p = 0.173), with a significant increase in the incidence of target lesion revascularization (TLR) (21.0 vs. 12.6; p = 0.033), but no difference in stent thrombosis (ST). Patients with CTO receiving a BES demonstrated a lower incidence of MACE (22.2% vs. 38.9%; p = 0.147) with a significant reduction in TLR compared to patients receiving a SES (11.1% vs. 33.3%, p = 0.0214) with an incidence similar to that observed in the non-CTO group treated with BES (11.6%). Definite ST at 5 years nearly halved in the BES group (4.4% vs. 8.3%, p = 0.478) with no ST in the BES group after the first year (0% vs. 8.3%, p for interaction = 0.009).*

Conclusions: *The use of a BES showed a reduction in MACE, TVR, TLR, and ST over time in the CTO subset with similar outcome as for non-CTO lesions.* (Cardiol J 2016; 23, 6: 626–636)

Key words: chronic total occlusion, biodegradable polymer biolimus-eluting stents, percutaneous coronary interventions

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Introduction

Revascularization of chronic total occlusion (CTO) is grossly underutilized in patients who undergo percutaneous coronary interventions (PCI) [1–3]. The initial success is lower and a high rate of re-occlusion burdened the initial experiences with balloon angioplasty and bare metal stents (BMS) [4, 5]. The introduction of new devices, such as dedicated guidewires, low profile balloons, or microcatheters [6] has increased the immediate success rate, however greater complexity of lesions treated may potentially exacerbate the risk. Drug-eluting stents (DES) have reduced restenosis and reocclusion when compared with BMS [7–11], but a recent publication of long-term data still reports worse results than those expected in non-CTO lesions [12]. Although second generation DES have greater polymer biocompatibility and different mechanical properties than first generation paclitaxel- and sirolimus-eluting stents (PES and SES), there are few data on long-term results obtained with these devices in patients with CTO [13, 14] and on the differences with non-CTO lesions or CTO lesions treated with first generation DES.

The LEADERS CTO sub-study is a post-hoc analysis of a randomized multicenter trial and was designed to compare the results after 5 years of follow-up of CTO lesions treated with a Biolimus A9-eluting stent with abluminal biodegradable polymer coating (BES) and a sirolimus-eluting permanent polymer stent (SES).

Methods

Study design and population

LEADERS was a prospective, multi-center, assessor-blind, non-inferiority trial involving 12 European centers (Belgium, France, Germany [3 centers], Netherlands, Poland, Switzerland [2 centers] and the United Kingdom), designed to compare the safety and efficacy of a BES with a biodegradable polymer (BioMatrix Flex™, Biosensors Europe SA, Morges, Switzerland) with a SES with durable polymer (Cypher® Select™, Cordis, Miami, USA) in a "real world, all-comers" patient population. The LEADERS trial study design is reported elsewhere [15]. The LEADERS trial was approved by all institutional Ethics Committees.

Unlike most other DES studies, CTO was not an exclusion criterion. CTO subgroup analysis is a post-hoc analysis performed on the LEADERS data set. Patients were divided according to the presence or absence of pre-procedural CTO, based on the pre-procedure angiogram and technical details of the intervention. Patients with at least one treated CTO lesion were classified as treated CTO patients. CTO was defined as a 100% coronary artery occlusion, with thrombolysis in myocardial infarction (TIMI) flow grade equal to 0 and duration of minimum 3 months. The occlusion duration was either angiographically proven or clinically estimated, according to the onset of symptoms or the timing of acute coronary events in the territory subtended by the CTO artery.

Angiography was analyzed at one core laboratory (Cardialysis, Rotterdam, The Netherlands) with the assessor blinded to the allocated stent.

Procedures and devices

Biolimus-eluting stents were available in diameters of 2.25, 2.5, 3.0, and 3.5 mm and in lengths of 8, 11, 14, 18, 24, and 28 mm. Sirolimus-eluting stents were available in diameters of 2.25, 2.5, 2.75, 3.0, and 3.5 mm and in lengths of 8, 13, 18, 23, 28, and 33 mm. Both platforms are made of stainless steel but BES struts are thinner (120 μm) than SES struts (140 μm). The main difference is represented by the drug, i.e. biolimus A9 versus sirolimus, and polymer used, i.e. a biodegradable polylactic acid coating in the BES versus a durable polymer covering in the SES.

