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DRUG ELUTING STENTS

Two-Year Clinical Outcomes with Paclitaxel-Eluting Coronary Stents in Patients with Chronic Total Occlusions: Analysis from the TAXUS ARRIVE Program

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Aims: *To examine the incidence of clinical events after implantation of the TAXUS Express paclitaxel-eluting stent (PES) in chronic total occlusions (CTO) in an unselected patient population.*
Methods and Results: *The TAXUS ARRIVE registries compiled data on 7,492 patients, including 113 patients with CTO (TIMI flow 0). Patients enrolled at procedure start with no mandated inclusion/exclusion criteria; all cardiac events were monitored with independent end-point adjudication. Two-year follow-up was 89% (101/113) for CTO patients who had significantly more baseline comorbidities/complex disease than simple-use patients undergoing native coronary intervention (N = 2,698) and significantly longer lesions/smaller vessels than other expanded-use patients (N = 4,681 without CTO). Among CTO patients the rate of 2-year major cardiac events (MCE, including cardiac death, myocardial infarction, and target vessel revascularization) was 22.3%, significantly higher than in simple-use patients (10.3%, P < 0.001). CTO MCE was similar to that for other expanded-use patients (16.5%, P = 0.14) but target lesion revascularization was significantly higher in year 2 (6.9% vs. 2.7%, P = 0.02). Academic Research Consortium definite/probable stent thrombosis through 2 years was 5.7%, significantly higher than simple-use patients but similar to other expanded-use cases.*
Conclusion: *In a "real-world" setting, PES use in CTO was associated with increased MCE compared to simple-use patients, but achieved long-term outcomes similar to that observed in other complex patient/lesion cases.*
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Introduction

Chronic total occlusions (CTO), defined as the total absence of antegrade flow (Thrombolysis In Myocardial Infarction [TIMI] flow grade 0) for ≥3 months duration[1,2] represent one of the most difficult coronary lesions to recanalize in interventional cardiology. Successful revascularization of CTO lesions in areas of viable myocardium remains relevant because a favorable angiographic result can decrease anginal symptoms, improve left ventricular function, and in some cases increase overall survival while decreasing the need for future surgical revascularization.[3–10] The technical challenges involved in reopening CTO account for poor primary success rates[11,12] and successful recanalization is often associated with subsequent restenosis even with bare metal stents (BMS).[1,13] The use of sirolimus-eluting (SES) or paclitaxel-eluting stents (PES) has reduced restenosis and clinically driven

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revascularization at 6 months and/or 1 year as reported in a number of nonrandomized or retrospective observational studies.[14–24] Based on a subset of patients from the TAXUS Peri-Approval Registry: A Multi-Center Safety Surveillance (ARRIVE) Program, the present study examines the performance of the TAXUS™ Express™ PES in CTO through 2 years of follow-up.

Methods

Study Design, Data Collection, Monitoring, and Follow-Up. The ARRIVE Program, consisting of 2 prospective multicenter US registries, was designed to study usage patterns and clinical outcomes for patients treated with the TAXUS Express[2] Coronary Stent System (Boston Scientific Corporation, Natick, MA, USA). ARRIVE 1 (2,487 analyzed patients; 48 sites) and ARRIVE 2 (5,005 analyzed patients; 53 sites) were similarly designed to enroll consecutive patients with no specific inclusion/exclusion criteria and follow-up through 2 years. Patients were enrolled at the time of procedure initiation after providing informed consent for participation under a protocol approved by the local Institutional Review Board in conformity with the Declaration of Helsinki and FDA guidelines. Follow-up angiography was performed per local practice. Dual anti platelet therapy (DAPT) was begun before or immediately after the procedure; aspirin was continued indefinitely and thienopyridine (clopidogrel/ticlopidine) was recommended for 6 months. Both studies are registered at www.Clinicaltrials.gov (identifiers NCT00569491 and NCT00569751).

