Zilver® PTX® Drug Eluting Peripheral Stent

Panel Package

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1. Executive Summary

The Zilver® PTX® Drug-Eluting Peripheral Stent (Zilver PTX stent) is coated on the outer surface with a small amount of paclitaxel that is locally delivered to the vessel walls and was first used to treat patients in 2005. Since that time, greater than 300,000 devices have been supplied for patient treatment globally, and there has been no signal of an increased mortality rate in any pre-market studies or post-market surveillance (PMS) data (e.g., clinical studies, complaint data, review of published literature). Results from the Zilver PTX randomized controlled trial (RCT) and Japan PMS, which included large patient populations with completed 5-year follow-up, demonstrate no increased risk of mortality with the Zilver PTX stent compared to angioplasty with a bare balloon (PTA) or placement of a BMS. These conclusions are supported by consistent results from numerous additional analyses, including propensity score analysis, covariate analysis, evaluation for a paclitaxel dose effect, and evaluation of cause of death.

2. Device Description

The Zilver PTX stent is a self-expanding nitinol stent coated on its outer surface with a thin layer of the drug paclitaxel. It is indicated in the US for improving luminal diameter for the treatment of *de novo* or restenotic symptomatic lesions in native vascular disease of the above-the-knee femoropopliteal arteries having reference vessel diameter from 4 mm to 7 mm and total lesion lengths up to 300 mm per patient. The Zilver PTX stent was CE Marked in 2009 and approved in the US and Japan in 2012.

There are several technological differences that distinguish the Zilver PTX stent from other currently approved paclitaxel-coated stents and balloons. In comparison to other approved paclitaxel-eluting stents, the coating on the Zilver PTX stent consists only of paclitaxel, without the presence of any polymer, binder, or excipient, and is applied only to the outer surface of the stent at a dose density of 3 $\mu g/mm^2$ (the inner lumen of the stent is uncoated). The solid state phase of the paclitaxel coating on the Zilver PTX stent is primarily amorphous. As a result of the open-cell stent design and coating only of the outer stent surface, the total amount of paclitaxel on the Zilver PTX stent is low, ranging from 0.4 mg for the 40 mm length stent to 1.3 mg for the 140 mm length stent. The maximum total amount of paclitaxel that a patient receives when a 300 mm lesion length is treated is approximately 3 mg (0.01 mg/mm vessel). In comparison to drug-coated balloons (DCB), the total amount of paclitaxel on the Zilver PTX stent is approximately 5 to 10 times lower.

In contrast to DCBs, the Zilver PTX stent is protected by a retractable sheath during delivery through the body. Once deployed, the paclitaxel on the stent remains between the stent struts and the vessel wall, with minimal downstream delivery; nearly all (typically >98%) of the coating remains on the stent during delivery and deployment. Due to the amorphous form of the paclitaxel, any paclitaxel particles that may travel downstream quickly dissolve in the blood (approximately 80% dissolved after 40 minutes in non-clinical testing). After the paclitaxel coating is eluted, only a bare metal stent remains, with no polymer or long-term drug release.

3. Animal Safety and Pharmacokinetics

Animal studies to support approval of the Zilver PTX stent were extensive; studies were conducted in accordance with Good Laboratory Practices (21 CFR 58) and included placement of approximately 450 stents in 190 animals with follow-up durations through 6 months. Study endpoints were relevant to the safety, performance, and pharmacokinetics (PK) of the Zilver PTX stent, and included animal health observations and clinical pathology, as well as thorough necropsies under the supervision of board-certified veterinary pathologists.

The studies included a range of dose densities and a range of total doses per animal and per hindlimb. Studies included the commercial paclitaxel dose density of 3 µg/mm^2, as well as overdose densities of 9 and 12 µg/mm^2. To establish a drug safety margin with respect to regional and systemic effects, an *in vivo* study evaluated the regional and systemic effects of a total paclitaxel dose >3X what a patient would receive when treated for the maximum indicated 300 mm lesion length. Specifically, Zilver PTX stents were used to provide a dose of approximately 10.5 mg paclitaxel per animal (equivalent to a total stent length >1,000 mm). The assessments of local effects included quantitative angiography, quantitative histomorphometry, and qualitative and semiquantitative histopathology. The assessments of regional and systemic effects included hematology, serum chemistry, and thorough necropsies (including gross and histologic evaluation of all major body systems [integumentary, musculoskeletal, respiratory, cardiovascular, digestive, genitourinary, lymphatic, endocrine, and nervous systems] to look for potential systemic effects, and detailed evaluation of the downstream, hindlimb tissues to look for potential regional effects).

The animal studies showed no evidence of health problems or negative sequelae associated with Zilver PTX stents, including no safety concerns at total paclitaxel doses >3X what a patient would receive when implanted with the maximum number of stents allowable per the IFU. There were no systemic or regional paclitaxel effects; no thromboses, occlusions, vessel ruptures, aneurysms, pseudoaneurysms, or drug-related medial thinning; no evidence of variable paclitaxel effect along the stented length; and no edge effect stenoses. The results also demonstrated adequate local healing responses and endothelialization of the stented vessels at all dose densities evaluated, without negative sequelae. Thorough necropsies revealed no adverse effects associated with the devices tested.

PK evaluations assessed the paclitaxel levels locally on the stent and in the stented vessel wall, regionally in the proximal and distal reference vessel wall and the adjacent and downstream skeletal muscle, and systemically in the plasma. This included a 24-hour PK study and a 2-month PK study to further define the timing of the peak plasma paclitaxel level. The PK data showed that paclitaxel was locally delivered to the stented arterial wall with very limited regional and systemic delivery. Specifically, the paclitaxel remaining on the stent decreased rapidly at first, dropping to approximately 34% at 30 minutes and 7% at 6 hours after implantation. Beyond 6 hours, the paclitaxel remaining on the stent decreased gradually, to approximately 0.1% of the initial amount at 56 days. Locally, the paclitaxel levels in the stented arterial wall peaked immediately after stent implantation, dropped off rapidly to approximately 44% of peak at 6 hours, leveled off at around 20% of peak from 1 to 14 days, then tapered off gradually to approximately 0.2% of peak by 56 days. Regionally, in adjacent and downstream skeletal muscle, paclitaxel levels were low, at less than 3% of those in the stented artery and dropped below the assay limit of quantification after 56 days in adjacent muscle and after 7 days in downstream muscle, respectively. Systemically, in the plasma, the paclitaxel levels were extremely low, at less than 0.007% of those in the stented arterial wall and dropped below the limit of quantification after 6 hours.

In summary, these extensive animal PK studies support the safety of the Zilver PTX stent and showed no safety concerns at total paclitaxel doses >3X what a patient would receive when implanted with the maximum number of stents allowable per the IFU. The PK studies also showed that paclitaxel was locally delivered to the stented arterial wall with very limited regional and systemic delivery.

4. Clinical Evidence

A literature review was performed to identify 5-year mortality rates for peripheral arterial disease (PAD) patients who underwent revascularization, and the results are shown in Table 4-1.