Balloon angioplasty and stent implantation were performed according to standard techniques. In the CTO group, either anterograde or retrograde recanalization strategies were allowed, no restrictions were applied to the material used. Full lesion coverage with the index stent was the routine strategy.

Before or at the time of the procedure, patients were given at least 75 mg of acetylsalicylic acid (ASA), 300–600 mg loading dose of clopidogrel, and unfractionated heparin in a dose of at least 5,000 IU or 70–100 IE/kg. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator.

All patients were discharged on at least 75 mg daily ASA indefinitely and clopidogrel 75 mg daily for at least 12 months.

Outcomes

In-hospital adverse events were assessed and clinical follow-up was planned up to 5 years.

The primary endpoint was a composite of cardiac death, myocardial infarction (MI), and clinically indicated target vessel revascularization (TVR). The definition of cardiac death included

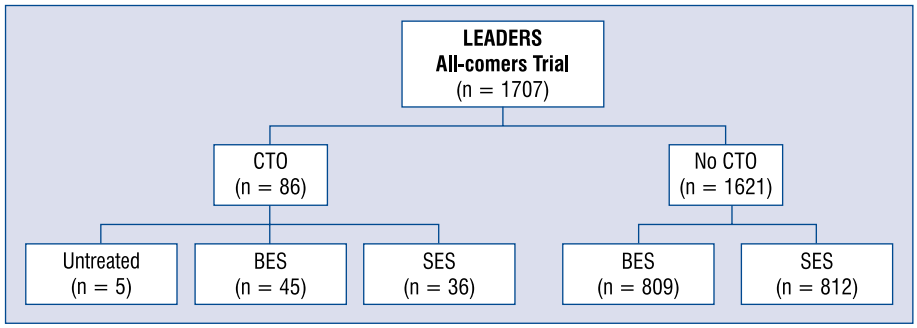

Figure 1. Study flow chart; BES — biodegradable polymer biolimus-eluting stents; CTO — chronic total occlusion; SES — sirolimus-eluting stent.

any death due to immediate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), deaths related to the procedure, including those related to concomitant treatment, unwitnessed death, and death of unknown cause. MI was defined using the electrocardiographic criteria of the Minnesota code manual or as a measurement of creatine kinase concentrations to more than double normal, with positive concentrations of creatine kinase-MB or troponin I or T. TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target lesion, including upstream and downstream branches and the target lesion itself. Revascularization was regarded as clinically indicated if the stenosis of the treated lesion was at least 50% of the lumen diameter on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms, or if the diameter stenosis was at least 70% irrespective of the presence or absence of ischemic signs or symptoms.

Secondary endpoints were cardiac death, death from any cause, MI, clinically-indicated target lesion revascularization (TLR) defined as a repeated revascularization due to a stenosis within the stent or within a 5 mm border proximal or distal to the stent, repeated PCI (re-PCI), any TVR, or stent thrombosis (ST) according to the definitions of the Academic Research Consortium [16].

Statistical analysis

The statistical design of the LEADERS trial is described elsewhere [15].

A stratified post hoc analysis of clinical and angiographic outcomes was performed within the treated CTO and non-CTO groups, with patients compared based on the randomized study stents (BES or SES) implanted.

Discrete data were summarized as frequencies (n, %) and compared by Fisher's exact test. Continuous data were expressed as mean ± standard deviation and compared by Student's t-test. The Cox proportional hazards model was used to compare clinical outcomes among groups. Survival curves were constructed for time-to-event variables using Kaplan-Meier estimates, and compared by the log-rank test. All p-value and confidence intervals are two-sided at 5% level.

Results

A total of 1,707 patients were enrolled in the LEADERS trial. Among them 86 had a CTO lesion, of which 81 patients were successfully treated with either the study or comparator stent (45 patients with BES vs. 36 patients with SES). The non-CTO group included 1,621 patients, of which 809 were treated with BES versus 812 with SES (Fig. 1).

Baseline characteristics

Baseline characteristics according to CTO and non-CTO group and type of stent implanted in each group are shown in Table 1.

There were no major baseline clinical differences between patients with and without CTOs, except for a greater frequency of ST segment elevation MI in the non-CTO group and a higher incidence of prior MI in the CTO group.