An independent Clinical Events Committee (CEC) determined the relationship of the study device to reported major cardiac events (MCE; cardiac death, myocardial infarction, [MI], target vessel revascularization [TVR]). Target lesion revascularization (TLR) was defined as "TAXUS-stent-related" TVR, given the absence of a central angiographic core laboratory. Stent thrombosis (ST) was defined per the Academic Research Consortium (ARC) definition of "definite/probable."[25] An event was considered related to TAXUS if it occurred at the stented segment or if the relationship to the stent could not be excluded based on existing information. All data for MCE and ST were source verified and there was an additional 10–20% per site random sampling of patients. Other details pertaining to the design of these registries and validation for combined analysis have been described previously.[26,27]

Statistical Analysis. Continuous variables are presented as mean ± standard deviation (SD) and were compared by Student's *t*-test. The significance of differences in categorical variables was determined using the Fisher exact test or chi-square test. Time-to-event curves were generated by the Kaplan–Meier product method with differences assessed by the log-rank test. A two-sided P value of <0.05 was considered statistically significant. All analyses were performed using SAS System Software, Version 8.0 or higher (SAS Institute, Cary, NC, USA).

The following patient subgroups were compared: (a) CTO patients with TIMI flow grade 0; (b) simple-use cases; and (c) expanded-use cases minus the CTO/TIMI 0 flow patients. Simple-use cases (N = 2,698), with or without diabetes, excluded one or more of the following: acute myocardial infarction, bifurcation, cardiogenic shock, CTO, prior brachytherapy, vein graft stenting, in-stent restenosis, large vessel (RVD > 3.75 mm), left main disease/stenting, long lesion (>28 mm), moderate/severe calcification, multivessel stenting (mean of 2.1 vessels per patient), ostial lesion, renal disease (serum creatinine >3.0 mg/dL or dialysis), severe tortuosity, small vessel (RVD < 2.5 mm) as classified by the investigator. Expanded-use cases (N = 4,794) are those not described as simple-use.

Results

Baseline Characteristics. Of 7,492 analyzed patients in the ARRIVE Program, 161 (2.1%) were classified by the investigator as having a successfully treated CTO, which could have included lesions with distal TIMI flow grade 1 and duration <3 months.[27] In this study, however, we used the more strict definition of CTO with TIMI flow grade 0 and we identified a target study population of 113 (1.5%) patients, all of whom were successfully revascularized with TAXUS stents implanted. These CTO patients were part of a large subgroup of expanded-use ARRIVE cases (N = 4,794; 64%)[27] with patient and/or lesion characteristics outside the simple-use cohort (N = 2,698) who would have met the criteria for inclusion in the TAXUS IV pivotal trial.[28]

Table 1 compares baseline patient and lesion characteristics among the CTO, simple-use, and other

Table 1. Comparison of Baseline Patient and Lesion Characteristics in ARRIVE CTO, Simple-Use, and Other Expanded-Use (Excluding CTO) Subgroups