Table 4-1 Literature-reported 5-year mortality rates in PAD patients

Citation		Number of Patients	Disease State	Mortality Rate	
				Annualized	5-year
Rantner B, et al. Sci Rep. 2017;8:45833		255	IC	1.7%	8.6%
Rana H, et al. J Vasc Surg. 2013;57:28-36[a]		564	IC	3.2%	16%
Pande RL, et al. Circulation. 2011;124:17-23[b]		647	IC	4.5%	22.6%
Mueller T, et al. J Vasc Surg 2014;59:1291-1299		487	IC	4.7%	23.4%
Heikkila K, et al. BJS Society. 2018;105:1145–1154[c]		26579	IC	4.9%	24.7%
Pereg D, et al. Coron Artery Dis. 2014;25:79–82		1708	IC	5.2%	25.9%
Sigvant B, et al. Eur J Vasc Endovasc Surg. 2016;51:395-403[d]		57,322	IC	5.4%	27%
Chen DC, et al. Am J Cardiol. 2017;119:1146-1152		382	IC	4.8%	24%
		497	CLI	10.2%	51%
Secemsky E, et al. J Am Coll Cardiol. E-pub ahead of print	DES	4105	60%	10.3%	51.7%
01March2019. doi https://doi.org/10.1016/j.jacc.2019.02.020[e]	BMS	47351	CLI	10.0%	50.1%

IC = Intermittent Claudication; CLI = Critical Limb Ischemia; DES = Drug-eluting Stent
[a] 2-year mortality rate was reported as 6%.
[b] Mean follow-up of 4.4 years.
[c] 1-year and 3-year mortality rates were reported as 7.6% and 16.5%, respectively.
[d] Meta-analysis included studies with follow-up ranging from 1-13 years.
[e] 60% of patients had CLI; median follow-up was reported as 2 years; mortality rate estimate was 4.1 years, corresponding to the maximum follow-up duration; the only peripheral DES available during the study period was the Zilver PTX stent.

The Zilver PTX stent has been evaluated in multiple clinical investigations enrolling more than 2,000 patients. Table 4-2 provides an overview of mortality rates in Cook-sponsored studies of the Zilver PTX stent and the Zilver BMS. Table 4-3 presents mortality rates for investigational studies of a Cook paclitaxel-eluting renal stent and a Cook paclitaxel-coated balloon; the paclitaxel coating on these devices is comparable to that on the Zilver PTX stent. All deaths in each of these studies underwent adjudication by an independent clinical events committee (CEC), including an assessment of relationship to the device. Importantly, no deaths were adjudicated as device-related, including no paclitaxel-related deaths.

Table 4-2. Mortality rates for Zilver PTX and Zilver BMS studies

Study	Device	Follow-up	# of Patients	Kaplan-Meier Mortality Rate				
				Annualized	1-year	2-year	3-year	5-year
RCT[a]	Zilver PTX	5 years	336	3.7%	2.4%	5.8%	10.5%	18.7%
	PTA/BMS	5 years	143	3.5%	2.8%	6.1%	9.8%	17.6%
Japan PMS[b]	Zilver PTX	5 years	904	5.1%	5.4%	11.4%	15.6%	25.7%
	BMS	3 years	190	5.1%	4.7%	9.5%	15.3%	
EU BMS	BMS	5 years	110	3.3%	0.9%	2.8%	4.8%	16.7%
US PAS[c]	Zilver PTX	5 years	200	3.1%	2.6%	5.3%	9.4%	TBD
Single-arm Study	Zilver PTX	2 years	787	3.0%	3.2%	5.9%		
French Reimbursement	Zilver PTX	2 years	119	3.2%	3.4%	6.3%		
China[d]	Zilver PTX	1 year	178	0.6%	0.6%			
REAL PTX[e]	Zilver PTX	3 years	75	1.5%	2.7%		4.6%	
	DCB[f]		75	3.9%	6.9%		11.6%	

[a] Consistent with the ICHE9 guidance further described in Section 4.1.4, patient groups follow "as-treated" principle.
[b] Concurrently enrolled, non-randomized studies; sequential enrollment with no exclusion criteria; substantial rate of CLI.
[c] 5-year follow-up ongoing.
[d] Non-Kaplan-Meier rate; mortality calculated as 1/178.
[e] Physician-sponsored study funded by Cook; patients were randomized to the Zilver PTX stent or commercially available DCBs.
[f] 77.3% InPact, 21.3% Lutonix, 1.4% Other.

Table 4-3. Mortality rates for other Cook paclitaxel device studies

Study	Device	Follow-up	# of Patients	Kaplan-Meier Mortality Rate				
				Annualized	1-year	2-year	3-year	5-year
Renal	Paclitaxel-eluting Renal Stent[a]	5 years	81	2.8%	5.1%	7.8%	7.8%	14.1%
	Bare Renal Stent		39	3.0%	0%	5.7%	8.8%	15.2%
Advance 18 DCB	Paclitaxel-coated PTA balloon[a]	2 years	78	1.3%	2.6%	2.6%		
	Bare PTA balloon		73	1.5%	1.4%	2.9%		

[a] Paclitaxel coating is comparable to that on the Zilver PTX stent.

Overall, the 5-year mortality rates reported in the literature are consistent with each other. Furthermore, the rates for the Zilver PTX stent fall within the literature-reported mortality ranges summarized in Table 4-1, thus supporting the safety of the Zilver PTX stent.

Analyses in the subsequent sections focus on the pivotal RCT study and the large real-world all-comers study in Japan. Both of these studies enrolled patients with superficial femoral artery (SFA) disease, have adequate non-paclitaxel-coated comparators, and have completed 5-year follow-up. Additional analyses for these studies include propensity matching, covariate analysis, dose analysis, and an evaluation of causes of death. A PK analysis and a review of all adverse events are also included for the RCT.

4.1 Zilver PTX RCT

The Zilver PTX RCT was a prospective, multinational, randomized study designed to compare the safety and effectiveness of the paclitaxel-eluting Zilver PTX stent to PTA and provisional BMS placement in patients with femoropopliteal PAD. Randomization was stratified based on lesion length to help ensure the patient cohorts were appropriately balanced for the primary effectiveness outcome. A total of 479 patients were enrolled at 55 sites in the United States, Japan, and Germany. Five-year follow-up is complete, and results have been published.[1] At the time the RCT was initiated, there was no approved BMS available in the US for SFA treatment. Therefore, the study had a unique design, developed in conjunction with FDA, that included a primary randomization to the Zilver PTX stent or PTA (standard-of-care at the time) followed by a secondary randomization to the Zilver PTX stent or BMS for patients who had suboptimal acute PTA results. The study also allowed crossover to treatment with the Zilver PTX stent for PTA patients who subsequently required reintervention within the first year post-procedure. The secondary randomization was driven by a need from the medical community to have a direct comparison of drug-eluting stent versus BMS, and the crossover allowed patients the opportunity to receive the Zilver PTX stent in the event that their primary treatment failed. Notably, as a result of this study design, per the protocol, 40% of patients in the primary PTA randomization group were actually treated with a Zilver PTX stent at the time of the procedure (n=63) or within the first year (n=31). Overall, 70% (n=336) of patients in the study were treated with a Zilver PTX stent and 30% (n=143) of patients were treated with PTA only or BMS. Figure 4.1-1 provides a schematic demonstrating the overall flow of patients within the Zilver PTX RCT.

[1] Dake MD, et al. Circ Cardiovasc Interv. 2011;4:495-504; Dake MD, et al. J Am Coll Cardiol. 2013;61:2417-2427; Dake MD, et al. [published erratum in Circulation. 2019;139:e42] Circulation. 2016;133:1472-1483.