Compared to non-CTO lesions, CTO lesions were significantly more complex as reflected by greater lesion length with a higher Syntax score, resulting in a greater number of stents implanted. Within the CTO group, there was a higher number of lesions treated in the SES group compared to the BES group (1.89 ± 1.04 vs. 1.44 ± 0.66;

Table 1. Baseline characteristics. The groups are divided according to the type of revascularization and stent.

	Treated CTO (n = 81)			No CTO (n = 1621)			P: Treated CTO vs. no CTO
	BES (n = 45)	SES (n = 36)	P: BES vs. SES	BES (n = 809)	SES (n = 812)	P: BES vs. SES	
Age [years]	62.0 ± 10.5	64.9 ± 12.4	0.264	64.7 ± 10.8	64.5 ± 10.6	0.658	0.277
Male	38 (84.4)	27 (75.0)	0.401	602 (74.4)	605 (74.5)	1	0.294
Diabetes	12 (26.7)	5 (13.9)	0.182	210 (26.0)	185 (22.8)	0.148	0.595
Hypertension	28 (62.2)	27 (75.0)	0.242	600 (74.3)	589 (72.7)	0.499	0.303
Hypercholesterolemia	36 (80.0)	27 (75.0)	0.603	522 (64.6)	552 (68.1)	0.141	0.039
Currently smoking	9 (20.0)	9 (25.0)	0.603	195 (24.1)	205 (25.3)	0.604	0.693
Family history	22 (48.9)	19 (52.8)	0.824	316 (39.1)	355 (43.8)	0.055	0.107
Unstable angina	5 (11.1)	5 (13.9)	0.745	185 (22.9)	175 (21.6)	0.550	0.038
STEMI	0 (0)	1 (2.8)	0.444	135 (16.7)	139 (17.1)	0.843	< 0.001
Chronic heart failure	3 (6.7)	1 (2.8)	0.625	20 (2.5)	29 (3.6)	0.246	0.316
Prior MI	24 (53.3)	17 (47.2)	0.658	251 (31.1)	259 (32.0)	0.708	< 0.001
Prior PCI	18 (40.0)	10 (27.8)	0.347	294 (36.4)	300 (37.0)	0.797	0.725
Prior CABG	5 (11.1)	7 (19.4)	0.354	85 (10.5)	100 (12.3)	0.274	0.372
LV ejection fraction [%]	52.8 ± 12.7	57.6 ± 12.9	0.250	56.0 ± 11.2	55.3 ± 12.4	0.360	0.613
Multivessel disease	14 (31.1)	12 (33.3)	1	192 (23.7)	164 (20.2)	0.093	0.040
Number of lesions*	1.44 ± 0.66	1.89 ± 1.04	0.029	1.46 ± 0.69	1.41 ± 0.70	0.113	0.037
Lesions length† [mm]	45.4 ± 24.9	44.4 ± 23.1	0.843	21.0 ± 15.0	19.5 ± 13.5	0.029	< 0.001
Long lesion (> 20 mm)	35 (79.6)	27 (77.1)	1	223 (27.8)	192 (23.9)	0.087	< 0.001
Severe calcification	5 (17.9)	7 (28.0)	0.514	141 (20.8)	147 (22.0)	0.595	0.865
Syntax score	15.2 ± 8.7	20.0 ± 8.6	0.048	13.2 ± 8.6	13.1 ± 8.7	0.819	< 0.001
Number of stents implanted per patient‡	2.96 ± 1.46	3.14 ± 1.64	0.597	1.90 ± 1.20	1.80 ± 1.09	0.081	< 0.001
Total stent length [mm]	65.5 ± 37.0	68.0 ± 35.6	0.945	34.2 ± 22.1	33.3 ± 20.6	0.440	< 0.001

N (%) or mean ± standard deviation; *Number of lesions according to Core Lab (QCA data), regardless if they were total occluded pre-procedure; †Sum of the length of the lesions according to QCA analysis, regardless if they were total occluded; ‡Investigator reported per lesion the number of stents and the stent length per used stent. The total number of stents and total stent length per patient is calculated, regardless if the lesions were total occluded pre-procedure; BES — biodegradable polymer biolimus-eluting stents; CABG — coronary artery bypass grafting; CTO — chronic total occlusion; LV — left ventricular; MI — myocardial ibfarction; PCI — percutaneous coronary intervention; SES — sirolimus-eluting stent; STEMI — ST elevation myocardial infarction

p = 0.029), as well as the Syntax score (20.0 ± 8.6 vs. 15.2 ± 8.7; p = 0.048). No significant differences were found with regard to stent length and number of stents implanted (Table 1).