Variable	CTO N = 113 Patients N = 128 Lesions	Other Expanded Use (Excluding CTO) N = 4,681 Patients N = 7,365 Lesions	Simple Use[a] N = 2,698 Patients N = 3,112 Lesions	P value CTO vs. Other Expanded Use (Excluding CTO)	P value CTO vs. Simple Use
Patient characteristics					
Male	74.3 (84)	68.0 (3,182)	65.9 (1,777)	0.15	0.06
Age, mean ± SD (years)	60.4 ± 12.0 (113)	65.1 ± 11.8 (4,681)	63.0 ± 11.5 (2,698)	<0.001	0.02
Smoker	31.9 (36)	23.0 (1,076)	24.2 (652)	0.03	0.06
Hypercholesterolemia	75.2 (85)	76.6 (3,585)	74.4 (2,007)	0.74	0.84
Hypertension	71.7 (81)	76.4 (3,576)	75.4 (2,034)	0.24	0.37
Diabetes[b]	27.4 (31)	32.7 (1,532)	29.8 (805)	0.24	0.58
Medically treated	23.0 (26)	29.4 (1,376)	26.3 (710)	0.14	0.43
Prior MI	36.3 (41)	41.8 (1,956)	26.9 (725)	0.24	0.03
Prior stroke	0.9 (1)	7.1 (331)	5.0 (135)	0.01	0.046
Acute/chronic renal disease	0.9 (1)	4.1 (190)	0.0 (0)	0.14	0.04
Known multivessel disease	31.0 (35)	42.7 (1,997)	27.2 (733)	0.01	0.37
Prior CABG	15.0 (17)	25.2 (1,178)	11.4 (307)	0.01	0.23
Prior PCI	20.4 (23)	37.9 (1,772)	34.5 (930)	<0.001	0.002
Known left main disease	5.3 (6)	7.5 (353)	0.0 (0)	0.37	<0.001
Congestive heart failure	2.7 (3)	8.0 (374)	5.0 (134)	0.04	0.26
Preprocedure characteristics					
Lesion RVD (mm)	2.9 ± 0.4 (128)	3.0 ± 0.5 (7,365)	3.0 ± 0.4 (3,110)	<0.001	0.002
<2.5 mm	7.8 (10)	3.7 (272)	0.0 (0)	0.03	<0.001
≥2.5 mm–<2.75 mm	29.7 (38)	25.5 (1,877)	27.3 (850)	0.30	0.56
≥2.75 mm–<3.0 mm	18.0 (23)	11.5 (846)	11.6 (360)	0.02	0.03
≥3.0 mm–<3.25 mm	29.7 (38)	29.3 (2,158)	35.9 (1,118)	0.92	0.15
≥3.25 mm–<3.5 mm	2.3 (3)	3.1 (226)	3.7 (115)	>0.99	0.63
≥3.5 mm	12.5 (16)	27.0 (1,986)	21.4 (667)	<0.001	0.02
Lesion length (mm)	26.8±19.5 (126)	16.3 ± 9.9 (7,339)	13.7 ± 5.8 (3,103)	<0.001	<0.001
Vessel location					
LAD	31.3 (40)	32.9 (2,423)	34.4 (1,072)	0.69	0.46
LCx	39.1 (50)	33.6 (2,476)	39.5 (1,228)	0.20	0.93
RCA	26.6 (34)	23.5 (1,729)	26.1 (812)	0.41	0.91
LM	0.8 (1)	2.2 (164)	0.0 (0)	0.53	0.04
Graft	2.3 (3)	7.8 (574)	0.0 (0)	0.02	<0.001

Data are % (n) or mean ± SD (n); P values are chi-square test (binary) or *t*-test (continuous).
[a]Simple-use and expanded-use cases are described in the Methods section.
[b]Includes patients treated with diet/exercise plus those treated with oral mediations and/or insulin.
Abbreviations: CABG = coronary artery bypass graft; CTO = chronic total occlusion with TIMI = 0; MI = myocardial infarction; LAD = left anterior descending; LCx = left circumflex; LM = left main; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter.

expanded-use (excluding CTO, N = 4,681) subgroups. CTO patients were significantly younger than either of the other two subgroups, with less prior percutaneous coronary intervention (PCI) and longer lesions in smaller vessels and received more TAXUS stents per lesion. Table 2 compares procedural characteristics among these 3 cohorts. The stented length per lesion was significantly greater in the CTO subgroup compared to either of the other 2 subgroups and there were significantly more dissections in the CTO cohort. Side branch occlusion was not significantly different across groups. Post-procedure flow was TIMI 3 in 95.3% of CTO lesions.

Clinical Outcomes. Among ARRIVE CTO patients, clinical follow-up was available in 93% (105/113) at 1 year and 89% (101/113) at 2 years. As shown in Figure 1, the cumulative incidence of MCE through 2 years in the CTO cohort was 22.3%, which was significantly higher than the simple-use cohort (10.3%, P < 0.001) but similar to the subgroup of expanded-use patients excluding CTO cases (16.5%, P = 0.14). Among CTO patients, all deaths