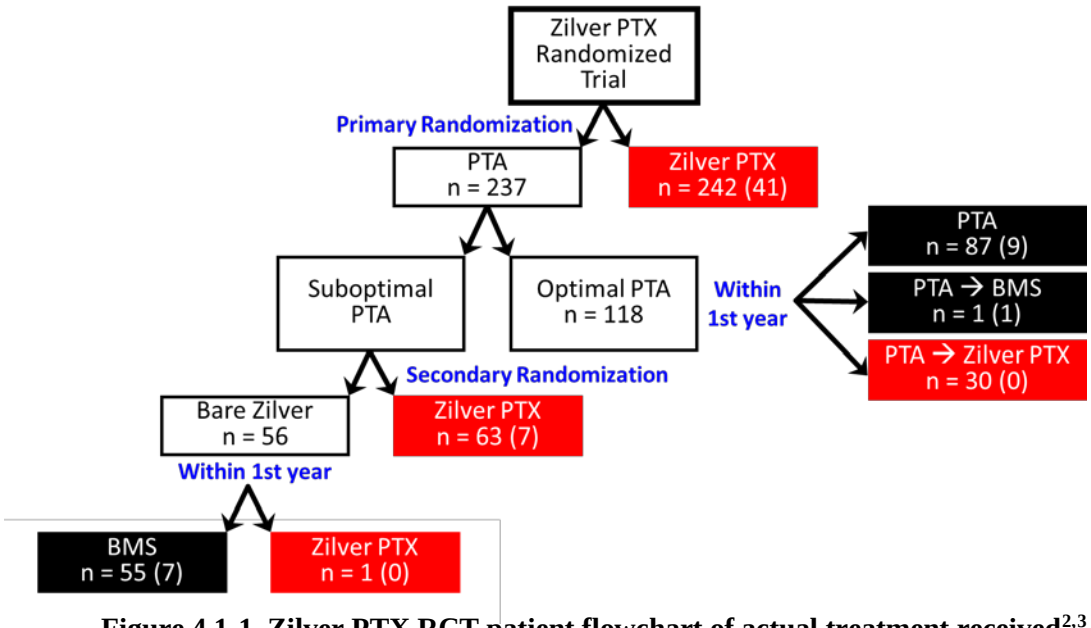

Figure 4.1-1. Zilver PTX RCT patient flowchart of actual treatment received[2,3]

Prior to the Zilver PTX RCT and throughout the enrollment and follow-up periods, there were no other peripheral paclitaxel-coated devices available in the US or Japan. Therefore, patients were not treated with a peripheral paclitaxel-coated device prior to study enrollment, nor were they treated with a peripheral paclitaxel-coated device during reintervention of the study limb or non-study limb other than the protocol-defined use of the Zilver PTX stent.[4] As a result, there is no confounding effect on mortality in the control group of the Zilver PTX RCT due to the use of paclitaxel-coated devices for reintervention or treatment of the contralateral leg.

4.1.1 Clinical Pharmacokinetics

A subgroup of 60 Zilver PTX patients from the RCT were included in a PK substudy to evaluate systemic paclitaxel delivery. Patients were divided into two groups based on the number of stents with which they were implanted. A parametric curve was fit to the data, and the maximum observed plasma paclitaxel concentration (C_{max}), time to maximum concentration (T_{max}), area under the plasma concentration-time curve (AUC), half-life ($t_{1/2}$), and paclitaxel total clearance (CL_{plasma}) were estimated, along with 95% confidence intervals (Table 4.1.1-1). Additionally, clinical results were compared to previous animal study results.

[2] Numbers in parentheses represent the number of deaths within each group.
[3] The Zilver PTX study allowed for treatment of 2 lesions in separate procedures. For 2 patients who had 2 lesions treated, lesion 1 was treated with PTA, but lesion 2 was treated with primary PTX. In this flowchart for consideration of paclitaxel-related mortality, these patients are included in the primary PTX group since they underwent primary PTX treatment for lesion 2. Additionally, 1 patient who was initially assigned to the primary PTX group was treated with a primary BMS due to unavailability of the necessary Zilver PTX device size at the time of treatment. In this flowchart, this patient is included in the primary PTA/BMS group. None of these 3 patients died during the study. The primary PTX group includes 5 live case patients enrolled as part of national continuing medical education conferences; none of these 5 patients died during the study. In the secondary randomization to Zilver PTX or BMS, 3 patients were randomized to BMS but were treated with Zilver PTX and are included in the Zilver PTX group in this flowchart; 1 of these patients died at 1542 days. Additionally, 1 patient was randomized to the Zilver PTX group but was treated with a BMS and is included in the BMS group in this flowchart.
[4] There was late commercial availability of paclitaxel DCBs in Germany prior to the completion of the Zilver PTX RCT follow-up in 2013. There were no deaths in the PTA/BMS group in Germany.

Table 4.1.1-1. Pharmacokinetic parameters (with 95% confidence intervals)

Parameter	One Stent (n=42 patients)	Two Stents (n=16 patients)	Animal PK Study (n=2 animals)
Paclitaxel dose range (mg)	0.3 - 0.9 (mean ± SD: 0.7 ± 0.2)	1.1 - 1.7 (mean ± SD: 1.4 ± 0.2)	0.9
T_{max} (min)	20	22	20
C_{max} (ng/mL)	4.4 (4.2 - 4.6)	6.6 (6.3 - 6.9)	7.1
$AUC_{0\text{-}last}$ (ng·h/mL)[a]	6.5 (4.7 - 8.5)	14.0 (10.7 - 17.2)	12.8
$AUC_{0\text{-}inf}$ (ng·h/mL)[a]	6.5 (4.7 - 8.5)	14.9 (11.2 - 18.7)	12.8
$t_{1/2}$ (h)	2.4 (1.8 - 3.3)	7.0 (5.2 - 10.8)	1.6
CL_{plasma} (L/h)	107 (81.4 - 147.3)	93.3 (74.6 - 124.7)	68.5

[a] AUC (area under the plasma concentration-time curve) from time zero to time of last measured concentration or time zero to infinity.

The clinical PK results were in close agreement with previously reported results from the animal PK studies. Minimal paclitaxel was delivered systemically (C_{max} <10 ng/mL), and only trace levels (less than 1 ng/mL) remained in the plasma at the 8- and 12-hour time points. The very low concentration and short duration of paclitaxel in the blood support the safety of the Zilver PTX stent.

In contrast to chemotherapeutic use, the total amount of paclitaxel on the Zilver PTX stent is low. Typical cumulative systemic intravenous doses of paclitaxel over the course of 12 weeks for the treatment of breast cancer are approximately 1,120 to 1,536 mg (1.1 to 1.5 g).[5] This compares to the maximum locally delivered paclitaxel dose of approximately 3 mg (0.003 g) for the treatment of a 300 mm SFA lesion with the Zilver PTX stent, which is <0.3% of the chemotherapeutic dose. A recent review[6] indicated that for a single treatment of the most commonly used chemotherapeutic dose (175 mg/m^2 given as a 3-hour infusion), C_{max} was 4400 ng/mL, which is approximately 500-1000 times greater than levels measured with the Zilver PTX stent; CL_{plasma} was 20 L/h, which is approximately 5 times lower than with the Zilver PTX stent; and plasma levels were >40 ng/mL through 24 hours in comparison to levels of <1 ng/mL at 12 hours with the Zilver PTX stent.