Angiographic and procedural characteristics for the CTO group demonstrate that the right coronary artery was more frequently targeted in the BES group (Table 2).

CTO versus non-CTO lesions

At 5-year follow-up, the incidence of overall major adverse cardiac events (MACE) was similar between the CTO and non-CTO groups (29.6% vs. 23.3%; p = 0.173). Likewise, no significant differences were found in the rate of cardiac death, MI and both clinically-indicated and any TVR (Table 3). Clinically-indicated TLR did not show any statistical significant difference in the CTO and non-CTO groups (16% vs. 10.5%; p = 0.13), but the number of any TLR was significantly higher in the CTO group (Fig. 2A). The incidence of definite ST and definite plus probable ST was percentually higher, yet not significant in the CTO compared to non-CTO group (Table 3).

CTO lesions: BES versus SES

Patients with CTO treated with BES had a non-significant lower incidence of MACE (22.2% vs. 38.9%; HR 0.549, 95% CI 0.243–1.236; p = 0.147). With regard to other clinical endpoints, such as cardiac death, clinically-indicated TVR and TLR, the rate of events was numerically lower in

Table 2. Procedural and angiographic characteristics in the CTO group.

	BES (n = 45)	SES (n = 36)	P: BES vs. SES
CTO lesion coronary artery:			
Left main	0 (0)	0 (0)	NA
Left anterior descending	15 (33.3)	13 (36.1)	0.818
Left circumflex	7 (15.6)	12 (33.3)	0.071
Right coronary artery	23 (51.1)	9 (25.0)	0.023
Bypass graft	0 (0)	2 (5.6)	0.194
Presence of stump	27 (60)	17 (47.2)	0.251
Bridging collateral	14 (31.1)	9 (25.0)	0.544
Retrograde filling	23 (51.1)	21 (58.3)	0.517
Anterograde approach	44 (97.8)	36 (100)	NA
Bilateral injection	10 (22.2)	9 (25.0)	0.769
Number of stents implanted	2.36 ± 1.40	2.00 ± 1.01	0.205
Total stent length [mm]	55.5 ± 34.6	46.3 ± 25.3	0.194
RVD [mm]:			
In-stent	2.63 ± 0.53	2.59 ± 0.45	0.751
In-segment	2.54 ± 0.58	2.46 ± 0.49	0.501
MLD post-procedure [mm]:			
In-stent	2.10 ± 0.66	2.11 ±0.53	0.985
In-segment	1.79 ± 0.62	1.78 ±0.58	0.944
MLA post procedure [mm^2]:			
In-stent	3.59 ± 1.87	3.37 ± 1.58	0.585
In-segment	2.66 ± 1.58	2.54 ± 1.53	0.730

N (%) or mean ± standard deviation; CTO — chronic total occlusion; BES — biodegradable polymer biolimus-eluting stents; SES — sirolimus-eluting stent; NA — not assessed; RVD — reference vessel diameter; MLD — minimal lumen diameter; MLA — minimal lumen area