Table 2. Procedural Characteristics

Variable	CTO N = 113 Patients N = 128 Lesions	Other Expanded Use (Excluding CTO)[a] N = 4,681 Patients N = 7,365 Lesions	Simple Use[a] N = 2,698 Patients N = 3,112 Lesions	P value CTO vs. Other Expanded Use (Excluding CTO)	P value CTO vs. Simple Use
Stent utilization					
TAXUS stented length per lesion, mm	33.5 ± 25.4 (127)	21.67 ± 11.63 (7,256)	18.71 ± 7.11 (3,108)	<0.001	<0.001
Stents implanted per lesion	1.4 ± 0.9 (127)	1.2 ± 0.4 (7,256)	1.1±0.2 (3,108)	<0.001	<0.001
Procedural outcomes					
Any dissection	13.3% (17/128)	4.6% (341/7,366)	3.5% (110/3,112)	<0.001	<0.001
At target lesion	35.3% (6/17)	38.4% (131/341)	28.2% (31/110)	0.80	0.57
Proximal	29.4% (5/17)	40.2% (137/341)	34.5% (38/110)	0.38	0.68
Distal	58.8% (10/17)	30.5% (104/341)	39.1% (43/110)	0.01	0.12
Postprocedure TIMI flow					
0	0.0% (0/128)	0.2% (15/7,364)	0.3% (8/3,112)	1.00	1.00
1	2.3% (3/128)	0.1% (5/7,364)	0.1% (2/3,112)	<0.001	<0.001
2	2.3% (3/128)	0.9% (65/7,364)	0.5% (16/3,112)	0.11	0.04
3	95.3% (122/128)	98.8% (7,279/7,364)	99.2% (3,086/3,112)	0.004	0.001
Side branch occlusion	1.6% (2/128)	1.1% (83/7,366)	0.9% (29/3,112)	0.66	0.35
Side branch flow impairment	0.8% (1/128)	2.1% (154/7,366)	1.4% (45/3,112)	0.53	1.00
Visible thrombus at treated site	3.1% (4/128)	2.0% (145/7,366)	1.2% (37/3,112)	0.33	0.08

Data are % (n) or mean ± SD (n); P values are chi-square or Fisher exact test (binary) or *t*-test (continuous).
[a]Simple-use and expanded-use cases are described in the Methods section.
Abbreviations: CTO = chronic total occlusion with TIMI = 0; TIMI = thrombolysis in myocardial infarction.

were cardiac deaths, there were no Q wave MIs, and all revascularizations were TLR. The CTO cohort had significantly more MI, revascularization, and ST than the simple-use subgroup through 2 years (Fig. 1). Outcomes in the CTO population were generally similar to the expanded-use excluding CTO cohort. There was, however, a trend toward significantly more TLR in the CTO cohort compared to the expanded-use minus CTO subgroup through 2 years (14.8% vs. 9.0%, respectively, P = 0.052, Fig. 1). Annual cardiac event rates for the CTO cohort and the expanded-use minus CTO cohort in the first and second year after stenting are shown in Table 3. The CTO event rates were numerically higher for all events at all time points but were significantly higher for TLR in year 2 (6.9% [7/101] vs. 2.7%, [115/4261] P = 0.02). ST in the CTO cohort was 3.8% in the first year with similar rates of early (<30 days) and late (≥31 days−1 year) ST (1.8% and 1.9%, respectively).

Effect of Diabetes in CTO. Figure 2 shows outcomes among CTO patients with and without medically treated diabetes. Due to the small size of the groups these comparisons are intended to be hypothesis-generating analyses. Among diabetic patients, all deaths were cardiac deaths and all revascularizations were TLR. The overall incidence of MCE through 2 years was higher among diabetic patients versus the nondiabetic subgroup (37.9% vs. 17.9%, respectively) as were the individual event rates which had diverged by 6 months.