4.1.2 Primary Endpoints

The RCT included a primary safety hypothesis of noninferior (i.e., equivalent or superior) event-free survival (defined as freedom from the CEC-adjudicated major adverse events of death, target lesion revascularization (TLR), target limb ischemia requiring surgical intervention or surgical repair of the target vessel, and freedom from worsening of the Rutherford classification by 2 classes or to class 5 or 6) at 1 year for the primary Zilver PTX randomization group compared to the primary PTA randomization group. The primary effectiveness hypothesis was superior primary patency at 1 year for the primary Zilver PTX randomization group compared to the primary PTA randomization group. Secondary analyses evaluated effectiveness of the Zilver PTX stent compared to a BMS, including assessment of primary patency and freedom from TLR.

The 1-year primary endpoints of event-free survival and patency showed superiority of the primary Zilver PTX randomization group compared to the primary PTA randomization group, and these results were sustained through 5 years. Through 5 years, rates for primary patency (66.4% versus 43.4%, p<0.01) and freedom from TLR (83.1% versus 67.6%, p<0.01) for the Zilver PTX stent group (primary plus provisional) were superior to rates for the PTA/BMS group. Similarly, rates for patency (72.4% versus 53.0%, p=0.03) and freedom from TLR (84.9% versus 71.6%, p=0.06) with provisional Zilver PTX stent placement were improved over those for provisional BMS placement in a randomized comparison. These results represent a >40% relative risk reduction

[5] Mayer E. Uses of Paclitaxel as a Primary Therapy in Oncology: Outcomes, Benefits, Adverse Events and Doses Compared to Devices. Presented at: Vascular Leaders Forum; 01 March 2019; Washington, D.C.
[6] Stage TB et al. Clin Pharmacokinet. 2018;57:7–19

for both restenosis and TLR through 5 years for the Zilver PTX stent compared to PTA/BMS, reflecting the long-term benefits of the Zilver PTX stent.[7]

4.1.3 Primary Randomization Mortality Analysis

A comparison of unadjusted mortality for the primary randomization groups is shown in Figure 4.1.3-1 and Table 4.1.3-1. Mortality through 5-year follow-up was 22.1% for the primary Zilver PTX randomization group and 15.3% for the primary PTA randomization group (log-rank p=0.04). However, per the study protocol, 40% (94/237) of the primary PTA randomization group patients were actually treated with a Zilver PTX stent (63 patients following acute PTA failure and secondary randomization during the initial procedure and 31 patients following failure of their original therapy in the first year). Therefore, this mortality comparison of primary randomization groups is confounded by inclusion of Zilver PTX patients in the primary PTA randomization group; an as-treated analysis of mortality is described in Section 4.1.4.

Despite randomization, the observed mortality difference between the primary randomization groups is thought to be related to imbalances in patient comorbidities and demographics that were not addressed by stratification. Randomization and stratification are intended to result in cohorts of patients that are comparable. However, it is not always possible to ensure balance between randomized groups across many variables (e.g., demographics such as age and comorbidities such as diabetes) that may influence an outcome of interest, such as all-cause mortality, for which the RCT was not designed. Propensity matching is a well-known and widely used method that reduces potential bias due to known confounding factors and provides highly comparable and well-balanced cohorts of patients on which to perform comparative analyses.[8] Therefore, this method was used to evaluate mortality results for the primary Zilver PTX and primary PTA randomization groups.

For this propensity score analysis, a Cox proportional hazards model using stepwise variable selection identified the following variables related to mortality to use for patient matching: age, total lesion length, diabetes, carotid disease, congestive heart failure, arrhythmia, prior tissue loss, renal disease, smoking status, and hypercholesteremia. Additional variables included in the Cox model but not selected for patient matching were claudication/critical limb ischemia (CLI), body mass index, gender, previous myocardial infarction (MI), pulmonary disease, hypertension, and country. Of the 479 RCT patients, 372 (78%) were matched (186 pairs). Mortality for these propensity-matched patients through 5-year follow-up was 18.3% for the primary Zilver PTX randomization group and 18.7% for the primary PTA randomization group (log-rank p=0.79). Therefore, when patients are matched using baseline variables resulting in two comparable groups, there is no difference in mortality between the primary randomization groups through 5 years.

[7] Dake MD, et al. [published erratum in Circulation. 2019;139:e42] Circulation. 2016;133:1472-1483
[8] Rubin DB, Ann Intern Med. 1997;127:757-763; Stürmer T, et al. J Intern Med. 2014;275:570-580; Williamson EJ, et al. Stat Med. 2014;33:721-737

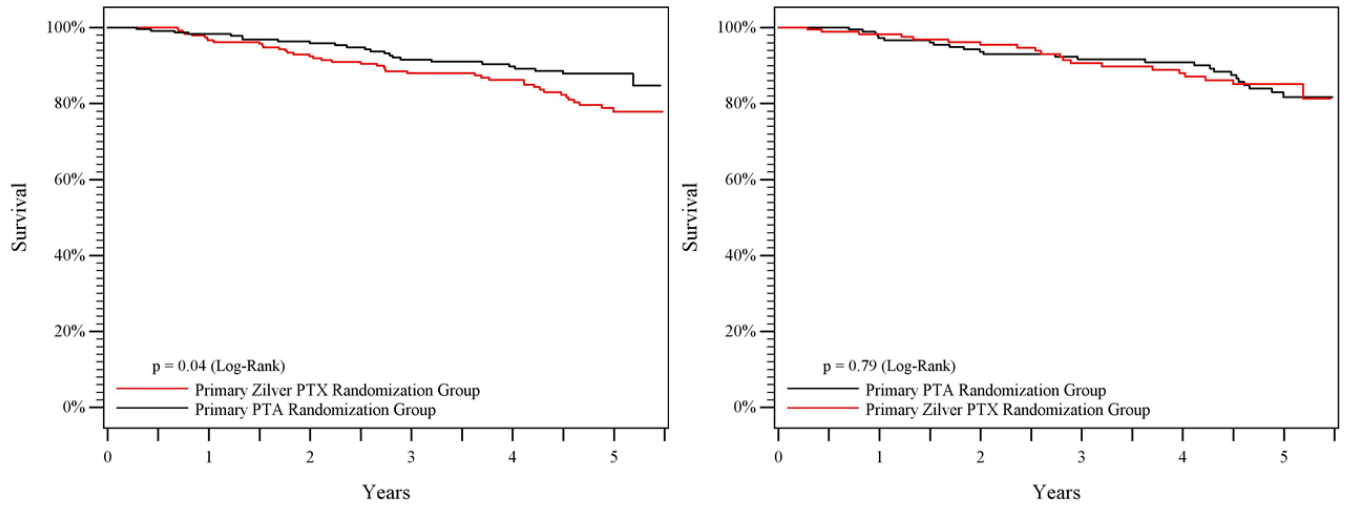

Figure 4.1.3-1. Kaplan-Meier survival analyses for the RCT primary randomization groups (left: unmatched groups; right: matched groups)