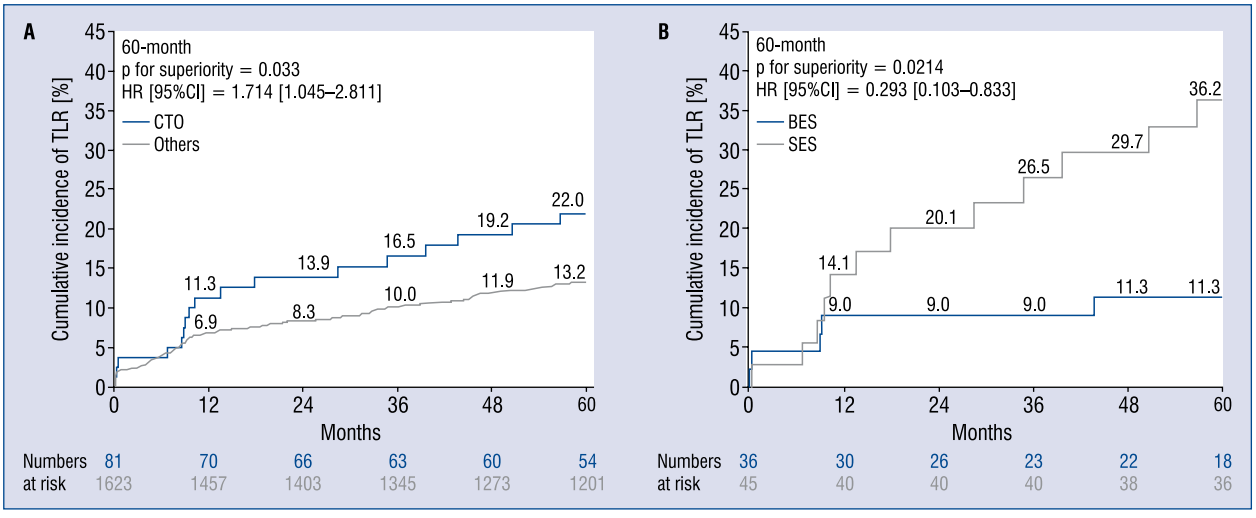

Figure 2. A. Kaplan-Meier curves show the incidence of target lesion revascularization (TLR) in chronic total occlusion (CTO) group vs. non-CTO group; **B.** Kaplan-Meier curves show the incidence of TLR within the CTO group between biodegradable polymer biolimus-eluting and sirolimus-eluting stents (BES and SES); HR — hazard ratio; CI — confidence interval.

Table 3. Events at 5-year follow-up.

	Treated CTO (n = 81)					No CTO (n = 1621)					P: ALL
	All (n = 81)	BES (n = 45)	SES (n = 36)	HR [95% CI] (BES vs. SES)	P: BES vs. SES	All (n = 1621)	BES (n = 809)	SES (n = 812)	HR [95% CI] (BES vs. SES)	P: BES vs. SES	Treated CTO vs. no CTO
MACE	24 (29.6%)	10 (22.2%)	14 (38.9%)	0.549 [0.243–1.236]	0.147	377 (23.3%)	175 (21.6%)	202 (24.9%)	0.850 [0.694–1.040]	0.115	0.173
Cardiac death	6 (7.4%)	2 (4.4%)	4 (11.1%)	0.384 [0.070–2.097]	0.269	129 (8.0%)	64 (7.9%)	65 (8.0%)	0.981 [0.695–1.385]	0.913	0.819
MI (Q-wave + non-Q--wave)	10 (12.3%)	6 (13.3%)	4 (11.1%)	1.228 [0.346–4.353]	0.751	155 (9.6%)	75 (9.3%)	80 (9.9%)	0.931 [0.679–1.276]	0.656	0.408
Clinical TVR	14 (17.3%)	5 (11.1%)	9 (25.0%)	0.411 [0.138–1.229]	0.112	214 (13.2%)	99 (12.2%)	115 (14.2%)	0.845 [0.646–1.106]	0.220	0.303
MI											
Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	24 (1.5%)	8 (1.0%)	16 (2.0%)	0.496 [0.212–1.158]	0.105	NA
Non-Q--wave MI	10 (12.3%)	6 (13.3%)	4 (11.1%)	1.228 [0.346–4.353]	0.751	135 (8.3%)	67 (8.3%)	68 (8.4%)	0.982 [0.701–1.377]	0.918	0.208
All death	10 (12.3%)	5 (11.1%)	5 (13.9%)	0.760 [0.220–2.625]	0.664	205 (12.6%)	97 (12.0%)	108 (13.3%)	0.895 [0.680–1.177]	0.426	0.882
Revascularization											
All clinical TLR	13 (16.0%)	5 (11.1%)	8 (22.2%)	0.468 [0.153–1.433]	0.184	171 (10.5%)	78 (9.6%)	93 (11.5%)	0.827 [0.612–1.118]	0.217	0.130
PCI	12 (14.8%)	5 (11.1%)	7 (19.4%)	0.544 [0.173–1.717]	0.299	156 (9.6%)	71 (8.8%)	85 (10.5%)	0.826 [0.602—1.132]	0.234	0.135
CABG	2 (2.5%)	0 (0.0%)	2 (5.6%)	NA	NA	24 (1.5%)	11 (1.4%)	13 (1.6%)	0.846 [0.379–1.889]	0.684	0.506
Any TLR	17 (21.0%)	5 (11.1%)	12 (33.3%)	0.293 [0.103–0.833]	0.0214	204 (12.6%)	94 (11.6%)	110 (13.5%)	0.843 [0.640–1.110]	0.225	0.033
Any TVR	16 (19.8%)	5 (11.1%)	11 (30.6%)	0.326 [0.113–0.942]	0.038	232 (14.3%)	108 (13.3%)	124 (15.3%)	0.858 [0.663–1.110]	0.244	0.178
Any re-PCI	21 (25.9%)	7 (15.6%)	14 (38.9%)	0.350 [0.141–0.870]	0.024	394 (24.3%)	187 (23.1%)	207 (25.5%)	0.884 [0.725–1.077]	0.221	0.762

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Table 3. (cont.) Events at 5-year follow-up.