Discussion

The present study examined the performance of PES through 2 years postimplantation in CTO lesions and represents one of the few published experiences including only CTO lesions with TIMI flow 0. The 113 study patients were part of the TAXUS Express ARRIVE registries, which gathered data on 7,492 patients in routine practice.[26,27] Compared to the cohort of simple-use patients (N = 2,698) who would have been eligible for the TAXUS IV pivotal trial,[28] CTO patients had a significantly higher incidence of MCE and ST (Fig. 1). When compared to the expanded-use excluding the CTO cohort, however, the CTO subgroup did not have significantly different outcomes for cardiac death, MI, TVR, or ST. Only TLR rates were significantly higher with CTO and only in the second year (Table 3). These findings underscore the possibility that although CTO represent one of the most complex coronary lesions, PES implantation in CTO can achieve outcomes

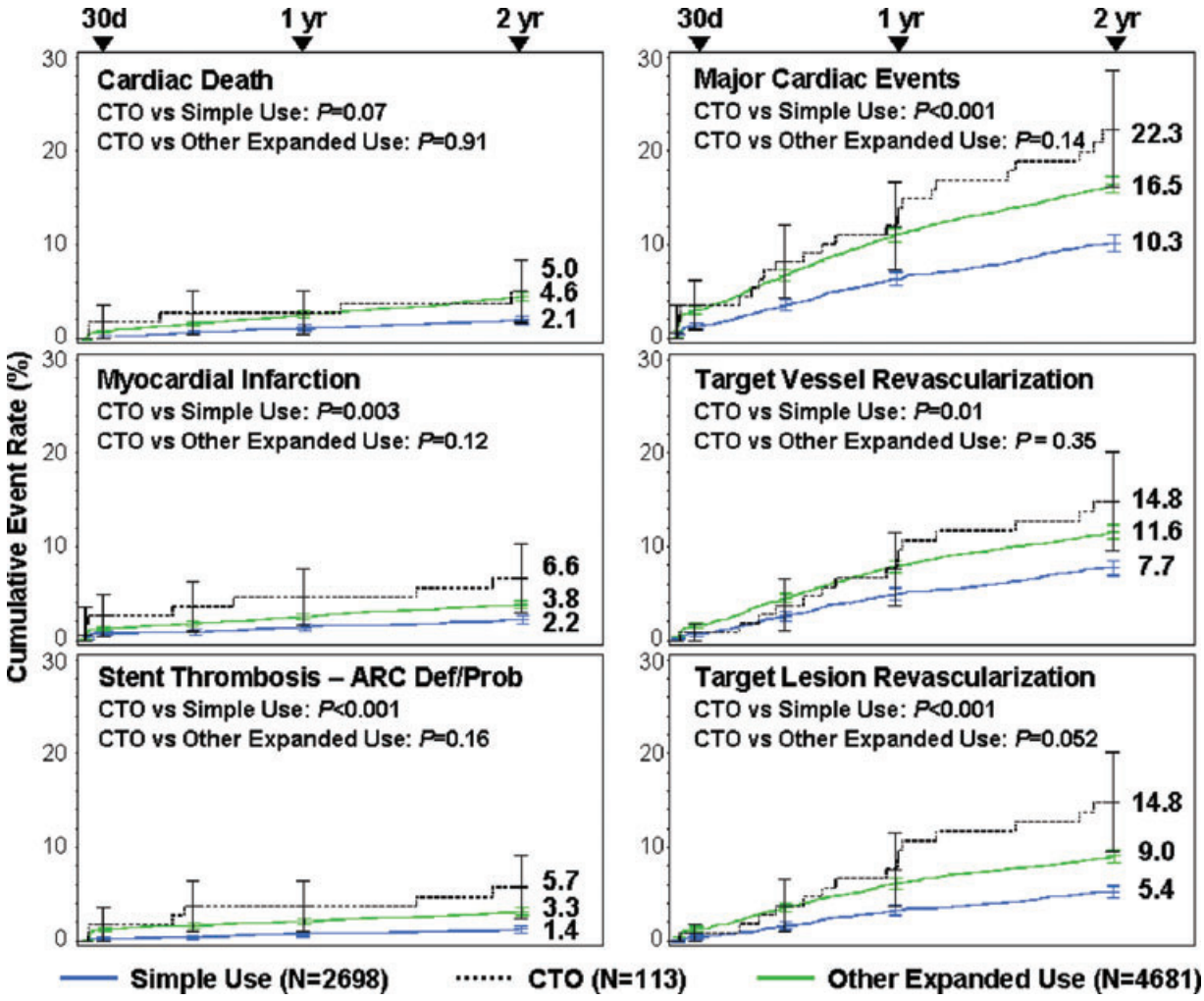

Figure 1. Time-to-event comparison of outcomes in CTO, simple-use, and other expanded-use patients. Cohorts shown are CTO with TIMI Flow Grade 0 (N = 113), Simple-Use (N = 2,698, defined in Table 1), and Other Expanded-Use (N = 4,681). ST is per ARC definite/probable definitions.[25] P values are log-rank; error bars are ± 1.5 SE. These data result from the Kaplan–Meier product method analysis and are slightly different from that reported in Table 3, which shows output from binary proportion analysis.