Table 4.1.3-1. Kaplan-Meier estimates for the RCT primary randomization groups

Years	Mortality Estimate		Standard Error		Failed		Censored		Remaining	
	Primary PTX	Primary PTA	Primary PTX	Primary PTA	Primary PTX	Primary PTA	Primary PTX	Primary PTA	Primary PTX	Primary PTA
Unmatched Primary Randomization Groups										
0	0%	0%	0%	0%	0	0	0	0	242	237
1	3.4%	1.7%	1.2%	0.9%	8	4	10	15	224	218
2	7.6%	4.1%	1.8%	1.4%	17	9	31	36	194	192
3	12.0%	8.4%	2.4%	2.1%	26	17	50	55	166	165
4	13.8%	10.2%	2.6%	2.3%	29	20	70	68	143	149
5	22.1%	12.1%	4.1%	2.7%	41	23	126	131	75	83
Final	22.1%	15.3%	4.1%	6.4%	41	24	-	-	-	-
Propensity-Matched Primary Randomization Groups										
0	0%	0%	0%	0%	0	0	0	0	186	186
1	2.8%	1.7%	1.2%	1.0%	5	3	7	31	174	152
2	6.4%	4.6%	1.9%	1.8%	11	7	25	47	150	132
3	8.3%	9.4%	2.3%	2.6%	14	13	41	63	131	110
4	9.1%	12.0%	2.5%	3.1%	15	16	57	72	114	98
5	18.3%	14.9%	4.4%	3.5%	25	19	101	102	60	65
Final	18.3%	18.7%	4.4%	7.7%	25	20	-	-	-	-

4.1.4 As-Treated Mortality Analysis

When considering mortality potentially related to treatment with a paclitaxel-eluting device, it is of utmost importance to consider all patients treated with the paclitaxel device compared to patients treated only with non-paclitaxel devices (i.e., PTA or BMS). This as-treated analysis for safety is supported by the International Conference on Harmonisation Guideline, *E9 Statistical Principles for Clinical Trials*, which includes a description of the set of subjects who should be evaluated for safety. This internationally harmonized standard endorsed by multiple regulatory bodies, including the United States FDA, states, "For the overall safety and tolerability assessment, the set of subjects to be summarized is usually defined as those subjects who received at least one dose of the investigational drug."[9] Therefore, when considering potential paclitaxel-related mortality, the

[9] International Conference on Harmonisation. E9 Statistical principles for clinical trials. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf. September 1998. Accessed May 10, 2019.

most appropriate analysis is to compare all patients treated with the Zilver PTX stent in the study (n=336; groups identified in red in Figure 4.1-1) to those treated only with PTA or BMS (n=143; groups identified in black in Figure 4.1-1). Figure 4.1.4-1 and Table 4.1.4-1 provide the Kaplan-Meier estimates of survival and the corresponding life table for these groups. The unadjusted risk of mortality through 5-year follow-up was 18.7% for patients treated with the Zilver PTX stent and 17.6% for patients treated with only PTA or BMS. There is no increased risk of long-term mortality for patients treated with the Zilver PTX stent compared to patients treated with PTA or BMS (log-rank *p*=0.53).

The same propensity score analysis used for the primary randomization analysis was also used to identify appropriately matched patients to help ensure a balanced comparison in the as-treated analysis. Up to a 2:1 matching was used since the number of Zilver PTX patients in the study was more than twice the number of PTA/BMS patients. A total of 211 PTX patients (63%) were matched to 129 PTA patients (91%). As shown in Figure 4.1.4-1 and Table 4.1.4-1, mortality through 5 years for the propensity-matched patients was 20.7% for the Zilver PTX stent and 18.6% for PTA/BMS (log-rank *p*=0.53). These results are comparable to the results prior to matching and further confirm that there is no difference in mortality for the Zilver PTX stent compared to PTA/BMS.

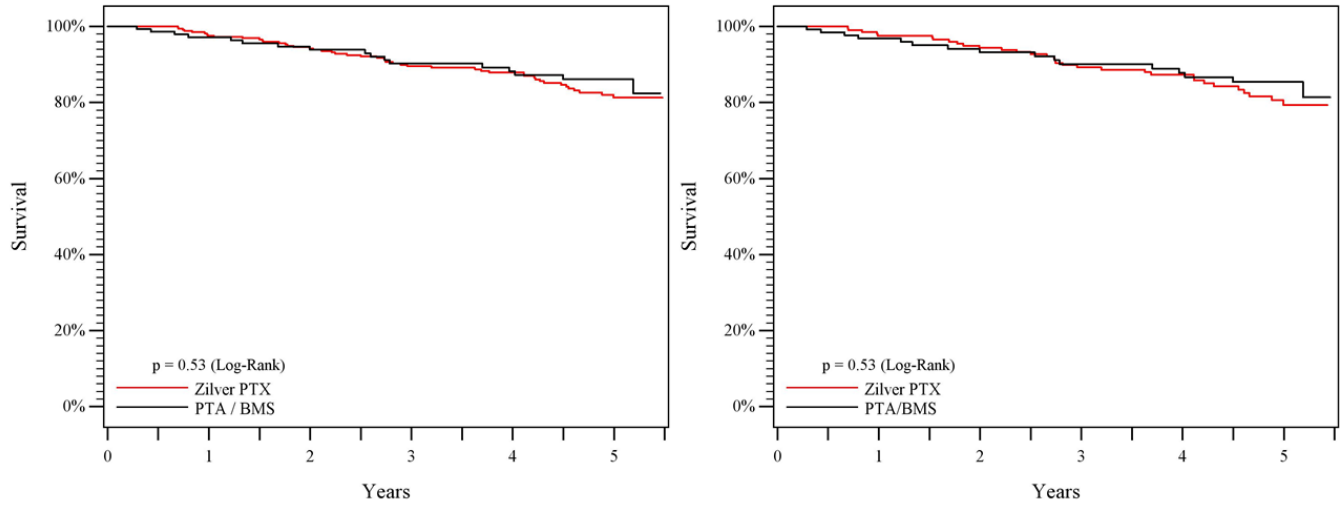

Figure 4.1.4-1. Kaplan-Meier survival analyses for the RCT as-treated groups (left: unmatched groups; right: matched groups)

Table 4.1.4-1. Kaplan-Meier estimates for the RCT as-treated groups

Years	Mortality Estimate		Standard Error		Failed		Censored		Remaining	
	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS
Unmatched As-treated Groups										
0	0%	0%	0%	0%	0	0	0	0	336	143
1	2.4%	2.8%	0.9%	1.4%	8	4	13	12	315	127
2	5.8%	6.1%	1.4%	2.2%	18	8	43	24	275	111
3	10.5%	9.8%	1.9%	2.8%	31	12	69	36	236	95
4	12.1%	11.8%	2.1%	3.2%	35	14	97	41	204	88
5	18.7%	13.9%	3.4%	3.6%	48	16	186	71	102	56
Final	18.7%	17.6%	3.4%	7.4%	48	17	-	-	-	-

Years	Mortality Estimate		Standard Error		Failed		Censored		Remaining	
	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS	Zilver PTX	PTA/ BMS
Propensity-Matched As-treated Groups										
0	0%	0%	0%	0%	0	0	0	0	211	129
1	2.4%	3.2%	1.1%	1.6%	5	4	8	11	198	114
2	5.6%	6.8%	1.7%	2.5%	11	8	25	23	175	98
3	10.8%	9.9%	2.4%	3.0%	20	11	40	35	151	83
4	12.7%	12.2%	2.7%	3.5%	23	13	63	39	125	77
5	20.7%	14.6%	4.6%	3.9%	32	15	121	64	58	50
Final	20.7%	18.6%	4.6%	7.9%	32	16	-	-	-	-

4.1.5 Covariate and Dose Analysis

In addition to the propensity analysis, a Cox proportional hazards model considered all variables simultaneously to ascertain which factors may influence mortality. As shown in Table 4.1.5-1, treatment arm (Zilver PTX vs. PTA/BMS; as-treated) was not a predictor of mortality (HR=1.076 (0.592, 1.956)); only age and prior tissue loss were significant predictors of mortality.