	Treated CTO (n = 81)					No CTO (n = 1621)					P: ALL
	All (n = 81)	BES (n = 45)	SES (n = 36)	HR [95% CI] (BES vs. SES)	P: BES vs. SES	All (n = 1621)	BES (n = 809)	SES (n = 812)	HR [95% CI] (BES vs. SES)	P: BES vs. SES	Treated CTO vs. no CTO
Definite ST	5 (6.2%)	2 (4.4%)	3 (8.3%)	0.523 [0.087–3.132]	0.478	53 (3.3%)	20 (2.5%)	33 (4.1%)	0.603 [0.346–1.050]	0.074	0.177
Definite + probable ST	5 (6.2%)	2 (4.4%)	3 (8.3%)	0.523 [0.087–3.132]	0.478	70 (4.3%)	29 (3.6%)	41 (5.0%)	0.704 [0.438–1.133]	0.148	0.447
Acute (0 to 1 days)											
Definite ST	1 (1.2%)	1 (2.2%)	0 (0.0%)	NA	NA	11 (0.7%)	7 (0.9%)	4 (0.5%)	1.757 [0.514–6.003]	0.368	0.566
Definite or probable ST	1 (1.2%)	1 (2.2%)	0 (0.0%)	NA	NA	11 (0.7%)	7 (0.9%)	4 (0.5%)	1.757 [0.514–6.003]	0.368	0.566
Sub-acute (2 to 30 days)											
Definite ST	1 (1.2%)	1 (2.2%)	0 (0.0%)	NA	NA	16 (1.0%)	5 (0.6%)	11 (1.4%)	0.454 [0.158–1.306]	0.143	0.835
Definite or probable ST	1 (1.2%)	1 (2.2%)	0 (0.0%)	NA	NA	22 (1.4%)	9 (1.1%)	13 (1.6%)	0.691 [0.295–1.616]	0.394	0.919
Early (0 to 30 days)											
Definite ST	2 (2.5%)	2 (4.4%)	0 (0.0%)	NA	NA	26 (1.6%)	12 (1.5%)	14 (1.7%)	0.860 [0.398–1.859]	0.701	0.558
Definite or probable ST	2 (2.5%)	2 (4.4%)	0 (0.0%)	NA	NA	32 (2.0%)	16 (2.0%)	16 (2.0%)	1.003 [0.502–2.005]	0.994	0.761
Late (31 to 360 days)											
Definite ST	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	7 (0.4%)	3 (0.4%)	4 (0.5%)	0.754 [0.169–3.367]	0.711	n.a.
Definite or probable ST	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	9 (0.6%)	5 (0.6%)	4 (0.5%)	1.257 [0.338–4.681]	0.733	n.a.
Very late (361 to 1800 days)											
Definite ST	3 (3.7%)	0 (0.0%)	3 (8.3%)	NA	NA	21 (1.3%)	5 (0.6%)	16 (2.0%)	0.308 [0.113–0.842]	0.022	0.093
Definite or probable ST	3 (3.7%)	0 (0.0%)	3 (8.3%)	NA	NA	30 (1.9%)	8 (1.0%)	22 (2.7%)	0.359 [0.160–0.807]	0.013	0.262

BES — biodegradable polymer biolimus-eluting stent; CABG — coronary artery bypass graft; CI — confidence interval; CTO — chronic total occlusion; HR — hazard ratio; MACE — major adverse cardiac events; MI — myocardial infarction; NA — not assessed; PCI — percutaneous coronary interventions; SES — sirolimus-eluting stent; ST — stent thrombosis; TLR — target lesion revascularization; TVR — target vessel revascularization

Table 4. All stent thrombosis (ST) and dual antiplatelet (DAPT) discontinuation (d/c) for chronic total occlusion (CTO) patients.