similar to implantation in other types of expanded-use lesions and clinical subsets.

Revascularization. Cumulative Kaplan–Meier rates for MCE in the CTO cohort were 12.0% through 1 year and 22.3% through 2 years (Fig. 1), reflecting the relatively high incidence of TLR in the first and second years after stenting (7.6% and 6.9%, respectively, Table 3). Unlike with some other high-risk patient subgroups in ARRIVE,[27] TLR rates among CTO patients did not drop over time, as has also been reported for SES.[29] These rather high rates in part reflect the comorbidities and complex coronary disease inherent in this patient population (Table 1). The technical difficulties encountered in recanalization of these lesions may contribute to higher event rates, especially revascularization, when compared to interventions on simpler lesions. Although the CTO lesion itself independently predicts restenosis, a variety of other factors have also been associated with higher restenosis rates in drug-eluting stent (DES) implantation including target vessel location, reference vessel diameter, lesion length, stent diameter, stent length, stented length, and number of implanted stents.[30–34] Our CTO cohort exhibited some of these high-risk features, including significantly longer lesions in smaller vessels, longer

stent length, and more stents per lesion, as compared to the simple-use and expanded-use excluding the CTO groups, which may contribute to the increased rates of TLR.

Comparison with Other CTO Studies. While differences in selection criteria, CTO definition/characteristics, and stenting technique make it difficult to compare directly across studies, ARRIVE CTO MCE rates were similar to that reported by others for PES and SES, with revascularization accounting for most of the total composite events. The effect of SES versus BMS in CTO was evaluated directly in the randomized controlled trial (RCT) PRISON II (N = 200 total) where CTO patients receiving SES had significantly lower TVR compared to those with BMS (8% vs. 22% at 6 months, P = 0.009).[35] The ongoing CIBELES study (anticipated enrollment of 208; www.clinicaltrials.gov Identifier NCT00793221) will compare the everolimus-eluting stent with SES in nonacute CTO and will provide additional RCT data. ARRIVE rates for mortality, MI, and TVR were comparable to that reported for DES in CTO (n = 124 at 2 years) in the STENT registry.[36] In the ACROSS/TOSCA-4 study, MCE with SES was 10.3% at 1 year, driven by a TLR rate of 9.8%.[24] Through 5 years in the RESEARCH registry, though, clinically-driven TLR in the CTO group was only slightly lower with SES versus a consecutive historical control BMS group (N = 140 total).[37] Werner et al. reported significantly reduced 1-year MACE for PES (N = 48) compared to matched cases treated with BMS (12.5% vs. 47.9%, P < 0.001).[15] Outcomes were similar in a subsequent cohort study where 12-month MCE was significantly lower with PES (N = 82) versus BMS (13.3% vs. 56.7%, P < 0.001) driven by TLR (10.0% vs. 53.4%, P < 0.001).[23] Werner et al. also found that rates were lower for patients in whom the diffuse atherosclerosis associated with the CTO was completely covered by PES rather than by a hybrid approach of PES and BMS.[23]

Diabetic Patients. Diabetic patients undergoing PCI typically have more coronary disease, an increased propensity for restenosis, and a higher risk of subsequent cardiac death and MI than nondiabetic patients.[38,39] In the ARRIVE registry overall, medically treated diabetes was associated with higher 2-year mortality but comparable MI, ST, and TLR rates.[40] Diabetic ARRIVE CTO patients experienced more major cardiac events overall compared to nondiabetic CTO patients and rates for the individual events were