To analyze the potential for a paclitaxel dose-dependent mortality response, the total paclitaxel dose per patient (ranging from 0 to 3.5 mg paclitaxel) was input into the Cox model in place of treatment arm (due to the highly correlated nature of treatment arm and dose, both variables were not considered simultaneously in the model). The results demonstrate that paclitaxel dose was not a predictor of mortality (HR=0.987 (0.948, 1.028)); age and prior tissue loss remained the only significant variables (Table 4.1.5-1).

Table 4.1.5-1. Results of Cox proportional hazards model for Zilver PTX RCT

Covariate		Treatment Arm Analysis[a]		Dose Analysis[b]	
		P-value	HR (95% CI)	*P*-value	HR (95% CI)
Age		0.001	1.059 (1.022, 1.096)	0.002	1.057 (1.021, 1.095)
Prior tissue loss		0.01	2.662 (1.249, 5.674)	0.007	2.855 (1.333, 6.112)
Diabetes		0.08	1.618 (0.945, 2.769)	0.09	1.597 (0.932, 2.737)
Congestive heart failure		0.13	1.741 (0.855, 3.543)	0.10	1.815 (0.891, 3.697)
Carotid disease		0.13	1.564 (0.871, 2.810)	0.13	1.583 (0.880, 2.848)
Lesion length (mm)		0.21	1.003 (0.998, 1.009)	0.14	1.005 (0.998, 1.011)
Renal disease		0.22	1.538 (0.776, 3.051)	0.22	1.532 (0.774, 3.034)
Cardiac arrhythmia		0.22	1.558 (0.767, 3.167)	0.25	1.516 (0.747, 3.076)
Smoking	Never vs. quit	0.30	0.902 (0.400, 2.037)	0.32	0.922 (0.409, 2.079)
	Never vs. current		0.569 (0.227, 1.430)		0.587 (0.234, 1.472)
	Quit vs. current		0.631 (0.341, 1.169)		0.636 (0.343, 1.179)
Body mass index		0.33	0.971 (0.915, 1.030)	0.34	0.972 (0.916, 1.031)
Hypercholesterolemia		0.41	1.329 (0.678, 2.607)	0.37	1.364 (0.694, 2.678)
Gender (male)		0.44	1.247 (0.709, 2.193)	0.42	1.263 (0.719, 2.220)
Pulmonary disease		0.51	1.237 (0.658, 2.324)	0.52	1.234 (0.654, 2.329)
Country	Germany vs. US	0.59	0.509 (0.115, 2.255)	0.59	0.517 (0.117, 2.289)
	Japan vs. US		0.741 (0.292, 1.878)		0.723 (0.286, 1.828)
Hypertension		0.68	1.191 (0.519, 2.731)	0.59	1.256 (0.545, 2.894)
Paclitaxel[a,b]		0.81	1.076 (0.592, 1.956)	0.54	0.987 (0.948, 1.028)
CLI vs. claudication		0.89	1.061 (0.455, 2.477)	0.99	1.007 (0.429, 2.363)
Previous MI		0.92	1.033 (0.537, 1.986)	0.88	1.051 (0.550, 2.011)

HR = hazard ratio; CI = confidence interval.
[a] Treatment arm (Zilver PTX vs. PTA/BMS, as-treated).
[b] Paclitaxel dose; unit size = 0.1 mg paclitaxel.

The results from these covariate analyses provide additional evidence demonstrating that there is no increased risk of mortality with the Zilver PTX stent.

4.1.6 Causes of Death

A summary of causes of death during the study based on information provided by the sites and the CEC adjudications is provided in Table 4.1.6-1 below. The most prevalent causes of death were cardiovascular disease and cancer. The rate of cardiovascular death was higher in the PTA/BMS group compared to the Zilver PTX group. Therefore, there is no indication of an increased rate of cardiovascular mortality associated with the Zilver PTX paclitaxel drug coating. Although the rate of cancer death was higher in the Zilver PTX group compared to the PTA/BMS group, the difference is not statistically significant (p=0.11). Additionally, the rate of cancer death was somewhat lower than the rate observed in a separate evaluation of 110 patients with 5-year follow-up treated with the Zilver BMS in Europe, as also shown in Table 4.1.6-1. Furthermore, McDermott et al.[10] reported a 3-year cancer mortality rate of 3.0% in a cohort of 1,314 PAD patients, corresponding to a 1-year annualized rate of 1.0% (i.e., approximately 5% through 5 years). Rantner et al.[11] reported that cancer was the leading cause of death in a population of 255 intermittent claudication patients, occurring in 3.9% of patients (10/255) within 5 years. These rates are comparable to that seen in the Zilver PTX RCT for cancer deaths. Therefore, there is no indication of an increased rate of cancer-related mortality associated with the Zilver PTX stent. Rates for other causes of death are low and similar between the groups and also similar to the rate observed in a separate study of the Zilver BMS.

Table 4.1.6-1. CEC-adjudicated causes of death

Cause	Zilver PTX RCT			Zilver BMS Europe
	PTX	PTA/BMS	*P*-value	BMS
Cardiovascular	4.8% (16/336)	5.6% (8/143)	0.66	4.5% (5/110)
Cancer[a]	4.8% (16/336)	1.4% (2/143)	0.11	6.4% (7/110)
Pulmonary	1.8% (6/336)	1.4% (2/143)	>0.99	1.8% (2/110)
Stroke	0.6% (2/336)	0.7% (1/143)	>0.99	0% (0/110)
Trauma/accident	0% (0/336)	1.4% (2/143)	0.09	0% (0/110)
Gastrointestinal	0.3% (1/336)	0% (0/143)	>0.99	0.9% (1/110)
Multiple/unknown	2.1% (7/336)	1.4% (2/143)	>0.99	0.9% (1/110)

[a] History of cancer was not collected prior to patient enrollment.

4.1.7 Adverse Events

Adverse events reported during the study were compared for patients treated with the Zilver PTX stent to patients treated with PTA/BMS. As shown in Table 4.1.7-1, there was no increase in any specific category of adverse events for patients treated with the Zilver PTX stent. Additionally, adverse event rates were compared for 60 prespecified event types within the cardiovascular, pulmonary, renal, gastrointestinal, wound, vascular, and miscellaneous categories. These 60 event types were defined prospectively in the study protocol based on previous experience with vascular stent studies, reporting standards, and considerations specific to peripheral vascular disease and the presence of a drug coating. The only event types with significant differences between the Zilver PTX group and the PTA/BMS group were “Vascular Other” and “Pulmonary COPD,” both of which occurred at higher rates in the PTA/BMS group. Therefore, there is no indication of an increased rate of any adverse event type for patients treated with the Zilver PTX stent.

[10] McDermott MM, et al. Vasc Med. 2016;21:120-129.
[11] Rantner B, et al. Sci Rep. 2017;8:45833.

Table 4.1.7-1. Adverse events for RCT

Event Category	Zilver PTX[a]	PTA/BMS	*P*-value
Cardiovascular	36.9% (124/336)	37.8% (54/143)	0.92
Pulmonary	19.3% (65/336)	21.0% (30/143)	0.71
Renal	14.3% (48/336)	13.3% (19/143)	0.89
Gastrointestinal	19.3% (65/336)	16.8% (24/143)	0.61
Wound	9.2% (31/336)	9.1% (13/143)	>0.99
Vascular	71.4% (240/336)	70.6% (101/143)	0.91
Miscellaneous	55.4% (186/336)	55.9% (80/143)	0.92

[a] All adverse events for patients who crossed over to the Zilver PTX stent are counted in the Zilver PTX group.