Overall population†	BES (n = 45)	SES (n = 36)	P: BES vs. SES*
9 months	2 (4.4%)	0 (0%)	0.500
1 year	2 (4.4%)	0 (0%)	0.500
2 years	2 (4.4%)	2 (5.6%)	1
3 years	2 (4.4%)	3 (8.3%)	0.651
4 years	2 (4.4%)	3 (8.3%)	0.651
5 years	2 (4.4%)	3 (8.3%)	0.651
Patients who d/c DAPT < 12 months‡	**BES (n = 10)**	**SES (n = 11)**	**P: BES vs. SES***
9 months	0 (0%)	0 (0%)	NA
1 year	0 (0%)	0 (0%)	NA
2 years	0 (0%)	1 (9.1%)	1
3 years	0 (0%)	2 (18.2%)	0.476
4 years	0 (0%)	2 (18.2%)	0.476
5 years	0 (0%)	2 (18.2%)	0.476
Patients who d/c DAPT ≥ 12 months‡	**BES (n = 31)**	**SES (n = 23)**	**P: BES vs. SES***
9 months	0 (0%)	0 (0%)	NA
1 year	0 (0%)	0 (0%)	NA
2 years	0 (0%)	1 (4.3%)	0.426
3 years	0 (0%)	1 (4.3%)	0.426
4 years	0 (0%)	1 (4.3%)	0.426
5 years	0 (0%)	1 (4.3%)	0.426

*Fisher's exact test; †All ST are reported, regardless if patient discontinued DAPT and if the ST took place before or after d/c DAPT; ‡Only reported if the ST took place after date of d/c DAPT; BES — biodegradable polymer biolimus-eluting stents; NA — not assessed; SES — sirolimus-eluting stent

the BES, while the percentage of MI was slightly higher (Table 3). The incidence of clinically-indicated TLRs was halved in the BES group (11% vs. 22%; HR 0.468, 95% CI 0.153–1.433; p = 0.184). However, all TLRs had a significantly higher rate in the patients receiving a SES (Fig. 2B). Of interest, in the long-term follow-up the rate of any TLR was similar between the BES CTO group and overall non-CTO group (11.1% vs. 12.6%). Moreover, the use of a BES in the CTO group reduced by almost two thirds the risk of any TVR (HR 0.326, 95% CI 0.113–0.942; p = 0.038) and any repeated PCI (HR 0.350, 95% CI 0.141–0.870; p = 0.024).

The incidence of definite ST was nearly halved in the BES group (4.4% vs. 8.3%; HR 0.523, 95% CI 0.087–3.132; p = 0.478). These results were also maintained regardless of dual antiplatelet therapy compliance (Table 4).

However, although BES had a higher rate of early (≤ 30 days) definite ST (4.4% vs. 0%), no events were recorded in the late and very late period. Definite ST occurred more frequently in the very late period for the SES (p for interaction = 0.009). The same trend was also found in the 30 days landmark analysis for MACE, significantly lower between 30 days and 5 years in the BES group (p for interaction = 0.042) (Fig. 3).

Discussion

Patients with CTO are often denied angioplasty because the immediate success rate is lower than in conventional PCI [17, 18] and the long-term durability is questioned. Limited data are available for comparison of long-term follow-up in CTO and non-CTO patients. In the j-Cypher registry [19], 1,210 patients with CTO (defined as complete obstruction with TIMI flow grade 0 or 1 and an estimated duration > 1 month) were compared to 9,549 patients who underwent PCI on a non-occlusive lesion or a recent occlusion. After 5 years of follow-up, the rate of TLR was significantly higher if a CTO lesion was treated. However, the incidence of all-cause death and cardiac death was similar between CTO and non-CTO patients. This study confirms the higher incidence of late events, especially TLR, in CTO patients treated