Table 3. Cardiac Outcomes in ARRIVE CTO Compared to Simple-Use and Other Expanded-Use (Excluding CTO) Subgroups

	CTO[a] N = 113 Patients		Other Expanded Use (Excluding CTO)[b] N = 4,681 Patients		Simple Use[b] N = 2,698 Patients		P value CTO vs. Other Expanded Use (Excluding CTO)		P value CTO vs. Simple Use	
Variable	0–1 Yr	1–2 Yr	0–1 Yr	1–2 Yr	0–1 Yr	1–2 Yr	0–1 Yr	1–2 Yr	0–1 Yr	1–2 Yr
Cardiac death	2.9% (3/105)	2.0% (2/101)	2.7% (123/4,546)	1.8% (78/4,261)	1.3% (33/2,623)	0.8% (21/2,520)	0.76	0.71	0.16	0.22
MI[c]	4.8% (5/105)	2.0% (2/101)	2.5% (114/4,546)	1.2% (52/4,261)	1.4% (36/2,623)	0.8% (20/2,520)	0.19	0.36	0.02	0.21
TVR	7.6% (8/105)	6.9% (7/101)	7.8% (355/4,546)	3.4% (146/4,261)	4.9% (129/2,623)	2.7% (68/2,520)	0.94	0.09	0.21	0.02
TLR[d]	7.6% (8/105)	6.9% (7/101)	6.1% (276/4546)	2.7% (115/4261)	3.4% (89/2623)	1.9% (48/2520)	0.51	0.02	0.03	0.005
ST[e]	3.8% (4/105)	2.0% (2/101)	2.2% (100/4546)	1.0% (43/4261)	0.9% (24/2623)	0.5% (13/2520)	0.30	0.28	0.02	0.09

Data are from simple proportion analysis and are presented as % (n/N); P values are Fisher exact test or chi-square test. Note that these data are slightly different from that reported in Figure 1, which shows output from the Kaplan–Meier product method.

[a]Classified by the investigator as having CTO plus TIMI flow grade 0 and estimated occlusion duration of ≥3 months.

[b]Expanded use and simple use are defined in the Methods section.

[c]There were no Q wave MIs in the CTO cohort.

[d]With no central angiographic core laboratory, TLR was defined as "TAXUS-stent-related" TVR.

[e]Per ARC definite/probable definitions.[25]

Abbreviations: ARC = Academic Research Consortium; MI = myocardial infarction; TVR = target vessel revascularization; TLR = target lesion revascularization; ST = stent thrombosis.