4.1.8 Additional Data Collection for Lost-to-Follow-up Patients

Of the 479 patients enrolled in the RCT, 238 patients completed 5-year follow-up, 65 patients died, 55 patients withdrew, and 121 patients were lost to follow-up (LTF). Cook has requested information on the current status of LTF patients and patients who completed the study from sites in the US and Germany; there were no LTF patients in Japan. Additional follow-up information was not requested for the 55 patients who actively withdrew from the study. To date, additional follow-up information has been obtained for 88/121 LTF patients, and Cook is continuing to pursue data for the remaining patients.

4.2 Japan Post-Market Surveillance Study

In addition to the Zilver PTX RCT results, Cook analyzed results from the PMS of the Zilver PTX stent and the Zilver BMS in Japan. Both studies were conditions of approval in Japan and are complete with follow-up through 5 years for the Zilver PTX study and through 3 years for the BMS study. The Japan PMS studies had no inclusion/exclusion criteria, which resulted in inclusion of patients treated outside the indications for use. The studies enrolled 904 consecutive patients treated with the Zilver PTX stent and 190 consecutive patients treated with the Zilver BMS[12]. These were non-randomized studies that enrolled concurrently.

4.2.1 Mortality Analysis

Figure 4.2.1-1 and Table 4.2.1-1 provide the Kaplan-Meier estimates of survival and the corresponding life table for the Zilver PTX and Zilver BMS patients. The risk of mortality through 3 years was 15.6% for Zilver PTX patients and 15.3% for Zilver BMS patients (i.e., 5.2% vs. 5.1% annualized rates, respectively). The risk of mortality through 5 years was 25.7% for Zilver PTX patients (5.1% annualized rate; the BMS study follow-up ended at 3 years). There was no difference in mortality between Zilver PTX stent and Zilver BMS patients (log-rank p=0.92). Both groups have an approximately 5% annual mortality rate over the available follow-up periods with no apparent increase in the annual mortality rate beyond 3 years with the Zilver PTX stent. The mortality rates in the Japan PMS studies for both the Zilver PTX stent and Zilver BMS were higher compared to the rates in the Zilver PTX RCT, likely reflecting that the patients enrolled in these all-comers studies had overall poorer health and more challenging lesions, including having a higher incidence of CLI, than the patients enrolled in the Zilver PTX RCT.[13]

Similar to the Zilver PTX RCT, a propensity score analysis was used to match Zilver PTX and Zilver BMS patients in the Japan PMS studies. Based on the variables available from the Japan PMS studies, the following were used for patient matching: age, diabetes, carotid disease, claudication/CLI, renal failure, smoking status,

[12] 18 additional patients enrolled in the BMS study were also treated with Zilver PTX at the time of the procedure. To maintain a group consisting only of BMS, these patients were excluded from this analysis. Two of these 18 patients died within 3 years (3.7% annual rate).
[13] Yokoi H, et al. J Am Coll Cardiol Intv. 2016;9:271-277

hypercholesteremia, and gender. Up to 4:1 matching of Zilver PTX to Zilver BMS patients was used since the number of Zilver PTX patients in the study was more than 4 times the number of BMS patients. A total of 547 Zilver PTX patients (61%) were matched to 165 Zilver BMS patients (89%). As shown in Figure 4.2.1-1 and Table 4.2.1-1, the propensity-matched results demonstrate no difference in mortality (log-rank *p*=0.80) for patients treated with the Zilver PTX stent or Zilver BMS, and these results are comparable to the results prior to matching.

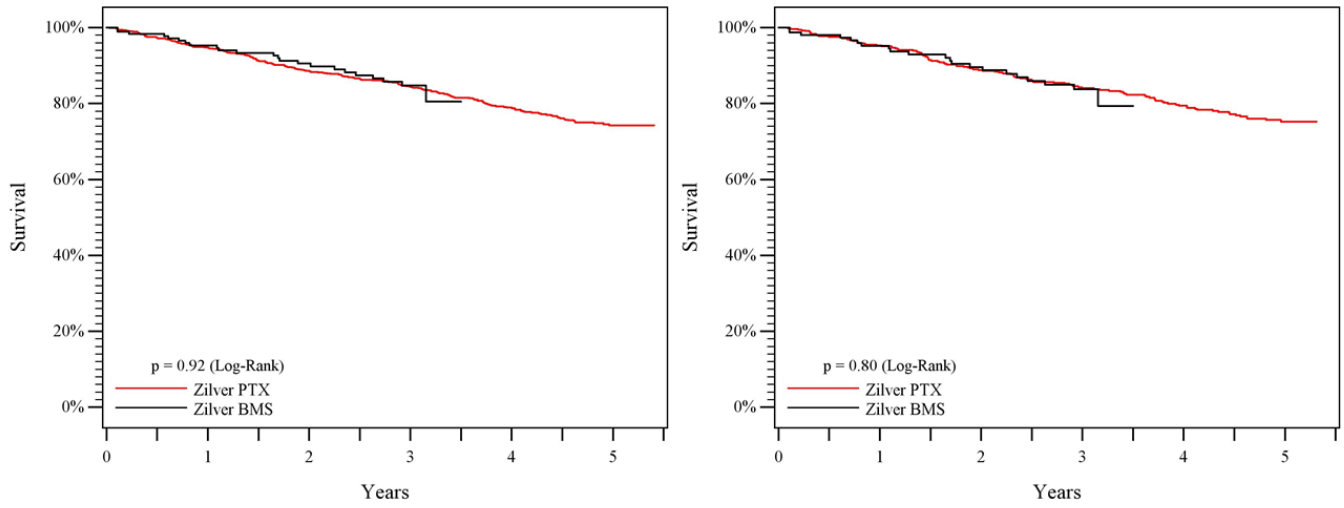

Figure 4.2.1-1. Kaplan-Meier survival analyses for the Japan PMS studies (left: unmatched groups; right: matched groups)

Table 4.2.1-1. Kaplan-Meier survival analysis estimates for the Japan PMS

Years	Mortality Estimate		Standard Error		Failed		Censored		Remaining	
	Zilver PTX	BMS	Zilver PTX	BMS	Zilver PTX	BMS	Zilver PTX	BMS	Zilver PTX	BMS
Unmatched Japan PMS Groups										
0	0%	0%	0%	0%	0	0	0	0	904	190
1	5.4%	4.7%	0.8%	1.6%	47	8	47	29	810	153
2	11.4%	9.5%	1.1%	2.5%	96	15	132	52	676	123
3	15.6%	15.3%	1.4%	3.6%	126	22[a]	211	108	567	60
4	21.1%		1.7%		160		273		471	
5	25.7%		2.3%		185		499		220	
Propensity-Matched Japan PMS Groups										
0	0%	0%	0%	0%	0	0	0	0	547	165
1	4.7%	4.8%	0.9%	1.8%	25	7	31	27	491	131
2	11.2%	10.4%	1.4%	2.8%	57	14	68	47	422	104
3	15.9%	16.2%	1.8%	4.0%	78	20	117	95	352	50
4	20.6%		2.1%		96		154		297	
5	24.8%		2.9%		110		297		140	

[a] One additional event occurred after 3 years (1095 days).