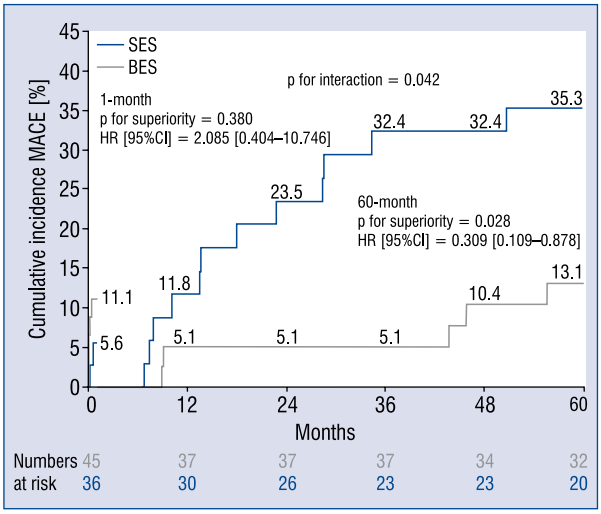

Figure 3. Landmark analysis at 30 days for major adverse cardiac events (MACE); BES — biodegradable polymer biolimus-eluting stents; CI — confidence interval; HR — hazard ratio; SES — sirolimus-eluting stent.

with SES. The similar outcome observed in CTO and non-CTO groups treated with BES suggests that second generation DES should be preferred in these complex lesions to preserve the clinical benefit conferred by a successful CTO recanalization. Multiple registries have indicated that a restored patency of a complete occlusion may translate into a greater clinical benefit than treatment of other non-occlusive lesions in stable syndromes [20–22]. ST, especially in the late and very late period, represents one of the main limitations of DES [23–25]. In our study, the overall incidence of all ST and of definite ST was similar between the CTO and non-CTO groups. These data are in line with the findings of the j-Cypher registry where the definite/probable ST did not differ according to the groups. However, in that study, the only device employed was a SES.

In our study, we tested two different DES platforms, from polymers and type of drug eluted to mechanical properties. In recent studies comparing first versus second generation DES for the treatment of CTOs [10, 11], a favorable trend was observed for second generation DES in short-term follow-up. These promising results were also confirmed by our study. In fact, in the CTO lesion subset, our data showed a notable reduction of events in favor of the biodegradable polymer Biolimus A9-coated stent with a higher reduction mainly in the long-term follow-up, equalizing the outcome between CTO and non-CTO groups.

This represents one of the main findings of our study. In fact, initial experiences in the POBA/BMS era showed that outcome of CTO was worse than non-CTO lesions [26]. This worse outcome was improved but not fully corrected by the introduction of first generation DES [27].

Several factors may explain these results. Sirolimus-eluting stents show histologic evidence of poor biocompatibility with hypereosinophilic infiltrates [28] and slow incomplete strut coverage which has been confirmed with OCT [29]. Evaginations between struts are a quite specific feature of the Cypher stent and a 9-month OCT substudy of LEADERS was the first to show a difference in strut coverage between BES and SES [30], with late catch-up shown at 2 years [31]. The rigidity and great thickness of Cypher also predispose this stent to late fracture, often associated to restenosis and re-occlusion. CTO recanalization is associated with the frequent use of long stents in vessels with most treatments performed in the right coronary artery, a vessel characterized by large systo-diastolic excursions. A DES with a bioabsorbable polymer has the advantage of the polymer gradually degrading and eventually disappearing over the course of several months, limiting the risk of the late thrombotic events in the durable polymer group, especially in complex lesions, such as the CTOs.

Limitation of the study

Our study has several limitations. First, the LEADERS CTO study, as a post-hoc analysis of a randomized controlled trial, was not powered to test the difference between CTO and non-CTO groups. Although the trial was undertaken in 10 European centers where high volume PCI procedures were performed by experienced operators using modern approaches, patients with at least one CTO treated were less than 5% of all the lesions treated. The lack of sub-randomization for CTO explains some discrepancies in the basal characteristics of the SES and BES groups but the fact lesions come from an all-comers registry improves homogeneity, making the groups more comparable and the selection process more rigorous than in other retrospective registries.

The main strength of this sub-study is represented by the confirmation of the type of lesion treated by an independent Core Lab, with nearly complete, well documented and fully monitored follow-up.

Conclusions

Chronic total occlusion subgroup of the LEADERS all-comers trial showed that BES may reduce at 5-year follow-up MACE, TVR, TLR and ST when compared to SES. For ST, the benefit of DES with biodegradable polymer seems to emerge in the late and very late phase, after the polymer is fully degraded.

These results of the CTO group are consistent with the overall trial but tested in a small subgroup and a larger trial is needed to explore these hypotheses.

Moreover, our data suggest that patients with a successful recanalization of a CTO lesion with BES may have similar outcome to patients without CTO treated with PCI, encouraging a more liberal use of PCI in CTOs.

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