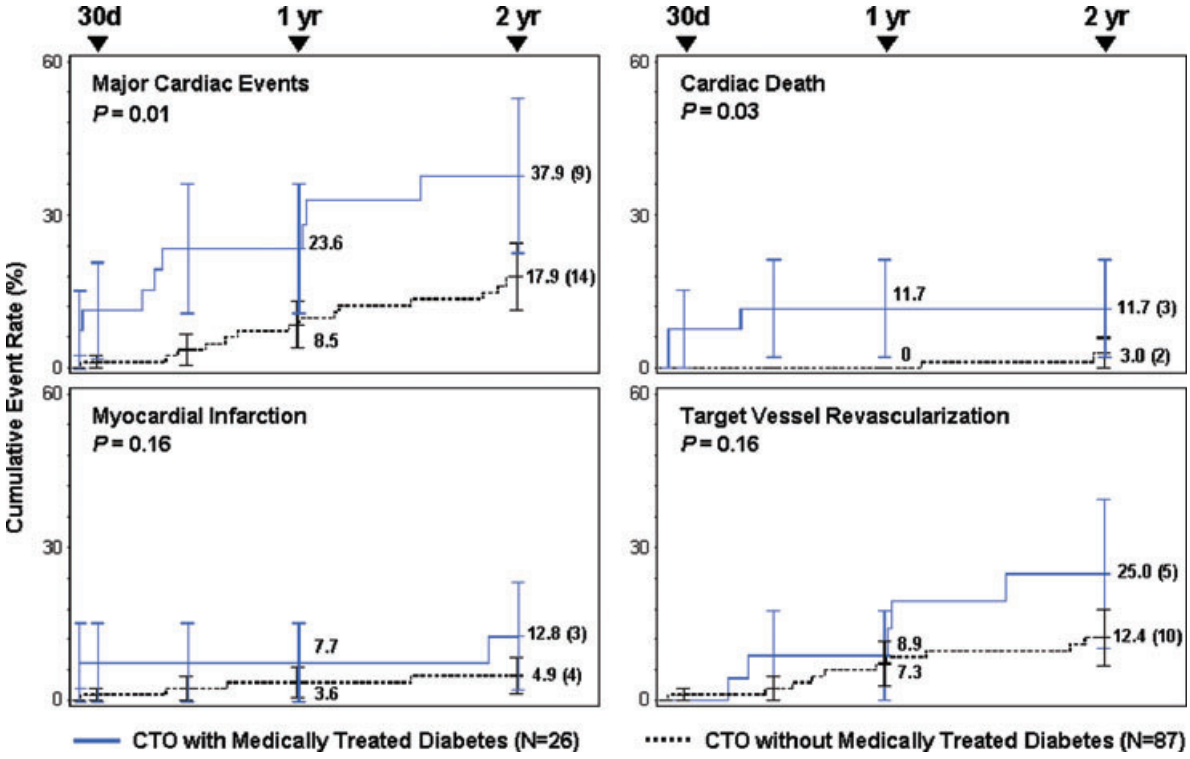

Figure 2. Time-to-event comparison of outcomes in ARRIVE CTO patients with and without medically treated diabetes. Cohorts included patients with (N = 26) and without (N = 87) medically treated diabetes in the ARRIVE CTO with TIMI Flow = 0 subgroup. P values are log-rank; error bars are ± 1.5 SE.

numerically higher in the diabetic group. Revascularization was not statistically significantly higher in diabetic versus nondiabetic CTO patients, though TLR was more common in the overall CTO subgroup versus the expanded-use excluding CTO cohort. This may suggest that in CTO patients, as in the overall ARRIVE population, PES can abrogate the increased risk of restenosis among diabetic patients previously seen with BMS[31,40,41] though the small sample size here limits the interpretation of these hypothesis-generating analyses. A number of studies evaluating SES use in diabetic patients have not demonstrated a similar reduction of restenosis rates compared to nondiabetic patients[42–45] though recent registry reports have suggested similar restenosis rates with PES and SES among diabetic patients.[46–48]

Study Limitations. ARRIVE has several limitations inherent in registries including lack of a control group, use of site-specific angiographic assessment rather than core laboratory analysis, absence of protocol-mandated serial cardiac enzyme or electrocardiographic measurements which may introduce multiple interpreter variability due to the lack of standardization and less monitoring than would be found with traditional RCTs. Lack of intravascular ultrasound use for evaluating stent apposition (only in 1.6% of CTO patients) especially in CTO lesions potentially contributed to the registry's event rates. This study provides no information on the angiographic success rate of CTO recanalization as patients were only included by definition if a PES was implanted. Multiple testing is a limitation in the diabetic analysis as the relatively small CTO sample size is further subdivided by these comparisons. Finally, ARRIVE allowed site investigators to define a CTO lesion, though the outcome data reported here were confined to TIMI flow grade 0 cases.

Conclusions

In conclusion, when compared to the cohort of other expanded-use patients in the ARRIVE registry, the CTO subgroup yielded comparable results in terms

of cardiac death, MI, TVR, and ST. Revascularization was similar among diabetic and nondiabetic CTO patients suggesting that PES can abrogate the increased risk of restenosis among diabetic patients. These "real-world" results show that PES can be safely implanted across CTO with favorable long-term outcomes.

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Author Contributions

Drs. Lasala and Cox contributed to study conception/design and collection; Drs. Lasala, Cox, Huang, Yeung, Starzyk, Bowman, and Dawkins contributed to data analysis and interpretation; Drs. Huang, Yeung, and Starzyk drafted the manuscript; Drs. Lasala, Cox, Bowman, and Dawkins provided critical review/revision of the manuscript; all authors approved the final manuscript version.

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