4.2.2 Covariate and Dose Analysis

Similar to what was previously described for the Zilver PTX RCT, a Cox proportional hazards model was also developed for the Japan PMS studies incorporating the variables available from these studies. As shown in Table 4.2.2-1, paclitaxel treatment (Zilver PTX stent vs. Zilver BMS stent) was not a predictor of mortality (HR=1.160 (0.724, 1.859)). Age, CLI, renal failure, male gender, and no hypercholesterolemia were significant predictors for mortality, reflecting the overall poorer health in these all-comers studies compared to the RCT.

To analyze the potential for a paclitaxel dose-dependent mortality response, the total paclitaxel dose per patient (ranging from 0 to 8.3 mg paclitaxel) was input into the Cox model in place of treatment arm (due to the highly correlated nature of treatment arm and dose, both variables were not considered simultaneously in the model). The results demonstrate that paclitaxel dose was not a predictor of mortality (HR=1.015 (0.996, 1.035)); age, CLI, renal failure, gender, and hypercholesterolemia remained significant (Table 4.2.2-1).

Table 4.2.2-1. Results of Cox proportional hazards model for Japan PMS

		Treatment Arm Analysis[a]		Dose Analysis[b]	
Covariate		***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**
CLI vs. claudication		<0.0001	2.984 (2.207, 4.034)	<0.0001	3.011 (2.231, 4.065)
Renal failure[c]		<0.0001	2.473 (1.839, 3.326)	<0.0001	2.453 (1.825, 3.298)
Age		<0.0001	1.045 (1.026, 1.064)	<0.0001	1.046 (1.027, 1.065)
Gender (male)		0.001	1.833 (1.264, 2.658)	0.001	1.859 (1.281, 2.696)
Hypercholesterolemia		0.004	0.641 (0.473, 0.870)	0.004	0.640 (0.472, 0.868)
Diabetes		0.12	1.283 (0.938, 1.757)	0.15	1.262 (0.922, 1.726)
Carotid disease		0.19	1.223 (0.907, 1.649)	0.17	1.233 (0.915, 1.662)
Smoking	Never vs. quit	0.23	1.312 (0.922, 1.867)	0.18	1.344 (0.945, 1.914)
	Never vs. current		1.013 (0.658, 1.557)		1.021 (0.664, 1.571)
	Quit vs. current		0.772 (0.519, 1.147)		0.760 (0.510, 1.131)
Hypertension		0.43	0.859 (0.588, 1.255)	0.44	0.862 (0.590, 1.259)
Paclitaxel[a,b]		0.54	1.160 (0.724, 1.859)	0.12	1.015 (0.996, 1.035)
Lesion length (mm)		0.57	1.004 (0.991, 1.016)	0.41	0.991 (0.971, 1.012)
Pulmonary disease		0.95	1.019 (0.593, 1.750)	0.96	0.987 (0.574, 1.698)

HR = hazard ratio; CI = confidence interval.
[a] Zilver PTX vs. Zilver BMS.
[b] Paclitaxel dose; unit size = 0.1 mg paclitaxel.
[c] eGFR <60 mL/min/1.73m^2 and/or on dialysis.

Similar to the Zilver PTX RCT results, the results of these covariate analyses for the Japan PMS provide additional evidence demonstrating that there is no increased risk of mortality with the Zilver PTX stent.

4.2.3 Causes of Death

A summary of causes of death for the Zilver PTX Japan PMS study based on information provided by the sites and CEC adjudications is provided in Table 4.2.3-1 below. The most prevalent cause of death was cardiovascular disease. The mortality rates are comparable to the rates seen in the Zilver PTX RCT, which are included for ease of comparison. Since rates for the Zilver BMS PMS study are only available through 3 years, they are not included in this table.

Table 4.2.3-1. CEC-adjudicated causes of death

Cause	Zilver PTX Japan PMS	Zilver PTX RCT
Cardiovascular	6.1% (55/904)	4.8% (16/336)
Cancer	2.9% (26/904)	4.8% (16/336)
Pulmonary	2.7% (24/904)	1.8% (6/336)
Stroke	1.5% (14/904)	0.6% (2/336)
Trauma/accident	0.2% (2/904)	0.0% (0/336)
GI	0.2% (2/904)	0.3% (1/336)
Infection	0.2% (2/904)	0.0% (0/336)
Renal	0.8% (7/904)	0.0% (0/336)
Multiple/unknown	5.9% (53/904)	2.1% (7/336)

5. Next Steps

Proposed recommendations for next steps include the following:

1. **Guideline Enhancement:** Review and update as needed, in collaboration with physician societies, to clarify the appropriate follow-up for PAD patients to optimally manage the overall complexity and range of co-morbidities found in this patient population.
2. **Future PAD studies:** Ensure consistent follow-up and visit compliance in both control and treatment arms, as appropriate. Ensure adequate reporting of contralateral limb revascularization and pharmacologic regimen used. Provide additional guardrails to minimize loss-to follow-up, in particular for mortality outcomes, (e.g., update informed consent language to allow withdrawal from study procedures but continued visibility to vital status).
3. **Large datasets:** As an achievable goal, Cook supports an industry-wide partnership with key stakeholders (physician societies, FDA, etc.) to further interrogate existing, large, observational datasets (e.g., CMS data, RAPID) to confirm lack of a mortality signal over an extended period (e.g., 5 years).

6. Conclusions

In conclusion, based on an extensive review of the available data, there is no increased mortality risk with the Zilver PTX stent compared to PTA/BMS. Importantly, the Zilver PTX stent provides a sustained clinical benefit, providing a >40% relative risk reduction for both restenosis and TLR through 5 years compared to PTA/BMS. The Zilver PTX stent is coated with a small amount of paclitaxel, with minimal paclitaxel delivered systemically, and only trace levels remaining in the plasma at 12 hours. Furthermore, the mortality rates observed for the Zilver PTX stent are within the rates reported in the literature for PAD patients undergoing revascularization.

The Zilver PTX RCT study design included a protocol-specified secondary randomization and cross-over to Zilver PTX treatment within the first year. As a result, per the protocol, 40% of patients in the primary PTA randomization group were actually treated with a Zilver PTX stent in the study. In unmatched groups, mortality through 5-year follow-up was 22.1% for the primary Zilver PTX randomization group and 15.3% for the primary PTA randomization group. After propensity matching, there is no difference in mortality between the primary randomization groups (18.3% for the primary Zilver PTX randomization group vs. 18.7% for the primary PTA randomization group, log-rank p=0.79).

An as-treated analysis of all patients treated with the Zilver PTX stent compared to those treated only with PTA or BMS demonstrates no increased risk of long-term mortality with the Zilver PTX stent (18.7% vs. 17.6%; log-rank p=0.53). Covariate analyses support the conclusion that the Zilver PTX stent does not increase the risk of mortality, and there is no association of paclitaxel dose with mortality. There was no indication of an increased rate of any specific cause of death for the Zilver PTX stent, and no deaths have been CEC-adjudicated as paclitaxel-related or device-related. Additionally, there is no increased rate of any category of adverse events or specific adverse event type for patients treated with the Zilver PTX stent compared to PTA/BMS.

Furthermore, results from large real-world all-comers studies in Japan also showed no increased risk of mortality for the Zilver PTX stent compared to the Zilver BMS stent. Similar to the Zilver PTX RCT, covariate analyses of data from Japan support the conclusion that there is no relationship between the Zilver PTX stent and mortality.

Taken together, the extensive analyses of the clinical evidence are consistent and support the conclusion that there is no increased risk of mortality for the Zilver PTX stent compared to non-paclitaxel devices.